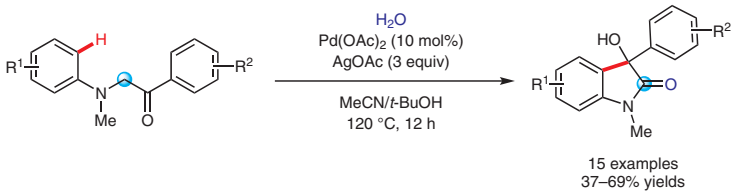
Synthesis Y.-Y. Liao et al. Paper

Palladium-Catalyzed Selective Synthesis of 3-Hydroxy-2-oxindoles via Cascade C–H Cycloaddition and Oxidation of α-Aminoacetophenones

Yan-Yan Liao
Li Xu
Ri-Yuan Tang*
Wen-Xu Zheng*

Department of Applied Chemistry, College of Materials and Energy, South China Agricultural University, Guangzhou 510642, P. R. of China
rytang@scau.edu.cn
wzheng@scau.edu.cn



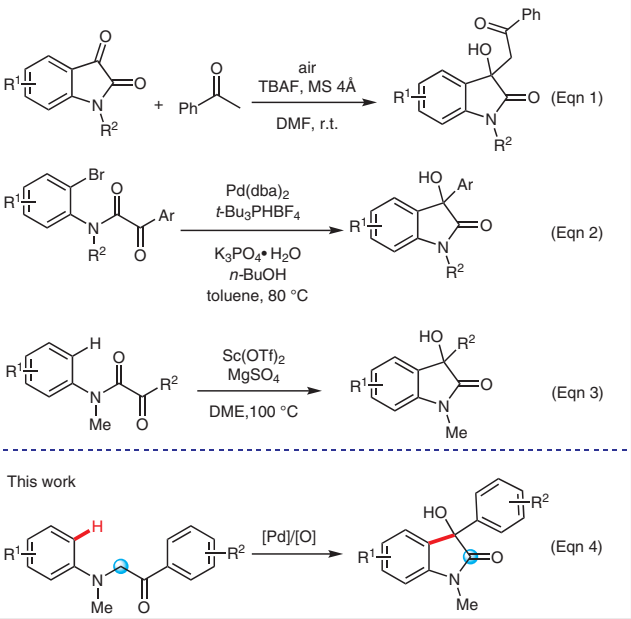
Received: 18.05.2018
Accepted after revision: 06.07.2018
Published online: 08.08.2018
DOI: 10.1055/s-0037-1610537; Art ID: ss-2018-h0346-op

Abstract A novel method for the synthesis of 3-hydroxy-2-oxindole (3-hydroxyindolin-2-one) derivatives by palladium-catalyzed tandem C–H cycloaddition and oxidation of α-aminoacetophenone has been developed. In the presence of $Pd(OAc)_2$ and AgOAc, a variety of 3-hydroxy-2-oxindoles were synthesized in moderate yields. Control experiments show that the selective cycloaddition occurs prior to the oxidation is crucial for this successful chemical transformation.

Key words palladium, indole, cyclization, oxidation, C–H functionalization

The indolin-2-ones are an important class of drug skeleton that have a wide range of excellent biological activity, being found in many natural products as well as pharmaceuticals.[1] 3-Hydroxyindolin-2-ones derived from indolin-2-ones are privileged scaffolds for drug development,[2] which have been used as kinase inhibitors and protease inhibitors.[3] Owing to their versatility in medicinal application, significant effort has been devoted to the development of synthetic methods for 3-hydroxyindolin-2-ones. The aldol reaction of indoline-2,3-diones is an effective pathway towards 3-hydroxyindolin-2-ones.[4] However, indoline-2,3-diones bearing functional groups are not easily accessible,[5] the limited scope is insufficient for diversity synthesis of 3-hydroxyindolin-2-ones. Endeavors for the pursuit of more efficient synthetic methods have been made in recent years.[6–8] For example, in 2016, Liu and co-workers[6a] disclosed an interesting tandem autoxidation/aldol reaction of 2-oxindoles with ketones leading to the formation of 3-hydroxyindolin-2-ones under mild reaction conditions (Scheme 1, eq. 1). In 2011, Kündig and co-workers[7a] reported a Pd-catalyzed efficient synthesis of 3-hydroxyindolin-2-ones via an intramolecular nucleophilic addition of aryl halides to α-ketoamides. However, the methodology required the pre-bromination of substrates and the use of an expensive catalyst (Scheme 1, eq. 2). Direct C–H cyclization of α-ketoamides into 3-hydroxyindolin-2-ones has also been developed.[8] This methodology requires the use of expensive Lewis acids such as scandium(III) triflate[8a] or corrosive trifluoroacetic acid[8b,c] (Scheme 1, eq. 3). Thus far, transition-metal-catalyzed C–H addition to ketones remains scare.[9] As our ongoing interest is in the chemical transformation of α-aminoacetophenone derivatives,[10,11] we envisioned that tandem C–H cycloaddition/oxidation of α-aminoacetophenones enables access to 3-hydroxyindolin-2-ones. The reaction selectivity is crucial for this transformation because α-aminoacetophenones could be converted into an indole[10] or an α-ketoamide,[11] and even undergo an oxidative cleavage of the C–N bond. Thus selective C–H cycloaddition to the ketone of α-aminoacetophenone remains challenging. A solution to this problem is to develop a transition-metal-catalyzed selective tandem C–H activation system.[12] Herein, we report a palladium-catalyzed selective synthesis of 3-hydroxyindolin-2-ones via tandem C–H cycloaddition and oxidation of α-aminoacetophenones (Scheme 1, eq. 4).

Our investigation began with the cyclization of α-aminoacetophenone **1a** under different reaction conditions (Table 1). Initially, $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) were applied as the catalyst and oxidant for the reaction development. The solvent effect, including toluene, dioxane, NMP, DCE, DMAc, DMSO, $MeNO_2$, *t*-BuOH, and MeCN, was evaluated at 100 °C for 12 hours (entries 1–9). MeCN is a preferable solvent for the reaction, affording product **2a** in 44% yield (entry 9). Other silver salts, such as AgOTf, Ag_2O, and $AgBF_4$, are not suitable for this transformation (entries 10–12). When the reaction was carried out in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$, α-ketoamide (*N*-methyl-2-oxo-



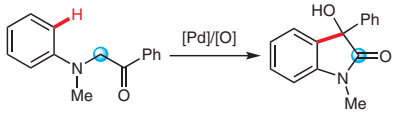
Scheme 1 Synthetic methods for 3-hydroxyindolin-2-ones

N,2-diphenylacetamide) was obtained as the major byproduct in 65% yield, whereas only 5% yield of desired product **2a** was obtained (entry 13).[11] Next, other palladium catalysts were also examined. Both $Pd(OCOCF_3)_2$ and $PdCl_2$ were suitable for this reaction, affording product **2a** in 45% and 25% yields, respectively (entries 14 and 15).

The mixed solvent of MeCN and *t*-BuOH was also studied (entries 16–18). The product yield was increased to 50% when the reaction was carried out in MeCN/*t*-BuOH (5:1) (entry 17). No target product was observed in the mixed solvent of MeCN and HFIP (entry 19). The mixed solvent of MeCN/EtOH was also effective, but only a 36% yield of product **2a** was obtained (entry 20). The reaction temperature also affects the transformation. The reaction at 80 °C gave a lower yield (entry 21). To our delight, the product yield increased to 56% when the reaction was carried out at 120 °C (entry 22). The product yield increased to 65% when 3 equivalents of AgOAc were used (entry 24), whereas the reaction with 1.5 equivalents of AgOAc led to a lower yield (entry 23). In the absence of $Pd(OAc)_2$, the reaction did not occur (entry 25). Without the addition of AgOAc, only a 5% yield of product **2a** was obtained (entry 26). These results demonstrate that both $Pd(OAc)_2$ and AgOAc are essential for this chemical transformation.

With the optimized reaction conditions in hand (Table 1, entry 24), we investigated the scope of this tandem C–H cycloaddition and oxidation reaction (Scheme 2). α-Aminoacetophenones bearing either an electron-withdrawing or electron-donating substituents on the benzene ring were tolerated to afford the corresponding products **2a–o** in moderate yields. Initially, substituents on the benzene ring adjacent to the ketone were examined. The methyl-substituted substrate delivered the desired product **2b** in 69% yield at 120 °C for 12 hours. The methoxy group appeared to have good compatibility, affording product **2c** in 55% yield. Halo groups, such as chloro and fluoro, were also tolerated, providing the corresponding products **2d** and **2e** in 51% and 56% yields, respectively. Next, the effect of substituents on the aniline motif was investigated (products **2f–m**). The presence of halo groups, such as bromo, fluoro, and chloro, on the benzene ring of aniline would decrease the

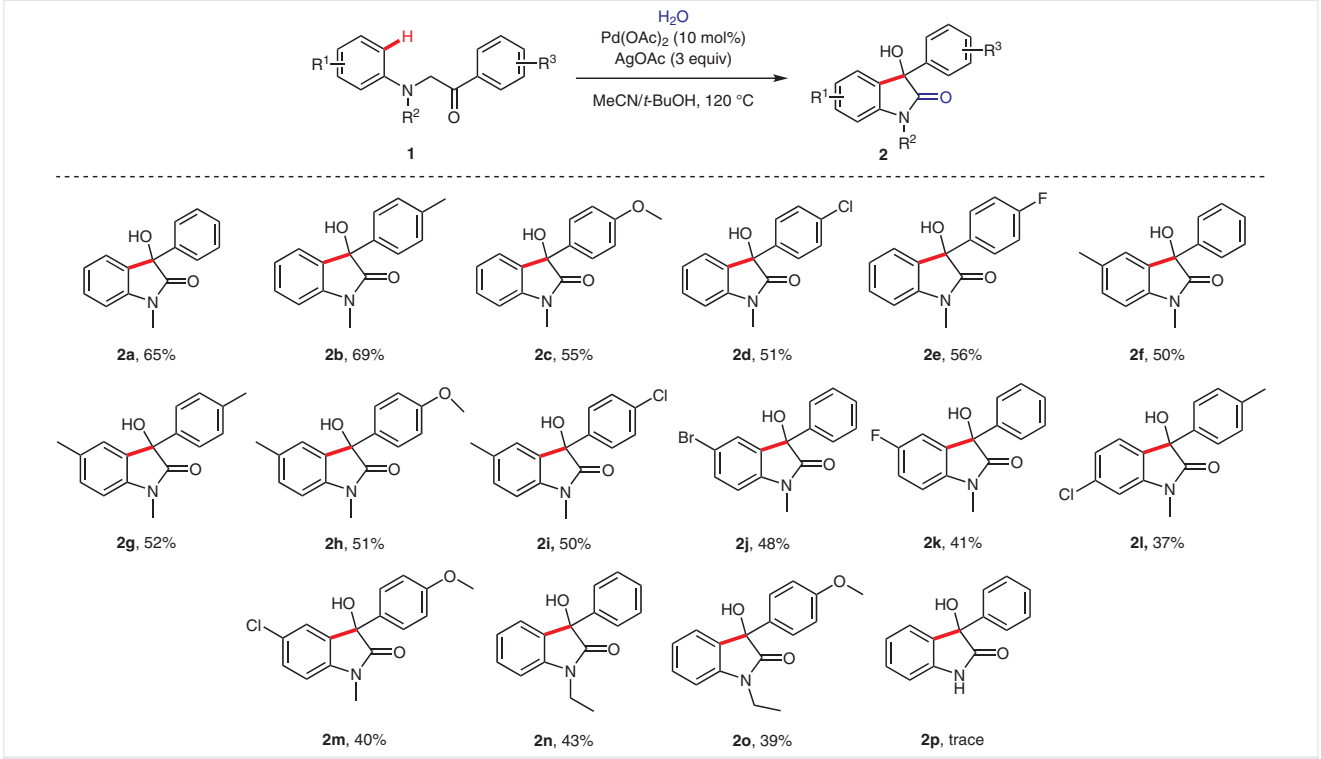
Table 1 Screening of Optimal Conditions[a]



1a **2a**

Entry	Catalyst	Oxidant (equiv)	Solvent	Isolated yield (%)
1	$Pd(OAc)_2$	AgOAc (2)	toluene	15
2	$Pd(OAc)_2$	AgOAc (2)	dioxane	18
3	$Pd(OAc)_2$	AgOAc (2)	NMP	trace
4	$Pd(OAc)_2$	AgOAc (2)	DCE	12
5	$Pd(OAc)_2$	AgOAc (2)	DMAc	27
6	$Pd(OAc)_2$	AgOAc (2)	DMSO	trace
7	$Pd(OAc)_2$	AgOAc (2)	$MeNO_2$	trace
8	$Pd(OAc)_2$	AgOAc (2)	*t*-BuOH	trace
9	$Pd(OAc)_2$	AgOAc (2)	MeCN	44
10	$Pd(OAc)_2$	AgOTf (2)	MeCN	trace
11	$Pd(OAc)_2$	Ag_2O (2)	MeCN	trace
12	$Pd(OAc)_2$	$AgBF_4$ (2)	MeCN	trace
13	$Pd(OAc)_2$	$Cu(OAc)_2$ (2)	MeCN	5
14	$Pd(OCOCF_3)_2$	AgOAc (2)	MeCN	45
15	$PdCl_2$	AgOAc (2)	MeCN	25
16	$Pd(OAc)_2$	AgOAc (2)	MeCN/*t*-BuOH (2:1)	32
17	$Pd(OAc)_2$	AgOAc (2)	MeCN/*t*-BuOH (5:1)	50
18	$Pd(OAc)_2$	AgOAc (2)	MeCN/*t*-BuOH (10:1)	45
19	$Pd(OAc)_2$	AgOAc (2)	MeCN/HFIP (5:1)	0
20	$Pd(OAc)_2$	AgOAc (2)	MeCN/EtOH (5:1)	36
21[b]	$Pd(OAc)_2$	AgOAc (2)	MeCN/*t*-BuOH (5:1)	48
22[c]	$Pd(OAc)_2$	AgOAc (2)	MeCN/*t*-BuOH (5:1)	56
23[c]	$Pd(OAc)_2$	AgOAc (1.5)	MeCN/*t*-BuOH (5:1)	40
24[c]	$Pd(OAc)_2$	AgOAc (3)	MeCN/*t*-BuOH (5:1)	65
25[c]	–	AgOAc (3)	MeCN/*t*-BuOH (5:1)	trace
26[c]	$Pd(OAc)_2$	–	MeCN/*t*-BuOH (5:1)	5

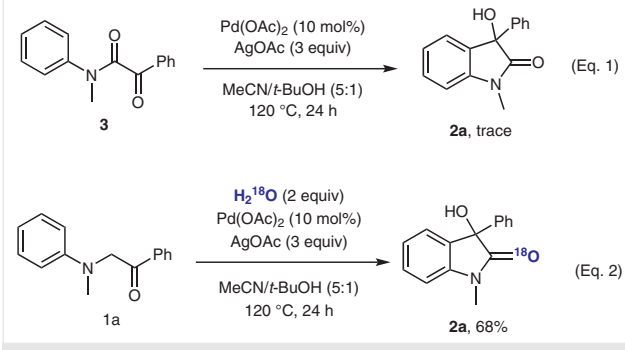
[a] Reaction conditions: **1a** (0.2 mmol), H_2O (0.4 mmol, 2 equiv), solvent (2 mL), 100 °C, 12 h; unless otherwise stated.
[b] At 80 °C.
[c] At 120 °C.



Scheme 2 Substrate scope. *Reagents and conditions*: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (3 equiv), H_2O (0.4 mmol, 2 equiv), MeCN/*t*-BuOH (5:1, 2 mL), 120 °C, 12 h.

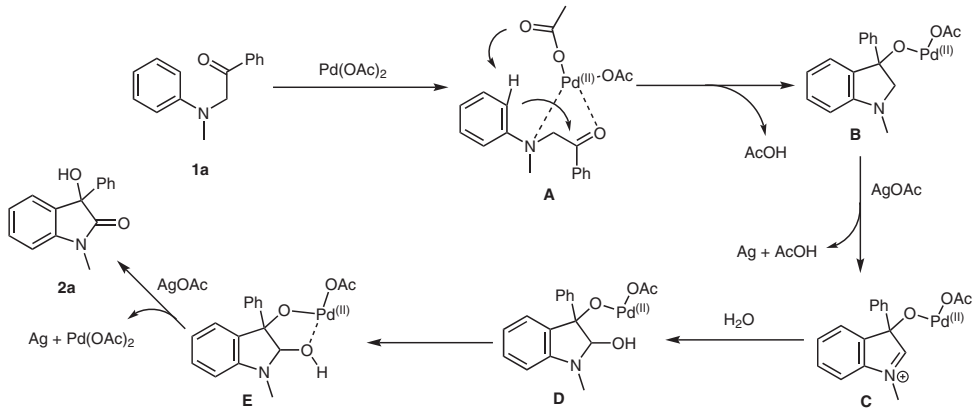
reactivity to some extent, leading to lower yields (products **2j–m**). These results demonstrate that the electron-withdrawing groups on the aniline disfavor the C–H cycloaddition. Compared with the *N*-methyl-substituted substrate **1a**, the *N*-ethyl substituted substrates were less effective (products **2n** and **2o**). In this reaction, the *N*-protecting group is essential for the successful transformation. The reaction did not occur when there was no protecting group on the amide (product **2p**). However, neither *N*-benzyl- nor *N*-allyl-substituted substrates were compatible with the reaction conditions. The majority of the substrates decomposed under the reaction conditions, and the reactions were messy, only a small amount of desired products were observed on GC-MS.

Subsequently, control experiments were conducted to gain insight into the reaction mechanism (Scheme 3). During the reaction development, a small amount of diketone **3** was observed by GC-MS analysis, suggesting that diketone **3** might be the reaction intermediate. Thus diketone **3** was subjected to the reaction conditions. However, no desired product **2a** was observed in the reaction of diketone **3**, suggesting that the formation of the amide completely suppress the C–H cycloaddition to the ketone (Scheme 3, eq. 1). In order to confirm the origin of the oxygen atom in the amide, two equivalents of $H_2{}^{18}O$ was added to the reaction. The ^{18}O labeled 3-hydroxyindolin-2-one **2a** was observed on GC-MS (Scheme 3, eq. 2), suggesting that the oxygen atom came from water.



Scheme 3 Control experiments

Based on the present results, a possible reaction mechanism is proposed as shown in Scheme 4. The cycloaddition of compound **1a** should occur prior to the formation of amide. Initially, $Pd(OAc)_2$ chelates with compound **1a** to afford a complex **A**, followed by hydrogen abstraction and a cycloaddition process to produce an intermediate **B**. Intermediate **B** then is oxidized by AgOAc to afford an imine cation **C**. The imine cation **C** undergoes hydrolysis to produce an intermediate **D**. The newly formed hydroxyl group may



Scheme 4 A possible reaction mechanism

chelate with $Pd(OAc)_2$ to give a complex **E**. Finally, intermediate **E** is further oxidized by AgOAc to afford the target product **2a**.

In summary, a novel method for the selective synthesis of 3-hydroxyindolin-2-ones through palladium-catalyzed tandem C–H bond cycloaddition and oxidation of α-aminoacetophenones has been established. Although α-aminoacetophenones have multiple reactive sites for different chemical transformation,[10,11] the reaction selectivity was controlled well in the presence of $Pd(OAc)_2$ and AgOAc. However, the reaction scope and efficiency are not satisfactory. Significant effort is needed to improve the reaction.

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-III 600 instrument (600 MHz for ^{1}H, 151 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ as the solvent. Chemical shifts for ^{1}H and ^{13}C NMR were referred to internal TMS (δ = 0) as the standard. Mass spectra were measured on an Agilent GC-MS-5975C Plus spectrometer (EI). HRMS (ESI) analysis was measured on a Bruker micrOTOF-Q II instrument.

3-Hydroxy-1-methyl-3-phenylindolin-2-one (2a); Typical Procedure[13]

To a flame-dried Schlenk tube with a magnetic stirring bar charged with **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), AgOAc (0.6 mmol, 3 equiv) under an air atmosphere was added MeCN/*t*-BuOH (5:1, 1 mL). The mixture was stirred at 120 °C for 12 h. When the reaction was complete, the mixture was filtered and purified by column chromatography (petroleum ether/EtOAc) to afford **2a** as a yellow solid; yield: 31.1 mg (65%); mp 136.6–138.0 °C (Lit. 137.5–138.4 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 7 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 3.48 (s, 1 H), 3.17 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.5, 143.5, 140.1, 131.6, 129.9, 128.6, 128.3, 125.3, 124.9, 123.5, 108.7, 78.0, 26.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 239 (66), 211 (56), 210 (100), 195 (17), 194 (65), 134 (24), 105 (20), 77 (36).

3-Hydroxy-1-methyl-3-*p*-tolylindolin-2-one (2b)[7a]

Yellow solid; yield: 34.9 mg (69%); mp 197.4–198.5 °C (Lit. 191.4–192.9 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21–7.19 (m, 3 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 3.24 (s, 1 H), 3.17 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.6, 143.5, 138.1, 137.1, 131.6, 129.8, 129.3, 125.3, 124.9, 123.5, 108.6, 77.8, 26.5, 21.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 253 (63), 224 (100), 210 (42), 208 (62), 165 (13), 91 (30).

3-Hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (2c)[13]

Yellow solid; yield: 30.0 mg (55%); mp 147.3–148.1 °C (Lit. 142.5–143.7 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 4 H), 7.11 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 6.89–6.84 (m, 2 H), 3.79 (s, 3 H), 3.39 (s, 1 H), 3.25 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.7, 159.6, 143.5, 132.1, 131.6, 129.8, 126.9, 124.9, 123.5, 114.0, 108.7, 77.6, 55.3, 26.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 269 (55), 241 (48), 240 (100), 226 (33), 224 (56), 135 (25), 77 (27).

3-(4-Chlorophenyl)-3-hydroxy-1-methylindolin-2-one (2d)[7d]

Yellow solid; yield: 27.8 mg (51%); mp 171.5–172.3 °C (Lit. 174.5–175.5 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.31–7.29 (m, 2 H), 7.27–7.25 (m, 1 H), 7.12 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 3.57 (s, 1 H), 3.26 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.1, 143.4, 138.6, 134.3, 131.2, 130.2, 128.7, 126.9, 124.9, 123.7, 108.8, 77.6, 26.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 273 (62), 244 (100), 228 (65), 210 (17), 193 (21), 152 (17), 134 (26), 111 (24), 77 (25).

3-(4-Fluorophenyl)-3-hydroxy-1-methylindolin-2-one (2e)[14]

Yellow solid; yield: 28.8 mg (56%); mp 170.3–172.4 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44–7.33 (m, 3 H), 7.29 (dd, *J* = 7.4, 0.7 Hz, 1 H), 7.12 (s, 1 H), 7.02 (t, *J* = 8.7 Hz, 2 H), 6.94 (s, 1 H), 3.50 (s, 1 H), 3.26 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.3, 162.7 (d, *J* = 247.6 Hz, 1 C), 143.4, 135.9, 131.3, 130.1, 127.4 (d, *J* = 9.1 Hz, 1 C), 124.9, 123.7, 115.5 (d, *J* = 22.6 Hz, 1 C), 108.8, 77.5, 26.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 257 (61), 229 (60), 228 (100), 212 (83), 134 (19), 123 (20), 95 (26).

3-Hydroxy-1,5-dimethyl-3-phenylindolin-2-one (2f)[13]

Yellow solid; yield: 25.3 mg (50%); mp 124.4–125.9 °C (Lit. 116.2–117.1 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.8 Hz, 2 H), 7.31 (dt, *J* = 19.7, 9.4 Hz, 3 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.11 (s, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 3.96 (s, 1 H), 3.23 (d, *J* = 0.7 Hz, 3 H), 2.31 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.7, 141.0, 140.3, 133.2, 131.8, 130.0, 128.5, 128.1, 125.6, 125.3, 108.4, 78.2, 26.5, 21.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 253 (71), 225 (57), 224 (100), 209 (19), 208 (74), 148 (23), 91 (22), 77 (39).

3-Hydroxy-1,5-dimethyl-3-*p*-tolylindolin-2-one (2g)

Yellow solid; yield: 27.8 mg (52%); mp 155.2–157.6 °C.

IR (KBr): 3368, 1696, 1624, 1599, 1494, 1356, 999 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.20–7.19 (m, 2 H), 7.07–7.05 (m, 3 H), 7.02 (s, 1 H), 6.71 (d, *J* = 7.9 Hz, 1 H), 3.31 (s, 1 H), 3.15 (s, 3 H), 2.25 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.6, 141.1, 138.0, 137.3, 133.2, 131.6, 130.0, 129.3, 125.6, 125.2, 108.4, 78.0, 26.5, 21.1, 21.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 267 (66), 239 (53), 238 (100), 224 (33), 223 (16), 222 (63), 119 (19), 91 (38).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_2$: 268.1326; found: 268.1332.

3-Hydroxy-3-(4-methoxyphenyl)-1,5-dimethylindolin-2-one (2h)

Yellow solid; yield: 28.9 mg (51%); mp 155.2–157.6 °C.

IR (KBr): 3376, 1694, 1623, 1601, 1491, 1352, 1242, 1032 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.9 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.13 (s, 1 H), 6.90–6.83 (m, 2 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 3.79 (s, 3 H), 3.38 (s, 1 H), 3.24 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.6, 159.5, 141.0, 133.1, 132.3, 131.6, 130.0, 126.8, 125.6, 114.0, 108.4, 77.7, 55.3, 26.5, 21.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 283 (64), 267 (38), 255 (60), 254 (100), 240 (27), 238 (69), 224 (28).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_3$: 284.1280; found: 284.1281.

3-(4-Chlorophenyl)-3-hydroxy-1,5-dimethylindolin-2-one (2i)

White solid; yield: 28.9 mg (50%); mp 188.2–189.2 °C.

IR (KBr): 3362, 1692, 1603, 1498, 1486, 1356, 1093, 829 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 4 H), 7.15 (d, *J* = 7.9 Hz, 1 H), 7.05 (s, 1 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 3.91 (s, 1 H), 3.22 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.3, 140.9, 138.8, 134.1, 133.5, 131.3, 130.3, 128.7, 126.9, 125.6, 108.6, 77.8, 26.6, 21.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 289 (28), 287 (82), 261 (25), 260 (43), 259 (24), 258 (100), 244 (26), 242 (100), 207 (21), 918 (25).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClNO_2$: 288.0785; found: 288.0788.

5-Bromo-3-hydroxy-1-methyl-3-phenylindolin-2-one (2j)[2c]

Yellow solid; yield: 30.4 mg (48%); mp 154.4–156.2 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.40 (d, *J* = 1.9 Hz, 1 H), 7.39–7.30 (m, 5 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 3.83 (s, 1 H), 3.23 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.1, 142.4, 139.5, 133.5, 132.6, 128.7, 128.6, 128.2, 125.2, 116.2, 110.2, 77.9, 26.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 317 (80), 291 (70), 290 (100), 289 (68), 288 (88), 274 (25), 272 (27), 194 (22), 193 (95), 165 (23), 152 (25), 151 (16), 133 (24), 105 (64), 104 (20), 78 (16), 77 (96), 76 (24), 75 (17).

5-Fluoro-3-hydroxy-1-methyl-3-phenylindolin-2-one (2k)[13]

Yellow solid; yield: 21.0 mg (41%); mp 163.3–165.9 °C (Lit. 169.5–171.0 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 7.06 (m, 2 H), 6.85 (dd, *J* = 8.4, 4.0 Hz, 1 H), 3.67 (s, 1 H), 3.26 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.4, 160.0 (d, *J* = 243.1 Hz, 1 C), 139.6, 139.3, 133.1 (d, *J* = 7.5 Hz, 1 C), 128.7, 128.5, 125.2, 116.1 (d, *J* = 24.1 Hz, 1 C), 113.2 (d, *J* = 24.1 Hz, 1 C), 109.3 (d, *J* = 9.1 Hz, 1 C), 78.1, 26.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 257 (68), 229 (52), 228 (100), 213 (13), 212 (68), 105 (33), 77 (40).

6-Chloro-3-hydroxy-1-methyl-3-*p*-tolylindolin-2-one (2l)

White solid; yield: 21.2 mg (37%); mp 143.6–143.8 °C.

IR (KBr): 3302, 1703, 1609, 1493, 1370, 1070, 813 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 2 H), 7.06 (dd, *J* = 7.9, 1.7 Hz, 1 H), 6.91 (d, *J* = 1.7 Hz, 1 H), 3.84 (s, 1 H), 3.22 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.8, 144.6, 138.3, 136.7, 135.5, 130.2, 129.3, 125.9, 125.2, 123.3, 109.4, 77.5, 26.6, 21.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 289 (22), 287 (63), 261 (16), 260 (41), 259 (50), 258 (100), 246 (16), 244 (64), 242 (53), 207 (20), 91 (24).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClNO_2$: 288.0786; found: 288.0789.

5-Chloro-3-hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (2m)[15]

White solid; yield: 24.2 mg (40%); mp 160.0–161.2 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.07 (dd, *J* = 7.9, 1.8 Hz, 1 H), 6.89 (d, *J* = 1.7 Hz, 1 H), 6.84 (d, *J* = 8.9 Hz, 2 H), 4.06 (s, 1 H), 3.78 (s, 3 H), 3.19 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.7, 159.7, 144.6, 135.5, 131.6, 130.1, 126.8, 125.9, 123.3, 114.0, 109.4, 55.3, 26.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 305 (18), 303 (53), 277 (14), 276 (41), 275 (44), 274 (100), 261 (26), 260 (47), 259 (78), 258 (100), 135 (24).

1-Ethyl-3-hydroxy-3-phenylindolin-2-one (2n)[16]

Yellow solid; yield: 20.2 mg (43%); mp 151–152 °C (Lit. 153–154 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 7 H), 7.11–7.05 (m, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 3.90–3.73 (m, 2 H), 3.43 (s, 1 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.2, 142.6, 140.3, 131.9, 129.8, 128.6, 128.2, 125.2, 125.1, 123.3, 108.8, 77.9, 35.0, 12.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 253 (79), 225 (50), 224 (36), 210 (100), 208 (26), 206 (22), 146 (30), 132 (26), 105 (30), 91 (19), 77 (49).

1-Ethyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one (2o)

White solid; yield: 22.1 mg (39%); mp 127.1–127.7 °C.

IR (KBr): 3386, 1709, 1617, 1506, 1468, 1253, 1174, 914 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.33 (dt, *J* = 9.4, 4.3 Hz, 4 H), 7.11–7.06 (m, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.88–6.82 (m, 2 H), 3.89–3.70 (m, 5 H), 3.62 (s, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.3, 159.5, 142.5, 132.3, 132.0, 129.7, 126.7, 125.1, 123.3, 114.0, 108.8, 77.5, 55.3, 35.0, 12.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 283 (91), 267 (20), 255 (92), 254 (62), 240 (100), 238 (53).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}NO_3$: 284.1281; found: 284.1283.

2-[(3-Chlorophenyl)(methyl)amino]-1-*p*-tolylethanone (1l)

White solid; yield: 202 mg (78%); mp 76.0–76.9 °C.

IR (KBr): 1688, 1599, 1559, 1500, 1222, 983, 953 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.11 (t, *J* = 8.1 Hz, 1 H), 6.69 (dd, *J* = 7.8, 1.2 Hz, 1 H), 6.65 (t, *J* = 2.1 Hz, 1 H), 6.52 (dd, *J* = 8.4, 2.5 Hz, 1 H), 4.76 (s, 2 H), 3.10 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.3, 150.4, 144.6, 135.1, 132.8, 130.1, 129.5, 127.9, 116.8, 112.1, 110.3, 58.5, 39.6, 21.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 275 (6), 273 (19), 156 (64), 155 (19), 154 (100), 141 (4), 140 (12), 139 (12), 138 (15).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}ClNO$: 274.0993; found: 274.0996.

Funding Information

We gratefully acknowledge the financial support of South China Agricultural University and the Science Technology Program Project of Guangdong Province (No. 2016B020204005).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610537.

References

(1) (a) Prakash, C. R.; Raja, S. *Mini-Rev. Med. Chem.* **2012**, *12*, 98. (b) Pandeya, S. N.; Smitha, S.; Jyoti, M.; Sridhar, S. K. *Acta Pharm. (Weinheim, Ger.)* **2005**, *55*, 27.

(2) (a) England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805. (b) Ghosh, S.; Kinthada, L. K.; Bhunia, S.; Bisai, A. *Chem. Commun.* **2012**, *48*, 10132. (c) Zhou, F.; Cao, Z.-Y.; Zhang, J.; Yang, H.-B.; Zhou, J. *Chem. Asian J.* **2012**, *7*, 233. (d) Kinthada, L. K.; Ghosh, S.; De, S.; Bhunia, S.; Dey, D.; Bisai, A. *Org. Biomol. Chem.* **2013**, *11*, 6984. (e) Kinthada, L. K.; Babu, K. N.; Padhi, D.; Bisai, A. *Eur. J. Org. Chem.* **2017**, 3078. (f) Kinthada, L. K.; Medisetty, S. R.; Parida, A.; Babu, K. N.; Bisai, A. *J. Org. Chem.* **2017**, *82*, 8548.

(3) (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247.

(4) (a) Gutierrez, E. G.; Franz, A. K. *e-EROS Encycl. Reagents Org. Synth.* **2013**, 1. (b) Flores, M. F.; Pena, J.; Garcia-Garcia, P.; Garrido, N. M.; Diez, D. *Curr. Org. Chem.* **2013**, *17*, 1957.

(5) (a) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900. (b) Satish, G.; Polu, A.; Ramar, T.; Ilangovan, A. *J. Org. Chem.* **2015**, *80*, 5167.

(6) (a) Zhang, Q.-B.; Jia, W.-L.; Ban, Y.-L.; Zheng, Y.; Liu, Q.; Wu, L.-Z. *Chem. Eur. J.* **2016**, *22*, 2595. (b) Wang, B.; Zhu, J.; Wei, Y.; Luo, G.; Qu, H.; Liu, L.-X. *Synth. Commun.* **2015**, *45*, 2841. (c) Buckley, B. R.; Fernández, D.-R. B. *Tetrahedron Lett.* **2013**, *54*, 843.

(7) (a) Jia, Y.-X.; Katayev, D.; Kündig, E. P. *Chem. Commun.* **2010**, *46*, 130. (b) Shin, I.; Ramgren, S. D.; Krische, M. J. *Tetrahedron* **2015**, *71*, 5776. (c) Yin, L.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7620. (d) Hu, J.-X.; Wu, H.; Li, C.-Y.; Sheng, W.-J.; Jia, Y.-X.; Gao, J.-R. *Chem. Eur. J.* **2011**, *17*, 5234.

(8) (a) Wang, H.-L.; Li, Y.-M.; Wang, G.-W.; Zhang, H.; Yang, S.-D. *Asian J. Org. Chem.* **2013**, *2*, 486. (b) Gorokhovik, I.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 5536. (c) Sai, K. K. S.; Esteves, P. M.; Tanoue da Penha, E.; Klumpp, D. A. *J. Org. Chem.* **2008**, *73*, 6506.

(9) (a) Ren, H.; Wang, P.; Wang, L.; Tang, Y. *Org. Lett.* **2015**, *17*, 4886. (b) Zhang, X.-S.; Zhu, Q.-L.; Luo, F.-X.; Chen, G.; Wang, X.; Shi, Z.-J. *Eur. J. Org. Chem.* **2013**, 6530. (c) Shibata, T.; Hashimoto, Y.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075.

(10) Ji, X.-M.; Zhou, S.-J.; Deng, C.-L.; Chen, F.; Tang, R.-Y. *RSC Adv.* **2014**, *4*, 53837.

(11) Tang, R.-Y.; Guo, X.-K.; Xiang, J.-N.; Li, J.-H. *J. Org. Chem.* **2013**, *78*, 11163.

(12) (a) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578. (b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (c) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146.

(13) Liu, M.; Zhang, C.; Ding, M.; Tang, B.; Zhang, F. *Green Chem.* **2017**, *19*, 4509.

(14) Zhu, F.; Zhou, F.; Cao, Z.-Y.; Wang, C.; Zhang, Y.-X.; Wang, C.-H.; Zhou, J. *Synthesis* **2012**, *44*, 3129.

(15) Yamamoto, Y.; Yohda, M.; Shirai, T.; Ito, H.; Miyaura, N. *Chem. Asian J.* **2012**, *7*, 2446.

(16) Liao, Y.-J.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2003**, *59*, 3511.