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Copper-catalyzed arylation of indolin-2,3-ones with arylboronic acids

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ABSTRACT

A convenient and efficient $Cu(OTf)_2$-catalyzed arylation of indolin-2,3-ones with arylboronic acids using cheap 1,10-phenanthroline hydrate as ligand was developed under air atmosphere, achieving 3-aryl-3-hydroxy-2-oxindoles in good to excellent yields. This catalytic system shows broad functional group tolerance. Moreover, the rigorous exclusion of air/moisture is not required in these transformations.

1. Introduction

3-Aryl-3-hydroxy-2-oxindoles, and derivatives thereof, are encountered in a large variety of natural products with a wide spectrum of biological activities.[1] Common synthetic routes for preparation of these compounds involve the addition of organometallic reagents, such as organomagnesium[2] and organolithium[3] to indolin-2,3-ones. However, these organometallic reagents are either toxic, poor functional group compatibility, or are sensitive to air and moisture. Some other general methods to construct 3-aryl-3-hydroxy-2-oxindoles include metal-catalyzed intramolecular coupling reactions. For example, Kündig[4] and Jia[5] have developed a new method for the synthesis of 3-aryl-3-hydroxy-2-oxindoles from the direct intramolecular nucleophilic addition of aryl halides to α-ketoamides catalyzed by palladium or nickel. Recently, Kanai and Shibasaki have reported intramolecular arylation of aryl triflate to α-ketoamides catalyzed by a palladium–difluorPhos complex.[6]

Organoboron reagents enjoy great prestige due to their advantages of stability to air or moisture and good functional group tolerance.[7] In 2006, Hayashi[8] and Minnaard[9] independently reported direct access to 3-aryl-3-hydroxy-2-oxindoles from indolin-2,3-ones via rhodium-catalyzed cross-coupling reaction with arylboronic acids. Since then, synthetic method by palladium-catalyzed[10] approaches for such transformations have been developed. The high availability of indolin-2,3-ones renders this route particularly attractive.

However, palladium and rhodium is very expensive compared with copper. Recently, the use of copper salts as catalysts has gained much prominence in addition reactions of organoboron reagents, which commonly used *N*-heterocyclic carbene or phosphines as a ligand.[11] In 2010, Hayashi and Shintani reported copper-catalyzed asymmetric addition reactions of arylboronates to indolin-2,3-ones by the use of a chiral *N*-heterocyclic carbene ligand.[12] We have reported the copper-catalyzed synthesis of carbinols[13a] and diaryl ketones[13b] by addition of arylboronic acids to aromatic aldehydes using dppf and xantphos as a ligand, respectively. A continuation of our interest in the development of organoboron reactions led us to explore the potential reactions between organoboron reagents and aldehydes, aldimines, alkynes or nitroarenes.[14] Herein, we report a new method for the synthesis of 3-aryl-3-hydroxy-2-oxindoles by copper-catalyzed arylation of arylboronic acids with indolin-2,3-ones in the presence of bisdentate pyridine ligands (Scheme 1).

2. Results and discussion

Initial studies of the reaction conditions were conducted by using the common PPh_3 as ligand and the addition of phenylboronic acid to *N*-methylindoline-2,3-dione as a model reaction. However, despite extensive investigation with a variety of parameters, such as Cu sources, bases, solvents, and PPh_3/Cu ratios, no synthetically useful results were obtained with use of this approach. Since ligands always play important roles in metal-catalyzed chemistry,[15] we then turned our attention to the

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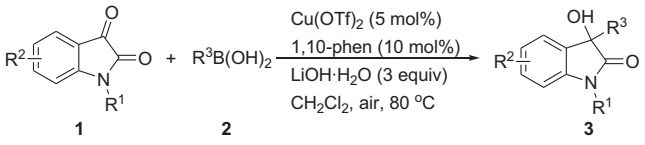


1a: R^1 = CH_3 **2a**: R^3 = Ph
1b: R^1 = n-C_4H_9 **2b**: R^3 = p-(Me)C_6H_4
1c: R^1 = n-C_6H_{13} **2c**: R^3 = m-(Me)C_6H_4
1d: R^1 = $PhCH_2$ **2d**: R^3 = o-(Me)C_6H_4
1e: R^1 = $Ph(CH_2)_3$ **2e**: R^3 = p-(OMe)C_6H_4
1f: R^1 = Ph **2f**: R^3 = m-(OMe)C_6H_4
1g: R^1 = CH_2=CHCH **2g**: R^3 = p-(Cl)C_6H_4
1h: R^1 = n-C_4H_9, R^2 = 5-Me **2h**: R^3 = p-(Br)C_6H_4
1i: R^1 = n-C_4H_9, R^2 = 5-OMe **2i**: R^3 = p-(CF_3)C_6H_4
1j: R^1 = n-C_4H_9, R^2 = 5-NO_2 **2j**: R^3 = m-(NO_2)C_6H_4
1k: R^1 = n-C_4H_9, R^2 = 5-F **2k**: R^3 = p-(NO_2)C_6H_4
1l: R^1 = n-C_4H_9, R^2 = 7-F **2l**: R^3 = 2-naphthyl
1m: R^1 = n-C_4H_9, R^2 = 5-Cl **2m**: R^3 = p-(Ph)C_6H_4
1n: R^1 = n-C_4H_9, R^2 = 5-Br **2n**: R^3 = 3-thienyl
1o: R^1 = n-C_4H_9, R^2 = 6-Br **2o**: R^3 = p-(F)C_6H_4
1o: R^1 = n-C_4H_9, R^2 = 4-Br **2p**: R^3 = *trans*-PhCH=CH

Scheme 1. Copper-catalyzed synthesis of 3-aryl-3-hydroxy-2-oxindoles.

screening of ligands (Table 1, entries 1–10). Among the ligand tested, 1,10-phenanthroline hydrate (**L1**) was the best, affording the desired product **3aa** in 62% yield (Table 1, entry 5).

Encouraged by this promising result, the reaction conditions were further optimized including the effect of bases, copper sources, and solvents. The results suggested that the base used had a dramatic effect on the yields. Among the base screened, $LiOH·H_2O$ turned out to be the best (Table 1, entries 5, 11–21). Then using $LiOH·H_2O$ as the base we screened the influence of the copper sources, $Cu(OTf)_2$ was superior to others, such as $Cu(OAc)_2·H_2O$, CuI, $CuBr_2$, CuF_2, $Cu(acac)_2$, and $CuCl_2·2H_2O$ (Table 1, entries 5, 22–27). Next, we studied the solvent effect and found that CH_2Cl_2 was superior to xylene, toluene, chlorobenzene, DMF, THF, and CH_3CN (Table 1, entries 5, 28–34). When conducted under air atmosphere, **3aa** was obtained in 70% yield. The comparable result indicated inert atmosphere was not essential for this transformation. To our delight, the yield of **3aa** was improved to 91% by changing the ratio of *N*-methylindoline-2,3-dione and phenylboronic acid (Table 1, entry 34).

With optimal conditions in hand, the scope of copper-catalyzed coupling of various *N*-substituted indoline-2,3-diones with different arylboronic acids was investigated.

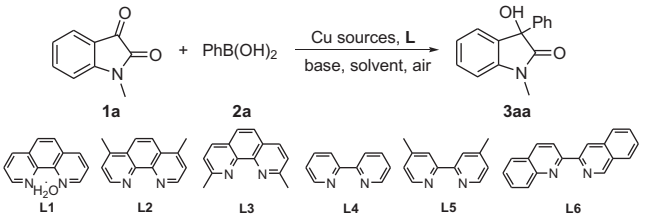
As shown in Table 2, a range of functional groups, such as methyl, methoxy, fluoro, chloro, bromo, nitro, trifluoromethyl, and thienyl groups, were tolerated in this procedure. However, the steric hindrance had obvious effects on the yields of the reaction. For example, the arylation of *N*-methylindoline-2,3-dione with *ortho*-, *meta*-, and *para*-tolylboronic acid was examined, 92% of **3ab** and 85% of **3ac** were isolated, while the yield of **3ad** was decreased to 31% (Table 2, entries 2–4).

On the other hand, the electronic effect of substituents on the arylboronic acids had some influence on the reaction. The electron-donating substituents on the phenyl ring of arylboronic acids were beneficial for the transformation, whereas arylboronic acids bearing an electron-withdrawing decreased slightly the efficiency. These reasons may be as follows: electron-withdrawing arylboronic acids, which are less nucleophilic, and hence transmetalate more slowly than their electron-neutral analogues, are prone to homocoupling and protodeboronation side reactions.[15] However, in our catalytic system, arylboronic acids containing a strongly electron-withdrawing group, such as 4-(trifluoromethyl) phenylboronic acid (**2i**), 4-nitrophenylboronic acid (**2j**), and 4-nitrophenyl-boronic acid (**2k**) reacted with **1a** to afford **3ad**, **3ae**, **3af**, and **3ag** in 70%, 83%, and 77% yields, respectively (Table 2, entries 9–11). Moreover, 2-naphthylboronic acid (**2l**) and 4-phenylphenylboronic acid also gave the corresponding **3ah** in 79% and 85% yields, respectively (Table 2, entries 12 and 13). The result was unsatisfactory using a heteroarylboronic acid, such as 3-thienylboronic acid (**2n**) with **1a**, affording the corresponding arylation product **3an** in 45% yield (Table 2, entry 14). Notably, the products of **3ah** and **3eh** had the bromo group untouched, showed high selectivity (Table 2, entries 8 and 21).

Further investigation showed that the arylation of arylboronic acids with other *N*-substituent groups, such as *N*-butyl, *N*-hexyl, *N*-benzyl, *N*-phenylpropyl, *N*-phenyl, and *N*-allyl indoline-2,3-dione analogues did not cause any difficulties for this transformation (Table 2, entries 15–23).

Next, we explored the effect of the arylation of phenylboronic acid with *N*-butylindoline-2,3-dione containing various substituent groups on the phenyl ring (Fig. 1). As expected, the various substrates

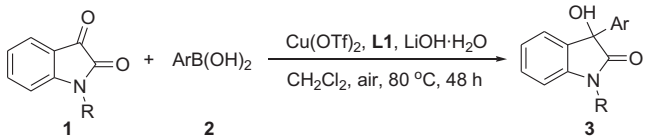
Table 1
Selected results of screening for optimal conditions[a]



Entry	Cu sources	Ligand	Base	Solvent	Yield[b] (%)
1	$Cu(OTf)_2$	PPh_3	$LiOH·H_2O$	Xylene	Trace
2	$Cu(OTf)_2$	dppb	$LiOH·H_2O$	Xylene	18
3	$Cu(OTf)_2$	dppf	$LiOH·H_2O$	Xylene	25
4	$Cu(OTf)_2$	binap	$LiOH·H_2O$	Xylene	15
5[c]	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	Xylene	62
6	$Cu(OTf)_2$	**L2**	$LiOH·H_2O$	Xylene	58
7	$Cu(OTf)_2$	**L3**	$LiOH·H_2O$	Xylene	NR
8	$Cu(OTf)_2$	**L4**	$LiOH·H_2O$	Xylene	44
9	$Cu(OTf)_2$	**L5**	$LiOH·H_2O$	Xylene	50
10	$Cu(OTf)_2$	**L6**	$LiOH·H_2O$	Xylene	10
11	$Cu(OTf)_2$	**L1**	Li_2CO_3	Xylene	Trace
12	$Cu(OTf)_2$	**L1**	K_2CO_3	Xylene	30
13	$Cu(OTf)_2$	**L1**	Cs_2CO_3	Xylene	58
14	$Cu(OTf)_2$	**L1**	Rb_2CO_3	Xylene	30
15	$Cu(OTf)_2$	**L1**	NaOAc	Xylene	Trace
16	$Cu(OTf)_2$	**L1**	$KF·2H_2O$	Xylene	Trace
17	$Cu(OTf)_2$	**L1**	LiF	Xylene	Trace
18	$Cu(OTf)_2$	**L1**	LiBr	Xylene	Trace
19	$Cu(OTf)_2$	**L1**	Et_3N	Xylene	Trace
20	$Cu(OTf)_2$	**L1**	NaOH	Xylene	22
21	$Cu(OTf)_2$	**L1**	KOH	Xylene	38
22	$Cu(OAc)_2·H_2O$	**L1**	$LiOH·H_2O$	Xylene	51
23	CuI	**L1**	$LiOH·H_2O$	Xylene	57
24	$CuBr_2$	**L1**	$LiOH·H_2O$	Xylene	55
25	CuF_2	**L1**	$LiOH·H_2O$	Xylene	54
26	$Cu(acac)_2$	**L1**	$LiOH·H_2O$	Xylene	59
27	$CuCl_2·2H_2O$	**L1**	$LiOH·H_2O$	Xylene	51
28	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	Toluene	58
29	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	PhCl	61
30	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	DMF	Trace
31	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	THF	33
32	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	CH_3CN	29
33	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	CH_2Cl_2	71(70)[d]
34[c]	$Cu(OTf)_2$	**L1**	$LiOH·H_2O$	CH_2Cl_2	91[e]

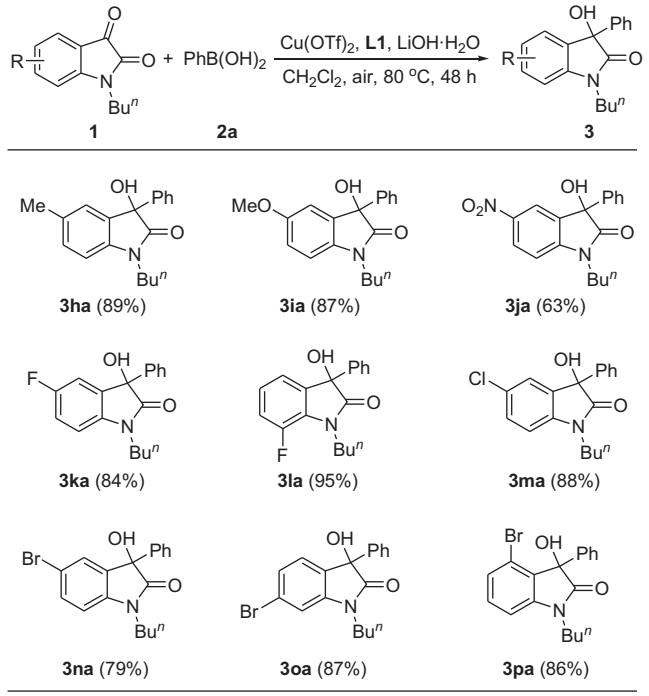
NR=No reaction.
[a] All reactions were run with **1a** (0.3 mmol), **2a** (0.6 mmol), **L** (10 mol %), Cu source (5 mol %), and base (3 equiv) in undried solvent (3 mL) at 80 °C for 48 h under N_2.
[b] Isolated yields.
[c] Identical result was obtained using anhydrous **L1** or $LiOH·H_2O$ instead of **L1** or LiOH.
[d] Under air.
[e] Compounds **1a** (0.3 mmol) and **2a** (1.2 mmol).

Table 2
Arylation of *N*-substituted indoline-2,3-diones with arylboronic acids[a]



Entry	R	Ar	Product	Yield[b] (%)
1	CH_3 (**1a**)	Ph (**2a**)	**3aa**	91
2	CH_3 (**1a**)	*p*-(Me)C_6H_4 (**2b**)	**3ab**	92
3	CH_3 (**1a**)	*m*-(Me)C_6H_4 (**2c**)	**3ac**	85
4	CH_3 (**1a**)	*o*-(Me)C_6H_4 (**2d**)	**3ad**	31
5	CH_3 (**1a**)	*p*-(OMe)C_6H_4 (**2e**)	**3ae**	80
6	CH_3 (**1a**)	*m*-(OMe)C_6H_4 (**2f**)	**3af**	90
7	CH_3 (**1a**)	*p*-(Cl)C_6H_4 (**2g**)	**3ag**	73
8	CH_3 (**1a**)	*p*-(Br)C_6H_4 (**2h**)	**3ah**	81
9	CH_3 (**1a**)	*p*-(CF_3)C_6H_4 (**2i**)	**3ai**	70
10	CH_3 (**1a**)	*m*-(NO_2)C_6H_4 (**2j**)	**3aj**	83
11	CH_3 (**1a**)	*p*-(NO_2)C_6H_4 (**2k**)	**3ak**	77
12	CH_3 (**1a**)	2-Naphthyl (**2l**)	**3al**	79
13	CH_3 (**1a**)	*p*-(Ph)C_6H_4 (**2m**)	**3am**	85
14	CH_3 (**1a**)	3-Thienyl (**2n**)	**3an**	45
15	*n*-C_4H_9(**1b**)	Ph (**2a**)	**3ba**	89
16	*n*-C_6H_{13} (**1c**)	Ph (**2a**)	**3ca**	83
17	$PhCH_2$ (**1d**)	Ph (**2a**)	**3da**	84
18	$Ph(CH_2)_3$ (**1e**)	Ph (**2a**)	**3ea**	91
19	$Ph(CH_2)_3$ (**1e**)	*p*-(F)C_6H_4 (**2o**)	**3eo**	81
20	$Ph(CH_2)_3$ (**1e**)	*p*-(Cl)C_6H_4 (**2g**)	**3eg**	81
21	$Ph(CH_2)_3$ (**1e**)	*p*-(Br)C_6H_4 (**2h**)	**3eh**	80
22	Ph (**1f**)	Ph (**2a**)	**3fa**	71
23	CH_2=$CHCH_2$ (**1g**)	Ph (**2a**)	**3ga**	76

[a] All reactions were run with *N*-substituted indoline-2,3-dione **1** (0.3 mmol), arylboronic acid **2** (1.2 mmol), **L1** (10 mol %), $Cu(OTf)_2$ (5 mol %), $LiOH·H_2O$ (3 equiv), and CH_2Cl_2 (3 mL) at 80 °C for 48 h under air.
[b] Isolated yields.

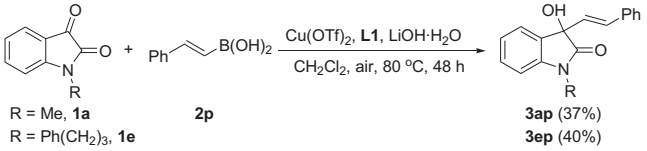


[a] Reaction conditions: indoline-2,3-dione **1** (0.3 mmol), phenylboronic acid **2a** (1.2 mmol), $Cu(OTf)_2$ (5 mol%), **L1** (10 mol%), $LiOH·H_2O$ (3 equiv) and CH_2Cl_2 (3 mL), air, 80 °C, 48 h.
[b] Isolated yields were given in parenthesis.

Fig. 1. Arylation of *N*-butylindoline-2,3-diones with phenylboronic acids.[a]

worked well under the optimized conditions. However, electronic affected the efficiency. For example, *N*-butylindoline-2,3-dione containing a strongly electron-withdrawing group, such as *N*-butyl-5-nitroindoline-2,3-dione (**1j**) produced the corresponding product **3ja** in 63% yield. Moreover, the influence of a mono-substituent bromo group at the 4-, 5- and 6-position for *N*-butylindoline-2,3-diones was investigated to examine the steric effect in our system. For example, **2a** proceeded with **3n**, **3o**, and **3p** efficiently, affording the desired product **3na**, **3oa**, and **3pa** in 79%, 87%, and 86% yields, respectively (Table 2, entries 2, 10, and 11), demonstrating little steric hindrance effect on the yields in this transformation. Similarly, the products **3na**, **3oa**, and **3pa** leaving the C–Br bond intact, which is attractive for further synthetic elaboration.

Finally, we investigated the treatment of *trans*-2-phenylvinylboronic (**1p**) with *N*-methylindoline-2,3-dione (**1a**) or *N*-phenylpropylindoline-2,3-dione (**1e**) under the optimized conditions. As shown in Scheme 2, the desired products **3ap** and **3ep** were obtained in 37% and 40% yields, respectively.



Scheme 2. Copper-catalyzed coupling of indoline-2,3-dione with *trans*-2-phenylvinylboronic.

3. Conclusion

In summary, we have developed a new protocol for the synthesis of 3-aryl-3-hydroxy-2-oxindoles from the reaction of various indoline-2,3-diones and arylboronic acids in the presence of $Cu(OTf)_2$ and 1,10-phenanthroline hydrate under air atmosphere. The present catalytic system provides easy access to a variety of biologically relevant 3-aryl-3-hydroxy-2-oxindoles in good to excellent yields. Importantly, this transformation is very practical since it does not require the use of expensive ligands.

4. Experimental section

4.1. General

Chemicals and solvents were either purchased or purified by standard techniques. Melting points were uncorrected and recorded on Digital Melting Point Apparatus WRS-1B. IR spectra were recorded on an AVATAR 370 FI-Infrared Spectrophotometer. NMR spectroscopy was performed on both a Bruck-500 spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). TMS (tetramethylsilane) was used as an internal standard and $CDCl_3$ or DMSO-d_6 was used as the solvent. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. Elemental analysis was determined on a Carlo-Erba 1108 instrument.

4.2. General procedure for the synthesis of 3-aryl-3-hydroxy-2-oxindoles

A sealed reaction tube was charged with indolin-2,3-ones (0.3 mmol), arylboronic acids (1.2 mmol), $Cu(OTf)_2$ (5 mol %), **L1** (10 mol %), and $LiOH·H_2O$ (0.9 mmol) in 3 mL of CH_2Cl_2 at 80 °C for 48 h under air atmosphere. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2–3 mL), and filtered through a plug of silica gel, eluting with additional ethyl acetate (10–20 mL). The filtrate was concentrated and the resulting residue was purified by column chromatography on silica gel (300–400 mesh) with petroleum ether/EtOAc as eluent to provide the desired product.

*4.2.1. 3-Hydroxy-1-methyl-3-m-tolylindolin-2-one (**3ac**) (Table 2, entry 3).* Solid; mp 75.1–76.3 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.25 (3H, s), 3.15 (3H, s), 6.66 (1H, s), 7.00–7.19 (7H, m), 7.33–7.36 (1H, m). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.2, 26.2, 77.1, 108.9, 122.6, 122.8, 124.4, 126.0, 128.1, 128.3, 129.4, 133.2, 137.3, 141.3, 143.4, 176.8. IR (KBr): 3402, 2982, 2783, 1704, 1614, 1358, 1221, 1086, 747 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=253 (M$^+$, 100), 237 (45), 224 (82), 208 (99), 134 (32), 91 (51), 77 (30). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.93; H, 6.02.

*4.2.2. 3-Hydroxy-1-methyl-3-o-tolylindolin-2-one (**3ad**) (Table 2, entry 4).* Solid; mp 231.6–233.4 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.66 (3H, s), 3.19 (3H, s), 6.70 (1H, s), 6.87 (1H, d, *J*=10 Hz), 6.97–7.09 (3H, m), 7.18–7.21 (1H, m), 7.28 (1H, t, *J*=5 Hz), 7.33–7.36 (1H, m), 7.88–7.89 (1H, m); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.6, 26.0, 76.2, 108.6, 122.7, 123.9, 125.5, 126.4, 127.6, 129.5, 131.0, 131.5, 134.0, 139.0, 143.9, 176.0; IR (KBr): 3320, 2987, 2622, 1699, 1615, 1460, 1120, 1090, 1029, 918, 770, 753 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=253 (M$^+$, 100), 237 (24), 224 (47), 210 (75), 91 (51), 77 (26). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.94; H, 5.92.

*4.2.3. 3-Hydroxy-3-(3-methoxyphenyl)-1-methylindolin-2-one (**3af**) (Table 2, entry 5).* Solid; mp 141.0–141.1 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.14 (3H, s), 3.72 (3H, s), 6.67 (1H, d, *J*=5 Hz), 6.72 (1H, s), 6.82–7.37 (7H, m); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 26.2, 55.1, 77.0, 108.9, 111.7, 112.6, 117.7, 122.8, 124.4, 129.3, 129.5, 133.0, 142.9, 143.4, 159.2, 176.6; IR (KBr): 3212, 2785, 1699, 1610, 1488, 1470, 1371,1349, 1256, 1033, 753, 691 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=269 (M$^+$, 83), 253 (30), 240 (100), 224 (50), 210 (48), 134 (25), 77 (38). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.42; H, 5.68.

*4.2.4. 3-(4-Bromophenyl)-3-hydroxy-1-methylindolin-2-one (**3ah**) (Table 2, entry 8).* Solid; mp 166.3–166.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.15 (3H, s), 3.93 (1H, s), 6.83 (1H, d, *J*=10 Hz), 7.02 (1H, t, *J*=10 Hz), 7.14–7.17 (3H, m), 7.27–7.35 (3H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.6, 77.7, 108.8, 122.4, 123.8, 124.8, 127.2, 130.1, 131.2, 131.6, 139.1, 143.3, 177.2; IR (KBr): 3286, 2991, 1698, 1612, 1470, 1350, 1090, 815, 754 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=319 ([M+2]$^+$, 78), 317 (M$^+$, 76), 301 (55), 289 (100), 272 (75), 222 (45), 193 (63), 165 (43), 134 (53), 77 (73). Anal. Calcd for $C_{15}H_{12}BrNO_2$: C, 56.62; H, 3.80. Found: C, 56.69.42; H, 3.74.

*4.2.5. 3-Hydroxy-1-methyl-3-(3-nitrophenyl)indolin-2-one (**3aj**) (Table 2, entry 10).* Solid; mp 164.8–165.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.20 (3H, s), 4.21 (1H, s), 6.89 (1H, d, *J*=5 Hz), 7.04 (1H, t, *J*=10 Hz), 7.15–7.61 (5H, m), 8.05–8.16 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.7, 77.5, 109.2, 120.7, 123.2, 124.0, 124.8, 129.5, 130.5, 130.7, 131.7, 142.4, 143.4, 148.3, 176.7; IR (KBr): 3387, 3028, 1699, 1611, 1527, 1470, 1346,1091, 754, 734 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=284 (M$^+$, 100), 256 (81), 239 (85), 209 (44), 134 (65), 77 (46). Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25. Found: C, 63.43; H, 4.31.

*4.2.6. 3-Hydroxy-1-methyl-3-(4-nitrophenyl)indolin-2-one (**3ak**) (Table 2, entry 11).* Solid; mp 165.6–166.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.19 (3H, s), 4.13 (1H, s), 6.88–7.33 (4H, m), 7.45–8.07 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.7, 77.8, 109.1, 123.7, 124.0, 124.8, 126.5, 130.5, 130.8, 143.3, 147.2, 147.7, 176.6; IR (KBr): 3217, 2988, 1703, 1611, 1517, 1343, 1096, 753 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=284 (M$^+$, 100), 256 (99), 239 (86), 209 (74), 134 (55), 77 (50). Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25. Found: C, 63.44; H, 4.20.

*4.2.7. 3-Hydroxy-1-methyl-3-(naphthalene-2-yl)indolin-2-one (**3al**) (Table 2, entry 12).* Solid; mp 166.0–166.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.20 (3H, s), 3.65 (1H, s), 6.86 (1H, d, *J*=5 Hz), 7.01 (1H, t, *J*=10 Hz), 7.22–7.39 (5H, m), 7.67–7.83 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.6, 78.2, 108.8, 123.1, 123.6, 124.3, 125.0, 126.2, 126.3, 127.6, 128.2, 128.5, 129.9, 131.5, 133.0, 133.1, 137.4, 143.5, 177.5; IR (KBr): 3324, 3057, 2352, 1699, 1611, 1470, 1354, 1222, 1098, 752, 694 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=289 (M$^+$, 36), 273 (100), 260 (50), 244 (84), 127 (25), 77 (20). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23. Found: C, 78.94; H, 5.28.

*4.2.8. 3-(Biphenyl-4-yl)-3-hydroxy-1-methylindolin-2-one (**3am**) (Table 2, entry 13).* Solid; mp 174.0–174.2 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.18 (3H, s), 3.65 (1H, s), 6.85 (1H, d, *J*=5 Hz), 7.04 (1H, t, *J*=10 Hz), 7.25–7.38 (7H, m), 7.45–7.46 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.5, 77.9, 108.7, 123.6, 125.0, 125.8, 127.1, 127.3, 127.4, 128.7, 129.9, 131.5, 139.1, 140.5, 141.2, 143.5, 177.5; IR (KBr): 3059, 2319, 1700, 1612, 1471, 1366, 1223, 1089, 750, 695 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=315 (M$^+$, 80), 286 (100), 270 (68), 210 (28), 152 (32). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43. Found: C, 79.94; H, 5.49.

*4.2.9. 3-Hydroxy-1-methyl-3-(thiophen-3-yl)indolin-2-one (**3an**) (Table 2, entry 14).* Solid; mp 155–158 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.22 (3H, s), 3.62 (1H, s), 6.89 (1H, d, *J*=10 Hz), 7.11–7.43 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.5, 75.8, 108.7, 123.0, 123.4, 124.8, 125.7, 126.7, 130.0, 130.7, 140.8, 176.9; IR (KBr): 2981, 1704, 1357, 1220, 1094, 758 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=245 (M$^+$, 78), 229 (28), 200 (60), 184 (100), 111 (25), 77 (33). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52. Found: C, 63.72; H, 4.47.

*4.2.10. 1-Hexyl-3-hydroxy-3-phenylindolin-2-one (**3ca**) (Table 2, entry 16).* Solid; mp 82.2–82.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (3H, t, *J*=10 Hz), 1.21–1.29 (6H, m), 1.61–1.64 (2H, m), 3.52–3.73 (2H, m), 3.82 (1H, s), 6.83 (1H, d, *J*=5 Hz), 6.97 (1H, t, *J*=10 Hz), 7.17–7.29 (7H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 22.5, 26.5, 27.3, 31.4, 40.3, 77.9, 108.9, 123.3, 125.0, 125.2, 128.1, 128.5, 129.7, 131.9, 140.3, 142.9, 177.5; IR (KBr): 2987, 2818, 1699, 1466, 1354, 1166, 1098, 748, 695 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=309 (M$^+$, 38), 210 (100), 194 (24), 146 (25), 132 (33), 105 (25), 91 (23), 77 (31). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.71; H, 7.53.

*4.2.11. 3-Hydroxy-3-phenyl-1-(3-phenylpropyl)indolin-2-one (**3ea**) (Table 2, entry 18).* Solid; mp 96.6–98.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.88–2.02 (2H, m), 2.59–2.62 (2H, m), 3.69–3.75 (2H, m), 6.71 (1H, d, *J*=10 Hz), 6.95–7.11 (4H, m), 7.16–7.23 (7H, m), 7.27–7.29 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.8, 33.1, 39.8, 77.9, 108.8, 123.4, 125.1, 125.2, 126.1, 128.2, 128.3, 128.4, 128.5, 129.7, 131.9, 140.2, 140.9, 142.7, 177.5; IR (KBr): 2987, 1704, 1358, 1221, 1090, 754, 699 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=343 (M$^+$, 74), 327 (22), 221 (100), 183 (75), 132 (43), 105 (40), 91 (62), 77 (41). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16. Found: C, 80.49; H, 6.22.

*4.2.12. 3-(4-Fluorophenyl)-3-hydroxy-1-(3-phenylpropyl)indolin-2-one (**3eo**) (Table 2, entry 19).* Solid; mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.95–2.02 (2H, m), 2.61–2.64 (2H, m), 3.57 (1H, s), 3.60–3.66 (1H, m), 3.70–3.76 (1H, m), 6.74 (1H, d, *J*=10 Hz), 6.91–7.15 (6H, m), 7.17–7.28 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7, 33.1, 39.9, 77.4, 109.0, 115.5 (1C, d, $^2J_{C-F}$=21 Hz), 123.5, 125.0, 126.2, 127.3 (1C, d, $^3J_{C-F}$=7.5 Hz), 128.4 (1C, d, $^2J_{C-F}$=21 Hz), 130.0, 131.5, 136.0, 140.8, 142.7, 162.6 (1C, d, $^1J_{C-F}$=246.3 Hz), 177.2; IR (KBr): 3185, 2987, 1699, 1611, 1506, 1488, 1359, 1224, 1159, 829, 747, 700 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=361 (M$^+$, 74), 345 (26), 239 (100), 228 (75), 201 (65), 132 (50), 123 (36), 91 (50) 77 (23). Anal. Calcd for $C_{23}H_{20}FNO_2$: C, 76.44; H, 5.58. Found: C, 76.49; H, 5.64.

*4.2.13. 3-(4-Chlorophenyl)-3-hydroxy-1-(3-phenylpropyl)indolin-2-one (**3eg**) (Table 2, entry 20).* Solid; mp 100–102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.92–2.02 (2H, m), 2.59–2.63 (2H, m), 3.57 (1H, s), 3.59–3.64 (1H, m), 3.68–3.74 (1H, m), 6.73 (1H, d, *J*=5 Hz), 6.98–7.01 (1H, m), 7.09–7.24 (11H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7, 33.1, 39.9, 77.5, 109.0, 123.5, 125.0, 126.2, 126.8, 128.3, 128.5,

128.7, 130.0, 131.4, 134.2, 138.7, 140.8, 142.7, 177.1; IR (KBr): 3208, 2913, 1704, 1612, 1221, 1467, 1362, 1224, 1090, 1014 cm^{-1}; MS (EI, 70 eV): *m/z* (%)=379 ($[M+2]^+$, 19), 377 (M^+, 60), 361 (26), 255 (100), 244 (73), 217 (62), 161 (36), 132 (56), 91 (54) 77 (23). Anal. Calcd for $C_{23}H_{20}ClNO_2$: C, 73.11; H, 5.33. Found: C, 73.19; H, 5.39.

*4.2.14. 3-(4-Bromophenyl)-3-hydroxy-1-(3-phenylpropyl)indolin-2-one (**3eh**) (Table 2, entry 21).* Solid; mp 123–125 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.08 (2H, m), 2.67–2.70 (2H, m), 3.64 (1H, s), 3.66–3.72 (1H, m), 3.77–3.81 (1H, m), 6.80 (1H, d, *J*=10 Hz), 7.05–7.08 (1H, m), 7.17–7.33 (9H, m), 7.42–7.43 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7, 33.1, 39.9, 77.5, 109.0, 122.4, 123.5, 125.0, 126.2, 127.1, 128.3, 128.5, 130.0, 131.4, 131.7, 139.3, 140.8, 142.7, 177.0; IR (KBr): 3184, 2936, 1698, 1611, 1486, 1466, 1358, 1161, 1010, 815, 750, 700 cm^{-1}; MS (EI, 70 eV): *m/z* (%)=423 ($[M+2]^+$, 72), 421 (M^+, 70), 301 (100), 288 (58), 261 (57), 183 (22), 161 (56), 146 (61), 132 (74), 91 (79), 65 (18). Anal. Calcd for $C_{23}H_{20}BrNO_2$: C, 65.41; H, 4.77. Found: C, 65.35; H, 4.83.

*4.2.15. 1-Allyl-3-hydroxy-3-phenylindolin-2-one (**3ga**) (Table 2, entry 23).* Solid; mp 134.5–135.5 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.45 (1H, s), 4.26–4.31 (1H, m), 4.44–4.49 (1H, m), 5.25–5.30 (2H, m), 5.83–5.90 (1H, m), 6.91 (1H, d, *J*=5 Hz), 7.06–7.09 (1H, m), 7.28–7.41 (7H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 42.6, 77.9, 109.6, 117.9, 123.5, 125.0, 125.3, 128.3, 128.6, 129.8, 131.0, 131.5, 140.2, 142.7, 177.2; IR (KBr): 3298, 2927, 1699, 1612, 1467, 1367, 1177, 931, 753, 698 cm^{-1}; MS (EI, 70 eV): *m/z* (%)=265 (M^+, 81), 237 (72), 221 (35), 146 (100), 132 (43), 105 (62), 90 (30), 77 (71). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 77.03; H, 5.64.

*4.2.16. 1-Butyl-3-hydroxy-5-methyl-3-phenylindolin-2-one (**3ha**) (Fig. 1, entry 1).* Solid; mp 103.6–106.3 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88 (3H, t, *J*=10 Hz), 1.29–1.35 (2H, m), 1.60–1.64 (2H, m), 2.20 (3H, s), 3.51 (1H, s), 3.54–3.59 (1H, m), 3.67–3.73 (1H, m), 6.73 (1H, d, *J*=5 Hz), 7.00–7.05 (2H, m), 7.18–7.30 (5H, m). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.7, 20.1, 21.0, 29.4, 40.1, 78.0, 108.7, 125.2, 125.7, 128.1, 128.6, 130.0, 131.9, 132.9, 140.5, 177.4. IR (KBr): 3098, 2926, 1703, 1492, 1356, 1221, 700 cm^{-1}. MS (EI, 70 eV): *m/z* (%)=295 (M^+, 52), 267 (17), 224 (100), 146 (28), 105 (24), 77 (28). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.31; H, 7.23.

*4.2.17. (E)-3-Hydroxy-1-methyl-3-styrylindolin-2-one (**3ap**) (Scheme 1, entry 1).* Solid; mp 156–158 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 3.14 (3H, s), 6.34 (1H, d, *J*=16 Hz), 6.46 (1H, s), 6.57 (1H, d, *J*=16 Hz), 7.04–7.11 (2H, m), 7.24–7.41 (6H, m). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 25.6, 75.6, 108.3, 122.1, 123.8, 126.0, 127.4, 128.2, 128.4, 128.9, 129.1, 130.5, 135.4, 142.6, 175.5; IR (KBr): 3098, 2725, 1704, 1613, 1471, 1367, 1223, 1090, 891 cm^{-1}. MS (EI, 70 eV): *m/z* (%)=265 (M^+, 100), 248 (25), 160 (68), 146 (21), 91 (30), 77 (28). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 76.89; H, 5.74.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.135.

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