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Article

Chitosan-supported cinchonine as an efficient organocatalyst for direct asymmetric aldol reaction in water

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ABSTRACT

Chitosan-supported succinic anhydride-cinchonine (CTS-SA-CN) was synthesized via a two-step route with succinic anhydride as the linker. The catalyst was used to promote the direct asymmetric aldol reaction between cyclohexanone and a variety of aromatic aldehydes in aqueous medium. Aldol adducts were obtained in excellent yields (up to 99%) and good enantioselectivities (up to 96% ee). The CTS-SA-CN catalyst was successfully recycled simply by filtration after use, and was reused 5 times without any significant loss of activity.

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1. Introduction

Among the huge variety synthetic organic reactions, asymmetric aldol reactions are effective in achieving important and straightforward routes to desired C–C backbones, while also affording valuable optically active β -hydroxyl carbonyl compounds [1–6]. With the introduction of increasingly stringent environmental protection laws, there is significant pressure on synthetic chemists to develop highly efficient synthetic routes that exert minimal influence on the environment. The development of highly stereoselective aldol reactions is a part of this trend, and interest in this area has soared in the past few decades [7,8]. Therefore, considerable research effort has been devoted to the development of commercial biocatalysts such as proline, proline derivatives, and cinchona alkaloid [9–13]. Cinchona alkaloids, although less popular than proline or proline derivatives, have also aroused much interest as potential organocatalysts for aldol reactions [14,15]. For example, Paradowska et al. [16] reported that quinine or quinidine is able to

catalyze the aldol reaction with modest yield and stereoselectivity. Liu's group [17] and Kacprzak's group [18] prepared cinchona-derived amines, and found that they mediated aldol reactions between cyclohexanone or acetol and aromatic aldehydes with high enantioselectivity.

According to previous reports [14,19], small organic molecules such as amino acids and cinchona alkaloids with important applications in the field of asymmetric catalysis are difficult to recycle and reuse, which detracts from the sustainability of the resources and the process. To overcome these deficiencies, researchers have turned to the immobilization of small organic molecules [20] with the assistance of organic synthetic polymers [21] such as polystyrene [22–25] and polyethylene glycol [26,27], as well as inorganic materials like silicone [28–30] or ionic liquids [31,32]. Thus, it is expected that the environmental advantages of biopolymers will see them recognized as viable alternative supports of small organic molecules used for asymmetric catalysis [33].

Chitosan (CTS), obtained by the deacetylation of chitin, is

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the most abundant biopolymer in nature after cellulose. This material is of special interest [34] because it can be used as an active support for polymer-supported metal catalysts [35–37], while chitosan hydrogel and aerogel can be used as green and recyclable catalysts for aldol or Knoevenagel reactions [38,39]. However, less work is currently devoted to the preparing chitosan-supported organocatalysts and evaluating the performance for asymmetric aldol reactions in water (an environmentally friendly solvent) than in organic solvents. In our current work, chitosan-supported cinchonine (CN) was prepared with succinic anhydride (SA) as the linker, and its catalytic performance in asymmetric aldol reactions between cyclohexanone and various aromatic aldehydes in water was investigated. Our main focus was on providing an efficient, recyclable, operationally simple, and environmentally friendly catalyst for the aldol protocol.

2. Experimental

2.1. General procedures and instruments

Commercial grade reagents and solvents were used as received except when specific purification procedures were recommended. Thin layer chromatography (TLC) was conducted on GF254 silica gel plates. Infrared spectra were recorded with an Avatar 360 Fourier transform infrared spectrometer (FTIR; Nicolet). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400M spectrometer (Bruker), and the chemical shifts of ^1H NMR spectra were reported in relation to tetramethylsilane ($\delta = 0$). Analytical high-performance liquid chromatography (HPLC) was performed on an Agilent 1100 system (Agilent) equipped with a diode array ultraviolet detector. Separation was achieved using a Chiralpak AD column (Daicel).

2.2. Synthesis of succinic anhydride-cinchonine (SA-CN)

Cinchonine (1.2 g) and dichloromethane (10 mL) were added to a 50 mL round-bottomed flask with stirring. Succinic anhydride (0.8 g) was dissolved in 25 mL of dichloromethane and the solution was added dropwise into the reaction flask with 4-dimethylaminopyridine (DMAP, 0.0244 g) as the catalyst. The reaction mixture was magnetically stirred at 50 °C for 5–6 h. Upon completion, the solvent was removed in vacuo to leave the crude target product as a light yellow solid. The crude product was dissolved in 25 mL of water and the solution was heated at 95 °C for 5–10 min in a water bath, followed by cooling to room temperature, and extraction with chloroform (3 × 20 mL). The organic fractions were combined, dried over anhydrous Na_2SO_4 , and filtered before the solvent was evaporated to give 1.32 g of white solid product (final purified target product) in 84% yield. The purified product was directly used for structural characterization and evaluation of catalytic performance. FTIR: 3439, 3072, 2938, 2878, 1744, 1637, 1593, 1571, 1510, 1459, 1384, 1239, 1204, 1151, 993, 924, 840, 805, 764, 638, 470 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta = 8.85$ (d, $J = 4.4$ Hz, H), 8.22 (d, $J = 8.4$ Hz, H), 8.05–8.01 (m, 1H), 7.67–7.62 (m, 1H),

7.56–7.52 (m, 1H), 7.38 (d, $J = 4.4$ Hz, 1H), 6.83 (d, $J = 2.8$ Hz, 1H), 6.09–5.99 (m, 1H), 5.24–5.18 (m, 2H), 3.38–3.28 (m, 1H), 3.17 (m, 2H), 2.81 (m, 2H), 2.73–2.59 (m, 3H), 2.41 (m, 1H), 2.18 (m, 1H), 1.89 (m, 1H), 1.72–1.53 (m, 3H), 1.24 (m, 1H). Mass spectrometry (MS) (ESI, m/z): $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$ $[\text{M}-\text{H}]^-$ calculated 393.19, found 392.9.

2.3. Preparation of CTS-SA-CN catalyst

Dicyclohexylcarbodiimide (DCC, dehydrating agent, 0.82 g), SA-CN (1.32 g), CTS (0.6 g), and dichloromethane (15 mL) were added to a 50 mL round-bottomed flask in the presence of a small amount of triethylamine as the catalyst. The mixture was stirred at 40 °C for 48 h. Upon completion of the reaction, the mixture was filtered, and the residue was sequentially washed with dimethylformamide, dichloromethane, and ethanol. The residue was dried under vacuum to give the target product CTS-SA-CN (0.76 g) as a light yellow solid.

2.4. General procedure for direct aldol reaction

Substituted benzaldehyde (0.2 mmol) was added to a reaction solution that contained cyclohexanone, a known amount of catalyst, and water or alternative solvent. The reaction was allowed to proceed at room temperature with stirring for a set duration while the reaction system was monitored by TLC. Upon completion of the reaction, the mixture was filtered and the filtrate was extracted with ethyl acetate. The organic fractions were combined, dried over anhydrous Na_2SO_4 , filtered, and the solvent removed. The concentrate was purified by TLC on silica gel (ethyl acetate/petroleum ether eluent) to give pure aldol adducts. Characterization of aldol products was performed according to published procedures [40].

2.5. Recyclability of CTS-SA-CN catalyst

After the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone, the CTS-SA-CN catalyst was collected by vacuum filtration. The filtered CTS-SA-CN catalyst was washed with ethanol and dichloromethane, and then oven-dried for 24 h to be ready for reuse without further purification.

3. Results and discussion

Scheme 1 shows the two-step route to synthesize the chiral CTS-SA-CN organocatalyst. Briefly, SA-CN is synthesized in the first step using DMAP as catalyst. SA-CN is then allowed to react with CTS and DCC in dichloromethane as the second step to obtain chiral CTS-SA-CN catalyst, which was confirmed by FTIR spectroscopy. Figure 1 shows the FTIR spectra for chitosan and CTS-SA-CN catalyst. In the spectrum of the catalyst, the broad band at around 3448 cm^{-1} was attributed to hydroxyl stretching, while the sharper absorption at 3328 cm^{-1} was assigned to the amide. The absorptions at 2928 and 2851 cm^{-1} were ascribed to aliphatic stretching of the CH_2 in the SA-CN. The enhanced absorption at 1627 and 1575 cm^{-1} were assigned to the amide ($\nu_{\text{N-H}}$) and amino groups, while the peak at 642 cm^{-1} was

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