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Efficient Asymmetric Epoxidation of α,β-Unsaturated Ketones Using a Soluble Triblock Polyethylene Glycol–Polyamino Acid Catalyst

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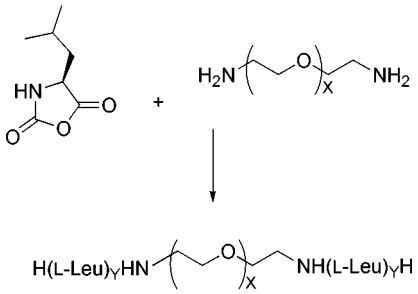
ABSTRACT



Polyethylene glycol (PEG)-bound poly-L-leucine acts as a THF-soluble catalyst for the Juliá–Colonna asymmetric epoxidation of enones. Excellent enantioselectivities may be obtained even with short chain length polyleucine. FT-IR investigations have determined that the catalytically active polyleucine components of these copolymers have an α-helical structure.

The polyamino acid catalyzed asymmetric epoxidation of α,β-unsaturated ketones was discovered[1] and developed[2] by Juliá and Colonna. Modifications to the original protocol have been reported which allow the epoxidation of a wide range of substrates.[3]

The polyamino acid remains insoluble under all the reaction conditions reported thus far. Immobilization of the polyamino acid on silica provides the optimum heterogeneous catalyst in terms of efficiency, stability, and ease of recycling.[4]

In this paper, we report the preparation, conformational analysis, and synthetic use of the first soluble version of the Juliá−Colonna catalyst, thus adding a new example to the armory of "liquid phase" synthetic technology.[5]

Poly-L-leucine, for synthetic applications, is normally prepared from the *N*-carboxyanhydride of L-leucine (L-Leu NCA) by adding a nucleophilic initiator to effect polymerization. Using standard initiators such as benzylamine, 1,3-diaminopropane, or cross-linked aminomethyl polystyrene,[6] the polyamino acid obtained is insoluble in water and organic solvents. We reasoned that if the chosen initiator is an appropriate organic solvent-soluble polymer, the resulting

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(2) (a) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317−1324. (b) Colonna, S.; Molinari, H.; Banfi, S.; Juliá, S.; Masana, J.; Alvarez, A. *Tetrahedron* **1983**, *39*, 1635−1641.

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(5) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (b) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917−1924. (c) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546−554.

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copolymeric catalyst might also be soluble in the same organic solvents.[7] The initiator chosen for this work was the commercially available *O*,*O*′-bis(2-aminoethyl)polyethylene glycol (diaminoPEG) of average molecular weight 3350, which is a conveniently handled solid at room temperature. DiaminoPEG was preferred to PEG as an initiator because the amide linkage formed to the polypeptide should be stable under the basic epoxidation conditions.

Interestingly, such diaminoPEG/polyleucine copolymers have been constructed before[7] and studied in connection with their potential use as wound dressings.[8] Soluble polypeptides rich in L-leucine residues have also been prepared by the strategic placement of aminoisobutyric acid (Aib) residues within the peptide chains. These polymers have been tested for activity in Juliá−Colonna epoxidations.[9]

A series of copolymers **1**−**4** was prepared by polymerization of L-Leu NCA in THF using PEG:NCA ratios of 1:10 (**1**), 1:20 (**2**), 1:30 (**3**), and 1:40 (**4**). After polymerization, addition of diethyl ether caused precipitation of a white solid which was collected, washed with ether, and filtered[10] to give the THF-soluble triblock copolymers $H(L\text{-Leu})_YNHCH_2CH_2(OCH_2CH_2)_XNH(L\text{-Leu})_YH$. The *average* chain lengths of polypeptide on diaminoPEG (*Y*) for the copolymers **1**−**4** were determined by microanalysis on the basis of the known value for the average chain length of the diaminoPEG ($X = 71$):[11]

1: $H(L\text{-Leu})_{3.9}NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_{3.9}H$

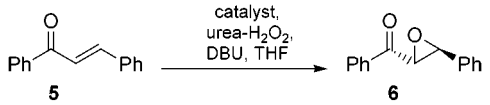
2: $H(L\text{-Leu})_{7.5}NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_{7.5}H$

3: $H(L\text{-Leu})_{11.6}NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_{11.6}H$

4: $H(L\text{-Leu})_{12.2}NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_{12.2}H$

Each of the catalysts **1**−**4** was tested for the epoxidation of chalcone (**5**) (Scheme 1), and the extent of conversion to,

Scheme 1



and the enantiomeric excess of, epoxychalcone **6** was determined by chiral HPLC (Table 1). The reaction conditions involved prestirring the oxidant (urea−H_2O_2) in THF for 20 min to generate a solution of H_2O_2 and then removing

Table 1. Epoxidation of Chalcone (**5**) with Soluble Polyleucine Catalysts

	catalyst							
	1		**2**		**3**		**4**	
time (h)	c[a] (%)	ee (%)	c[a] (%)	ee (%)	c[a] (%)	ee (%)	c[a] (%)	ee (%)
1	39	97	39	97	36	98	34	97
24	80	98	80	97	63	95	58	96

[a] c = conversion.

the insoluble peroxide carrier by filtration, rendering the reaction homogeneous.[12]

Remarkably, the catalysts **1** and **2**, containing smaller quantities of polypeptide, were efficient catalytic agents, the conversion of **5** to **6** being greater than for catalysts **3** and **4** (for the same amount of soluble polymer). This increased catalytic activity may reflect the greater number of amino termini present for the lower molecular weight materials, since the catalysts contained the same weight of polyamino acid in each experiment. This provides further evidence that the region adjacent to the *N*-terminus is responsible for catalytic activity and stereocontrol in the Juliá−Colonna epoxidation.[13]

The catalytic activity of the copolymers containing short polyamino acid chains compares very favorably with insoluble short chain poly-L-leucines prepared using a peptide synthesizer. Thus, for comparison, a series of oligoleucines $H(L\text{-Leu})_X\text{-R}$ (*X*-mers) was constructed[14] and used to epoxidize chalcone (**5**) under biphasic conditions[15] (comparable to the homogeneous conditions used for the soluble polymers above).

For example, the 6-mer gave epoxychalcone **6** with an ee of only 8% after 1.5 h at which point the conversion was 33%. Even the 18-mer only gave epoxide with an ee of 77% (also after 1.5 h, conversion 34%). For intermediate chain lengths, the ee ranged smoothly between these limits and the extent of conversion after 1.5 h never exceeded 40%.

Even accounting for the slightly different[16] ratios of polyamino acid:chalcone involved in these experiments, the difference in stereoselectivity between the soluble and insoluble catalysts is clear. For a direct comparison, some of the soluble catalysts were tested for the epoxidation of

(7) Kricheldorf, H. R.; Müller, D. *Int. J. Biol. Macromol.* **1983**, *5*, 171−178.

(8) Kim, H.-J.; Choi, E.-Y.; Oh, J.-S.; Lee, H.-C.; Park, S.-S.; Cho, C.-S. *Biomaterials* **2000**, *21*, 131−141.

(9) Takagi, R.; Shiraki, A.; Manabe, T.; Kojima, S.; Ohkata, K. *Chem. Lett.* **2000**, 366−367.

(10) Some THF insoluble product was present. As this was also shown to be a good catalyst for asymmetric epoxidation presumably it arose from polymerization of the L-leucine NCA by adventitious water.

(11) Determined by the % N in the copolymers. The amino-PEG is assumed to be fully bifunctionalized. Obviously, the polyleucine units on each end of the copolymers are not necessarily the same length.

(12) **Typical procedure:** urea−H_2O_2 (0.5 g) was stirred in THF (49.5 mL) and DBU (0.5 mL) under N_2 at rt for 20 min. The solution was filtered, and 1.7 mL of the filtrate was added to a vial containing copolymer including polyleucine (17 mg) and chalcone (17 mg). A second aliquot of oxidant and base in THF (1.7 mL) was added after 4 h.

(13) Bentley, P. A.; Cappi, M. W.; Flood, R. W.; Roberts, S. M.; Smith, J. A. *Tetrahedron Lett.* **1998**, *38*, 9297−9300.

(14) R refers to the solid support, see Supporting Information.

(15) **Biphasic conditions:** To a stirred solution of chalcone (**1**) (50 mg) in dry THF (1.5 mL) at rt was added polyleucine (100 mg). Urea−H_2O_2 (28 mg, 1.2 equiv) and DBU (56 μL, 1.5 equiv) were added. After 30, 90, and 150 min the same quantities of urea−H_2O_2 and DBU were added.

(16) By mass the PLL:chalcone ratio varied from ca. 1:5 (for the 6-mer) to 1:2 (for the 18-mer) and was always 1:1 in the experiments with the soluble polymer. More importantly, the ratio (number of polypeptide chains): chalcone was not varied significantly using this protocol.

chalcone (**5**) under the standard biphasic conditions, in which the peroxide carrier is not separated by filtration. After 30 min the conversion was at least 50% and the enantioselectivities remained high; for example, catalyst **1** gave a 57% conversion to epoxychalcone **6** (93% ee). For catalyst **3**, the corresponding figures were 70% conversion and 95% ee, and for catalyst **4**, 94% conversion and 97% ee were observed after this time.

To test just how short the average polypeptide unit can be while still maintaining catalytic activity, another soluble polymer was prepared with a different initiator:L-Leu NCA ratio. The structure of the resulting polymer (**7**) was determined, by microanalysis, to be $H(L\text{-Leu})_{1.8}NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_{1.8}H$. This proved too short a chain length for good enantioselectivity to be obtained in the epoxidation reaction, with chalcone epoxide **6** being generated with an ee of only 5% when material **7** was used as the catalyst.[17]

Juliá and Colonna have speculated that the α-helical structure of catalysts such as polyleucine and polyalanine is a necessary requirement for their activity.[2b] The newly prepared soluble polyamino acids provided an opportunity to investigate the relationship between length, conformation, and activity.

Consequently, the conformations of the PEG-bound polyleucines were investigated by FTIR spectroscopy.[18] The frequency of the amide I band of peptides and proteins is known to be a sensitive indicator of secondary structure.[19] Two reference compounds (**8** and **9**) were prepared by stepwise addition of leucine residues to diaminoPEG:[20]

8: $H(L\text{-Leu})NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})H$

9: $H(L\text{-Leu})_2NHCH_2CH_2(OCH_2CH_2)_{71}NH(L\text{-Leu})_2H$

The FTIR spectra of the polyamino acids **2**−**4** and **7** show distinct differences to those for **8** and **9** (Figure 1). Whereas the short oligoleucines (**8** and **9**) have a broad absorbance, centered near 1657 cm^{-1}, the longer chain catalysts (**2**−**4**) are characterized by a narrow band with a maximum around 1652 cm^{-1}. Clearly, the amide I band of the shortest polyamino acid prepared by NCA polymerization (**7**) is a composite of these two features.

For a more quantitative analysis, the spectra were fitted to a number of Lorentzian bands in a global fit procedure.[21]

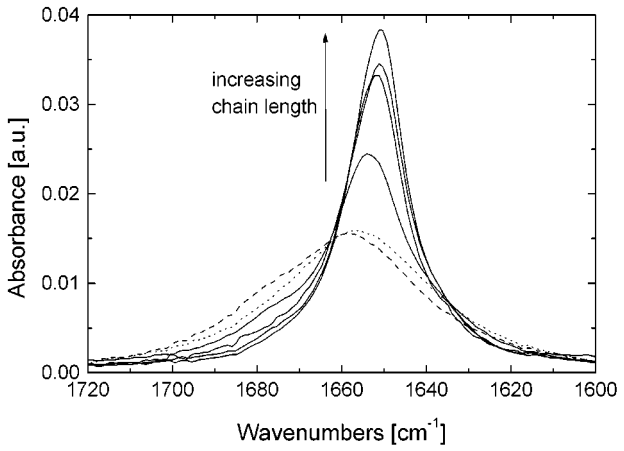


Figure 1. FTIR spectra of catalysts **2**−**4** and **7** (solid lines, different chain lengths as indicated in figure) and compounds **8** (dashed line) and **9** (dotted line) in the amide I region. For better comparability, the spectra have been normalized to the same total absorbance (area under the spectrum).

It was found that all the spectra can be reproduced simultaneously with a minimum of five Lorentzians. Representative deconvoluted spectra are shown (Figure 2), and the fit results are summarized (Table 2).

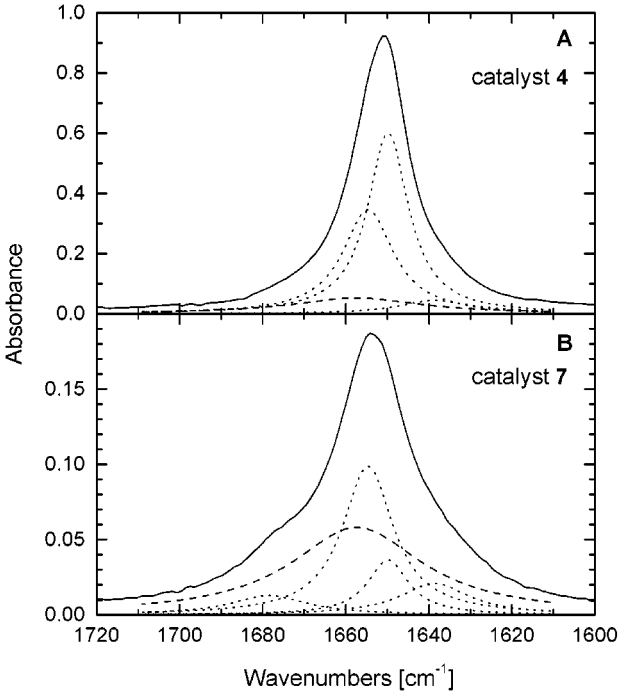


Figure 2. FTIR spectra of catalysts **4** (A) and **7** (B) in the amide I region, showing the deconvolution into separate Lorentzian bands (dotted and dashed lines, with the dashed line indicating the broad band centered at 1657.3 cm^{-1}, which dominates the amide I band of compounds **8** and **9**), as obtained from the global fit of all data (Table 2).

(17) This ee was obtained under a different set of homogeneous conditions involving an anhydrous solution of H_2O_2 in a mixture of TBME and THF. Catalysts **1**−**4** gave significantly higher ees of epoxide **6** when tested under this protocol.

(18) FTIR measurements were made using samples dissolved in chloroform (10−50 mg/mL) and a 150 μm path length cell with CaF_2 windows. FTIR spectra were measured with a Bio-Rad FTS-40 spectrometer, averaging over 1000 scans at a resolution of 2 cm^{-1} and subtracting any residual water vapor lines.

(19) (a) Arrondo, J. L. R.; Muga, A.; Castresana, J.; Goñi, F. M. *Prog. Biophys. Mol. Biol.* **1993**, *59*, 23−56. (b) Krimm, S.; Bandekar, J. *Adv. Protein Chem.* **1986**, *38*, 181−364. (c) Surewicz, W. K.; Mantsch, H. H.; Chapman, D. *Biochemistry* **1993**, *32*, 389−394.

(20) Compounds **8** and **9** show no catalytic activity, but were prepared to provide short reference polyleucine samples unable to form a well-defined secondary structure, in particular unable to form an α-helix. Their preparation is given in the Supporting Information.

Table 2. Results of a Global Fit of the FTIR Spectra of the Polymers **2**−**4** and **7**−**9** in the Amide I Region[a]

		band center, width (cm^{-1})				
polymer	chain length	1638.6, 20.5	1649.8, 12.0	1654.7, 14.8	1657.3, 38.5	1678.5, 22.8
8	1[b]	0.5			89.3	10.2
9	2[b]	5.2	1.3		90.7	2.8
7	1.8[c]	8.8	9.0	30.1	46.0	6.1
2	7.5[c]	3.0	31.3	34.9	27.5	3.3
3	11.6[c]	7.6	36.7	34.6	19.5	1.5
4	12.2[c]	6.0	46.9	33.4	13.1	0.5

[a] Shown are the center frequencies and widths of the five Lorentzian bands needed to obtain a satisfactory simultaneous fit of all spectra and the relative contributions of these bands to the total absorbance of each sample (in %) (as determined by the area under each band). [b] Exact length of polypeptide chain on each end of PEG. [c] Average length of polypeptide chain on each end of PEG.

Compounds **8** and **9**, with only one or two leucines coupled to diaminoPEG, are unable to form significant secondary structure, and their FTIR spectra are dominated by one broad band at 1657 cm^{-1}. This corresponds to the amide I frequency previously reported for unordered peptide structures.[19,22]

Some contribution of this band is also observed for polymers **2**−**4** and **7**, although its relative importance decreases for the longer chain catalysts. Thus, with increasing average chain length the amount of disordered structure decreases, probably due to the smaller number of polyleucine chains with less than four residues, the minimum number of residues for forming an α-helix.

For the longer chain catalysts, two narrow bands at 1649.8 and 1654.7 cm^{-1} become dominant. These bands fall into the spectral region which is typical of the amide I frequency of α-helices.[19,23] Most likely, the two bands should not be interpreted as two distinct bands but as representing a distribution of bands, which are too close to be resolved, reflecting the distribution of peptides of differing lengths in the samples. Upon increasing the average chain length, the center of this distribution shifts from 1654 to 1650 cm^{-1} (see Table 2). This corresponds to the shift of the α-helix amide I frequency toward smaller values with growing chain length, which has been predicted on theoretical grounds[24] and observed for helical peptides in aqueous solution.[25] These results indicate that polyleucine chains attached to diamino-PEG predominantly adopt an α-helical structure in organic solvents,[26] provided the chain length exceeds the minimum number of residues required for forming one helical turn.[27] This minimum number here is four residues, assuming that the first helical hydrogen bond is formed from the *N*-terminal residue carbonyl to the amide group of PEG. Chains shorter than this minimum length, on the other hand, form a disordered structure.

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Supporting Information Available: Experimental procedures for the synthesis of the oligopeptides used. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The amide I spectra of all compounds were fitted simultaneously to the sum of a variable number of Lorentzian bands, using a nonlinear least-squares (Levenberg−Marquardt) fitting routine. The same Lorentzian band centre frequencies and widths, but different relative amplitudes, were used for all spectra. It was found that a minimum of five Lorentzians was needed to obtain a satisfactory fit. The use of six or more Lorentzians did not significantly improve the quality of the fit.

(22) Chirgadze, Y. N.; Shestopalov, B. V.; Venyaminov, S. Y. *Biopolymers* **1973**, *12*, 1337−1351.

(23) Chirgadze, Y. N.; Brazhnikov, E. V. *Biopolymers* **1974**, *13*, 1701−1712.

(24) Nevskaya, N. A.; Chirgadze, Yu. N. *Biopolymers* **1976**, *15*, 637−648.

(25) Graff, D. K.; Pastrana-Rios, B.; Venyaminov, S. Y.; Prendergast, F. G. *J. Am. Chem. Soc.* **1997**, *119*, 11282−11294.

(26) These conclusions are in general agreement with those obtained in a recent publication on insoluble oligo-L-leucines of varying chain lengths, where it was shown that the efficiency of oligo-L-leucine as a Juliá−Colonna catalyst is related to its α-helical structure: Takagi, R.; Manabe, T.; Shiraki, A.; Yoneshige, A.; Hiraga, Y.; Kojima, S.; Ohkata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2115−2121. Insoluble oligo-L-leucines show a significant contribution of *β*-sheet structure, which is thought to be formed upon aggregation of the insoluble polymer chains. No significant aggregation is observed for the soluble poly-L-leucines investigated here.

(27) Two minor bands at 1638.6 and 1678.5 cm^{-1} are needed to obtain a satisfactory fit (Table 2). Although these wavelengths are characteristic of *β*-sheet structures (see refs 19, 22), at the present moment it is not clear whether these bands indicate a minor population of *β*-sheet structures for amino-PEG bound polyleucine or are due to some artifact, possibly related to the insoluble product found during catalyst synthesis. A more detailed investigation of these minor contributions is currently in preparation. The main conclusion, namely, that PEG-bound polyleucine is found to adopt a predominantly α-helical structure, is not affected by these minor bands.