Enantiocomplementary asymmetric epoxidation of selected enones using poly-L-leucine and poly-D-leucine

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The use of poly-leucines for asymmetric epoxidations has been broadened to include a variety of α,β-unsaturated ketones and dienones.

Enantioselective epoxidation constitutes an extremely appealing strategy for the synthesis of optically active organic compounds. This is well illustrated by the dramatic emergence of the titanium tartrate-catalysed epoxidation of allylic alcohols as one of the most widely applied reactions in asymmetric synthesis.[1] In our search for non-enzymic biocatalysts we became interested in the use of poly-amino acids to control the course of oxidation reactions. The use of synthetic chiral polypeptides for the asymmetric epoxidation of α,β-unsaturated ketones has been reported by Juliá et al.[2] However, high enantioselectivities appeared to be limited to *trans*-chalcone derivatives.[3] We felt that poly-amino acids had a greater synthetic potential and we started an investigation into the scope and versatility of this reaction. Our initial results are reported herein.

The D- and L-enantiomers of a range of chiral epoxy ketones have been prepared in good to excellent yield and excellent optical purity (Table 1). All the epoxidations were carried out at ambient temperature in a three-phase system with an organic solvent, a catalytic amount of poly-L-leucine[4] or poly-D-leucine[+] and a large excess of oxidant (30% aqueous H_2O_2–NaOH). It was found that pre-activation of the catalyst by stirring the mixture for 6 h before addition of the α,β-unsaturated ketone resulted in shorter reaction times and reactions were typically finished in 1–3 days. During this pre-activation time the polymer swells and apparently adopts a more reactive physical state. The initial solvent of choice was hexane. However substrates that did not undergo epoxidation in hexane were easily oxidised in dichloromethane with good chemical yield and high enantioselectivity. The optical purity of the products was determined by chiral HPLC[‡] using the racemates[§] as reference standards. For epoxidations with poly-L-leucine the 2R,3S configuration was assigned to the epoxides based upon optical rotation measurements[¶] and NMR experiments using Eu(hfc)$_3$. The use of poly-D-leucine always resulted in the formation of the complementary enantiomers. The catalyst was recovered after oxidation of the enone 1a and was re-used in a second reaction with no adverse effect on the rate or enantioselectivity of the reaction, as observed previously.

Scheme 1 *Reagents:* i, poly-L-leucine + H_2O_2–NaOH–CH_2Cl_2; ii, poly-D-leucine + H_2O_2–NaOH–CH_2Cl_2

The results summarised in Table 1 and Scheme 1 indicate that the epoxidation has a broad substrate specificity and, therefore, is not restricted to chalcones. Satisfactory enantioselectivities were obtained for substrates with heteroaromatic substituents (entries 1c–e) and with a second conjugated double bond (entries 1h–i). The epoxides 2c–e and 2h–i are of special interest since they allow further functionalisation of the molecule (*e.g.* furan hydrolysis to the carboxylic acid,[5] 2c–e, and ozonolysis of the double bond, 2h, i). Epoxidation of the p-MeSC$_6$H$_4$ derivative 1f led to the isolation of the sulfoxide 3 as a by-product in 22% yield.** This observation opens a potential area of application of poly-amino acids to other asymmetric oxidations and further work towards the asymmetric oxidation of sulfides is in progress in these laboratories.

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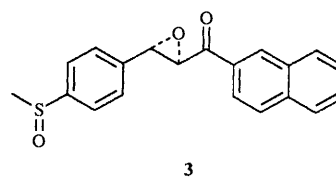
The reactions of other substrates were also examined. As shown in Scheme 2 the olefins 4 and 6 afforded the corresponding diepoxides with good diastereoselectivity and excellent enantioselectivity. The formation of the diepoxide 5 is the first example indicating that an aromatic or conjugated alkene substituent is not necessary for the epoxidation to occur. We are currently investigating the oxidation of other alkyl substituted α,β-unsaturated ketones.

Epoxidations have also been carried out in a triphase system of aqueous sodium perborate, dichloromethane and poly-L-leucine or poly-D-leucine. A catalytic amount of a phase-transfer catalyst such as aliquat 336 was needed for the reaction to occur. The epoxides 2a and 2b have been obtained in enantiomeric excesses of up to 90% under non-optimised reaction conditions. Further investigations in this area will be reported in due course.
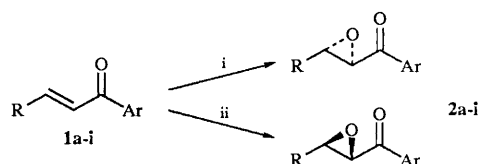

[†] Synthesised in the same way as poly-L-leucine according to ref. 4.

[‡] The optical purities of the chiral epoxy ketones 2a–i were determined using a Chiralpak AD column at the wavelength of 254 nm.

[§] The racemic epoxy ketones were prepared by epoxidation of the α,β-unsaturated ketones with 30% aqueous H_2O_2 and toluene using a phase-transfer catalyst according to ref. 4.

[¶] The absolute configuration of the epoxy ketone 2a had been determined by X-ray crystal structure (see ref. 3d) and the compound showed a negative optical rotation.

All the L-epoxy ketones derived from poly-L-leucine (including compound 2a) behaved in a similar manner in the presence of the chiral shift reagent; the epoxy ketones derived from reactions catalysed by poly-D-leucine showed different behaviour in terms of the chemical shift of protons adjacent to the carbonyl group.

** For the epoxidation with poly-D-leucine a shorter reaction time reduced the amount of sulfoxide formed. After 40 h, only a trace of this by-product was observed.

Table 1 Epoxidation of the enones 1a–i

Entry	R	Ar	Catalyst	Yield (%)	ee (%)
1a	Ph	2-Naphthyl	poly-L-leucine	85	93
1b	Ph	2-Naphthyl	poly-D-leucine	67	93
1c	2-Furyl	2-Naphthyl	poly-L-leucine	75	>96
1d	Ph	2-Furyl	poly-L-leucine	85	87
1e	Ph	2-Furyl	poly-D-leucine	98	93
1f	p-MeSC$_6$H$_4$	2-Naphthyl	poly-L-leucine	65	96
1g	p-MeSC$_6$H$_4$	2-Naphthyl	poly-D-leucine	82	>96
1h	PhCH=CH	2-Naphthyl^a	poly-L-leucine	78	>96
1i	PhCH=CH	2-Naphthyl^a	poly-D-leucine	76	>96

^{a} Reaction performed in hexane.
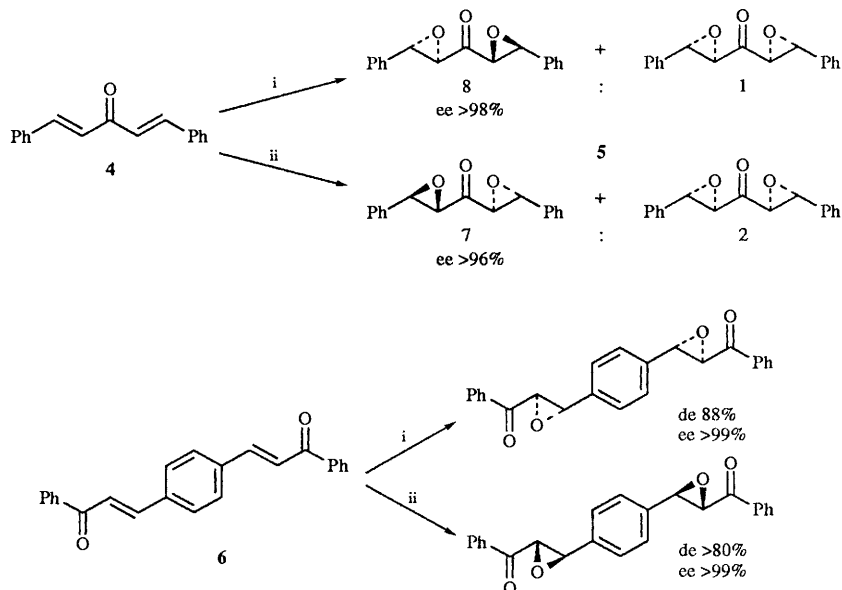
Scheme 2 *Reagents:* i, poly-L-leucine + H$_2$O$_2$–NaOH–CH$_2$Cl$_2$; ii, poly-D-leucine + H$_2$O$_2$–NaOH–CH$_2$Cl$_2$

In summary, we believe the use of poly-amino acids for the catalysis of asymmetric oxidations is dramatically under-exploited. Perceived advantages of these catalysts are as follows. (i) They are cheap, easy to prepare and indeed commercially available.†† (ii) They are recoverable, reusable and applicable to large-scale reactions. (iii) Changing from the poly-L- to the poly-D-system switches the enantiomer of the epoxide. (iv) They allow a range of simple and achiral starting materials to be converted into chiral products in excellent yield and high optical purity. (v) Oxidations can be accomplished using peroxide or perborate.

Experimental

General procedure for the epoxidation of enones using peroxide.

To a solution of NaOH (206 mg, 5.15 mmol) in distilled water (0.5 cm^3), cooled in an ice-bath, were added CH$_2$Cl$_2$ (1.8 cm^3), poly-L-leucine (111 mg) and 30% aqueous H$_2$O$_2$ (1 cm^3, 9 mmol). The mixture was allowed to warm to room temperature and then stirred for 6 h to allow the polymer to swell. The α,β-unsaturated ketone (0.43 mmol) was then added to it. If after 18 h the reaction was incomplete, a solution of NaOH (30 mg) in 30% aqueous H$_2$O$_2$ (0.3 cm^3) was added to the reaction mixture and stirring was continued until the reaction was complete. After dilution of the reaction mixture with ethyl acetate (10 cm^3) the catalyst was filtered off and the filtrate was washed with water and brine, dried and

evaporated to afford the crude product, which was purified by recrystallisation or column chromatography.

References

1 E. N. Jacobsen, *Catalytic Asymmetric Synthesis*, ed. I. Ojima. VCH, Weinheim, 1993, 159.
2 S. Juliá, J. Masana and J. C. Vega, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 929.
3 (a) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1317; (b) S. Colonna, H. Molinari, S. Banfi, S. Juliá, J. Masana and A. Alvarez, *Tetrahedron*, 1983, **39**, 1635; (c) S. Banfi, S. Colonna, H. Molinari, S. Juliá and J. Guixer, *Tetrahedron*, 1984, **40**, 5207; (d) P. W. Baures, D. S. Eggleston, J. R. Flisak, K. Gombatz, I. Lantos, W. Mendelson and J. J. Remich, *Tetrahedron Lett.*, 1990, **31**, 6501; (e) S. Itsuno, M. Sakakura and K. Ito, *J. Org. Chem.*, 1990, **55**, 6047.
4 J. R. Flisak, K. J. Gombatz, M. M. Holmes, A. A. Jarmas, I. Lantos, W. L. Mendelson, V. J. Novack, J. J. Remich and L. Snyder, *J. Org. Chem.*, 1993, **58**, 6247.
5 A. Dondoni, F. Junquera, F. L. Merchán, P. Merino and T. Tejero, *Tetrahedron Lett.*, 1994, **35**, 9439.

†† A range of poly-L- and poly-D-amino acids is available from Anelko Ltd.