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An effective heterogeneous L-proline catalyst for the direct asymmetric aldol reaction using graphene oxide as support

Rong Tan [a], Chengyong Li [a], Jianqing Luo [a], Yu Kong [a], Weiguo Zheng [a], Donghong Yin [a,b,*]

[a] Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha, Hunan 410081, China
[b] Technology Center, China Tobacco Hunan Industrial Corporation, No. 426 Laodong Road, Changsha, Hunan 410014, China

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ABSTRACT

Pristine L-proline was non-covalently loaded on the graphene oxide (GO) sheet in a simple route by mixing them in aqueous solution. Technologies of characterization well suggested that L-proline was efficiently loaded on the two sides and edge of the GO sheet through hydrogen-bonding or/and ionic interaction, giving the excellent **L-proline/GO** hybrid catalyst for the direct asymmetric aldol reaction. The unique multilayered structure of the GO carrier with sufficient interlayer space favored reagents' diffusion toward L-proline chiral moiety and therefore resulted in the high catalytic efficiency of the heterogeneous L-proline. Excellent yield (96%) with high enantiomeric excess (79% *ee*) was obtained in the direct aldol reaction of 2-nitrobenzaldehyde with acetone catalyzed by **L-proline/GO** hybrid, which was comparable to that observed in the reactions promoted by L-proline itself. Furthermore, the **L-proline/GO** hybrid used as a heterogeneous catalyst could be easily recovered and recycled for seven times without significant loss of the reactivity.

1. Introduction

The direct asymmetric aldol reaction is one of the most important C—C bond-forming reactions in organic synthesis and is of much importance in the pharmaceutical, agrochemical, and fine chemical industries [1–4]. In 2000, List et al. demonstrated the use of proline as an efficient catalyst for the direct asymmetric aldol reaction between unmodified ketone and a variety of aldehydes [5]. The proline used as an important chiral small-molecule organocatalyst has been drawn much attention since it is easily accessible, environmentally safe, and available in both the enantiomeric forms [6–8]. However, it suffered from the unavoidable drawbacks of homogeneous catalytic processes (e.g., lower thermal stability and difficulties in catalyst separation and recovery). Immobilization and recycling of L-proline have received considerable concerns in recent years. Several types of supports, such as polymer [9–12], silica [13–17], ionic liquid (IL) [18,19], β-cyclodextrin [20], Merrifield resin [21] and magnetite [22], are usually considered for the immobilizations of proline and its derivatives. Gruttadauria and his co-workers [9–11] used polystyrene-supported proline-based organic catalysts for the direct asymmetric aldol reaction. Zou et al. [12] investigated the catalytic behaviors of PVC-TEPA-supported L-proline in the aldol reaction. Lu et al. [13] synthesized L-proline-functionalized polymers as supported organocatalysts. Bae et al. [14,15] grafted L-proline onto the heterogenized silica for catalyzing the asymmetric aldolization. Calderón et al. [16,17] catalyzed the asymmetric aldol reaction by proline on mesoporous materials. Miao and Chan [18] prepared an IL-anchored proline catalyst, which was efficient and recyclable for asymmetric aldol reaction. The heterogeneous catalysts indeed can be recycled for reuse, but some of them are less efficient due to the low accessibility of substrates. Recently, layered double hydroxides (LDHs) have emerged as an attractive support to develop the L-proline/LDHs hybrid using intercalation of L-proline in Mg—Al LDH through ion-exchange method [23]. It is found that the immobilization of L-proline on LDHs has no adverse effect on the catalytic activity of L-proline. Thus, this represents a fascinating strategy for developing the heterogeneous L-proline catalyst with high efficiency and easy reusability by supporting the L-proline on layered materials.

Recently, a newly layered material-graphene oxide (GO) has attracted much attention of scientists all over the world, since it exhibits unique surface properties (oxygenated functional groups on the basal planes and edge), high-specific surface area, and easy exfoliation into monolayers under water [24–26]. In particular, the GO consists of intact graphitic regions interspersed with sp^3-hybridized carbons containing carboxyl, hydroxyl, and epoxide functional groups on the edge, top, and bottom surface of each sheet and sp^2-hybridized carbons on the aromatic network [26].

* Corresponding author at: Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha, Hunan 410081, China. Fax: +86 731 88872531.
E-mail address: yindh@hunnu.edu.cn (D. Yin).

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The presence of the abundant oxygen functional groups provides GO sheet with large capability of loading organic molecules through covalent or non-covalent approaches, facilitating development of a broad novel class of materials with enhanced properties and even introducing new functionalities to GO sheet [27,28]. Yang et al. have reported high-efficiency loading of doxorubicin hydrochloride (DXR) on GO sheet (0.91 mg/mg) through hydrogen-bonding interaction between GO and DXR, as well as the π–π stacking interaction [29]. Apart from the abundant oxygen functional groups, the key to understanding the large loading capability of GO sheet lies in the large theoretical specific surface area (up to 400–1500 $m^2 g^{-1}$) [30], as well as the high efficient utilization of surface area because both sides of the nanosheet are accessible.

Based on the fascinating layered structure of GO material, as well as the large capability of loading organic molecules, we reason that the GO can be used as an efficient support for L-proline and allows for desirable catalytic properties. It is well known that the carboxyl and secondary amine groups of the L-proline are capable of participating in hydrogen bond [31], and we thus decide to introduce the L-proline into the GO sheet through the hydrogen-bonding interaction between the L-proline and the GO sheet to prepare the **L-proline/GO** hybrid. We envision that the GO sheet can efficiently load L-proline molecular on its two sides and edge, resulting in a sandwich-like hybrid (**L-proline/GO**) where layers of GO sheet alternate with layers of L-proline. The intercalated L-proline component serves as the catalytic sites, and the GO sheet as support is expected to favor accessibility of reagents, which in turn increases the catalytic efficiency of the heterogeneous L-proline catalyst. Furthermore, the non-covalent method, which does not need to tune the structures of the L-proline and the GO sheet, represents an interesting strategy for the attachment of active sites on the GO sheet for use in catalytic reactions. Herein, L-proline was efficiently loaded on GO sheet simply by using the non-covalent approach. It is interesting that the layered **L-proline/GO** hybrid, in which reagents can free access interlamellar space, functions as the heterogeneous catalyst, but behaves as the homogeneous catalyst. Thus, it presents comparable catalytic activity and enantioselectivity relative to the pristine L-proline and can be easily separated for reuse by centrifugation.

2. Experimental

2.1. Materials and methods

4-nitrobenzaldehyde, 2-chlorobenzaldehyde, and 4-acetamidobenzaldehyde were obtained by TCI. 2-nitrobenzaldehyde, 2-naphthaldehyde and 4-bromobenzaldehyde were bought from Acros. 3-pentanone, cyclohexanone, and cyclopentanone were purchased from Aldrich. Other commercially available chemicals were laboratory grade reagents from local suppliers. They were used without further purification, except for the aromatic aldehyde, which was purified by distillation.

^{1}H NMR spectra of samples were recorded at a Varian-500 spectrometer. Tapping mode atomic force microscopy (AFM) measurements were performed using a multimode SPM from Digital Instruments with a Nanoscope IIIa Controller. X-ray diffraction (XRD) patterns were recorded on a Philips X'PERT-Pro-MPD diffractometer using Cu K_α radiation (λ = 1.542 Å). A continuous scan mode was used to collect 2θ from 5° to 40°. Fourier transform infrared (FT-IR) spectra were obtained as potassium bromide pellets with a resolution of 4 cm^{-1} and 32 scans in the range 400–4000 cm^{-1} using an AVATAR 370 Thermo Nicolet spectrophotometer. Elemental analyses of N were carried out on Vario EL III Elemental analyses made in Germany. The thermogravimetric and differential thermogravimetric (TG–DTG) analysis was performed on Netsch STA449c. The sample weight was *ca.* 10 mg and was heated from room temperature up to 800 °C with 10 °C/min using alumina sample holders. Analytical high performance liquid chromatography (HPLC) was carried out on Waters 2695 Separations Module with Waters 2996 photodiode array detector using Daicel chiralpak OB-H, AD-H or AD columns.

2.2. Preparation of L-proline/GO hybrid

In the experiments, GO was prepared by the oxidation of high-purity graphite powder (99.9999%, 200 mesh) with H_2SO_4/$KMnO_4$ according to the method of Hummers and Offeman [32]. After repeated washing of the resulting yellowish-brown cake with hot water, the powder of GO was dried at room temperature under vacuum overnight. FT-IR (KBr): 3390, 3132, 1735, 1621, 1224, 1050, 581 cm^{-1}.

The mixture of the dried GO (0.1 g) and L-proline (0.2 g) was sonicated in deionized water for 0.5 h and further stirred at room temperature for 24 h. After centrifugal separation by using an Eppendorf 5804 centrifuge operated at 10,000 rpm for 15 min, the precipitate was collected and dried overnight under vacuum to give brown flake solid of **L-proline/GO** hybrid. FT-IR (KBr): 3369, 2976, 2741, 2301, 1617, 1398, 1326, 1163, 1036, 837, 775, 673, 620 cm^{-1}. The L-proline content in the **L-proline/GO** hybrid is 4.06 mmol/g, which was determined according to the content of nitrogen element in **L-proline/GO** hybrid analyzed by elemental analyses.

For comparison, we also prepared the graphite-supported L-proline catalyst (L-proline/graphite) and the active carbon-supported L-proline catalyst (L-proline/AC) according to the above similar preparation procedure. L-proline content in the prepared catalysts was also measured in terms of nitrogen element percentage as obtained from nitrogen elemental analyses results. The results are listed in Table 1.

2.3. General procedure for the direct asymmetric aldol reaction

2.3.1. Typical procedure for the asymmetric aldol reactions of acetone with various aryl aldehydes

A mixture of catalyst (0.035 g, 0.14 mmol L-proline content in the **L-proline/GO** hybrid) and acetone (4 ml) was stirred at 30 °C for 10 min. Subsequently, the corresponding aromatic aldehyde (0.5 mmol) was added. The resulting mixture was stirred at room temperature until the reaction was judged to be complete based on TLC analysis. The catalyst was then separated by centrifugation. The upper organic phase with the product was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel (Acros, 40–60 μm, 60 Å, eluent hexane/ethyl acetate 5:1). Enantiomeric excess (*ee* value) was determined by HPLC on Daicel chiralpak OB-H or AD columns.

2.3.1.1. (4R)-Hydroxy-4-(2-nitrophenyl)-butan-2-one 1. Enantiomeric excess was determined by HPLC with a Daicel chiralpak OB-H column (i-PrOH/hexane = 15:85), 25 °C, 254 nm, 1 ml/min; major antienantiomer t_R 8.4 = min and minor antienantiomer t_R = 7.3 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95–7.42 (m, 4H), 5.68 (d, J = 10.7 Hz, 1H), 3.73 (s, 1H), 3.15–2.72 (m, 2H), 2.24 (s, 3H).

2.3.1.2. (4R)-Hydroxy-4-(4-nitrophenyl)-butan-2-one 2. Enantiomeric excess was determined by HPLC with a Daicel chiralpak OB-H column (i-PrOH/hexane = 15:85), 25 °C, 254 nm, 1 ml/min; major antienantiomer t_R = 14.0 min and minor enantiomer t_R = 16.1 min. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.22–7.28 (m, 4H), 5.27 (s, 1H), 3.67 (s, 1H), 2.87 (d, J = 6.7 Hz, 2H), 2.23 (s, 3H).