

# Are deep eutectic solvents a real alternative to ionic liquids in metal-catalysed reactions?

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## Abstract

This microreview tries to answer the question: *Are Deep Eutectic Solvents a real alternative to Ionic Liquids in metal-catalysed reactions?* We have gathered the outstanding results of the use of DES in metal-catalysed processes and we have compared them to the ones with ILs. The huge possibilities of combinations of the components of the DES provides a vast number of different solvents with tunable properties. These DES have been successfully applied to different reactions such as, coupling or hydrogenation, among others. But work still be necessary to explore the use of DES in other reactions and to go in depth in the study of the influence of the nature of the DES. Finally, we also present the rise in a new family of solvents, bio-based ionic liquids, complementary to the use of DES in order to fully substitute traditional ILs.

**Keywords:** *DES, ionic liquids, bio-based ionic liquids, coupling reactions, hydrogenation*

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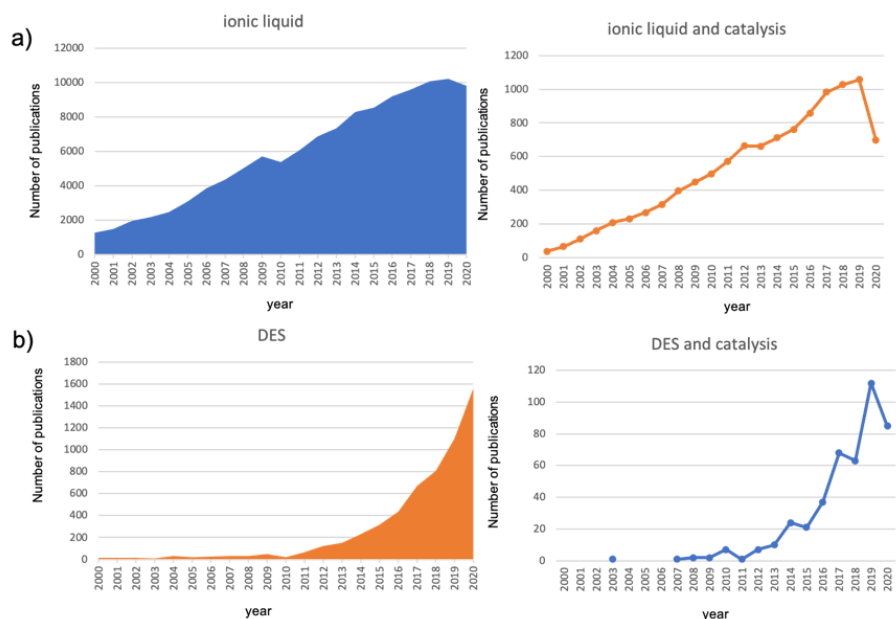
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## 1 Introduction

The advent of sustainable chemistry at the end of the 20<sup>th</sup> century sparked an intense search for greener reaction media in order to substitute conventional solvents charged of being volatile, flammable or toxic. Thus, an increasing interest arose in using water as solvent or supercritical and fluorinated fluids as hydrophobic media, but above all ionic liquids (ILs) attracted the most attention. This statement is supported by the number of publications per year devoted to ionic liquids since 1999, (figure 1a) reaching a plateau of around 10000 pub/year since 2016. The same trend is observed if we consider the publications dealing with IL and catalysis (figure 1a). However, after this boom of ILs, some dissenting voices appeared questioning their toxicity,[1] price and sometimes arduous synthesis. The scientific community diverted then its attention to deep eutectic solvents (DES), much easier to prepare and handle and with tunable properties depending on their components.[2–4]. Deep eutectic solvents are formed by two components, normally a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA). Sometimes the difference between ILs, DES and Low Melting Mixtures (LLMs) has been controversial and some authors have tried to shed light on these aspects.[5] Since 2011 an exponential growth on DES publications has been observed (figure 1b), and the same trend can be noted when analysing the publications dealing with DES and catalysis (figure b). Although the overall numbers are currently far from those related to ILs publications.

**Figure 1**

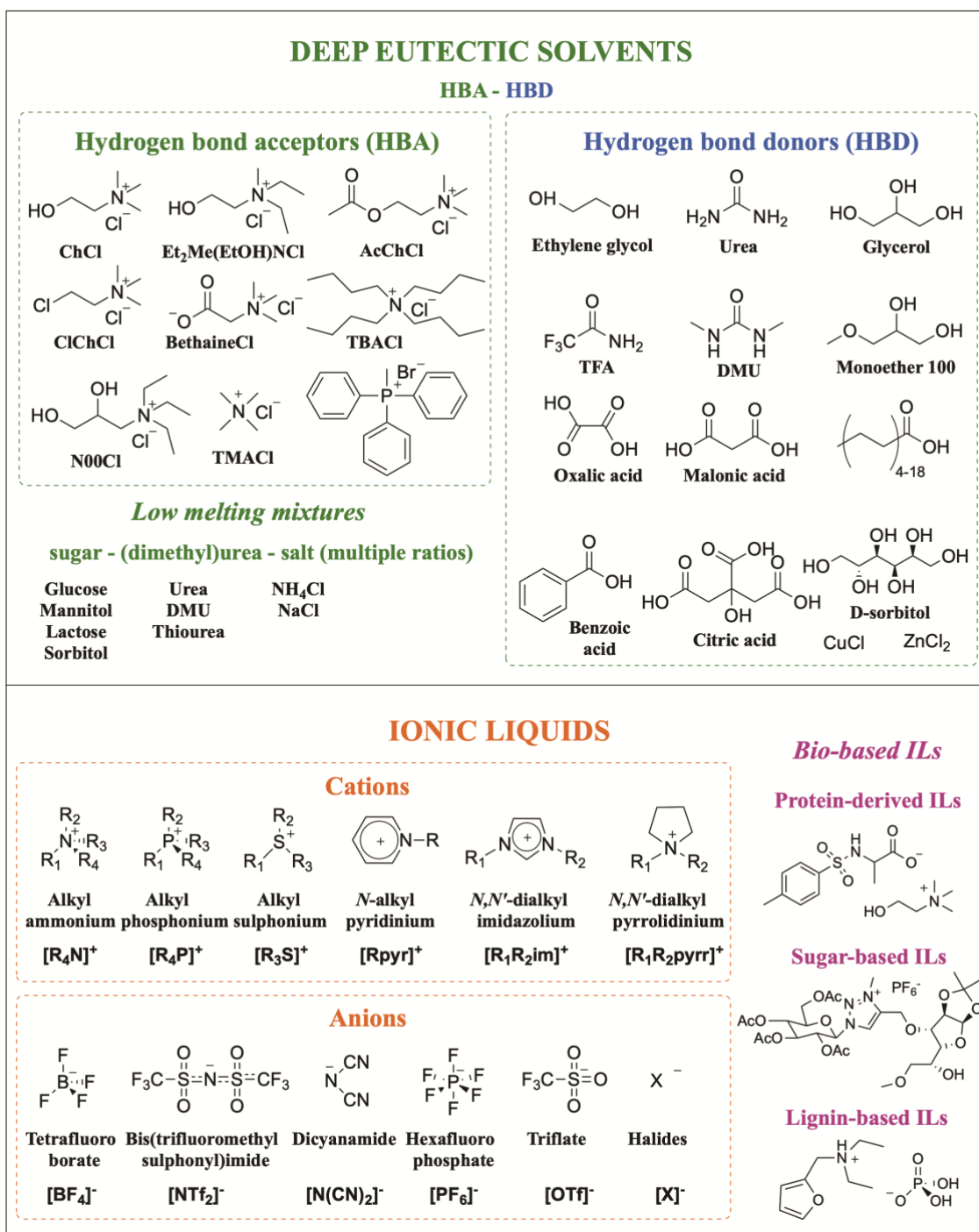
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Number of publications related to ILs and DES (source WOS)

As Alonso et al. stated in 2016 “*The ideal situation would be to perform metal-catalysed reactions in DES. However, the number of reactions explored until now is very small, with the scope of reactions of this class thus remaining unknown*” [6] Nevertheless, it is noteworthy the number of recent reviews devoted to the use of DES in catalysis. [7–10] Herein we present a comparative study of metal-catalysed reactions both in ILs and DES (figure 2) in order to point out the viability and the future perspectives in the use of DES as reaction media.

**Figure 2**

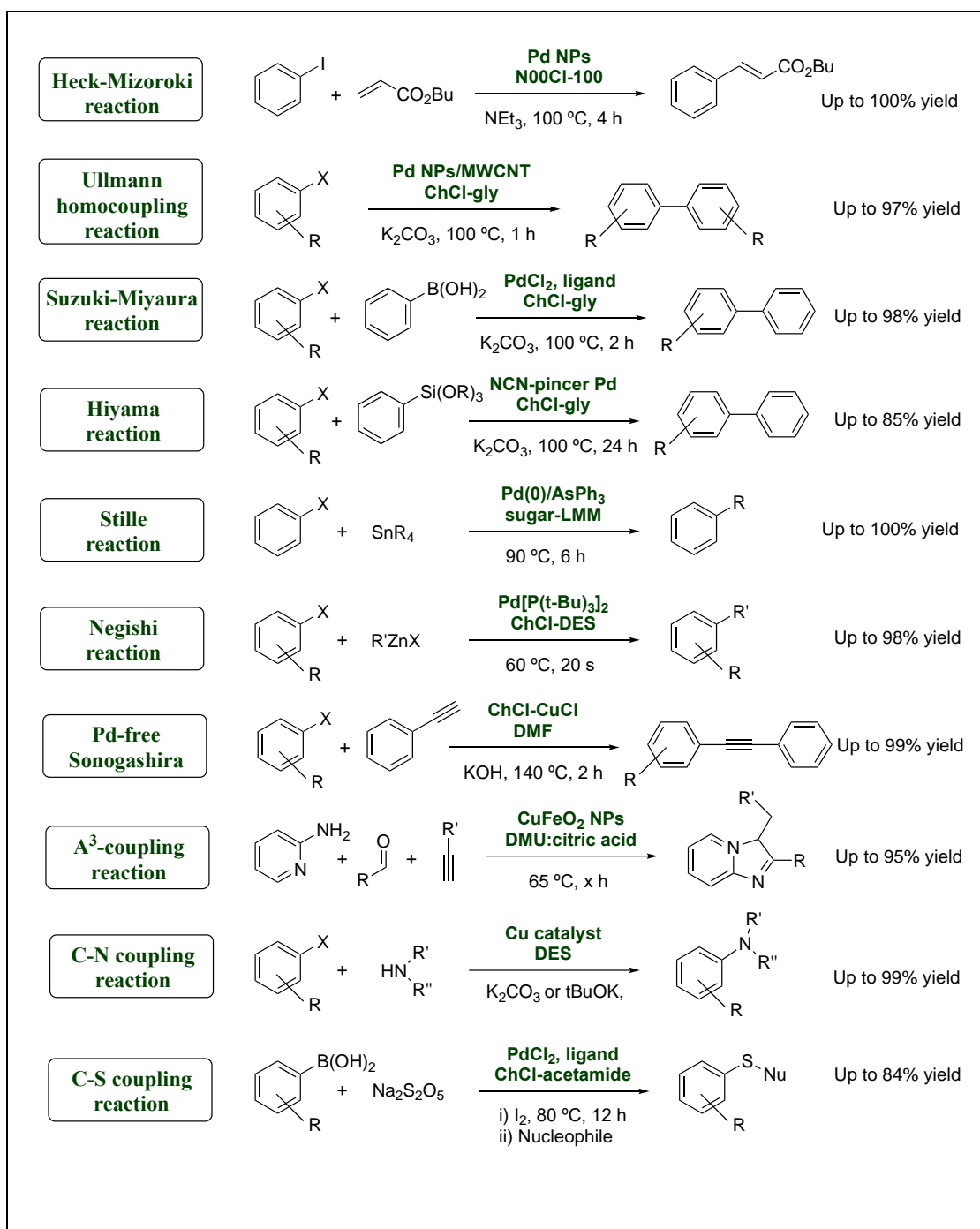


Structure of the main types of DES, LMM and conventional ILs FIGURE 2 HAS BEEN MODIFIED

## 2 DES vs ILs in metal-catalysed coupling reactions

Metal-catalysed coupling reactions have become a powerful tool for the efficient and sustainable synthesis of organic compounds. Organic solvents, water, ILs, DES and supercritical fluids have been widely used in this kind of processes [7,11]. But a growing interest in the use of DES in coupling reactions has arisen since the first works of Imperato et al. in 2006 [12].

Figure 3



Outstanding results of metal-catalysed cross-coupling reactions carried out in DES.[8,9,13]

## 2.1 C–C coupling reactions

Both ILs and DES are suitable solvents for coupling reactions, acting sometimes not only as a solvent but also as a catalyst stabilizer and by tuning the reaction selectivity thus adding additional advantages with respect to the use of conventional solvents [6,9,11,14,15]. In addition, their low-volatility and high-viscosity facilitates the catalytic system recoverability and the catalyst reuse, increasing the sustainability of the process. Starting with homocoupling reactions, excellent results have been reported for aryl homocoupling reactions, catalysed by Pd\_NPs in ILs [11], but scarce works describe the use of DES as the reaction media. The use of DES for promoting the **Ullmann** reaction has been reported just in two preliminary works [16,13]. In the case of Afshari et al., the

immobilization of the NPs onto a carbonaceous-solid support in ChCl-Glycyl DES (Glyceline) has led to the synthesis of biaryl derivatives in 1 h with up to 97% yields [16]. Pd catalyzed **Heck-Mizoroki** reaction between unsaturated halides and alkenes has been successfully carried out in LMMs [17,18] and DES [16,19–22]. As can be seen in Saavedra et al. works, not all the DES are able to promote the desired coupling, for instance, no conversion was observed in the Heck reaction when using hydrophobic DES. Nevertheless, in most cases, these solvents overcome the results achieved with conventional solvents [19,21]. Recently, Leal-Duaso et al. have systematically studied the role of the solvent in the Heck-Mizoroki reaction between iodobenzene and *n*-butyl acrylate [13]. These DES, formed by glycerol and glycerol ethers as HBD and ChCl and N00Cl as HBA, have provided better results than those using the IL [bmim]PF<sub>6</sub> as reaction media. This study reveals that the nature of the DES allows to fine-tune both the Heck-coupling selectivity and the catalyst recoverability [13,22]. Although excellent results have been described in the abovementioned Pd-NPs/DES systems, it is still necessary to test the DES suitability on Heck reaction using less activated halides such as chlorinated ones. It is also relevant to mention that all the examples of the application of DES in Heck-Mizoroki reactions encompass the use of palladium as catalyst, ignoring the possibilities of low-cost metals, such as nickel, iron and cobalt, which have been successfully tested in ILs [23,24].

The use of ionic solvents together with metal complexes have been profusely described in the **Suzuki-Miyaura** reaction [19,21,25]. In general, the best results in this reaction have been obtained using ChCl-DES and LMMs. And this process has been applied to the selective synthesis of valuable chemicals [11,15]. For instance, Capriati and col. prepared benzodithiophene derivatives for optical applications [26], terpenyl compounds were obtained by using a ligand-free Pd-catalyst in Glyceline [27] and Delaye et al. have prepared imidazo-fused heterocycles using carbohydrate-based LMMs [28]. Similar results can be achieved by using Pd-NPs in LMMs, reducing the palladium loading up to 0.05% and increasing the catalyst recyclability [18]. Interestingly, the linkage of Pd NPs to a support such as graphene oxide allows the magnetically recovering of catalyst in the DES [29].

Ramón and col. raised the issue of designing specific catalysts for the **Hiyama** cross-coupling reaction in DES [20,21,30]. NCN-pincer, bipyridine and mesoionic carbene ligands in palladium complexes have been studied and moderate yields were obtained in ChCl derived DES, not always improving previous results in conventional solvents and ILs [15,30]. Biaryl compounds are also available *via* **Stille** reaction between iodo- and bromobenzene and tetraalkylstannanes or phenyltrialkylstannanes. LMMs composed of sugar-(dimethyl)urea-NH<sub>4</sub>Cl have been successfully applied to this reaction with comparable results to ILs or conventional organic solvents and with additional advantages such as catalyst recoverability improvement [12]. A scalable and air-tolerant catalytic system for **Negishi** coupling of aryl bromides and organozinc substrates has been described by Dilauro et al. [31]. The use of a palladium catalyst in ChCl-based DES provided excellent yields under mild conditions, and much shorter reaction times compared to the ones reported for ILs.

Finally, **Sonogashira** coupling of terminal alkynes with aryl or vinyl halides for the creation of valuable C(sp)–C(sp<sup>2</sup>) bonds is being intensively studied using Pd catalysts in DES. Among them, carbohydrate-based LMMs [17], urea and glycerol derived DES [19,20,22,32,33]. In general, the excellent results are comparable to those provided by ILs [9,15]. More interestingly, an example of palladium-free Sonogashira reaction has been reported using ChCl-CuCl [34]. In this case, the metal-containing DES acts both as the catalyst and the solvent.

## 2.2 C–N coupling reactions

Arylated amines are a chemical leitmotiv in many pharmaceuticals, organic materials, natural products and catalysts, that is why a great attention is paid to the development of catalysed synthetic pathways for their obtaining.

Although Buchwald-Hartwig Pd-catalysed cross-coupling of amines and aryl halides is one of the most useful tool for the preparation of aromatic amines,[35] Ullman-type reaction using copper catalysts has been preferred when using DES as reaction media. The works of Varma [9] and Capriati[8] gather the scarce works dealing with the use of DES in C–N bond formation. Thus, Shaabani and col. [16] presented the first example of Ullmann reaction using a recyclable catalytic system composed of magnetic carboxamide-functionalized graphene oxide with Cu\_NPs. A synergetic effect of ChCl-Gly DES with the catalyst was responsible for the good yields observed. Capriati and col. described the use of CuI as catalyst in ChCl-Gly for a broad scope of substrates with excellent yields by just tuning the base (tBuOK or K<sub>2</sub>CO<sub>3</sub>) depending on the nature of the amine. These results improved the ones described in phosphonium derived ILs using CuO<sub>2</sub> clusters as catalysts.[36]

Amide formation by an aminocarbonylation reaction has also successfully been addressed using DES. The utilization of Pd(OAc)<sub>2</sub> as catalyst, together with ChCl-urea (reline) or ChCl-Gly (Glyceline), provided good yields for a wide scope of substates. The catalyst-solvent system was easily recycled and reusable.[37]

## 2.3 C–S and C–O coupling reactions

Thioethers are fundamental building blocks for the synthesis of biologically active molecules. Copper catalysts in ILs have been proposed as sustainable and efficient systems for its obtaining[38,39] and Pd catalysts have been used in three-component reactions in IL for C–S bond formation in a IL.[40]

In this case, the use of ChCl-urea as solvent has permitted to carry out the synthesis of thioethers in excellent yield without the need of metal species, thus DES acting both as solvent and catalyst.[41] The same S<sub>N</sub>Ar protocol has also been applied to C–O bond formation with excellent results.[42]

A wide scope of sulfones have been obtained applying a jigsaw-synthesis using ChCl-acetamide as solvent and PdCl<sub>2</sub>-Phosphine ligand as catalyst,[43] improving the results previously described using IL as an additive in copper-catalysed coupling reaction of aryl halides with PhSO<sub>2</sub>Na.2H<sub>2</sub>O.[44]

## 3 DES vs ILs in metal-catalysed hydrogenations

Metal-catalysed hydrogenation reactions are processes with a huge interest for food, pharmaceutical and petrochemical industry. The use of ionic solvents in these reactions improves the solubility of hydrogen, thus increasing the reactivity. Different ILs have been applied to hydrogenation reactions, revealing the importance of the solvent design. It is relevant to note that the presence of irremovable impurities in ILs negatively affects the hydrogenation efficiency [45], this would give a good opportunity to the utilization of DES, easily available in a high purity.

However, scarce hydrogenations have been described using DES as reaction media. The first example, reported the homogeneous hydrogenation of methyl cinnamate in urea-carbohydrate LMMs using the Wilkinson's catalyst. [25] Recently, nine glycerol-based DES have been applied to the Pd\_NPs catalysed hydrogenation of alkenes, alkynes and carbonyl compounds [46]. Improved results compared to previous works were described [47] especially in the semi-hydrogenation of alkynes to alkenes.

DES can be also the H<sub>2</sub>-source, as in the Ru-catalysed transfer hydrogenation of carbonyl compounds under mild conditions [48].

#### 4 Bio-based ionic liquids: a new alternative?

As discussed herein, DES present advantages that make them a good alternative to traditional organic solvents and ILs. However, DES sometimes present some disadvantages, such as a moderate viscosity, the temperature stability or the difficulty in the recovery due to the loss of one of its components in extraction processes.

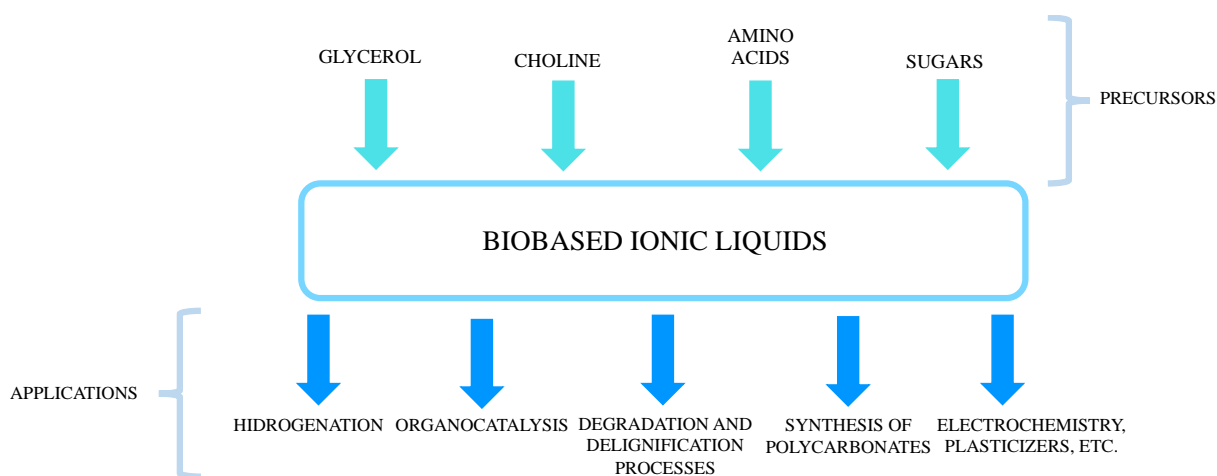
In order to overcome the drawbacks of ILs and DES a new family of solvents is being developed: *biobased ionic liquids*.

The number of publications dealing with biobased-ILs still low, although increasing in the last years. Regarding the synthesis of biobased ILs, amino acids, sugars, choline chloride or glycerol derivatives have been used as platform molecules.[48-52]

Some applications for this new solvents have been described, such as in catalysts,[53-55] and in the degradation of organophosphorus pesticides,[56] or as solvents for electrochemistry.[57]

Up to now only few examples of the use of biobased-ILs in metal-catalysed reactions have been reported. All of them are related to the stabilization of Pd-NPs and their application to catalytic processes. Thus, Gómez et al.[58] described the use of Pd-NPs in choline-based ILs as catalysts for hydrogenation reactions and Gaikwald et al [22] designed glycerol-derived ILs for in situ generation of Pd-NPs and their application in Heck coupling.

**Figure 4**



Sources and applications of bio-based ILs.

#### 5 Conclusions and perspectives

The works published up to date have demonstrated that the use of DES is a real alternative to traditional ILs metal-catalysed reactions. DES improves the activity, stability and recoverability of metal catalysts thanks to their ability to interact with metal species and in some cases, the use of DES improved both reaction yields and selectivity. The fine tuning of the most important DES properties can be done by choosing the right HBA and HBD. DES components are easily available and the purity of the solvent is guarantee. These aspects are the main advantages of DES compared to ILs. Only two main drawbacks of DES should be addressed: the moderate viscosity of some DES and some difficulties upon extraction processes. Both issues can be solved by the use of designer

DES or biobased ILs or applying to alternative extraction techniques such as the use of supercritical fluid extraction. However, the use of DES remains unexplored in less common cross-couplings such as Kumada, Corey-House, Fukuyama, Liebeskind-Srogl (C–C), Castro-Stephens, Cadiot-Chodkiewicz (C–Csp), Glaser (Csp–Csp), Buchwald-Hartwig and Chan-Lam (C–N) among others.

Future works should include computational studies of the role of DES in the reactions pathways, broaden the scope of DES (NaDES, chiral DES or DES including metals), catalytic studies with other metals apart from copper or palladium and finally try to apply green activation methods in DES.

### **List of Abbreviations**

DES: Deep Eutectic Solvents

NaDES: Natural Deep Eutectic Solvents

LMMs: Low Melting Mixtures

IL: Ionic Liquid

ChCl: Choline chloride

AcChCl: Acetyl choline chloride

DMU: Dimethylurea

Gly: Glycerol

Im: Imidazolium

N00Cl: *N,N,N*-Triethyl-2,3-dihydroxypropan-1-aminium chloride

Pyr: Pyridinium

Pyr: Pyrrolidinium

TBACl: Tetrabutylammonium chloride

TFA: Trifluoroacetamide

BmimPF<sub>6</sub>: Buthyl Methyl Imidazolium Hexafluorophosphate

DMF: Dimethylformamide

TMACl: Tetramethylammonium chloride

100: 3-Methoxy-1,2-propanediol

### **Conflict of interest statement**

Nothing declared.

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This review gathers the use of DES as reagents, catalysts and solvent in organic chemistry. Useful publication to get familiar with DES and their uses in organic synthesis.

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This article describes the preparation of Palladium nanoparticles from a Pd (II) precursor in a choline-based ionic liquid. These nanoparticles were used as catalysts in hydrogenation reactions for a large number substrates with high yields.