

Note

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# Synthesis of 2-Amino-3-Hydroxy-3*H*-Indoles via Palladium-catalyzed One-Pot Reaction of Isonitriles, Oxygen and *N*-tosylhydrazones Derived from 2-Acylanilines

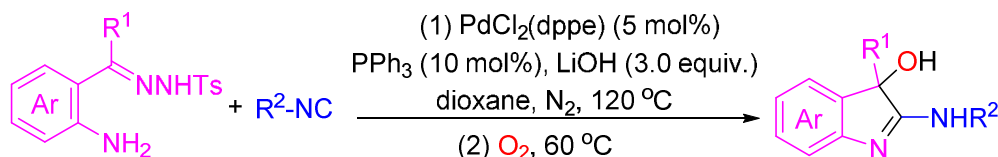
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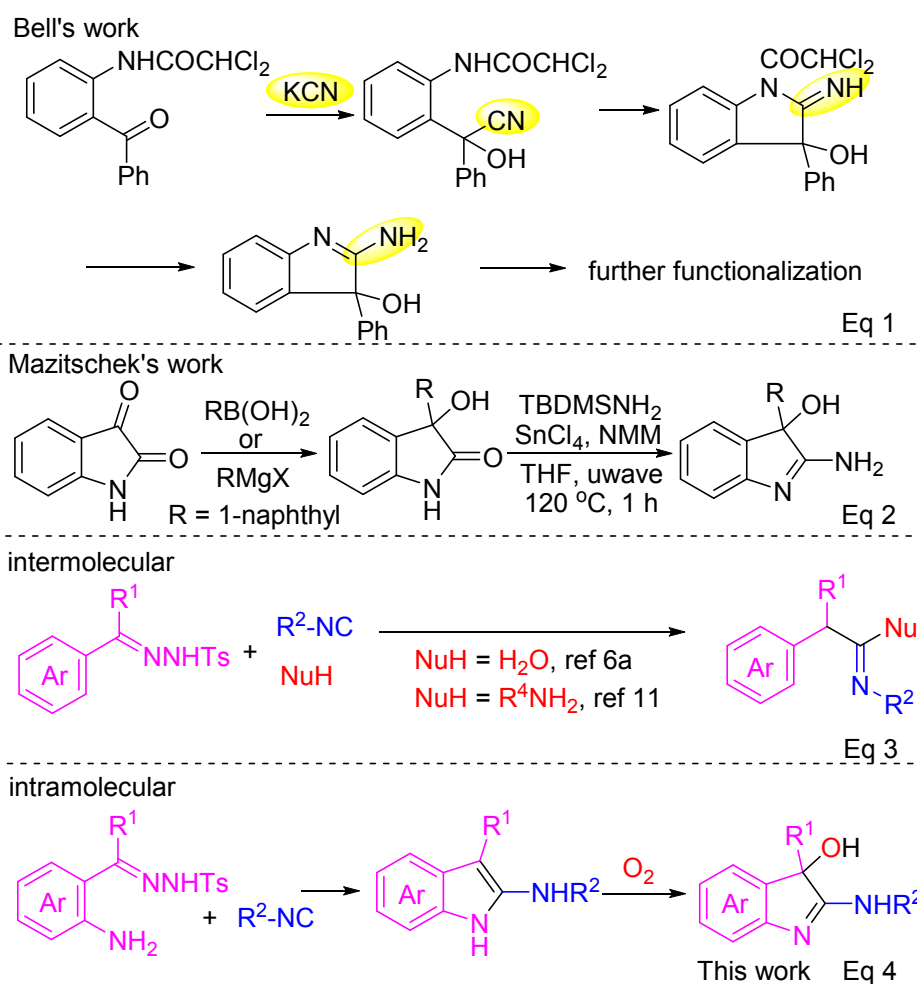
## ABSTRACT



A cyanide-free one-pot procedure was developed to access 2-amino-3-hydroxy-3*H*-indoles, which involved: 1) *in situ* formation of ketenimines by the reaction of *N*'-(1-(2-aminophenyl)ethylidene)-*p*-tosylhydrazones with isonitriles; 2) the intra-molecular nucleophilic attack of ketenimines by the amino in phenyl furnishing the ring closure leading to 2-aminoindoles; 3) the oxidation of 2-aminoindoles by O<sub>2</sub> leading to 2-amino-3-hydroxy-3*H*-indoles. This strategy represents not only a key compliment to the sporadic synthetic methods towards 2-amino-3-hydroxy-3*H*-indoles but also a progress in *N*-tosylhydrazone, isonitrile and ketenimine chemistry.

2-Amino-3-hydroxy-3*H*-indoles possess activity against plasmodium falciparum, serving as antimalarials with potent *in vivo* activity.<sup>1</sup> However, its biological activity is virtually unexplored, which is at least partly due to sporadic synthetic methodologies.<sup>2</sup> To date, only two practical methods were reported. One is the annulation of 2'-aroylacylanilides with cyanide developed by Bell (Scheme 1, Eq 1).<sup>3</sup> Mazitschek demonstrated the other procedure involving the addition of aryl boronic acids to isatins followed by treatment with *tert*-butyldimethylsilyl amine (Scheme 1, Eq 2).<sup>4</sup> Therefore, further development of practical methods involving either new reaction partners or pathways towards such frameworks kept highly desired goal for organic chemists.

Meanwhile, ketenimines are versatile intermediates in organic synthesis.<sup>5</sup> Cai pioneered the study on *in situ* formation of ketenimines<sup>6</sup> whereby direct reaction between isonitriles<sup>7,8,9</sup> and *N*-tosylhydrazones<sup>10,11,12</sup> as the carbene precursors. Afterwards, inter-molecular nucleophilic attack of the *in situ* formed ketenimines by H<sub>2</sub>O produced amides (Scheme 1, Eq 1).<sup>6a</sup> This strategy was further developed by us in a palladium-catalyzed MCRs to access amidines, where amines served as nucleophiles (Scheme 1, Eq 3).<sup>13</sup> We expect the intra-molecular nucleophilic attack on the *in situ* formed ketenimines, albeit no reports before, could furnish ring closure towards 2-aminoindoles, which, subsequently, is oxidized by O<sub>2</sub> allowing to access 2-amino-3-hydroxy-3*H*-indoles quickly (Scheme 1, Eq 4).<sup>14</sup> Herein, we wish to report such a synthetic pathway, which represents not only a key compliment to the sporadic synthetic methods towards 2-amino-3-hydroxy-3*H*-indoles but also a progress in *N*-tosylhydrazone, isonitrile and ketenimine chemistry.



**Scheme 1.** The nucleophilic attack on *in situ* formed ketenimine via reaction of *N*-tosylhydrazone and isonitrile.

Initially, we tested the reaction of *N*-(1-(2-aminophenyl)ethylidene)-*p*-tosylhydrazone (**1a**, 1.0 equiv.), 2,6-diisopropylphenyl isonitrile (**2a**, 1.2 equiv.) in the presence of Pd(OAc)<sub>2</sub> (5 mol%), PPh<sub>3</sub> (10 mol%) and LiOH (3.0 equiv.) in dioxane under N<sub>2</sub> at 120 °C for 5 h (Table 1, entry 1). To our delight, 2-((2,6-diisopropylphenyl)amino)-3-

methyl-3-hydroxy-3*H*-indole **3aa** was isolated in 44% yield after further heating the reaction mixture under O<sub>2</sub> at 60 °C for 1 h (Table 1, entry 1). Pd(acac)<sub>2</sub> provided a comparable yield (50%, Table 1, entry 2). Pleasingly, Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> increased the yield to 70% (Table 1, entry 3) and PdCl<sub>2</sub>(dppe) was the best (73%, Table 1, entry 4). PdCl<sub>2</sub>(dppf)•CH<sub>2</sub>Cl<sub>2</sub> and Pd(cod)Cl<sub>2</sub> slightly decreased the reaction efficiency to 62% and 58%, respectively (Table 1, entries 5 and 6). The ligands, such as tri(4-methylphenyl)phosphine (36%, Table 1, entry 7), tri(2-furyl)phosphine (68%, Table 1, entry 8) and tricyclohexylphosphine (45%, Table 1, entry 9) were inferior to PPh<sub>3</sub>. In the absence of PPh<sub>3</sub>, the yield dramatically decreased to 33% (Table 1, entry 10); while no reaction took place in the absence of both palladium and PPh<sub>3</sub> (Table 1, entry 11). Replacing dioxane with THF slightly decreased the reaction efficiency (65%, Table 1, entry 12); while DMF and toluene resulted in no reaction (Table 1, entries 13 and 14). The reaction was inhibited when LiOH was replaced with Cs<sub>2</sub>CO<sub>3</sub> or LiO<sup>t</sup>Bu (Table 1, entries 15 and 16).

**Table 1.** Selected results for screening the optimized reaction conditions <sup>a</sup>

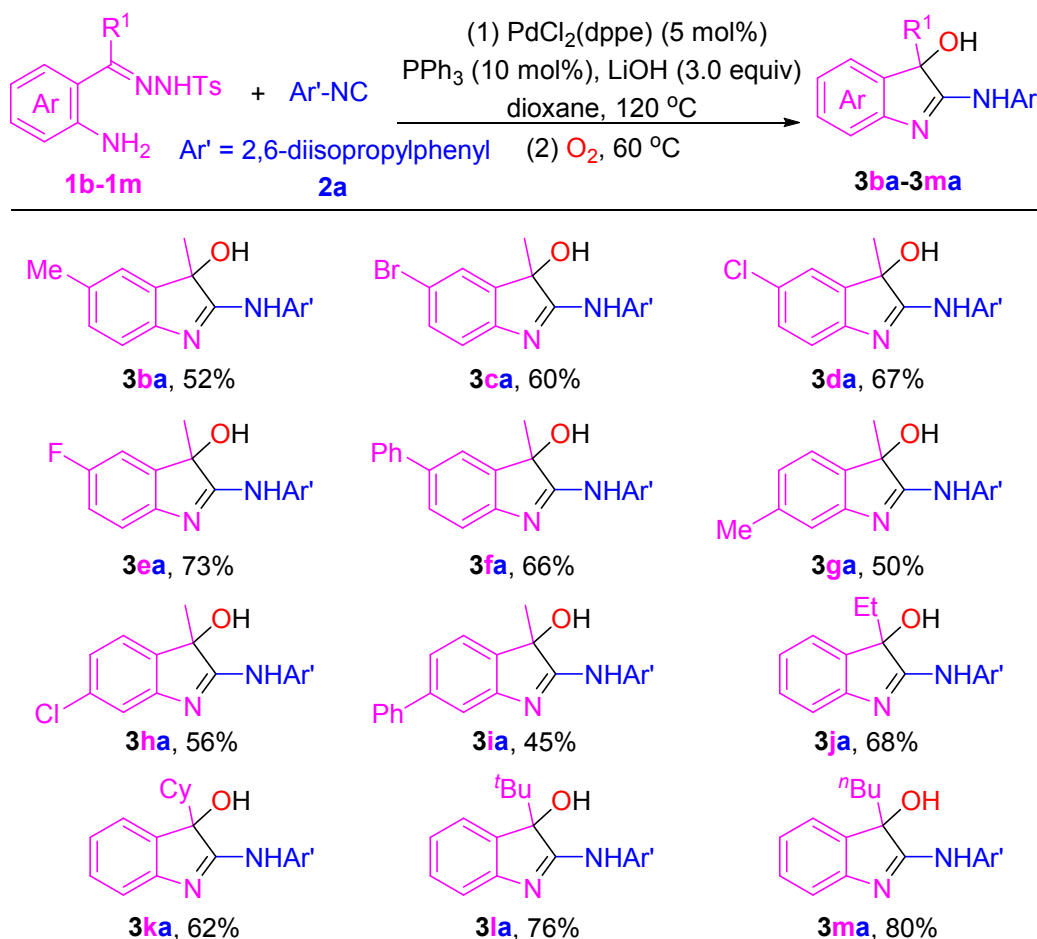
Entry	Catalyst	Ligand	Solvent	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	dioxane	44
2	Pd(acac) <sub>2</sub>	PPh <sub>3</sub>	dioxane	50
3	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub>	PPh <sub>3</sub>	dioxane	70
4	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	dioxane	73
5	PdCl <sub>2</sub> (dppf)•CH <sub>2</sub> Cl <sub>2</sub>	PPh <sub>3</sub>	dioxane	62
6	Pd(cod)Cl <sub>2</sub>	PPh <sub>3</sub>	dioxane	58
7	PdCl <sub>2</sub> (dppe)	P( <i>p</i> -tolyl) <sub>3</sub>	dioxane	36
8	PdCl <sub>2</sub> (dppe)	P(2-furyl) <sub>3</sub>	dioxane	68
9	PdCl <sub>2</sub> (dppe)	PCy <sub>3</sub>	dioxane	45
10	PdCl <sub>2</sub> (dppe)	--	dioxane	33
11	--	--	dioxane	NR
12	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	THF	65
13	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	DMF	<5
14	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	toluene	<5
15 <sup>c</sup>	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	dioxane	27
16 <sup>d</sup>	PdCl <sub>2</sub> (dppe)	PPh <sub>3</sub>	dioxane	<5

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Pd catalyst (0.01 mmol, 5 mol%), ligand (0.02 mmol, 10 mol%) and LiOH (0.6 mmol, 3.0 equiv.) in solvent (2 mL) under N<sub>2</sub>, 120 °C for 5 h in a sealed tube, then under O<sub>2</sub>, 60 °C for 1 h Cs<sub>2</sub>CO<sub>3</sub>. <sup>b</sup> Isolated yield. <sup>c</sup> Cs<sub>2</sub>CO<sub>3</sub> instead of LiOH. <sup>d</sup> LiO<sup>t</sup>Bu instead of LiOH.

Once the optimized conditions were established, the scope and limitation of substituted *N'*-(1-(2-aminophenyl)ethylidene)-*p*-tosylhydrazones were studied (Scheme 2). As expected, the procedure ran smoothly to access 2-amino-3-methyl-3-hydroxy-3*H*-indole derivatives with various substituents at the 5- and 6- position in moderate to good yields (**3ba-3ia**). A series of functional groups, such as methyl, bromo, chloro and fluoro were

compatible with the reaction conditions, which provided handles for potentially further functionalization. Notably, the diversity was further increased as the 3-alkyl in 2-amino-3-hydroxy-3*H*-indoles was not limited to methyl. The 3-ethyl (**3ja**, 68%), cyclohexyl (**3ka**, 62%), *t*-butyl (**3la**, 76%) and *n*-butyl (**3ma**, 80%) analogues were all isolated in good yields, while 3-aryl products was isolated in trace disappointedly. The structure of **3aa** was established by X-ray crystallographic analysis (see Supporting Information).<sup>15</sup>

**Scheme 2.** The substrate scope of substituted *N*-tosylhydrazones<sup>a</sup>



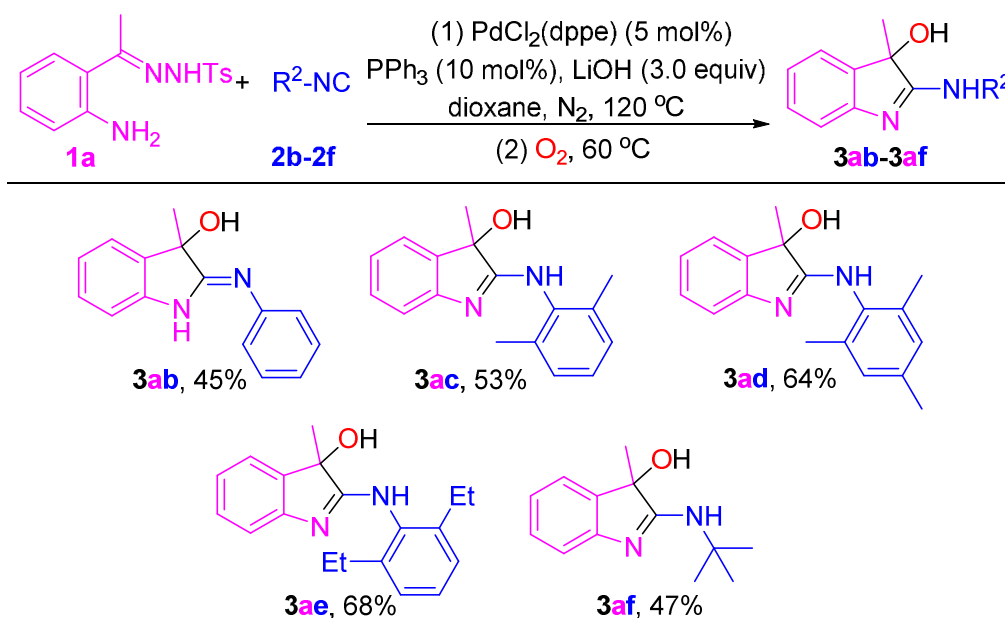
<sup>a</sup> Reaction conditions: **1b-1m** (0.2 mmol), **2a** (0.24 mmol), PdCl<sub>2</sub>(dppe) (0.01 mmol, 5 mol%), PPh<sub>3</sub> (0.02 mmol, 10 mol%) and LiOH (0.6 mmol, 3.0 equiv.) in dioxane (2 mL) under N<sub>2</sub>, 120 °C for 5 h in a sealed tube, then under O<sub>2</sub>, 60 °C for 1 h.

Afterwards, the scope of isocyanides was studied (Scheme 3). The hindrance on the phenyl of isocyanide was beneficial for this transformation. For example, phenyl isocyanide provided **3ab** in 45% yield; while the 2,6-dimethyl, 2,4,6-trimethyl and 2,6-diethyl analogues produced the corresponding 2-amino-3-hydroxy-3*H*-indoles in 53% (**3ac**), 64% (**3ad**) and 68% (**3ae**) yields, respectively. Notably, *t*-butyl isocyanide took part in this transformation, and 2-*t*-butylamino-3-methyl-3-hydroxy-3*H*-indole **3af** was isolated in 47% yield. *n*-Hexylisocyanide did not work under the

procedure. The structure of **3ab** was established by X-ray crystallographic analysis (see Supporting Information).<sup>16</sup>

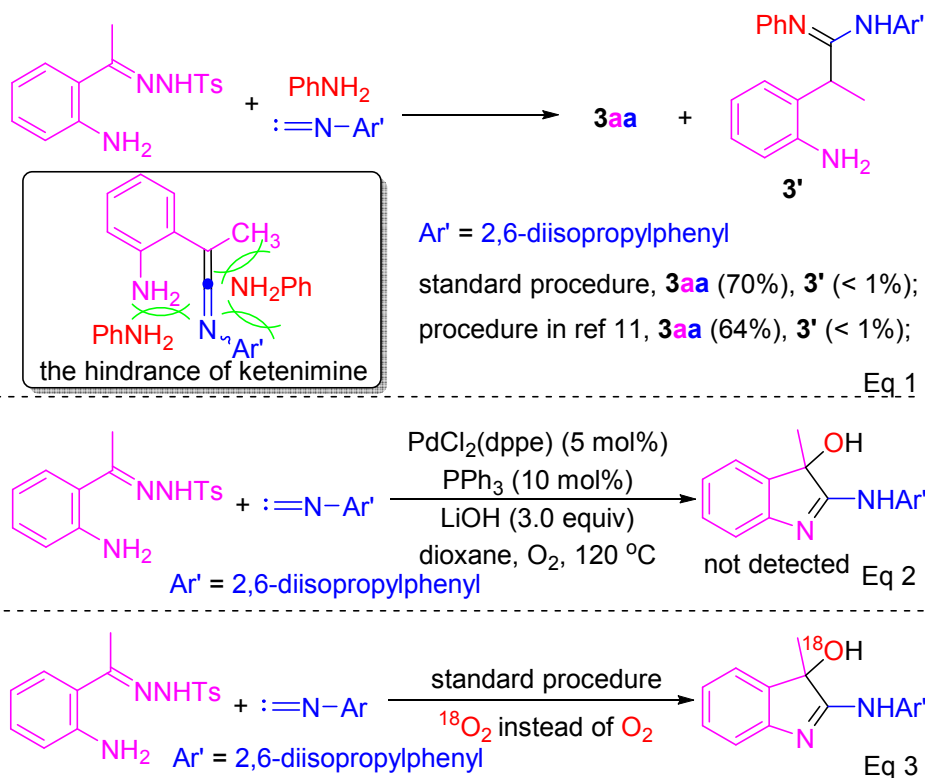
Notably, in this case, the C=N bond in N-C=N linkage located in out of the ring.

**Scheme 3.** The substrate scope of isonitriles <sup>a</sup>



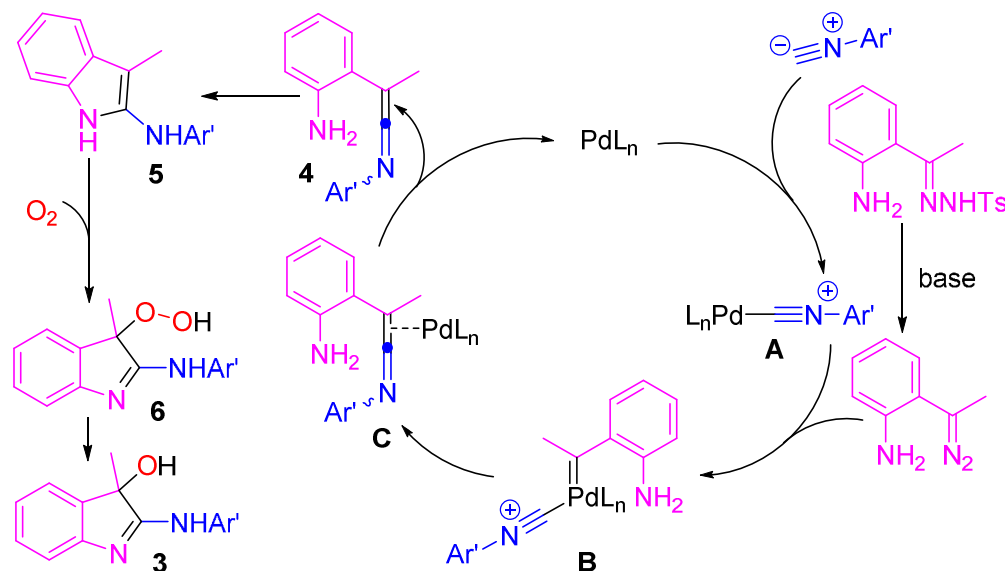
<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2b-2f** (0.24 mmol), PdCl<sub>2</sub>(dppe) (0.01 mmol, 5 mol%), PPh<sub>3</sub> (0.02 mmol, 10 mol%) and LiOH (0.6 mmol, 3.0 equiv.) in dioxane (2 mL) under N<sub>2</sub>, 120 °C for 5 h in a sealed tube, then under O<sub>2</sub>, 60 °C for 1 h.

Some experiments were conducted to get some insights into this procedure. In the competitive experiments, under either the standard procedure or the procedure in ref 11, 2-((2,6-diisopropylphenyl)amino)-3-methyl-3H-indole **3aa** was isolated as the sole product and no product whereby the inter-molecular nucleophilic attack was detected at all (Scheme 4, Eq 1). This may be ascribed to the hindrance of the presumed ketenimine intermediate (Scheme 4, Eq 1). During the transformation, 2-aminoindoles were occasionally detected, which were not stable enough to be isolated. The product **3aa** could not be detected when the reaction was conducted in one-pot under oxygen atmosphere (Scheme 4, Eq 2). Moreover, no <sup>18</sup>O was detected in the final product by adding H<sub>2</sub><sup>18</sup>O to the standard procedure. However, <sup>18</sup>O was totally incorporated in the hydroxy group of the product when the reaction was conducted under <sup>18</sup>O<sub>2</sub> atmosphere (Scheme 4, Eq 3).



Scheme 4. Preliminary mechanism study.

Based on the experimental results, a proposed mechanism was outlined in Scheme 5. Firstly, the coordination of palladium with isonitrile formed complex **A**. Then, under basic conditions, sequential deprotonation and detosylation of *N'*-(1-(2-aminophenyl)ethylidene)-*p*-tosylhydrazone took place to produce a diazo compound, which reacted with palladium complex **A** towards a palladium carbene **B**, along with the extrusion of N<sub>2</sub>. Secondly, **B** converted to the palladium complex **C** via migratory insertion. After the dissociation of palladium to enter the catalytic cycle, the intramolecular attack of ketenimine **4** by the amino in the phenyl ring furnished the ring closure leading to 2-aminoindole **5**. Finally, the oxidation of **5** by O<sub>2</sub> produced the final product 2-amino-3-hydroxy-3*H*-indole via the formation of 2-amino-3-peroxy-3*H*-indole.<sup>14</sup>



Scheme 5. A tentative mechanism.

In conclusion, we have developed a palladium-catalyzed cascade one-pot reaction of *N'*-(1-(2-aminophenyl)ethylidene)-*p*-tosylhydrazones, isonitriles and O<sub>2</sub> towards 2-amino-3-hydroxy-3*H*-indoles. This procedure involved: the sequential *in situ* formation of ketenimines; intra-molecular nucleophilic attack of ketenimines by amino; and oxidation by O<sub>2</sub>. It represents a practical synthetic method towards 2-amino-3-hydroxy-3*H*-indoles, rendering a progress in *N*-tosylhydrazone, isonitrile and ketenimine chemistry.

## EXPERIMENTAL SECTION

**General Information:** Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at ambient temperature on a 300 or 400 MHz (75 or 100 MHz for <sup>13</sup>C) NMR spectrometer. NMR experiments are reported in δ units, parts per million (ppm), and were referenced to CDCl<sub>3</sub> (δ 7.26 or 77.0 ppm), acetone-*d*<sup>6</sup> (δ 7.26 or 77.0 ppm) or DMSO-*d*<sup>6</sup> (δ 2.50 or 39.50 ppm) as the internal standard. The coupling constants *J* are given in Hz. Column chromatography was performed using EM Silica gel 60 (300-400 mesh). High-resolution mass spectra (HRMS) were obtained using a micro TOF II focus spectrometer (ESI).

## Experimental Procedure:

### General Procedure for 2-Amino-3-hydroxy-3*H*-indoles.



A 20 mL Schlenk tube equipped with a stir bar was charged with **1** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv.), PdCl<sub>2</sub>(dppe) (5.8 mg, 5 mol%), PPh<sub>3</sub> (5.2 mg, 10 mol%), LiOH (48.0 mg, 0.6 mmol) and dioxane (2 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred under N<sub>2</sub> at 100 °C in oil bath. After 5 h, the tube was cooled to room temperature, and poured with O<sub>2</sub>. The mixture was stirred at 60 °C for another 1 h. After completion, 5 mL of brine was added, and the mixture was extracted with EtOAc (3 × 2mL). The organic layer was collected and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc as the eluent to give the desired product.

**2-((2,6-Diisopropylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3aa):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3aa** (47.0 mg, 73% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42 (d, *J* = 7.2 Hz, 1H), 7.22-7.15 (m, 4H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.52 (s, 1H), 4.09 (s, 1H), 3.12-3.02 (m, 2H), 1.83 (s, 3H), 1.25-1.16 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.6, 143.0, 141.3, 139.6, 139.1, 132.2, 129.4, 124.1, 123.8, 123.6, 123.3, 121.8, 109.0, 75.4, 28.2, 27.7, 27.3, 23.8, 23.8, 23.6, 23.2; GCMS (EI) calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O 322, found 322; HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>O (M + H)<sup>+</sup> 323.2118, found 323.2119; IR (KBr) 3414, 3060, 2962, 2926, 2867, 1687, 1620, 1588, 1484, 1471, 1384, 1362, 1325 cm<sup>-1</sup>.

**2-((2,6-Diisopropylphenyl)amino)-3,5-dimethyl-3-hydroxy-3H-indole (3ba):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ba** (35.1 mg, 52% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28 (s, 1H), 7.22-7.16 (m, 3H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 6.40 (s, 1H), 3.76 (s, 1H), 3.11-3.02 (m, 2H), 2.34 (s, 3H), 1.84 (s, 3H), 1.25-1.15 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.7, 143.2, 139.5, 139.0, 139.0, 132.1, 131.4, 129.7, 124.5, 124.0, 123.5, 123.3, 108.7, 75.4, 28.2, 27.7, 27.3, 23.7, 23.7, 23.6, 23.2, 20.9; GCMS (EI) calcd for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub>O 336, found 336; HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub>O (M + H)<sup>+</sup> 337.2274, found 337.2274; IR (KBr) 3474, 3415, 2961, 1637, 1617, 1458, 1384, 1339 cm<sup>-1</sup>.

**5-Bromo-2-((2,6-diisopropylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3ca):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ca** (48.2 mg, 60% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38 (s, 1H), 7.20-7.13 (m, 4H), 6.56 (d, *J* = 8.1 Hz, 1H), 6.47 (s, 1H), 3.94 (s, 1H), 3.05-2.95 (m, 2H), 1.80 (s, 3H), 1.22-1.12 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.2, 142.7, 139.8, 139.4, 138.9, 133.8, 129.3, 127.1, 124.4, 124.3, 123.6, 123.4, 110.0, 75.4, 29.7, 28.2, 27.8, 27.3, 23.7, 23.6, 23.2;

GCMS (EI) calcd for  $C_{21}H_{25}BrN_2O$  400, found 400; HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{26}BrN_2O$  ( $M + H$ )<sup>+</sup> 401.1223, found 401.1212; IR (KBr) 3416, 2962, 2926, 2868, 1685, 1638, 1618, 1560, 1459, 1384, 1326  $cm^{-1}$ .

**5-Chloro-2-((2,6-diisopropylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3da):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3da** (47.7 mg, 67% yield) as yellow solid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.12 (s, 1H), 7.45 (s, 1H), 7.28 (d,  $J = 7.7$  Hz, 1H), 7.12-7.04 (m, 3H), 6.72 (d,  $J = 7.2$  Hz, 1H), 6.09 (s, 1H), 3.11-2.97 (m, 1H), 2.96-2.76 (m, 1H), 1.61 (s, 3H), 1.12-1.08 (m, 12H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  131.4, 123.1, 122.7, 74.8, 27.8, 27.0, 23.9, 23.6, 23.3, 23.0; GCMS (EI) calcd for  $C_{21}H_{25}ClN_2O$  356, found 356; HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{26}ClN_2O$  ( $M + H$ )<sup>+</sup> 357.1728, found 357.1730; IR (KBr) 3547, 3474, 3414, 3235, 2958, 2866, 1668, 1638, 1616, 1478, 1457, 1436, 1384, 1322  $cm^{-1}$ .

**2-((2,6-Diisopropylphenyl)amino)-5-fluoro-3-methyl-3-hydroxy-3H-indole (3ea):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ea** (49.6 mg, 73% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.20-7.12 (m, 4H), 6.86 (t,  $J = 8.7$  Hz, 1H), 6.56-6.53 (m, 1H), 6.48 (s, 1H), 3.09-2.98 (m, 2H), 2.03 (s, 1H), 1.81 (s, 3H), 1.23-1.13 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.8, 158.7 (d,  $J_{C-F} = 239.0$  Hz), 142.8, 139.3 (d,  $J_{C-F} = 53.0$  Hz), 137.2, 133.6, 124.3, 123.6, 123.4, 115.8, 115.6, 111.8, 111.6, 109.5 (d,  $J_{C-F} = 7.0$  Hz), 75.6, 28.2, 27.7, 27.3, 23.7, 23.6, 23.2, 21.0; GCMS (EI) calcd for  $C_{21}H_{25}FN_2O$  340, found 340; HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{26}FN_2O$  ( $M + H$ )<sup>+</sup> 341.2024, found 341.2022; IR (KBr) 3436, 2963, 2928, 2868, 1691, 1629, 1488, 1438, 1384, 1362, 1327  $cm^{-1}$ .

**2-((2,6-Diisopropylphenyl)amino)-3-methyl-5-phenyl-3-hydroxy-3H-indole (3fa):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3fa** (52.6 mg, 66% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.68 (s, 1H), 7.56-7.54 (m, 2H), 7.44-7.41 (m, 3H), 7.32 (t,  $J = 7.3$  Hz, 1H), 7.22-7.16 (m, 3H), 6.72 (d,  $J = 7.8$  Hz, 1H), 6.56 (s, 1H), 3.08-3.02 (m, 2H), 2.04 (s, 1H), 1.87 (s, 3H), 1.24-1.17 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.4, 143.0, 140.9, 140.7, 139.5, 139.0, 135.5, 132.6, 128.8, 128.4, 126.8, 126.8, 124.2, 123.6, 123.4, 122.8, 109.3, 75.4, 28.2, 27.8, 27.3, 23.7, 23.6, 23.6, 23.2; GCMS (EI) calcd for  $C_{21}H_{30}N_2O$  398, found 398; HRMS (ESI)  $m/z$  calcd for  $C_{27}H_{31}N_2O$  ( $M + H$ )<sup>+</sup> 399.2431, found 399.2437; IR (KBr) 3435, 3060, 2962, 2926, 2867, 1691, 1623, 1600, 1508, 1479, 1464, 1438, 1384, 1362, 1326  $cm^{-1}$ .

**2-((2,6-Diisopropylphenyl)amino)-3,6-dimethyl-3-hydroxy-3H-indole (3ga):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ga** (33.8 mg, 50% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (d,  $J = 7.5$  Hz, 1H), 7.20-7.11 (m, 3H), 6.81 (d,  $J = 7.5$  Hz, 1H), 6.46 (s, 1H), 6.43 (s, 1H), 3.39 (s, 1H), 3.04-2.98 (m, 2H), 2.29 (s, 3H), 1.80 (s, 3H), 1.21-1.14 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.5, 143.2, 141.6, 139.8, 139.4, 139.0, 129.1, 124.0, 123.6, 123.5, 123.3, 122.4, 109.8, 75.2, 29.7, 28.2, 27.8, 27.2, 23.6, 23.6, 23.2, 21.7; GCMS (EI) calcd for  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$  336, found 336; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  337.2274, found 337.2276; IR (KBr) 3463, 2961, 2926, 2867, 1686, 1654, 1630, 1559, 1507, 1458, 1384, 1326  $\text{cm}^{-1}$ .

**6-Chloro-2-((2,6-Diisopropylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3ha):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ha** (40.1 mg, 56% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 7.8$  Hz, 1H), 7.18-7.12 (m, 3H), 6.96 (d,  $J = 7.9$  Hz, 1H), 6.64 (s, 1H), 6.51 (s, 1H), 3.56 (s, 1H), 3.02-2.94 (m, 2H), 1.79 (s, 3H), 1.21-1.14 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.9, 142.7, 142.5, 139.3, 138.9, 135.1, 130.4, 124.8, 124.4, 123.6, 123.4, 121.9, 109.7, 74.9, 29.7, 28.2, 27.8, 27.2, 23.6, 23.5, 23.2; GCMS (EI) calcd for  $\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}$  356, found 356; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{26}\text{ClN}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  357.1728, found 357.1727; IR (KBr) 3438, 2962, 2926, 2968, 1693, 1617, 1560, 1485, 1458, 1325  $\text{cm}^{-1}$ .

**2-((2,6-Diisopropylphenyl)amino)-3-methyl-6-phenyl-3-hydroxy-3H-indole (3ia):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ia** (36.0 mg, 45% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55-7.51 (m, 3H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 1H), 7.28-7.21 (m, 4H), 6.91 (s, 1H), 3.10-3.00 (m, 2H), 2.08 (s, 1H), 2.07 (s, 1H), 1.90 (s, 3H), 1.24-1.19 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.2, 140.8, 131.3, 128.8, 127.6, 127.1, 125.0, 124.1, 123.8, 123.5, 121.4, 75.6, 29.7, 28.3, 27.8, 27.0, 23.8, 23.5, 23.4; GCMS (EI) calcd for  $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}$  398, found 398; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  399.2431, found 399.2427; IR (KBr) 3463, 2961, 2927, 1685, 1626, 1560, 1507, 1458, 1437, 1384, 1339  $\text{cm}^{-1}$ .

**2-((2,6-Diisopropylphenyl)amino)-3-ethyl-3-hydroxy-3H-indole (3ja):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ja** (45.9 mg, 68% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J = 7.2$  Hz, 1H), 7.20-7.12 (m, 4H), 6.99 (t,  $J = 7.4$  Hz, 1H), 6.63 (d,  $J = 7.5$  Hz, 1H), 6.48 (s, 1H), 3.37 (s, 1H), 3.10-3.01 (m, 2H), 2.23-2.18 (m, 2H), 1.23-1.12 (m, 12H), 0.91 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.8, 142.9, 141.8, 139.1, 138.6, 129.9, 129.1, 124.1, 123.8, 123.2, 123.0, 121.4, 108.6, 76.4, 33.2, 27.7, 27.4, 23.6, 23.3, 23.2, 23.0, 7.5; GCMS (EI) calcd for  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$  336, found 336;

HRMS (ESI)  $m/z$  calcd for  $C_{22}H_{29}N_2O$  ( $M + H$ )<sup>+</sup> 337.2274, found 337.2274; IR (KBr) 3456, 2962, 2918, 2849, 1685, 1637, 1622, 1470, 1384, 1325  $cm^{-1}$ .

**3-Cyclohexyl-2-((2,6-diisopropylphenyl)amino)-3-hydroxy-3H-indole (3ka):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ka** (48.4 mg, 62% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42 (d,  $J$  = 7.3 Hz, 1H), 7.20-7.10 (m, 4H), 6.98 (t,  $J$  = 7.4 Hz, 1H), 6.62 (d,  $J$  = 7.7 Hz, 1H), 6.44 (s, 1H), 3.11 (hept,  $J$  = 6.7 Hz, 1H), 2.95 (hept,  $J$  = 6.7 Hz, 1H), 2.87 (s, 1H), 2.17-2.09 (m, 2H), 1.86-1.68 (m, 4H), 1.34-1.10 (m, 17H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.3, 143.2, 142.4, 139.4, 138.8, 129.8, 129.3, 124.9, 124.0, 123.5, 123.3, 121.5, 108.8, 80.5, 48.3, 28.1, 27.8, 26.9, 26.5, 26.3, 26.1, 26.0, 23.9, 23.6, 23.5, 23.3; GCMS (EI) calcd for  $C_{26}H_{34}N_2O$  390, found 390; HRMS (ESI)  $m/z$  calcd for  $C_{26}H_{35}N_2O$  ( $M + H$ )<sup>+</sup> 391.2744, found 391.2744; IR (KBr) 3466, 3059, 2960, 2929, 2854, 1725, 1686, 1619, 1470, 1384, 1325  $cm^{-1}$ .

**3-(tert-Butyl)-2-((2,6-diisopropylphenyl)amino)-3-hydroxy-3H-indole (3la):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3la** (55.5 mg, 76% yield) as yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (d,  $J$  = 7.5 Hz, 1H), 7.21-7.10 (m, 4H), 6.95 (t,  $J$  = 7.5 Hz, 1H), 6.59 (d,  $J$  = 7.8 Hz, 1H), 6.31 (s, 1H), 3.12 (hept,  $J$  = 6.8 Hz, 1H), 3.06 (s, 1H), 2.88 (hept,  $J$  = 6.7 Hz, 1H), 1.26-1.12 (m, 21H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.1, 143.3, 142.7, 139.3, 138.6, 130.4, 129.2, 126.1, 124.0, 123.6, 123.3, 121.0, 108.6, 82.5, 38.8, 28.3, 27.7, 24.1, 23.8, 23.7, 23.4, 23.3; GCMS (EI) calcd for  $C_{24}H_{32}N_2O$  364, found 364; HRMS (ESI)  $m/z$  calcd for  $C_{24}H_{33}N_2O$  ( $M + H$ )<sup>+</sup> 365.2587, found 365.2591; IR (KBr) 3474, 2961, 2929, 2869, 1683, 1638, 1618, 1469, 1384, 1362, 1325  $cm^{-1}$ .

**3-(n-Butyl)-2-((2,6-diisopropylphenyl)amino)-3-hydroxy-3H-indole (3ma):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ma** (58.3 mg, 80% yield) as yellow solid: <sup>1</sup>H NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 (d,  $J$  = 7.4 Hz, 1H), 7.20-7.11 (m, 4H), 6.99 (t,  $J$  = 7.4 Hz, 1H), 6.63 (d,  $J$  = 7.8 Hz, 1H), 6.49 (s, 1H), 3.09 (s, 1H), 3.07-2.97 (m, 2H), 2.20-2.16 (m, 2H), 1.27-1.12 (m, 16H), 0.89 (t,  $J$  = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.9, 143.2, 142.1, 139.3, 138.9, 130.4, 129.4, 124.3, 124.0, 123.5, 123.3, 121.7, 109.0, 78.3, 40.4, 28.0, 27.8, 25.7, 23.9, 23.5, 23.5, 23.3, 22.9, 13.9; GCMS (EI) calcd for  $C_{24}H_{32}N_2O$  364, found 364; HRMS (ESI)  $m/z$  calcd for  $C_{24}H_{33}N_2O$  ( $M + H$ )<sup>+</sup> 365.2587, found 365.2589; IR (KBr) 3416, 2959, 2931, 2868, 1685, 1638, 1619, 1470, 1384, 1325  $cm^{-1}$ .

**3-Methyl-2-(phenylamino)-3-hydroxy-3H-indole (3ab):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ab** (21.3 mg, 45% yield) as yellow solid:  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  7.93 (s, 1H), 7.36-7.28 (m, 3H), 7.22-7.16 (m, 1H), 7.10 (d,  $J$  = Hz, 1H), 7.04-6.99 (m, 1H), 6.97-6.92 (m, 1H), 5.10 (s, 1H), 1.58 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  129.9, 129.6, 123.2, 122.8, 122.6, 120.2, 25.9; GCMS (EI) calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$  238, found 238; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  239.1179, found 239.1181; IR (KBr) 3450, 3418, 2935, 1642, 1617, 1450, 1380, 1333  $\text{cm}^{-1}$ .

**2-((2,6-Dimethylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3ac):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ac** (28.1 mg, 53% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 7.1 Hz, 1H), 7.16 (t,  $J$  = 7.5 Hz, 1H), 7.09-7.07 (m, 2H), 6.99-6.95 (m, 2H), 6.64 (s, 1H), 6.51 (s, 1H), 4.43 (s, 1H), 2.15 (s, 6H), 1.81 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.55, 129.4, 128.3, 123.7, 121.8, 109.0, 75.4, 27.3, 17.7; GCMS (EI) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$  266, found 266; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  267.1492, found 267.1500; IR (KBr) 3457, 2926, 1685, 1621, 1560, 1469, 1384, 1326  $\text{cm}^{-1}$ .

**2-((2,4,6-Trimethylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3ad):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ad** (35.8 mg, 64% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (d,  $J$  = 7.0 Hz, 1H), 7.16 (t,  $J$  = 7.6 Hz, 1H), 6.96 (t,  $J$  = 7.4 Hz, 1H), 6.90 (s, 2H), 6.62 (s, 1H), 6.49 (s, 1H), 4.35 (s, 1H), 2.29 (s, 3H), 2.12 (s, 6H), 1.80 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 129.3, 128.9, 123.7, 121.8, 60.4, 21.0, 20.7, 17.6, 14.1; GCMS (EI) calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$  280, found 280; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  281.1648, found 281.1652; IR (KBr) 3415, 2966, 2924, 2855, 1684, 1637, 1620, 1570, 1470, 1384, 1325  $\text{cm}^{-1}$ .

**2-((2,6-Diethylphenyl)amino)-3-methyl-3-hydroxy-3H-indole (3ae):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3ae** (40.0 mg, 68% yield) as yellow solid:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J$  = 7.1 Hz, 1H), 7.19-7.05 (m, 4H), 6.98 (t,  $J$  = 7.4 Hz, 1H), 6.61 (d,  $J$  = 7.2 Hz, 1H), 6.50 (s, 1H), 3.92 (s, 1H), 2.58-2.49 (m, 4H), 1.81 (s, 3H), 1.17 (t,  $J$  = 7.4 Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.3, 144.5, 141.3, 134.9, 134.4, 132.1, 129.4, 126.5, 126.3, 123.8, 121.8, 109.0, 75.3, 27.2, 24.6, 24.0, 14.4, 14.2; GCMS (EI) calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$  294, found 294; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  295.1805, found 295.1806; IR (KBr) 3439, 3061, 2966, 2930, 2873, 1686, 1620, 1589, 1471, 1452, 1384, 1326  $\text{cm}^{-1}$ .

**2-(tert-Butylamino)-3-methyl-3-hydroxy-3H-indole (3af):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 10) give **3af** (20.5 mg, 47% yield) as yellow oil:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20-7.13 (m, 3H), 6.86 (t,  $J = 7.2$  Hz, 1H), 4.93 (s, 1H), 2.90 (s, 1H), 1.44 (s, 9H), 1.41 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.2, 155.3, 136.8, 129.8, 121.4, 121.2, 117.0, 80.6, 52.0, 28.7, 25.7; GCMS (EI) calcd for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$  218, found 218; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}$  ( $\text{M} + \text{H}$ ) $^+$  219.1492, found 219.1497; IR (KBr) 3408, 2970, 2928, 1623, 1599, 1574, 1532, 1458, 1384, 1366, 1339  $\text{cm}^{-1}$ .

## ASSOCIATED CONTENT

### Supporting Information:

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxx.

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds (PDF)

X-ray crystallographic data for **3aa** and **3ab** (CIF)

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15. The molecular structure of **3aa** was determined by X-ray crystallo-graphic analysis. CCDC 1497965 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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