



Showcasing a review on deep eutectic solvents by
Graziano Di Carmine, Andrew P. Abbott, and
Carmine D'Agostino from Università di Ferrara,
University of Leicester, and University of Manchester:

Deep eutectic solvents: alternative reaction media for
organic oxidation reactions

Deep Eutectic Solvents (DESs) have recently gained interest
as reaction media for organic oxidations, displaying a series
of advantages over conventional solvents. In this review we
critically highlight the state-of-the-art in this emerging area,
focusing on sustainability and enhancement in reactivity.

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Deep eutectic solvents: alternative reaction media for organic oxidation reactions

Graziano Di Carmine, ^{ab} Andrew P. Abbott ^c and Carmine D'Agostino ^{*b}

Deep eutectic solvents (DESs) have emerged as an alternative to ionic liquids (ILs). DESs share with ILs some appealing features, such as low vapor pressure, capability to dissolve reagents insoluble in common organic solvents, and the possibility to tune the overall pH of the medium by replacing one of the constituents of the mixture. Furthermore, DESs can be prepared by combining molecules that come from natural sources (*i.e.*, glycerol, glucose), making them biodegradable. DESs have already been used for a variety of reactions and protocols since they were reported for the first time by A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70, and among the reactions studied, organic oxidation has recently gained much attention. In particular, the recyclability of these ionic compounds makes it possible to achieve anchoring of organic oxidants, such as TEMPO and peroxydisulfate, directly onto one species of the DES mixture components. In addition, their solubility properties play a crucial role in organic oxidation since DESs have the ability to dissolve both organic lipophilic and hydrophilic species, making the oxidation of organic compounds mediated by hydrogen peroxide more efficient. Herein we report the state of the art of this developing field, focusing on the benefits of substituting common organic solvents with DESs, especially in terms of sustainability, enhancement of reactivity, and recyclability.

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^a Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Via Luigi Borsari, 46, I-44121 Ferrara, Italy

^b Department of Chemical Engineering and Analytical Science, The University of Manchester, The Mill, Sackville Street, Manchester, M13 9PL, UK.

E-mail: carmine.dagostino@manchester.ac.uk

^c School of Chemistry, University of Leicester, Leicester, LE1 7RH, UK

1. Introduction

Ionic liquids (ILs) have been of interest for more than 40 years as alternative media for a wide variety of applications¹ and they have attracted significant attention in the past two decades in many areas of chemistry such as materials,² gas



Graziano Di Carmine

Graziano Di Carmine obtained his Bachelor's Degree from the University of Rome "Tor Vergata", a Master's Degree at the University of Bologna and a PhD in chemistry at the University of Ferrara under the supervision of Prof. Olga Bortolini working on umpolung reactivity promoted by organocatalysts. He was a Research Fellow at the ISOF CNR of Bologna and then moved to the University of Manchester as a

Research Associate in the group of Dr Carmine D'Agostino working on NMR methods for the investigation of reactions promoted by solid-supported organocatalysts. He is currently a Research Fellow at the University of Ferrara.



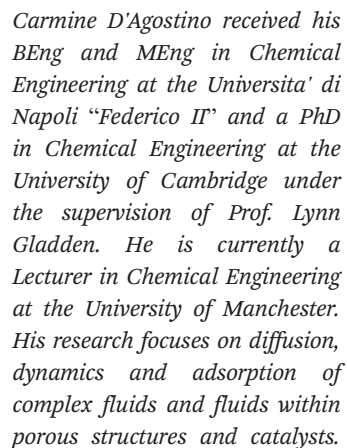
Andrew Abbott

Andrew Abbott is Professor of Physical Chemistry at the University of Leicester where he has been since 1993. He started research into ionic liquids and deep eutectic solvents in 1999 and launched the spin-out company Scionix in 2000. He has research interests in electrodeposition, mineral and natural product extraction and biomaterials.



While the first definition of DESs involved quaternary ammonium salt and hydrogen bond donor mixtures, they can be more generally described as mixtures of Brønsted and Lewis acids and bases. In all these systems strong hydrogen bonds develop and these deviate from ideal mixtures, resulting in a significant depression of freezing point. Similar mixtures of Brønsted and Lewis acids and bases are commonly found in nature and the term natural DESs has been coined, although this should only be applied to naturally occurring mixtures rather than those synthesized from naturally occurring starting materials.¹³

Table 1 Common halide salts and HBDs used in the preparation of DESs



He received several awards, including the Young Scientist Award at the International Congress on Catalysis, the Reaction Chemistry & Engineering Emerging Investigator award and a prestigious Junior Research Fellowship at the University of Cambridge.



Table 2 Classification of deep eutectic solvents depending on their composition

Eutectic	Acid	Base
1	Lewis MClx M = Zn, Sn, Fe, ¹⁴ Al, ¹⁵ Ga, ¹⁶ In (ref. 17)	Lewis R ₄ NCl
2	Lewis MClx·yH ₂ O, M = Cr, Co, Cu, Ni, Fe (ref. 18)	Lewis R ₄ NCl
3	Brønsted RZ, Z = CONH ₂ , COOH, OH (ref. 19)	Lewis R ₄ NCl
4	Lewis MClx or MClx·yH ₂ O M = Al, ²⁰ Zn, ²¹ Cr (ref. 22)	Lewis RZ, Z = CONH ₂ , COOH, OH
5	Brønsted ROH RZ, Z = COOH (ref. 23)	Lewis RZ, Z = CONH ₂ , COOH, OH

Table 2 lists the different types of Brønsted and Lewis acid and base mixtures which have been studied together with examples of the components used.

Generally, an appreciable depression of the freezing point is observed and the magnitude of that depression is related to the strength of the bond formed between the two components, *i.e.* AlCl₃ will exhibit a greater depression of freezing point than an alcoholic HBD such as glucose.

DESSs have been used in numerous applications, such as for metal-organic framework (MOF) synthesis, nanoparticle preparation and gasoline desulfurization and as a medium for organic reactions.^{11b,24,25} Among organic reactions, oxidation reactions are well-known to be fundamental transformations in both industry and academia due to their capability to turn inert molecules into more reactive analogues prone to undergo further transformations. For example, hydrogen atom transfer (HAT) in free radical halogenation is a well-known protocol to prepare chlorinated solvents (chloroform, hexachlorobutadiene and dichloromethane) starting from fossil resources;²⁶ ozonolysis is generally employed to fragment alkynes to prepare carboxylic acids,²⁷ and the hydroxylation of the C-H bond is used to convert lipophilic compounds into hydrophobic analogues for environmental and pharmaceutical purposes (Scheme 1).²⁸

2. Physicochemical properties of DESSs

Ionic fluids have different solvent-solvent-solute interactions and this results in significantly different physicochemical properties. These properties are easily tuned by changing the type and composition of the constituents. Among these, freezing point, viscosity, conductivity and pH have to be well characterized since they can significantly affect the reactivity and mass transport.

Freezing point and vapor pressure

Freezing point is among the most important properties as this can limit the temperature range during the reaction screening in the optimization stage. Freezing-point depression upon formation of DESSs is related to the magnitude of the interaction between the components being mixed. For example, in the formation of relene, which is a mixture of ChCl and urea, the

lattice energy of ChCl, which is a measure of the cohesive forces that bind the ions to each other, is perturbed by the urea molecules present in the mixture, which disrupt the original framework by mutual interaction between halide anions (ChCl) and the hydrogen atoms attached to the nitrogen atom (urea). When choline chloride and urea are mixed together (in a molar ratio of 1:2), the resulting freezing point of the mixture is 12 °C, whereas the melting points of ChCl and urea are 302 and 133 °C, respectively.^{11a} Generally, room temperature DESSs are the most desirable ones because they allow performing reactions at lower temperature for minimizing the energy requirements of the process. Unfortunately, the number of DESSs that are liquid at room temperature is still very limited. In Table 3 the freezing point of several DESSs reported in the literature is shown.

It is clear, by looking at the structure of the HBDs capable of forming room-temperature DESSs that molecules able to sequester the halide anion by a strong hydrogen bond are good candidates (urea, 2,2,2-trifluoroacetamide, levulinic acid, xylitol, D-sorbitol, *etc.*). In the context of organic

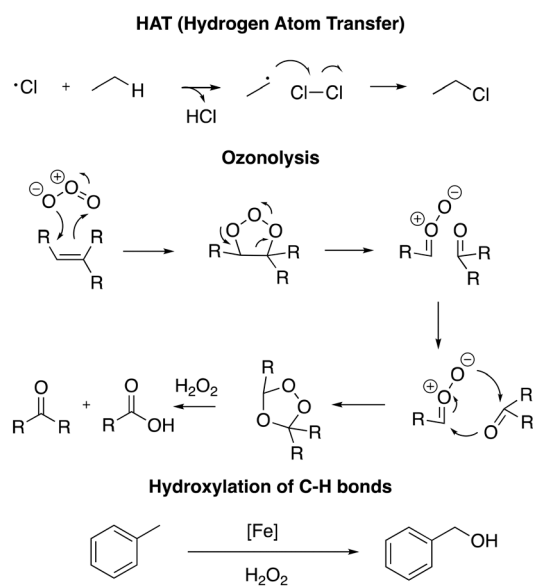
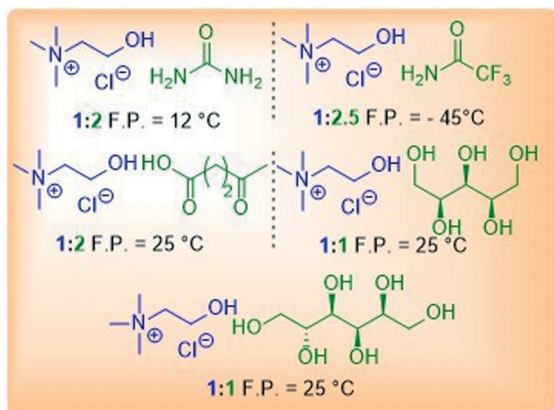
**Scheme 1** Selected examples of key oxidation processes in organic chemistry.

Table 3 Freezing points of some room-temperature liquid DESs

reactions, the capability of the solvent to remain liquid at low temperatures is sometimes crucial in order to minimize the side reaction pathways. Among the physical properties, vapor pressure is closely related to environmental concerns. Solvents exhibiting a low vapor pressure can be more easily separated from much more volatile reaction species, hence recovered. This makes DESs ideal from this perspective since they have a negligible vapor pressure.

Viscosity

Most DESs have viscosities in the range of 10 to 1000 cP at room temperature, which is significantly higher than that of molecular solvents, typically 1 cP. The high viscosity results from the large size of the solvent molecules (ions) and the extensive hydrogen bonding network which results in a low molar volume and a small free volume in the liquid. The viscosity of DESs has been modelled using hole theory which assumes that the movement of charges is limited by the availability of free volumes large enough to accept the ions.²⁹ Most reactions are mass transport limited so solvent viscosity is important in controlling reaction rates.^{30,31} The viscosity of DESs can be significantly decreased by the addition of even a small amount of a molecular solvent, particularly water or even the reagent itself.

It has been shown that molecular liquids are heterogeneous with DESs. Water is found to form a microemulsion when mixed with DESs using dynamic light scattering and NMR spectroscopy.^{30b,32} This has been shown to be important for the electropolymerization of aniline and could control the mechanism of other reactions in mixed media.³³

Conductivity

Numerous studies have shown that the conductivity of ionic liquids and DESs does not follow the classical model for ionic strength but instead it has been shown by numerous groups that conductivity is proportional to fluidity (1/viscosity). Accordingly, since the liquids are relatively viscous

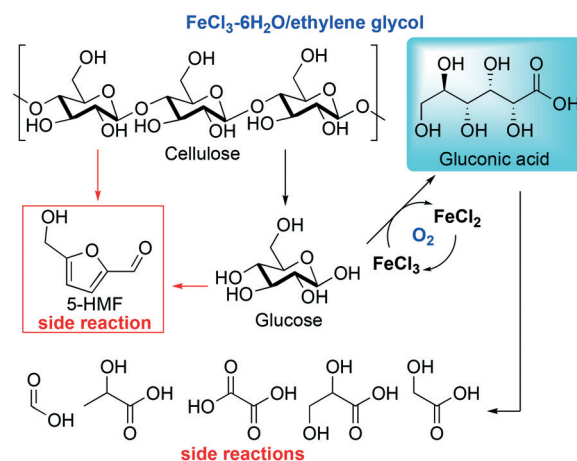
Table 4 Examples of pH values and Kamlet–Taft parameters (π^* , α , β) for commonly used DESs

DES	pH	π^*	α	β
1ChCl:1 oxalic acid	1.32	—	—	—
1ChCl:1 malonic acid	2.39	—	—	—
1ChCl:1 citric	2.84	—	—	—
1ChCl:2 ethylene glycol	6.89	0.96 ± 0.001	1.02 ± 0.02	0.33 ± 0.007
1ChCl:2 glycerol	7.50	0.96 ± 0.04	1.04 ± 0.06	0.32 ± 0.01
1ChCl:2 urea	8.91	0.98 ± 0.02	1.05 ± 0.02	0.30 ± 0.04

they have conductivities which are significantly lower than that expected for a solution with an ionic strength in the range 4–6 mol dm⁻³. Typically the conductivities of DESs are in the range 0.1 to 5 mS cm⁻¹. The conductivity of ionic liquids and DESs has been accurately predicted using hole theory.³⁴

Polarity

Polarity is another property that must be carefully evaluated before designing a reaction, especially organic reactions, since it can affect the solubility of the reactants and change the activation energy drastically. It is possible to understand the polarity effect on some reactions considering as examples the S_N1 and S_N2 reaction mechanisms. S_N1 reactions occur considerably faster in polar solvents since the first step involves the formation of a carbocation, which can be stabilized by a polar solvent decreasing the activation energy Δ , whereas no significant effect can be observed in S_N2 reactions, which do not involve charged intermediates.³⁵ Owing to their composition, DESs have high polarity, which can be evaluated using the E_T (30) scale (electronic transition energy of a probe dye in a solvent).³⁶ Similar data have been obtained for Kamlet and Taft polarity parameters (Table 4) and these also show that all DESs have similarly high values for all parameters.³⁷

**Scheme 2** Cellulose conversion into gluconic acid catalyzed by FeCl₃ proposed by Mu et al.⁴⁰

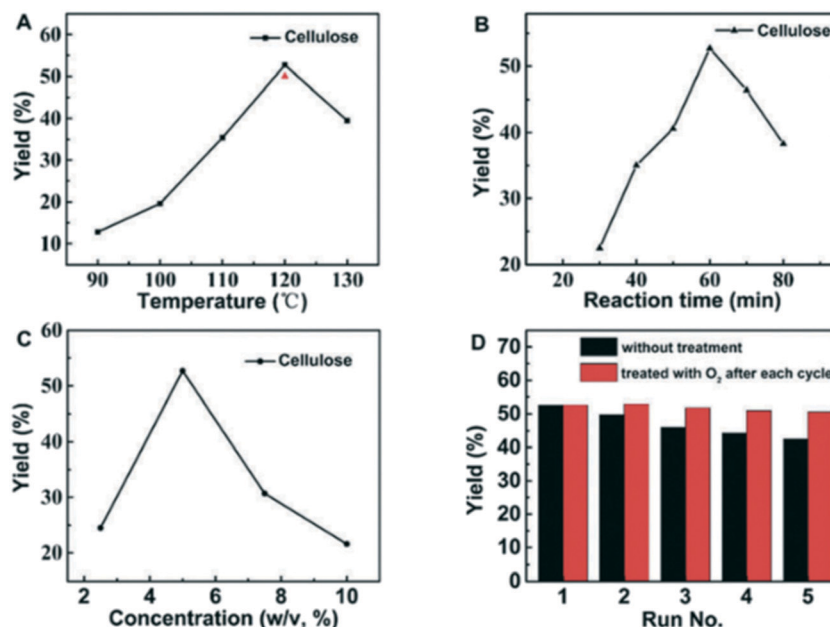


Fig. 1 Temperature (A), reaction time (B) and concentration effect (C) on the yield of reaction and recycling test (D). Reproduced from ref. 40 with permission from The Royal Society of Chemistry.

pH

While pH is a difficult concept to characterize in non-aqueous solutions, a recent study³⁸ used a classic colorimetric indicator, bromophenol blue, to quantify the pK_a of organic acids in ionic liquids and deep eutectic solvents. The pK_a values for 9 organic acids were found to be about 0.5 units higher than that of the corresponding aqueous solution which was rationalized in terms of the different concentrations of bases when comparing DESs with water. As would be expected, the addition of more ChCl to the DES makes the mixture more basic. The same was found for more traditional ionic liquids where the basicity of the anion controlled the overall pH, although [Bmim] [BF₄] was found to be more acidic than expected due to the hydrolysis of the anion forming HF. pH values for pure DESs were determined using a glass electrode and found to be in good agreement with colorimetric measurements. Some examples of DES pH are given in Table 4. Clearly, HBDs which are carboxylic acids have a much lower pH than HBDs with OH moieties. Those with amides tend to be slightly alkaline as might be expected.

Recently the dissolution behavior of a variety of d- and p-block metal oxides was studied in DESs and it was found that for non-coordinating acids the solubility of the metal oxides was directly correlated with the acid strength as the proton acts as an oxygen acceptor. This understanding of DES pH should be directly transferrable to an understanding of organic reactivity.

The following sections provide an overview of the state of the art of organic oxidations performed in DESs. Through selected examples found in the most recent literature, we highlight the benefits of substituting volatile organic solvents with DESs, not only in terms of overall sustainability achieved but also in terms of improved efficiency and recyclability.

3. Organic oxidation in DESs

3.1. Metal-promoted oxidation in DESs

Due to the increasing demand of new transformations of renewable resources, many efforts have been dedicated to the design of new processes for a more sustainable valorization

Table 5 Selected results for toluene oxidation promoted by FeCl₃ reported by Guajardo *et al.*⁴³

DES	Cat	S_{Bzh} [%]	S_{BzAc} [%]	S_{BzCl} [%]	S_{BzOH} [%]	Conv [%]
None	FeCl ₃	69	0	26.5	4.4	8.4
URA ^a	FeCl ₃	87	0	9	4	5
ETA ^b	FeCl ₃	73.5	13.9	10.1	2.5	18
ChCl ^c	FeCl ₃	66.3	5.3	5.3	2.8	10.5

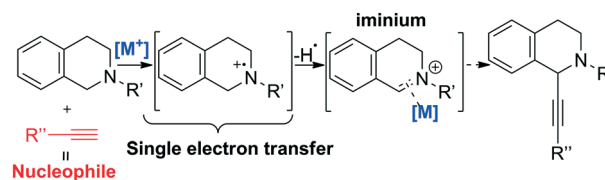
^a ChCl/urea. ^b ChCl/ethylene glycol. ^c ChCl is a DES obtained by mixing choline chloride and FeCl₃. All reactions were performed at 60 °C.

of raw materials. Within this realm, the processing of lignocellulosic biomass has gained attention as a renewable alternative to fossil resources.³⁹ In this context, Mu and co-workers reported an efficient catalytic method to convert cellulose, the most abundant component in lignocellulosic biomass, into gluconic acid in DESs, employing FeCl₃ as a catalyst for the aerobic oxidation step. The reaction is followed by a spontaneous self-precipitation of the products, which makes the process appealing for industrial purposes.⁴⁰ Aware of the capability of highly concentrated FeCl₃ aqueous solutions to catalyze the oxidation of cellulose into gluconic acid, the authors designed a protocol using DESs as reaction media in order to overcome the reuse of the FeCl₃ and the separation of the gluconic acid, which is not trivial.⁴¹ Scheme 2 shows the reaction proposed by Mu *et al.*⁴⁰

The authors prepared several DESs by mixing FeCl₃ with different HBDs (ethylene glycol (EG), malonic acid, glycine and xylitol, to mention some), obtaining DESs with low viscosity and good conductivity when compared to other common DESs. Furthermore, these DESs exhibited a relatively high acidity, a crucial feature to promote the first step of the reaction, that is, the hydrolysis of cellulose into monomeric glucose. The temperature effect was investigated as well, and it was found that the best conditions in terms of conversion and selectivity were achieved using FeCl₃-EG as a DES at 120 °C. Full conversion was achieved in one hour with a 52.7% yield of gluconic acid that can be simply collected by filtration due to its insolubility in the medium after cooling.

Despite the DESs used exhibiting a low freezing point (−55 °C to −66 °C), high temperatures were required in order to increase the selectivity; the concentration of cellulose played an important role as well, as shown in Fig. 1.

Among the oxidation reactions catalyzed by FeCl₃, oxidation of toluene into benzaldehyde is another important key transformation in the chemical industry, toluene being the cheapest and primary source of aromatic compounds. Unfortunately, the selective partial oxidation still remains a great challenge, partly due to the more favorable tendency of the aldehyde to undergo overoxidation to benzoic acid. Operationally this requires performing the reaction while keeping the concentration of toluene very high.⁴² Guajardo and co-workers reported a protocol to convert toluene into benzaldehyde with hydrogen peroxide in DESs.⁴³ Despite hydrogen peroxide being often recognized as a green reactant, it is poorly soluble in organic solvents and, in some cases, the reaction must be performed under a PTC (phase transfer catalysis) regime, with water having a detrimental effect on the selectivity by promoting the oxidation of benzaldehyde into the undesirable benzoic acid. It is well-known that ILs allow the capture of water formed, decreasing the side reaction.⁴⁴ The work disclosed by Guajardo represents an alternative in which the more desirable DESs are used instead of ILs. Sodium tungstate (ST), iron(III) chloride (FeCl₃), phosphotungstic acid (PT), and phosphomolybdic acid (PM) were tested as catalysts in different DESs. FeCl₃ was selected as the most promising for



Scheme 3 Mechanism of generic C-C coupling in vicinal nitrogen C-H activation by metal.

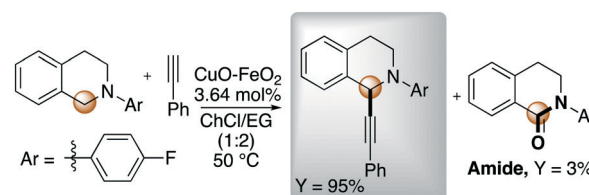
the next screening step. The results of such solvent screening are summarized in Table 5.

The authors studied the intrinsic catalytic activity of DES but no reactivity was observed. Iron(III) chloride was the only catalyst able to promote the oxidation, presumably by a Fenton-like mechanism. The ETA-FeCl₃ system showed higher conversion ($S_{Bzh} = 73\%$, conv = 18%) when compared to the neat system ($S_{Bzh} = 69\%$, conv = 8.4%), but the URA-FeCl₃ couple was able to give the highest selectivity, despite lower conversion ($S_{Bzh} = 87\%$, conv = 5%). The authors investigated the temperature effect as well, observing conversion decreasing when reaching temperatures above 60 °C. This is probably due to the faster decomposition of hydrogen peroxide.

Iron-based catalysis finds several applications in organic synthesis and C-C bond formation reactions are undoubtedly among key transformations due to their intrinsic capability to increase the framework complexity of molecules. In particular, C-C bond formation through C-H activation is one of the great challenges in organic synthesis.⁴⁵ One example is the mechanism of C(sp³)-H bond activation at the α -position of nitrogen, which is well-known and proceeds through two consequent single electron transfer (SET) reactions generating an iminium intermediate, as shown in Scheme 3.⁴⁶

In this context, Zhang reported the synthesis of imidazo[1,2-*a*]pyridines promoted by CuFeO₂ nanoparticles in DES.⁴⁷ In 2016, Ramón *et al.* presented for the first time the cross-dehydrogenative coupling between 1,2,3,4-tetrahydroisoquinoline and phenylacetylene through C-H bond activation promoted by copper impregnated on magnetite (CuFeO₂) in DES using atmospheric oxygen as the oxidant.⁴⁸ The optimized reaction is shown in Scheme 4.

To prove the essential role of DESs in the reaction the authors reported the reactivity in other common organic solvents. They observed that in all the cases the yield is lower



Scheme 4 Cross-dehydrogenative coupling reported by Ramón *et al.* through C-H bond activation promoted by copper impregnated on magnetite (CuFeO₂) in ChCl:EG.⁴⁸

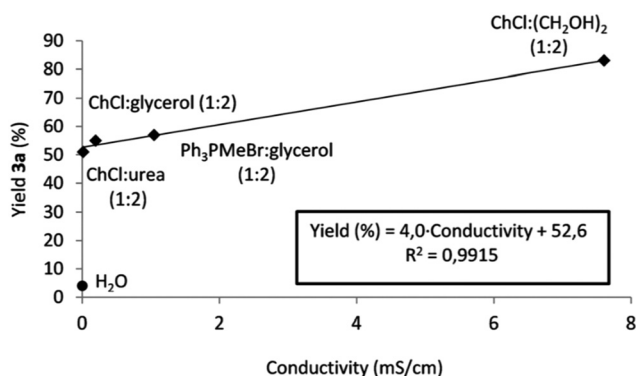


Solvent	3a Yield (%)	4a Yield (%)
DMSO	45	35
MeOH	5	10
PhMe	5	10
Water	5	25
THF	5	5
DMF	5	40
DCE	25	5
1,4-Dioxane	5	65
CHCl ₃ :(CH ₂ OH) ₂ (1:2)	75	5

than that in the reaction performed in the DES. Furthermore, a better selectivity was observed for the reaction in the DES as shown in Fig. 2.

Finally, the recyclability of the DES-catalyst mixture was tested as well; the results showed that the mixture could be reused up to ten times without appreciable decrease of reactivity.

FeCl₃ also plays a crucial role in the synthesis of polymers in modern industrial chemistry. Some particular features of these materials are required nowadays, particularly in



specific applications such as photoluminescence and electrochemistry.⁴⁹ For example, poly(3-alkylthione)s are a class of important polymers that exhibit electro- and photo properties, which make them attractive for manufacturing of semiconductor polymers and dyes. FeCl₃ oxidative polymerization is the protocol mainly adopted to prepare these polymers on a large-scale process, affording the desired product in high yield employing a low-cost catalyst.⁵⁰

FeCl₃ (4 equiv.) reaction performed at 25 °C.

The results summarized in Fig. 4 and Table 6 show that ChCl/urea is the most efficient solvent for the FeCl₃-promoted oxidative polymerization of 3-octylthiophene, performing better than ILs and chloroform.

Despite iron being more preferable than palladium for abundance reasons, the latter remains ubiquitous in organic synthesis due to its versatility. In 2017, Ramón *et al.* reported the palladium catalyzed C-S bond formation in the presence of sodium metabisulfite as a SO₂ source.⁵³ Exploiting the ability of DESs to dissolve organic substrates, catalysts, ligands and the inorganic salt, the authors obtained an improvement when the reaction was performed in DESs instead of common organic solvents. The most promising

Table 6 Summary of yield, molecular weight and polydispersity index of P3OT prepared through the DESs-based protocol of Lee *et al.*⁵¹

Solvent	Time [h]	M_w [g mol ⁻¹]	PDI [M_w/M_n]	Yield [%]
ChCl : urea	1	13 466	6.7	59
ChCl : urea	4	27 787	13.7	81
ChCl : urea	10	44 179	12.9	100
[Bmim][SbF ₆]	48	42 584	15.9	99
Chloroform	48	34 672	12.9	87

DES was a mixture of ChCl and acetamide (1:2), whereas, 2-(dicyclohexylphosphanyl)-1-phenylpyridin-1-ium chloride was selected as the best ligand. The reaction is shown in Scheme 5.

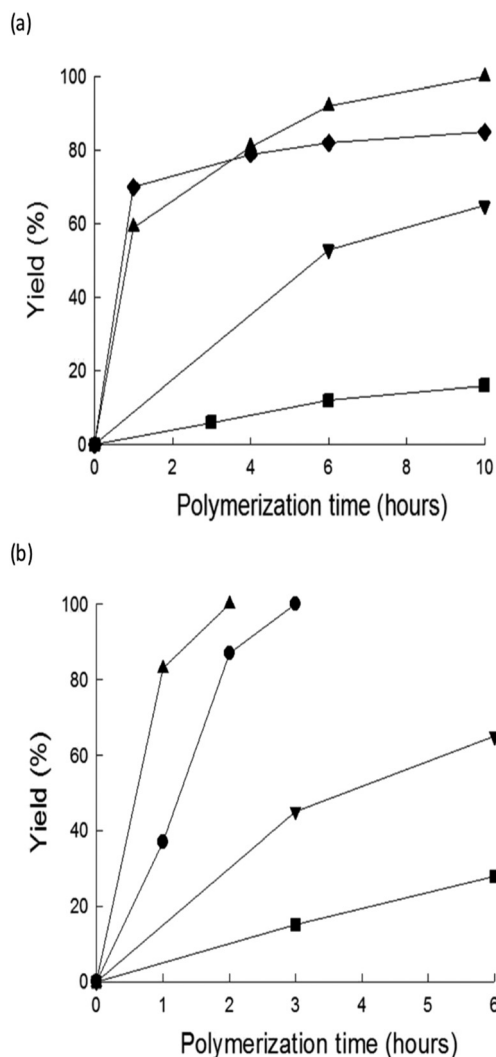


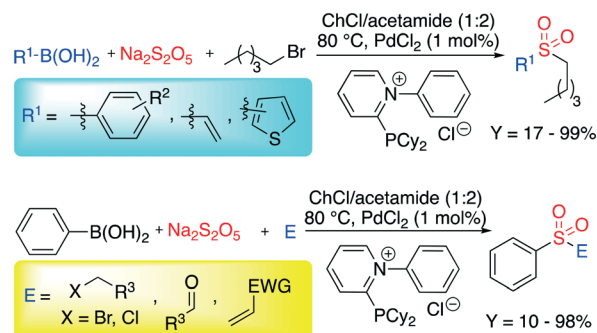
Fig. 4 Time-yield curves for P3OT prepared by FeCl₃-catalyzed oxidative polymerization (a) at 25 °C in DESs, IL and chloroform and (b) at 50 °C in DESs and IL (▲: [Ch]Cl:U, ●: [Ch]Cl:U:TU, ▼: [Bmim][SbF₆], ■: [Ch]Cl:F:TU, ◆: CHCl₃). Reproduced from ref. 51 with permission from The Royal Society of Chemistry.

In their studies, the authors focused on the C–S coupling, keeping the pentyl bromide as the electrophile and investigating the scope of the reaction by varying the aryl boronic acid. Aryl boronic acid-based compounds bearing both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) were tested, showing that the reactivity varies from poor to excellent (17–99%). Other electrophiles were tested among the most commonly used in organic synthesis such as Michael acceptors, alkyl chloride and aldehydes, showing the great flexibility of the protocol.

The recycling of the catalyst was also studied. The products were extracted using 2-MeTHF, a sustainable organic solvent, whereas the catalyst remained in the DES. The authors observed that the DES–catalyst medium could be reused three times without adding the catalyst, ligand or solvent.

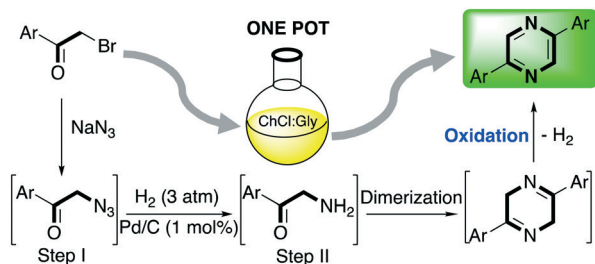
3.2. One-pot oxidative processes in DESs

One-pot processes involve two or more chemical reactions which take part in a single reactor and the product of the previous reaction acts as a substrate for the next one. These processes are highly desirable since they eliminate the need for time- and energy-consuming separation processes and purification of the intermediates.⁵⁴ Recently, Capriati and co-workers reported the synthesis of 2,5-diarylpyrazines employing DESs as media with the purpose of exploring a well-known reaction using non-conventional reaction solvents.⁵⁵ 2,5-Diarylpyrazines are extensively studied scaffolds due to their properties in medicinal chemistry, such



Scheme 5 Palladium-catalyzed C–S bond formation in DESs.⁵³

Review



Scheme 6 One-pot (2 steps) synthesis of 2,5-diarylpyrazines in DES starting from 2-bromo-1-arylethan-1-ones.⁵⁵

as anti-inflammatory, anti-diabetic, anti-bacterial and anti-fungal, and as dyes.⁵⁶ The authors envisaged the possibility of performing a one-pot process starting from affordable substituted ketones for obtaining the desired product in two steps followed by two spontaneous transformations (dimerization and aerobic oxidation) as shown in Scheme 6.

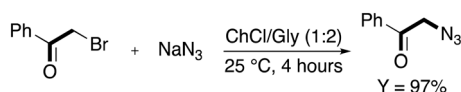
They started investigating the nucleophilic substitution of the halide in DES after considering that the reaction works very well in ILs and that it is classically performed in solvents with high polarity.⁵⁷ The use of a ChCl/Gly eutectic mixture (1:2) at room temperature allowed obtaining the desired product in 4 h with 97% yield (Scheme 7).

The authors suggested that a cooperative effect of the CHCl_3 is involved in the mechanism, observing that in the presence of pure Gly the yield drops down to 23%. After examining the scope and limitation of this reaction, varying the substituents on the aromatic ring and finding that no detrimental effects were observed with both electron-poor and electron-rich rings, the authors carried out a subsequent investigation of the chemoselective reduction of the azido functional group. Classical reductive systems were tested such as $\text{Zn}/\text{ammonium formate}$, Zn/HCl , $\text{Zn}/\text{NH}_4\text{Cl}$, Ph_3P , and $\text{D-glucose}/\text{KOH}$ without any significant results. The use of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ smoothly promoted the reduction of the azido group, whilst the subsequent use of Pd/C (1 mol%) in the presence of hydrogen (3 atm) promoted the dimerization/oxidation to 2,5 diphenylpyrazine, obtained in 89% yield (Scheme 8).

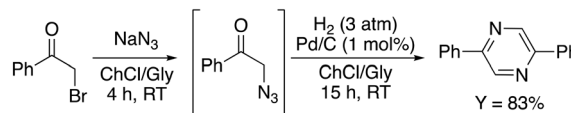
Finally, the authors presented the scope and limitations of the telescoped one-pot synthesis tested using different bromide ketones as shown in Table 7.

The authors did not investigate the reuse of the DES, probably because the mixture, which was contaminated with palladium, necessary to trigger the next step, was not as efficient as the pure one for the nucleophilic substitution.

Continuing with the preparation of heteroaromatic compounds, pyrimidine is broadly recognized as a privileged



Scheme 7 Synthesis of 2-azido-1-phenylethan-1-one from 2-bromo-1-phenylethan-1-one in CHCl_3/Gly .⁵⁵



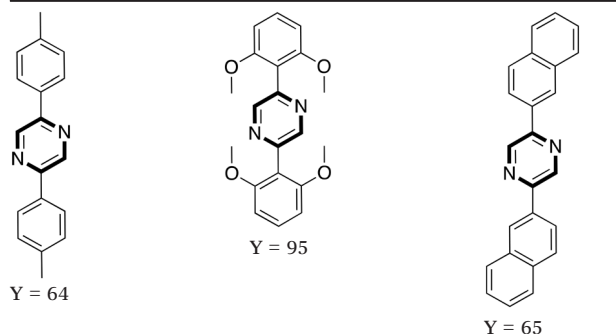
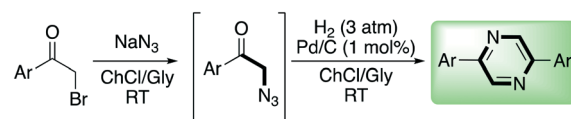
Scheme 8 Telescoped one-pot synthesis of 2,5-diphenylpyrazine in a ChCl/Gly deep eutectic mixture.⁵⁵

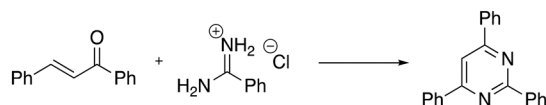
scaffold for important drugs, which exhibit biological activities in several diseases. In addition, pyrimidine analogues find broad applications in polymer chemistry and materials science.⁵⁸ A variety of protocols has been reported during these years on the preparation of pyrimidines. However, the reported methods often suffer from drawbacks such as the need to use rare or toxic metals as catalysts, expensive or moisture-sensitive starting materials, longer reaction times, harsh reaction conditions and poor recycling of the catalyst. Thus, new economical and environmentally friendly methods for the synthesis of substituted pyrimidines are much sought-after. Recently, Chaskar and co-workers disclosed a new and affordable method to prepare this class of molecules in DESs.⁵⁹ The authors selected the reaction of 1,3-diphenyl-2-en-1-one with benzamidine hydrochloride as a model system (Scheme 9).

The authors investigated the reactivity by screening several common organic solvents such as EtOH, toluene, DMF and acetonitrile. They reported that the reaction affords the desired product up to 83% yield using a strong base such as NaH and NaOH at very high temperature (80–110 °C) in a reasonably short reaction time (1–2 hours). The reaction was seen to be more efficient in choline hydroxide (ChOH) (Table 8). In particular, in ChOH the reaction gave a yield of 90% in a shorter reaction time (30 min) and under milder conditions (60 °C) without strong bases as additive.

The recyclability of the DESs was also studied showing that it was possible to reuse the DES five times without any appreciable loss of activity (90% to 87%). The authors

Table 7 Selected examples of the scope of telescoped one-pot synthesis of 2,5-diarylpyrizanes⁵⁵





Scheme 9 Model reaction chosen for the preliminary study of the pyrimidine one-pot protocol in DESs reported by Chaskar *et al.*⁵⁹

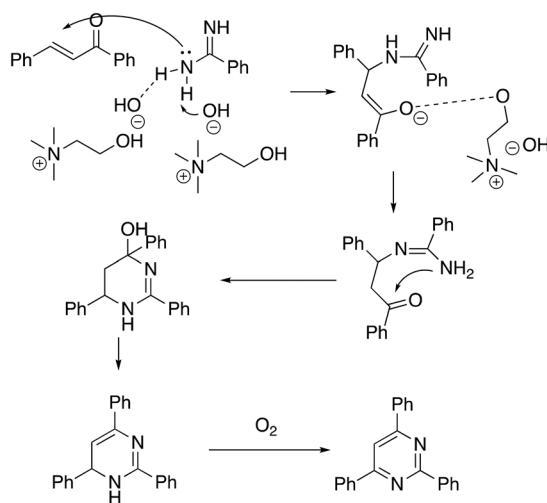
Table 8 Selected results of the optimization screening. Pyrimidine tandem reaction in DESs⁵⁹

Time [h]	Additive/solvent	Temp [°C]	Yield [%]
24	EtOH	80	NR
1.5	NaOH/EtOH	80	83
5	NaH/THF	80	59
2.5	Toluene	110	43
0.5	ChOH	60	90

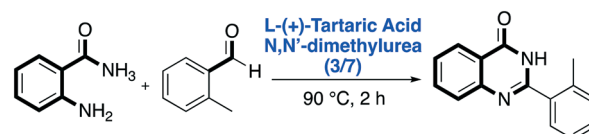
Reaction conditions: 1,3-diphenyl-2-en-1-one (1.0 mmol), benzamidine hydrochloride (1 mmol), base (2 mmol) and solvent 5 mL.

proposed a mechanism whereby ChOH seems to play a crucial role in promoting the reaction (Scheme 10).

Regarding diazo-heterocyclic compounds, in 2016 Nagarajan and co-workers reported a metal-free DES-mediated cyclization strategy to prepare substituted and unsubstituted quinazolinones, well-known molecular scaffolds that can be further elaborated for the synthesis of various natural products and drugs.⁶⁰ They screened several sugar-based DES mixtures such as citric acid/*N,N'*-dimethylurea, D(-)-fructose/*N,N'*-dimethylurea, L-(+)-tartaric acid/*N,N'*-dimethylurea and mannose/*N,N'*-dimethylurea/ $\text{NH}_4\text{-Cl}$ employing anthranilamide and *o*-tolualdehyde as model substrates. L-(+)-tartaric acid/*N,N'*-dimethylurea (3 : 7) (F.P. 90



Scheme 10 Proposed mechanism for the [3 + 3] tandem pyrimidine synthesis in ChOH.⁵⁹



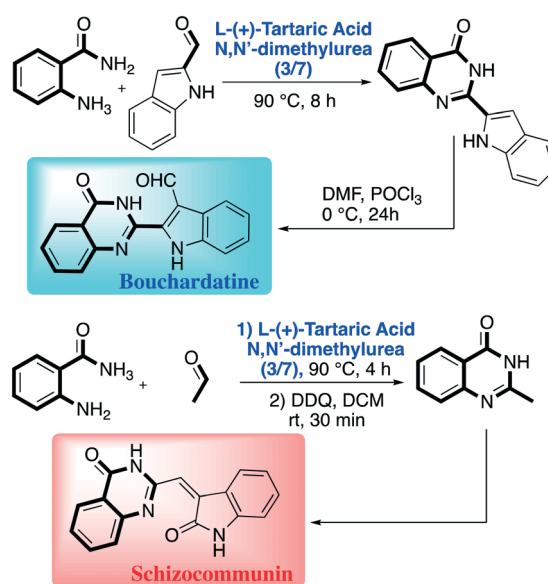
Scheme 11 Dihydroquinazolinone one-pot synthesis in L-(+)-tartaric acid/*N,N'*-dimethylurea.⁶⁰

°C) was found to be the most promising DES for the reaction, affording the desired product in 78% yield. The reaction required to be performed in an open air atmosphere to allow the aromatization of the initially formed dihydroquinazolinone to quinazolinone through aerobic oxidation (Scheme 11).

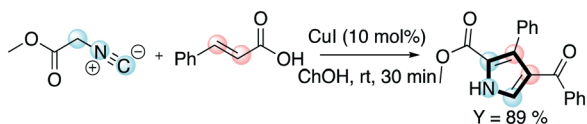
The robustness and the limitations of the methods were tested by varying the substituents on the reagents. Interestingly, the authors proved the utility of the protocol in preparing APIs (active pharmaceutical ingredients) (Scheme 12).⁶¹

Pyrroles are another class of molecules of interest in several areas of chemistry and materials science. They have found promising applications as organic semiconductors and in OLED (organic light-emitting diode) applications.⁶² Chaskar and co-workers reported a one-pot method employing DESs for the synthesis of these important scaffolds.⁶³ The one-pot procedure consists of a [3 + 2] cycloaddition between a chalcone and a isocynoacetate promoted by a copper(i) salt followed by aerobic oxidation to access the tri-substituted pyrrole (Scheme 13).

In the reported paper, the authors showed the benefit of moving from classical to DES-based solvents. The reaction in DESs proceeded faster and under milder conditions when compared with the use of classical organic solvents (THF, DMF, MeOH) that all require strong bases to trigger the



Scheme 12 Dihydroquinazolinone derivate elaboration towards pharmaceutically relevant compounds reported by Nagarajan *et al.*⁶⁰

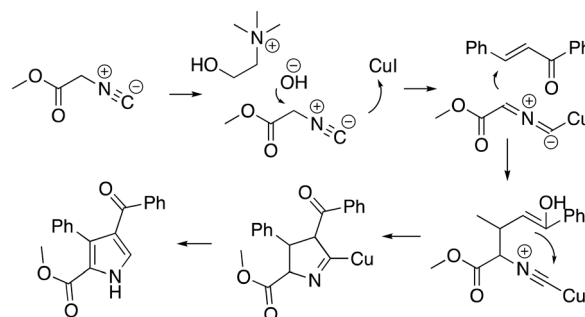


Scheme 13 The one-pot protocol disclosed by Chaskar for the preparation of tri-substituted pyrroles.⁶³

reaction. The authors investigated the scope of the reaction as well, as shown in Table 9.

The protocol was shown to be robust and applicable for both electron-withdrawing and electron-donating groups bearing on the aryl moiety of the olefin. Replacing the aryl moiety with the alkyl onto the ketone did not change dramatically the reactivity. The recycling test showed that the DESs could be reused five times without loss of reactivity. The mechanism proposed by the authors was also reported (Scheme 14), whereby the role of the CHOH is thought to be the deprotonation of the isocyanooacetate in order to generate the dipole for the cyclization.

C–N and C–C bond oxidation by atmospheric oxygen is easy to observe when a re-aromatization occurs. However, in other cases a stronger oxidant is required. Oxidation by hypervalent iodine compounds is one of the most used methods to oxidize selectively organic compounds. This class of reactions has been widely used in research laboratories since the first reactions, under mild conditions, were discovered by Dess and Martin.⁶⁴ Within this class, *o*-iodoxybenzoic acid is one of the most prominent and interesting reactants. It is one of the cheapest hypervalent iodine reagents and it can be reused by treating the derived reduced by-product with aqueous oxone, after recovery and separation by the crude reaction. In 2017, Sharma and co-workers, intrigued by previously reported studies on oxidation in DESs, decided to explore the oxidation of primary amines into imines promoted by IBX (2-iodoxybenzoic acid),⁶⁵ extending the concept to the Ugi



Scheme 14 Proposed mechanism for the one-pot pyrrole synthesis in CHOH.⁶³

reaction, a one-pot process featuring reorganization of imine, organic acid and isocyanide to obtain bis-amide analogues *in situ*. Selected results about the first step of the Ugi collected by Sharma are summarized in Table 10.

The authors found that the addition of an additive (benzoic acid) is crucial to obtain the desired product. Otherwise, the absence of the acid afforded a mixture of the corresponding aldehyde and nitrile. It is worth noting that substitution of classical organic solvents (entries 1, 2 and 3) with DESs significantly boosted the reactivity (entry 4 in Table 10). The authors rationalized this behavior, observing a better solubility of IBX in the DES compared to some organic solvents (DCM, CH₃CN, toluene). After finding the optimized condition for the oxidation, the authors investigated its implementation in the Ugi reaction. Ugi reaction involves the condensation of a carbonyl and an amine in order to generate an imine as an intermediate followed by the addition of isocyanide and a carboxylic acid. Some examples are shown in Scheme 15.

Phenylamine and benzylamine bearing electron-donating substituents (*p*-methoxy) reacted under standard conditions and afforded the target product in very good yield (82% and 80%, respectively). The authors reported that the reaction remains effective when varying the substituents on both the acid and the isocyanide species. A complete study was performed to investigate the reusability of the DESs. Water

Table 9 Selected examples of the scope of tri-substituted pyrrole synthesis in CHOH (ref. 63)

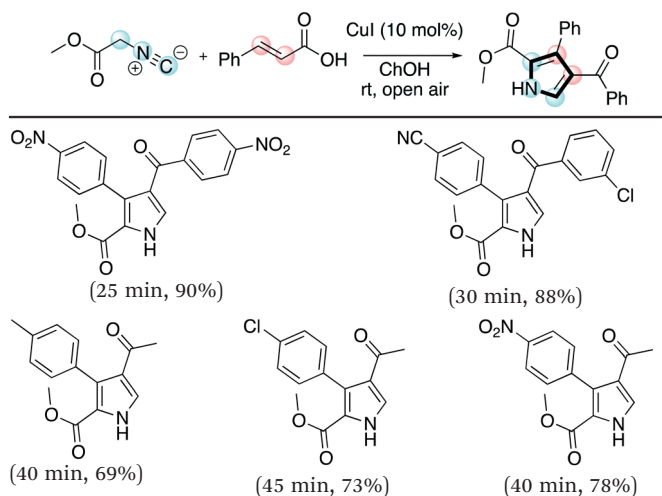
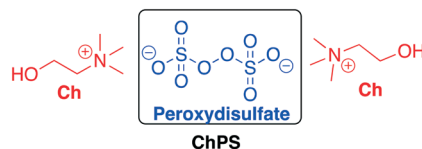


Table 10 Selected results of the optimization screening of IBX-promoted oxidation of primary amines in DES⁶⁵

Entry	Solvent	Additive	Yield [%]
1	DCM	None	17
2	DCM	BA	54
3	CH ₃ CN	BA	39
4	ChCl/urea	BA	84

Reaction conditions: benzylamine, IBX (0.1 equiv.), additive (0.1 equiv.). Solvent (0.4 M). BA (benzoic acid), DCM (dichloromethane).

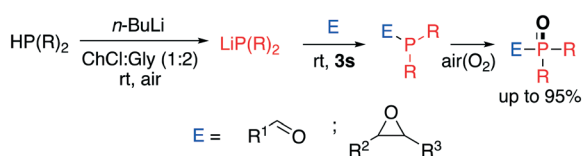




Chemical structures of six amide products from the reaction of 2,2,6,6-tetramethyl-4-piperidinone with various aldehydes. The products are:

- Top Left:** N-benzyl-2-phenyl-2-phenylacetamide (Y = 82%)
- Top Right:** N-benzyl-2-phenyl-2-(4-methoxyphenyl)acetamide (Y = 80%)
- Middle Left:** N-benzyl-2-phenyl-2-(furan-2-ylmethyl)acetamide (Y = 76%)
- Middle Right:** N-benzyl-2-phenyl-2-(4-nitrophenylmethyl)acetamide (Y = 82%)
- Bottom Left:** N-benzyl-2-phenyl-2-(cyclohexylmethyl)acetamide (Y = 85%)
- Bottom Right:** N-benzyl-2-phenyl-2-(4-fluorophenylmethyl)acetamide (Y = 83%)

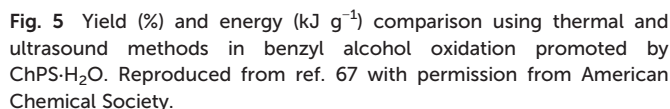
The protocol consists of three steps. Firstly, the reactive lithium phosphide is generated by adding 1 equivalent of *n*-BuLi to a solution of phosphine in DES (ChCl:Gly, 1:2); the electrophile (epoxy or aldehyde) is then added, affording either the α - or β -hydroxy-phosphine analogue, which spontaneously undergoes oxidation at the phosphorus centre in excellent yield (up to 95%). Surprisingly, the reaction works in DESs containing a HBD despite the lithium





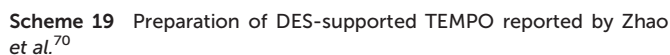
 12 examples, 90-97% Yield

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In general, the selective oxidation of alcohols to aldehydes in DESs is a topic that is currently attracting much interest.⁶⁹ The group of Zhao reported a selective oxidation of both primary and secondary alcohols to aldehydes and ketones promoted by TEMPO supported onto a DES employing oxygen as a sacrificial reactant.⁷⁰ The authors reported the synthesis of the modified DES as well (Scheme 19).

This DES was tested in the aerobic oxidation of benzyl alcohol in the presence of several metallic co-catalysts with air at ambient pressure (Table 11).



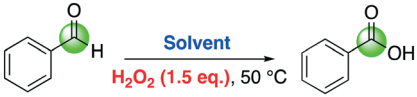
Time [h]	Co-catalyst	Conv. [%]	Selec [%]
1	None	0.4	>99
1.5	FeCl ₃ ·6H ₂ O	3.1	>99
1.5	Fe(NO ₂) ₃ ·9H ₂ O	>99	>99
17.5	Cu(NO ₂) ₃ ·3H ₂ O	24.0	>99
1.5	Co(NO ₂) ₃ ·6H ₂ O	3.1	>99

The co-catalyst is crucial to trigger the reaction and in its absence the conversion after 1 hour was below 1%. Among the most used metals in the TEMPO oxidation $\text{Fe}(\text{NO}_2)_3 \cdot 6\text{H}_2\text{O}$ was the most active, boosting the reactivity to 99% conversion, whereas the selectivity remained the same as that of the other entries.

The applicability of the protocol was studied by testing more than 20 types of alcohols, both primary and secondary, showing a broad range of application with conversion over 90% and almost full selectivity towards the aldehyde or ketone products. A recyclability study was reported as shown in Table 12. The system solvent/catalyst was reused up to five times without significant loss of reactivity, although fresh co-catalyst ($\text{Fe}(\text{NO}_2)_3 \cdot 6\text{H}_2\text{O}$) had to be added after each run. After the seventh cycle, the conversion decreased more drastically and the DES-supported TEMPO could not be used again.

Carboxylic acids are recognized as pivotal intermediates in organic and industrial chemistry and they allow access to more complex frameworks. Carboxylic acids are prepared mainly using sacrificial reagents and transition metal catalysts starting from alcohols or aldehydes.⁷¹ Hydrogen peroxide is one of the most commonly used oxidative agents along with atmospheric oxygen. It is low-cost and the by-product generated is water, which does not pose particular issues in terms of disposal.

Run	Conversion [%]	TOF [h ⁻¹]	Selec [%]
1	>99	26.4	>99
2	>99	26.4	>99
3	>99	26.4	>99
4	>99	26.4	>99
5	>99	26.4	>99
6	85	22.7	>99
7	66	17.6	>99
8	27	7.2	>99

Table 13 Solvent study on the oxidation of benzaldehyde by hydrogen peroxide investigated by Nagarkar *et al.*⁷²


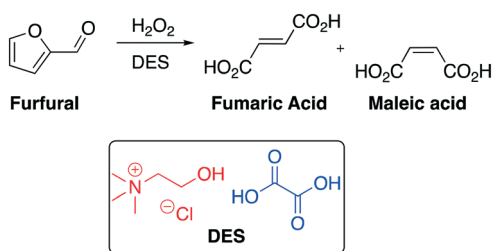
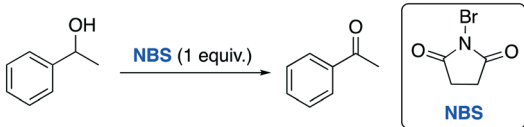
Entry	Solvent	Conv. [%]	Select. [%]
1	ChCl/urea	100	100
2	MeCN	66	66
3	MeOH	55	55
4	Toluene	49	49
5	H ₂ O	50	50

Reaction conditions: benzaldehyde (1 mmol), solvent (2.0 mL), 30% H₂O₂ (1.5 equiv.), reaction time 2 h.

In 2018, the Nagarkar's group reported the oxidation of aldehydes to carboxylic acids using H₂O₂ in DESs.⁷² The authors used benzaldehyde as a model substrate and found that by maintaining the reaction temperature at 50 °C in ChCl/urea the number of equivalents of hydrogen peroxide dramatically affected the reactivity. The conversion was seen to increase from 38% to 100% when moving from 1 equiv. to 1.5, respectively. Keeping the reaction running for more than 2 hours resulted in a drop of yield due to degradation of the benzoic acid previously formed. A comparative study showing the effect of replacing common solvents with the DESs was performed (Table 13). The recycling experiments showed that the activity within the DESs reaction media remained the same for five cycles.

The preparation of organic acids, especially those used as bulk chemicals, from renewable resources is a very attractive topic nowadays. In this context, maleic acid and fumaric acid along with their anhydrides are well-known as important C₄ chemical intermediates within the chemical industry, such as resins, lubricant additives, surface coatings and pharmaceuticals. In 2013 Yan and co-workers disclosed a protocol to convert furfural, one of the most important intermediates which comes from lignocellulose, into maleic and fumaric acid employing ChCl-oxalic acid DESs as both solvent and catalyst (Scheme 20).⁷³

Carboxylic acids play a crucial role in the oxidation of furfural due to their capability to be oxidized to organic peracids by H₂O₂ and then efficiently oxidize furfural to maleic acid and fumaric acid. Based on this observation,

**Scheme 20** Furfural conversion into fumaric acid and maleic acid promoted by hydrogen peroxide and ChCl-oxalic acid DES.⁷³**Table 14** Results on the optimization of the condition of the oxidation of 1-phenylethanol promoted by NBS⁷⁴


Entry	Solvent	Time [min]	Yield [%]
1	ChCl/urea	5	100
2	DCM	80	45
3	MeOH	80	65
4	MeCN	80	55
5	H ₂ O	80	80

Reaction conditions: 1-phenylethanol (1 mmol) and NBS (1 mmol), solvent (0.5 mL), temperature 60 °C.

the authors designed a DES with one organic acid that can catalyze the reaction. They selected oxalic acid as the key component of the DES due to its strong acidity ($pK_a = 1.13$). A conversion of 100% of furfural into maleic and fumaric acid was achieved in six hours under mild conditions (50–60 °C).

In 2014 the Azizi group reported a very fast and selective oxidation of primary and secondary alcohols promoted by *N*-bromosuccinimide (NBS) in DESs.⁷⁴ The reaction was observed to be faster in DESs than in common organic solvents when 1-phenylethanol was used as a model starting material (Table 14).

The authors found that the ChCl/urea DES was a more efficient medium compared to other solvent media, remarking the absence of overoxidative side-products. Interestingly, the high chemoselectivity of the protocol towards primary alcohols was proved in an experiment in which a mixture of benzyl alcohol and 1-phenylethanol was used (Scheme 21).

3.5. Phenol preparation in DESs

The preparation of phenols has always held a role of great importance in industrial chemistry and continues to attract the attention of the chemical and engineering communities. Recently, several reports have been disclosed about aromatic boronic acids as synthons for the synthesis of phenols through catalytic oxidative hydroxylation. In 2013, He and co-workers reported the oxidation of boronic acid into phenol in DESs employing hydrogen peroxide in the absence of a catalyst.⁷⁵ Phenylboronic acid was chosen as a model reagent, with the reaction proceeding at room temperature in water in

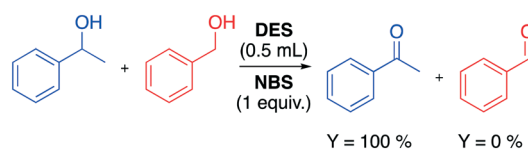
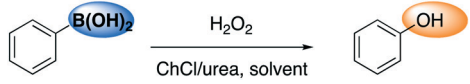
**Scheme 21** Chemoselective test for the oxidation of alcohols promoted by NBS in ChCl/urea DES.⁷⁴

Table 15 Optimized conditions for the oxidation of phenylboronic acid into phenol as reported by He *et al.*⁷⁵

			
ChCl/urea [mol%]	Solvent	Time [min]	Yield [%]
—	H ₂ O	60	Trace
10	H ₂ O ^a	5	92
10	EtOH	30	80
10	THF	30	73
10	CH ₃ CN	30	84

Reaction conditions: phenylboronic acid (1 mmol), solvent (2 mL), H₂O₂ 20 equiv. ^a H₂O₂ 5 equiv.

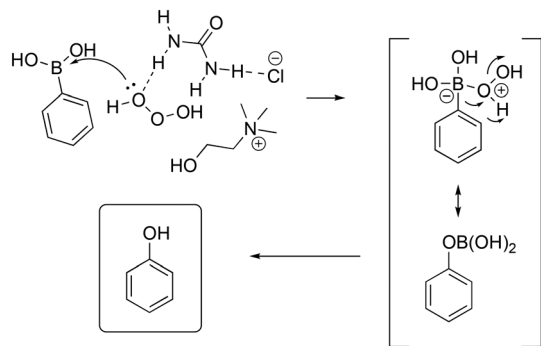
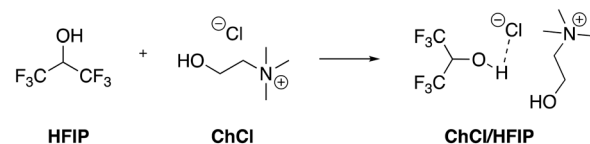
the presence of catalytic amounts of DES ChCl/urea (yield = 92%). The selected screening of reaction conditions is shown in Table 15, whereby the reaction in DESs appears faster and requires less amount of hydrogen peroxide in water, whereas the absence of DESs results in a drop of reactivity in any solvent.

The authors explored the scope of the reaction using different aryl boronic acid compounds by varying the substituent on the aromatic ring. Electron-rich aryl boronic acids exhibited high yield (90 to 96%), showing complete consumption of the reagents in five minutes, whereas electron-poor boronic acids required a longer reaction time (15 minutes) with lower yield (82 to 90%). The authors proposed a mechanism to explain the role of the DES as the catalyst (Scheme 22) in which the DES activates the hydrogen peroxide by polarization of the peroxide bond through hydrogen bonding.

A similar protocol using ChCl/HFIP (Scheme 23) was reported, studying in this case the reuse of the catalyst, which showed a reusability for five cycles.⁷⁶

4. Summary and outlook

Deep eutectic solvents (DESs) have emerged as more affordable alternatives to ionic liquid (IL) solvents, whilst sharing with them some desirable physicochemical

**Scheme 22** Proposed mechanism for the oxidation of aryl boronic acids promoted by hydrogen peroxide and ChCl/urea.⁷⁵**Scheme 23** Preparation of the ChCl/HFIP.⁷⁶

properties, such as similar viscosities, pH, and capability to dissolve both organic and hydrophilic compounds. Their use as solvent media for organic reactions has been growing rapidly, with organic oxidations carried out in DESs emerging in recent years. The work reported in this area has shown promising results, highlighting several benefits in using DESs over conventional ILs and fossil fuel-based organic solvents, which can be summarized as:

- Enhancement in reactivity.
- Easier recyclability.
- Possibility to bind organic reactants, such as oxidative reagents, and catalyst functionalities to the DES framework.
- Easier separation and purification of reaction products.
- Possibility to operate under a wide temperature range.

Whilst some issues remain for a much wider use at a larger scale, such as the high viscosity of some DESs, commercial applications seem to be on the doorstep and we believe that their use for organic oxidations will lead to new processes for the manufacture of chemical commodities.

Conflicts of interest

There are no conflicts to declare.

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