

A new procedure for the Juliá–Colonna stereoselective epoxidation reaction under non-aqueous conditions: the development of a catalyst comprising polyamino acid on silica (PaaSiCat)

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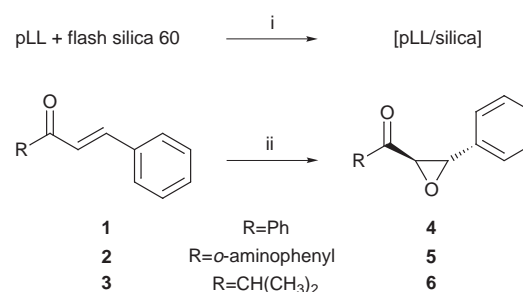
Polyleucine adsorbed onto silica provides a robust, readily-recycled, highly active catalyst for the asymmetric epoxidation of the α,β -unsaturated ketones 1, 2, and 3.

The asymmetric epoxidation of α,β -unsaturated ketones using peroxide anion in the presence of a polyamino acid (paa) such as poly-L-alanine or poly-L-leucine was discovered by Juliá and Colonna.¹ In this original procedure the substrate in a water-immiscible organic solvent, for example toluene, was treated with aqueous sodium hydroxide containing hydrogen peroxide and the paa. The insoluble paa was present as a gel-like third phase. Though this procedure was used by several workers,² several problems were presented by this protocol, not least the harsh reaction conditions employed, the limited range of (chalcone-like) substrates that could be oxidized, the lengthy reaction times that were needed and, most importantly, the difficulty in recovery of the gel-like catalyst.

A more recently developed procedure overcame some of these problems.³ The new protocol employed a two-phase system, comprising substrate and a peroxide donor (e.g. urea-hydrogen peroxide complex) in an organic solvent containing a base such as diazabicycloundecene (DBU) in the presence of the insoluble paa. The catalyst was present as a thick paste coating the inside of the reaction flask. Several advantages of the two-phase system were immediately apparent. First the reaction times were decreased by one to two orders of magnitude; secondly the substrate range was broadened since the use of aqueous base had been eliminated.⁴ Thirdly, recovery of product was straightforward, involving simple decantation of solvent and product from the paste-like catalyst.

One problem remained, that is the recovery of catalyst. Although it was established that the catalyst could be recycled,⁵ losses of catalyst amounted to ca. 10% per run. Moreover, after some time, the catalyst had to be reactivated before re-use.⁶ In this paper we present a solution to this problem, by translocating a strategy successfully employed in the field of biotransformations.

Within the field of biocatalysis it has been demonstrated that immobilization of enzymes onto a solid support yields material which normally exhibits an increased degree of activity in organic solvents.⁷ Moreover the recycling of an immobilized enzyme is much easier. The concept of immobilization of enzymes was applied to the synthetic polyamino acid poly-L-leucine (pLL). In initial adsorption experiments several materials were tested as solid carriers for pLL.⁸ The ratio of polyamino acid to solid support was chosen to be similar to the ratio used by Carrea for the immobilization of lipase PS.⁹ The new materials were compared to the parent (unmodified) pLL in the "standard"¹⁰ test reaction, namely Weitz–Scheffer epoxidation of enone **1** to give the epoxide **4** (Scheme 1). From among these new materials the silica-based catalyst is outstanding. Besides demonstrating a significantly increased catalytic activity the physical properties of the new material are (as expected) totally different from the unmodified pLL. Whereas unmodified pLL forms a paste during the course of the reaction the new catalyst retained its granular appearance; also there is no observable swelling of the catalyst. When the stirring is stopped



Scheme 1 Catalyst preparation and standard test reaction. *Reagents and conditions:* i, THF, 48 h; ii, pLL/silica, UHP, DBU, THF.

phase-separation is rapid and filtration, as part of the work-up procedure, is much easier to achieve. The Juliá–Colonna epoxidation employing the polyamino acid-on-silica catalyst (PaaSiCat) could be accomplished in a wide range of solvents. In terms of rate of the reaction (complete conversion in less than 50 min) and enantiomeric excess ($\geq 93\%$ ee) tetrahydrofuran, pyridine and *tert*-butyl methyl ether were found to be excellent solvents.

Remarkably the standard test reaction can be carried out using the PaaSiCat with only 23% of the pLL normally employed, without any significant influence on the rate of the reaction and enantiomeric excess of the resultant material.¹¹ In addition to these advantages the catalyst is extremely robust. In contrast to unmodified pLL,¹² it can be heated at 150 °C for 12 h under vacuum and retain full catalytic activity! The recyclability of the new catalyst was investigated for the standard test reaction. In contrast to our reported⁶ results with pLL, no increase in the reaction time for the epoxidation was observed, even after six runs with the recycled silica-supported catalyst. The substantial loss of catalyst observed under normal biphasic conditions was eliminated. The average mechanical loss per run of the new material (which contains only 23% of pLL, it should be emphasized) is about 3%. Recycled material exhibits equally high catalytic activity when compared to freshly-prepared catalyst, the enantiomeric excess of epoxide remaining at a remarkably high level ($\geq 93\%$ ee). The new procedure was tested with other substrates, namely 1-(2-aminophenyl)-3-phenylprop-2-en-1-one (**2**) and 4-methyl-1-phenyl-pent-1-en-3-one (**3**) (Table 1). From Table 1 it is obvious that the employment of the procedure decreases the reaction time significantly while retaining a very high degree of face-selectivity in the oxidation of the enone.

In conclusion we believe that this new protocol is the method of choice for conducting the Juliá–Colonna epoxidation of enones. The new catalyst is easy to prepare and has a significantly higher activity than the non-adsorbed pLL. Furthermore the work-up procedure is very much easier making recycling of the catalyst very simple, such that the loss of catalyst is minimized. In general the yields are higher with the PaaSiCat than those obtained with unmodified pLL. This discovery gives access to a robust, simple-to-use, highly active asymmetric epoxidation catalyst from commercially

Table 1 Epoxidation of enone **2** and **3** using pLL or PLL on silica

Entry	Enone	Catalyst	t/h	Conversion (%) ^a	Epoxide (ee) (%) ^a
1	2	pLL	3	35	5 (n.e.)
2	2	PLL/silica	3	85	5 (93)
3	3	pLL	26	56	6 (89)
4	3	PLL/silica	14	78	6 (93)

^a Conversion and ee determined by HPLC; n.e. - not evaluated.

available pLL and commonly used "flash" silica, and further investigations are in progress to define the range of substrates undergoing reaction. All the details will be described in a forthcoming full paper, but even at this early stage it is quite clear that the method compares favourably with other recently published methods for the asymmetric epoxidation of α,β -unsaturated ketones.¹³

Experimental

Preparation of catalyst

pLL (1 g) and silica gel 60 (3.4 g, 230–400 mesh, Merck) were mixed in a 100 ml round bottomed flask and then suspended in THF (30 ml anhydrous). The flask was sealed with a septum and the mixture stirred in the dark for 48 h (magnetic stirrer, slow stirring rate). The suspension was then filtered (glass sinter porosity 3) and the solid residue washed with 2×10 ml of anhydrous THF. The catalyst was dried under vacuum (1 h, 11 mbar, room temp., then 1 h, 0.08 mbar, 50 °C).

Typical procedure for an epoxidation reaction

A mixture of the enone (8.6×10^{-5} mol), urea–hydrogen peroxide adduct (10 mg, 1.2 equiv.) and catalyst (155 mg) were suspended in THF (1 ml, anhydrous) and DBU (15 μ l, 1.2 equiv.) was added. After the completion of the reaction the mixture was filtered and the solid residue washed with EtOAc (5×2 ml). The organic phase was treated with aqueous Na₂SO₃ (20% solution). After phase-separation, the organic phase was washed with brine, dried (MgSO₄) and the solvent evaporated under reduced pressure. Measurements of enantiomeric excess were conducted by HPLC (Chiralpak AD, Daicel): a) epoxide **4**: 254 nm, EtOH–hexane 1:9, 1.0 mL min⁻¹, b) epoxide **5**: 230 nm, EtOH–hexane 7:43, 1 mL min⁻¹, c) epoxide **6**: 230 nm, EtOH–hexane 0.5:9.5, 0.7 mL min⁻¹. EtOH contains 0.7% of H₂O.

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