SPECTRUM OF ENGINEERING SCIENCES
ISSN (E) 3007-3138 (P) 3007-312X VOLUME 4, ISSUE 3, 2026

MECHANISTIC INSIGHTS, CATALYTIC PERFORMANCE, AND SUSTAINABILITY ASSESSMENT OF WATER VERSUS DEEP EUTECTIC SOLVENTS IN ORGANOCATALYSIS

Shehreen Fatima[*1], Muhammad Jawad[2]

[*1]*B's chemistry University of Sargodha*
[2]*BS organic Chemistry Karakoram international university Gilgit*

[*1]shehreenfatima624@gmail.com, [2]mjawad.chemist@gmail.com

DOI: https://doi.org/10.5281/zenodo.23661749

Keywords

Article History
Received: 01 January 2026
Accepted: 16 March 2026
Published: 31 March 2026

Copyright @Author
Corresponding Author: *
Shehreen Fatima

Abstract

Organocatalysis has become one of the three principal pillars of modern asymmetric catalysis, alongside metal catalysis and biocatalysis. However, the environmental sustainability of its design relies on the reaction medium, as well as the design of the catalyst. Water and deep eutectic solvents (DESs) are two of the most promising green alternatives to traditional volatile organic solvents due to their low toxicity to the environment and special physicochemical characteristics. These media, with their common sustainability goals, have different mechanistic pathways and significant advantages and disadvantages in catalytic performance. In this review, the pros and cons of the use of water and DESs as reaction media in sustainable organocatalysis activities are critically examined and compared. It analyzes the rate-enhancing hydrophobic effect and interfacial catalysis of aqueous systems as well as the solvation by the hydrogen-bond-network, pre-organization of substrates and dual solvent–catalyst functionality of DESs. They are systematically tested on representative carbon–carbon and carbon–heteroatom bond-forming reactions such as aldol, Michael, Mannich and Diels–Alder reaction with a focus on reaction yield, stereoselectivity, catalyst recyclability, and operational efficiency. Both solvent systems are additionally assessed for their sustainability measure through green chemistry parameters, LCA (life-cycle assessment) and existing data on toxicity and biodegradability. The literature surveyed shows that neither water nor DES is superior in all respects, but rather the environment and catalytic properties are very much reaction type dependent, substrate compatible and process dependent. Finally, this review pinpoints the challenges that need to be addressed in future research: comprehensive life cycle data on DESs, hydrated DES–water hybrid systems and optimisation of scale up strategies. These challenges will enable to make informed choices for solvents and contribute to the development of sustainable organocatalytic processes.

1. INTRODUCTION

In the early 2000s, organocatalysis, which involves the acceleration of chemical transformations by small, metal-free molecules, became a new star, and is now essential for the development of chiral building blocks in the synthesis of pharmaceuticals and fine chemicals. Most often, the catalysts used are simple, non-

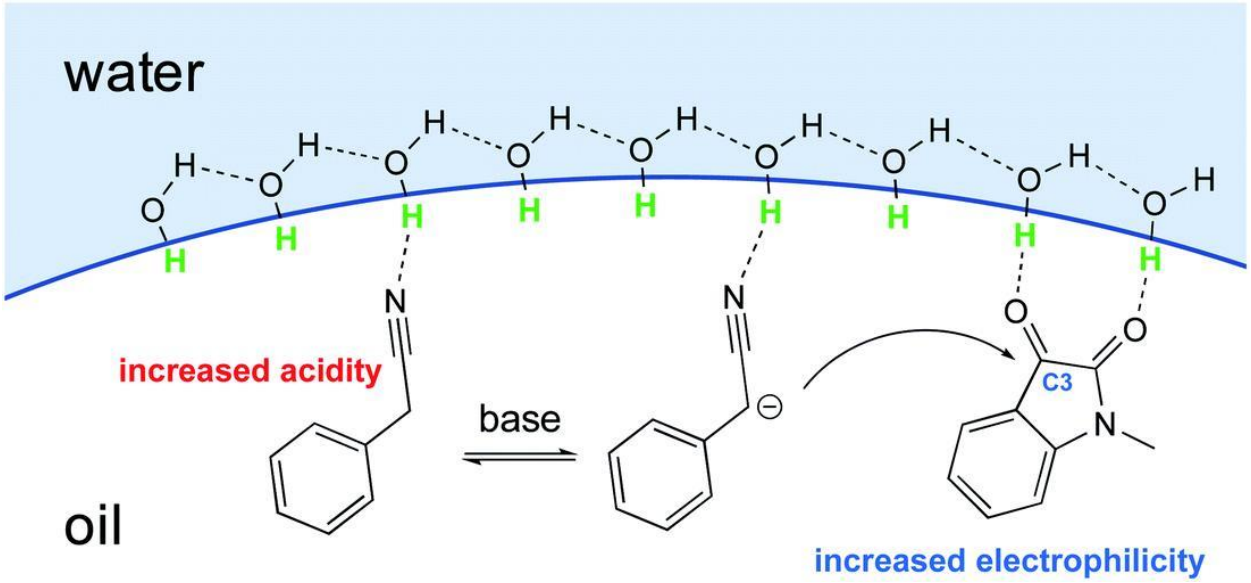
toxic and commercially available, and thus organocatalysis has been linked to the goals of green chemistry. But a significant part of the environmental impact of the field is not from the catalyst – it is from the reaction medium: conventional organocatalytic methods have frequently employed organic solvents like dichloro methane, dimethylformamide or toluene which are volatile, flammable or toxic. Two classes of solvents have come into the spotlight as alternatives. The most abundant, the cheapest, and the least toxic of the liquids available is water, and it has been demonstrated in many instances that water does not just tolerate organocatalytic reactions, but actually accelerates them via the hydrophobic effect and 'on-water' catalysis, both of which were first rationalized by Breslow (1991) and elaborated by Narayan et al. (2005). Deep eutectic solvents are second type of EES which are eutectic mixtures of a hydrogen-bond donor (HBD, e.g., urea, glycerol, carboxylic acids) and a hydrogen-bond acceptor (HBA, e.g., quaternary ammonium salts such as choline chloride) and were first systematically described by Abbott et al. (2004). DESs are also tunable for polarity, volatility and in some cases are intrinsically chiral, meaning they can act as both solvent and co-catalyst or even as the exclusive catalytic component of asymmetric transformations (Alonso et al., 2021; Ashworth et al., 2016; "Recent Impact of Natural Deep Eutectic Solvents," 2026). Although both media have been adopted with great enthusiasm there is very little direct comparison between the two media in a single mechanistic and sustainability framework. This review will close this gap by (i) summarizing the mechanistic understanding of catalysis in water and in DES, (ii) surveying representative catalytic performance data for both media for common classes of organocatalytic reactions, and (iii) critically evaluating the sustainability of these reactions using green metrics, life-cycle assessment and toxicological evidence.

2. Water as a Reaction Medium for Organocatalysis

2.1 Mechanistic Basis: Hydrophobic Effects and "On-Water" Catalysis

The hydrophobic effect was first proposed by Breslow (1991) as a possible explanation for the rate acceleration of organic reactions in water, because, when the reactants are more soluble in the organic transition state than in the water, the water pushes the reactants together, decreasing the activation entropy and in some cases the activation enthalpy for the reaction. The Diels-Alder cycloaddition was shown by Rideout and Breslow (1980) to exhibit dramatic rate enhancements in water compared to organic solvents; and this result was expanded to many other pericyclic and polar reactions. On-water catalysis is another conceptually similar yet distinct phenomenon defined by Narayan et al. (2005) as the rapid reaction of water-insoluble organic reactants when they are stirred in water, but not when completely dissolved in water. Jung and Marcus (2007) later gave a theoretical treatment, which indicates that the reactive species are located at the organic–aqueous interface, where non-hydrogen-bonded O–H groups of interfacial water molecules can participate as hydrogen-bond donors to stabilize the developing charge in the transition state. Since then, this interfacial hydrogen-bonding activation has been used to describe the rate and selectivity increases of aldol, Mannich and Michael reactions performed by amines, ureas and thioureas (Cortes-Clerget et al., 2021; van der Helm et al., 2019). The effects of kosmotropic (NaCl) versus chaotropic (LiClO4) additives, studied in this case, and the use of denser D2O as solvent, have shown that large rate accelerations in the synthesis of spirooxindole-γ-butyrolactone derivatives are directly caused by hydrophobic hydration (Suresh et al., 2018). Finally, in-depth mechanistic analyses have led to classification of aqueous organocatalysts on the basis of the activation process they undergo in aqueous solution (enamine/iminium, hydrogen-bonding, Brønsted acid/base, or NHC catalysis), with clear parallels to enzymatic catalytic mechanisms in

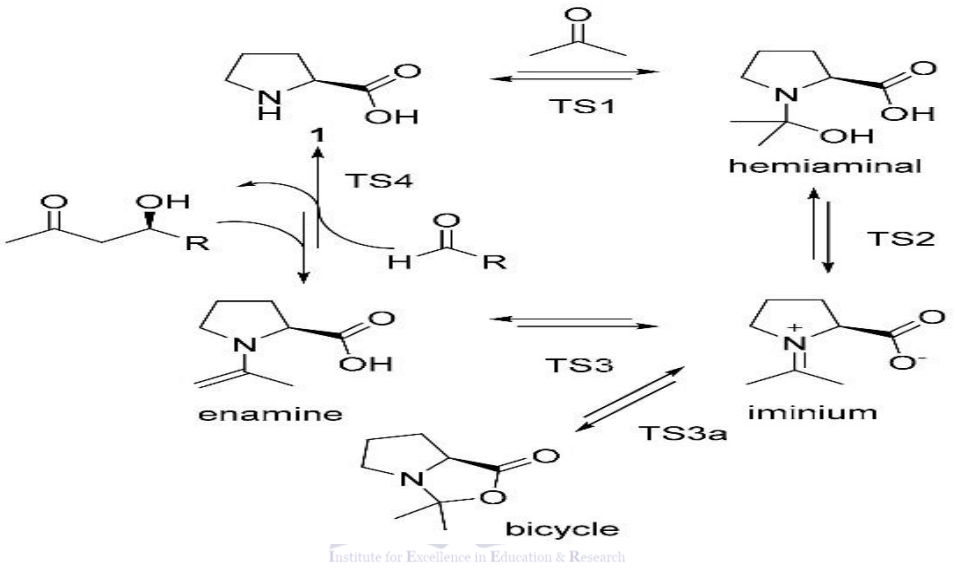
physiological water (van der Helm et al., 2019). Supramolecular strategies, in which the hydrophobic cavity of macrocycles like calixarenes and cyclodextrins sequester substrate molecules from bulk water, represent another way to exploit and amplify the intrinsic hydrophobic effect, mimicking the active sites of enzymes (De Rosa et al., 2018). However, it is important to note that the magnitude and even the nature of the solvent effect on the rate of cycloaddition reactions can vary from one reaction to another: For some reactions, the solvent effect on the rate is small, and, in some cases, the effect is even more pronounced specifically in water, due to the hydrophobic effect, while for other reactions dominated by simple polarity effects, the solvent effect is much smaller, or even inverse (Cortes-Clerget et al., 2021; Narayan et al., 2005). This mechanism diversity is the reason that "water effects" cannot be considered as a uniform phenomenon.



2.2 Catalytic Performance in Aqueous Organocatalysis

Practically, aqueous organocatalysis has successfully been applied to many types of C–C and C–heteroatom bond-forming reactions. L-Proline and its derivatives catalyse direct asymmetric aldol reactions "in water, on water, and by water" depending on the reaction circumstances, the performance of the catalyst is strongly dependent of its amphiphilicity, as the purely hydrophilic proline would be problematic when applied to poorly soluble substrates, thus, surfactant-tailored or amphiphilic proline derivatives that self-assemble at the oil–water interface have been developed (Mase & Barbas, 2010). Well-designed aqueous organocatalytic systems can achieve yields and enantioselectivities equal to those obtained in organic solvents for aldol reactions, Mannich reactions and Michael reactions, and more importantly, the catalyst can be easily recovered and the product isolated by phase separation (Kitanosono et al., 2018). The rate acceleration of the Diels–Alder cycloaddition, the most prototypic class of reactions that exemplify water-induced rate acceleration, was reported early on, with several orders of magnitude of enhanced rates over nonpolar organic media, and this effect was attributed to the hydrophobic stabilisation of the compact transition state (Rideout & Breslow, 1980). More recent quantum-chemical and molecular-dynamics studies have refined this picture, revealing that further lowering of the activation barrier is possible with organocatalysts that act as hydrogen-bond donors, this effect being complementary to the bulk aqueous

acceleration ("Bifunctional Hydrogen Bond Donor-Catalyzed Diels–Alder Reactions," 2021). Since then, the on-water approach has been broadened to transition-metal-catalysed couplings (Suzuki–Miyaura, Mizoroki–Heck, Mizoroki–Mizuno, Kumada–Grignard), and the physical phenomenon is now generally applicable to various catalyst types (Wei et al., 2024). Recyclability of the catalyst in aqueous media is generally good, if the organocatalyst is water-soluble or attached to a hydrophilic support, as it can be simply separated from the aqueous phase for reuse without the need to extract the water containing the catalyst; however, if the organocatalyst is hydrophobic and the substrate is poorly soluble in water, the use of co-solvents or surfactant additives will have to compromise the simplicity and green approach of recycling in the aqueous media (Kitanosono et al., 2018; van der Helm et al., 2019).



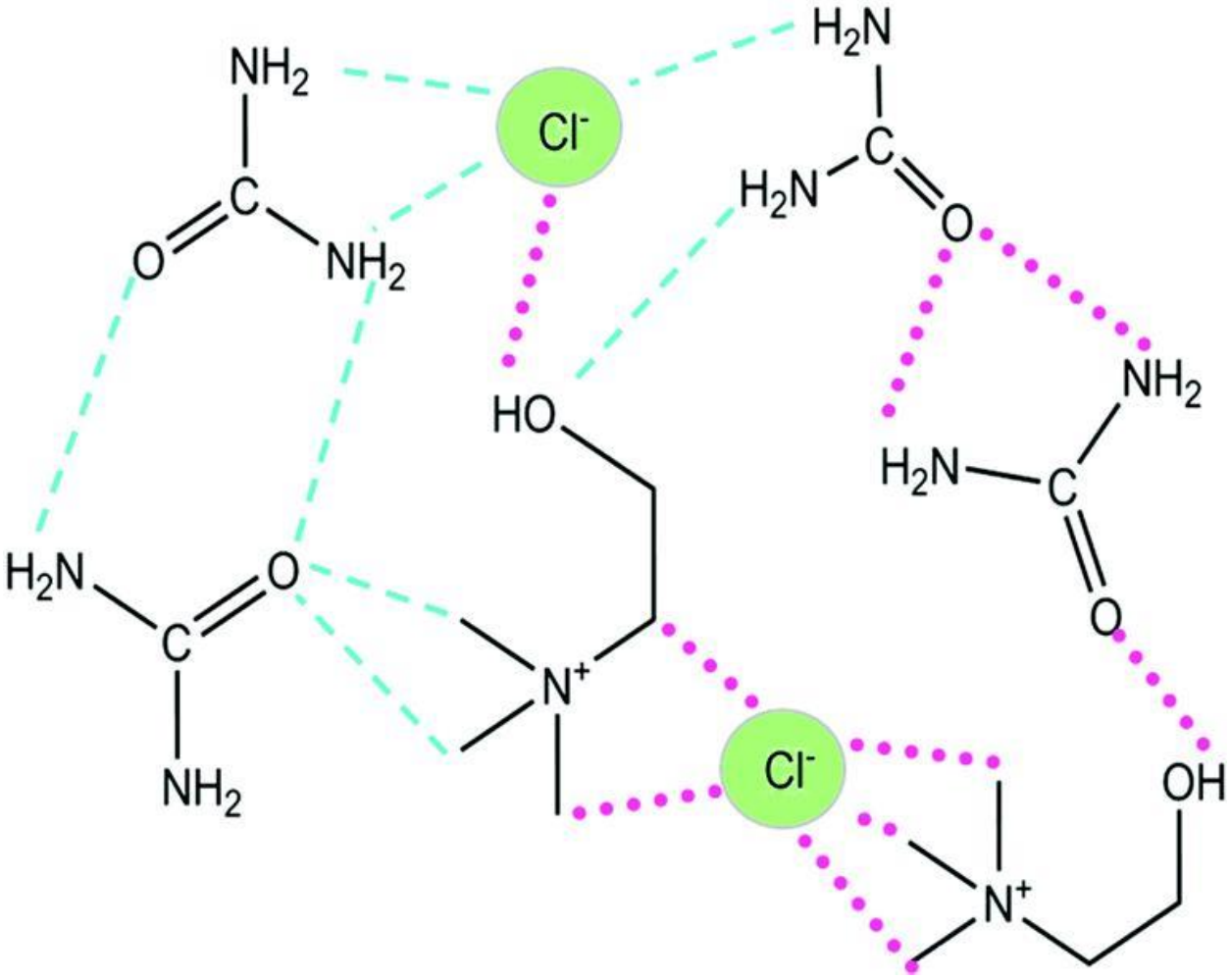
Institute for Excellence in Education & Research

3. Deep Eutectic Solvents in Organocatalysis

3.1 Structure, Formation, and Hydrogen-Bond Network of DES

DESs consist of a mixture of a hydrogen-bond acceptor (usually a quaternary ammonium or phosphonium salt) and a hydrogen-bond donor (usually an amide, carboxylic acid, polyol or sugar) in a specific molar ratio that results in a eutectic composition with a melting point that is significantly lower than either of the individual components. For example, the archetypal example "reline" (choline chloride:urea, 1:2) melts at about 12 °C although the parent components melt at 302 °C and 133 °C, respectively (Abbott et al., 2004). This melting-point depression has been suggested by multiple studies using neutron diffraction, ab initio molecular dynamics, and Raman spectroscopy to arise from an extensive dynamic hydrogen-bond network in which the HBD is able to interact with the halide anion (and in some systems, the cation), via multiple competing hydrogen bonds, thereby destroying ordered lattice structures of the separate crystalline components and increasing the configurational entropy (Ashworth et al., 2016; Hammond et al., 2016; "First-Principles Molecular Dynamics Study of a Deep Eutectic Solvent," 2018). In particular, the ab initio studies of reline have shown that the charge delocalisation between the anion and the HBD is reduced as compared to the original proposal, and that competitive HBD–anion and HBD–cation interactions and new type C–H hydrogen bonds also play an important role in the structure of the liquid ("Polymer Solvation in Choline Chloride Deep Eutectic Solvents," 2019; "First-Principles Molecular Dynamics Study of a Deep Eutectic Solvent," 2018). The low vapour pressure and non-flammability of DESs make them ideal for catalytic applications, while the

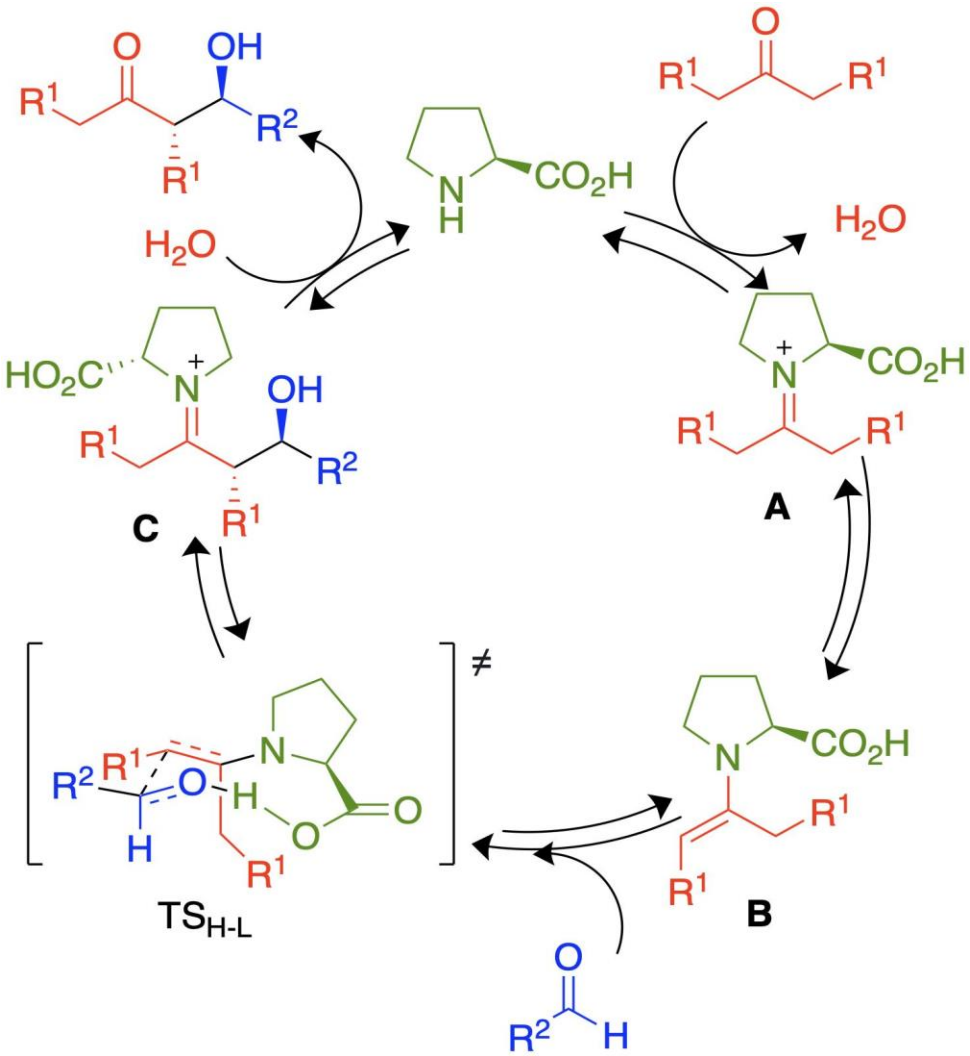
tunable polarity and viscosity resulting from variations in HBA:HBD identity and ratio, and, in the case of chiral components (e.g., L-proline, L-prolinol, or natural sugars), an inherent chiral solvation environment, render them of catalytic relevance (Alonso et al., 2021; "Recent Impact of Natural Deep Eutectic Solvents," 2026).



3.2 Mechanistic Roles of DES: Solvent, Co-catalyst, and Chiral Inductor

Chiral inductor, co-catalyst, and solvent roles of DES in synthesis. One of the key mechanistic differences between DES-mediated organocatalysis and aqueous organocatalysis is that the solvent may often be directly involved in the catalytic cycle as opposed to being a passive or hydrophobically structuring medium. For the first time, protonated L-proline has been used as the reaction medium and the source of chirality, with the hydrogen-bond-donor parts of the DESs acting directly on the enamine (or iminium) intermediate to control the facial selectivity (L-Proline Based Deep Eutectic Solvents, 2024). Mechanistic studies of aldol reaction in natural deep eutectic solvents (NADES) reveal that the choice and stereochemistry of the HBD can have a significant impact on the diastereo- and enantioselectivity: For instance, excellent yield and selectivity in the cross-aldol reaction between acetone and 4-methylbenzaldehyde have been obtained in a D-glucose/racemic-malic-acid NADES using L-proline as catalyst, which was found to be poor in conventional choline-chloride-based DESs, suggesting specific

hydrogen-bonding interactions between the sugar/acid HBD network and the developing transition state, and not bulk polarity alone, to be the origin of the selectivity (Alonso et al., 2021). A new innovation is the development of eutectogels ("EutectoGels") where a gelator (usually a chiral amino acid or derivative thereof) self assembles within a NADES to form a soft, structured three dimensional matrix that traps both substrate and catalyst. It is similar in spirit to the supramolecular cavities that have been employed in aqueous macrocyclic catalysis (Section 2.1) and has been successfully applied to enhance the stereocontrol for benchmark aldol and Michael reactions with enantioselectivities up to 97% ee for L-proline/choline chloride:urea eutectogel systems (Abbott et al., 2004; "How Deep Eutectogel Systems are Shaping Organocatalytic and Enzymatic Asymmetric Catalysis," 2025). Furthermore, Chiral DESs based on L-prolinol and related ammonium-pyrrolidine salts have been designed to carry both the eutectic medium and the organocatalyst in a single molecular framework, and solid–liquid equilibrium and DSC data of these systems confirm that they exhibit genuine eutectic (and not merely mixture) behaviour (Alonso et al., 2021). Differently from the aqueous organocatalysis, these systems do not follow the classical definition of "catalyst" and "solvent".



3.3 Catalytic Performance in DES-Mediated Organocatalysis

The catalytic activities of the DES in organocatalysis are summarized.The catalytic activities of the DES in organocatalysis are summarized. The asymmetric aldol reaction is always the major benchmark throughout the DES literature. The quantitative yields, diastereomeric ratios up to 25:1 favouring anti-isomer, and enantiomeric excesses above 90% without use of auxiliary toxic solvents or additives ("L-Proline-Based Deep Eutectic Solvents," 2024) have been achieved using chiral DESs based on L-proline and various glycols (diethylene glycol, ethylene glycol, triethylene glycol, glycerol). However, the use of classical (non-chiral, non-proline-derived) choline-chloride-based DESs with externally added chiral amine catalysts showed poor catalytic performance even in the presence of water as co-additive, indicating that it is not sufficient to simply replace an organic solvent with a DES to achieve good catalytic performance; rather the DES must be rationally matched to or be the catalyst itself (Alonso et al., 2021). Beyond the aldol reaction, DES have been found to be useful for a variety of organocatalytic asymmetric conjugate additions, including isobutyraldehyde/β-nitrostyrene Michael reactions catalysed by diarylprolinol ethers, aldehyde–maleimide conjugate additions catalysed by primary-amine monocarbamates, and 1,3-dicarbonyl α-amination reactions catalysed by chiral benzimidazoles, all with good to excellent enantioselectivity and with the added advantage that most DES components are non-volatile and may be easily recovered from the reaction flask by simple product extraction ("Organocatalytic Asymmetric Conjugate Addition," 2019). Comparative studies of DES media to solvent-free conditions for aldol reactions reveal that hydrophobic DES (HDES) based on L-proline can provide beneficial intermolecular interactions, electronic properties and thermophysical characteristics compared to the solvent-free conditions, indicating that the advantage of DES is not just a mere dilution effect, but a genuine solvation advantage (2019). Lipase-catalysed (biocatalytic) aldol additions have also shown that product distribution is closely related to the hydrophilicity/hydrophobicity of the DES used, with hydrophilic ChCl:glycerol DES being less soluble for hydrophobic substrates like 4-nitrobenzaldehyde, an important cautionary parallel to the substrate-solubility limitations noted for purely aqueous systems in Section 2.2 ("Comparison of Deep Eutectic Solvents and Solvent-Free Reaction Conditions," 2019).

Overall, recent reviews of DES-mediated organocatalytic and enzymatic asymmetric catalysis conclude that, while the number of reaction classes explored remains smaller than for aqueous organocatalysis, the results obtained—particularly for aldol and Michael-type C–C bond formation—are competitive with, and in several chiral DES cases superior to, both organic-solvent and aqueous benchmarks, with the important added feature of intrinsic (rather than externally supplied) chirality ("How Deep Eutectic Solvents Are Currently Shaping Organocatalytic and Enzymatic Asymmetric Catalysis," 2025).

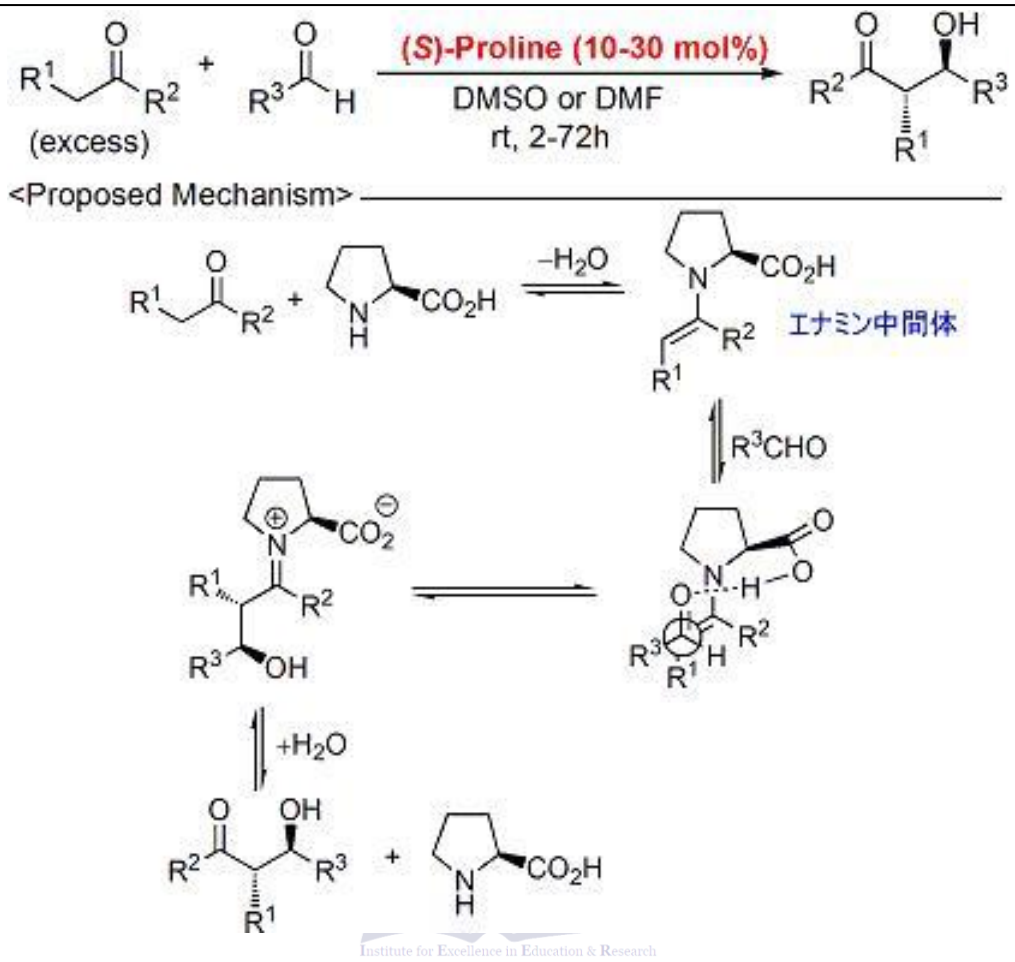


Table 1

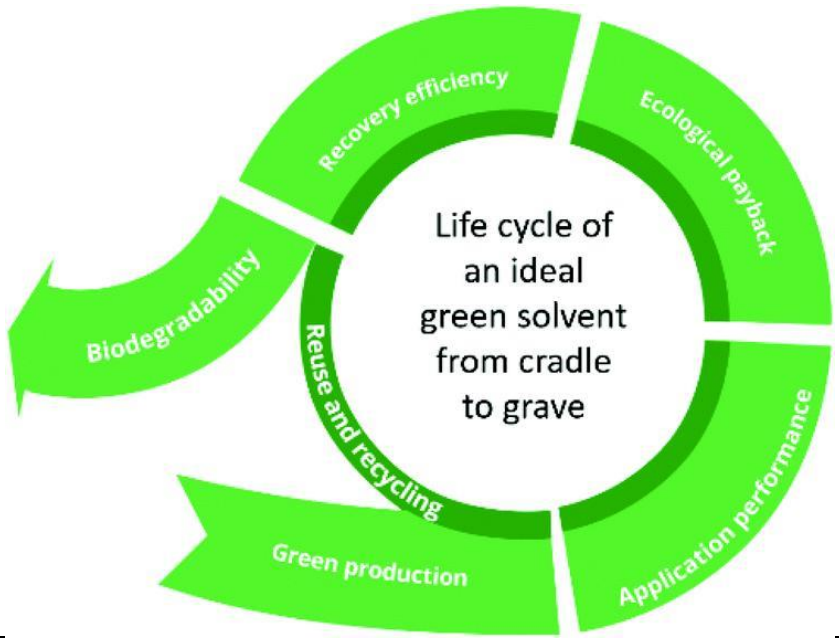
Parameters	Water	Deep eutectic solvents (DES)
Mechanistic basis	Hydrophobic packing ("on-water" effect)[a]; interfacial concentration of reactants; limited solvation of enamine/iminium intermediates	The H-bond donor–acceptor network is large, which is ideal for the stabilization of polar/charged transition states; can serve as a co-catalyst
Catalytic yield	Moderate–high; substrate-solubility limited	High; can degrade both polar and nonpolar substrates
Enantioselectivity	Variable; H-bonding may disrupt chiral organization	Often enhanced; H-bond network rigidifies TS geometry
Reaction rate	This can be accelerated for certain reactions (such as Diels-Alder).	Activated by H-bond; Diffusion is limited by viscosity.

Catalyst recyclability	Limited; leaching into aqueous phase	Retention of catalyst in DES phase after cycles; high
Substrate scope	Moderately hydrophobic restriction of substrate	Broad; polar, ionic, and hydrophobic substrates
E-factor[b]	Very low	Low - recycled; higher - single use
Biodegradability	Complete	Generally high (esp. natural DES); component-dependent
Toxicity	Negligible	Low (choline-based/natural DES); HBD-dependent
Viscosity/processing	Low; easy phase separation	High - complicates mass transfer and isolation

4. Sustainability Assessment

4.1 Green Chemistry Metrics and Process Considerations

Water and DES do well with several of the traditional green chemistry metrics including low volatility, non-flammability (or, in the case of water, complete non-flammability) and, for many DES formulations, the use of natural or renewable materials, such as choline, sugars, and amino acids, as reported in "Recent Impact of Natural Deep Eutectic Solvents" (2026) and in Zaib et al. (2022). However, green metrics for the whole process, like the E-factor (mass of waste per mass of product) and process mass intensity are not only influenced by the intrinsic solvent, but also the ease of product isolation, recovery of the solvent and the number of purification steps necessary will vary significantly between the two media. While the neat solvents are benign, the reaction work-up steps are often simple phase-separation for aqueous reactions, or require additional extraction or chromatography steps, which increases the overall process mass intensity, although some DES reactions do not require extra steps, such as "Deep Eutectic Solvents for Protein Extraction," 2025 and "Organocatalytic Asymmetric Conjugate Addition," 2019.



4.2 Life-Cycle Assessment

A complete life-cycle assessment (LCA) would be needed to assess the environmental advantages of DES use over conventional solvents, as DES components (choline chloride, urea, ethylene oxide and related precursors) are produced by traditional and often energy- and resource-intensive chemical processes. In an LCA study which was well cited, Zaib et al. (2022) compared the environmental impact of the DES (choline chloride:urea, 1:2) with that of methanol, ethanol, dichloromethane, and ethyl acetate for the oxidation reaction of an alcohol. Reline was shown to have lower environmental impacts than dichloromethane and ethyl acetate, but higher than methanol and ethanol, suggesting that the sustainability of a DES is not absolute, but highly dependent on the type of solvent with which it is compared. The same study examined a family of choline-chloride-based DESs, though, and found that the natural DES composed of citric acid (ChCl:citric acid) had the largest environmental footprint among all of the DESs studied, largely due to the water used and CO2 emissions generated for fermentation-based production of citric acid—which again highlights that "natural" doesn't mean "low environmental impact" (Zaib et al., 2022). Complementary LCA research into DES-based pretreatment for nanocellulose production also emphasizes that there is a lack of standardized and comprehensive life-cycle data for DES systems, compared with the amount of synthetic and catalytic literature – which is limiting the ability to confidently make sustainability claims at this time ("Life Cycle Assessment of DES systems for nanocellulose production," 2025).

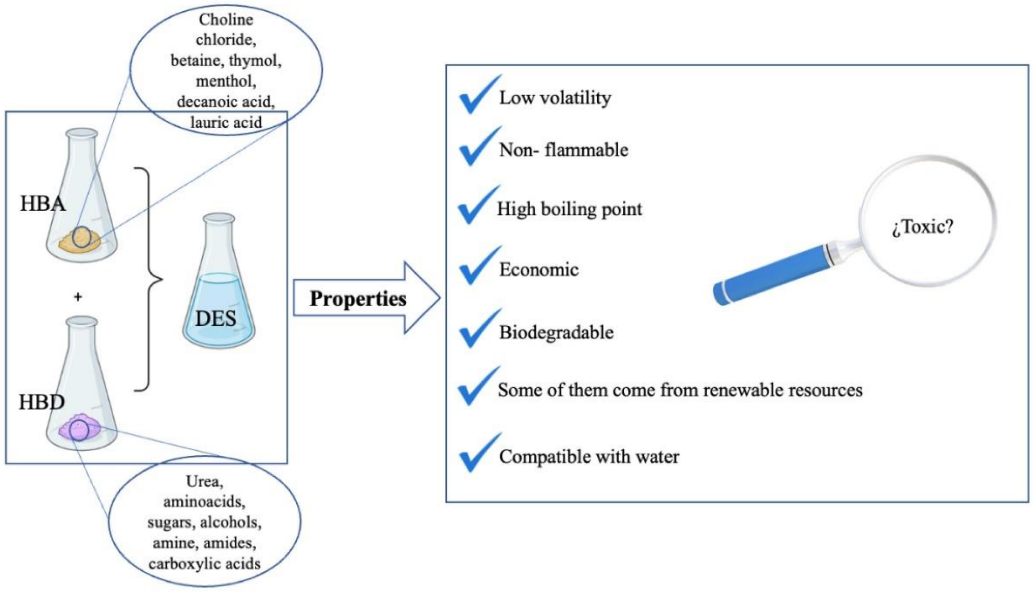
4.3 Toxicity, Biodegradability, and Emerging Assessment Frameworks

It is often claimed in early literature that DESs are biologically easily degradable and low toxicity, based mainly on qualitative arguments; more recent critical reviews give a different view. The four sustainability attributes most frequently attributed to DES – namely, low toxicity, good biodegradability, renewable sourcing and low cost – have been found to be class-assumed and must be verified on a case by case basis "Critical Assessment of the Sustainability of Deep Eutectic Solvents" (2022). Toxicological and bioremediation tests with the haloarchaeon Haloferax mediterranei also highlight that DES toxicity is still a significant, unaddressed challenge for large-scale application and DESs are frequently labeled as "green" without thorough testing (Martínez et al., 2025). Recognizing this vacuum, quantitative tools are starting to come into being. A recently proposed method, termed "DES Ecoscale," relies on green chemistry metrics and LCA methodology and on the principles of safe-and-sustainable-by-design (SSbD), allows to associate component sustainability, synthesis conditions, physicochemical performance, application-phase considerations, and end-of-life behaviour into a single quantitative score, which ranges between 66 and 98 points for 15 representative DES/NADES systems, suggesting that meaningful discrimination between DES formulations which are "sustainable" or "problematic" is possible when appropriate, solvent-specific metrics are used, rather than relying on the generic green-solvent assumption (dela-Huerta-Sainz et al., 2026). In comparison, the sustainability profile of water is relatively easy to quantify: it is non-toxic, it is universally biodegradable (in the sense that it is already the main component of the biosphere), and it has no synthesis-related environmental footprint. Its main sustainability costs are on the other hand, downstream: energy for heating/distillation-based recovery, generation of aqueous wastes that may be contaminated with organic residues, and water-footprint implications of using a resource that is scarce in many locations where it is used, costs qualitatively different from, and in most process contexts smaller than, those associated with DES synthesis and disposal (Kitanosono et al., 2018; Zaib et al., 2022).

5. Comparative Analysis: Water versus DES

In terms of the mechanism, the water and DES both catalyse and steer the reactions in organocatalytic reactions in largely complementary ways, rather than identical ways. The influence of water is mostly a

bulk/interfacial phenomenon in which the main driving forces are the hydrophobic effect and interfacial hydrogen bonding, which are largely independent of the specific chemistry of the catalyst, and depend on the polarity of the substrate and its aggregation behaviour (Breslow, 1991; Jung & Marcus, 2007; Narayan et al., 2005). In contrast, DES effects are often more specific and structural; the HBD/HBA hydrogen-bond network can be involved in the direct coordination of reaction intermediates, provide chirality and, if present as eutectogel, physically contain reactants, which makes DES more mechanistically complex and system-specific (Alonso et al., 2021; "How Deep Eutectic Solvents Are Currently Shaping Organocatalytic and Enzymatic Asymmetric Catalysis", 2025; "L-Proline Based Deep Eutectic Solvents", 2024). The catalytic performance of water and DES is similar in reactions where the aggregation of the two species is inherently catalytic, such as Diels–Alder cycloadditions or many aldol and Mannich reactions that can be performed with amphiphilic catalysts; DES, and especially chiral DES, has demonstrated strong catalytic ability in asymmetric aldol and conjugate-addition chemistry where the solvent's own chirality and hydrogen-bonding capacity can be used for stereocontrol without requiring elaborate, externally added chiral catalysts (Kitanosono et al., 2018; "L-Proline Based Deep Eutectic Solvents," 2024; "Organocatalytic Asymmetric Conjugate Addition," 2019). Both media are similarly constrained by a lack of solubility in the media for both the substrates and the catalysts, which can lead to reduced yields and necessitate compromise approaches (such as co-solvents and amphiphilic catalyst design) (van der Helm et al., 2019; "Comparison of Deep Eutectic Solvents and Solvent-free Reaction Conditions," 2019). Sustainability-wise, neither of the two media is better than the other in general. Water has virtually no upstream manufacturing burden, but can have downstream energy and/or wastewater costs; DES has an upstream synthetic burden (raw-material sourcing, sometimes energy-intensive HBD production from fermentation, as in the case of citric acid) that must be balanced against the advantages of its non-volatility, recyclability and, in several reported protocols, easy extraction of the product with retention of DES and its reuse in subsequent catalytic cycles ("Organocatalytic Asymmetric Conjugate Addition," 2019; Zaib et al., 2022; "Critical Assessment of the Sustainability of Deep Eutectic Solvents," 2022). Only the available LCA evidence suggests that DES is a 'better' solvent than chlorinated solvents or ester solvents, but it is 'worse' than water, which stands out as a simple, ubiquitous and low synthesis impact solvent in general, and becomes more 'worthy' of use when its use is driven by the structural/chiral desolvation properties that give it catalytic advantages (e.g., enantioselectivity) which could otherwise be obtained using additional chiral catalyst or additive input (Kitanosono et al., 2018; dela-Huerta-Sainz et al., 2026; Zaib et al., 2022).



6. Challenges and Future Perspectives

There are a number of weaknesses in the confident and generalisable comparison of water and DES in organocatalysis. Second, existing studies have typically investigated only a limited number of representative DES/solvent pairs, and existing LCA standardized data for DES are still limited compared to the number of synthetic applications that have been reported (Zaib et al., 2022; "Life Cycle Assessment of Deep Eutectic Solvent Employment," 2025). Second, toxicological and biodegradability data for DES are also not complete, and recent critical reviews have warned of overgeneralisation of 'green' attributes based on a few 'glowing reviews' in the field (Martínez et al., 2025; Critical Assessment of the Sustainability of DES, 2022). Third, hybrid water/DES systems, where controlled amounts of water are deliberately added to modulate the viscosity, polarity, and hydrogen-bond network of DES, are also of great promise but remain largely under-explored because water is known to competitively disrupt the DES hydrogen-bond network in a manner that can be tuned rather than simply avoided ("Polymer Solvation in Choline Chloride Deep Eutectic Solvents," 2019; "First-Principles Molecular Dynamics Study of a Deep Eutectic Solvent," 2018). Fourth, the majority of reported DES catalytic organocatalytic protocols are at the laboratory (milligram-to-gram) scale, and the process-scale viscosity, mass-transfer, and DES-recovery data required for scale-up to an industrial level are still limited. New quantitative sustainability tools that are currently developing like DES Ecoscale provide a promising pathway for more rigorous and comparable assessment in both future DES studies and potentially adapted analogues of aqueous organocatalytic processes (dela-Huerta-Sainz, 2026).

REFERENCES

Abbott, A. P., Boothby, D., Capper, G., Davies, D. L., & Rasheed, R. K. (2004). Deep eutectic solvents formed between choline chloride and carboxylic acids: Versatile alternatives to ionic liquids. Journal of the American Chemical Society, 126(29), 9142–9147 .

Alonso, D. A., Baeza, A., Chinchilla, R., Guillena, G., Pastor, I. M., & Ramón, D. J. (2021). Asymmetric organocatalysis in deep eutectic solvents. European Journal of Organic Chemistry. https://doi.org/10.1002/ejoc.202100385

Ashworth, C. R., Matthews, R. P., Welton, T., & Hunt, P. A. (2016). Doubly ionic hydrogen bond interactions within the choline chloride–urea deep eutectic solvent. Physical Chemistry Chemical Physics, 18(26), 18145–18160.

Bifunctional hydrogen bond donor-catalyzed Diels–Alder reactions: Origin of stereoselectivity and rate enhancement. (2021). [Journal article, PubMed Central record PMC8049058].

Breslow, R. (1991). Hydrophobic effects on simple organic reactions in water. Accounts of Chemical Research, 24(6), 159–164.

Comparison of deep eutectic solvents and solvent-free reaction conditions for aldol production. (2019). [Journal article].

Cortes-Clerget, M., Yu, J., Kincaid, J. R. A., Walde, P., Gallou, F., & Lipshutz, B. H. (2021). Water as the reaction medium in organic chemistry: From our worst enemy to our best friend. Chemical Science, 12(12), 4237–4266. https://doi.org/10.1039/D0SC06000C

dela-Huerta-Sainz, S., Diez-Cabanes, V., Santamaría, S., Escobedo, M., Marcos, P. A., Bol-Arreba, A., Trenzado, J. L., Atilhan, M., & Aparicio, S. (2026). DES Ecoscale: A quantitative sustainability assessment framework for deep eutectic solvents. ACS Sustainable Chemistry & Engineering, 14(26), 11573–11590. https://doi.org/10.1021/acssuschemeng.6c01738

De Rosa, M., La Manna, P., Talotta, C., Soriente, A., Gaeta, C., & Neri, P. (2018). Supramolecular organocatalysis in water mediated by macrocyclic compounds. Frontiers in Chemistry, 6, Article 84. https://doi.org/10.3389/fchem.2018.00084

Deep eutectic solvents for protein extraction: Mechanisms, performance, and green metrics. (2025). [Journal article].

First-principles molecular dynamics study of a deep eutectic solvent: Choline chloride/urea and its mixture with water. (2018). Journal of Physical Chemistry B. https://doi.org/10.1021/acs.jpcb.7b10422

Hammond, O. S., Bowron, D. T., & Edler, K. J. (2016). Liquid structure of the choline chloride–urea deep eutectic solvent (reline) from neutron diffraction and atomistic modelling. Green Chemistry, 18(9), 2736–2744.

How deep eutectic solvents are currently shaping organocatalytic and enzymatic asymmetric catalysis. (2025). RSC Sustainability, 3, 3883.

Jung, Y., & Marcus, R. A. (2007). On the theory of organic catalysis "on water." Journal of the American Chemical Society, 129(17), 5492–5502.

Kitanosono, T., Masuda, K., Xu, P., & Kobayashi, S. (2018). Catalytic organic reactions in water toward sustainable society. Chemical Reviews, 118(2), 679–746.

Life cycle assessment of deep eutectic solvent employment for sustainable nanocellulose production from biomass: A systematic review. (2025). https://doi.org/10.1080/17518253.2025.2507283

L-proline-based deep eutectic solvents as green and enantioselective organocatalyst/media for aldol reaction. (2024). Journal of Molecular Liquids.

Martínez, G., Guillena, G., & Martínez-Espinosa, R. M. (2025). Toxicity assessment and bioremediation of deep eutectic solvents by Haloferax mediterranei: A step toward sustainable circular chemistry. ChemSusChem. https://doi.org/10.1002/cssc.202500825

Narayan, S., Muldoon, J., Finn, M. G., Fokin, V. V., Kolb, H. C., & Sharpless, K. B. (2005). "On water": Unique reactivity of organic compounds in aqueous suspension. Angewandte Chemie International Edition, 44(21), 3275–3279. https://doi.org/10.1002/anie.200462883

Mase, N., & Barbas, C. F., III. (2010). In water, on water, and by water: Mimicking nature's aldolases with organocatalysis and water. Organic & Biomolecular Chemistry, 8(18), 4043–4050. https://doi.org/10.1039/C004970K

Organocatalytic asymmetric conjugate addition of aldehydes to maleimides and nitroalkenes in deep eutectic solvents. (2019). [Journal article, PubMed Central record PMC6891809].

Critical assessment of the sustainability of deep eutectic solvents: A case study on six choline chloride-based mixtures. (2022). ACS Omega. https://doi.org/10.1021/acsomega.2c06140

Polymer solvation in choline chloride deep eutectic solvents modulated by the hydrogen bond donor. (2019). Journal of Molecular Liquids.

Recent impact of natural deep eutectic solvents on asymmetric organocatalysis. (2026). Catalysts. https://doi.org/10.3390/catal16050413

Rideout, D. C., & Breslow, R. (1980). Hydrophobic acceleration of Diels–Alder reactions. Journal of the American Chemical Society, 102(26), 7816–7817.

Suresh, P., Thamotharan, S., & Ganesan, S. S. (2018). Driving NHC organocatalysis on water through hydrophobic hydration for the synthesis of diverse heterocycles and carbocycles. Catalysis Communications, 111, 47–51.

van der Helm, M. P., Klemm, B., & Eelkema, R. (2019). Organocatalysis in aqueous media. Nature Reviews Chemistry, 3(8), 491–508. https://doi.org/10.1038/s41570-019-0116-0

Wei, Y., et al. (2024). Recent advances in Pd-catalyzed reactions involving the "on-water" mechanism. Chinese Journal of Chemistry. https://doi.org/10.1002/cjoc.202300489

Zaib, Q., Eckelman, M. J., Yang, Y., & Kyung, D. (2022). Are deep eutectic solvents really green?: A life-cycle perspective. Green Chemistry, 24(20), 7924–7930. https://doi.org/10.1039/D2GC01752K

IEER
Institute for Excellence in Education & Research