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How deep eutectic solvents are currently shaping organocatalytic and enzymatic asymmetric catalysis

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Asymmetric catalysis is a key technology that provides enantiomerically pure compounds that are vital for the pharmaceutical, agrochemical and food and fragrance industries. It has been recently observed that asymmetric catalysis can be successfully conducted in sustainable systems known as Deep Eutectic Solvents (DESs) or natural deep eutectic solvents (NADESs) when biobased materials are used. This paper provides a critical perspective on these systems, exploring their limitations and relevance for the production and development of new pharmaceuticals and other high-value-added substances. It also looks are very recent developments in this area, whereby, the actual DES can act as the catalyst, the reactant and be part of a supramolecular construct, known as EutectoGel that enhances the sustainability of the process.

Sustainability spotlight

The focus of this article is on the applications and benefits that Deep Eutectic Solvents (DESs) and principally Natural DESs (NADESs, which are derived from biomass chemicals, like amino acids, sugars, *etc.*) have and will continue to have on asymmetric catalysis, principally with an eye on potential industrial applications. Currently at the industrial level there is enormous pressure to reduce the consumption of non-renewable solvents, which present significant disposal issues and contribute substantially to the global carbon-footprint. We show how NADESs can reverse this situation, making chemical processes more sustainable at both industrial and non-industrial scales. This article ties in closely with the UN Sustainable Development Goal 12, which is concerned with sustainable consumption and production with a particular focus on chemical waste disposal. Additionally, it also is linked to the UN Sustainable Development Goal 9, which focuses on sustainable industrialization and innovation.

1. Introduction

The compositions known as Deep Eutectic Solvents (DESs) are obtained from a combination of a hydrogen-bond donor (HBD) compound with a hydrogen-bond-acceptor (HBA) compound, and due to the formation of a network of random weak interactions, a regular crystal lattice cannot be achieved, and a liquid is obtained (Fig. 1(i)). These are highly tunable systems, obtained from various combinations of HBD and HBA and possess many significant advantages that include recyclability, non-flammability, non-toxicity and a low ecological footprint.[1,2] Those that are obtained from biomass derived renewable resources, like sugars, amino acids, or organic acids are called Natural Deep Eutectic Solvents (NADESs). Some of the most common HBD-based NADESs include urea, glycerol, malic acid, tartaric acid, *etc.*, and common HBAs include trimethylglycine (betaine), choline chloride, proline, alanine, *etc.* Several reactions have already been successfully carried out in NADESs,[3,4] including catalytic asymmetric reactions using enzymes[5] and organocatalysts.[6–8] The main advantages of using NADESs in catalysis, are that they become even more sustainable in the sense that they are renewable, and that the catalyst can be recycled (by immobilization in the NADES). In some cases, the NADESs function themselves as the catalyst (*vide infra*) and have been used for producing Active Pharmaceutical Ingredients (APIs). A very attractive approach is the use of Reactive DESs (RDESs) (*vide infra*) which has been applied particularly in biocatalysis. Chiral RDESs also exist but have had only moderate success (see below for an example).[6] Our group has been very active in this area having developed a novel RDES for a multi-component reaction. Reports on biocatalysis with DESs have increased exponentially in the last 20 years.[5]

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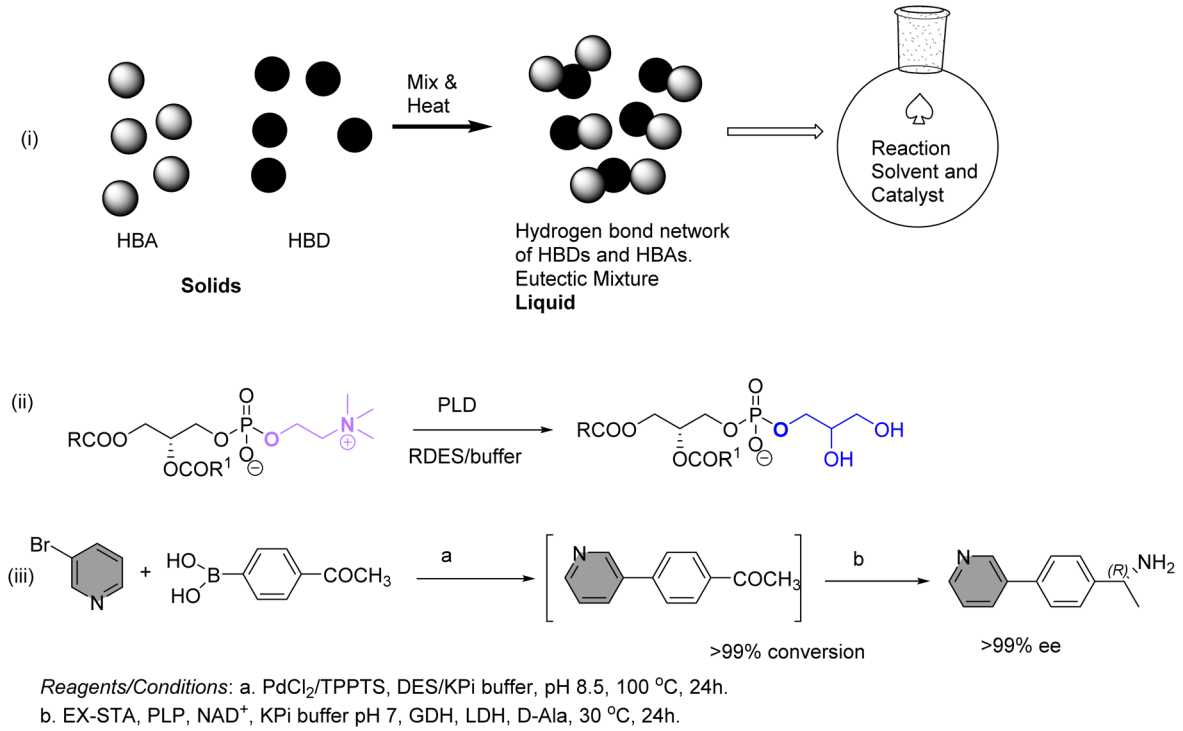

Fig. 1 (i) Formation of NADESs from HBA and HBD building blocks. (ii) The use of RDES in biocatalytic phospholipid preparation. (iii) A sequential metal-catalyzed/biocatalyzed transamination.

2. Bio- and organocatalysis as enabling technologies

Biocatalysis and organocatalysis are key tools for producing chiral non-racemic compounds in the pharmaceutical, flavor, fragrance and agrochemical industries. Due to the inherent advantages of NADESs, several biocatalytic and organocatalytic reactions have already been performed with great success in NADESs. In the case of biocatalytic reactions the key advantage is the stabilization conferred to the enzyme by the NADES, eliminating the need for performing complex immobilization steps. The reaction types studied to date include redox, transamination, hydrolysis, and chemo-enzymatic cascades.[5] Allegretti *et al.* reported groundbreaking work on the preparation of polar head modified phospholipids using a phospholipase D (PLD)-catalyzed biotransformation in a reactive NADES composed of choline chloride and glycols.[9] The glycol component acts as the nucleophile that substitutes the choline unit (Fig. 1(ii)). Yield enhancements were observed due to mass effects and product precipitation.

Chemo-enzymatic cascades are a very powerful approach to producing important enantiopure targets, like drugs, agrochemicals, *etc.* This approach has been used by various groups over the last decade and has found an ideal match with continuous flow methods. By the same token, chemo-enzymatic methods are also very well suited to NADESs.[5] One very nice example is the report by the groups of Gröger and González-Sabín, who performed enantioselective sequential one-pot synthesis of biaryl-substituted amines using a combination of a Suzuki–Miyaura reaction and an enzymatic transamination in a NADES–buffer mixture (Fig. 1(iii)).[10] It should be noted that the biarylmethyl amine motif is an important pharmacophore, as it is present in a host of APIs like, *Valsartan* (treatment of high blood pressure), *Odanacatib* (osteoporosis in post-menopausal women), *Vancomycin* (microbial infections), *BIIB042* (Alzheimer's disease), *etc.* In their approach these workers used a limited number of bromophenylacetophenones and phenylboronic acids (or bromopyridines and *p*-$(B(OH)_2$-acetophenone) for the palladium catalyzed coupling (with triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt hydrate (TPPTS), as the ligand), choline chloride (ChCl)/glycerol (Gly) (1/2) and phosphate buffer (ratio 1 : 4). The reaction was run for 24 h at 100 °C before the transaminase enzymes (EX-STA or EX-wt), with the co-factors NAD^+, pyridoxal-5′-phosphate (PLP), D-alanine (amine source), glucose dehydrogenase (GDH) and lactate dehydrogenase (LDH)) were added, and the reaction was run at 30 °C for 24 h (Fig. 1(iii)). Quantitative conversions and enantioselectivities, as well as high yields, were obtained with EX-STAT. In the case of EX-wt (the wild type enzyme) the results were more disappointing, *i.e.* the conversions were low. One of the key advantages of using the NADES was the ability to overcome solubility hurdles, as the Suzuki–Miyaura reaction could be run at a substrate load of 200 mM and the enzymatic reaction at 25 mM. Besides, this study underscores the importance of medium engineering for optimizing chemical reactions.

Organocatalytic applications in NADES are less developed and have been limited to a few reaction types. At the outset, the catalysts were added to the NADES (*e.g.*, cinchona and proline

catalysts) generally in ChCl based NADES.[7,8] Some excellent enantioselectivities could be obtained for a Michael addition using a cinchona-amine.[6,7] Later, organocatalysts, like proline and sugars were used as part of the NADES composition, and this is currently a hot area of interest. Unfortunately, to date the results are not very satisfactory, in that the stereoselectivities are not very high and the reactions require long reaction times. Our research group is currently developing novel tailor-made chiral NADESs that can be used in synthesizing single enantiomers for pharmaceutical applications. The control of the enantioselectivity is non-trivial, and there have been some attempts using analytical approaches (NMR, ATR-FTIR, DSC (Differential Scanning Calorimetry), *etc.*) to gain a better understanding of the dynamics involved at the molecular level so that the stereoselectivities can be improved.[9] Computational methods have also been used.[11]

One approach to control enantioselectivity is the use of supramolecular constructs known as eutectogels. These are soft-material versions of NADESs, obtained by adding an appropriate gelator to the NADES, thereby forming a supramolecular structure that can confine both the substrates and the catalyst thus providing better stereocontrol in the reaction. They can improve organization and grouping of the reactants and reagents, with better interactions so that higher yields and selectivities can be achieved. D'Anna and Ramón's groups successfully developed a ChCl/urea and L-proline Eutectogel system that gave very promising results in an Aldol reaction (20 °C, 24 h, enantioselectivities up to 97% ee).[12] Chiral EGs have also been reported, with a view to their application as novel chiroptical materials but they have never been used as catalysts.[13,14]

As regards the future, it is expected that further reaction types will be studied, particularly those leading to APIs and other valuable targets. There is also anticipation of a greater role for artificial intelligence (AI) and machine learning in NADES optimization and in tailoring the reactions conditions to suit the NADES composition. That said, these tools can also be applied for the optimization of the NADES composition for biocatalytic and other reactions. There have already been key developments in the application of AI and machine learning to assist with NADES property design and to tailor the physicochemical properties for specific applications, mainly in the fields of extraction, biocatalysis and pharmacology.[15]

3. Challenges and opportunities

The introduction of deep eutectic solvents (DESs) and their natural counterparts NADESs, has brought new opportunities to the industry in the search for chemical reaction systems capable of addressing weaknesses and unmet needs in areas such as environmental impact, safety, and cost. Partially, this has been achieved by virtue of their superb solubilization properties for a variety of compounds such as organic molecules and drugs.[16] Their applications are manifold as demonstrated by examples from biodiesel production, bioproduct extractions, organic synthesis, catalysis, electrochemistry, and metal processing.[17] Thus, there are areas which offer a perfect match with technologies in high demand for the manufacture of active pharmaceutical ingredients (APIs), particularly in general synthetic organic chemistry and catalysis. This aligns well with the tremendous development experienced over the past 5 decades or so in designing production methods for medicinally relevant molecules of ever-increasing complexity.

To date, we have already witnessed the profound influence exerted by (NA)DESs in the chemical synthesis arena, not least in the pharmaceutical space. It feels as though we are still in the early stages of exploring these unique solvents and have only begun to examine the advantages they may offer over more conventional counterparts. With the introduction of the concept of green chemistry in the 1990s, the guiding principles[18] expressed therein have been adopted virtually across the whole world, all the way from bench chemistry to full scale commercial production.[19] When specifically focusing on catalysis, the preparation of modern small molecule APIs (typically with molecular weight <500–800 Dalton) often relies on one or several catalytic reaction steps, be it in chemo-, bio- or organocatalysis mode, driven by the steadily increasing structural complexity of target medicines. This scenario is even more pronounced in the portfolio of drug molecules still in the R&D phase on their path to become approved medicines. Therefore, the industry is in urgent need of technologies, entirely novel or modified, that can respond in a positive way to future demands.

With solvents taking on the role of enablers of chemical transformations, it is, no doubt, very logical to put a major emphasis on their properties and performance. It does, however, not stop here, as, especially when contemplating use on larger scales, a range of critical parameters such as environmental impact, recyclability, safety and hazards features, commercial availability, and cost must be factored in. Furthermore, pharmaceutical products are expected to match the highest quality standards and, therefore, components used in their manufacture, for example starting materials, auxiliaries, protecting groups, solvents, *etc.* must be either absent from the final drug product or proven non-harmful. These criteria being maintained rigorously by authorities worldwide are in place due to patient safety and will, consequently, also apply to NADES.

As far as we are aware, NADES use within the chemical and pharmaceutical industry establishment is still scarce, whether for drug discovery/development or production, but academic research suggests that this will be a key enabling technology on an industrial scale in the future – due to their green chemistry attributes, biocompatibility and environmental friendliness, for instance, as well as their reactivity in certain cases (RNADES). A very recent example providing strong reasons to adopt an optimistic view in this regard has gained further momentum as showcased by promising examples from areas such as motion sensing and wound healing.[20] As shown by *in vivo* studies, conductive hydrogels based on DES demonstrate excellent biocompatibility and low cost, underpinning their suitability as entities for advanced materials, for example in the form of eutectogels (*vide infra*) which nicely combine properties of hydrogels and eutectic solvents. Moreover, the area of biocatalysis has benefited greatly from these tools in the last few years and it can be anticipated that key biocatalytic production

routes using NADES will be developed for operation on an industrial scale in the foreseeable future. Suffice it to say, we are only at the beginning of reaping the fruits in the form of a diverse range of applications offered by eutectic solvents in general and NADES in particular.

4. Chemistry as an enabler of novel medicines

The past few decades have seen a stunning development of novel medical treatment paradigms that now provide patients with efficient drugs in many therapeutic areas, for example in the cardiovascular space, cancer prevention, metabolic diseases, pain relief, infectious challenges, psychiatry, and neurology. This has revolutionized health care and improved quality of life in ways that seemed improbable only one or two generations ago. Major contributing factors to this are of course the deeper understanding of the underlying causes for diseases, their possible genetic background, and biochemical mechanisms involved together with the plethora of risks originating from external sources, *e.g.* bacteria and viruses. Equally important, however, is highlighting the essential role of chemistry, at large, in the elucidation of how molecular entities interact with specific biological targets, for example, enzymes, responsible for maintaining and controlling the functions of life. This requires an in-depth understanding of such interactions at the atomic level—how they function and can be controlled or manipulated to achieve the desired effect.

There is one aspect of pharmacologically active compounds that has profoundly changed the roadmap in medicinal and process chemistry alike – the phenomenon of chirality or the handedness of molecules (analogous to left and right hands, feet or ears). While historically the medicines provided to patients were racemic (50 : 50 mixture of stereoisomers) in many cases, unless they represented achiral moieties (featuring identical mirror images), the 2nd half of the 20th century experienced a pronounced shift towards using only the enantiomer responsible for the desired pharmacological effect, at the same time avoiding toxicity or other potentially harmful side-effects.[21] This development has posed considerable challenges for the entire drug industry and especially for synthetic chemists, whose foremost task is to devise reliable methods on how to prepare active molecules with the right structure and quality taking the desired stereochemical aspects into account. At present, after considerable time spent on the discovery and exploration of novel methods in joint efforts by the scientific community in academia and industry, procedures are available to prepare life-saving compounds and medicines at virtually any scale.[22]

Of the three previously mentioned catalytic categories, two dominate the playing-field entirely – the use of metals in various shapes and forms (homogenous/heterogenous) and enzymes from natural sources or prepared *via* evolutionary techniques. However, the third technology in the toolbox, organocatalysis, is now an established area which has undergone an amazing journey from its original discovery in the early 1970s to the current days, receiving a lot of attention and demonstrating many practical applications. Thus, over the years we have seen the addition of a variety of specific catalysts and families of catalysts, capable of enabling highly efficient transformations across a broad range of organic substrates. More recently it has been shown that organocatalytic reactions can be conducted in DESs and are not restricted to more traditional conditions relying on standard solvents. Based on these very promising findings, the green profile of "classical" DESs and their natural analogues NADESs has begun to be explored more widely – an endeavor entirely in the interest of chemical and pharmaceutical industries.[23] The capability of tailoring the physicochemical parameters (particularly, polarity and viscosity) of NADESs through a judicious choice of starting components in a combinatorial manner, makes them an excellent choice for chemical processes.

The organocatalyzed asymmetric Michael reaction is a very useful tool, especially when aiming for C–C bond formation, providing key APIs, like, Telcagepant (antimigraine), (*S*)-Pregabalin (anticonvulsant, analgesic), (−)-Paroxetine (antidepressant), Baclofen (muscle relaxer, antispasmodic), *etc.*[24] The ability of conducting such reactions within NADES systems is very attractive. In fact, very promising performance of an asymmetric Michael addition using a chiral cinchonasquaramide catalyst in a betaine-reduced sugar NADES was recently demonstrated (Fig. 2).[25] It was proposed that the betaine unit probably acts as the Hydrogen Bond Acceptor (HBA), whilst sugars, like D-sorbitol, D-mannitol, and D-xylitol act as the Hydrogen Bond Donor, HBD. Experimental evidence supported the transient formation of a catalyst–substrate–reagent complex where NADES confers a stabilizing influence and a three-dimensional bias favoring one of the stereoisomers. A particularly attractive feature is the easy work-up of the reaction mixture which allows operation in standard process equipment. The absence of metals, especially the transition/rare types, *e.g.* Pd, Rh, and Ir, provides the benefit of eliminating the need for sophisticated work-up to ensure their residual content in the product remains below the accepted tolerance level (frequently in the low ppm range). Ignoring metals of this kind also has a positive impact on the cost of goods as they often contribute significantly to the price of the API due to their high expense.

5. Impacting chemical and pharmaceutical production

Manufacturing active pharmaceutical ingredients (APIs) has seen a tremendous development of methods and technologies over the past 5 decades or so. This has been driven by a whole raft of factors, for example increasing molecular complexity of the target molecules, higher quality demands, pressure on cost of goods, environmental concern forcing producers to prioritize catalytic solutions in favor of traditional stoichiometric counterparts, and sustainability to mention some of the more impactful ones. An overarching trend in this space has, no doubt, been the introduction of the green chemistry paradigm

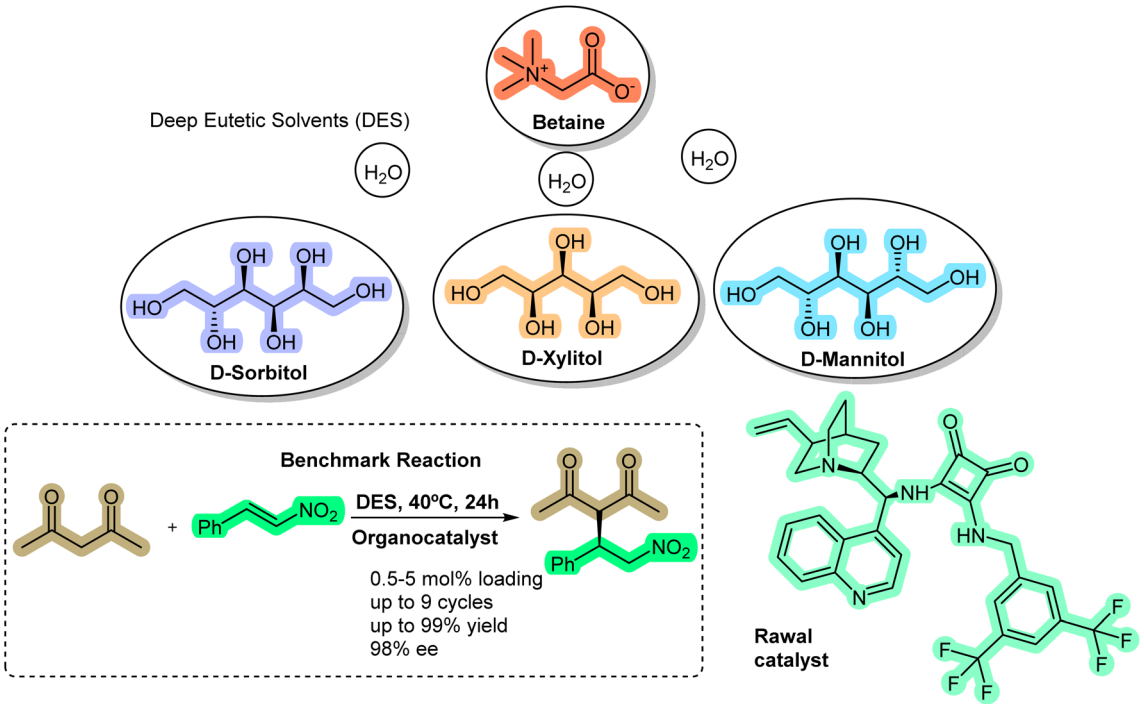

Fig. 2 Classical Michael reaction as a model to demonstrate the performance and outcome of the organocatalytic synthesis strategy in a variety of NADES systems based on betaine and reduced C_5/C_6 sugar alcohols.

as mentioned before.[18] Putting emphasis on chemical synthesis inevitably brings catalysis into focus. Thus, in a synthetic sequence of a small molecule API (molecular weight of 300–600 Dalton), it is, nowadays, customary to find at least one catalytic step, if not multiple. This situation applies not only to the R&D phase of a drug project but continues into the full-scale manufacturing arena and currently many of the top-line medicines marketed world-wide follow this scenario.

One basic factor to be mindful of in this context is the far-reaching regulatory rules that govern the pharmaceutical business in most countries worldwide. In essence, this means that the chemical manufacturing process of an active ingredient in a medicine must be validated as safe and of the appropriate quality for the intended use. As all components introduced in the manufacture – starting materials and building blocks, solvents, auxiliaries, *etc.* – inevitably leave their fingerprint on the finished product, it is an onerous task to attempt changes to already registered synthetic routes. Therefore, the upfront design of a process must take into account as many of the quality-affecting parameters as possible; preferably all of them. Focusing specifically on solvents, which find abundant use as reaction media for pharmaceutical manufacture, it is not uncommon that many of these are associated with an unwanted environmental impact. Thus, there is an inherent desire to find better alternatives and the outlook for success, given that the chemical reaction performance is not affected in an overly negative way, is higher when shifting to a solvent with a proven track record of being harmless. Altogether, these circumstances underpin the operation of organocatalytic chemistry in NADESs[16] by virtue of their excellent match with crucial parameters guiding the preparation of pharmaceuticals. Besides the intrinsic environmental friendliness of these versatile solvents, their recovery and recyclability is essential.

6. Academic–industrial liaison to drive technical capabilities forward

One of the key messages of the above commentary is the desire to implement chemical production in a sustainable, efficient, economical and environmentally friendly manner. The use of highly active cheap catalysts and renewable, environmentally friendly solvents is one way to achieve this objective.

During the post-pandemic period several academic laboratories have actively developed Reactive NADES (RNADES) and Chiral NADES (CNADES) to resolve the above issues. The use of NADES for the synthesis of pharmaceuticals has already emerged as a clear game-changer[26] and NADES for asymmetric organocatalytic synthesis of pharmaceuticals has already been identified as an emerging field.[27]

The harnessing of RNADES platforms is very attractive, particularly from a process intensification point of view. By creating a NADES system from reaction components (reactant or reagent) it helps address the issue of solvent waste disposal (to a certain degree, less solvent usage). It can also increase the reaction rate, through reactant/reagent concentration. The other aspect is that the solvent can be renewed by replenishing the consumed component, allowing further reaction cycles o easily be carried out. Although some biocatalytic asymmetric catalytic reactions using RNADES are known, there have been no reports on the non-biocatalytic asymmetric reactions in

RNADES. Nonetheless, there have been interesting applications in the pharmaceutical context, like the report by Di Giola and co-workers, on the synthesis of racemic *Atenolol* (Fig. 3(a)), an anti-hypertension drug developed in the 70's.[28] One of the key steps involved the synthesis of an epoxide intermediate using epichlorohydrin, and it was found that best results (>99% conversion, 95/5 selectivity in favor of the glycidyl ether as opposed to the halohydrin) were obtained using ChCl/ethylene glycol (1 : 2) at 40 °C for 6 h. Amazingly, the reaction could be repeated up to 3 times! The NADES is proposed to have a catalytic effect, namely through nucleophilic catalysis, forming a key dichloropropanol intermediate (activated by glycol) that reacts with the phenyl-amide, yielding an halohydrin that undergoes ring closure to form the glycidyl ether (Fig. 3(a)). The process could be run at a 10 g scale, and several cycles could be accomplished which indicates the potential of NADES in scaled-up industrial processes. Remarkably the process mass intensity (PMI) metric (that gauges the greenness of a chemical process) was superior to that of some equivalent patented methods. The main advantages included eliminating the need for purification of the product using expensive chromatography, reduced reaction times, mild conditions, no need for additional bases and other additives, and the capability to perform multiple reactions in the same NADES. Under the descriptive label of Green Amide Synthesis, the same group also used this approach to access amides, a frequently appearing functionality in molecules of pharmaceutical interest.

Molnar's group reported the use of several RNADESs for the synthesis of thiazolidine-2,4-dione lipoxygenase inhibitors with yields of up to 90% *via* a classical organocatalyzed Knoevenagel reaction (Fig. 3(b)).[29] The reactions could be repeated up to 5 times. The proposed catalytic action is suggested to come from the *N*-methylurea component that can establish key hydrogen bonds with the aldehyde reactant and the choline component.

Lignin valorization[30,31] is an important academic and industrial endeavor and, in this context, Joshi and Tiwari reported the esterification of lignin-derived eugenol to eugenol benzoate using another type of RNADES that is acidic in nature (Fig. 3(c)).[32] Eugenol has diverse properties ranging from medicinal, dental, to flavoring agents. Surprisingly eugenol benzoate exhibits improved properties over eugenol. The process worked best (conversion of 90%) with an acidic RNADES catalyst, ChCl-*p*-toluenesulfonic acid (1 : 4), using a 1 : 5 molar ratio of eugenol to benzoic acid in toluene at 110 °C for 3 h. The main advantage of this method is that the NADES catalyst could be recovered. Obviously, this process can be optimized, using lower temperatures and omitting non-environmentally friendly solvents like toluene; nonetheless

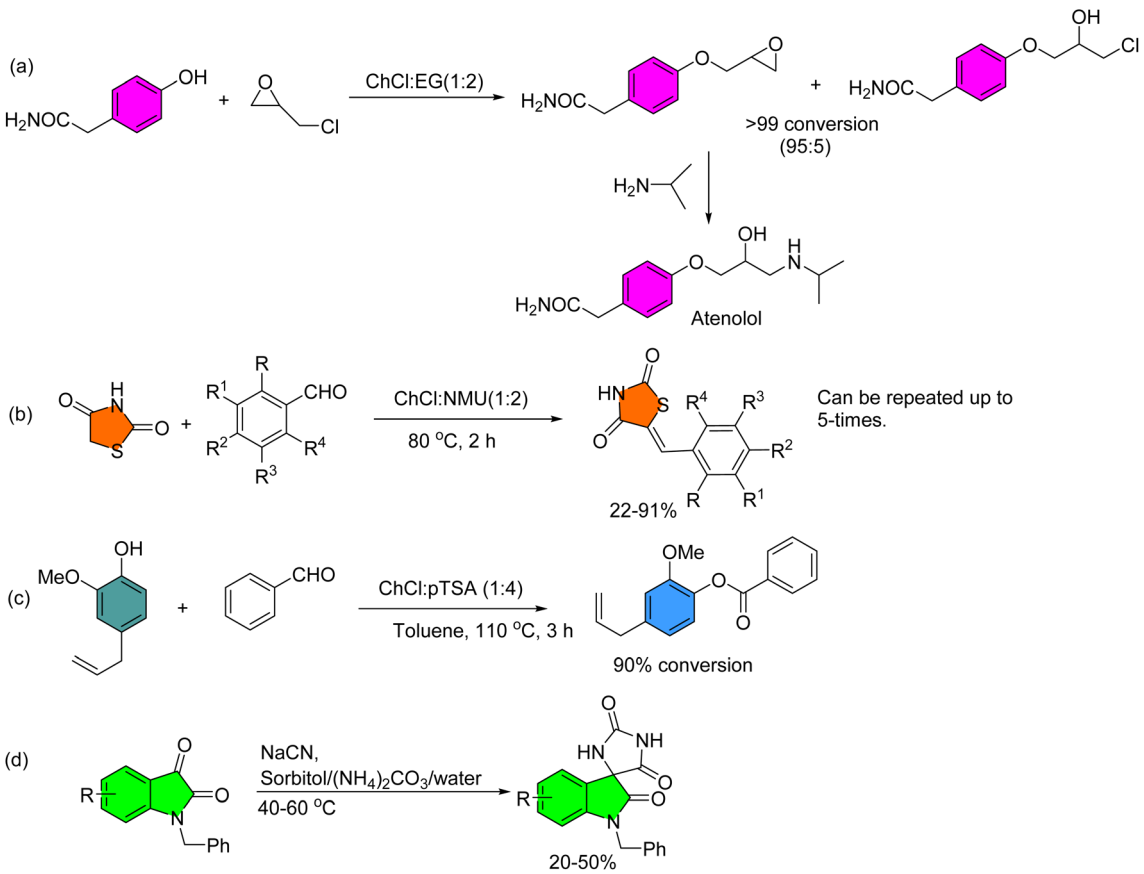

Fig. 3 (a) The synthesis of the drug Atenolol using a RNADES system. (b). The synthesis of thiazolidine-2,4-dione lipoxygenase inhibitors with RNADES; NMU = *N*-methylurea. (c) Synthesis of eugenol benzoate using an acidic RNADES. (d) The use of a novel carbonate based RNADES for a Bucherer–Bergs multicomponent reaction.

this example shows the potential of RNADES in industrial processes.

With the aim of developing spirocyclic hydantoin compounds with biological activities (for cancer, Alzheimer's, leishmania, *etc.*), the Burke group developed a highly efficient Bucherer–Bergs reaction (a simple multicomponent reaction with simple reagents) to produce spirocyclic hydantoin-oxindoles (known Valladolid receptor 1 inhibitors, with anti-inflammatory applications) in a RNADES, consisting of sorbitol/ammonium carbonate/water (1 : 1 : 3) (Fig. 3(d)). Recently, the first Bucherer–Bergs reaction in deep eutectic solvents offering biologically active spiro-oxindole-hydantoins in moderate to good, unoptimized yields of 48% has been demonstrated.[33] Attempts to induce enantioselectivity with NADES have so far failed for this reaction, but the Burke group is currently optimizing this process. The group is also exploring asymmetric kinetic resolutions in CNADES.

Unfortunately, the number of examples in the literature on the use of CNADES is still limited, generally restricted to conjugate additions, aldol, α-amination and reduction reactions, and even in reported cases, the enantioselectivities are far from optimal. The key benefit of using NADES is the ability to conduct reaction cycles (addition of fresh reagents for consecutive reaction cycles). Nevertheless, substantial research needs to be conducted at the academic level before this technology will be of practical use at the industrial level.

As a final remark, one can see that there is a bright future for the application of NADESs in the industrial context, and it is expected that several important industrial applications will emerge soon.

7. Conclusions

In summary, since the introduction of organocatalysis as a novel catalytic principle about five decades ago, this methodology has become a useful and valuable addition to the organic synthesis toolbox. Over this period, many examples have been published which highlight features of applying organocatalysts to achieve desired transformations. The development has involved both the inclusion of novel and unprecedented organic moieties as effective catalysts, and the shift from traditional solvents to unconventional rection media such as NADES to carry out synthetic manipulations of ever-increasing complexity. Given their environmentally friendly profiles, NADESs provide an additional advantage to industrial manufacturing, especially in pharmaceutical manufacturing, where traditionally >50% of the process mass intensity (PMI) originates from the use of solvents.[34] NADESs have obvious potential to become the gamechanger the pharmaceutical industry needs and the future will reveal how quickly the expected benefits can be delivered.[35] At the end, achieving a deep impact will depend on the preparedness and willingness of the manufacturing industry to implement the necessary changes. To achieve this, more high-quality examples like the ones discussed here must be created and shared across the scientific community.

Declaration of interests

EdPC, AJB, and HJF are shareholders of Chiratecnics.

Data availability

No primary research results, software or code have been included in support of this paper. Furthermore, no new data were generated or analysed as part of preparing this Perspective.

Author contributions

AJB and HJF worked out the concept for the article and drafted the text, illustrations, and references. EdPC conducted a thorough fact-check and offered improvements to the content. All authors were engaged in the final proof-reading. HJF amalgamated all aspects relevant to the final version and submitted the manuscript with full support from the team of authors.

Conflicts of interest

All authors declare that they are not aware of any conflicts of interest. All authors are shareholders of Chiratecnics.

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