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# Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by silica-grafted poly-(L)-leucine catalysts

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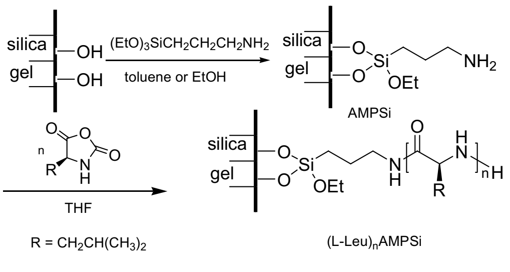
**Abstract**—A practical procedure has been developed for grafting poly(amino acid) on silica gel as an efficient and recoverable catalyst in the Juliá–Colonna asymmetric epoxidation with high enantioselectivities. Separation and recovery of the catalyst of poly(amino acid) have been remarkably improved by grafting on silica gel without a significant loss of enantioselectivity and activity.

Alkenes epoxidation is among the most widely useful asymmetric transformations. This reflects both the effectiveness of existing epoxidation protocols and the versatility of epoxides as intermediates for biologically active target molecules. The Juliá–Colonna asymmetric epoxidation of α,β-unsaturated ketones, catalyzed by poly-(amino acid) such as poly-(L)-leucine or poly-(L)-alanine, is one of the most efficient methods for epoxidation of electron-deficient substrates.[1,2] In recent years, the scope of the Juliá–Colonna asymmetric epoxidation has been extended largely including α,β-unsaturated ketones, esters, and amides.[3–12] 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[13,14] or inorganic materials through simple physical absorption[3,5,15,16] have been explored. However, immobilization of poly(amino acid) on inorganic materials, such as silica gel, through covalent binding has not been explored. Binding of an organic functional group to silica surface via a covalent bond is the most reliable method for modification and functionalization of silica surface.[17] The covalent bond used for the binding is mostly the Si–O–Si bond, where one of the silicon atoms is on the silica surface and the other comes from organosilicon compounds. The Si–O–Si bond could be readily formed by the reaction of a Si–OH group on the silica surface with organosilicon compounds. In this letter, we report the grafting of poly-(L)-leucine on silica gel through the Si–O–Si bond and Juliá–Colonna asymmetric epoxidation of (*E*)-α,β-unsaturated aromatic ketones catalyzed by the silica-grafted poly-(L)-leucine.

Grafting poly-(L)-leucine on silica gel was readily effected as shown in Scheme 1. The silica functionalized with primary 3-aminopropyl groups (AMPSi) was prepared through the treatment with (3-amino-propyl) triethoxysilane as reported in the literature.[18,19]

Polymerization of the amino acid *N*-carboxyanhydride (NCA) using functionalized silica gel (AMPSi) as an initiator was conducted in THF at room temperature similar to the procedures used in the homogeneous



**Scheme 1.** Preparation of poly-(L)-leucine-silica.

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*Keywords*: Asymmetric epoxidation; Grafted; Poly-(L)-leucine; α,β-Unsaturated ketone.

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system.[20] Using this silica-grafted primary amine, AMPSi, as an initiator, *N*-carboxyanhydride (NCA) of L-leucine were polymerized in THF, with AMPSi:NCA ratios of 1:*n* at room temperature for 72 h under a nitrogen atmosphere providing silica-grafted poly-(L-leucine), (L-Leu)$_n$AMPSi, with degrees of polymerization (*n*). A series of the silica-grafted poly-(L)-leucine catalysts were prepared with NCA of L-Leucine in THF using AMPSi:NCA ratios of 1:6, 1:15, 1:30, and 1:45.

The representative catalyst chosen for the characterization was that with ratio AMPSi/NCA = 1:30. The infrared spectroscopy showed the characteristic absorption of L-leucine at 3314, 2962, 2874, 1660, 1470, and 1440 cm$^{-1}$ for the N–H, C–H, and C=O, respectively.[1d] In the $^{13}$C CP-MAS NMR spectroscopy, signals at 173–178, 50–60, 36–44, and 16–26 ppm were assigned to the carbon atoms of poly-(L)-leucine. The peaks at 8.8, 20.5, and 43.0 ppm in the $^{13}$C CP-MAS NMR spectroscopy were attributed to the Si–C, Si–C–C, and Si–C–C–C–N of the 3-aminopropyl groups, respectively.[18,19] The terminal amino groups, which were determined by non-aqueous titration, were also in good agreement with the number of amino groups of the initiator (AMPSi).

The performance of the silica-grafted poly-(L)-leucine catalyst in the oxidation of (*E*)-α,β-unsaturated ketones was evaluated in the epoxidation of benzalacetophenone under various conditions. The results are summarized in Tables 1 and 2. In the model reaction of benzalacetophenone epoxidation,[21] the enantioselectivity increased with the degrees of the polymerization of poly(L-leucine), reaching 93% ee with $n = 45$ (Table 1, entry 4) similar to the homogeneous catalyst. However, the enantioselectivity of the reaction was independent on the change of reaction conditions, such as oxidants and solvents. Thus, almost the same enantioselectivities and yields were obtained by using different protocols (Table 2): a triphasic system, consisting of the insoluble catalyst, a solution of the enone in toluene, and an aqueous layer containing $H_2O_2$ and NaOH (Table 2, entry 1); the biphasic protocol, consisting of the insoluble catalyst and a solution of the benzalacetophenone and DBU in THF (Table 2, entry 2); or utilizing sodium percarbonate as both oxidant and base, the percarbonate protocol (Table 2, entries 3–5). Considering the ease of the catalyst recovery and the reaction time, we chose the percarbonate protocol to further investigate oxidation of (*E*)-α,β-unsaturated ketones with the poly-(L)-leucine-silica catalysts.

Reusability of the (L-Leu)$_n$AMPSi catalyst in both anhydrous and hydrous systems was also demonstrated by the reactions using benzalacetophenone as the substrate. The results are summarized in Tables 3 and 4, respectively.

In the anhydrous system, the weight of the recovered catalyst, (L-Leu)$_n$AMPSi, increased with recycling while enantioselectivity remarkably decreased due to the urea adsorbed on the surface of the silica gel. However, after the catalyst was washed with methanol, the catalytic activity and enantioselectivity were retained (Table 3, entry 5). In the hydrous system, the (L-Leu)$_n$AMPSi catalyst could be recycled several times, although the weight of the recovered catalyst and the enantioselectivity of

**Table 1.** Asymmetric epoxidation of benzalacetophenone catalyzed by (L-Leu)$_n$AMPSi under different degrees of polymerization[a]

| Entry | DF[b] | *n* | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 0.3 | 6 | 23 | 20 |
| 2 | 0.3 | 15 | 80 | 81 |
| 3 | 0.3 | 30 | 92 | 92 |
| 4 | 0.3 | 45 | 90 | 93 |

[a] General epoxidation procedure is described in Ref. 21.

[b] Degree of functionalization.

**Table 2.** Asymmetric epoxidation of benzalacetophenone catalyzed by (L-Leu)$_n$AMPSi under different protocols[a]

| Entry | Oxidation/base | *T* (h) | Solvent | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | $H_2O_2$/NaOH[b] | 48 | Toluene | 92 | 92 |
| 2 | UHP/DBU[c] | 6 | THF | 92 | 92 |
| 3 | $Na_2CO_3 \cdot 1.5H_2O_2$[d] | 2 | DME | 93 | 92 |
| 4 | $H_2O_2/Na_2CO_3$ (satd aq)[e] | 2 | DME | 93 | 93 |
| 5 | $H_2O_2/Na_2CO_3$ (10% aq)[e] | 2 | DME | 94 | 92 |

[a] Benzalacetophenone 0.5 mmol, catalyst 0.04 mmol, ambient temperature.

[b] Toluene 2 mL, $H_2O_2$ (30%) 0.5 mL, NaOH (10%) 0.25 mL.

[c] UHP 0.06 g (0.62 mmol), DBU 0.08 mL (0.53 mmol), anhydrous THF 2 mL.

[d] $Na_2CO_3 \cdot 1.5H_2O_2$ 0.12 g (0.8 mmol), DME 1 mL.

[e] The solution of $Na_2CO_3$ 1 mL, $H_2O_2$ 0.1 mL, DME 1 mL.

**Table 3.** Reusability of the (L-Leu)$_n$AMPSi catalyst in anhydrous system[a]

| Run | Catalyst (g) | Yield (%) | ee (%) |
|---|---|---|---|
| 1 | 0.70 | 90 | 93 |
| 2 | 0.80 | 93 | 82 |
| 3 | 0.89 | 92 | 78 |
| 4 | 0.99 | 90 | 56 |
| 5 | 0.65 | 93 | 93[b] |

[a] Benzalacetophenone 1.2 mmol, catalyst, urea–$H_2O_2$ 1.5 mmol, THF 3 ml, DBU 0.21 ml, ambient temperature, 6 h.

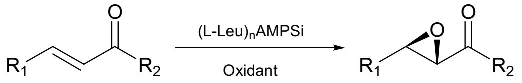
[b] The catalyst was washed with methanol after four times recycling.

**Table 4.** Reusability of the (L-Leu)$_n$AMPSi catalyst in hydrous system[a]

| Run | Catalyst (g) | Yield (%) | ee (%) |
|---|---|---|---|
| 1 | 0.50 | 94 | 93 |
| 2 | 0.49 | 92 | 90 |
| 3 | 0.49 | 93 | 91 |
| 4 | 0.48 | 90 | 89 |
| 5 | 0.47 | 83 | 86 |
| 6 | 0.47 | 80 | 85 |
| 7 | 0.46 | 78 | 83 |
| 8 | 0.45 | 80 | 82 |
| 9 | 0.44 | 78 | 82 |
| 10 | 0.43 | 83 | 80 |

[a] 1.0 mmol benzalacetophenone, catalyst, 1.68 mmol sodium percarbonate, 2 ml DME, 2 ml $H_2O$, ambient temperature, 2 h.

**Table 5.** Enones epoxidized using the (L-Leu)$_n$AMPSi catalyst[a]



| Entry | $R_1$ | $R_2$ | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | Ph | Ph | 94 | 93 |
| 2 | *p*-$MeOC_6H_4$ | Ph | 80 | 82 |
| 3 | *p*-$O_2NC_6H_4$ | Ph | 80 | 92 |
| 4 | *o*-$MeOC_6H_4$ | Ph | 54 | 70 |
| 5 | *o*-$EtOC_6H_4$ | Ph | 50 | 73 |
| 6 | *p*-$ClC_6H_4$ | Ph | 90 | 92 |
| 7 | Ph | *o*-$MeOC_6H_4$ | 70 | 80 |
| 8 | Ph | *p*-$ClC_6H_4$ | 88 | 93 |

[a] 1.0 mmol substrate, 0.06 mmol catalyst, 1.6 mmol sodium percarbonate, 2 mLDME, 2 mL $H_2O$, ambient temperature, 2 h.

epoxidation decreased with the recycling. Indeed, after 10 recycles α,β-epoxyketone was obtained in 83% yield in 80% ee under a constant condition (Table 4). The average loss of catalyst amounted to ca. 1.4% per run.

The epoxidation of various (*E*)-α,β-unsaturated ketones was examined using the silica-grafted poly(L-leucine). All of the olefins tested afforded the corresponding epoxides in good yields and enantioselectivities (Table 5). Electron-donating groups, such as MeO, decreased the enantio-selectivity of the asymmetric epoxidation significantly while electron-withdrawing ones showed little effects (Table 5, entries 2, 3, and 6). Ortho-substitutents, namely steric hindrance, lowered both the yields and enantioselectivities of the reactions catalyzed by the silica-grafted poly-(L)-leucine (Table 5, entries 4, 5, and 7).

In conclusion, we have developed a silica-grafted poly-(L)-leucine that could act as an efficient chiral catalyst in the epoxidation of (*E*)-α,β-unsaturated aromatic ketones with the percarbonate protocol to yield optically active epoxy ketones in high enantioselectivities up to 93% ee. Separation and recovery of the poly-(L)-leucine catalyst has been remarkably improved in this system, and the catalyst could be reused without a significant loss of activity. The good substrate compatibility would enable the synthesis of a variety of optically active epoxy ketones.

## Acknowledgments

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20. Synthesis of silica-grafted poly(L-leucine) catalysts. The AMPSi 3.2 g (0.3 mmol of $NH_2$/g) was dried under vacuum (0.5mmHg) at 110 °C for 2 h prior to use. The AMPSi and L-leucine NCA (5.0 g, 32 mmol) were mixed in anhydrous tetrahydrofuran (80 mL) at room temperature for 72 h with stirring. After stirring, the solid was filtered, thoroughly washed with methanol (60 mL, stirring 6 h) and diethyl ether (60 mL, stirring overnight) and dried under vacuum at room temperature (6.6 g). IR ($cm^{-1}$) 3314, 2962, 2874, 1660, 1470, 1440, 1219, 1086, 963, 799, 465; $^{13}C$ CP-MAS $\delta$ (ppm) = 8.8, 20.5, 24.3, 39.4, 43.0, 55.9, 175.9. Anal. Calcd for $C_{183}H_{338}N_{31}O_{30}@SiO_2$: C, 32.67; N, 6.45. Found: C, 32.04; N, 6.21.
21. (a) Typical epoxidation procedure under a hydrous condition:
To a solution of the enone (0.5 mmol) in DME (1 mL) and $H_2O$ (1 mL) was added percarbonate (0.76 mmol) and the grafting poly(L-leucine)-silica (0.04 mmol). The mixture was stirred for 6 h at room temperature until the reaction was completed (TLC). The catalyst was removed by rapid filtration and washed with ethyl acetate. The combined organic fractions were evaporated in vacuo to yield crude epoxide;
(b) Typical epoxidation procedures under an anhydrous condition:
A solution of the substrate (1.2 mmol) in anhydrous THF were added urea–hydrogen peroxide (1.5 mmol), DBU (1.5 mmol) and the grafting poly(L-leucine)-silica (0.06 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 crude epoxide; (c) The enantiomeric excess was determined by chiral-phase HPLC analysis with a Chiralpak$^{®}$ AD column (fluent: 10% *i*-PrOH in hexane, UV detection at 254 nm).