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Copper-Catalyzed Activation of Dioxygen: Oxidative Cyclization of 2-Arylindoles

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Abstract: A series of unusual six-ring-fused heterocycles containing indole and quinoline skeletons was successfully synthesized by a copper-catalyzed reaction from 2-arylated indoles. Two new bonds were regioselectively formed from C–H and C–H coupling. ^{18}O-Labelled experiments revealed that the dioxygen is not only the oxidant but also the reactant.

Keywords: copper; heterocycles; oxidative cyclization; oxygen

Oxidative C–H bond functionalization is one of the most important and attractive strategies in organic synthesis.[1] In most of these transformations, it is necessary to reoxidize the reduced catalyst to its oxidized state.[2] For these transformations, molecular oxygen (O_2) is an ideal oxidant, since it is inexpensive and environmentally friendly. The use of dioxygen activation for functionalization reactions represents one of the most ideal processes in organic synthesis.[3] Activation of O_2 by copper enzymes has been observed in some biological oxygenase systems, such as monooxygenase tyrosinase and dopamine β-monooxygenase that effect the hydroxylation of C–H bonds.[4] Recently, copper-catalyzed reactions that involve dioxygen activation and use rather simple models to realize biomimetic syntheses have been intensively studied.[5] Although remarkable success has been achieved, to the best of our knowledge, it is still challenging to develop aerobic oxidation systems employing low-cost copper as catalyst to convert commercially available or readily accessible materials in one step to target compounds.

The construction of nitrogen heterocycles is an important goal in organic synthesis due to their occurrence in many natural products and biologically active molecules and the fact that they play important roles in the pharmaceutical and agrochemical industries.[6] Indole[7] and quinoline[8] nuclei are privileged scaffolds that occupy a central role in many medicinally relevant compounds. Indole derivatives are known to exert antitubercular,[9] anticancer,[10] antiviral,[11] and antioxidant activities.[12] Some of them are used to lower cholesterol and prevent cardiovascular disease; for example, fluvastatin, which includes an indole moiety, is a synthetic member of the statin class of drugs. The indole pharmacophore is even found in a variety of antiobesity agents.[13] The quinoline ring system is also prevalent in numerous marketed drugs such as antibacterials, antimalarial agents, HIV-1 integrase inhibitors,[14] and other compounds of pharmaceutical interest.[15] Molecules containing a combination of indole and quinoline frameworks (Figure 1) are interesting synthetic target owing to their various biological activities including antimalarial, anticancer, DNA binding and cytostatic activities.[16] Herein, we report the efficient cyclization of 2-arylindoles to the six-ring-fused heterocycles in the presence of 20 mol% $Cu(OH)_2{\cdot}CuCO_3$ catalyst under an oxygen atmosphere without the use of ligands and additional bases or acids. The synthesized new motif has the potential to exhibit biological activity. The mechanistic

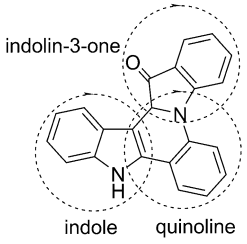
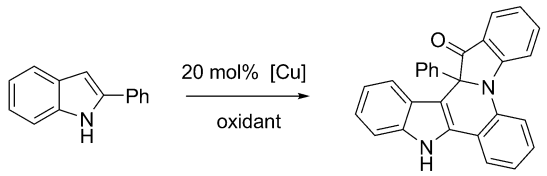


Figure 1. Structure of a conjugate containing indole and quinoline frameworks.

studies on the formation of these fused heterocycles have been performed to provide valuable mechanistic insights into the cyclization.

Our initial attempt started with the reaction of 2-phenyl-1*H*-indole (**1a**) at 130 °C in DMSO under O_2 atmosphere by the use of CuBr as the catalyst which afforded the fused heterocyclic product **2a** in 18% yield (Table 1, entry 1). Screening of the copper catalysts revealed that both $Cu(OAc)_2$ and $Cu(OH)_2{\cdot}CuCO_3$ were active and that $Cu(OH)_2{\cdot}CuCO_3$ was the best to give the product **2a** in 79% yield (Table 1, entries 1–7). No reaction was observed in the absence of copper catalyst (Table 1, entry 8). A 77% yield was obtained when the reaction was carried out in air (Table 1, entry 9). However, no product was found when the reaction was carried out under an N_2 atmosphere (Table 1, entry 10). Oxidants such as *tert*-butyl hydroperoxide (TBHP), *t*-BuOO-*t*-Bu, DDQ and Oxone showed poor efficiency (Table 1, entries 11–14). The yield decreased when the reaction temperature was decreased (Table 1, entries 15 and 16). Other solvents such as DMF, toluene, and dioxane furnished the product in poor yields (Table 1, entries 17 and 18).

Table 1. Screening for optimal conditions.[a]



1a **2a**

Entry	Catalyst	Oxidant	Yield [%][b]
1	CuBr	O_2	18
2	CuI	O_2	22
3	CuCl	O_2	39
4	CuO	O_2	42
5	$Cu(OAc)_2$	O_2	77
6	$Cu(OAc)_2{\cdot}H_2O$	O_2	55
7	$Cu(OH)_2{\cdot}CuCO_3$	O_2	79
8	–	O_2	n.r.
9	$Cu(OH)_2{\cdot}CuCO_3$	air	77
10	$Cu(OH)_2{\cdot}CuCO_3$	N_2	n.r.
11	$Cu(OH)_2{\cdot}CuCO_3$	*t*-BuOOH	n.d.[c]
12	$Cu(OH)_2{\cdot}CuCO_3$	*t*-BuOO-*t*-Bu	n.d.[d]
13	$Cu(OH)_2{\cdot}CuCO_3$	DDQ	n.d.[d]
14	$Cu(OH)_2{\cdot}CuCO_3$	Oxone	n.d.[d]
15	$Cu(OH)_2{\cdot}CuCO_3$	O_2	77[e]
16	$Cu(OH)_2{\cdot}CuCO_3$	O_2	11[f]
17	$Cu(OH)_2{\cdot}CuCO_3$	O_2	67 g]
18	$Cu(OH)_2{\cdot}CuCO_3$	O_2	n.r.[h]

[a] *Reaction conditions:* **1a** (0.3 mmol), catalyst (0.06 mmol), solvent (DMSO, 2 mL), air and O_2 (1 atm) for 48 h.
[b] Yield of isolated product.
[c] *t*-BuOOH (1.5 equiv., 0.45 mmol) 0.30 mL, 5–6 M in decane, under a nitrogen atmosphere.
[d] Oxidant (1.5 equiv., 0.45 mmol) under a nitrogen atmosphere.
[e] The reaction was carried out at 110 °C.
[f] The reaction was carried out at 90 °C.
[g] The reaction was carried out in DMF.[h] The reaction was carried out in toluene or dioxane. *t*-BuOOH = *tert*-butyl hydroperoxide, *t*-BuOO-*t*-Bu = di-*tert*-butyl peroxide, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, Oxone = potassium peroxomonosulfate.

With the optimal reaction conditions in hand, we next examined the scope of various 2-arylindoles as summarized in Table 2. It is found that a variety of substituted 2-arylindoles can be converted to the desired products in modest to good yields, showing good functional group tolerance. 2-Arylindoles with both electron-withdrawing substituents (F, Cl, Br, I and CF_3) and electron-donating substituents (OMe and Me) participated in the reaction smoothly to give the fused heterocycles in good yields (**2c**, **2d**, **2g–2l** and **2n–2r**). It should be noted that 2-*o*-tolyl-1*H*-indole gave no product, indicating that the steric hindrance played a role (**2b**). Two products were obtained when 2-*m*-tolyl-1*H*-indole was introduced as substrate (**2c** and **2c′**), and again the less hindered product **2c** was favored. The tolerance of halogen substituents provides this process with potential for further synthetic transformations. The structure of the product was further confirmed by an X-ray crystallographic study of **2a** (Figure 2).[20] It was seen that the fused rings were not in the same plane.

To gain insight into the reaction features, 2-phenylindole and 2-*p*-tolyl-1*H*-indole were treated in one-pot under the reaction conditions. A cross-over product was indeed detected by HR-MS, supporting an intermolecular process [Eq. (1)]. Moreover, when **1a**

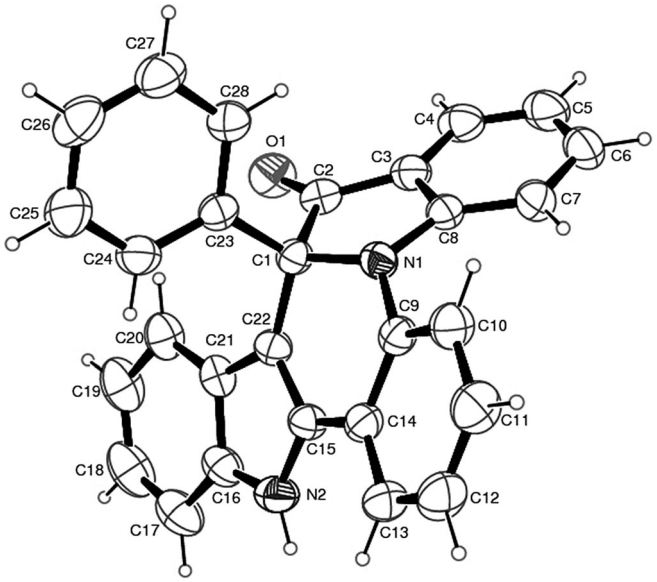
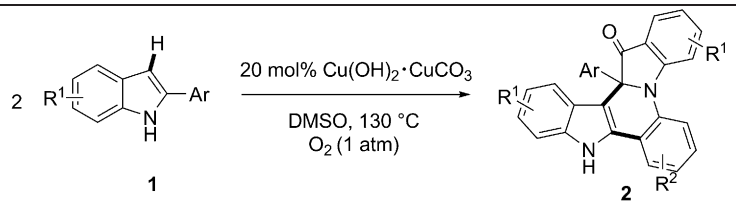
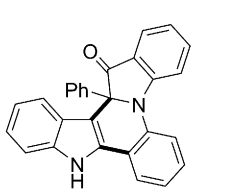


Figure 2. The X-ray single crystal structure of product **2a**.

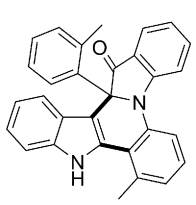
Table 2. Copper-catalyzed oxidative cyclization of various 2-arylindoles.[a,b]



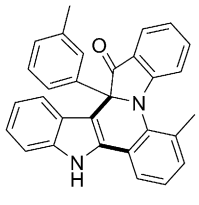
1 2



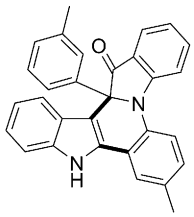
2a 79%



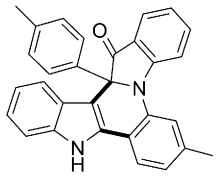
2b 0%



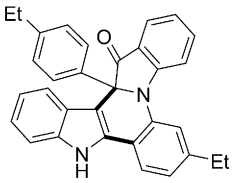
2c 16%



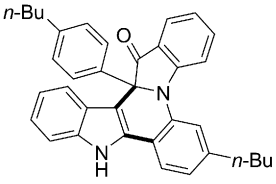
2c' 53%



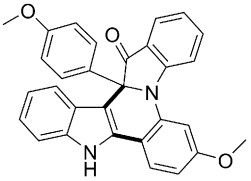
2d 53%



2e 59%



2f 63%



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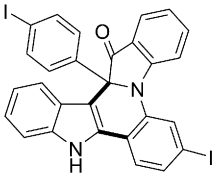

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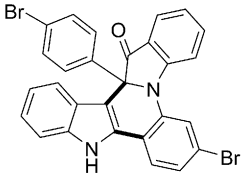

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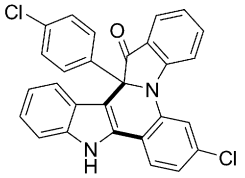

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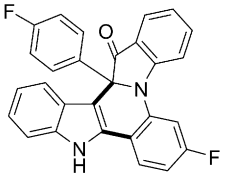
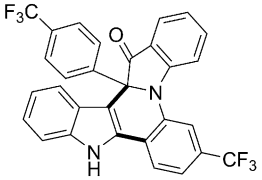
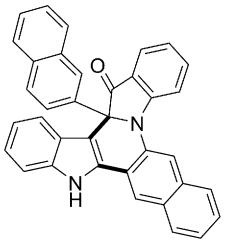


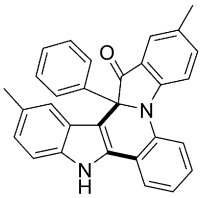
2k 58%



2l 49%



2m 90%



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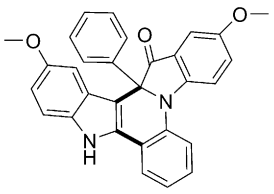
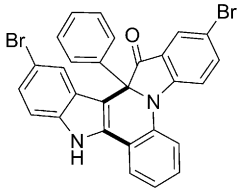


2o 65%



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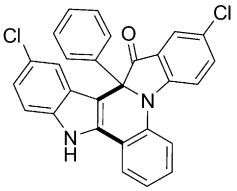
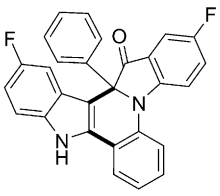


2q 66%



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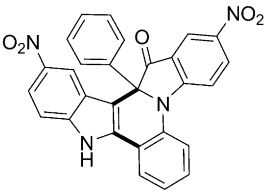
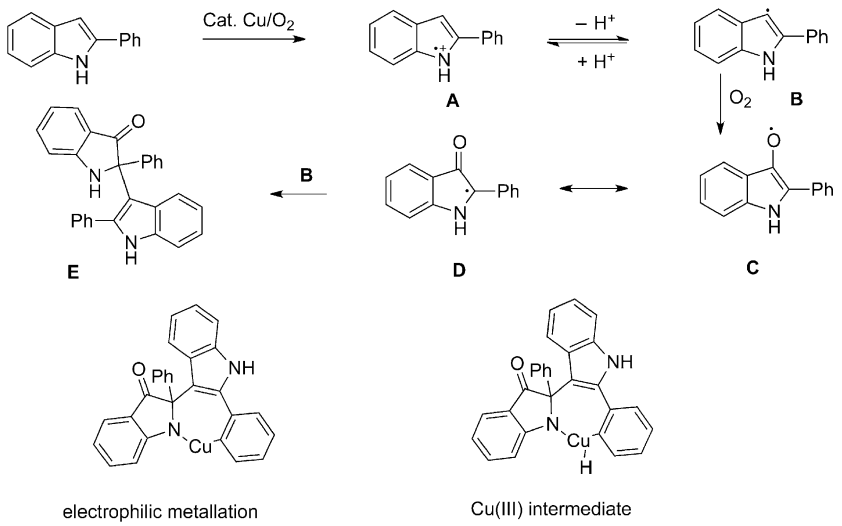


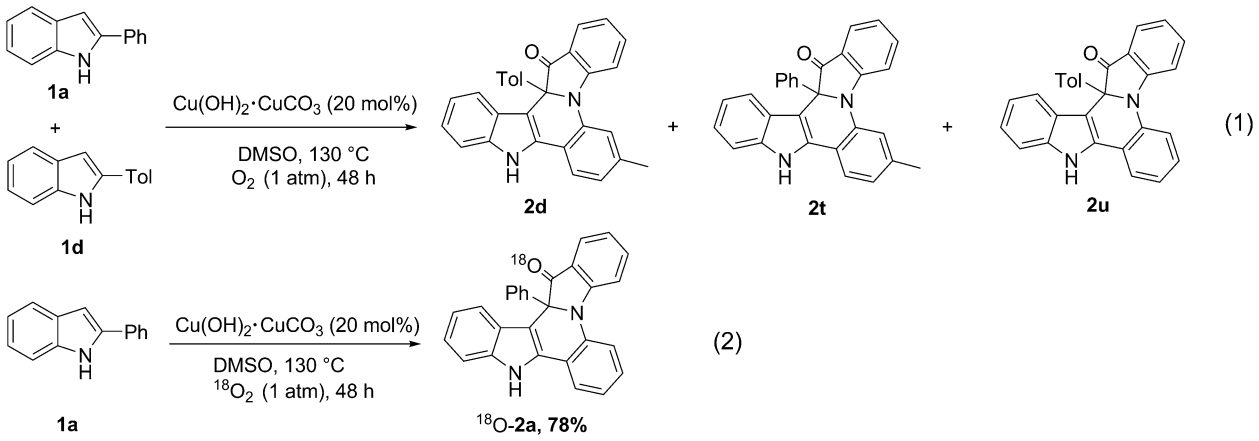
2s 0%

[a] *Reaction conditions:* **1a** (0.3 mmol), $Cu(OH)_2 \cdot CuCO_3$ (0.06 mmol), DMSO (2 mL), O_2 (1 atm), 130 °C, 48 h.
[b] Isolated yield.

was subjected to the reaction conditions employing a nitrogen rather than an oxygen atmosphere, formation of **2a** did not take place (Table 1, entry 10). In addition, a labelling experiment was performed using an $^{18}O_2$ atmosphere in anhydrous DMSO. About 78% of the product had O^{18} incorporated, thus indicating that the carbonyl oxygen in the product derives from dioxygen [Eq. (2)]. On the basis of these experimental results and a previous report,[17] a plausible reaction mechanism was proposed as shown in Scheme 1. First, the indole radical cation **A** is formed in the presence of copper catalyst and oxygen *via* the electron transfer process. The subsequent deprotonating equilibrium gives the indolyl radical **B**, which is oxidized by the oxygen/copper system to afford intermediate **C**. The combination of intermediate **C** and **D** delivers the oxidized dimer of 2-phenylindole **E**, which is indeed detected in the reaction solution by HR-MS. The subsequent cyclization might occur *via* the oxidative addition and reductive elimination process of a Cu(I)/Cu(III) cycle, where the oxygen drives the process forward.[18] The electrophilic metallation and reductive elimination pathway is another possible route.[19]



Scheme 1. Plausible reaction mechanism.



In summary, we have developed a copper-catalyzed method for the dimerization of 2-arylindoles. This transformation provides a novel route for accessing fused nitrogen-containing heterocycles. The use of an inexpensive copper catalyst and O_2 or air as the oxidant is a practical advantage. The incorporation of an oxygen atom into the organic frameworks from atmospheric molecular oxygen (O_2) offers the most ideal oxidation process. Further studies to elucidate the detailed reaction mechanism and the synthetic applications are ongoing in our group.

Experimental Section

Typical Procedure for the Preparation of 2a

To an oven-dried Schlenk tube under an O_2 atmosphere were sequentially added $Cu(OH)_2{\cdot}CuCO_3$ (13.3 mg, 0.06 mmol) and the 2-phenylindole (57.9 mg, 0.3 mmol), followed by DMSO (2 mL). The reaction vessel was immersed in an oil bath preheated to 130 °C and allowed to stir for 48 h. Saturated aqueous NaCl (10 mL), and EtOAc (10 mL) were added to the cooled reaction mixture successively. The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was subjected to flash column chromatography (sila gel, petroleum ether/ethyl acetate = 5:1, v/v) to obtain the desired products in 79% yield.

Acknowledgements

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[20] CCDC 862203 contains the supplementary crystallographic data for this paper (compound **2a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.