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Review Article

Polyamino Acids as Catalysts in Asymmetric Synthesis

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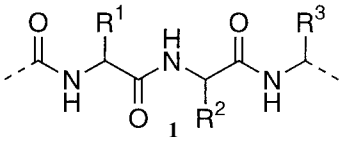
Abstract—The use of polyamino acids in asymmetric organic synthesis is reviewed. Particular emphasis is placed on the asymmetric epoxidation of α,β-unsaturated ketones with hydrogen peroxide in the presence of polyalanine or polyleucine, and further transformations of the epoxide products.

Introduction

Enzymes are complex macromolecules consisting of up to 20 different amino acids. Typically, neighbouring amino acid residues are different [(**1**) $R^1 \neq R^2 \neq R^3 \ldots$], and an enzyme contains few regions of homogeneity. This structural diversity leads to the wide variety of enzymes that are found in microorganisms, plants and animals. However the very complexity of protein structure has the consequence that the vast majority of enzymes are not amenable to chemical synthesis; recourse to cloning of the gene and over-expression of the protein is normally the mechanism by which large quantities of enzymes are obtained.



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Enzymes are able to catalyse a wide range of reactions.[1–3] The hydrolysis of esters and amides, the esterification of alcohols and the reduction of ketones are popular biotransformations amongst synthetic organic chemists, not least because enzymes frequently confer a high degree of chemo-, regio- and/or stereoselectivity to the process. Furthermore, the use of bio-hydroxylation reactions is widespread in academia and industry. The conversion of acyclic, heterocyclic and alicyclic molecules (e.g. steroids) into alcohols is well established;[4] the employment of mono-oxygenases in whole cells often leads to hydroxylation at a position remote from pre-existing functionality.[5–7] The oxidation of aromatic compounds to provide phenols is also an important transformation and has been carried out on a large scale.[8] The conversion of aromatic compounds into cyclohexadienediols is a biotransformation that is impossible to emulate in one step using other chemical technology. Such dienediols have been exploited in a most elegant fashion in organic synthesis.[9,10]

One area of biotransformation that is notably uncommon is the conversion of alkenes into epoxides (oxiranes). While there are isolated examples of epoxidations (Scheme 1) giving optically active products, these usually involve terminal alkenes and certainly the biocatalytic process does not have wide applicability.[11,12]

In contrast to the dearth of naturally occurring proteins which can catalyse epoxidation, Juliá reported in 1980 that a *synthetic* polypeptide consisting solely of alanine residues, i.e. (**1**) $R^1 = R^2 = R^3 = CH_3$, is able to catalyse the epoxidation of chalcone (**4**) and similar enones (Scheme 2).[13] It was demonstrated that the oxidation reaction occurs with a high degree of enantioselectivity; the authors concluded, however, that the protocol was only applicable to chalcones, that is compounds of the type $Ar^1COCH{=}CHAr^2$.

This reaction was the first example of asymmetric catalysis by a synthetic polypeptide; subsequent to this work, a number of further examples have been reported. In this review we shall survey the preparation and use of polyamino acids in asymmetric synthesis.[14,15] The review focuses largely on asymmetric epoxidation of enones, highlighting recent developments that expand the range of epoxides which may be generated.[16–21]

Key words: Amino acids and derivatives; peptides and polypeptides; polymers; reviews.

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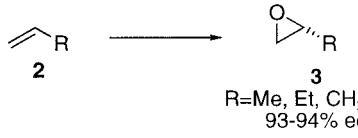
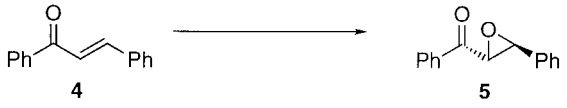


Scheme 1. *Reagents and conditions: Micrococcus* sp. M90C, 30°C, 14–24 h.



Scheme 2. *Reagents and conditions*: aq. H_2O_2, poly-L-alanine, aq. NaOH, toluene, 24 h, 85% yield, 93% ee.

In addition, we shall discuss briefly some of the reactions which have been performed on the chiral α,β-epoxy-ketones so produced.

Preparation of Poly-α-amino Acids

The most commonly used method for polymerisation of α-amino acids involves initial activation of the amino acid **6** towards nucleophilic attack by formation of an *N*-carboxyanhydride (NCA, **7**) (Scheme 3). This is achieved by use of phosgene[22,23] or an equivalent such as diphosgene[24,25] or triphosgene;[26] alternatively an *N*-alkoxycarbonyl-protected amino acid **8** may be cyclised using thionyl chloride.[27,28] Polymerisation is then initiated by addition of a nucleophile, typically water,[29] an amine[30] or diamine[31] to give polymer **9**.[32,33] This method gives a range of chain lengths in the polymer product, although the average length can be controlled by varying the ratio of NCA to initiator.

The polymers prepared using simple initiators have proved difficult to separate from the reaction products. This problem can to some extent be alleviated by use of polyamino acids attached to a polystyrene support; these are prepared by use of a hydroxy-[34] or amino-functionalised[35] cross-linked polystyrene as the initiator.

An alternative method of polyamino acid synthesis, and one which may prove most useful in the elucidation of reaction mechanisms, is the controlled generation of defined chain length polymers using standard solid-phase peptide synthesis techniques.[36]

Applications of Poly-α-amino Acids in Synthesis

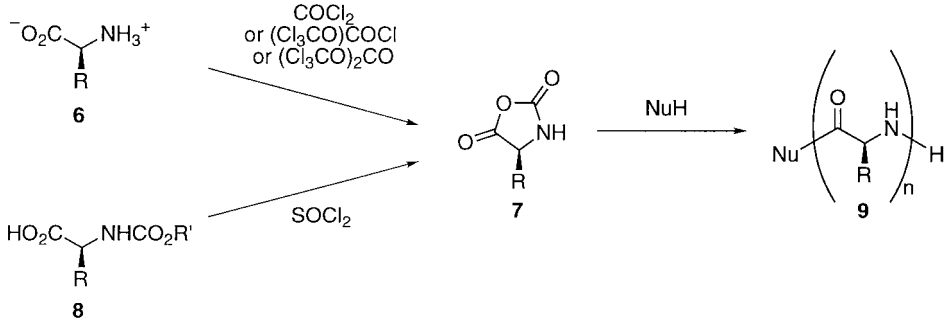
Synthetic polyamino acids have found various applications including use as chiral stationary phases for chromatography[37,38] and as matrices for controlled drug delivery systems.[39,40] In this review, however, we shall concentrate on their use as catalysts in asymmetric synthesis.

The first report detailing the use of a polypeptide in asymmetric synthesis was by Akabori et al. in 1956.[41] Using palladium supported on the structural protein silk fibroin, moderate enantiomeric excesses were obtained in the hydrogenation of prochiral carbon–carbon and carbon–nitrogen double bonds (Scheme 4). For example, hydrogenation of the oxazolinone **10** followed by hydrolysis afforded unnatural D-phenylalanine (**11**) in 16% yield with 36% ee. Similarly, hydrogenation of oxime derivative **12** afforded L-glutamic acid (**13**) in 39% yield with ca. 7% ee.

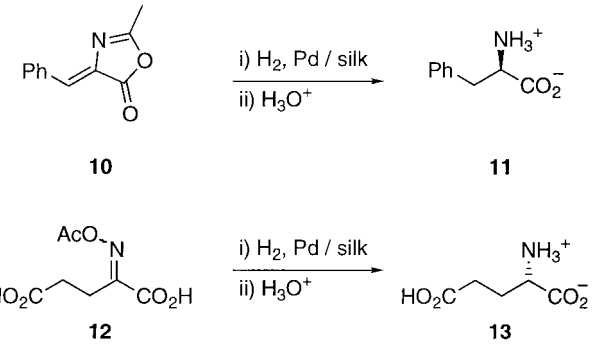
The use of polyamino acids as ligands for palladium was also reported by Alper et al.[42] The palladium-catalysed carbonylation of but-2-en-1-ol (**14**) proceeds in the presence of high molecular weight (ca. 22,000) poly-L-leucine to give (*R*)-α-methyl-γ-butyrolactone (**15**) in 49% yield and 61% ee (Scheme 5). This optical purity was superior to those obtained with "conventional" ligands such as diethyl tartrate or BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene).

Nonaka and co-workers have reported the use of polyamino acids as electrode coatings for asymmetric electrochemical oxidations and reductions. Thus, reduction of 4-methylcoumarin (**16**) on a graphite cathode coated with poly-L-valine afforded (*S*)-3,4-dihydro-4-methylcoumarin (**17**) in 43% ee, albeit with a chemical yield of only 8% (Scheme 6).[43] Likewise, reduction of citraconic acid (**18**) yielded (*S*)-methylsuccinic acid (**19**) with an ee of 25%.[43–45] Curiously, use of a poly-D-valine-coated electrode was reported to give the *same* enantiomer of **19** with lower optical purity.[44]

Reductions of α-keto acids, oximes and a geminal dibromide were less successful than the conjugate reductions, with the reported enantiomeric excesses being in the range 0–17%.[46]



Scheme 3.



10 **11** **12** **13**

Scheme 4.

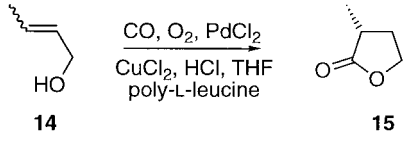
Similarly, the asymmetric oxidation of alkyl aryl sulphides to sulphoxides using a platinum electrode coated first with polypyrrole and then with a poly-L-amino acid proceeds with good enantioselectivity (Scheme 7).[47,48] The highest ee, 93%, was obtained in the oxidation of *tert*-butyl phenyl sulphide (**20**) to the corresponding (*S*)-sulphoxide **21** on a poly-L-valine-coated electrode.

The most extensively studied reaction that uses a polyamino acid as a catalyst is the asymmetric epoxidation of conjugated enones discovered by Juliá et al. in 1980.[13] Initial results showed that poly-L-alanine could catalyse the epoxidation of chalcone (**4**) (for example by using hydrogen peroxide and sodium hydroxide in a toluene–water mixture), affording (2*R*,3*S*)-epoxychalcone (**5**) in good yield and 93% ee (Scheme 8). More details of this reaction are documented in the following section.

Juliá–Colonna Epoxidation

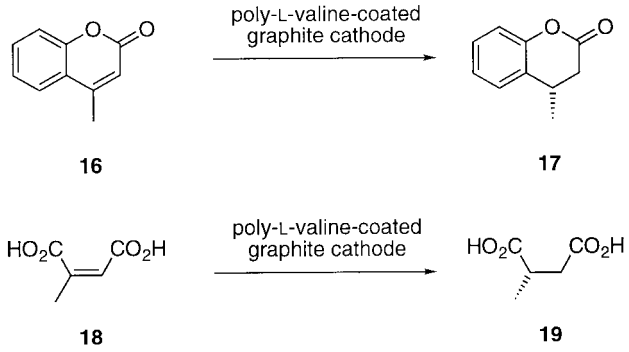
The initial report of asymmetric epoxidation by Juliá and co-workers utilised insoluble poly-L-alanine as catalyst and aqueous hydrogen peroxide as oxidant in a mixture of aqueous sodium hydroxide and toluene. In a series of papers, Juliá and Colonna systematically examined and optimised the conditions for this transformation:[13,34,49–51]

- Carbon tetrachloride and toluene were reported as the optimal organic solvents for the reaction, whilst cyclohexane and *n*-hexane were found to give poor asymmetric induction.[49] Juliá and Colonna also reported that the use of methanol as a solvent results in racemic product; it was suggested that the alcoholic solvent disrupts hydrogen bonding which was postulated to be important in setting up the chiral environment essential for an asymmetric reaction. In a subsequent study (by Lantos, Novak et al.) on the asymmetric epoxidation of the naphthyl ketone **30** (Table 1), different solvent effects were found.[52] In this case *n*-hexane was reported to be the optimal organic solvent with carbon tetrachloride and cyclohexane also being effective, whilst toluene gave little or no reactivity. The origin of these differing solvent dependences is not clear.
- It was found that the relative proportions of the three phases (solid catalyst, organic solvent and aqueous) has a significant effect on the chemical yield and optical purity. Optimum conditions for the epoxidation of 1 g of chalcone were reported to be 8.8 cm^3 of water, 13.9 cm^3 of toluene and 800 mg of catalyst.[13]
- The length of the polyamino acid chain has a significant bearing on the outcome of the reaction. Initial studies were carried out using a polymer with a mean length, *n*, of 10 residues;[53] subsequently it was reported that, on examination of a range of polymers with $n = 5$–30, increased polymer length resulted in an increase in the optical purity of the product.[49]
- A range of different amino acid monomers was investigated;[51] it was found that poly-L-alanine, poly-L-leucine and poly-L-*iso*-leucine are good catalysts for the epoxidation of chalcone (**4**). Poly-L-valine was also reported to catalyse the reaction but with reduced rate and optical purity of product (4% yield and 30% ee after 12 days reaction). Poly-L-phenylalanine and poly-L-proline were found to give essentially racemic product.[34] Interpretation



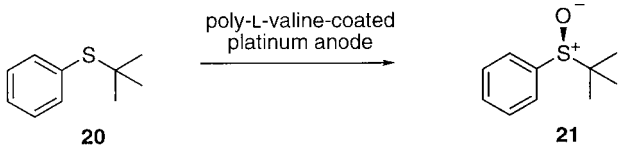
14 **15**

Scheme 5.



16 **17** **18** **19**

Scheme 6.



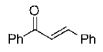
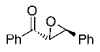
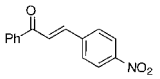
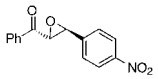
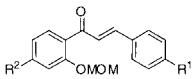
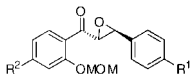
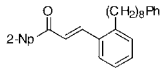
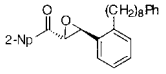
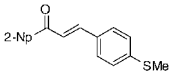
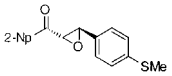
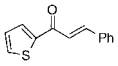
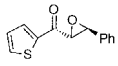
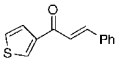
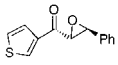
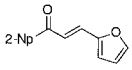
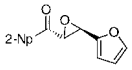
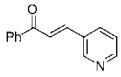
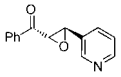
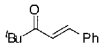
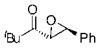
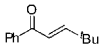
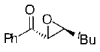
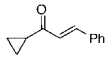
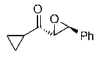
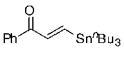
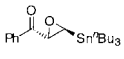
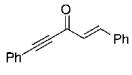
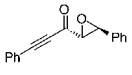
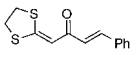
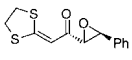
20 **21**

Scheme 7.

4 **5**

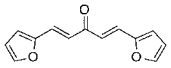
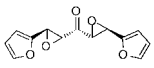
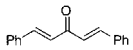
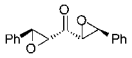
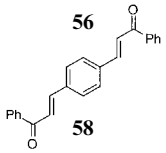
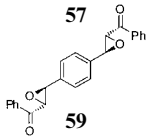
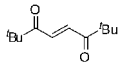
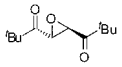
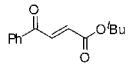
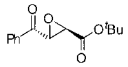
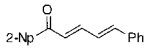
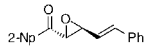
Scheme 8. *Reagents and conditions:* aq. H_2O_2, poly-L-alanine, aq. NaOH, toluene, 24 h, 85% yield, 93% ee.

Table 1. Substrates epoxidised under triphasic reaction conditions[a]

Substrate	Product	Method	Yield %	ee %	Ref
		a	85	93	[13]
4	**5**				
		a	83	82	[49]
22	**23**				
					
24 $R_1 = R_2 = H$	**25** $R_1 = R_2 = H$	b	65	38	[55]
26 $R_1 = OMe$, $R_2 = H$	**27** $R_1 = OMe$, $R_2 = H$	b	64	66	[55]
28 $R_1 = R_2 = OMe$	**29** $R_1 = R_2 = OMe$	b	74	84	[55]
		c	82	95	[52]
30	**31**				
		d	82	> 96	[59]
32	**33**				
		a	96	80	[49]
34	**35**				
		a	30	70	[49]
36	**37**				
		e	75	> 96	[59]
38	**39**				
		d	70	94	[31]
40	**41**				
		e	92	> 98	[31]
42	**43**				
		e	85	90	[31]
44	**45**				
		e	85	77	[62]
46	**47**				
		f	90	> 99	[63]
48	**49**				
		g	57	90	[62]
50	**51**				
		e	51	> 94	[62]
52	**53**				

(continued on next page)

Table 1 (*continued*)

Substrate	Product	Method	Yield %	ee %	Ref
 **54**	 **55**	e	60	90	[60]
 **56**	 **57**	e	—	> 98	[59]
 **58**	 **59**	e	74	> 99	[31]
 **60**	 **61**	g	100	> 95	[62]
 **62**	 **63**	g	66	> 95	[62]
 **64**	 **65**	f	78	> 96	[31]

[a] *Reagents and conditions:* a. aq. H_2O_2, aq. NaOH, toluene, poly-L-alanine; b. aq. H_2O_2, aq. NaOH, CCl_4, poly-L-alanine; c. aq. NaOH, *n*-hexane, EDTA, poly-L-leucine; d. aq. H_2O_2, aq. NaOH, DCM, poly-D-leucine; e. aq. H_2O_2, aq. NaOH, DCM, poly-L-leucine; f. aq. H_2O_2, aq. NaOH, *n*-hexane, poly-L-leucine; g. aq. H_2O_2, aq. NaOH, toluene, CLAMPS-poly-L-leucine.

of these results in terms of the expected secondary structure of the various polyamino acids was attempted. Poly-L-alanine and poly-L-leucine are reported to form α-helices, whereas poly-L-valine is known to adopt a β-sheet structure. This suggests that increased α-helical character might be associated with catalytic function and degree of asymmetric induction. Further support for this hypothesis was provided in the form of results obtained with poly-DL-alanine; this is known to adopt the β-sheet conformation and, as expected, generates **5** in poor yield. Not all the results were consistent with the α-helix hypothesis: poly-L-*iso*-leucine is reported to exist as a β-sheet; however it proved to be an excellent catalyst. Moreover, poly-β-benzyl-L-aspartate and poly-γ-benzyl-L-glutamate adopt α-helices with opposite handedness, but each gives the same major enantiomer in the epoxidation reaction. Unfortunately both were relatively poor catalysts for the reaction (enantiomeric excesses 3 and 11.6%, respectively). In a later study Lantos and Novak[52] examined a range of polyamino acids and reported that poly-L-leucine consistently gave the highest yields and enantioselectivities.

- As the polyamino acid catalysts are insoluble in the reaction medium it is possible to filter, wash and then re-use them. Juliá and Colonna reported reduced catalytic ability and asymmetric induction with recycled poly-L-alanine.[51] The reduction in catalytic ability was less if a longer polymer was employed or if poly-L-leucine was used instead of poly-L-alanine. It was suggested that the reduced effectiveness of the recycled catalyst stems from degradation of the catalyst *via* hydrolysis. The increased stability of poly-L-leucine under the reaction conditions was ascribed to its greater steric bulk. In contrast to these results Lantos and Novak[52] found that they could re-use poly-L-leucine (the polymer length was not reported) six times and observed no erosion in either yield or ee.
- The physical form of the polyamino acid catalysts changes under the triphasic conditions; the catalyst swells to form a gel. A number of authors recommend an initial swelling stage to the reaction, prior to addition of the substrate, in which the catalyst, oxidant, base and solvents are stirred for a number of hours.[52]
- In early work little attention was paid to the nature of the initiator employed in the polymerisation reaction used to generate the catalyst (vide supra), with some workers employing water[52] and others amine nucleophiles.[13] However, in 1990 Itsuno and co-workers[35] examined the use of a cross-linked aminomethyl polystyrene (CLAMPS) polymer as an initiator. Polyamino acids generated with this initiator are easier to handle due to the larger particle size which facilitates rapid and easy filtration of the catalyst after the reaction has finished.
- Generally the oxidant employed is an excess of aqueous hydrogen peroxide, which has the advantage of being cheap and readily available. Attempts have been made to extend the methodology to allow the use of hydrogen peroxide

adducts which are more easily and safely handled than aqueous hydrogen peroxide. Roberts et al. have shown that sodium percarbonate and sodium perborate can both be used. There is some variation in ee and reaction time with different oxidants; indeed on some occasions sodium perborate and sodium percarbonate have proved the more effective.[31] A number of attempts have been made to use *tert*-butyl hydroperoxide and, although it has been shown to effect the Juliá–Colonna reaction, greatly reduced enantioselectivities are observed.[31,49]

Triphasic conditions — substrate range

Juliá and Colonna employed a relatively narrow range of substrates; essentially all reported examples were analogues of chalcone (**4**). Subsequent workers have expanded the substrate range somewhat; Ferreira and Bezuidenhoudt[54–58] and Lantos and Novak[52] have reported a number of examples with different aryl substituents. In a series of papers[31,59–62] Roberts et al. reported the results of a systematic attempt to extend the substrate range and to find the limits of reactivity. Recently, in a paper concerned with the development of copper catalysed epoxy-stannane cross-coupling, Falck has demonstrated the first example of a vinyl stannane **48** undergoing the Juliá–Colonna epoxidation.[33] Table 1 illustrates selected results from all these workers.

In addition to chalcone, a range of aryl-substituted substrates, bearing both electron-donating and electron-withdrawing groups has been reported. It is possible to replace either aryl substituent with a heteroaryl ring, such as pyridine, thiophene or furan. Introduction of aliphatic chains can result in reduced enantioselectivity, although *tert*-butyl and cyclopropyl ketones are particularly good substrates. A number of sulphur(II) containing compounds have been epoxidised without oxidation of the sulphur moiety. Roberts et al. have oxidised a range of substrates containing more than one double bond and/or carbonyl group clearly mapping out the selectivities obtainable with such systems.

Biphasic conditions

Despite the range of substrates which can be oxidised using the Juliá–Colonna procedure a number of problems limit the applicability of the methodology. The reaction times are long; reactive enones, such as chalcone (**4**), can be epoxidised in 24 h but a significant number of substrates prove to be essentially unreactive or are prohibitively slow to react. For example, oxidation of the diene **64** afforded the epoxide **65** in 78% yield and >96% ee under the triphasic conditions, but the reaction took 72 h. In particular, enolisable substrates, such as the *iso*-propyl **66** and methyl **68** ketones were found to be epoxidised very slowly or not at all (Scheme 9).[62] Furthermore, additional equivalents of aqueous hydrogen peroxide must be added at regular intervals. The triphasic conditions also limit the potential range of substrates to which the methodology may be applied, i.e. to those compounds which are stable in the presence of nucleophilic, aqueous base.

66 R=^{i}Pr **67** 60%, 62% ee

68 R=Me **69** No reaction

Scheme 9. *Reagents and conditions:* aq. H_2O_2, aq. NaOH, DCM, poly-L-leucine, 168 h.

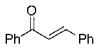
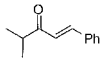
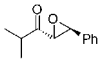
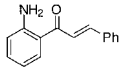
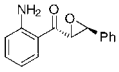
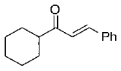
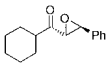
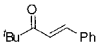
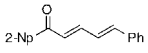
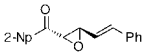
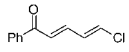
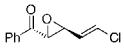
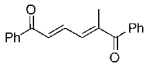
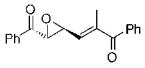
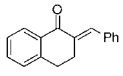
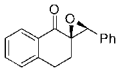
In 1997 a modified Juliá–Colonna epoxidation protocol was reported which served to overcome these limitations.[64] Under the new "biphasic conditions" the reaction is performed in a non-aqueous solvent, using a water-free source of hydrogen peroxide and a non-nucleophilic amine base. A range of solvents was surveyed and tetrahydrofuran, 1,2-dimethoxyethane, *tert*-butyl methyl ether, dimethylsulphoxide, *N*,*N*-dimethylformamide and ethyl acetate were all found to be suitable; less effective solvents included dichloromethane, acetonitrile and toluene. The most effective base of those tested was DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). In order to minimise the amount of water in the reaction, it was necessary to add the oxidant in the form of a complex; examples of such complexes include those formed with urea[65] and DABCO (1,4-diazabicyclo[2.2.2]octane).[66] The ready availability of the urea–hydrogen peroxide complex (popularised by Heaney and commonly known as UHP) made this the oxidant of choice.

Under the biphasic conditions reaction times are greatly reduced; for example the epoxidation of chalcone (**4**) is complete in 30 min and the diene **64** is converted to the mono-epoxide **65** (85% conversion, >95% ee) in 3 h. Moreover, previously unreactive substrates could be oxidised, for example the methyl ketone **68** was converted into **69** in 70% yield and 80% ee in 4 h. Table 2 illustrates the range of substrates that has been epoxidised under the new conditions.[64,67,68]

In addition to a wider range of alkyl substituents, the new conditions may be used to oxidise dienones. Epoxidation of trisubstituted double bonds is slower than disubstituted cases, thus it is possible to oxidise **77** selectively. One case of a relatively reactive trisubstituted enone is the α-tetralone derivative **79**.

Even under these accelerated conditions various classes of substrate remain unreactive; thus far, attempts to epoxidise cinnamate esters and vinyl chlorides have proved unsuccessful,[67] whilst an α,β-unsaturated nitro compound has been readily epoxidised but with no enantioselectivity. Unlike the triphasic case the poly-amino acid catalyst appears not to swell appreciably under the biphasic conditions, instead the polymer adopts the appearance of a paste. Interestingly, it has been found that the rate and enantioselectivity of the reaction are maximised if the poly-L-leucine catalyst is first activated by stirring in a mixture of aqueous sodium hydroxide and an organic solvent, then filtered, washed and dried before use. The exact effect of this activation procedure is currently unclear.[72]

Table 2. Substrates epoxidised under biphasic conditions[a]

Substrate	Product	Method	Yield %	ee %	Ref
 **4**	 **5**	a	85	>95	[64]
 **66**	 **67**	a	100	97	[69]
 **68**	 **69**	a	70	80	[68]
 **70**	 **71**	a	81	>98	[70]
 **72**	 **73**	a	91	89	[68]
 **42**	 **43**	a	76	94	[68]
 **64**	 **74**	b	80	90	[67]
 **75**	 **76**	a	57	86	[67]
 **77**	 **78**	a	70	92	[67]
 **79**	 **80**	c	60	86	[71]

[a] *Reagents and conditions*: a. UHP, DBU, CLAMPS-poly-L-leucine, THF; b. UHP, DBU, CLAMPS-poly-D-leucine, THF; c. UHP, DBU, CLAMPS-poly-L-leucine, EtOAc.

Noting that under the biphasic conditions the poly-L-leucine does not swell appreciably it has been postulated that the modified Juliá–Colonna epoxidation might be applicable to a fixed-bed reactor approach to epoxide synthesis. In an initial small-scale study the epoxidation of chalcone (**4**) was found to be most effective on a column of CLAMPS-poly-L-leucine and DABCO-hydrogen peroxide using *tert*-butyl methyl ether containing DBU (0.5% v/v) as the eluent. A residence time of 20 min ensured the generation of epoxychalcone (**5**) in >97% conversion and >98% ee.[36]

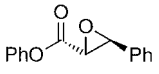
Elaboration of the epoxides

Epoxides generated using the Juliá–Colonna reaction have been elaborated into a number of optically active structures of biological interest, including Diltiazem,[68] the Taxol® side chain,[68] (+)-clausenamide[36] and a number of flavonoid derivatives.[54–58]

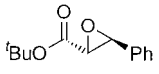
This section is not intended to be an exhaustive review of the chemistry of α,β-epoxy-carbonyl compounds. It concentrates on transformations reported on the products of Juliá–Colonna epoxidation reactions rather than the substrate class in general. The chemistry can be classified into two main areas, namely reaction at the carbonyl group and opening or rearrangement of the epoxide. Often the latter transformations are performed after manipulation of the ketone moiety, i.e. a typical approach is to elaborate the carbonyl group prior to opening the epoxide ring. This reflects the relative paucity of regioselective epoxide ring openings that may be accomplished at the ketone oxidation level. A third class of reaction, currently limited to a single example, involves carbon–carbon bond formation via an epoxy-stannane.[63]

Reaction at the carbonyl group. The three main transformations of the carbonyl moiety are Baeyer–Villiger oxidation, addition of alkyl metal reagents and reduction.

Flisak, Lantos et al. have reported the Baeyer–Villiger oxidation of a number of epoxychalcones prepared by Juliá–Colonna oxidation of the corresponding enones.[73] Oxidation was performed using *m*-CPBA (3-chloroperoxybenzoic acid) in dichloromethane and afforded the corresponding aryl esters in 57–80% yield and 87–>99% ee after recrystallisation (e.g. **81** is produced from **5** in 74% yield and >99% ee); as expected the oxidation does not affect the optical purity of the epoxide. The methodology was subsequently extended by Roberts and co-workers to include the readily available *tert*-butyl ketones; for example **82** is generated from **43** in 94% yield.[68] Thus, it is possible to convert epoxy ketones into either acid or base labile esters maximising the efficiency of the methodology for the synthesis of complex molecules.



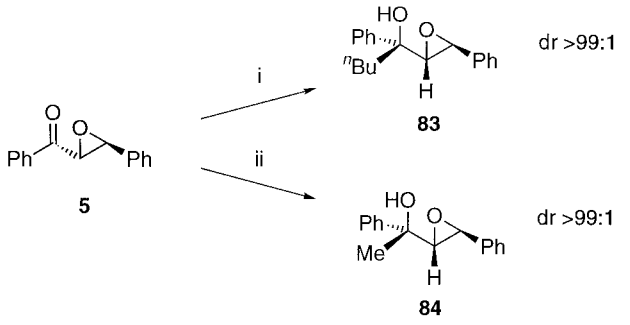
81



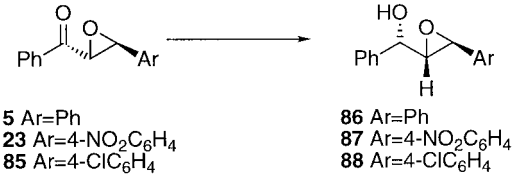
82

Roberts has also examined the addition of alkyl metal reagents to the ketone. Alkyl lithium, organocerium and Grignard reagents have been studied with the latter giving the best diastereoselectivities.[74,75] For example, epoxychalcone **5** was treated with *n*-butyl and methyl Grignard reagents to afford the corresponding tertiary alcohols **83** and **84** in reasonable yields and excellent diastereoselectivities (Scheme 10).

Stereoselective hydride reduction of the ketone has been studied by Colonna et al.[76] It was discovered that treatment of epoxychalcones **5**, **23** and **85** with zinc borohydride in ether afforded the corresponding *erythro*-configured secondary alcohols **86–88** with good stereocontrol and quantitative yields (Scheme 11).



Scheme 10. *Reagents and conditions:* i. *n*-BuMgI, diethyl ether, −78°C, 60%; ii. MeMgI, diethyl ether, −78°C, 89%.

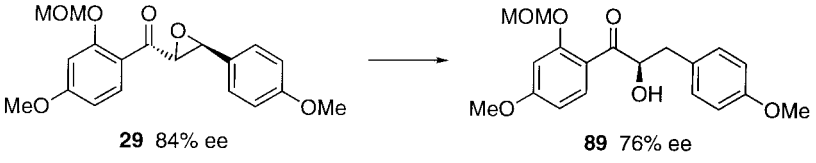


Scheme 11. *Reagents and conditions:* $Zn(BH_4)_2$, Et_2O, 0°C, 100%.

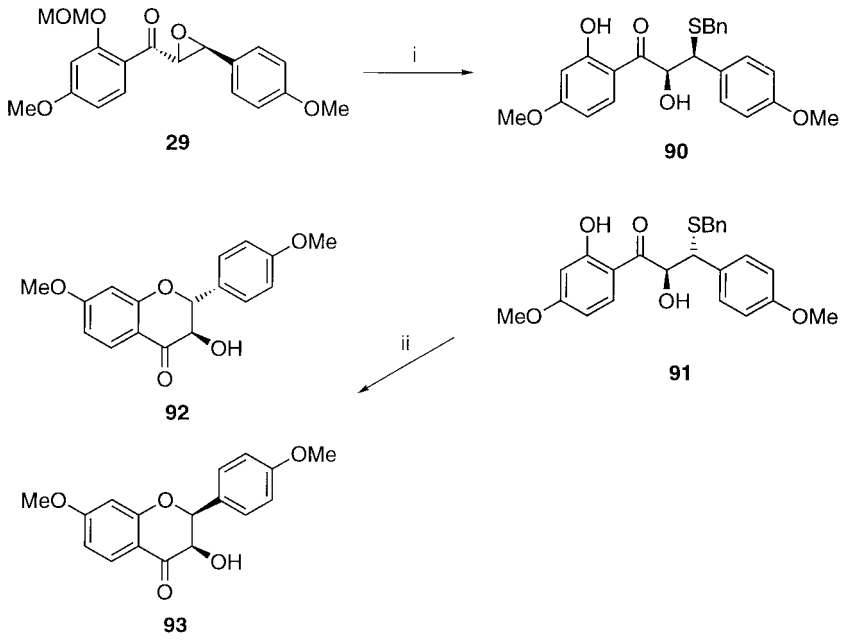
Transformation of the epoxide. Relatively little work has been reported on the selective intermolecular opening of the epoxide moiety of homochiral α,β-epoxy ketones. In a series of papers Ferreira has investigated the conversion of protected, polyoxygenated epoxychalcones, generated via Juliá–Colonna epoxidation, into flavonoids. Hydrogenolysis of epoxychalcones generates the α-hydroxydihydro-chalcone derivatives with little or no loss of optical purity.[56] For example, **29**, available in 84% ee from the corresponding chalcone, can be converted into **89** (ee 76%) by catalytic hydrogenolysis using palladium on barium sulphate (Scheme 12).

Initial attempts to deprotect the MOM group of **29** and to cyclise directly onto the epoxide moiety using the phenol nucleophile led to low optical and chemical yields of the desired product **92**.[55] These problems were overcome by the development of a two step protocol,[58] the first step consisting of opening the epoxide with concomitant deprotection of the MOM group using benzylthiol in the presence of tin tetrachloride. For example, treatment of **29** under these conditions afforded a mixture of the two diastereomeric sulphides **90** and **91** in a ratio of ca. 2.3:1 and an overall yield of 93%. Subsequent cyclisation of this mixture using a thiophilic Lewis acid, silver tetrafluoroborate, generated a mixture of the separable diastereomeric dihydroflavonoids **92** and **93** in an overall yield of 71% and a ratio **92**:**93** of 79:21 (Scheme 13).

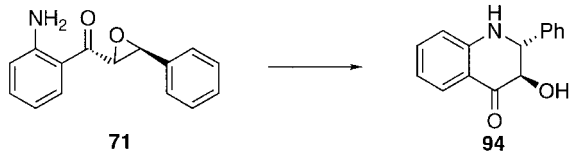
Roberts has also prepared cyclic derivatives by reaction of the epoxides with internal nucleophiles; amino chalcone **70** is readily converted to the epoxide **71** under the biphasic conditions (Table 2). Subsequent cyclisation proceeds smoothly with inversion to afford the chiral tetrahydroquinolone **94** in 52% yield over two steps and with >98% ee (Scheme 14).[70]



Scheme 12. *Reagents and conditions:* H_2, $Pd/BaSO_4$, MeOH, 88%.



Scheme 13. *Reagents and conditions:* i. BnSH, $SnCl_4$, DCM, −20 to 0°C, 93%; ii. $AgBF_4$, DCM, 71%.



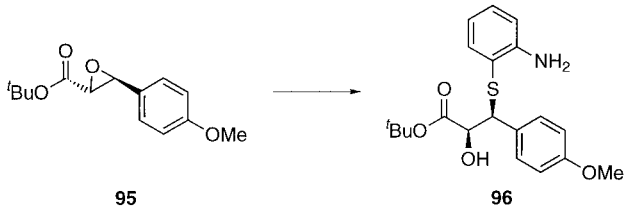
Scheme 14. *Reagents and conditions: n*-butanol, 85°C, 64%.

The only examples of selective, intermolecular opening of the epoxide moiety have been performed at the carboxylate oxidation state. In an efficient synthesis of the calcium channel blocker Diltiazem, Roberts' group utilised Inoue's epoxide opening[77,78] which proceeds with retention of configuration to convert epoxide **95** into **96** in 90% yield (Scheme 15).[68]

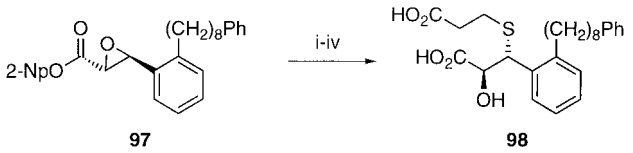
In their synthesis of SK&F 104353 (**98**) Lantos and Novak converted the ester **97** into a carboxylate salt then used a thiolate to selectively attack the β-carbon of the epoxide, with inversion of stereochemistry (Scheme 16).[52]

Roberts has also examined chemistry of the epoxide after addition to the carbonyl group; the tertiary alcohols generated by the previously described Grignard additions can be isomerised to the corresponding secondary alcohols via a silyl chloride-mediated Payne rearrangement; for example treatment of **84** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in DMF afforded the alcohol **99** in 69% yield. In addition, the epoxide was opened by reaction with tin tetrachloride at −78°C to afford the chloro-diol **100** with retention of configuration (Scheme 17).[74]

Carbon–carbon bond formation. Falck has recently reported a cross-coupling of epoxy-stannanes and reactive



Scheme 15. *Reagents and conditions: o*-aminothiophenol, PhMe, 110°C, 90%.

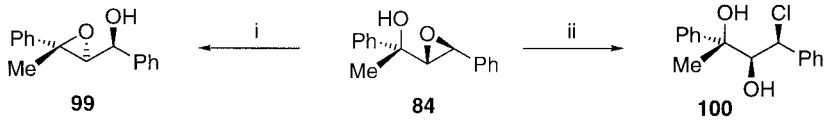


Scheme 16. *Reagents and conditions:* i. LiOH, H_2, MeOH, 95%; ii. $MeO_2C(CH_2)_2SH$, NaOMe, THF, MeOH; iii. NaOH, H_2O; iv. HCl, H_2O, 76%.

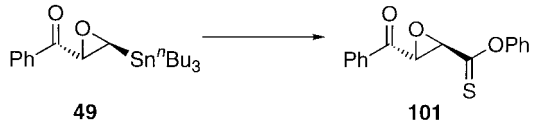
electrophiles mediated by copper (I) sulphide.[63] For example, epoxide **49**, obtained in >99% ee from vinyl stannane **48**, was coupled with phenyl chlorothionoformate to afford thionoester **101** in good yield (Scheme 18).

Mechanism of polyleucine-catalysed epoxidation reactions

A discussion of the mechanistic investigations into polyamino acid-catalysed epoxidation of electron-poor alkenes is beyond the scope of this review.[79,80] However, in the light of the catalytic activity of homogeneous poly-L-leucine[36] it is now possible to make selected "mutations" of the peptide to investigate the mode of action of the polymer in detail. We are currently active in this area.



Scheme 17. *Reagents and conditions:* i. TBDMS-Cl, imidazole, DMF, 69%; ii. $SnCl_4$, DCM, −78°C, 86%.



Scheme 18. *Reagents and conditions:* PhOC(=S)Cl, Cu_2S, THF, 60°C, 89%.

Conclusion

The Juliá–Colonna oxidation has emerged as a useful methodology for the preparation of optically active epoxides from α,β-unsaturated ketones. Given the commercial availability of the active catalyst[81] it is clear that further examples of the use of this simple protocol will appear. However the application of polyamino acid catalysis to other stereoselective oxidations and, indeed, to completely different processes must await a clear understanding of the ordering of the reactants on the chiral surface of the catalyst.

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Biography

Mike Porter was born in Harrogate, Yorkshire, UK on 2nd August 1970. From 1988 he studied at Merton College, the University of Oxford, where he received his B. A. degree in 1992. He remained in Oxford for his D. Phil. studies, investigating the biosynthesis of penicillins under the supervision of Professor Sir Jack Baldwin. In 1996 he was awarded a NATO Postdoctoral Fellowship to work with Professor Philip Magnus at the University of Texas at Austin, researching methods for the synthesis of *Amaryllidaceae* alkaloids. In February 1998 he returned to the United Kingdom to take up a post as a Senior Research Assistant at the University of Liverpool.

John Skidmore was born in Macclesfield, Cheshire, UK on January 13th 1972. He studied for his B. A. at St. Peters' College, the University of Oxford, graduating in 1994. Remaining at Oxford, he carried out research for his D. Phil. under the supervision of Dr. J. M. Peach, investigating the synthesis and properties of spin-labelled calcium ionophores. In 1997 he moved to the University of Liverpool where he currently holds the position of Senior Research Assistant, working with Professor S. M. Roberts on the chemistry of polyamino acids.

Stan Roberts was born in Hale, Cheshire, UK in 1945. After leaving school he joined ICI as a technician and studied for two years part-time to gain a Higher National Certificate in Chemistry. Two years of full time study at the University of Salford, UK led to the award of a first-class Honours degree. After studying polyhaloaromatic chemistry at Salford under the supervision of Professor Hans Suschitzky the award of Ph.D was made in 1969. Post doctoral periods with Professors Dreiding (Zurich) and Woodward (Harvard) followed. In 1972, Dr. Roberts was appointed lecturer in biochemistry and organic chemistry at Salford University, where he developed his interest in prostaglandin synthesis. Industry then beckoned again and, shortly after being appointed Reader, he left Salford in 1980 to join Glaxo (Greenford) as Head of Chemical Research. During the next six years Stan led teams involved in antimicrobial and anti-cancer chemotherapy. In 1986 he joined Exeter University as Professor of Organic Chemistry and set up a team in the area of biotransformations. Finally, in 1995 he joined Liverpool University as Heath Harrison Professor of Organic Chemistry, and has become fascinated, over this latter period, in biomimetic catalysis.