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Catalytic Procedures for the Synthesis of Pharmaceutical Active Compounds in Deep Eutectic Solvents

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Review

Stereoselective Catalytic Synthesis of Bioactive Compounds in Natural Deep Eutectic Solvents (NADESs): A Survey across the Catalytic Spectrum

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Abstract: Deep eutectic solvents (DESs) are a mixture of two or more components, and at a particular composition, they become liquids at room temperature. When the compounds that constitute the DESs are primary metabolites namely, amino acids, organic acids, sugars, or choline derivatives, the DESs are called natural deep eutectic solvents (NADESs). NADESs fully represent green chemistry principles. These solvents are highly welcome, as they are obtained from renewable resources, and gratifyingly are biodegradable and biocompatible. They are an alternative to room-temperature ionic liquids (RTILs). From the pharmaceutical industry's point of view, they are highly desirable, but they unfortunately have been rarely used despite their enormous potential. In this review, we look at their impact on the asymmetric catalytic synthesis of key target molecules via metal-based catalysis, biocatalysis, and organocatalysis. In many cases, the NADESs that have been used are chiral and can even promote enantioselective reactions; this crucial and very exciting aspect is also discussed and analyzed.

Keywords: natural deep eutectic solvents (NADESs); asymmetric catalysis; organocatalysis; biocatalysis; metal-based catalysis



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1. Introduction

The vast majority of drugs launched on the market over the recent 2-to-3 decades exists as single enantiomers (or are achiral); this stems from the fact that for chiral molecules one enantiomer brings the therapeutic benefit whilst the other has no effect, or can have deleterious effects, as is the case for thalidomide (commercialized as Contergan[®]) administered in the 1960s as a racemate to pregnant women, where the (*R*)-enantiomer is a sedative and the (*S*)-enantiomer a teratogen in a number of countries [1]. (It must be pointed out that, in the special case of thalidomide, just administering the (*R*)-isomer to patients would not suffice from a safety point of view, as the molecule is sterically unstable under physiological conditions, leading to bio-inversion and formation of the undesired (*S*)-enantiomer.) The current market for single enantiomer drugs is more than EUR 300 billion. Many stereoselective methods are available to make single-enantiomer chiral drugs, but the most promising by far is via asymmetric catalysis. Many important and even block-buster drugs have been obtained using this methodology [2,3]. Asymmetric catalytic synthesis can be achieved

through three principally distinct methods: metal-based catalysis, organocatalysis, and biocatalysis. Although catalysis, in general, is a green methodology, the overarching considerations in all of these approaches are the (1) cost of the catalyst, (2) catalytic activity throughout the reaction, and (3) recycling of the catalyst. There are many solutions; the catalyst can be immobilized—and traditionally, this was achieved via its attachment to an appropriate solid support [4]—and then used either under batch conditions or in continuous flow. Under these conditions, the reactions are heterogeneous and entail certain disadvantages (support type, pore size, stability of catalyst, immobilization method, existence of linker, and interactions between the solid support and the components); this can be overcome by using liquids to immobilize the catalysts, the most common being ionic liquids [5], or biphasic fluorinated liquids [6], but the most recent is the Deep Eutectic Solvent (DES) category [7]. DESs have emerged as very useful liquids for many applications, but their most striking contribution is in the field of catalysis, particularly biocatalysis [7] and organocatalysis [8]. What is a DES? A DES is a liquid that is obtained when a hydrogen-bond acceptor (HBA), like a quaternary ammonium salt, is mixed with a hydrogen bond donor (HBD) [9]. Their melting points are lower than those of their components, and they readily mix with water but gratifyingly are immiscible with most organic solvents. DESs are recyclable, reusable, stable, non-flammable, biodegradable, and non-toxic mixtures. They have properties similar to ionic liquids, but unlike ionic liquids, they are non-toxic and are not biodegradable. One other significant advantage is their solubility properties, as well as their ability to stabilize transition states, particularly for organocatalyzed reactions. Some informative reviews on the subject have been published by the Alicante/Perugia groups [8], del Amo [9], and Domínguez de María [10].

In this review, we look at the use of promising asymmetric catalytic reactions that lead to Active Pharmaceutical Ingredients (APIs) that have been successfully conducted in NADESs.

2. Deep Eutectic Solvent (DES) Characteristics

The excellent physicochemical properties of DESs allow for the possibility of being used as greener solvents and an alternative to those commonly used in chemical synthesis. As shown above, DESs are built from hydrogen-bond donor and hydrogen-bond acceptor components and can be easily adapted for specific applications. The most widely used hydrogen bond donor components include urea, thiourea, phenol, glucose, citric acid, malonic acid, sorbitol, and glycerol. The most commonly used hydrogen bond acceptors (HBA) are choline chloride, betaine, glycine, and proline [9]. DESs have been applied in numerous chemical operations, including polymerizations, biotransformations, metal-catalyzed reactions, sample preparations, and catalytic techniques, as well as in the design of new pharmaceutical formulations [11]. Traditionally, the HBA was a halide salt, like choline chloride (ChCl), but recently, other types of DESs—the so-called Natural DESs or NADESs, which are obtained from organic acids, amino acids, and sugars, have been used more often [11]. One excellent example is the NADES developed from the HBA: *N,N,N*-trimethylglycine (betaine) [12]. The solvent category with the most similarity to NADES is the room-temperature ionic liquid (RTIL) category, which has enjoyed much success and application in stereoselective transformations over the last several decades, over time; however, the observations and evidence accumulated indicated that members of the RTIL family were tainted by the lack of certain green features and technical applicability, a high perceived cost, and poor biodegradability and biocompatibility, pointing in the direction of unsatisfactory sustainability and, thus, making the case for substitution by NADES.

3. Asymmetric Organocatalysis in DESs

The area of organocatalysis is perhaps the newest member to the field of asymmetric catalysis. Although various types of organocatalytic transformations have been used over the last 100 years, including the landmark Hajos–Parrish–Wiechert–Eder–Sauer intramolecular Aldol reaction used as an inspiration in the 1970s to make drug molecules. It, however, only became an important catalytic tool two decades ago with the developments of the 2022 Nobelists in chemistry, Benjamin List and David MacMillan [13]. More re-

cently, asymmetric organocatalysis has been hooked up with DESs. The 2021 review by the Alicante/Perugia group provides a number of interesting examples of the application of asymmetric organocatalysis in NADESs for accessing some key target molecules (Figure 1) [8]. Most of the reactions that have been studied to date fall into the very limited categories of Aldol condensation [14], Michael addition [15], and α -aminations [16], as well as a report on an integrated biocatalytic/organocatalytic sequence that provides chiral 1,3-diols with yields of up to 70% and 99% ee. In fact, prior to 2016, there were no reports on the application of NADES to support organocatalysis [10], and the expectations were very high.

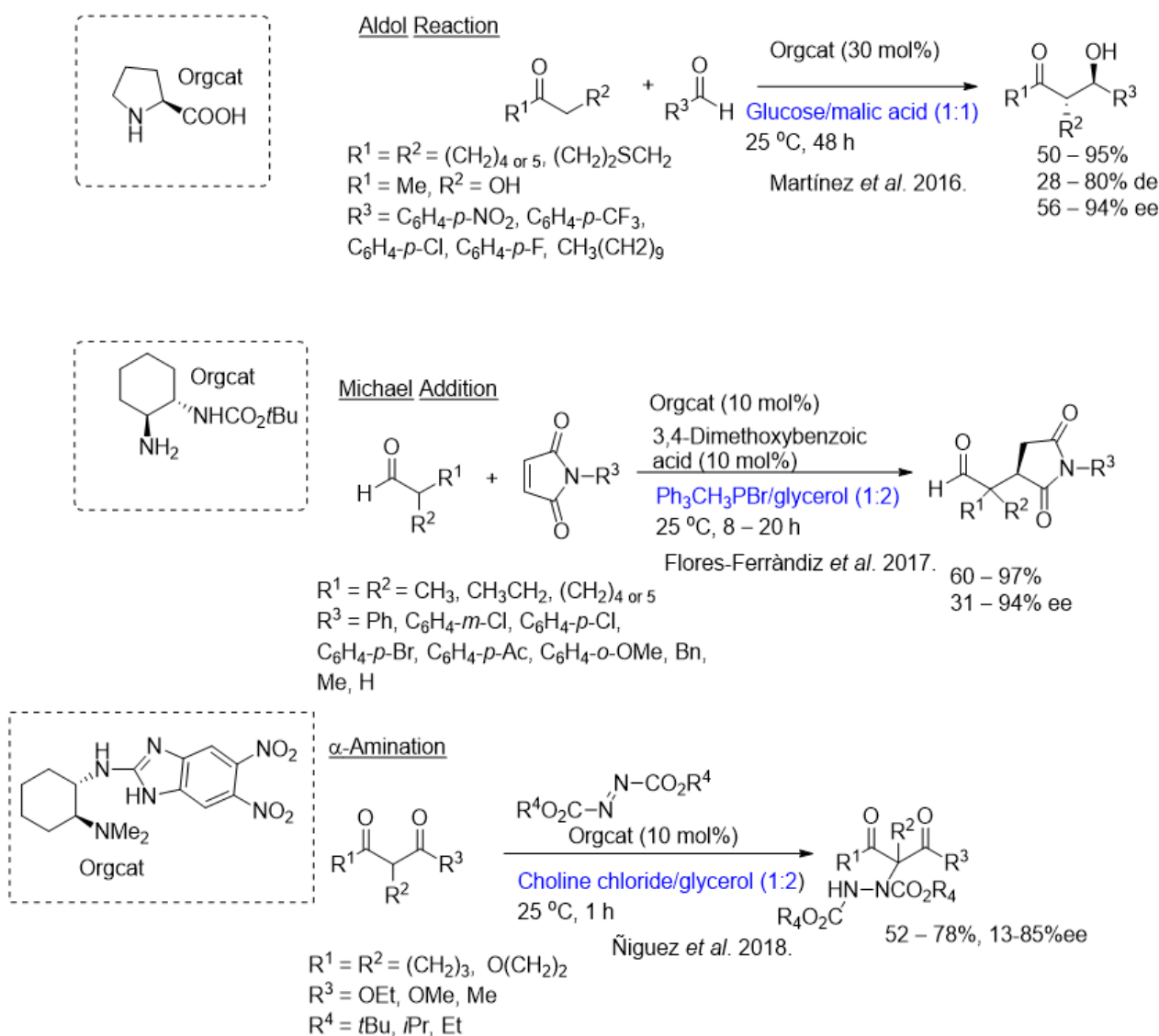
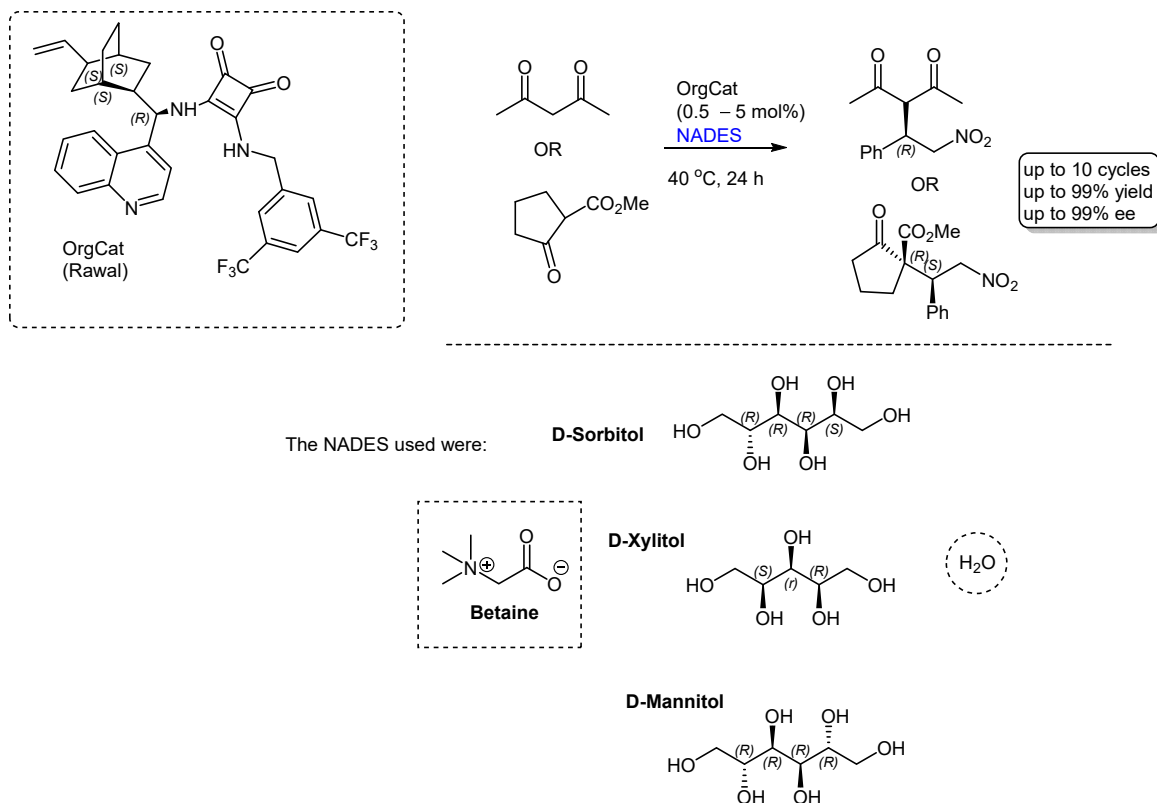


Figure 1. Examples of some organocatalyzed reactions conducted in different NADESs (blue) [14–16]. (In the case of the α -amination, the stereochemical configuration of the product was not indicated by the authors).

More recently, our group successfully immobilized cinchona-squaramides to size-controlled porous glass beads and effectively used them in Michael additions of acetylacetone and methyl 2-oxocyclopentane-1-carboxylate to *trans*- β -nitrostyrene [17]. We further showed the application of this catalyst in the same reactions, but using NADES systems [18]. The results were highly enlightening, affording the Michael adducts in very high yields and stereoselectivities (Scheme 1). Yields of up to 99% and enantioselectivities of up to 99% ee could be achieved after 24 h at 40 °C (the reaction had to be run at this temperature to main-

tain the NADES in the liquid form and as viscous as possible). Three types of NADESs were investigated: betaine/sorbitol/water, betaine/xylitol/water, and betaine/mannitol/water. It was with the former that the best results were achieved; this was presumed to be due to the structural characteristics of the sorbitol. In the interest of recyclability, several reaction cycles were conducted with the same NADES and organocatalyst; in the case of methyl 2-oxocyclopentane-1-carboxylate, up to 10 cycles could be successfully performed without any significant drop in yield and stereoselectivities.

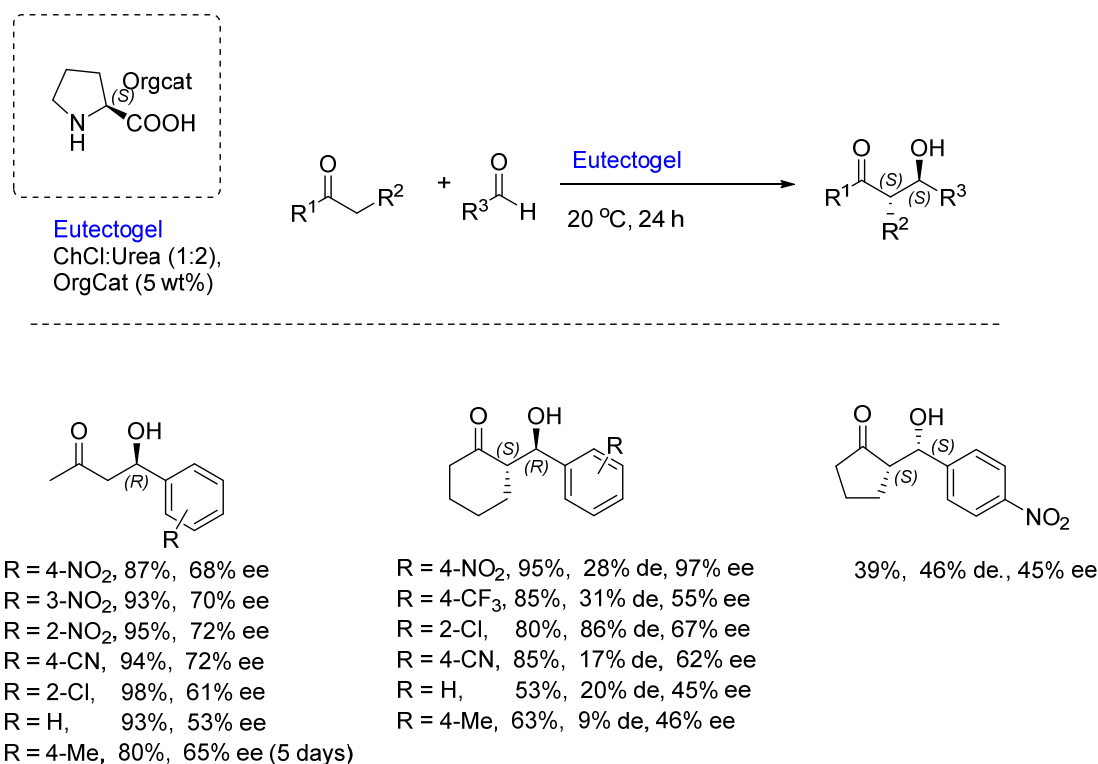


Scheme 1. Examples of Michael reactions with the Rawal Organocatalyst conducted in betaine-derived NADESs [17,18].

One other question is the role of the NADES solvent in organocatalyzed reactions. Our recent experience in the Michael reaction is that the solvent or the components of the solvent compete with the organocatalyst. For example, the Michael reaction with methyl 2-oxocyclopentane-1-carboxylate occurred in betaine/sorbitol/water with a yield of 99% and a diastereoselectivity of 58% ee without any catalyst present. Some good support for this conjecture came from our density functional theory (DFT) calculations, which showed that there was a lowering of the reaction transition state by the sorbitol component. This was assumed to be due to key H-bonding between the sorbitol and the reaction transition state complex. Even stronger support came from the observation that one of the reactions in the betaine/sorbitol/water was highly enantioselective (for acetylacetone) with 75% ee. This phenomenon is not uncommon, and in fact both base and acid catalyzed reactions have been successfully executed in NADES (reactions like Perkin, Knoevenagel, and Aldol condensations) [10]. It appears, in fact, that NADESs are not “non-innocent” solvents, manifesting subtle interactions with the reaction intermediates, possibly also stabilizing the transition states via H-bond interactions. This discussion naturally leads to the role of chiral NADES as a medium for conducting asymmetric organocatalysis. A good example was the use of various L-proline-derived NADESs (as the HBA component) in asymmetric Michael reactions that involved butan-2-one and nitrostyrene [19]. Amongst the NADESs that were tested, the best performers consisted of diethyleneglycol/proline

(3/1) (92% yield, syn/anti 85/15, ee 26/rac) and glycolic acid/proline (3/1) (15% yield, syn/anti 60/40, ee 86/95). This exciting aspect was also reviewed in 2022 by Tang and Yao [20], who alerted us to the paucity of examples currently known and mentioned that there were decreases in the enantioselectivity of the reaction due to NADES recycling.

A more recent development has been with eutectogels and their use in asymmetric organocatalysis. In 2021, the group of Ramón and D'Anna reported on the application of these materials for asymmetric Aldol reactions [21]. These materials have been categorized as “catalytic soft materials” and are a combination of Low-Molecular-Weight Gelators (LMWGs) and NADES. They were designed to act as specific organized vessels to perform organocatalytic reactions. In this work, a variety of canonical amino acids, like proline, cysteine, asparagine, etc. (all of *L*-configuration), were used for a variety of Aldol reactions between ketones and aldehydes—employing initially the reagents acetone and *p*-nitrobenzaldehyde as the benchmark (Scheme 2). To determine the best LMWG and NADES combination, using the reaction of acetone with *p*-nitrobenzaldehyde indicated that a gel derived from using *L*-proline (5 wt%) in the NADES, ChCl/Urea (1:2) at 20 °C for 24 h, afforded the aldol product in an 87% yield and 68% ee (Scheme 2). The scope of the reaction was evaluated, and in some cases, enantioselectivities of up to 95% could be achieved; however, although in those cases where diastereomers were formed, the diastereoselectivities were only moderate. Michael additions were also conducted, using isobutyraldehyde or maleimide with *trans*- β -nitrostyrene, a base additive or an acid additive and 5 mol% proline, but unfortunately the yields were very poor.



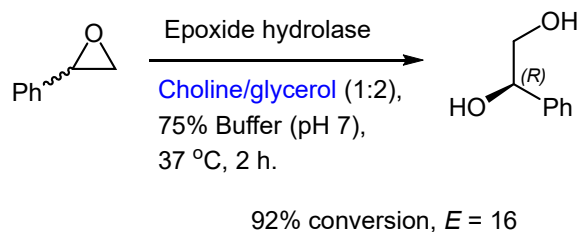
Scheme 2. The application of an *L*-proline-based eutectogel in the Aldol reaction.

Overall, this is a very promising, enabling technology that has much potential to offer for the synthesis of biologically active compounds but is still in its infancy.

4. Biocatalysis in DESs

The long-lasting paradigm that enzymes could actually function in a strictly aqueous environment was finally debunked in the mid-1980s by Klivanov and co-workers when they showed that the reactions could be run in organic solvents [22,23]. Since then, it has been shown by numerous examples how efficient biocatalytic reactions can be performed

in “unconventional” systems such as “classical” organic solvents, room-temperature ionic liquids (RTIL), supercritical fluids, and of course, NADESs [24]. The latter category, along with RTILs, has brought several advantages for conducting enzyme-driven transformations, having enjoyed enormous attention as being broadly useful in organic chemistry. The ground-making work on the use of NADES in biocatalysis was performed by Kazlauskas’s group in 2008; they demonstrated that it was entirely feasible to run biocatalysis in these nonconventional systems, as was showcased by different biotransformations relying on hydrolases (CALB type) as catalytic species in a variety of choline chloride-based NADESs (Scheme 3) [25]. It was found that the catalytic activity was 20-fold better in the NADES system than in the original aqueous system.



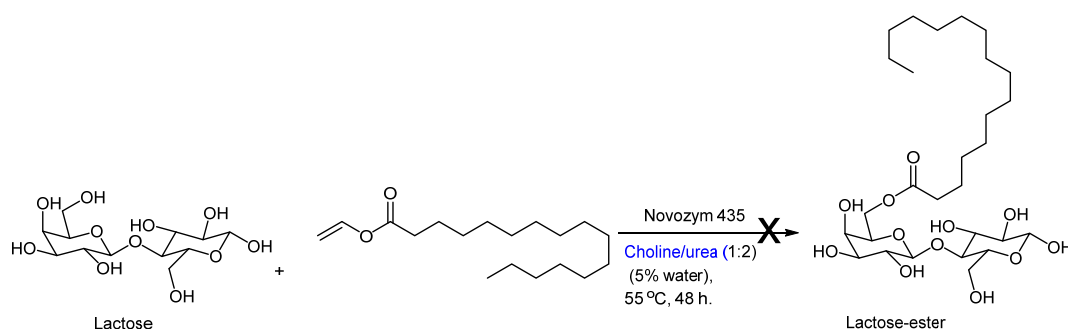
Scheme 3. Pioneering work from Kazlauskas’s group on the deracemization of styrene oxide [25].

This pioneering work showed the far superior performance in the NADES chosen to conduct this ring-opening hydrolysis, with 92% conversion in comparison to <5% in a “standard” aqueous buffer. It seems that the (*R*)-enantiomer was the favored isomer, and the enantioselectivity of the kinetic resolution was moderate ($E = 16$).

They have also been used successfully in *trans*-esterification reactions. Several articles disclose the use of glucose and several acyl donors for enzymatic transesterifications in DESs. For example, in 2015, Pöhnlein et al. reported the transesterification of glucose with vinyl hexanoate, using immobilized CALB (Novozym 435) in different DESs [26]. Ester products were obtained in the reactions that used both ChCl/urea and ChCl/glucose DESs. The beauty of this approach was that, in one case, the NADES behaved as the solvent and the substrate. In 2020, the same two hydrophilic DESs were reported for the transesterification of glucose with vinyl decanoate [27].

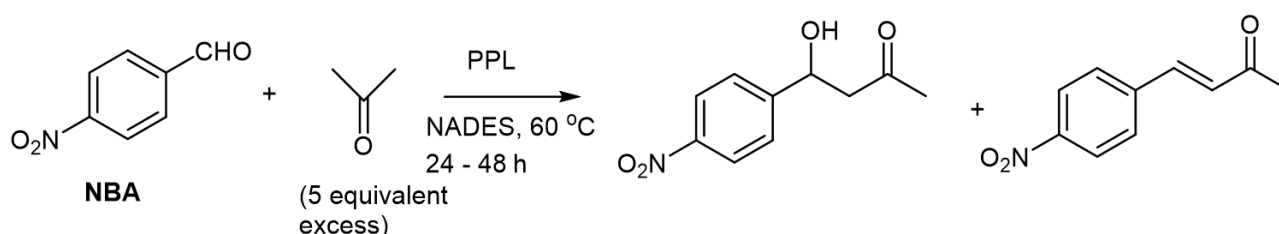
The same group also explored, for the first time, the use of a hydrophobic DES (menthol/decanoic acid) as a suitable reaction medium for sugar ester production [28]. The yields obtained with these NADESs were significantly higher than with hydrophilic NADESs. Different reaction parameters were investigated to optimize the synthesis further. Twenty milligrams/mL iCALB and 0.5 M glucose resulted in the highest initial reaction velocity for the esterification reaction, and the highest initial reaction velocity was observed with 1.5 M glucose in the transesterification reaction. The enzyme was reusable for at least five cycles, without significant loss of activity.

On the downside, a recent study from Ubiali’s group addressed the problems involved in the synthesis of sugar fatty acid esters from disaccharides, like lactose, using choline chloride-based NADES [29]. They encountered difficulties in conducting this transformation using standard Novozym lipases (Scheme 4). An important point was raised by these authors, where they correctly recognized that the NADES does not behave as a simple solvent, but in fact, its individual components interact with the reaction system’s constituents. (“Overall, the conclusion is that DESs are not innocent solvents because they interact with the substrates and the catalysts and influence the reaction outcome or directly hamper it”.) They also linked the choice of DES to the choice of catalyst for a reaction, particularly a chiral catalyst, where there is no such thing as a ‘one-size-fits-all’ solution. “Rather than being a simple ‘one-size-fits-all’ solution, incorporating a DES in a reaction needs a profound study for each particular case, starting from the genuine motivation to use them (solubility, sustainability, etc.), considering the enzyme and substrate compatibility, and eventually the ease of a downstream unit”.



Scheme 4. Failed transesterification of lactose with vinyl palmitate (acyl donor) by Ubielli and co-workers [29].

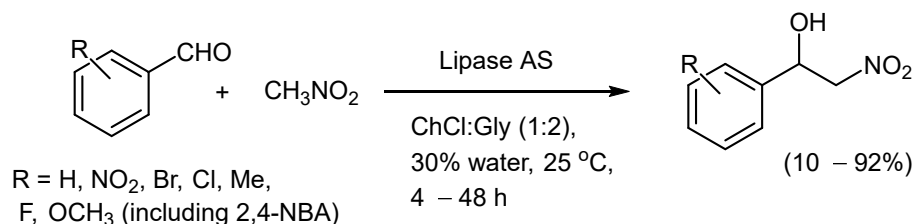
The enzyme porcine pancreas lipase (PPL) was used in the enzymatic catalysis of the aldol reaction condensation of *p*-nitrobenzaldehyde and acetone in the same NADES ChCl/glycerol, as described above (Scheme 5) [30].



Scheme 5. PPL catalyzed aldol reaction in NADES [30].

It was noted that the product composition could be directly correlated with the choice of DES, as the DESs differ in their hydrophobicity. The initial reaction velocity of the aldol addition was higher in the hydrophilic NADES, ChCl:Gly (1:1.5). Unfortunately, this DES was limited by the solubility for the *p*-nitrobenzaldehyde (4-NBA) substrate. To overcome this problem, a NADES consisting of tetrabutylammonium chloride/4-NBA (2.2:1.5) was prepared and evaluated. The 4-NBA containing DES exhibited the highest solubility for 4-NBA. However, the fastest reaction with a final yield of 1296.5 mM, or 71% yield and 82% conversion after 32 h, was achieved when no NADES was used (solvent-less reaction conditions) and improving the productivity up to 40.5 mM h^{−1} compared to reactions performed in NADES. An enone side-product was obtained in most cases, but particularly for the more hydrophilic NADES, like ChCl/glycerol. BSA-catalyzed aldol additions were also investigated but did not exhibit specificity either for an aldol or olefin formation. Unfortunately, the authors did not discuss the stereochemical aspects of the reaction, such as the configuration of the major enantiomer or the direction of enantioselectivity.

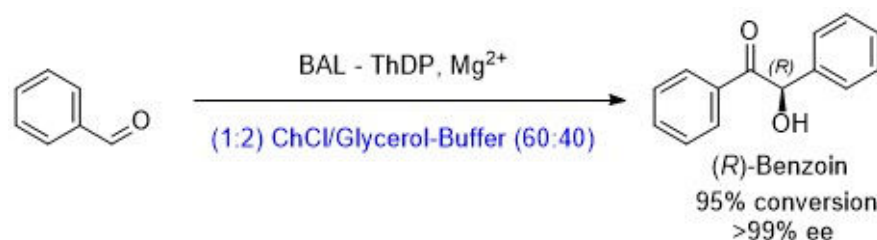
The Henry reaction has also been explored in NADES. The Henry reaction is simple, but it is useful from a pharmaceutical point of view due to the presence of a vicinal benzylic chiral alcohol and a nitro group when aldehydes are used and nitro-amino compounds when imines are used (*aza*-Henry variant). The useful lipase-catalyzed (*Aspergillus niger* [lipase AS “Amano”]) C-C bond forming Henry reaction between nitromethane and carbonyl acceptors (4-NBA and other aromatic aldehydes) has been demonstrated to proceed in an excellent manner in DESs, such as ChCl/glycerol (1:2). By the addition of up to 30 vol% of H₂O, it was found that the lipase activity could be improved, and under optimized conditions, a best yield of >92% was achieved (Scheme 6) [31].



Scheme 6. Lipase-catalyzed Henry reactions, as reported by Zhang and co-workers [31].

Interestingly, when the *aza*-Henry reaction was conducted between benzaldehyde *N*-tosyl imine and nitromethane in ChCl:Gly (1:2), the product was obtained in 17% yield after 40 h, proving that the NADES could catalyze the reaction. This is a similar observation to one of ours for a Michael addition reaction [18]. The reactions with the Lipase present gave slightly better yields (up to 39%). Unfortunately, the reactions were not enantioselective, but the authors expressed a desire to use site-directed mutagenesis and alterations in the reaction medium to make the outcomes enantioselective.

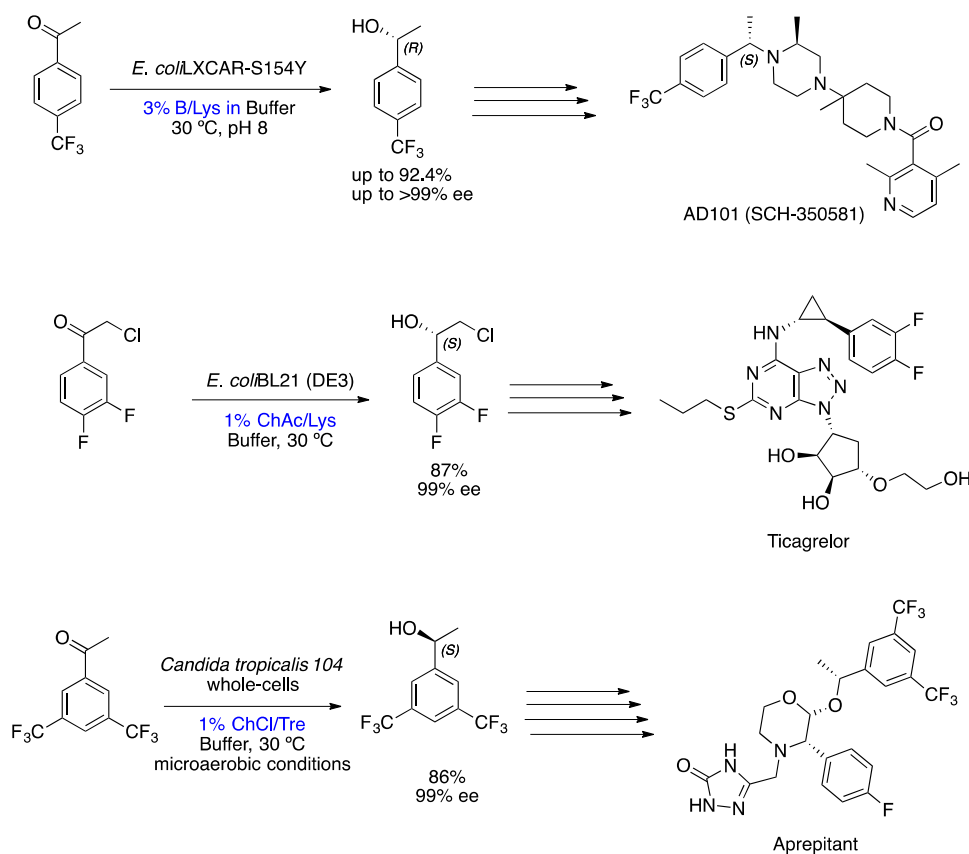
It was demonstrated that the “classical” benzoin condensation can operate at high efficiency under DES conditions (Scheme 7). As shown by Maugeri and Domínguez de María, benzaldehyde gives (*R*)-benzoin in a benzaldehyde lyase (BAL)-catalyzed enantioselective C-C bond-forming reaction in NADES/buffer mixtures in the presence of thiamine diphosphate (ThDP) and Mg²⁺ ions. The enzyme at hand is a thiamine diphosphate-dependent lyase (ThDP-lyase). The NADES/buffer mixtures were selected according to their composition and proportion. Three different NADES mixtures were studied, ChCl/glycerol, ChCl/urea, and ChCl/xylitol, and the best was ChCl/glycerol (1:2). Due to the high viscosity of NADESs coupled with the stability/activity of the enzyme, a certain quantity of buffer is required in the reaction; the best ratio found was 60:40 *v/v*. The reaction proceeds with 95% conversion and offers the product in an outstanding enantiopurity of >99% (*R*-isomer) [32].



Scheme 7. BAL-catalyzed enantioselective C-C bond formations in DES/buffer mixtures [32].

The preparation of chiral bioactive compounds, in many instances, requires enantiopure precursors, consequently implying that stereoselective reactions that can be catalyzed by biocatalysts in unconventional solvents, such as NADES solvents. As already mentioned, these solvents are very viscous and sometimes compromise the activity of the biocatalyst and, consequently, the productivity and enantioselectivity of the reaction. However, NADESs are increasingly being used in biocatalytic reactions, even though in smaller quantities than the buffer co-solvents. Further examples of the great potential of NADESs for biocatalysis are shown in Scheme 8. All of these examples are bioreductions of acetophenone derivatives, which have provided key enantiopure intermediates to important bioactive compounds, such as AD101 (SCH-350581) [33,34], Ticagrelor [35] and Aprepitant [36,37]. Xia et al. reported the preparation of (*R*)-1-[4-(trifluoromethyl)phenyl]ethanol through the bioreduction of 4-(trifluoromethyl)acetophenone biocatalyzed by recombinant *E. coli* LXCAR-S154Y and *Geotrichum* ZJPH1810, using 3% NADES/DES as co-solvents in a buffer (Scheme 8). The Betaine (B)/Lysine (Lys) (NADES) was chosen from the four DESs and 13 NADESs examined in this reaction, providing the desired product in up to 92.4% yield and up to 99% ee (preparative scale) at a substrate concentration of 400 mM [34]. He et al. described a stereoselective bioreduction of 2-chloro-1-(3,4-difluorophenyl)ethanone to (*S*)-

2-chloro-1-(3,4-difluorophenyl)ethanol catalyzed by recombinant *Escherichia coli* cells in reaction media containing 1% choline acetate (ChAc)/Lys with a buffer (Scheme 8). This ChAc/Lys mixture was selected from several NADESs due to enhanced coenzyme regeneration and improved cell membrane permeability during bioreduction, which explains the high conversion. The result was excellent, and the enzymatic reduction of the keto-molecule precursor made it possible to obtain the (S)-chlorohydrin with a yield of 87% and enantioselectivity of 99% ee with 1 M of substrate. Furthermore, the substrate loading in the established ChAc/Lys buffer mixture was increased 3.3-fold compared to the aqueous medium [35]. Another example reported by Zhu et al. was the enantioselective synthesis of (S)-1-[3,5-bis(trifluoromethyl)phenyl]ethanol in 86% yield and 99% ee through the bioreduction of the corresponding carbonyl group promoted by whole cells of *Candida tropicalis* 104 in 1% *w/v* NADES (mixture of ChCl/Trehalose (Tre) (1:1)) in a buffer (Scheme 8). The use of NADES as a reaction medium has been shown to be advantageous, increasing yield, cell viability, and cell membrane permeability to the substrate and, at the same time, protecting the cell [37].



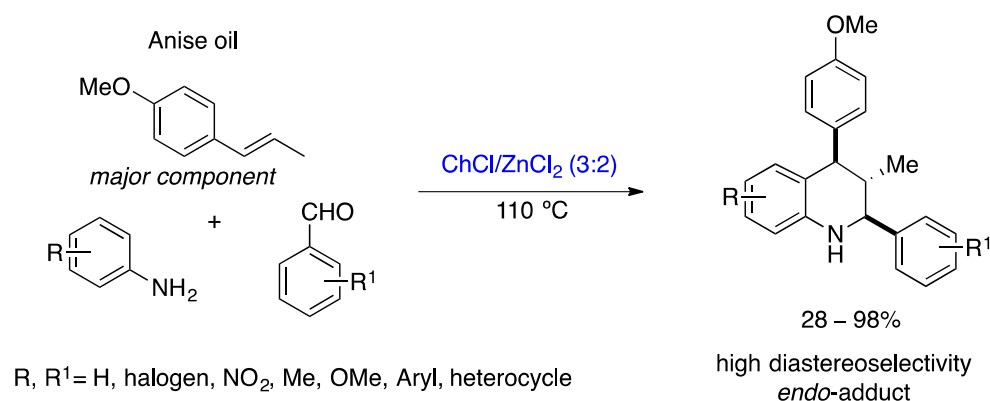
Scheme 8. Preparation of enantiomerically enriched intermediates through the bioreduction of acetophenone derivatives [34,35,37].

The examples showcased here provide convincing evidence of the influence that NADESs—in their various compositions—have on the outcomes of different biocatalytic processes. Moreover, the main message to be transmitted in these examples is that by carefully choosing the most appropriate NADES, we can get the most out of the enzymatic reactions at hand.

5. Metal-Based Asymmetric Catalysis (MBAC) in DES

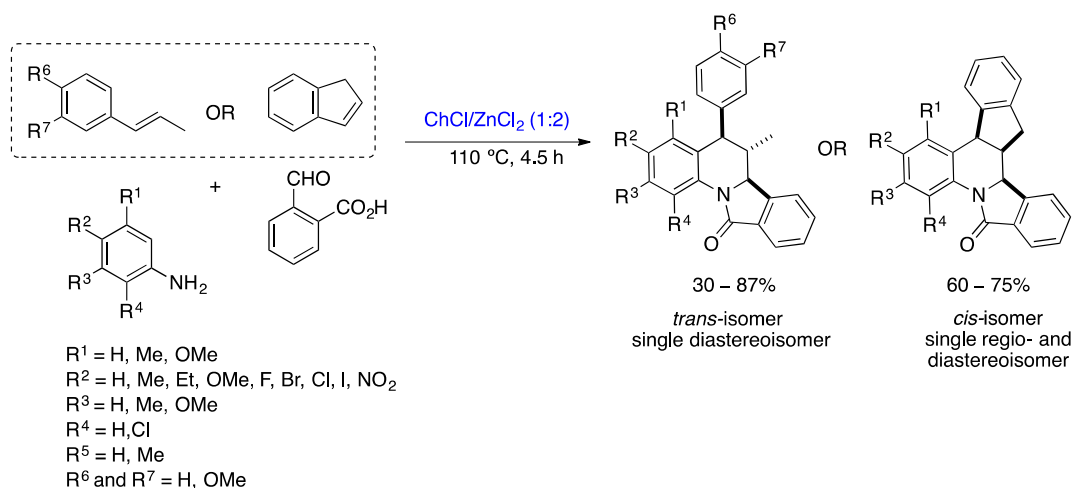
Metal-based asymmetric catalysis is very important for the preparation of bioactive chiral compounds in the pharmaceutical industry, but the toxicity of heavy metals and the volatile organic solvents jeopardizes its sustainability [38]. The use of DESs in asymmetric metal-based catalysis is the way to make these reactions more sustainable since

both the solvent and the metal catalyst can be reused several times. So far, DESs have shown their versatility in coupling reactions based on transition metals (Suzuki, Hiyama, Heck, and Sonogashira) and aminocarbonylations or Pd-catalyzed C-S bond formation reactions, among others. In most of these reactions, the DESs performed well, in that they gave very good-to-excellent yields, and it was possible to reuse the solvents and the catalysts several times, while maintaining the activity [38,39]. Furthermore, these reactions are part of the synthetic pathway for various bioactive compounds [40,41]. Despite its extraordinary performance in metal-based catalysis reactions, its application in asymmetric catalytic synthesis based on metals is rare. So far, only a few examples have been reported in the literature, and the metals have been used in stoichiometric quantities rather than catalytic. Peñaranda-Gómez et al. reported a sustainable and diastereoselective method for the preparation of tetrahydroquinoline derivatives from star anise oil, using a mixture of choline chloride (ChCl)/zinc chloride as the DES (Scheme 9) [42]. This diastereoselective synthesis is a multicomponent inverse electron-demand *aza*-Diels–Alder reaction, carried out with anise oil (the main component is *trans*-anethole), anilines, and aromatic aldehydes in ChCl/ZnCl₂ mixtures (3:2) at 110 °C for 3 h, providing a total of 22 tetrahydroquinoline derivatives in low-to-excellent yields with high diastereoselectivity [42]. The diastereoisomers formed have the *cis*-(2*e*,4*e*) configuration, which was determined by NMR analysis. In addition, DESs can be recycled for three cycles and still maintain their activity. The DESs in this reaction act as a solvent and catalyst and are crucial to the reaction. It should be emphasized that tetrahydroquinoline derivatives are value-added compounds in the field of medicinal chemistry. Differential scanning calorimetry (DSC) determined the best temperature and composition of DESs for this multicomponent reaction.



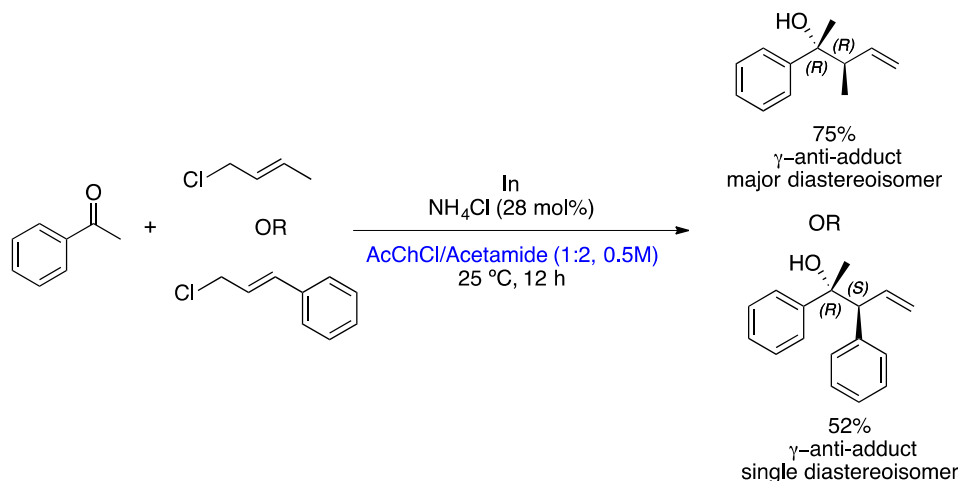
Scheme 9. Diastereoselective synthesis of tetrahydroquinoline derivatives in DES described by Peñaranda-Gómez et al. [42].

Recently, Sanabria-Sánchez et al. developed a multicomponent, diastereoselective, one-pot Povarov reaction in DESs for the preparation of a wide variety of dihydroisoindolo[2,1-a]quinolin-11-ones derivatives. Similar to the methodology described by Peñaranda-Gómez et al. [42], the DESs act as both the solvent and catalyst. Various DESs consisting of Lewis or Brønsted acids were studied, such as ChCl/ZnCl₂, Urea/ZnCl₂, ChCl/MgCl₂, ChCl/SnCl₂, ChCl/APTS, ChCl/CF₃SO₃H, and ZnCl₂/ethylene glycol and reaction conditions to choose the best system, ChCl/ZnCl₂ (1:2) at 110 °C for 4.5 h (Scheme 10) [43]. Twenty dihydroisoindolo[2,1-a]quinoline-11-one derivatives were prepared with yields of up to 87% and high diastereoselectivities by reacting a wide variety of anilines, alkenes (*trans*-anethole, methyl eugenol, and indene), and 2-formylbenzoic acid in ChCl/ZnCl₂ (1:2) at 110 °C for 4.5 h. ¹H NMR analysis of the compounds confirmed the production of a single diastereoisomer, the 6,6*a*-*trans* isomer. In addition, the DES mixture could be reused for six cycles without loss of activity.



Scheme 10. Synthesis of dihydroisoindolo[2,1-a]quinolin-11-one derivatives via the Povarov reaction in DESs [43].

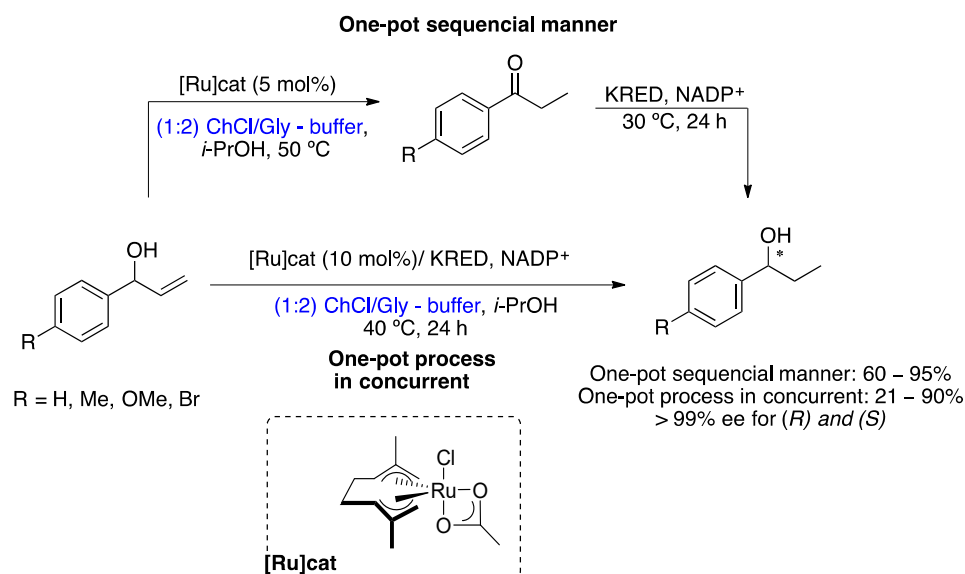
The development of more sustainable methods for the preparation of homoallylic alcohols is of great interest to the pharmaceutical industry. González-Gallardo et al. reported the allylation of various carbonyl compounds via indium organometallic and allyl chloride derivatives in DESs. Several DESs were studied for this reaction, such as choline chloride (ChCl)/ethylene glycol (1:2), acetylcholine chloride (AcChCl)/acetamide (1:2), ChCl/glycerol (1:2), ChCl/urea (1:2), MePPh₃Br/glycerol (1:2), ChCl/L-malic acid (1:1), and ChCl/D-galactose (5:2). To the reactions carried out with the DESs ChCl/ethylene glycol (1:2) and AcChCl/acetamide (1:2), ammonium salts (NH₄Cl or NH₄OAc) were added to stabilize the species of In, furnishing the desired product with excellent yields. Once both of the DESs gave excellent yields, the AcChCl/acetamide mixture was selected as a solvent due to its lower toxicity [44]. Twenty homoallyl alcohol derivatives were prepared in moderate-to-excellent yields through the Barbier allylation of a wide range of carbonyl derivatives and chloroallyl substrates mediated by indium (stabilized by NH₄Cl) in DESs at 25 °C for 12 h. However, only two of them showed diastereoselectivity, those prepared from γ -substituted allyl chloride derivatives (crotyl chloride and cinnamyl chloride). In both cases, the *anti*-adduct was the sole or the major diastereoisomer formed according to Scheme 11. The recyclability of DESs and NH₄Cl was studied over six cycles, but performance was only maintained over four cycles. In any case, it can be emphasized that DESs perform well in organometallic reactions, making these reactions more sustainable due to their lower toxicity and good recyclability.



Scheme 11. Barbier allylation of acetophenone mediated by In in DESs [44].

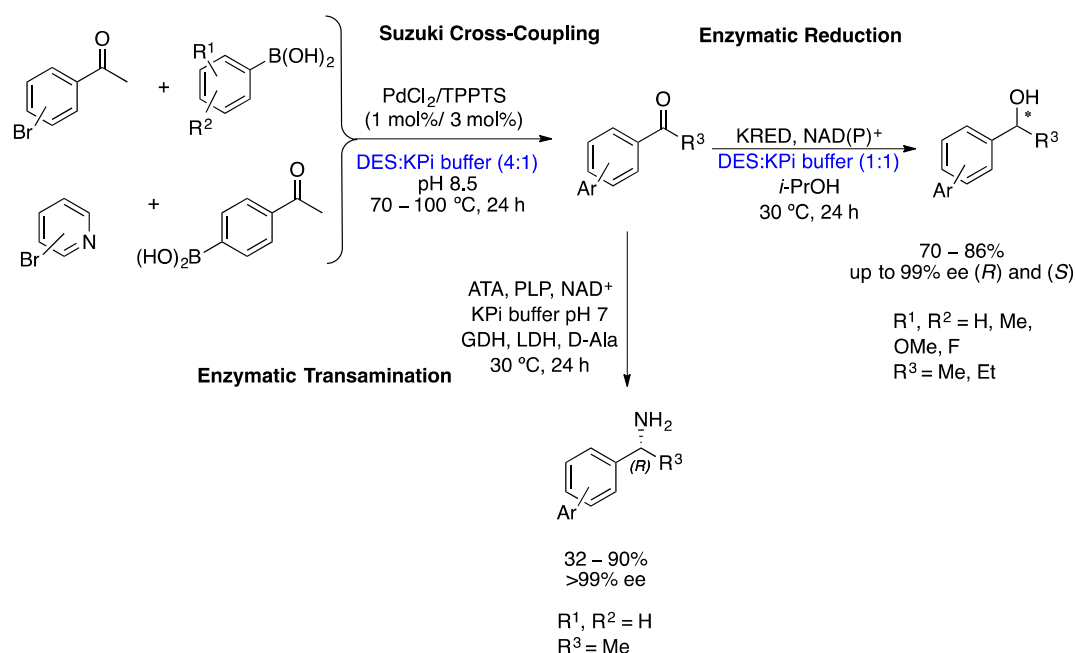
Another promising approach is the chemoenzymatic cascade, which combines transition metal catalysis and biocatalysis for the asymmetric synthesis of bioactive molecules [45]. Basically, metal/enzymatic cascades and sequential transformations consist primarily of the role of metal species (Pd, Ru, Au, Ir, and Fe) in catalyzing various organic reactions (C-C couplings, isomerizations, and hydrations) and their combination with stereospecific enzymes, including alcohol dehydrogenases, alcohol oxidases, aldolases, amine dehydrogenases, and amino acid dehydrogenases, among others. The use of DESs in metal/enzymatic cascades and sequential transformations is rare, but the few results that have been reported are very promising for the pharmaceutical industry.

The first successful example of the integration of metal and biological catalysis in DESs/buffer mixtures was reported in 2018 [46]. This chemoenzymatic cascade consists of the ruthenium-catalyzed isomerization reaction of allylic alcohols to an α,β -saturated ketone, followed by enantioselective enzymatic reduction promoted by ketoreductases (KREDs), providing enantiopure alcohols (Scheme 12). This chemoenzymatic cascade was carried out using two different approaches, a sequential reaction (one-pot in two steps) and a simultaneous (concurrent) reaction (one-pot in one step). The choice of solvent mixture, based on DESs and buffers, was made carefully, making it possible for both reactions to take place without inhibiting the metal catalyst or the enzyme. The best mixture of DESs was ChCl/glycerol (1:2) or ChCl/sorbitol (1:1) for enantioselective bioreduction; however, for the chemoenzymatic reactions, the first mixture of DESs was chosen due to the high viscosity of the sorbitol-based DES, even at 40 °C. In the case of the sequential approach (one-pot in two stages), the first stage involves the Ru-catalyzed isomerization of racemic allylic alcohols in DESs buffer, *i*-PrOH at 50 °C, after consumption of the starting material; for the second stage, the temperature was reduced to 30 °C and KRED and its cofactor (NADP⁺), obtaining the desired chiral alcohols in good-to-excellent yields and high enantioselectivities. With regard to the second approach, the simultaneous reaction (one pot in one step), both catalysts were added at the start of the reaction; for this reason, the enzyme showed poor stability in the aqueous buffer, resulting in incomplete reactions, providing the desired product mixed with unreacted ketone, and in some cases, allyl alcohol was also obtained, indicating slow isomerization. However, five chiral saturated alcohols were prepared in low-to-excellent yields and with excellent enantioselectivities via the chemoenzymatic reaction of allylic alcohols catalyzed by KRED and Ru complex (10% mol) at 40 °C in ChCl/Gly (1:2)/buffer (4:1) (Scheme 12).



Scheme 12. Chemoenzymatic cascade for the preparation of enantiopure saturated alcohols from racemic allylic alcohols in DES/buffer mixtures [46].

In 2018, Paris et al. described the first application of DESs as a solvent in Suzuki coupling, followed by bioreduction for the preparation of enantiopure biaryl alcohols in very good yields (up to 86%) and excellent ee (>99%) (Scheme 13) [47]. The two-step method consists of the palladium-catalyzed Suzuki coupling of 4'-haloacetophenones with arylboronic acids at 70–100 °C in a choline chloride/glycerol (Gly) buffer mixture, followed by the enzymatic reduction of the ketone formed catalyzed by alcohol dehydrogenases at 30 °C. Separately, both the palladium-catalyzed coupling reactions and the bioreductions were previously carried out in mixtures of DES and DES/buffer. Subsequently, the reaction conditions were optimized with regard to the choice of components and the proportion of DES mixture: the proportion of DES and buffer and also the substrate concentration. Using these ChCl/Gly (1:2)/buffer (4:1) conditions at 100 °C for the Suzuki coupling step for a 200 mM substrate, it was possible to prepare 10 biaryl ketone derivatives in high yields. In addition, the reaction conditions for enzymatic reductions were optimized, requiring dilution to 75 mM with a buffer containing *i*-PrOH, ketoreductases (KREDs), and cofactor (NADP⁺) to establish an efficient bioreduction of the transiently formed ketone. Using these conditions, it was possible to reduce a wide variety of substrates. Furthermore, using the stereocomplementary ADH enzymes of *Lactobacillus kefir* and *Rhodococcus ruber*, it is possible to obtain enantiopure (*R*)- and (*S*)-biaryl alcohols.



Scheme 13. One-pot chemoenzymatic cascade for preparation of enantiopure biaryl alcohols [47] and enantiopure biaryl amines [48].

Later, the same groups of Gröger and González-Sabín reported the preparation of enantiopure biaryl amines through a chemoenzymatic cascade in DESs/buffer mixture, which consists of a palladium-catalyzed cross-coupling reaction followed by enantioselective enzymatic amination (Scheme 13) [48]. As described above, the first step was the optimization of the reaction conditions by choosing the most suitable solvent for both reactions to take place in excellent yields. The best DES (co-solvent) for this chemoenzymatic cascade was (1:2) ChCl/Gly. In addition, biocatalysis using amine transaminases (ATAs) in DESs has not been reported before. The reactions were carried out according to the schematic representation (Scheme 13), the Pd-catalyzed step was carried out at 200 mM substrate loading in a DES/buffer mixture (4:1), and the biocatalysis step was carried out at 25 mM before dilution to a buffer containing 10% *w/w* DES due to enzyme stability problems. Five (*R*)-biaryl amines were prepared using this methodology in low to very good yields with excellent enantioselectivities (>99% ee) [48].

The preparation of chiral compounds through asymmetric catalytic syntheses carried out in DESs has not been widely explored so far, perhaps because, in general, chiral metal complexes (consisting of a chiral ligand coordinated to a metal) are probably very sensitive to the aqueous medium and end up decomposing; another aspect is that most DESs contain other components that coordinate with the metal, giving rise to racemic products. An alternative is to resort to the chemoenzymatic cascade or the use of organocatalysts for the preparation of chiral compounds, since both approaches have shown very promising results using DESs as reaction media.

6. Conclusions

In this review, we looked at recent developments in the use of NADES in asymmetric catalysis, from the point of view of metal-based catalysis, organocatalysis, and biocatalysis. By far, perhaps for historical reasons, this alternative solvent system has been used more frequently in biocatalysis than other catalytic reactions. Despite the great potential of this alternative medium, the number of asymmetric reactions so far examined has been limited, being restricted mainly to Aldol, Henry, Michael, α -aminations, asymmetric hydrolysis, benzoin condensation, Barbier allylation, and some others, but this will undoubtedly improve in the coming years.

With regard to the use of NADES in metal-based catalysis for the preparation of chiral bioactive compounds, we can see that it has been very little explored. However, the few examples in the literature have shown that DESs help to stabilize catalysts and could also be recycled many times, maintaining their activity. Chemoenzymatic cascade reactions are another alternative approach for the enantioselective preparation of bioactive compounds in which NADES have been successfully used.

Many challenges and opportunities remain—the most intriguing of which is their application as both solvent and catalyst—to provide single enantiomer or scalemic products without the requirement for the addition of a chiral catalyst, as our group previously showed for a simple organocatalyzed Michael reaction [18]. This, in fact, is something we are actively working on at the current time.

There have been some reports of solid-supported NADES in the literature [49], signifying a very exciting sustainable approach to performing chemical reactions, and we expect that there will be further developments in this field in the near future.

The ability to use the NADES as both a solvent and reagent is very appealing from a sustainability point of view, and some examples are known (see Section 4 above). This approach should become more common in the near future, with a goal towards plug-and-play-type chemistry; this becomes even more interesting when the catalyst is also incorporated into the NADES.

Besides being renewable, NADES components are also biodegradable and cheaper than their petroleum-based solvent counterparts. And from a production point of view, they are safer to transport than classical industrial solvents, such as ethers and aromatic and chlorinated hydrocarbons.

The effect of the NADES on the reaction system was briefly discussed in this report, and it would be honest of us to say that NADES are “non-innocent” solvents. This is something that will need to be seriously addressed so that the advantages of NADES can be maximized for efficient and selective chemical synthesis. The problem with restricted mass-transfer is also an issue that will need to be carefully resolved or at least improved as we go forward.

As far as we are aware, there have been no reports on the use of NADES in photoredox and continuous flow processes, due to certain practical issues, but one can predict that such applications will be inevitable in the near future.

On a final note, we expect that there will be further and more frequent applications of NADES in stereoselective transformations in the coming years, including larger-scale applications, which, to the best of our knowledge, have not been intensely studied yet.

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