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Copper-Catalyzed Oxidative Dearomatization/Spirocyclization of Indole-2-Carboxamides: Synthesis of 2-Spiro-pseudoindoxyls

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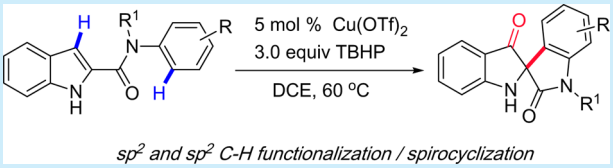
Supporting Information

ABSTRACT: A copper-catalyzed oxidative dearomatization/spirocyclization of indole-2-carboxamides using *tert*-butyl hydroperoxide (TBHP) as the oxidant has been developed that provides rapid and efficient access to C2-spiro-pseudoindoxyls. Two of the sp^2 C−H bonds are functionalized during the reaction process, and the reaction likely proceeds via the formation of a highly reactive 3*H*-indol-3-one intermediate followed by aromatic electrophilic substitution with the *N*-aryl ring of the amide moiety.



Spiro-pseudoindoxyls that contain a C2 spirocyclic quaternary carbon center are common structural subunits found in a variety of indole alkaloids such as fluorocurine,[1] mitragynine pseudoindoxyl,[2] and rauniticine pseudoindoxyl[3] (Figure 1), and some of them are found to exhibit important

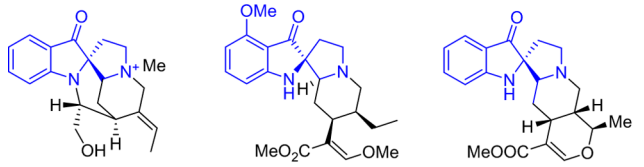
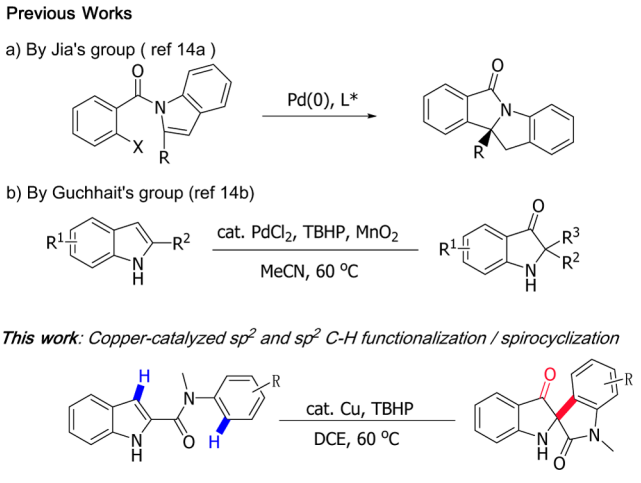


Figure 1. Representative indole alkaloids containing the spiro-pseudoindoxyl core structure.

biological properties. For example, mitragynine pseudoindoxyl has potent opioid agonistic activity in the guinea pig ileum and in mouse vas deferens.[2b] Compared with the intensively studied and biologically interesting spirooxindoles bearing a spiro center at C3,[4] the synthetic procedures for C2-spiro-pseudoindoxyls are far less developed. The main approach to these compounds is based on oxidative rearrangement of the corresponding indole derivatives, which has been successfully used in the synthesis of a series of indole alkaloids.[5] Other methods include Smalley cyclization,[6] gold-catalyzed cycloisomerization of 3-phenoxy alkynyl indoles[7] or nitroalkynes,[8] N-heterocyclic carbene (NHC)-catalyzed annulation of enals with azaaurones,[9] Ugi reactions,[10] etc. However, these methods usually suffer from multistep synthesis of substrates, utilization of hazardous azide compounds, or limited reaction scope. Thus, the development of straightforward and facile methods for the synthesis of spiro-pseudoindoxyls from easily accessible starting materials is highly desired.

Recently, the copper-catalyzed oxidative C−H bond functionalization reaction has emerged as an attractive methodology for constructing C−C and C−heteroatom bonds not only because of its low cost and low toxicity but also because of its high efficiency in redox catalysis.[11] During the course of our ongoing program on copper-catalyzed cyclization reactions to form nitrogen heterocycles, we found that spiro-pseudoindoxyls can be conveniently formed under copper redox conditions. Herein we report a new and efficient route to spiro-pseudoindoxyls via copper-catalyzed oxidative dearomatization/spirocyclization of indole-2-carboxamides using TBHP as the oxidant (Scheme 1). It turned out that both the C−H bond at C3 of the indole moiety and one of the C−H bonds on the *N*-aryl ring were activated to allow construction of the target products. Indoles are known to undergo dearomatization under dioxygen, catalyzed by CuCl, to

Scheme 1. Construction of C2 Quaternary Indolines



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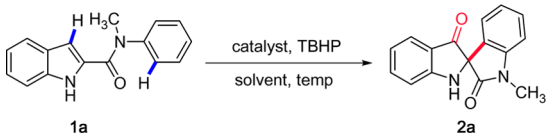
give 2,3-dioxygenated cleavage products[12] or 3-oxo-3*H*-indoles[13] via the intermediacy of 3*H*-indol-3-one. Recently, Jia's group disclosed a Pd-catalyzed construction of C2 quaternary indoline for the synthesis of fused-ring compounds.[14a] A Pd-catalyzed oxidation of indoles to C2 noncyclic quaternary indolin-3-ones has been reported by Guchhait's group.[14b] Oxidative di- or trimerization of indoles catalyzed by copper salts[15a,b] or copper oxidase[15c] has also been described.[15] However, to the best of our knowledge, transition-metal-catalyzed oxidative dearomatization of indole followed by spirocyclization by means of intramolecular nucleophilic attack of the reactive intermediates has not been established.

Initially, we investigated the copper-catalyzed reactions of 1*H*-indole-2-carboxamide **1a** bearing an *N*-phenyl ring (Table 1). When **1a** was treated with 10 mol % CuCl and 3.0 equiv of TBHP in DCE at 60 °C for 6 h, the spirocyclized product, spiro-pseudoindoxyl **2a**, was obtained in 27% yield (entry 1). Structural identification of **2a** was carried out by X-ray crystallography. Although the yield was low, the result was highly attractive since it revealed that two of the sp^2 C−H bonds were functionalized during the reaction process. Inspired by these initial results, we next screened various Cu(II) salts. It was found that $CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$ all could catalyze the reaction. However, the yields of **2a** were in the range of 21−38% (entries 2−4). To our delight, when $Cu(OTf)_2$ was employed as the catalyst, the desired product **2a** was obtained in a high yield of 85% (entry 6). Interestingly, the reaction could also proceed in the presence of 10 mol % $FeCl_3$, and **2a** was formed in 47% yield (entry 7). The catalyst loading of $Cu(OTf)_2$ could be reduced to 5 mol %, in which case **2a** was isolated in 86% yield (entry 8). Decreasing the amount of TBHP to 2.0 equiv resulted in a lower product yield (65%; entry 9). Changing the substrate concentration from 0.05 to 0.1 or 0.03 M afforded **2a** in slightly lower yields (entries 11 and 12). Only a trace amount of **2a** was observed when the reaction was carried out at the lower temperature of 40 °C (entry 13). Other solvents such as toluene, THF, DMF, DMAc, CH_3CN, and 1,4-dioxane were also tested. However, they are not effective for this reaction (entries 15−20). The use of 3.0 equiv of TBHP in a decane solution (5−6 M) was also found to be effective for this reaction, leading to **2a** in 84% yield (entry 21). In the absence of copper catalyst or TBHP, no reaction was observed (entries 22 and 23).

Table 1. Optimization Studies for the Formation of 2a[a]



1a 2a

entry	catalyst (mol %)	equiv of TBHP	solvent	temp (°C)	time (h)	yield (%)[b]
1	CuCl (10)	3	DCE	60	6	27
2	$CuCl_2$ (10)	3	DCE	60	6	21
3	$CuBr_2$ (10)	3	DCE	60	5	38
4	$Cu(OAc)_2$ (10)	3	DCE	60	5	24
5	$Cu(acac)_2$ (10)	3	DCE	60	6	messy
6	$Cu(OTf)_2$ (10)	3	DCE	60	3	85
7	$FeCl_3$ (10)	3	DCE	60	4	47
8	$Cu(OTf)_2$ (5)	3	DCE	60	4	86
9	$Cu(OTf)_2$ (5)	2	DCE	60	8	65
10	$Cu(OTf)_2$ (5)	4	DCE	60	4	79
11[c]	$Cu(OTf)_2$ (5)	3	DCE	60	4	78
12[d]	$Cu(OTf)_2$ (5)	3	DCE	60	4	84
13	$Cu(OTf)_2$ (5)	3	DCE	40	6	trace
14	$Cu(OTf)_2$ (5)	3	DCE	80	2	80
15	$Cu(OTf)_2$ (5)	3	toluene	60	6	27
16	$Cu(OTf)_2$ (5)	3	THF	60	6	trace
17	$Cu(OTf)_2$ (5)	3	DMF	60	3	–
18	$Cu(OTf)_2$ (5)	3	DMAc	60	4	–
19	$Cu(OTf)_2$ (5)	3	CH_3CN	60	6	34
20	$Cu(OTf)_2$ (5)	3	1,4-dioxane	60	6	NR
21[e]	$Cu(OTf)_2$ (5)	3	DCE	60	3	84
22	–	3	DCE	60	4	NR
23	$Cu(OTf)_2$ (5)	–	DCE	60	4	NR

[a]Reactions were run on a 0.2 mmol scale using 4 mL of solvent. [b]Isolated yields. [c]Using 2 mL of solvent. [d]Using 6 mL of solvent. [e]Using 5−6 M TBHP in decane.

Encouraged by the above results, we next examined the substrate scope for accessing diversely substituted spiro-pseudoindoxyls by varying the substituents on the indole and amide moieties under the conditions shown in Table 1, entry 8 (Figure 2). First, we investigated the effect of different *N*-alkyl substituents (R^1) on the amide group. It was found that in addition to an *N*-methyl substituent, *N*-ethyl- or *N*-benzyl-substituted substrates also underwent the reaction smoothly to afford **2b** and **2c** in 89% and 72% yield, respectively. Next, the electronic effects of different *N*-aryl substituents (R^2) were studied. With an electron-donating group at the *para* position of the *N*-phenyl ring, such as *p*-CH_3, *p*-^{n}Bu, or *p*-MeO, the corresponding products **2d−f** were obtained in 63−71% yield.

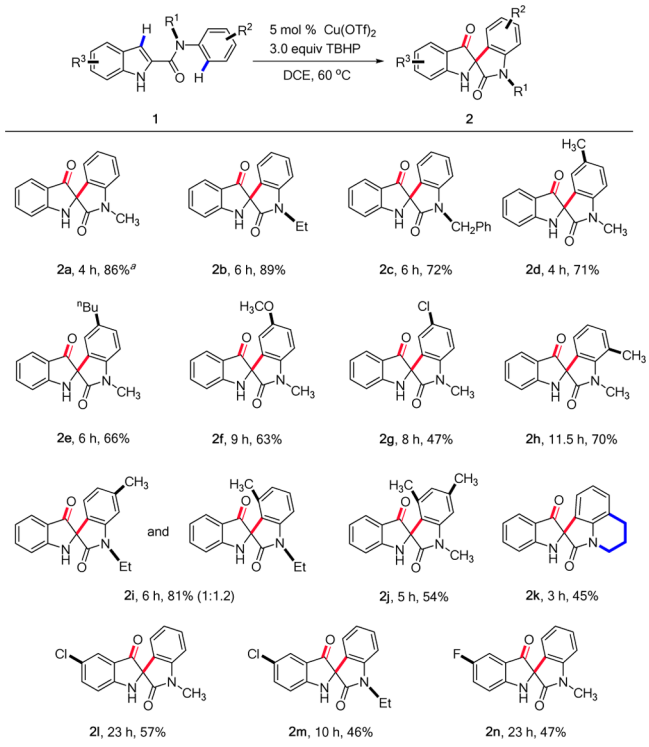


Figure 2. Substrate scope of the dearomatization/spirocyclization reaction. Unless otherwise noted, the reactions were carried out using 3.0 equiv of TBHP and 5 mol % $Cu(OTf)_2$ in DCE at 60 °C under N_2 on a 0.3 mmol scale. Isolated yields are shown. [a]The reaction was run on a 0.2 mmol scale.

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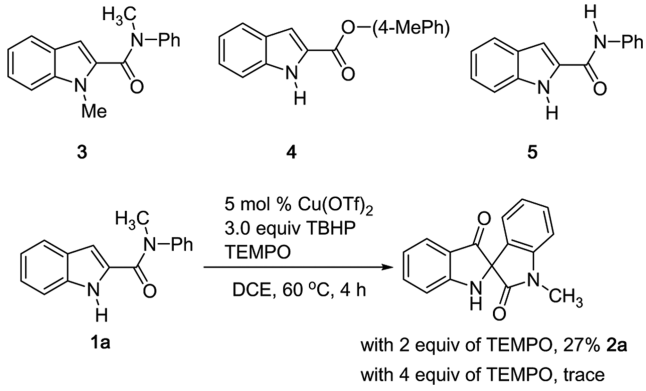
An electron-withdrawing *p*-Cl substitution afforded **2g** in a lower yield of 47%, possibly becausse of the lower nucleophilicity of the *N*-aryl ring in this case (compare **2f** with **2g**). An *N*-methyl,*N*-(*o*-methylphenyl)-substituted substrate was transformed into **2h** in a good yield of 70%. With a methyl group at the *meta* position of the *N*-phenyl ring, two spirocyclized products **2i** and **2i′** were obtained in a combined yield of 81% in a ratio of 1:1.2. The results indicated that both of the *ortho* C−H bonds on the *N*-aryl ring could be competitively functionalized. With methyl groups at the 3- and 5-positions of the *N*-phenyl ring, the desired product **2j** could be obtained in a moderate yield. Interestingly, indole-2-carboxamide bearing a tetrahydroquinoline moiety on the amide moiety cyclized readily under the standard reaction conditions to afford the highly strained polycyclic spiroindole **2k** in 45% yield, demonstrating the synthetic potential for the construction of complex organic molecules by this method. A chlorine or fluorine substituent on the indole moiety was tolerated well during the reaction, and the corresponding products **2l**−**n** were obtained in 46−57% yield.

To understand the reaction mechanism, we carried out the following control experiments (Scheme 2). It was found that

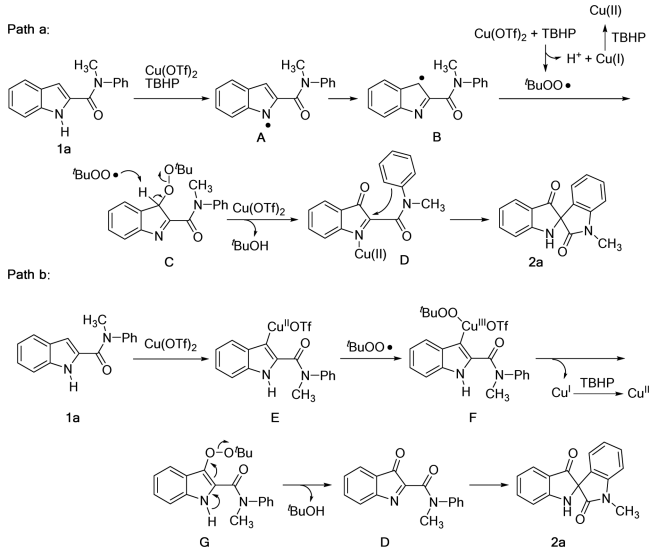
Scheme 2. Control Experiments



when *N*-Me-protected indole **3** or substrate **4** containing a $-CO_2$(4-MePh) group was employed under the standard reaction conditions, no reaction occurred, indicating that the presence of the free *N*-H indole and amide moiety in **1** are crucial for the success of this reaction. Substrate **5** bearing an *N*-H amide group resulted in a complex reaction mixture. When the reaction was performed in the presence of a radical scavenger such as TEMPO, the yield of **2a** was decreased significantly to 27%. Increasing the amount of TEMPO to 4.0 equiv resulted in only traces of the desired product of **2a**. The results implied that radical species might be involved in the reaction process.

On the basis of the above results and literature reports, we propose the following reaction mechanism involving two possible pathways for this novel transformation (Scheme 3). In path a, N-centered indole radical **A** might be generated in the presence of $Cu(OTf)_2$/TBHP,[16] and it could isomerize to form C3 radical **B**. Intermediate **B** would couple with *tert*-butylperoxy radical (*t*-BuOO·) produced through the reaction of Cu(II) and TBHP according to the study by Sasson et al.[17] to afford indole 3-*tert*-butylperoxide **C**. Elimination of *t*-BuOH from **C** would furnish 2-substituted 3*H*-indol-3-one **D**,[14,18] which would then undergo aromatic electrophilic substitution with the *N*-aryl ring of the amide moiety to produce the

Scheme 3. Possible Reaction Mechanism



product **2a**. Alternatively, in path b, indolylcopper(II) intermediate **E** might be formed in the presence of $Cu(OTf)_2$.[19] **E** could react with *tert*-butylperoxy radical to give the Cu(III) intermediate **F**.[20] Reductive elimination followed by elimination of *t*-BuOH would deliver the same intermediate **D** as in path a. The produced Cu(I) would subsequently be oxidized by TBHP to regenerate the Cu(II) catalyst for the next catalytic cycle.

In summary, we have developed a novel copper-catalyzed oxidative dearomatization/spirocyclization of indole-2-carboxamides using TBHP as the oxidant. The method provides rapid and efficient access to C2-spiro-pseudoindoxyls, which are common structural units prevalent in indole alkaloids but are usually difficult to prepare. Two of the sp^2 C−H bonds are functionalized during the reaction process, and the reaction likely proceeds via the formation of a highly reactive 3*H*-indol-3-one intermediate followed by aromatic electrophilic substitution with *N*-aryl ring of the amide moiety. This method offers several advantages such as easily accessible starting materials, good functional group tolerance, and mild reaction conditions. Further studies to elucidate the reaction mechanism and extend this chemistry are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03131.

X-ray crystallographic data for **2a** (CIF)
Experimental details and spectroscopic characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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