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Synthetic applications of polymeric α-amino acids

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1. Introduction

If chemists could combine the available 'toolkit' of amino acids and assemble polypeptide structures as complex as enzymes then we would have access to an almost limitless range of novel asymmetric catalysts. As well as high catalytic activities, we would also benefit from catalysts which exhibit high substrate selectivity — a feature which presently eludes synthetic catalysts.

As methods for the preparation of synthetic reagents are developed it is inevitable that chemists will eventually be able to prepare polypeptides of equal complexity and activity to naturally-occuring enzymes. This review describes some of the progress which has been made to date using simple polymers of single amino acids, which are not unknown in biological systems.[1] Some of this work has also featured in earlier reviews.[2–4]

2. Methods for the preparation of polymers of α-amino acids

Whilst automated peptide synthesis represents an attractive method for the synthesis of reagents of known length and purity, it is limited by the scale on which material can be prepared. In general the favoured method which has been adopted in the literature is the simple polymerisation of the amino acid N-carboxyanhydride (NCA) derivatives, which are generally crystalline and available in one step from amino acids (Scheme 1).

The subsequent polymerisation may be achieved by either reaction with a suitable amine or through the use of a humidity tank. The former method initiates the polymerisation through a nucleophilic attack followed by loss of carbon dioxide and subsequent further polymerisations. In general the average length of the polyamino acid chain thus formed is simply assumed to be directly related to the mole percentage of initiator amine employed. This crude method has obvious limitations but

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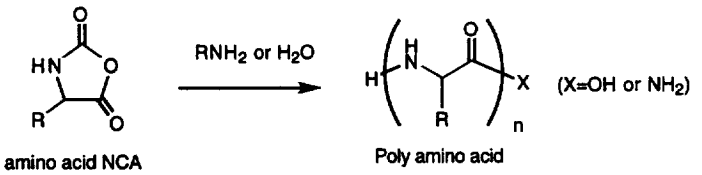


Scheme 1. Preparation of polymers of α-amino acids.

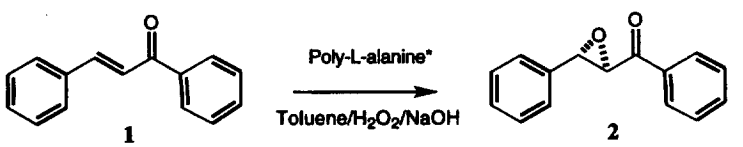
provided that an initiator of higher reactivity than the resulting amine of the chain is employed then it is generally reliable.[5] The reproducible formation of polymers of much over 20 amino acid units is somewhat limited due to potential hindrance of reactions at the amine terminus due to the developing secondary structure of the polymer chain.

A further advantage of the amine-initiated polymerisation method is that copolymers may be prepared simply by the sequencial reaction of quantities of amino acid NCAs with growing polymer chains. In a similar way, the reactive amine termini of extending polymers may be 'capped' or otherwise functionalised. This approach has been employed to prepare modified derivatives of polyamino acid catalysts.

The polymerisation of amino acids to give polymers is a spontaneous, although slow, process even within the solid crystalline material. This can be accelerated through the use of a humidity chamber in which very large quantities of polymer can be prepared. Some researchers prefer this method, however it should be noted that the use of *extremely* pure NCA derivatives is critical for the formation of good quality material.[6] Methods for the analysis of the product, such as MALDI-MS, give an indication of the molecular weight distribution but are limited by the extreme insolubility of the polyamino acid chains in all but the most polar of solvents.[7,8]

3. Polymers of α-amino acids as synthetic catalysts for epoxidation reactions

The use of polyalanine for the control of the asymmetric epoxidation of chalcone **1** was first reported in 1980 (Scheme 2).[9] A product **2** of up to 97% 'optical yield' was formed from a triphasic system of toluene, water, and polyalanine, which dissolves in neither solvent.[9–12] Attempts at the transformation in the absence of water failed.[10]



* Polymerisation initiated by action of n-BuNH$_2$ on L-alanine-NCA.

Scheme 2. Asymmetric epoxidation of chalcone mediated by polyalanine.

Notably it appeared that the strongly hydrophobic polyalanine was superior to polyglutamates and that the polymer was essential for the reaction to actually take place, as well as for asymmetric induction.[9,10] The latter result clearly implies that the oxidation reaction takes place on the surface of the polyleucine, i.e. it acts as a phase transfer catalyst. The reaction times, typically 48 hours, were relatively long and it often proved necessary to add further quantities of hydrogen peroxide to replace that which decomposes naturally under the reaction conditions. Polyalanines of a length of 10 amino acid units were commonly employed, although it appears that, up to a point, slightly longer polymers of 30 amino acid units had a slight advantage.[10,13] Later reports indicated that whilst poly-L-leucine and poly-L-isoleucine gave good results, polyvaline and polyphenylalanine were inferior reagents.[13]

Toluene and carbon tetrachloride appear to be the solvents of choice, whilst in contrast hexane and cyclohexane gave poor results. Hydrogen peroxide/sodium hydroxide as oxidant gave superior results compared to a number of other oxidants such as mCPBA, and *tert*-butyl hydrogen peroxide in combination with a variety of bases.[10] Some competitive results were reported for the use of sodium percarbonate as oxidant provided that aliquat 336 was added to the reaction mixture.[14] The reaction may be conveniently carried out at room temperature.[10]

The polymer could be recovered and reused after the first application, although at a small cost to conversion and asymmetric induction. It appears that the polymer is slowly digested by the strongly basic reaction conditions hence best results were obtained with recycled catalyst of long original chain length and with the bulkier poly-L-leucine reagent.[13] A relatively large quantity of polymer was required; typically 0.4 g polymer to 0.5 g substrate, although this could be reduced to some extent at the cost of yield but without a great loss of asymmetric induction.[9,10]

4. Mechanism of epoxidation

The exact mechanism by which the epoxidation is catalysed and the asymmetric induction generated remain somewhat unclear. Initial speculations were that hydrogen bonding between the chalcone and the polymer chain are important, since performing the reaction in methanol resulted in the formation of racemic product. Furthermore the use of poly-L-proline, which lacks N–H bonds, also gave poor results in terms of conversion and e.e., although it should be noted that it is likely to have a dramatically different secondary structure to that of most polypeptides.[15] The hydrophobic catalysts may assist the reaction by providing a suitable stabilising environment for the hydrophobic substrate.

It has been further speculated that polymers with a high degree of α-helical structure, which includes polyleucine and polyalanine, give the best results.[13] This may also explain the requirement, at least in early work in the area, for the polymers to contain at least 10 amino acid units, i.e. long enough to form distinct secondary structure. X-Ray powder diffraction studies suggest a certain degree of crystallinity in the polymers[5a] but more recent results have suggested that the polymer may actually be predominantly a β-sheet structure.[8] A physiochemical study of the polyleucine surface during the reaction showed enhanced stabilisation of water–solvent emulsions. Together with other observations this supports the operation of a mechanism which takes place in a monolayer.[16]

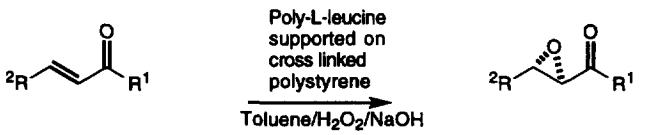
5. Variation of catalyst structure and use of polymer bound materials

For the majority of the early work on epoxidations Julia *et al.* favoured the use of poly-L-alanine derived from the action of n-$BuNH_2$ on the alanine NCA precursor. The corresponding polymers derived from initiation of the same polymerisation with N,N-diethylethylenediamine and a derived cationic catalyst proved to be inferior both in terms of yield and asymmetric induction.[10] In contrast the use of simple diamines as initiators gives polymers which furnished excellent results in the epoxidation reaction.[14] Simple variations of the N- and O-terminal groups of the polypeptide appear to have little effect on the activity of the catalyst; different N-terminal groups may be introduced by employing a different amine, or water if a carboxylic terminus is required, as the polymerisation initiator, whilst alkylation of the N-terminus may be achieved through the reaction with formaldehyde and formic acid.[15]

Latitude of this type in a synthetic catalyst has many potential advantages when it comes to practical utility. It has been noted that polyleucine of chain lengths of ca. 10–30 units, which are typical for the applications described above, tend to be of a particle size which commonly blocks filter devices. In view of this the anchorage of the polymer chains to a larger inert support such as polystyrene, appears attractive. In an early paper this was achieved through the reaction of a hydroxy-loaded polystyrene with polyalanine-NCA to give a polymer which performed almost as well as the non-bound version in the prototype reaction.[15]

However perhaps the most effective polymer-bound polyamino acid system is that reported by Itsuno *et al.* in 1990.[17] In this work a simple benzylamine-loaded cross-linked polystyrene was used

to initiate the polymerisation of alanine and leucine-NCAs to form polymers with various lengths of appended amino acid chains. Of these the best examples featured poly-L-leucine of chain lengths ca. 30 units proved to be the most effective in terms of activity and practical utility. Indeed the polymer supporting process significantly increases the stability of the polyamino acids, although beyond a certain limit of surface functionalisation this advantage is lost. Using the optimal solvent toluene in the three-phase process it was possible to obtain products of 94% e.e. in 95% yield after 12 recycles of the catalyst! A series of epoxidations were described in this paper (Scheme 3). Later results following on from this work in which the block copolymers were prepared and used in the epoxidation suggest that the region of the peptide nearest the amino terminus of the polymer is responsible for the greater part of the observed asymmetric induction.[8]



R^1=Ph, R^2=Ph	94% yield	97% e.e.
R^1=Ph, R^2=p($MeOC_6H_4$)	89% yield	90% e.e.
R^1=Ph, R^2=p($NO_2C_6H_4$)	90% yield	99% e.e.
R^1=Ph, R^2=o($MeOC_6H_4$)	56% yield	76% e.e.
R^1=Ph, R^2=o($EtOC_6H_4$)	56% yield	83% e.e.
R^1=Ph, R^2=p(ClC_6H_4)	98% yield	99% e.e.
R^1=p($MeOC_6H_4$), R^2=Ph	83% yield	87% e.e.
R^1=p(ClC_6H_4), R^2=Ph	98% yield	99% e.e.

Scheme 3.

A similar approach to the support of polyalanine was achieved through the use of a polymethacrylate polymer system bearing polyalanine side chains. Although it worked well shortcomings in terms of stability were noted.[18]

6. Substrate variation

The oxidation reaction shown in Scheme 2 appears to be particularly selective and suitable for the oxidation of enones. Quite a large degree of variation of structure is tolerated provided that the 1,3-diphenyl substituted, or similar, motif is retained in the substrate. In a series of studies by Julia which followed up his initial work a number of chalcone derivatives were successfully oxidised in high enantiomeric excesses using the aforementioned triphasic conditions (Figure 1).[10] In the cases illustrated, the enantiomeric excesses were determined through the use of a chiral shift reagent. In contrast, the oxidations of electron poor double bonds within substrates of dramatically different structure gave inferior results (Figure 1).[10,13]

In a series of recent reports by Roberts, the methodology (using humidity-tank generated poly-L-leucine) has been extended to the epoxidation of a further series of compounds including furyl and pyridyl substituted substrates (Figure 1).[10,14,19] The oxidation of the sulphide-substituted substrate **3** gave the product of double bond epoxidation in good yield before side products from the oxidation of the sulfide were formed. The bis-epoxidation of dieneones was also found to be a remarkably selective reaction (Scheme 4). This transformation benefits from the mathematical advantage afforded to the e.e. when two new chiral centres are created in one operation on the same molecule, hence the asymmetric inductions are some of the highest ever observed for this process.[14,19,20] In the example shown good results were achieved using dichloromethane as solvent, which is in contrast to many early reports, and the addition of the phase transfer catalyst aliquat 336 was demonstrated to provide a significant advantage in some cases.[14,19] Conjugated enones are epoxidised at the double bond adjacent to the carbonyl group (Scheme 5).[14]

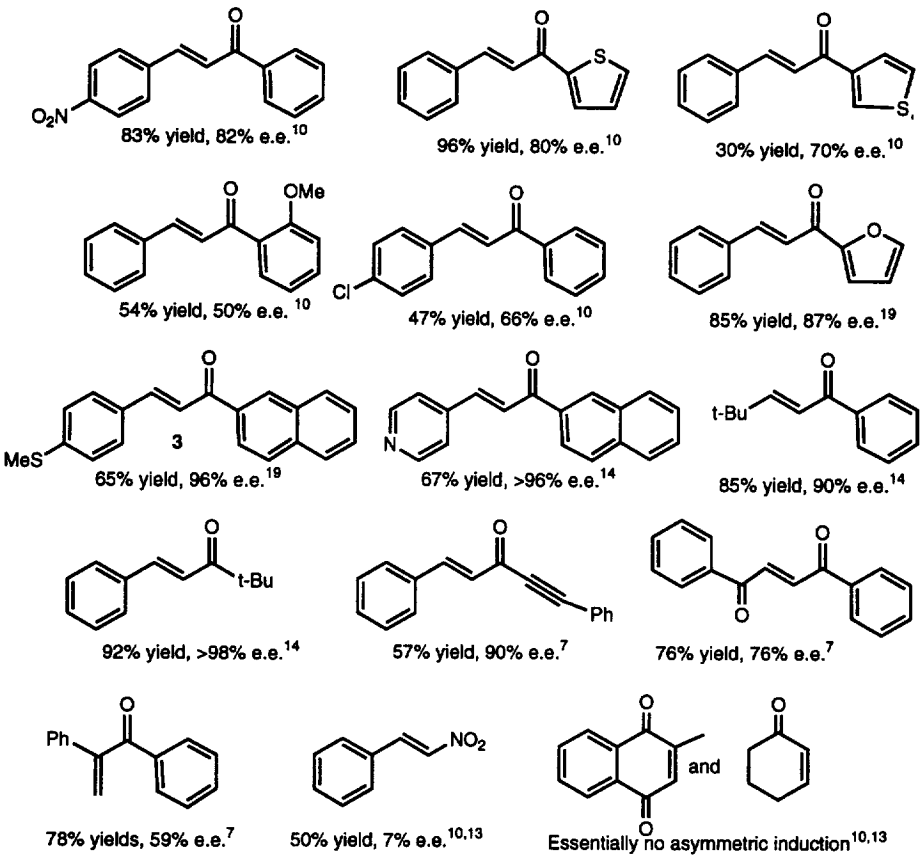
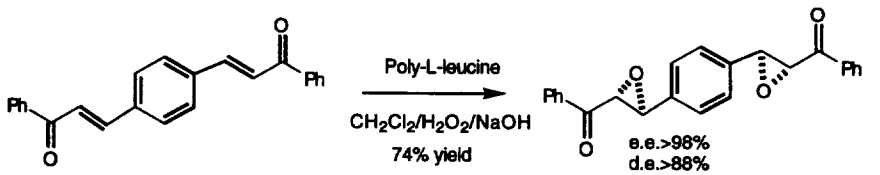
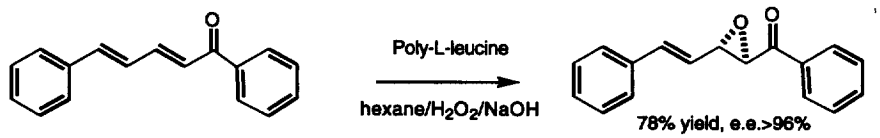


Figure 1. Further enones epoxidised using the triphasic method.



Scheme 4.

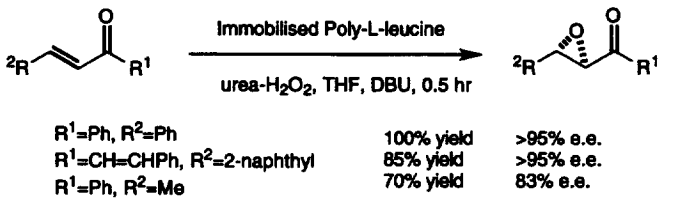


Scheme 5.

7. Reaction in non-aqueous media

Perhaps one of the most significant advances to be made in recent years in this area is the report by Roberts on the use of non-aqueous conditions to achieve the chalcone epoxidation.[21] Thus the use of urea-hydrogen peroxide complex in an organic solvent such as THF in the presence of DBU and

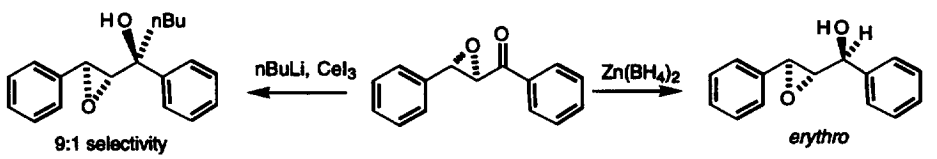
poly-L-leucine results in epoxidation of a range of substrates within 30 minutes and with high levels of asymmetric induction (Scheme 6). This modification effectively solves the problems of oxidant decomposition, long reaction times and difficulty of workup associated with the traditional three phase system. The recent reports on the combination of this approach with the use of polymer bound polyleucine[21,22] delivers a truly practical oxidation system which remains competitive with alternative methods recently reported for the transformation.[23]



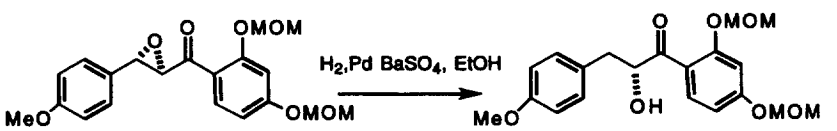
Scheme 6. Epoxidation of enones under non-aqueous conditions.

8. Specific synthetic applications

One of the earliest synthetic applications of the chalcone epoxidation methodology was in the asymmetric synthesis of enantiomerically enriched α,β-epoxy alcohols, i.e. by the stereoselective reduction of the epoxidation products with zinc borohydride (Scheme 7).[24] This reduction is selective for the *erythro* diastereoisomer and forms a complementary approach to the Sharpless epoxidation for the synthesis of this class of molecules. Highly diastereoselective additions (up to 9:1) of organometallic reagents to the ketones have also been reported recently (Scheme 7).[21] In addition, the reduction of the chalcone epoxides via catalytic hydrogenation with palladium on barium sulfate provides a simple entry to α-hydroxy ketones (Scheme 8).[25]



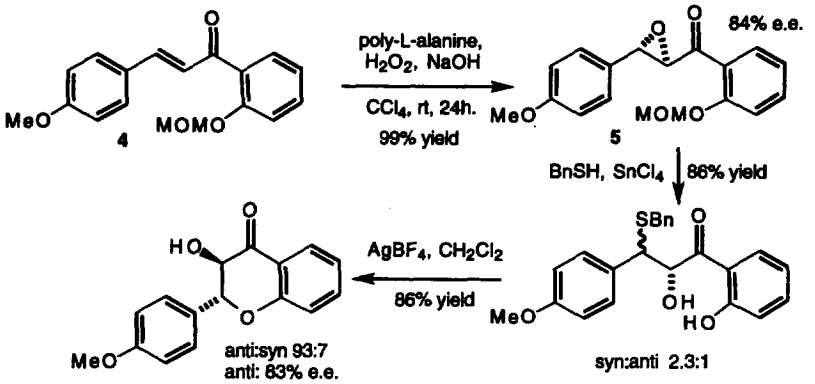
Scheme 7.



Scheme 8.

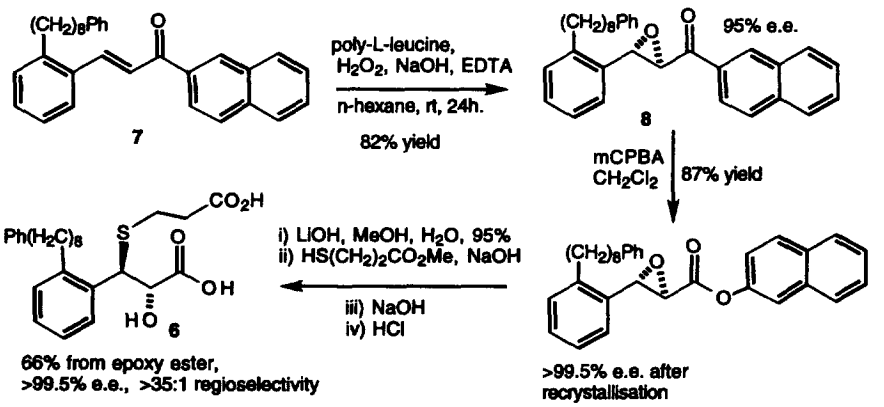
Chiral flavanols **4** and related materials have been prepared via the intermediacy of poly-oxygenated chalcone epoxides. The epoxidation of chalcones was carried out using poly-L- or -D-alanine in the previously reported triphasic system (i.e. aqueous basic hydrogen peroxide) and gave products with enantiomeric excesses in the range of 32–84% e.e. which appeared to decrease with increased oxygenation.[26a] In the example in Scheme 9, which features one of a series of polyoxygenated chalcones employed in this application, the acid catalysed method initially employed for cyclisation of the phenol derived from **5** (i.e. the deprotected epoxidation substrate) resulted in some loss of enantiomeric purity.[26a] This problem has been largely surmounted though the stereoselective epoxide opening with a thiol and subsequent cyclisation illustrated.[26b] A similar approach to chiral flavanols,

using an alternative chiral phase transfer catalysis system and an analogous sequence of reactions, has been reported.[27]



Scheme 9.

Perhaps the most significant single application of polymeric α-amino acid catalysed epoxidation to a commercial target is the synthesis of the leukotriene antagonist molecule SK and F104353 **6** as reported by Lantos *et al.*[6,28] Key to this was the epoxidation of the 2-naphthyl substituted enone **7** via the established triphasic conditions but with poly-L-leucine prepared in large quantities by the humidity tank method. Slightly less than 1:1 w:w of the polymer was employed relative to enone. The importance of highly pure L-leucine NCA precursor was stressed. The SK and B group found that, in contrast to the initial reports, hexane was a superior solvent to toluene in this particular application. In addition the rate of decomposition of the hydrogen peroxide could be reduced by the addition of EDTA to the mixture, thus reducing reaction times and avoiding the need to replenish the oxidant throughout the process. Pre-swelling of the polymeric α-amino acid was also found to be advantageous and reduced the reaction times for the large scale applications from 72 to 24 hours. In addition it was found that the poly-L-leucine was entirely reusable (up to six consecutive reuses reported) after the reaction. Using the optimised conditions the epoxide **8** was isolated in 82% yield and 95% enantiomeric excess (Scheme 10).

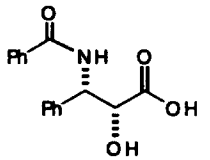


Scheme 10.

A number of key further steps included a selective Baeyer–Villiger oxidation to furnish the ester, ester hydrolysis and then a mild (THF, 5°C, 4 h) selective ring opening of the epoxide of the *carboxylate*

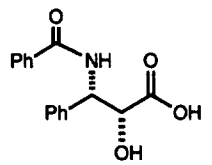
salt with a thiol. Subsequent ester hydrolysis and neutralisation furnished the target molecule **6** in excellent overall yield.

In a very recent paper,[22] Roberts has described an approach to the side chain **9** of the important anti-cancer compound taxol via a key polyleucine mediated epoxidation process.

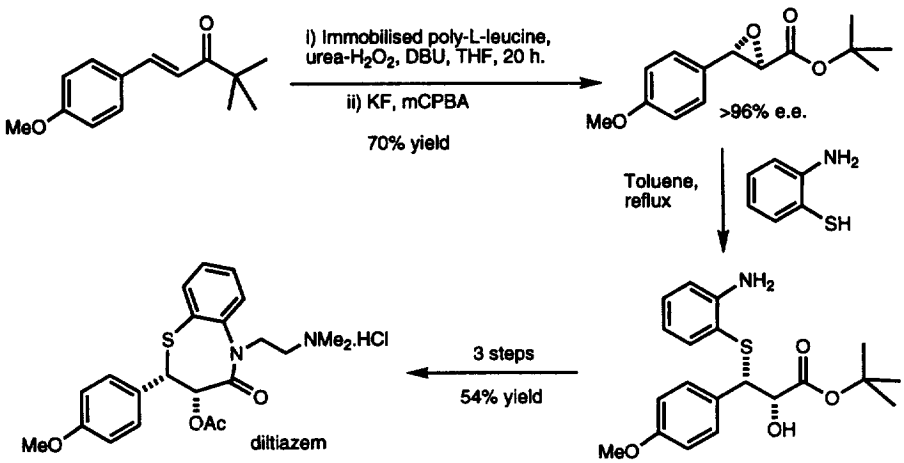


9 (Taxol side chain)

In addition the synthesis of diltiazem, a blood pressure lowering agent, has been prepared by a concise sequence from a simple enone precursor (Scheme 11).



9 (Taxol side chain)

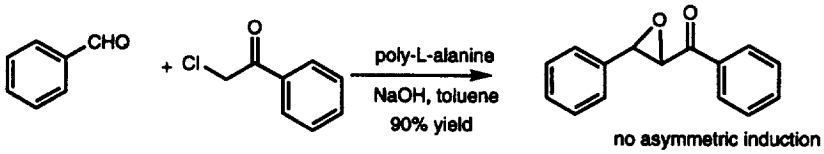


Scheme 11.

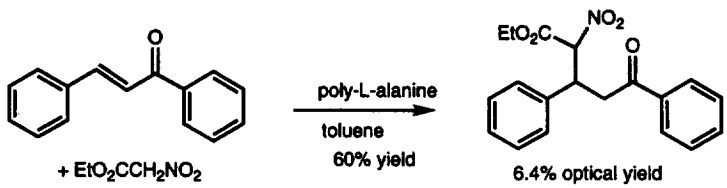
9. Other reactions catalysed by polymeric α-amino acids

A number of other reactions have been attempted with the use of polymeric α-amino acids as catalysts, although with rather moderate success. The Darzens reaction of phenacyl chloride with benzaldehyde (Scheme 12) gave essentially no asymmetric induction, although the addition of ethyl nitroacetate to chalcone (Scheme 13) proceded with 6.4% optical yield.[10] The low asymmetric induction, and reaction time of 31 days, essentially renders the latter process impractical. Attempts at kinetic resolution through the dehydrohalogenation of racemic chlorohydrins have also been attempted, but with little success.[10] Catalysis of the asymmetric addition of thiols to enones using polyleucine has been attempted but products of low e.e. were obtained,[29] as was the case when a number of other proteins were employed to the same end.[30]

Poly-L-leucine has found use as a chiral additive for the asymmetric carbonylation reaction of allylic alcohols (Scheme 14).[31] In the 1990 report by Alper and Hamel it was found that the polymer

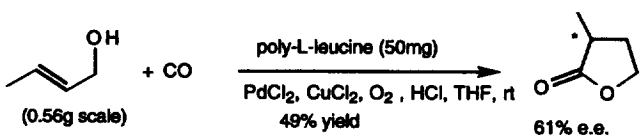


Scheme 12.



Scheme 13.

outperformed a number of chiral alcohols and phosphines in this application, furnishing the product lactone in 49% yield and 61% e.e.



Scheme 14.

Some very early reports described the use of polyamino acids to control asymmetric hydrogenations using either palladium catalyst (in the case of α-acylamino acrylates) or a carbon electrode (for unsaturated esters).[4] Products of ca. 5% e.e. were obtained in the former process, and a result of 43% e.e. was claimed in the latter case. A recent paper has described the combination of polyamino acids with iron(III) porphyrins on electrode surfaces to give well characterised products which have been demonstrated to be effective at dioxygen reduction.[32]

10. Conclusion

The use of polymeric α-amino acids remains a research area with a great deal of potential. The development of these reagents has now reached a point where many of the initial difficulties involved with their preparation and use have now been overcome through the use of supported reagents and non-aqueous reaction conditions. The methodology has proved itself to be a valuable synthetic tool for large scale as well as small laboratory scale applications, as demonstrated by the synthesis of SK and F104353. Present interest now lies in the extension of polyamino acid methodology to other asymmetric applications, and to the preparation and evaluation of more complex catalysts. The potential for modification through the incorporation of other amino acids and organometallic groups is obvious and will no doubt occupy researchers in this area for many years to come.

Acknowledgements

The author wishes to thank Professor S. M. Roberts (Liverpool) for helpful discussions and for providing preprints.

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