EurJOC
European Journal of Organic Chemistry

Minireviews
doi.org/10.1002/ejoc.202100385

Chemistry Europe
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Asymmetric Organocatalysis in Deep Eutectic Solvents

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The recent advances in asymmetric organocatalysis using eutectic mixtures as a reaction medium are revised in this mini-review. In addition, the first enantioselective transformations using chiral eutectic solvents, which play the role of a green medium and organocatalyst, are described. In this minireview we intend to deepen not only in the synthetic aspects of asymmetric organocatalysis in eutectic mixtures, but also in the fundamental issues that seem to be essential for a successful development of this promising, and at the same time challenging, methodology.

1. Introduction

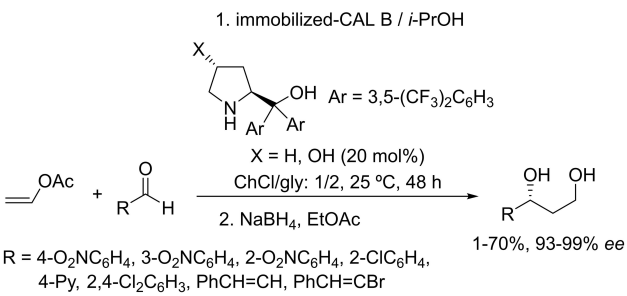
Asymmetric organocatalysis is an exceptionally attractive methodology for the preparation of functionalized chiral compounds, since small purely organic molecules are used as catalysts under mild and simple reaction conditions.[1–3] This metal-free methodology is often employed to prepare compounds that do not tolerate metal contamination such as pharmaceutical products, but also provides a certain degree of sustainability within the synthetic process. Different methodologies have already been reported with the aim of improving the sustainability of organocatalytic processes.[4] The application of alternative and greener solvents in asymmetric organocatalysis enables the reduction of waste formation generally attributed to the employment of volatile organic compounds (VOCs) as a reaction medium.[5] Deep eutectic solvents (DESs) have recently emerged as promising alternative solvents in organic chemistry since they share the advantages of ionic liquids, such as low vapor pressure and non-flammability, but are inexpensive and easy to recycle, have a low ecological footprint and their synthesis is straightforward. Despite these advantages, the use of DESs in asymmetric organocatalyzed reactions remains very scarce. In this mini-review, we briefly discuss the recent advances on asymmetric organocatalysis using eutectic mixtures as a reaction medium.[6,7]

2. Asymmetric Aldol Reactions in DESs

The organocatalyzed enantioselective cross-aldol reaction is probably the paradigm of this type of processes.[8] The first reported transformation using L-proline as organocatalyst, acetone in large excess and 4-nitrobenzaldehyde, had intrinsic contradictions with the Twelve Principles of Green Chemistry, as VOC solvents were mandatory for the reaction and at the following work-up steps. Further modifications of catalysts and/or reaction conditions (neoteric solvents, absence of solvent, etc.) somehow overcome the lack of sustainability of the first reported process.

A real breakthrough in the field of DESs as media for this type of transformation started with the studies of Domínguez de María group.[9] This research group developed a tandem process involving an integrated bio- and organocatalyzed process, rendering aldol products, which were isolated as diols after reduction with $NaBH_4$, in moderate to good yields (Scheme 1).

Thus, after preliminary studies, the immobilized lipase B from *Candida antartica* (CAL-B) was found as the enzyme able to perform the in situ production of acetaldehyde by the



Scheme 1. Tandem bio- and organocatalyzed cross-aldol reaction.

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transesterification of vinyl acetate with isopropanol, giving as by-product the expected isopropyl acetate. This biocatalyzed reaction was carried out in a choline chloride (ChCl) and glycerol (gly) DES mixture. The in situ formed acetaldehyde is the nucleophilic partner in the subsequent cross-aldol reaction. The unstable aldol was extracted from the DES using ethyl acetate and reduced to the corresponding diol. The DES and CAL-B could be reused up to six times without observing any

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Sarah Jayne Burlingham received her BSc in Chemistry at the University of Alicante in 2019 and went on to obtain her MSc in Medicinal Chemistry at the same University the following year. She is currently working toward her Ph.D. under supervision of Rafael Chinchilla and Diego A. Alonso, working on the development of Photocatalytic Alkylations and Decarboxylations as well as the synthesis of chiral Deep Eutectic Solvents.

Rafael Chinchilla was born in Alicante and studied chemistry at the University of Alicante, from which he graduated in 1985 and received his doctorate in 1990. After a postdoctoral stay at the University of Uppsala (1991–1992) with Prof. J.-E. Bäckvall, he moved back to the University of Alicante, where he was appointed associate professor in 1997 and full professor in 2012. His research interests are mainly focused on enantioselective syntheses by use of organocatalysis.

Gabriela Guillena was born in Alicante (Spain) in 1970 and received her B. Sc. degree (1993) from the University of Alicante. After spending one year as postgraduate student in the group of Prof. D. Seebach (ETH, Zürich), she returned to the University of Alicante and received her M.Sc. (1995) and Ph.D. (2000) degrees. After two years as a postdoctoral fellow in the research group of Prof. G. van Koten (University of Utrecht, Netherlands), she returned to the University of Alicante where she became assistant professor (2003), associate professor (2007) and Professor (2017) through the National Habilitation process. Her current research interest is focused on new sustainable methodologies in organic synthesis based on the use of deep eutectic mixtures as media for the synthesis of molecules with industrial interest.

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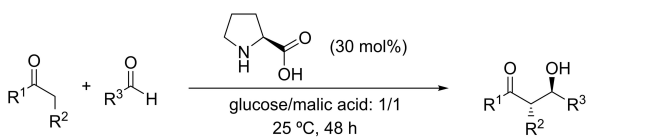
Matteo Tiecco was born in Perugia (Italy) and he studied Chemistry at the University of Perugia. Here he received his PhD in 2008 with a thesis on surfactants-DNA interactions (Prof. G. Savelli as supervisor). After his PhD, he spent his post-doc activity in different workgroups at University of Perugia, at the University of Chieti-Pescara (Italy) and atUniversidad de Alicante, Alicante (Spain) working with Prof. R. Germani, Prof. G. Cruciani, Prof. G. Cardinali, Dr. P. Di Profio and Prof. D. A. Alonso. His research interests are about Deep Eutectic Solvents (DESs) and their structural and catalytic properties, organocatalysis made by DESs, surfactants and micellar aggregates, ionic liquids, surfactants as biocides, polymers and polymer recycle green processes. Currently he's post-doc at University of Perugia, Italy. He obtained the habilitation for becoming associate professor in 2019.

loss of enzymatic activity. However, the addition of fresh catalyst in each reaction run was compulsory in order to keep the initial level of enantioselectivity. This suggested that the organocatalyst was partially soluble in the DES as well as in ethyl acetate. In order to solve this problem, the 4-hydroxyprolynol derivative (X = OH) was used as a catalyst alternative, as it can form more and stronger hydrogen bond interactions with the DES, highlighting the importance of the catalyst's design in order to maximize its compatibility with the reaction medium. Also, changing the VOC solvent to 2-methyl tetrahydrofuran for the reduction process assured the retention of the catalyst in the DES phase.[10]

The classical aldol reaction using ketones as nucleophilic partners, was tested in a set of seven ChCl-based DESs and 12 different chiral amines as organocatalysts, obtaining poor results in all cases, even in the presence of water as an additive.[11] However, when the natural deep eutectic solvent (NADES) mixture of D-glucose and racemic malic acid was used as reaction media, the process took place in excellent yields, moderate diastereomeric ratios, and good to excellent enantioselectivities (Scheme 2).

The influence of the stereochemistry of the malic acid on the reaction was studied by performing these reactions using D-glucose/D-malic acid or D-glucose/L-malic acid in a 1/1 mixture as a DES. The enantiomeric excess was similar to that obtained when the standard D-glucose/*rac*-malic acid was used. Additionally, the molar ratio of the components of the DES was varied giving worse results to those achieved using the eutectic ratio. The obtained results found were homogenous with all kind of aromatic aldehydes, but slightly lower selectivities were observed when aliphatic aldehydes were employed. A clear negative non-linear effect was detected when the results were correlated with the enantiomeric excess of the catalysts. This effect could be explained as a consequence of a kinetic conglomerate phase effect. The DES and the catalyst were recycled by performing the reaction at 5 g scale. Both, the organocatalysts and the DES, could be recovered and reused at least three times with similar results. Under these conditions, the addition of water, after completion of the reaction, dissolved the DES and the catalyst, leading to two phases, with the upper one containing only the aldol product. In some cases, a small amount of starting ketone was also observed. This remaining ketone could be removed by simple distillation, obtaining the pure product without using any type of VOC solvent. The aqueous layer was then distilled to remove the water, giving the recovery of the starting DES and the catalyst which could then be reused in another cycle. This protocol could be extended to the aldol reaction between a non-enolizable aldehyde and aliphatic aldehydes, obtaining similar results but in longer reaction times.



Scheme 2. Cross-aldol reaction catalysed by L-proline.

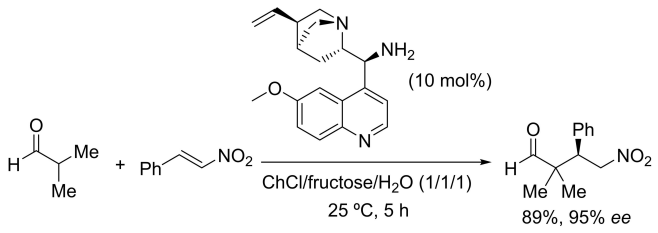
The Benaglia group found an ingenious form to carry out the classical aldol reaction depicted in Scheme 2 in a continuous way by using a biphasic system and a pump forcing the interaction of both phases.[12] The organic upper phase was initially constituted by the aldehyde and a large excess of ketone, which was forced to flow through the lower phase formed by the DES [ChCl/urea/H_2O (1/2/1.5 molar ratio)] and L-proline (35 mol%) by means of a simple tube and a pump. Under these custom conditions (of exchange and flow phases), it was possible to conduct the reaction giving good to excellent enantioselectivities for aldol products. The distillation of the large excess of ketone (20 equivalents) gave the product without the need of using VOC solvent, with the DES and organocatalyst being recovered and reused one more time without depletion of the results.

Finally, the group of Concellón and Del Amo were able to perform the typical aldol reaction (Scheme 2), using cyclohexanone as the only nucleophile and different aromatic aldehydes, obtaining the corresponding aldols with yields in the range of 63–99%, 64–86% diastereomeric ratio, and 66–99 ee.[13] The reaction was carried out in the ChCl/ethylene glycol (1/2 molar ratio) eutectic mixture using L-isoleucine (20 mol%) as a chiral amine catalyst, and 10 equivalents of water. Both, the organocatalyst and the DES medium could be recycled and reused at least five times without observing changes in the results. For this purpose, aqueous extraction with ethyl acetate was performed, isolating the product in the organic layer by removing all of the volatiles, and recovering the DES/catalyst via water removal.

3. Asymmetric Conjugate Additions in DESs

Choline chloride-based DESs have been studied as reaction medium in asymmetric organocatalyzed conjugate additions. The first examples were reported by Benaglia and Capriati groups using chiral primary amines such as 9-amino-9-deoxy-epi-cinchona derivatives as organocatalysts, which were known to promote reactions via enamine, dienamine and iminium ion formation.[14] Regarding the enamine activation, an efficient conjugate addition of isobutyraldehyde to β-nitrostyrene in ChCl/fructose/H_2O (1/1/1 molar ratio) afforded the corresponding Michael adduct in 89% yield and 95% enantioselectivity (Scheme 3). Interestingly, the reaction in the eutectic mixture was faster and more stereoselective than in organic solvents (toluene, glycerol) or water, which is consistent with a positive cooperative effect of the DES with the organocatalyst.[15] The reusability of the catalytic system was demonstrated by carrying out up to three reaction cycles reducing the reaction time to 2 h which led to a reduction in yield by half, although the selectivity was maintained.

The same cinchona-derived organocatalyst was also successfully used for the conjugate addition of ethyl *E*-3-methyl-3-



Scheme 3. Conjugate addition of isobutyraldehyde to β-nitrostyrene in a ChCl/fructose/H_2O DES.

nitroacrylate (dienamine activation) and 4-hydroxycoumarin (iminium activation) to benzalacetone in ChCl/urea (1/2 molar ratio), which demonstrated the versatility of the optimized catalytic system.[15]

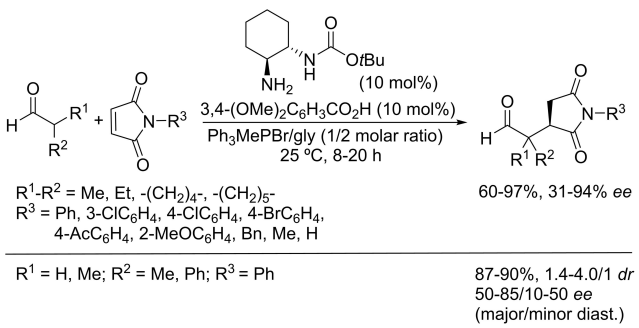
The enantioselective conjugate addition of aldehydes to *N*-substituted maleimides, leading to enantioenriched succinimides, has also been achieved in DESs at room temperature using chiral 1,2-diaminocyclohexane-derived organocatalysts (10 mol%), obtained from enantiomerically pure (1*S*,2*S*)-cyclohexane-1,2-diamine by monoprotection with the *tert*-butoxycarbonyl (Boc) group (Scheme 4).[16] Among all the employed DESs, the best results, concerning yield and enantioselectivity, were achieved using the combination Ph_3MePBr/gly (1/2 molar ratio). The influence of the acid and basic additives was also assayed, observing that the addition of a carboxylic acid such as 3,4-dimethoxybenzoic acid in an equimolecular amount relative to the catalyst (10 mol%) improved the results. Mainly α,α-disubstituted aldehydes were employed, affording up to 94% *ee* of the final adduct, whereas when some α-monosubstituted aldehydes were assayed, moderate to low diastereomeric ratios were obtained in generally lower *ee*'s. Remarkably, this reaction performed in a DES gave a better enantioselection than when using conventional organic solvents.[17]

The reusability of the DES and the catalytic system was explored by carrying out different reaction cycles of the model conjugate addition reaction between isobutyraldehyde and *N*-phenylmaleimide. Thus, once the reaction was finished, the corresponding final adduct was extracted with a mixture of ethyl ether/*n*-hexane. However, attempting to directly reuse the remaining DES layer in another reaction cycle by adding new aldehyde and maleimide resulted in low yields and moderate enantioselectivities of the resulting product. This was explained after observing the presence of the acid additive in the recovered organic layer (via NMR). It was found that refreshing the catalytic system by means of the addition of new additive (but no new chiral organocatalyst) to the recovered deep eutectic solvent allowed the obtention of the addition product with almost identical enantioselectivity and yield than when used for the first time. Following this recovery procedure, the DES containing the organocatalyst could be reused four times without diminishing its enantioinduction. However, a fifth reaction cycle led to a decrease in the catalytic activity. The (*R*)-sense of the enantioselectivity in this reaction was the same as when the same catalyst was employed using conventional polar solvents. This was explained through theoretical calculations,[17b] which revealed that, under these conditions, the organocatalyst cannot be considered as "bifunctional", as no additional coordination via hydrogen-bond between the transient nucleophilic enamine and the maleimide electrophile takes place.

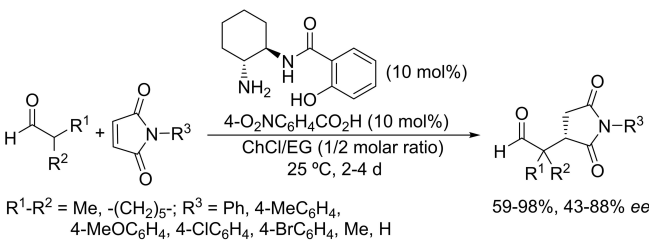
This enantioselective Michael addition reaction between α,α-disubstituted aldehydes and N-substituted maleimides have also been carried out in DESs at room temperature using a monosalicylamide derived from (1*R*,2*R*)-cyclohexane-1,2-diamine as an organocatalyst (10 mol%) (Scheme 5).[18] In this case, the chosen DES was formed by the combination of ChCl/ethylene glycol (1/2 molar ratio), and the presence of 10 mol% of 4-nitrobenzoic acid improved both yield and enantioselectivity. The obtained enantioselections for the final adducts were generally slightly lower than when using the former organocatalyst in the same process.

The DES, containing the organocatalyst was reused in the model reaction between isobutyraldehyde and *N*-phenylmaleimide. Thus, the final adduct was extracted using 2-methyltetrahydrofuran, and the catalytic system was refreshed by the addition of new acid additive (but no new chiral organocatalyst) to the recovered DES, allowing the accomplishment of a second reaction cycle with similar conversion and identical enantioselectivity as when used for the first time. Following the same recovery procedure, the DES containing the organocatalyst was used in a third cycle, but the conversion diminished, whilst maintaining the enantioinduction.

The asymmetric conjugate addition to nitroalkenes is a very interesting tool for the construction of highly functionalized synthetic building blocks. Although significant progress has

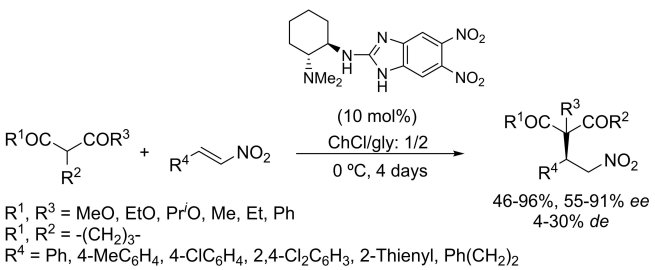


Scheme 4. Asymmetric Michael addition of aldehydes to maleimides organocatalyzed by a chiral amino monocarbamate.



Scheme 5. Enantioselective Michael addition of aldehydes to maleimides in DES.

been made over the last years in the achievement of highly efficient asymmetric organocatalyzed conjugate additions to these activated double bonds,[19] very few catalytic systems have shown good selectivity when using eutectic mixtures as reaction media. Chiral 2-aminobenzimidazoles have recently been shown as very active and selective organocatalysts for the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins[20] and maleimides[21] in toluene. Although these benzimidazole-derived organocatalysts base their catalytic activity on weak interactions with the reagents involved in the reaction such as hydrogen bonds, this catalytic system has been successfully modulated in such a way that they can also be used in eutectic media. Thus, the enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitrostyrenes catalyzed by a bifunctional chiral 2-aminobenzimidazole-derivative has been carried out in the mixture ChCl/gly (1/2 molar ratio) yielding the corresponding adducts in good yields, low diastereoselectivities and moderate to good enantioselectivities (Scheme 6).[22] Interestingly, the process is gram-scalable and the catalyst and reaction media can be recovered and reused at least four times since the chiral organocatalyst is engaged in the eutectic mixture by a hydrogen-ionic bond interaction as demonstrated with NOESY experiments (Figure 1).[22]



Scheme 6. Enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroolefins organocatalyzed by a chiral 2-aminobenzimidazole catalyst in DES.

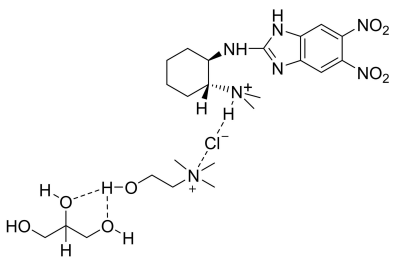


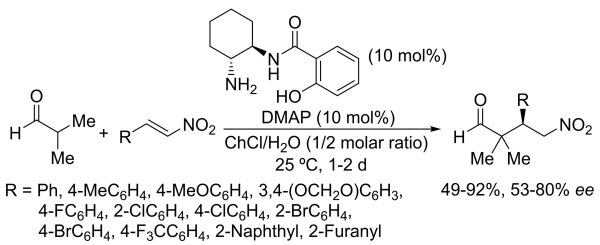
Figure 1. Proposed interaction of chiral 2-aminobenzimidazole-derived catalyst with the ChCl/gly eutectic mixture.

Chiral monosalicylamides have also been employed as organocatalysts (10 mol%) in the enantioselective Michael addition reaction of isobutyraldehyde and different β-arylated nitrostyrenes in DESs at room temperature, leading to the corresponding enantioenriched γ-nitroaldehydes with up to 80% *ee* (Scheme 7).[18] The DES giving the best results was formed by the combination ChCl/H_2O (1/2 molar ratio), containing a basic additive such as *N*,*N*-dimethylaminopyridine (DMAP, 10 mol%) necessary to improve yield and enantioselectivity.

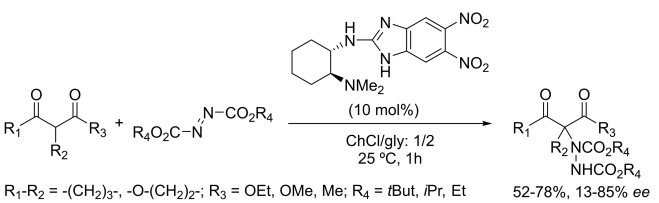
In reference to the reusability of the catalytic system, the corresponding final adduct was extracted from the DES using 2-methyltetrahydrofuran, observing via ^{1}H NMR in this organic phase the necessity of adding new additive (DMAP) after the first reaction cycle, although no leaching of the organocatalyst was detected. Again, refreshing the catalytic system by the addition of new DMAP as an additive (but no fresh catalyst) to the recovered DES, allowed to obtention of the corresponding adduct in a second reaction cycle with identical enantioselectivity as in the first one. The DES containing the organocatalyst was reused in an additional cycle with a decrease in the conversion but essentially without diminishing the achieved enantioinduction.

4. Asymmetric α-functionalization in DESs

The enantioselective α-amination of 1,3-dicarbonyl compounds to give highly functionalized chiral molecules has been carried out using DESs as a reaction medium by involving chiral 2-amino benzimidazole-derived compounds as a catalytic system. Thus, the electrophilic α-amination of ethyl 2-oxocyclopentane-1-carboxylate with di-*tert*-butylazodicarboxylate (10 mol%) was studied in different DESs such as ChCl/urea, ChCl/ethylene glycol and ChCl/tartaric acid amongst others, but gave the best results using ChCl/urea (1/2 molar ratio) and ChCl/gly (1/2 molar ratio) as a reaction media with up to 94% conversion and a 75% ee on average in the presence of a chiral 2-amino-benzimidazole-derived organocatalysts (10 mol%, Scheme 8).[23] The influence of the temperature in these reactions was also studied, achieving generally higher enantioselectivities when carrying out the reaction at 0 °C rather than the initial 25 °C. The



Scheme 7. Enantioselective Michael addition of isobutyraldehyde to β-arylated nitroolefins in ChCl/H_2O DES.



Scheme 8. Enantioselective α-amination of 1,3-dicarbonyl compounds in a ChCl/gly eutectic mixture.

reaction time could also be reduced from 5 to 1 h by carrying out the reaction using ultrasounds (360 W) at 25 °C.

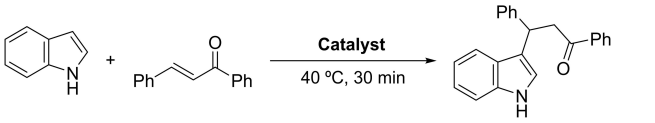
Concerning the recyclability of the organocatalyst and the DES, when the product was extracted from the reaction medium using hexane or ether, it was observed that the catalytic system could be recycled for up to five reaction runs whilst maintaining the enantioselectivity but with a decreased activity, requiring a vigorous stirring to maintain the desired conversion. A variety of dicarbonyl compounds were studied as electrophiles, including benzofused dicarbonyl compounds, also studying the variation of the azodicarboxylate group, obtaining isolated yields between 52–78% and 13–85% ee with the best results being acquired with the basic ethyl 2-oxocyclopentane-1-carboxylate and di-*tert*-butylazodicarboxylate.

5. Chiral Deep Eutectic Solvents (CDESs) in Asymmetric Organocatalysis

A peculiar and relevant aspect of asymmetric synthesis in green media is represented by the use of chiral liquids to develop asymmetric transformations without the use of any added organocatalyst, by namely exploiting the chirality of the solvent itself.[24] Chiral Ionic Liquids (CILs), as *de facto* forerunners of DES, have already been explored in asymmetric catalysis.[25] These chiral liquids showed two different cases: the chirality of the medium itself, made with the introduction of chiral centers in the anionic, cationic or in both portions of the liquids, or tailored liquids with the introduction of specific chiral portions (i.e. L-proline derivatives) that could act as organocatalysts in asymmetric reactions. In the first cases low enantiomeric excesses were observed in model transformations, while higher ones were observed in the cases when the use of "specific interacting" liquids were employed.[26]

Generally, the catalytic activity of the DESs is dependent on the catalytic properties of the molecules forming them.[27] However, the mechanisms follow different rules from ILs, since the interactions between the components have a higher complexity compared to the ones between the components of ILs.[28] This is because not only electrostatic interactions (or the weakening of them) occur in DESs but also H-bonds which have a higher directionality and specificity.[29]

The case of chiral DESs and their use as organocatalytic green liquids is a peculiar and relevant case of catalysis operated by this innovative class of liquids. So far, only two studies on asymmetric organocatalysis achieved by these solvents have been reported.[30,31] Thus, the use of (+)-camphorsulfonic acid (+CSA) as hydrogen bond donor (HBD) gave liquids at room temperature when mixed with easily one-step synthesized molecules from commercially available compounds (*S*)- and (*R*)-*N*,*N*,*N*-trimethyl-(1-phenylethyl)ammonium methanesulfonate, (FR and FS, respectively) as hydrogen bond acceptors (HBAs) (Scheme 9). The two liquids formed by +CSA mixed with the two HBA enantiomers FR and FS were used as green solvents, acid catalysts and chiral organocatalysts in an asymmetric Michael-type Friedel-Crafts addition of indole to chalcone. The results were comparable with those obtained when the reaction was performed in acetonitrile with the addition of +CSA as catalyst.[30]

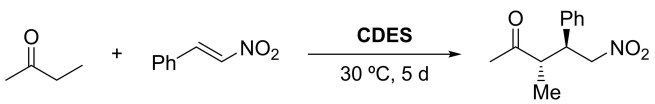


Scheme 9. Michael-type Friedel-Crafts reaction of indole to chalcone in chiral DES.

The results showed that the two DESs formed with the two enantiomers as HBAs were diastereomerically different liquids because of the inconsistent yields observed, whereas the enantiomeric excesses observed in the reactions performed in the DES +CSA/FR and in acetonitrile are identical. The differences in configuration on the chiral centre of the HBAs also determined different enantiomeric excesses between the DESs +CSA/FR and +CSA/FS. Structural studies via NMR and DFT showed that the main difference between the structure of these two DESs relied on the intimacy of the HBD-HBA couples in the liquids.[30]

The same structural approach was applied using L-proline as HBA in combination with various non-chiral HBD molecules. In this case, it was observed that the association constant, therefore the synergistic interactions between HBD and HBA molecules, can determine the activity and selectivity of L-proline in these mixtures.[31] The DESs made from mixtures of L-proline with glycolic acid, glycerol, 1,4-butanediol, *p*-toluenesulfonic acid, thymol, and diethylene glycol were used both as green and organocatalytic solvents in the Michael addition of butanone to *trans*-β-nitrostyrene, taking into account the double role of L-proline as an organocatalyst as well as the DES component (Scheme 10).

Additionally, NMR and theoretical DFT studies showed 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 organocatalyst seems to be



Scheme 10. Asymmetric conjugate addition of butanone to β-nitrostyrene in chiral DESs.

more tightly involved in the CDES formation (especially with the nitrogen, as emerged from DFT data), therefore this liquid showed lower reactivity. On the other hand, the high structuration and the high affinity of glycolic acid with the amino acid led to higher enantiomeric excesses: once the enamine is formed, the glycolic acid interacts specifically with L-proline, favouring the enantioselectivity of the addition to *trans*-β nitrostyrene. The other liquids with weaker interactions between L-proline and the HBDs (such as the case of gly/L-proline) led to racemates, since the HBDs do not selectively interact with one enantioface of the enamine, but favour the reactivity because of the higher availability of the nitrogen in the amino acid.[31]

This mini-review have brought forward the interest in the use of DESs in asymmetric organocatalyzed processes that has grown significantly throughout the last years. Definitely, DESs represent a sustainable alternative to VOCs as reaction media. However, despite the remarkable advantages of the use of DESs as reaction media in asymmetric organocatalytic processes, there are many questions still to be solved mainly associated with the low knowledge about the structural organization of these solvents especially in the presence of an organocatalyst with activation modes closely related with the interactions responsible for the formation of the eutectic mixture. Finding the right balance in this complex process seems to be crucial to develop active and highly selective organocatalytic processes in eutectic mixtures under low loading conditions.

Novel Chiral Deep Eutectic Solvents (CDESs) have very recently been revealed as promising high-structured liquids for organocatalyzed enantioselective transformations. While relevant, the use of chiral DESs is highly challenging and yet to be fully explored in the field of green asymmetric synthesis with major efforts directed towards the achievement of tailor-made CDESs specific for asymmetric carbon–carbon and carbon–heteroatom bond-forming transformations.

Acknowledgements

This work was supported by the Spanish Ministerio de Ciencia, Innovación y Universidades (MICINN, PGC2018-096616-B–I00), the University of Alicante (VIGROB-173 and VIGROB-316FI), and the University of Pisa (PRA_2018_36).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Active solvents · Asymmetric organocatalysis · Deep eutectic solvents · Enantioselectivity · Green chemistry

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Manuscript received: March 29, 2021
Revised manuscript received: April 20, 2021
Accepted manuscript online: May 4, 2021