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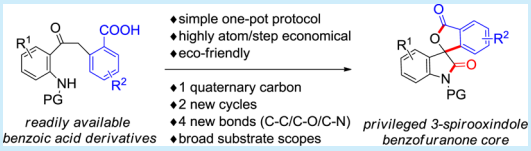
# A Tandem Oxidative Annulation Strategy for the Synthesis of Tetracyclic 3-Spirooxindole Benzofuranones

Chunxia Zhang,[†] Min Liu,[†] Mingruo Ding, Hao Xie, and Fengzhi Zhang*

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

Supporting Information

**ABSTRACT:** A simple and efficient method was developed for the construction of the medicinally important tetracyclic 3-spirooxindole benzofuranones. In this highly atom- and step-economical one-pot protocol, one quaternary carbon center, two new cycles, and four new bonds (C−C/C−O/C−N) were formed under simple ligand-free copper-catalyzed conditions through a novel tandem oxidative annulation strategy.




The polycyclic 3-spirooxindole cores are privileged motifs in bioactive molecules, pharmaceuticals, and natural products.[1] For example, 3-spirooxindole lactones **1**[2] and **2**[3] (Figure 1) have shown potential anticancer and cytotoxic activities, respectively. 3-Spirooxindole ether **3** was reported to be a CB2 agonist and could be a potential drug candidate for reducing neuropathic and bone pains.[4] The tetracyclic 3-spirooxindole benzoether **4** (Funapide) is a novel analgesic under development by Xenon Pharmaceuticals in partnership with Teva Pharmaceutical Industries for the treatment of a variety of chronic pain conditions.[5] Tryptoquivaline **5** are a group of indole alkaloids that belong to tremorgenic mycotoxins which are capable of eliciting intermittent or sustained tremors in vertebrate animals by acting on the central nervous system.[6]

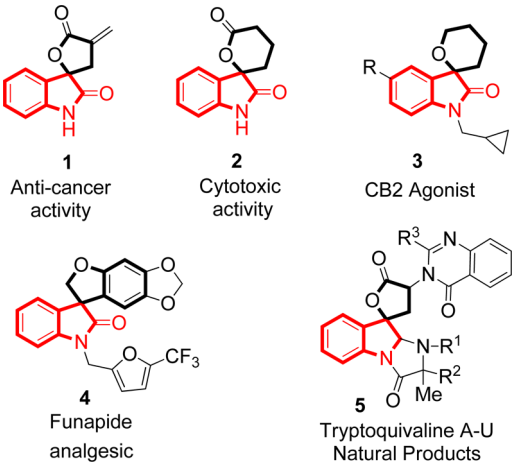
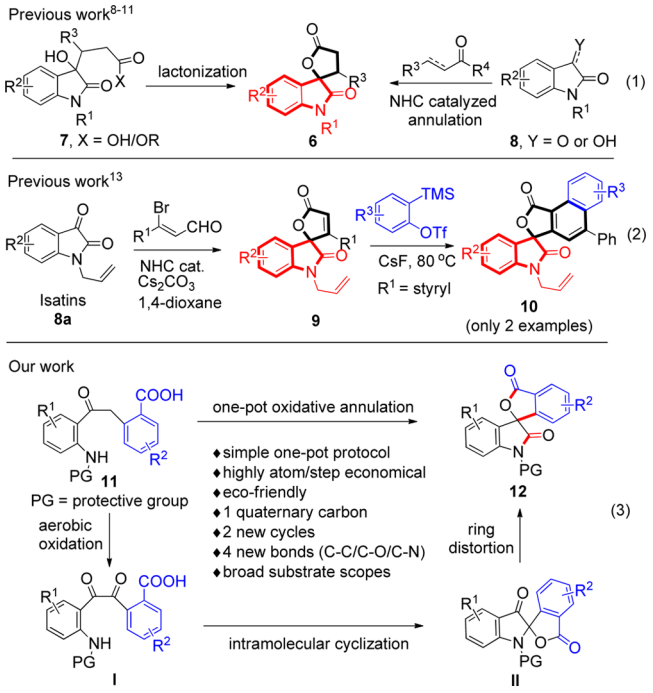



**Figure 1.** Representative examples of bioactive polycyclic spirooxindole derivatives.

Due to the polycyclic 3-spirooxindole core's appealing structures and significant biological activities, there has been an intense interest in the development of efficient strategies for the construction of these privileged heterocyclic systems.[7] Previously reported methods for the construction of the tricyclic 3-spirooxindole lactones **6** mainly employ the functionalized indoles or oxindoles as the starting materials (Scheme 1, eq 1), for example, (i) the intramolecular lactonization of 3-hydroxyoxindole esters **7**,[8] (ii) the intramolecular oxidative lactonization of 3-indolepropionic acids,[9] (iii) *N*-heterocyclic carbene (NHC) catalyzed annulations of

**Scheme 1. Synthetic Strategies for the 3-Spirooxindole Lactone Synthesis**

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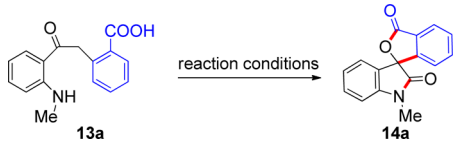
isatins/3-hydroxyoxindoles **8** with enals or propionic acids,[10] (iv) and Michael/cyclization of 3-hydroxyoxindoles.[11] Recently with linear aniline derivatives as starting materials, Du and co-workers reported a chiral aryliodine-mediated enantioselective synthesis of 3-spirofurooxindoles via cascade oxidative C−O and C−C bond formation.[12] Despite these reports, methods for the construction of the tetracyclic 3-spirooxindole lactones are limited. To the best of our knowledge there is only one example of the synthesis of tetracyclic 3-spirooxindole benzofuranone **10** through benzannulation of spirooxindole butenolides **9** with benzynes, which was limited by the availability of suitable dienes and aryne precursors (Scheme 1, eq 2).[13] Therefore, more general and efficient synthetic methodology is still required for the synthesis of tetracyclic 3-spirooxindole benzofuranones. During our investigation of Pd/Cu catalyzed intramolecular decarboxylative amination reaction with benzoic acid derivatives **11** as the starting materials, we accidentally detected the formation of a trace amount of tetracyclic 3-spirooxindole benzofuranones **12**. Despite the challenge to inhibit the amide formation and decarboxylative related side reactions etc.,[14] we envisioned that the 3-spirooxindole benzofuranone **12** could be prepared through aerobic oxidation of readily available benzoic acid derivatives **11**, intramolecular cyclization of the possible intermediate diketone **I**, and ring distortion of the spiro[indoline-2,1′-isobenzofuran]-3,3′-dione **II** (Scheme 1, eq 3), which would provide a highly atom- and step-economical one-pot protocol for the synthesis of this fairly complex and valuable heterocyclic system.

We initiated the study of this reaction with readily available benzoic acid derivative **13a** as the starting material (Table 1). After intensive screening of catalytic systems (see Supporting Information), we are pleased to find the desired tetracyclic spirooxindole benzofuranone **14a** could be obtained in 44% yield with CuCl as the catalyst (Table 1, entry 1). By switching to another Cu(I) catalyst such as CuCN, CuBr, or CuI, the reactions gave better yields (Table 1, entries 2−4). The yield could be improved to 65% by using $CuBr_2$ as the catalyst (Table 1, entry 5). By conducting the reaction under an air atmosphere the yield was decreased to 53% (Table 1, entry 6). Only trace amounts of product were obtained if the reaction was carried out under a nitrogen atmosphere (Table 1, entry 7), which demonstrated oxygen is required as a green oxidant in this reaction. The yield could be further improved to 75% yield under the ligand-free copper-catalyzed condition under an oxygen atmosphere (Table 1, entry 8). Interestingly the reaction also could be conducted under the metal-free condition though the yield was decreased significantly (Table 1, entry 9). Next we carried out the base screening. With KOH as the base only trace amounts of product were obtained (Table 1, entry 10). The yield was dropped to 36% with $Cs_2CO_3$ as the base (Table 1, entry 11). The yield could be improved to 80% with NaOMe as the base (Table 1, entry 12). By switching to DCE as solvent, the yield decreased to 40% (Table 1, entry 13). Finally, we found the yield could be further improved to 84% with DMF as solvent (Table 1, entry 14).

With the optimum conditions in hand, we then prepared various benzoic acid derivatives **13** according to the known procedure and subjected to the reaction conditions.[15] First, we examined the substrates with substituents on the aniline ring (Table 2). For the substrates with a simple methyl substituent,

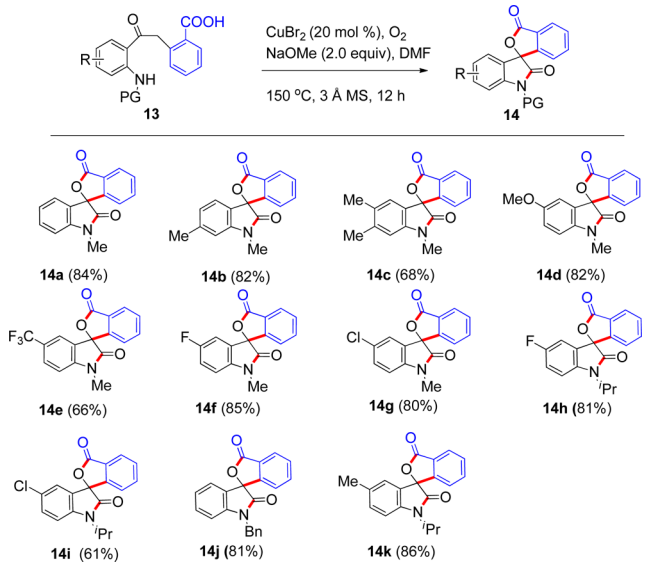
**Table 1. Optimization of Reaction Conditions**




| entry[a] | cat. | ligand | base | solvent[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | CuCl | Phen | $K_3PO_4$ | DMA | 44 |
| 2 | CuCN | Phen | $K_3PO_4$ | DMA | 47 |
| 3 | CuBr | Phen | $K_3PO_4$ | DMA | 53 |
| 4 | CuI | Phen | $K_3PO_4$ | DMA | 55 |
| 5 | $CuBr_2$ | Phen | $K_3PO_4$ | DMA | 65 |
| 6 | $CuBr_2$ | Phen | $K_3PO_4$ | DMA | 53[d] |
| 7 | $CuBr_2$ | Phen | $K_3PO_4$ | DMA | trace[e] |
| 8 | $CuBr_2$ | – | $K_3PO_4$ | DMA | 75 |
| 9 | – | Phen | $K_3PO_4$ | DMA | 39 |
| 10 | $CuBr_2$ | – | KOH | DMA | trace |
| 11 | $CuBr_2$ | – | $Cs_2CO_3$ | DMA | 36 |
| 12 | $CuBr_2$ | – | NaOMe | DMA | 80 |
| 13 | $CuBr_2$ | – | NaOMe | DCE | 40 |
| 14 | $CuBr_2$ | – | NaOMe | DMF | 84 |

[a]0.2 mmol of benzoic acid **13a**, 20 mol % of catalyst, 20 mol % of 1,10-phenanthroline (phen), 2.0 equiv of base, 150 mg of 3 Å molecular sieves, $O_2$ atmosphere, 1.0 mL of solvent, 150 °C, 12 h. [b]Anhydrous solvent. [c]Isolated yields. [d]Air atmosphere. [e]$N_2$ atmosphere.

**Table 2. Substrate Scopes with Substitution Variation on the Aniline Ring**




the yields are generally good (**14b** and **14c**). The substrate with a highly electron-donating group gave a much higher yield than those with a highly electron-withdrawing group (**14d** and **14e**). The substrates with halogen groups such as F and Cl on the aniline ring are effective (**14f−i**). By changing the protecting group on the nitrogen to an isopropyl or a benzyl group, the reactions gave the corresponding products in good yields (**14h−k**).

Next, we examined the substrates with substituents on the benzoic acid ring (Table 3). Generally, the substrates with either electron-donating or -withdrawing groups are effective and gave the corresponding products in good yields under the optimum conditions (**16a−e**). Halogens such as F, Cl, and Br



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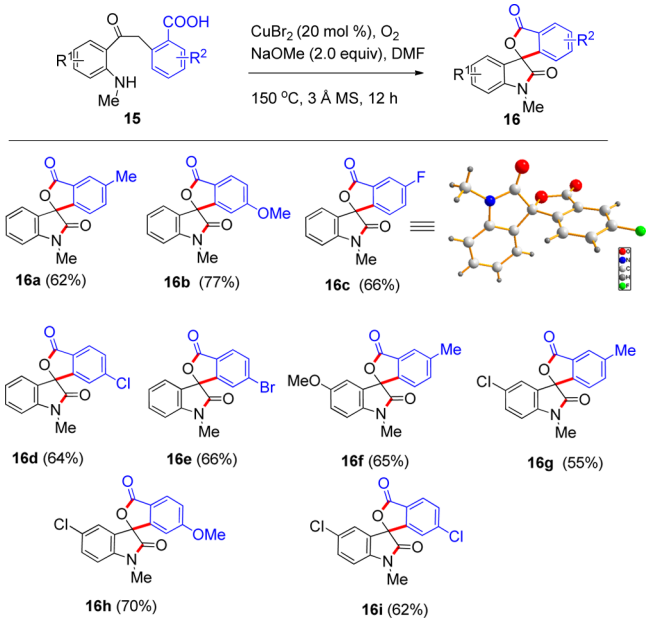
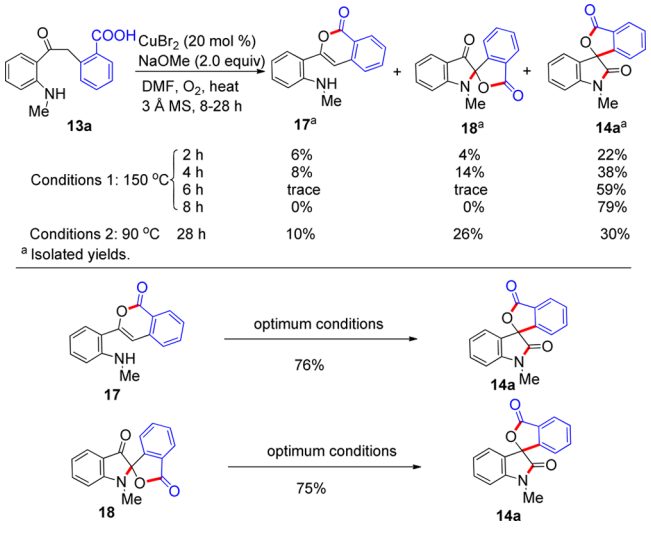
**Table 3. Substrate Scopes with Substitution Variation on Both Aromatic Rings**




are tolerated under the optimum conditions, which could be used as functional handles for further transformations. The structure of **16c** was further confirmed by X-ray analysis.[16] Finally, we tested the substrates with substituents on both aromatic rings, which also afforded the desired products in good yields under the optimum conditions (**16f–i**).

In order to identify the possible reaction intermediates and further understand this multistep annulation reaction, we carried out the following experiments (Scheme 2). First, we

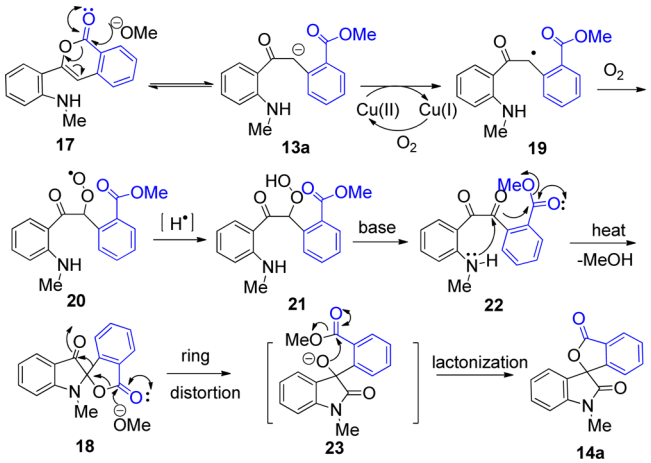
**Scheme 2. . Mechanistic Studies**




treated the substrate **13a** under the optimum conditions and monitored the reaction every 2 h. After 2 h, small amounts of the isochromenone intermediate **17** and spiro[indoline-2,1′-isobenzofuran]-3,3′-diones **18** were isolated along with the remaining starting material **13a** and the desired 3-spirooxindole benzofuranone product **14a**. Within 4 h, the amounts of compounds **17** and **18** reached the maximum. The starting material **13a** and compounds **17** and **18** then disappeared after 8 h affording the only desired product **14a** in 79% yield, which shows the compounds **17** and **18** might be the intermediates of this annulation reaction. If this reaction was conducted at 90 °C, even after 28 h, the starting materials still remained along with the compounds **17** (10%), **18** (26%), and **14a** (30%). By treatment of compounds **17** and **18** under the optimum conditions respectively, as we expected, both of them could be converted into the desired 3-spirooxindole benzofuranone product **14a** completely. Furthermore, small amounts of compound **18** were detected during the transformation of **17** to **14a**, which might indicate the isochromenone **17** was converted to 3-spirooxindole benzofuranone **14a** via spiro-[indoline-2,1′-isobenzofuran]-3,3′-diones **18** as well.

Based on the above experiments and previous reports,[15,17] a proposed reaction pathway for this annulation is depicted in Scheme 3.

**Scheme 3. Proposed Reaction Pathway**




Under the optimum conditions the benzoic derivative **13a** might be exchangeable with the isochromenone **17**. Under the aerobic oxidation conditions the starting material **13a** could be oxidized to give the diketone **22** via a pathway reported by Wang and Zhang through intermediates **19–21**.[18] The diketone **22** could be cyclized to give the 2-spirocyclic compound **18**. Finally the desired 3-spirooxindole benzofuranone **14a** could be obtained through ring distortion and lactonization via intermediate **23**.[19] These simple reaction conditions allow the formation of a fairly complex structure in a single step that involves an aerobic oxidation/cyclization/rearrangement/lactonization sequence. It is worth noting that the 2-spirocyclic compound **18** was obtained as the final product when Letcher and co-workers treated the 5-methyldibenz[*b*,*f*]azocin-6,12-dione with sodium metaperiodate in boiling 50% aqueous methanol.[15] Even though the same diketone **22** was proposed as the same intermediate, the ring distortion did not happen and the 3-spirooxindole benzofuranone **14a** was not obtained under their reaction conditions.

In summary, we have developed a highly atom- and step-economical method for the synthesis of various complex and valuable tetracyclic spirooxindole benzofuranones from readily available benzoic acid derivatives. This multistep one-pot protocol could be carried out under simple ligand-free copper-catalyzed conditions with oxygen as the oxidant, in which one quaternary carbon center, two new cycles, and four



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new bonds were formed during this robust tandem oxidative rearrangement reaction.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01374.

General experimental procedures, characterization details, and $^{1}H$ and $^{13}C$ NMR spectra of compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: zhangfengzhi@zjut.edu.cn.

### ORCID

Fengzhi Zhang: 0000-0001-9542-6634


### Author Contributions

†C.Z. and M.L. contributed equally.

### Notes

The authors declare no competing financial interest.

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