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Calixarene-proline functionalized iron oxide magnetite nanoparticles (Calix-Pro-MN): An efficient recyclable organocatalyst for asymmetric aldol reaction in water

Ezgi Akceylan[a], Arzu Uyanik[a], Serkan Eymur[b], Ozlem Sahin[a], Mustafa Yilmaz[a,*]

[a] Selcuk University, Department of Chemistry, 42031 Konya, Turkey
[b] Giresun University, Department of Energy Systems Engineering, 28200 Giresun, Turkey

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ABSTRACT

Calix[4]arene-based chiral organocatalyst derived from *L*-proline supported onto well-defined (15 ± 3 nm) magnetic Fe_3O_4 nanoparticles was used as a highly active, recoverable, and reusable catalyst for the asymmetric aldol reaction in water without need for organic solvents. The chiral organocatalyst showed high catalytic activity (up to 94%), enantioselectivity (up to 93%) and diastereoselectivity (up to 97:3) for the reaction between cyclohexanone and aromatic aldehydes. The catalyst could easily separated using an external magnetic field and reused for several times without any significant loss of activity.

1. Introduction

The asymmetric aldol reaction has widely been considered as one of the most important carbon–carbon bond-forming reactions applied in the synthesis of β-hydroxy carbonyl compounds, which are valuable synthetic building blocks [1,2]. Since List and Barbas described the direct aldol reaction catalyzed by *L*-proline in the early of 2000s [3], *L*-proline has attracted great attention in asymmetric synthesis because it is efficient, inexpensive, environmentally safe, and available in both enantiomeric forms [4–6]. Unlike natural aldolases that efficiently catalyze the aldol reaction in an aqueous environment, organocatalytic reactions catalyzed by *L*-proline and its derivatives have typically been carried out in polar organic solvents such as DMSO, DMF, or $CHCl_3$. The catalytic inefficiency of *L*-proline in water is mainly due to the fact that the high dielectric constant of water screens charge-charge interactions and disrupts hydrogen bonds [7–11] Instead, water is an ideal solvent for chemical transformations due to its environmentally benign nature, safety, and low cost. Therefore, it is highly desirable to develop new organocatalysts that can carry out organic transformations efficiently and selectively in water media. A thorough literature study shows that the attachment of hydrophobic fragments to the catalyst structure is a key concept for obtaining a high stereoselectivity in water media [12–14].

There have been fruitful developments of various *L*-proline derivatives for a wide variety of fundamental transformations in the presence of water in synthetic organic chemistry. However, poor recovery of these organocatalysts from the reaction medium has often hindered their use in many applications, including fine chemical synthesis. By far, one of the most efficient ways to address these restrictions is the heterogenization of active catalytic molecules, thus generating easily recoverable and reusable catalysts. In this regard, heterogeneous proline catalysis via covalent bonding interaction has recently been reported using a wide variety of supports, such as polymer, silica, ionic liquid, and cyclodextrin [15–18]. However, the main disadvantage associated with the immobilization of organocatalysts on these supports is the need to filtrate the catalyst from the reaction mixture. In the field of sustainable organocatalytic processes, the development of an efficient and water-compatible *L*-proline catalyst for direct asymmetric aldol reaction in water still remains challenging.

Magnetic nanoparticles (MNPs), especially Fe_3O_4 coated with silica ($SiO_2@Fe_3O_4$), are considered as interesting supports for the immobilization of homogeneous catalysts. MNPs are easily dispersed in the reaction medium, they have a large surface area, and they are simply separated via magnetic force from the reaction medium [17,19–25]. Therefore, the use of magnetically separable nano-organocatalysts has emerged as a powerful tool for

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* Corresponding author. Tel.: +90 332 2233873; fax: +90 332 2412499.
E-mail address: myilmaz42@yahoo.com (M. Yilmaz).

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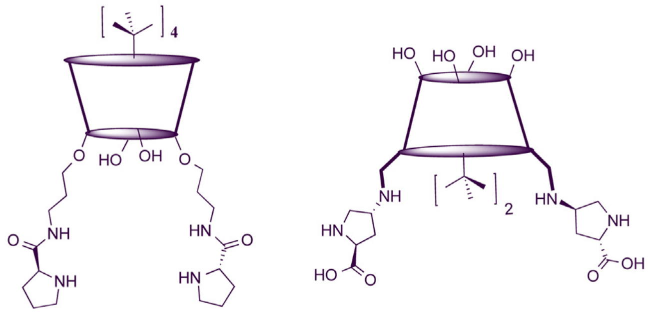
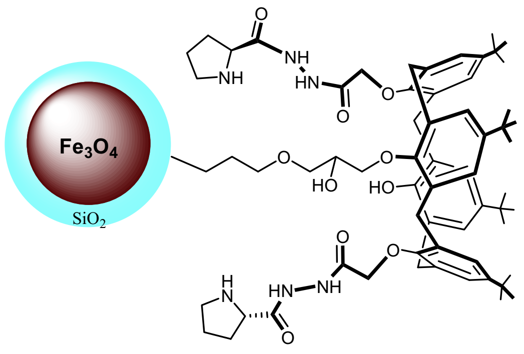


Lower rim functionalized calixarene

Upper rim functionalized calixarene

Fig. 1. Structure of proline-substituted calixarene derivatives as organocatalysts for aldol reactions in water.



Calix-Pro-MN

Fig. 2. Schematic representation of magnetically recoverable organocatalysts.

asymmetric catalysis in recent years [19–25]. However, among all of the reported systems, most catalysts work in only organic solvents, and only few of them work well in the presence of water. For example, Wang et al. prepared Fe_3O_4@SiO_2-supported *S*-diarylprolinol trimethylsilyl ether, which is efficient and recyclable for asymmetric Michael addition reaction in dichloromethane [26]. However, the nanocatalyst is not active when only water is used as a solvent. Kong et al. very recently developed *L*-proline-based ionic-liquid-functionalized MNPs as a catalyst for asymmetric aldol reaction in water [27]. While previous studies highlighted the inspiring possibilities with recyclable catalysts, there is still a need to investigate novel nanoparticle-supported organocatalysts for the enantioselective reactions in water.

Calixarenes, with their conformational and structural flexibility, are one of the best-known supramolecular organizations, along with cyclodextrins, cucurbiturils, and crown ethers [28]. Since they can be modified at both the upper and lower rims, calixarenes have generated great interest as important receptors in organic synthesis and for applications as supramolecular receptors for molecular recognition, self-assembly, catalysis, and separation science [29–32]. We have recently reported a direct aldol reaction in water using *p*-tert-butylcalix[4]arene-based chiral organocatalysts bearing a chiral proline moiety at both the upper and lower rims of the calix[4]arene units (Fig. 1) [33,34]. When considering the catalytic inefficiency of the *L*-proline for the aldol reaction in water, we can easily assume that the hydrophobic part of the functionalized calix[4]arene is responsible for the observed high reactivity and selectivity in water.

In ongoing study for the improvement of sustainable and benign protocols for asymmetric synthesis, we envisioned: (i) using the hydrophobic cavity of calixarenes as a platform for the aldol reaction in water, (ii) calixarene-functionalized iron oxide magnetite nanoparticles as a platform for magnetic separation, and (iii) *L*-proline moiety as an active organocatalyst. As shown in Fig. 2, we investigated the use of calix[4]arene-based *L*-proline-modified magnetic nanoparticles as a sustainable organocatalyst.

2. Experimental

2.1. Materials and reagents

Thin layer chromatographic (TLC) analyses were carried out on precoated $60F_{254}$ slides (Merck). Generally, reagent grade solvents were dried by standard procedures, and then distilled prior to use. Commercially available chemicals were used without any purification. When required, reactions were conducted under a nitrogen atmosphere employing oven-dried glassware. Analytical normal phase high performance liquid chromatography (HPLC) was carried out using an Agilent 1200 instrument equipped with a diode array detector (214 and 254 nm). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained at ambient temperature on a Varian spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal reference. Coupling constants (J) are reported in Hz. Elemental analyses were obtained on a Leco CHNS-932 analyzer. Perkin Elmer 100 FTIR spectrometer was used for FTIR spectra.

2.2. Synthesis

The compounds **1**–**3** were synthesized by procedures published in the literature [35,36]. Silica based magnetic nanoparticles (Fe_3O_4-MN) was prepared according to literature procedure [37]. Compound **4** and magnetic derivatives of calix[4]arene (Calix-Pro-MN) are herein reported for the first time.

2.3. Synthesis of compound 4

Boc-*L*-Proline (1.05 g, 4.2 mmol) and N,N′-dicyclohexylcarbodiimide (DCC) (1.2 g) were dissolved in dichloromethane (20 mL) and cooled down to 0 °C. After the solution was stirred for 30 min, a solution of compound **3** (1.55 g, 1.96 mmol) in dichloromethane (100 mL) was added and the mixture was stirred 60 h at room temperature. Solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and the organic layer extracted three times with water. The combined organic phases were dried (anhydrous $MgSO_4$), the solvent was removed under reduced pressure. Compound **4** was obtained in 73% yield; m.p. 132–134 °C. IR: 1665, 1698 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.05 (s, 18H, But), 1.27 (s, 18H, But), 1.44 (s, 18H, But), 1.70–1.98 (m, 8H, CH_2CH_2), 3.45–3.72 (m, 8H, $ArCH_2Ar$, CH_2N), 4.10–4.33 (bs, 4H, $ArCH_2Ar$), 4.46 (bs, 2H, N*CH*CO), 4.71 (s, 4H, CH_2O), 6.96 (s, 4H, ArH), 7.04 (s, 4H, ArH), 8.10 (s, 2H, NHCO), 8.80–9.20 (bs, 2H, NHCO), 9.55–9.86 (bs, 2H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): 171.64 (NHCO), 166.01 (NHCO), 157.13 (NCOO), 154.96, 154.17, 149.42, 142.85, 132.48, 127.03, 126.26, 125.72, 80.20, 58.40, 54.37, 50.0, 49.11, 47.44, 34.15, 33.85, 31.60, 31.00, 29.10, 28.40 and 24.58. Anal. Calcd for: $C_{67}H_{92}O_{12}N_6$: C, 68.78; H, 7.98; N, 7.08%. Found: C, 68.32; H, 7.54; N, 7.50%.

2.4. Synthesis of compound 5

Compound **4** (0.25 g, 0.21 mmol) was dissolved in mixture of TFA/CH_2Cl_2 (1:4) (20 mL), and stirred for 10 h at room temperature. The mixture was basified with concentrated ammonia solution and extracted with dichloromethane (3× 15 mL). After the removal