The Juliá-Colonna epoxidation: Access to chiral, non-racemic epoxides

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Available online 9 March 2006

Abstract

The co-catalysis of the Juliá-Colonna epoxidation with selected phase transfer catalysts results in a dramatic increase of reactivity and sometimes also in a higher enantiomeric excess of the product. The required amount of polyamino acid can be significantly reduced under the new conditions, such that large scale industrial application of the method is now feasible. Highly active catalyst can be prepared via a statistical polymerisation of leucine-*N*-carboxyanhydride at elevated temperature.
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Keywords: Epoxidation; Asymmetric; Polyamino acid; Peptide; Phase transfer catalysis

1. Introduction

A variety of stereoselective reactions in which (synthetic) polyamino acids (PAA) take part as catalysts is known [1]. Among these reactions the enantioselective epoxidation of α, β-unsaturated ketones attracted most attention. In 1980 Juliá et al. reported the first example of an enantioselective epoxidation of chalcone, using synthetic, chiral, non-racemic PAAs [2] as catalysts.

The original triphasic conditions entail taking a homochiral D- or L-PAA, normally poly-leucine, allowing it to swell to form a gel in the presence of an organic solvent (e.g. toluene, CH_2Cl_2, etc.), aqueous NaOH and aqueous H_2O_2 (Scheme 1). After several hours of pre-activation [3] the formation of the desired epoxide takes place. The epoxidation itself is a rather slow reaction, which takes up to several days [4]. Nevertheless, the enantioselectivity achieved is normally very good and both enantiomers are accessible via the selection of the PAA.

Even though the reaction is already under the original triphasic conditions a very valuable method for the synthesis of epoxides there are some limitations [5]. The range of substrates is limited due to the aqueous alkaline conditions. Therefore, compounds sensitive to hydroxide ions are no viable starting materials. Typically ca. 10 mol% of the catalyst have to be used, which resembles ca. 200 wt.% due to the high molecular weight. The high catalyst loading and the gel-formation might cause problems during work-up and catalyst recovery [6].

To overcome some of these limitations improved protocols for the enantioselective epoxidation have been developed by Roberts and co-authors, the so called biphasic conditions [5], the *PaaSiCat*-conditions (*PaaSiCat* = polyamino acid on Silca as Catalyst [7]) and the percarbonate conditions [8]. Under these conditions a broader range of substrates can be selectively epoxidised. Using the biphasic- or the *PaaSiCat* conditions it is even possible to epoxidise substrates with active hydrogen atoms adjacent to the carbonyl group. Despite of all progress, from an industrial point of view the various improved procedures of the Juliá-Colonna epoxidation are still hampered. Most of the problems are related to the PAA used as catalyst, especially the necessity of rather large quantities of the catalyst, the time-consuming pre-activation of the catalyst, which has to be carried out separately [9] and difficulties in the work-up process due to the gel-like nature of the catalyst [6]. Beside these problems related to the method the availability of highly active catalyst is limited.

The Juliá-Colonna epoxidation is a very interesting reaction since chiral, non-racemic epoxides may serve as building blocks for the synthesis of a wide variety of optically active compounds. Several examples have been published to illustrate the value of such building blocks [10,1] (Scheme 2).

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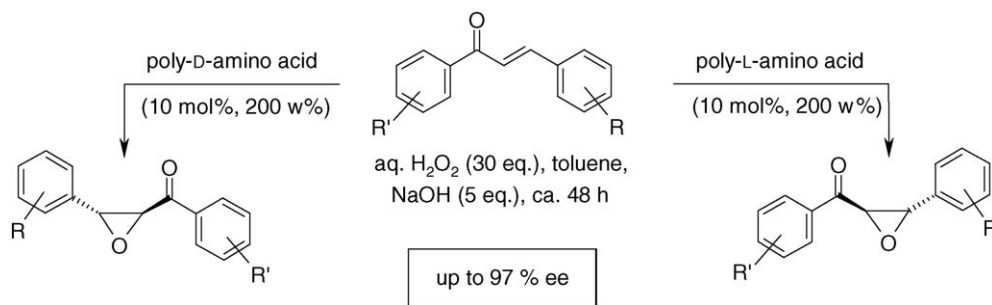
Scheme 1. Enantioselective epoxidation of chalcones (triphasic conditions).

2. Results and discussion

2.1. Hypothesis and initial testing

In view of an industrial application the triphasic conditions appeared most attractive as a starting point for an optimisation. These conditions are especially interesting since no separate pre-activation of the catalyst is required and the base and the oxidant used are rather inexpensive chemicals.

As a working hypothesis for the optimisation of the Juliá-Colonna epoxidation it was assumed that in the reaction mixture the PAA is the only source of chirality and therefore the oxidant or the substrate or both have to co-ordinate with it. Evidence for the formation of such complexes has been described just recently [11]. For the formation of such a complex the generated hydrogen peroxide anion has to be transferred through at least one phase interface. Following this lead a phase transfer catalyst (PTC) should be able to accelerate this central step of the reaction.

In the first experiment we tested our hypothesis under triphasic conditions using the standard test system, namely the epoxidation of *trans*-chalcone [e.g. 2,5,7,8,12] with poly-L-leucine (poly-L-leu) as catalyst.

To our surprise the addition of just 11 mol% tetrabutylammonium bromide (TBAB) as co-catalyst resulted in a dramatic acceleration of the reaction (Table 1) [13]. The reaction proceeds with high enantioselectivity (94% ee). Within 1.5 h virtually

Table 1
Comparison of the standard triphasic protocol with a PTC co-catalysed system on *trans*-chalcone (**1**)
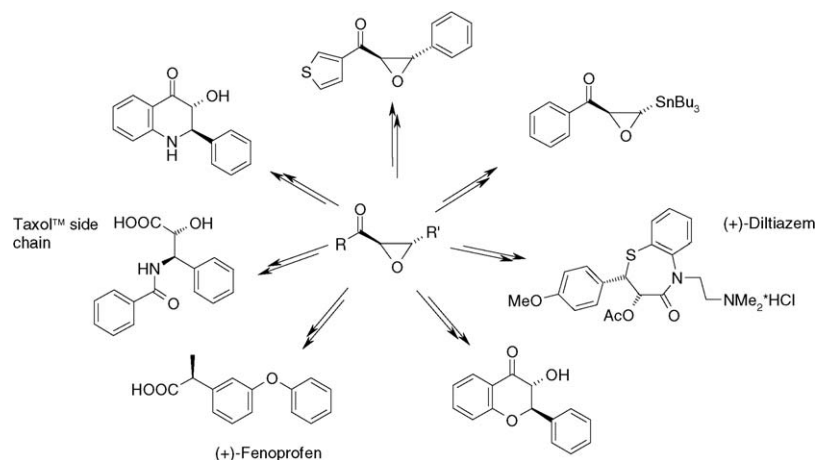
Conditions	Result
1.5 h, room temp.	2% conversion, ee not evaluated
+TBAB, 1.5 h, room temp.	>99% conversion, ee = 94%

Conditions: experimental procedure 4.3.3, 200 wt.% unactivated standard poly-L-leu (100 mg), 11 mol% TBAB, 28.5 equiv. H_2O_2, 4.2 equiv. NaOH, reaction time as indicated.

complete conversion to the desired epoxide **2** was observed while under standard triphasic conditions only 2% of the product were detected. Under these conditions the previously described pre-activation time of several hours [3,4b] is reduced to only minutes.

2.2. Catalyst preparation and testing

For all Juliá-Colonna protocols developed so far the employed PAA and the manner of its preparation turned out to be of crucial importance [14]. Therefore, the supply with a reliable poly-L-leu source was required for further investigations. Very pure and crystalline L-leucine-*N*-carboxyanhydride (L-leu-NCA) was obtained on a multi 100 g scale by phosgenation of L-leucine (L-leu) in THF, using 2 equiv. of L-leu as acid scavenger. Under these conditions the L-leu-NCA was not accompanied by a dark brown oil as described for a similar procedure [12c]. Alternatively the L-leu-NCA can be synthesised

Scheme 2. Selected examples.
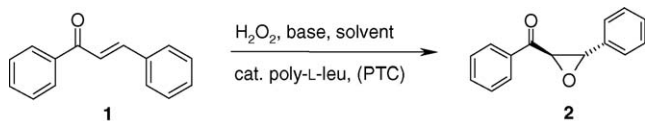
Scheme 3. Standard test reaction for the Juliá-Colonna epoxidation.

Table 2
Comparison of catalysts and the effect of PTC co-catalysis using *trans*-chalcone (**1**) as substrate

Entry	Catalyst	Time (min)	Result
1	Standard poly-L-leu	90	2% conversion, ee not evaluated
2	ht-Poly-L-leu	90	59% conversion, ee = 91%
3	ht-Poly-L-leu + TBAB	7	>99% conversion, ee = 94%

Conditions: experimental procedure 4.3.3 (Entry 1 + 2) and 4.3.1 (Entry 3), 200 wt.% poly-L-leu (100 mg,), 11 mol% TBAB, 28.5 equiv. H_2O_2, 4.2 equiv. NaOH, reaction times as indicated.

Table 3
Optimisation of the amount of poly-L-leu required, *trans*-chalcone (**1**) as substrate

| Catalyst type	Concentration (mol%)	Concentration (wt.%)	Conversion (%)	ee (%)
ht-Poly-L-leu type 1	0.28	5	96	90
	0.11	2	93	90
	0.03	0.5	52	83
ht-Poly-L-leu type 2	0.20	2	97	93
	0.05	0.5	89	90
	0.02	0.2	77	84
	0.01	0.1	61	80

Conditions: experimental procedure 4.3.1, 3 mol% TBAB, 4.2 equiv. NaOH, 5 equiv. H_2O_2, 1 h reaction time.

using stochiometric amounts of L-leu followed by a thorough re-crystallisation of the resulting L-leu-NCA. The L-leu-NCA was then polymerised in a statistical manner using a primary amine as initiator. To minimise the required time for the preparation of poly-L-leu the polymerisation was carried out in toluene at elevated temperature. Under the new conditions for the preparation of poly-L-leu the PAA forms a gel. After some optimisation it turned out that the isolation of the poly-L-leu can be done easily by precipitation with methanol or centrifugation and subsequent drying. In summary, the new procedure for the catalyst preparation allowed the reliable preparation of several highly active poly-L-leu types with different chain lengths on a multi 100 g scale (Scheme 4) [15].

A poly-L-leu variant polymerised at higher temperature (ht-poly-L-leu) was tested using the standard test reaction (Scheme 3). In comparison with the standard catalyst [14] the ht-poly-L-leu possesses a significantly higher activity. Whereas the standard poly-L-leu gave almost no conversion within 90 min reaction time the use of ht-poly-L-leu led in the same time to a conversion of 59% and an ee of 91% (Table 2). Even more interesting the combination of the PTC co-catalysis and the new ht-poly-L-leu under standard conditions resulted in a

dramatic accelerated reaction. In just 7 min complete conversion to the epoxide with an enantiomeric excess of 94% was achieved.

Under the PTC co-catalysis (PTC/triphasic-conditions) the previously described pre-activation time of several hours [3] is reduced to a few minutes and the reaction mixture appears as a thick emulsion with a small aqueous phase.

Having access to a very active catalyst and the knowledge regarding the PTC-co-catalysis the scope of the reaction was evaluated. In a first step the amount of catalyst was lowered (Table 3). Two different batches of ht-poly-L-leu were used for the testing. The ht-poly-L-leu type 1 was prepared using 1,3-diaminopropane as initiator in an L-leu-NCA/initiator ratio of 66:1, ht-poly-L-leu type 2 was prepared using 1-butylamine as initiator in an L-leu-NCA/initiator ratio of 18:1. Again the epoxidation of *trans*-chalcone (**1**) was used as standard test reaction (Scheme 3).

Interestingly a significant reduction in the amount of ht-poly-L-leu required was achieved for both poly-L-leu types. Using the triphasic/PTC conditions, a reduction of ht-poly-L-leu quantity by a factor of 100 was possible without significant loss of enantiomeric excess. Even with just 0.1 wt.% of the catalyst (type 2) a reasonable enantiomeric excess could be achieved. Due to the reduction of the amount of the catalyst, mixing and work-up of the reaction system is no longer a problem; the reaction mixture appears as a "2-phase-system" with only a trace of the
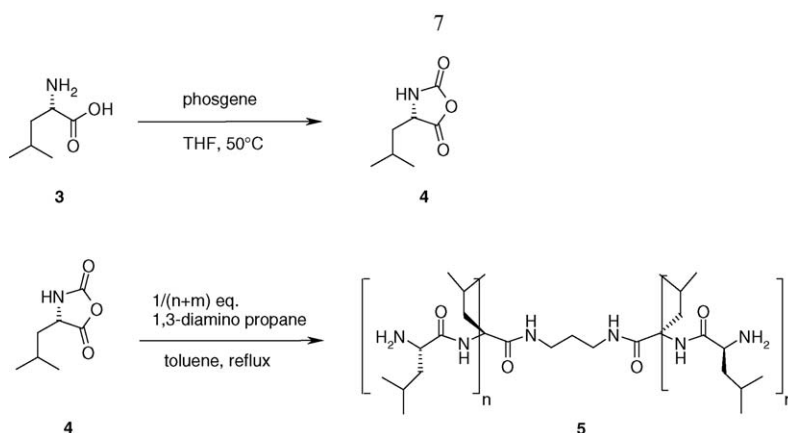
Scheme 4. Synthesis of L-leu-NCA and statistical polymerisation to poly-L-leu.
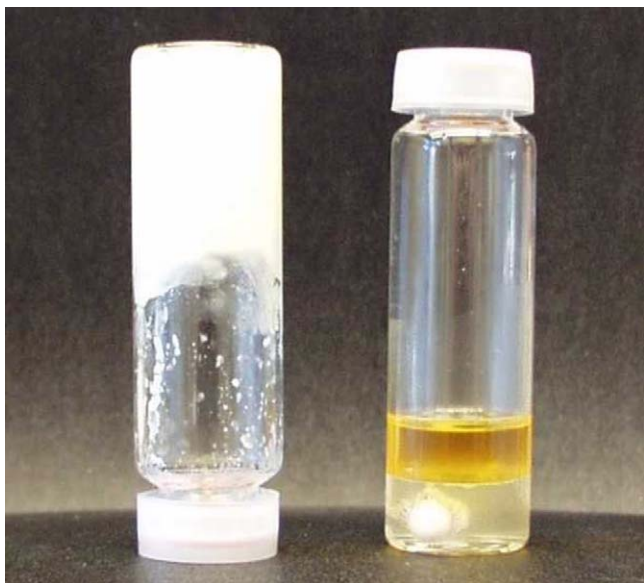
Picture 1. Appearance of a triphasic- and a PTC/triphasic system. Conditions: experimental procedure 4.3.3 (left); 500 mg chalcone, 25 mg poly-leucine, 23 mg TBAB, 2 ml toluene, 1.3 equiv. NaOH (5 M), 1.3 equiv. aq. H_2O_2 (30%), instant mix, aqueous phase diluted for the photo (right).

catalyst at the phase boundary, rather than the usual voluminous gel (Picture 1).

Beside the reduction of the amount of catalyst the amounts of oxidant and base can also be reduced significantly. In initial experiments the excess of H_2O_2 normally used was reduced from ca. 30 equivalents (equiv.) to 1.3 equiv. and the excess of

NaOH from 4 equiv. also to 1.3 equiv. without any detrimental effect.

2.3. Influence of the PTC

The influence of the amount of the PTC on the rate of reaction and the enantiomeric excess of the chalcone epoxide was also examined using the standard test reaction (Scheme 3). As expected it was found that the rate of reaction decreases with a reduction in the amount of PTC, but the enantiomeric excess remains high. It is interesting to note that even 0.1 mol% of the catalyst is sufficient to co-catalyse the reaction. With no PTC, less than 1% conversion to the epoxide was observed during the same reaction time (Fig. 1).

The properties of the PTC are important for the outcome of the epoxidation. PTCs more hydrophilic than TBAB, e.g. benzyltriethylammonium chloride have very little influence on the speed and enantiomeric excess of the reaction. In strong contrast very hydrophobic PTCs (e.g. $(Oct_4N)^+Br^-$) induce a very fast but significantly less selective reaction if all ingredients are present straight from the beginning. Noteworthy in this case is that the selectivity can be improved if the substrate is added after a short induction period of the poly-L-leu in presence of the PTC. The epoxidation proceeds then with a reasonable enantiomeric excess (Fig. 2, Table 4). The positive effect of a pre-activation of the catalyst in presence of a more lipophilic PTC is rather general [16].

The dramatic increase of the racemic "background" epoxidation under the co-catalysis with very lipophilic PTCs indicates
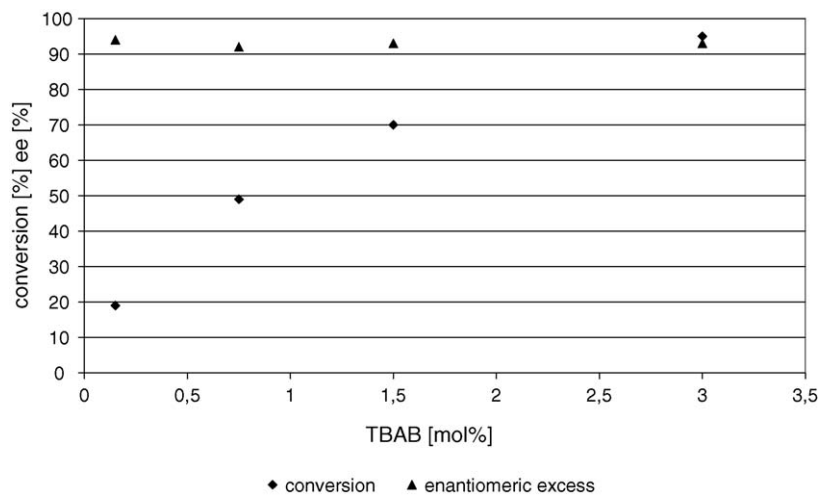

Fig. 1. Influence of the PTC concentration on the rate of reaction and enantiomeric excess. Conditions: experimental procedure 4.3.1, 3 wt.% ht-poly-L-leu type 1, TBAB as indicated, 1.5 equiv. NaOH, 1.5 equiv. H_2O_2, 2 h reaction time.
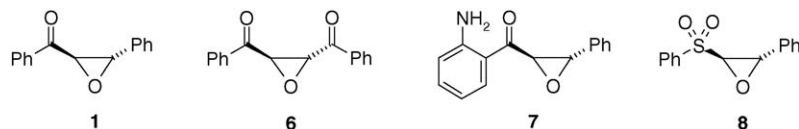

Fig. 2. Products.

Table 4
Influence of pre-activation of the PAA for selected PTCs

Entry	Epoxide formed	PTC/procedure	Time (min)	H_2O_2 (equiv.)	NaOH (equiv.)	Conv. (%)	ee (%)
1	**1**	Oct$_4$N)$^+$Br$^-$, a	30	5	4.2	75	7
2	**1**	Oct$_4$N)$^+$Br$^-$, b	30	5	4.2	>99	84
3	**6**	Oct$_4$N)$^+$Br$^-$, a	15	1.3	1.3	>99	82
4	**6**	Oct$_4$N)$^+$Br$^-$, b	15	1.3	1.3	>99	95
5	**7**	Aliquat336$^®$, a	30	5	4.2	74	55
6	**7**	Aliquat336$^®$, b	30	5	4.2	>99	91
7	**8**	Aliquat336$^®$, a	120	5	4.2	92	22
8	**8**	Aliquat336$^®$, b	30	5	4.2	95	64

Conditions: 200 wt.% poly-L-leu type 1, 11 mol% PTC; procedure a: instant mix (experimental proc. 4.3.1); procedure b: with pre-activation (experimental proc. 4.3.2).
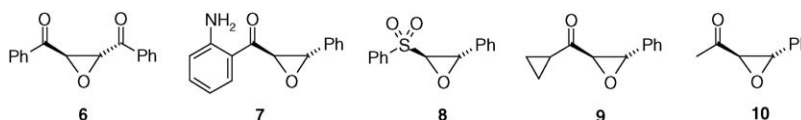

Fig. 3. Products.

Table 5
Comparison of the triphasic/PTC-conditions with other Juliá-Colonna epoxidation protocols

Entry	Prod.	Time (min)	H_2O_2 (equiv.)	NaOH (equiv.)	Conv. (%)	ee (%)	Ref. experiment
1	**6**	8	1.3	1.3	>99 (76)	92 (76)	15 h, triphasic [6]
2	**7**	15	5	4.2	97 (81)	93 (98)	2 h, biphasic [5]
3	**8**	120	5	4.2	82 (61)	68 (21)	cond. not publ. [7]
4	**9**	300	28	4.2	40 (85)	90 (77)	18 h, triphasic [6]
5	**10**	60	5	4.2	64 (70)	77 (80)	4 h, biphasic [3b]

Conditions: experimental proc. 4.3.1, 200 wt.% poly-L-leu type 1, 11 mol% TBAB; results of the reference experiments are given in parenthesis.

that poly-L-leu is not initially ready to catalyse the reaction. However, after a short induction time the poly-L-leu adopts a form, which is able to catalyse the reaction in a very efficient way. This might correlate with the observation that the poly-L-leu changes its appearance at the beginning of the reaction. A swelling of the PAA in the solvent can be observed during the induction period. This swelling might be explained by solvation of the poly-L-leu and/or the incorporation of the hydrogen peroxide or its anion into the polymer [11]. It is interesting to note that the required time for this swelling is much shorter in the presence of a PTC like TBAB.

2.4. Scoping the new conditions

In order to scope the new conditions, some further epoxidation reactions were carried out to broaden the substrate range and to draw comparisons to the results published in the literature for the epoxidation process (Fig. 3, Table 5) [16]. As test compounds substrates were chosen, which either exhibited low reactivity or

were not epoxidisable at all under the standard triphasic conditions. For these experiments the same catalyst loading was used as described in the literature.

As seen previously under the new triphasic/PTC conditions the conversions were generally much faster than under the published conditions, even though the ht-poly-L-leu was used as it was produced. The enantiomeric excess was in the same range as the reported results, sometimes significantly higher. In the cases of the epoxidation of the 1-alkyl enones (Table 5, Entries 4 and 5) some side reactions were observed, especially in the case of the epoxidation of (3*E*)-4-phenylbut-3-en-2-one (Table 5, Entry 5). However, it is noteworthy that this substrate type has not been epoxidised at all under the triphasic conditions [5].

In a further test (2*E*)-1-phenyl-3-pyridin-2-yl-prop-2-en-1-one (**11**) was epoxidised under improved triphasic/PTC conditions with just 5 wt.% poly-L-leu type 1 (Scheme 5, experimental proc. 4.3.1). The reaction with this substrate is known to be slow under standard conditions (16 h, 115 wt.% poly-L-leu, 84% conv., 72% ee, triphasic conditions [4c]). The
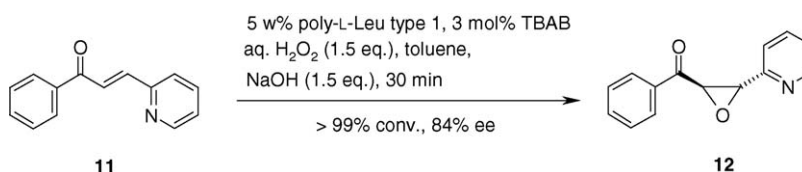
Scheme 5. Epoxidation of (2*E*)-1-phenyl-3-pyridin-2-yl-prop-2-en-1-one (**11**).

Table 6
Scale-up study using enone **13** as test substrate

Entry	Substrate (g)	ht-Poly-L-leu (wt.%)	Time (h)	Conv. (%)	Yield (%)[b]	ee (%)[b]
1	100	20	20	>99	77	96
2[a]	100	20	12	>98	76	97
3	100	15	20	>99	78	97
4	100	10	20	>99	75	96
5	100	5	20	>99	77	92
6	100	20 (recycl.)	20	>99	75	97

Conditions: analogous to experimental proc. 4.3.4, amounts ht-poly-L-leu (Fluka, poly-L-leucine-1,3-diaminopropane, prod.no. 93197) and reaction time as indicated.

[a] Experiment carried out in a sealed glass autoclave.

[b] Enantiomeric excess and yield after crystalisation from toluene.
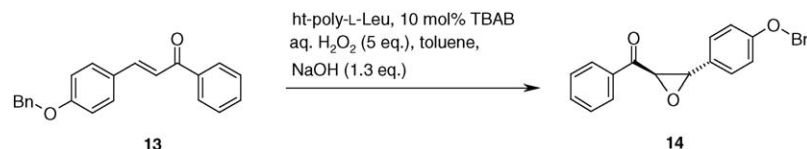
Scheme 6. Scale-up study.

outcome of the reaction confirmed the observation achieved with *trans*-chalcone.

Attempts to scale-up the Juliá-Colonna epoxidation under the triphasic/PTC-conditions to a 100 g scale led initially to a significant increase of the overall reaction time [17] when the epoxidation of (2*E*)-3-[4-(benzyloxy)phenyl]-1-phenylprop-2-en-1-one (**13**) was used as a test reaction.

It turned out that the epoxidation rate under the triphasic/PTC conditions is strongly dependent on the efficiency of stirring. Therefore, a jacketed glass reactor with glass baffles at the reactor inner walls has been employed for a first scale-up study in order to ensure efficient radial and axial flow within the heterogeneous reaction mixture. As stirrer a pitched-blade glass impeller was used at a stirring rate of 700–800 rpm. However, with 20 wt.% of ht-poly-L-leu up to 20 h (overnight) at room temperature were required to ensure full conversion of the enone **13** (Table 6, Entry 1), albeit epoxy ketone **14** was obtained in good optical purity. When the same reaction was performed in a sealed glass autoclave providing more efficient mixing (stirring rate ca. 700 rpm) the reaction time could be reduced to just 12 h (Table 6, Entry 2). A further reduction of the amount of poly-L-leu employed for the epoxidation is possible (Table 6, Entries 3–5). With only 5 wt.% pll the reaction was also finished in 20 h (overnight), although, the enantiomeric excess dropped to 92%. If required, a recycling of the catalyst is possible under the triphasic/PTC conditions (Entry 6) (Scheme 6).

3. Conclusion

In summary, the PTC co-catalysed Juliá-Colonna epoxidation is normally much faster and the enantiomeric excess sometimes higher than under previously published conditions. These effects are rather general. The necessary amount of poly-L-leu can be reduced significantly yielding an almost biphasic system. Therefore, mixing, work-up and catalyst recovery are no limitations any longer. Under the new conditions a separate pre-activation of the catalyst is not required. The catalyst itself can be prepared

very fast in a reliable way via a high temperature polymerisation of L-leucine-NCA resulting in a highly active poly-L-leucine. A scale-up study indicated that a scale-up is possible. On a 100 g substrate scale with only 10 wt.% of poly-L-leucine as catalyst the epoxidation of (2*E*)-3-[4-(benzyloxy)phenyl]-1-phenylprop-2-en-1-one (**13**) resulted in 75% yield and 96% ee [18].

4. Experimental

4.1. General information

The reactions were carried out at room temperature. During the reaction light was excluded. The conversions were monitored by TLC or HPLC. Samples for the HPLC were prepared by filtration of a sample of the reaction mixture in EtOAc/petrol ether (1:2) through a small layer of silica (Pasteur pipette), evaporation of the solvent and re-dissolving the material in the HPLC-solvent. The enantiomeric excess was determined by chiral HPLC or via ^{1}H NMR using Eu(hfc)$_3$ as shift reagent. The racemic epoxides were used as standards.

4.2. The catalysts

The standard-poly-L-leu was prepared in THF at room temperature via statistical polymerisation of L-leu-NCA with 1,3-diaminopropane (1,3-diaminopropane/leu-NCA = 1:66) as initiator [14].

For the preparation of ht-poly-L-leu, the initiator and leu-NCA were dissolved at room temperature in toluene and subsequently heated to reflux for 24 h. Two types of catalyst were prepared, differing in the amine used to initiate the polymerisation and the amine/leu-NCA ratio: poly-L-leu type 1 (1,3-diaminopropane/leu-NCA = 1:66), poly-L-leu type 2 (1-amino butane/leu-NCA = 1:18). Due to the initiator used for the preparation of poly-L-leu type 1 two active centers per molecule were assumed for the calculation of the mol%-figures for this catalyst.

For work-up the ht-poly-L-leu can be isolated via centrifugation of the resulting gel and subsequent drying or via precipitation with methanol [17]. ht-Poly-leu prepared similarly to the procedure described in this article is now available from Fluka (poly-L-leucine-1,3-diaminopropane, prod.no. 93197).

4.3. Reaction conditions

4.3.1. Triphasic/PTC-conditions, procedure a, (instant mix)

The indicated amount of poly-leu, 0.24 mmol of the substrate and the given amount of PTC were mixed. Subsequently 0.8 ml toluene, the indicated amounts of NaOH (5 M, aq.) and H_2O_2 (30%, aq.) were added. This mixture was stirred for the indicated time at a rate of approximately 1250 rpm. For work-up the mixture was diluted with 1 ml of EtOAc and poured slowly into 4 ml of a stirred ice-cold aqueous $NaHSO_3$ solution, 20%. After 5 min the mixture was centrifuged. The organic phase was separated and the solvent evaporated under reduced pressure.

4.3.2. Triphasic/PTC-conditions, procedure b (pre-activation)

The poly-leu and the PTC were placed in a sample vial. Subsequently toluene and NaOH (5 M, aq.) were added (ratios see procedure a). This mixture was stirred at a rate of approximately 1250 rpm for 1.5 h before the substrate was added. After the indicated reaction time the work-up was carried out as described above.

4.3.3. Triphasic conditions ([14], work-up modified)

As triphasic/PTC, procedure a, but without phase transfer catalyst.

4.3.4. Scale-up studies

A 2000 ml jacketed glass vessel was successively charged with tetrabutylammonium bromide (TBAB) (11 g, 0.032 mol, 10 mol%), ht-poly-L-leu (Fluka, poly-L-leucine-1,3-diaminopropane, prod.no. 93197, 10 g, 1.1 mmol, 0.35 mol%), toluene (1600 ml) and 5 M aqueous sodium hydroxide (82 ml, 0.410 mol, 1.3 equiv.). After cooling to 15 °C 30% hydrogen peroxide (162 and 1.57 mol, 5 equiv.) 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 h before enone **13** (100 g, 0.318 mol, 1.0 equiv.) was added as a solid. Subsequently, the reaction was stirred for 20 h in the dark at 25 °C. The reaction 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 **14** 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 sulfate, filtered and concentrated in vacuo to afford a beige solid. This material was crystallised from toluene (300 ml) to furnish epoxy ketone **14** (79 g, 75%) as a white solid. Analysis by chiral HPLC indicated 96% ee.

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