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Green Oxidation of Indoles Using Molecular Oxygen over a Copper Nitride Nanocube Catalyst

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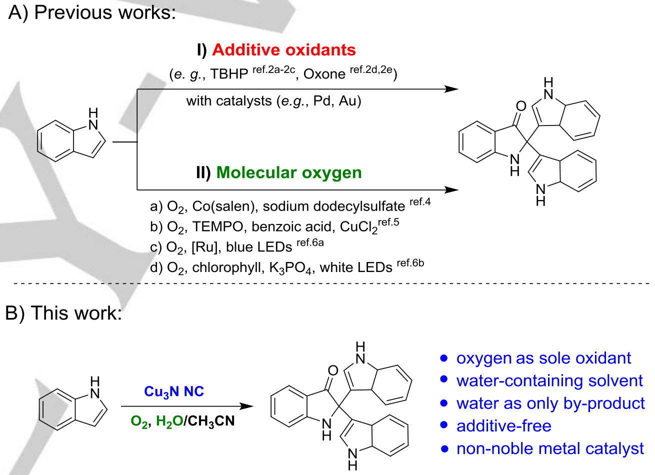
Abstract: Oxidative transformation of indoles is a promising approach for synthesizing valuable nitrogen-containing compounds; however, conventional methods use toxic oxidants and additives. Herein, we report for the first time the catalytic oxidative trimerization and the oxygenative cleavage (Witkop oxidation) of indoles using molecular oxygen under additive-free conditions accomplished by a copper nitride nanocube (Cu_3N NC) catalyst. The Cu_3N NC catalyst exhibits excellent activity to produce various indolin-3-ones and 2-ketoanilides with high functional group tolerance. Owing to this excellent catalytic performance, the Cu_3N NC catalyst is distinguished from the conventional copper catalysts, demonstrating the high catalytic potential of metal nitride in organic synthesis.

Introduction

Functionalization of indoles is important for synthesizing various nitrogen-containing compounds. In particular, oxidative trimerization of indoles is a useful method for preparing indolin-3-one skeleton, which exists in natural bioactive compounds and has wide applications in pharmaceutical chemistry against infectious diseases such as hepatitis, mumps, pneumonia, and influenza.[1] Several studies have been reported on the trimerization of indoles using homogeneous and heterogeneous catalysts (Scheme 1 A-I).[2] However, these catalytic systems inevitably require organic and inorganic oxidants such as *tert*-butyl hydroperoxide (TBHP)[2a-c] and oxone[2d,2e], respectively, which produce large amounts of waste. From the atom efficiency and environmental viewpoint, molecular oxygen (O_2) has been considered an ideal oxidant. Moreover, it has been widely used in green oxidative organic reactions because water is theoretically the sole co-product of the reactions.[3] Therefore, several efforts have been made for the green oxidation of indoles with O_2 (Scheme 1A-II). Inada et al. reported a Co(salen)-catalyzed trimerization of indoles with sodium dodecylsulfate as surfactant under O_2 bubbling.[4] Recently, the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated oxidation of indoles with O_2 using benzoic acid as an additive was also reported.[5] In addition, a visible-light photoredox catalysis has been developed for the trimerization of indoles with ruthenium or natural chlorophyll as photocatalyst.[6] Despite the use of O_2, these reaction systems still require additives or expensive catalysts containing noble metals and the non-noble metal catalyst system with O_2 under additive-free conditions has not been achieved yet. Hence, the development of such catalyst system is strongly desired for establishing a green and sustainable methodology of indoles oxidation.



Scheme 1. Oxidative trimerization of indole to [3,2':2',3''-terindolin]-3'-one.

Recently, we found that metal–non-metal alloy nanoparticles (NPs) serve as a new class of catalytic materials in liquid-phase organic synthesis. The alloying of non-metals, such as phosphorous atom with metal NPs significantly enhanced the catalytic activity.[7] We have also demonstrated that nanosized copper nitride (Cu_3N) exhibits catalytic activity in the hydroxylation of aryl halides to phenols, which is the first application of Cu_3N in organic reactions.[8] The regularly arranged Cu and N atoms of a Cu_3N crystallite surface can be regarded as the N–Cu^I–N complex array that allows the concerted effect between the copper and nitrogen atoms. This finding encouraged us to further investigate the catalytic potentials of Cu_3N for other important organic reactions. Herein, we demonstrate the first example of using a Cu_3N nanocube (Cu_3N NC) in the oxidative transformation of indoles (Scheme 1B). The Cu_3N NC exhibited high catalytic activity in the oxidative trimerization with O_2 under additive-free conditions, providing a simple and atom-economical methodology for the

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synthesis of various indolin-3-ones. Furthermore, this catalytic system was applicable in the oxygenative C=C bond cleavage (Witkop oxidation) of indoles for the synthesis of amide derivatives.

Results and Discussion

Cu_3N NC was prepared by the solvothermal method with a slight modification of the reported procedure using $Cu(NO_3)_2{\cdot}3H_2O$, octadecylamine, and oleylamine (for details, see Experimental Section).[9] The powder X-ray diffraction (PXRD) pattern of the prepared Cu_3N NC exhibited five peaks at 23.1, 33.2, 40.9, 47.6, and 53.7° indexed to the standard diffraction data for Cu_3N (JCPDS No. 47-1088) (Figure 1a). The representative transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images are shown in Figures 1b and 1c, respectively, revealing the formation of cubic Cu_3N particles with an average edge length of 67 nm (standard deviation = 15.7 nm) (Figure S1). To gain further insights into the Cu species present in the Cu_3N NC, a Cu *K*-edge X-ray absorption fine structure (XAFS) analysis was performed. The X-ray absorption near-edge structure (XANES) spectrum of the Cu_3N NC is shown in Figure 1d, along with the spectra of Cu foil, CuO, and Cu_2O as references. It can be seen that the absorption edge energy of the Cu_3N NC is similar to that of Cu_2O, suggesting that the oxidation state of Cu species in the Cu_3N NC is +1.

The catalytic activity of the Cu_3N NC was initially investigated for the trimerization of indole (**1a**) in an aqueous acetonitrile solution (H_2O/CH_3CN, v/v = 2/3) under 3 bar of O_2 atmosphere at 60 °C for 12 h (Table 1). It is noteworthy that the Cu_3N NC exhibited excellent catalytic performance, providing the desired product [3,2':2',3''-terindolin]-3'-one (**2a**) in 84% yield (entry 1). This is the first example of a non-noble-metal catalyst for promoting the O_2-mediated trimerization of indole under additive-free conditions (Table S2). On the other hand, using commercial Cu_3N, Cu_2O, CuCl, CuO, and Cu_3P resulted in lower activity compared to the Cu_3N NC (entries 2–6 vs 1). Indeed, the catalytic performance of the Cu_3N NC was significantly affected by the oxidant; for example, using TBHP instead of O_2 did not afford **2a**, confirming the indispensable role of O_2 in this transformation (entry 7). No desired product was obtained in the absence of the Cu_3N NC catalyst or O_2 (entries 8 and 9). These observations clearly demonstrate the excellent catalytic activity of a Cu_3N NC in the trimerization of indole.

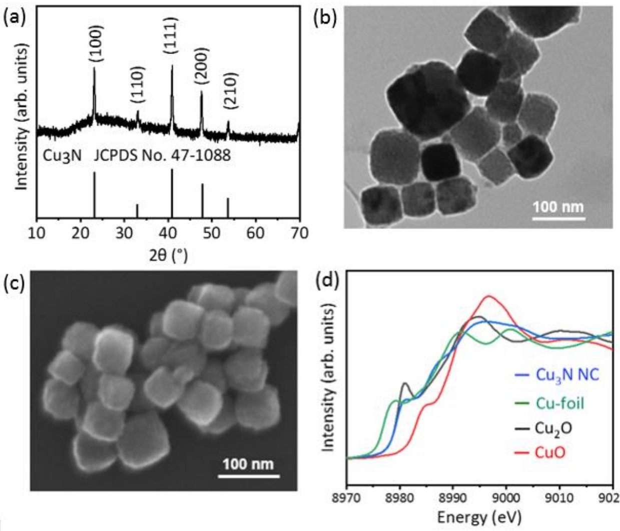
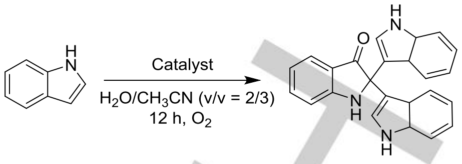


Figure 1. (a) PXRD patterns, (b) TEM, and (c) SEM images of the Cu_3N NC. (d) Cu *K*-edge XANES spectra of the Cu_3N NC and the reference Cu compounds.

Table 1. Oxidative trimerization of indole with the Cu_3N NC and other copper catalysts.[a]



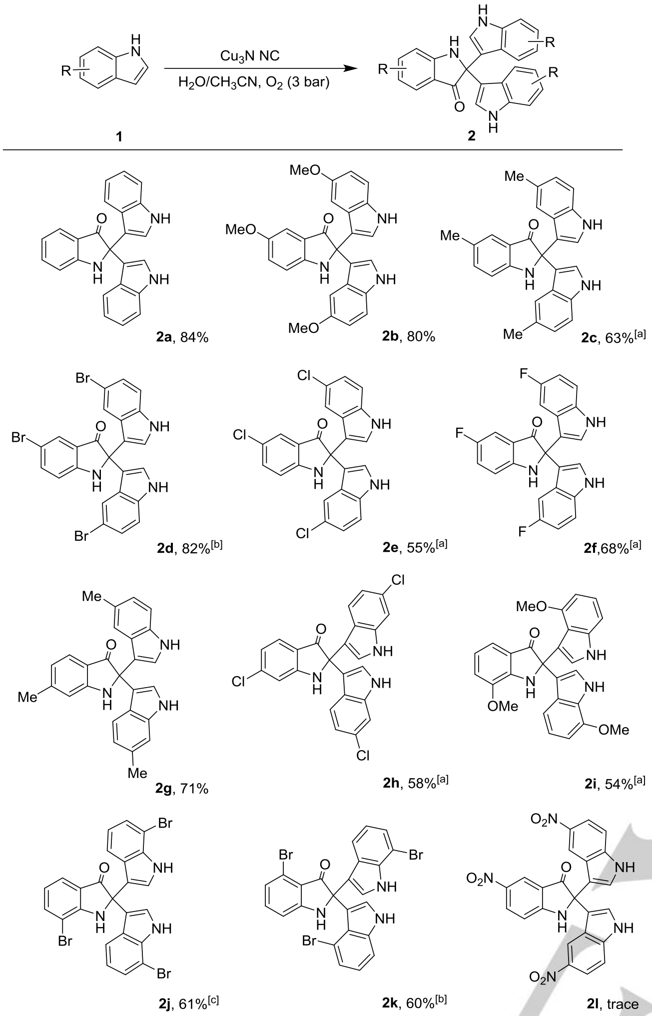
1a **2a**

Entry	Catalyst	O_2 (bar)	Isolated yield of **2a** (%)
1	Cu_3N NC	3	84
2	Cu_3N (commercial)	3	28
3	Cu_2O	3	26
4	CuCl	3	23
5	CuO	3	18
6	Cu_3P	3	18
7[b,c]	Cu_3N NC	-	N. R.
8[b]	Cu_3N NC	-	N. R.
9	-	3	N. R.

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (5 mol% Cu), H_2O/CH_3CN (v/v = 2/3, 2 mL), 60 °C. [b] Ar (3 bar). [c] TBHP (2.0 eq.). The abbreviation N. R. indicates No Reaction. The detailed results for reaction condition optimization are summarized in Table S1.

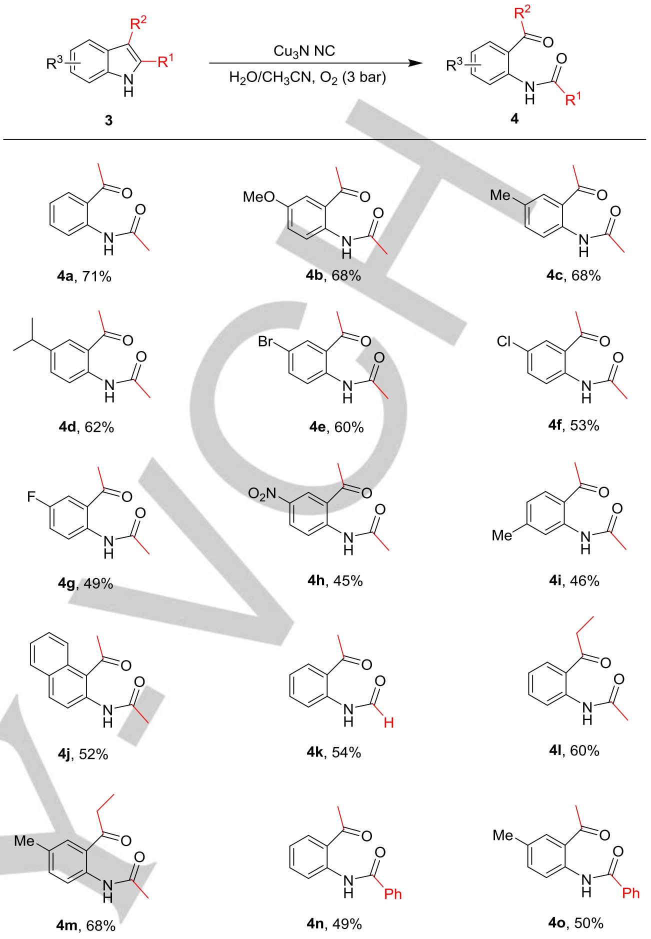
The substrate scope of the oxidative trimerization of indoles using a Cu_3N NC was investigated (Scheme 2). Indoles with electron-donating groups (–OMe and –Me) and electron-withdrawing groups (–Br, –Cl, and –F) at the C5 position were successfully converted to the desired products in 55%–82% isolated yields (**2b**-**2f**). The oxidative coupling for other position-substituted indoles also proceeded smoothly, resulting in moderate to good yields of trimerization products (**2g**–**2k**). In contrast, no desired oxidative product was observed when indole with a strong electron-withdrawing group (–NO_2) (**2l**) was used (see Scheme S1 for detailed results of the limitation of substrates).

The Cu_3N NC catalyst was also tested for the Witkop oxidation, which is an oxidative cleavage reaction of the C2-C3 C=C double bond of indoles to generate 2-ketoanilides as the important intermediates for drug syntheses.[10,11] As the model compound, 2,3-dimethylindole (**3a**) was used to evaluate the Cu_3N NC catalysis. The Cu_3N NC catalyst efficiently promoted the Witkop oxidation to produce *N*-(2-acetylphenyl)acetamide (**4a**) in 71% isolated yield under 3 bar of O_2 atmosphere without any additive in an aqueous CH_3CN solvent. Thus, using the Cu_3N NC catalyst provides a green oxidation protocol for the Witkop oxidation (Scheme 3, Tables S3 and S4). The high efficiency of the Cu_3N NC–O_2 catalyst system was illustrated in



Scheme 2. Substrate scope of the oxidative trimerization of indoles. Reaction conditions: **1** (0.5 mmol), Cu_3N NC (5 mg, 5 mol% Cu), H_2O/CH_3CN (v/v = 2/3, 2 mL), 60 °C, 12 h, isolated yield. [a] 60 °C, 24 h. [b] 80 °C, 12 h. [c] 80 °C, 24 h.

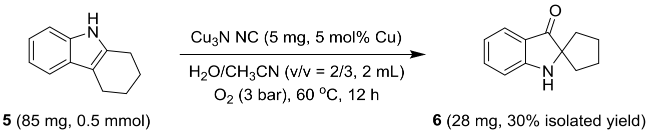
the gram-scale synthesis by converting 1.0 g of **3a** to **4a** in 60% isolated yield (0.76 g) (Scheme S2). Moreover, the reaction of various 2,3-dimethylindole derivatives containing electron-donating groups (–OMe, –Me, and –*i*Pr) and electron-withdrawing groups (–Br, –Cl, and –F) at the C5 position produced the corresponding oxygenated products in good yields (**4b–4g**). 5-Nitro-substituted dimethylindole, that is, 2,3-dimethyl-5-nitroindole, was transformed to **4h** in a 45% yield. The C6-position-substituted indole, 2,3,6-trimethyl-1H-indole, and naphthylindole underwent the C=C oxygenation to provide **4i** and **4j** in 46% and 52% yields, respectively. When mono-substituted indole of 3-methylindole was used in the Witkop reaction, 2-acetyl formanilide **4k** was obtained in a 54% yield. Furthermore, other C2, C3-disubstituted indoles such as 3-ethyl-2-methyl-1H-indole (**3l**) were successfully converted into the corresponding Witkop cleavage products (**4l–4o**) with acceptable yields (49%–68%). Therefore, the Cu_3N NC catalyst was first applied to the additive-free Witkop oxidation with a broad substrate scope under an O_2 atmosphere (Table S4). The difference in mass balance may be caused by the generation of insoluble organic compounds (see Figure S2 and Table S5 for details).



Scheme 3. Substrate scope of the Witkop oxidation of indoles. Reaction conditions: **3** (0.5 mmol), Cu_3N NC (5 mg, 5 mol% Cu), H_2O/CH_3CN (v/v = 2/3, 2 mL), 60 °C, 12 h, isolated yield.

We further investigated the applicability of the Cu_3N NC in the oxidative rearrangement of C2-C3 cyclic-substituted indole, 2,3,4,9-tetrahydro-1*H*-carbazole (**5**). This reaction produced spiro-[cyclopentane-1,2'-indolin]-3'-one (**6**) in 30% yield, although a lower selectivity was obtained due to the formation of by-products (Scheme 4) (see Figures S3 and S4, and Scheme S3 for details). Previously reported reaction systems required acid or base as additives;[12] however, the Cu_3N NC catalyst promoted the oxidative rearrangement without any additive. This demonstrates the versatility of Cu_3N NC for the green oxidative functionalization of indole derivatives.

The reusability of the Cu_3N NC was also investigated. After the Witkop oxidation of **3a**, the Cu_3N NC catalyst was separated from the reaction mixture through centrifugation. The Cu_3N NC maintained its activity up to the second reuse experiment, providing an approximately 60% yield of **4a** for 0.5 h (Figure S5a). The third reuse resulted in a slight decrease of **4a** yield.



Scheme 4. Oxidative rearrangement of 2,3,4,9-tetrahydro-1*H*-carbazole (**5**).

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The PXRD patterns and TEM image of the recovered Cu_3N NC indicated that its cubic morphology was gradually converted to amorphous during the reaction. This morphology change may decrease the catalytic performance in the third run (for details, see Figures S5b and S6).

To gain insights into the reaction mechanism of oxidative trimerization, TEMPO was added as a radical scavenger under the standard trimerization conditions of **1a** (Scheme S4). No desired product **2a** was obtained, indicating that the Cu_3N NC-catalyzed trimerization reaction involves a free radical process. This observation agrees well with the result of the gas chromatography–mass spectrometry (GC-MS) analysis conducted during the reaction (Figures S7 and S8), in which the intermediates generated through a free radical process were detected (for mechanism, see Scheme S5).[2,10,13] The Witkop oxidation was also suppressed by the addition of TEMPO (Scheme S6), suggesting the contribution of oxygen radical species in the Witkop oxidation (for mechanism, see Scheme S7).[10] Hence, the Cu_3N NC catalyst was expected to promote a broad range of oxidation reactions via a radical-mediated pathway.

Conclusion

In summary, we successfully performed the Cu_3N NC-catalyzed green oxidative functionalization of indoles with O_2 as a sole oxidant under additive-free conditions in an aqueous solvent. This is the first application of the Cu_3N NC to oxidative reactions. For oxidative trimerization and Witkop oxidation of indoles, the Cu_3N NC catalyst outperformed other Cu-based catalysts such as Cu_2O, CuCl, and CuO. Moreover, it exhibited good functional group tolerance to produce the desired indolin-3-ones and 2-ketoanilide derivatives in moderate to good yields. The Cu_3N NC catalyst could be recovered and reused without significant loss in its catalytic activity.

Experimental Section

Preparation of a Cu_3N NC. In a 50 mL Schlenk flask, $Cu(NO_3)_2{\cdot}3H_2O$ (120 mg) and octadecylamine (2.5 g) were added to 2.5 mL of oleylamine. The mixture was stirred at 150 °C for 1 h under Ar flow. Then, the obtained yellow solution was heated to 260 °C and kept at this temperature for 20 min. As a result, a brown colloidal solution was obtained. After cooling the solution to room temperature, the solid was isolated by precipitation in 2-propanol. The obtained solid was further washed several times with ethanol/toluene (v/v = 1/1) to afford the Cu_3N NC as a brown powder.

General procedure for the oxidation of indoles. In a 50 mL stainless-steel autoclave, indoles (0.5 mmol) and Cu_3N NC (5 mg, 5 mol% Cu) were added to 2 mL of H_2O/CH_3CN mixture (v/v = 2/3). The autoclave was purged and filled with O_2 until the pressure reached 3 bar, and then the mixture was stirred at 60 or 80 °C. After the reaction, the mixture was concentrated *in vacuo*. The residue was subjected to the silica gel flash chromatography with hexane/ethyl acetate to yield the desired products.

A gram-scale experiment of the Witkop oxidation of 2,3-dimethylindole. In a 100 mL stainless-steel autoclave, 2,3-dimethylindole (7 mmol, 1.015 g) and Cu_3N NC (35 mg, 3 mol% Cu) were added to 10 mL of H_2O/CH_3CN (v/v = 2/3). The autoclave was purged and filled with O_2 until the pressure reached 3 bar. The mixture was then stirred at 60 °C for 24 h and was concentrated *in vacuo*. The residue was subjected to the silica gel flash chromatography with hexane/ethyl acetate to yield the desired products.

Control experiments. In a 50 mL stainless-steel autoclave, indoles (0.5 mmol), Cu_3N NC (5 mg, 5 mol% Cu) and TEMPO (1.0 mmol) were added to 2 mL of H_2O/CH_3CN (v/v = 2/3). The autoclave was purged and filled with O_2 until the pressure reached 3 bar. The mixture was then stirred at 60 °C for 12 h and was concentrated *in vacuo*. The residue was subjected to the silica gel flash chromatography with hexane/ethyl acetate to yield the desired products.

Acknowledgements

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Keywords: copper nitride nanocube • indoles • molecular oxygen • trimerization • witkop oxidation

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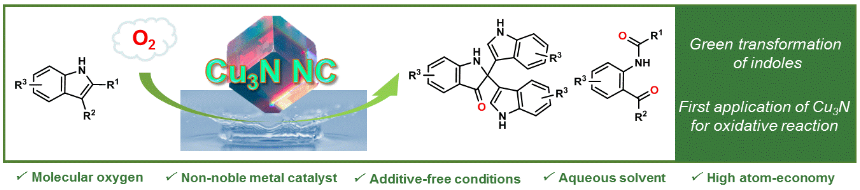

A green, sustainable, and highly efficient method for the oxidative transformation of indoles was established over a copper nitride nanocube (Cu_3N NC) catalyst. This is the first report on the additive-free trimerization and Witkop oxidation of indoles using molecular oxygen, which will greatly contribute to the oxidative functionalization of indoles in academic and practical aspect.

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