

# Metal-Free Base-Mediated Oxidative Annulation Cascades to 3-Substituted-3-Hydroxyoxindole and its 3-Spirocyclic Derivative

Min Liu,<sup>†, a</sup> Chunxia Zhang,<sup>†, a</sup> Mingruo Ding,<sup>a</sup> Bencan Tang<sup>\*, b</sup> and Fengzhi Zhang<sup>\*, a</sup>

**Abstract:** A simple and efficient method was developed for the construction of the medicinally important 3-substituted-3-hydroxyoxindole and its 3-spirocyclic derivatives with readily available aniline derivatives as starting materials. This highly atom- and step-economical one-pot protocol was carried out under metal-free base-mediated conditions through a novel oxidative annulation strategy with oxygen as the oxidant. The key intermediates were isolated and confirmed. A reasonable reaction pathway was proposed and supported by both the preliminary experiments and computational studies.

The 3-substituted-3-hydroxyoxindole and its synthetic derivatives have been well documented for various biological activities.<sup>1</sup> This promising motif has been encountered in a large variety of natural products and pharmaceuticals. For example, convolutamydine A-E are a family of alkaloids containing a dibromohydroxyoxindole moiety, which were isolated from the Floridian marine bryozoans *Amathia convolute* and exhibited a potent activity in the differentiation of HL-60 cells.<sup>2</sup> Maremycin A-D were isolated from a marine *Streptomyces* species, and some of them exhibited cytotoxicity to K562 human leukemia cell line etc.<sup>3</sup> NSC635473 and YK-4-279 inhibit Ewing's sarcoma family tumor cell growth and induce apoptosis.<sup>4</sup> SM-130686 is a highly potent and orally active nonpeptidic growth hormone secretagogue.<sup>5</sup> 3-Substituted-3-hydroxyoxindole's synthetic derivatives such as the spirocyclic analogue have shown potential anti-cancer activity.<sup>6</sup>

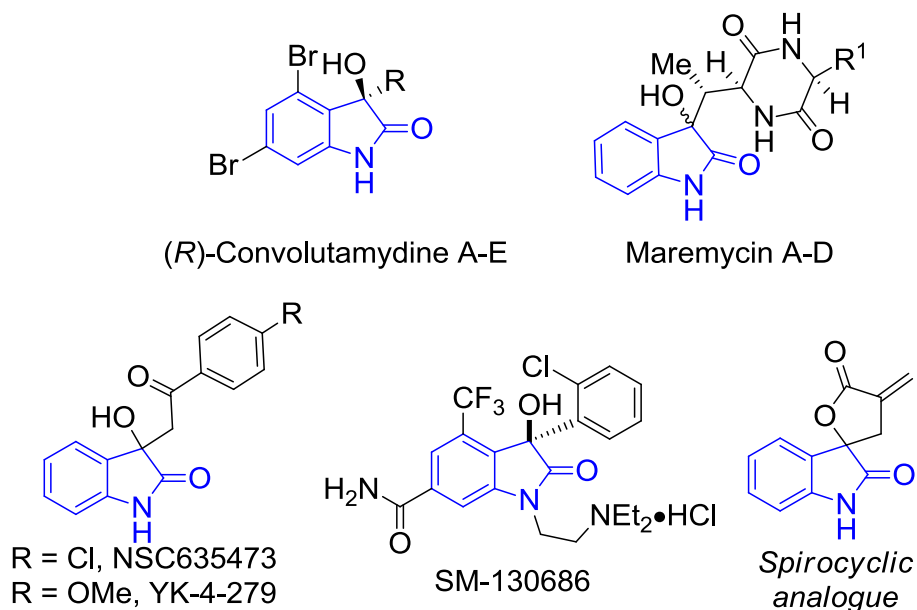
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<sup>†</sup> These authors contributed equally to this work

<sup>a</sup> College of Pharmaceutical Science & Green Pharmaceutical Collaborative Innovation Center of Yangtze River Delta Region, Zhejiang University of Technology, Hangzhou, 310014, P. R. China

<sup>b</sup> Department of Chemical and Environment Engineering, Science and Engineering Building, The University of Nottingham Ningbo China, 199 Taikang East Road, Ningbo, 315100, P. R. China

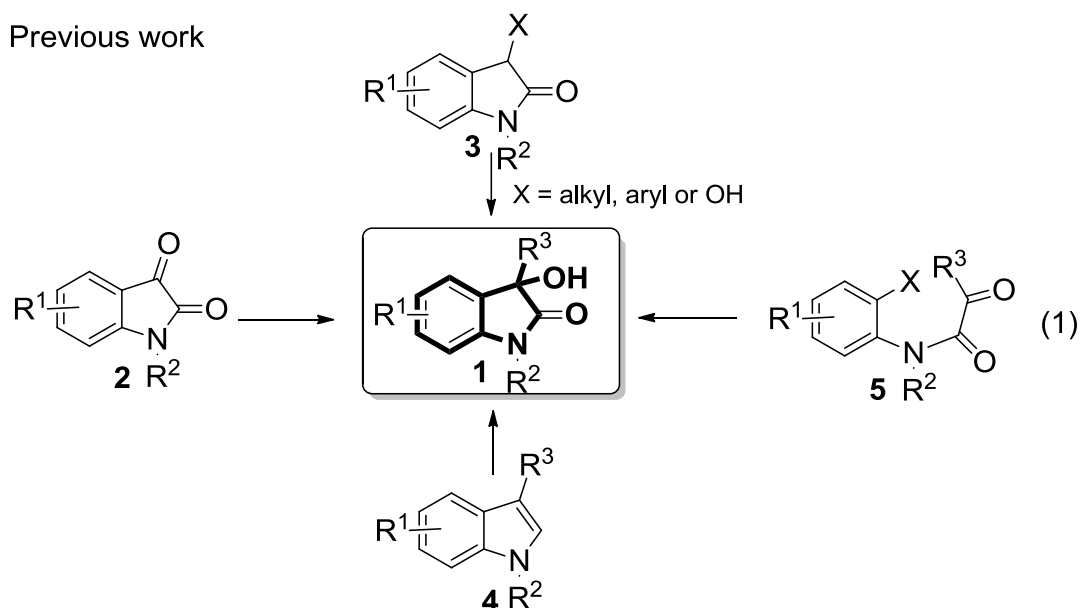
\* Corresponding authors: [bencan.tang@nottingham.edu.cn](mailto:bencan.tang@nottingham.edu.cn), [zhangfengzhi@zjut.edu.cn](mailto:zhangfengzhi@zjut.edu.cn)



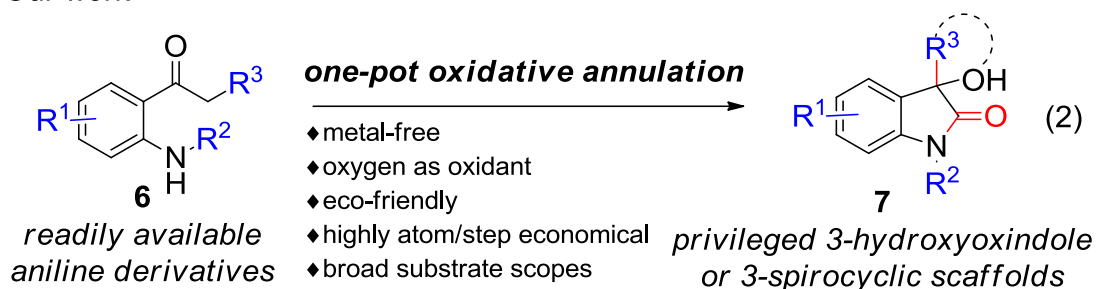
**Figure 1. Representative examples of bioactive 3-substituted-3-hydroxyoxindole and its synthetic derivatives**

The general class of 3-substituted-3-hydroxyoxindole possess appealing structure and a wide range of biological activities, and as such have been the focus of many methodological efforts.<sup>7</sup> Previously reported methods for the synthesis of 3-substituted-3-hydroxyoxindole **1** mainly employ the functionalized isatins, oxindoles or indoles as the starting materials through metal catalysis or organocatalysis (Scheme 1, eq 1),<sup>8</sup> for example, (i) the nucleophilic addition of isatins **2**,<sup>9</sup> (ii) the electrophilic addition of 3-hydroxyoxindoles **3**,<sup>10</sup> (iii) the hydroxylation of 3-substituted oxindoles **3**,<sup>11</sup> (IV) oxidation of indoles.<sup>12</sup> Despite these methods, examples for the construction of the 3-substituted-3-hydroxyoxindole or its 3-spirocyclic analogue with linear starting materials are limited, which include Kündig's Pd-catalyzed asymmetric intramolecular  $\alpha$ arylation of amide enolates,<sup>13</sup> Shibasaki's Cu-catalyzed enantioselective intramolecular arylation of  $\alpha$ -keto amides,<sup>14</sup> Jia and Gao's Ni-catalyzed intramolecular nucleophilic addition of aryl chlorides to  $\alpha$ -keto amides,<sup>15</sup> Xu's novel synthesis of various 3-aryl-3-hydroxyoxindole derivatives *via* Rh-catalyzed asymmetric arylation-cyclization sequence with *ortho*-ketoester anilines as substrates<sup>16</sup> and Du's metal-free chiral aryl iodine-mediated enantioselective synthesis of 3-spirofurooxindoles *via* cascade oxidative C-O and C-C bond formation.<sup>17</sup> Though these methods are generally efficient for the synthesis of 3-substituted-3-hydroxyoxindole, our interest in atom- and step-economical cascade reactions<sup>18</sup> led us to investigate whether we could achieve the rapid synthesis of both 3-substituted-3-hydroxyoxindole and its 3-spirocyclic derivative **7** *via* metal-free oxidative annulation/ring distortion sequence with readily available aniline derivatives **6** as starting materials (Scheme 1, eq 2).

Previous work

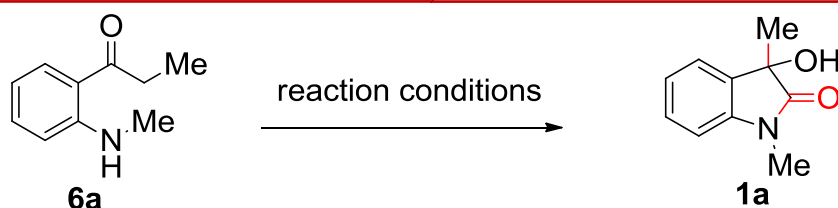


Our work



**Scheme 1. Synthetic strategies for the 3-substituted-3-hydroxyoxindole and its derivatives**

We initiated the study of this reaction with readily available aniline derivative **6a** as the starting material (Table 1). Firstly, with CuI as catalyst and K<sub>3</sub>PO<sub>4</sub> as base a screening of organic solvents was conducted. We found there is no desired product with THF as solvent (Table 1, entry 1). The reaction afforded the desired product in 24% yield with 1,4-dioxane as solvent (Table 1, entry 2). By screening the other solvents the yield was only improved to 43% with DMF as solvent (Table 1, entries 3-6). It was found the reaction was effective as well in the absence of copper catalyst (Table 1, entry 7). We then conducted a base screening. Unfortunately there is no any improvement by switching to the other bases (Table 1, entries 8-11). Gratifyingly the yield was boosted to 84% by adding 0.2 equiv DABCO (Table 1, entry 12). By reducing the amount of K<sub>3</sub>PO<sub>4</sub> the yield was decreased to 73% (Table 1, entry 13). The reaction can be carried out at lower temperature. However, the yield was decreased to 75% at 120 °C and 64% at 60 °C (Table 1, entries 14-15). Pleasingly, this reaction was equally effective on gram scale; 1.03 g of product **1a** was easily prepared in 81% yield on 5 mmol scale (entry 16).

**Table 1. Optimization of Reaction Conditions**

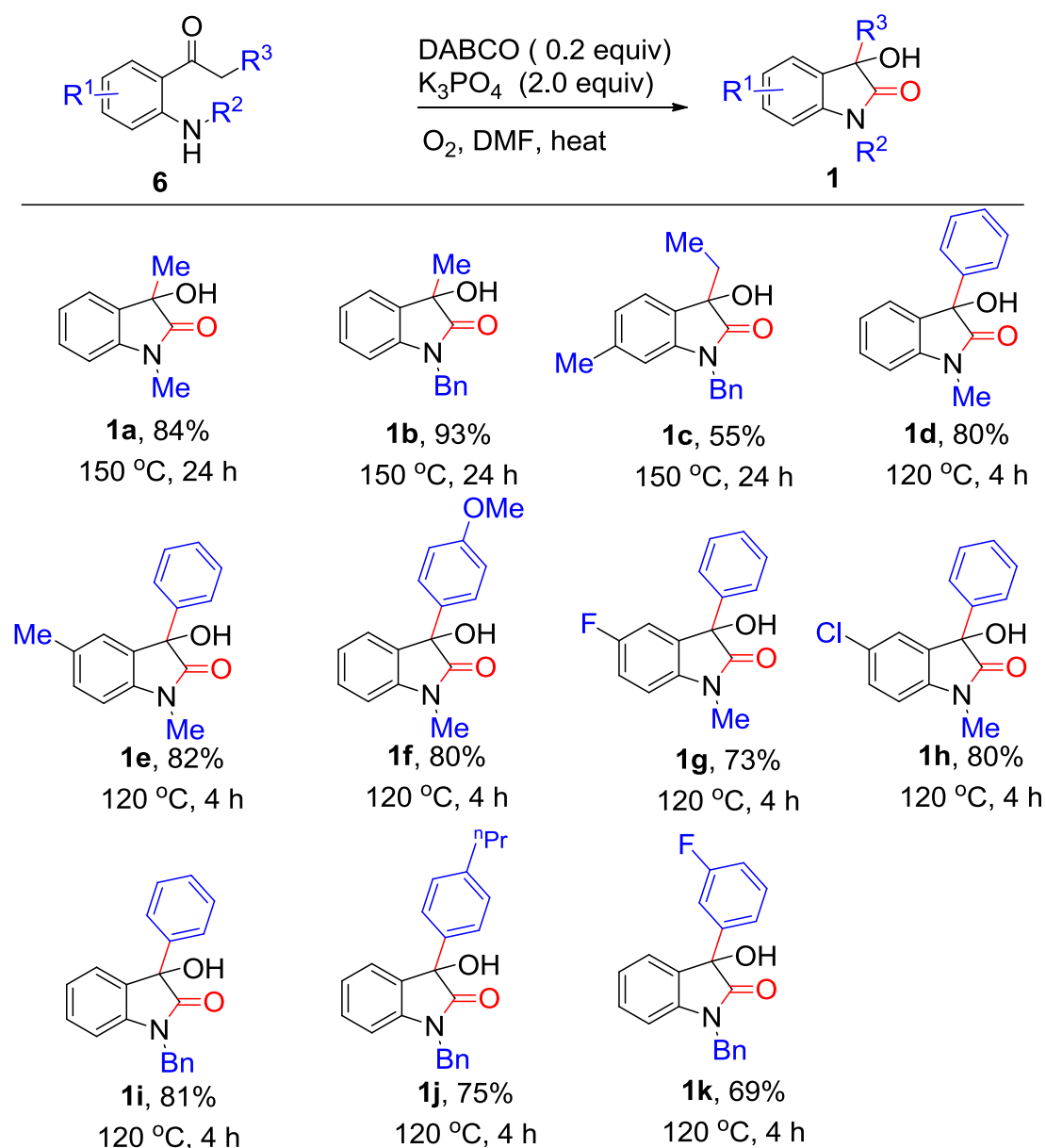
entry <sup>a</sup>	cat. (0.2 equiv)	base (2.0 equiv)	additive (0.2 equiv)	solvent <sup>b</sup>	yields (%) <sup>c</sup>
1	CuI	K <sub>3</sub> PO <sub>4</sub>	–	THF	0
2	CuI	K <sub>3</sub> PO <sub>4</sub>	–	1,4-dioxane	24
3	CuI	K <sub>3</sub> PO <sub>4</sub>	–	toluene	20
4	CuI	K <sub>3</sub> PO <sub>4</sub>	–	CH <sub>3</sub> CN	18
5	CuI	K <sub>3</sub> PO <sub>4</sub>	–	DMA	36
6	CuI	K <sub>3</sub> PO <sub>4</sub>	–	DMF	43
7	–	K <sub>3</sub> PO <sub>4</sub>	–	DMF	40
8	–	NaOH	–	DMF	18
9	–	Cs <sub>2</sub> CO <sub>3</sub>	–	DMF	39
10	–	KOH	–	DMF	trace
11	–	Cs <sub>2</sub> CO <sub>3</sub>	–	DMF	36
12	–	K <sub>3</sub> PO <sub>4</sub>	DABCO	DMF	84
13 <sup>d</sup>	–	K <sub>3</sub> PO <sub>4</sub>	DABCO	DMF	73
14 <sup>e</sup>	–	K <sub>3</sub> PO <sub>4</sub>	DABCO	DMF	75
15 <sup>f</sup>	–	K <sub>3</sub> PO <sub>4</sub>	DABCO	DMF	64
16 <sup>g</sup>	–	K <sub>3</sub> PO <sub>4</sub>	DABCO	DMF	81

<sup>a</sup>0.2 mmol **6a**, 2.0 equiv base, 0.2 equiv DABCO, O<sub>2</sub> atmosphere, 1.0 mL solvent, 150 °C, 4-24 h.

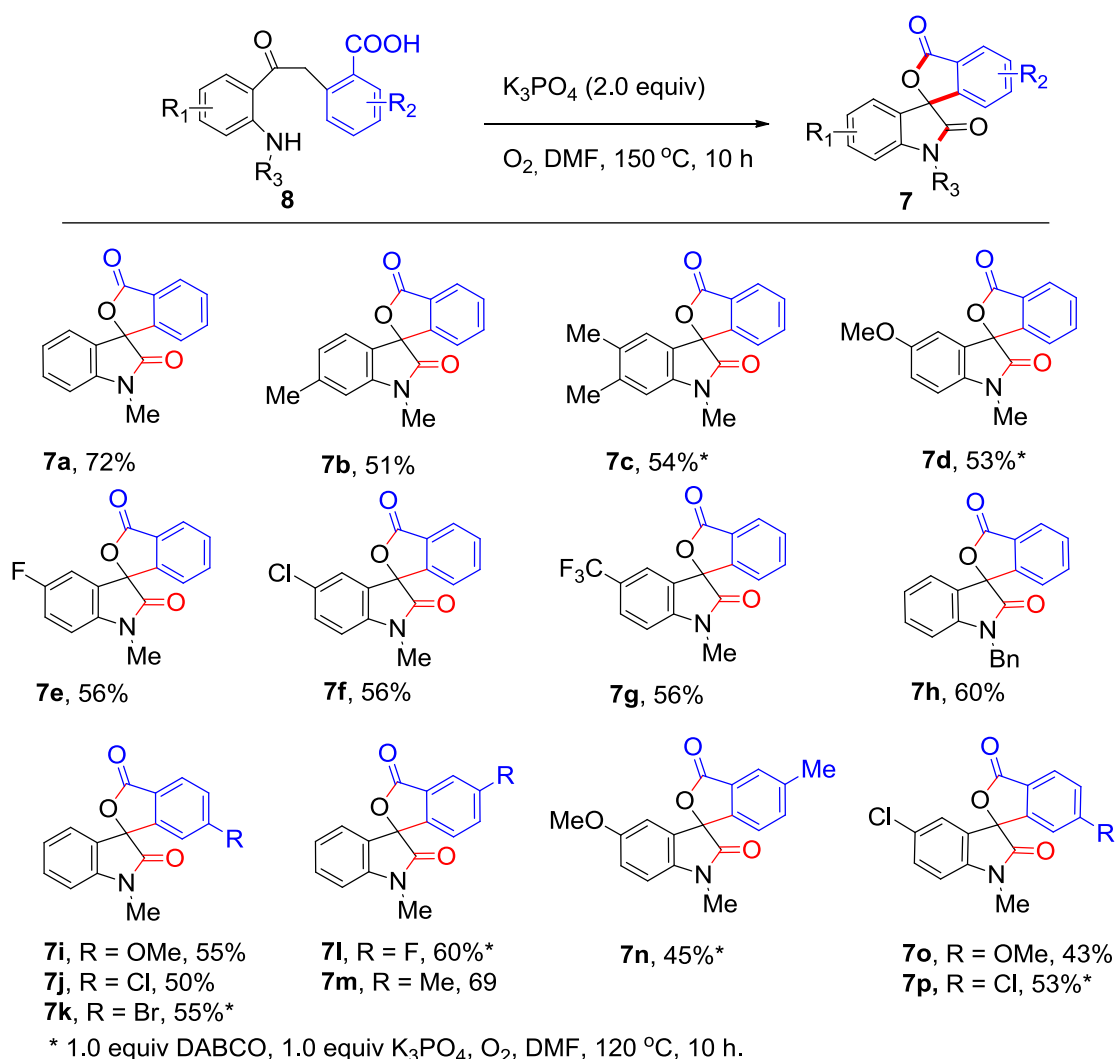
<sup>b</sup>Anhydrous solvent. <sup>c</sup>Isolated yields. <sup>d</sup>1.0 equiv K<sub>3</sub>PO<sub>4</sub>. <sup>e</sup>120 °C. <sup>f</sup>60 °C. <sup>g</sup>5 mmol Scale, 1.03 g **1a** was prepared.

With the optimum conditions in hand, we then prepared various aniline derivatives **6** according to the known procedure and subjected to the reaction conditions (Table 2).<sup>19</sup> First, we examined the substrates with an alkyl substituent  $\alpha$  to the carbonyl group. The substrates are effective with either alkyl or benzyl substituent on the nitrogen (**1a-c**), although the reactions require higher temperature and longer reaction time. The substrates with a phenyl substituent  $\alpha$  to the carbonyl group were then investigated. For the substrates with a methyl group on the nitrogen, all the reactions gave the desired products in good yields at 120 °C in 4 h (**1d-h**). The substrates with a phenyl group on the nitrogen are effective as well (**1i-k**). Both electron withdrawing and donating groups are tolerated under the optimized reaction conditions. Halogen such as chlorine and fluorine are compatible with the reaction conditions (**1g-h** and **1k**), which could be used for the functional handles for further transformations.

**Table 2. Substrate scopes for the synthesis of 3-hydroxyoxindoles**

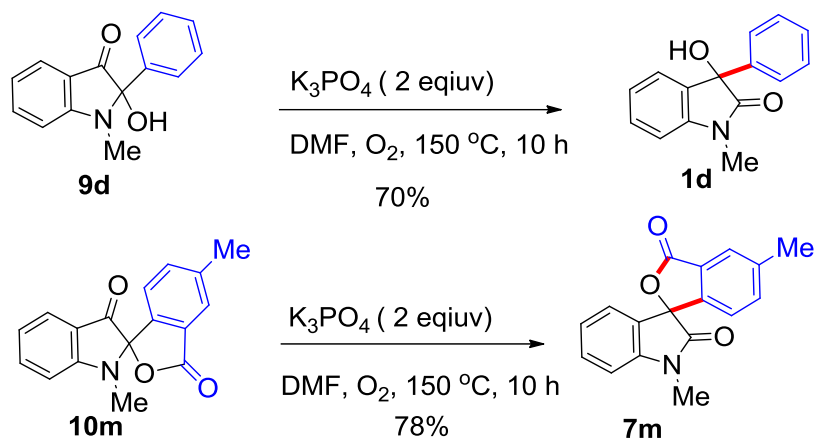


Next, we prepared various aniline derivatives with benzoic acid ring  $\alpha$  to the carbonyl group according to the known procedure and subjected to the reaction conditions (Table 3).<sup>20</sup> Interestingly, these substrates could undergo further lactamization to give the tetracyclic 3-spirooxindole benzofuranones successfully. Most of the substrates could undergo the oxidative cyclization successfully even in the absence of DABCO (such as **7c** and **7d** etc). However, some of the substrates do need stoichiometric amount of DABCO to deliver the corresponding products in moderate yields (such as **7c** and **7d** etc). Generally the substrates with either electron donating or electron withdrawing groups are effective and gave the corresponding products in good yields under the optimum conditions (**7b-g**). Halogens such as F, Cl and Br are tolerated under the reaction conditions (**7e-f**, **7j-l**), which could be used as functional handle for the further transformations. The structure of **7l** was further

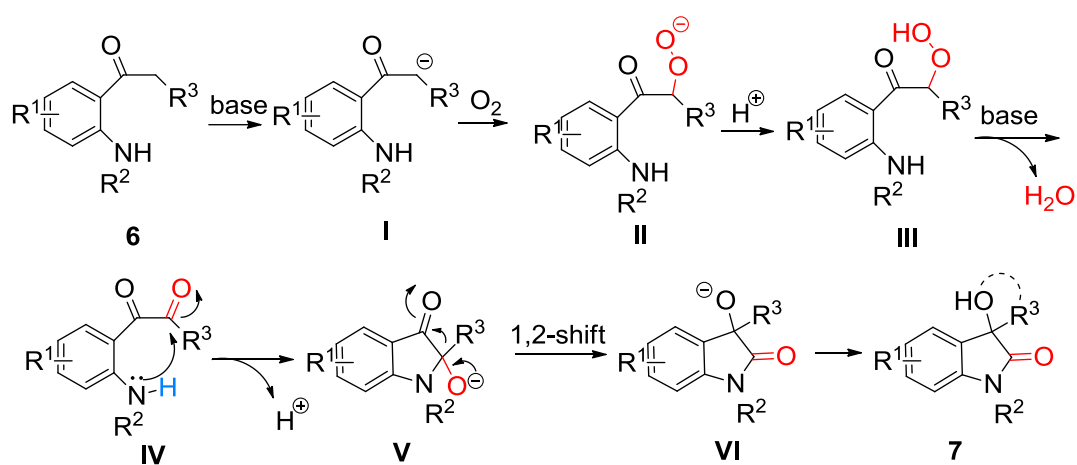
**Table 3. Substrate scopes for the synthesis of 3-spirooxindole benzofuranones**

confirmed by X-ray analysis.<sup>21</sup> Finally, we tested the substrates with substituent on both aromatic rings, which also gave the desired products in good yields under the optimum conditions (**7m-o**).

During the annulation reactions small amounts of 2-hydroxy-1-methyl-2-phenylindolin-3-one **9d** or spiro[indoline-2,1'-isobenzofuran]-3,3'-diones **10m** were detected except the remaining starting material and the desired product. To demonstrate whether compounds **9d** and **10m** are the intermediates of this annulation reaction, we managed to isolate these two compounds and treated them under the reaction conditions respectively (Scheme 2). As we expected, both compounds **9d** and **10m** could be converted into the desired 3-phenyl-3-hydroxy oxindole **1d** and 3-spirooxindole benzofuranone product **7m** in good yields respectively.



Scheme 2. Reaction intermediates confirmation

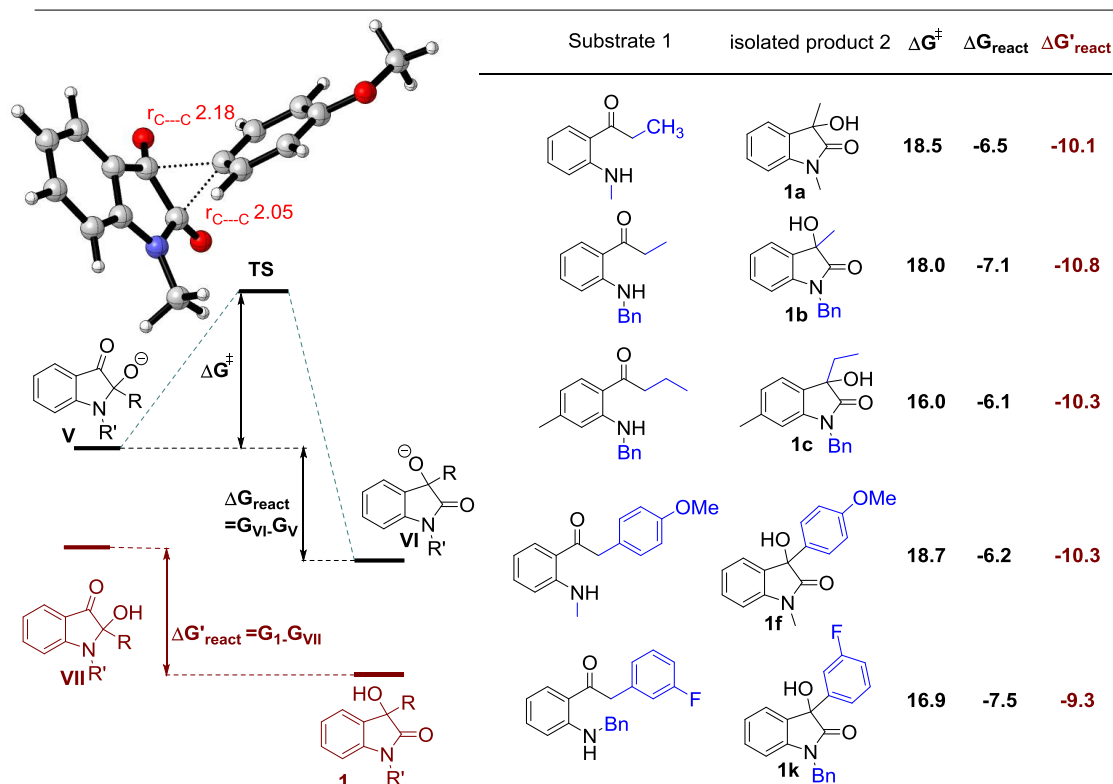


Scheme 3. Proposed reaction pathway

Based on the above experiment results and previous reports from the other groups,<sup>20, 22</sup> a plausible reaction pathway for this annulation is depicted in Scheme 3. In the presence of base the aniline derivative **1** could be oxidized to give the diketone **IV** *via* intermediates **I-III** under the aerobic oxidation condition in a pathway reported by Wang and Zhang.<sup>23</sup> The diketone **IV** was then cyclized to give the 2-substituted-2-hydroxy-3-indolinone **V**. Followed by a 1,2-migration or ring distortion the 3-substituted-3-hydroxy-2-oxindole or its 3-spirocyclic derivative **7** could be obtained in a similar pathway as described by Kafka and co-workers.<sup>22</sup>

In order to understand the energetics of this rearrangement from **V** to **VI**, we performed density functional theory (DFT) calculations using Gaussian09 program.<sup>24</sup> All stationary point structures were optimized using B3LYP<sup>25</sup> functional and 6-31+G(d) basis set with a conductor like polarizable continuum model (CPCM)<sup>26</sup> solvation model in DMF in Gaussian09. Both local minima and transition structures are confirmed by vibrational frequencies with 0 and 1 imaginary frequency, respectively. All transition structures are checked by intrinsic reaction coordinate (IRC) calculation. Hence, the barrier for this base-catalyzed  $\alpha$ -ketol rearrangement from **V** to **VI** was found to be

very low, i.e. 16.0-18.7 kcal mol<sup>-1</sup> for the examples we calculated, which is for **1a**, **1b**, **1c**, **1f** and **1k** (see **Table 2** and **Scheme 3**). This process was found to be in favor of the deprotonated form of 3-substituted-3-hydroxyoxindole **VI** by 6-7.5 kcal mol<sup>-1</sup> (see  $\Delta G_{\text{react}}$  in Scheme 3), making the reverse process a barrier of 22.1-24.1 kcal mol<sup>-1</sup>. Moreover, their protonated structures 2-substituted-2-hydroxyoxindole **VII** and 3-substituted-3-hydroxyoxindole **1** were also studied, with **1** being found to be more thermodynamically stable than **VII** by ca 10 kcal mol<sup>-1</sup> (see  $\Delta G'_{\text{react}}$  in Scheme 3). Similar result was also found when comparing the free energy of **10** and **7** (Scheme 2) and their analogues, in which **7** has lower free energy by ca 11 kcal mol<sup>-1</sup> (see SI for more information). Overall, calculations suggested that the thermodynamic stability of the lactam **VI** or **1** was the driven force for this rearrangement.



**Scheme 3. Computational studies of base-mediated  $\alpha$ -ketol rearrangement reaction.** CPCM(DMF)-B3LYP/6-31+G(d) free energies are quoted in kcal mol<sup>-1</sup> and selected distances are shown in Å. Computed structures are displayed with CYLview.<sup>27</sup>

In summary, we have developed a novel and efficient method for the synthesis of both 3-substituted-3-hydroxyoxindole and its 3-spirocyclic derivative with readily available linear aniline derivatives as starting materials. This highly atom- and step-economical one-pot protocol was carried out under metal-free base-mediated conditions through a novel oxidative annulation strategy with oxygen as the oxidant. One quaternary carbon center, more than one new cycle and three new bonds were formed in only one synthetic step to give the privileged heterocyclic systems with high selectivity and atom economy.



## ACKNOWLEDGMENT

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