Deep Eutectic Solvents and Heterogeneous Catalysis with Metallic Nanoparticles: A Powerful Partnership in Sustainable Synthesis

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Abstract

The last decade has seen a remarkable interest in *Deep Eutectic Solvents* (*DESs*), usually obtained from biorenewable, cheap and non-toxic precursors, as effective environmentally responsible reaction media for transition-metal-catalyzed organic transformations. One of the main advantages associated with the use of these neoteric solvents is the ease of recyclability of both the catalytic system under study and the eutectic mixture, which paves the way for their implementation in heterogeneous catalysis. In this *Current Opinion*, a discussion is offered to highlight recent studies published, in particular since 2018, in which transition-metal-based nanoparticles have been efficiently coupled with *DESs* in the following synthetic protocols: *i*) C–C and C–X (X = N, O, S) coupling reactions; *ii*) oxidation/reduction processes; *iii*) synthesis of heterocycles/cycloisomerizations; and *iv*) polymerization reactions.

Keywords

Deep Eutectic Solvents; Heterogeneous catalysis; Nanocatalysts; Metallic nanoparticles; Sustainable synthesis.

Graphical abstract

Heterogeneous
Catalysis

Green Chemistry

Organic
Synthesis

Deep Eutectic
Solvents
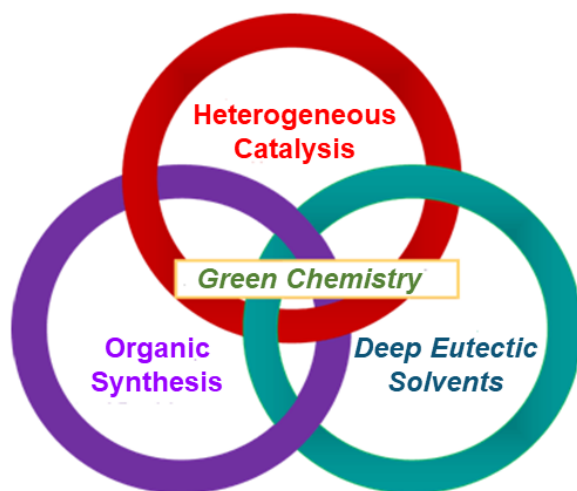
1. Introduction

Over the last two centuries, humans have impacted heavily on the environment giving rise to global warming, the gradual consumption of deposits of raw materials, and the change of various natural ecosystems [1,2]. Thus, actions are urgent and necessary to face climate-health threats; for example, switching from a linear to a circular economy, limiting the use of hazardous substances or reducing the employment of non-biorenewable raw materials [3,4]. The concept of Green Chemistry emerged in the 1990s. It is based on 12 basic principles [5], whose practical application means achieving a more sustainable synthetic work methodology [6–10]. Currently, solvents account for a high percentage of waste generated in different chemical processes, both at laboratory and industrial level [11]. In addition, a large part of organic solvents traditionally used in synthesis are volatile organic compounds (*VOCs*), which are often toxic and/or flammable (e.g., *n*-hexane, toluene, dichloromethane, tetrahydrofuran) [12,13].

Since the pioneering work of Abbott [14], Deep Eutectic Solvents (*DESs*) have emerged as a new class of sustainable reaction media because of the following properties: *i*) negligible vapor pressure; *ii*) high-thermal stability; *iii*) nonflammability; and *iv*) easy recycling. *DESs* are binary or ternary mixtures comprising at least one hydrogen bond donor (*HBD*) and at least one hydrogen bond acceptor (*HBA*), which are strongly associated with each other *via* hydrogen bond interactions [15,16]. Figure 1 depicts some of the most common *HBAs* and *HBDs* used in the synthesis of *DESs*. [17]. In the portfolio of green solvents, *DESs* are rapidly evolving as privileged reaction media replacing *VOCs* in a variety of chemical transformations [18–25].
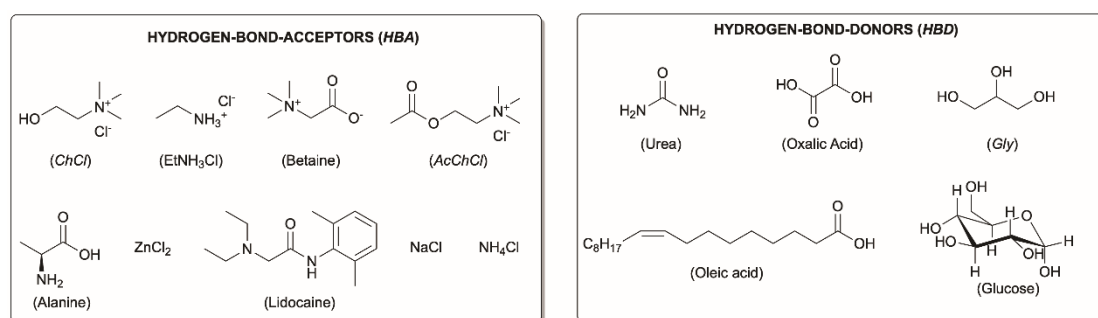

Figure 1. Common *HBA* and *HBD* components used in the synthesis of *DESs*. *ChCl* = choline chloride; *AcChCl* = acetylcholine chloride; *Gly* = glycerol.

Despite these advantages, however, there is still controversy about their toxicity. Thus, new guidelines have recently been released for *DESs* toxicity monitoring [26]. Particular care should be taken to *DES* components especially if they bear a risk of nitrosamine formation (e.g., amides of dialkanolamines) [27,28].

In his book on Catalysis, G. Rothenberg stated "*catalysis is the key to sustainability*" [29]. A catalyst is a chemical substance that accelerates a chemical reaction without changing its thermodynamic parameters, often improving the selectivity of a process, with fewer by-products and waste generated, in line with the aforementioned Principles of Green Chemistry [5,30,31]. In the field of sustainable chemistry, the use of heterogeneous catalysis [32,33] is highly pursued for the development of *greener* catalytic systems and synthetic methodologies, since it allows the straightforward separation of the catalytic system, thereby opening the door to recyclability studies that would increase the turnover numbers of the catalytic system [34]. It is hard to find advanced syntheses in which heterogeneous catalysts are not being used in any of their stages, as they often have been found to unlock the discovery of novel synthesis processes [35,36].

In this brief *Opinion*, we will be tackling the sustainability challenges in cross-coupling and other reactions (*i.e.*, oxidations, cicloisomerizations, polymerizations) by focusing on the partnership formed between eutectic mixtures and heterogeneous catalysts, basically, metallic nanoparticles (NPs) for a sustainable catalysis.

2. Applications of metallic NPs in cross-coupling reactions in *DESs*: C–C and C–heteroatom bond formation

Since the pioneering work of Corey and Posner [37] in 1970, cross-coupling reactions have made great progress. They are nowadays considered one of the most reliable tools in modern organic synthesis as they allow the straightforward and selective formation of C–C, C–N, C–O or C–S bonds [38–40]. The use of heterogeneous catalysts (basically metallic NPs) has dominated the field during the last decades [41], leading to the publishing of a variety of C–C cross-coupling processes catalyzed by metallic NPs, while using *DESs* as sustainable solvents [42]. Zhao and Ramón paved the way in this field by reporting the first ligand-free Suzuki and Heck couplings (Figure 2a) [43] and cross-dehydrogenative couplings between a variety of tetrahydroisoquinolines and terminal alkynes (Figure 2b) [44], respectively. Recently Capriati, Salomone and co-workers revisited this field by describing ligand-free heterogeneous Pd-catalyzed

Sonogashira reactions in the eutectic mixture 1choline chloride (*ChCl*)/2glycerol (*Gly*). In this case, the commercially available and cheap Pd/C was found to promote the desired couplings between (hetero)aryl iodides and both aromatic and aliphatic alkynes in good to quantitative yields (50 to 99%) (3 h at 60 °C) (Figure 2c), with *DES* and the catalyst being successfully recycled for up to 4 times [45]. As limitations, the catalytic systems required the presence of a base (NEt$_3$) and higher temperatures (80 ºC), giving rise to undesired side reactions (formation of enynes/enediynes). Not only Pd NPs but also other Pd-containing heterogeneous catalysts have successfully been applied to C–C cross-coupling reactions. Heydari and co-workers demonstrated that it is possible to trigger an imidazole-aryl coupling reaction (*via* regioselective C–H bond activation at the C5 position of the starting imidazole) by using the Pd heterogeneous catalyst MRGO@DAP-AO-Pd (Figure 2d). The latter is based on modified magnetic reduced graphene oxide (MRGO) containing a diaminopyridine (DAM)/amidoxime (AO) mixed ligand which is able to anchor the Pd precursor [PdCl$_2$(CH$_3$CN)$_2$] to the structure of MRGO [46]. In this case, an alkaline *DES* (1K$_2$CO$_3$/5*Gly*) and 130 ºC are required to obtain the final biaryl products. The catalytic system reduces its: *i*) selectivity, when increasing the loading (1 mol%); and *ii*) activity, when decreasing the temperature (90 ºC). More recently, Doan and co-workers demonstrated that a Pd-incorporated Zr-based Metal-Organic-Framework (*MOF*) containing sulfone groups (Pd@MOF) behaved as an efficient heterogeneous catalyst for the synthesis of a wide variety of stilbene-type derivatives through the Heck reaction, by using a ternary and a basic DABCO-based eutectic mixture (DABCO = 1,4-diazabicyclo[2.2.2]octane) as the solvent [47]. However, the use of an external base was mandatory, while the presence of amino groups and substituents in *ortho*-position had a negative effect. The catalyst and the eutectic mixture could be recovered and reused up to 5 catalytic cycles (Figure 2e).
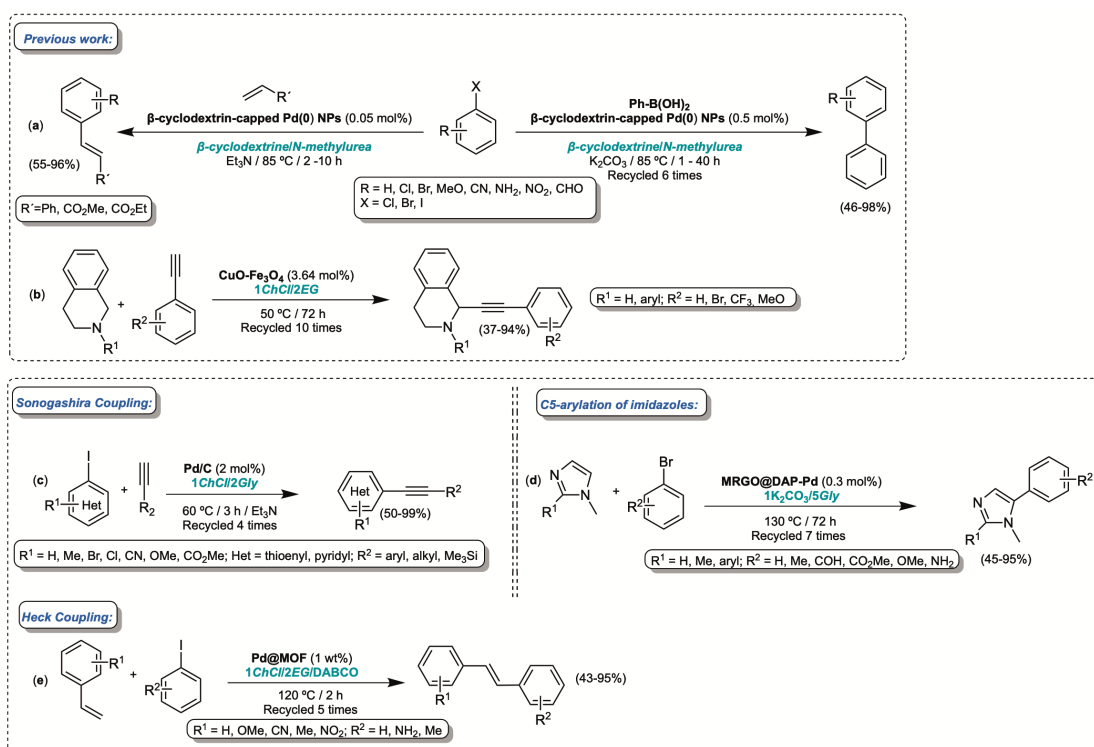
Figure 2. Various Pd-catalyzed C–C cross-coupling reactions performed in *DESs* (a–e). *ChCl* = choline chloride; *EG* = ethylene glycol; *Gly* = glycerol. DABCO = 1,4-diazabicyclo[2.2.2]octane.

Since the pioneering studies performed by Ramón and co-workers on C–S bond formation (catalyzed by *in-situ* formed Pd NPs), the partnership formed between metallic NPs and *DESs* continues to be a blossoming field (Figure 3a) [48]. Regarding the C–N bond formation, Afshari and co-workers reported the interesting use of carboxime-functionalized graphene oxide (carboxamide-f-GO), containing copper nanoparticles (CuNPs) on its surface covered with Fe_3O_4, to yield a new mixed nanocatalytic system (CuNP-carboxamide-f-GO@Fe_3O_4), useful for the Ullmann cross-coupling (Figure 3b), which was synthesized from natural graphite using water as the solvent [49]. In this case, both secondary and primary amines and aryl iodides were coupled by using 1*ChCl*/2*Gly* as sustainable solvent with a low catalyst loading (0.05 mol%), although both an external base (K_2CO_3) and a high temperature (110 ºC) were required. By employing this methodology, a plethora of tertiary and secondary amines were synthesized in good to excellent yields (75–99%). However, the catalytic process did not take place in the absence of base, while the use of lower temperatures (80 ºC) decreased considerably the observed catalytic activity. It is worth highlighting that both the nanocatalytic system (CuNP-carboxamide-f-GO@Fe_3O_4) and the eutectic

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solvent (1*ChCl*/2*Gly*) could be recycled for up to 5 consecutive cycles. Heydari and co-workers later described the possibility to use a heterogeneous and magnetic Cu catalyst [Fe_3O_4@creatine-Cu(I)] in the coupling of bromoarenes with aniline-type derivatives (Figure 3c) using the basic eutectic mixture 1K_2CO_3/4*Gly* as the solvent at 80 ºC, with the catalytic system being recycled for up to 5 consecutive runs [50]. Remarkably, the authors also extended their studies to the formation of C–O bonds by replacing anilines with phenol-type coupling partners (Figure 3d). However, trisubstituted phenols (*i.e.*, picric acid) gave only moderate yields due to steric hindrance. The coupling of anilines and bromoarenes was then revisited by the same authors, however, using a Cu(I) acyclovir complex supported on silica/silane-recovered magnetic Fe_3O_4 nanoparticles [Fe_3O_4@SiO_2-Si(CH_2)$_3$N-acyclovir-Cu(I)] (Figure 3e), being its synthesis performed in water or ethanol [51]. In this case, ethylene glycol was chosen as the *HBD* of the basic eutectic mixture. Again, the catalytic system could easily be recovered and reused for 5 new rounds of reactions when working at 80 ºC, whereas the use of lower temperatures (25–60 ºC) dramatically decreased the final yields. Finally, it is worth mentioning the use of: *i*) CuO-supported on γ-Fe_2O_3 for the synthesis of carbamates or *N*-acylureas in 1*ChCl*/2*Gly* (recycled up to 6 runs, Figure 3f) [52]; and *ii*) Fe_3O_4 superparamagnetic NPs (MNP-Fe_3O_4) for the synthesis of ureas or carbamates using the 1*ChCl*/1$ZnCl_2$ eutectic mixture as the solvent (recycled up to 5 runs; Figure 3g) [53].
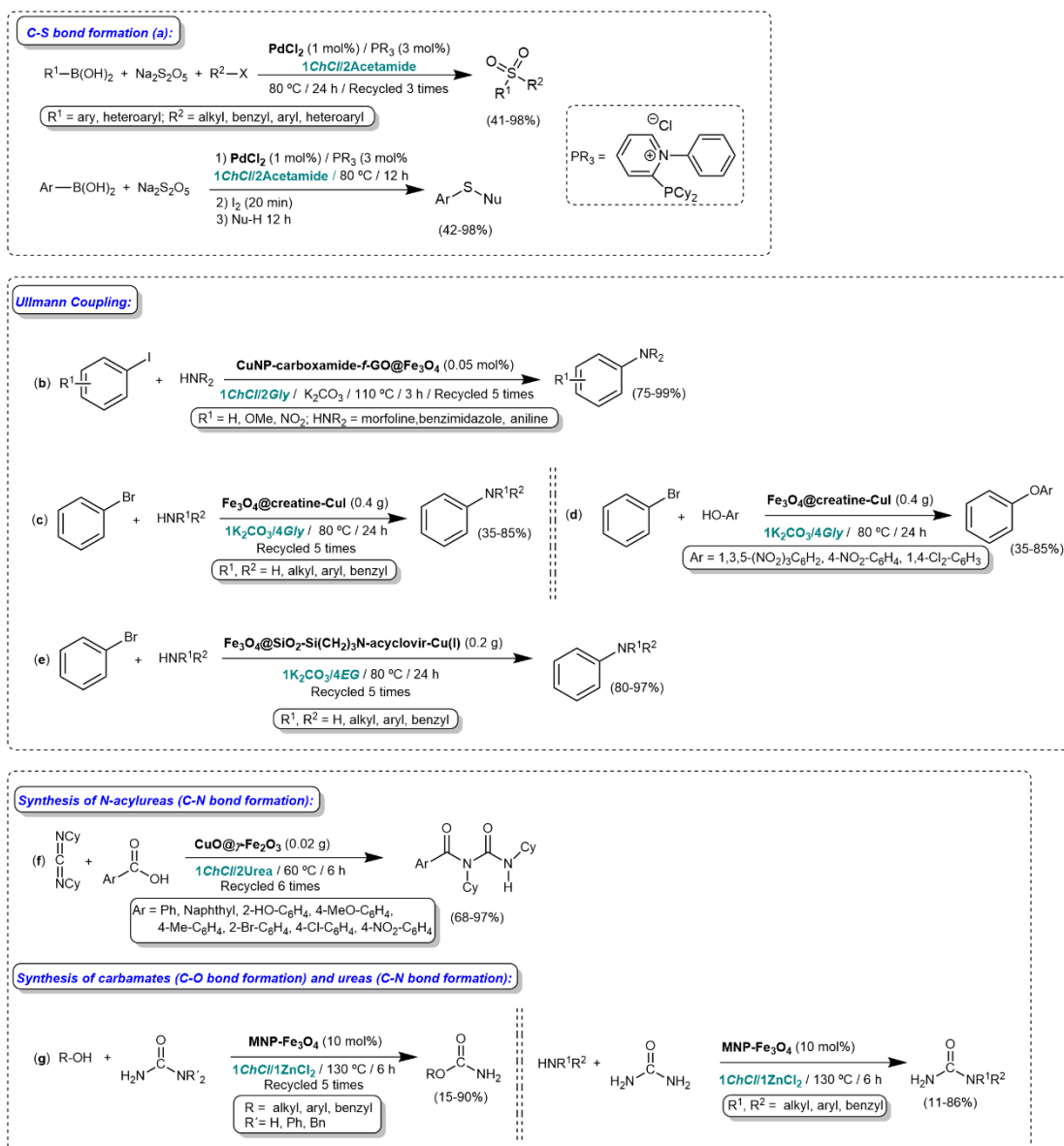
Figure 3. Various C-heteroatom bond formation reactions (a–g) performed in *DESs*. *ChCl* = choline chloride; *EG* = ethylene glycol.

3. Other applications of metallic NPs and DESs

In order to give the reader an overview on the use of metal nanocatalysts to promote different organic transformations, in this section, miscellaneous examples are discussed.

Reduction/oxidation reactions: In 2014, Carrier and co-workers reported the hydrogenation of butadiene in 1*ChCl*/2Urea catalyzed by gold NPs supported on TiO_2 [54]. König and co-workers then described the synthesis of a supported Pd/NCO heterogeneous catalyst (Pd/NCO = Palladium on supporting material composed of Carbon, Nitrogen and Oxygen), obtained by pyrolysis of a mixture containing

palladium acetate and different sugar-based *DESs*, and its use for the hydrogenation of 1-dodecene under a H_2 atmosphere at room temperature (Figure 4a) [55]. More recently, many groups have turned their attention to the possibility to promote catalytic oxidation reactions by employing the partnership formed by metallic heterogeneous catalysts and eutectic mixtures. Xiong, Cheng and co-workers described a Co-based MOF $[Co_3(BTC)_2(urea)_2] \cdot 2H_2O$ (H_3BTC = 1,3,5-benzenetricarboxylic acid), which was synthesized directly in 1*ChCl*/2Urea, and its use in the catalytic oxidation of styrene to the corresponding mixture of benzaldehyde and styrene oxide when using TBHP (*t*-butylhydroperoxide) as the external oxidant at 75 ºC for 24 h in CH_3CN (Figure 4b), the catalytic system being recycled for up to 3 cycles [56]. Although conversion rate could be enhanced by increasing the reaction temperature, a decrease on the selectivity of benzaldehyde was observed. Ammozadeh and co-workers also demonstrated that the same heterogeneous TiO_2-DES-based catalyst [*n*-TiO_2-P25@TDI@DES(1$ZnCl_2$/4Urea), Figures 4c,d], obtained by mixing commercially available *n*-TiO_2-P25 NPs with TDI (toluene diisocyanate) in 1$ZnCl_2$/4Urea, was able to catalyze: *i*) the photocatalytic oxidation of benzylic alcohols to benzaldehydes (a gradual increase of the steric hindrance produced a concomitant decrease of the reaction yield; Figure 4c) [57]; and *ii*) the chemoselective oxidation of sulfides to the corresponding sulfoxides by using H_2O_2 as the co-oxidant under neat conditions, the catalytic system being recycled up to 6 consecutive cycles (Figure 4d) [58].

Synthesis of heterocycles/cycloisomerization processes: The combination of eutectic mixtures and metal-based NPs has been successfully employed in the synthesis of different *N*-heterocyclic compounds. Lu and co-workers first described a one-pot strategy for the synthesis of imizado[1,2]pyridines by reacting 2-aminopyridines, aldehydes and terminal alkynes in the presence of the superparamagnetic $CuFeO_2$ NPs as catalyst (Figure 4e) [59]. Both the superparamagnetic NPs and the eutectic mixture could be recovered and reused for up to 6 consecutive cycles. A similar one-pot four-component protocol was also reported by Manocheri and co-workers for the efficient synthesis of tetrasubstituted imidazoles by using Fe_3O_4 NPs as catalyst, while working in 1*ChCl*/2Urea at 60 ºC (Figure 4f) [60]. Recently, Ramón, García-Álvarez and co-workers proved that Pd(II) oxide, impregnated on magnetite (PdO-Fe_3O_4), was an efficient and selective catalyst for the cycloisomerization of a variety of alkynoic acids and alkynyl imides in *ChCl*-based eutectic mixture or aqueous media, working at 90 ºC and in the absence of any co-catalyst, giving rise to five-membered lactones or lactams

(Figure 4g) [61]. The reaction selectivity was preserved with aliphatic substituents by working at lower temperatures (50 °C). The catalytic system could be recycled up to 4 consecutive times without any decrease in catalytic activity or selectivity.

Polymerization: Presa Soto, García-Álvarez and co-workers reported the possibility to promote a heterogeneous Atom Transfer Radical Polymerisation (ATRP) of methyl methacrylate under ARGET conditions (ARGET = Activators ReGenerated by Electron Transfer) by using the Cu(II)-MOF [Cu$_2$(bdc)$_2$(DABCO)] (bdc = terephthalic acid) as a recyclable catalyst in the absence of organic ligands. This Cu(II)-MOF works in combination with Sn(EH)$_2$ as a reducing agent (EH = 2-ethylhexanoate), under an air atmosphere and in 1*ChCl*/2*Gly* [62]. Under these experimental conditions, a well-defined poly(methyl methacrylate) (PMMA) was obtained. Importantly, both the MOF catalyst and DES were successfully recycled for up to 6 consecutive catalytic cycles.
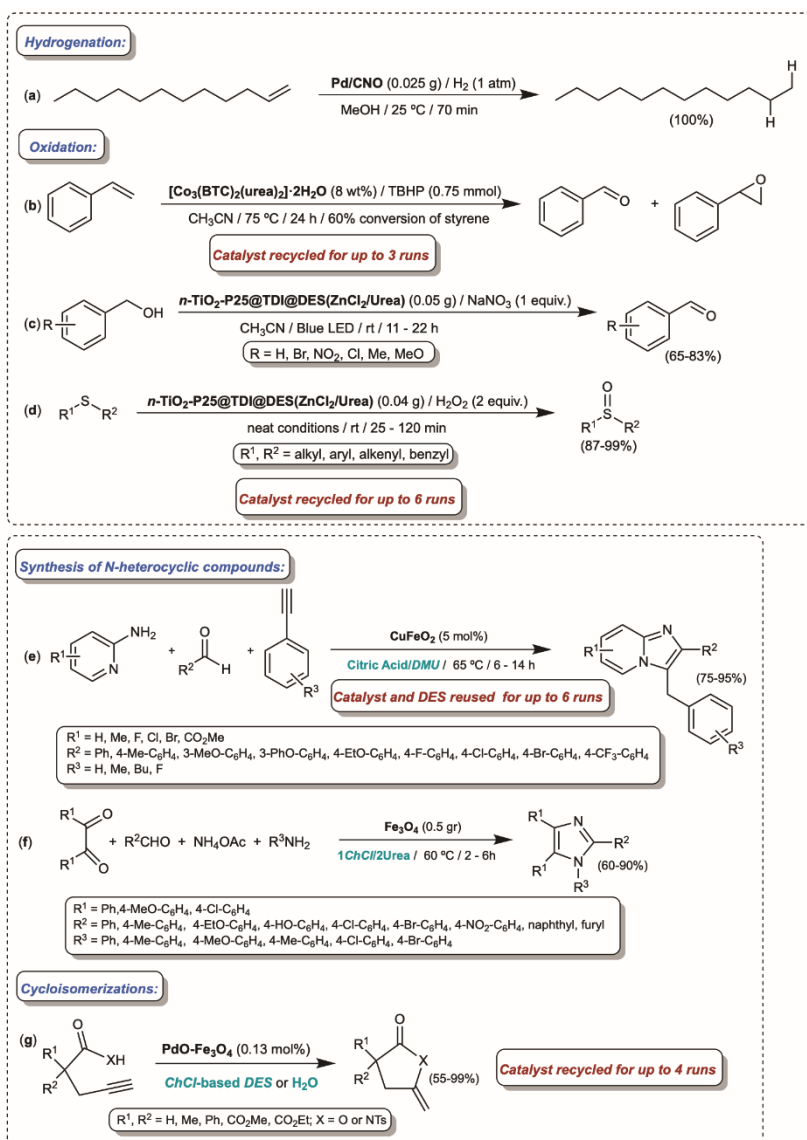
Figure 4. Miscellaneous application of NPs and *DESs* in organic synthesis (a–g). rt = room temperature; *ChCl* = choline chloride; *DMU* = 1,2-dimethyl urea; Pd/CNO = active palladium on supporting material composed of Carbon, Nitrogen and Oxygen (CNO).

5. Conclusions and opportunities

In this *Current Opinion*, recent reports dealing with a partnership formed by highly active and selective heterogeneous NPs and eutectic mixtures have been highlighted. Several advanced heterogeneous catalysts including Pd, Cu or Fe as active species have been shown to trigger a wide variety of important chemical transformations ranging from the formation of C–C/C–heteroatom bond to oxidation/reduction protocols or even cycloisomerizations/polymerizations of unsaturated organic substrates. In most of the reported cases, reactions took place in the presence of air and at room temperature/pressure, with the heterogeneous catalysts being reusable without suffering a strong erosion of their activity or selectivity. Although the catalytic performance of heterogeneous catalysts in *DESs* has been greatly advanced, the design of new efficient heterogeneous nanocatalysts, especially based on earth-abundant metals [63], as well as biocompatible metal NPs [64], in combination with environmentally responsible solvents, is highly sought after for developing a more sustainable commercial production of organic commodities [3,4]. Interaction effects between *DESs* and metallic NPs are also worth deepening [65].

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This work describes, as a proof of concept, the synthesis of biocompatible nanomaterials by combining Deep Eutectic Solvents with carrageenan as capping agent for nanoparticles. Not only carrageenan ensures the safety and has the potential to act as antibacterial and antiviral agent, but it also adds enhanced stability to the nanoparticles, thereby opening a new field of research in this field.

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