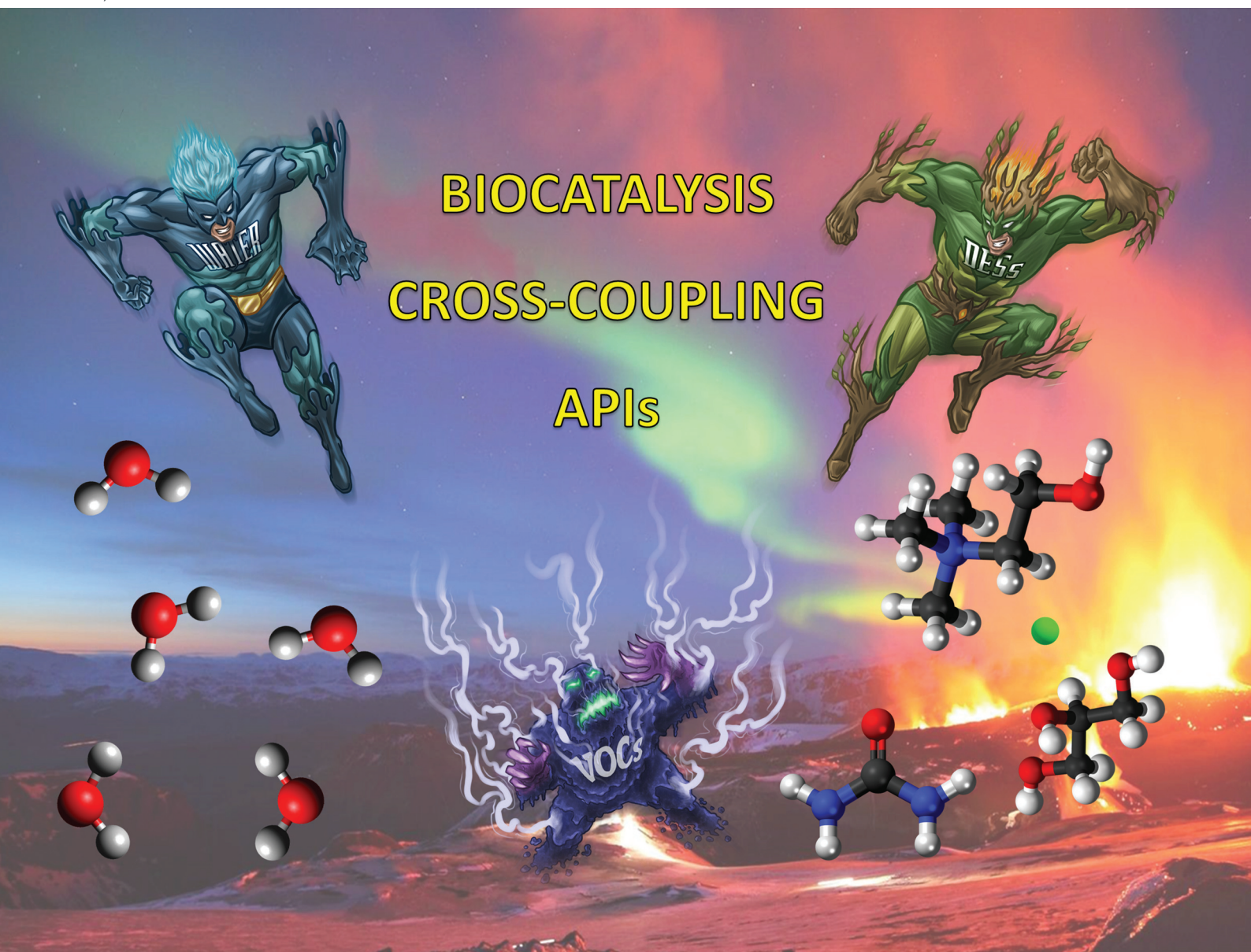


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REVIEW ARTICLE

Filippo Maria Perna, Paola Vitale, Vito Capriati *et al.*
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REVIEW

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Advances in deep eutectic solvents and water: applications in metal- and biocatalyzed processes, in the synthesis of APIs, and other biologically active compounds

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Owing to a growing awareness towards environmental impact, the search for “greener”, safer, and cost-effective solvents able to replace petroleum-derived solvents has never been greater today. In this context, the use of environmentally responsible solvents like water and the so-called deep eutectic solvents (DESs), constructed from bio-based compounds, has recently experienced important growth in several fields of sciences. This short review highlights the key features of the chemistry of water and (hydrated) DESs when applied to metal- and biocatalyzed transformations as well as to the synthesis of active pharmaceutical ingredients (APIs) and other biologically relevant compounds by providing, through discussion of all relevant literature over the past five years, a comparison of the outcomes of the reactions when carried out in one or the other solvent.

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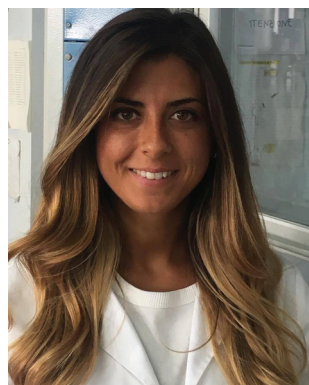
1. Introduction

The growing environmental concerns in society, which are mainly related to the increase of pollution, the climate change and resource depletion, a combination of factors that are plaguing people's and animal's lives and affecting their health, has impelled chemistry research in developing products and

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synthetic protocols from renewable resources.¹ In this context, the search for cost-effective and more environmentally responsible and safe solvents, in place of toxic and often harmful fossil-generated volatile organic compounds (VOCs), is central as solvents represent the largest source of waste associated with chemical production, accounting for more than 80% of the total mass used in a synthetic process carried out in batch reactors.²

It was thus with no surprise that in recent years an explosive growth of publications has focused on the use of bio-based solvents like deep eutectic solvents (DESs) and water, both conforming to the principles of green chemistry.³ DESs and water share several physicochemical properties (*e.g.*, negligible vapour pressure, thermal stability, non-flammability, cheapness), and are both characterized by a strong hydrogen-bond network. DESs are, indeed, usually formed by binary or ternary mixtures comprising at least one hydrogen bond donor (HBD) and at least one hydrogen bond acceptor (HBA). When these components are mixed in a proper molar ratio, the corresponding mixtures have a melting point much lower than that of either of the individual components and, per definition, also to that of an ideal liquid mixture.⁴ DESs are tunable solvents par excellence exhibiting a broad set of polarities because of the possible inclusion of either hydrophilic or hydrophobic components in their structure.⁵ In addition, those coming from renewable sources also show low toxicity and high biodegradability.⁶

Intriguingly, water and DESs do have another aspect in common: they are both key players in nature's game. Indeed, if it is true, on the one hand, that water has been (and still is) the "universal solvent" on Earth for several biosynthetic processes for millions of years, on the other hand, DESs formed from primary metabolites (*e.g.*, sugars, natural amino alcohols and carboxylic acids, amino acids, vitamins) (sometimes called natural deep eutectic solvents, NADESs) seem to be the

missing link in understanding cellular metabolism and plant physiology. By acting as the third liquid state in the living organisms besides water and lipid, DESs may similarly allow biological processes to take place, while also facilitating the storing and the transportation of poorly water-soluble macromolecules, and the protection of living organisms from cold and drought stresses.⁷ At the same time, water has also been proven to play a major role in DES formation by modifying the physicochemical properties of the corresponding supramolecular network. This, in turn, affects DES interactions with natural and bioactive molecules (*vide infra*).⁸ However, if a small amount of water in hydrated DESs appears to strengthen the hydrogen-bond network, recent studies have disclosed that DES nanostructure is retained up to 42 wt% water. At 51 wt% water, the solution starts exhibiting a behaviour closer to that of solutes in an aqueous solution.⁹

Several outstanding reviews and book chapters are today already available on the chemistry of both DESs¹⁰ and water¹¹ as these are hot topics in many academic workplaces, with new and emerging applications, in particular, in the fields of main group chemistry,¹² metal,¹³ bio,¹⁴ and organocatalysis,¹⁵ electrochemistry,¹⁶ photosynthesis,¹⁷ and solar technology.¹⁸ The reader is referred to these publications for more detailed information. Notwithstanding the similarities existing between DESs and water, these "solvents", likewise in nature, sometimes offer complementary performances on organic reactivity when tested individually in certain reactions. The reasons are still not clear, and the knowledge of mechanisms of action at a molecular level have become an intense matter of investigation amongst researchers.¹⁹

This short review collects and discusses recent progresses over the past five years in (a) cross-coupling processes, (b) biocatalyzed transformations promoted by whole-cell microorganisms, and (c) the synthesis of active pharmaceutical ingredients (APIs) and other biologically active compounds, show-



Filippo Maria Perna

the use of sustainable solvents in organometallic chemistry, metal-, bio-, and organocatalyzed reactions, and the asymmetric and green synthesis of target molecules with pharmacological importance.

Filippo M. Perna received his Ph.D. from the University of Bari (Italy) in 2004 under the supervision of Professor S. Florio. He has been a Visiting Researcher at the University of Oviedo in Spain working in the group of Professor J. Barluenga. In 2006 he became Assistant Professor in Organic Chemistry at the University of Bari and joined the research groups of Professors V. Capriati and S. Florio. His current research interests are focused on



Paola Vitale

new synthetic methodologies of heterocycles in several interdisciplinary projects. Her research is mainly focused on developing new "green" approaches for the preparation of fine chemicals and APIs by combining biocatalysis and organometallic chemistry.

Paola Vitale graduated in 2000 at the University of Bari (Italy) (summa cum laude) in Chemistry and Pharmaceutical Technologies, and was awarded as the Best Graduate student of her course. She received her Ph.D. at the University of Bari, carrying out a research on new heterocyclic NSAIDs. From 2004 to 2006 she worked as a Postdoctoral Researcher, and then became Researcher at the University of Bari, developing

casing topics/reactions where comparison between water and DESs are available. The aim is to give the reader an overview of the great assortment of reactions feasible, and the potential benefits thereof, when synergistically or singularly using DESs and/or water in (bio)synthetic processes. On the other hand, micelle-promoted transition metal-catalyzed cross-couplings “in water” will not be detailed here, and the interested reader is referred to the comprehensive reviews/monographies already available in the literature.²⁰

2. Cross-coupling reactions in DESs and water

Over the years, transition-metal-catalyzed cross-coupling reactions have become ubiquitous in organic chemistry as they provide an impressive and powerful tool for forging C–C bonds.^{20e,21} The direct formation of C(sp²)–C(sp²), C(sp)²–C(sp²) or C(sp³)–C(sp²) bonds is, indeed, central to natural product synthesis, materials science, biological-, medicinal-, and supramolecular chemistry, and also to catalysis, coordination chemistry and polymer synthesis.²² In this context, solvents are crucial because of the considerable influence they have on the rate and selectivity of such processes as well as on their equilibria.²³ The stability of catalysts, in turn, can be influenced by coordinating solvents used in the synthesis, which compete with the ligands (if any), whereas the function of acids and bases could alternatively be played by a complementary hydrogen bond-donor or hydrogen bond acceptor functionality, if present on the solvent. In order to minimize industrial waste and to promote a sustainable environment,²⁴ many efforts have been made over the last decade to accomplish transition-metal catalyzed cross-couplings in more environmentally benign protocols, like those based on nature-inspired reaction media.²⁵ Remarkable developments have

been achieved, especially when using green solvents such as water or DESs. The field of cross-coupling reactions in DESs has been recently reviewed by Varma, Ramón and co-workers.²⁶ Thus, in this section, we summarize and discuss only selected examples of metal-catalyzed cross-couplings where a comparison of the reactivity and the outcome of the reaction in water and in DES is available.

2.1 The Suzuki–Miyaura reaction

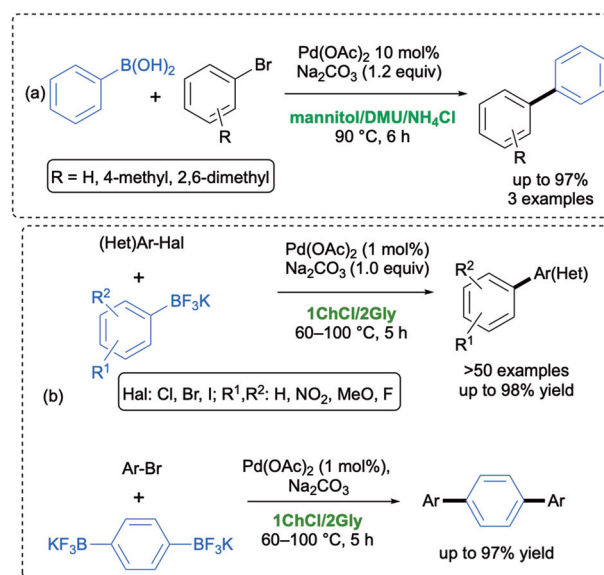
The Suzuki–Miyaura (SM) reaction has been heavily exploited in this decade because of several advantages over other similar reactions, such as mild reaction conditions, the commercial availability of an array of precursors, functional group tolerance, and the deployment of nontoxic and easily synthesized boronic acids and their derivatives (*e.g.*, potassium organotri-fluoroborates, boronate esters). A survey of the literature disclosed many examples of Pd, Ni and Au complexes as efficient catalysts for such cross-couplings.²⁷ In 2006, König and co-workers first reported that phenyl boronic acid could be successfully coupled with three aryl bromides at 90 °C in a low-melting sugar–urea–salt mixture made by mannitol-*N,N'*-dimethyl urea (DMU)–NH₄Cl (50:40:10 w/w) as an eco-friendly solvent, in the presence of 10 mol% of Pd(OAc)₂ as a catalyst and Na₂CO₃ as a base. A quantitative conversion was achieved after 6 h, and the hydrodeboration reaction was not observed as a competing process (Scheme 1a).²⁸

In the following years, numerous papers have been published on such a cross-coupling reaction in DESs, mostly using boronic acids as the nucleophilic partners, a large amount of electrophile, and palladium catalysts often associated with structurally engineered phosphine ligands in order to obtain good yields in short reaction times. Ramón and co-workers, in particular, introduced three different protocols: (a) the use of



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Vito Capriati is full Professor of Organic Chemistry at the University of Bari (Italy). He has been Visiting Scientist at the Ohio State University (USA) (2001, with Professor G. Fraenkel) and Visiting Professor at the Göthenburg University (Sweden) (2003). Since 2016 he is the Director of the Interuniversity Consortium CINMPIS. His awards include the 2009 CINMPIS Prize and the 2014 Prize of the Division of Organic Chemistry of the Italian Chemical Society. Current research interests revolve around the chemistry of *s*-block elements, and the development of novel sustainable chemical transformations. Since 2019 he is Fellow of the Royal Society of Chemistry.



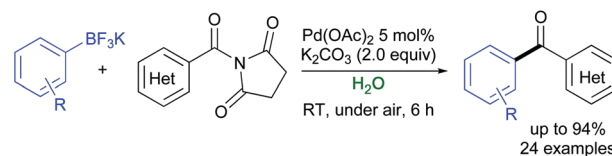
Scheme 1 Examples of Suzuki–Miyaura cross-coupling reactions in (a) low-melting mixtures and (b) in DESs.

PdCl_2 as a catalyst, K_2CO_3 as a base, and cationic structurally engineered phosphine ligands in a choline chloride (ChCl)-based DES;²⁹ (b) the use of a *N*-heterocyclic carbene (NHC)-Pd complex as a catalyst, K_2CO_3 as a base in a ChCl/ethylene glycol (EG) (1 : 2 mol/mol) eutectic mixture, in the presence of 10 equiv. of water;³⁰ and (c) the employment of a DES-compatible bipyridine palladium complex as a general pre-catalyst, K_2CO_3 as a base in a ChCl/EG (1 : 2 mol/mol) mixture at 100 °C.³¹

In 2018, Capriati and co-workers developed a Pd-catalyzed SM reaction between (hetero)aryl halides (Cl, Br, I) and air- and moisture-stable mono- and bifunctional potassium aryltrifluoroborates (employed in a strict 1 : 1 stoichiometric ratio). Under these conditions, the coupling was found to proceed efficiently and chemoselectively in air and under generally mild conditions (60 °C), using 1 mol% of $\text{Pd}(\text{OAc})_2$ as a catalyst, Na_2CO_3 as a base in a ChCl/glycerol (Gly) (1 : 2 mol/mol) eutectic mixture, which is used as a recyclable, sustainable and environmentally responsible medium (Scheme 1b).³² The same ligand-free approach has been then applied to promote smooth SM coupling reactions, under aerobic conditions, between dihalogeno-substituted benzodithiophenes (BDTs) and aryl-, alkenyl- and alkynyltrifluoroborate salts in a ChCl/Gly eutectic mixture to synthesize valuable π -conjugated BDT adducts in up to 79% yield, whose optical and electrochemical properties have been deeply investigated by means of absorption and cyclic voltammetry measurements.³³

The use of potassium aryltrifluoroborates in pure water was less effective. In 2015, Schatz and co-workers described an efficient, broadly applicable and sustainable SM protocol in pure water with a Pd loading as low as 0.4 mol%, without any ligand or organic co-solvent, working with a range of activated and nonactivated aryl halides (Scheme 2). Nevertheless, quantitative conversions could not be achieved when using the easy-to-handle and air-stable potassium phenyltrifluoroborate in place of the corresponding phenylboronic acid. The catalytic activity was boosted by using NHC ligand precursors and/or supramolecular additives.³⁴

In 2018, an efficient and ligandless catalytic protocol was developed for the coupling between potassium aryltrifluoroborates with various aryl and heteroaryl bromides in water with Na_2CO_3 as a base. Using tetraethylammonium tetrahydroborate (TEAB) as an additive and $\text{Pd}(\text{OAc})_2$ as a catalyst, the desired adducts were isolated in moderate to excellent yields (up to 94%).³⁵ In 2020, a green general strategy for the synthesis of aryl ketones from twisted amides and air- and moisture-stable potassium aryltrifluoroborates has been set up by



Scheme 3 Water phase, room temperature, and ligand-free Suzuki–Miyaura cross-coupling reaction.

Liu, Zhu, Zeng and co-workers using $\text{Pd}(\text{OAc})_2$ as a catalyst and K_2CO_3 as a base. The reported protocol showed a high functional group tolerance, with a variety of ketones synthesized in very good yields (up to 94%) under air, and within 6 h reaction time (Scheme 3). Of note, this approach, which relied on the high reactivity of *N*-acylsuccinimides, also demonstrated the first water phase, room temperature, and ligand-free Suzuki–Miyaura coupling successfully taking place through a C–N bond cleavage.³⁶

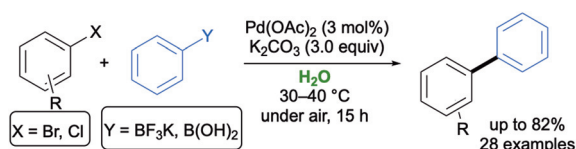
2.2 The Sonogashira–Hagihara reaction

The Sonogashira–Hagihara (SH) reaction is the cross-coupling reaction between terminal alkynes and aryl or vinyl halides (pseudohalides) to generate conjugated enynes. This represents one of the most powerful methods for the rapid build up of $\text{C}(\text{sp}^2)\text{--C}(\text{sp})$ bonds in synthetic chemistry. This methodology has been widely applied to prepare biologically active molecules, natural products, conducting polymers/engineering materials, and macrocycles with acetylene links.^{37,38} After pioneering studies by König,³⁹ different copper-free procedures between aryl iodides or bromides and terminal aromatic and/or aliphatic alkynes have been developed in DESs.^{40,41}

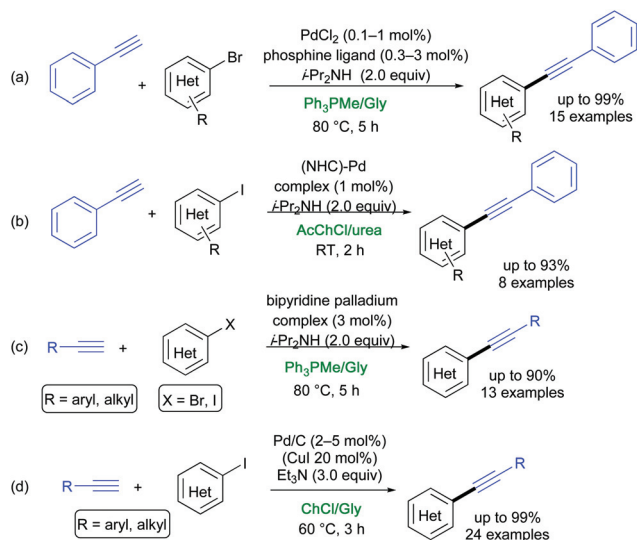
(Hetero)aryl bromides and iodides were successfully cross-coupled to terminal alkynes in DESs by Ramón, Alonso and co-workers according to the following approaches: (a) use of PdCl_2 associated to cationic structurally engineered phosphine ligands and *i*- Pr_2NH as a base in $\text{Ph}_3\text{PMeBr}/\text{Gly}$ (1 : 2 mol/mol) (Scheme 4a);²⁹ (b) use of a NHC-Pd complex and *i*- PrNH_2 in $\text{AcChCl}/\text{urea}$ (1 : 2 mol/mol) (Scheme 4b);³⁰ and (c) use of a bipyridine palladium complex as a pre-catalyst in $\text{Ph}_3\text{PMeBr}/\text{Gly}$ (1 : 2 mol/mol) in the presence of *i*- Pr_2NH (Scheme 4c).³¹

A highly efficient, recyclable and ligand-free protocol was developed by Salomone, Capriati and co-workers. Working under heterogeneous conditions, the commercially available Pd/C was found to be an effective catalyst for promoting the coupling between (hetero)aryl iodides (including electron-rich iodides) and aromatic and aliphatic alkynes, within 3 h at 60 °C in yields ranging from 50 to 99%, in the ChCl/Gly eutectic mixture using Et_3N as a base (Scheme 4d).⁴²

Notwithstanding the well-known poor solubility of organic substrates in water, Bhattacharya and Sengupta first demonstrated the feasibility of running the alkynylation of aryl iodides and bromides in pure water without any organic co-solvent, phase-transfer catalysts or water-soluble phosphine ligands.⁴³ These couplings, which took place under truly heterogeneous conditions, are remarkably fast (30 min at



Scheme 2 Pd acetate-catalyzed on-water Suzuki Miyaura reactions.



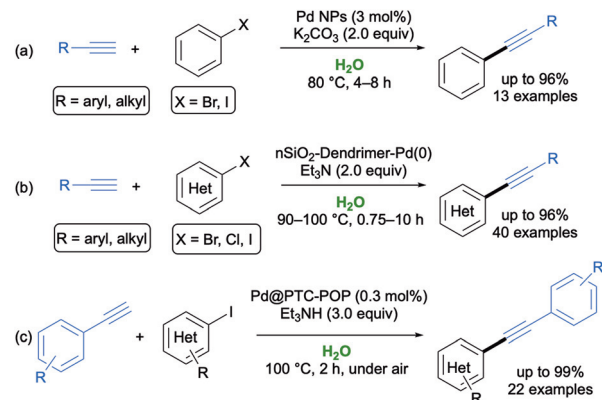
Scheme 4 Examples of Sonogashira–Hagihara coupling reactions in DESs (a) in the presence of a phosphine ligand, (b) using a NHC–Pd or (c) a bipyridine Pd complex, or (d) under ligand-free conditions.

70 °C) affording aryl alkynes in 75–92% yield when using 0.5 mol% of $\text{Pd}(\text{PPh}_3)_4$, 1 mol% CuI, and Et_3N or *N,N*-diisopropylethylamine (DIEA) as a base. The reaction showed excellent group tolerance and sensitive functionalities like an aldehyde group were also tolerated. It is worth noting that the addition of an organic solvent like DMF (DMF/ H_2O 9:1) slowed down the reaction rate and led to the appearance of side-products.

The synthesis of arylpropargylic amines was then achieved by Costa and co-workers *via* the SH coupling of aryl iodides with propargylic amines,⁴⁴ working under the so-called “on water” conditions.⁴⁵ The desired adducts were isolated in up to 85% yield in 24–48 h when using less than 0.2 mol% of Pd ($\text{PPh}_3)_4$ and 1.5 mol% CuI in the presence of DIEA at 95 °C.⁴⁴

In 2015, Nasrollahzadeh and colleagues set up an easy and cost-effective synthesis of Pd nanoparticles (NPs) *via* the reduction of aqueous Pd^{2+} ions using *Piper longum* fruit extracts without any surfactant or stabilizer, most probably because the flavonoid present in the extract acted themselves as both reducing and stabilizer agents. The synthesized Pd NPs (stable and storable for months under inert atmosphere) proved to be effective catalysts (loading up to 3 mol%) to perform ligand-, amine- and copper-free SH couplings between aromatic aryl halides and terminal alkynes in neat water under aerobic conditions at 80 °C in the presence of K_2CO_3 as a base. The expected adducts were isolated in 84–96% yield with the tolerance of a variety of functional groups, and the catalyst was recycled up to five times without any loss of catalytic activity (Scheme 5a).⁴⁶

In 2016, Sardarian and co-workers reported the synthesis of novel dendrimer-encapsulated Pd(0) nanoparticles immobilized on nanosilica with surface amino groups using natural and waste material from rice husk as the source of the silica



Scheme 5 Examples of Sonogashira–Hagihara coupling reactions run in water catalyzed by (a) Pd NPs, or (b) dendrimer-encapsulated Pd(0) nanoparticles immobilized on nanosilica, or (c) a porous organic polymer with *in situ* generated Pd NPs (Pd@PTC-POP).

components.⁴⁷ This catalytic system revealed to be an efficient catalyst for promoting copper- and phosphine-free SH couplings between aryl halides and terminal alkynes in water at 90–100 °C in the presence of Et_3N , with the desired internal alkynes isolated in 62–97% yield. The robustness of the methodology was further highlighted by the reuse of the catalyst over five cycles without any significant loss in its catalytic activity (Scheme 5b).⁴⁷

In 2019, a novel highly active and reusable solid phase-transfer catalyst, consisting of a porous organic polymer with *in situ* generated Pd NPs (Pd@PTC-POP), was fabricated by Dong and co-workers by exploiting a one-pot Suzuki cross-coupling approach. This catalyst promoted SH cross-coupling reactions in aqueous phase, especially from iodo-substituted aromatic substrates and alkynes, with the corresponding adducts being synthesized in very good yields (up to 99%) within 2 h at 100 °C in the presence of Et_3N and with a broad substrate scope (Scheme 5c).⁴⁸

2.3 The Murahashi coupling

Organolithium compounds are one of the most important classes of organometallic compounds as they are ubiquitous in organic synthesis.⁴⁹ These cheap, commodity reagents are either commercially available or can be easily accessed by halogen-metal exchange or a direct metalation reaction. Because of their high reactivity, cross-coupling of organolithium species were often proven to suffer from either a fast lithium-halogen exchange, leading to homocoupled products, or a β -hydride elimination reaction, responsible for the formation of dehalogenated products.⁵⁰ Seminal contributions by Murahashi and co-workers to this field disclosed that Pd(0)-catalyzed cross-couplings between alkenyl halides and organolithium reagents are indeed feasible, though only at high temperature, long reaction time, and at high catalyst loading.⁵¹

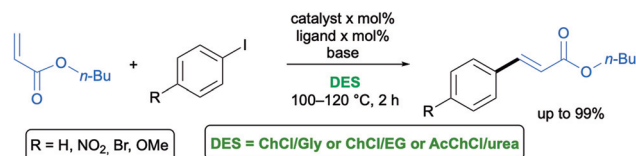
The Murahashi coupling has been recently revised by Feringa and co-workers who disclosed that several alkyl-, alkenyl-, and (hetero)aryllithium reagents could be directly

cross-coupled with aryl and alkenyl (pseudo)halides in the presence of palladium or nickel complexes, not experiencing the above drawbacks, when (i) using a nonpolar solvents (toluene), which affects the reactivity of the organolithium reagents, or working with no additional solvents, in conjunction with a Pd catalyst with bulky electron-rich ligands (e.g., Pd/*Pt*-Bu₃), and (ii) performing a slow addition of the organolithium reagent to the reaction mixture.⁵² Feringa, Hornillos and co-workers also reported that the slow addition (20 min reaction time) of an excess PhLi (2–10 equiv.) to 1-bromonaphthalene using 10 mol% of Pd-PEPSI-*i*-Pr in a ChCl/Gly eutectic mixture produced the desired adduct, though in low yield (28–53% conversion) (Scheme 6a).⁵³ On the other hand, when alkyl- or aryllithium reagents were added over a mixture of arylbromide and the Pd-catalyst (down to 0.1 mol%) with no additional solvents, cross-coupling reactions were found to proceed fast (10 min) at ambient temperature and also in open air, thereby providing the desired adducts in high yields (81–98%), excellent selectivities, and high scalability.⁵³

In 2019, Capriati and co-workers reported a direct Pd-catalyzed cross-coupling between organolithium reagents and a variety of (hetero)-aryl halides (Br, Cl), taking place at ambient temperature under air, with water as the only reaction medium and in the presence of NaCl as a cheap additive (Scheme 6b).⁵⁴ A water-accelerated catalysis was the key for achieving C(sp³)-C(sp²), C(sp²)-C(sp²), and C(sp)-C(sp²) cross-coupling reactions, which proceeded fast (20 s reaction time), in yields up to 99%, in competition with protonolysis, and in the absence of dehalogenated/homocoupling side products. Both the catalyst and water could be easily recycled up to 10 times, with an *E*-factor as low as 7.35. Several eutectic mixtures were also tested, though with both lower yields and selectivity.⁵⁴

2.4 The Heck–Mizoroki reaction

The Heck–Mizoroki (HM) reaction is generally referred to as the Pd-catalyzed C–C coupling between aryl or vinyl (pseudo)halides and activated alkenes in the presence of a base to form a substituted alkene.⁵⁵ Cross-coupling reactions between aryl iodides with different substitution patterns and methylacrylate have been successfully carried out by Ramón and co-workers in various eutectic mixtures like ChCl/Gly (1 : 2), ChCl/EG (1 : 2) and AcChCl/urea (1 : 2) using cationic pyridiniophosphine



Scheme 7 Pd-Catalyzed Heck–Mizoroki cross-coupling reaction between aryl iodides and methyl acrylate in DESs.

or bipyridine or strong σ -donor carbene ligands for palladium in the presence of NaOAc as a base at 100–120 °C with good to excellent results (Scheme 7).^{29–31}

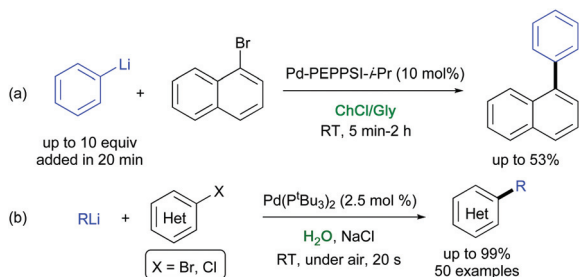
Among Pd-catalyzed cross-coupling reactions, the Heck coupling turned out to be one of the most challenging in an aqueous environment, and several homogeneous and immobilized catalysts, including nanoparticles, have been developed.⁵⁶ An environmentally friendly Pd-catalyzed Matsuda–Heck reaction between arenediazonium tosylates and different activated alkenes has been first developed by Postnikov and co-workers in water. Under optimized conditions, arylation of aldehydes took place with a broad substrate scope with the desired products isolated with a high purity and in a considerable short reaction time (up to 1 min) when using microwave irradiation (Scheme 8a).⁵⁷

In 2017, Tsai and co-workers reported that mono or double Pd-catalyzed MH couplings between dialkyl vinylphosphonates and aryl halides could be carried out in water under air using *i*-Pr₂NH as a base, by simply selecting aryl halides or dialkyl vinylphosphonates as the limiting reagent. A plausible mechanism was also reported. When aryl iodides were used as the electrophiles, the coupling could be run at 80 °C under a low catalyst loading (0.1–1 mol%), whereas aryl bromides required a higher temperature (120 °C), a catalyst loading up to 5 mol%, and a longer reaction time. The greenness of the reaction was showcased by an effective reuse of the residual aqueous solution for both the reported couplings (Scheme 8b).⁵⁸

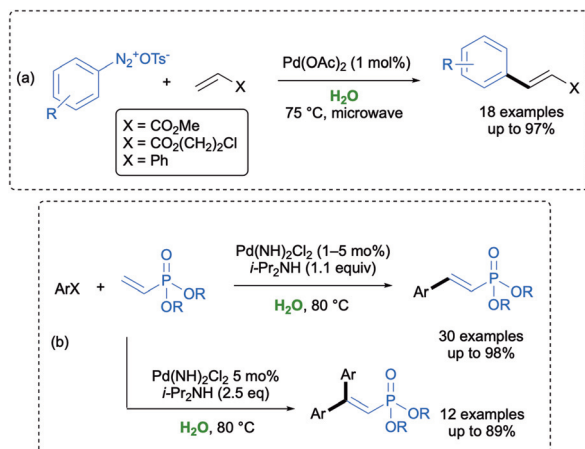
2.5 The Ullmann-type reaction

In contrast to the “classical” Ullmann reaction, which is the direct synthesis of symmetric biaryls *via* copper-catalyzed coupling at elevated temperature (>180 °C),⁵⁹ the so-called “Ullmann-type” reaction encompasses copper-catalyzed nucleophilic aromatic substitution between aryl halides and various nucleophiles.⁶⁰ Key aspects of all these reactions are the use of (a) polydentate auxiliary ligands with oxygen- or nitrogen coordination sites (e.g., diols, diamines, oximes) aimed at improving the solubility of the copper precursors and the stability of the active catalyst, and/or (b) toxic VOCs (e.g., DMSO, DMF, dioxane, THF).

Copper-catalyzed couplings in aqueous media are known, though they often require harsh conditions (high temperatures up to 100–130 °C) and the presence of phase-transfer catalysts and ligands.⁶¹ In 2011, Wei and co-workers reported the copper powder-catalyzed ligand-free amination of aryl halides with aliphatic amines under aerobic conditions in pure water



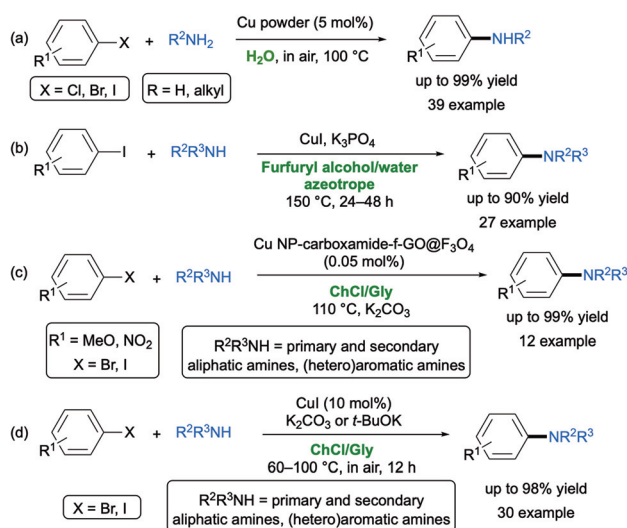
Scheme 6 Pd-Catalyzed Murahashi cross-coupling using (a) DES or (b) water as the reaction medium.



Scheme 8 Pd-Catalyzed (a) Matsumada–Heck reaction with arendiazonium tosylates, and (b) Heck–Mizoroki reaction with dialkyl vinylphosphonates in water.

at 100 °C. Under these conditions, however, although sensitive functional groups were tolerated (*e.g.* CHO, MeCO, CN), secondary amines and aniline derivatives were proven to be unreactive (Scheme 9a).⁶²

In 2018, Vaccaro and co-workers developed a waste-minimized protocol to promote the Ullmann-type copper-catalyzed coupling between aryl halides and heteroaromatic or aliphatic amines in the biomass-derived furfuryl alcohol (FA) as an effective bio-based co-solvent/bidentate ligand for Cu(I) catalyst. The reaction showed a broad substrate scope, with the corresponding adducts being isolated in generally good yields.



Scheme 9 Cu-Catalyzed Ullmann amine cross-coupling between aryl halides and amines (a) in water, (b) in bio-based solvents, (c) in DES, in the presence of Cu NP carboxamide functionalized magnetic graphene oxide as a nanocatalyst, and (d) in DES, with no additional ligands under air.

Of note, when the FA was mixed with water, it formed an azeotrope (20 wt% of FA), and thus it could be easily recovered and reused (Scheme 9b).⁶³

In 2018, Shaabani and co-workers reported the Ullmann C–N coupling of aryl halides with *N*-heterocycles or aniline derivatives in ChCl/Gly (1:2), taking place in high yields (75–99%) and short reaction times, catalyzed by a new copper nanoparticle (Cu NP) modified carboxamide-functionalized magnetic graphene oxide (carboxamide-*f*-GO@Fe₃O₄) nanocatalyst, which in turn was synthesized *via* a one-pot four component UGI reaction. The Cu NP-carboxamide-*f*-GO@Fe₃O₄ nanocomposite and DES were easily recovered and reused for five consecutive runs. The authors related the high efficiency of the *N*-arylation process to the combination of the synthesized nanocatalyst with DES whose extensive hydrogen-bonding network creates a strain inside its cavity so as to trigger the coupling process (Scheme 9c).⁶⁴

A practical and efficient protocol for performing CuI-catalyzed Ullmann amine synthesis between (hetero)aryl halides (Br, I) and a variety of aromatic or aliphatic primary and secondary amines has been then developed in the same biodegradable ChCl/Gly mixture by Capriati and co-workers. Notable features of this report are (a) a broad substrate scope starting from both electron-deficient and electron-rich (hetero) aryl halides with the tolerance of several functional groups, and with the desired adducts isolated in up to 98% yield; (b) mild conditions (60–100 °C) in air, with K₂CO₃ or *t*-BuOK (in the case of aromatic amines) as a base, and a catalyst loading of CuI up to 10 mol%; and (c) an effective recycling of the DES, the catalyst and the base over 6 cycles with an excellent performance of the copper species in the employed eutectic mixture (Scheme 9d).⁶⁵

3. Sustainable synthesis of active pharmaceutical ingredients (APIS) and biologically active compounds

Recommendations by institutions and organizations, such as The American Chemical Society's (ACS) Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) (whose aim is to catalyze the integration of green chemistry and engineering in the pharmaceutical industry), and the European Union and the United States Environmental Protection Agency (EPA), are concerned with the need to replace conventional hazardous VOCs in favour of safer and bio-based reaction media.^{2a,66} Indeed, as has been pointed out in the introduction, the appropriate selection of a solvent with a low ecological footprint in a synthetic strategy not only is important for solving global sustainability issues, but also for improving the sustainability of a chemical production process. This is because solvents are heavily used in the pharmaceutical industry as reaction media and in designing purification steps. As a consequence, a number of solvent selection guides have been produced over the years by pharmaceutical industries (*e.g.*,

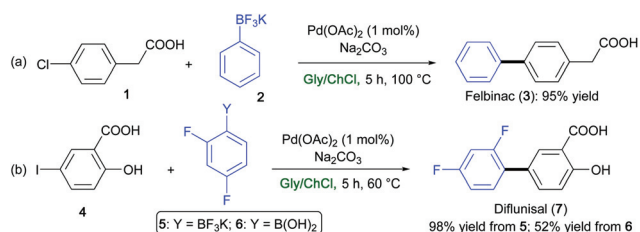
GSK,^{2d,67} Sanofi,⁶⁸ Pfizer⁶⁹), which are useful both for academia and industrial manufacture.

In the last two decades, DESs have gained a lot of momentum in the realm of APIs as nanocarriers for increasing the drug delivery and its bioavailability either by creating new formulations or by forming novel eutectic mixtures with APIs themselves.^{10g,i,70} In this context, the development of sustainable protocols for synthesizing relevant APIs directly in DESs are emerging more and more also for the unique catalytic properties displayed by these mixtures, often resulting in higher selectivities, conversions and yields, shorter reaction times than in conventional VOCs, as well as simpler work-ups and purification procedures.

In the field of transition-metal-catalyzed transformations (see section 2), Pd-catalyzed Suzuki–Miyaura coupling reactions have proven to be effective for synthesizing the analgesic, nonsteroidal, anti-inflammatory drugs Felbinac (**3**)⁷¹ and Diflunisal (**7**).⁷² These drugs were prepared in high yields (95–98%) in a ChCl/Gly eutectic mixture and in the absence of additional ligands, by reacting 2-(4-chlorophenyl)acetic acid (**1**) (Scheme 10a) or 2-hydroxy-5-iodobenzoic acid (**4**) (Scheme 10b) with potassium phenyltrifluoroborate (**2**) or potassium 2,4-difluorophenylborate (**5**), respectively. Of note, the reaction yield of Diflunisal dropped down to 52% starting from the corresponding 2,4-difluoroboronic acid (**6**).³²

Similarly, the commercially available and cheap Pd/C was found to promote a ligand-free Sonogashira coupling in ChCl/Gly in the presence of CuI (20 mol%) and Et₃N between the 6-iodouracil derivative **8** and phenylacetylene (**9**) to afford the desired alkynylated adduct **10** in 50% yield (Scheme 11).⁴² Uracil derivatives are privileged structures in drug discovery with a wide array of biological and pharmacological activities.⁷³

The nucleophilic addition of Grignard and organolithium reagents to chiral non-racemic aromatic and aliphatic *N*-tert-



Scheme 10 Synthesis of (a) Felbinac (**3**), and (b) Diflunisal (**7**) via a Pd-catalyzed Suzuki–Miyaura coupling reaction in ChCl/Gly.

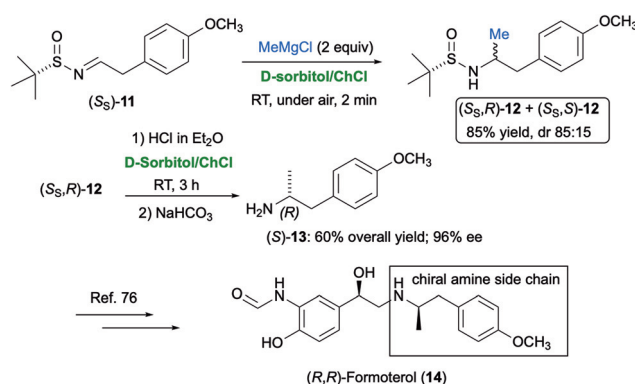


Scheme 11 Synthesis of uracil derivative **10** via a Pd-catalyzed Sonogashira cross-coupling reaction in ChCl/Gly.

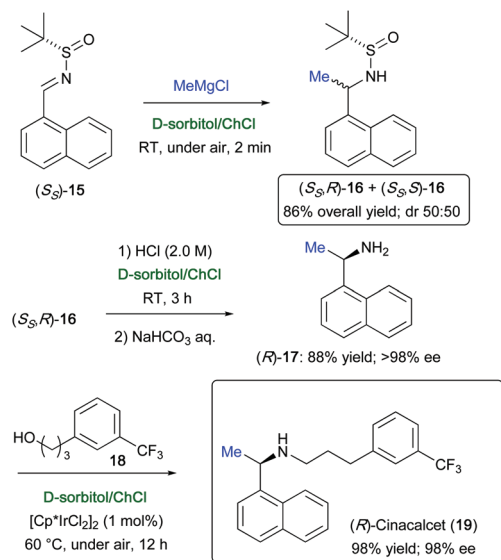
butanesulfinyl imines was found to proceed smoothly and quickly (2 min reaction time) in the biodegradable eutectic mixture *D*-sorbitol/ChCl, at ambient temperature and under air, to provide a mixture of diastereomeric sulfinamides in very good yields (74–98%) and with a broad substrate scope.⁷⁴ Scaling up the process on a gram-scale was also successful. This methodology was applied to the synthesis of the chiral amine side-chain of (*R,R*)-formoterol (**14**) (Scheme 12), which is a β_2 -agonist useful as a bronchodilator in the management of asthma and chronic obstructive pulmonary disease.⁷⁵

To this end, sulfinyl imine (*S_S*)-**11** was reacted with MeMgBr to provide a mixture of the two diastereomeric sulfinamides (*S_{S,R}*)- and (*S_{S,S}*)-**12** [85% overall yield; diastereomeric ratio (dr) = 85 : 15]. After separation by flash chromatography, the two diastereomers could be deprotected with an acid treatment in the same eutectic mixture, at ambient temperature and under air, to afford the corresponding enantioenriched free amines. Chiral, *p*-methoxyphenyl-substituted amine (*S*)-**13**, which is an important chiral intermediate en route to (*R,R*)-formoterol (**14**),⁷⁶ was isolated in 60% yield and 96% enantiomeric excess (ee) from (*S_{S,R}*)-**12** (Scheme 12).⁷⁴

The enantiopure (*R*)-cinacalcet (**19**) (98% ee), which is a blockbuster drug used as calcimimetic to treat secondary hyperparathyroidism,⁷⁷ was prepared in only three steps in *D*-sorbitol/ChCl. First, the enantiopure amine (*R*)-1-(1-naphthyl)ethylamine (**17**) was synthesized by reacting MeMgBr with sulfinyl imine (*S_S*)-**15**, which furnished a mixture of the two diastereomeric sulfinamides (*S_{S,R}*)- and (*S_{S,S}*)-**16** [86% overall yield; dr = 50 : 50], with the auxiliary group being removed by acidifying the eutectic mixture with a solution of HCl (2.0 M). Then, the amine (*R*)-**17**, obtained from (*S_{S,R}*)-**16**, was straightforwardly *N*-alkylated with alcohol **18** in the presence of the iridium catalyst [Cp*IrCl]₂ (1 mol%) to furnish the target drug (*R*)-**19** in 98% yield and 98% ee, after 12 h reaction time at 60 °C working under aerobic conditions (Scheme 13). By performing the above alkylation in toluene at 100 °C for 17 h, in a sealed reactor and under argon, (*R*)-**19** was isolated in an overall yield of only 50%.⁷⁸ Amine alkylation with alco-



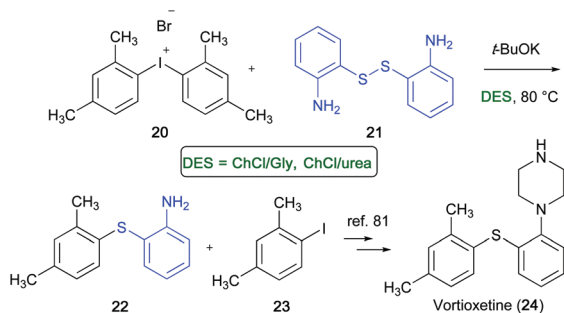
Scheme 12 Synthesis of the chiral amine side-chain of (*R,R*)-formoterol (**14**) via nucleophilic addition of MeMgCl to sulfinyl imine (*S_S*)-**11** in *D*-sorbitol/ChCl.



Scheme 13 Asymmetric synthesis of (*R*)-cinacalcet (**19**) in a *D*-sorbitol/ChCl eutectic mixture.

hols has also been achieved with good results by Williams and co-workers using 1 mol% $[\text{Cp}^*\text{IrI}_2]_2$ in water, in the absence of base or other additives.⁷⁹

Vortioxetine (**24**) is a multi-modal acting drug with high affinity towards a range of serotonergic targets, and is now on the market for the treatment of major depressive disorder.⁸⁰ A transition-metal-free synthesis of thioether **22**, which is an important precursor of Vortioxetine,⁸¹ has been developed by Gallos and co-workers in ChCl-based eutectic mixtures, like ChCl/Gly or ChCl/urea.⁸² The reaction occurred between bis(2,4-dimethyl)iodonium bromide (**20**) (easily accessible from *m*-xylene) and the commercially available 2-aminothiophenol disulfide (**21**) using *t*-BuOK as a base, which was added under stirring at 40–45 °C to the aforementioned mixture in DES in a sealed tube. After 3 h at 80 °C, thioether **22** was isolated in 85–88% yield. The iodoxylenes **23**, formed as a by-product, could be recycled to **20**. The synthesis is also applicable in multi-gram scale (Scheme 14).

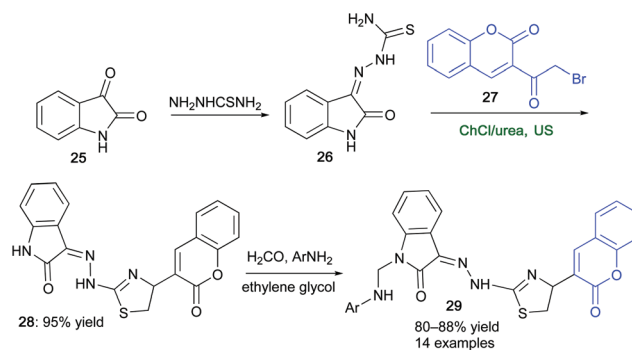


Scheme 14 Synthesis of unsymmetrical thioether **22** en route to Vortioxetine (**24**).

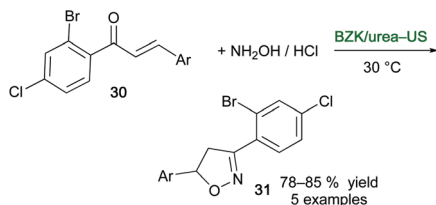
Indole ring and its derivatives have emerged as privileged pharmacophores in thousands of compounds exhibiting a plethora of biological and pharmaceutical activities (*e.g.*, anti-inflammatory, analgesic, antimicrobial, antitumor, and anti-convulsant).⁸³ An improved synthesis of a key thiazole-indole intermediate (**28**) en route to selected indolin-2-one derivatives **29**, has been set up by synergistically combining the action of a ChCl/urea eutectic mixture with ultrasound (US).⁸⁴ By reacting 3-bromoacetyl coumarin (**27**) with hydrazine thioamide (**26**), in turn prepared from isatin (**25**), under the aforementioned conditions, compound **28** was isolated in a yield as high as 95% after only 1 h (Scheme 15). On the other hand, by performing the same organic transformation in conventional VOCs (*e.g.* dioxane), adduct **28** was isolated in 44–68% yield after 3–4 h.⁸⁴ It was envisaged that the extended network of hydrogen bonds typical of DES may be playing a key role in catalyzing the transformation. This was supported by DFT calculations at the B3LYP/6-31+G(d,p) level of theory. The synthesized indolin-2-one derivatives **29** showed good anti-inflammatory and/or analgesic activity as compared to the standard drugs.

Isoxazoline derivatives are biologically important scaffolds with antibacterial, analgesics, anti-inflammatory, antitubercular, and anticancer activity.⁸⁵ With the aim of synthesizing selected derivatives in an eco-friendly manner, novel DESs formed by mixing benzalkonium chloride (BZK) and urea in different molar ratios were prepared and physically and spectroscopically characterized by Bakht and co-workers.⁸⁶ By reacting chalcone derivatives **30** with hydroxylamine hydrochloride, it was found that the best performance in the synthesis of isoxazoline derivatives **31**, in terms of reaction time (up to 60 min), yield (up to 85%) and energy utilization (up to 88% energy saved), were achieved using the combination BZK:urea (1:2)-US. By applying the nonultrasonic thermal method, lower yields of **31** were obtained (up to 71%) with longer reaction times ranging from 15 to 4–5 h if conventional VOCs or the above DES are used, respectively (Scheme 16).

Fused pyrazolopyranopyrimidines are interesting compounds displaying a wide spectrum of biological and pharmacological activities.⁸⁷ A multicomponent domino reaction,



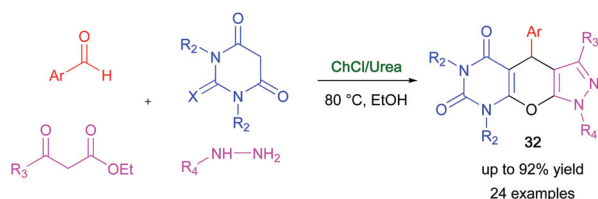
Scheme 15 Synthesis of a key thiazole-indole derivative (**28**) by combining ChCl/urea and US towards indolin-2-ones **29**.



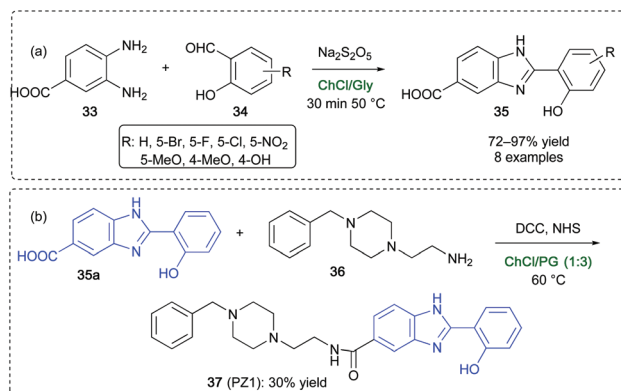
Scheme 16 Synthesis of isooxazolines **31** from chalcone derivatives **30** using a combination of benzalkonium chloride (BZK)/urea and US.

aimed at obtaining biologically active tricyclic-fused pyrazolo-pyranopyrimidines, has been devised by Bhosle and co-worker using DESs as environmentally benign reaction media with the dual role of solvents and catalysts.⁸⁸ After extensive screening, it was found that the cyclocondensation of various aromatic aldehydes, barbituric acid, hydrazine hydrate, and ethyl acetate took place smoothly in a ChCl/urea (1 : 2) eutectic mixture, in the presence of EtOH, to provide valuable pyrazolo-pyranopyrimidine derivatives **32** with a broad substrate scope and very good yields (75–92%) within 1 h at 80 °C (Scheme 17).⁸⁸ Lower yields (21–34%) were instead obtained after heating the reaction mixture at 80 °C for several hours using VOCs as reaction media. The feasibility of recycling the above eutectic mixture was evaluated, and a plausible reaction mechanism for the DES-catalyzed domino reaction was also proposed.

Benzimidazole-based structures are found in many drugs and drug-like candidates⁸⁹ (like the antihypertensive Telmisartan and the antiviral compound Maribavir), in anti-ulcer agents (like the blockbuster drug Omeprazole),⁹⁰ and in several β -secretase inhibitors and Alzheimer's disease targets.⁹¹ An efficient cyclodehydration reactions for the synthesis of 2-hydroxybenzimidazoles **35** has been developed by Capriati and coworkers by reacting 3,4-diaminobenzoic acid **33** with a variety of salicylaldehyde derivatives **34** in ChCl/Gly (1 : 2) using $\text{Na}_2\text{S}_2\text{O}_5$ as the oxidant.⁹² Compared to VOCs, the synthesis of **35** in the above DES occurs in better yields (up to 97%), and has the advantage of shorter reaction time (30 min vs. 12 h) and milder reaction conditions (50 vs. 100 °C) (Scheme 18a). In addition, the whole synthesis of the Donepezil-like, hit compound PZ1 (**37**), which is known to be a new promising multi-target directed compound in Alzheimer's disease treatment,⁹³ has been performed and optimized in DESs taking advantage of shorter reaction time in each single



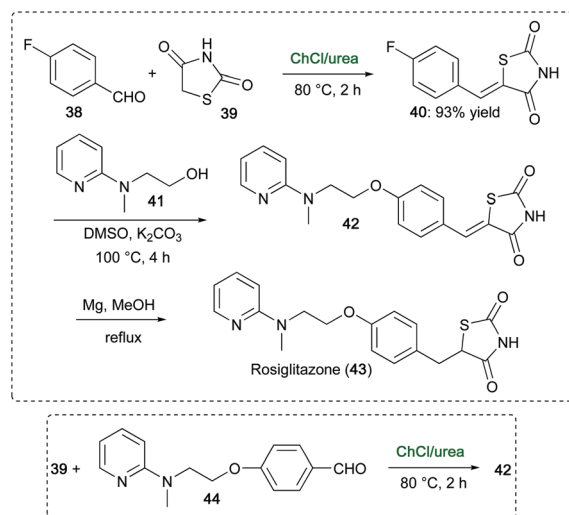
Scheme 17 Synthesis of fused pyrazolo-pyranopyrimidines **32** in ChCl/urea.



Scheme 18 Synthesis of (a) 2-hydroxyphenyl benzimidazole derivatives **35** and (b) Donepezil-like compound PZ1 **37** in DES.

step and/or the avoidance of harsh conditions and toxic and harmful reagents/VOCs.⁹² The one-pot two-step synthesis of PZ1 has also been achieved in a ChCl/propylene glycol (PG) (1 : 3) by reacting the *N*-benzylated adduct **36** with 2-hydroxyphenylbenzimidazole derivative **35a** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS), with an overall yield of 30% at 60 °C after 60 h reaction time, compared to the 21% yield obtained when working in DMF at 25 °C for 60 h (Scheme 18b).

An attractive, scalable route for the synthesis of rosiglitazone (**43**), a drug used to treat type 2 diabetes mellitus,⁹⁴ has been developed by Mane and co-workers avoiding toxic/hazardous chemicals/solvents reported for other routes.⁹⁵ This multistep route made use of ChCl/urea in a key step to promote the Knoevenagel condensation of 4-fluorobenzaldehyde (**38**) with 2,4-thiazolidinedione (**39**), which furnished **40** in 93% yield within 2 h at 80 °C (Scheme 19). Compound **40** was then condensed with pyridinylamino alcohol **41** to give adduct **42**,



Scheme 19 Sustainable and improved synthesis of rosiglitazone drug using ChCl/urea in the synthesis of key intermediates **40** and **42**.

which on reduction with Mg-MeOH gave rosiglitazone (43). Intermediate 42 could also be synthesized in $\text{CHCl}_3/\text{urea}$, within 2 h at 80 °C, *via* condensation of 39 with pyridinyl-amino benzaldehyde 44, thereby avoiding the use of toluene and piperidine, which are recommended in similar condensation reactions reported by Cantello and co-workers (Scheme 19).⁹⁴

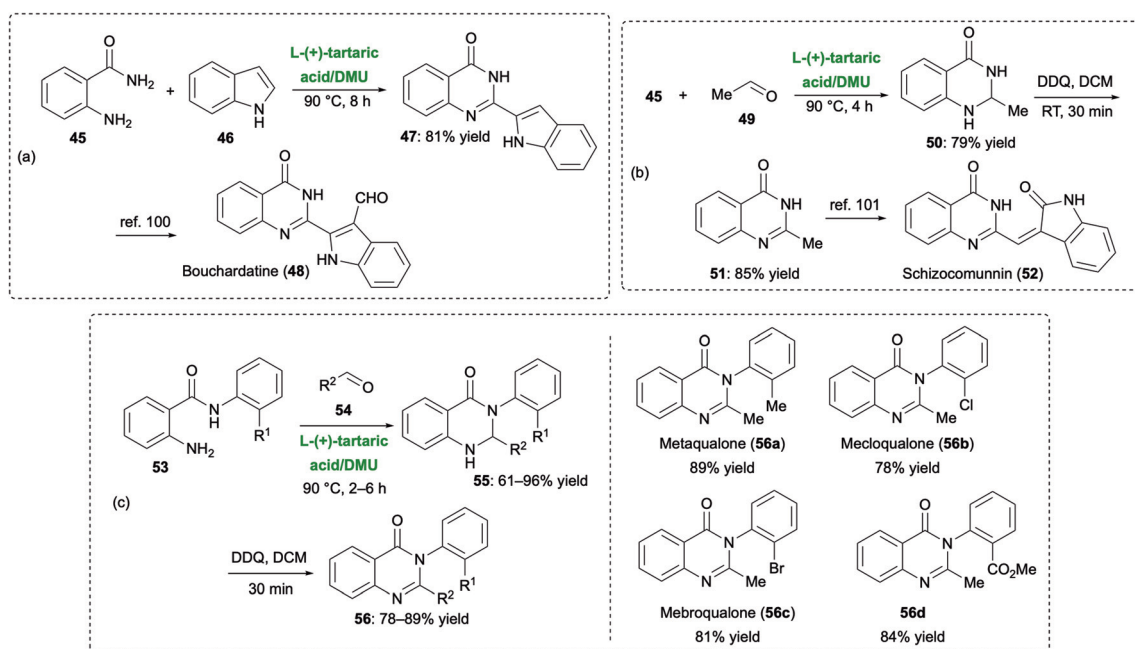
Quinazolinones are key heterocyclic cores in many naturally occurring alkaloids and marketed drugs [*e.g.*, methaqualone (quaalude), mebroqualone, mecloqualone (Casfen)] with sedative, hypnotic and anxiolytic properties.⁹⁶ Nagarajan and Ghosh have recently reported on a DES-mediated synthesis of two important natural alkaloids like bouchardatine and schizocommunin,⁹⁷ the former known to have biological properties as anti-cancer, anti-inflammatory and anti-tubercular activities,⁹⁸ the latter showing a cytotoxic activity against murine lymphoma cells and human hepatoma cells, and also knowing to be a potent activator of the aryl hydrocarbon receptor.⁹⁹

The quinazolinone skeleton of bouchardatine (48) was obtained by preliminarily reacting anthranilamide (45) with indole-2-carboxaldehyde (46) in a 1-(+)-tartaric acid-DMU (3 : 7) melt at 90 °C for 8 h to give the quinazolinone intermediate 47 in 81% yield, which was finally formylated at indole C3 position to provide 48, according to a procedure previously reported by the same research group (Scheme 20a).¹⁰⁰ Schizocommunin (52), in turn, was prepared by first treating 45 with acetaldehyde (49) in the above green melt at 90 °C for 2 h to give dihydroquinazolinone 50 in 79% yield. Next, 50 was aromatized with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to furnish quinazolinone 51 in 85% yield. Target drug

52 was finally obtained in one-step from 51, following Nishida's procedure (Scheme 20b).¹⁰¹ In a similar way, drugs like methaqualone (56a), mecloqualone (56b), mebroqualone (56c), and the alkaloid methyl 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) benzoate 56d, all featuring the 2,3-disubstituted quinazolinone skeleton (56), could be prepared in good overall yields (78–89%) by reacting in the aforementioned low melting mixture at 90 °C for 2–6 h the selected 2-amino-*N*-(substituted) benzamide 53 with the appropriate aldehyde 54, followed by aromatization with DDQ of the corresponding dihydroquinazolinones 55 (Scheme 20c).⁹⁷

4. Biocatalyzed transformations in aqueous DES mixtures

Biocatalytic reactions carried out in DESs as unconventional reaction media have experienced an accelerated development over the last years as testified by the impressive number of papers published dealing with either biocatalysis promoted by whole-cell microorganisms¹⁰² or by isolated enzymes (*e.g.*, alcohol-dehydrogenases,^{14c,103} lyases,¹⁰⁴ lipases,¹⁰⁵ laccases,¹⁰⁶ hydrolases,¹⁰⁷ decarboxylases,¹⁰⁸ *etc.*).¹⁰⁹ In this section, some important points and updates related to whole-cell biocatalysis in DESs over that run in an aqueous environment will be discussed, paying particular attention (a) to the green aspects and cost-benefits resulting from this catalysis as compared to that of isolated enzymes, and (b) to the biocatalyst performance when using environmentally responsible DES media¹¹⁰ due to higher substrate loadings¹¹¹ and stability,¹¹² and an improved (or opposite) selectivity displayed by the biocatalyst itself.¹¹³



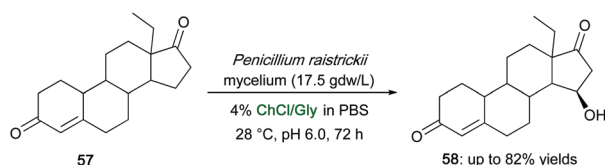
Scheme 20 Synthesis of (a and b) 2-substituted quinazolinone alkaloids bouchardatine (48) and schizocommunin (52), and (c) 2,3-disubstituted quinazolinones (56) (drugs and natural products).

The behaviour of lipases and oxidoreductases in DESs and in DES/aqueous mixtures has been thoroughly investigated,^{105,114} also with the support of molecular dynamics simulations, that have revealed the importance of the role of “water content” in these systems,^{103,115} thereby confirming that water layer is necessary for achieving an efficient conformational flexibility of the biocatalyst, which is the key to maintain its catalytic activity.¹¹⁶

Water addition to DES mixtures allows a lower viscosity of the medium, while preserving the supramolecular network of DES with percentage up to 42 wt% water,^{8a,9} with the resulting biotransformations often displaying an increased productivity yield in comparison with water or buffer as the sole reaction medium. Solvent choice in organic reactions is also known to influence green chemistry metrics, which are used to evaluate the real sustainability of biocatalytic processes. These include, among others, productivity (g product per L reactor per h), the *E*-factor (kg waste per kg product), water intensity (g water used per g product), and solvent intensity (g solvent used per g product).

The ideal medium of enzymes and cells is water, but in many synthetic processes it has been seen that organic reagents and catalysts are much more prone to non-polar or even anhydrous solvents.^{111a} Compared to bio-transformations mediated by isolated enzymes, whole cell biocatalytic processes have major advantages such as low costs, an easier catalyst preparation, intracellular enzymes stability in their natural environment, and an accessible cofactors regeneration *in situ*.

Biocatalyzed synthesis of steroids, which are worldwide used in clinical therapy as endocrine regulators, allow higher stereo- and regioselectivity and efficiency when compared to other synthetic approaches. Different DESs have been screened to overcome the problem of the poor solubility of steroids in aqueous solutions. The addition of 6% (v/v) of ChCl/urea (1 : 2) boosted the dehydrogenation of cortisone acetate into prednisone acetate by *Arthrobacter simplex*,¹¹⁷ whereas the mixture ChCl/Gly (1 : 2) was found to improve the 15 α -hydroxylation of Δ -ethylgonendione (57) to the corresponding 15 α -hydroxy- Δ -ethylgonendione (58), mediated by *Penicillium raistrickii*. This is a key biotransformation in the industrial synthesis of Gestodene steroids (Scheme 21).¹¹⁸ In the absence of DESs, 58 was isolated in 33% yield only, after 72 h incubation of *Penicillium raistrickii* mycelium with 57 (2 g L⁻¹). On the other hand, the suspension of this microorganism in a solution containing 4% (v/v) ChCl/Gly (1 : 2) improved the conversion up to



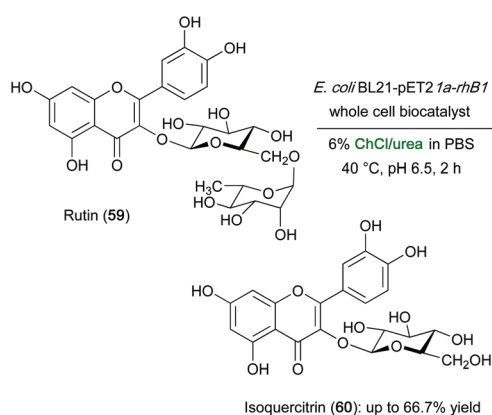
Scheme 21 Biotransformation of Δ -ethylgonendione (57) to 15 α -hydroxy- Δ -ethylgonendione (58), mediated by *Penicillium raistrickii* in ChCl/Gly.

82% thanks to a beneficial effect of DES on the substrate solubility, and the mass transfer within mycelium cells.

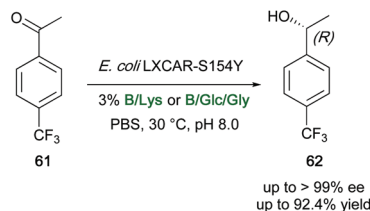
DESs have been recently employed also in the flavonoids synthesis, which is an important process in the production of APIs, flavors and fragrances. The production of L-rhamnose and isoquercitrin from the enzymatic hydrolysis of rutin by recombinant *Aspergillus niger* α -L-rhamnosidase glycosyl hydrolase was recently reported in a buffer mixture with ChCl-urea. The latter mixture, which was selected as the best co-solvent among other 24 different DESs tested, was found to increase by 1.12 times the synthesis of both L-rhamnose and isoquercitrin from rutin. ChCl/urea was also proven to be an efficient extractive solvent for L-rhamnose and isoquercitrin, which were isolated in 96% and 94% purity, respectively, by an aqueous two-phase systems technology.¹¹⁹

The aforementioned biotransformation of rutin (59) into isoquercitrin (60) was also investigated using whole cells in various eutectic mixtures, which were added to the aqueous medium containing *E. coli* cells expressing α -L-rhamnosidase. While the observed catalytic activity in ChCl/Gly (1 : 2), ChCl/EG (1 : 2) and ChCl/acetamide (1 : 2) resulted only slightly higher compared to the PBS control (52.9%), the yield of isoquercitrin increased to up to 66.7% when using ChCl/urea (Scheme 22). The latter mixture was also found to increase the cell permeability of the *E. coli* BL21-pET21a-rhaB1 whole-cell biocatalyst by increasing the contact between the enzyme and the substrate, thereby improving the catalytic performance in the isoquercitrin production.¹²⁰

Similarly, four DESs and 13 NADESs have been screened in the bioreduction of 4-(trifluoromethyl)acetophenone (61) to (*R*)-1-[4-(trifluoromethyl)phenyl]ethanol (62) promoted by the recombinant *E. coli* LXCAR-S154Y and *Geotrichum* ZJPH1810 biocatalysts (Scheme 23).¹²¹ Compound 62 is a key intermediate in the preparation of several pharmaceuticals, including the chemokine CCR5 antagonist, which is widely used for the treatment of AIDS, the DP1 receptor antagonist, and the anti-fungal econazole.¹²¹ The desired secondary alcohol was isolated in high yields (up to 92.4%) and enantioselectivity (up to



Scheme 22 Enzymatic hydrolysis of rutin (59) to isoquercitrin (60) using recombinant *E. coli* whole cells in aqueous DESs.

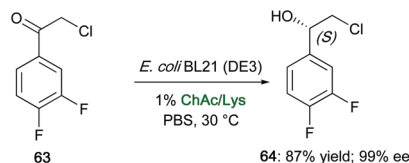


Scheme 23 Bioreduction of acetophenone derivative **61** to the secondary alcohol **62** by recombinant *E. coli* cells in various aqueous eutectic mixtures.

>99%), also on a preparative scale. The best results were obtained when betaine (B), L-proline (Pro) and L-carnitine were used as HBAs in place of ChCl, with an improved catalytic efficiency due to the preservation of cell membrane integrity by the above DES components and an effective coenzyme regeneration. In addition, lysine (Lys)-based NADES were found to reverse the enantioselectivity of the bioreduction when the reaction was carried out with high water content in the reaction medium. With the B/Lys (1:2) mixture, yields improved up to 88.1% in the presence of 400 mM of substrate, whereas the product was isolated in 85.2% yields when using the B:glucose (Glc):Gly (1:1:2) mixture. A lower yield (77%) was observed when the biotransformation was carried out in an aqueous buffer system, with the same 400 mM substrate concentration.¹²¹

Various NADESs have also been screened in the bioreduction of 2-chloro-1-(3,4-difluorophenyl)ethanone (**63**) to (*S*)-2-chloro-1-(3,4-difluorophenyl)ethanol (**64**), which is a key chiral synthon for the synthesis of P2Y₁₂ receptor antagonist Ticagrelor (Brilinta[®]), by the recombinant *E. coli* BL21 (DE3), expressing a carbonyl reductase from *Leifsonia xyli* HS0904.¹²² Mixtures of ChCl salts and amino acids [e.g., ChCl/glycine (Gly), ChCl/glutathione (GSH), ChCl/Glc, ChCl/alanine (Ala), choline acetate (ChAc)/GSH, ChAc/glutamic acid (Glu)] were found to affect strongly the pH of the medium when amounts up to 1% w/v were added to cells suspension with respect to buffer solution, in many cases with a decreased reaction yield, probably due to a change of the binding of carbonyl reductase to the substrate. Conversely, *E. coli* BL21 (DE3) efficiently allowed the asymmetric production (also on a preparative scale) of (*S*)-**64** after incubating cells in a reaction medium containing ChAc/Lys, the substrate loading being 3.3-fold higher than in a pure aqueous mixture. The enantiopure chloridrin was isolated in a yield (87%) higher than that obtained when the biotransformation was run in a buffer solution (68%), and with an enantioselectivity up to 99% ee (Scheme 24). It was also demonstrated that the eutectic mixture ChAc/Lys improved NADH coenzyme regeneration of 1.4–2.0-fold, compared to that resulting by the addition of the single components of the eutectic mixture at the same molar ratio.

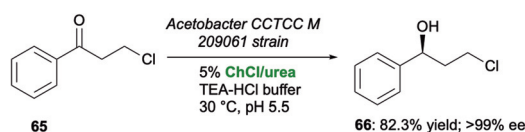
Similar results have been reported by Lou and co-workers,¹²³ who investigated the bioreduction of 3-chloropropiophenone (**65**) to (*S*)-3-chloro-1-phenylpropanol (**66**) by means of immobilized whole cells of *Acetobacter* CCTCC M



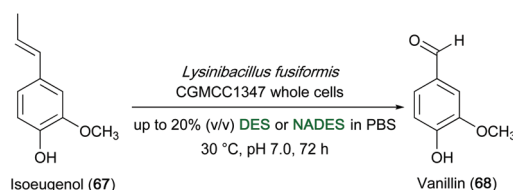
Scheme 24 Bioreduction of α -chloro ketone **63** to the chloridrin **64** by the recombinant *E. coli* BL21 (DE3) whole cells in the presence of ChAc/Lys as a co-solvent.

209061 in the presence of different DESs as co-solvents. The results collected showed that while acidic HBDs strongly inactivated the carbonyl reductase of *Acetobacter*, secondary alcohol **66** was produced in the highest yield of 82.3% (>99% ee) in the presence of 5% v/v of ChCl/urea, with an increased ketone concentration up to 3-fold with respect to buffer control (Scheme 25).

The impact of 24 DESs and 21 NADESs as co-solvents (up to 20% v/v) was examined in the biotransformation of isoeugenol (**67**) to vanillin (**68**) catalyzed by *Lysinibacillus fusiformis* CGMCC1347 whole cells (Scheme 26).¹²⁴ Both types of solvents improved the production yields up to 142% and 132% compared to the ones obtained in (NA)DES-free aqueous systems (Scheme 26). The reaction yields, in particular, were found to depend on the nature of the HBD component of the NADES. The order of efficiency was organic acids < alcohols < sugars, since HBDs affected the pH of the reaction medium. The results showed that a pH = 7.0 was the optimal for the bioconversion of isoeugenol into vanillin. Cell immobilization in polyvinyl alcohol-alginate beads increased even more the production yield than in pure water (up to 181%), with the catalytic activity still maintained for at least 13 cycles. NADESs used as cosolvents also increased both the solubility of isoeugenol up to 1.9–2.7 fold and the production yield with respect



Scheme 25 Bioreduction of β -chloroketone **65** to β -chloroalcohol **66** by immobilized whole cells of *Acetobacter* CCTCC M 209061 in the presence of ChCl/urea as a co-solvent.



Scheme 26 Bioconversion of isoeugenol (**67**) to vanillin (**68**) catalyzed by *Lysinibacillus fusiformis* CGMCC1347 whole cells in DES or NADES mixtures.

to the same transformation run in aqueous systems, thanks to an improved permeability of the cell membrane, resulting by the combination of a surfactant action without decreasing the cell viability.

The exploitation of the biocatalysis in NADES by the *Candida tropicalis* 104 whole cells was investigated in the asymmetric synthesis of (*S*)-1-[3,5-bis(trifluoromethyl)phenyl] ethanol (**70**), which is a key intermediate towards pharmaceutical lipid-lowering agents,¹²⁵ from the corresponding carbonyl compound **69** (Scheme 27). The reaction yield increased from 74% to 86% when such a bioreduction was carried out in the presence of 1% w/v of ChCl:trehalose (Tre) (1 : 1) mixture, with respect to the sole PBS buffer medium. ChCl:Tre, like other DES mixtures, enhanced the cell viability and the cell membrane permeability to the substrate, while exerting a protective effect against ketone cytotoxicity. This allowed an higher substrate charge up to 200–300 mM, with a consequent 6-fold increase of the substrate-to-catalyst ratio of the process with respect to that performed in water alone.¹²⁶

Chemo-enzymatic multi-step processes represent a new challenge in the “green chemistry” approach, since they require the use of chemical and biological catalysts together. Biphasic systems are, in general, the way to carry out such processes,¹²⁷ using batch conditions and discontinuous systems, although non-continuous processes represent a limitation for semi-preparative or large-scale syntheses.¹²⁸ Since the first pioneering works of Domínguez de María and co-workers on the tandem combination of proline-based organocatalytic and lipase transesterification reactions in DES mixtures,¹²⁹ other research groups have reported on the successful combination of various DES/water monophasic systems for organo-, bio-, and metal-catalyzed transformations. Several sustainable bioreductions promoted by isolated enzymes jointly with metal-catalyzed reactions have been carried out in eutectic mixtures and/or water to obtain enantioenriched chiral products by means of well-projected chemo-enzymatic sequences in which the compatibility of each catalyst with previous catalysts/reagents has been carefully evaluated.^{14b,d,19d,130}

On the other hand, the use of whole-cell biocatalysts within multistep cascade processes is still in its infancy. To date, there are only a few examples in which the addition of bio-sourced eutectic mixtures to the reaction medium was proven to increase the biocatalytic efficiency of a whole-cell-mediated process, without other complicated strategies.¹³¹ A low efficiency was often observed especially when heating or monophasic media were required, either because of the

incompatibility/toxicity of metal- or chemical catalysts for the cells viability or because of the metal catalyst inactivation/chelation/leaking in the presence of proteins or metabolites.¹³² Thus, major efforts need to be made towards this direction, in order to benefit of the advantages of whole cells also in chemo-enzymatic processes.¹³³

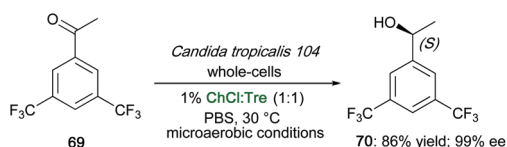
5. Conclusions

The main purpose of this short review has been to give the reader an overview on the feasibility of performing sustainable metal- and biocatalyzed reactions as well as the synthesis of relevant APIs and other biologically active compounds when using water or DESs as privileged reaction media. All through this review, we have tried to trace a comparison between the different solvent performances, which sometimes are similar, other times are different. Although water and DESs share several physicochemical properties (see Introduction), the solubility of substrates/catalysts is not always the same in these solvents. Thus, the fact of working under homogeneous/heterogeneous conditions should be, each time, carefully evaluated in order to provide a rationalization of the observed results, and to get an understanding of the mechanisms thereof.

Major breakthroughs are expected to come (a) by the use of cheap earth-crust abundant metals in place of noble and expensive metals as catalysts in cross-coupling reactions performed directly in DES mixtures or water, at ambient temperature and in air, and (b) by scaling up DES/water-based processes, which are traditionally carried out in batch reactors, operating under a continuous flow regime. This is important to boost a sustainable industrial production of pharmaceutically relevant drugs. As for this last point, recent papers highlighting the possibility of (a) achieving an efficient continuous synthesis of DESs,¹³⁴ or (b) combining DESs with the micro-flow technology,^{15b,135} are truly inspiring and encouraging towards this goal.

Thanks to the biotechnological progresses over the last decades, a number of recombinant biocatalysts expressing the enzymes necessary for the desired transformations have been engineered, with reduction of side reactions. The benefits arising from this technology could be hopefully expanded in DES media, with potential amazing outcomes. Medium engineering¹³⁶ and recombinant biocatalysts engineering will certainly allow in the next future more improvements in multistep chemo-enzymatic stereoselective processes with whole cells, through a rationale project of high-tolerant and more efficient whole-cell catalysts, even immobilized on natural supports. If successful, this will reduce the number of reaction steps, thereby avoiding the use of additional VOCs for the purification or extraction of products and intermediates, and will certainly contribute to solve the problem of the environmental impact of many synthetic processes.

We hope that this review can contribute to further raise the interest of researchers and practitioners turning their attention



Scheme 27 Bioreduction of acetophenone derivative **69** to the corresponding secondary alcohol **70** by *Candida tropicalis* 104 whole cells in the presence of ChCl/Tre as a co-solvent.

on the possibility (and the advantages) of building a truly sustainable chemistry for the studied transformations based on water or bio-based solvents.

Author contributions

All authors contributed to all aspects of manuscript preparation, revision and editing.

Conflicts of interest

There are no conflicts to declare.

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