

Asymmetric epoxidation of enones employing polymeric α -amino acids in non-aqueous media

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Urea-hydrogen peroxide complex in an organic solvent and in the presence of DBU and poly-(L)-leucine causes rapid asymmetric epoxidation of the enones **1a**, **b** and **d**.

Poly(amino acid)s are cheap surrogates of enzymes for promoting some stereoselective organic reactions.¹ For example, Banfi *et al.* have described a method for the asymmetric epoxidation of chalcones using these polymeric catalysts; thus the enone **1a** was transformed into the chiral epoxy ketone **2a** (Scheme 1 and Table 1, entry 1).² The reaction involved a triphasic system comprising alkaline aqueous hydrogen peroxide, an organic solvent and the insoluble polymer. Subsequently the asymmetric epoxidation has been shown to be a reliable, robust reaction and the range of enones undergoing oxidation has been extended considerably; for example the dienone **1b** affords the unsaturated epoxy ketone **2b** in good yield and excellent enantiomeric excess (Table 1, entry 2).³

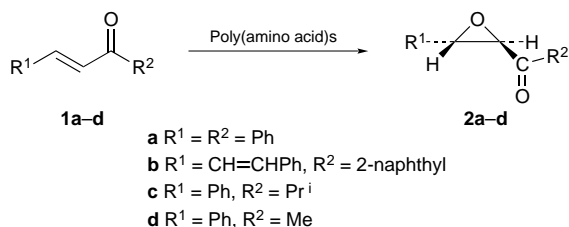
Nevertheless, several limitations to the protocol became evident. First, reaction times were often unacceptably long (≥ 3 days; Table 1, entry 2) and all of these reactions required continuous addition of oxidant and base. The use of aqueous

sodium hydroxide caused slow degradation of the poly(amino acid) and precluded the epoxidation of compounds possessing alkali-sensitive functionality. Secondly, the polymer, prepared as an amorphous solid, required swelling (to form a gel) through contact with aqueous organic solvent for a period of 6 h. Thirdly, compounds of the type $R^1CH=CHCOHR^2R^3$ or $R^1COCH=CHCHR^2R^3$, *i.e.* with 'active' hydrogen atoms, were oxidized slowly [often with poor selectivity (Table 1, entry 3)], or not at all (Table 1, entry 4).⁴

We have now found a satisfactory solution to many of these problems by conducting the asymmetric epoxidation in a two-phase non-aqueous system made up of oxidant, a non-nucleophilic base, immobilised poly(amino acid)⁵ and an organic solvent.

Thus chalcone **1** (0.24 mmol) was added to dry THF (0.8 cm³), immobilised poly-(l)-leucine⁵ (PLL) (100 mg), urea-hydrogen peroxide complex (UHP)⁶ (1.2 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 equiv.). The ensuing reaction was complete in 30 min and provided the epoxyketone **2a** in high yield and excellent optical purity after column chromatography (Table 1, entry 5). Use of immobilised poly-(d)-leucine (PDL) gave rise to the enantiomeric epoxy ketone *ent-2a* (Table 1, entry 6). The use of more solvent (2.0 cm³) resulted in a slower reaction (96% conversion after 1 h) but no diminution in the optical purity of the product (96% ee). For these reactions the work-up procedure is very straightforward; the insoluble polymer is simply filtered off and, indeed, may be recycled (at least six times) without reduction in the rate of the epoxidation, the yield or the optical purity of the product.

Preliminary investigations also showed that changes could be made to the nature of the solvent, the base and the oxidant. Thus, repeating the non-aqueous Juliá oxidation of chalcone **1a** in 1,2-dimethoxyethane, *tert*-butyl methyl ether and ethyl acetate



Scheme 1

Table 1 Asymmetric epoxidation of some α,β -unsaturated ketones using oxidant and poly(amino acid) catalyst

Entry	Enone	Epoxy ketone	Poly(amino acid) ^a	Solvent	Oxidant	Base	t/h	% Conversion (% yield)	Enantiomeric excess
1	1a	2a	PLL or PLA	CH ₂ Cl ₂ or hexane	30% H ₂ O ₂	NaOH-H ₂ O	18	(87)	88
2	1b	2b	PLL	hexane	30% H ₂ O ₂	NaOH-H ₂ O	72	(78)	> 95
3	1c	2c	PLL	CH ₂ Cl ₂	30% H ₂ O ₂	NaOH-H ₂ O	168	(60)	62
4	1d	2d	PLL	CH ₂ Cl ₂	30% H ₂ O ₂	NaOH-H ₂ O	168	(0)	—
5	1a	2a	PLL	THF	NH ₂ CONH ₂ -H ₂ O ₂	DBU	0.5	100 (85)	> 95
6	1a	<i>ent-2a</i>	PDL	THF	NH ₂ CONH ₂ -H ₂ O ₂	DBU	0.5	> 90 (85)	94
7	1a	2a	PLL	THF	NH ₂ CONH ₂ -H ₂ O ₂	DBN	0.5	> 95	> 90
8	1a	2a	PLL	THF	NH ₂ CONH ₂ -H ₂ O ₂	Humig's base	0.5	37	50
9	1a	2a	PLL	THF	DABCO-1.5H ₂ O ₂	DBU	0.5	95	95
10	1a	2a	PLL	THF	90% H ₂ O ₂	DBU	0.5	77	65
11	1b	2b	PLL	THF	NH ₂ CONH ₂ -H ₂ O ₂	DBU	3	85	> 95
12	1d	2d	PLL	THF	NH ₂ CONH ₂ -H ₂ O ₂	DBU	4	(70)	83

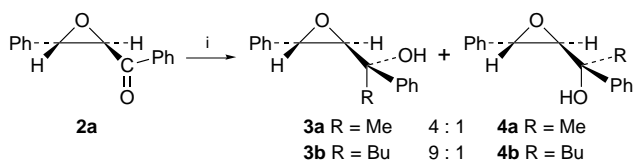
^a PLL: poly-(l)-leucine; PLA: poly-(l)-alanine; PDL = poly-(d)-leucine.

gave results which were almost identical to those obtained using THF. Polar aprotic solvents such as dimethyl sulfoxide and dimethylformamide gave equally good results but dichloromethane, acetonitrile and toluene were less satisfactory, giving rise to longer reaction times and/or less enantioselective reactions.

While DBU can be replaced with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), Hunig's base (*N,N*-diisopropylethylamine) is much less effective (Table 1, entries 7 and 8); triethylamine gave no reaction. 1,4-Diazabicyclo[2.2.2]octane-peroxide complex (DABCO-1.5H₂O₂)⁷ may be used as the oxidant (Table 1, entry 9) but, in contrast, 90% hydrogen peroxide gave rise to a slower reaction and a product that was less optically pure (Table 1, entry 10).

It is very significant that α,β -unsaturated ketones, which required long reaction times when employing the Juliá triphasic conditions, were transformed quickly, with great selectivity, in the new biphasic system (Table 1, entry 11). Furthermore, styryl methyl ketone **1d** was oxidized to the epoxy ketone **2d** over 4 h in moderate yield and optical purity (Table 1, entry 12; cf. entry 4). Hence it seems that the new reaction conditions will broaden the range of epoxy ketones that can be prepared using this methodology.

In a parallel research programme we are investigating the further reactions of the chiral epoxy ketones available from the Juliá methodology. For example, we have shown that the epoxy ketone **2a** is alkylated diastereoselectively using methyllithium or butyllithium and CeI₃,⁸ giving rise to compounds **3a** and **3b** as the major products which were separated from the minor isomers **4a** and **4b** by chromatography (Scheme 2). The structural identity of compound **3b** was elucidated by X-ray crystallography (Fig. 1).[†] This methodology gives rise to epoxides formally derived from allylic tertiary alcohols, compounds not readily obtainable in optically active form using the Sharpless technology.⁹



Scheme 2 Reagents and conditions: i, MeLi or BuLi, CeI₃, THF, -70 °C

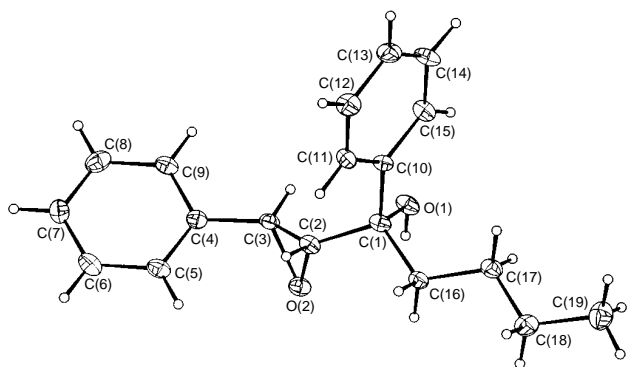


Fig. 1 X-Ray crystal structure of compound **3b**

Footnotes

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[†] Crystal data for C₁₉H₂₂O₂, *M* = 282.37, monoclinic, space group *P*2₁, *a* = 10.753(2), *b* = 5.6320(10), *c* = 13.403(2) Å, β = 104.930(4)° (by least-squares refinement of the setting angles for 250 reflections within θ = 1.96–24.98°), *V* = 784.3(2) Å³, *Z* = 2, *D*_c = 1.196 g cm⁻³, *T* = 150 K, μ(Mo-Kα) = 0.76 cm⁻¹, *F*(000) = 304, crystal size = 0.5 × 0.6 × 0.5 mm.

Data were collected on a FAST TV Area detector diffractometer following previously described methods (ref. 10). From the ranges scanned, 3383 data were recorded (1.96 < θ < 24.98°; index ranges: -11 < *h* < 4, -4 < *k* < 6, -14 < *l* < 14) and merged to give 2170 unique [*R*(int) = 0.0653].

The structure was solved *via* direct methods (ref. 11) and refined on *F*_o² by full-matrix least-squares (ref. 12) using all unique data corrected for Lorentz and polarisation factors. All non-hydrogen atoms were anisotropic. The hydrogen atoms were inserted in idealised positions with *U*_{iso} set at 1.5 times the *U*_{eq} of the parent. The weighting scheme used was *w* = 1/[σ²(*F*_o)² + (0.0137*P*)²], where *P* = [max(*F*_o)² + 2(*F*_c)²]/3; this gave satisfactory agreement analyses. Final *R*₁ (on *F*) and *wR*₂ (on *F*_o²) values were 0.0544 and 0.0647 for all 2170 data and 192 parameters. The corresponding *R* values were 0.0355 and 0.0615 for 1498 data with *I* > 2σ(*I*). Sources of scattering factors as in ref. 12. The numbering of the atoms is shown in Fig. 1.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/394.

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