



# The role of deep eutectic solvents in catalysis. A vision on their contribution to homogeneous, heterogeneous and electrocatalytic processes

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## ABSTRACT

Deep eutectic solvents (DESs) are a group of eco-friendly, low-cost and tuneable solvents that have gained significant attention in recent years due to their remarkable properties including high solubility and conductivity, low toxicity and easy recovery. DESs have also demonstrated outstanding catalytic activity, especially as a green alternative to traditional solvents and catalysts in several chemical reactions including organic synthesis, biomass conversion and pharmaceutical manufacturing, among others. In this review, we explore the potential of DESs as co-solvents in reaction media or catalysts in a diversity of organic reactions, focusing on both homogeneous and heterogeneous catalysis and electrocatalysis during the last quinquennium.

The review article is organised in three main sections: homogeneous catalysis, heterogeneous catalysis and electrocatalysis. In each section, the most significant and recent research regarding versatile types of organic synthesis reactions is presented and discussed. Furthermore, this review offers insights into the future perspectives of DESs in organic catalysis.

## Introduction

With the growing awareness of environmental issues and needing to develop efficient and environmentally sustainable synthetic protocols, the efforts of the scientific community have focused on the search for alternative solvents allowing to mitigate their pernicious effects on both human health and the environment.

Taking into consideration the abovementioned, two main paths towards eco-friendly solvents have been developed: i) the replacement of hazardous solvents with ones showing better environmental, health and safety properties [1] and ii) the substitution of solvents derived from petroleum by those with a biodegradable nature or attained from renewable resources [2]. It is well known that supercritical fluids, fluorinated solvents, ionic liquids or water have been widely used in chemical syntheses and hold a remarkable place in chemical research with green technology (both in syntheses and catalysis) [3]. Although these new generations of solvents are more aligned with the principles of green chemistry [4], it is worth mentioning that they are still subjected to strict

limitations, like the demand of sophisticated equipment for supercritical fluids, high prices or toxicity of some families of ionic liquids or the instability and low solubility of some substrates in water. Thus, efforts should be focused on the search of the most suitable reaction medium required for each circumstance, both from the point of view of sustainability and applicability.

Ionic liquids (ILs) gained prominence with respect to other contemporary solvents in several fields such as catalysis (or biocatalysis), chemical applications, extraction and separation processes or advanced materials [5], due to their attractive properties like negligible volatility, non-flammability, high capacity for solubilizing a wide range of compounds, their ability to be tuned and tailor their thermophysical properties by ions selection, thermal and chemical stability, good electrical conductivity, high viscosity, as well as their ability to act as catalysts [6,7]. These characteristics have labelled these designer solvents as the “solvents of the future”. However, it has been observed that different imidazolium, phosphonium- and pyridinium-based ILs are not as environmentally friendly as initially considered, showing a wide

**Abbreviations:** ChCl, Choline chloride; ZrOCl<sub>2</sub>·8H<sub>2</sub>O, Zirconyl chloride octahydrate; TfOH, Trifluoromethanesulfonic acid; ZnCl<sub>2</sub>, Zinc chloride; Ph<sub>3</sub>PMeBr, Methyltriphenylphosphonium bromide; DMC, Dimethyl carbonate; FeCl<sub>3</sub>, Iron trichloride; AlCl<sub>3</sub>, Aluminum chloride; CeCl<sub>3</sub>·7H<sub>2</sub>O, Cerium chloride heptahydrate; Metf-Pec, Metformin-pectin; Fe<sub>3</sub>O<sub>4</sub>/GO@CL-Pd, Magnetite-graphene oxide/palladium nanocomposite; Ni(OH)<sub>2</sub>, Nickel hydroxide (II); CTAB, Cetyltrimethylammonium bromide; GA, Gluconic acid; PtCu, Platinum-Copper; MWCNTs, multi-walled carbon nanotubes; Co-P, cobalt-phosphorous.

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range of toxicities in living organisms due to their relatively high solubility in water, high thermal and chemical stability and low biodegradability [8]. Additionally, the synthesis of some ILs is not environmentally friendly and generally requires a large amount of salts and solvents in order to completely exchange the anions. These drawbacks together with tedious preparation and purification processes and the high price of biocompatible ILs restrict their industrial application.

At this point, deep eutectic solvents (DESs) have emerged as versatile alternatives to conventional ILs since they were presented as a new class of solvents at the end of the Twentieth century, as firstly reported by Abbott and collaborators [9]. As compared to ILs, DESs show similar physicochemical properties like negligible vapor pressure (reduced air pollution), non-flammability (process safety) or the ability to tune their thermophysical properties. However, notable advantages such as (i) their convenient synthesis (100 % atom economy), (ii) their very low price since most of DESs can be prepared from readily accessible chemicals, (iii) simple reaction workup and (iv) their low toxicity, make DESs, especially those derived from ammonium cation and renewable chemicals, which makes them a sustainable and green alternative [10–12]. As a consequence, DESs were introduced in several applications, including organic synthesis [13], polymer chemistry [14], analytical chemistry [15] or biomass valorization [16].

The vast utilization and scope of DESs in a variety of fields have been presented based upon available literature and displayed in Fig. 1.

#### Deep eutectic solvents and their properties

By definition, DESs are liquid systems formed by the interaction of two or more components, typically a hydrogen bond donor (HBDs) and a hydrogen bond acceptor (HBAs), at a molar ratio where a eutectic mixture is formed, resulting in a liquid state with unusual solvent properties (a lower melting point than either of the individual components) [17]. In fact, the term ‘deep eutectic solvent’ was initially used to describe eutectic mixtures with a melting point much lower than that of the pure constituents. However, there is no clear correlation between the freezing point of DESs and melting points of the pure components, since the freezing point of the eutectic mixture depends on the lattice energy of DESs, interaction between couple HBA-HBD and entropy changes arising from the formation of liquid phase [18,19]. Nevertheless, this explanation was used for all eutectic-based solvents leading to a general classification that follows a common formula of  $\text{Cat}^+\text{X}^-z\text{Y}$  for DESs, where  $\text{Cat}^+$  mainly refers to ammonium cation, while X usually represents a halide anion and Y either Lewis or Brønsted acid (z refers to the

number of Y molecules that interact with the anion) [12]. Recently, a new class of DESs filed as Type V has been included in the general classification. Unlike the previous ones, DESs Type V lack an ionic contribution but exhibit melting point characteristics of DES. This new class is formed by non-ionic molecules where HBDs are characterized by having an asymmetric configuration (due to the asymmetric charge distribution) like thymol or phenolic based compound, and HBAs components that do not provide hydrogen bond donor sites, (also known as lone HBAC components) like ethers, ketones, esters or aldehydes, among others [20].

Hence, DESs are classified into five principal classes obtained by combinations of HBAs and HBDs (Table 1). Generally, as representative of HBAs are choline chloride, tetraalkylammonium halides, tetrabutylphosphonium bromide, and metal halides/hydrated metal halides and typical HBDs used for its design are carboxylic acids alcohols, carbohydrates, amides, or amino acids.

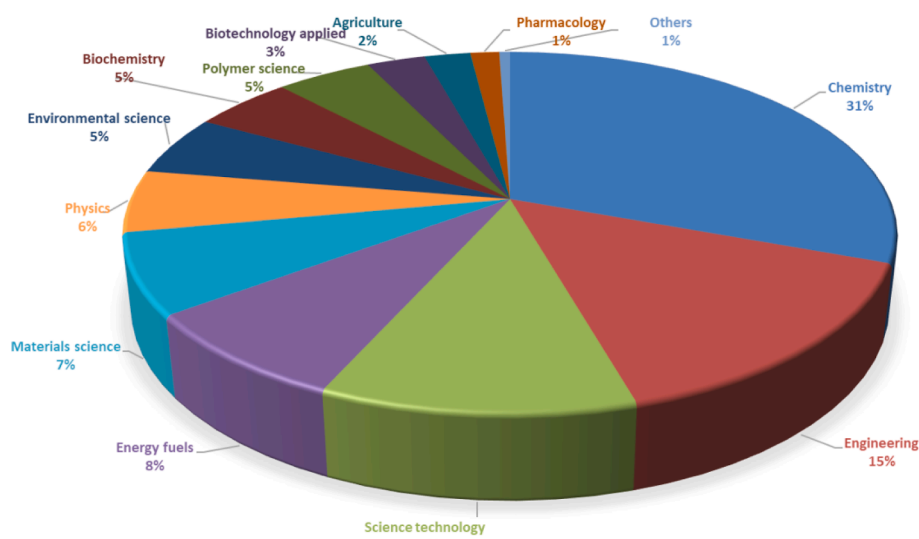
Since DESs can be designed by modifying the HBAs or HBDs or the molar ratio of the pure components and taking into account the hydrogen bonding interactions and the degree of solubility of the pure components in water, they have been classified as hydrophilic or hydrophobic DESs (HDESs) with particular physicochemical properties [21].

In terms of density and viscosity, hydrophilic DESs present higher values of these properties than water or organic solvents and similar to homologous ILs. This phenomenon may be due to the difference in their packing, and can be explained using the hole theory as DESs are composed of empty spaces created during the melting process in the liquid and the size of these holes determines their density with values

**Table 1**  
General classification of DESs.

Type	Composition	General formula
I	QAS + metal chloride	$\text{Cat}^+\text{X}^- + z\text{YCl}_x$ (Y = Zn, Sn, Al, Ga)
II	QAS + metal chloride hydrate	$\text{Cat}^+\text{X}^- + z\text{YCl}_x \cdot w\text{H}_2\text{O}$ (Y = Cr, Co, Fe)
III	QAS + HBD	$\text{Cat}^+\text{X}^- + z\text{RY}$ (Y = $\text{CONH}_2$ , $\text{COOH}$ , OH)
IV	Metal chloride hydrate + HBD	$\text{MCl}_x + \text{RY}$ (M = Al, Zn; Y = $\text{CONH}_2$ , OH)
V	Non-ionic compounds of HBA and HBD	$\text{L} + \text{A}$ (L = lone HBA, A = asymmetric HBD)

\* QAS: Quaternary Ammonium Salt. HBA: Hydrogen Bond Acceptor. HBD: Hydrogen Bond Donor.



**Fig. 1.** Application of DESs in different industrial areas.

higher than the pure components [18]. Density and viscosity are drastically changed when combining different HBDs or HBAs due to hydrogen bond interaction between them, van der Waals interactions or the molecular organization or packing [22,23]. The chemical structure of the HBAs and HBDs that constitute the DES also influence the experimental data observed in the electrical conductivity of these solvents. Therefore, this transport property is extremely sensitive to the concentration of pure conducting species existing in the eutectic mixture formed. Besides, lower electrical conductivity was observed for the majority of DESs maybe related with their higher viscosity values, which can be attributed of the ions or molecules moving [24]. Similar behaviour of viscosity is observed in HDESs, being these higher values strongly related to the nature of the pure constituents of the eutectic mixture. On the contrary, HDESs display density values lower than hydrophilic DESs and they decrease with increased alkyl chain length of HBDs or HBAs [21].

In general, the experimental values of the physicochemical properties of these solvents can be altered by several factors. Hence, the importance of developing molecular-based mathematical models for their prediction is pivotal [25].

The acidity and basicity of DESs is an important parameter to consider in many extraction processes and organic reactions, even more when DESs are used as catalysts, as the acidity/alkalinity of the components played a major role in modifying reactions efficiency. The Bronsted acidity/basicity of DESs could be evaluated by measuring the pH or by the Hammett acidity function (by determining tendency of the solution to capture protons) [26,27]. Reports where are studied the acidity/basicity properties of DES are quite limited to date in the literature and these can be summarized in the application of spectroscopic methods as infrared spectroscopy or nuclear magnetic resonance or electrochemical sensors which providing information about pH values of DESs, thereby endorsing that the acidity or basicity of DESs are mainly influence by the pH values of their individual constituent components [28]. However, knowledge about this property is no less interesting since the acidity/basicity condition can allow the use of these alternative

**Table 2**  
Physicochemical properties of representative DESs used in catalysis.

DESs	Molar ratio	Viscosity (Pa·s)	Density (g·cm <sup>-3</sup> )	Conductivity (μS·cm <sup>-1</sup> )	Ref.
[ChCl][urea]	1:2	0.214 <sup>a</sup>	1.1879 <sup>a</sup>	1287 <sup>a</sup>	[31]
[ChCl] [ethylene glycol]	1:2	0.025 <sup>a</sup>	1.1139 <sup>a</sup>	9730 <sup>a</sup>	[31]
[ChCl] [glycerol]	1:2	0.177 <sup>a</sup>	1.1854 <sup>a</sup>	1647 <sup>a</sup>	[31]
[ChCl] [malonic acid]	1:1	0.616 <sup>a</sup>	1.2112 <sup>a</sup>	732.0 <sup>a</sup>	[31]
[ChCl] [levulinic acid]	1:2	0.119 <sup>a</sup>	1.1320 <sup>a</sup>	1422 <sup>a</sup>	[31]
[ChCl][tartaric acid]	2:1	66.44 <sup>a</sup>	1.2735 <sup>a</sup>	14.30 <sup>a</sup>	[31]
[ChCl][citric acid]	1:1	45.01 <sup>a</sup>	1.3313 <sup>a</sup>	18.40 <sup>a</sup>	[31]
[ChCl][oxalic acid]	1:1	0.089 <sup>a</sup>	1.2371 <sup>a</sup>	2350 <sup>a</sup>	[31]
[ChCl] [glucose]	2:1	8.000 [25] <sup>b</sup>	1.2422 [26] <sup>b</sup>	nd	[32,21]
[ZrOCl <sub>2</sub> ·8H <sub>2</sub> O] [urea]	1:5	0.052 <sup>b</sup>	1.4901 <sup>b</sup>	nd	[33]
[ZrOCl <sub>2</sub> ·8H <sub>2</sub> O] [glycerol]	1:2	0.533 <sup>b</sup>	1.5700 <sup>b</sup>	nd	[33]
[ZrOCl <sub>2</sub> ·8H <sub>2</sub> O] [ethylene glycol]	1:2	0.149 <sup>b</sup>	1.5700 <sup>b</sup>	nd	[33]
[ChCl][TfOH] <sub>2</sub>	2:1	0.233 <sup>a</sup>	1.5302 <sup>a</sup>	nd	[34]
[urea][ZnCl <sub>2</sub> ]	3.5:1	nd	1.6500 <sup>c</sup>	7400 <sup>c</sup>	[35]

nd: no determined; Measurement at: <sup>a</sup> 30 °C; <sup>b</sup> 25 °C; <sup>c</sup> 35 °C.

solvents in processes to dissolve metals or remove oxides [29,30].

In Table 2 are displayed the most significant physicochemical properties of representative DESs report in this review.

Following a concise introduction to Deep Eutectic Solvents (DESs) as a novel class of contemporary solvents exhibiting substantial potential for replacing traditional solvents, the primary objective of this manuscript is to elucidate the advantages of DESs in prevalent organic catalysis reactions. These include cross-coupling reactions, multicomponent reactions, and Friedel-Crafts reactions. Furthermore, this work aims to underscore the potential of DESs in these well-established domains of organic synthesis, while also shedding light on areas necessitating further exploration, such as heterogeneous catalysis and electrocatalysis within eutectic mixtures. These insights are intended to contribute to the ongoing discourse surrounding the utilization of DESs in sustainable chemical processes.

### Deep eutectic solvents in catalytic reactions

DESs have gained increasing attention in recent years as potential solvents for catalysis reactions due to their remarkable properties including high solubility, wide range of viscosity, low toxicity and easy recovery. DESs have also demonstrated outstanding catalytic activity, especially as a green alternative to traditional solvents and catalysts in various chemical reactions [13,36]. These eutectic mixtures have been found to be effective as solvents or as catalysts, both in organic synthesis and catalytic reactions, including esterification, amidation, condensation, cross-coupling, cycloaddition and oxidation, highlighting its reuse in both homogeneous and heterogeneous catalytic reactions.

Besides, they have evidenced several advantages over traditional solvents and catalysts like easy synthesis from cheap and renewable starting materials, low toxicity and biodegradable nature (specially, natural deep eutectic solvents), easy recycling and reuse in several reaction cycles, which makes them a sustainable and green alternative [37].

However, there are also some challenges associated with using DESs as catalysts. Their high viscosity can sometimes limit mass transfer and diffusion of reactants and products, which may in turn affect reaction kinetics. Additionally, their high sensitivity to water and other impurities can alter their stability and catalytic activity.

With a naked eye, Fig. 2 displayed the progress of DESs used in catalytic reactions during the last decade, highlighting a boom in publications in the last four years.

### Homogeneous catalysis

Homogeneous catalysis is commonly used in organic chemistry reactions and in this type of catalysis, the catalyst and the reactants are in the same phase (usually liquid) and both interact to form intermediates complexes that are then converted into the desired product. One advantage of homogeneous catalysis is that it allows for more precise control over reaction conditions, such as temperature, pressure and amount of catalysts [38]. This allows a better selectivity and efficiency in the reaction as compared to heterogeneous catalysts. However, one of the limitations of homogeneous catalysis is the difficulty of separating and/or recovering the catalyst from the reaction mixture as it is in the same phase as the reactants. This can significantly increase the cost of the process. However, many examples of organic syntheses reported in the literature stand out disadvantages like long reaction times, harsh reaction conditions, unsatisfactory yields or the need of excess catalysts, among which acids, bases and metal complexes are highlighted [39,40]. Therefore, the development of an efficient, low-cost, and environmentally benign synthesis still remains an urgent task.

Traditionally, organic solvents have been proposed as media for catalytic reactions but the growing concern for the environment has attracted an increased interest in the development of protocols for efficient and environmentally friendly organic synthesis. As part of this

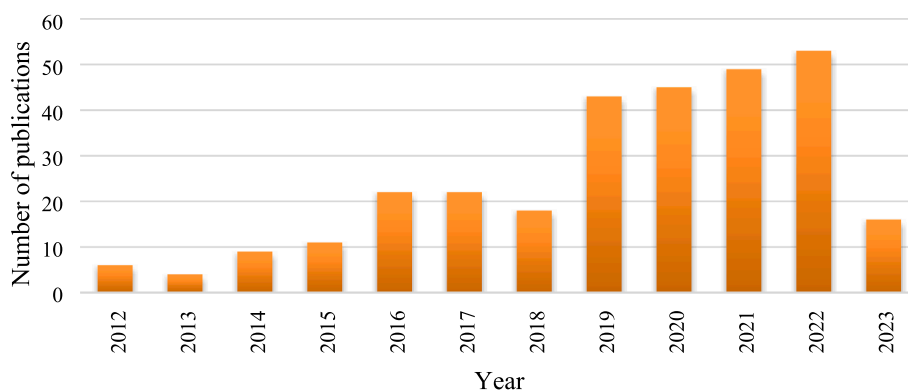


Fig. 2. The number of published papers on DESs in catalysis reactions in the last decade (adapted from ISI Web of Knowledge).

green concept, DESs have emerged as an interesting type of neoteric solvents present in many organic reactions. Moreover, DESs have demonstrated a dual role in catalytic reactions since they can act both as reaction media and catalysts. In this section, the role of DESs in catalytic reactions are discussed.

#### Cross-coupling reactions in DESs

The cross-coupling reactions are considered a class of versatile and efficient reactions in organic synthesis where palladium (salts or complexes) is commonly used as catalyst. Despite the existence of significant advances in the field, various hazardous organic solvents, like toluene or benzene are employed, making this synthesis tool unattractive to green chemistry. Thus, neoteric solvents like ILs [41] and DESs have acquired prominence as reaction media, providing advantages over traditional organic solvents, like the use of low catalyst concentrations, negligible formation of homocoupling products and easy reuse and recycling of catalyst. Focusing on DESs as reaction medium, Pelliccioli and co-workers [42] reported the successful use of eutectic mixture [ChCl][glycerol] (1:2, molar ratio) as unconventional solvent in Suzuki–Miyaura cross-coupling reaction by palladium-catalyzed ligand-free for the synthesis of  $\pi$ -conjugated heteroaryl systems, obtaining selective 2,7-diaryl-substituted under mild conditions (60 °C, 60 W, under air). The same DES was selected by Delaye et al. [43] for the synthesis of imidazo-fused heterocycles present in drugs as gastroprotectives or anticancer treatments like imidazo[1,2-a]pyridines and imidazo[1,2-b]pyridazines. Both substrates led to yields close to 90 % for the coupling with aryl boronic acids. The recycling of palladium acetate catalyst from the DES was optimum over five cycles, as no loss of activity was detected at 90 °C. The formation of heterocyclic compounds is of relevant interest in organic synthesis since these compounds are of great importance in pharmaceutical chemistry or agrochemistry. A recent review on the synthesis of these compounds in DES was addressed in detail by Molnar and collaborators [44].

Subsequent research work from Saavedra and collaborators [45] reported a pre-catalyst based on bipyridine-palladium derivative for various coupling reactions. In this work, they tested the effectiveness of Pd-catalyst in the presence of hydrophilic and hydrophobic DESs. Thereby, [ChCl][glycerol] (1:2, molar ratio) was found to be an efficient reaction medium for Hiyama coupling reaction and [ChCl][ethylene glycol] (1:2, molar ratio) was found to be a better reaction medium for both Suzuki–Miyaura and Heck–Mizoroki coupling reactions. On the other hand, [Ph<sub>3</sub>PMeBr][glycerol] (1:2, molar ratio) was found to be an efficient medium for the Sonogashira coupling reaction leading to yields higher than 80 % in all cases after operation at 100 °C for 24 h. In turn, [decanoic acid:menthol](1:2, molar ratio) was the most effective hydrophobic DES (98 % yield, 100 °C, 1 h). It should be noted that the catalyst remained active and could be efficiently recycled up to five consecutive cycles in Hiyama and Suzuki reactions. In the case of Sonogashira reactions, the catalyst could be recycled for three

consecutive cycles.

In order to scrutinize novel catalytic reactions in the presence of DES, Messa et al. first explored the aminocarbonylation of (hetero)aryl iodides using Pd-catalyst with choline-based DES [ChCl][urea] and [ChCl][glycerol] (both 1:2, molar ratio) as solvent for the catalytic reaction under mild reaction conditions (60 °C, 12 h). In this research, a high chemoselectiveness towards the aryl carbon–iodine was evidenced when the reaction was carried out in the presence of eutectic mixtures in comparison with other conventional solvents like tetrahydrofuran, dimethylformamide or water. Additionally, the potential for recycling both the catalyst and DES after cross coupling reaction of aminocarbonylation of (hetero)aryl iodide was demonstrated [46].

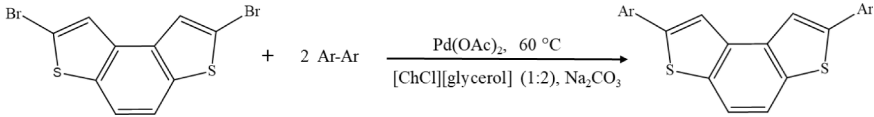
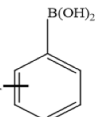
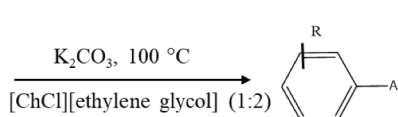

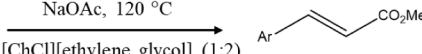
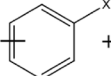
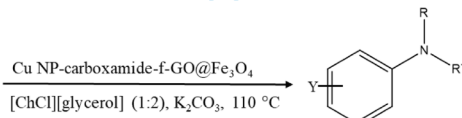
Although salts and complexes of Pd are the most common catalysts in cross coupling reactions, the search of novel catalysts with magnetic properties have aroused interest in recent years mainly due to the easy recovery of these catalysts from the reaction medium. In this line, Leal-Duaso et al. [47] immobilized palladium nanoparticles in glycerol-based DESs used as suitable media in Benchmark Heck – Mizoroki coupling reaction between iodobenzene and n-butyl acrylate to obtain n-butyl ciammate. The presence of these glycerol-based DESs improved the regeneration of the Pd-catalyst by observing a complete dissolution of the triethylammonium iodide salt formed during the cited coupling reaction. Subsequently, the authors used these glycerol-based DESs to demonstrate its high catalytic activity in a hydrogenation reaction of conjugated and non-conjugated alkenes and carbonyl compounds where these eutectic mixtures proved to be good supports for nanocatalysis, as they played a key role in the activity and the recyclability of the catalytic systems [48].

The DES [ChCl][glycerol] (1:2, molar ratio) was used as an efficient medium for C–N Ullmann coupling reaction catalyzed by copper nanoparticle-modified carboxamide- functionalized magnetic graphene oxide for replacing organic solvents. Again, the feasibility of recovering and recycling both the solvent and the catalyst up to five cycles was demonstrated [49]. Some of Cross-coupling reactions in DES are summarized in Table 3.

#### Friedel-Crafts and Diels-Alder reactions in DESs

Friedel-Crafts (F-C) and Diels-Alder (D-A) are some of the most useful carbon–carbon bond forming reactions in organic chemistry. In F-C reaction, two main reactions (alkylation and acylation) are involved for the preparation of alkyl substituted arenes using alkyl halide, alkyl sulfonate or alkene as alkylation reagents. The D-A reaction consists of converting a conjugated diene to a cyclic olefin. In the last times, F-C and D-A have been pointed out due to their application in the synthesis of natural products present in plants and animals like isoprenoid alcohols, alkaloids, carbazoles or diterpenes with interest in the formulation of pharmaceuticals and chemical intermediates [50,51]. In both cases, traditional catalysis included Lewis Brønsted acids, but the ongoing interest in applying green chemistry in organic synthesis seeks to replace

**Table 3**  
Illustrations of Cross-coupling reactions performed in DESs.

General scheme	Ref
<p>Synthesis of bis(hetero)aryl-substituted benzodithiophenes</p> <p>Suzuki-Miyaura reaction:</p> 	[42]
<p>Synthesis of bipyridine-palladium derivatives</p> <p>Suzuki-Miyaura reaction: Ar-Br + </p> 	[45]
<p>Heck-Mizoroki reaction: Ar-I + </p> 	
<p>Synthesis of N-aryl amines</p> <p>Ullman couplin reaction:  + RR'NH</p> 	[49]

these compounds with others with the same functionality and biocompatibility.

In this context, tunable solvents like ILs and DESs are proposed as advantageous substitutes to play a prominent role in these reactions. Nonetheless, few investigations were carried out where DESs are applied in these reactions, unlike ILs. On this way, choline-based DESs were selected in the benzylation of *p*-xylene with benzyl alcohol. Finally, Brønsted acidic DES catalysts [ChCl][ TfOH]<sub>2</sub> (2:1, molar ratio) were selected for the benzylations of various benzene compounds, achieving 100 % conversion of benzyl alcohol and over 90 % monobenylation selectivity in 1 h. In addition, the catalytic DES could be recovered from the organic phase and six-run recycling tests without loss of effectiveness were reported [52].

Wang et al. [53] investigated the obtaining of triarylmethanes and diarylalkanes (important intermediates in medicinal, materials chemistry and dye precursors) by F-C alkylation reactions. For making a green process, they evaluated different DES types such as urea [Urea][ZnCl<sub>2</sub>] (3.5:1, molar ratio), [Acetamide][ZnCl<sub>2</sub>] (4:1, molar ratio), [tetramethylammonium chloride][ZnCl<sub>2</sub>]<sub>2</sub> (1:2, molar ratio), [ChCl][ZnCl<sub>2</sub>]<sub>2</sub> (1:2, molar ratio). According to the results, [tetramethylammonium chloride][ZnCl<sub>2</sub>]<sub>2</sub> and [ChCl][ZnCl<sub>2</sub>]<sub>2</sub> provided 72 % and 94 % yields, respectively, while ZnCl<sub>2</sub> alone provided only 40 % yield making it patent the improvement in the catalytic process when DES is present in the reaction medium. As evidenced in other works, the catalytic activity of DES remained very high (from 89 % to 94 %) after several cycles of use.

In line with this work, Jin et al. synthesized six DESs-catalysts for the preparation of intermediate aromatic ketones by F-C acylation reaction [54]. As HBAs, ChCl, benzyltrimethylammonium chloride and triethylamine borane were selected, and they were combined with HBDs such as ZnCl<sub>2</sub>, trifluoromethanesulfonic acid and *p*-toluenesulfonic acid, concluding that the DES [ChCl][ZnCl<sub>2</sub>]<sub>2</sub> presented the best catalytic effect under optimum reaction (30 min and 70 °C), in agreement with a previous work [53]. Moreover, the catalytic activity of DES did not significantly decrease after five cycles of reuse (80–85 %). Previously, the DES [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> (1:3, molar ratio) was proposed as catalyst and

green solvent under microwave irradiation in F-C acylation with high regio- and chemoselectivity in reactions using acid anhydrides to provide ketone products [54]. According to the results, the disadvantages of moisture sensitive Lewis acids and also those of volatile organic solvents were overcome with the use of DESs and moreover high yields were reported with short reaction times (from 5 to 20 min). On the other hand, three new ketone products were reported to be synthesized under the catalytic effect of DES, concluding that [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> DES offered many advantages such as low toxicity, low cost, easy handling and preservation of its catalytic activity after reuse. Later on, the same authors investigated the use of the same DES as a Lewis acid compound for the acylation of secondary alcohols, phenols and naphthols with acid anhydrides [55]. They utilized [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> both as catalyst and reaction medium at room temperature. According to the authors, Lewis acidity of [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> (1:3, molar ratio) was clearly robust for the promotion of acylation of sterically hindered secondary alcohols to yield acylated products. As a result, 96 % yield was achieved in the propionylation of 1-phenylethanol with propionic anhydride in 30 min of reaction time. [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> could be recycled many times and no significant activity loss was detected.

Although D-A reaction is one of the most useful reactions in synthetic organic chemistry and material design, a particular focus is placed on the synthesis of intermediates in drugs formulations, the preparation of functionalized surfaces, bioconjugation techniques, and in nanotechnology or polymers design [56]. However, the use of the new generation of solvents in the D-A reaction has been minimally studied.

In 2018, Le et al. [57] proposed the choline-based DES [ChCl][ethylene glycol] and [ChCl][malonic acid], both 1:2 M ratio, as reaction medium for grafting of novel polymeric materials (Poly(ionic liquid)s) (PILs) onto multiwalled carbon nanotubes, which have several applications like additives in polymers, batteries or solar cells. The results demonstrated that DESs play an important role in dispersing multiwalled carbon nanotubes (MWNTs) and catalysing D-A reactions, leading to a significant improvement in the grafting density of PILs on MWNTs and their reaction time (regarding water as control).

The following year, Grosso and collaborators [58] presented for the

first time the DES [ChCl][glycerol] (2:1, molar ratio) as reaction medium in the synthetic approach to bis(indolyl) methanes (BIMs) based on bis-hetero-Diels–Alder/conjugate addition reactions of nitroso- and azoalkenes with indoles, that led to a marked improvement in the efficiency and sustainability of the organic synthesis. In fact, it was shown that the use of these DES as a reaction medium for the synthesis of BIMs allowed obtaining higher reaction yields than what was shown in previous works where a mixture of H<sub>2</sub>O/DMC was used as a reaction medium. Nevertheless, in this research the authors have not evaluated the DES recycling.

The first study about interactions behaviour between solute–solvent (DES) in D-A reactions was approached by Torres et al. [59]. Eutectic mixtures with lactic acid, glycerol and ethylene glycol as HBDs were selected for studying the reaction between cyclopentadiene and ethyl acrylate or butyl acrylate in typical cycloadditions. As concluded by the authors, the *endo/exo*-selectivity of D-A reactions in the presence of eutectic mixtures seem to depend on the hydrogen-bond donating capacity of the DESs, the molar ratio of HBA/HBD, and the synergistic effect between DES components. Finally, they concluded that DESs exhibited a better *endo*-selectivity and a higher or comparable yield than similar reactions already described using conventional or other ionic solvents.

For the sake of process greenness, it is desirable a reduction in reaction times and temperatures or recycling the reaction system and as a consequence, saving in energy consumption and cost. With this assumption, the combined use of techniques like microwave-assisted or ultrasounds and non-conventional solvents like DESs was applied for more efficient samples pretreatment or extractions. This strategy was put into practice by Marullo and coworkers in the D-A reaction using N-ethylmaleimide as dienophile and changing the nature of the dienes

selected in a media with deep eutectic solvents (DES) under ultrasonic activation [60]. Once 10 different DESs were evaluated, [ChCl][ethylene glycol] (1:2, molar ratio) was found to be the best reaction solvent since it allows drastically reducing the reaction time (from 24 h to 70 min) and more than 99 % of energy saving without loss in yield. Moreover, the solvent could be reused at least eight times.

Some of F-C and D-A reactions in DES are displayed in Table 4.

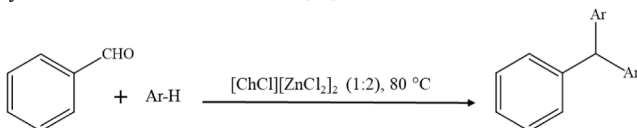
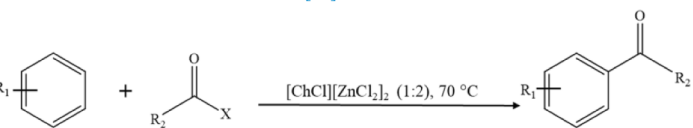
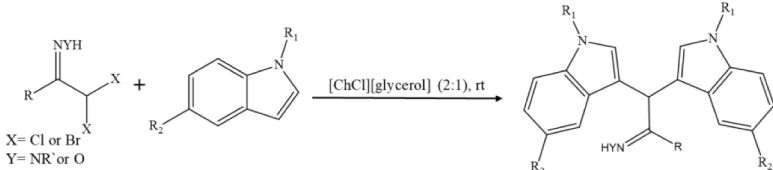
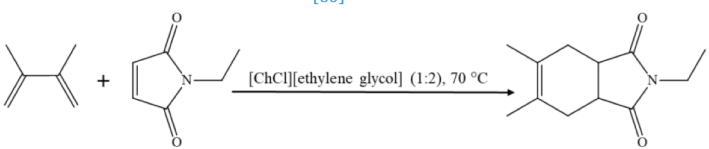
#### Multicomponent reactions in DES

Multicomponent reactions (MCRs) have become a very important tool in organic synthesis in which three or more starting molecules react to form the corresponding product in a one-pot reaction, usually with high atom economy. The MCR approach provides atom economy, reduced reaction time, high yields, eco-friendliness, and robustness for designing new chemical molecules, particularly in drugs synthetic processes [61].

Albeit, a solvent is the common medium for carrying out organic reactions due to factors like easy control over mass and heat transfer, stabilization of transition states, and fast modification of reactivity (rate, selectivity, etc.). To avoid the drawbacks of conventional organic solvents, new tailor-made and “greener” solvents have been investigated as sustainable media, and also as catalysts, among which DESs can be highlighted.

The scope of the multicomponent reaction in the presence of DESs was investigated in the synthesis of pyrazoles as these molecules have important biological and analytical applications. An efficient and environmentally benign one-step three-component reaction of aldehyde, 3-oxopropanenitrile and 1H-pyrazol-5-amine was reported by Ge et al. [62] for the synthesis of 4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile derivatives using the natural DESs [L-proline][oxalic acid]

**Table 4**  
Illustrations of Friedel-Crafts and Diels-Alder reactions performed in DES.

General scheme	Ref
Synthesis of triarylmethanes and diarylalkanes	[53]
Friedel-Crafts alkylation reaction: 	
Synthesis of intermediate aromatic ketones	[54]
Friedel-Crafts acylation reaction: 	
Synthesis of bis(indolyl)methanes	[58]
Diels-Alder addition reaction: 	
Synthesis of Diels-Alder adduct	[60]
Diels-Alder cycloaddition reaction: 	

(1:1, molar ratio) as catalyst. After evaluating different solvents, the selected DES allowed obtaining yields higher than 90 % and a successful reuse for five times without loss of activity. They concluded that the hydrogen bonding nature of DES facilitates the electrophilic activation of the carbonyl groups in three steps: Knoevenagel condensation, Michael addition and intramolecular cyclization. In order to optimize benign processes for pyrazole synthesis, Kamble & Shankarling [63], reported the production of 4,4-(arylmethylene) -bis- (3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives in water as solvent, catalyzed by [ChCl][tartaric acid] (1.5:3, molar ratio) DES and ultrasounds irradiation. For that purpose, the authors proposed a Knorr pyrazole synthesis for obtaining 3-methyl-1-phenyl-5-pyrazolone where DESs act as catalysts in aqueous medium, following a Knoevenagel-Michael Addition reaction in ultrasound with DES as reaction medium. The optimization of reaction conditions, allowed concluding that low catalysts concentration (10 % versus 30 %) is enough for obtaining reaction yields close to 95 %. Moreover, the unique combination of DES and ultrasound results in a significant enhancement in product yield and a decrease in reaction time at RT.

A plausible mechanism for indoles synthesis was carried out in the Than and Nagre research groups. The former [64] focused on the DES type I [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> (1:3 M ratio) as catalyst in the MCR of aldehydes, indoles and activated methylene compounds for synthesizing 3-substituted indoles at room temperature and solvent-free under sonication. The reaction tolerated various substrates without any additives, recording about 70 % of isolated yield under optimal conditions (30 % catalyst load, 6 h). The recovery of [ChCl][ZnCl<sub>2</sub>]<sub>3</sub> was easily accomplished through liquid–liquid extraction and a slight loss of catalytic activity was detected after four runs. Later on, a strategy for the synthesis of 3-substituted indoles via multicomponent reaction of malononitrile, aromatic aldehyde, and indole under ultrasonic irradiation using the common DES type III [ChCl][urea] (1:2 M ratio) was investigated [65]. They demonstrated that the catalytic effect of selected DES allowed to obtain 75 % reaction yield with 4 times shorter reaction time than that recorded for conventional Lewis acid catalysts like FeCl<sub>3</sub> or AlCl<sub>3</sub>.

In the same way, Nguyen & Tran [66] developed the synthesis of thieno [2,3-b]indole using cheap chemicals like sulfur, acetophenones, and indoles via magnetic silica-coated Fe<sub>3</sub>O<sub>4</sub> nanoparticles-supported [Urea]<sub>4</sub>[ZnCl<sub>2</sub>] eutectic mixture as catalyst. The magnetic DES turned out to be an effective catalyst to activate the reaction leading to high conversions levels, unlike various Brønsted/Lewis acids and conventional DES or magnetic supports. The prominent feature of the current method is the ease of catalyst recovery by an external magnet.

Efficient protocols via MCRs have been explored for the synthesis of pyrimidine derivatives, a class of molecules with a wide spectrum of biological and pharmacological activities [67]. Paying attention to these applications, Aryan et al. developed an efficient synthesis of pyrido[2,3-d]pyrimidine derivatives through reaction of 4(6)-aminouracil derivatives, aromatic aldehydes and three different active methylene compounds using [ChCl][urea] (1:2 M ratio) as co-solvent [68]. The authors argued that this synthesis showed a high degree of steric and electronic tolerance for the substituted aromatic aldehydes used, without the need of any extra oxidant and/or catalyst, in the presence of the selected DES. Moreover, the authors tested the antifungal and antibacterial effects of the product with excellent results compared to previous work in the presence of conventional solvents. In relation to that, Tipale et al. used the same DES for the synthesis of pyrazolopyrimidines [69]. They evaluated the dual role of [ChCl][urea] to act as catalyst in an ethanolic medium, and as solvent, achieving 92 % reaction yield in both cases. As in Arya's work, the DES was successfully recovered and reused three times with a minimum loss of catalytic activity.

In 2021, Shaibuna and collaborators explored the role of various type IV DESs in MCRs for the synthesis of molecules like cyclophanes, dihydropyridines or dihydropyrimidinone, all of them with applicability

in areas like electrooptic devices, as photorefractive materials or therapeutic targets. In this regard, the authors checked the suitability of DESs based on ZrOCl<sub>2</sub>·8H<sub>2</sub>O and CeCl<sub>3</sub>·7H<sub>2</sub>O in combination with urea, ethylene glycol, glycerol as HBDs for the synthesis of 1,8-dioxooctahydroxanthenes by the reaction of various aldehydes and dimedone at room temperature [70]. The eutectic solvent [ZrOCl<sub>2</sub>·8H<sub>2</sub>O][ethylene glycol] (1:2 M ratio) involved product conversions of about 96 % and showed a dual role (as catalyst and reaction medium). The results can be explained by the strong hydrogen bonding ability of DES, favouring its activity as a catalyst, while its lower viscosity eased its performance as solvent. Moreover, the authors highlight that cited DES provide better results in terms of easy preparation, high yields, and dual role in comparison with other catalysts and solvents. After the previous research work, the authors published the positive role of [ZrOCl<sub>2</sub>·8H<sub>2</sub>O][ethylene glycol] (1:2 M ratio) for the synthesis of symmetric dihydropyridine derivatives from aldehyde, ethyl acetoacetate and ammonium acetate via the Hantzsch reaction at room temperature [71].

A subsequent research work from Shaibuna [72], pointed another one-pot multicomponent reaction between ethyl acetoacetate, various aldehydes and urea/thiourea for the synthesis of dihydropyrimidinones/thiones via Biginelli reaction using various type IV DESs. As the authors demonstrated in their prior works, the eutectic mixture composed of [ZrOCl<sub>2</sub>·8H<sub>2</sub>O][ethylene glycol] ((1:2 M ratio) promoted excellent yield (higher than 90 %) in mild conditions (30 °C, 30 min). For example, the presence of DESs [ZrOCl<sub>2</sub>·8H<sub>2</sub>O][urea] (1:5 M ratio) and [CeCl<sub>3</sub>·7H<sub>2</sub>O][urea] (1:5 M ratio) allowed the synthesis of a mixture of both 3,4-dihydropyrimidinones (Biginelli product) and 1,4-dihydropyridines (Hantzsch product), respectively. On the contrary, low reaction yields were obtained with DESs [ZrOCl<sub>2</sub>·8H<sub>2</sub>O][glycerol], [CeCl<sub>3</sub>·7H<sub>2</sub>O][ethylene glycol], [CeCl<sub>3</sub>·7H<sub>2</sub>O][glycerol], all with (1:2 M ratio) or [CeCl<sub>3</sub>·7H<sub>2</sub>O][lactic acid] (1:4 M ratio). Further, stability, reactivity, and other structural parameters were calculated and the catalyst was reused up to four cycles. Examples of multicomponent reactions in DESs are shown in Table 5.

For all the above, it can be concluded that the presence of these neoteric solvents in organic reactions for the synthesis of different molecules not only does not alter the final product of the synthesis but also promotes short reaction times, biodegradability, low-cost reagents and recyclability of the catalyst making these solvents more attractive for homogeneous catalysis.

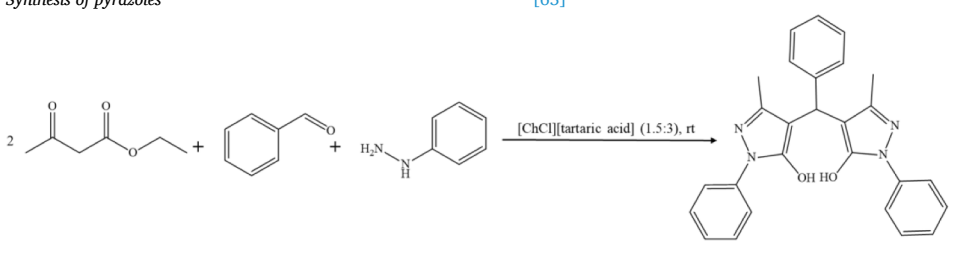
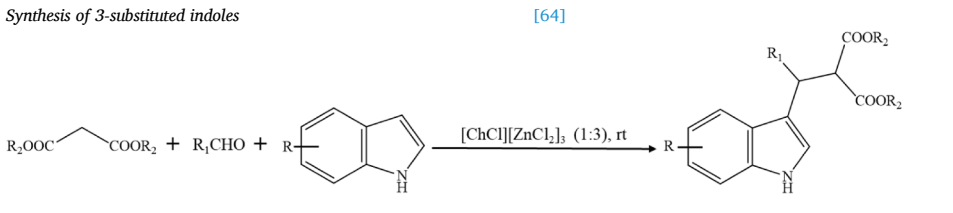
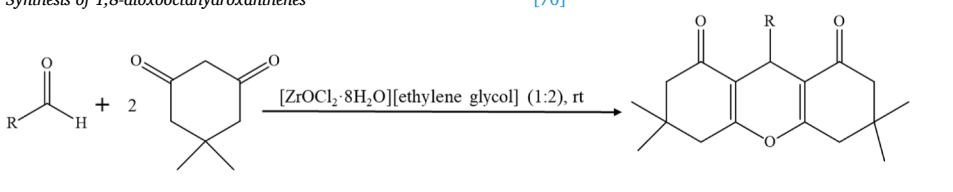
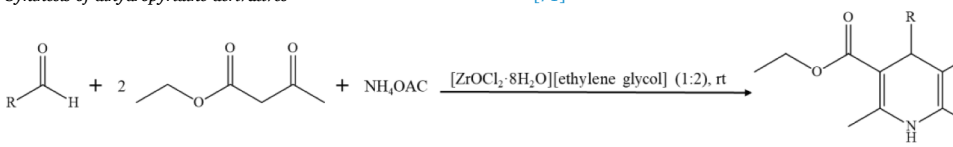
#### Heterogeneous catalysis

Twinned with homogeneous catalysis, heterogeneous catalysis is one of the pillars both in the synthesis of bulk and fine chemicals or in catalytic reactions involved in a plethora of industrial applications, among which oil refining industry, wastewater treatment, the production of polymers, biomass transformation reactions or automobile industry can be cited [73].

Heterogeneous catalysis is defined as a chemical reaction in which a catalyst is present in a different phase (solid, liquid, or gas) to that of the reactants, which target is to accelerate chemical reactions and reduce the amount of energy required. In heterogeneous catalysis, the reactants are adsorbed onto the surface of the catalyst, undergoing chemical reactions that transform them into products. Although homogeneous catalysts are usually more active and selective than heterogeneous catalysts, the latter are preferable in industrial processes due to advantages like their easy handling, separation from the reaction mixture, recovery and reuse, thus simplifying the process design and reducing the overall cost [74].

In order to address this matter in the field of sustainable chemistry, the use of heterogeneous catalysis is highly researched for the development of greener catalytic systems and synthetic methodologies, because it allows the straightforward recovery and recycling of the catalytic system, that would increase the lifetime of the catalytic system and decrease both residues from the catalytic reaction and production

**Table 5**  
Illustrations of Multicomponent reactions performed in DESs.

General scheme	Ref
<p>Synthesis of pyrazoles</p> 	[63]
<p>Synthesis of 3-substituted indoles</p> 	[64]
<p>Synthesis of 1,8-dioxooctahydroxanthenes</p> 	[70]
<p>Synthesis of dihydropyridine derivatives</p> 	[71]

costs [75,76].

In an attempt to give an overview on the application of DESs as an attractive alternative for replacing volatile organic compounds in the portfolio of green solvents, in this section miscellaneous examples of DESs application in heterogeneous catalytic reactions are discussed. In Fig. 3 is displayed a graphical example of a heterocatalytic reaction bearing DES.

The analysis of literature data reveals that choline-based DESs is the most common eutectic mixture researched in heterogeneous catalysis. For instance, Shaabani & Afshari [49] explored different choline-based

DESs as reaction solvents for catalysing the synthesis of carboxamide-functionalized graphene oxide as nanocatalyst. The authors demonstrated that the eutectic combination [ChCl][glycerol] (1:2, molar ratio) was more effective than [ChCl][urea] (1:2, molar ratio) with 97 and 70 % conversion yields, respectively. This research makes clear the advantages, in terms of temperature and lower reaction times, obtained in the Ullman C-N coupling reaction carried out in the presence of DESs compared to previous research works employing conventional solvents. Moreover, the catalyst and eutectic solvent were recycled and reused with a slight loss of activity of the former of 10 % after 5 cycles, which



**Fig. 3.** Schematic heterogeneous catalysis process with DES.



confirms the benign nature of these eutectic solvents for a catalyst.

Analogously, Messa et al. [77] proved the effect of [ChCl][glycerol] (1:2, molar ratio) eutectic mixture in Sonogashira cross-coupling reaction between (hetero)aryl iodides and terminal aryl- or alkyl-substituted alkynes by using palladium on activated charcoal (Pd/C) (2 mol%) as a heterogeneous catalyst under mild conditions. They reasoned that the higher yields obtained (98 %) may be due to the strong and extended hydrogen bond network of glycerol that may influence the activity of both the triethylamine base and the catalyst. In so far as, DESs like [ChCl][urea] and [ChCl][lactic acid], both (1:2, molar ratio) resulted in lower or null yield values.

Contrarily to the results obtained by Messa and Shaabani, the pioneering research work by Zhang et al. [78] bet in the synthesis of spirooxindole dihydropyridines via MCRs of isatins, malononitrile and anilinolactones with graphene oxide supported molybdenum as magnetic catalyst and [ChCl][urea] (1:2, molar ratio) as co-solvent under microwave irradiation. The authors managed to improve the optimal conditions (microwave power, 500 W; temperature, 90 °C; time, 50 min) when the magnetic catalyst was in contact with the selected DES to obtain conversion yields near 100 %. However, unpromising results were obtained in this organic catalysis with other choline-based DESs like [ChCl][glycerol], [ChCl][citric acid] or [ChCl][glucose]. Once again, the possibility of recovering and reusing the catalyst and DES was investigated without a noticeable loss in its activity.

DES [ChCl][urea] (1:2, molar ratio) was also selected as a green reaction medium, with easy handling, low cost, and environmentally friendly, for the synthesis reaction of tetrazolic acids (5-substituted 1H-tetrazoles), a group of bioactive molecules bearing pharmacological activity with potential applications in medicinal chemistry [79]. The main aim of this study was to optimize the conditions of tetrazolic acids synthesis by combining different catalysts and reaction solvents. The most promising results were attained with copper acetate (20 % load) as catalyst using the above cited DES as the solvent recording an isolated yield of 90 % in just 12 h at 100 °C. The authors emphasize that the proposed method avoids the usage of toxic chemicals/high-boiling-point organic solvents and prevents formation of highly volatile and toxic  $\text{HN}_3$  by-product being this a greener procedure in synthetic organic chemistry.

In the line of exploring the applicability of DES [ChCl][urea] (1:2, molar ratio) the scientific work of Arangadi and coworkers [80] evaluate the possibility of modifying activated carbon electrodes obtained from residual biomass with DESs with the purpose of adding active sites by introducing additional intermolecular interactions to the hydrogen bond network. The designed catalysts showed greater capacity for the removal of ions through physisorption. The authors justify their results by restructuring the charges via the complexed anion  $[\text{Cl}(\text{urea})_2]^-$  and cation urea  $[\text{choline}]^+$ . As a result, the anion complexed  $[\text{Cl}(\text{urea})_2]^-$  moves toward the positive electrode, and the urea  $[\text{choline}]^+$  complexed cation into the solution, which causes a restructuring of the charges allowing the movement of more  $\text{Cl}^-$  ions towards the positive electrode. In like manner, the cation complexed with urea  $[\text{choline}]^+$  moves into the negative electrode and the complexed anion  $[\text{Cl}(\text{urea})_2]^-$  toward the solution, moving more  $\text{Na}^+$  ions. shown improvement by 85 % for DES added on modify biomass-derived porous activated carbon. The described mechanism to desalination processes shown improvement by 85 % when DES was added on modify biomass-derived porous activated carbon.

Focus in the idea of sustainable chemistry, Marullo and coworkers investigated the best procedure to convert fructose and sucrose into 5-hydroxymethylfurfural using DESs as a reaction media [81]. They evaluated how the structural components of eight DESs with different HBAs and HBDs played a significant role in influencing the reaction, specifically the HBDs components. The eutectic solvent [ChCl][GA] (1:1, molar ratio) was identified as a suitable compromise between catalytic ability and stability in presence of resin amberlyst-15 with considerably improve in reaction yields to 78 %, much higher than that

found without catalyst (10 %). Moreover, the catalytic system was recycled for five cycles without a loss in yields for both sucrose and fructose transformation into 5-hydroxymethylfurfural.

Although urea and glycerol were the most commonly selected HBDs, natural compounds as caffeic acid or pectin were chosen for preparing DESs with application in heterogeneous catalysis.

In the research work of Sun & Hou [82], a novel DES was prepared using solid caffeic acid as HBD with choline chloride. This eutectic mixture was used as caffeoyl donor in glycerol caffeates synthesis. The transesterification reaction of [ChCl][caffeic acid] DES (1:2, molar ratio) with glyceryl monooleate was performed in the presence of solid acids resin NKC-9 as catalyst. [ChCl][caffeic acid] DES increased the poor solubility of solid caffeic acid, avoiding great mass transfer limitation and enhancing initial reaction rate, especially at low temperature (70 °C). These results were ascribed to more active sites at high catalyst load and greater miscibility of caffeic acid-based DES achieving the maximum caffeic acid conversion (91 %). A subsequent research work from Wang et al. [83] used the same DES in the synthesis of caffeoyl alkyl ester with cation-exchange resin A-35 as catalyst. After an exhaustive analysis of various reaction parameters like temperature, substrate ratio, catalyst load or reaction time, it was found that the caffeic acid conversion was 95 % with [ChCl][caffeic acid] DES (8:1, molar ratio) at 85 °C for 24 h. It is also noteworthy the double role of caffeic acid-based DES which can act as both the reactant and solvent. In brief, both research works concluded that caffeic acid-based DESs showed some advances: environmentally friendly and cheap catalyst, minimization of mass transfer resistance and short reaction time in catalytic reactions where caffeic acid acts as caffeoyl donor.

In line with designing DESs with natural-based sources Bakhtiarian & Khodaei synthesized for the first time a magnetic DES formed by choline chloride as HBA and metformin immobilized on pectin as HBD [84]. The magnetic [ChCl][Metf-Pec] was tested in the synthesis of 2,3-dihydro-4(1H)-quinazolinones, a molecule with a wide spectrum of medical applications, by MCRs using isatonic anhydride, aryl/heteroaryl aldehydes and ammonium acetate. After a series of experiments, the authors argued that catalyst loading, temperature and solvent play a significant role for obtaining the optimum results, highlighting the sensitivity of reaction yield to time. Thus, the yield was increased 1.2 times when the reaction time raised 15 min (from 45 to 60 min) at mild conditions (70 °C) without solvent. Also, the magnetic nature of the DES allowed to provide a simple and clean recovery by running the catalytic reaction six times as well as its sustainability for the scale-up synthesis of quinazolinones derivatives.

In 2021, Niakan et al. utilized the catalyst  $\text{Fe}_3\text{O}_4/\text{GO}/\text{CL-Pd}$  for the reaction of various aryl boronic acids with aryl halides through Suzuki-Miyaura cross-coupling reaction in the presence of hydrophilic and hydrophobic DESs in order to propose a sustainable synthesis of bi-phenyls. According to the authors data, the magnetic catalyst revealed higher activity in hydrophilic DESs (especially with dimethylammonium chloride as HBA) than hydrophobic one, which can be attributed to the better dispersion of the catalyst in hydrophilic eutectic mixtures. Moreover, both DESs and magnetic catalysts were attained to be efficiently reused after five cycles and the product yield remained as 90 % [85].

Likewise, DESs have acquired interest in the cycloaddition reactions with  $\text{CO}_2$  and epoxides to obtain cyclic carbonates, the latter with great application as precursor or intermediate molecules in various fields. Although the role of these alternative solvents in this area of catalysis is not yet remarkable, Gu and collaborators report in their work the use of DESs as precursors for the formation of nanocomposites [86]. The eutectic mixtures formed by [urea][melanine][ $\text{ZnCl}_2$ ] (24:1:2, molar ratio) was integrated into the synthesis of nanocomposites based on graphitic carbon nitride ( $\text{g-C}_3\text{N}_4$ ) giving rise to heterogeneous catalysts with dual Lewis acid-base functionalities. The incorporation of DES in the catalyst design gives it a homogeneous distribution of the active sites allowing simultaneous activation of  $\text{CO}_2$  and epoxides. The authors

concluded their work with results of efficient activities towards the cycloaddition of CO<sub>2</sub> with epoxides to cyclic carbamates under mild conditions (90 °C, 3 h) without solvents in reaction media. Another advantage highlighted by the authors in the process of adding DES to the heterogeneous catalyst was the high selectivity that the latter showed after five cycles of reuse in cycloaddition reactions.

The use of DESs as precursors in the design of catalytic materials with specific properties has also been demonstrated by Mou et al., who explored this approach for nitrogen fixation by a process where a series of (g-C<sub>3</sub>N<sub>4</sub>)/metal oxide nanocomposites were used as photocatalysts [87]. They used the DES composed by [urea][melanine][FeCl<sub>2</sub>] as a reaction media where metal oxide and g-C<sub>3</sub>N<sub>4</sub> precursors are incorporated, which after a pyrolysis process are decomposed in metal oxide nanoparticles and the g-C<sub>3</sub>N<sub>4</sub> nanosheets, respectively, that then are coupled each other homogeneously. The authors demonstrated that the presence of DES in this reaction contributed in an improvement of the coupling between the precursors. The process described allows obtaining a catalyst with a major surface area increasing the photocatalytic activity sites.

At a later date, Igual and collaborators focussed their study on synthesizing a more efficient catalysts of nitrogen-doped ceria nanomaterials for its use in the degradation of sulfamethoxazole through a photocatalytic reaction [88]. A hydrothermal treatment of ammonium cerium (IV) nitrate and urea in presence of eutectic solvent [acetic acid][CTAB] (1:1, molar ratio) and then doping with nitrogen enable to obtain nanoparticles exhibited high stability, photocatalytic efficiency, uniform surface and small size, achieving a photocatalytic efficiency in remediation and detoxification of sulfamethoxazoles close to 100 %. This work underscores the significance of exploring innovative approaches to catalyst synthesis like ceria nanomaterials but the influence of DESs in achieving desirable catalytic properties is still very slight explored in this area [89].

As already stated throughout these sections, DESs have shown to have a dual function as both a reaction solvent and a catalyst. Nonetheless, making libraries with new classes of heterogeneous catalysts with similar specificities to homogeneous catalysts continues to be a challenge, but newer synthetic procedures and nanotechnologies have infused new points of view into this context towards more sustainable and greener catalytic processes at industrial scale.

Although some review can be found in the literature focused on the use of DES in heterogeneous catalysis [90], research in this field is currently scarce, so it is important to place the emphasis on this lack and urge the scientific community to continue exploring the possible improvements that these alternative solvents can contribute to the catalysts used in heterogeneous catalysis.

### Electrocatalysis

Electrocatalysis is a type of catalysis in which an electric current is used to drive a chemical reaction. It involves the use of an electrode that is coated with a catalyst, which facilitates the reaction by lowering the energy barrier required for the reaction to occur. Electrocatalysis plays an important role in many industrial and technological applications, including electrochemical energy storage (such as batteries) [91], fuel cells, and fossil fuel-free chemical production [92]. In these processes, the electrode serves as both a support for the catalyst and a conductive interface for the flow of electrons between the reactants and the catalyst, allowing for the efficient conversion of chemical energy into electrical energy, and vice versa.

The design and development of efficient electrocatalysts is crucial for improving the performance of electrochemical systems. This has led to significant research efforts in the field of electrocatalysis, with a focus on identifying new catalyst materials, optimizing catalyst structures, and understanding the fundamental mechanisms of electrocatalytic reactions. This has led to the enhancement of new strategies so the application of computer science technology for the design of

electrocatalysts is essential [93].

Although few research works have evaluated the ability of DESs as appropriate reaction medium for electrocatalysis, the implementation of these neoteric solvents is still in its beginnings. Characteristics of these eutectic mixtures like the compositions of DESs, large surface tension or highly ordered hydrogen bonds make these new solvent candidates attractive for electrocatalysis (Fig. 4).

In 2009, Boggs et al. studied hydrogen production via electrolytic conversion of urine and urea in alkaline media using non-expensive catalysts [94]. This technique stands out for the low-cost hydrogen production process in comparison with conventional water electrolysis. Sun et al. [95] explored the urea-assisted water electrolysis and the catalytic mechanism potentiodynamic deposition of the Co-doped Ni (OH)<sub>2</sub> catalyst carried out in [ChCl][ethylene glycol] (1:2, molar ratio). As a result, the electrocatalysts exhibited superior electrocatalytic activity towards hydrogen evolution reaction and urea oxidation reaction. These observations may be due to the porous network with large surface area and, as a consequence, accessible active sites, robust structural stability, and the presence of species with enhanced charge transfer, in contrast with nickel-based oxide/hydroxide or metal-organic frameworks (Zn/Ni) catalysts [96]. The same DES system was selected by Guo and collaborators to promote electrochemical water oxidation by using an easy electrodeposition approach performed in [ChCl][ethylene glycol] (1:2, molar ratio) with thiourea as an additive [97]. This improved structural stability was responsible for the enhanced intrinsic catalytic activity as well as long-term stability. The behaviour is explained by the DESs unique solvent environment, such as highly ordered hydrogen bonding, low water activity and large surface tension, to guide the formation of electrodeposits with controllable shape, size and composition toward enhanced catalytic activity. As a conclusion of both research works, it can be argued that DESs are an adequate medium for synthesizing electrocatalysts with high catalytic performance.

The role of DESs in reactions of water splitting electrolysis is summarised in a recent review [98].

Even more, the potential of these neoteric solvents has been explored with other targets too. By way of illustration, Ron et al. demonstrated the applicability of [glucose][urea] (1:2 M ratio) DES for generating molecular oxygen through the electrochemical oxygen evolution reaction by the calcining method [99]. Glucose-based DES showed a high capacity to solubilize metallic salts of nickel, cobalt and ruthenium, which, after dissolving and carbonizing together under N<sub>2</sub> atmosphere, were transformed into several highly active transition metal oxide nanostructures. In this work, the use of [glucose][urea] DES as a carbon resource allowed to synthesize the N,O-doped graphene sheets efficiently. In addition, the high durability of the generated electrocatalysts suggested that the DES calcining method is competitive for transition metal oxide nanomaterials production to be used as energy storage and conversion devices.

In the light of this, Elsharkawya and coworkers [100] synthesised nanostructured Ni films to assessed as electrocatalysts for hydrogen

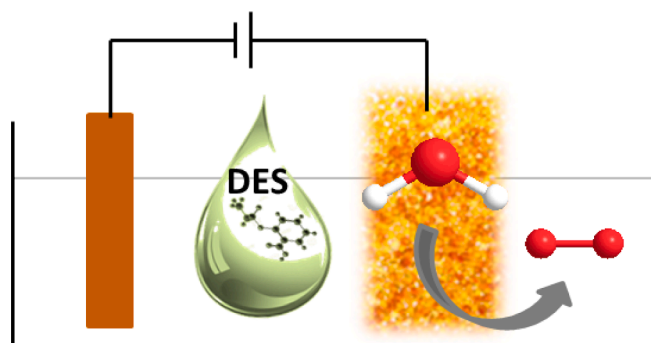


Fig. 4. Representative scheme of an electrocatalytic process bearing DES.

evolution reaction and oxygen evolution reaction. DES [ChCl][ethylene glycol] (1:3, molar ratio) and conventional aqueous acetate buffer were proposed to investigate the electrodeposited nickel (Ni) on graphite electrode. The differences in properties and morphologies between the two films, as well as the evaluations of catalytic activity, kinetics, and efficiency were notable between both solvents. It's interesting to note that the fabricated Ni electrode from [ChCl][ethylene glycol] solvent exhibits better performance in terms of current density and overpotential as well as higher kinetics and higher stability for both the hydrogen evolution reaction and the oxygen evolution reaction compared to the electrode prepared from the aqueous acetate buffer. This underscores the potential of eutectic mixtures as valuable tools in catalysis reactions and their role in advancing sustainable and efficient chemical processes.

The same DES was selected by Protsenko et al. [101] to evaluate the more effective electrocatalysts for the hydrogen evolution reaction by electrochemical deposition of nanocrystalline nickel and composite nickel-titania films. As previously mentioned, the stake of DES during the fabrication of the electrode ensures that they acquire improved electrocatalytic properties towards the hydrogen evolution reaction, previously mentioned. It was also shown that the introduction of more water into the electroplating electrolyte resulted in an appreciable increase in the content of embedded TiO<sub>2</sub> particles. The embedded TiO<sub>2</sub> particles can have various applications and properties, depending on their size and distribution in the coating. This relevant information can be used to optimize electroplating processes.

A DES-electrolysis strategy for degrading organic pollutants like dyes and antibiotics was presented by Jia et al. where the eutectic solvent [Ch-phosphate][urea] (1:2 M ratio) played the role of electrolyte for synthesizing N and P co-loaded titanic oxides [102]. This strategy consisted of introducing high purity titanium plates that would act as cathode and anode in an electrolytic solution formed by DES and co-charged titanic oxides. After the oxidation reaction occurs, the titanium ions combine with the active oxygen generated by the electrolysis of DES and form N, P co-doped titanium dioxide that will act as a photocatalyst to carry out a rapid photocatalytic degradation of organic pollutants. As conclusion, results revealed that the resultant N, P co-doped titanium dioxide was considerably competitive regarding pure TiO<sub>2</sub> or similar doped ones in photocatalysis reaction and the opportunity for using eutectic solvents as electrolytes.

The research work of Wang et al. describe a simple and effective one-step chemical reduction strategy for fabricating a promising catalyst for the methanol oxidation reaction of Pt nanoparticles with hollow-opened structures (Pt HOSs) using the eutectic mixture [ChCl][ethylene glycol] (1:2, molar ratio) that serves as the reducing agent [103]. The electrocatalytic evaluations demonstrated that the as-synthesized Pt HOSs nanoparticles exhibited enhanced electrocatalytic activity, stability, and resistance to toxicity for the methanol oxidation reaction when compared to commercial Pt black catalysts. These superior catalytic properties were attributed to the unique structural features of the Pt HOSs by using DES as reaction media. The study suggests that this synthesis method offers a promising avenue for designing and fabricating Pt-based nanostructures with tailored catalytic properties.

A novel green synthesis method to develop electrocatalysts of PtCu nanoclusters on MWCNTs within a DES as reaction media was introduced by Zhong and collaborators. The widely used DES [ChCl][ethylene glycol] (1:2, molar ratio) was chosen as synthesis medium to control the dispersion of Pt-based nanoparticles and enhance the electronic interaction between the catalytic nanoparticles and the MWCNT support. Besides, the incorporation of alloyed copper to the system reduced the size of the catalytic particles, forming cluster nanostructures with a less refined surface. In addition, the authors found that the electrocatalytic activity of the PtCu/MWCNT nanohybrids was composition-dependent. In this configuration, the nanohybrids exhibited an approximately 2.5-fold increase in mass activity compared to carbon nanotube-supported monometallic Pt catalysts. The study

concludes that the synthesis strategy using deep eutectic solvents is crucial for designing and fabricating high-performance electrocatalysts, particularly for fuel cell applications. The PtCu/MWCNT nanohybrids developed in this study offer improved electrocatalytic activity, CO tolerance, and durability compared to monometallic Pt catalysts [104].

The same eutectic system was selected for to prepare efficient and durable catalytic electrodes for the electrocatalytic oxidation of 5-hydroxymethylfurfural into 2,5-furandicarboxylic acid. The catalytic electrodes create by electrodeposition of Co-P using [ChCl][ethylene glycol] (1:2, molar ratio) as reaction media exhibit enhanced performance in the electrocatalytic 5-hydroxymethylfurfural oxidation helps to avoid the complexity of multiple alkylations and offers advantages like lower pH which prevent the denaturation of 5-hydroxymethylfurfural, high durability in contrasts with the short lifetime of conventional catalytic electrodes in oxidation reactions and the ability to simplify the reaction pathway. On the whole, the employ of DES as a strategy to prepare efficient and durable catalytic electrodes in the electrocatalytic oxidation reaction presented in this research led to a high 5-hydroxymethylfurfural conversion rate of 99 % with 85.3 % 2,5-furandicarboxylic acid yield [105].

This section aims to give an overview of the different applications of DESs in electrocatalysis field as well as the benefits they bring to the catalytic reaction. As reaction media for functional material preparation, DESs help achieve preparing morphology-controlled nanostructures or electrodeposited thin film.

Despite that, collaborative research and development in interdisciplinary areas will play a crucial role in unlocking the full potential of DESs since it has been noticed that most of the studies are focused on water splitting or hydrogen/oxygen evolution reactions most of them focused on research with a single type of eutectic mixture. So, there are still significant challenges to overcome in order to fully harness their potential like screening new DESs.

### Future perspectives of DES in catalysis

Even though catalysis effects are known from the antiquity, the knowledge of the phenomenon did not begin until the end of the 18th century and the beginning of the 19th century, when deepening the understanding of the modification of various chemical reactions by the presence of small amounts of additional substances that would later be called catalysts. Catalytic processes contribute significantly to the world economy since they are the pillar of basic processes for daily life such as the refining of crude oil and the synthesis of basic chemical products, in pharmaceutical compounds to synthesize molecular skeletons of chemical substances used in drugs.

With the growing awareness of environmental concerns, a major effort is required to replace toxic chemicals with more environmentally friendly ones. This challenge demands an imperative turn in the discovery of new catalytic processes, which entails new intellectual and technological challenges. Processes of low economic and energy cost, chemical reactions or catalysts in shorter times or techniques for the recovery of catalysts, requires designing, developing and applying new research methods taking advantage of new emerging technologies.

DESs have triggered a surge of interest and opened up appealing prospects in green processes since they share the remarkable attributes of both IL and green materials and even replacing them due to outstanding advantages like simple synthesis, low price of raw materials or high biodegradability.

Recent important progress in catalytic organic reactions are systematically summarized where DESs are introduced as reaction media, catalyst and advanced electrolyte and particular focus is paid on the fundamental understanding of the role it plays their structure-composition-properties-yields in catalysis.

However, the significant drawbacks of DESs in general and in specific in catalysis are related to their physical properties like high viscosity, which alter other physicochemical properties like transport properties as

conductivity, their hygroscopic nature, the lack of studies on storage time of the eutectic mixtures in optimal conditions or the fundamental knowledge of the intrinsic reactions between the components of eutectic mixtures should not be ignored. In order to mitigate this gap in literature is relevant the use of computer technology tools to predict the molecular behaviour of these new solvents with respect to their pure components.

Since the main objective of the application of alternative solvents such as DESs in organic catalysis is to replace conventional solvents and propose more sustainable processes, conducting techno-economic analyses and addressing the economic feasibility of DESs in organic catalysis is essential for their adoption as sustainable alternatives to conventional solvents. To address this concern, future research efforts should not only focus on the scientific aspects of DES-assisted catalysis but also on the economic and sustainability aspects for improving catalytic reaction under mild conditions to minimize energy costs to drive their industrial implementation. Very few techno-economic studies on the use of DESs in industrial processes have been carried out and all focused on the bio-refinery field [106,107], and several reviews in the field are useful tools to get further insight on the topic [108–113].

Further investigation by the academy would be interesting for performing boost research to fully understand the effects of DES on catalytic processes and provide new synthetic procedures, organometallic complexes from eutectic mixtures, information on the enantioselectivity of reactions in the presence of DESs, design more effective catalysts in reaction media of eutectic mixtures, etc., to increase the range of catalytic transformations that are possible with the use of deep eutectic solvents.

## Conclusions

This review article addresses the role of Deep Eutectic Solvents (DESs) in both homogeneous and heterogeneous catalysis, as well as briefly touches upon their emergence in the field of electrocatalysis. The inclusion of DESs in catalytic reactions has demonstrated the potential to reduce reaction times without altering the observed yields compared to reactions conducted without the presence of these eutectic mixtures. Many reported DESs have exhibited the capacity to function as catalysts, solvents, or both, thereby positioning them as viable alternatives to traditional methods. Consequently, their catalytic applications have garnered significant attention, offering the prospect of replacing numerous volatile organic solvents.

However, it is worth noting that a primary limitation associated with deep eutectic solvents lies in their high viscosity, primarily stemming from the robust hydrogen bonding interactions among their constituents. This issue can be mitigated by incorporating water as a cosolvent, thereby lowering properties such as melting point, density, and viscosity of the DES. Nevertheless, this solution necessitates careful evaluation, as it has the potential to impact the hydrogen bonding network, either reinforcing or disrupting the DES structure, which in turn may affect the catalytic reaction in unintended ways.

Conversely, the extensive range of applications documented in the literature underscores the promise of deep eutectic solvents in catalysis. Most studies to date have focused on choline chloride-based eutectic mixtures, frequently proposing acid catalysis through hydrogen bond activation. Nevertheless, the sheer multitude of ionic liquids and their corresponding DESs suggests that this field remains in its infancy, warranting further investigations involving different types of DESs to arrive at robust conclusions regarding their transformative potential in electrocatalysis, homogeneous, and heterogeneous catalysis.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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