Pergamon

Tetrahedron Letters 40 (1999) 5417–5420

TETRAHEDRON
LETTERS

Polyamino Acid-Catalysed Asymmetric Epoxidation: Sodium Percarbonate as a Source of Base and Oxidant

Joanne V. Allen,[a] Karl-Heinz Drauz,[b] Robert W. Flood,[a] Stanley M. Roberts,[a]* John Skidmore.[a]

a) Department of Chemistry, University of Liverpool, Liverpool, U.K., L69 7ZD.
b) Degussa-Hüls AG, Postfach 13 14, D-63403 Hanau, Germany.

Received 29 April 1999; accepted 19 May 1999

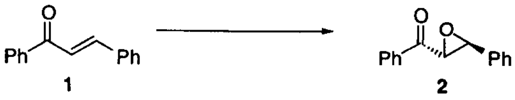
Abstract: New reaction conditions, using sodium percarbonate, are reported for the polyamino acid-catalysed asymmetric epoxidation of enones. Under these new conditions the rate of the uncatalysed reaction is reduced allowing an increased ratio of substrate to catalyst compared with previous protocols.

Keywords: Asymmetric reactions; Enones; Epoxidation; Peptides and polypeptides.

The polyamino acid-catalysed asymmetric epoxidation of enones was first reported by Juliá in 1980.[1] This method, now known as the Juliá-Colonna epoxidation, consists of a triphasic system comprising an insoluble polyamino acid catalyst, such as poly-L-leucine (PLL), an aqueous solution of NaOH and H_2O_2 and an organic solvent such as toluene in which the substrate is dissolved. More recently we have reported a biphasic protocol utilising PLL, urea-H_2O_2[2] and DBU in an organic solvent, such as THF.[3] Under these conditions reaction times are greatly reduced and the range of substrates which can be epoxidised is expanded.[4]

In an effort to elucidate the role of the polyamino acid catalyst in this transformation we have prepared a number of fixed-length polymers of leucine using a peptide synthesiser.[5,6] By virtue of the defined nature of these catalysts we have been able to examine the effect of making single changes to the sequence of the peptide. Some of the catalysts generated in this way have proved to be considerably less active than the normal peptide used for preparative chemistry.[7] We have found the biphasic protocol less than ideal as a probe for the activity of a given catalyst due to the rate of the uncatalysed epoxidation which occurs concurrently with the catalysed reaction. Chalcone (**1**) is epoxidised under standard biphasic conditions in 20 minutes to afford the epoxide **2** in 85% yield and >95% ee (scheme 1).[3] If the catalyst is omitted from such an epoxidation the rate shows an initial lag phase followed by a more rapid reaction resulting in a 91% conversion to racemic epoxide after 225 minutes (table 1). During epoxidation of **1** catalysed by a 20-mer of PLL capped with two methyl groups on the *N*-terminus[6] (*N,N*-dimethyl PLL) the ee of the product **2** drops from 85 to 44% as the reaction proceeds.

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)01021-7



Scheme 1

Table 1 The uncatalysed and *N,N*-dimethyl PLL catalysed epoxidation of chalcone (**1**).[a]

Time (min.)	Background Reaction Conversion to *rac*-**2** (%)[c]	*N,N*-dimethyl PLL catalysed[b] Conversion to **2** (%)[c]	ee of **2** (%)[c]
30	3	29	85
90	34	54	70
150	69	73	58
210	-	86	50
225	91	-	-
360		97	44

a) *Reagents and conditions:* chalcone (**1**) (0.24 mmol), urea-H_2O_2 (0.30 mmol), DBU (0.36 mmol), THF (1 cm^3). Further portions of urea-H_2O_2 (0.30 mmol) and DBU (0.36 mmol) were added after 30, 90 and 150 minutes.

b) 100 mg of supported catalyst (bound to polystyrene *via* a hydroxymethylphenoxyacetic acid linker and a PEG graft with a density of attachment of 0.17 mmol/g.)

c) Determined by hplc using a Chiralpak® AD column (eluent: 10% EtOH in hexane, UV-detection at 254 nm).

We now report a new protocol for polyamino acid-catalysed enone epoxidation in which sodium percarbonate[8,9] serves a dual role of oxidant and base. These new conditions are characterised by a diminished background reaction and an enantioselectivity which remains constant throughout the course of a reaction. Moreover, this method is more environmentally benign, cheaper and practically more convenient than the previously reported conditions.

Ando has reported the use of sodium percarbonate for enone epoxidation in aqueous ethanol[10] and it has previously been reported as an effective alternative to aqueous H_2O_2 for polyamino acid-catalysed epoxidation under the triphasic conditions.[11] However, under the biphasic conditions replacement of UHP with sodium percarbonate results in a slower epoxidation. It was envisaged that a miscible aqueous-organic solvent mixture might facilitate dissolution of the sodium percarbonate and release of hydrogen peroxide. A series of mixed solvent systems was examined (table 2). Ethereal-aqueous mixtures gave the highest enantioselectivities. In particular the water-1,2-dimethoxyethane (DME) mixture gave a rapid reaction and high ee, results comparable with the biphasic conditions.

A brief examination was made of the scope of this new protocol. It was found that in the absence of PLL the reaction was considerably slower than with the biphasic system. After 3.5 hours the conversion to the epoxide *rac*-**2** was 18% and even after 24 hours it was only 59%. The reduced rate of this background reaction proved particularly advantageous when examining less effective catalysts, such as the *N,N*-dimethyl PLL. In contrast to the variation in ee observed with the biphasic reaction using this catalyst, under the new procedure the ee remained constant throughout the course of the reaction at 60±2%.

Table 2 Organic-aqueous solvent systems for the PLL-sodium percarbonate epoxidation[a] of chalcone (**1**).

Organic Solvent	Time[b]	Conversion to **2** (%)[c]	ee of **2** (%)[c]
THF	3.5 h	92	96
MeCN	45 min[d]	12	79
DMF	4 h	87	41
DMSO	2.5 h	97	87
DME	20 min	>99	96

a) *Reagents and conditions:* chalcone (**1**) (0.24 mmol), $Na_2CO_3 \cdot 1.5H_2O_2$ (0.36 mmol), i-PLL,[12] organic solvent (0.5 cm^3), water (0.5 cm^3).

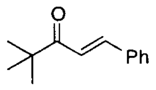
b) We have observed some variation in the length of time that polyleucine mediated reactions take to run to completion. The above reactions were performed using a batch of catalyst prepared on a 3 g scale and subsequently activated.[13]

c) Determined by hplc using a Chiralpak® AD column (eluent: 10% EtOH in hexane, UV-detection at 254 nm).

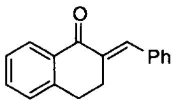
d) No further reaction occurred after this time.

The new conditions also allow an increased substrate to catalyst ratio without reducing the ee of the final product. A six-fold increase in the amount of substrate (1.44 mmol of chalcone (**1**), 100 mg of i-PLL[12], 1 cm^3 of solvent) resulted in a decreased ee of **2** under the biphasic conditions (92% isolated yield, 89% ee), whilst using the percarbonate protocol the ee remains excellent (87% isolated yield, 94% ee). This result, coupled with the low cost of the new procedure, makes it the method of choice for preparative scale work.

In addition to chalcone (**1**) a range of other enones can readily be epoxidised. For example, the *tert*-butyl ketone **3** was epoxidised in 94% isolated yield and 94% ee (biphasic protocol: 76% yield, 94% ee[3]). A more slowly epoxidised substrate is the tetralone **4**. A range of solvent ratios was surveyed and 1:2 DME:water proved to be the most effective; conversion was complete after 48 hours to afford epoxide with an ee of 87% (biphasic protocol: 62%[14]). In addition it was found that the rate of the epoxidation of this latter substrate could be increased by the addition of dicyclohexyl-18-crown-6 (1.6 equiv.) without any reduction in the ee of the product.



3



4

In summary, epoxidation of enones using sodium percarbonate and polyleucine in mixed DME/water solvent systems proceeds rapidly to afford the corresponding epoxides with high ee. It has been shown that these conditions have certain advantages over previously reported protocols; in particular they allow epoxidation to proceed with lower catalyst to substrate ratios and with less effective catalysts without seeing a diminished enantioselectivity caused by a rapid non-polyleucine-catalysed epoxidation.

Typical experimental procedure: To a stirred mixture of enone (0.24 mmol) and CLAMPS immobilised poly-L-leucine (100 mg) in DME (0.5 cm^3) and water (0.5 cm^3) was added sodium percarbonate (0.36 mmol). The reaction was monitored by tlc, when complete the reaction mixture was filtered and the residue washed with EtOAc (3 x 15 cm^3). The EtOAc solution was washed with water (30 cm^3), dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford the crude epoxide.

Acknowledgements: We thank the E.P.S.R.C. (studentship to R.W.F., fellowship to J.S.), Degussa-Hüls AG for a fellowship (J.V.A.) and Dr. J. A. Smith for the synthesis of the *N,N*-dimethyl-PLL.

References

1. Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 929.
2. Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett*, **1990**, 533.
3. 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.
4. A number of recent reviews have been published, see for example Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry*, **1997**, *8*, 3163; Pu, L. *Tetrahedron: Asymmetry*, **1998**, *9*, 1457.
5. Cappi, M. W.; Chen, W.-P.; Flood, R. W.; Liao, Y.-W.; Roberts, S. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M. *Chem. Commun.*, **1998**, 1159.
6. Bentley, P. A.; Cappi, M. W.; Flood, R. W.; Roberts, S. M.; Smith, J. A. *Tetrahedron Lett.*, **1998**, *39*, 9297.
7. The preparative scale catalysts are synthesised by polymerisation of the amino acid *N*-carboxyanhydride. The diminished activity shown by the defined length peptides reflects lower loading of the peptide on the support and in some cases, changes made to the peptide structure.
8. McKillop, A.; Sanderson, W. R. *Tetrahedron*, **1995**, *51*, 6145.
9. Muzart, J. *Synthesis*, **1995**, 1325.
10. Ando, T.; Cork, D. G.; Kimura, T. *Chem. Lett.*, **1986**, 665.
11. Lasterra-Sánchez, M. E.; Felfer, U.; Mayon, P.; Roberts, S. M.; Thornton, S. R.; Todd, C. J. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 343.
12. We typically use poly-L-leucine immobilised on a polystyrene support (i-PLL) see Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.*, **1990**, *55*, 6047.
13. We have found that the catalytic activity of polyamino acid catalysts can be improved by an activation procedure. This involves stirring the catalyst in a mixture of toluene (10 cm^3/g) and 4M sodium hydroxide (4 cm^3/g) for between 1 and 5 days. The catalyst is separated by filtration, washed with water, 1:1 water:acetone and acetone and dried before use. The mechanism of this activation procedure is currently not clear.
14. Bentley, P. A.; Roberts, S. M. unpublished results.