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Copper encapsulated alkaloids composite: an effective

heterogeneous catalyst for electrocatalytic asymmetric

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Abstract: A novel heterogeneous catalyst, alkaloid@Cu was prepared by the entrapment of commercially purchased alkaloids within non-noble metallic copper nanoparticles. This composite was compacted into a coin and directly used as cathode for electrocatalytic asymmetric hydrogenation of aromatic ketones. Using water as hydrogen source, optically active alcohols with 71% ee value and 93% yield were obtained under very mild conditions.

Keywords: Copper nanoparticles; Encapsulated alkaloids; Electrocatalytic hydrogenation; Asymmetric hydrogenation

1. Introduction

The catalytic asymmetric reduction of pro-chiral ketones, especially asymmetric hydrogenation and asymmetric transfer hydrogenation, has been recognized as one of the most important methods for the synthesis of chiral alcohols, which are widely-applied intermediates in the pharmaceutical, natural products, agrochemical, fragrance, and other fine chemical industries [1-2].

In both academic laboratories and industrial operations, homogeneous catalysts based on rare and expensive transition metals such as ruthenium, iridium and rhodium have typically been used in this context [3]. As for heterogeneous catalyst, the Pt/cinchona alkaloids catalyzed asymmetric hydrogenation of α -ketoester is one of the few successful examples with both high enantiomeric excess (ee value) and yield

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under favorable reaction conditions [4]. Although remarkable results have been obtained in some cases, the limited availability, high cost, and toxicity of these precious metals also brought some unsolved problems.

For this reason, asymmetric catalysts based on abundant, inexpensive, and nontoxic metals have attracted increasing attention [5]. In our former work, we successfully introduced metallic Ag and Cu instead of Pt into typical Pt/alkaloid catalyzed asymmetric hydrogenation of α -ketoesters using electrochemical methods [6-8]. Both Ag and Cu are far more abundant and cheaper than Pt. In addition, H₂O acted as hydrogen source in this procedure, which might be superior to the widely-used high pressure H₂. To the best of our knowledge, similar reports have never been seen anywhere. Alkaloids were put into the reaction solution and electroadsorbed onto the metallic Cu surface for asymmetric induction. The problem is that these modified electrodes could hardly be reused because of the facile desorption of the alkaloid. Similar issue also existed in homogeneous and Pt/alkaloid systems. Electrocatalytic asymmetric hydrogenation was also investigated by other groups, but the ee value were around 13% [9-11].

In our recent work, we further investigated the application of metallic Cu in asymmetric hydrogenation. Unlike electrochemical catalysis in our former reports, alkaloids were not adsorbed onto the surface but entrapped within Cu nanoparticles, producing an alkaloid@Cu composite. This alkaloid@Cu composite belongs to the so-called organically doped metals [12, 13], which have been demonstrated to be ideal cathode material for electrochemical catalysis by our former reports [7, 14, 15]. In our electrocatalytic asymmetric hydrogenation system, alkaloid@Cu composite directly acted as chiral inducer without any alkaloids in the reaction solution. Corresponding optically active products were successfully obtained under very mild conditions.

2. Experimental section

2.1. Apparatus and reagents

All reagents were used as received.

Electrocatalytic hydrogenation were performed with a direct-current-regulated

power supply (HY3002D, HYelec®, China). The yield and ee value of products were determined with a high-performance liquid chromatography (HPLC) instrument (DIONEX Ultimate 3000 pump). The microstructure, morphology and EDX were analyzed using Hitachi S-4800 field emission Scanning Electron Microscope (FE-SEM) equipped with an energy dispersive X-ray fluorescence spectrometer (EDX, Oxford; UK). X-ray diffraction (XRD) patterns were recorded with an Ultima IV x-ray powder diffractometer. N₂ adsorption-desorption was carried out at 77 K on a BELSORP-MAX instrument.

2.2. General procedure

Synthesis of aklaloid@Cu: A solution of 0.85 g of CuCl₂ in 25 mL of distilled water was poured into a stirred solution of 9 mg alkaloid and 0.9 g of sodium dodecyl sulfate in 25 mL of H₂O. 0.35 g of zinc powder was added and the combined slurry was stirred at room temperature for 6 h. The precipitate was filtered and washed with 10 mL 1 M HCl to remove zinc residues, then with 20 mL distilled water and acetonitrile (MeCN) for three times and dried under vacuum for 6 hours. Pure Cu nanoparticles (NPs) was prepared in the same way except for the absence of alkaloid in the reducing solution.

Typical electrochemical hydrogenation was conducted in a mixture of 50 mM substrate, 0.1 M tetraethylammonium iodide (TEAI) in a 20 mL co-solvent (MeCN/H₂O = 9/1) in an undivided glass cell with an alkaloid@Cu cathode and sacrificial magnesium (Mg) anode. The current density was 10 mA cm⁻² and the charge was 300 C. The electrolyte was bubbled with high purity N₂ throughout the electrolysis. All the procedure was performed at room temperature.

3. Results and discussion

The entrapment of alkaloids within Cu nanoparticles was carried out according to alkaloid (aq) + CuSO₄ (aq) + Zn (s) = alkaloid@Cu (s) + ZnSO₄ (aq). Cinchonidine (CD, Fig. 1A) was chosen as model dopant. The resulting material, CD@Cu composite, is a fine powder with the typical colour and shine of Cu, which was easily

compacted into a coin using a tablet press (Fig. 1B). According to former reports, metal crystallites act as a protecting matrix providing a confined environment around the dopant molecules, allows the diffusion of substrate and product molecules in and out the composite, yet not allowing the dopant to leach out [13]. Therefore, the two issues were most important in our current system. Was the CD dopant entrapped within the composite? Did the entrapped CD retain its property? We characterized CD@Cu composite with multiple methods to get an answer to these two questions.

The typical FE-SEM patterns (Fig. 1C) of the CD@Cu composite reveal that Cu nanograins gather into particles having an average size of 100 nm and aggregated further into a macroporous solid. EDX spectra (Fig. 1E) provides a direct proof that CD was entrapped within this composite: all relevant elements of this material are observed, including copper, carbon, oxygen and nitrogen. Fig. 1F displays the powder XRD patterns of pure CD (a), pure Cu NPs (b), and CD@Cu composite (c). Typical diffraction peaks of Cu are contained in (b) and (c). CD@Cu (c) feature the extra diffraction peaks (2θ =15-30), which are almost identical to those of pure CD (a). These are additional evidence that CD was indeed entrapped within the CD@Cu composite. It's notable that shifting of the peaks compared with pure Cu NPs reflections is very small. This finding is one of the indications that the CD molecules are immobilized not within the copper lattice but within the small cages of the aggregated nanocrystals [13].

Since CD@Cu composite would be applied to catalytic processes, this entrapment should be stable and CD must remain intact through the process. Firstly, we want to emphasize that the entrapment is completely different from adsorption [12, 13]. The adsorbed CD on Cu surface was unstable, which could be easily washed away by MeCN or water. In contrast, we washed the CD@Cu composite with water and MeCN many times in filtering, but the presence of CD dopant could still be confirmed by characterization methods as mentioned above, which revealed that entrapment was very stable. Although MeCN and water couldn't break the composite, dimethylsulfoxide (DMSO) was found to be a good solvent for extraction of dopant [13]. If CD@Cu composite was added into DMSO for extraction, distinct peaks were

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observed by FT-IR (Fig. 1G, a), which is the same as pure CD (Fig. 1G, b), indicating that CD was entrapped and retained its property throughout the entrapment and extraction process.

Beyond the preparation of a new organically doped metal composites, we wanted to probe the applicability of such materials in catalysis and study the advantages they offer with respect to the unsupported catalysts. With this aim, we describe herein the suitability of the CD@Cu composite as heterogeneous catalysts in the asymmetric electrocatalytic hydrogenation of aromatic ketones. CD@Cu powder has metallic character and could be easily compacted into coin for electrolysis. A typical asymmetric electrocatalytic hydrogenation was carried out in a mixture of 50 mM substrate, 0.1 M TEAI in a 20 mL co-solvent (MeCN/H₂O = 9/1), with a CD@Cu composite cathode and an Mg anode (Fig. 2A). Methyl benzoylformate (Fig. 2A, 1a) was used as a model substrate. It's notable that no CD was found in the reaction solution. Optically active R-methyl mandelate was obtained with a 78% ee and a 94% yield were detected by HPLC (Fig. 2B). No by-product was detected by HPLC (or below the limit of detection), asymmetric hydrogenation of 1a on CD@Cu composite shows excellent selectivity. As comparison, we also tested the catalytic activity of non-entrapped CD using metallic Cu cathode. Pure Cu NPs were also compacted into coin as CD@Cu composite for asymmetric hydrogenation with 1.5 mM CD in reaction solution as chiral inducer, other conditions being the same as with the CD@Cu system. A similar yield, 93%, but a significantly lower ee value, 23%, were obtained. For other entrapped-alkaloids, including cinchonine (CN), quinine (QN) and quinidine (QD), obviously higher ee value were also achieved with CN@Cu, QD@Cu and QN@Cu cathode, compared to non-entrapped ones, as shown in Fig. 2B. It's notable that R-configuration was observed using CD and QD catalysts; while S-configuration was predominant for CN and QN. What's more, 1b-1g were tested to examine the substrate scope of CD@Cu composite using reaction conditions of **1a**. The results summarized in Fig. 2C show that moderate or good yields and ee values could be obtained with all the substrates. Therefore, alkaloid@Cu composite could be effective in the electrochemical asymmetric hydrogenation with a wide range of substrates.

It's an interesting question why the much higher ee value was observed at CD@Cu system. CD@Cu and Cu NPs were prepared the similar way. According to N_2

adsorption-desorption, CD@Cu and Cu NPs have specific surface area of 3.2 and 2.9 m^2 g⁻¹, respectively. Larger specific surface area might explain part of the higher ee value obtained at CD@Cu cathode, but it is not the whole truth. In our former work, we synthesized a metallic nanostructure Cu NPs cathode with regular morphology, smaller particle size and 7.5 $m^2 g^{-1}$ specific surface area [8]. Under the same conditions, the best ee value achieved at this cathode was 61%, still lower than with the CD@Cu cathode. According to previous research, alkaloid could be electrosorbed on the metallic Cu surface [8, 16] and the ee value was shown to vary linearly with the adsorption amount in actual electrolysis [8]. We can infer that more CD on (or around) the cathode surface is conducive to accelerate electrolysis procedure. In this report, 1.2 g CD@Cu composite was compacted into a cathode coin, containing nearly 27 mg CD, which means 27 mg CD was around the inner surface of our CD@Cu cathode. As for physical adsorption, if pure 1.2 g Cu NPs cathode was put into 20 mL 1.5 mM CD solution for electrosorption, CD in solution only dropped less than 0.1 mg. What's more, the adsorbed CD was not stable and could be easily washed by MeCN, but the entrapped CD was very stable. In a word, CD on the CD@Cu cathode surface was 270 times more than these on pure Cu NPs, which might explain why the ee value obtained at CD@Cu composite cathode was much higher than the non-entrapped CD system.

The recyclability of the CD@Cu cathode was subsequently examined in the asymmetric hydrogenation of **1a**. After the reaction, the cathode was thoroughly washed with MeCN and then reused for a next reaction run under identical conditions with fresh reagents. As shown in Fig. 2D, the catalyst showed no appreciable reduction of activity even after ten runs. SEM images and for the reused catalyst suggested that the morphology and crystal structure was completely preserved after several reuses (Fig. 1D). XRD patterns revealed that CD still existed in the reused catalyst (Fig. 1F, d). What's more, CD was extracted from the composite and quantitate detected by HPLC, which was 27 mg, the same as that of the as-synthesized sample. These results indicated that no leak of CD occurred during the reaction. Hence, CD@Cu composite has excellent stability and reusability.

4. Conclusions

Compared to noble metal platinum, copper is far more abundant and non-expensive. Using electrochemical conditions, we successfully introduced metallic Cu instead of Pt into typical Pt-alkaloid catalyzed asymmetric hydrogen system. Alkaloid, the chiral inducer, was encapsulated within Cu particles rather than modified on the metal surface by physical adsorption, which means that this alkaloid@Cu composite is an absolute heterogeneous catalyst. Alkaloid@Cu composite could be directly used as cathode for the electrocatalytic asymmetric hydrogenation of aromatic ketones without any supporter or carrier, good ee value and excellent yield were obtained under mild conditions. In addition, the alkaloid@Cu composite shows remarkable stability and can be used multiple times, which would be crucial in possible practical applications.

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Fig. 1 A: Molecular structure of alkaloids; B: CD@Cu composite before (left) and after press (right); FE-SEM patterns of CD@Cu before (C) and after using (D); E: EDX spectra of CD@Cu; F: XRD patterns of pure CD (a), pure Cu NPs (b), CD@Cu before (c) and after using (d); G: FT-IR spectra of dopant extracted from CD@Cu composite (a) and pure CD (b).





Fig. 2 A: reaction pathway; B: comparison of entrapped and non-entrapped alkaloid catalysts using **1a** as substrate; C: asymmetric hydrogenation with different substrates at CD@Cu cathode; D: reuse test of CD@Cu composite using **1a** as substrate.

Graphical Abstract



Highlights

- Asymmetric electrocatalytic hydrogenation was carried out on modified Cu electrodes.
- Alkaloids were encapsulated within metallic Cu, alkaloid@Cu, instead of being physisorbed.
- > Alkaloid@Cu had a much higher activity than pure Cu NPs.
- > Alkaloid@Cu had excellent stability and reusability.