

Novel conditions for the Juliá–Colonna epoxidation reaction providing efficient access to chiral, nonracemic epoxides

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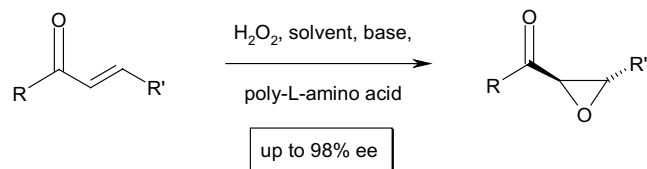
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Abstract—The addition of a phase-transfer catalyst significantly accelerates the Juliá–Colonna epoxidation reaction yielding chiral, nonracemic epoxy ketones. Furthermore, a reliable procedure for the preparation of highly active poly-L-leucine catalyst is reported.

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Stereoselective catalysts of pure organic origin have come sharply into focus in recent times.¹ In one of the early examples, the use of chiral polyamino acids as organic catalysts was reported by Juliá et al. in the epoxidation of chalcone with good enantioselectivity (Scheme 1).² Since then several groups, including Juliá and Colonna and later Roberts and co-workers, have shown that with respect to the original triphasic method (excess of inorganic base and hydrogen peroxide in an aqueous phase, the substrate dissolved in an organic phase and the insoluble polyamino acid as a third phase) several improvements can be gained.³ Under the new conditions of the Juliá–Colonna epoxidation a broad range of substrates bearing a substituted enone system as a prerequisite can be selectively epoxidized. However, from an industrial point of view even the various



Scheme 1. Juliá–Colonna epoxidation.

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

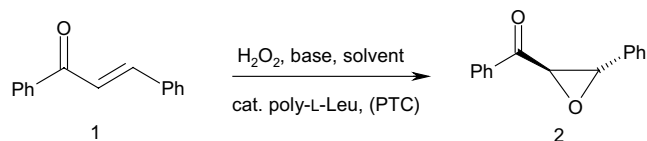
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improved procedures are hampered by several factors, for example, by the limited availability of the catalysts, which are used in rather large quantities, long reaction times and/or difficulties in the work-up process.

In a move to extend our chiral technologies we became interested in the Juliá–Colonna reaction since chiral, nonracemic epoxides may serve as building blocks for the synthesis of a wide variety of optically active compounds.⁴

Understanding the reaction mechanism of the Juliá–Colonna epoxidation should be key to further optimization and has been addressed by some research groups.⁵ Even so, very little is known about the active catalytic species. A key problem is that the most common and selective catalyst, poly-leucine, is virtually insoluble in organic and aqueous media. As a hypothesis we assumed that a phase-transfer catalyst (PTC) should be able to accelerate the reaction since for all existing Juliá–Colonna protocols the hydroperoxide anion is formed in one phase and has to be transferred through at least one phase interface in order to form the desired epoxide.⁶

In the first set of experiments we tested whether the addition of a PTC under triphasic conditions would have any influence on the epoxidation of *trans*-chalcone (the standard test system, Scheme 2).⁷ We chose these conditions for our first tests since unactivated poly-L-leucine (poly-L-Leu) can be used as the catalyst and



Scheme 2. Standard test reaction for the Juliá–Colonna epoxidation.

Table 1. Comparison of PTC/triphasic-conditions with the triphasic protocol on *trans*-chalcone **1**

Conditions ^a	Result
1.5 h, room temp	2% conversion, ee not evaluated
+TBAB, 1.5 h, room temp	>99% conversion, ee = 94%

^a See Ref. 8.

aqueous hydrogen peroxide as the oxidant. To our surprise the addition of tetrabutylammonium bromide (TBAB) as co-catalyst resulted in a dramatic acceleration of the reaction (Table 1).

The reaction proceeds with high enantioselectivity (94% ee). Within 1.5 h, virtually complete conversion to the desired epoxide **2** was observed while under standard triphasic conditions only 2% of the product was detected. Under these conditions the previously described pre-activation time of $\geq 6\text{ h}$ ⁹ is reduced to a few minutes. Our current understanding of the reaction with the PTC is that it increases the available peroxide concentration in the organic phase.¹⁰ Additionally, we could show that due to the very fast reaction, the amount of oxidant and base could be reduced significantly, from 30 equiv H_2O_2 and about 4 equiv of NaOH initially to 1.3 equiv of each.

Under all the published conditions hydrogen peroxide or a hydrogen peroxide generating agent is used as the oxidant. We therefore tested whether a somewhat safer and equally readily available aqueous NaOCl-solution could be used as the oxidizing reagent under the new PTC/triphasic-conditions.

Table 2. Epoxidation of *trans*-chalcone using an aqueous NaOCl-solution

Conditions ^a	Result
1.5 h, room temp	1% conversion, ee not evaluated
+TBAB, 1.5 h, room temp	32% conversion, ee = 90%

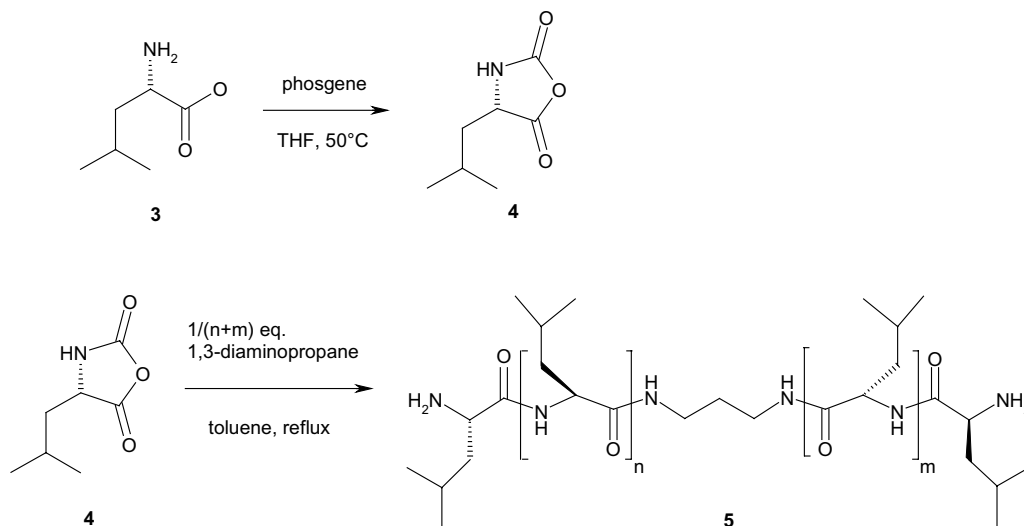
^a See Ref. 8.

Following the original protocol no reaction was observed with NaOCl.¹¹ However, considerable conversion and good enantioselectivity was obtained on using TBAB as a phase-transfer catalyst over the same reaction time of 1.5 h (Table 2, entry 2).

For all the Juliá–Colonna protocols developed so far, the polyamino acid employed and the manner of its preparation are of crucial importance.¹² Poly-L-Leu has been prepared in a conventional fashion by synthesis of the corresponding *N*-carboxyanhydride **4** (Leu-NCA) and subsequent amine induced polymerization.

In our hands some of the commercial poly-L-leucines did not deliver the required catalytic activity, so we investigated large-scale production of material for our developmental work. We obtained Leu-NCA on a multi 100 g scale in very pure and crystalline form by phosgenation of L-leucine **3** in THF, using 2 equiv of leucine as acid scavenger. Under these conditions the Leu-NCA was not accompanied by a dark brown oil as described earlier.^{12a} After some optimization it turned out that the subsequent statistical polymerization induced by 1,3-diaminopropane was preferably performed in refluxing toluene.¹³ The required poly-L-Leu **5** was isolated by precipitation with an alcohol or by centrifugation and subsequent drying. This procedure allowed the reliable preparation of several highly active poly-L-Leu types with different chain lengths on a multi 100 g scale (Scheme 3).

To our surprise poly-L-Leu that had been polymerized at higher temperatures (ht-poly-L-Leu) led to signifi-



Scheme 3. Preparation of Leu-NCA and statistical polymerization to poly-L-Leu **5**.

Table 3. Comparison of PTC/triphasic-conditions with the triphasic protocol on *trans*-chalcone

Catalyst	Conditions ^a	Result
Standard poly-L-Leu	1.5 h	2% conversion, ee not evaluated
Ht-poly-L-Leu	1.5 h	59% conversion, ee = 91%
Ht-poly-L-Leu + TBAB	7 min	>99% conversion, ee = 94%

^a See Ref. 8.

cantly more active catalysts as compared to the standard material.^{12d} In the triphasic epoxidation of *trans*-chalcone (Scheme 2) almost no conversion (2%, ee not evaluated) was observed after 1.5 h with standard poly-L-Leu while in the same time the ht-poly-L-Leu had already led to a conversion of 59% and an ee of 91% (Table 3). Obviously, the new catalyst material does not need a prolonged pre-activation period.⁹ The combination of ht-poly-L-Leu and TBAB led to full conversion of **1** in less than 10 min (Table 3, entry 3).

In summary, a new and efficient protocol for the Juliá-Colonna epoxidation has been developed. It was found that the addition of specific PTCs results in a significant acceleration of the reaction. One effect of the PTC is a sharp reduction of the catalyst pre-activation period that is otherwise needed. Thus under the triphasic conditions the principle of co-catalysis is very beneficial since the active poly-L-leucine can be used as it is produced. Ongoing research indicates that improved poly-L-leucine quality enables the epoxidation of a broader range of substrates and leads to significant reductions in catalyst loadings yielding a virtually biphasic system. These results are reported in the following publication.

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- PTCs have already been used for Juliá-Colonna reactions in order to utilize sparingly water-soluble oxidants such as Na-perborate or Na-percarbonate. However, no beneficial additional effects on reaction time, selectivity and catalyst loading have been reported.
- For example: (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929; (b) Bentley, P. A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E. *Chem. Commun.* **1997**, 739; (c) Geller, T.; Roberts, S. M. *Chem. Commun.* **1999**, 1397; (d) Takagi, R.; Manabe, T.; Shiraki, A.; Yoneshige, A.; Hiraga, Y.; Kojima, S.; Ohkata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2115; (e) Geller, T.; Gerlach, A.; Krüger, C. M.; Militzer, H.-C. EP-A-02015587.
- Poly-L-Leu*. All poly-L-Leu-batches used were prepared via statistical polymerization of Leu-NCA with 1,3-diaminopropane (1,3-diaminopropane/Leu-NCA = 1:66). The standard-poly-L-Leu was prepared in THF at room temperature.^{12d} For the preparation of ht-poly-L-Leu, 1,3-diaminopropane and Leu-NCA were dissolved at room temperature in toluene and subsequently heated to reflux for 24 h.
Triphasic/PTC-conditions. Poly-L-Leu (100 mg, 11 mol%, 200 wt%), 50 mg (0.24 mmol) of *trans*-chalcone and 8.5 mg (11 mol%) of TBAB were mixed. Subsequently 0.8 mL toluene, 4.2 equiv NaOH (5 M) and 28.5 equiv H₂O₂ (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 NaHSO₃ solution (20%). After 5 min the mixture was centrifuged. The organic phase was separated and the solvent evaporated under reduced pressure.
Triphasic/PTC-conditions, NaOCl. As before but with 6 mL NaOCl-solution (aq 7.5% NaOCl) instead of H₂O₂ and NaOH. This mixture was stirred at a rate of approximately 1250 rpm for 1.5 h. For work-up of the mixture see above.
Triphasic conditions. As Triphasic/PTC but without phase-transfer catalyst.
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 the HPLC were prepared by filtration of a solution of the material (EtOAc/pet. 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 determined by chiral HPLC employing racemic epoxides as standards.
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- Geller, T.; Gerlach, A.; Vidal-Ferran, A.; Militzer, H.-C.; Langer, R. *PCT Int. Appl.* **2003**, WO 2003070808 (Priority: DE 2002-10206793 20020219, Bayer AG). Later Baars et al. also reported polymerizations of Leu-NCA at elevated temperature.^{12a} Ht-poly-L-Leu made similar to the procedure described in this article is now available from Fluka (Poly-L-leucine-1,3-diaminopropane, Prod. no 93197).