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Study of C–C bond forming reactions towards improved performances by organocatalyst.

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Abstract

Organocatalysts may be retained in the DES phase during biphasic extractive work-up (e.g. with biogenic 2-methyl-tetrahydrofuran), enabling product recovery and organocatalyst recycling within the DES phase simultaneously. Herein, the proof-of-concept of designing organocatalysts—sspecifically tailored for DES—that may be properly retained in the DES phase (immobilized) among extractive cycles is demonstrated for the first time. To this end, the incorporation of novel hydrogen-bond donor groups (e.g.−OH) in the organocatalyst structure appears as a promising option to achieve improved results, leading to 1.5-fold higher conversions and yields, together with excellent chemoselectivities (>90%) for the new organocatalyst. Reactions are conducted using different bio-based DES, showing the broad applicability and possibilities that these processes may have. In this work it is demonstrated that organocatalysts can be tuned to be used in different DES. This first proof-of-concept may trigger new research and applications of DES as sustainable solvents for enantioselective C–C bond forming reactions, whereby the organocatalyst design can play an important role for optimized integrated process.

Keywords: Organocatalyst, C-C Bond, DES

Introduction:

Deep Eutectic Solvents (DES) have emerged as promising neoteric solvents for different chemical segments, e.g. using them as solvents for organic synthesis, as additives, or as extractive phases, among some relevant uses [2]. Previously, eutectic mixtures comprising substrates (e.g. composed of amino acids for peptide synthesis) had been reported to perform solvent-free biocatalytic processes [3]. In the novel applications, DES are typically formed by combination of a halide salt (e.g. choline chloride) with hydrogen-bond-donor molecules, such as (biobased) alcohols, carboxylic acids, amines, etc. DES may be cost-effective solvents, environmentally-friendly, tunable and biodegradable, and thus their use in different synthetic reactions is gaining particular attention, stimulated by the above-described potential advantages [4]. With regard to organic compounds solubilities, DES enable often the dissolution of hydrogen-bonding molecules, such as alcohols, carboxylic acids, amines, etc., whereas non-hydrogen bonding compounds tend to form a second phase. That feature has further allowed several promising strategies, ranging from biphasic forming systems with many

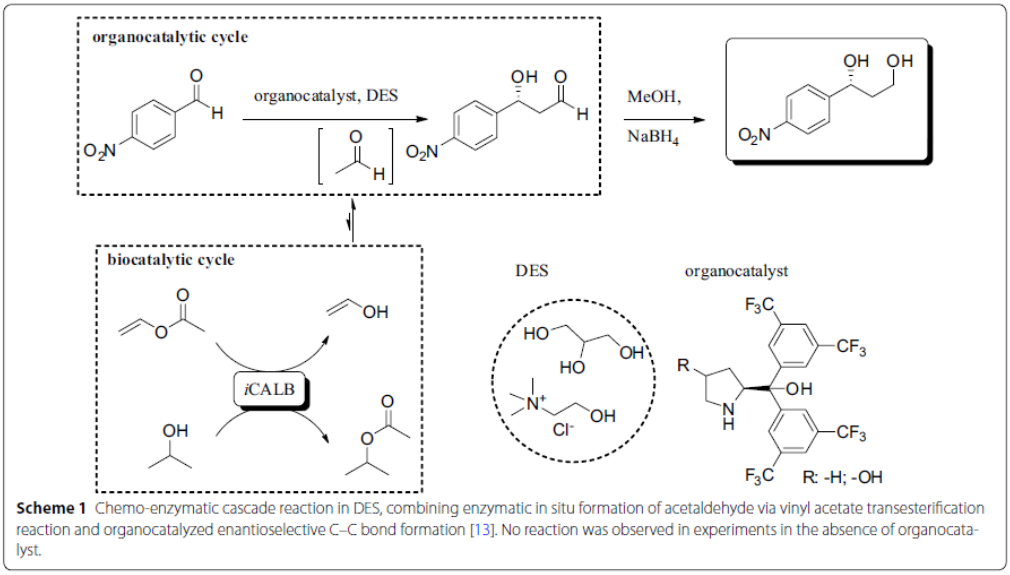
commonly used extractive solvents (e.g. ethyl acetate, 2-MeTHF) to unique extraction properties towards alcohol separation from esters [5]. Due to the high tune ability of DES, many options and creative innovations are possible.

The set-up of combined multi-step enzyme-organocatalytic reactions has also emerged as a promising branch of catalysis, synergistically using biocatalysis together with small molecules as catalysts for many (enantioselective) processes, e.g. efficient C–C bond formations under rather mild reaction conditions [6]. In this area, we have successfully reported the first chemo-enzymatic cascade reaction in DES recently. Using immobilized lipase B from Candida Antarctica (iCALB), in combination with vinyl acetate and 2-propanol, an transesterification occurs, acetaldehyde is produced in situ [7] and subsequently undergoes an organocatalytic cycle—based on enamine-iminium intermediates—to afford the final aldol product in an enantioselective fashion. For this purpose diaryl prolinols catalysts showed the best results, giving the final product in high yields and excellent enantioselectivities (Scheme 1) [8].

Apart from the observed high yields and selectivities (Scheme 1), the above-reported process was also promising in terms of organocatalyst recycling, as the used diaryl prolinol organocatalyst bears different hydrogen-bond donor groups, which lead to strong interactions with the DES. When ethyl acetate was used for extractive purposes as second phase, the organocatalyst remained partly immobilized in the DES phase [9]. Thus, the DES phase could be used for two cycles without the need of adding fresh organocatalyst. Given the typically used high organocatalyst loadings, the recycling process may improve the overall economics. Based on these promising observed results in terms of yield and enantioselectivity, and on the prognosis on ecological footprints and recycling [10], it was hypothesized that the incorporation of further hydrogen-bond donor groups along the organocatalyst structure might lead to higher DES-organocatalyst interactions and hence a better catalyst immobilization, while keeping yields and enantioselectivities in the same level. In this article, a proof-of-concept in that direction is reported for the first time.

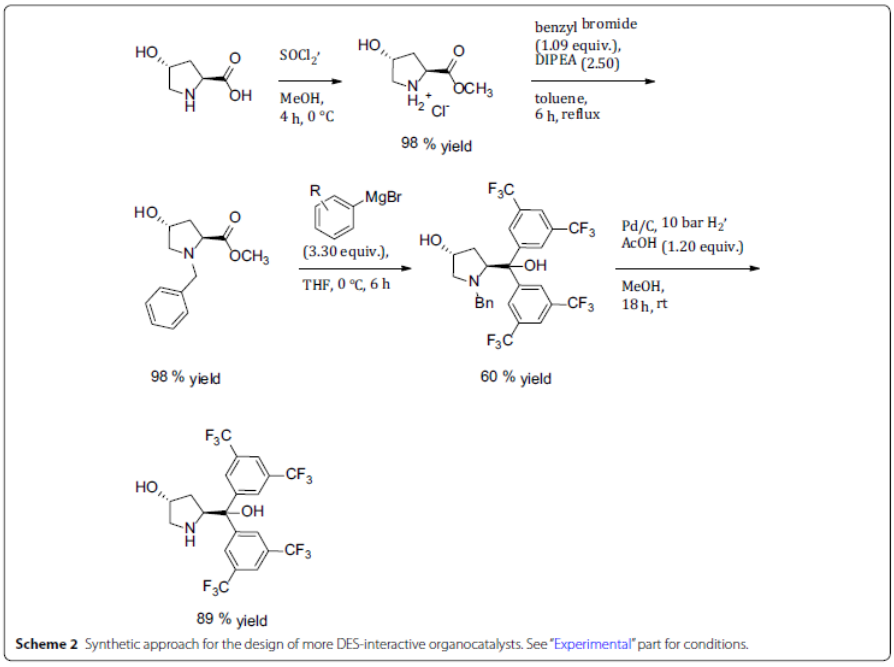
Results and Discussion

Starting from the diaryl prolinol as successful catalyst (Fig. 1) [11], the strategy consisted on incorporating an extra –OH moiety, leading to an organocatalyst with a further hydrogen-bond-donor group for the envisaged selective interaction with DES (Fig. 1).



Scheme 1 Chemo-enzymatic cascade reaction in DES, combining enzymatic in situ formation of acetaldehyde via vinyl acetate transesterification reaction and organocatalyzed enantioselective C–C bond formation [13]. No reaction was observed in experiments in the absence of organocatalyst.

With that goal in mind, the subsequent step was to envision an efficient approach to synthetize the desired organocatalyst. Based on previous literature [12], a synthetic strategy was successfully set, starting from commercially available 4-hydroxy-proline leading to the desired organocatalyst in good overall yield (Scheme 2).



Scheme 2 Synthetic approach for the design of more DES-interactive organocatalysts. See "Experimental" part for conditions.

Once the organocatalysts, Cat1 and Cat2 were synthetized, the multi-step enzyme-organocatalyst enantioselective aldol reaction (Scheme 1) was assessed to compare the performance of the two organocatalysts, and thus evaluate the influence of the extra –OH moiety in the performance and in the recyclability. As DES, the same 1:2 (mol:mol) ChCl:Gly was used. Yields, conversions and the respective chemoselectivity (yield over conversion) were studied along different cycles. Among each cycle, the DES-reactive phase was extracted with biobased 2-MeTHF [13]—to recover the aldol product—, and the DES phase was reused without addition of fresh organocatalyst or enzyme. The overall intended process concept is depicted in Fig. 2.

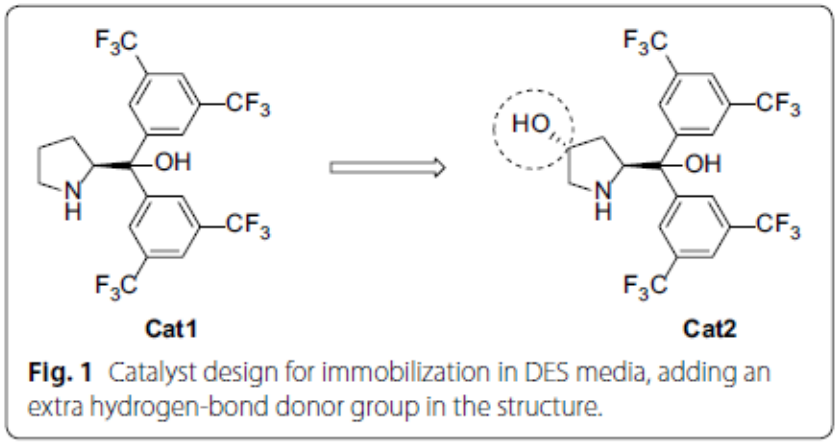


Fig. 1 Catalyst design for immobilization in DES media, adding an extra hydrogen-bond donor group in the structure.

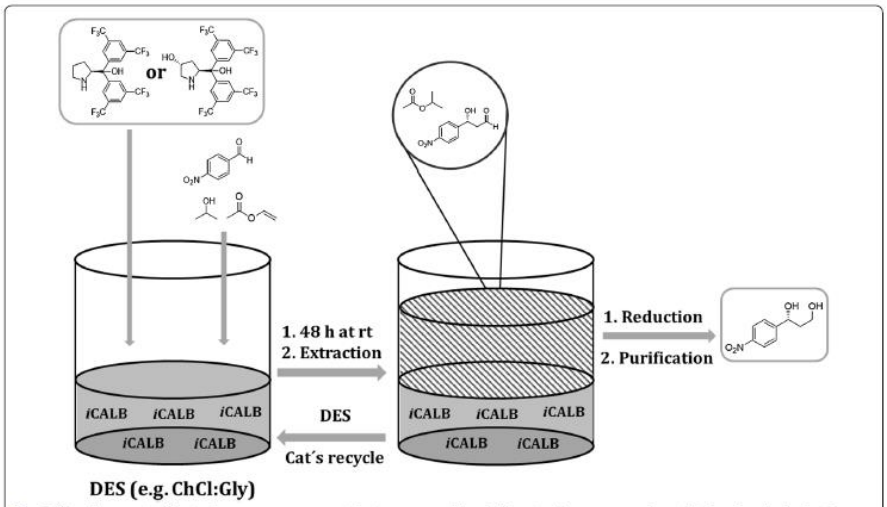


Fig. 2 Overall concept of the tandem enzyme-organocatalyst process combined with extraction among cycles and further chemical reduction. Immobilized CAL-B (iCALB) is suspended in the DES. Less than 1 wt% water is assumed in the reactive media.

Conclusions

The first time, leading to the proof-of-concept of an organocatalyst with improved performances (yield, conversion and chemoselectivities) in DES, by the incorporation of novel hydrogen-bond donor groups. Hence, triggering the catalyst immobilization via hydrogen bond interactions with the DES phase. Likewise, different DES have been tested for the reaction successfully. Overall, results suggest that the high tuneability of DES, combined with tailored organocatalyst-design, may lead to powerful synergies to perform selective organic reactions in non-hazardous environmentally-friendly media under rather mild reaction conditions. More research and design is needed to first understand the molecular interactions between DES and organocatalysts, and to ultimately exploit the tremendous potential that this multi-disciplinary field may have.

Chemicals

All chemicals were purchased from Sigma-Aldrich and used without further purification. Immobilized form of Candida antarctica Lipase B (iCAL-B) was purchased from c-LEcta GmbH (trade name CALB-immo).

DES preparation

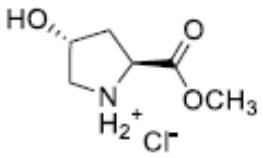
The components were mixed in the desired molar ratio and stirred at 60°C until a clear solution was obtained. After cooling down to room temperature, the DES was directly used. DESs were stored for maximum 1 month in a closed vessel.

Analytics

All NMR spectra were measured on a 400 MHz (1H-NMR: 400 MHz, 13C-NMR: 101 MHz), and 300 MHz (1H-NMR: 300 MHz, 13C-NMR: 75 MHz) Bruker device from BioSpin GmbH at 20°C. Chemical shifts are relative to the used solvents (CDCl3: 1H: δ = 7.26 ppm, 13C: δ = 77.16 ppm), indicated in ppm. Following abbreviations were used for the signal patterns: s = singlet, bs = broad signal, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets etc. for the 1H-spectra.

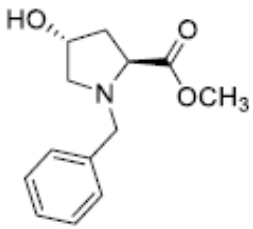
Cat2 synthesis

(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-ium chloride



Freshly distilled methanol (125 mL) was added to a round bottom flask and trans-4-hydroxy-l-proline (5.00 g, 38.13 mmol) was suspended. The slurry was cooled down to 0°C. After drop wise addition of thionyl chloride (2.78 mL, 38.2 mmol, 1.00 equiv.) the reaction mixture was stirred for 4 h at RT. Removal of the solvent under reduced pressure gave the product (6.80 g, 37.4 mmol, 98% yield) as a white solid. 1H-NMR (CDCl3, 300 MHz): δ = 2.08–2.18 (2H, m), 3.06 (1H, d, J = 12.0 Hz), 3.36 (1H, dd, J = 12.0, 4.4 Hz), 3.75 (3H, s), 4.41–4.48 (2H, m), 5.62 (1H, br-s), 9.91 (2H, br-s) ppm. 13C-NMR (CDCl3, 75 MHz): δ = 37.0, 53.0, 57.3, 68.4, 68.5, 169.0 ppm. Data are fully consistent with previous literature [16].

Methyl (2S,4R)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate



DES screening: 4-Nitrobenzaldehyde (1.00 mmol) was added with (S)-α,α-Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol (cat 1, 0.20 mmol), vinyl acetate (276 µL, 3.00 mmol, 3.00 equiv.), iso-propanol (230 µL, 3.00 mmol, 3.00 equiv.) and iCALB (3 mg) to 1 mL of 1:2 ChCl/glycerol DES in a G15 vial, equipped with a 15 mm × 4 mm magnetic stirring bar. The vessel was closed with a cap and gasket. After stirring (300 rpm) for 24 h at RT, methanol (2.00 mL) was added and the reaction mixture was transferred into a round bottom

flask and cooled down to 0°C. After slow addition of sodium borohydride (226 mg, 6.00 mmol over 30 min), the reaction was allowed to stir another hour at 0°C. Quenching was conducted by the addition of aqueous saturated ammonium chloride solution (15 mL) followed by the addition of ethyl acetate (15 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 15 mL). After washing of the combined organic layers with brine (15 mL), drying was proceed over sodium sulfate. Filtration of drying agent and solvent removal under reduced pressure led to the crude product which was purified via flash chromatography (eluent: 4:1 EtOAc/PE; Rf = 0.33) to give a colorless oil. 1H-NMR (CDCl3, 300 MHz): δ = 1.97 (q, J = 5.8 Hz, 2H), 2.18 (br-s, 1H), 3.50 (d, J = 2.9 Hz, 1H), 3.90–3.95 (m, 2H), 5.10 (t, J = 6.00 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H) ppm. 13C-NMR (CDCl3, 75 MHz): δ = 40.6, 61.7, 73.7, 124.1, 126.8, 147.6, 152.1 ppm.

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