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Screening of functional solvent system for automatic aldehyde and ketone separation in aldol reaction: A combined COSMO-RS and experimental approach

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HIGHLIGHTS

- The functional solvent system acts as an integrated reactor and separator.
- The computer-aided solvent selection efficiently reduces the experimental work.
- The aldol product is automatically purified in both batch and flow processes.
- The aldehyde reactant and the reaction solvent can be recycled after the reaction.
- A microflow process is developed using the new reaction/separation approach.

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ABSTRACT

An integrated reaction-separation process based on only solvents is presented, and thus without the need for related technical equipment (reactor-separator). Both product purification and reactant recovery are achieved automatically for an asymmetric aldol reaction employing a biphasic solvent system as compartmentalizing soft matter. Firstly, COSMO-RS based simulation is introduced as a theoretical guidance in the solvent selection for the reactant 3-chlorobenzaldehyde and non-solvent selection for the R-aldol product, (R)-4-(3-chlorophenyl)-4-hydroxybutan-2-one. This encompasses solubility as core critical parameter, as well as chemo-physical properties and environmental profiling. Such criteria-cascaded screening could effectively reduce a 7665 solvents-database into 1 candidate solvent, which is dodecane, before experimental process assessment. Secondly, this screening's top candidate was validated as the best reaction solvent by first a solubility test and then by a batch reaction, in which a conversion of 69% was achieved. As desired, the mono-phase reaction yielded spontaneously the product layer and the separate dodecane phase as the second layer, which indeed allowed facile separation of the product from the residual reactant. In a third step, a segmented flow process was developed giving a highest product yield of 63% and a total conversion 92% respectively after a 2 h residence time.

1. Introduction

Process intensification is defined as a game changer in both equipment design and processing for chemistry, breaking with former methodologies [1]. Reactive distillation, the integration of reaction and distillation into one system, is a key example [2]. The same goes for

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microreaction technology and microreactors [3–5]. In the janus-headed sense of the process intensification definition [1], this innovative equipment opens new avenues in chemical processing, so-called novel process windows [6,7].

A plethora of single chemical reactions has been performed with flow chemistry [8], and several benefits are reported [9]. Even several flow chemical reactions in series have been performed, i.e. multi-step reactions in continuous-flow [8,10]. Recently, impressive end-to-end processing of medicines from raw material in one run have been reported, which has even been connected with compounding/formulating equipment to deliver pills in a continuous fashion [11,12]. A high number of reactor and separator equipment and huge controlling tasks, i.e. high system complexity, is needed, however, which generally affects costs, reliability, and productivity; furthermore, there is still a lack of scale-up flow separators [11,12].

An alternative approach to address such complexity is currently investigated within a large collaborative project (FET-Open EU project ONE-FLOW) [13]. Key is to think of another way of compartmentalizing the reaction and separation spaces, as traditionally provided by the serial alignment of flow equipment. In this respect we can learn from nature, as within a living cell all processes are hierarchically compartmentalized [14,15].

Following this line, this paper explores to perform multistep reaction-purification flow processes by smart solvents and without the need for intermediate separation and purification modules. Those solvents shall be designed in such way that they can largely support and/or perform the functions of reaction and separation, in an integrated manner (coined as 'solvent factory' in 'ONE-FLOW' [13].Those solvents shall, at best, fluidically open and close interim reaction compartments, e.g. to facilitate transport of reaction species [16,17]. Such switching between one and two (or a few and more) phases can be induced by solubility or temperature [18,19].

Traditionally solvents are used only as the carriers for the reactants and product, and otherwise are a concern for sustainability and health in pharmaceutical processing [20,21]. The huge loads request massive recycling [21] and workup procedures, such as separation and purification [22,23]. To this end, two approaches have been considered by industry and researchers: solvent reduction (solvent-free, solvent recovery, etc.) and efficient and more powerful solvent selections (computer-aided molecular designs, etc.) [24–27].

Among the efficient solvent selection methods, the computer-aided modeling of thermodynamic properties opens a very large solvent design space, and consequently, the combination of computational methods with experiments has been suggested [25,26,28].

This integration of computational tools with experimental work can open new opportunities for solvents that have not been considered before [25,26]. Several computational models, such as PC-SAFT (Perturbed Chain Statistical Associating Fluid Theory), UNIFAC (Universal Quasichemical Functional-group Activity Coefficients), and COSMO-RS (COnductor like Screening MOdel for Real Solvents), have been introduced to predict phase equilibria and other thermodynamic properties of multicomponent mixtures. These models can drastically reduce the experimental effort in the solvent system selection process [19,29–32].

Many experts believe that neoteric solvents like ionic liquids are ideal choice here, as millions can be made by easy synthesis and hundreds are commercially available [33]. Moreover, the lego-type molecular structure allows a fine-tuning of polarity, size and shape and are commonly coined 'designer solvents' [34]. Yet and even simpler, there are also thousands of 'conventional solvents', if we consider all kinds of liquids and moldable solids as solvents (meaning much, much beyond the classical range of what is used in the lab). Many of them are also commercially available.

Aiming, as said, toward an advanced use of solvents as the integrated reactor-separator, modeling shall assist or even enable each solvent to be the exclusive or prime host of a guest species, e.g. one solvent for the reactants (actually best one for each reactant), another one for the catalyst, and one for the product when it is formed. Those solvents have then the function to host, release and finally trap the species, for means of recycling and product purification.

This new process concept has been tested with the aldol reaction. It is a well-known intermediate synthesis step in the pharmaceutical industry. The Barbas, Singh, and Gröger groups have demonstrated the synthetic power, by showing that the direct asymmetric aldol reaction between aldehydes and ketones can be developed into a highly efficient C−C bond-formation reaction catalyzed by the Singh catalyst [35–38]. The reaction is well explored, and co-solvents and co-catalysts have been widely reported in order to get high product yields. Also several methods have been developed to recycle catalysts [39–41].

The separation of the aldehyde reactant and ketone products as intended here, however, has been rarely reported. Only two publications from the Brindle group report about a bisulfite workup method, which thus needs a second reaction step. The bisulfite derivatives, created from the aldehydes and ketones, have changed structure and charges and are then separated by extractants relying on a solubility difference [42,43].

The aim of this study is accordingly to close the gap in the separation/recycling of the aldol reaction, in the frame of providing thereby proof of concept for the bigger picture (ONE-FLOW) [13], i.e. to use solvents as integrated reactor-separator (to simplify the equipment use). In order to truly learn about advantages and disadvantages of the new process approach, the aldol reaction is considered as a right reaction, because it is challenging. The aldehyde- and keto-bearing reactant and product possess similar thermodynamic properties, i.e. are difficult to separate directly by solubility (extraction).

2. Methodology

2.1. COSMO-RS based solvent modelling

The key performance parameter for the solvent screening is to determine solubility of the reactant and product among a high number of candidate solvents, which provides unique chances for optimizing desired solvent functionality, but which is however prohibitive for any experimental test.

Predictive thermodynamic models can be employed to estimate the solubilities of the aldol product and aldehyde reactant in various candidate solvents. Many papers in the literature use COSMO-RS theory to predict the solubilities of pharmaceuticals as part of a priori solvent screening, and compare to other thermodynamic models such as UNIFAC and other quantitative structure-property relationship methods [44–46]. The alluring feature of using COSMO-RS for solvent screening is the independence of experimental data and a feasible solubility estimation with the physically well-founded computational approach. For these reasons, the solubilities of product and reactant in solutions were predicted using COSMO-RS in the commercial software package COSMOtherm [47]. All calculations were made using the BP-TZVP 1701 parameterization (version C3.0, release 17.01). COSMO-RS is a continuum solvation model for predicting thermodynamic properties based on interacting molecular surfaces of pure liquids or liquid mixtures. Each desired molecule is modeled a perfect conductor in order to define the three-dimensional polarity of the molecule, σ [48]. This surface charge information is condensed into a certain interval, detailing the amount of surface segment type and the affinity for one system, termed the sigma-profile $p(\sigma)$ and chemical potential $\mu(\sigma)$. COSMO-RS then uses the data into a statistical thermodynamics approach, to calculate the relevant molecular interactions such as the electrostatic misfit and hydrogen bonding energy. Therefore, only the energetically optimized molecular structure of each molecule is necessary to make predictions of phase equilibria such as solubilities [29]. Wichmann and Klamt give a detailed description how to use the COSMO-RS method in solvent screening [49]. The conclusion is that COSMO-RS can qualitatively and

semi-quantitatively predict the solubility of drug and drug-like molecules in various solvents.

2.2. Turbomole modelling

The Turbomole software (TmoleX 18, version 4.4.0) was used to calculate the molecular model - the aldol product in this case with surface charge at the RI-DFT level of theory with the def-TZVP basis set [50–52]. This was done, since there is no major difference between TZVP and TZVPD-FINE in parameterization deviation; however, TZVP operation is significantly faster than TZVPD-FINE [53].

2.3. Chemicals

Singh catalyst (> 98.0%) was purchased from TCI; dodecane (≥99%) was purchased from Fisher Scientific; 3-chlorobenzaldehyde (97%), acetone (98.5%), cyclohexane (99.5%), S-1-phenylethanol (≥98.5%) were purchased from Sigma Aldrich. TLC plates were purchased from VWR. (R)-4-(3-chlorophenyl)-4-hydroxybutan-2-one ((R)-3-hydroxy ketone) used for calibration lines was synthesized (3-chlorobenzaldehyde: acetone = 1:9 mol/mol, 30 mol% proline, room temperature, 24 hrs) in batch and purified by column chromatography (ethyl acetate: cyclohexane = 1:9 v/v). ^{1}H NMR (400 MHz, Chloroform-d) δ(ppm): 7.32–7.15 (m, 4H), 5.07 (t, J = 4.7 Hz, 1H), 3.64 (d, J = 3.3 Hz, 1H), 2.81–2.77 (m, 2H), 2.16 (s, 3H); HPLC tp = 11.8 min (Fig. S1, Supporting Information).

2.4. Phase characterization

For solubility tests and batch reactions, the liquid reagents were shaken at 350 rpm for 24 h; in scale-up microflow processes, the phase separation only happened with 0.5 mol% Sigh catalyst and ≥ 8 h residence time or ≥ 5 mol% Sigh catalyst and ≥ 1 h (for the dissolution of the Singh catalyst, an extra 40 min ultrasonic solubilization was performed before the flow reaction). Afterwards 20 min centrifuging at 4000 rpm, the phasic systems were checked and photographed by a Nikon camera. The compounds in each phase were analyzed by HPLC methods and quantified by internal standard method for both reactant (3-chlorobenzaldehyde) conversion and product ((R)-3-hydroxy ketone) yield (Fig. S2, Supporting Information)). In addition, for flow, to ensure full phase separation and prevent further reactions or product decompositions, only 1.5 ml reaction samples were collected (average needed time: 15 mins) before the analysis of the phase.

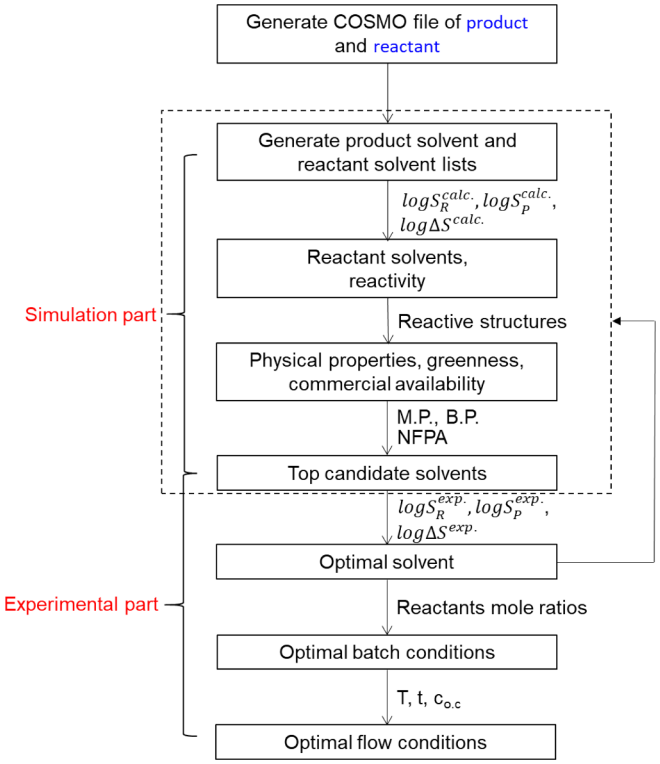
2.5. Flow reactor setup

The continuous microflow set-up consisted of a 750 µm inner-diameter, 5 ml PFA capillary and microfluidic connectors (LT-115X) and ferrules (P259X) [procured from IDEX]. The liquid reagents in disposable plastic syringes (6 ml, BD Discardit II) were fed using two syringe pumps (Fusion 720, Chemyx) and merged with a T-mixer.

2.6. Reaction analysis

In the batch experiment, 1 mmol 3-chlorobenzaldehyde, 1–9 mmol acetone and 0.5 mol% Singh catalyst were introduced into 1 ml dodecane or 1 ml dodecane & 1 ml water separately, with a 3 ml glass vial used as reactor. The mixture was stirred at room temperature with the stirring speed 350 rpm. After 24 h reaction, the bi-layer (dodecane-product) and triple-layer (dodecane-water-product) reaction mixture were centrifuged for 20 min at 10 °C with 4000 rpm and then each layer was carefully separated into different 3 ml glass vials. For the water layer, 1 ml ethyl acetate was used to extract the reaction mixture from water into organic phase, for 3 times.

In the flow experiment, 4 mmol 3-chlorobenzaldehyde, 4–36 mmol acetone and a certain amount of Singh catalyst (from 0.5 mol% to saturated mol%) were introduced into the micro-flow reactor, with 4 ml dodecane as reaction solvent. To keep the product fresh, only 1.5 ml reaction mixture was collected into 3 ml glass vials once the flow pattern became steady, followed by analysis and quantification by HPLC.



Scheme 1. Methodology scheme for cascaded solvent screening.

3. Results and discussion

3.1. Proposition of cascaded solvent selection scheme

A cascaded procedure for solvent screening was proposed and tested, reducing possible candidates, via stepwise applying performance thresholds and targets as well as exclusion criteria, down to a number which could be experimentally handled; see Scheme 1. This screening framework consisted of two major parts: the solvent screening based on COSMO-RS and the experimental validation in batch and flow. In the solvent screening section, several steps were presented in order to select a reasonable amount of candidate solvents. The first step was to generate the COSMO file of the aldol product using the Turbomole software. Then, the product and reactant solvents were calculated by the COSMOthermX software separately; the candidate solvent species were taken from the COSMO-RS database. Afterwards, the solubilities were ranked by reactant solubility ($logS_R^{calc}$), product solubility ($logS_P^{calc}$), and the solubility difference ($log\Delta S^{calc}$, $log\Delta S^{calc} = logS_R^{calc} - logS_P^{calc}$); if this value was large enough, one of the species was considered to be present and the other (practically) not. With the above simulation results, already a limited number of candidate solvents remained, which allowed other properties to be considered manually in following steps. Firstly, an orthogonality exclusion criterion was applied to narrow the screening space, i.e. rejecting solvents which could react themselves. For instance, for the aldol reaction considered, solvents with a ketone-moiety and other compounds such as aldehydes, alcohols, ammonia, which may interfere with the reactants, were eliminated. Furthermore, the physical properties needed to suit the flow operability, i.e. they should be easy to operate. As some of the solvents in the database are solids at room temperature which need to be molten for purpose, the melting point (M.P.) was considered. On the other hand, the boiling

point (B.P.) has to be high enough to allow a stable superheated flow operation with standard commercial equipment (back-pressure regulator). The viscosity should not be prohibitively high, to have a reasonably low pressure drop. After this manual screening, the next step in the solvent number reduction was a quick sustainability check applying threshold and exclusion criteria. The costs of the solvents have to be affordable for laboratory-scale tests, yet do not need to match economic criteria initially (to not suppress the innovation power of the approach). A basic consideration of greenness was ensured by employing the standards of the National Fire Protection Agency (NFPA). After the modeling-driven solvent screening procedure was concluded, the promising solvents were experimentally assessed in the second part of the framework. The solubility tests with each reaction compound ($logS_R^{exp}$, $logS_P^{exp}$) and reaction mixture ($logS_{mix}^{exp}$) in each chosen solvent candidate were performed as the first experimental step. This was considered as an intermediate step, because the best solvent had to be evaluated under reactions conditions afterwards; otherwise, if no suitable solvents were to be found, we could reset the above constraints like threshold values of solubilities. The solvent satisfying best the requirements was applied first for the batch process (optimizing reactant mole ratios) and, after process optimization, later for the flow process (reaction temperature, T; residence time, t; organic catalyst concentration, $c_{o.c.}$). Each step is explained in more detail in the following sections.

3.2. Generation of the COSMO file for the reaction product

The first task was to generate the COSMO files of the reactant and product which are necessary for solubility calculation. The reactant (3-chlorobenzaldehyde) was already available in the database, so only the product, (R)-4-(3-chlorophenyl)-4-hydroxybutan-2-one ((R)-3-hydroxy ketone) needed to be generated by the Turbomole software (TmoleX 18) [50–52]. The COSMO files of product and reactants contained all the required information for predicting the thermodynamic properties using COSMOtherm. The molecules were described by their sigma profiles, as seen in Fig. 1. The peak distributions of product and reactants were similar. The large broad peaks in the non-polar region between −0.01 and 0.01 e/Å [21,54,55] account for the negative p-orbitals and positive carbons of the phenyl groups, typically for aromatic compounds giving two distinct peaks instead of one. The small shoulder extending from 0.010 to about 0.015 e/Å^2 corresponds to the negative charge of the carbonyl oxygen and chlorine. This suggests that both product and reactant are dissolvable in the solvents from the ketone family chosen through hydrogen bond donor interactions. Yet there is also a small difference. The hydroxyl group in the product is a polar group [54,55], while the reactant has a more symmetric charge distribution and is accordingly less polar than the product. This

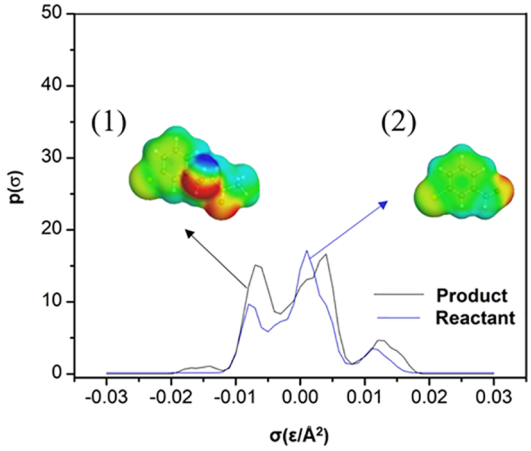


Fig. 1. Sigma profiles of (1) the (R)-aldol product and (2) the aldehyde reactant.

indicates that the reactant will show more affinity than the product with solvents, which are less and even non-polar or having broader profiles between the hydrogen bonding borders.

3.3. Pre-screening of candidate reaction solvents

To utilize the different polarities between the product and the reactant, possible functional solvents were explored to distinguish these two compounds. Since the aldol reaction was performed at one temperature, the temperature was held constant for the simulations. It was chosen to extract and separate the structurally simpler aldehyde reactant from the ketone product.

Initially, all candidate solvents from the COSMO-RS database (ver. C30_1701, COSMOlogic) were selected and generated as excel list, which included in total 7665 species. To intentionally maintain a large search space, only the solubility was considered as the screening scenario in the first step.

COSMOtherm can directly calculate the chemical potentials based on sigma profiles of the involved components [56]. The desired solubility was calculated from the difference between the chemical potentials of the solute in the solvent $\mu_j^{solvent}$ and in the pure solute μ_j^{pure} (Eq. (1)) [57]. For better comparability of the effects of the different molecular interactions on solubility, a non-iterative mode was utilized [58]. The obtained solubilities showed the following relation:

$$log_{10}(x_j) = log_{10}\left[\exp\left(\frac{\mu_j^{pure} - \mu_j^{solvent}}{RT}\right)\right] \quad (1)$$

The reactant and product solubilities in a large number of solvents were determined separately by an auxiliary batch-processing program in COSMOthermX, including CT_CREATE and RUN_CT, which only requires a template input file for solubility calculation and a list of the involved solvents. Once all calculations were complete, the reactant solvents list and product solvents list were written as excel tables with decadic logarithm $log_{10}(x_j)$.

$log_{10}(x_j)$ ($logS$) is the optimized mole fraction of solute in one solvent and chosen as the key parameter to characterize solubility in this work. The maximal value is 0, meaning total dissolution in the solvent; as the values of $logS$ decrease, the solubility tends to be smaller [57]. All $logS$ calculations were made considering a reaction temperature of 25 °C. In Fig. 2(a), an overview of the solvents in the COSMO-RS database is presented and ranked by $logS_R$ (black points, from largest to lowest) here, which shows the huge selection space considered.

The potential reaction solvents should comprise both big values of $logS_R$ and $log\Delta S$, while keeping very low $logS_P$. As the key scenario constraint, the cut-off values of these three parameters were arbitrarily chosen based on the U.S. Pharmacopoeia solubility definition (S_{std}) [59]: $logS_R > -1 (S_{std} < 10$, free soluble), $logS_P < -1.5 (S_{std} > 30$, sparingly soluble), . It decreased the total solvent candidates to 507. Interestingly, cyclohexane, used for the synthesis under investigation here by the Gröger group, was ranked as 212th among these solvents [60]. This is an indication that the common lab-practice solvent choice leaves good room for improvement through solubility modeling. So the candidates above cyclohexane (211th) were considered in the next step (shown in Fig. 2(b), Table S1, Supporting Information).

3.4. Chemo- and physical properties constraints

From the list of the 211 remaining candidates, it can be found that most of them belonged to the class of alkanes and halides. As mentioned in Scheme 1, solvent candidates had to be excluded that can interact with the aldol reaction. This demands the exclusion of highly active, acidic and basic groups. In particular, R-COOH, R−SO_3H, R−NH_2, pyridine, R−C(=O)R', R−C(=O)H, R-2-ol-R' were sorted out as they are prone to undergo unwanted chemical transformations, such as acetal reaction, acyloin condensation, Mannich reaction and catalyst

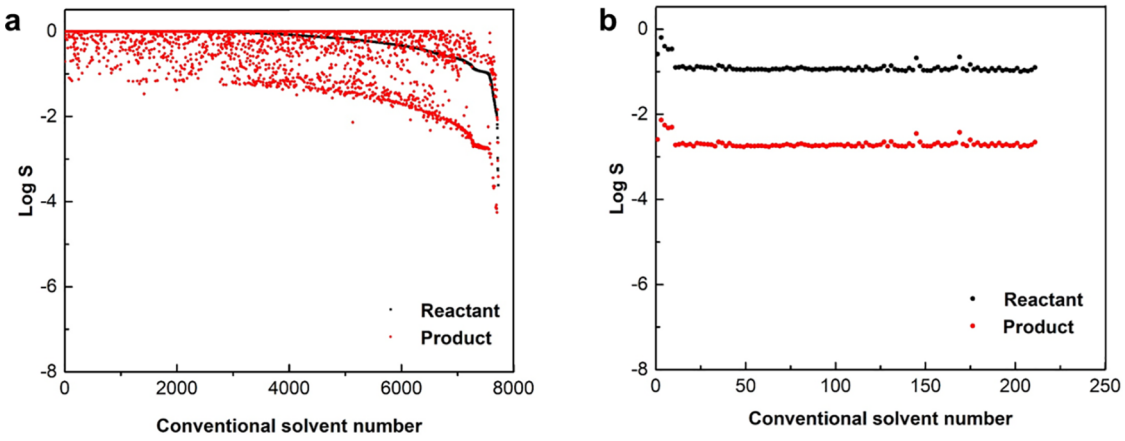


Fig. 2. The satisfied solvent numbers (a) before- and (b) after 1st step screening by log S.

decompositions.

After posing thermodynamic and molecular-structural thresholds, some physical properties, the melting point (T_m) and the boiling point (T_b), were considered as discussed for the scheme in Scheme 1. Considering the suitable reaction temperature range for this aldol reaction [37,39], we set $T_m < 0\,^{\circ}C$, $T_b > 80\,^{\circ}C$ for the reaction solvent. These chemo-physical constraints resulted in a shortlist of top 12 reaction solvents, shown in Table 1. This list comprises linear and branched alkanes.

3.5. Greenness and commercial availability

As depicted in Scheme 1, next a greenness check was executed following the MSDS hazard identification by the national fire protection association (NPFA) as established industrial standard. The solvents listed in Table 1 were evaluated by 4 NPFA factors, including toxicity, flammability, instability, and special hazards, using four levels 0–4 for evaluation. Solvents with any value > 2 were eliminated according to the above criteria.

Additionally, commercial availability for scale-up/industrial application was identified by the commercial supply of two most common chemicals suppliers, Sigma Aldrich and TCI. Passing this threshold, the top 5 solvents finally were tetradecane, heptadecane, tridecane, undecane, and dodecane; the linear alkanes. Since water is frequently considered as co-solvent with the organic media used in the aldol reaction to accelerate enantioselectivities [61], the water solubility ($logS_W$) (Table S2, Supporting Information) in these top 5 solvents was calculated as an extra step to ensure water will not dissolve in the targeted solvent. After all the above-mentioned screening steps (summarized in Table 2), dodecane was recognized as the optimal solvent to be applied in the following experimental validations.

3.6. Solubility test

Reactant/product solubility tests were done in parallel. The solubilities were estimated by adding reactant/product to 500 µL dodecane in steps of 10 µL, 20 µL, 50 µL, 100 µL, 200 µL, in total 380 µL ($S_{std} < 1$, very soluble) [59]. It was found that the reactant totally dissolved ($S_{std} \simeq 0.82$) and the product was only sparingly soluble in dodecane ($S_{std} \simeq 40$), in good agreement with the COSMO-RS prediction. Then, 1 ml dodecane and 1 ml distilled water were added to a vial and shaken at 350 rpm for 24 h as next test. After 20 min centrifuging at 4000 rpm a clear biphasic system was formed. Afterwards, the reaction mixture [1 mmol acetone (second reactant), 1 mmol 3-chlorobenzaldehyde, 1 mmol product, 1 ml water, without catalyst] was added to 1 ml dodecane to check the solubility, with the same procedure as above. The product automatically separated from the other two layers because of its very low solubility in both dodecane and water. Therefore a triple phasic system, consisting of the top layer dodecane, the middle layer product, and the bottom layer water, was formed (Fig. 3). This ensures the possibility for facile separation of the product layer and recycling of any remaining layers. HPLC analysis was performed on each layer, showing that the dodecane layer contained 80 mol% reactant and almost no product. No apparent compounds were shown in the water layer, and the product layer contained 90 mol% product.

Table 1
Top 12 reaction solvents.

Solvent shortlist	
Tetradecane	3-methyloctane
4-methyl-nonane	3-methylnonane
3-ethylheptane	3-ethylpentane
5-methyl-nonane	Undecane
Heptadecane	Dodecane
Tridecane	Decane

3.7. Batch reactions – Variation of reactant ratios of 3-clorobenzaldehyde (targeted aldehyde reactant, R_1) and acetone (second reactant, R_2) in batch

Standard batch conditions for the aldol reaction as proposed by the Gröger group were taken, which involves room temperature conditions, using a ratio of 1:9 of R_1 and R_2, and using a concentration of 0.5 mol% Singh catalyst in water for 24 h [39]. We were interested in how to adapt this batch condition in view of the new functional solvent system in the ONE-FLOW cascade, seeing the benefit that it adds a spontaneous separation function into the reaction system. The two most important factors (shown in Scheme 2) we considered were (1) whether the addition of aldehyde reaction solvent dodecane would affect the yield of the aldol product; (2) and whether we needed to lower the R_2 ratio, concerning the generally high compatibility/solubility of R_2 with other compounds, which would affect the steady formation of the multiple phasic system and partitioning of substrates in each phase. Thus, as equation shows, the following processing approaches were followed (1) both the biphasic system water-dodecane and the monophasic system dodecane were tested, (2) different reactant ratios ranging from 1:1 to 1:9 were applied. The before-reaction phase behaviors are shown in Fig. 4(a); Fig. 4(b) shows the reaction mixtures after reaction and centrifugation. Fig. 4(a) and (b) show that for all varied conditions the product can form an individual phase spontaneously, which is in line with the solubility predictions and tests. Accordingly, a triphasic system of dodecane, water and product, as well as a biphasic system of dodecane and product were obtained after reaction for the two process approaches, respectively.

Table 2
Number of solvents in different screening steps.

Step	Considerations	Constraints	Remaining Solvents
1	COSMO-RS database	–	7665
2	Solubility	$logS_R > -1$, $logS_P < -1.5$, $log\Delta S > 1.5$	507
3	Benchmark solvents	Cyclohexane and water	211
4	Chemical property	Exclude R−COOH, R-SO_3H, R-NH_2, pyridine, R−C(=O)R', R−C(=O)H, R-2-ol-R'	12
	Physical property	$T_m < 0$ °C, $T_b > 80$ °C	
5	Greenness	NPFA factors ≤ 2	9
6	Commercial availability and water solubility	Low price and $logS_W$	1

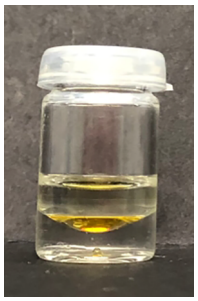
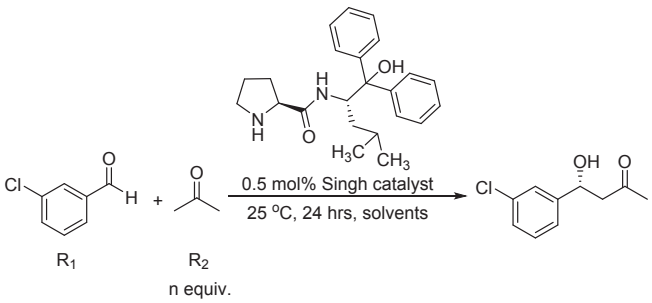


Fig. 3. The triphasic system formed by dodecane, aldol product and water.



Scheme 2. Aldol reaction scheme of 3-clorobenzaldehyde (R_1) with acetone (R_2) to produce R-aldol product, (R)-4-(3-chlorophenyl)-4-hydroxybutan-2-one.

Furthermore, fixing one specific reactant ratio, the multi-phase reaction system had one pure dodecane layer with more overall product content, as evident by the visibly larger volumes of the latter. Among the whole series of eight experiments undertaken, the protocol using the 1:9 reactant ratio and monophase operation delivered the maximal volume of the product phase.

The HPLC analysis was made to further determine the conversion of the reaction at different conditions, as shown in Fig. 4(c). Interestingly, we found that the 1:4 ratio (78 mol%) gave an even slightly higher conversion than the 1:9 (69 mol%) condition. This is because the high compatibility of R_2 for other substrates disturbs the liquid-liquid equilibrium of this biphasic system, in particular when it is occupied with a high mole ratio in the whole reaction system.

Having solved the product separation, the recycling of the catalyst remained an important process issue. The Singh catalyst has no solubility in dodecane and prefers staying with acetone in the water phase for the water-dodecane system, or in the product phase for the dodecane system. As a result, the excess acetone present in the reaction let to a lower reaction efficiency and conversion, because of the diminished interface between the phases of the Singh catalyst and aldehyde; assuming a mass-transfer driven process under effective kinetics. However, this factor could be avoided when the reaction was carried out in the segmented flow mode in a microflow reactor because of the expected efficient mixing through convection and high relative surface areas. Thus, the 1:9 reactant ratio in the monophasic system was still chosen as the right process approach for the microflow process.

The performance of this optimized batch condition in dodecane was

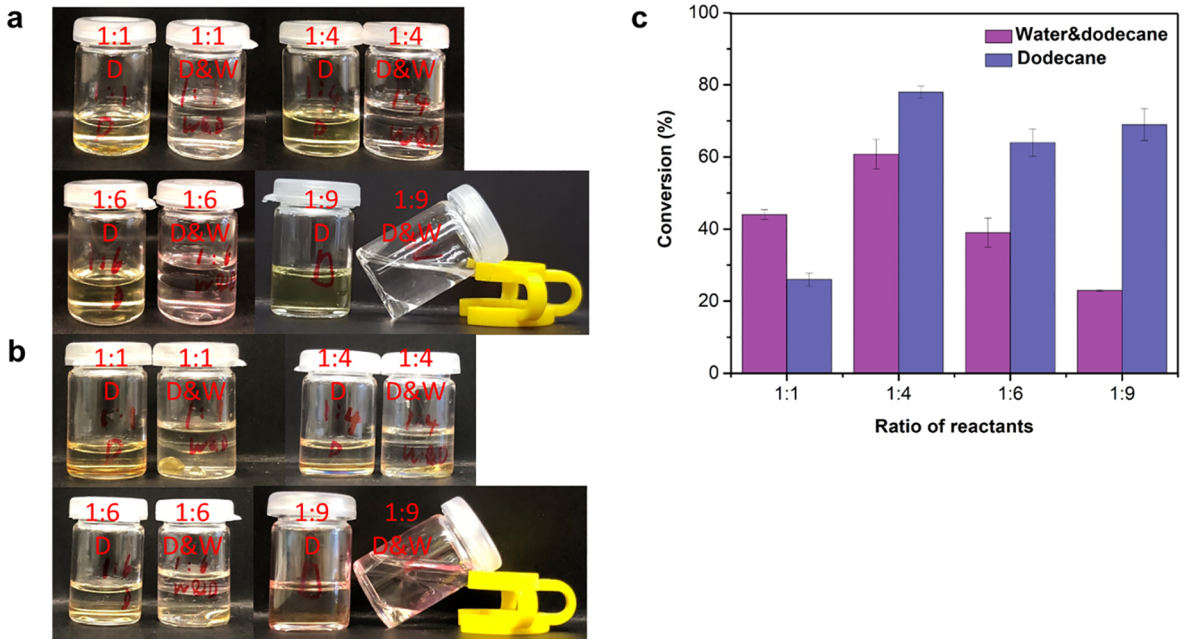


Fig. 4. The effect of solvents and reactant ratios on the reaction conversion catalyzed by 0.5 mol% Singh catalyst. (a) Phase behavior before reaction. (b) Phase behavior after reaction. (c) Aldehyde reactant conversions by mono- and bi-phasic system.

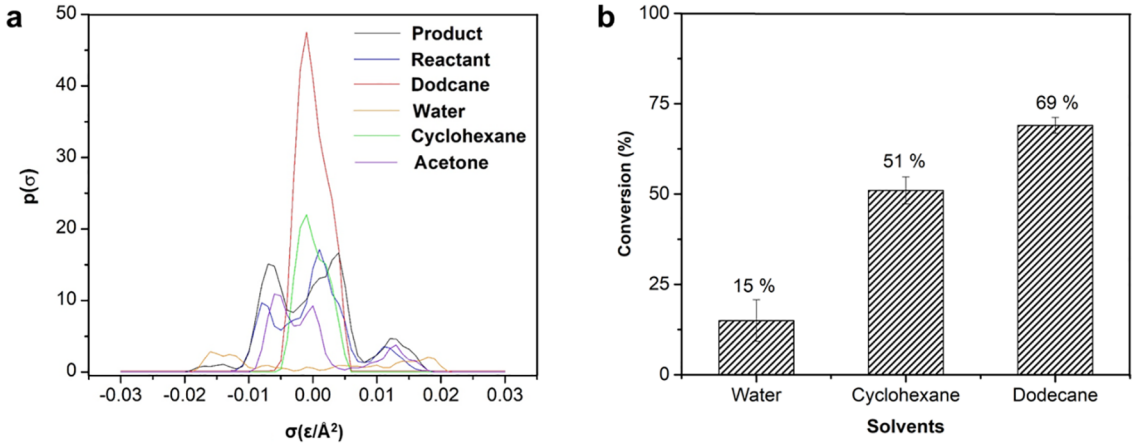


Fig. 5. Effect of reaction solvents and acetone for aldol reaction. (a) Simulation comparison by sigma profile, $p_i(\sigma)$. (b) Experimental comparison by aldehyde reactant conversion.

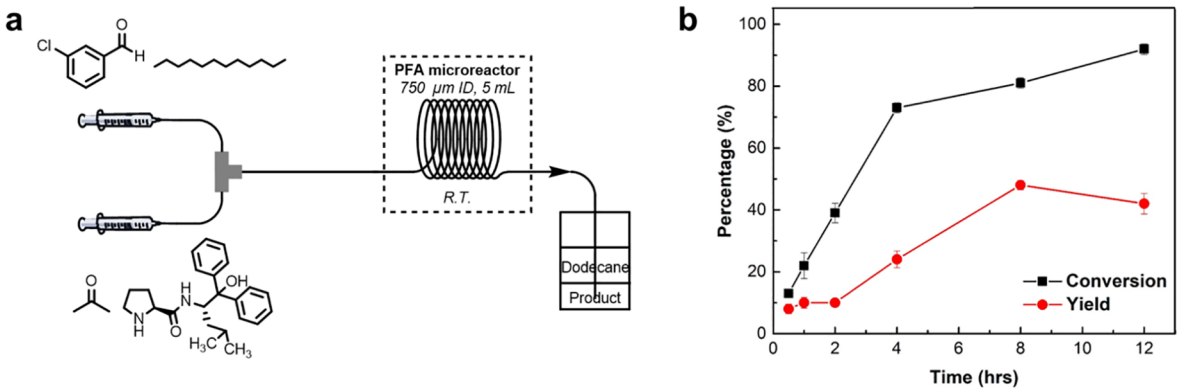


Fig. 6. (a) Microflow set-up scheme. (b) Residence time. (t) Effect on aldehyde reactant conversion and (R)-aldol product yield, flow rate varied from 9.6 ml/hr to 0.4 ml/hr.

compared to processing using the most common solvents, cyclohexane and water [60], to give some benchmark clues from both thermodynamic (solubility, COSMO-RS simulation) and chemical (experiments) point of view.

If we sort the calculated COSMO-RS results in 3.1 for the whole selection space of solvent candidates only by $logS_R$ (from largest to smallest) and regardless of other properties, water will rank as 7627th, cyclohexane as 255th, dodecane as 90th. It has also to be considered that the reactant will preferably stay in the non-polar phase different from the product, because of the symmetric carbonyl oxygen and chlorine groups. Therefore, if we summarize σ-profiles of these three solvents along with the reactants and product, more trends can be obtained, as seen in Fig. 5(a). There are the common slightly negative peaks assigned to hydrogen atoms and the slightly positive peaks denoted to the carbon atoms for all molecules. Along the X-axis, water has a very broad σ-profile around -1.6 e/Å^2 and $+1.8$ e/Å^2 resulting from the strongly polar hydrogen atoms and the oxygen atom, respectively; cyclohexane is almost nonpolar, which can be reflected from its narrow distribution around zero e/Å^2; the peak around $+1.3$ e/Å^2 corresponds to its carbonyl group. The same problem with these two solvents is the low distribution function sigma profile ($p_i(\sigma)$) on the Y-axis [29,62], compared to both reactant $p_R(\sigma)$ and product $p_P(\sigma)$. As discussed in 2.3, $p_i(\sigma)$ is indicative of a large difference of the screening charge densities by $\sigma = 0$ between reactant (less polar) and product (more polar) due to the hydroxyl group. In this case, only dodecane $p_D(\sigma)$ shows obviously the high non-polar probability distribution to distinguish reactant and product at a thermodynamic level (solubility). The information of the simulation check just reported was now used to set up comparative reactions to be processed under the exact same batch conditions except for the variations of solvent. The HPLC conversions in Fig. 5(b) show that processing in dodecane gave a significantly higher conversion than the other two solvents. This agrees perfectly with the simulation results.

3.8. Microflow processes – Residence time (t), temperature (T) and catalyst concentration variations ($c_{o.c.}$)

Despite the promising results obtained in batch, full conversion could not be reached. We surmise that the limited mass transfer and low specific interface between substrates cause the lower efficiency in the batch reactor, i.e. we were operating under effective kinetics [63]. Hence, processing in a continuous microflow reactor consisting of a 750 μm inner-diameter, 5 ml PFA capillary was undertaken. Varied with flow rates, the residence times were changed from 30mins to 12 hrs. However, compared to the batch process, only a two-phasic system was formed in the collection vial after under 8 hrs (Fig. 6(a)). The conversions of aldehyde reactant were increasing along with residence times, reaching a maximum of 92 mol% after 12 h; and the highest yield of pure R-aldol product is 48 mol% after 8 hrs, see Fig. 6(b). However, such long operational times do not really justify the terminology "flow" and are close to stop-flow, i.e. the operation of a microbatch. While still profiting from the large specific surfaces, there will be no strong mixing effects by convection at such low flow velocities. Also in more practical terms, productivity would be very low. In order to change the experiment thus to true microflow, two reaction parameters might be suited to speed up the aldol reaction, namely (1) the reaction temperature (T, from room temperature to 80 °C) and (2) Singh catalyst concentration

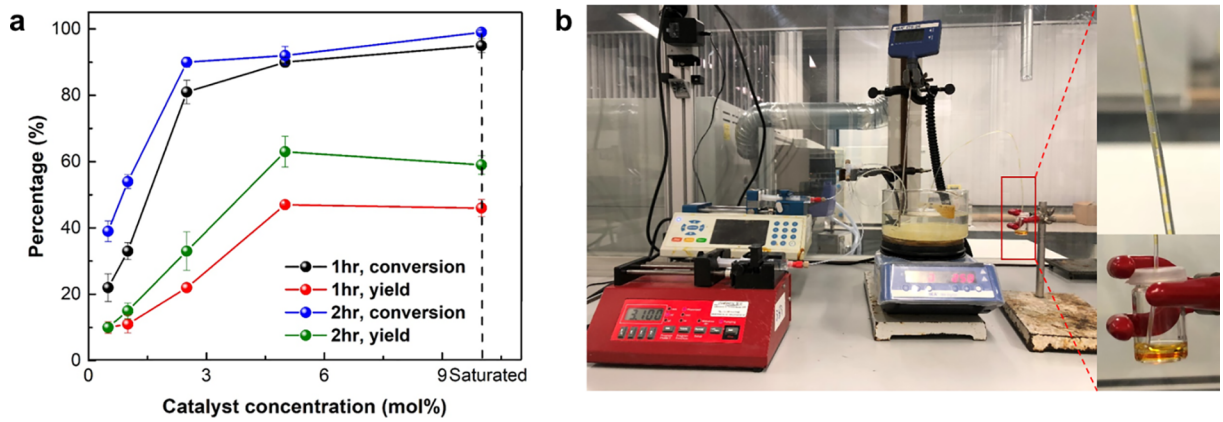


Fig. 7. (a) The effect of Singh catalyst concentration on the reaction conversion and yield. (b) Biphasic system and segmented flow formed during the reaction with $c_{cat} \geq 2.5$ mol%, t ≥ 1 hr.

($c_{o.c.}$, from 0.5 mol% to saturation conditions). The goal was to get maximal (R)-aldol product after ca. 1 hr reaction time. (1) Since the side product will be formed at high temperature, it was decided to restrict the maximal T to 80 °C. However, the high-temperature experiment showed hardly any increase in yield as compared to the first 'flow' experiment (80 °C, 5 mol% product yield). (2) The high-catalyst concentrations experiment delivered substantially larger yields instead (saturated Singh catalyst concentration, 46 mol% product yield). Secondly, the latter approach, 5 mol% $c_{o.c.}$, gave also a considerable 47 mol % product yield, the highest conversion 97% and highest productivity of 0.8 g/h (0.53 mol/(L × hr)). To increase the product yield, we extended the residence time from 1 hr to 2 hrs, leading to the optimal conditions with 5 mol% $c_{o.c.}$ (63 mol% product yield, conversion 92 mol %). All above results were analyzed by HPLC, as shown in Fig. 7(a). One point to highlight is that with ≥2.5 mol% catalyst and up to 1 hr, the formation of a segmented flow was observed, which is considered to provide efficient mixing through convection-induced recirculation (Fig. 7(b)). That might be in part responsible for the higher yields as well, besides the effect of having more catalyst.

4. Conclusions

We aimed to introduce a new reactor-separator concept which uses flexible soft matter compartmentalization to ensure orthogonality for reaction and subsequent separation. The soft matters used are multiphasic solvent systems which can be switched upon need. Designer solvents are a crucial part for reasons of ensuring a phase number ≥2 and, most notably, because of their fine-tunable solvent properties and availability in excessive number (> 10,000 species). The ideal scenario is to separate reactant(s), product and catalyst, each in their own phase, and, as the solvents play different roles in the process, they are called 'functional'. As the opening and closing of spaces is the key to our concept, we have coined the approach the "Spaciant Solvent Factory".

The aldol reaction was chosen as model reaction and the conceptual approach of a 'soft-integrated reactor-separator' could be verified. This is even more remarkable, as this reaction presents a difficult separation problem. The aldehyde and ketone (reactant and product) have similar physical properties, especially regarding their solubilities; nonetheless, automatic spontaneous separation could be achieved. The large reactant load, due to the need of an excess of one of the reactants, made the separation issue even more challenging.

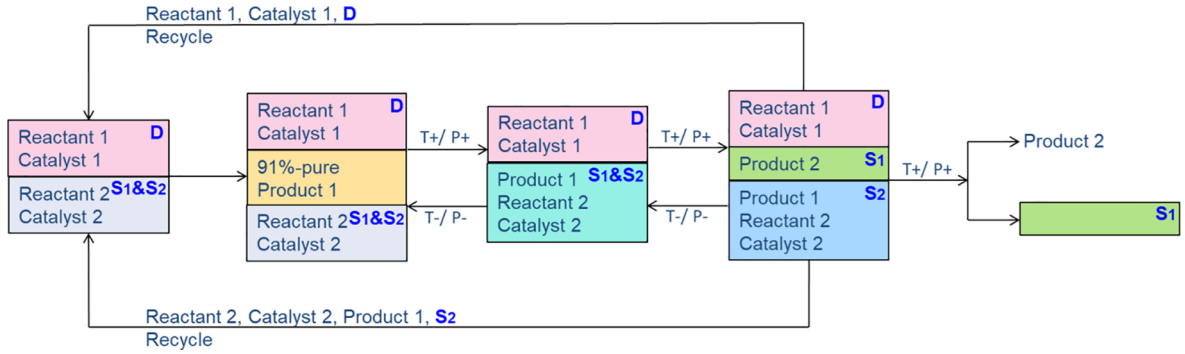
We selected the functional solvent dodecane as the most promising reaction solvent among > 7000 candidates after having run our proposed COSMO-RS based solvent screening methodology. Compared to the benchmark solvents water and cyclohexane, dodecane can act as both reaction media and extractant, and shows much better performance for the batch reaction. A transfer to a flow process (2 hrs) was achieved in a micro capillary system at high aldehyde reactant conversion (92 mol%) and reasonable (R)-aldol product yield (63 mol%). Most notably and as proof of the new process concept, this allows the separation of product (91 mol% product in product layer); and meanwhile recycling of the reactant(s), which were not consumed in the reaction.

5. Outlook

We think this combined thermodynamic simulation and experimental methodology is applicable to the separation of aldehyde and ketone species in other reaction systems, as the thermodynamic properties are ruled largely by the functional group. In future, the simulation selection scope should cover more solvents species such as ionic liquids and other thermodynamic properties. For the experimental part, we are underway to explore model reactions with easier separation tasks and at stoichiometric ratio, which are preferably run on reasonably large industrial scale. This shall turn this proof of concept study for automatic separation towards a fully systemic study with all functions running continuously (with recycling integrated) and allowing a quantification of relevant process parameters to map sustainability. We are also already underway to combine our approach with other compartmentalization approaches such as immobilized catalysts with polymersomes (which form the 'compartmentalized smart factory' in the ONE-FLOW project, investigated by the van Hest group) [40,64]. In the long run, we may automate the whole processing system, which is coined 'the digital machinery factory' (use of microcontrollers), e.g. to include analytical (camera) inspection of phase changes [65].

Our final goal is to achieve multi-step (catalytic) reactions in one run (ONE-FLOW) in multi-phasic systems using this methodology, i.e. to mimic the metabolic cascades of nature. In Scheme 3, we have envisioned how such Spaciant Solvent Factory for a two-step catalytic reaction may look alike.

The 2-step cascade from 3-chlorobenzaldehyde to (1R,3S)-1-(3-chloro-phenyl)butane-1,3-diol is an extension of the reaction presented here and that experimental study is currently under investigation. The aldol reaction reported here is the first step of the cascade, and the second step is an enzymatic reduction. The latter is investigated following the same solvent screening methodology as reported here. This



Scheme 3. Outline of the ONE-FLOW Spaciant Solvent Factory. Reactant 1, Catalyst 1 and Product 1 are compounds in the first-step aldol reaction. The rests are compounds in the second-step enzyme reduction. D: dodecane; S: solvent; T: temperature; P: pressure.

shall lead to the process design of a multi-phasic solvent system for automatic reaction-separation of the 1,3-diol formation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2019.123399.

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