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SUSTAINABLE CHEMICAL PROCESSES

RESEARCH ARTICLE

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Multi-step enzyme-organocatalyst C–C bond forming reactions in deep-eutectic-solvents: towards improved performances by organocatalyst design

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Abstract

Background: Deep eutectic solvents (DES) have recently emerged as promising non-hazardous environmentally-friendly solvents. In this respect, the use of DES as media for multi-step enzyme-organocatalysis (C–C bond formation via aldol-type reactions) represents a promising sustainable option. Being soluble in DES, 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.

Main results: 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.

Conclusions and implications: 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 set-up.

Keywords: Biocatalysis, Lipases, Deep-eutectic-solvents, Recycling, Multi-step cascade reaction

Background

The quest for novel bio-based and environmentally-friendly solvents for synthetic processes is presently an important trend in chemistry, as solvents typically account for a significant part of the pollution produced through chemical reactions [1]. In this area, very recently 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 [2–5].

Previously, eutectic mixtures comprising substrates (e.g. composed of amino acids for peptide synthesis) had been reported to perform solvent-free biocatalytic processes [6]. 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 (bio-based) 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 [7]. With regard to organic compounds solubilities, DES enable often the dissolution of hydrogen-bonding molecules, such as alcohols, carboxylic acids, amines, etc.,

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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) [7] to unique extraction properties towards alcohol separation from esters [8, 9]. Due to the high tuneability of DES, many options and creative innovations are possible.

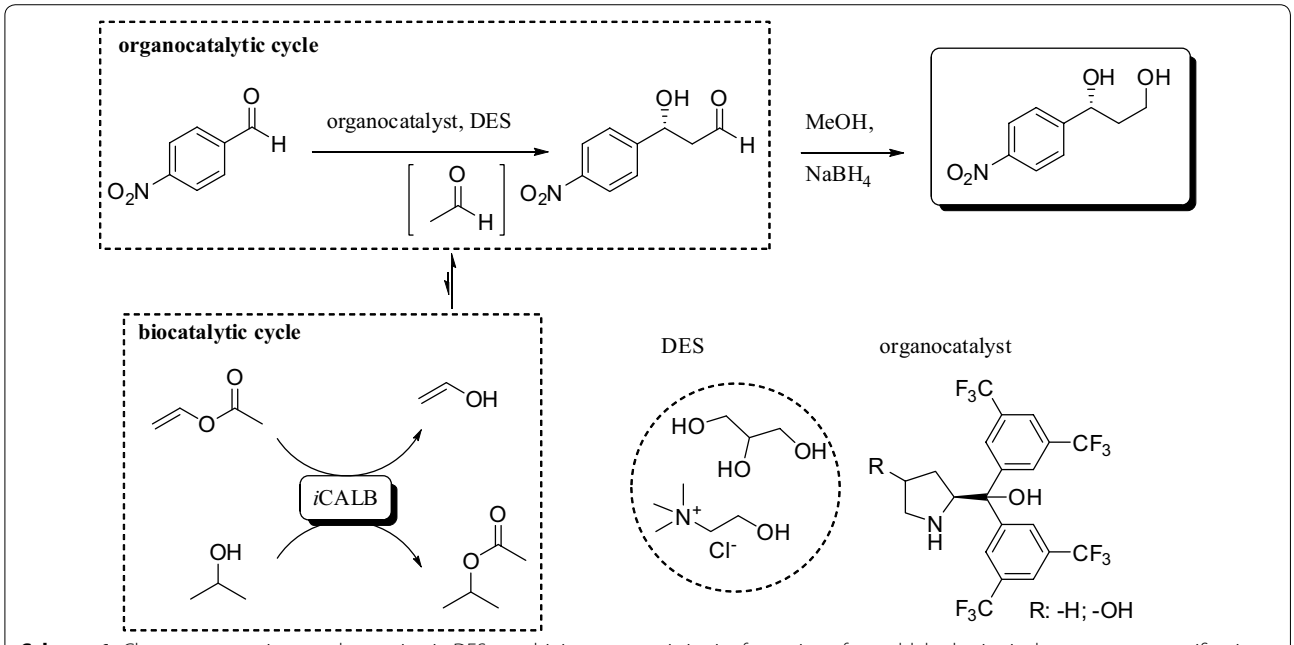
In recent years, the set-up of combined multi-step enzyme-organocatalytic reactions has also emerged as a promising branch of catalysis, synergistically using biocatalysis together with small molecules as catalysts for many (enantioselective) processes, e.g. efficient C–C bond formations under rather mild reaction conditions [10, 11]. In this area, we have successfully reported the first chemo-enzymatic cascade reaction in DES recently. Using immobilized lipase B from *Candida antarctica* (*i*CALB), in combination with vinyl acetate and 2-propanol, an transesterification occurs, acetaldehyde is produced in situ [12] 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) [13].

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 [13]. 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 [13], 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) [13], 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.

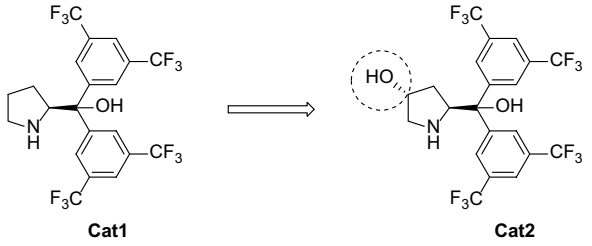
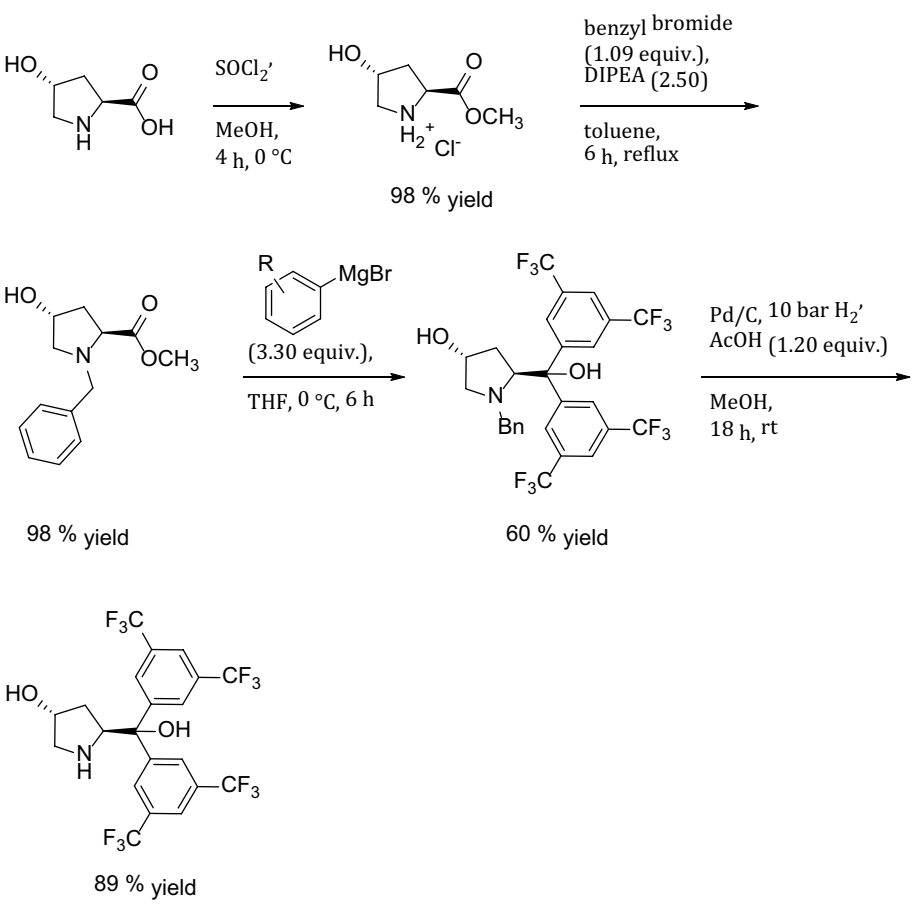


Fig. 1 Catalyst design for immobilization in DES media, adding an extra hydrogen-bond donor group in the structure.

With that goal in mind, the subsequent step was to envision an efficient approach to synthetize the desired organocatalyst. Based on previous literature [14], a synthetic strategy was successfully set, starting from commercially available 4-hydroxy-proline leading to the desired organocatalyst in good overall yield (Scheme 2).

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 bio-based 2-MeTHF [15]—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.

Upon addition of substrates (vinyl acetate, *iso*propanol and *p*-nitrobenzaldehyde) and organocatalysts to the DES phase (containing iCALB), the reaction was conducted for 48 h, after which the addition of 2-MeTHF followed. While organocatalyst and enzymes remained in the DES phase, the organic phase extracted the aldol product, together with other side-products such as isopropyl acetate. Overall results of the reaction are shown in Fig. 3.



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

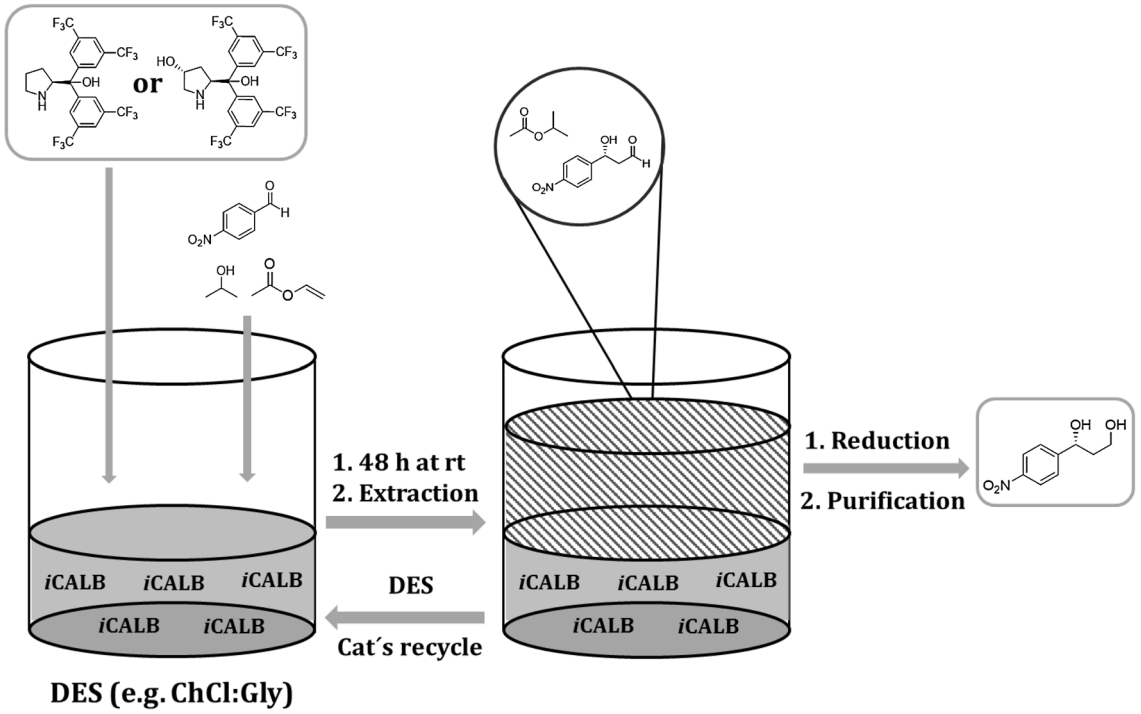


Fig. 2 Overall concept of the tandem enzyme-organocatalyst process combined with extraction among cycles and further chemical reduction. Immobilized CAL-B (iCALB) is suspended in the DES. Less than 1 wt% water is assumed in the reactive media.

As it can be observed (Fig. 3), the envisioned Cat2—bearing an extra hydrogen-bond donor group in the structure—led not only to better recycling profiles than Cat1, but also to higher yields, conversions and chemoselectivities. This finding clearly shows that the subtle incorporation of an extra −OH group exerts a beneficial effect in the organocatalytic process performed in DES media. The effect is particularly relevant within the first two reaction cycles, where Cat2 virtually led to 1.5-fold improved performance compared to that of Cat1 (yields of 43–52% for Cat1 and 71–74% for Cat2). After the third cycle, however, both catalysts showed a significant decrease in yield and conversion, albeit chemoselectivity remained outstanding, especially in the case of Cat2 (>90% along cycles), suggesting a cleaner and more efficient overall synthetic process. Despite results are still non-optimized, to our knowledge this represents the first proof-of-concept of organocatalyst specifically tailored to DES media. As it can be envisaged, the incorporation of further hydrogen-bond donor groups—or other beneficial moieties—, in the structure might lead to improved and tailored outcomes for proper *immobilized* organocatalysts in DES.

Apart from envisaging organocatalyst-design as an option to improve multi-step organocatalytic reactions in DES, another line of research is to broaden the type of DES used as non-hazardous, environmentally-friendly media for multi-step reactions. In this case, many halide salts, as well as hydrogen-bond donor (HBD) compounds can be envisaged. Along this line, different choline-chloride-based DES combined with a range of different HBDs—covering polyols, urea, sugar-based alcohols—, were subsequently used for the intended multi-step reaction (Scheme 1). Results are depicted in Fig. 4.

As observed (Fig. 4), the reaction media played an important role in the outcomes of the enzyme-organocatalyst reaction. Glycerol-based DES (comprising 1:2 and 1:1.5) led to excellent results, and even the subtle change of proportion (from 2 to 1.5 mol of glycerol) led to improved results in yields and chemoselectivities. The substitution of glycerol (as hydrogen-bond donor) by ethylene–glycol gave, however, lower yields and chemoselectivities, emphasizing the interactions that DES have with the catalytic process. Likewise, detrimental effects were more dramatic when using ChCl:urea and sugar-based DES, presumably due to enzyme denaturation. In the case of xylitol as hydrogen-bond donor, the reaction mixture froze within the first minutes of reaction, thus rapidly invalidating this option for a combined enzyme-organocatalyst process. Overall, the choice of DES media appears as a relevant matter as well for the setup of these enzyme-organocatalyst multi-step combined reactions.

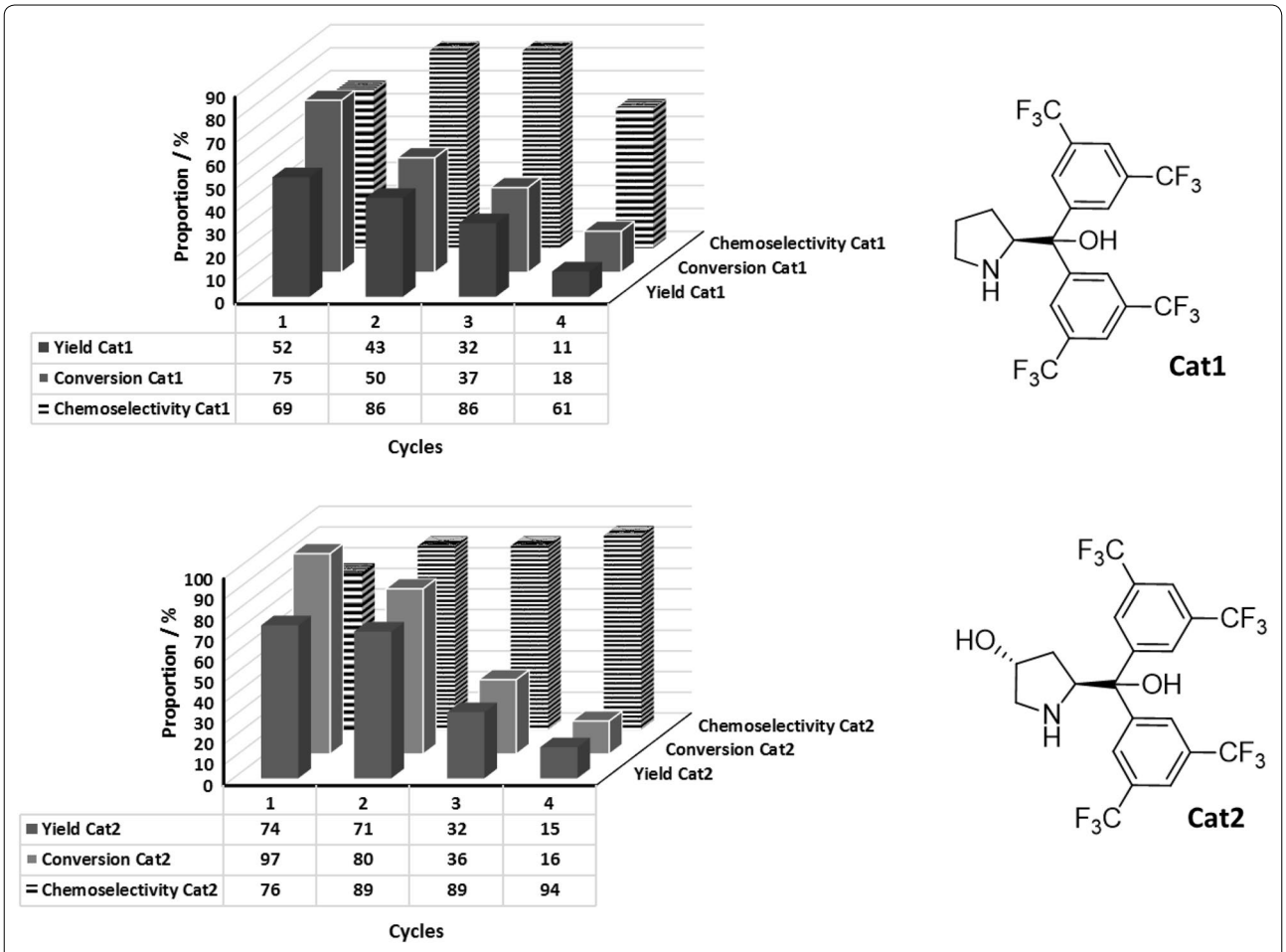


Fig. 3 DES and catalyst recycling. Reaction conditions: 1.00 mmol *p*-nitrobenzaldehyde, 3.00 mmol vinyl acetate, 3.00 mmol *i*-PrOH, 3 mg *i*CALB, 0.20 mmol catalyst, 1 mL 1:2 ChCl/glycerol DES, 48 h, RT; Extraction with 3 × 2 mL 2-MTHF; Reduction of the organic phase phase with 2.0 mL MeOH, 6.00 mmol $NaBH_4$, 1 h, 0°C to yield the reduced alcohol. Less than 1 wt% water is assumed in the reactive media.

Conclusions

In this paper the use of Deep Eutectic Solvents (DES) for multi-step enzyme-organocatalyst processes—leading to selective C–C bond forming aldol-type reactions—has been assessed. The design of organocatalysts specifically designed for DES media has been envisioned for 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.

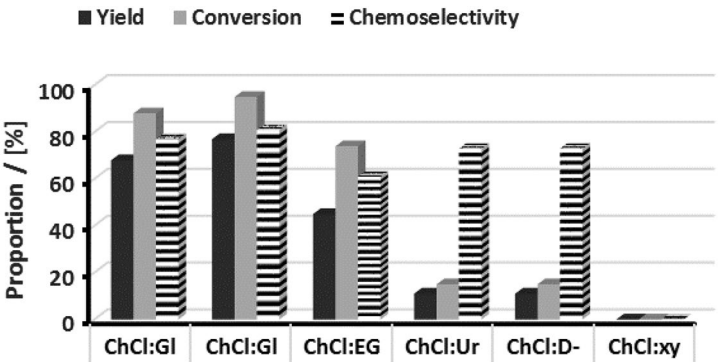
Experimental section

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.



	ChCl:Gly 1:2	ChCl:Gly 1:1.5	ChCl:EG 1:2	ChCl:Urea 1:2	ChCl:D-sorbitol 1:1	ChCl:xylitol 1:1
Yield	68	77	45	11	11	0
Conversion	88	95	74	15	15	0
Chemoselectivity	77	81	61	73	73	0

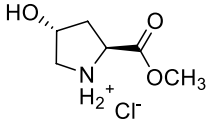
Fig. 4 DES screening. Reaction conditions: 1.00 mmol *p*-nitrobenzaldehyde, 3.00 mmol vinyl acetate, 3.00 mmol *i*-PrOH, 3 mg *i*CALB, 0.20 mmol Cat1, 1 mL DES, 48 h, room temperature; Reduction with 2.0 mL MeOH, 6.00 mmol $NaBH_4$, 1 h, 0°C. *Gly* glycerol, *EG* ethylene glycol. Less than 1 wt% water is assumed in the reactive media.

Analytics

All NMR spectra were measured on a 400 MHz (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 101 MHz), and 300 MHz (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz) Bruker device from BioSpin GmbH at 20°C. Chemical shifts are relative to the used solvents ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: 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 ^{1}H-spectra.

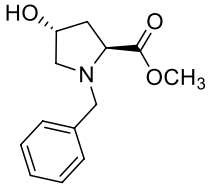
Cat2 synthesis

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



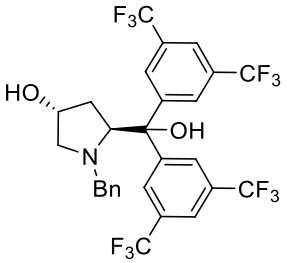
Freshly distilled methanol (125 mL) was added to a round bottom flask and *trans*-4-hydroxy-L-proline (5.00 g, 38.13 mmol) was suspended. The slurry was cooled down to 0°C. After drop wise addition of thionyl chloride (2.78 mL, 38.2 mmol, 1.00 equiv.) the reaction mixture was stirred for 4 h at RT. Removal of the solvent under reduced pressure gave the product (6.80 g, 37.4 mmol, 98% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 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*. ^{13}C-NMR ($CDCl_3$, 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



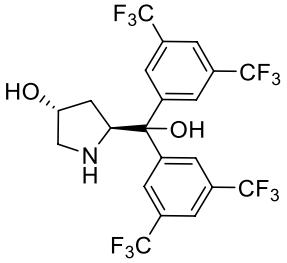
Toluene (30 mL) was added to a round bottom flask and (2*S*,4*R*)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-ium chloride (5.30 g, 29.2 mmol) was suspended. The mixture was cooled down to 0°C. Firstly *N*,*N*-Diisopropylethylamine (DIPEA, 12.60 mL, 72.34 mmol, 2.48 equiv.) was added drop wise and then followed by benzyl bromide (3.80 mL, 31.92 mmol, 1.09 equiv.). The reaction mixture was refluxed for 6 h and quenched with saturated aqueous ammonium chloride solution (30 mL). The aqueous solution was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over sodium sulfate. Filtering of the drying agent and solvent removal under reduced pressure gave the product (6.74 g, 28.7 mmol, 98% yield) as yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.75 (1H, br-s), 2.02–2,13 (1H, m), 2.18–2.33 (1H, m), 2.48 (1H, dd, *J* = 10.2, 3.7 Hz), 3.33 (1H, dd, *J* = 10.2, 5.6 Hz), 3.58–3.70 (2H, m), 3.66 (3H, s), 3.90 (1H, d, 12.9 Hz), 4.45 (1H, br-s), 7.20–7.38 (5H, m) *ppm*. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 39.6, 51.9, 58.2, 61.3, 63.7, 70.4, 127.36, 128.4, 129.2, 138.2, 174.1 *ppm*. Analytic data agree with literature [17].

(3R,5S)-1-benzyl-5-(bis(3,5-bis(trifluoromethyl)phenyl) (hydroxy) methyl)pyrrolidin-3-ol



Dry THF (20 mL) was added to a round bottom flask under argon atmosphere and magnesium turnings (1.70 g, 70.00 mmol, 5.00 equiv.) were suspended. A solution of 1-bromo-3,5-bis(trifluoromethyl) benzene (7.97 mL, 46.20 mmol, 3.30 equiv.) in dry THF (180 mL) was added drop wise at 0°C. The reaction mixture was refluxed for 2 h, transferred into a dropping funnel and added drop wise to a solution of methyl (2*S*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (3.29 g, 14.00 mmol) in dry THF (60 mL) at 0°C over 30 min. The mixture was stirred 4 h at RT, before it was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL) and subsequently neutralized with aqueous 10% HCl solution. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. Filtering of the drying agent and solvent removal under reduced pressure gave the crude product, which was purified via flash column chromatography (eluent: EtOAc/PE 1:6; $R_f = 0.22$). The final product (5.29 g, 8.37 mmol, 60% yield) was obtained as yellowish oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.67–1.75 (1H, m), 1.76–1.85 (1H, m), 2.68–2.76 (1H, m), 3.12–3.26 (2H, m), 3.52 (1H, d, *J* = 13.0 Hz), 3.49–3.55 (1H, m), 4.53 (1H, dd, *J* = 8.7, 7.5 Hz), 5.55 (1H, br-s), 6.97–7.00 (2H, m), 7.19–7.29 (3H, m), 7.75 (2H, d, *J* = 11.6 Hz) 8.06 (2H, s), 8.24 (2H, s) *ppm*. ^{13}C-NMR ($CDCl_3$, 101 MHz): δ = 38.9, 61.8, 62.7, 70.8, 71.1, 76.2, 121.5, 121.7, 121.9, 124.6, 125.7, 126.1, 127.7, 128.3, 128.7, 132.2, 138.5, 147.2, 149.4 *ppm*. Analytic data agree with literature results [18].

(3R,5S)-5-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy) methyl) pyrrolidin-3-ol



To a suspension of acetic acid (106 µL, 1.86 mmol, 1.20 equiv.) and palladium on carbon (10 wt% Pd/C, 100 mg), and dry methanol (3.0 mL) (3*R*,5*S*)-1-benzyl-5-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy) methyl) pyrrolidin-3-ol (1.00 g, 1.55 mmol) was added. The reaction was stirred in a hydrogen atmosphere (18 bar) for 18 h at RT. Filtering over Celite and removal of the solvent under reduced pressure gave an oil which was solubilized in ethyl acetate (15 mL). Saturated aqueous $NaHCO_3$ solution (15 mL) was added and neutralized to pH 7. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over sodium sulfate. Filtering of the drying agent and solvent removal under reduced pressure gave the product (748 mg, 1.38 mmol, 89% yield) as yellowish solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.40–1.52 (1H, m), 1.67–1.77 (1H, m), 3.05-3.22 (2H, m), 4.41–4.47 (1H, m), 4.72 (1H, dd, *J* = 10.1, 6.3 Hz), 7.76 (1H, s), 7.79 (1H, s), 7.94 (1H, s), 8.06 (1H, s) *ppm*. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 36.5, 55.6, 63.3, 72.6, 76.5, 125.7, 126.3, 132.2, 146.1, 149.2 *ppm*. Analytic data agree with previous literature [19].

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; $R_f = 0.33$) to give a colorless oil. ^{1}H-NMR ($CDCl_3$, 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. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 40.6, 61.7, 73.7, 124.1, 126.8, 147.6, 152.1 ppm.

Recycling system

4-Nitrobenzaldehyde (1.00 mmol) was added with organocatalyst (0.20 mmol), vinyl acetate (276 μL, 3.00 mmol, 3.00 equiv.), *iso*-propanol (230 μL) and iCALB (3.00 mg) to 1 mL of 1:2 ChCl/glycerol DES in a G15 vial, equipped with a 15 mm × 4 mm stirring bar. The vessel was closed with a cap and gasket. After stirring for the 48 h at 300 rpm, the DES phase was extracted with the 2-MTHF (3 × 2 mL). The combined organic layers were separated and methanol was added, while the mixture was cooled down to 0°C. After slow addition of sodium borohydride (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. Removal of drying agent and solvent under reduced pressure led to the crude product which was purified via flash chromatography (eluent: 4:1 EtOAc/PE; $R_f = 0.33$) to give a colorless oil. The extracted DES was directly used in the next cycle.

Authors' contributions

CRM and AR performed the experimental work. CRM and PDdM designed the experiments, interpreted the results, and wrote the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical guidelines

Competing interests

The authors declare that they have no competing interests.

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