Scale-Up Studies for the Asymmetric Juliá–Colonna Epoxidation Reaction

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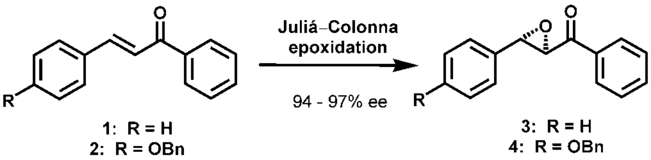
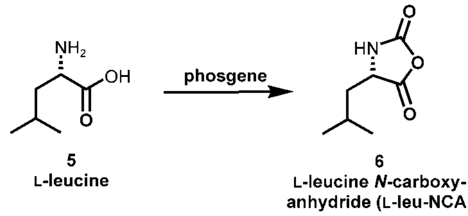
Abstract: The asymmetric Juliá–Colonna epoxidation reaction under triphasic/PTC conditions has been successfully scaled-up to a one-hundred gram substrate level providing the corresponding epoxy ketone with high optical purity (up to 97% ee) and in good yield (75–78%). The amount of polyamino acid catalyst could be reduced leading to a simplified reaction work-up. In order to minimise the overall reaction time baffled reactors with pitched-blade impellers have been employed.

Keywords: amino acids; asymmetric catalysis; epoxidation; heterogeneous catalysis; phase-transfer catalysis



Scheme 1. Reaction conditions: Poly-L-leucine (pll), aqueous H_2O_2/NaOH, tetrabutylammonium bromide (TBAB), toluene, rt.



Scheme 2. Reaction conditions: **5** in THF, 3.4 equivs. phosgene (gaseous, addition over 6.5 h, at 22–33 °C), 16 h rt, 35 °C/80 mbar (–THF), then addition of *n*-hexane, 85% yield.

The poly-α-amino acid-catalysed asymmetric Juliá–Colonna epoxidation has emerged as an efficient synthetic method for the enantioselective functionalisation of α,β-unsaturated ketones. Since its discovery in 1980,[1] the heterogeneous catalyst and the oxidant/solvent system has been optimised further so that now a broad range of substrates containing a substituted enone system can be epoxidised in high yield and with high enantioselectivity.[2]

Recently, we have developed a new protocol for the Juliá–Colonna epoxidation reaction under triphasic conditions[3] employing our own polyamino acid catalyst. The addition of small amounts of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (PTC) to the heterogeneous reaction mixture resulted in a significant acceleration of the epoxidation reaction.[4] With this new protocol we could obtain complete conversion of chalcone **1** into epoxy ketone **3** with high chemo- and enantioselectivity (94% ee) within 7 minutes at room temperature. In contrast to our new procedure less than 60% conversion has been observed without TBAB under otherwise identical epoxidation conditions after 1.5 hours.

Some time ago we became interested in preparing enantiomerically pure epoxy ketone **4** as a valuable synthetic intermediate. Using our newly developed triphasic/PTC conditions **4** could be obtained successfully from enone **2**[5] with 97% ee on a small scale.[6]

In order to prepare larger quantities of epoxy ketone **4** we subsequently investigated the synthesis of the poly-α-amino acid catalyst, which is usually obtained by amine-induced polymerisation of the corresponding *N*-carboxyanhydride.[7] Direct phosgenation[8] of L-leucine **5** in THF provided pure, crystalline L-leucine *N*-carboxyanhydride (L-leu-NCA, **6**) on a multi-100 g scale.[9]

After some optimisation it turned out that the subsequent statistical polymerisation initiated by 1,3-diaminopropane was preferably performed in toluene at elevated temperature.[7d] This method leads to a range of chain lengths in the polymer product **7**, although the average length can be controlled by varying the ratio of L-leu-NCA to 1,3-diamino propane.[7b, c]

After complete consumption of L-leu-NCA **6** and addition of methanol to the reaction mixture the product polyleucine **7** has been isolated on a 100-g scale. This material could be used directly without further purification[10] or pre-activation.[7d,11] Having established a relia-

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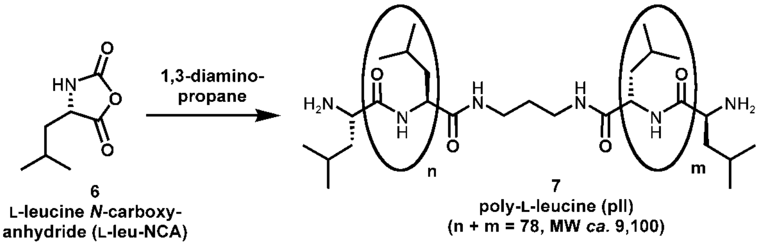
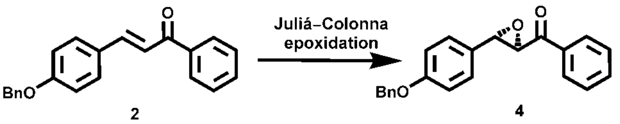


Scheme 3. Reaction conditions: **6** in toluene, addition of 0.0125 equivs. 1,3-diaminopropane, gradually heated to 80 °C (over 2 h), 1 h at 80 °C, then addition of methanol, 88% yield.

Table 1. Asymmetric Juliá–Colonna epoxidation reaction of chalcone **2** as per protocol at room temperature.



Entry	Substrate ([g])	pll [w/w %][a]	Time [h]	Conv. [%][b]	Yield [%][c]	ee [%][d]
1	**2** (100)	20	20	>99	77	95.9
2[e]	**2** (100)	20	12	>98	76	97.6
3[f]	**2** (17.5)	20	20	<50	--	93.9
4	**2** (100)	15	20	>99	78	97.3
5	**2** (100)	10	20	>99	75	95.5
6	**2** (100)	5	20	>98	77	92.0

[a] Based on chalcone **2**.
[b] Determined by HPLC analysis.
[c] Isolated yield of pure **4** after one crystallisation from toluene of the crude product.
[d] Ascertained by chiral HPLC analysis of isolated **4** and comparison to the racemic compound.
[e] This reaction has been performed in a sealed autoclave with efficient stirring.
[f] Reaction temperature has been kept at 15 °C.

ble access to larger quantities of poly-L-leucine (pll, **7**),[12] the stage was set for scaling-up the epoxidation of chalcone **2**.

For our triphasic/PTC conditions the epoxidation rate was found to have a strong dependency on the stirring speed. On a small scale highest reaction rates have been obtained when the epoxidation was performed in a 5-mL vial with maximum magnetic stirring (approximately 1250 rpm). For this scale-up study we have used jacketed glass reactors and, in order to ensure efficient radial and axial flow within the heterogeneous reaction mixture, glass baffles at the reactor inner walls have been employed in combination with pitched-blade glass impellers at a stirring rate of 700 to 800 rpm.

Scaling-up the Juliá–Colonna epoxidation of **2** from a 0.5 g, 5.0 g, 25 g, 50 g to a 100 g substrate level under triphasic/PTC conditions led to a significant increase of the overall reaction time to allow complete consumption of the starting material. With 20 w/w % of poly-L-leucine **7** up to 20 hours (overnight) at room temperature were required to ensure full conversion (Table 1, Entry 1), although epoxy ketone **4** was obtained in good optical purity. When the same reaction was performed in a sealed glass autoclave providing efficient mixing (stirring rate *ca.* 700 rpm) we could successfully reduce the reaction time to only 12 hours (Table 1, Entry 2). In an attempt to improve the enantioselectivity we lowered the reaction temperature to 15 °C. However, the conversion after 20 hours was below 50% and the optical purity of **4** was slightly diminished (Table 1, Entry 3). Next, we tried to reduce the amount of poly-L-leucine **7** employed for the epoxidation (Table 1, Entries 4–6). To our surprise even with only 5 w/w % pll the reaction was finished in 20 hours, although the enantiomeric excess dropped to 92%. With such low pll catalyst loadings, reaction work-up is dramatically simplified. The catalyst could easily be recovered by filtration and re-used after washing.[13]

In conclusion, we have demonstrated that the asymmetric Juliá–Colonna epoxidation reaction under triphasic/PTC conditions could be scaled-up successfully to a 100-g substrate level. With only 10 w/w % of poly-L-leucine catalyst epoxy ketone **4** could be obtained in 75% yield and 95.5% ee. Scaling-up the epoxidation resulted in prolonged reaction times even when baffled reactors were used.

Experimental Section

Protocol for the Asymmetric Juliá–Colonna Epoxidation Reaction of Chalcone 2

All reactions have been performed in jacketed glass vessels (250 mL, 1000 mL, 2000 mL) connected to a thermostat. To ensure efficient mixing the jacketed glass vessels were equipped with four glass baffles at the reactor inner walls and pitched-blade glass impellers. The stirring rate was usually kept at a range of 700 to 800 rpm.

A 2000-mL jacketed glass vessel was successively charged with tetrabutylammonium bromide (TBAB) (11 g, 0.032 mol, 10 mol %), poly-L-leucine (pll, **7**; 10 g, 1.1 mmol, 0.35 mol %), toluene (1600 mL) and 5 M aqueous sodium hydroxide

(82 mL, 0.410 mol, 1.3 equivs.). After cooling to 15 °C 30% hydrogen peroxide (162 mL, 1.57 mol, 5 equivs.) was added at that temperature (slightly exothermic) and the resulting heterogeneous mixture was warmed to 25 °C again. This mixture was then kept at 25 °C for 1 hour before chalcone **2** (100 g, 0.318 mol, 1.0 equiv.) was added as a solid. Subsequently, the reaction was stirred for 20 hours in the dark at 25 °C. The reaction mixture was diluted with ethyl acetate (1500 mL) and quenched by addition of ice-cold 20% aqueous $NaHSO_3$ solution (100 mL). A peroxide test of the aqueous layer was negative. After addition of water (1000 mL) a phase separation furnished an organic layer containing epoxide **4** and an aqueous layer containing insoluble poly-L-leucine. Poly-L-leucine was then filtered out and washed with ethyl acetate (100 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated under vacuum to afford a beige solid. This material was crystallised from toluene (300 mL) to furnish epoxy ketone **4** as a white solid; yield: 79 g (75%). Analysis by chiral HPLC indicated 95.5% ee.

Preparation of Poly-L-leucine (pll) 7

To a stirred suspension of L-leucine (**5**; 200 g, 1.51 mol, 1.0 equiv.) in THF (2000 mL) gaseous phosgene (507 g, 5.13 mol, 3.4 equivs.) was added continuously over 6.5 h. During this period the reaction mixture became homogeneous and the reaction temperature was allowed to rise to 33 °C. Stirring at ambient temperature was maintained for additional 16 h. Subsequently, most of the solvent THF and excess phosgene was distilled off at 35 °C/80 mbar. At this point *n*-hexane (1100 mL) was added and a precipitate was formed. After stirring for 1 h the precipitate was filtered off and washed with *n*-hexane (2×600 mL). Drying provided pure, crystalline L-leucine *N*-carboxyanhydride (L-leu-NCA, **6**); yield: 203 g (85%). Analytical data were in agreement with reported values.[8]

Freshly prepared L-leucine *N*-carboxyanhydride (L-leu-NCA, **6**; 100 g, 0.636 mol, 1.0 equiv.) was dissolved in anhydrous toluene (1500 mL) under argon at ambient temperature. To this homogeneous solution was added the initiator 1,3-diaminopropane (0.589 g, 0.008 mol, 0.0125 equiv.). Subsequently, the reaction mixture was gradually heated to 80 °C over 2 h. During this period CO_2 was liberated. Stirring was maintained for 1 h at 80 °C. After cooling down to 60 °C methanol (1000 mL) was added. This heterogeneous reaction mixture was stirred for 1 h at 60 °C before the solid was filtered off. Drying furnished poly-L-leucine (pll, **7**); yield: 63 g (88%). The product structure has been confirmed by MALDI-MS.

References and Notes

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[3] The reaction mixture observed by following the original protocol[1] consists of an organic phase (toluene and starting material/product), an inorganic aqueous phase (sodium hydroxide and hydrogen peroxide) and a third solid phase (insoluble polyamino acid catalyst).

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[6] Early screening experiments were conducted in magnetically stirred vials (5 mL) using 75 mg (0.24 mmol) of chalcone **2**.

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[9] Under the used conditions (see Scheme 2 and experimental section) L-leu-NCA **6** was not accompanied by a dark brown oil as described earlier.[7d]

[10] Further washings or grinding of the crude poly-L-leucine **7** had no effect on enantioselectivity or reaction rate.

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[12] This poly-L-leucine-1,3-diaminopropane catalyst is commercially available from Fluka (product number: 93197).

[13] A single re-use of recovered poly-L-leucine catalyst **7** furnished epoxy ketone **4** in 75% yield with 97.3% ee after 20 hours on a 100 g substrate scale.