An efficient silica-grafted poly-(L)-leucine catalyst for asymmetric epoxidation of α,β-unsaturated ketone

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Abstract

A new efficient covalent immobilization method for preparation of silica-grafted poly-(L)-leucine catalyst AP-PLL-Silica gel was developed. The AP-PLL-Silica gel catalyzed asymmetric epoxidation of benzalacetophenone, yielding optically active epoxy ketone in high enantioselectivity up to 97% e.e. The catalyst was easily separated and reused several times with no significant loss of activity and enantioselectivity.
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1. Introduction

The Juliá-Colonna reaction, catalyzed by poly(amino acid) such as poly-(L)-leucine or poly-(L)-alanine, is one of the most efficient methods for asymmetric epoxidation of electron-deficient α,β-unsaturated ketones [1–5]. In recent years the scope of the Juliá-Colonna asymmetric epoxidation has been extended largely including α,β-unsaturated ketones, esters and amides [6–15]. However, the most serious problem of the protocol is to handle the gel- or paste-like catalyst. To circumvent this problem, poly(amino acid) supported onto organic polymers through covalent bonds [16,17] or inorganic materials through simple physical absorption [6,8,18,19], and efficient procedure for the Juliá-Colonna expoxidation through poly-leucine catalysis have been explored [20–27]. We have reported the immobilization of poly(amino acid) on silica gel through covalent binding for the first time [28]. First, the silica was functionalized through the treatment with (3-aminopropyl)triethoxysilane (APTESi), and then the polymerization of (L)-leucine *N*-carboxyanhydride (NCA) was conducted using the functionalized silica as initiator to give

the silica-grafted poly-(L)-leucine catalyst Slilica gel-AP-PLL (Fig. 1).

Thus prepared covalently grafted catalyst Silica gel-AP-PLL has good activity, and could be separated easily from the reaction system. However, the enantioselectivity of epoxidation decreased evidently with the recycling. After two recycles the e.e.% was lower than 90% while after eight recycles the e.e.% dropped to 82%.

To improve the performance of the silica-grafted poly-(L)-leucine catalyst, herein we reported an ameliorative method for the covalent grafting of poly-(L)-leucine on silica gel. First, the polymerization of L-leucine NCA was initiated by APTESi which led to the formation of AP-PLL, and then the AP-PLL was covalently grafted on silica gel surface by the reaction of the Si–OH group with the terminal $(EtO)_3Si$ group to give the catalyst AP-PLL-Silica gel (Fig. 2).

2. Experimental

2.1. General

IR spectra of the catalyst in KBr pellets were measured on a Nicolet Nexus 670 FT-IR spectrometers. NMR spectra were obtained at a controlled temperature of 300 K on a Bruker Advance DXS 300 NMR spectrometer (7 T mag-
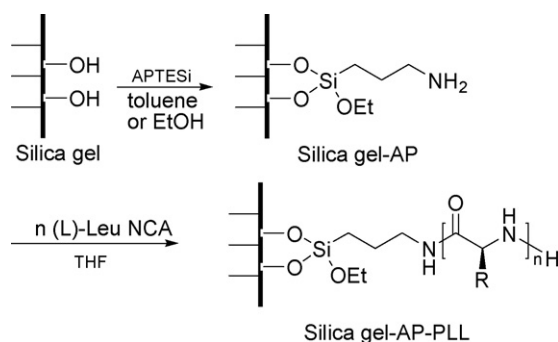
Fig. 1. Preparation of Silica gel-AP-PLL.

net) using a combination of cross polarization and magic angle spinning (CP/MAS). The enantiomeric excess was determined by chiral phase HPLC analysis with a Chiralpak AD-H column (fluent: 10% *i*-PrOH in hexane, UV detection at 254 nm).

2.2. Synthesis of AP-PLL-Silica gel catalyst

Under N_2 atmosphere, L-leucine NCA (5.0 g, 32 mmol) was dissolved in anhydrous THF (80 mL). APTESi was added, and the mixture was stirred for 72 h at room temperature. The silica gel (8.0 g, dried under vacuum at 120–140 °C for 6 h prior to use) was added, and stirred for another 24 h. After stirring anhydrous toluene (250 mL) was added, and then 200 mL solvent was distilled through water trap. The reaction mixture was cooled to room temperature, filtered, and the solid was thoroughly washed with methanol (60 mL) and diethyl ether (60 mL, stirring overnight) and dried under vacuum at room temperature (10.7 g).

2.3. Typical epoxidation procedure

To a solution of the benzalacetophenone (1.0 mmol) in DME (5 mL) and H_2O (5 mL) was added percarbonate (1.6 mmol). The mixture was stirred at room temperature until the reaction was complete (TLC). The catalyst was removed by rapid filtration and washed with ethyl acetate. The combined organic fractions were evaporated in vacuo to yield the crude epoxide.
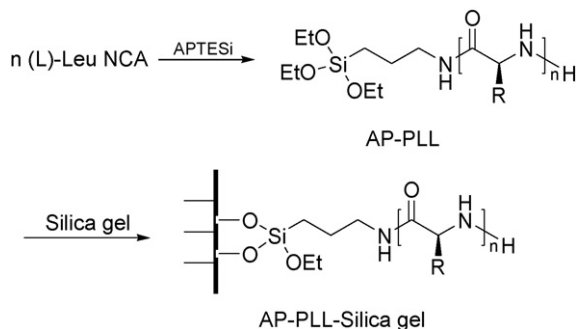

Fig. 2. Preparation of AP-PLL-Silica gel.

3. Results and discussion

### 3.1. Preparation of the AP-PLL-Silica gel catalyst

Using APTESi:L-leucine NCA ratio of 1:10, 1:30, 1:50, the polymerization of L-leucine NCA was initiated in anhydrous THF under N_2 atmosphere. After stirring for 72 h at room temperature, the silica gel was added, and the mixture was stirred sequentially for 24 h. Then the covalent silica-grafted AP-PLL-Silica gel catalyst was obtained after treatment with DME/H_2O.

The operational sequence greatly influenced the properties of catalysts. In our previous report [28], the covalently grafted catalyst Silica gel-AP-PLL was prepared as shown in Fig. 1. First, the silica gel was functionalized with APTESi to give Silica gel-AP, and then the Silica gel-AP was used to initiate the polymerization of L-leucine NCA. However, besides $-NH_2$, Si–OH group existing in Silica gel-AP could also initiate the polymerization of L-leucine NCA. Hence, the average chain length of poly-(L)-leucine was decreased, which directly influenced the properties of catalyst. In this paper, we have developed a new method; firstly using APTESi initiating the polymerization of L-leucine NCA led to the formation of AP-PLL, and then the AP-PLL was covalently grafted on silica gel (Fig. 2). The influence of the Si–OH group on the polymerization was avoided, which improved the performance of the catalysts.

It is worthy of pointing out that the treatment with DME/H_2O is necessary for improving the enantioselectivity of the catalyst, presumably because the treatment was favorable for opening the β-folded peptide chain to α-spiral ones [4]. Meanwhile, it was beneficial to the dissociation of the molecular cluster, which made the active point exposed.

3.2. Characterization of the AP-PLL-Silica gel catalyst

The infrared spectroscopy showed the characteristic absorption of L-leucine at 3308, 2960, 2869, 1654, 1541 and 1471 cm^{-1} for the N−H, C−H and C=O stretching bands, respectively. The solid state ^{29}Si CP/MAS NMR spectrum provided direct evidence for the incorporation of the covalently linked organic system (Fig. 3). For the grafting catalyst AP-PLL-Silica gel, besides the silica gel absorption peak at −90 to −110 ppm, three
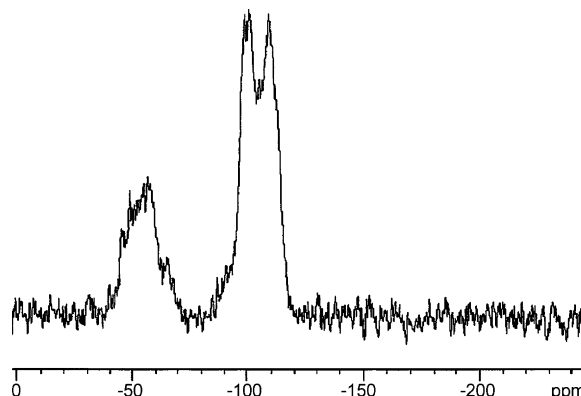
Fig. 3. The solid state ^{29}Si CP/MAS NMR spectrum of AP-PLL-Silica gel.

additional broad and overlapping signals appeared at -67, -57, and -46 ppm, which can be assigned to T_3, T_2 and T_1 organosilica species $[T_m = RSi(OSi)_m(OEt)_{3-m}, m = 1-3]$, respectively [29], with T_2 being the major organosilica species.
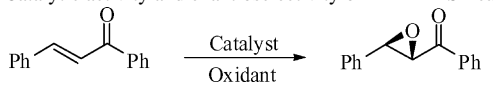
3.3. Performance of the AP-PLL-Silica gel catalyst

Using benzalacetophenone epoxidation in the Allen's system [30] as model reaction, the catalytic activity and enantioselectivity of the newly prepared catalyst AP-PLL-Silica gel, with a degree of polymerisation, $n = 30$, were evaluated through comparing with Silica gel-AP-PLL, silica-adsorbed catalyst Silica gel-Adsorb-PLL, and non-grafted catalyst n-BuNH-PLL, prepared by polymerization of L-leucine initiated with n-butylamine. The results are listed in Table 1.

Table 1 shows that the new silica-grafted catalyst AP-PLL-Silica gel efficiently catalyzed the chiral epoxidation of benzalacetophenone, and that the e.e.% of the product was up to 95% with 91% isolated yield (entry 1). The enatioselectivity of AP-PLL-Silica gel was notably high when compared with that of n-BuNH-PLL (entry 4), Silica gel-Adsorb-PLL (entry 3) and Silica gel-AP-PLL (entry 2), which indicated that the new grafting method was better than either the adsorbing method or the functionalized-silica gel initiating method.

To investigate the relationships between average chain length with catalytic property of AP-PLL-Silica gel, we contradistinguished the results of chiral epoxidation of benzalacetophenone, in the Allen's system with degree of polymerization $n = 10$, 30, 50 (Table 2). The influence of average chain length on the catalytic property was consistent with the results obtained with Silica gel-AP-PLL [28]. The catalytic activity and enantioselectivity improved with increasing chain length; when the degree of polymerization of poly-(L)-leucine (n) changed from 10 to 30, the yield was elevated from 86% to 91% (entries 1 and 2). The enantioselectivity also increased from 81% to 95% e.e. When the degree of polymerization was further increased to 50, the yield was increased to 95% with the enantioselectivity hardly improved (entry 3).

Table 1
Catalytic activity and enantioselectivity of AP-PLL-Silica gel[a]

Entry	Catalyst	Yield (%)[b]	e.e. (%)[c]
1	AP-PLL-Silica gel	91	95
2	Silica gel-AP-PLL	92	91
3	Silica gel-Adsorb-PLL	88	79
4	n-BuNH-PLL	93	87
5	AP-PLL-Silica gel[d]	92	84

[a] Benzalacetophenone 0.208 g (1.0 mmol), catalyst (treatment with DME/H$_2$O) 0.1 mmol, sodium percarbonate 0.24 g (1.6 mmol), DME 5 mL, H$_2$O 5 mL, stirring 4 h at room temperature, degree of polymerisation, $n = 30$.
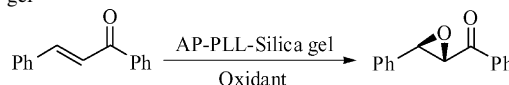[b] Isolated yield.
[c] HPLC analysis, Chiralpak AD-H chiral phase, mobile phase: n-hexane/isopropanol (90:1, v/v).
[d] Non-pretreated catalyst was used.

Table 2
Influence of average chain length on the catalytic property of AP-PLL-Silica gel[a]

Entry	Catalyst	n[b]	Yield (%)[c]	e.e. (%)[d]
1	AP-PLL-Silica gel	10	86	81
2	AP-PLL-Silica gel	30	91	95
3	AP-PLL-Silica gel	50	95	95

[a] Benzalacetophenone 0.208 g (1.0 mmol), catalyst (treatment with DME/H$_2$O) 0.1 mmol, sodium percarbonate 0.24 g (1.6 mmol), DME 5 mL, H$_2$O 5 mL, ambient temperature, 4 h.
[b] Degree of polymerization.
[c] Isolated yield with column chromatograph.
[d] HPLC analysis with Chiralpak AD-H chiral phase, mobile phase: n-hexane/isopropanol (90:1, v/v).

Table 3
Reusability of the AP-PLL-Silica gel catalyst[a]

Run	Catalyst (g)	Yield (%)[b]	e.e. (%)[c]
1	2.01	91	95
2	1.98	93	96
3	1.93	90	97
4	1.90	89	97
5	1.87	89	95
6	1.82	90	95

[a] Benzalacetophenone 0.208 g (1.0 mmol), catalyst (treatment with DME/H$_2$O) 0.07 mmol, sodium percarbonate 0.24 g (1.6 mmol), DME 5 mL, H$_2$O 5 mL, ambient temperature, 4 h.
[b] Isolated yield.
[c] HPLC analysis with Chiralpak AD-H chiral phase, mobile phase: n-hexane/isopropanol (90:1, v/v).

Reusability of the catalyst AP-PLL-Silica gel was demonstrated in the Allen's reaction system with $n = 30$. The results are summarized in Table 3. The recycled catalyst AP-PLL-Silica gel displayed excellent catalytic activity and enantioselectivity; the e.e.% was higher than 95%, and attained 97%. After recycle of six times, the catalytic activity and enantioselectivity were not notably decreased. The average loss of catalyst amounted to ca. 2% per run.

4. Conclusions

(1) The covalently silica-grafted catalyst AP-PLL-Silica gel was prepared by a new method; first, the polymerization of L-leucine NCA was initiated by APTESi which led to the formation of AP-PLL, and then the AP-PLL was covalently grafted on silica gel surface by the reaction of the Si–OH group with the terminal (EtO)$_3$Si group to give the catalyst AP-PLL-Silica gel. By this method the influence of –SiOH on the polymerization was avoided.

(2) The treatment with DMF/H$_2$O improved the enantioselectivity of the covalently silica-grafted AP-PLL-Silica gel catalyst.

(3) The AP-PLL-Silica gel catalyzed asymmetric epoxidation of benzalacetophenone yielded optically active epoxy ketone in high enantioselectivity up to 97% e.e. The cata-

lyst was easily separated and reused several times with no significant loss of activity and enantioselectivity.

Acknowledgments

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