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Research Note

An unexpected inversion of enantioselectivity in direct asymmetric aldol reactions on a unique L-proline/γ-Al_2O_3 catalyst

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Abstract

L-proline adsorbed on γ-Al_2O_3 unexpectedly switches the enantioselectivity of the direct asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde from 68% ee (*R* configuration for free L-proline catalyst) with 80% yield to 21% ee (*S* configuration) with 78% yield. The inversion of enantioselectivity was also observed in the direct asymmetric aldol reactions of acetone with several other aromatic aldehydes catalyzed by the L-proline adsorbed on γ-Al_2O_3. This inversion phenomenon is found to be general for different types of amino acids adsorbed on γ-Al_2O_3. The hydroxyl groups on γ-Al_2O_3 are found to be involved in the inversion induction of enantioselectivity in these direct asymmetric aldol reactions.

Keywords: Asymmetric catalysis; Aldol reactions; L-Proline/γ-Al_2O_3 catalyst; Inversion; Enantioselectivity

1. Introduction

The aldol reaction is one of the most important transformations in organic synthesis due to its usefulness in constructing stereochemically complex natural and nonnatural products [1,2]. Over the past decades, asymmetric methodologies for this reaction have been developed, of which preformed enolate is an unavoidable necessity in most cases [3]. In 1997, Yamada et al. reported the first direct asymmetric aldol reactions of aldehydes with unmodified ketones catalyzed by heterobimetallic bifunctional transition-metal complexes [4]. Recently, List et al. [5] reinvestigated the Hajos–Eder–Sauer–Wiechert reaction [6,7] and found that the amino acid proline is an effective organocatalyst for intermolecular direct asymmetric aldol reactions. However, 20–30 mol% proline was required, and only modest enantioselectivity was obtained for most of the aldol reactions [5,8]. Several proline derivatives and their structural analogues have been synthesized, with the aim of improving catalyst activity and enantioselectivity [9–12]. To further improve and recycle the amino acid catalyst for direct asymmetric aldol reaction, proline and its derivatives have been covalently immobilized on solid supports [13–16]. Compared with covalent immobilization, adsorption of a chiral molecule onto a solid surface could be a more simple and promising means for heterogenizing chiral catalysts [17–21]. An attractive feature of this method is that the major enantiomer can be reversed under certain conditions [19,20,22–27]. The extensive studies on this chiral inversion on a solid surface help clarify the adsorption mode of modifier and its interaction with reactant and hence are helpful in explaining the origin of the reaction enantioselection.

Some attempts to immobilize L-proline on silica by simple adsorption for direct asymmetric aldol reactions have been reported [8], and lower chemical and optical yields were obtained compared with those obtained using free L-proline as catalyst. However, an inversion phenomenon was not observed. Herein, we report that a novel catalyst for direct asymmetric aldol reactions is formed on the adsorption of L-proline on γ-Al_2O_3, which unexpectedly affords products with the absolute configuration opposite to that obtained with free L-proline as the catalyst. Our finding may generate a new opportunity for understanding and designing organo-inorganic hybrid catalysts for chiral synthesis.

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2. Experimental

Chemicals and γ-Al_2O_3 (Sasol, BET: 209 m^2/g) were commercially obtained. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in δ relative to TMS, and coupling constants J are given in Hz. Infrared spectra were recorded on a Nicolet Nexus 470 spectrometer. HPLC was performed on an HPLC 1100 device using Chiralpak AD-H (5 μm, 4.6 × 250 mm, Daicel Chemical Industries, Ltd.) and Hypersil ODS (5 μm, 4.6 × 100 mm, Agilent) columns. UV-Raman spectra were recorded at room temperature using a Jobin–Yvon T64000 triple-stage spectrograph with a spectral resolution of 2 cm^{-1}. The 244-nm line from a Coherent Innova 300 Fred laser was used as excitation source, and the power of the laser at the sample was <1.0 mW.

γ-Al_2O_3 was silylated as described previously [28,29]. The γ-Al_2O_3 was preheated at 150 °C for 3 h under vacuum. After 1 g of γ-Al_2O_3 was dispersed in 20 ml of toluene, 5 ml of the silylating agent chlorotrimethylsilane (TMSCl) was added to the mixture. The suspension was refluxed for 12 h under N_2 atmosphere, and then the sample was filtered, washed several times with ethanol, and dried in vacuo (60 °C) overnight.

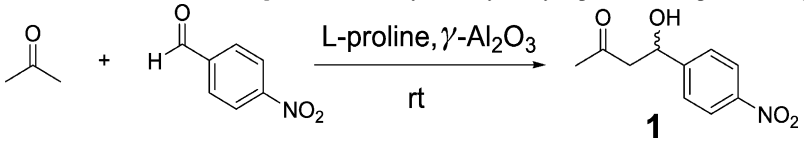
To a mixture of acetone (2 ml) and γ-Al_2O_3 (129 mg), L-proline (17.2 mg, 0.15 mmol) was added, followed by the corresponding aldehyde (0.5 mmol). The resulting mixture was stirred at room temperature for 5.5–48 h. The reaction mixture was treated with saturated ammonium chloride solution, and then γ-Al_2O_3 was filtered off. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layers were dried with anhydrous $MgSO_4$ and evaporated. Purification by silica gel column chromatography gave the pure aldol product. Ee was determined by HPLC on a Chiralpak AD-H column. Enantioselectivity is expressed as ee (%) = 100 × |R − S|/(R + S).

3. Results and discussion

Initially, we investigated the model aldol reaction of acetone with *p*-nitrobenzaldehyde catalyzed by L-proline in the presence of γ-Al_2O_3 (Table 1). The L-proline-catalyzed aldol reaction gave the aldol product **1** with *R* configuration and 68% ee, whereas racemic **1** was observed for the γ-Al_2O_3-catalyzed aldol reaction (Table 1, entries 1 and 2). When γ-Al_2O_3 was added to the aldol reaction mixture (0.5 mmol *p*-nitrobenzaldehyde, 2 ml acetone, and 30 mol% L-proline) at room temperature, the ee value of **1** was reduced, and the reaction became racemic when the ratio of L-proline and γ-Al_2O_3 reached 6.0 (Table 1, entries 3–5). When the concentration of γ-Al_2O_3 was increased further, **1** was unexpectedly obtained with an *S* configuration, and its ee values increased from 4 to 21% (Table 1, entries 6–8). The L-proline/γ-Al_2O_3 catalyst, prepared by a simple adsorption of L-proline on γ-Al_2O_3, showed the *S* configuration again and approximately the same enantioselectivity as that for the mixture of L-proline and γ-Al_2O_3 at a ratio of 3.3 (Table 1, entries 7 and 9). These results suggest that a unique catalyst is formed on the adsorption of L-proline on γ-Al_2O_3.

To investigate the adsorption of L-proline on γ-Al_2O_3, UV-Raman spectra of L-proline in solid form and on γ-Al_2O_3 were obtained (Fig. 1). The band at 1380 cm^{-1} corresponding to the symmetric stretching vibration of the carboxylate group of free L-proline shifted to 1390 cm^{-1} after L-proline was adsorbed on γ-Al_2O_3. The Raman bands of L-proline became broad, and some characteristic bands disappeared for the adsorbed L-

Table 1
Aldol reaction of acetone with *p*-nitrobenzaldehyde catalyzed by L-proline in the presence of γ-Al_2O_3



Entry	L-Prolin: γ-Al_2O_3 (molecules/nm^2)	Reaction time (h)	Yield (%)[a]	Ee (%)	Config.
1	0[b]	48	68	0	*Rac.*
2	No γ-Al_2O_3	8	80	68	*R*
3	25.0	5.5	67	52	*R*
4	7.2	5.5	61	22	*R*
5	6.0	5.5	68	0	*Rac.*
6	5.0	5.5	80	4	*S*
7	3.3	5.5	78	21	*S*
8	2.5	5.5	80	18	*S*
9	3.3[c]	5.5	65	20	*S*
10	3.3[d]	5.5	60	0	*Rac.*
11	3.3[e]	5.5	62	64	*R*
12	3.3[f]	27	78	64	*R*

[a] Isolated yield after separation by silica gel.
[b] γ-Al_2O_3 as catalyst.
[c] The as-synthesized catalyst.
[d] γ-Al_2O_3 was preadsorbed by pyridine as described in Ref. [30].
[e] α-Al_2O_3, BET: 4 m^2/g.
[f] Silylated γ-Al_2O_3.

proline. These changes indicate that L-proline strongly interacts with γ-Al_2O_3 and that the carboxylate groups are involved in the interaction [31–33]. The L-proline/γ-Al_2O_3 preadsorbed with pyridine resulted in the aldol product **1** with a dramatically reduced ee value, clearly showing that the acidic sites on γ-Al_2O_3 play an important role in the aldol reaction, because the preadsorbed pyridine can occupy these sites (Table 1, entry 10). To further clarify the roles of the surface sites in the asymmetric aldol reaction, α-Al_2O_3 and silylated γ-Al_2O_3 (both of which have much less surface hydroxyl groups and hence are less likely to interact with proline) were used as supports; they both gave results similar to those obtained with the free L-proline (Table 1, entries 11 and 12). These results suggest that the surface hydroxyl groups on γ-Al_2O_3 are essential to induce the inversion of enantioselectivity. It is also interesting that the inversion of enantioselectivity occurred for a L-proline/γ-Al_2O_3 ratio of about 3–5 molecules/nm^2 (Table 1, entries 6–9). This value is in accordance with the surface hydroxy concentration of γ-Al_2O_3 (about 4 molecules/nm^2) [34], suggesting that the new catalyst is formed only when L-proline interacts with surface hydroxyl group. The chiral inversion phenomenon was also observed for other natural amino acids adsorbed on γ-Al_2O_3. Fig. 2 shows that seven other natural amino acids, when adsorbed on γ-Al_2O_3, can induce the inversion of enantioselectivity and give aldol product **1** with an *S* configuration and ee values of 3–16%.

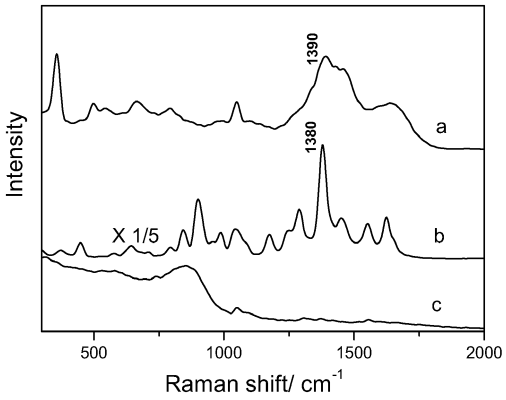
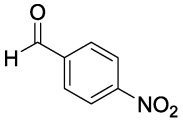
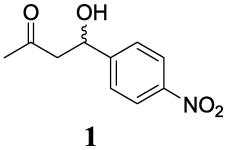
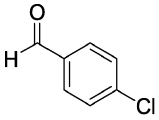
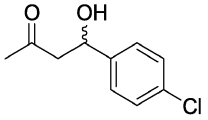
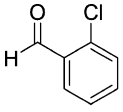
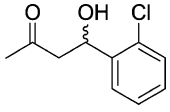
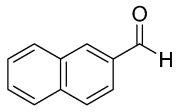
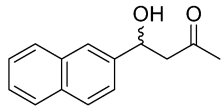
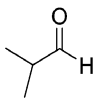
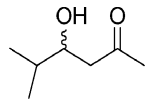


Fig. 1. UV-Raman spectra of (a) L-proline adsorbed on γ-Al_2O_3, (b) L-proline in solid form, and (c) γ-Al_2O_3.

The aldol reactions of acetone with several other aldehydes catalyzed by L-proline/ γ-Al_2O_3 were also examined (Table 2). The results demonstrate that the aldol reactions of all the aromatic aldehydes with acetone can be catalyzed by L-proline/ γ-Al_2O_3 to give the corresponding aldol products **1–4** with a reversed *S* configuration, except for the aliphatic isobutylaldehyde (Table 2). Therefore, it seems that the inversion phenomenon is quite general—namely, the coupling of L-proline with

Table 2
Cross aldol reactions of acetone with aldehydes catalyzed by free L-proline and L-proline adsorbed on γ-Al_2O_3

Aldehyde acceptor	Product	Catalyst	Reaction time (h)	Yield[a]	Ee (%)	Config.
	 **1**	L-proline	8	80	68	*R*
		L-proline/γ-Al_2O_3	5.5	78	21	*S*
	 **2**	L-proline	40	78	4	*R*
		L-proline/γ-Al_2O_3	31	38	19	*S*
	 **3**	L-proline	29	78	65	*R*
		L-proline/γ-Al_2O_3	23	27	14	*S*
	 **4**	L-proline	48	52	60	*R*
		L-proline/γ-Al_2O_3	40	18	8	*S*
	 **5**	L-proline	24	85	83	*R*
		L-proline/γ-Al_2O_3	18	57	9	*R*

[a] Isolated yield after separation by silica gel.

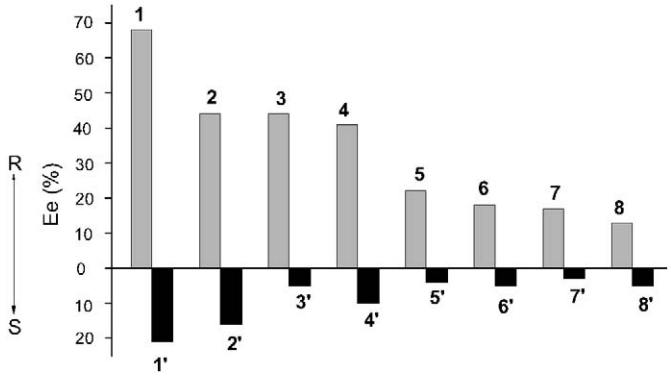
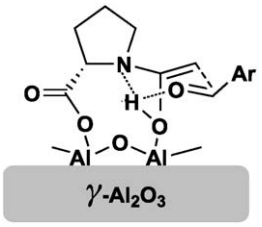


Fig. 2. Ee values of the direct asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde catalyzed by free natural amino acids (light gray bars) and by the adsorbed natural amino acids on γ-Al_2O_3 (black bars). 1: L-proline; 1′: L-proline/γ-Al_2O_3; 2: L-leucine; 2′: L-leucine/γ-Al_2O_3; 3: L-alanine; 3′: L-alanine/γ-Al_2O_3; 4: L-tryptophan; 4′: L-tryptophan/γ-Al_2O_3; 5: L-phenylalanine; 5′: phenylalanine/γ-Al_2O_3; 6: L-threonine; 6′: L-threonine/γ-Al_2O_3; 7: L-glutamine; 7′: L-glutamine/γ-Al_2O_3; 8: L-lysine; 8′: L-lysine/γ-Al_2O_3.



Scheme 1. The assumed intermediate complex of the asymmetric aldol reaction catalyzed by L-proline adsorbed on γ-Al_2O_3.

the γ-Al_2O_3 surface gives a organo-inorganic bifunctional catalyst for direct asymmetric aldol reactions. We assume that this catalyst functions via a proline–Al_2O_3 dual activation mechanism (Scheme 1). The amine group of the adsorbed proline activates acetone, and the hydroxyl group on γ-Al_2O_3 activates the carbonyl of *p*-nitrobenzaldehyde through hydrogen bonding [5,35,36]. The *Si* face of the aldehyde may be more easily attacked by the enamine on γ-Al_2O_3, resulting in formation of the product with an *S* configuration.

In conclusion, a functionally different catalyst from free L-proline is formed when L-proline absorbs on γ-Al_2O_3. The direct aldol reactions of acetone with aromatic aldehydes on the L-proline/γ-Al_2O_3 catalyst give products with configuration opposite to that observed with free proline as the catalyst. The hydroxyl groups on the γ-Al_2O_3 surface seem to be essential for the induction of inversion of enantioselectivity in these asymmetric aldol reactions. Although improvement of enantioselectivity remains necessary, the results should be significant in understanding and designing organo-inorganic hybrid catalysts for chiral synthesis.

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