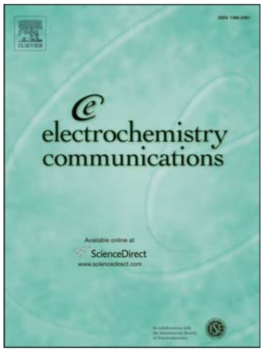

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Alkaloid-induced asymmetric hydrogenation on a Cu nanoparticle cathode by electrochemical conditions

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Abstract: Copper nanoparticles were prepared in an aqueous solution, compacted into a coin, and used as cathode for asymmetric hydrogenation by the electrochemical method for the first time. A good ee value and excellent yield were obtained under mild conditions. Electrochemical conditions were crucial for alkaloid adsorption on metallic Cu, which is a key process of asymmetric induction. Furthermore, the ee value was linear with an adsorption amount.

Keywords: Copper nanoparticles; Asymmetric hydrogenation; Electrochemical conditions; Alkaloids; Adsorption

1. Introduction

Asymmetric synthesis is a fundamental part of the pharmaceutical and agrochemical industries [1]. Asymmetric hydrogenation occupies a particularly important position in asymmetric synthesis, which provides an effective route for chiral compounds， but a majority of these reactions are homogeneously catalyzed by transition metal complexes such as Rh, Ir, and Ru catalysts, which are always expensive and hardly recyclable [2–9]. Heterogeneous catalysts have clear advantages compared with homogeneous catalysts. However, successful heterogeneous asymmetric catalysts are currently confined to several specific metals.

One of the most effective and well-document heterogeneous asymmetric catalysts are Pt/Al_2O_3 (or Pd) modified with alkaloids, which is used for the asymmetric hydrogenation of α-ketoesters, despite the use of noble metals [10–14]. Since the original discovery of this catalytic system, its mechanism has been studied thoroughly

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with both theoretical and experimental methods. Alkaloids can be adsorbed on the supported metal and quinoline moiety of alkaloids that lie parallel to the metal surface through a π-electron interaction, which is important for the formation of a preferential enantiomer [15–18].

Because of its rarities and large potential application in extensive fields, to explore a novel heterogeneous catalyst for asymmetric hydrogenation has both commercial and academic value. Metallic Ag or Cu, which are abundant and relatively cheap, can be alternative heterogeneous asymmetric catalysts; these metals are types of face-centered cubic metals，just like Pt and Pd. However, to the best of our knowledge, there is no report on the application of metallic Ag or Cu in heterogeneously asymmetric hydrogenation as active substance. No proof also exists on alkaloid adsorption on metallic Ag or Cu surface by typical methods.

In our previous research, alkaloids were electrosorbed on metallic Ag for heterogeneously asymmetric hydrogenation by electrocatalysis; moderate to suitable ee values were obtained under mild conditions [19–21]. For metallic Cu, the cinchonidine (CD) adsorption on the Cu (111) electrode surface was investigated by *in-situ* scanning tunneling microscopy (STM) in an aqueous solution by the electrochemical method, but not involving any actual catalysis [22]. We further explored the application of metallic Cu in asymmetric hydrogenation by the electrochemical method under the guidelines of this strategy.

2. Experimental

2.1. Apparatus and reagents

All reagents were used as received.

Galvanostatic electrohydrogenation and electrosorption of alkaloids were performed with a direct-current-regulated power supply (HY3002D, HYelec®, China). The product yield, ee value, and adsorption amount were determined with a high-performance liquid chromatography (HPLC) instrument (DIONEX Ultimate 3000 pump) equipped with a UV (RS variable wavelength) detector and a chiralcel OD-H column (DAICEL Chiral technologies Co., Ltd., China). The microstructure and morphology were analyzed with a Hitachi S-4800 field-emission scanning electron microscope. X-ray diffraction (XRD) patterns were recorded with an Ultima IV x-ray powder diffractometer with Cu Kα radiation (k = 1.5406 Å).

2.2. General procedure

The synthesis of Cu (Pt) NPs was performed as follows. 5 g of $CuSO_4 \cdot 5H_2O$ (2.07 g $H_2PtCl_6 \cdot 6H_2O$) was dissolved in 100 mL deionized water. 8 mL of ethylene glycol was then added into the solution. After 10 min of stirring, 50 mL of hydrazine hydrate solution (10%) was slowly added. The mixture was then stirred at 25 °C for 4 h. Cu (Pt) was precipitated immediately. The precipitate was filtered, washed with 10 mL water and 10 mL anhydrous ethanol for 4 times each, and dried for 12 h under vacuum.

The electrohydrogenation procedure is as follows. Cu NP powder was pressed into a coin and used as a cathode. Typical galvanostatic electrohydrogenation was conducted in a mixture of 50 mM substrate, certain concentration of alkaloid and 0.1 M tetraethylammonium iodide (TEAI) in a 20 mL co-solvent (MeCN/H_2O = 9/1) in an undivided glass cell with a Cu NP cathode and sacrificial magnesium (Mg) anode.

3. Results and discussion

First, Cu NPs and Pt NPs were characterized by multiple methods. The typical diffraction peaks of Cu (Fig. 1D, a) and Pt (Fig. 1D, c) were observed in the XRD patterns, and no trace of metal oxides was noted. The SEM pattern shows that Cu NPs have nanostructures (Fig. 1A) that were aggregated from Cu nanograins in the ~20 nm size range, similar to Pt NPs (Fig. 1B).

As previously mentioned, alkaloid adsorption on metallic Pt is a key step for chiral induction in a typical system. Can this adsorption be possible on metallic Cu similar to a Pt–alkaloid system? Contrastive experiments were performed to explore this scenario. Alkaloid adsorptions on both Pt NPs and Cu NPs were conducted in a mixture of 0.1 M TEAI and 1.5 mM CD in 20 mL MeCN under N_2 atmosphere for 30 mins. The alkaloid adsorption amount was calculated from the alkaloid concentration differences before and after the addition of 0.5 g Pt NPs or Cu NPs, which was detected by HPLC. The concentration differences show that 168 μg g^{-1} CD was adsorbed on Pt NPs, but the CD concentration remained unchanged after the addition of Cu NPs. This phenomenon indicates that the CD cannot be adsorbed on Cu NPs as Pt NPs by the typical method. Thus, electrochemical conditions were introduced to the asymmetric hydrogenation on metallic Cu and were demonstrated to be very efficient in our work.

Typical asymmetric hydrogenation was conducted in a mixture of 50 mM substrate and certain CD concentration as a chiral inducer in an undivided glass cell with a Cu NP cathode and Mg anode. Methyl benzoylformate (**1a**) was selected as the model substrate to optimize the reaction conditions. The influence of alkaloid concentration, electric charge, current density, and cathode was investigated (Table 1). Optically active methyl mandelate (**2a**) was obtained with a 40% ee and a 95% yield (Table 1 entry 2) under optimized conditions. Certain ee values and yield could also be achieved with other alkaloids (Table l), such as cinchonine (CN), quinine (QD), and quinidine (QN) (Table 1 entries 12–14).

Encouraged by the suitable results achieved with **1a**, the preparative scope of substrates was further studied under the reaction conditions in Table 1, entry 2. The results summarized in Table 2 show that moderate or good yields and ee values could be obtained with substituted ketones, including both electron withdrawing and electron-donating groups. Therefore, Cu NPs electrosorbed with alkaloids could be effective in the heterogeneous asymmetric hydrogenation of carbonyl with a wide range of substrates.

Given that alkaloids could not be adsorbed on the Cu surface by the typical method, investigating alkaloid behavior on the Cu surface under electrochemical conditions is necessary to understand the mechanism of this system. CD adsorption on the Cu (111) electrode surface was confirmed qualitatively by *in-situ* STM [22], which was performed in an aqueous solution unlike the actual reaction condition. In our work, we investigated the adsorption of alkaloids on Cu electrode quantitatively, which was performed under actual catalytic condition except for the absence of substrates. We detected the alkaloid concentration before and after adsorption by HPLC [21]. The concentration differences show that the adsorption amounts were 28, 10, 14, 18, 23, and 28 μg cm^{-2} under the conditions listed in Table 1 (entries 2, 7, 8, 9, 10, and 11, respectively) in the absence of substrates. It is quantitative evidence that CD can be adsorbed on the Cu NP surface under actual reaction conditions, and the adsorption amount is in the μg cm^{-2} levels. An interesting phenomenon was observed under the conditions of Table 1 entries 2, 7, 8, 9, 10, and 11, wherein the ee values of 40%, 14%, 21%, 27%, 32%, and 39%, respectively, increased with the adsorption amount. We plot the ee value versus the adsorption amount to further understand the relationship between the adsorption amount and ee value (Fig. 2A). A straight line could be achieved; thus, we can infer that the alkaloid adsorption was in favor of chiral induction and the ee value was linear with an adsorption amount.

Moreover, 50 mM **1a** was added for asymmetric hydrogenation after CD adsorption; 93% yield and 61% ee value were obtained (Table 1, entry 15). Compared with the **1a** added with CD (Table 1, entry 2), the yield was similar but the ee value was clearly higher. With a pre-adsorbed Cu NP electrode, a similar yield but much higher ee value could also be achieved with other alkaloids (Table 1, entries 16–18). In summary, alkaloids could be adsorbed on the Cu NP surface and the adsorbed alkaloids contributed to the formation of a preferential enantiomer.

The major disadvantage of homogeneous asymmetric hydrogenation involves the utilization of valuable and hardly recyclable transition metal complexes. By contrast, cheap alkaloids were used as chiral inducers in our catalytic system. Unlike a typical Pt/Al_2O_3 (or Pd) system, the Cu NPs used in our system were non-noble, abundant, and easily prepared. Furthermore, the Cu NP cathode has remarkable stability and reusability, can be easily cleaned after the previous run, and then reused for the next catalytic procedure. It was tested for recycle times under the reaction conditions of Table 1, entry 2. The yields and ee values of **2a** can be maintained at approximately 94% and 60% for 10 times (Fig. 2B). The Cu NP electrode stability was characterized by XRD before (Fig. 1D, a) and after (Fig. 1D, b) hydrogenation for 10 times. The XRD patterns show that the Cu NP electrode is stable and its components do not change. Cu NPs can also maintain its nanostructures and size range after recycling (Fig. 1C). Therefore, the Cu NP electrode we prepared is stable and reusable. Moreover, water was employed as a hydrogen source in our system without high-pressure and high-temperature hydrogen in a typical Pt/Al_2O_3 (or Pd) system. All procedures can be performed under mild conditions.

4. Conclusions

Alkaloids cannot be adsorbed on metallic Cu, such as metallic Pt, by the typical method, which is important for chiral induction. Metallic Cu was successfully introduced to heterogeneous asymmetric hydrogenation for the first time by electrochemical conditions. Furthermore, alkaloid adsorption on the metallic Cu surface was quantitatively investigated by HPLC under actual catalytic conditions and the ee value was linear with an adsorption amount. Unlike noble metallic Pt, metallic Cu is abundant, relatively cheap, and highly reusable. Metallic Cu could be an alternative option for heterogeneous asymmetric hydrogenation.

Acknowledgements

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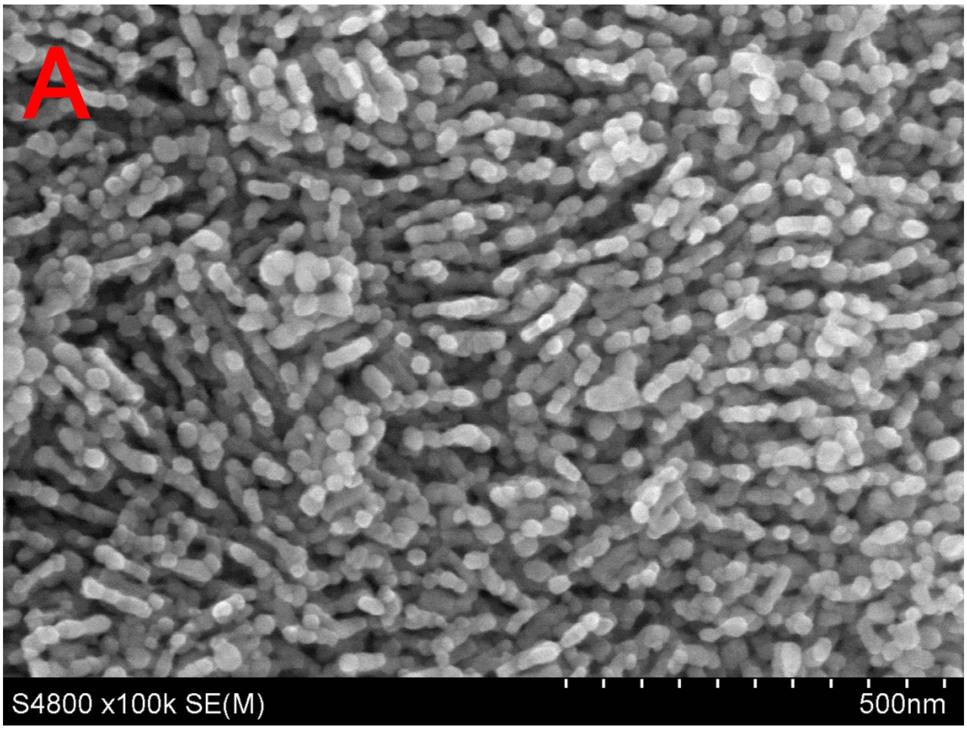
A
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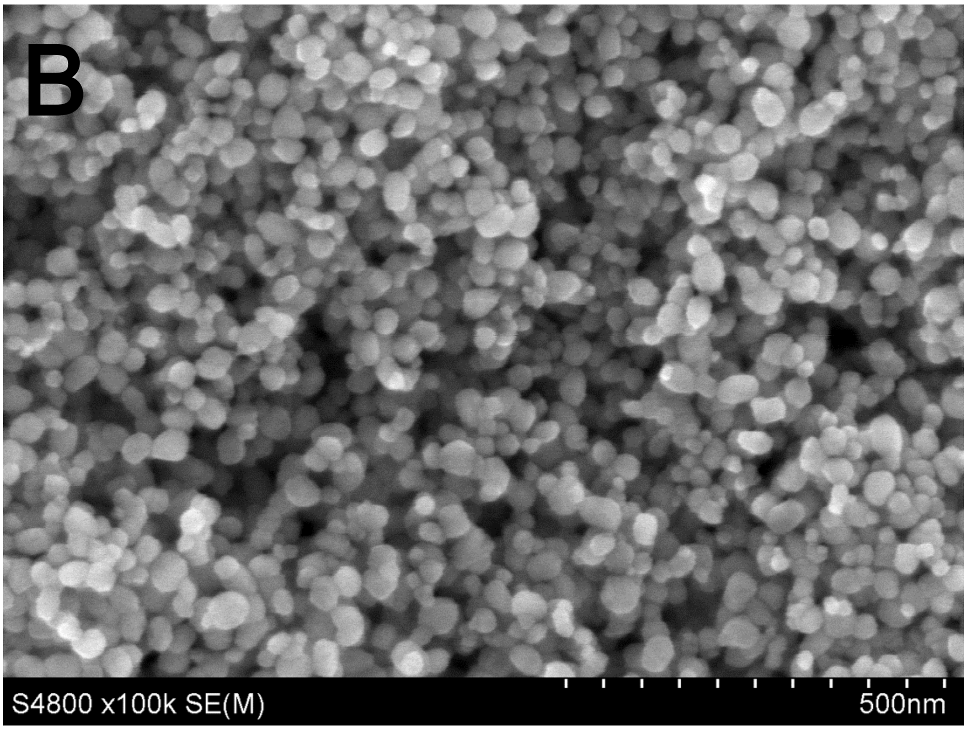
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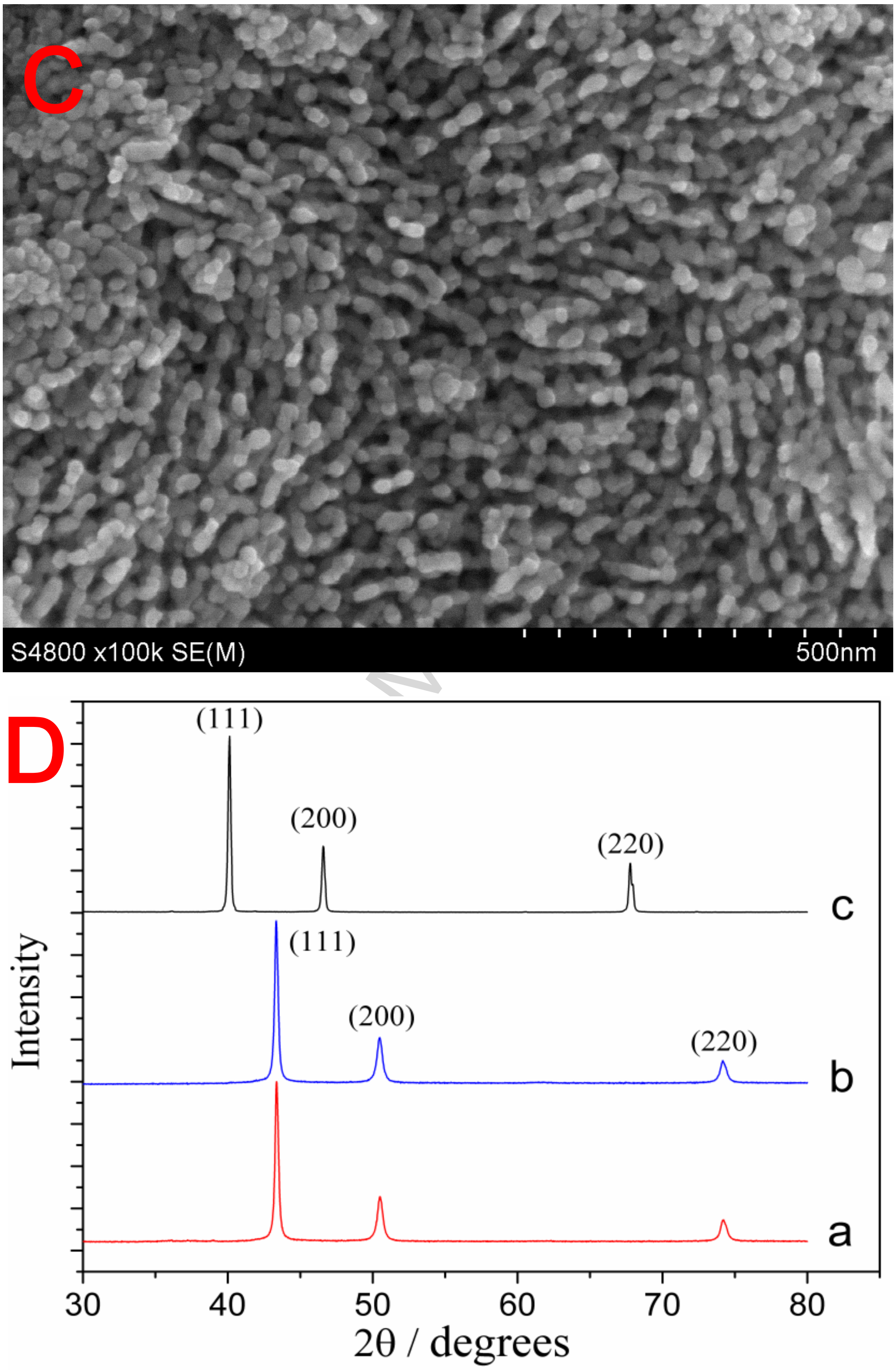


Fig. 1 Characterization of metal NPs. FE-SEM patterns of Cu NPs before using (A), Pt NPs (B), and Cu NPs after using for 10 times (C); D: XRD patterns of Cu NPs before using (a), after using for 10 times (b) and Pt NPs (c).

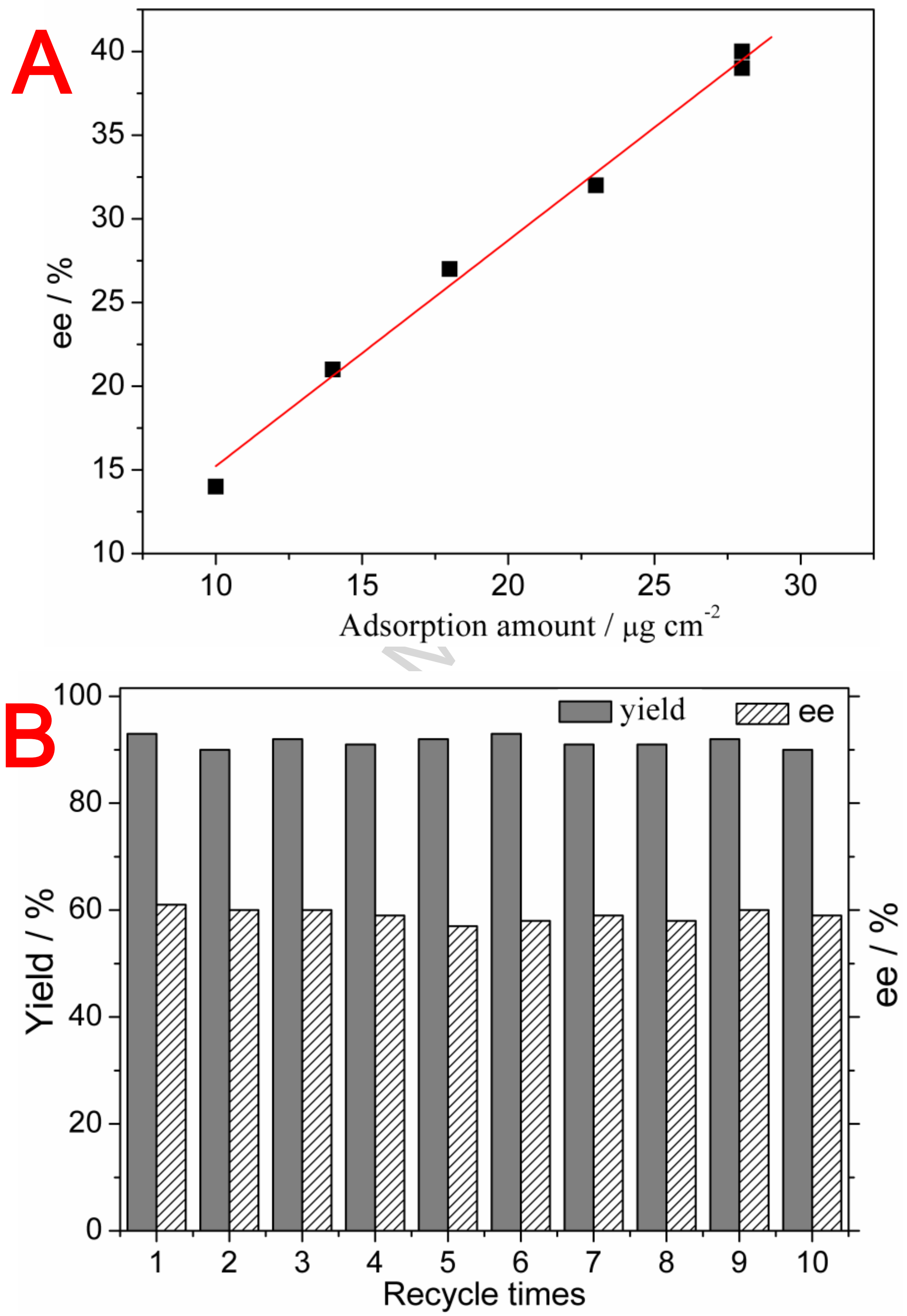
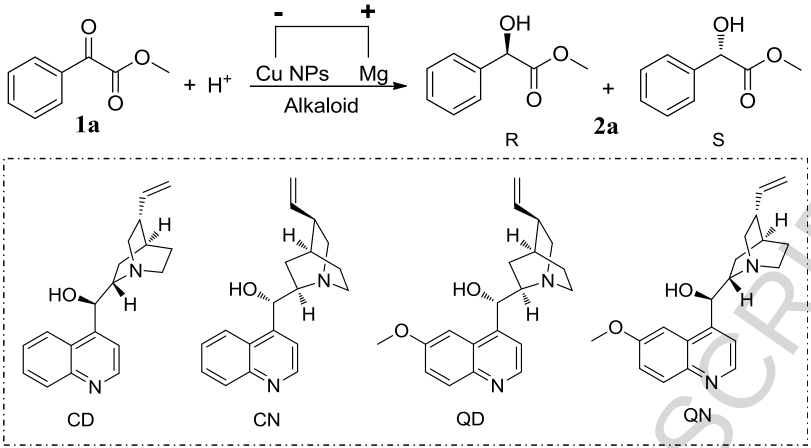


Fig. 2 ee value of **2a** versus CD adsorption amount (A); Reuse of Cu NPs electrode, reaction conditions as Table 1 entry 2 (B).

Table 1 Asymmetric hydrogenation of **1a** on various reaction conditions[a].

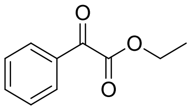
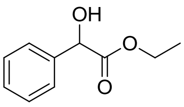
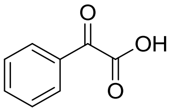
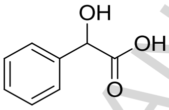
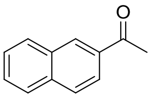
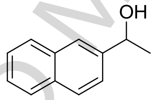
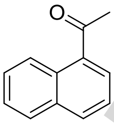
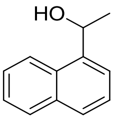
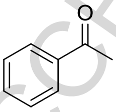
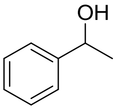
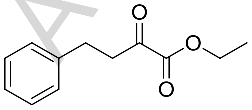
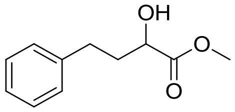


Entry	C_{CD} (mM)	Yield[b] (%)	R-ee[b] (%)
1[c]	1.5	93	38
2	1.5	95	40
3[d]	1.5	57	29
4[e]	1.5	11	24
5[f]	1.5	95	36
6[g]	1.5	94	39
7	0.5	92	14
8	0.75	92	21
9	1.0	93	27
10	1.25	91	32
11	2.0	90	39
12	1.5[h]	94	38(S)
13	1.5[i]	90	33
14	1.5[j]	87	31(S)
15	1.5[k]	93	61
16	1.5[l]	92	63(S)
17	1.5[m]	86	52
18	1.5[n]	85	50(S)

[a] Cathode: Cu NPs, anode: Mg, 20 mL co-solvent (MeCN/H_2O=9/1), 0.05 M **1a**, supporting electrolyte: 0.1 M TEAI, current density: 10 mA cm^{-2}, charge: 3 F mol^{-1}. [b] Determined by HPLC with a chiral column. [c] current density: 5 mA cm^{-2}, [d] current density: 15 mA cm^{-2}, [e] current density: 20 mA cm^{-2}, [f] charge: 4 F mol^{-1}, [g] charge: 5 F mol^{-1}, [h] Alkaloid: CN. [i] Alkaloid: QD. [j] Alkaloid:

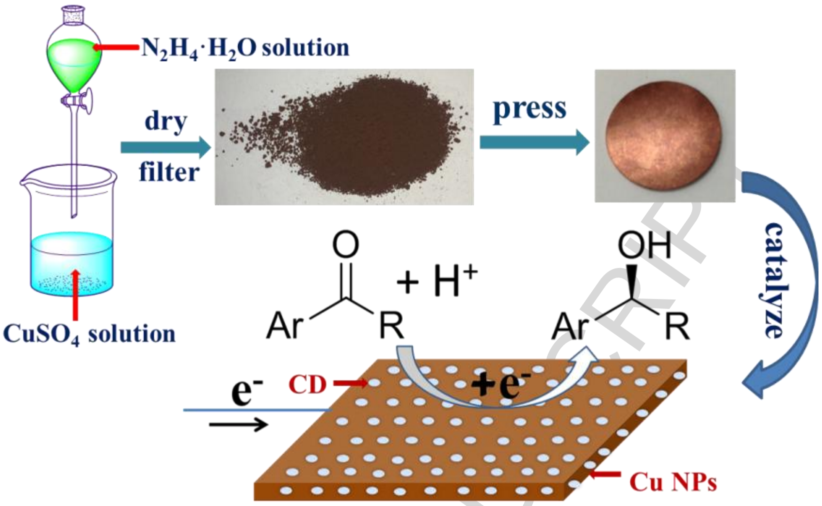
QN. [k] Alkaloid: CD, pre-adsorbed. [l] Alkaloid: CN, pre-adsorbed. [m] Alkaloid: QD, pre-adsorbed. [n] Alkaloid: QN, pre-adsorbed.

Table 2 Asymmetric hydrogenation of several substrates on Cu NPs electrode[a].

Entry	Substrate	Product	Yield[b] (%)	R-ee[b] (%)
1	 **1b**	 **2b**	86	33
2	 **1c**	 **2c**	88	36
3	 **1d**	 **2d**	4	16
4	 **1e**	 **2e**	7	20
5	 **1f**	 **2f**	6	28
6	 **1g**	 **2g**	89	47

[a] Cathode: Cu NPs, anode: Mg, 20 mL co-solvent (MeCN/H_2O=9/1), 0.05 M substrate, 0.1 M TEAI, 1.5 mM CD, current density: 10 mA cm^{-2}, charge: 300 C. [b] Determined by HPLC with a chiral column.

Graphical Abstract



Highlights

- Metallic Cu was used for heterogeneous asymmetric hydrogenation for the first time.
- All the preparation of Cu NPs and catalysis procedure were performed under mild conditions.
- Electrochemical conditions were crucial for alkaloid adsorption on metallic Cu and the ee value was proved to be linear with an adsorption amount.
- Cu NPs are much more abundant, relatively cheap, and remarkable reusable.