

## Scoping the triphasic/PTC conditions for the Juliá–Colonna epoxidation reaction

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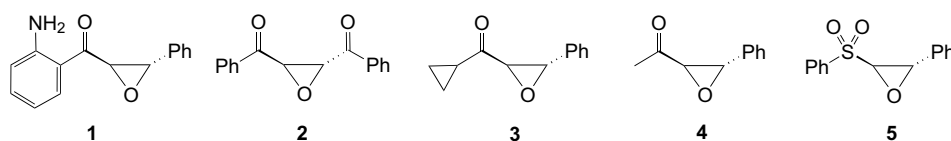
**Abstract**—A new, highly efficient procedure for the Juliá–Colonna epoxidation is reported. Based on the original triphasic protocol it is shown that the co-catalysis of the reaction with phase transfer catalysts results in a dramatic increase of reactivity and sometimes also in a higher enantiomeric excess of 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.

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We have reported previously, in brief, that the Juliá–Colonna epoxidation can be co-catalysed with phase transfer catalysts (PTCs) resulting in a dramatic increase in the rate of the reaction.<sup>1</sup> In order to scope the new conditions, some further epoxidation reactions were carried out to broaden the substrate range and to draw comparison to the results published in the literature for

the epoxidation process (Scheme 1, Table 1). Note that as test substrates, compounds were chosen, which either exhibit low reactivity or were not epoxidisable at all under the standard triphasic conditions.

As seen previously under the new triphasic/PTC conditions the conversions were generally much faster than



**Scheme 1.** Products.

**Table 1.** Comparison of the triphasic/PTC-conditions<sup>2</sup> with other Juliá–Colonna epoxidation protocols

Entry	Epoxide formed	Time	H <sub>2</sub> O <sub>2</sub> [equiv]	NaOH [equiv]	Conv. [%]	Ee [%]	Ref. experiment
1	<b>1</b>	15 min	5	4.2	97 (81)	93 (98)	(2 h, biphasic) <sup>5</sup>
2	<b>2</b>	8 min	1.3	1.3	>99 (76)	92 (76)	(15 h, triphasic) <sup>6</sup>
3	<b>3</b>	5 h	28	4.2	40 (85)	90 (77)	(18 h, triphasic) <sup>6</sup>
4	<b>4</b>	1 h	5	4.2	64 (70)	77 (80)	(4 h, biphasic) <sup>3b</sup>
5	<b>5</b>	2 h	5	4.2	82 (61)	68 (21)	Cond. not publ. <sup>7</sup>

Conditions:<sup>2</sup> procedure a, 11 mol% poly-L-Leu type 1, 11 mol% TBAB used; results of the reference experiments are given in brackets.

**Keywords:** Juliá–Colonna epoxidation; Epoxides; Asymmetric reactions; Asymmetric synthesis; Polyamino acid; Peptide; Phase transfer catalysis.

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**Table 2.** Influence of pre-activation of the polyamino acid for selected PTC's

Entry	Epoxide formed	PTC/procedure	Time [min]	H <sub>2</sub> O <sub>2</sub> [equiv]	NaOH [equiv]	Conv. [%]	Ee [%]
1	<b>1</b>	Aliquat336 <sup>®</sup> , a	30	5	4.2	74	55
2	<b>1</b>	Aliquat336 <sup>®</sup> , b	30	5	4.2	100	91
3	<b>2</b>	(Oct <sub>4</sub> N) <sup>+</sup> Br <sup>-</sup> , a	15	1.3	1.3	100	82
4	<b>2</b>	(Oct <sub>4</sub> N) <sup>+</sup> Br <sup>-</sup> , b	15	1.3	1.3	100	95
5	<b>5</b>	Aliquat336 <sup>®</sup> , a	120	5	4.2	92	22
6	<b>5</b>	Aliquat336 <sup>®</sup> , b	30	5	4.2	95	64

Conditions:<sup>2</sup> 11 mol% poly-L-Leu type 1, 11 mol% PTC; procedure a: instant mix; procedure b: with pre-activation.

under the published conditions, even though the poly-L-leucine (poly-L-Leu) was used as it was produced.<sup>2</sup> The enantiomeric excess (ee) was at least in the same range as the reported results, sometimes significantly higher. In the cases of the epoxidation of the 1-alkyl enones (Table 1, entries 3 and 4) some side reactions were observed, especially in the case of the epoxidation of 3-phenyl-2-butenone (Table 1, entry 4). However, it is noteworthy that this substrate type has not been epoxidisable at all under the triphasic conditions so far.<sup>3b</sup>

As reported for *trans*-chalcone, the type of PTC used has a profound influence on the outcome of the reaction.<sup>1</sup> The use of a more lipophilic catalyst results in a dramatic loss of enantiomeric excess. However, this effect can be minimised if the polyamino acid is pre-activated<sup>2</sup> in the presence of the PTC, whereupon the enone (or sulfone) is added later. In order to ascertain whether this effect can also be observed with other substrates further tests were carried out (Table 2).

For all the substrates epoxidised in the presence of a lipophilic PTC a significant positive influence on the ee was observed when pre-activation of poly-L-Leu was performed.

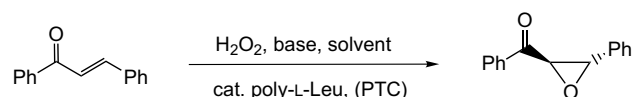
Under the previously published conditions, the usual amount of poly-L-Leu needed for efficient catalysis was in the range of ca. 10 mol%, which translates to ca. 200 wt%. Due to the very fast reaction under the triphasic/PTC-conditions it was interesting to determine whether the amount of the polyamino acid could be reduced (Table 3). Chalcone was used in the standard test reaction (Scheme 2).<sup>3</sup>

Interestingly a significant reduction in the amount of poly-L-Leu required was achieved for both poly-L-Leu

**Table 3.** Reduction of the amount of poly-L-Leu required

Catalyst type	Concentration [mol%]	Concentration [wt%]	Conversion [%]	Ee [%]
Poly-L-Leu type 1	0.28	5	96	90
	0.11	2	93	90
	0.03	0.5	52	83
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: procedure a, 3 mol% TBAB, 4.2 equiv NaOH, 5 equiv H<sub>2</sub>O<sub>2</sub>, 1 h reaction time.<sup>2</sup>

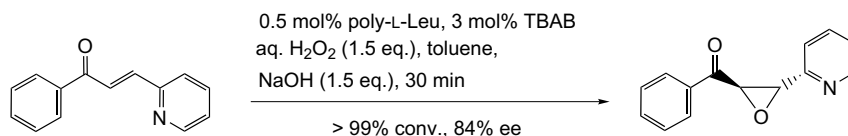
**Scheme 2.** Standard test reaction for the Juliá-Colonna epoxidation.

types. Using the triphasic conditions, a reduction of poly-L-Leu by a factor of 100 was possible without significant loss of enantiomeric excess. Even with poly-L-Leu amounts of just 0.1 wt%, a reasonable enantiomeric excess could be achieved. Due to the reduction of poly-L-Leu, the mixing and work-up of the reaction system was no longer a problem; the reaction mixture appears as a '2-phase-system' with only a trace of the catalyst at the phase boundary, rather than the usual voluminous gel.

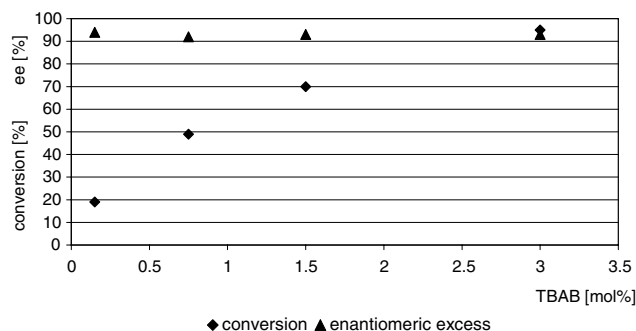
In a further test (*2E*)-1-phenyl-3-pyridin-2-yl-prop-2-en-1-one was epoxidised under the new conditions with just 0.5 mol% (9 wt%) poly-L-Leu type 1 (Scheme 3). The reaction with this substrate is known to be slow under standard conditions (16 h, 115 wt% poly-L-Leu, 84% conv., 72% ee, triphasic conditions).<sup>8</sup> The outcome of the reaction confirmed the observation achieved with *trans*-chalcone.

The influence of the amount of the PTC on the rate of reaction and the enantiomeric excess of the chalcone epoxide was also tested using the standard test reaction (Scheme 2). 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 was sufficient to co-catalyse the reaction. With no PTC, less than 1% conversion to the epoxide was observed in the same reaction time (Fig. 1).

The principle of co-catalysis is also applicable to other reaction conditions in the Juliá-Colonna epoxidation, that is, biphasic conditions and protocols involving silica-supported polyamino acids (PaaSiCat). Normally for these conditions pre-activated poly-L-Leu is required.<sup>9</sup> Of interest is the fact that, under the new PTC co-catalysed conditions a reasonable enantiomeric excess can be achieved even with unactivated poly-L-Leu (i.e., as produced directly from the polymerisation reaction). As under the triphasic conditions the reaction time as well as the enantiomeric excess is enhanced by the PTC (Table 4). This fact might be explained by a faster formation of the 'real' catalyst<sup>1</sup> and therefore a reduced (unselective) background reaction.



**Scheme 3.** Epoxidation of (2E)-1-phenyl-3-pyridin-2-yl-prop-2-en-1-one.



**Figure 1.** Influence of the PTC concentration on the rate of reaction and enantiomeric excess. Conditions<sup>2</sup>: Standard test reaction, procedure a, 0.3 mol% poly-L-Leu type 1, indicated amount of TBAB, 1.5 equiv H<sub>2</sub>O<sub>2</sub>, 1.5 equiv NaOH, 2 h reaction time.

**Table 4.** Influence of the PTC under biphasic- and PaaSiCat-conditions using unactivated poly-L-Leu, standard test (epoxidation of *trans*-chalcone)

Conditions	Results
Biphasic	>99% conversion, 53% ee
Biphasic/PTC	>99% conversion, 78% ee
PaaSiCat	>99% conversion, 86% ee
PaaSiCat/PTC	>99% conversion, 92% ee

Conditions: 30 min room temp; biphasic;<sup>3b</sup> PaaSiCat;<sup>3c</sup> biphasic/PTC and PaaSiCat/PTC as before but with 11 mol% TBAB.

In summary, the PTC co-catalysed Juliá–Colonna epoxidation is normally much faster and the enantiomeric excess higher than under previously documented conditions. The effect is generally observable under all tested protocols for the Juliá–Colonna epoxidation. In particular, under the triphasic conditions, the principle of co-catalysis is very beneficial since downstream work-up is very simple and only cheap ingredients are required. The necessary amount of poly-L-Leu can be reduced significantly to 2–5 wt%, thus mixing and catalyst recovery is no longer a limitation.

## References and notes

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- Poly-Leu: All poly-L-Leu-batches used were prepared via statistical polymerisation of L-leucine-NCA (leu-NCA) with an amine at high temperature. Two types of catalyst were prepared, differing in the amine used to initiate 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).<sup>4</sup> Due to the initiator used for the preparation of poly-L-Leu type 1, two active centres per molecule were assumed for the calculation of the mol% figures for this catalyst. ht-poly-Leu made using a procedure similar to that described in this article is now available from Fluka (Poly-L-leucine-1,3-diaminopropane, Prod. no 93197).
- Triphasic/PTC-conditions, procedure a, (instant mix): The indicated amount of poly-L-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) and H<sub>2</sub>O<sub>2</sub> (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<sub>3</sub> solution, 20%. After 5 min the mixture was centrifuged. The organic phase was separated and the solvent evaporated under reduced pressure.
- 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) 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.
- General remarks: (1) the reactions were carried out at room temperature; (2) during the reaction light has to be excluded; (3) the reactions were monitored by TLC or HPLC; (4) samples for HPLC were prepared by filtration of a solution of the material (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; (5) enantiomeric excess was determined by chiral HPLC or <sup>1</sup>H NMR (using Eu(hfc)<sub>3</sub>) employing racemic epoxides as standards.
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