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The effect of the primary structure of the polypeptide catalyst on the enantioselectivity of the Juliá–Colonna asymmetric epoxidation of enones

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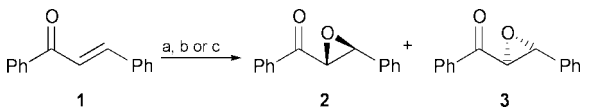
Epoxidation of chalcone (1), using basic hydrogen peroxide, catalysed by polypeptides with defined primary structures demonstrates that the residues in the chain near to the *N*-terminus determine the stereochemical outcome of the reaction.

In recent years there has been an increase in the application of peptides as catalysts for asymmetric reactions.[1] One of the first reported examples was the asymmetric epoxidation of chalcones, catalysed by polyamino acids in a triphasic system, discovered and developed by Juliá and Colonna.[2] Advances in this field have been made through the introduction of biphasic protocols, leading to an expansion in the range of enones which can be epoxidised with good stereoselectivity.[3] These methodologies have been successfully applied to reach various synthetic targets.[4]

For such synthetic work, the preferred catalyst is polyleucine prepared by the polymerisation of leucine *N*-carboxyanhydride (Leu-NCA), in an organic solvent, using a nucleophilic initiator (typically 1,3-diaminopropane or cross-linked aminomethyl polystyrene).[5] This polymerisation generates a mixture of oligomers with a distribution of chain lengths. Epoxidation of chalcone (**1**) using a catalyst prepared from L-Leu-NCA (15 equivalents compared to the initiator) at the start of the process followed by D-Leu-NCA (5 equivalents) provided the first indication that the *N*-terminal region of the chain has a disproportionately large influence on the stereochemical outcome of the reaction.[6]

In order to investigate more thoroughly the influence of the primary structure of a given polypeptide on its activity as an epoxidation catalyst, selected oligoleucines were prepared using an automated peptide synthesiser. It was shown that H-(L-Leu)$_{20}$-R† catalyses the epoxidation of chalcone (**1**), to afford the (2*R*, 3*S*)-epoxide **2**, in a similar manner to the NCA-derived polymer having an *average* chain length of twenty residues.[7] A peptide was then prepared in which the five *N*-terminal L-Leu residues were replaced by D-Leu: H-(D-Leu)$_5$-(L-Leu)$_{15}$-R. This material catalysed the epoxidation of chalcone (**1**) to give the antipodal (2*S*, 3*R*)-epoxide **3** with 85% conversion and 45% ee after 32 hours under the Juliá–Colonna triphasic conditions (Scheme 1).[8] In this last catalyst, the D-Leu residues make up only 25% of the total polyamino acid, however they dictate the stereochemical outcome of the reaction.

In this paper the use of other polypeptides as epoxidation catalysts is reported, in order to investigate in detail which residues in the *N*-terminal region are responsible for determining the origin of the stereocontrol exhibited by these catalysts.



Scheme 1 *Reagents and conditions*: (a) aq. NaOH, aq. H_2O_2, catalyst, toluene; (b) DBU, urea–H_2O_2, catalyst, THF; (c) $Na_2CO_3{\cdot}1.5H_2O_2$, catalyst, DME, water.

First, in order to determine whether the terminal amine group plays a defining role in the action of the peptide catalyst, three derivatives of H-(L-Leu)$_{20}$-R were prepared. In the first, one of the terminal amine hydrogens was substituted by an acetyl group [Ac-(L-Leu)$_{20}$-R]. The second oligomer had the same hydrogen replaced by a methyl group [Me-(L-Leu)$_{20}$-R] while the third had both amine hydrogens replaced by methyl groups [Me$_2$-(L-Leu)$_{20}$-R].‡ The peptides were tested as catalysts for the epoxidation of chalcone (**1**) under mild reaction conditions in order to minimise the possible cleavage of the sterically unhindered acetyl moiety (Table 1). The biphasic conditions[3a] utilise urea–H_2O_2 and DBU in THF, whilst the percarbonate conditions[3b] employ sodium percarbonate as both base and oxidant, in a DME–water solvent mixture.

Table 1 Epoxidation of chalcone (**1**) using selected catalysts

Catalyst[a]	Conditions[b]	Time/h	Conversion[c] (%)	Ee[d] (%)
H-(L-Leu)$_{20}$-R	Percarbonate	7	94	88
Ac-(L-Leu)$_{20}$-R	Percarbonate	5	96	50
Me-(L-Leu)$_{20}$-R	Percarbonate	5	98	67
Me$_2$-(L-Leu)$_{20}$-R	Percarbonate	6	82	58
H-(L-Leu)$_{20}$-R	Biphasic	1.07	100	92
Me$_2$-(L-Leu)$_{20}$-R	Biphasic	1.5	78	78

[a] For the reactions under the biphasic conditions the catalyst was activated before use by stirring with toluene–aq. NaOH for 18 h, filtered and then washed with water, acetone and hexane. [b] Ref. 3. [c] Determined by HPLC. [d] Determined by chiral HPLC.

All three polymers gave significant enantioselectivities (50–78% ee). The polymer Ac-(L-Leu)$_{20}$-R gave the lowest ee but clearly this modification (which markedly reduces the basicity and nucleophilicity of the terminal nitrogen atom) does not render the catalyst wholly inactive. This result is in agreement with the observation by Ohkata[9] that a 20-mer of L-Leu, protected at the amino-terminus with a Boc group and at the carboxylate end as a benzyl ester, when used as an epoxidation catalyst, affords chalcone epoxide **2** in 41% ee.

Next, a series of five peptides, H-(L-Leu)$_n$-(D-Leu)$_5$-(L-Leu)$_{15-n}$-R where n = 1–5 was prepared (these are referred to as *n*L/5D/(15 − *n*)L). These peptides were used to catalyse the epoxidation of chalcone (**1**) under the triphasic conditions[2] and the results are summarised in Table 2. On using the peptide L/5D/14L as a catalyst, the major product was epoxide **3** (*i.e.* that normally generated under poly-D-leucine catalysis), with an ee somewhat greater than that observed for the 5D/15L polymer.[8] In contrast, utilisation of the polymer 2L/5D/13L led to a sharp drop in the ee of the product; however the major enantiomer was still the epoxide **3**. Moving the block of five D-Leu residues one step further away from the amino terminus had another dramatic effect on the outcome of the epoxidation. Thus the 3L/5D/12L catalyst provided the epoxide **2** (normally generated using the

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Table 2 Epoxidation of chalcone (**1**) using mixed D- and L-Leu catalysts under triphasic[a] conditions over 32 h

Catalyst	Major product	Conversion[b] (%)	Ee[c] (%)
1L/5D/14L	**3**	99	67
2L/5D/13L	**3**	96	11
3L/5D/12L	**2**	100	89
4L/5D/11L	**2**	99	86
5L/5D/10L	**2**	99	88

[a] Ref. 2. [b] Determined by HPLC. [c] Determined by chiral HPLC.

poly-L-leucine catalyst) in 89% ee; the oligomers 4L/5D/11L and 5L/5D/10L gave very similar results. From this study it appears that the penultimate and antepenultimate residues from the *N*-terminus play a dominant role in determining the stereoselectivity of the Juliá–Colonna reaction.

We reasoned that, given the above results, the inclusion of glycine residues close to the *N*-terminus might have a significant effect on the catalytic activity of the peptide. Three catalysts H-(L-Leu)-Gly-(L-Leu)$_{18}$-R, H-(L-Leu)-Gly$_2$-(L-Leu)$_{17}$-R and H-(L-Leu)-Gly$_3$-(L-Leu)$_{17}$-R were prepared. Inclusion of three glycine residues reduces the ee of the epoxide **2** significantly; the effect of incorporating two glycine residues is more modest and the substitution of Gly for L-Leu in the penultimate position has relatively little effect, when compared to the polymer containing only L-Leu residues (Table 3). Interestingly, incorporation of the glycine residues results in a reduced conversion to the epoxide as well as diminishing the enantioselectivity.

Table 3 Epoxidation of chalcone (**1**) using selected catalysts under triphasic[a] conditions over 24 h

Catalyst	Conversion[b] (%)	Ee[c] (%)
H-(L-Leu)$_{20}$-R	97	88
H-(L-Leu)-Gly-(L-Leu)$_{18}$-R	90	70
H-(L-Leu)-Gly$_2$-(L-Leu)$_{17}$-R	79	52
H-(L-Leu)-Gly$_3$-(L-Leu)$_{17}$-R	60	29

[a] Ref. 2. [b] Determined by HPLC. [c] Determined by chiral HPLC, in each case epoxide **2** was the major enantiomer.

Finally, on the evidence that the residues close to the amino terminus of the polypeptide chain have the primary influence on the stereochemistry of the oxidation reaction, the peptides H-(L-Leu)$_n$-(D-Leu- L-Leu)$_8$-R, where n = 3–6, were prepared. These have an equal mixture of the two enantiomers of leucine in the bulk of the peptide chain and a different number of residues of the L-enantiomer at the amino terminus.

Table 4 shows that the polymers with five or six consecutive L-Leu residues at the amino terminus are excellent catalysts. Surprisingly, even the polymer with just three L-Leu residues at the amino terminus generates **2** with significant ee. It is noteworthy that this polymer has only one change (D- to L-Leu) from a polymer with residues of alternating stereochemistry, adding a little more weight to the postulate that polyamino acids could potentially have been prebiotic catalysts,[10] in as much as these results show that even a small excess of one enantiomer in an oligomeric structure, when correctly assembled, can lead to an amplification and a diversification of chirality.

Overall, it appears that the enone substrate and/or the peroxide reagent binds to the polyleucine near the *N*-terminus. It may well be pertinent that the final four N–H groups of an α-helical peptide are not able to act as hydrogen bond donors to carbonyl groups within the helix, thus providing a possible explanation for the differentiation between the terminal region and the bulk of the peptide. Kinetics and spectroscopy experiments are being undertaken (using PEG-bound polyamino acids that are soluble in organic solvents[11]) to ascertain which species is complexed to the chiral environment of the polymer. Such experimentation seems prudent before more detailed modelling can commence.

Table 4 Epoxidation of chalcone (**1**) using selected catalysts under triphasic[a] conditions over 18 h

Catalyst	Conversion[b] (%)	Ee[c] (%)
H-(L-Leu)$_3$-(D-Leu-L -Leu)$_8$-R	55	64
H-(L-Leu)$_4$-(D-Leu-L -Leu)$_8$-R	52	64
H-(L-Leu)$_5$-(D-Leu-L -Leu)$_8$-R	95	92
H-(L-Leu)$_6$-(D-Leu-L -Leu)$_8$-R	98	91

[a] Ref. 2. [b] Determined by HPLC. [c] Determined by chiral HPLC, in each case epoxide **2** was the major enantiomer.

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Notes and references

† The oligoleucines were linked *via* a hydroxymethylphenoxyacetic acid linker to PEG and thence to polystyrene resin (loading 0.18 mmol g^{-1}). These oligomers are represented as H-(Leu)$_n$-R where R = linker–PEG-resin.

‡ Strictly speaking this material is Me$_2$NCH(CH$_2$CHMe$_2$)CO(L-Leu)$_{19}$R, the nomenclature Me$_2$-(L-Leu)$_{20}$-R is used for convenience.

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