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SYNTHETIC ENZYMES—4[1]

HIGHLY ENANTIOSELECTIVE EPOXIDATION BY MEANS OF POLYAMINOACIDS IN A TRIPHASE SYSTEM: INFLUENCE OF STRUCTURAL VARIATIONS WITHIN THE CATALYSTS

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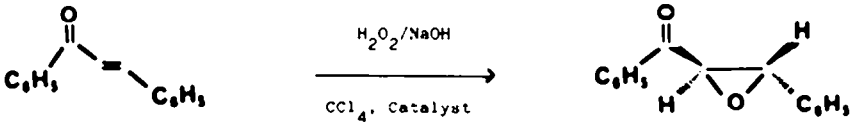
Abstract—The asymmetric epoxidation of chalcone and other electron-poor olefins in a triphase system (water-organic solvent-polyaminoacid) affords optically active oxiranes. The influence of the molecular structure of catalysts and of their secondary conformation on the enantioselectivity of the reaction has also been examined.

Asymmetric syntheses performed in the presence of synthetic or natural polypeptides are a subject of growing interest,[2] since these can be considered as simplified models of enzymatic reactions.

On the other hand, the epoxide functional group is one of the most useful intermediates in organic synthesis. For this reason the synthesis of chiral oxiranes is still a challenging target in the area of asymmetric induction. Having recently discovered a highly enantioselective method for epoxidizing electron-poor olefins[1] in a triphase system (polyaminoacid/aqueous phase/organic phase) it seems necessary to investigate the structural requirements of polyaminoacids used as catalysts, in order to enlarge the scope of this synthetic method.

We have prepared and tested, in the epoxidation of chalcone **1**, the series of poly-L-α-aminoacids **3–13** (Scheme 1). Catalysts **3–7** have been obtained from the corresponding L-aminoacids according to Scheme 2.



$H[HN-\underset{\underset{R}{|}}{CH}-CO]_m NH-Bu^n$

3 - 9

3,a ; R = CH_3 ; n = 10
3,b ; R = CH_3 ; n = 30
4,a ; R = $CH-(CH_3)_2$; n = 10
4,b ; R = $CH-(CH_3)_2$; n = 30
5,a ; R = $CH_2-CH-(CH_3)_2$; n = 10
5,b ; R = $CH_2-CH-(CH_3)_2$; n = 30
6 ; R = $CH(CH_3)CH_2-CH_3$; n = 10
7 ; R = CH_2Ph ; n = 10
8 ; R = CH_2COOCH_2Ph ; n = 10
9 ; R = $CH_2CH_2COOCH_2Ph$; n = 10

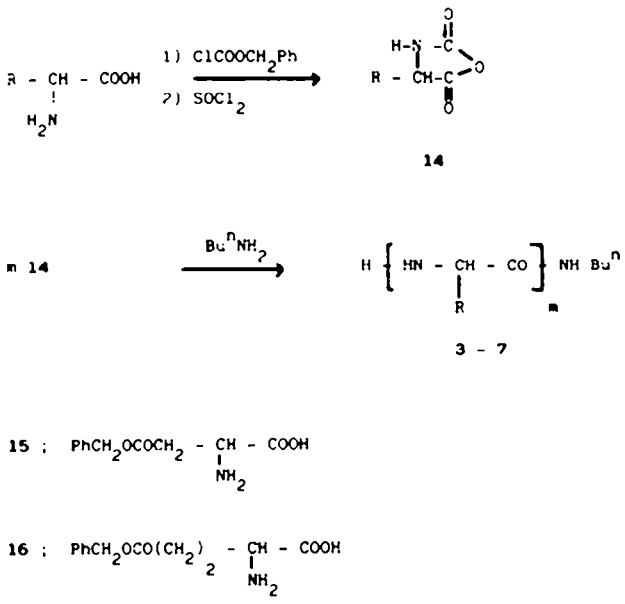
10 ; (L)-Ala-(L)-Ala
11 ; $[(L)\text{-Leu}_1\text{-(L)-Ala}_1]_{10}$ random
12 ; $[(L)\text{-Val}_x\text{-(L)-Ala}_y]_{10}$ random

12,a ; x = 1 ; y = 1
12,b ; x = 7 ; y = 3
12,c ; x = 9 ; y = 1

$C_6H_5\ CO-\left[HN-\underset{\underset{CH_3}{|}}{CH}-CO\right]_2-NH-Bu^n$

13

Scheme 1.



Scheme 2.

Catalysts **8** and **9** have been prepared similarly from 4-L-benzyl aspartate **15** and 5-L-benzyl glutamate **16** respectively. The L-α-aminoacids have been converted into the corresponding N-carboxyanhydride **14** (NCA) by reaction with benzylchloroformiate and thionyl chloride. The subsequent polymerization of **14** has been performed using n-butylamine as initiator.

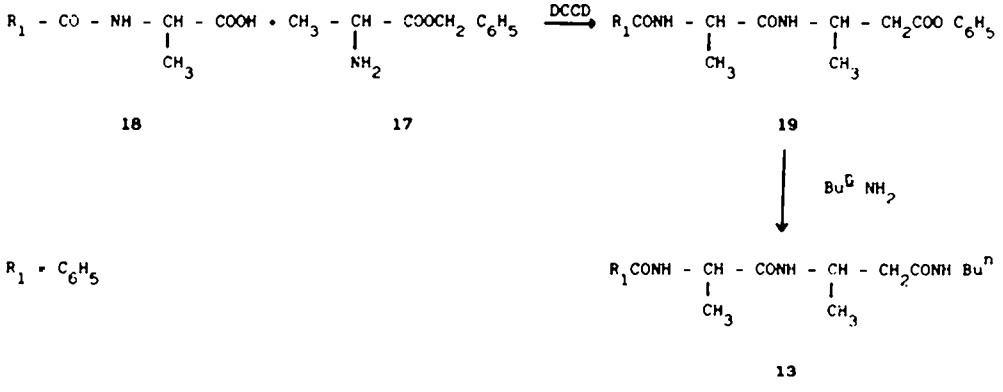
In compounds **3–9** m represents the mole-ratio of NCA to initiator, corresponding to the number average degree of polymerization.[1] Random copolymers **11** and **12a,b,c** of L-leucine and L-valine with L-alanine have been prepared according to literature,[3] using n-butylamine as initiator.

Compound **13** has been prepared from L-benzyl-alaninate **17** according to Scheme 3. Reaction of **17** with N-benzoyl-L-alanine **18** in the presence of dicyclohexyl-carbodiimide affords the benzyl ester **19** which by aminolysis with n-butylamine yields the compound **13**.

RESULTS AND DISCUSSION

All the epoxidations have been carried out at room temperature in a triphase system with carbon tetrachloride, water, catalytic amount of polypeptide and a large excess of oxidant (H_2O_2/NaOH) (unless otherwise stated). The results, reported in Table 1, indicate that epoxidation of chalcone **1** generally occurs with good chemical conversions and high optical yields. When poly-L-alanine **3b** is employed, the reaction is practically stereospecific with an enantiomeric excess (e.e.) of 96%.

Similar good results are obtained with poly-L-leucine **5a,b** and poly-L-isoleucine **6**, whereas poly-L-valine **4a,b** not only reduces the chemical yields, but also greatly affects the asymmetric synthesis. The same trend is shown by random copolymers **11** and **12a–c**: increasing the content of valine incorporated in the copolymer, chemical and optical yields progressively decrease (Table 2). Both poly-L-phenylalanine **7** and the dipeptide L-



Scheme 3.

Table 1. Epoxidation of chalcone 1 performed in CCl_4 at room temperature in the presence of catalysts 3–9

Catalyst	Time (hr)	Yield[a] (%)	$[\alpha]_{578}^{20}$ (CH_2Cl_2)	e.e. (%)
3,a (L)	28	75	- 199.5°	93
3,a (D)[b]	37	53	+ 193.5	90
3,a (D,L)[b]	24	5	0	0
3,b	28	77	- 205.4	96
4,a	168	5.5	- 22.0	10
4,b	144	4	- 70.5	33
5,a	28	60	- 181.2	84
5,b	28	44	- 189.8	88
6	72	76	- 204.5	95
7	72	32[c]	- 1.9	1
8	456	7.5	- 7.4	3
9	144	12	- 23.4	11.6

a) Calculated on the product recovered after purification by column chromatography.

b) Reaction performed in Toluene.

c) Calculated by ^1H n.m.r.

Table 2. Epoxidation of chalcone 1 performed in CCl_4 at room temperature in the presence of copolymers 10–13

Catalyst	Time (hr)	Yield (%)[a]	$[\alpha]_{578}^{20}$ (CH_2Cl_2)	e.e. (%)
10[b]	144	41	+ 5°	2
11	24	67	- 204	95
12,a	96	39	- 190.2	88
12,b	192	14	- 83.9	39
12,c	168	9	- 25.8	12
13	24	5	- 1.4	0.7

a) Calculated on the product recovered after purification by column chromatography.

b) Reaction performed in Toluene.

alanyl-L-alanine **10** (soluble in the aqueous phase) give almost racemic epoxichalcone **2**. The same occurs when catalyst **13** is used.

It is important to mention that chemical and optical yields are closely related in all cases. In the reactions examined, the predominant optical antipode of epoxichalcone **2** is levorotatory and according to Wynberg[4] it must have absolute configuration (2*R*, 3*S*). As expected, if poly-D-alanine is employed as catalyst, instead of poly-L-alanine **3a**, the degree of asymmetric induction is similar, but the sign of optical rotation is reversed. Poly-D,L-alanine does not afford appreciable amounts of epoxichalcone **2** even after long reaction time (chemical yields less than 10%).

The catalysts being insoluble in the reaction medium, are easily recovered from the epoxidation and recycled (Table 3): a decrease in chemical and optical yields is observed with poly-L-alanine **3a** whereas less substantial changes in the e.e. of **2** are seen with poly-L-alanine **3b**, with poly-L-leucine **5b** and with the copolymer of L-leucine with L-alanine **11**.

These results are explained by the fact that the polyaminoacids are partially degraded by hydrolysis in the basic reaction media. Catalysts with higher molecular weight[5] (**3b** in front of **3a**) or more sterically hindered (**5b** in front of **3b**) afford better results when they are recycled, being more resistant to the hydrolysis.

The high degree of asymmetric induction allows a tentative interpretation of its occurrence. We think that the H-bonding between the CO function of chalcone **1** and the peptide group of catalysts **3–9**, **11**, **12a–c** is responsible for the asymmetric synthesis of the epoxide **2**. Similar interactions between carboxylic acids and the peptide group of poly-L-alanine have been proved by Stephens *et al.*[6]

An indirect support of this hypothesis is given by the isolation of a racemic epoxichalcone **2**, when the reaction is performed in methanol with poly-L-alanine **3b** as catalyst. In this solvent, the interactions between the CO compound and the poly-α-aminoacid are broken. Since it is very likely that the actual oxidizing species is the hydroperoxide anion, this is, in turn, H-bonded to the

Table 3. Epoxidation of chalcone 1 performed in CCl_4 at room temperature in the presence of recycled catalysts

Recycled catalyst	Time (hr)	Yield[a] (%)	$[\alpha]_{578}^{20}$ (CH_2Cl_2)	e.e. (%)
3,a	28	70[b]	- 97.1°	45
3,b	66	75	- 151	70
5,b	240	64	- 180.6	84
11	24	11	- 184	86

a) Calculated on the product recovered after purification by column chromatography.
b) Calculated by ^1H n.m.r.

amido group of the catalyst. In spite of these considerations it is still very difficult to account for the influence of the secondary structure of the poly-α-aminoacid on the degree of asymmetric induction.

The conformations of poly-α-aminoacids **3–9**, **11**, **12a–c**, in the solid state, have been extensively investigated.[7] Poly-L-alanine **3a,b**, poly-L-leucine **5a,b**, and the copolymer of L-leucine with L-alanine assume the α-helical structure,[7,8] while poly-L-valine **4a,b**, poly-L-isoleucine **6** and poly-L-phenylalanine **7** are in the β-structure.

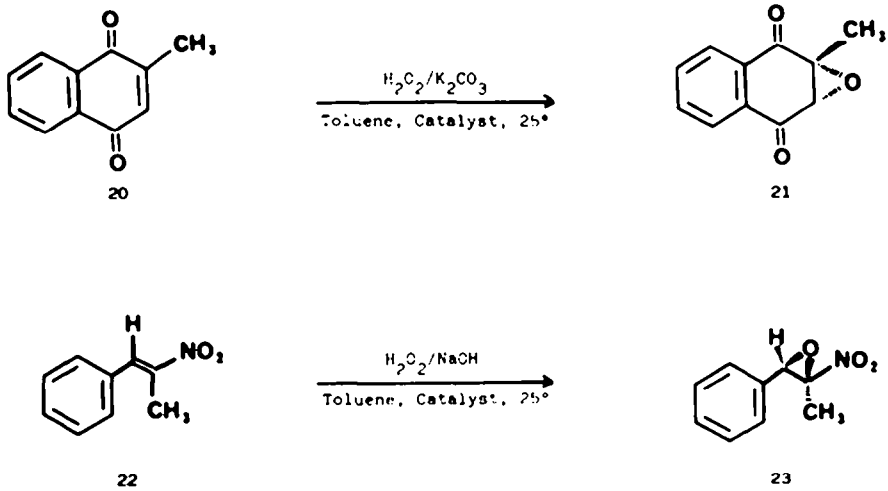
Poly-4-L-benzylaspartate **8** and poly-5-L-benzylglutamate **9** assume left handed and right handed α-helical structures respectively.[2] In the copolymers of L-valine with L-alanine the content of the α-helix local conformation and that of the β-form structure can be estimated by means of IR spectra, the far IR region being very sensitive to the conformational changes of polyaminoacids backbone.[8]

Our preliminary results[1] indicated that the enantioselectivity reaches its maximum with catalysts having a high content of α-helical conformation. This is the case with poly-L-alanine **3a,b**, with poly-L-leucine **5a,b** and with the copolymer of L-leucine with L-alanine **11**. The values of enantiomeric excess of epoxichalcone **2** obtained with the different copolymers of L-valine with L-alanine **12a–c** are also in this line: an increase in β content at the expense of the helical structure corresponds to a proportional decrease of the optical yield.

The results obtained from short length oligoaminoacids such as **13**, which cannot adopt α-helical conformation should favour this hypothesis as well as the poor results obtained using poly-D,L-alanine which is in conformation β[2,9] in contrast with optically active L and D polymers. Poly-L-valine **4a,b**, the most stable conformation of which, in these degrees of polymerization, is the β-pleated sheet,[8] is an inefficient catalyst, both from the chemical and from the chiral point of view.

This explanation, based on the α-helix content of the poly-α-aminoacids, does not account for the experimental results with poly-L-isoleucine **6** which behaves like poly-L-leucine **5a,b** and poly-L-alanine **3a,b**, and gives high e.e. even if it has a β-structure. Moreover the optical purity of the epoxichalcone is low with poly-4-L-benzylaspartate **8** and poly-5-L-benzylglutamate **9**, which have definitely an α-structure. It may well be that the actual amount of asymmetric induction in the epoxidation is influenced by the local ordering of the polypeptide matrix, as already found by Solladié[10] in the asymmetric synthesis performed in the presence of cholesteric liquid crystals.

On the other hand, the correlation observed in this epoxidation between chemical and optical yield, suggests that the triphasic system plays an important role. In fact,



Scheme 4.

Table 4. Epoxidation of substrates 20, 22 performed in toluene at room temperature

Substrate	Catalyst	Time (hr)	Yield[a] (%)	$[\alpha]_{436}^{20}$ (acetone)	e.e (%)
16	3,a	24	100	0	-
"	4,a	24	50	0	-
"	5,b	24	65	0	-
"	6	384	16	- 1.19	0.8
18	3,a	24	50	- 1.3	7[b]
"	5,b	24	50	0	-
"	9	24	67	- 0.7	4[b]

a) Calculated on the product recovered after purification by column chromatography.

b) Enantiomeric excess has been determined by ^{1}H n.m.r. using Eu(hfc)$_3$ as shift reagent.

the system is an emulsion of the organic phase in the aqueous phase, part of the polyaminoacid being placed as solid phase in the interface. The rest of solid catalyst is microdispersed into this system.[11] The physicochemical properties of such a system determines the velocity of the reaction, and depends on the polyaminoacid employed.

The predominant enantiomer of epoxichalcone 2 is independent on the secondary structure of the polypeptide used as catalyst, in the sense that the same levorotatory product is obtained both with poly-4-L-benzylaspartate 8 and poly-5-L-benzylglutamate 9 which assume left handed and right handed α-helix structures respectively. The structure of the substrate also plays an important role in determining the amount of asymmetric induction. Apart from chalcone and other related electron-poor olefins,[1] poly-α-aminoacids 3a, 4a, 5b, 6 and 9 are much less effective catalysts in the epoxidation of systems such as 2-methyl-1,4-naphthoquinone 20 and 1-phenyl-2-nitropropene 22 (Scheme 4).

The results, reported in Table 4, show that the epoxides obtained are either racemic or exhibit a very low enantiomeric excess. However, in these substrates, no relation between chemical and optical yield is observed, being the reaction favoured in the presence of polypeptides.[5]

A similar trend has been observed previously in some base-catalysed reactions such as Darzens condensation, the hydrogenation of halohydrins and the Michael addition of ethyl nitroacetate to the chalcone.[1] All these reactions afford almost racemic products.

The specific behaviour in the epoxidation of chalcone and other electron-poor olefins, namely the high enantiomeric excess obtained with H_2O_2/NaOH in a triphase system, seems to indicate that not only poly-L-alanine, but also the other poly-L-aminoacids described in this paper, act like synthetic enzymes, and may be valuable tools to perform organic reactions. Indeed this method is complementary to the Sharpless asymmetric epoxidation of allylic alcohols,[12] both systems affording almost optically pure oxiranes.

EXPERIMENTAL

M.ps are uncorrected. The optical rotations were determined with a Perkin–Elmer P-141 and P-241 polarimeters. IR spectra were recorded on a Perkin–Elmer 157 and 377 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 90 instrument, using TMS as internal standard and chemical shifts are expressed as values. Enantiomeric excess was determined by ^{1}H NMR with the use of europium Eu(hfc)$_3$ using a Varian 390 instrument.

Starting materials. Compounds 1, and 20, were commercial products, 22 was prepared according to the lit.[13], 65° (lit.[13], m.p. 64–65°). All products showed IR and ^{1}H NMR spectra in agreement with the proposed structure.

Synthesis of catalysts

N-Benzyloxycarbonyl-L-alanine [L-Alanine NCbzo] was prepared according to the lit.[14] The compound (60% yield) had m.p. 82° (lit.[14], m.p. 84°).

L-4-Methyl-1,3-oxazolidine-2,5-dione [*S-Alanine NCA*] was prepared according to the lit.[15] in 75% yield, m.p. 89° (lit.[16], m.p. 92°, ^{1}H NMR ($CDCl_3$): δ 1.6 (d, 3H), 4.35 (9, 1H), 6.6 (s, 1H).

Poly-L-alanine 3a. A soln of n-butylamine (0.337 g, 4.61 mmol) in 20 ml anhydrous acetonitrile was added to a soln of L-alanine NCA (5.3 g, 46.1 mmol) in 40 ml of the same solvent. The reaction was stirred for 4 days at room temp. The solvent was then eliminated in vacuum, the solid residue washed with CH_2Cl_2, Et_2O and dried under vacuum for 5 hr at 40°. Compound 3a (85% yield) had $[\alpha]_D^{20} = -120.5°$ (*c*, 0.996 in CF_3COOH); IR (KBr) 3270, 3060, 1655, 1630, 1540 and 1305; ^{1}H NMR (CF_3COOH): δ 0.50 (d, 3H), 1.1 (m, 34H), 3.0 (m, 2H), 4.2 (br, 1H).

Poly-D-alanine 3a was obtained identically (70% yield) from D-alanine. $[\alpha]_D^{20} = +131°$ (*c*, 0.475 in CF_3COOH); IR (KBr) 3290, 3070, 1665, 1640, 1545 and 1310; ^{1}H NMR (CF_3COOH) identical poly-L-alanine.

Poly-DL-alanine 3a was synthesized like poly-L-alanine starting from DL-alanine (60% yield).

Poly-L-alanine 3b was synthesized, using a NCA/initiator ratio 30:1. Compound 3b (yields 89%) had $[\alpha]_D^{20} = -153.15$ (*c*, 0.2455 in CF_3COOH).

N-Benzyloxycarbonyl-L-valine [L-*valine* NCbzo] was prepared following the procedure described for N-benzyloxycarbonyl-L-alanine. The product obtained in 65% yield had m.p. 56° (benzene-n-hexane) (lit.[17], m.p. 59°), ^{1}H NMR ($CDCl_3$): δ 1.0 (2d, 6H), 2.26 (m, 1H), 4.33 (m, 1H), 5.2 (s, 2H), 7.40 (s, 5H).

L-4-Isopropyl-1,3-oxazolidine-2,5-dione [*S-valine* NCA] was prepared according to the lit.[15] The anhydride obtained (65% yield) had m.p. 62–63° (lit.[18], m.p. 65°), ^{1}H NMR ($CDCl_3$): δ 1.0 (2d, 6H), 2.2 (m, 1H), 4.2 (d, 1H), 7.05 (s, 1H).

Poly-L-valine 4a,b were synthesized following the procedure described for 3a,b, using the appropriate NCA/initiator ratio. Compound 4a (yield 82%) had $[\alpha]_D^{20} = -122.03$ (*c*, 0.3786 in CF_3COOH); ^{1}H NMR (CF_3COOH) δ 1.0 (br, 63H), 2.2 (m, 14H), 3.3 (m, 2H), 4.4 (m, 10H). Compound 4b: yield 70%, $[\alpha]_D^{20} = -147.9°$ (*c*, 0.02799 in CF_3COOH); ^{1}H NMR (CF_3COOH): δ 1.0 (br, 183H), 2.2 (m, 34H), 3.3 (m, 2H), 4.4 (m, 30H).

N-benzyloxycarbonyl-L-leucine [L-*leucine* NCbzo] was prepared following the procedure described for N-benzyloxycarbonyl-L-alanine. The product (76.5% yield) is an oil[17]; ^{1}H NMR ($CDCl_3$): δ 0.9 (d, 6H), 1.6 (m, 3H), 4.3 (m, 1H), 5.1 (s, 2H), 7.2 (s, 5H), 10.2 (s, 1H).

L-4-*Isobuthyl*-1,3-*oxazolidine*-2,5-*dione* [L-*leucine* NCA] was prepared as described.[15] The anhydride obtained (58% yield) had m.p. 71° (lit.[19] 65–70°); ^{1}H NMR ($CDCl_3$): δ 1.0 (2d, 6H), 1.75 (m, 3H), 4.3 (m, 1H), 7.05 (s, 1H).

Poly-L-leucine **5a,b** were synthesized following the procedure described for **3a,b**, using the appropriate NCA/initiator ratio. Compound **5a** (84% yield) had $[\alpha]_D^{20} = -98.3$ (*c*, 0.2126 in CF_3COOH); ^{1}H NMR (CF_3COOH): δ 1.0 (s, 63H), 1.65 (s, 344), 3.45 (m, 2H), 4.6 (m, 10H). Compound **5b**: yield 85%; $[\alpha]_D^{20} = -99.08$ (*c*, 0.3048 in CF_3COOH) ^{1}H NMR (CF_3COOH): δ 1.0 (s, 183H), 1.70 (s, 94H), 3.45 (m, 2H), 4.6 (m, 30H).

N-Benzyloxycarbonyl-L-isoleucine was prepared following the procedure described for N-benzyloxycarbonyl-L-alanine. The product (76%) yield is an oil[20]; ^{1}H NMR ($CDCl_3$): δ 1.0 (m, 6H), 1.4 (m, 2H), 2.0 (m, 1H), 4.3 (d, 1H), 5.15 (s, 2H), 5.3 (d, 1H), 7.3 (s, 5H).

L-4-(2-*Butyl*)-1,3-*oxazilidine*-2,5-*dione* [L-*isoleucine* NCA]. The white crystalline solid (60% yield) had m.p. 66–68°; (lit.[19], 70–72°); ^{1}H NMR ($CDCl_3$) δ 1.0 (m, 6H), 1.40 (m, 2H), 2.0 (m, 1H), 4.30 (d, 1H), 7.25 (s, br 1H).

Poly-L-isoleucine **6**.[21] A soln of n-butylamine (0.0314 g, 0.429 mmol) in 20 ml anhyd acetonitrile was added under N_2 to a soln of L-isoleucine NCA (2.7 g, 17.2 mmol) in 40 ml of the same solvent. The reaction was stirred for 7 days at room temp. Anhyd diethyl ether was then added and the ppt filtered off, washed with ether and dried under vacuum for 5 hr at 40°. Compound **6** (1.3 g) had $[\alpha]_D^{20} = -127.35$ (*c*, 0.2764 in CF_3COOH); ^{1}H NMR (CF_3COOH) δ 1.0 (d, br 69H), 1.40 (m, br 26H), 2.0 (m, br, 11H), 3.5 (m, 2H), 4.5 (d, 11H).

Poly-L-phenylalanine **7** *and L-alanyl-L-alanine* **10** were commercial products.

β-Benzyl-L-aspartate was obtained in 50% yield as described.[22] m.p. 218° (lit.[22], 218–220°).

β-Benzyl N-carbobenzoxy-L-aspartate was prepared according as described.[22] (60% yield). It had m.p. 105–107° (lit.[22], 107–108°). ^{1}H NMR ($CDCl_3$) δ 2.95 (m, 2H); 4.6 (m, 1H); 5.1 (s, 4H); 5.8 (d, 1H); 7.2 (s, 10H); 10.2 (s, 1H).

β-Benzyl N-carboxy-L-aspartate anhydride (*β-Benzyl-L-aspartate* NCA) was prepared according to the lit.[23] (89% yield). The compound had m.p. 121 (lit.[23], 121°). ^{1}H NMR ($CDCl_3$) δ 2.9 (2d, 2H), 4.5 (m, 1H), 5.15 (s, 2H), 7.3 (s, 5H).

Poly 4-L-*Benzyl aspartate* **8**. A soln of n-butylamine (0.043 g, 0.6 mmol) in 5 ml of solvent (THF: 1.2-dichloroethane 1:4) was added under stirring at room temp. to a soln of β-benzyl-L-aspartate NCA (1.5 g, 6 mmol) in 25 ml of the same solvent. The polymerisation occurred in an homogeneus phase within 5 days. Then 400 ml of anhyd n-hexane were added, the ppt was filtered off and dried under vacuum at 40° for 5 hr. Compound **8** (78.5% yield) had $[\alpha]_{436}^{20} = -23.53°$ (*c*, 0.255 in CF_3COOH); ^{1}H NMR (CF_3COOH) δ 3.1 (m, br, 24H), 5–5.2 (m + s, 30H), 7.3 (s, 50H).

Poly 5-L-*benzyl glutamate* **9** was prepared as described.[1]

Random copolymer-L-leucine-L-alanine **11**[18] A soln of n-butylamine (0.185 g, 2.54 mmol in 10 ml anhyd acetonitrile was added to a soln of N-carboxy-L-alanine anhydride (1.46 g, 12.7 mmol) and N-carboxy-L-leucine anhydride (2 g, 12.7 mmol) in 90 ml of the same solvent. The reaction was stirred for 7 days at room temp. Then anhyd diethyl ether was added and the ppt dried in vacuum at 40° for 5 hr. Compound **11** (2.1 g) had $[\alpha]_D^{20} = -103.41$ (*c*, 0.5106 in CF_3COOH).

Random copolymers L-*alanine-L-valine* **12a–c**[18] were prepared following the procedure described for **11** using anhyd dioxane as solvent. The following molar concentrations were used: for compounds **12a–c** the molar ratio L-Ala NCA/L-Val NCA were 1:1, 3:7 and 1:9 respectively. Compound **12a** had $[\alpha]_D^{20} = -109.19$ (*c*, 0.272 in CF_3COOH), compound **12b** had $[\alpha]_D^{20} = -109.98$ (*c*, 0.2473 in CF_3COOH), compound **12c** had $[\alpha]_D^{20} = -104.95$ (*c*, 0.2565 in CF_3COOH).

Benzoyl-L-alanyl-L-alanine, benzyl ester **19**. 3.62 g L-benzyl alaninate (20.2 mmol) was dissolved in 10 ml CH_2Cl_2. The mixture was cooled on and 5.00 g of dicyclohexylcarbodiimide (24.3 mmol), 10 ml CH_2Cl_2, and 4.18 g (21.7 mmol) of N-benzoyl-L-alanine were added. The mixture was stirred at room temp during 12 hr. Then 1.1 ml AcOH was added and the solid filtered off. The remaining soln was washed with NH_3 5N (20 ml), H_2O (2 × 20 ml), dried and evaporated, yielding an oil which was solidified crushing with EtOAc. The solid was crystallized from EtOAc-hexane (84%); m.p. 137–8°; $[\alpha]_{578}^{20} = -20°$ (*c*, 1.15, Cl_2CH_2); ^{1}H NMR (d$_6$DMSO) 1.4 (d, 6H), 4.55 (m, 2H), 5.2 (s, 2H), 7.3–8.2 (m, 10H), 8.5 (br, 2H). (Found: C, 67.66; H, 6.63; N, 8.29. Calc for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90%).

N-Butyl-benzoyl-L-alanyl-L-alaninamide **13**. 1.6 g (5.01 mmol) of **19** was dissolved in 10 ml of butylamine, stirring magnetically. In a few min the formation of a white solid was observed. The reaction was prolonged at room temp for 12 hr. The solid was filtered off and crystallized from MeOH (65%); m.p. 255–6°; $[\alpha]_{578}^{20} = -24.8°$ (*c*, 0.476 MeOH); IR (KBr) 3270, 3050, 1630, 1530 and 690; ^{1}H NMR (d$_6$DMSO) 0.6–1.6 (m, 13H); 3.1 (br, 2H); 4.4 (m, 2H); 7.3–8.3 (m, 5H); 8.7 (br, 3H). (Found C, 64.26; H, 7.89, N, 13.07. Calc for $C_{17}H_{25}N_3O_3$: C, 63.93 H, 7.89, N, 13.15%).

Epoxidation of chalcone in the presence of catalysts **3–12**

General procedure.[1] The catalyst (400 mg) was added to a soln of **1** (2.4 mmol) in CCl_4 (6.00 g). Then, 4.4 ml of a soln of NaOH in H_2O_2 (0.08 g ml^{-1}) was added and the mixture was stirred at room temp for the appropriate time (Table 1). The reaction was monitored by TLC and when necessary, 2.2 ml of the alkaline soln was added after 24 hr. The catalyst was filtered off and washed with CH_2Cl_2 (50 ml). The organic phase was washed with water (3 × 25 ml), dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography on SiO_2 using petroleum ether–diethyl ether 9:1 as eluent. Reaction times, optical rotations, chemical yields and e.e. are depicted in Tables 1–3.

Epoxidation of substrates other than chalcone. Substrate **22** (780 mg; 4.8 mmol), toluene (6.00 g) and catalyst (400 mg) and 4.4 ml of the soln of NaOH in 30% H_2O_2 were stirred at room temp for the appropriate time (Table 4). The mixture was worked up as described and the crude product was eluted on SiO_2 (10 g) using CH_2Cl_2 as eluant. Optical rotations, chemical yields and e.e. are depicted in Table 4.

Compound **20** (413 mg, 2.5 mmol), toluene (6 g), catalyst (200 mg) and 4 ml of a soln of K_2CO_3 in 30% H_2O_2 (0.15 g ml^{-1}) was stirred for 24 hr. The mixture was worked up to give a solid free from starting material, m.p. 94–96°. Optical rotations, chemical yields and e.e. are depicted in Table 4.

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