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# Stereoselective organocatalysed reactions in deep eutectic solvents: highly tunable and biorenewable reaction media for sustainable organic synthesis

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Three distinct stereoselective reactions, catalysed by a chiral primary amine through different activation methods, have been successfully carried out for the first time in bio-based eutectic mixtures, thereby affording functionalised molecules in very high enantioselectivity. The use of these unconventional and biorenewable reaction media also provides opportunities for facilitating the recovery and the recycling of the chiral catalyst.

## Introduction

In the last decade, organocatalysis has become an established and powerful synthetic tool for the stereoselective synthesis of highly functionalized molecules, and has been already successfully employed for the preparation of natural products, intermediates for pharmaceuticals, and other biologically active compounds.[1] The extremely fast growth of metal-free catalytic methodologies has offered unique possibilities to develop more sustainable chemical processes.[2] In fact, since simple organic molecules are used as catalysts, the contamination of final products with heavy metals is intrinsically avoided. The great benefits of all recently developed metal-free catalysts make organocatalysis a very appealing and powerful technology platform for industry.[3] A few issues, however, still limit the application of such a valiant methodology to the synthesis of industrially relevant targets: two of the major problems concern the low catalyst activity,[4] generally displayed by most of the successful catalysts, and the need to operate very often in conventional, hazardous volatile organic solvents (e.g., toluene) in order to maximize the stereochemical efficiency of the catalyst. The improvement of the catalyst efficiency can be realized in different ways; for example, by studying the catalyst stability and through the optimization of its structure which, in turn, influences its mode of action. The immobilization of the chiral catalyst on solid support,[5] as well as its recycle exploiting flow reactor technologies,[6] represent alternative, attractive approaches to address the problem of high catalyst loading especially for industrial purposes.

Herein, we wish to report an alternative and almost totally unexplored approach to realize metal-free catalytic enantioselective transformations in not-hazardous reaction media, employing the so-called "deep eutectic solvents" (*DESs*). The concept of *DES* was firstly introduced by Abbott and co-workers to describe the formation of a liquid eutectic mixture (mp 12 °C) starting from two solid materials with high melting points: choline chloride (ChCl, mp 133 °C) and urea (mp 302 °C) in a molar ratio 1:2 (1ChCl/2Urea).[7] *DESs* [also known in the literature as Low-Transition-Temperature Mixtures (*LTTMs*) if their phase transition is identified by a melting point or by a glass transition] are today generally referred to as combinations of two or three safe and inexpensive components which are able to engage in hydrogen-bond interactions with each other to form an eutectic mixture with a melting point lower than either of the individual components. Thanks to their low ecological footprint and attractive low price,[8] *DESs* are today attaining increasing interest in both academia and industry as promising "green" alternative solvents in a variety of organic reactions as well as in process technology for their unusual solvent properties.[9]

It is worth mentioning that the concept of DESs is quite different from that of traditional ionic liquids[10] because the former are not entirely composed of ionic species, and can also be obtained from non-ionic species by gentle thermal mixing. In addition, *DESs* require (a) no purification, (b) their physicochemical properties can be easily and widely tuned to meet specific reaction requirements, and (c) they offer convenient methods of product isolation simply based on organic phase extraction or even precipitation upon addition of water, which can be subsequently removed thereby restoring a reusable *DES*. Emerging applications are in particular in the fields of biotransformations,[9g] metal-catalysed reactions,[9g,11] organometallic chemistry[12] and also organocatalysis. As for the latter, to the best of our knowledge, only a single example has been reported dealing with an enzyme-based secondary amine-catalysed cascade reaction (which allows *in situ* production of acetaldehyde) followed by an enantioselective aldol condensation in a ChCl/Glycerol(Gly)-based reaction medium.[13] The *DES* medium containing the enzyme and the organocatalyst

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Electronic Supplementary Information (ESI) available: DES preparation, synthesis of the catalyst, experimental details for organocatalytic reactions, product characterization, HPLC traces, recycling protocol. See DOI: 10.1039/x0xx00000x.

(L-proline derivative) could then be recycled up to six times, although partial extraction of the organocatalyst in the solvent used for product extraction (EtOAc) was observed as well.

In order to investigate more in detail the behaviour of organocatalytic systems in these innovative eco-friendly solvents and to evaluate the general applicability of such a strategy, here we discuss the use of a chiral primary amine successfully promoting three stereoselective transformations, which proceed through different pathways, in three diverse ChCl-based *DESs*, with the same excellent levels of stereo- and enantioselectivity compared to that of the traditionally employed organic solvents. Moreover, in some cases, the reaction was proven to be even accelerated, thereby affording the expected product in shorter reaction times and without any loss of stereoselectivity. Finally, the recycling of the chiral catalyst was also successfully achieved with a very simple operational procedure.[14]

## Results and discussion

We focused our attention on one of the most effective metal-free catalytic systems known to date for promoting reactions via enamine, iminium ion formation, and also through dienamine activation: the chiral primary amines 9-amino-9-deoxy-*epi*-cinchona derivatives,[15] whose efficiency was screened in three different ChCl-based eutectic mixtures (Table 1). The great versatility and the excellent levels of enantioselectivity reached in several reactions, indeed, makes the use of this class of catalysts extremely attractive especially in view of possible industrial applications, once the problem of the high catalyst loading will be positively solved.

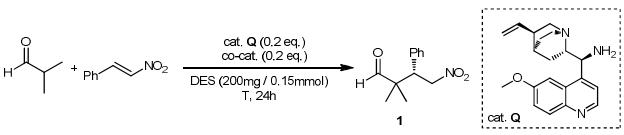
**Table 1** *DES* mixtures used in this work.

| *DES*[a] | components | molar ratio |
|---|---|---|
| *DES* **A** | CHOLINE CHLORIDE : UREA | 1:2 |
| *DES* **B** | CHOLINE CHLORIDE : FRUCTOSE : $H_2O$ | 1:1:1 |
| *DES* **C** | CHOLINE CHLORIDE : GLYCEROL | 1:2 |

[a] Typically, 1 g of *DES* per 0.6 mmol of substrate was used; for the synthesis of *DES* mixtures, see the Supporting Information.

We first investigated the conjugate addition of isobutyraldehyde to nitrostyrene to give adduct **1**,[16] catalysed through an enamine activation mode by the 9-amino-9-deoxy-epi-quinine (cat. **Q**, Scheme 1) in the presence of an acid additive, like benzoic acid.

**Scheme 1** Addition of isobutyraldehyde to β–nitrostyrene.




When the same organocatalytic Michael addition was performed in a *DES* mixture, in all investigated cases, a complete conversion was observed at both 25 and 50 °C employing *DESs* **A**–**C** (Table 2). In particular, employing *DESs* **A** and **B**, up to 85% enantiomeric excess (e.e.) was obtained (Table 2, entries 1 and 2).

Interestingly, the reaction was found to proceed in excellent yields and enantioselectivities in both the above *DESs* even without the addition of the acidic co-catalyst (Table 2, entries 7 and 8), which is typically required in the enamine activation mode. Of note, in the case of the fructose-based *DES* **B**, the reaction led to the formation of the expected product at room temperature, in quantitative yield, and with 95% e.e. (Table 2, entry 9).

**Table 2** Organocatalytic Michael addition in *DESs* **A**–**C**.

| entry [a] | *DES* | co-cat. | *T* (°C) | conv. [b] (%) | e.e. [c] (%) |
|---|---|---|---|---|---|
| 1 | *DES* **A** | PhCOOH | 25 | 75 | 80 |
| 2 | *DES* **B** | PhCOOH | 25 | >99 [d] | 85 |
| 3 | *DES* **C** | PhCOOH | 25 | >99 | 62 |
| 4 | *DES* **C** | PhCOOH | 0 | 27 | 21 |
| 5[e] | *DES* **C** | - | 25 | - | - |
| 6 | *DES* **A** | PhCOOH | 50 | >99 [d] | 81 |
| 7 | *DES* **A** | - | 50 | >99 [d] | 88 |
| 8 | *DES* **B** | - | 50 | >99 [d] | 85 |
| 9 | *DES* **B** | - | 25 | >99 [d] | 95 |
| 10[e] | *DES* **B** | - | 50 | - | - |

[a] Typical reaction conditions: 0.75 mmol aldehyde, 0.15 mmol nitrostyrene in 0.2 g of *DES,* 20 hours. [b] Conversions determined by $^1$H NMR. [c] Determined by HPLC on a chiral stationary phase. [d] Confirmed as isolated yields after chromatographic purification. [e] Reaction was performed without the catalyst.

Prompted by the above excellent results, and in view of the development of a recycling protocol of the chiral catalyst, we further investigated the experimental parameters of the transformation performed in *DES* **B**, like *concentration* and *reaction time* (Table 3).[17] For the sake of comparison, a few data of the corresponding reactions run in toluene (a typically used solvent in the transformations promoted by catalyst **Q**) are also reported. The concentration of the reaction mixture seems to have an effect on the reaction rate, but not a remarkable influence on the enantioselection of the transformation. Indeed, stopping the reaction after 3 and 5 hours, higher yields were obtained operating in 1 M solution rather than in 0.1 M solutions (Table 3, entries 1 and 2 vs entries 6 and 7). A similar trend was also observed in toluene (Table 3, entries 4 and 5 vs entries 8 and 9), but the reactions proved to be slower than those run in *DES* **B**. In fact, in 1 M solution of *DES* **B**, the product was isolated in 65% yield after 3 hours and in 89% yield after 5 hours (Table 3, entries 1 and 2), whereas the corresponding yields in toluene were 45% and 67%, respectively (Table 3, entries 4 and 5).

**Table 3** Optimization studies on the Michael addition in *DES* **B**.

| entry [a] | solvent | *t* (h) | conc. | conv. [b] (%) | e.e. [c] (%) |
|---|---|---|---|---|---|
| 1 | *DES* **B** | 3 | 1 M | 65 | 91 |
| 2 | *DES* **B** | 5 | 1 M | 89 [d] | 95 |
| 3 | *DES* **B** | 20 | 1 M | >99 [d] | 95 |
| 4 | toluene | 3 | 1 M | 45 | 95 |
| 5 | toluene | 5 | 1 M | 67 | 98 |
| 6 | *DES* **B** | 3 | 0.1 M | 27 | n.d. [e] |
| 7 | *DES* **B** | 5 | 0.1 M | 47 [d] | 89 |
| 8 | toluene | 3 | 0.1 M | 9 | n.d. [e] |
| 9 | toluene | 5 | 0.1 M | 15 | 97 |
| 10 | water | 3 | 1 M | 21 [d] | 61 |
| 11 | glycerol | 3 | 1 M | 51 [d] | 91 |

[a] Typical reaction conditions: aldehyde/nitrostyrene molar ratio 5/1 at 25 °C. [b] Conversions determined by $^1$H NMR. [c] Determined by HPLC on a chiral stationary phase. [d] Confirmed as isolated yields after chromatographic purification. [e] Not determined.

These results are consistent with a positive cooperative effect of the *DES* system with the chiral catalyst in promoting the transformation. The same reaction run in water afforded the product in low yield and modest enantioselectivity, while in pure glycerol the product could be isolated in 51% yield and 91% e.e. after 3 h (Table 3, entries 10-11). It is also remarkable that, in any conditions, excellent levels of enantioselectivity were always maintained in *DES* **B** (up to 95% e.e., Table 3).

The recycle of the precious chiral catalyst was realized by exploiting the different solubility properties the amino-Cinchona derivative proved to exhibit in *DESs* and in other organic solvents. In fact, in the product isolation procedure, once the stirring was stopped and the reaction mixture was washed once with 1 mL of 7/3 hexane/diisopropyl ether mixture, the product could be quantitatively extracted leaving the catalyst in the *DES* mixture.[18] Then, upon simply adding new, fresh reagents, the latter could be successfully re-used for further reaction runs. A few selected data are reported in Table 4. In preliminary experiments, the reaction was stopped after 24 hours, thereby affording the product in quantitative yield and in 95% e.e. (Table 4, entry 1).[18] In the second cycle, fresh reagents were added to the catalyst still present in *DES* **B**, and the reaction run for additional 24 hours, leading to the formation of the expected Michael adduct in quantitative yield and in 93% e.e. (Table 4, entry 2). However, starting from the third cycle, a drop in the chemical yield was observed (37% yield, Table 4, entry 3).[19] In the attempt to optimize the recyclability of the chiral catalyst **Q**, further studies were performed, by interrupting the reaction after 5 hours; also in this case, at the third cycle, the yield decreased (Table 4, entries 4–6). However, it was possible to further improve the productivity of the recycling protocol: shortening the reaction time to only 2 hours, three cycles (6 hours overall) allowed to obtain almost the double amount of product produced in the 5 hours reaction (Table 4, entries 7–9 vs entry 4), with an enantioselectivity constantly higher than 93%.

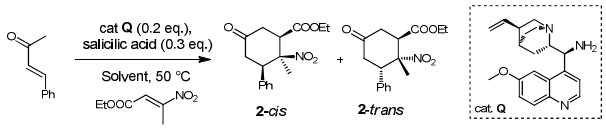
**Table 4** Recycle of the chiral catalyst in the addition of isobutyraldehyde to β–nitrostyrene in *DES* **B**.

| entry [a] | N. of cycles | *t* (h) | conv. [b] (%) | e.e. [c] (%) |
|---|---|---|---|---|
| 1 | 1 | 24 | >99 [d] | 95 |
| 2 | 2 | 24 | >99 [d] | 93 |
| 3 | 3 | 24 | 37 | 92 |
| 4 | 1 | 5 | 89 | 95 |
| 5 | 2 | 5 | 88 | 92 |
| 6 | 3 | 5 | 44 | 91 |
| 7 | 1 | 2 | 57 | 95 |
| 8 | 2 | 2 | 55 | 95 |
| 9 | 3 | 2 | 55 | 93 |
| 10 | 4 | 2 | 38 | 93 |
| 11 | 5 | 2 | 27 | 92 |

[a] Typical reaction conditions: aldehyde/nitrostyrene molar ratio 5/1 at 25 °C. [b] Conversions determined by $^1$H NMR. [c] Determined by HPLC on a chiral stationary phase. [d] Confirmed as isolated yields after chromatographic purification.

Finally, in order to demonstrate the general applicability of *DESs* as suitable solvents in organocatalytic reactions, we performed other two stereoselective transformations catalyzed by the same Cinchona catalyst **Q**, but through different activation mechanisms.

**Scheme 2.** Addition of *E*-3-methyl-3-nitroethylacrylate to benzalacetone.




The addition of *E*-nitroacrylates to α,β-unsaturated ketones, promoted by amino-Cinchona alkaloid derivatives in the presence of acidic additives,[20] was performed in *DESs* **A**–**C** (Scheme 2, Table 5). Also for this reaction, which is known to proceed through the formation of a dienamine intermediate, excellent enantioselections were observed in all the eutectic mixtures (Table 5). The highly functionalized cyclohexanones **2** were isolated in yields and diastereoselectivities (up to 76/24, Table 5, entry 7) comparable to those observed for the reaction in toluene (Table 5, entry 4). Enantioselectivities up to 97% for the *cis* adduct could be detected (Table 5, entry 1), thus demonstrating the possibility to successfully use *DESs* as reaction media also for multistep enantioselective catalytic reactions.[21]

**Table 5** Organocatalytic nitroacrylate addition to benzalacetone.

| entry [a] | solvent | *t* (h) | conv[b] (%) | *cis* / *trans* | e.e. [c] (%) *cis*/*trans* |
|---|---|---|---|---|---|
| 1 | *DES* **A** | 20 | 43 | 70/30 | 97/75 |
| 2 | *DES* **B** | 20 | 40 [d] | 75/25 | 93/n.d. |
| 3 | *DES* **C** | 20 | 37 | 70/30 | 91/n.d. |
| 4 | toluene | 20 | 57 | 66/34 | 92/68 |
| 5[e] | *DES* **C** | 20 | 60 [d] | 72/28 | 85/70 |
| 6[f] | *DES* **C** | 20 | - | - | - |
| 7[g] | *DES* **A** | 2 | 50 [d] | 76/24 | 94/72 |
| 8[h] | *DES* **A** | 20 | - | - | - |

[a] Typical reaction conditions: benzalacetone/nitroalkene molar ratio 2/1 at 50 °C. [b] Conversions determined by $^1$H NMR. [c] Determined by HPLC on a chiral stationary phase. [d] Confirmed as isolated yields after chromatographic purification. [e] Reaction run at 0 °C. [f] Reaction run without acid additive. [g] Reaction run with a 3/1 benzalacetone/nitroalkene molar ratio. [h] Reaction was performed without the catalyst.

Finally, the reaction between benzalacetone and 4-hydroxycumarin was investigated.[22]

**Scheme 3** Addition of 4-hydroxycoumarin to benzalacetone

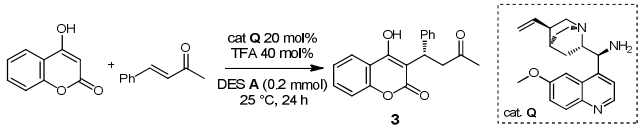



**Table 6** Organocatalytic 4-hydroxycoumarin addition to benzalacetone.

| entry [a] | solvent | yield [b] (%) | e.e. [c] (%) |
|---|---|---|---|
| 1 | *DES* **A** | 70 | 87 |
| 2[d] | *DES* **A** | 41 | 11 |
| 3 | *DES* **B** | 61 | 66 |
| 4 | *DES* **C** | 31 | 62 |
| 5[e] | *DES* **B** | - | - |

[a] Typical reaction conditions: benzalacetone/4-hydroxycoumarin molar ratio 2/1 at RT for 24 hours. [b] Confirmed as isolated yields after chromatographic purification. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction run at 50 °C. [e] Reaction was performed without the catalyst.

This organocatalyzed transformation, which involves the activation of the carbonyl substrate as iminium species, leads to the anticoagulant drug Warfarin 3 (Scheme 3). This reaction worked well in all the three tested *DESs*, but it afforded the best result in *DES* **A**. In fact, after 24 hours at room temperature, product **3** could be isolated in 70% yield and in 87% e.e. (for further details, see the Supporting Information).[23]

## Conclusions

In a world with dwindling petroleum resources, the ever-growing employment of unconventional, green solvents is taking the stage. In the present work, we report an alternative and almost totally unexplored approach to realize metal–free catalytic enantioselective transformations employing natural DESs as new potential, biorenewable, and environmentally-friendly reaction media. Three different eutectic mixtures were screened in this study as representative DES systems. By studying three model reactions catalysed by different mechanisms, excellent yields and stereoselectivities were obtained in the expected adducts. The recyclability of the chiral catalyst by a simple extraction protocol was also successfully accomplished especially in the addition reaction to β-nitrostyrene. There is no doubt that the positive features of such highly tunable and versatile *DESs* also in catalysis may contribute to pave the way towards new and unforeseen perspectives in the achievement of more industrially appealing organocatalytic synthetic methodologies.

## Experimental section

### General Methods

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 $F_{254}$ pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Melting point were determined with Branstead Electrothermal 9100 capillary melting point apparatus. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). $^{13}$C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). $^{19}$F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell 1 dm long. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Microwaves assisted reactions were performed in MW instrument CEM Discover S.

**Materials**

Commercial grade reagents and solvents were used without further purifications. Quinine (anhydrous, technical grade 98%), *trans*-β-nitrostyrene (technical grade 97%), trifluoroacetic acid (99%), were purchased from Sigma-Aldrich. Silica (Apex Prepsil Silica Media 8 μm) was purchased from Grace.

*Trans*-ethyl-3-nitrobut-2-enoate was prepared according to published procedures (see the Supporting Information). Isobutyraldehyde, was purified by distillation under atmospheric pressure and under nitrogen atmosphere before use. Cyclohexanone was purified by distillation under reduced pressure before use. 4-Hydroxycoumarin was recrystallized from EtOAc before use. Benzalacetone was recrystallized from hexane before use.

***DES* Preparation**

The employed Deep Eutectic Solvents (*DESs*)[9] [*DES* **A** choline chloride/urea 1/2; *DES* **B** choline chloride fructose/water 1/1/1; *DES* **C** choline chloride /glycerol 1/2)] were prepared by gentle heating under stirring at 70 °C for 15 min the corresponding individual components until a clear solution was obtained. Density of *DES* **B** was determined to be 1.21 g/mL. For this determination, the *DES* (1.21 g) was weighted directly in a 1 mL volumetric flask.

**General procedure for stereoselective organocatalyzed conjugate addition of isobutyraldehyde to nitrostyrene in *DESs***

Catalyst **Q** (17 mg, 0.053 mmol, 20 mol%) and benzoic acid (0.053 mmol 20 mol%; while investigating reaction conditions, it was observed that the desired product is formed even in the absence of the benzoic acid; see Table 2) were dissolved in the desired *DES* (353.3 mg – for optimization studies about reaction concentration in *DESs,* see Table 3) and kept under stirring. After 5 min, freshly distilled isobutyraldehyde (1.325 mmol, 5 equiv) was added and the reaction mixture was kept under stirring for further 5 min. Nitrostyrene (0.265 mmol, 1 equiv) was finally added and the reaction mixture was stirred for the reported time at the desired temperature (see Tables 2 and 3). After this period, the mixture was treated with water and the desired product was extracted with $Et_2O$. The collected organic phases were dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as the eluent. The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. When the reaction was subjected to microwave irradiation, it was run in proper MW vial.

**General procedure for stereoselective organocatalyzed conjugate addition of nitroacrylate to benzalacetone in *DESs***

Catalyst **Q** (20 mg, 0.063 mmol, 20 mol%), salicylic acid (0.094 mmol, 30 mol%) and *trans*-ethyl-3-nitrobut-2-enoate (0.314 mmol, 1 equiv) were dissolved in the desired *DES* (314 mg) and stirred for 10 minutes; benzalacetone (0.628 mmol, 2 equiv) was finally added. The reaction mixture was stirred at the desired temperature for the reported time (see Table 5) and after this period was treated with water. The desired product was extracted with $Et_2O$. The collected organic phases were dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as the eluent. The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. When the reaction was subjected to microwave irradiation, it was run in proper MW vial.

**General procedure for stereoselective organocatalyzed conjugate addition of 4-hydroxycoumarin to benzalacetone in *DESs***

Catalyst **Q** (10 mg 0.031 mmol, 20 mol%), benzalacetone (0.31 mmol, 2 equiv) 4-hydroxycoumarin (0.155 mmol, 1 equiv) and trifluoroacetic acid (0.062 mmol, 40 mol%) were dissolved in the desired *DES* (155 mg). The reaction mixture was kept under constant stirring for 24 h at room temperature. After this period, the reaction mixture was treated with water and the desired product was extracted with $Et_2O$. The collected organic phases were dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 70/30 as the eluent. The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

**General procedure for recycle experiments**

Catalyst **Q** (43 mg, 0.133 mmol, 20 mol%) and benzoic acid (0.133 mmol, 20 mol%) were dissolved in the desired *DES* (886.7 mg) and kept under stirring. After 5 min, freshly distilled isobutyraldehyde (3.325 mmol, 5 equiv) was added and the reaction mixture was kept under stirring for further 5 min. Nitrostyrene (0.665 mmol, 1 equiv) was finally added and the reaction mixture was stirred for the reported time at room temperature (see Table 4). After this period, hexane/$iPr_2O$ 7/3 (1 mL) was added and the mixture was stirred for further 2 min. The stirring was stopped to allow phase separation. The organic layer was removed through settling, and the solvent evaporated under reduced pressure. This procedure was repeated twice. The desired product, extracted through this procedure in the organic phase, was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as the eluent. The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. The catalytic system (i.e. catalyst and acidic co-catalyst) was regenerated by benzoic acid addition (20 mol%), in the *DES* phase, where catalyst **Q** was still dissolved. Thus, a further reaction was performed within this *DES*, where isobutyraldehyde (5 equiv) and *trans*-β-nitrostyrene (1 equiv) were added. This reaction mixture was subjected to the above described procedure and further reaction cycles were repeated within the same *DES* phase.

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