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Synthesis, characterization and organocatalytic activity of novel chiral (ammoniummethyl)pyrrolidine-derived deep eutectic solvents

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ABSTRACT

The present investigation centers on synthesizing, characterizing, and exploring the organocatalytic potential of a novel series of chiral deep eutectic solvents based on chiral (ammoniummethyl)pyrrolidine derivatives **1**–**3**. Using the theoretical solid–liquid equilibrium curves, we have been able to identify three chiral deep eutectic solvents (CDESs) that have been thermally and structurally characterized and used as reaction medium in the conjugate addition of cyclohexanone to *trans*-β-nitrostyrene. Among these chiral deep eutectic solvents, the mixture **2**/EG: 1/3, where a chiral choline bromide surrogate is employed as the HBA, has shown good organocatalytic activity and recyclability in the studied model organocatalyzed process. Notably, this CDES exhibited higher activity and selectivity compared to organocatalyst **2**, and at the same level as that exhibited by the **2**/TFA catalyst under neat conditions.

1. Introduction

Over the past decades, scientists have faced a challenge with the environmental implications of chemistry, particularly concerning the use of common solvents in chemical reactions. These volatile organic compounds (VOCs) present certain disadvantages, such as their high toxicity, volatility, non-biodegradability, and non-recyclability, creating a large amount of waste matter. Recently, Deep Eutectic Solvents (DESs) [1–3] and Ionic Liquids (ILs) [4] have been developed to help combat these drawbacks due to their sustainability advantages. DESs are formed by combining two or more Hydrogen Bond Acceptors (HBA) and Hydrogen Bond Donors (HBD): the weak interactions occurring between the different species (HBD-HBA) as well as the ones occurring between the same species (HBD-HBD and HBA-HBA) lead to an impossible regular crystal lattice formation, therefore to liquid systems. Additionally, this is not the sole requirement for a eutectic mixture to attain classification as a DES; it must also exhibit a lower eutectic point than of the ideal mixture [5]. Not only are DESs more sustainable, but they also present other advantages such as their recyclability, non-flammability, and low ecological footprint. Common reactions previously carried out in standard VOCs have been studied in various DESs with great success, including asymmetric organocatalytic reactions [6]. Conversely, not all aspects of conducting organocatalytic reactions in DESs can be considered advantageous; there are also notable disadvantages to consider. For instance, the necessity to replenish the reaction with organocatalyst during the recycling process, as the organocatalyst may also be extracted along with the product, resulting in a subsequent reduction in its activity [7,8].

The role that DESs play in organic reactions can be classified as "active" or "innocent", depending on whether they participate in the chemical transformation (former) or solely act as reaction media (latter). Accordingly, a specific subcategory of active DESs has been developed, known as Chiral Deep Eutectic Solvents (CDESs), where not only does the DES act as a reaction medium but also as an internal chiral organocatalyst, allowing reactions to be carried out in an enantio- and diastereoselective manner without the use of additional organocatalyst, therefore reducing the cost and increasing atom efficiency of the reaction. In this context, Tiecco et al. utilized both enantiomers of camphorsulfonic acid as hydrogen bond donors in conjunction with ammonium methanesulfonates as hydrogen bond acceptors to produce chiral liquids at room temperature. Despite displaying limited enantioselectivity, these chiral liquids functioned effectively as organocatalysts,

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eco-friendly solvents, and acid catalysts in the asymmetric Friedel-Crafts addition of indole to chalcone [9]. More recently, our group showcased the potential of L-Proline [10] and L-Prolinol [11] when forming room temperature chiral mixtures, serving as environmentally friendly solvents in the enantioselective conjugate addition of ketones to nitroolefins through enamine activation.

In this study, while preserving the chiral structure of L-Proline and thereby its inherent enamine activity, we present the synthesis of chiral ammonium salts **1**–**3** (Fig. 1) that mimic the widely recognized HBA choline chloride [12] and their use as HBAs in creating novel chiral eutectic liquids which have been characterized and employed in the asymmetric conjugate addition of ketones to nitroolefins.

2. Experimental

2.1. General

Unless otherwise noted, all commercial reagents and solvents were employed without further purification. Reactions under Argon atmosphere were carried out in oven-dried glassware sealed with a rubber septum. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra for catalytic experiments were recorded on a Bruker AC-300, employing $CDCl_3$ as solvent and TMS (0.003 %) as reference. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm values relative to TMS. Coupling constants (*J*) are reported in Hz. Chiral HPLC analyses were performed on an Agilent 1100 Series (Quat Pump G1311A, DAD G1315B detector and automatic injector) equipped with a Chiralpack AS-H chiral column using mixtures of hexane/isopropanol as mobile phase, at 25 °C. Differential Scanning Calorimetry (DSC) studies were carried out on a DSC heat Flow equipment with MDSC temperature from TA Instruments, model Q250. Viscosity analyses were performed on a Brookfield high torque viscosimeter CAP 1000+, the measurements were performed at 50 °C, 750 rpm with a 10 s hold time and 25 s run time using spindle 5.

2.2. Characterization data of novel ammoniummethylpyrrolidine bromides

Full detailed synthetic procedures of *ammoniummethylpyrrolidine bromides **1**–**3*** are described in the Supporting Information.

(S)-N,N,N-trimethyl-1-(pyrrolidin-2-yl)methanaminium bromide (**1**). ^{1}H NMR (300 MHz, CD_3OD) δ_H 3.84 (td, *J*=7.8, 4.2 Hz, 1H), 3.67 – 3.51 (m, 2H), 3.28 (s, 9H), 3.18 – 3.00 (m, 2H), 2.23 (ddt, *J*=12.5, 7.6, 3.9 Hz, 1H), 2.02 – 1.71 (m, 2H), 1.57 (dq, *J*=12.6, 8.6 Hz, 1H).

(S)-2-Hydroxy-N,N-dimethyl-N-(pyrrolidin-2-ylmethyl)ethan-1-ammonium bromide (**2**). ^{1}H NMR (400 MHz, CD_3OD) δ_H: 4.16 – 4.03 (m, 2H), 3.82 – 3.44 (m, 5H), 3.32 (d, *J*=3.3 Hz, 6H), 3.10 – 2.89 (m, 2H), 2.18 (m, *J*=12.2, 7.8, 4.0 Hz, 1H), 1.83 (m, 2H), 1.55 – 1.41 (m, 1H) ppm.

*(S)-(1-Pyrrolidin-2-ylmethyl)quinuclidine-1-ium bromide (**3**).* ^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.37–1.5 (m, 1H), 1.7–2.19 (m, 11*H*), 2.96–3.01 (m, 2H), 3.19–3.27 (m, 1H), 3.33–3.37 (m, 1H), 3.48–3.73 (m, 7H) ppm.

2.3. Solid-liquid phase curves determination

The DESs were characterized in terms of comparison between the theoretical solid–liquid phase diagrams with the experimental melting points at different molar ratios [5]. The melting points were measured with a thermometer via immersion of the samples in a Dewar with liquid nitrogen. The melting points were taken in triplicate to avoid kinetic effect on the melting of the mixtures.

The solid–liquid theoretical curves were determined by using the equation (1) that represents the solid–liquid equilibrium curve:

$$ln(\chi_i \hat{A} \cdot \gamma_i) = \frac{\Delta_m h_i}{R} \hat{A} \cdot \left(\frac{1}{T_{m,i}} - \frac{1}{T}\right) + \frac{\Delta_m Cp_i}{R} \hat{A} \cdot \left(\frac{T_{m,i}}{T} - ln\frac{T_{m,i}}{T} - 1\right) \quad (1)$$

where χ_i is the mole fraction of component i, γ_i is its activity coefficient in the liquid phase, $\triangle_m h_i$ and $T_{m,i}$ are its melting enthalpy and temperature, respectively, $\triangle_m Cp_i$ is its heat capacity change upon melting, R is the ideal gas constant, and T is the absolute temperature of the system. This equation can be simplified by considering the heat capacity change upon the melting of a substance as negligible, therefore equation (2) was used:

$$ln(\chi_i \hat{A} \cdot \gamma_i) = \frac{\Delta_m h_i}{R} \hat{A} \cdot \left(\frac{1}{T_{m,i}} - \frac{1}{T}\right) \quad (2)$$

The theoretical melting temperatures were determined from the theoretical curves by considering the activity coefficients $\gamma_i = 1$. The eutectic points were determined as the minimum in the experimental curves, and they were compared to the theoretical ones.

The experimental γ_i values were determined via equation (3) by using the experimentally observed melting temperatures:

$$\gamma_i = \frac{\exp\left[\frac{\Delta_m h_i}{R}\left(\frac{1}{T_{m,i}} - \frac{1}{T}\right)\right]}{\chi_i} \quad (3)$$

2.4. General procedure for the Michael addition reaction and recycling

Trans-β-nitrostyrene (14.9 g, 0.10 mmol, 1 equiv.) and cyclohexanone (19.6 g, 0.20 mmol, 2 equiv.) were added to the corresponding CDES (50 mg) and stirred at room temperature (25 °C) under Ar overnight. After this period, ethyl acetate (1 mL) was added, and the mixture was stirred for 1 min. Then, the organic phase was collected, and this procedure was repeated twice. The combined organic phases were evaporated under reduced pressure to give the crude reaction product, which was analyzed by ^{1}H NMR and chiral HPLC for reaction conversion, *dr* and *ee* determination.

Then, the next reaction cycle was performed with the remaining CDES after drying it under light vacuum, by adding fresh *trans*-β-nitrostyrene and cyclohexanone. This reaction mixture was subjected again to the above-described procedure and further reaction cycles were repeated using the recycled deep eutectic solvent phase in each case.

3. Results and discussion

3.1. Preparation of (ammoniummethyl)pyrrolidine bromides

Initially, we prepared chiral ammonium bromides **1**–**3**, which are required as HBAs for synthesizing the novel chiral liquids. As depicted in Scheme 1, the first step was the conversion of L-Proline into *N*-Cbz-2-

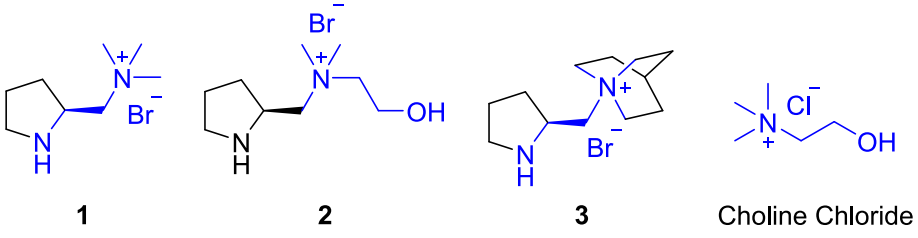
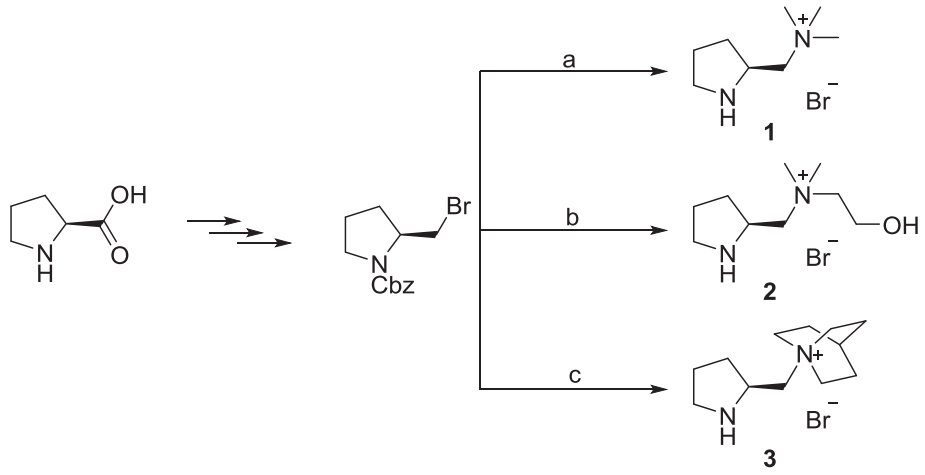


Fig. 1. Structures of L-Proline derived chiral ammonium salts **1**–**3** and Choline Chloride.



Scheme 1. Synthesis of pyrrolidine-derived chiral ammonium bromides. (a) 1. NMe_3 (1 M soln. in MeCN), 55 °C, 3 d. 2. H_2 (1 atm), Pd/C (10 % w/w), MeOH, RT, 24 h; (b) 1. $HNMe_2$ (40 % aqueous sol.), MeOH, 55 °C, 16 h. 2. $BrCH_2CH_2OH$, MeCN, 60 °C. 3. H_2 (1 atm), Pd/C (10 % w/w), MeOH, RT, 24 h; (c) 1. Quinuclidine, MeCN, 80 °C, 48 h. 2. H_2 (1 atm), Pd/C, MeOH, RT, 48 h.

(bromomethyl)pyrrolidine using the protocol reported in the literature [13,14]. From here on out, the conditions changed for synthesizing each chiral ammonium derivative. Thus, for the preparation of ammonium salts **1** and **3** [15], a nucleophilic substitution with trimethylamine or quinuclidine followed by hydrogenation afforded the expected salts in 47 % and 36 % overall yields, respectively (Scheme 1a and 1c). On the other hand, compound **2** was prepared from the corresponding bromide by two consecutive nucleophilic substitutions, first with dimethylamine as nucleophile and secondly with 2-bromoethanol as electrophile, followed by a deprotective hydrogenolysis, yielding salt **2** in a 42 % overall yield (Scheme 1b) [13].

3.2. Synthesis and characterization of novel (ammoniummethyl) pyrrolidine chiral eutectic mixtures

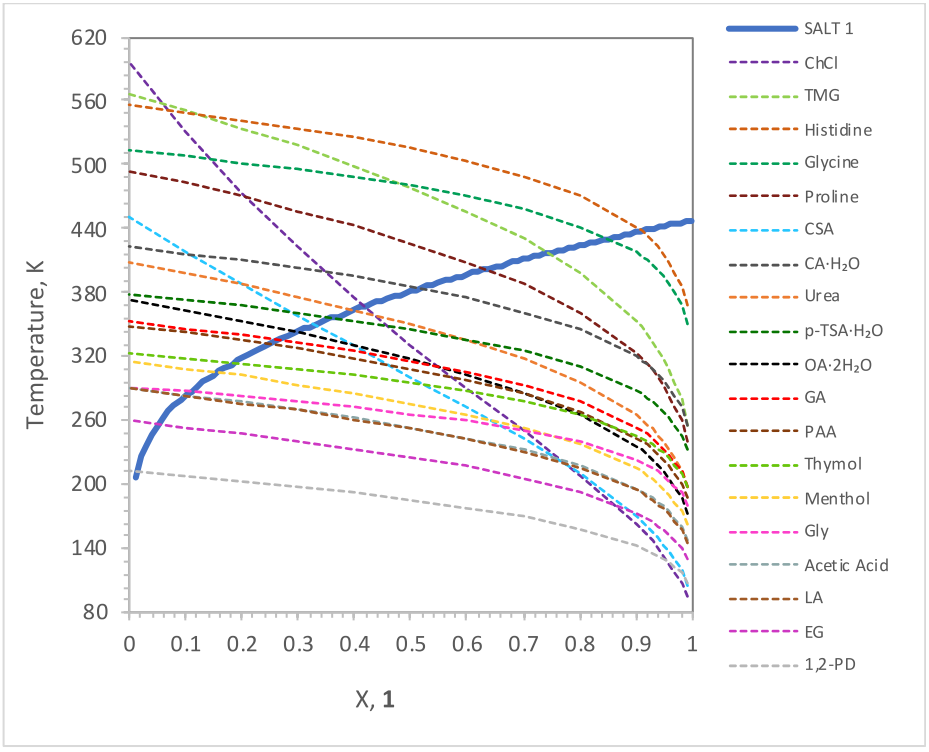
Once the chiral ammonium bromides **1**–**3** were obtained, we tested the possibility of forming CDESs by mixing them with different H-bond-capable molecules. We considered that when defining a liquid mixture as a DES, it is mandatory to compare the theoretical solid–liquid phase diagrams with the experimental melting points observed at different molar fractions of the components. A shift, specifically, a deepening in the experimental melting point of the eutectic mixture compared to the theoretical one, is proof of the non-ideality of the mixture, confirming the formation of a DES system [5,16]. However, if the theoretical and experimental curves are perfectly aligned, this indicates that the interactions occurring between the different species (HBA-HBD) have the same energies of the ones occurring between the same species (HBA-HBA and HBD-HBD), therefore this leads to ideal mixtures [17]. Peculiar is the case when one of the two components is already a liquid, because a solution of one molecule into the other can occur, and this can mistakenly consider a DESs rather than a solution, so it is mandatory a comparison of the theoretical melting curves with the experimental ones. Then, after experimentally determine the melting points of the three chiral ammonium bromides and the associated enthalpies [18], we initially represented the theoretical melting curves of the ammonium salts **1**–**3** with the ones of commonly reported H-bond-capable DES-forming molecules, such as choline chloride, urea, ethylene glycol, glycolic acid, and citric acid, amongst others (Fig. 2) [19]. Through this approach, we could filter out molecules from the testing set that lacked a theoretical crossing point, making them ineligible for comparison with the experimental data.

Due to their slopes, mainly determined by their fusion enthalpy values (see equations 1–3 in the Supporting Information), the theoretical melting curves of trimethylammonium-based compound **1** and cholinium-based compound **2** exhibited cross points with nearly all the theoretical curves of the analyzed HBD molecules. The sole exceptions were the L-Pro-cholinium salt **2** with glycine and with histidine, that did not exhibit any clearly detectable cross points with **2**. The quinuclidinium salt **3** curve showed crossing points with the theoretical curves of citric acid, camphorsulphonic acid, choline chloride, proline, TMG, and histidine. The lower fusion enthalpy of this molecule is the primary factor contributing to this lower slope, as indicated by the theoretical melting curve equation (see supporting information).

Therefore, we selectively opted for molecules with clearly defined crossing points to create novel chiral eutectic liquids, a strategy aimed at efficiency in both time and material utilization. Experimental melting points were initially determined visually by cooling 500 mg of the corresponding chiral mixture to −90 °C in an Eppendorf vial equipped with an internal thermometer, followed by allowing the mixture to reach room temperature until a liquid was observed, noting the thermometer temperature as the experimental melting point (Table 1). The comparison between the theoretical melting point curves and the experimental points revealed the identity of the formed liquids as DESs. This character is evident from the discrepancy between the eutectic points and the crossing points of the theoretical curves, along with a notable deepening of the values (Table 1). This behavior is observed when the eutectic profiles of the chiral mixtures are represented, as shown in Fig. 3 for the representative mixtures **1**/Gly: 1/2, **2**/EG: 1/3 and **3**/Urea: 1/2, which presented low experimental eutectic points (see Supporting Information for additional graphs). Moreover, all the activity coefficients, which were determined using the melting point values obtained via thermometer measures at the eutectic points, are lower than 1 indicating the non-ideality and the DES identity of the mixtures.

As it emerged from the melting point measurement data, all the studied CDESs showed a significant melting point depression compared to the starting materials and the crossing points of the theoretical melting curves (see Fig. 3 and Supporting Information for all the additional curves). All the CDESs showed very low melting points, spanning from −15 °C to −71 °C except for the mixture **3**/TMG: 1/5, which showed a value of 9 °C. The very low melting point values generally observed represent an advantage for their use in asymmetric synthesis as green organocatalytic media.

Subsequently, we performed a further thermal characterization of our novel chiral liquids using differential scanning calorimetry (DSC, non-hermetic vessel conditions, six heating cycles: −120 °C/120 °C/-120 °C/120 °C, 5 °C/min) using the chiral mixture **3**/Urea: 1/2. In these studies (Fig. 4 top), we noted a fluctuation in the experimental eutectic point throughout the cycles, ultimately stabilizing at 17.02 °C (dark blue



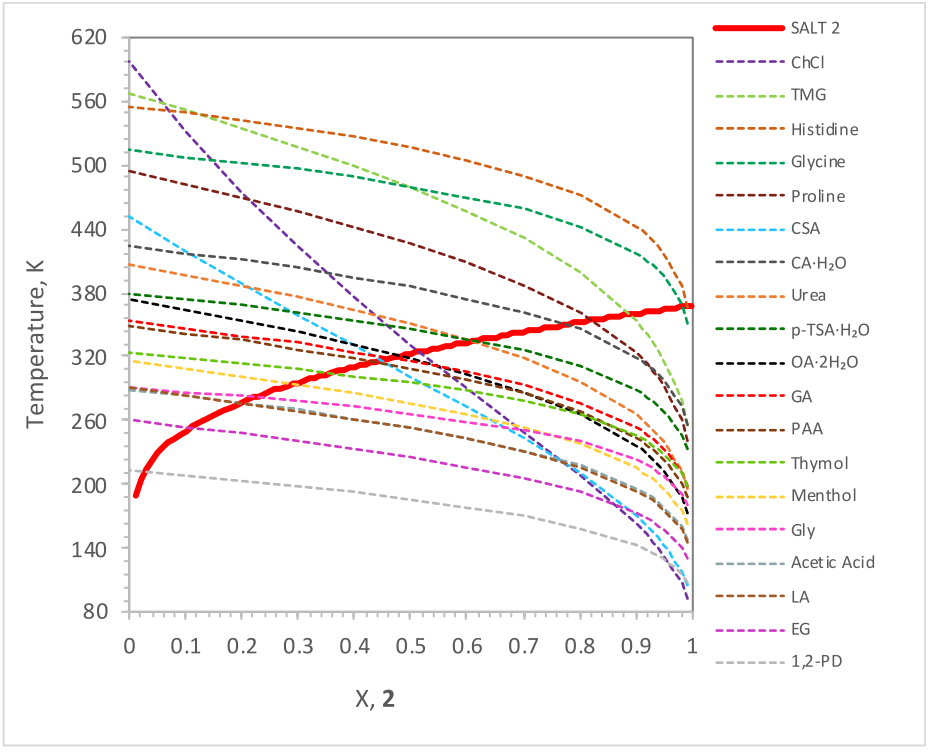


Fig. 2. Theoretical melting curves of the novel synthetic ammonium salts **1**–**3** (non-dashed lines) and of common DES-forming molecules (colored dashed lines). Abbreviations- CA: citric acid; ChCl: choline chloride; CSA: camphorsulphonic acid; EG: ethylene glycol; GA: glycolic acid; LA: lactic acid; OA: oxalic acid; PAA: phenylacetic acid; TMG: trimethylglycine; *p*-TSA: *p*-toluenesulfonic acid; 1,2-PD: 1,2-propanediol.

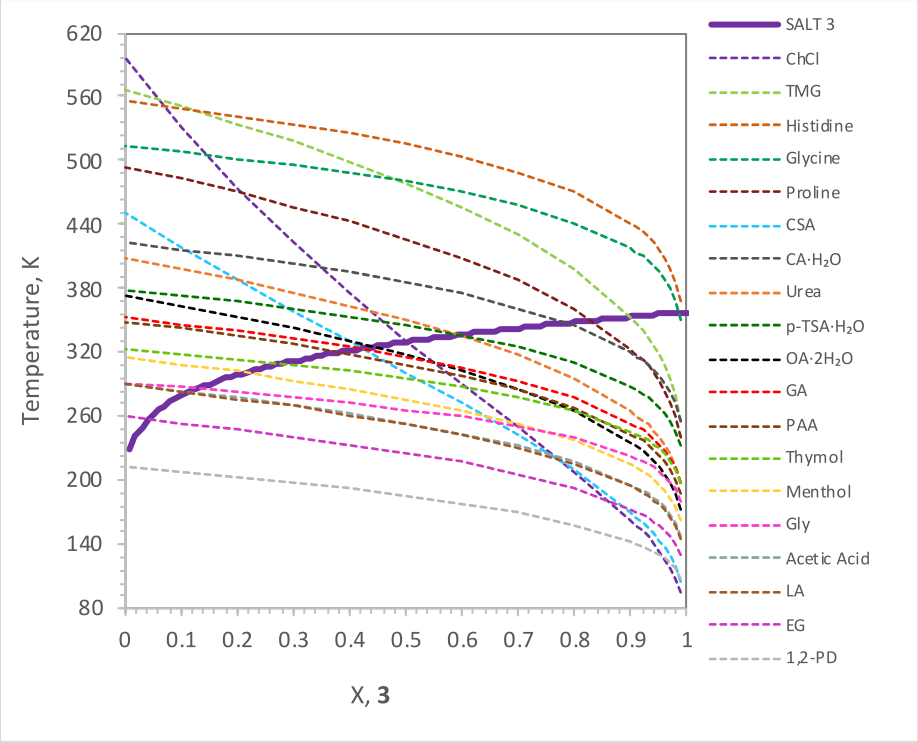


Fig. 2. (*continued*).

Table 1
Theoretical and experimental data for the formation of chiral mixtures.

Mixture	Theoretical curves crossing point[a] **Salt**/Counterpart	Theoretical crossing point temperature (°C)	Experimental Eutectic Point[a] **Salt**/Counterpart	Experimental eutectic point melting point (°C)
1/Glycerol	1/5	7	1/2	−51
1/PAA	1/2	47	1/3	−19
2/Urea	1/2	47	1/1	−17
2/EG	1/5	−23	1/3	−75
2/GA	5/4	37	1/3	−25
2/Glycerol	2/5	2	1/4	−57
2/TMG	10/1	57	11/1	−17
2/ChCl	5/4	37	4/1	−33
2/CA·H_2O	11/1	62	7/1	−10
2/ OA·$2H_2O$	5/4	37	5/1	−28
3/Urea	1/99	125	1/2	−15
3/TMG	3/2	187	5/1	9

[a] Mol ratio. Abbreviations: PAA: Phenylacetic acid; EG: Ethylene glycol; GA: Glycolic acid; TMG:Trimethylglycine; ChCl: Choline chloride; CA: Citric acid; OA: Oxalic acid.

curve) probably due to the presence of small amounts of water in the freshly prepared chiral mixture which were gradually evaporated. The ternary nature of the chiral mixture was corroborated by running the same DSC experiment under hermetic conditions where no variations of the eutectic points were observed from the second heating cycle, the eutectic point being established at −37.04 °C (Fig. 4 bottom). This value, while still being closer to the experimentally observed in our initial studies (−15 °C), differed probably due to several experimental variables, such as the amount of sample used in the thermal analyses.

The reason why a higher mass shows a higher eutectic temperature lies in the fact that heat transfer from the furnace or heat source to the sample is not instantaneous, and the sample has a finite thermal conductivity; therefore, there exists a thermal lag, which is proportional to the heating rate, sample and container mass, sample and container-specific heat capacity, and thermal resistance between the sensor and the sample [20]. This can cause the previously established melting points to differ from the DSC established values. In addition, this study was carried out with the other two combinations, **1**/Gly: 1/2 and **2**/EG: 1/3, observing similar behaviors between hermetically/non-hermetically sealed vessels and comparing them to the previously established temperatures (see Supporting Information).

DESs are mixtures that present a melting-crystallization behavior, which can be observed in DSC experiments by the presence of endothermic (melting)-exothermic (crystallization) peaks, revealing the formation of a highly ordered structure. In the case of LTTMs, only the transition from a solid glass to a liquid can be demonstrated, most often by the presence of a step in the DSC baseline due to the change of heat capacity observed when a solid glass transforms into a liquid, often referred to as the glass transition temperature (Tg). The fact that the mixtures in this study do not present a melting peak but only a glass transition does not necessarily mean that they are not DESs, but that they have been incapable of carrying out an arrangement in such a manner that they crystallize in the heating/cooling conditions tested in this study, possibly due to their rotation flexibility or even due to steric

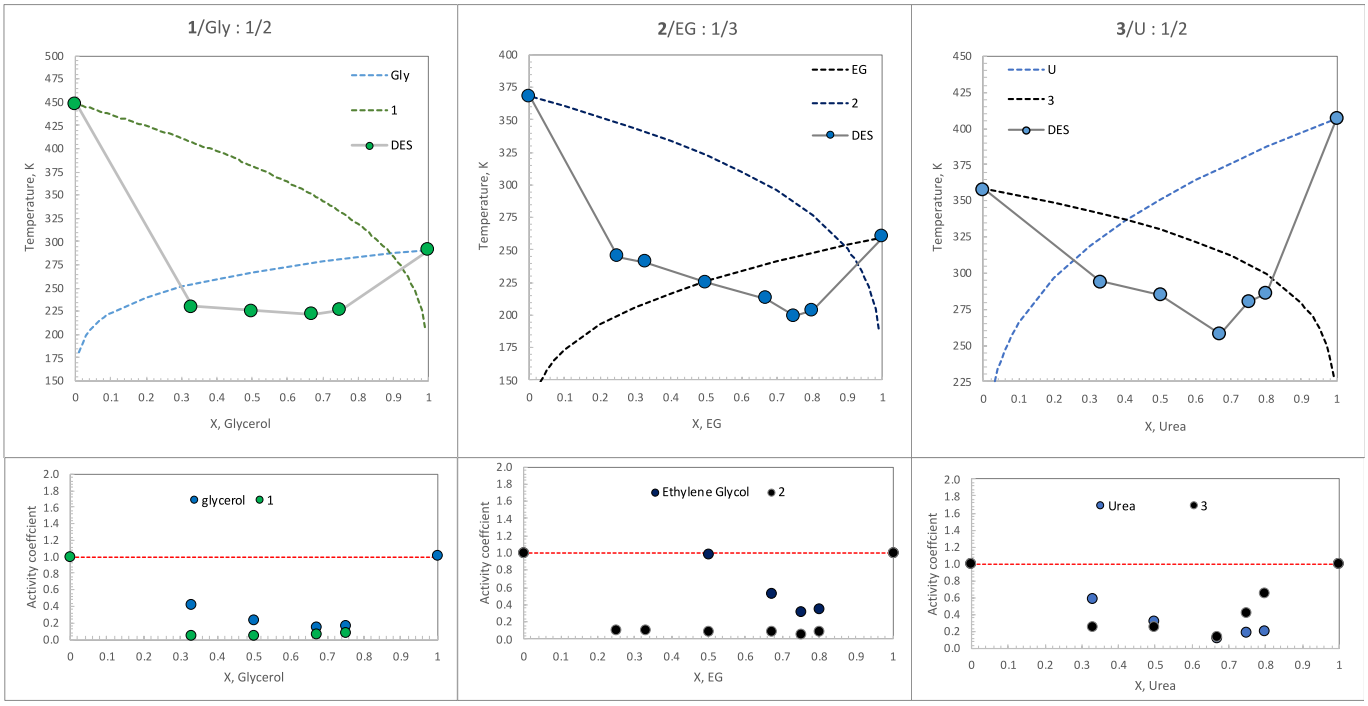


Fig. 3. TOP: Comparison of the theoretical melting curves of the components (dashed lines) with the experimental melting points (points) of **1**/Gly: 1/2, **2**/EG: 1/3 and **3**/urea: 1/2 CDESs; BOTTOM: Activity coefficients of the CDESs components. Experimental melting points determined with a thermometer after freezing the mixture in an Eppendorf vial with a nitrogen bath. Activity coefficients related to them.

hindrance. In fact, glass transitions of these mixtures are often accompanied by an enthalpic relaxation (an endothermic phenomenon in the DSC signal when the sample is heated through the Tg), which is a sign that the molecules were able to find energetically favorable orientations being closer to equilibrium [21]. Also, the activity coefficients calculated with the thermometer measures in Fig. 3 can be related to these glass transitions observed rather than to real melting phenomena, but we used them just do demonstrate the non-ideality of these mixtures as the values are under 1, even if they could be inaccurate.

^{1}H- and ^{13}C NMR studies were also carried out over the mixtures **1**/Gly: 1/2, **2**/EG: 1/3 and **3**/Urea: 1/2 using DMSO-d_6 and CD_3CN (Fig. 5 and Table 2). Thus, for the chiral mixture **1**/Gly: 1/2, the study was carried out in CD_3CN (a polar but aprotic solvent suitable for preserving H-bonds interactions) and the most significant shifts are that of 4 T and 6 T of **1** shifting upfield (Table 2, entries 1 and 3), signals 1T and 2G shifting downfield (Table 2, entries 2 and 4) and the complete disappearance of the OH signals of the glycerol, which implies interactions of the OH's with the NH group and with the ammonium salt moiety.

Similarly, for the mixture of **2**/EG: 1/3, the most significant shifts are those of 6C (Table 2, entry 6) in **2** and a very intense shift upfield of 2E (Table 2, entry 7), which implies interactions of the OH's ammonium salt moiety in a similar manner to the previous example. Lastly, the mixture **3**/Urea: 1/2 was analyzed in deuterated DMSO due to solubility issues with CD_3CN. The most significant shifts are those of 1Q, 4Q and 5Q in ^{1}H NMR (Table 2, entries 9–11). Signals 5Q of **3** shifted downfield, and urea presented significant shifting upfield in ^{13}C NMR (Table 2, entries 14 and 15), which implies interactions of the carbonyl moiety and the NH group of the ammonium salt **3**.

3.3. Organocatalytic study of the prepared novel chiral eutectic mixtures

Once the novel chiral mixtures were prepared, identified as CDESs and characterized, they were employed as a reaction medium in the model asymmetric conjugate addition of cyclohexanone to *trans*-β-nitrostyrene at 30 °C using a 5/1 chiral solvent/limiting reagent mass ratio (Table 3).

When using the CDES **1**/Gly: 1/2 (48 ± 21 cP at 50 °C), a conversion of just 17 % was obtained, nevertheless presenting a significant stereoselective induction, achieving 82/18 *dr* and 80 % *ee* for the major *syn* diastereomer (Table 3, entry 1), significantly improving the results obtained when employing **1** (15 mol %) as organocatalyst under neat conditions (entry 2) where a negligible conversion was observed. When the conjugate addition reaction was carried out with **1** as chiral organocatalyst (15 mol %) under neat conditions in the presence of 5 mol % of trifluoroacetic acid (TFA) as co-catalyst, the catalytic activity of **1** was improved although the selectivity of the process, especially for the major diastereomer, was not superior to that obtained with the CDES. (Table 3, entry 3). This result points to the plausible role played by the CDES in the reaction, promoting a faster imine-enamine equilibrium and stabilizing the intermediate nitronate, avoiding the formation of byproducts [22].

The CDES **2**/EG: 1/3 (135 ± 10 cP at 50 °C) gave excellent conversion, with moderate to good diastereo- and enantioselectivities (Table 3, entry 4), showing a dramatic improvement again compared to the lack of conversion when using only **2** as chiral organocatalyst (Table 3, entry 5). When the reaction was carried out employing the catalytic system **2** (15 mol %)/TFA (5 mol %), the result in terms of conversion was comparable to that obtained with the CDES, although the selectivity of the reaction was significantly improved, especially for the enantioselectivity of the major *syn* isomer (Table 3, entry 6). Finally, the **3**/Urea: 1/2 CDES (819 ± 18 cP at 50 °C) gave a quantitative conversion in the model reaction, with a 34 % *ee* for the major diastereomer (Table 3, entry 7).

Finally, the recyclability of chiral mixtures **1**/Gly: 1/2, **2**/EG: 1/3 and **3**/Urea: 1/2 was studied in the model conjugate addition reaction. For this purpose, we initially studied the solubility of the three CDES in cyclohexane, cyclopentyl methyl ether and *tert*-butyl methyl ether and it was observed by ^{1}H NMR analysis that only cyclohexane left the chiral mixtures intact after stirring for 1 min in this solvent (see SI), whilst the others dissolved one of both components of the CDES. Therefore, cyclohexane was the chosen solvent for the recyclability study. As depicted in Table 4, the second reaction cycle when using the chiral

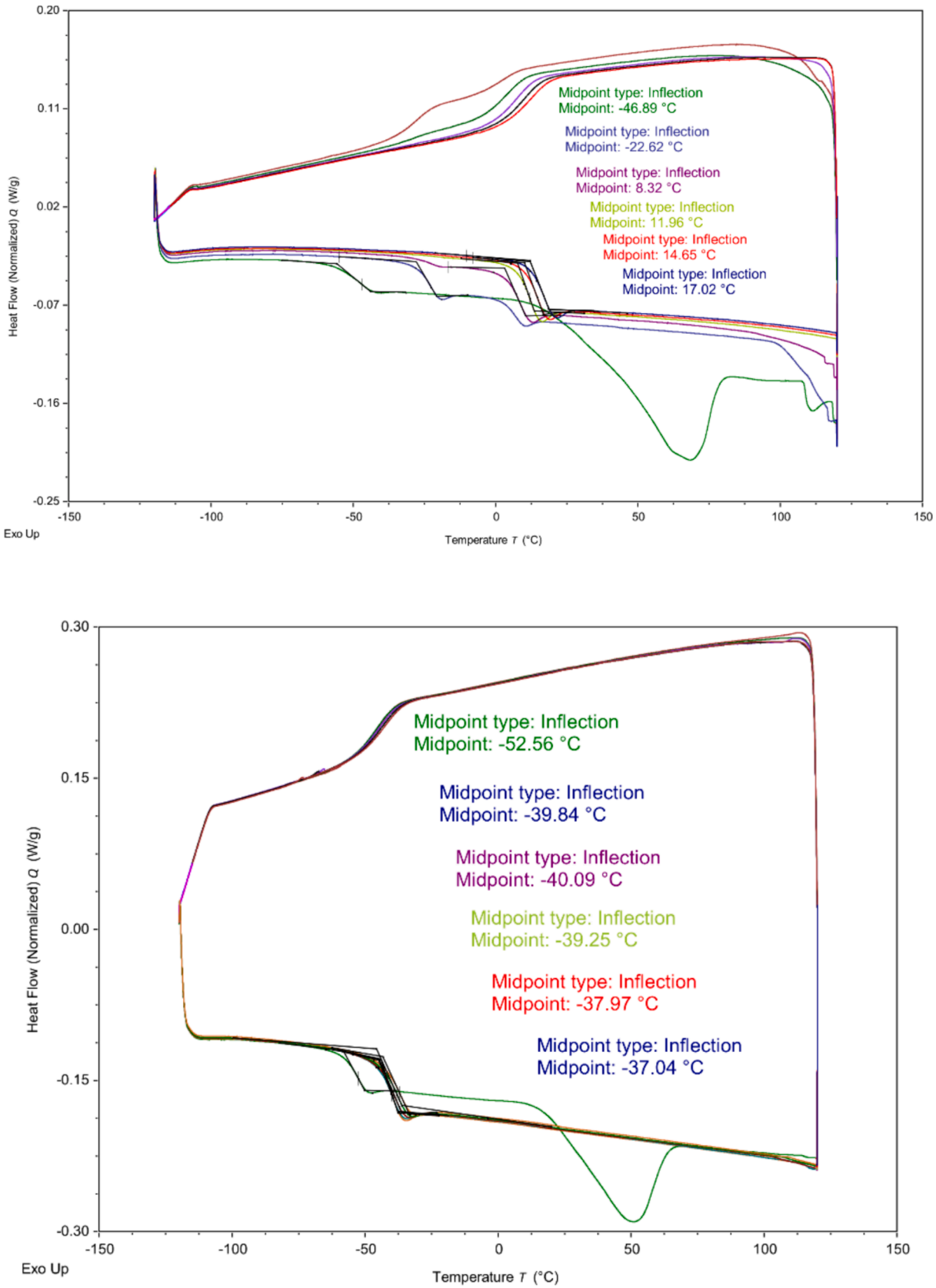


Fig. 4. DSC analysis of **3**/Urea: 1/2, six cycles, −120 °C/120 °C/-120 °C/120 °C, speed 5 °C/min. Top) non-hermetically sealed vessel. Bottom) Hermetically sealed vessel.

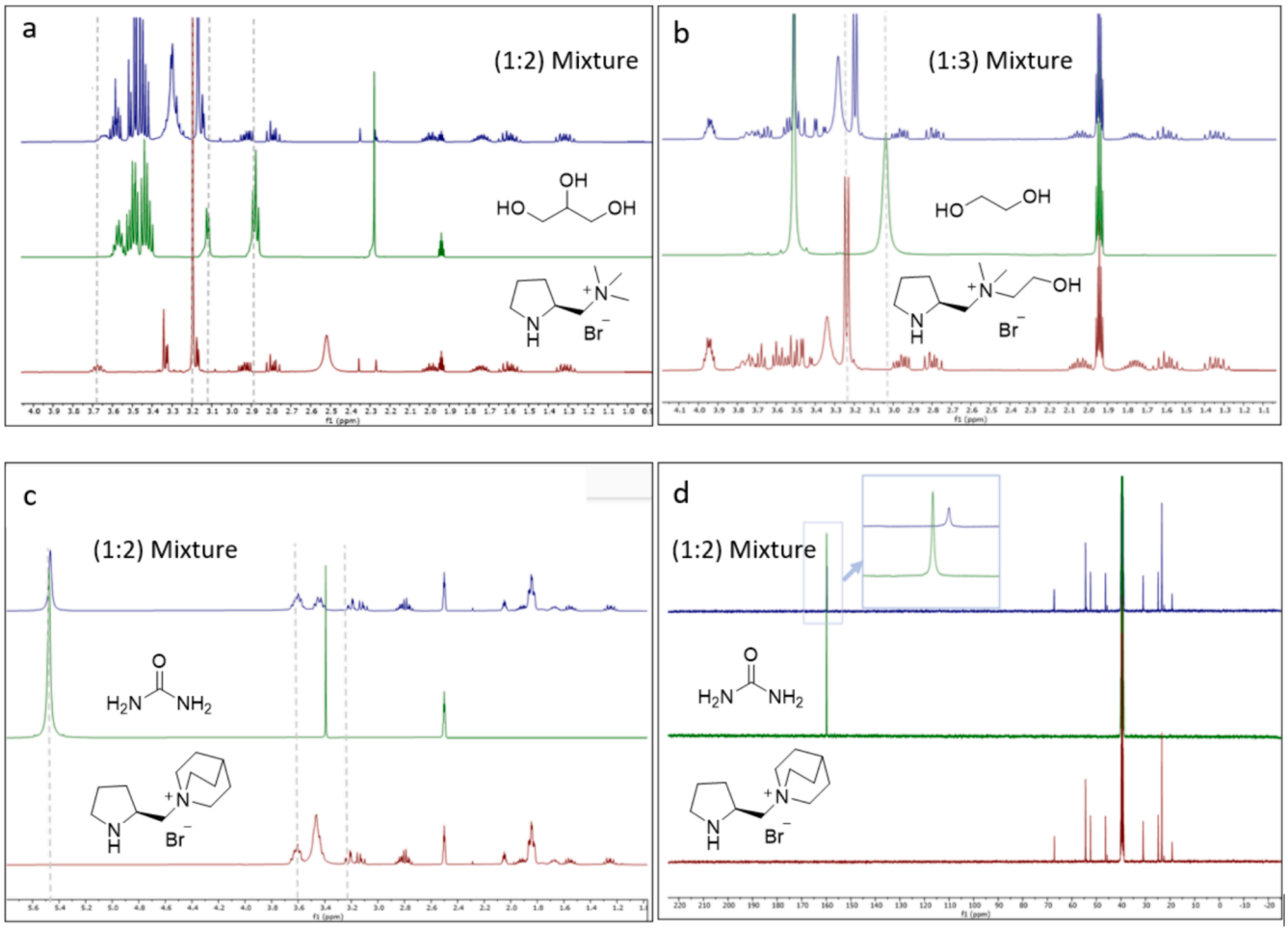
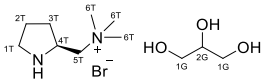
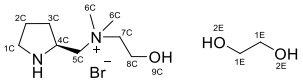
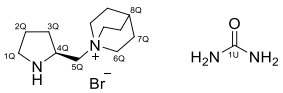


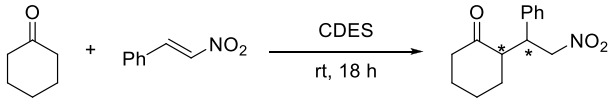
Fig. 5. NMR analysis of the corresponding mixtures. a) ^{1}H NMR spectra of **1** (red), Glycerol (green), **1**/Gly: 1/2 (blue) (400 MHz, CD_3CN); b) ^{1}H NMR spectra of **2** (red), EG (green), **2**/EG: 1/3 (blue) (300 MHz, CD_3CN); c) ^{1}H NMR spectra of **3** (red), urea (green), **3**/Urea: 1/2 (blue) (400 MHz, DMSO-d_6); d) ^{13}C NMR spectra of **3** (red), urea (green), **3**/Urea: 1/2 (blue) (101 MHz, DMSO-d_6).

Table 2
NMR coordination shifts (Δδ = Pure compound – Mixture).

Entry	Nucleus	CDES	Position	Δδ (ppm)
1	^{1}H		4 T	+0.04
2	^{1}H		1′T	−0.02
3	^{1}H		6 T	+0.03
4	^{1}H		2G	−0.02
5	^{1}H		6C	−0.05
6	^{1}H		2E	+0.34
7	^{1}H		1E	+0.01
8	^{1}H		5Q	+0.02
9	^{1}H		4Q	+0.03
10	^{1}H		1Q	+0.03
11	^{1}H		6Q	+0.01
12	^{1}H		NH_2	+0.01
13	^{13}C		5Q	−0.06
14	^{13}C		1U	+0.18

mixture **1**/Gly: 1/2 proceeded successfully but without any kind of stereoselectivity (Table 4, entry 2). On the other hand, the mixture **2**/EG: 1/3 could be recycled up to four times, which increased stereoselectivity (Table 4, entries 3–6). However, this came with a significant decrease in conversion, likely due to stronger interactions between the two DES components, appearing the chiral organocatalyst to be more tightly involved in the CDES formation with each reaction cycle [23].

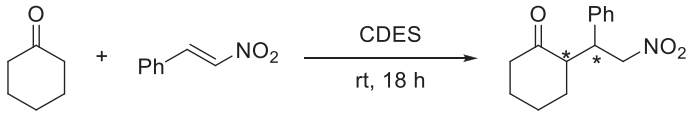
Table 3
Asymmetric conjugate addition of cyclohexanone to *trans*-β-nitrostyrene employing chiral eutectic mixtures.[a]



Entry	Chiral promoter	Time (h)	Conversion (%)[b]	*dr* (*syn*/*anti*)[c]	*ee* (*syn*/*anti*)[c]
1	**1**/Gly: 1/2	24	17	82/18	80/48
2	**1** (15 mol %)[d]	96	<5	Nd	Nd
3	**1**/TFA (5 mol %)[d]	96	48	63/37	56/68
4	**2**/EG: 1/3	24	>99	60/40	61/>99
5	**2** (15 mol %)[d]	96	<5	Nd	Nd
6	**2**/TFA (5 mol %)[d]	96	95	69/31	75/60
7	**3**/Urea: 1/2	24	>99	80/20	34/>99

[a] Reaction conditions: cyclohexanone (0.2 mmol), beta-nitrostyrene (0.1 mmol), chiral liquid/limiting reagent mass ratio of 5/1, rt, 18 h.
[b] Determined by ^{1}H-NMR analysis of the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture.
[d] Reaction carried out under neat conditions. Abbreviations: Gly (glycerol), TFA (Trifluoroacetic acid).

Table 4
Recyclability studies in the asymmetric conjugate addition of cyclohexanone to *trans*-β-nitrostyrene employing CDESs as reaction media.[a]



Entry	CDES	Cycle	Conversion (%)[b]	*dr* (*syn*/*anti*)[c]	*ee* (*syn*/*anti*)[c]
1	**1**/Gly:1/2	1	17	82/18	80/48
2	**1**/Gly:1/2	2	60	rac	rac
3	**2**/EG: 1/3	1	>99	60/40	61/>99
4	**2**/EG: 1/3	2	>99	65/35	65/8
5	**2**/EG: 1/3	3	28	75/25	79/72
6	**2**/EG: 1/3	4	14	80/20	95/54
7	**3**/Urea: 1/2	1	>99	80/20	34/>99
8	**3**/Urea: 1/2	2	<5	–	–

[a] Reaction conditions: cyclohexanone (0.2 mmol), β-nitrostyrene (0.1 mmol), chiral liquid/limiting reagent mass ratio of 5/1, rt, 18 h.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture. Abbreviations – EG: ethylene glycol; Gly: glycerol; rac: racemic mixture.

Finally, the chiral mixture **3**/Urea: 1/2 exhibited no recyclability, as the reaction failed to proceed in the second cycle.

4. Conclusions

Three different chiral ammonium salts have been successfully synthesized and employed as HBA in the formation of novel CDES later used as reaction medium in the asymmetric organocatalytic Michael reaction between cyclohexanone and *trans*-β-nitrostyrene. The new formed chiral eutectic solvents were thermally and structurally characterized via differential scanning calorimetry (DSC) and NMR. Chiral eutectic mixtures **2**/EG: 1/3 and **3**/Urea: 1/2 gave particularly good activity and good diastereo- and enantioselectivity in the studied model conjugate addition. Recyclability studies showed that the mixture **2**/EG: 1/3 could be reused up to 4 times without loss of *dr* or *ee*, but with significant deterioration in the reaction conversion after the second reaction cycle.

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CRediT authorship contribution statement

Sarah J. Burlingham: Writing – review & editing, Writing – original draft, Supervision, Investigation. **Jose A. Ñíguez:** Writing – review & editing, Investigation. **Alejandro Torregrosa-Chinillach:** Writing – review & editing, Investigation. **Diego Ros Ñíguez:** Investigation. **Rafael Chinchilla:** Writing – review & editing, Writing – original draft, Conceptualization. **Ion Such-Basáñez:** Investigation. **Matteo Tiecco:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation, Conceptualization. **Diego A. Alonso:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

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.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2024.125724.

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[23] We have previously demonstrated by NMR and theoretical DFT studies that stronger interactions between the two DES components (as in the case of the CDES formed by glycolic acid/L-proline) led to low conversions, due to the fact the chiral organocatalyst component seems to be more involved in the CDES formation (especially with the nitrogen, as emerged from DFT data), therefore this liquid showed lower reactivity. See reference 10.