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# Batch versus continuous mg-scale synthesis of chalcone epoxide with soluble polyethylene glycol poly-L-leucine catalyst

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**Abstract**

The polyethylene glycol poly-L-leucine catalysed asymmetric epoxidation of chalcone was carried out in a laboratory batch reactor. At initial concentrations of poly-L-leucine, chalcone, peroxide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) of 13.47 g/l, 0.0802 mol/l, 0.132 mol/l and 0.22 mol/l, respectively, the conversion was 94.9% and enantioselectivity was 90.3%. The peroxide deprotonation time by DBU and sequence of reactant addition were found to affect the reaction outcome. Based on these results, a suitable protocol for continuous runs was established. These were carried out in a setup comprising two micromixers and two tubular microreactors the first for deprotonation and the second for epoxidation. Slow mixing of the poly-L-leucine catalyst due to its low molecular diffusivity was identified as a potential cause for the worse performance of the continuous system compared to the batch reactor. This however was rectified when peroxide and poly-L-leucine were pre-mixed prior to entering the continuous reactor system.


*Keywords:* Asymmetric epoxidation; Microreactor; Polyleucine

## 1. Introduction

Batch reactors have been the dominant workhorse in the pharmaceutical and fine chemicals industry for decades, due to their flexibility and versatility for cost-effective manufacture of small quantities of chemicals with short product lifetime. This is in contrast to the bulk chemicals industry where dedicated continuous plants find widespread application as they offer the potential for lower manufacturing costs, improved safety, reduced variation in product quality (due to better control of reaction conditions) and reduction in down-time from batch to batch processing or plant reconfiguration.

The increasing competitiveness in the pharmaceutical industry has intensified the search for more efficient and economical production processes. This, coupled with recent developments in microreaction technology, has fueled interest in continuous processing [1–5]. Microreactors typically have sub-millimeter characteristic dimensions and hold-up volumes in the micro liter range. The high surface to volume ratio in such a miniaturized system facilitates intensified heat and mass transfer and precise control of operating conditions, expanding the range of chemistries resulting in better yield and selectivity. Microreaction technology could potentially revolutionize the pharmaceutical industry as it could combine the benefits of continuous processing with some of the flexibility required by the industry. Additionally, it also allows for potential savings in R&D costs and time, by rapid scale-up via numbering up.

In recent years, various types of reactions have been tested in microreactors which exploit the benefits offered by microreaction technology to enhance performance. A substantial number of these relate to liquid phase organic synthesis, demonstrating the growing interest to exploit microreactors for fine chemicals production [6–11].

In this work, the poly-L-leucine catalysed epoxidation of chalcone reaction is investigated. It allows access to highly enantioselective chalcone epoxides that are reactive intermediates used in the pharmaceutical industry [12–23]. The use of poly-L-leucine as a catalyst for epoxidation of chalcone was first reported by Julia and Colonna in 1980, in a triphasic reaction system with the chalcone substrate in a water-immiscible organic solvent such as hexane or toluene, aqueous sodium hydroxide containing hydrogen peroxide as oxidant and base and the

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**Nomenclature**

| | |
|---|---|
| ACN | acetonitrile |
| $d$ | tube diameter (m) |
| $D_{ab}$ | diffusivity of a in b ($m^2/s$) |
| $D_c$ | characteristic dimension (m) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| $Fo$ | Fourier number |
| $L$ | length (m) |
| $L_{mix}$ | mixing length (m) |
| PEG | polyethylene glycol |
| PLL | poly-L-leucine |
| $Re$ | Reynolds Number ($Re = \rho ud/\mu$) |
| $Sc$ | Schimdt Number ($Sc = \mu/\rho D_{ab}$) |
| $t$ | time (s) |
| THF | tetrahydrofuran |
| $u$ | average velocity (m/s) |
| $\rho$ | Density |
| $\mu$ | viscosity |

insoluble gel-like polyamino acid as catalyst [24–27]. However, this system did not gain widespread popularity because of the lengthy reaction time and difficulty in recovering the gel-like catalyst. Later, a nonaqueous biphasic system was reported, in which the aqueous sodium hydroxide and hydrogen peroxide were replaced with organic base and anhydrous urea-hydrogen peroxide. This improved reaction times to around 30 min but the paste-like form of the catalyst remained difficult to handle [28]. A "mild" biphasic system employing sodium percarbonate as both oxidant and base was also reported which diminishes the background epoxidation, resulting in improved enantioselectivity [29]. Immobilisation of the solid catalyst on silica [30,31] improved physical properties for handling, while tethering the catalyst to polyethylene-glycol allowed for the employment of homogeneous reaction conditions [32,33]. More recently, a modified triphasic procedure has been reported, in which addition of a phase transfer catalyst in the original triphasic procedure improved reaction rates rapidly [34,35].

From all the above reaction systems, the one selected is the polyethylene glycol-poly-L-leucine catalysed asymmetric epoxidation of chalcone, a liquid phase reaction in a mixed tetrahydrofuran (THF) and acetonitrile (ACN) solvent with urea-hydrogen peroxide as oxidant and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base to deprotonate the oxidant as depicted in Scheme 1. The reaction is strongly affected by the choice of solvent used. Acetonitrile was found to enhance the background reaction while THF appears to prevent the background reaction [36]. A THF:ACN ratio of 2.15 was selected for the reaction system to allow for comparisons of our experimental results with those from earlier kinetic studies which were carried out in a THF:ACN ratio of 2.15 [37]. Experimental results from these kinetic studies indicate a conversion of 87% and enantioselectivity of 95% in 16 min at 23.1 °C and at base case initial concentrations as shown in Table 1.

Table 1
Base case initial concentration of reactants in the reaction mixture

| | |
|---|---|
| PLL (g/l) | 13.47 |
| Peroxide (mol/l) | 0.132 |
| Chalcone (mol/l) | 0.0802 |
| DBU (mol/l) | 0.22 |

All the reactants are completely soluble in mixed THF/ACN, except for urea-hydrogen peroxide which leaves behind an insoluble solid, after the hydrogen peroxide is extracted with organic solvent [37].

This paper describes the transfer of the reaction from batch to continuous mode. For this purpose, batch and continuous experimental studies were carried out to help establish a protocol for a continuous system with similar performance characteristics as the batch process.

## 2. Experimental

### 2.1. Analytical conditions

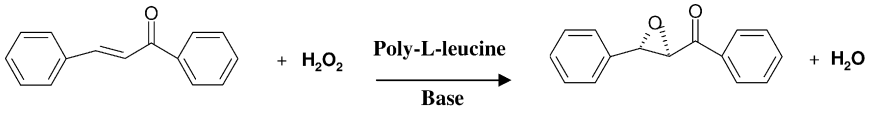
Chiral HPLC analyses were performed on a Jasco liquid chromatograph equipped with the chiral column Chiralpak® AD (VWR International). The mobile phase was 10% ethanol in hexane. The flowrate was set at 1.0 ml/min and the UV detector at 254 nm. The oven temperature was set at 10 °C and the sample was injected manually with a Rheodyne 7725i injection valve.

### 2.2. Determination of peroxide concentration

The peroxide concentration was determined using the procedure by Gonsalves et al. [38]. Each 0.5 ml aliquot was treated with 15 ml glacial acetic acid and 5 ml saturated potassium iodide solution, and left in the dark for approximately 10 min. The resulting solution was then titrated against 0.1 M sodium thiosulphate until a light yellow solution was obtained. A drop of starch solution was then added and the titration with 0.1 M sodium thiosulphate continued until a clear solution was obtained. All the chemicals were obtained from Sigma–Aldrich. The concentration of $H_2O_2$ was determined from this titration value based on the stoichiometric equations below:

$$H_2O_2 + 2HI \rightarrow I_2 + 2H_2O \quad (1)$$

$$2Na_2S_2O_3 + I_2 \rightarrow Na_2S_4O_6 + 2NaI \quad (2)$$




Scheme 1.

### 2.3. Batch experimental procedure

A batch of mixed solvents was prepared keeping the THF:ACN ratio at 2.15 (v/v). A solution of hydrogen peroxide was prepared by stirring 3 g of urea-hydrogen peroxide (Lancaster synthesis) in 20 ml of mixed THF/ACN for approximately 1 h. The mixture was then filtered to remove the undissolved solids and the clear solution was used in the reaction. This solution was titrated regularly and its concentration remained around 1 M. A 3.0 mol/l chalcone solution (Lancaster synthesis) was also prepared.

For every batch reaction, approximately 0.42 g of PEG-poly-L-leucine catalyst (PLL) (Lancaster synthesis) was used. The catalyst was dissolved in mixed THF/ACN and the peroxide and DBU (Lancaster synthesis) solutions were then added to this. The mixture was stirred for approximately 30 min and the reaction was initiated by adding the chalcone solution. The reactor was maintained at 30 °C by placing it in a water bath. After 16 min, a reaction sample was taken and quenched with saturated aqueous sodium sulphite solution (Sigma–Aldrich). The organic phase was extracted with ether, evaporated to dryness and the residue redissolved in 10% (v/v) ethanol in hexane for HPLC analysis.

### 2.4. Continuous experimental setup

An XP 3000 Modular digital pump (Cavro) with three 50-μl syringes was used to pump solutions of chalcone, peroxide and catalyst with DBU. Three solutions were prepared: a 0.16 mol/l chalcone solution, a 0.53 mol/l peroxide solution and a PLL/DBU solution of 53.88 g/l PLL and 0.88 mol/l DBU. Two micromixer chips were used to bring the reagents into contact. They are shown in Fig. 1 and consist of a 100 μm T-type micromixer channel (first section) followed by a larger serpentine delay loop channel (second section), dimensions of which are given in Table 2. Peroxide and PLL/DBU flows of 5 μl/min each joined in the first micromixer chip and entered a 0.3 ml Teflon tubular reactor with 30 min residence time. Subsequently, a 10 μl/min chalcone flow joined the combined streams in the second micromixer and entered a 0.32 ml Teflon tubular reactor with a total residence time of 16 min. The micromixers and Teflon tubular reactor were maintained at a temperature of 30 °C by placing them in a water bath. The reaction was quenched at the reactor outlet by collecting the outlet flow in a stirred vial containing sodium sulphite as quench.

Table 2
Channel dimensions of the mixing chips

| Dimensions | First chip | | Second chip | |
|---|---|---|---|---|
| | First section | Second section | First section | Second section |
| Width (μm) | 100 | 300 | 100 | 600 |
| Depth (μm) | 300 | 300 | 300 | 300 |
| Length (mm) | ~20 | ~288 | ~20 | ~198 |

The microreactor chips were fabricated by photolithography and deep reactive ion etching (DRIE) on 4 in. silicon wafers at the central microstructure facility (CMF, Rutherford Appleton Laboratory). The structured wafers, each containing nine micromixers were covered with a Corning 7740 glass wafer (1 mm thick, with holes pre-drilled as inlets and outlets) and sealed by anodic bonding. The bonded wafer was cut to obtain nine micromixers per wafer. For both the deprotonation and epoxidation reactions, 0.75-mm-ID Teflon tubes were used as reactors. The dimensions of these tubular reactors were selected so that their performance approximated plug flow. For plug flow to be applicable the following criteria must be met [39]:

$$\frac{d}{L} \ll Re_d Sc \ll \frac{L}{d} \tag{3}$$

For a 0.75 mm ID tube the length required for a 0.32 ml reactor volume is 0.724 m. In this case $Re_d\ Sc = 78.4$ based on chalcone molecular diffusivity of $7.22 \times 10^{-9}$ m$^2$/s, while the values of $d/L$ and $L/d$ are 0.001 and 966, respectively. Wilke and Chang correlations were used to estimate the binary diffusivity of chalcone in pure THF and pure acetonitrile while the method of Tang and Himmelblau was used to estimate diffusivity in a pair of mixed solvents [40].

## 3. Batch experiments

### 3.1. Effect of solvent pre-mixing

The batch reaction was initially carried out by first extracting the urea-hydrogen peroxide into pure acetonitrile. This was then pre-stirred with DBU and polyleucine catalyst in THF for 30 min

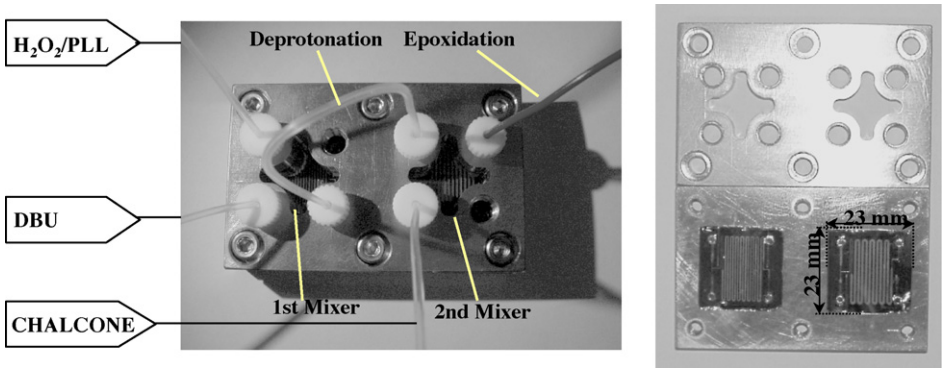



Fig. 1. Assembled continuous flow reactor and mixing chips used in this work (modified flow arrangement). A shorter deprotonation reactor is shown for illustration.

for deprotonation and the reaction was initiated by adding a solution of chalcone dissolved in THF, taking care to ensure that the THF to acetonitrile ratio was always maintained at 2.15 [37]. This protocol gave a conversion of 96% (±1.2%) and enantioselectivity of 90.2% (±1.1%) at 30 °C and 16 min reaction time.

Two main problems were apparent with this initial batch procedure. Extraction of hydrogen peroxide from urea-hydrogen peroxide using pure acetonitrile (while using pure THF for all other reactants) limited the maximum peroxide concentration to 0.132 mol/l, due to the need to maintain the THF:ACN ratio at 2.15. This ruled out the possibility of further optimizing the reaction for improved yields and production rate. Additionally, this also resulted in formation of a white precipitate on addition of hydrogen peroxide in acetonitrile solution to the reaction mixture in THF [37].

A new reaction protocol was devised in which a large batch of mixed THF and acetonitrile was prepared with a THF:ACN ratio of 2.15. This batch of mixed solvent was then used to prepare all reagent solutions as well as for extracting urea-hydrogen peroxide, therefore allowing a larger range of peroxide concentrations to be used while also avoiding formation of precipitate, which could potentially cause clogging of continuous equipment. While the rate of reaction is known to increase with increasing temperature up to 35 °C [23], the reaction was carried out at a temperature of 30 °C, which allows for a reasonably fast rate while avoiding potentially damaging operating conditions to catalyst lifetime (the catalyst is a polypeptide, which denatures at high temperatures).

A base case batch experiment using the modified procedure with pre-mixed THF and ACN at 30 °C, with pre-stir (deprotonation) time of 30 min resulted in a conversion of 94.9% (±2.6%) and enantiomeric excess of 90.3% (±0.5%) in 16 min, close to those obtained with the initial procedure, without formation of white precipitate, hence making the reaction feasible for continuous processing. The current procedure allows scope for further optimizing the reaction in a single continuous unit prior to numbering up, as we are now able to increase the peroxide concentration to higher levels.

### 3.2. Effect of deprotonation time

The first step of the reaction involves a pre-reaction equilibria. The concentration of the reactive species, which is the peroxy anion, is determined by the chemical equilibrium process:

$$H_2O_2 \Leftrightarrow OOH^- + H^+ \quad (4)$$

It was estimated that near complete deprotonation was achieved with the peroxide and DBU concentrations used, with final peroxy anion concentrations in excess of the stoichiometric requirements ($pK_a$ ($H_2O_2$) = 11.75, $pK_a$ (DBU) = 12) [23]. However, data on the rate at which the equilibrium concentration is reached was not available. A further complication exists, as hydrogen peroxide is prone to decomposition under basic conditions. To ensure that the initial concentration of the reactive species is constant, the effect of varying deprotonation reaction time was examined. The batch experiments were carried out with varying deprotonation reaction time, from 15 min to 60 min, to check for the optimum deprotonation reaction time.

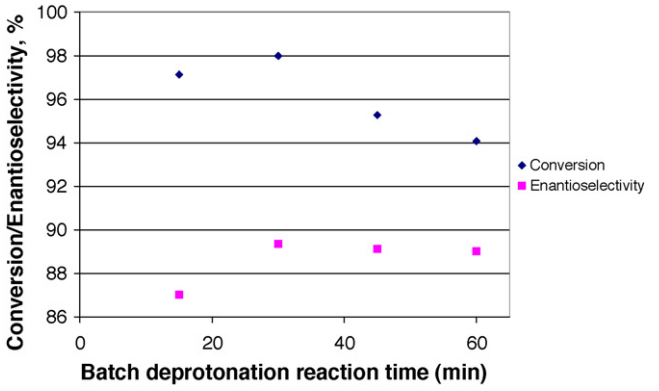



Fig. 2. Conversion and enantioselectivity of chalcone epoxidation as a function of deprotonation time (conditions: base case with pre-mixed THF/ACN at 30 °C).

From Fig. 2, the conversion was observed to be highest at a deprotonation time of 30 min, and dropped when the deprotonation time was increased further. The enantioselectivity increased to about 89% at 30 min, and remained fairly constant even when the deprotonation time was increased further. The difference may be due to different initial peroxy anion concentrations. At lower deprotonation time, deprotonation reaction is incomplete resulting in lower peroxy anion concentration, while at longer deprotonation time, deprotonation reaction is complete but peroxy anion starts to decompose due to the alkaline reaction conditions. The improvement in enantioselectivity from 15 min to 30 min and subsequent stabilisation after 30 min point to the possibility that a period of stirring the catalyst and peroxide prior to start of reaction may lead to improved enantioselectivity as it allows the peroxy anion to adsorb on the catalyst, reducing the amount of free peroxide available for the background reaction. However, the improvement of around 2% is probably statistically not significant enough for such a conclusion to be drawn.

### 3.3. Effect of reactant addition sequence

The effect of the order of reactant addition on the reaction performance was also investigated. The following cases were examined:

(I) Catalyst, peroxide and DBU pre-stirred for 30 min followed by addition of chalcone solution to start the reaction.
(II) Catalyst, chalcone and DBU pre-stirred for 30 min followed by addition of peroxide solution to start the reaction.
(III) Catalyst, chalcone and peroxide pre-stirred for 30 min followed by addition of DBU to start the reaction.
(IV) Catalyst solution pre-stirred with chalcone for 30 min. The peroxide solution was simultaneously pre-stirred with DBU for 30 min. The two solutions were then mixed to start the reaction.

The results show a significant change in conversion and enantioselectivity when the sequence of reactant addition was varied

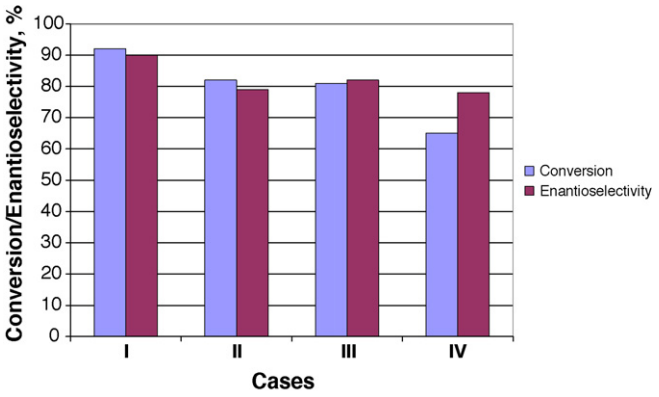



Fig. 3. Conversion and enantioselectivity of chalcone epoxidation for various reactant addition sequences. For details see text (conditions: base case with pre-mixed THF/ACN, 30 min pre-stir prior to epoxidation reaction at 30 °C).

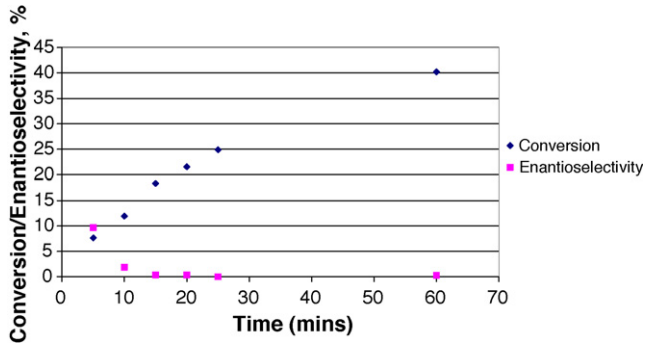



Fig. 4. Conversion and enantioselectivity of chalcone epoxidation in the absence of catalyst (conditions: base case with pre-mixed THF/ACN with 30 min deprotonation time at 30 °C).

(see Fig. 3). The drop in conversion when peroxide or DBU was added last (cases II and III) could possibly be due to incomplete deprotonation of the peroxide resulting in lower concentration of the reactive species (peroxy anion). A bigger drop in conversion was observed when pre-mixed DBU and peroxide was added last (case IV) and this could be due to faster decomposition of the peroxy anion in the absence of catalyst for the peroxy anion to adsorb to. The substantial drop in enantioselectivity in cases II–IV points to the possibility that a period of contacting the catalyst with peroxy anion could improve enantioselectivity by reducing the amount of free peroxide available for the background reaction.

### 3.4. Background reaction

The background reaction refers to the rate of the epoxidation reaction in the absence of poly-L-leucine catalyst. The rate of background reaction was examined and found to be relatively slow. The conversion of chalcone after 16 min was approximately 19% (see Fig. 4).

## 4. Continuous experiments

Having established the reaction protocol from the batch runs, the reaction was then performed in a continuous setup (see Fig. 5) at inlet reactor concentrations at base case conditions (see Table 1). Based on the results obtained from the batch reaction experiments, the continuous system was designed so that peroxide, poly-L-leucine catalyst and DBU were mixed first before entering the deprotonation tubular reactor with 30 min residence time. At the exit of the deprotonation reactor, the mixture was subsequently mixed with chalcone solution to start the reaction before entering the epoxidation reactor.

The conversion and enantioselectivity obtained for the continuous reaction system were 73.6% and 83.1%, respectively, much lower than those obtained from the batch system. This was thought to be due to incomplete mixing and confirmed from mixing length calculations. The molecular diffusivity of PEG-poly-L-leucine can be estimated to be $1.432 \times 10^{-10}$ m$^2$/s. This is a reasonable estimate as the diffusivity of polyethylene glycol with an average molecular weight of 15,500 was reported by Brandrup et al. [41] as $(6–8) \times 10^{-11}$ m$^2$/s.

The Fourier number is defined as

$$Fo = \frac{D_{ab}t}{D_c^2} \tag{5}$$

For substantial to complete mixing, the Fourier number should be in the range $(0.1 < Fo < 1)$ [42]. The mixing length can be calculated by multiplying the average velocity with the mixing time. The length, $L$ for complete mixing (at $Fo = 1$) can be obtained from:

$$L_{mix} = \frac{D_c^2 u}{D_{ab}} \tag{6}$$

The mixing lengths were calculated for the first and second mixing chips, and were found to be inadequate. For a characteristic dimension, $D_c = 100\,\mu$m, the required mixing lengths for the first and second chips are 388 mm and 776 mm, respectively.

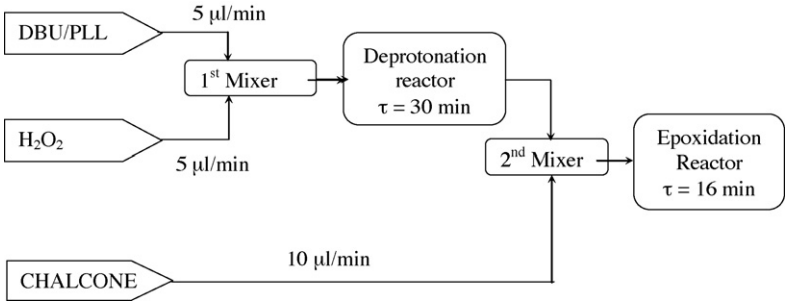



Fig. 5. Flow diagram of continuous experimental setup.

Table 3
Calculated required mixing lengths in the first and second micromixing chips based on poly-L-leucine and chalcone diffusivities

| | Molecular diffusivity ($m^2/s$) | Mixing length at $Fo = 1$ (mm) | |
|---|---|---|---|
| | | First micromixer | Second micromixer |
| Chalcone | $7.219 \times 10^{-09}$ | 7.7 | 15.4 |
| Poly-L-leucine | $1.432 \times 10^{-10}$ | 388 | 776 |

Table 4
Comparison of reaction performance with different micromixers

| | T-micromixers (%) | IMM micromixers (%) |
|---|---|---|
| Conversion | 74 | 76 |
| Enantioselectivity | 84 | 84 |

If the larger channel dimensions of the two chips are taken as characteristic length, this results in an even larger mixing length. In comparison, the required mixing lengths calculated based on chalcone diffusivity are 7.7 and 15.4 mm for the first and second micromixing chips, respectively (see Table 3) well within the available mixing length. This indicates that all other reagents except poly-L-leucine are well mixed (chalcone is expected to have lower molecular diffusivity compared to the other reagents due to its larger molecular size).

As the calculations indicate insufficient mixing, an experimental run using IMM standard slit interdigital micromixers was carried out. The two inlet feed streams come into contact in the interdigital-mixing element, creating a multi-laminated outlet flow with characteristic lamellae dimensions of 40 μm. The regular flow pattern created by multi-lamination is combined with geometric focusing and subsequent volume expansion which speeds up liquid mixing of the multi lamellae and leads to jet mixing [43]. The results however were similar to those obtained with the chip T-micromixers (see Table 4). The mixing time required based on lamellae width of 40 μm was estimated and shown in Table 5 (based on multi-lamination effect only. Semi-analytical calculation of mixing time is not possible due to complex interplay between focused interlamellae diffusion and jet mixing). In hindsight, the IMM mixers are probably not very good substitutes as the materials of construction of the mixing elements (nickel on copper for the first micromixer and silver on copper for the second micromixer) are known to catalyse peroxide decomposition.

Table 5
Calculated required mixing time for IMM slit interdigital micromixer based on poly-L-leucine and chalcone diffusivities

| | Molecular diffusivity ($m^2/s$) | Mixing time at $Fo = 1$ (s) |
|---|---|---|
| Chalcone | $7.219 \times 10^{-09}$ | 0.22 (1.39) |
| Poly-L-leucine | $1.432 \times 10^{-10}$ | 11.2 (69.8) |

Values in paranthesis are for characteristic dimension of 100 μm for comparison.

The setup was then modified such that the peroxide was premixed with the catalyst as shown in Fig. 6. This would allow the peroxide to be well dispersed with the catalyst molecule and adsorb on the catalyst on deprotonation instead of decomposing. Furthermore, the lack of free peroxy anions would reduce the background reaction rate. This modification resulted in conversion of 94.8% and enantioselectivity of 89.8%, closely matching those obtained in the batch experiments.

For near complete reaction, the production rate of this setup is approximately 1 g/day, making it suitable for bench-scale production of milligram quantities of chalcone epoxide. In comparison, CPC-System's CYTOS lab system with an internal volume of 1.1 ml is designed to handle flowrates of 0.2–40 ml/min, for production of the initial 40 g and up to kilogram quantities of product [44,4]. This easily meets the target for small scale production to supply pre-clinical and clinical phase I studies, where delivery time for kilogram quantities is in the order of 4–6 months [5].

While the production rate can be easily increased by increasing the number of reactors operating in parallel, clearly, for the existing unit to achieve the higher end of the production range, the reaction rate needs to be enhanced further. Numbering up may indeed prove beneficial for rapid scale-up; recent efforts to scale-up a modified triphasic epoxidation to 100 g substrate level have suffered from scale-up related problems, with significant increase of the overall reaction time [45]. A continuous chemzyme membrane reactor for PEG-poly-L-leucine catalysed epoxidation of chalcone in pure THF has also shown a decrease in reaction performance, when the reactor is operated for long times [46].

## 5. Concluding remarks

It was found that mixing needed to be enhanced as mixing by diffusion alone would require a very long channel due to the low molecular diffusivity of PEG-poly-L-leucine. The mix-

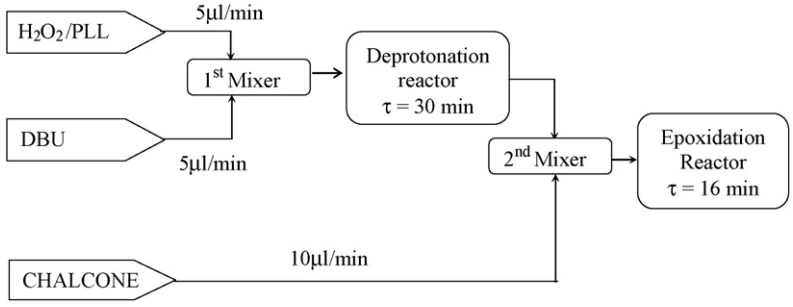



Fig. 6. Modified flow arrangement of continuous experimental setup.

ing problem was circumvented by feeding a mixture of peroxide and PEG-poly-L-leucine to the reactor system instead of feeding them separately. In this way, the peroxide adsorbed on the catalyst immediately after deprotonation, reducing the amount of free peroxide for the background reaction or decomposition. It may also be possible to improve the system further by reduction of the deprotonation reaction time, as the performance difference for 15 and 30 min is not significant and is well within limits of experimental error. A continuous system, by appropriate optimization and scale out provides the opportunity for higher throughputs.

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