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Proof of concept for continuous enantioselective liquid-liquid extraction in capillary microreactors using 1-octanol as a sustainable solvent

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Abstract

The use of capillary microreactors for enantioselective liquid-liquid extraction (ELLE) was successfully demonstrated using a model system consisting of a buffered aqueous amino acid derivative (3,5-dinitrobenzoyl-(*R*,*S*)-leucine) solution (phosphate buffer, pH 6.58) and a chiral cinchona alkaloid (CA) host in an organic solvent. It was shown that 1-octanol is a suitable replacement for the commonly used chlorinated solvents like 1,2-dichloroethane. Experiments were conducted in a capillary microreactor set-up (0.8 mm internal diameter) operated in the slug flow regime at 294 K (residence times between 12 and 900 s, 1:1 flow ratio of the aqueous to organic phases, 1 mM of host and 1 mM of amino acid derivative). The enantiomeric excess (*ee*) was shown to be a function of the solvent and residence time and varied between 37%-49% in 1,2-DCE and 28-46% in 1-octanol in the organic phase. The *ee* values in the organic phase at shorter residence times were higher than the independently determined equilibrium *ee* values (41% in 1,2-DCE and 31% in 1-octanol at a host concentration of 1 mM). This is an unprecedented observation with large implications for ELLE, as it implies that operation in the kinetic regime may lead to improved enantioseparation performance.

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Introduction

The availability of enantiopure compounds is of great importance for the pharmaceutical,[1,2] agrochemical,[3] flavor and fragrances industries,[4] as the individual enantiomers may show significant differences in biological activity. Synthesis of racemic compounds followed by a chiral separation is a well-established strategy to obtain enantiopure compounds.[5,6] Classical resolution for instance by crystallization is the most used technique for racemate separation.[7-10] However, this approach has a number of limitations, such as excessive solids handling.[7,11] Alternative methods have been developed such as kinetic resolution,[12-14] and physical separations. Examples of the latter are membrane separations,[15-18]chromatographic separation,[5] capillary electrophoresis,[7] and enantioselective liquid-liquid extraction (ELLE).[7,19-40]

ELLE involves contacting two immiscible liquid phases, one with the racemic mixture to be separated (usually in the aqueous phase) and an organic phase containing a soluble chiral host with a higher affinity for one of the enantiomers. After extraction, the enantio-enriched organic phase is back extracted to recover and recycle the host. The principle of ELLE is schematically shown in Figure 1.

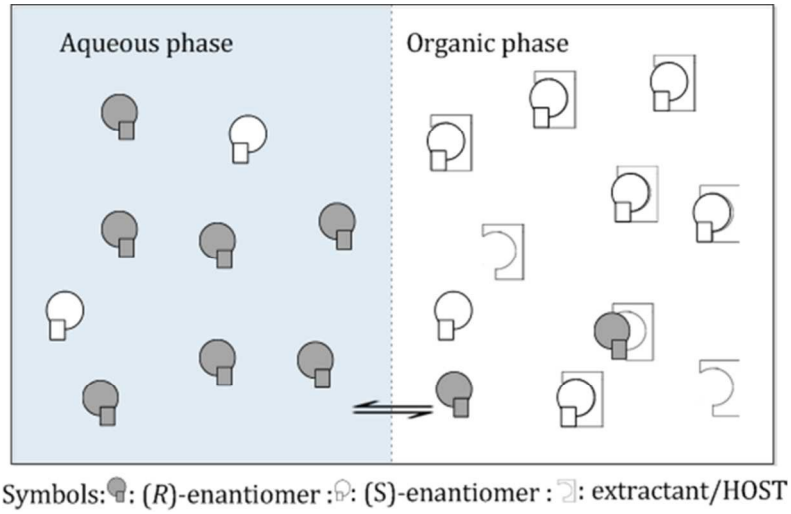

Figure 1. Schematic representation of ELLE.

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Advantages of ELLE include ease of scale up due to the fact that liquid-liquid extraction is a mature technology and the possibility to use one host family for the separation of multiple racemates.[7,41-42] Crystallization and filtration, which are the two major unit operations in classical resolutions are also the two most problematic ones, causing a lot of problems in the plant as a result of too small crystals, blocked filters and long filtration times. These problems are largely avoided with ELLE. We have recently shown the proof of concept for ELLE in a continuous mode using Centrifugal Contactor Separators (CCS), which are highly process intensified devices that combine mixing and phase separation. By using a countercurrent cascade of multiple CCS devices, good enantioselectivity and yield was obtained for the separation of an aqueous solution of 3,5-dinitrobenzoyl-(*R,S*)-leucine (DNB-(*R,S*)-Leu in Figure 2) with a cinchona alkaloid host (CA4 in Figure2) in 1,2-dichloroethane (1,2-DCE).[11,29,30] However, due to the relatively low selectivity, many stages are required to obtain both enantiomers in high-enantiopurity,[41,43] which has a negative effect on capital costs. In addition, there is a clear incentive to minimize the host inventory to reduce costs. Alternatives for CCS devices are intensified columns, as explored by Kockmann and co-worker,[22,23] and showing that a large number of stages is achievable per meter column.

Another possible alternative to intensify enantioseparation by liquid-liquid extraction is the use of microreactors.[44] The use of microreactors for liquid-liquid extractions has been reported,[45-55] examples are chip-based microreactors, high capacity mini extractors, and capillary or tubular microreactors (including coil-based flow reactors).[53] The use of such capillary microreactors offers good control over temperature and residence time, has shown to lead to enhanced mass transfer rates, and is relatively easy to scale-up.[51,54] Moreover, the use of microreactors may "green-up" ELLE e.g., by being more energy efficient (as compared to CCS) and reduced solvent use due to low reactor volume. This applies not only to the production phase, but also for the screening experiments in the lab. Although capillary microreactors are of great interest for ELLE, its use has never been reported in the literature and is an absolute novelty of this paper.

We here present an experimental study on enantioseparation by ELLE in capillary microreactors in the slug flow regime. This flow regime is expected to be advantageous as it is known to enhance mass transfer rates due to intensified circulation inside slugs and

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droplets.[51,56] The experiments were performed in an integrated setup which combines liquid-liquid extraction and separation.[56] A model system consisting of the separation of racemic 3,5-dinitrobenzoyl-*(R,S)*-leucine (DNB-(*R,S*)-Leu) using a chiral cinchona alkaloid host[11] was used. This reaction was selected as we have ample experience with it in CCS devices[11,57] and relevant thermodynamic data like complexation constants are available for the reference solvent (1,2-DCE).

Several derivatives of cinchona alkaloid (CA) chiral hosts have been successfully applied for the enantioseparation of DNB-(*R,S*)-Leu (Figure 2).[44]

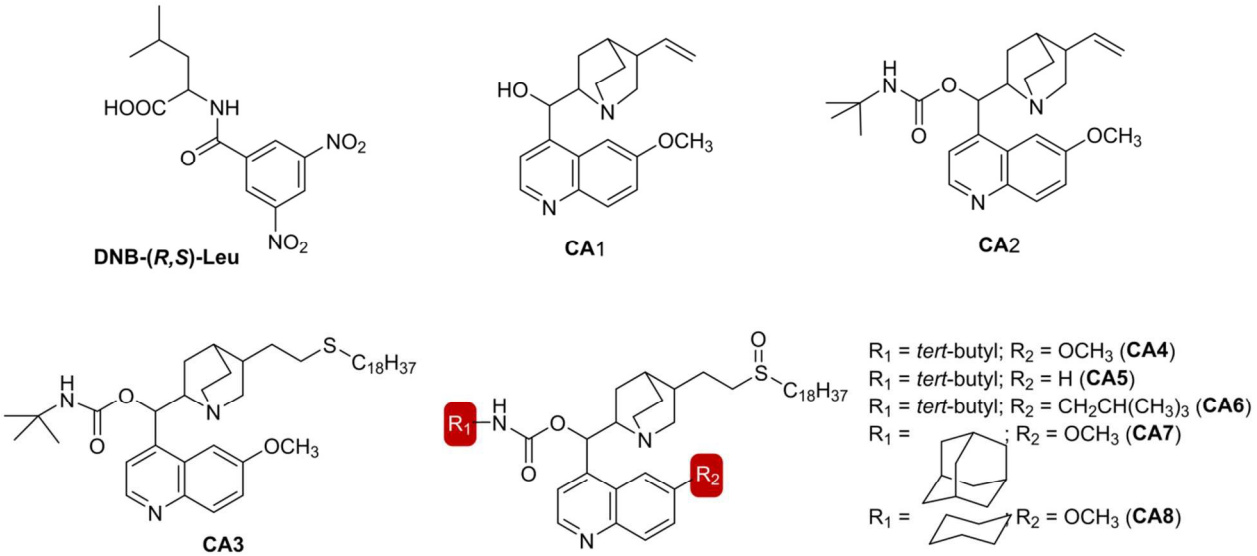

Figure 2. DNB-(*R,S*)-Leu and examples of cinchona-based chiral hosts for ELLE reported in the literature.[44]

In this study, we have used host CA3, the non-oxidized variant of the well-known extractant CA4. It is the precursor for CA4 and as such one synthetic step in the host synthesis may be eliminated. Two solvents were explored, viz. 1,2-DCE and 1-octanol. The former has been used extensively for ELLE, though its use has strong drawbacks when considering environmental performance. A such, the use of the environmentally more benign 1-octanol has also been investigated and its performance will be compared with 1,2-DCE. Higher alcohols are considered as green recommended solvents by a number of solvent selection guides.[58,59] In addition, 1-octanol is accessible from renewable resources ref.[60] Besides

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solvent effects, the influence of process variables and particularly the residence time on the separation performance was studied by varying the total flow rate and/or length of the capillary microreactors.

Material and Methods

Materials

The host CA3 was synthesized according to literature two-step procedure (Figure S1, Supplementary information).[61] NMR and elemental analysis data are provided in Figure S2, S3 and Table S1, Supplementary information. The amino acid derivative, 3,5-dinitrobenzoyl-(*R,S*)-leucine (DNB-(*R,S*)-Leu), was obtained from DSM. Organic diluents, viz. 1-octanol (99.8%) and 1,2-dichloroethane (1,2-DCE) (99.8%), were obtained from Sigma-Aldrich. Disodium hydrogen phosphate (≥ 99.5%) and potassium dihydrogen phosphate (≥ 99.5%), were obtained from Merck. All experiments were performed with Milli-Q water.

Experimental setup

Two set ups were used for the experimental study reported i.e. a batch set up and a continuous capillary microreactor. Experiments in the batch set up involved mixing an aqueous phase with the racemate and an organic phase with the host in a vial using a Teflon bar (1000 RPM) for a perdetermined amount of time. All continuous experiments were carried out in a capillary microreactor set up as schematically shown in Figure 3. The aqueous and organic phases were transferred to the capillary microreactor made of poly(tetrafluoroethylene) (PTFE) tubings (Bola, Germany, 1.6 mm outer diameter and 0.8 mm inner diameter) via a Y-junction (120˚ angle between branches, 1 mm inner diameter, made of polyether ether ketone (PEEK) for the use of 1,2-DCE and polymethylmethacrylate (PMMA) for 1-octanol) using syringe pumps (model No. LA30, HLL Gmbh, Germany). The end of the capillary microreactor was connected to a Y-splitter for the separation of both liquid phases. The outlets of the Y-splitter consist of a PTFE tube and a glass tube of the same dimension (i.e., 1.6 mm outer diameter and 0.8 mm inner diameter). The two tubes were positioned in a prefabricated Y-shaped splitter made from PEEK or PMMA. The

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separation in the splitter is based on the preferential wettability (aqueous phase: glass, organic phase: PTFE). The composition of the aqueous phase was analyzed (*vide infra*).

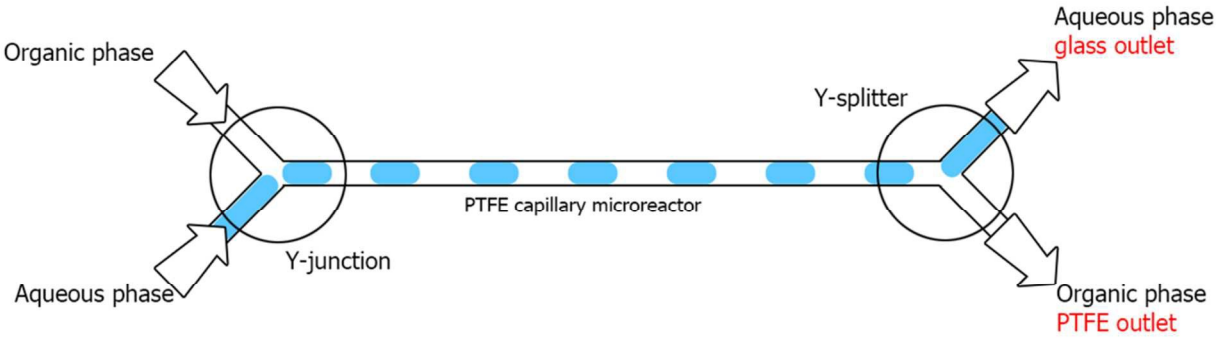

Figure 3. Schematic representation of the experimental setup.

Experimental procedure

ELLE experiments in the capillary microreactor

The experiments in the slug flow capillary microreactor were carried out using 1 mM DNB-(*R*,*S*)-Leu in an aqueous phosphate buffer (pH=6.58) as the feed solution and 1 mM CA3 in 1,2-DCE or 1-octanol as the extractant at room temperature. An overview of experimental conditions is given in Table 1.

Table 1. Experimental conditions for the enantioselective extraction DNB-(*R*,*S*)-Leu in a capillary microreactor.

	Value	**Ranges**
Temperature (K)	294	
Buffer concentration (M)	0.1	
Buffer, pH	6.58	
DNB-(*R*,*S*)-Leu concentration [mM]	1.01 ± 0.01	
Host, CA3 concentration [mM]	1.03 ± 0.04	
Capillary inner diameter (mm)	0.8	
Capillary length (cm)		10-250
Q_{aq}, Q_{org} [mL h^{-1}]		2.5-15.0
Q_{aq}/Q_{org}	1.0	

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For all experiments, a 1 to 1 flow ratio of the aqueous to organic phases was applied. The residence time (τ) is defined on the total flow rate and given in eq. 1.

$$\tau = \frac{V_c}{Q_{aq} + Q_{org}} = \frac{\frac{\pi}{4} d_c^2 L_c}{Q_{aq} + Q_{org}} \quad (1)$$

where V_c is the geometrical volume of the microreactor, d_c the inner diameter and L_c the length of the capillary microreactor and Q_{aq} and Q_{org} are the volumetric flow rates of the aqueous and organic phases, respectively. In the set-up, residence times between 12 and 900 s are attainable by combining different microreactor lengths and the total flow rates. All experiments were run for at least 2 residence times to ensure that the steady state was obtained. During an experiment, the aqueous phase was collected and analyzed by HPLC. All experiments were performed at least in duplicate. A good reproducibility of the experiments was observed, with a relative standard deviation (RSD) of less than 6%.

*ELLE experiments with DNB-(R,S)-Leu and **CA3** in a batch set-up*

To determine equilibrium concentrations and enantioselectivities, the extraction of DNB-(*R,S*)-Leu with CA3 was performed in a batch set-up. Experiments were performed in 20 mL vials, which were loaded with 5 mL of a 1 mM solution of CA3 in 1,2-DCE or 1-octanol and 5 mL of a buffered aqueous phase (pH 6.58) with a racemate concentration of 1 mM. The solution was stirred using a Teflon bar (1000 RPM) for at least 14 h. After extraction, the phases were allowed to settle and separated. The pH of the aqueous phase was measured and its composition was analyzed by HPLC. The concentration of analyte in the organic phase was calculated using an overall mass balance.

Analytical procedures

The concentration of DNB-(*R,S*)-Leu in the aqueous phase was analyzed by reversed phase HPLC (a Shimadzu SIL-20A, with a CTO-20AC column oven and LC-20AD pumps) using a chiral Astec Chirobiotic T column and a UV detector (270 nm). The eluent was a 3:1 (v/v) mixture of acetonitrile and methanol with 0.25 vol% triethylamine and 0.25 vol% acetic

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acid. The flow rate was set at 1 mL/min and the injection volume was 15 µL. Before injecting the aqueous phase samples to the column, the samples were filtered using a syringe filter with a pore size of 0.45 µm (Sartorius). A calibration curve using pure DNB-(*R,S*)-Leu was used to determine the concentrations in the samples.

The pH of the aqueous phase was measured using an InoLab pH 730 pH-meter equipped with a SenTix 81 probe (WTW, Germany).

Theory and definitions

The principle of ELLE with the extractant/host in the organic phase (C) and the racemate to be separated in the organic phase (R and S) is given in Figure 4.[11,32] It involves transfer of the enantiomers from the aqueous to organic phase followed by complexation to the chiral host. The complexation constant is different for both enantiomers and this leads to enentioselectivity.

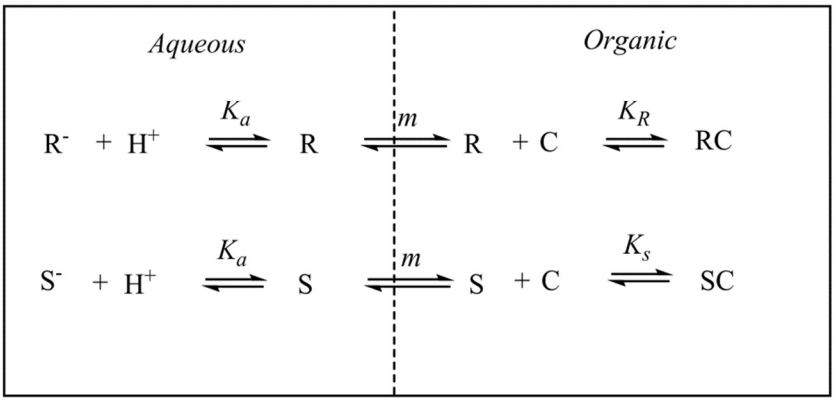

Figure 4. Relevant reactions for ELLE.[11]

The concentrations of both enantiomers in the water phase were determined experimentally (HPLC). Those in the organic phase were calculated by using overall mass balances (eqs. 2 for batch operation and eqs. 3 for continuous operation). [11,23]

$$V_{aq}[R]_{aq,o} = V_{aq}\left([R]_{aq} + [R^-]_{aq}\right) + V_{org}\left([R]_{org} + [RC]_{org}\right) \quad (2a)$$

$$V_{aq}[S]_{aq,o} = V_{aq}\left([S]_{aq} + [S^-]_{aq}\right) + V_{org}\left([S]_{org} + [SC]_{org}\right) \quad (2b)$$

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$$Q_{aq}[R]_{aq,o} = Q_{aq}\left([R]_{aq} + [R^-]_{aq}\right) + Q_{org}\left([R]_{org} + [RC]_{org}\right) \quad (3a)$$

$$Q_{aq}[S]_{aq,o} = Q_{aq}\left([S]_{aq} + [S^-]_{aq}\right) + Q_{org}\left([S]_{org} + [SC]_{org}\right) \quad (3b)$$

Here, $[R]_{aq,0}$ and $[S]_{aq,0}$ represent the inlet (continuous) or initial (batch) concentration of the *(R)*- and *(S)*-enantiomer, V_{aq} and V_{org} represent the volume of aqueous and organic phase in batch operation, Q_{aq} and Q_{org} are the volumetric flow rates of the aqueous and organic phases for continuous operation, [RC] and [SC] represent the concentration of the host-enantiomer complex .

The operational selectivity (α_{op}) is defined in eq. 4

$$\alpha_{op} = \frac{D_S}{D_R}, \text{ if } D_S > D_R \quad (4)$$

Here, D is the distribution of the enantiomers between the two liquid phases, which is defined as:

$$D_R = \frac{[R]_{org,all}}{[R]_{aq,all}} = \frac{[R]_{org} + [RC]_{org}}{[R^-]_{aq} + [R]_{aq}} \quad (5a)$$

$$D_S = \frac{[S]_{org,all}}{[S]_{aq,all}} = \frac{[S]_{org} + [SC]_{org}}{[S^-]_{aq} + [S]_{aq}} \quad (5b)$$

The enantiomeric excess, *ee*, is defined in eq 6.

$$ee_i = \frac{\left|[R]_{i,all} - [S]_{i,all}\right|}{[R]_{i,all} + [S]_{i,all}} \times 100\% \quad (6)$$

Here, subscript *i* represents the organic phase or the aqueous phase.

A good enantioselective extraction process is not only determined by a high *ee* but also by a high extraction yield, which is defined as the extracted amount into the organic phase

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compared with the inlet concentration in the aqueous phase.[11] The yield of an enantiomer is defined as:

$$Y_R = \frac{[R]_{org,all}}{[R]_{aq,0}}.SR = \frac{[R]_{org} + [RC]_{org}}{[R]_{aq,0}}.SR \quad (7a)$$

$$Y_S = \frac{[S]_{org,all}}{[S]_{aq,0}}.SR = \frac{[S]_{org} + [SC]_{org}}{[S]_{aq,0}}.SR \quad (7b)$$

Here SR is the solvent ratio, defined as V_{org}/V_{aq} for batch operation and Q_{org}/Q_{aq} for the continuous microreactor.

Results and Discussion

Equilibrium experiments in batch with 1,2-DCE and 1-octanol

Batch experiments were performed in both 1,2-DCE and 1-octanol to determine the equilibrium composition of the enantioselective extraction of DNB-(*R,S*)-Leu with CA3. 1,2-DCE was used as the benchmark and 1-octanol as an example of a greener, environmentally more benign solvent. Experiments were carried out with a fixed phase ratio of the aqueous and organic phase (1 to 1) at room temperature and DNB-(*R,S*)-Leu and host concentrations of 1 mM. To ensure equilibrium, the experiments were performed for at least 14 h. The results for both 1,2-DCE and 1-octanol are given in Table 2.

Table 2. Batch equilibrium extraction results for DNB-(*R,S*)-Leu with CA3[a]

Organic solvent (number of experiments, *n*)	α_{op} (± stdev)	Y_R (± stdev)	Y_S (± stdev)	ee_{aq} (%) (± stdev)	ee_{org} (%) (± stdev)
1,2-DCE (*n*=6)	3.2 ± 0.2	0.15 ± 0.01	0.36 ± 0.02	14 ± 1	41± 2
1-octanol (*n*=5)	3.2 ± 0.2	0.31 ± 0.02	0.58 ± 0.01	25 ± 2	31 ± 3

[a]Conditions: Vaq/Vorg = 1,phosphate buffer pH 6.58, 294 K, 1 mM DNB-(R,S)-Leu, 1 mM CA3

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The value for α_{op} was 3.2 ± 0.2 in both solvents. These values are close to those observed for the well-known extractant CA4 for this extraction system (α_{op} of 3.4) at similar conditions in DCE.[11] Thus, non-oxidized CA3 is a good alternative for CA4 with the advantage that one synthetic step in the host synthesis can be eliminated. CA3 is selective for the S-enantiomer, as is clear from the yield data in Table 2. When comparing performance of the two solvents, the data show that the equilibrium *ee* values in the organic phase are higher for 1,2-DCE (41%) than for 1-octanol (31%). However, the yield of the S enantiomer is higher in 1-octanol than in 1,2-DCE, which is a promising feature and shows the potential of 1-octanol to replace chlorinated solvents like 1,2-DCE.

Experiments in the continuous microreactor set-up

Experiments in 1,2-DCE

Enantioselective extraction of an aqueous solution of DNB-(*R,*S)-Leu with CA3 in 1,2-DCE were carried out in a slug flow capillary microreactor (Figure 3) using various residence times, by varying the flow rates and capillary lengths. All experiments were performed at room temperature and a fixed flow ratio of the buffered aqueous to organic phases (1:1), see the experimental section for details.

Initially, three experiments were performed to determine the effect of residence times on performance. A microreactor with a capillary length of 10 cm was applied and operated at three different flow rates (2.5-7.5 mL/h, residence times between 12 and 36 s). With these flow settings, the reactor is operated in the slug flow regime (Figure S4, Supplementary information). All experiments were run for at least 2 residence times to ensure that the steady state was obtained. The outlet concentrations of DNB-(*R,S*)-Leu in both phases *versus* residence times are shown in Figure 5.

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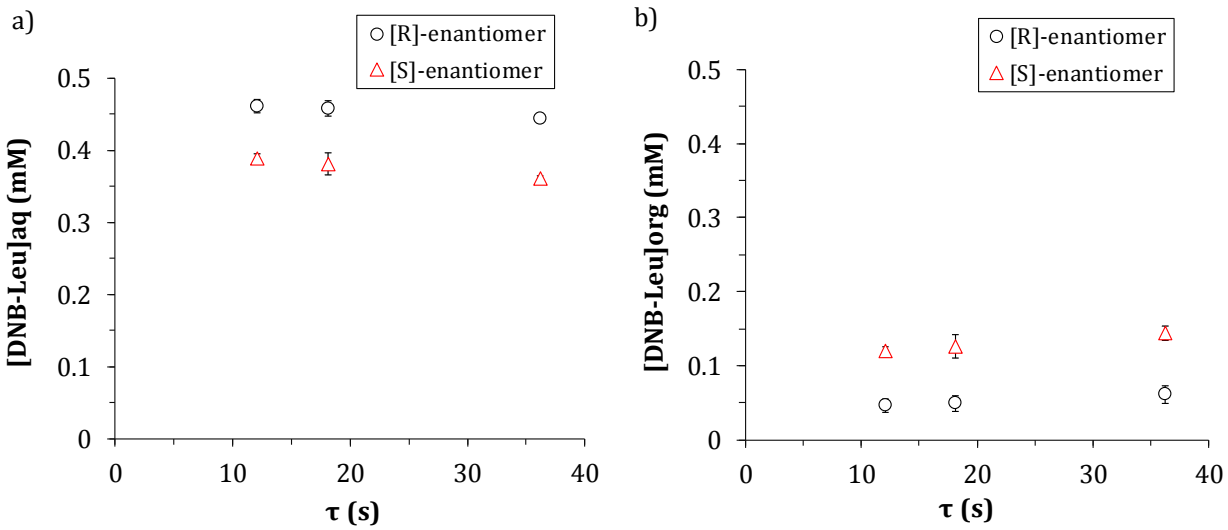

Figure 5. Outlet concentration of DNB-(*R,S*)-Leu in the aqueous phase (a) and organic phase (b) versus residence time in the capillary microreactor (Figure 3) for 10 cm capillary length. Conditions: see Table 1.

The results show that the *(S)*-enantiomer is preferentially extracted from the aqueous phase to the organic phase, indeed proving that enantioselective extraction is possible in the microreactor set-up. The *ee* values are calculated from the data presented in Figure 5 using eq. 6 and are provided in Figure 6a. The *ee* values are between 41-44 % for the organic phase, though the error in the values is relatively large. However, the values are within the range for the equilibrium value obtained in batch at similar conditions (41± 2 %, Table 2). The operational selectivity is between 2.9 and 3.1 (Figure 6b) and also comparable with the operational selectivity obtained in batch experiment (3.2 ± 0.2) at equilibrium conditions.

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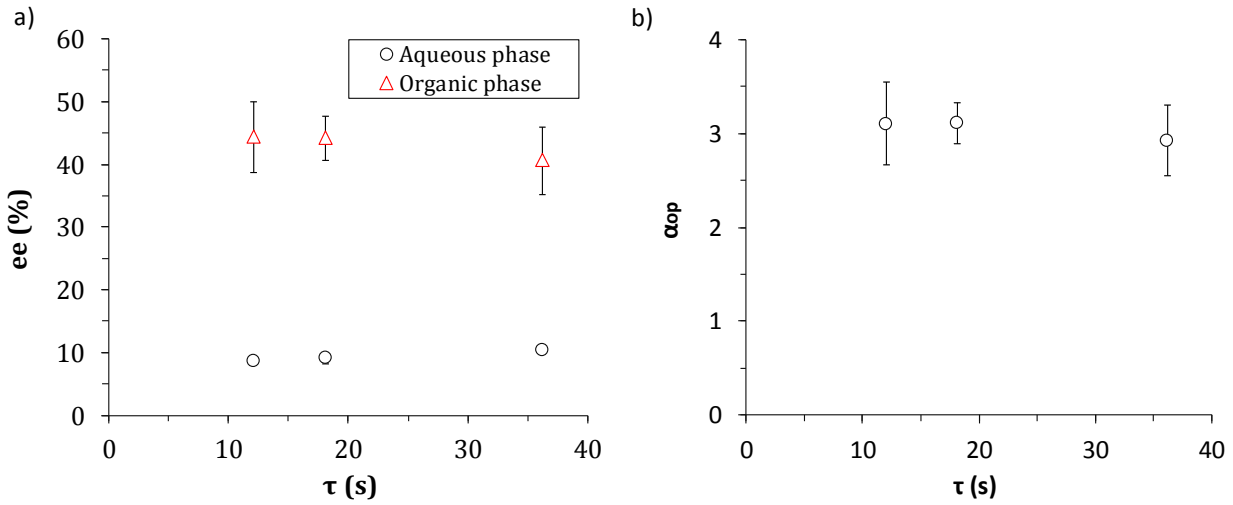

Figure 6. Enantiomeric excess (a) and operational selectivity (b) of enantioselective extraction of DNB-(R,S)-Leu and CA3 in DCE in a microreactor of 10 cm length. Conditions: see Table 1.

Though the operational selectivity and the *ee* values seem to be close to the equilibrium values obtained in batch, the concentration in the outlet are not constant and seem to be a function of the residence time, see Figure 5 for details. This is an indication that the experiments were not solely performed in the equilibrium regime. To further assess this, additional experiments (in total 57, see Supplementary Information Table S2) were performed at a wider range of residence times (12- 900 s). Residence times were set by changing either the flow rates or the length of the microreactor. The results are given in Figure 7 and indeed show that the concentrations in the outlet are not constant.

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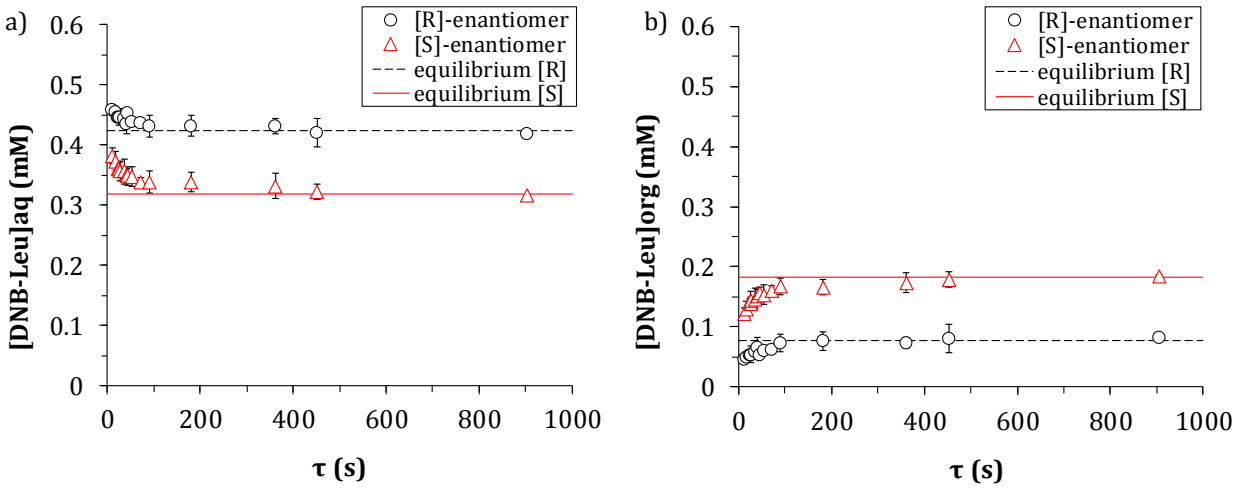

Figure 7. Concentration of DNB-(*R*,*S*)-Leu in the aqueous phase outlet (a) and organic phase outlet (b) versus residence time after extraction with CA3 in 1,2-DCE in the slug flow capillary microreactor. Conditions: see Table 1.

At low residence times, the concentrations are a function of the residence times, whereas the values become constant at higher residence times and about equal to the equilibrium values obtained in batch experiments. This implies that equilibrium is attained at higher residence times, typically above 200 s. A similar trend was found for the *ee* values and the operational selectivity (Figure 8). The *ee*'s varied between 37%-49% and of particular interest is the observation that the *ee* values in the organic phase are higher in the kinetic regime than at equilibrium. This implies that higher *ee*'s are possible when operating the microreactor set-up in the kinetic regime thus at low residence times. This remarkable aspect will be considered further when discussing the experiments with 1-octanol, which showed an even more profound effect of residence times on *ee*.

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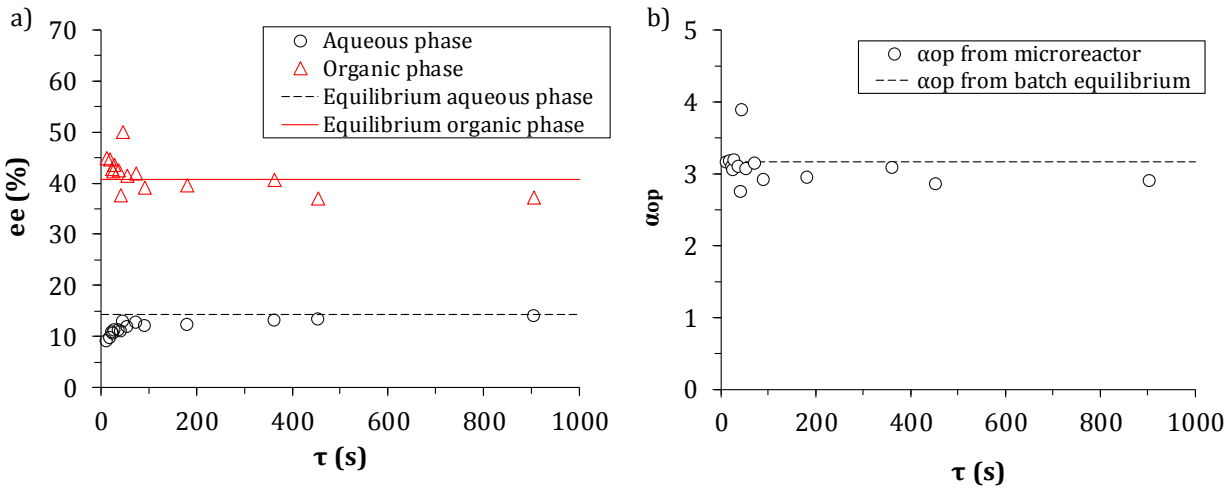

Figure 8. Enantiomeric excess (a) and operational selectivity (b) versus the residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1,2-DCE in the slug flow capillary microreactor. The values are calculated from the data presented in Figure. 7 using eq. 4 and eq. 6. Conditions: see Table 1.

Continuous experiments in 1-octanol

To find alternatives for 1,2-DCE and to probe solvent effect on separation performance, the use of 1-octanol as the organic solvent was explored. A total of 29 experiments were performed in the continuous set-up in the slug flow regime at a range residence times by varying the total flow rate and tube length (Table S3, Supplementary information). Conditions are given in Table 1.

The effect of residence times on the outlet concentrations are shown in Figure 9, and as with 1,2-DCE, the outlet concentrations are a function of the residence time. For residence times beyond about 300 s, the concentrations become constant and equilibrium is attained. The outlet concentrations in this regime are indeed equal to those obtained in the batch equilibrium studies (*vide supra*).

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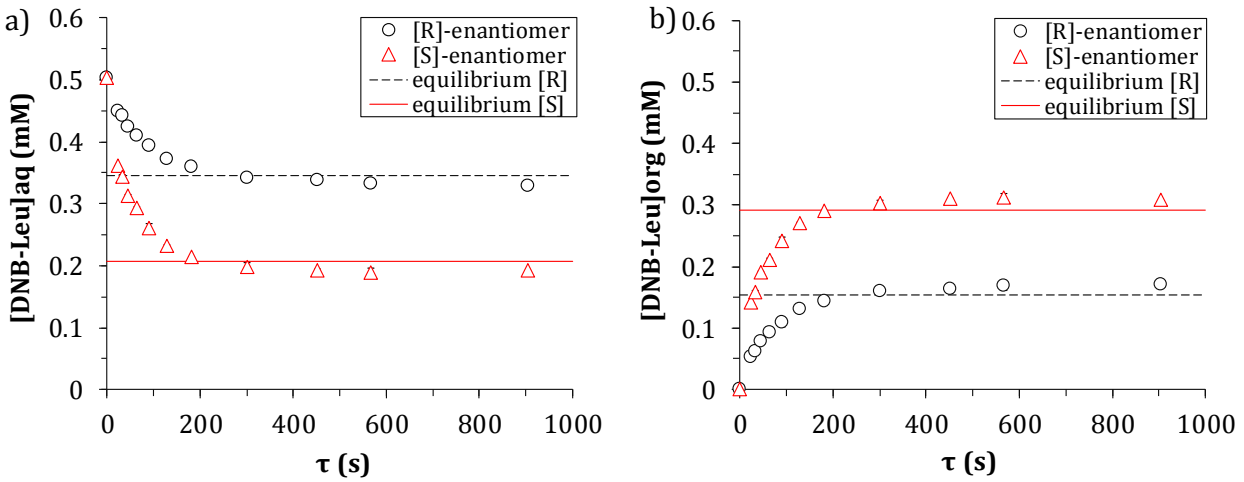

Figure 9. Aqueous phase outlet (a) and organic phase outlet (b) versus the residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octanol in the slug flow capillary microreactor. Conditions: see Table 1

Similar trends were observed for the *ee* values (Figure 10). The *ee*'s varied between 28-46% and are a clear function of the residence time. Values are highest at the shortest residence times and then level off to the equilibrium value (about 30%) at longer residence times. The *ee* values in the equilibrium regime are similar to those obtained in batch equilibrium studies (31%).

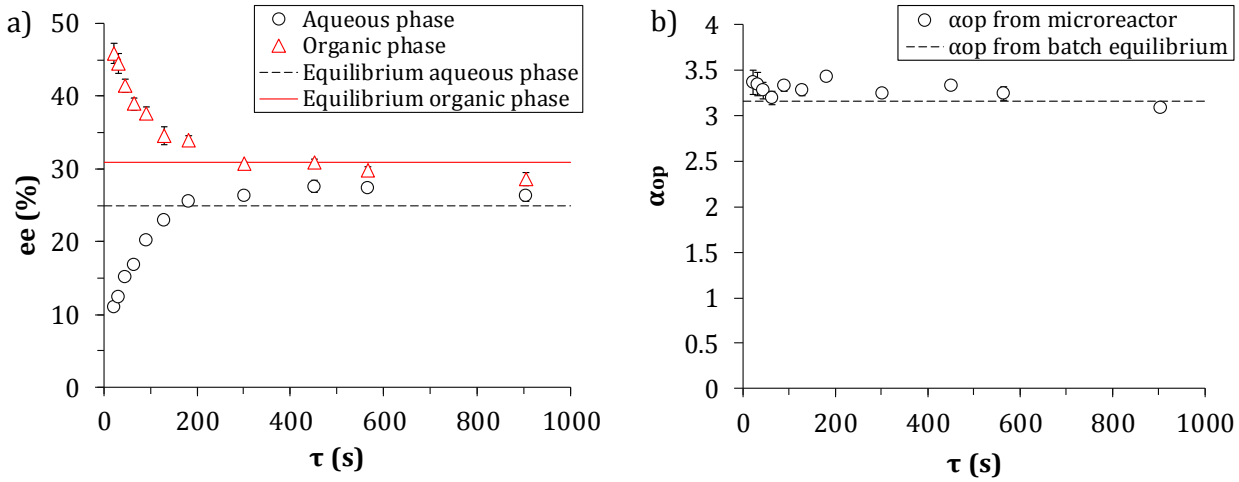

Figure 10. Enantiomeric excess (a) and operational selectivity (b) versus residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octano. The values are

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calculated from the data presented in Figure 9 using eq. 4 and eq. 6. Conditions: see Table 1.

The observation of high ee values at short residence times is more profound in 1-octanol than in 1,2-DCE. This kinetic effect may be explained by considering the intrinsic rates of the complexation reactions in the organic phase (Figure 1) and the mass transfer rates of both enantiomers from the aqueous to the organic phase. To gain insights in the intrinsic rates of the complexation reactions, a number of batch experiments were performed with DNB-(*R,S*)-Leu and CA3 in 1-octanol. The organic and aqueous phase were contacted intensively for about 6 s and then phase separated within 30 s. Analysis of the aqueous phase (HPLC) showed that equilibrium values were already attained within this timescale. This implies that the intrinsic kinetics for complexation in the organic phase are faster than the experimentally observed timescale of the kinetic regime in the microreactor (about 300 s in 1-octanol see Figure 9). As such mass transfer rates of the enantiomers from the aqueous phase to the organic phase are also of importance and affect the overall rate of the extraction processes. However, the extraction process in the kinetic regime in the microreactor is not solely governed by mass transfer processes as in this case chiral recognition is not possible and *ee* values at short residence times are expected to be zero.[43,62]

This suggests that the experiments were carried out in the intermediate regime where both mass transfer rates and intrinsic kinetics play a role and determine the overall rate of the transfer processes. In this regime, the observed transfer rates of the enantiomers are governed by physical properties of the system (diffusivities, mass transfer coefficients, etc.) which are equal for both enantiomers and by the rates and equilibrium constants of the complexation reactions. The latter are different for both enantiomers and will lead to differences in transfer rates and thus *ee* values in the experiments performed in the capillary microreactors. We have designated this as the kinetic regime, to make a distinction with the equilibrium regime, but it should be noted that the behaviour of the system is determined not only by the kinetics but also by the mass transfer characteristics. Extensive reactor engineering modeling activities to obtain a better understanding of the

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complex interplay between reaction and mass transfer are in progress and will be reported in due course.

Thus, we can conclude that higher *ee* values are attainable in the capillary microreactors in the kinetic regime. This unprecedented finding has high potential and justifies further studies as it suggests that equilibrium ELLE is not necessary the best when regarding ELLE performance. However, for ELLE, not only the *ee* is of importance but the yields of the individual enantiomers should also be considered and obviously a high yield is preferred. The yields of the *(R)*- and *(S)*-enantiomer versus the residence times for the experiments in 1-octanol are given in Figure 11. Clearly, the yields are lower in the kinetic regime, for which higher ee values are attainable. As such, a balance between *ee* and yield should be considered. In this respect, the development of multistage microreactor concepts in which each individual microreactor is operated in the kinetic mode to obtain high *ee* values holds great promise.

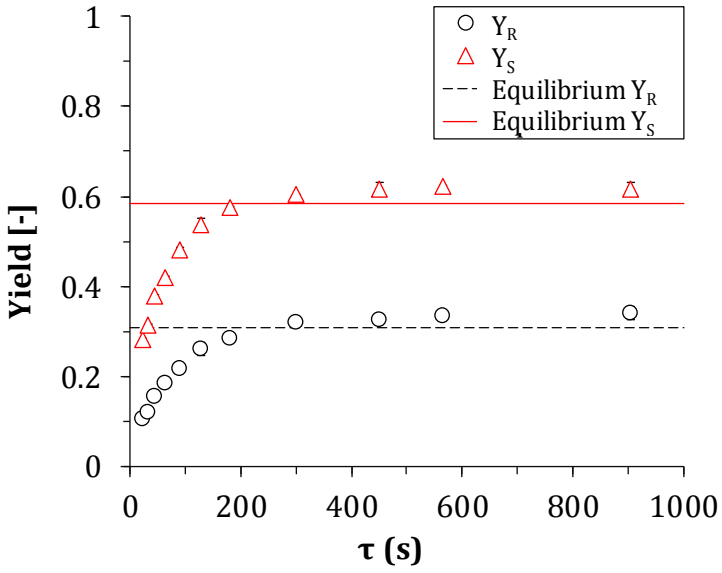

Figure 11. The extraction yields of both enantiomers for enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octanol. The values are calculated from the data presented in Figure 9 using eq. 7a and 7b. Conditions: see Table 1.

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The results provided above only involve a single extraction step. Higher ee's and yields are possible by performing multistage extractions using various configurations (co-cross and countercurrent operation). Prediction of ee's and yields in the equilibrium regime for such configurations by appropriate (reactor) engineering models are well established.[32,63] For instance, for an operational selectivity of 3 for a reactive extraction system, about 10 equilibrium stages are required in counter current operation to obtain *ee* values of 99%. However, the introduction of non-equilibrium operation (in the kinetic regime) significantly complicates the calculations. Here we want to discuss some preliminary results obtained with operating the system in the kinetic regime, i.e. at short residence times, and in combination with a multistage configuration for the system with 1-octanol as the organic solvent. As an example, a multistage concept was applied by taking each time the aqueous outlet to a next ELLE step where it is treated with a fresh organic stream containing only 1 mM of extractant, see Figure 12. In such a cross flow mode, it is possible to increase the yield of *(S)*-enantiomer, while at the same time having *ee* values higher than the equilibrium value for each step, by performing the extraction at a short residence time. Each extraction step then operates in the kinetic regime. However, the *ee* values at such short residence time will decrease from each step to the next due to the change in the aqueous inlet concentration of S and R where the excess of R will increase with each step.

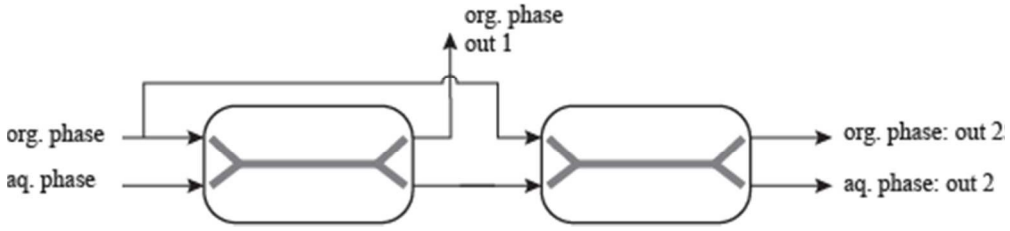

Figure 12. Multistage concept for ELLE using flow reactors applying fresh organic solution to each step

Finally, we mention here that by suitably rearranging the inflow and outflow connections, an overall countercurrent flow operation is possible, as illustrated in Figure 13. Reactor engineering modeling activities to obtain a better understanding of the complex interplay

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between reaction and mass transfer and the consequences of various multistep operation modes are in progress and will be reported separately.

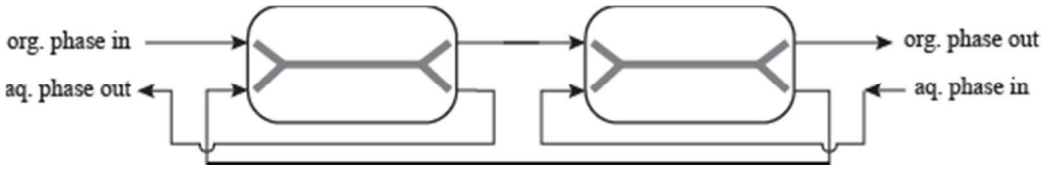

Figure 13. Multistage concept for ELLE using flow reactors applying a countercurrent scheme to the feed streams for each step.

Conclusions

We here report the proof of concept for ELLE in a capillary microreactor operated in the slug flow regime. 1-Octanol was shown to be a good, environmentally more benign alternative for conventionally used chlorinated solvents like 1,2-DCE. The use of microreactors holds great potential for future exploration as it allows for continuous operation, precise setting of residence times and small inventories of expensive host and solvents. Furthermore, for new chemistry systems, it allows for fast screening and optimization of process conditions. Of high interest is also the observation that the *ee* is higher in the kinetic regime than in the equilibrium regime for particularly 1-octanol, indicating that non-equilibrium ELLE may have high potential. Process studies are in progress to demonstrate the use of microreactors for multistage operation, including a host recycling step (back-extraction), to separate racemates and to give both enantiomers in high yields and purity.

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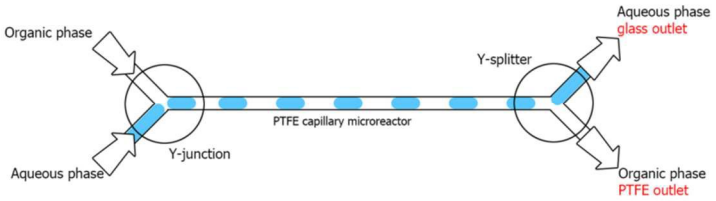

Separation of racemates in microreactors using liquid-liquid extraction with 1-octanol as the solvent is successfully demonstrated.