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Towards a Mechanistic Insight into the Juliá-Colonna Asymmetric Epoxidation of α, β-Unsaturated Ketones Using Discrete Lengths of Poly-leucine.

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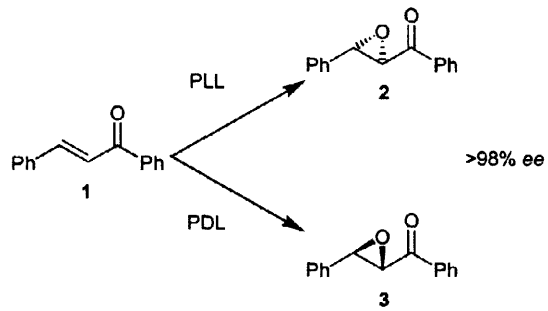
Abstract: Accurate length poly-leucines have been used to evaluate mechanistic features of the asymmetric epoxidation of chalcone. Studies have been directed towards the influence of the length of the chain, the stereochemistry of the amino acid residues and the nature of the terminal amino group.

The poly-leucine catalysed stereocontrolled epoxidation of chalcones was discovered by Juliá and Colonna[1] (Scheme 1) and successfully utilised by Flisak,[2] Ferreira *et al.*[3] Recently it has become clear that the epoxidation is not restricted to chalcones[4] and that the optically active epoxyketones produced are of considerable use in synthetic organic chemistry.[5] An understanding of the mechanism by which the polyamino acid catalyses the stereoselective epoxidation is crucial if the protocol is to be developed much further.



Scheme 1. Asymmetric Epoxidation of Chalcone Using Poly-L-leucine (PLL) or Poly-D-leucine (PDL). Triphasic conditions: H_2O_2 (aq), NaOH (aq), toluene. Biphasic conditions: Urea hydrogen peroxide adduct, DBU, THF.

The polymeric catalyst is normally synthesised by preparation of leucine-*N*-carboxyanhydride (leu NCA) and addition of an initiator, for example an amine, an alcohol or water.[6] The product is a mixture of oligomers, typically containing macromolecules with a molecular weight range 1500-3000 Da.[7] Recently we have made poly-leucines of specified chain length joined at the *C*-terminus *via* a hydroxybenzoic acid linker to polyethylene glycol and thence to a polystyrene resin (PEG-PS). We report preliminary studies with these polypeptides with a view to understanding the molecular interactions between polymer, peroxide and enone which lead to the often-exquisite stereocontrol.[4]

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Samples of H-L-Leu$_{10}$-PEG-PS (10L) and H-L-Leu$_{20}$-PEG-PS (20L) were prepared using a peptide synthesiser and used to catalyse the epoxidation of chalcone using the original triphasic procedure and the new biphasic conditions (Table 1).[8] As expected the biphasic protocol gave a faster reaction (Table 1, Entries 1,3) with both methods achieving similar enantioselectivities.

Entry	Conditions	Catalyst	Time (h)	Conversion (%)	Product *ee* (%)
1	Triphasic	10 mer	35	85	66
2	Triphasic	20 mer	9	96	91
3	Biphasic	10 mer	1.5	62	54
4	Biphasic	20 mer	1.5	48	59
5	Biphasic	Activated* 10 mer	1.5	90	85
6	Biphasic	Activated* 20 mer	1.5	57	89

Table 1. The Epoxidation of Chalcone Using PEG-PS Bound Oligo-L-leucine of Varying Lengths Giving Epoxychalcone **2**. * Poly-leucine stirred with toluene (70 mL) and NaOH (4M, aq, 30 mL) for approx. 18 h, washed with various solvents and dried *in vacuo* (12 h). Conversion and *ee* calculated by HPLC [Column: Chiralpak® AD; Eluent: ethanol (10%), hexane (90%); UV detector wavelength: 254nm].

We have noted previously that the polyamino acid performs much better in the biphasic reaction when "activated" by treatment with aqueous sodium hydroxide.[9] Not surprisingly, therefore, this procedure was found significantly to increase the rate of reaction and the enantiomeric excesses of epoxide **2** derived from the 10 mer and 20 mer catalysed reactions (Table 1, Entries 5 and 6). It is noteworthy that the 10 mer of leucine is capable of exerting significant stereocontrol.

Next a series of polymers modified by incorporation of D-leucine residues at the *N*-terminus [H-D-Leu$_X$-L-Leu$_Y$-PEG-PS (XD/YL)] were constructed. Three polymers, 5D/15L, 7D/13L and 9D/11L were used as catalysts for biphasic and triphasic epoxidations of chalcone (Table 2).

In contrast to H-L-Leu$_{20}$-PEG-PS (Table 1, Entry 2), the polymer 5D/15L produces the enantiomer of epoxychalcone normally derived from the poly-D-leucine series (**3**) with moderate *ee* (Table 2, Entry 1). An increase to 7 or 9 D-leucine residues at the *N*-terminus gives greater stereoselectivity for the epoxidation (Table 2, Entries 2 and 3). Similar results are obtained in the biphasic system for this series of peptides (Table 2, Entries 4, 5 and 6), confirming prior observations made using heterogeneous length D/L mixtures prepared *via* Leu NCA.[7] Thus the asymmetric epoxidation of chalcone (**1**) appears to be controlled by the stereochemistry of the amino acid residues in the *N*-terminal region of the oligomer chain.

Entry	Conditions	Catalyst	Time(h)	Conversion (%)	Major Product	*ee* (%)
1	Triphasic	5D/15L	32	85	**3**	(45)
2	Triphasic	7D/13L	32	100	**3**	(80)
3	Triphasic	9D/11L	32	98	**3**	(71)
4	Biphasic	5D/15L	1.5	68	**3**	(52)
5	Biphasic	7D/13L	1.5	81	**3**	(83)
6	Biphasic	9D/11L	1.5	87	**3**	(81)

Table 2. Comparison of 20 mer Oligo-leucine Chains Containing L- and D-Leu Residues for the Epoxidation of Chalcone. Conversion and *ee* calculated by HPLC [Column: Chiralpak® AD; Eluent: ethanol (10%), hexane (90%); UV detector wavelength: 254nm].

When D/L mixtures of 10 mers were studied it was evident that a single D-leucine residue at the *N*-terminus was not sufficient to give epoxide **3** as the major enantiomeric product (Table 3, Entries 2 and 6). The 3D/7L catalyst gave almost racemic products using both methods (Table 3, Entries 3 and 7). More surprisingly in light of the results using the 5D/15L catalyst, the 5D/5L oligomer also produced essentially racemic epoxide (Table 3, Entries 4 and 8).

Entry	Conditions	Catalyst	Time (h)	Conversion (%)	Major Product	*ee* (%)
1	Triphasic	10L	35	85	**2**	(66)
2	Triphasic	1D/9L	35	31	**2**	(29)
3	Triphasic	3D/7L	35	34	**2**	(5)
4	Triphasic	5D/5L	35	82	**3**	(5)
5	Biphasic	10L	2.5	98	**2**	(77)
6	Biphasic	1D/9L	2.5	94	**2**	(65)
7	Biphasic	3D/7L	2.5	73	**2**	(15)
8	Biphasic	5D/5L	2.5	96	**3**	(2)

Table 3. Comparison of 10 mer Oligo-leucine Chains Containing L- and D-Leu Residues for the Epoxidation of Chalcone. Conversion and *ee* calculated by HPLC [Column: Chiralpak® AD; Eluent: ethanol (10%), hexane (90%); UV detector wavelength: 254nm].

It seems that the *C*-terminal region is responsible for assembling the correct overall architecture so as to present the *N*-terminal region in an optimal way for it to dictate the stereochemistry of the resultant epoxide. Two experiments (*e.g.* Table 2, Entry 1 and Table 3, Entry 1) suggest the minimum size of the *C*-terminal domain must be between 5 and 15 residues to allow the *N*-terminal region to demonstrate its chiral control. Evidently the chiral induction of the peptide is not just dependent upon the primary structure of the peptide.

The 5D/15L catalyst was cleaved from the PEG-PS support using TFA (95%)(aq) to give H-D-Leu_5-L-Leu_{15}-OH, which provided the epoxide **3** (21% *ee*) upon oxidation of chalcone (**1**) under biphasic conditions.

The depreciation in enantioselectivity is undoubtedly due to the effect of TFA since poly-leucine produced by the NCA method lost its catalytic power on treatment with this acid.

Finally the oligo-leucine incorporating an *N,N*-dimethyl moiety at the *N*-terminus (Me_2N-L-Leu_{20}-PEG-PS) was synthesised and used as a catalyst for the epoxidation of chalcone (**1**); the *N,N*-dimethylpolyleucine gave comparable enantioselectivity to that obtained using H-L-Leu_{20}-PEG-PS under biphasic conditions, showing quite clearly that the free NH_2 group does not play a key role in the binding of peroxide and/or enone into position.

In summary this study highlights three facets of polyleucine catalysed epoxidation reactions. First a 10 mer of L-leucine effects good stereocontrol; secondly the 5 amino acid residues adjacent to the *N*-terminus dictate the stereochemistry of the product, but the NH_2 group itself is not crucial; thirdly the *N*-terminal region's influence is dependent on the presence of more than 5 and up to 15 residues adjacent to the *C*-terminus but the stereochemistries of the latter residues seems to be relatively unimportant. Other studies are ongoing utilising customised, discrete length peptides, effectively performing "point mutations" on the "synthetic enzymes (synzymes)".[1]

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References

1. Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929-931.
2. Flisak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmas, A. A.; Lantos, I.; Mendelson, W. L.; Novack, V. J.; Remich, J. J.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 6247-6254.
3. Nel, R.J.J.; van Heerden, P. S.; van Rensburg, H.; Ferreira, D. *Tetrahedron Lett.* **1998**, *39*, 5623-5626.
4. Pu, L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457-1477.
5. Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501-3507.
6. Kricheldorf, H. R. *α-Aminoacid-N-Carboxyanhydrides and Related Heterocycles*; Springer-Verlag: Berlin, 1987.
7. Bentley, P. A.; Kroutil, W.; Littlechild, J. A.; Roberts, S. M. *Chirality* **1997**, *9*, 198-202.
8. Bentley, P. A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E. *Chem. Commun.* **1997**, 739-740.
9. Allen, J.V., Roberts, S.M., Williamson, N.M., Advances in Biochem. Eng. Biotechnol., eds. Faber, K., Scheper, T., in press.