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Deep eutectic solvents: cutting-edge applications in cross-coupling reactions

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Abstract:

Deep eutectic solvents (DESs), surmised as "the organic reaction medium of the century", have reverberated a new symphony throughout the present green millennium. A brief historical account of the DESs systems, their physicochemical properties as task-specific and designer solvents for cross-coupling reactions, are appraised including the hole theory that explains the underlying mechanistic pathway for this emerging neoteric medium. The insights in to cross-coupling reactions and their applications are encapsulated highlighting the significant achievements pertaining to the dual role of DESs as solvent and catalyst; popular "name-reactions" for carbon-carbon and carbon-heteroatom bond formations relating to the nature of DESs and the core optimum conditions are included. The review also encompasses the novel approaches to privilege catalytic systems and identifying the voids left in cross-coupling reactions where DESs systems have not made inroads yet. Finally, the challenges of utilizing the neoteric derivatives of DES for these reactions is expounded.

Keywords: Deep eutectic solvents, Cross-coupling reactions, Transition metals, Carbon–carbon bond formation, Green solvents

1   Introduction

Human in 21st century has eventually come to realize that the dynamic, uncontaminated and orderly planet, a gift to mankind from Mother Nature, has been endangered to the fringe of annihilation with extravagance in developing unsustainable industries, pollutant production, and unrestrained generation of the greenhouse gases. Consequently, confronting these life/death scenarios of economic issues is a global public health emergency to salvage a pollution-free planet for the next generations. Encouragingly, more governments, industries, and citizens are searching for enhanced sustainable materials management systems, greater resource efficiency, less environmentally damaging chemistry, cleaner technologies, and more circular economies, as integral part of a comprehensive transformation towards a sustainable economy for tackling serious pollution problems. Furthermore, new chemical alternatives that contribute to the reduction of pollutant emissions are constantly being developed. In this context, intensifying efforts are continuously being made to replace harmful, carcinogenic, and fossil fuel-based solvents with an eco-friendly, recyclable and safer neoteric reaction mediums, as they are the largest contributors to the waste stream (over 80%).[1–3] Not surprisingly, multifarious approaches have been explored including the emergent utilization of ionic liquids (ILs),[4,5] polyethylene glycol (PEG),[6,7] supercritical carbon dioxide,[8] water,[9] solvent-free conditions[10] and alternative energy inputs systems, such as mechanochemical ball-mill operation,[11] ultrasound[12,13] and microwave,[14,15] and combination thereof,[6,16,17] as sustainable cutting-edge technologies.[18–20] In the interim, deep eutectic solvents (DESs) resounded a new masterwork during the contemporary green millennium.

1.1   Deep eutectic solvents (DESs): an overview and applications

An emerging trend has been the concept of "eutecticity", derived from Greek word for 'low melting'.[21] Eutectic system can be defined as the combination of two or more components in a specific molar ratio that instigate the decrease of the melting point to the lowest point in the whole phase diagram, even lower than the melting point of either of the constituents. One noteworthy and tangible example is "honey" which is a highly viscous eutectic mixture comprising fructose, glucose and sucrose. Undoubtedly, eutectic mixtures are the missing pieces in Nature's puzzle that significantly caught the attention of scientists in view of widespread possible applications.[22] DESs are a modern generation of eutectic solvents that have started a new and exciting journey in the realms of the environmentally-benign medium.[23] Historically, the applications of eutectic solvents in catalysis ensued by the utilization of $NaNH_2$-KNH_2 (1:1), the first observed eutectic mixture,[24] for the synthesis of alkylaminopyridine/quinolines in 1946.[25] Nevertheless, it took half a century until the eutectic mediums were used as organic solvents for enzymatic reactions.[26] Eventually, the concept of DES, as a green alternative for IL, was introduced by Abbott and co-workers in 2004[27] with the deployment of $ChCl$:$ZnCl_2$ acidic solvent in several reactions, including Diels-Alder cycloadditions,

Fischer indole annulations and polymerization reactions.[28,29] From then on, extensive and valuable reports have been published, highlighting the beneficial impact of DESs in organic reactions[30] and biotransformations.[31] The advent of DES has signified a profound influence on scientific development, not only for being a new greener and recyclable medium but also for their ever-burgeoning applications in the fields of extraction,[32] gas separation,[33] analytical chemistry,[34] renewable energy storage,[35] biomass valorization,[36] drug discovery and carriers,[37] as well as in biotechnology and bioengineering.[38]

The most widely deployed DESs are prepared by mixing a hydrogen bond acceptor (HBA), exemplified by an inexpensive quaternary ammonium salts such as choline chloride (ChCl, included in the so-called vitamin B_4) produced on a scale of millions of tons per year, with a hydrogen bond donor (HBD) such as sugars, organic and amino acids, urea (most of them are from renewable resources) or glycerol (a waste product from biodiesel production) (Fig. 1). DESs containing ionic species are spatially and temporally heterogeneous while those consisting of uncharged components are homogenous.[39] Notably, three procedures are recognized for the synthesis of DESs namely, simply mixing and heating,[40] grinding[41] and freeze-drying,[42] all of them being 100% atom economic that precludes further purification.

Notably, DESs integrate the outstanding physicochemical features of ILs with the superiority of biodegradable and non-toxic starting materials. Some drawbacks of ILs such as complicated synthesis procedure, difficult high purity, sensitivity to air and moisture, exothermic quaternization reaction which need temperature-controlled could be circumvented in DES mediums.[43] For instance, the melting points of the DESs are lower than the melting points of the ILs while the temperature stability of the eutectic mixtures is relatively lower compared to the ILs.[44] Also, DESs consists of compounds that they are relatively cheaper than ILs components. Additionally, solvation strength is among the most appreciated traits of DESs as it allows solvation of various solutes in high concentrations much more than their solubility in water.[45] On the other hand, compared to the conventional solvents, DESs are recognized as nonflammable, thermally stable, biodegradable, highly soluble, relatively less toxic, and non-volatile.[46]
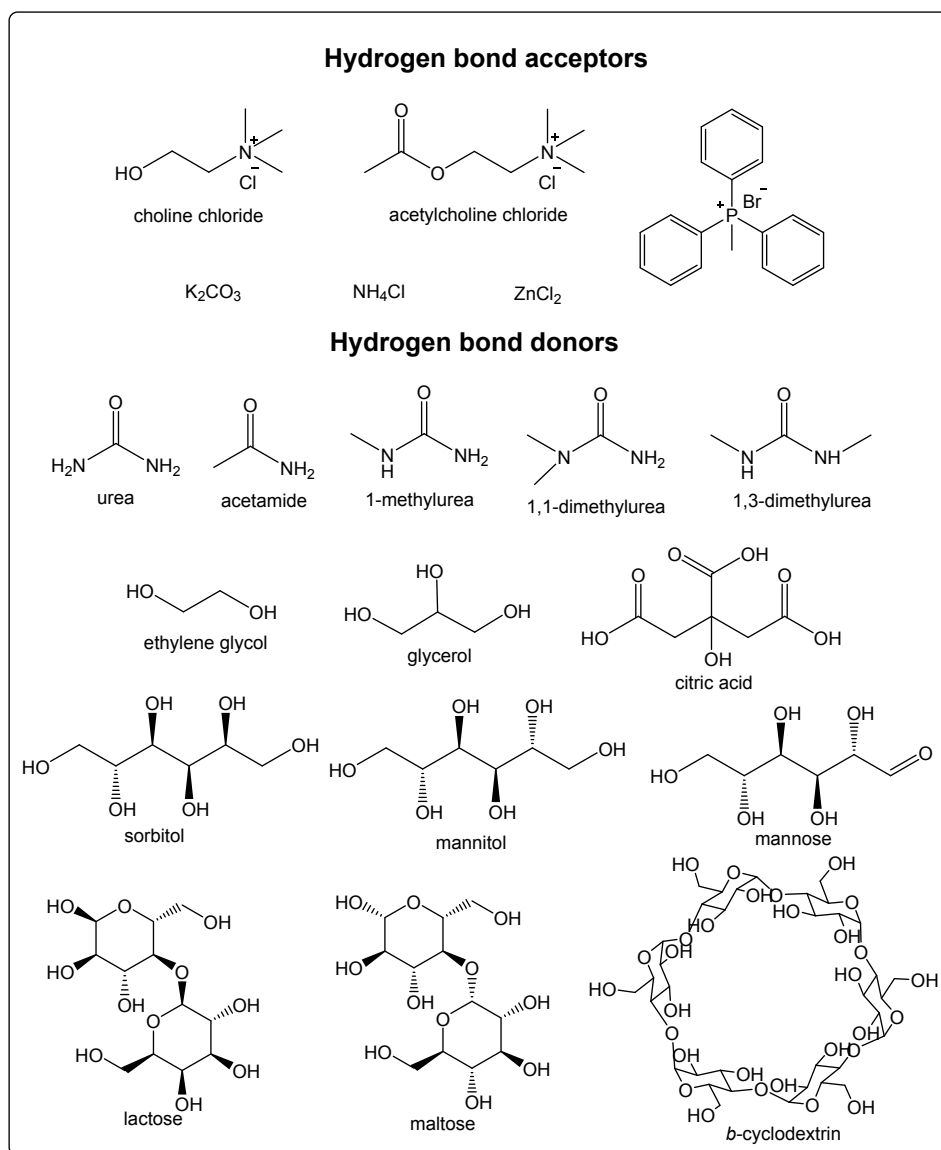
Figure 1 An assortment of some DES components accomplished in cross-coupling reactions

DESs have been developed expeditiously with a wide variety of classes being recognized, for instance: (i) "natural deep eutectic solvents" (NADES), synthesized from primary metabolites or bio-renewable resources such as amino acids, organic acids and sugars, and are being recognized as the third liquid in organisms besides water and lipid phase due to the solubility of intracellular compounds that have intermediate polarity and are otherwise insoluble in both water and lipid phases.[47] They play an important role in Nature, including solubility of animal metabolites, cryoprotection, dehydration and germination processes;[48,49] (ii) "therapeutic deep eutectic solvents" (THEDES), referred to DESs encompassing active pharmaceutical ingredients like ibuprofen or lidocaine-based DES, and (iii) deep eutectic solvent derivatives (DESD), also termed low transition temperature mixtures

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(LTTMs), such as ChCl:glycolic acid and ChCl:glycolic acid:oxalic acid, which are similar but distinct from eutectic point mixtures. Additionally, hydrophobic DESs as nascent subclass of DESs effectively empowered the utilization of these compounds in applications that need direct contact with water.[50]

1.2 Cross-coupling reactions: history and developments

Cross-coupling reactions have been touted within the last decade as an important synthetic chemist's toolbox in modern organic synthesis.[51,52] The resurgence of interest in coupling reactions has been driven, not only for producing unsaturated systems with defined stereochemistry and ease of implementation, but also because of their value to the medicinal and pharmaceutical industry for the construction of neoteric libraries of synthetic molecules. Additionally, this class of reaction produced the rapid formation of C-C, C-N, C-O and C-S bonds which are significant transformations in organic synthesis.[53,54] The year 2010 was a major milestone for the Nobel Prize winners in chemistry (Suzuki, Negishi, and Heck) for the development of the Pd-catalyzed cross-coupling reactions that have witnessed high impact and pivotal roles of these reactions.[55,56] Also, most of these reactions need a transition metal catalyst to proceed at an appropriate synthetic rate. Notably, this widely used and powerful method provides a practical synthetic route for the direct formation of carbon-carbon bonds like Csp^2-Csp^2, Csp-Csp^2 and Csp^3-Csp^2 bonds, which has found considerable academic and industrial usage for the production of polymers, fine chemicals, biologically active molecules[57] and materials in addition to the total synthesis[58] and has become a cornerstone for pharmaceuticals industry.[59]

Generally, the solvent is necessary for cross-coupling reactions to create a homogeneous mixture and stabilize the catalyst.[60] On the other hand, these reactions contain different substrates which make it a challenging proposition for designing and selecting the solvent. The designed medium must dissolve diverse types of solutes such as lipophilic reactants, organometallics, inorganic metal complexes or nanoparticles, bases and salts.[61] Although a variety of organic solvents have been conventionally used for cross-coupling reactions, they are not able to satisfy reactions rate or yield due to a low selectivity and the substrate limitations. Since, cross-coupling reactions are associated with negative activation volumes and decreasing entropy owing to the conversion of two substrates to one molecule of product, therefore the DESs with high-pressure cavities could be eminent candidates as solvent/catalyst for these reactions. The high strain cavities inside the matrix of the DES with extensive hydrogen-bonding network is responsible for providing the cross-coupling products with high yield in shorter duration thus promoting the efficiency of coupling reactions. Consequently, the emergence of task-specific deep eutectic solvents for cross-coupling reactions is an incessantly improving practice in organic and biochemistry.

1.3   Scope of the review

The present review provides, in the first instance, a brief description of the physicochemical properties of DESs systems that affect their efficiencies as task-specific and robust solvents in cross-coupling reactions. Then, the dependence of hole theory to the mechanistic catalytic pathway of this designer solvents has been deliberated. Besides, the review thoroughly highlights the journey of DES utilization as a solvent and co-catalyst for the accomplishment of cross-coupling reactions in several vital organic reaction categories. Although there are numerous books and reviews on the cross-coupling reactions or DESs systems, until now there is no critical review attributed to the applications of DESs as media in cross-coupling reactions; these reactions have had a tremendous impact not only on a plethora of studies in academic fields but also on industrial processes. Consequently, the need to review with a focus on the green and environmental-benign approaches for the accomplishing of these reactions is pivotal. In view of the stupendous growth of DESs as an environmentally-benign media for cross-coupling reactions in recent years, we are encouraged to summarize this hot topic from early works till now.

2 The effect of physicochemical properties of DESs on the chemical processes

The solvent selection is very delicate issue affected the chemical behavior of reagents and catalytic platform, therefore the correct choice of an appropriate solvent is of crucial importance for successful synthesis that allows superior selectivity and reactivity. Deep eutectic solvents may be deemed as sustainable designer task-specific solvents and the physicochemical properties of DESs are crucial for making a suitable selection. For instance, the classic mixture, ChCl:urea (1:2), wherein the melting point of the mixture (12 ^{o}C) is lower than the melting point of the comprising components, ChCl and urea (302 and 133 ^{o}C, respectively) resulting in a transparent liquid at room temperature. The extensive hydrogen bonding of eutectic mixture renders them as ideal solvents for conducting organic reactions while preventing the crystallization of the starting materials, catalysts and products in the liquid phase.[62] This hydrogen-bonding network is not only responsible for solubilizing substrates and reactants but also accountable for the role as a catalyst/co-catalyst in the direct synthesis of diverse molecules and materials[63] such as heterocyclic scaffolds,[64–66] metal complexes,[67] metal organic framework,[68] nanoparticles,[69] polymers[70] and for the functionalization of materials.[71] In addition, a vast variety of organic reactions,[72,73] such as asymmetric synthesis,[74] Diels–Alder reactions,[75] multicomponent reactions,[76–78] enzyme biotransformations[79] and oxidation/reduction processes[80–82] have been conducted in DESs besides been introduced for transition metal catalyzed reactions[83] as well as polar organometallic chemistry involving organolithium and Grignard reagents;[84–86] their deployment can initiate better and more favorable interactions between reactants and the catalyst, offering an easier work-up and recycling process compared to the traditional solvents.

DESs can play a triple role, as an active catalyst, as the solvent for the reaction and even as a substrate. Some of the inherent characteristic of DESs could influence the reaction conditions, mechanistic pathway, the rate of the reaction, product yields and formation of byproduct due to their specific properties, such as viscosity, water content, density, polarity and pH, molar ratio, concentration, conductivity, thermal stability, lipophilicity/hydrophilicity and biocompatibility/biodegradability. Interestingly, by fine-tuning the inherent nature and the molar ratio of DESs, their physicochemical properties, and ability to dissolve solutes and their overall phase behavior could be specifically transformed and designed to match the desired reaction conditions. In continuation, some of these operative physicochemical behaviors will be abridged.

First of all, viscosity is an importing factor in designing novel tailor-made solvents for organic reactions, due to some mass-transfer limitations and is dictated by the type of the ammonium salts and HBDs, their molar ratio's, the temperature, and the water content. For this reason, diverse HBDs, comprising DESs with varying viscosities, affect the mass transfer of reactants (substrates, products and catalysts) thus altering the reaction rate.[87] Except for ChCl:EG (1:2) (36 cP, 20 ^{o}C), most of the DESs exhibit high viscosities (> 100 cP) at room temperature. Viscosity of DESs is also reliant on the free volume and since the low viscosity DESs are in vogue these days, therefore the hole theory,[88] could be useful for designing such platforms. For instance, the deployment of small cations or fluorinated hydrogen-bond donors can initiate the preparation of low viscosity DESs.[89] Also, the presence of water could affect DESs viscosity. The presence of water can be a double-edged sword wherein its higher amount in DES decreases the viscosity and reduces the contact between the catalyst and substrates, thus improving the mass transfer. On the other hand, the presence of a higher amount of water destroys the hydrogen bonding framework of DES and may affect the catalytic efficiency of DES.[90] The other pivotal physical factor for choosing an appropriate solvent is density that is influenced by the nature and molar ratio of components. For example, the $ZnCl_2$-HBD systems exhibit densities higher than 1.3 g cm^{-3}. Most of the DESs show higher densities in comparison to water. Importantly, the increase of ChCl molar ratio in the eutectic mixture ChCl:gly (1:2) leads to decrease in density of the ensuing blend .[91] Moreover, the acidic or basic nature of DESs could be tailored to the catalytic necessities of the reactions; the presence of water in DESs could change the pH as has been suggested that a 20% water increase in ChCl:urea triggers an increase of one unit in the pH value.[92] The acidic behavior of DES could facilitate the breakage of the organic bonds.[30] As it is well known, the solvent polarity could significantly affect the course of the reaction. Notably, DESs are found to be dipolar based on the solvatochromic polarity scale; the polarities of ChCl:EG/gly/urea being 0.80, 0.86 and 0.84, respectively.[45]

Interestingly, the molar ratio portion of HBA:HBD could affect the viscosity, solvatochromic parameters, conductivity, density, polarity, freezing point of DESs and also the hydrogen bonding interactions between the mixed components.[93] Likewise, logical ordering is not found for the effect of altered salt/HBD molar ratio on the viscosity; increase in the salt/HBD molar ratio could

lead to a higher or lower viscosity. Since the salt/HBD molar ratio significantly impacts the viscosities of DES, it is clear that it could also influence the conductivities of DESs, wherein molar conductivity is inversely proportional to the viscosity. In the case of ChCl-based DESs, the conductivity increases with the increase in ChCl content;[94] thus, augmenting the molar fraction of ChCl to 25 mol% in ChCl:gly results in the conductivity of 0.85 mS cm^{-1}. On the other hand, DESs conductivities could significantly increase with temperature enhancement due to drop in DES viscosity that could be calculated via Arrhenius-like equation.[90]

Another aspect that may influence the appropriate design of the DES catalytic system is the decomposition temperature (T_{dcp}), melting temperature (T_m) and freezing point (T_f), which need to be considered. Most of the DESs exhibited a T_{dcp} about 200 °C, except for ChCl:EG which is 121 °C.[31] Due to the strong hydrogen bonding interactions, ChCl:urea could form a room temperature liquid DES (12 °C). Sugar-based polyols (*e.g.* xylitol, D-isosorbide, and D-sorbitol) and carboxylic acids (*e.g.* levulinic acid, malonic acid, phenylpropionic acid, *etc.* as HBDs) produced room temperature liquid DESs wherein the molar ratio of the components could affect the freezing point. Thus, for instance, ChCl:urea mixture has different freezing points depending on the ratio, higher than 50 ºC for mixture 1:1 and 12 ºC for the 1:2 eutectic mixture. It was observed that the number of hydroxyl group in the HBD also has some impact: The T_f of ChCl:gly mixture (with three OH) is -40 °C, while in ChCl:EG (with two OH) it is -66 °C;[90] generally, higher the number of hydroxyl groups, the lower and more intensive would be the decrease in the T_f .[95]

From another point of view, the appraisal of the biocompatibility and biodegradability of DES systems is important in designing synthetic platforms, especially for the synthesis of organic molecules with potent medicinal applications. Despite general assumption, although most of the DES components are bio-sourced, the eutectic mixtures are not necessarily eco-compatible and non-toxic in few cases. Hayyan *et al*. launched an expedient approach for determining the toxicity of DESs which confirmed that the toxicity varied depending on the nature and structures of constituents;[96] some reasoned that it may be due to their charge delocalization, salt's counter anion, redox-stress and lipid bilayer aggregation.[38] It is confirmed that most of the DESs exhibited high biodegradability, the highest one being ChCl:gly (96%), while few other DESs such as ChCl:gly and ChCl:EG are biocompatible. Importantly, Zhao and coworkers proved that most of the ChCl-based DESs showed more than 69% degradability after 28 days.[97]

2.1 Catalytic role of DESs based on "Hole Theory"

Apart from aforementioned concepts, the mobility of ions and the availability of holes in DESs has been rationalized using physical properties such as fluid viscosity via the hole theory. It was introduced by Fürth[98] as an alternate view of the liquid state advanced by Emi and Bockris[88,99] for use with molten salts and finally deployed by Abbot *et al.* for analyzing the properties of DESs.[94] Hole

theory has demonstrated that during the melting process, ionic materials have random size and location of empty vacancies and holes, generated by thermal fluctuations in available local density, which allows appropriate ionic motions.[89] This cavity formation may due to the presence of an extensive hydrogen-bonding network, relatively large ion sizes, and electrostatic forces within the liquid.[100] By decreasing of the average hole radius upon mixing two components, the DES density is increased.[101] In molten salts, the average size of the holes is the same as the corresponding ion. Therefore, small ions have easy mobility into a vacant site thus culminating in lower viscosity of the liquid. Also, the strength and nature of the intermolecular interactions lead to different numbers and sizes of holes resulting in higher or slower mobility of molecules and ions.[95] Since the average size of the holes at low temperatures is small, the combination with larger size ion hampers their mobility which explains the high viscosity of DESs $(10^1\text{-}10^3 \text{ Pa})$.[102] The Stokes–Einstein equation is used for the prediction of the average size of free volumes within such liquids and attributed density.[103,104]

Notably, pressure could affect the reactions that possess an entropy-decreasing value during the transformations. As mentioned before, the higher viscosity of DESs compared to traditional solvents might be attributed to the creation of high-pressure cavities. On the basis of this theory, the volumetric factors are more effective than interactions between salt and hydrogen bonding donor.[105] The presence of these high-pressure cavities, which could favor the reactions accompanied with entropy decreasing and high thermal stability,[106] renders DES an appropriate medium for organic reactions under high pressure and temperature, besides being environmentally benign.[107]

3   Suzuki–Miyaura reaction

Among all the classical cross-coupling reactions, the Suzuki-Miyaura reaction is the most widely exploited protocol, which was developed by these researchers in 1979. The ever-increasing attention paid to this reaction and its applications during the intervening 40 years of history, has augmented dramatically in the last decade[108–112] foreshadowing its efficiency and effectiveness. This broadly applied synthetic protocol establishes a practical approach for the straightforward C-C bond formation, which has found worldwide academic and industrial appliances for the synthesis of polymers,[113] fine chemicals, and functionalized materials, in addition to pharmaceuticals, as well as in total synthesis;[114] the use of nontoxic and privilege reactants, organoboron compounds, is another special attribute.[115]

König *et al.* have paved the way for the development of cross-coupling reactions in deep eutectic solvents.[116] As a first report, they introduced a DES-based system using eco-friendly sugar:urea derivative:salt, such as sorbitol/mannitol/lactose:DMU:NH$_4$Cl (7/5/6:2/4/3:1) for Pd-catalyzed Suzuki–Miyaura reaction. A few years later, a new DES based on β-cyclodextrin, α-1,4-linked

cyclic oligosaccharides produced from starch via enzymatic conversion, and *N*-methylurea (3:7), was described; cyclodextrin is extensively applied in food, pharmaceutical and chemical industries, and in agriculture and environmental domains.[117,118] Greener catalytic system, in the presence of fresh native β-CD-capped Pd^0 nanoparticles, was implemented for the ligand-free Suzuki-Miyaura and Mizoroki-Heck reaction. Next, Alonso, Ramón and co-workers illustrated choline ChCl-based DES system for the construction of C-C bonds and the preparation of a wide range of biaryls;[119] the reaction was undertaken at 100 °C using 0.1–1 mol% of $PdCl_2$ as the catalyst, K_2CO_3, and cationic phosphines as effective ligands (Scheme 1). Whilst several eutectic mixture systems tested, ideal results were acquired with ChCl:EG (1:2) closely followed by ChCl:gly (1:2). Since the eco-friendly factor for the glycerol is higher than that of ethylene glycol, and considering the minimal influence on the yields attained, the ChCl:gly system was chosen as the medium for this reaction. Notably, DES along with catalyst could be recovered and reused up to 5 times without a noticeable drop in the catalytic activity.
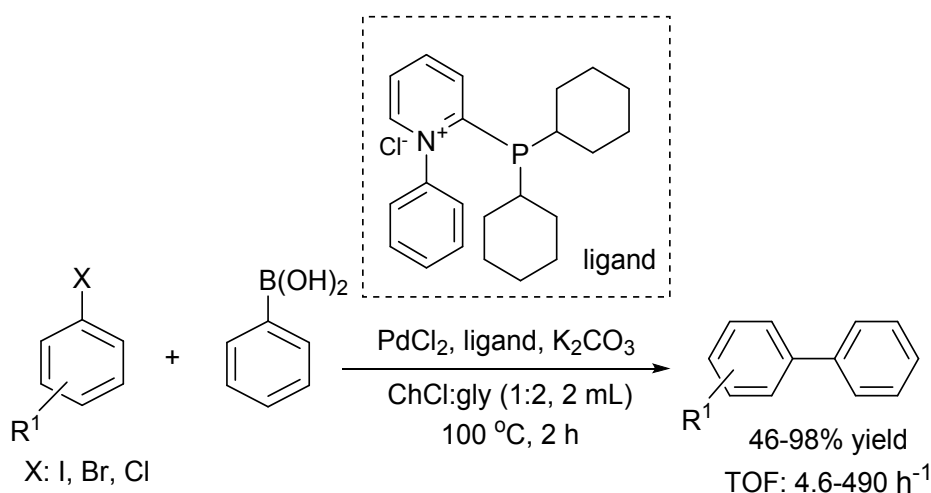
Scheme 1 Suzuki-Miyaura cross couplings in ChCl:gly (1:2)

In order to increase the activity of catalyst, in 2019, a palladium carbine catalyst was introduced[120] wherein the new complex could perform the Suzuki-Miyaura reaction using ChCl:EG (1:2) at room temperature in only 3 h with a broad scope of functionalized aryl bromide derivatives as substrates, and even with the related chlorides albeit with enhanced reaction time. The success of the reaction was due to the presence of 10 equivalents of water whereas its role not being clearly determined. However, the catalyst and the DES could not be recycled.

To avoid the aforementioned inconvenience, a new amino-bipyridine-palladium complex was designed.[121] Although the reaction temperature had to be increased up to 100 ºC, the catalyst and the DES could now be recycled and reused up to eight cycles

without any depletion in activity wherein the true catalyst was validated to be Pd(0) nanoparticle surrounded by the amino-bipyridine-Pd precatalyst.

In 2018, Capriati *et al.* disclosed ligand-free bio-inspired Suzuki–Miyaura reactions using aryltrifluoroborates as efficient partners in DES.[122] Pd-catalyzed Suzuki–Miyaura cross-couplings between (hetero)aryl halides (Cl, Br, I) and versatile, moisture-stable mono- and bi-functional potassium aryltrifluoroborates proceeded efficiently in air and under generally facile conditions, with a catalyst [Pd(OAc)$_2$] loading as low as 1 mol%, in the absence of any ligand, and employing Na$_2$CO$_3$, and ChCl:gly (1:2) system as an environmentally responsible solvent and co-catalyst (Scheme 2). Pd(OAc)$_2$ as catalyst comprising DES and base could be easily recycled up to six times with an E-factor as low as 8.74. Biaryls and terphenyl scaffolds could be obtained in yields of up to and above 98%; over 50 examples have been compared and investigated. This catalytic system was run in air and at 60 °C for (hetero)aryl bromides and iodides, and tolerated broad spectrum of functional groups namely nitro, cyano, carboxylic acids, halides, carbonyl derivatives and free hydroxy and amino functionalities. Eventually, this green methodology was used for the preparation of two non-steroidal anti-inflammatory drugs, Felbinac and Diflunisal.


Hal = Cl, Br, I; R = BF$_3$K, alkyl, aryl, various functional groups
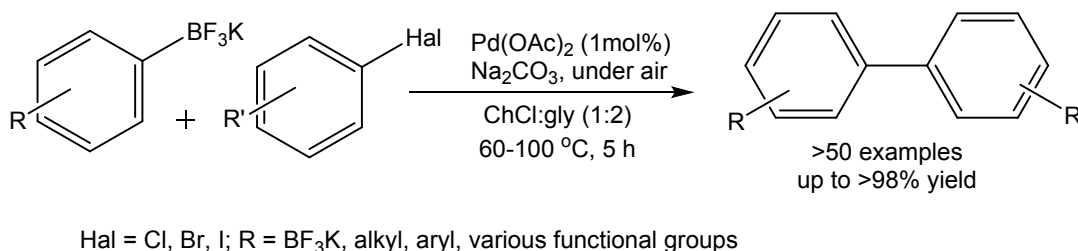
Scheme 2 Pd-catalyzed Suzuki-Miyaura couplings of aryltrifluoroborates in ChCl:gly (1:2)

Additionally, the synthesis of symmetrical triaryl derivatives has been described via one-pot double Suzuki–Miyaura cross-coupling reactions of bifunctional dipotassium phenylene-1,4-bis(trifluoroborate). Further, the authors reported a three-component assembly *via* two different aromatic moieties to generate unsymmetrical terphenyl derivatives with an adequate explanation as to how this reaction occurred in DESs. Their observations revealed no occurrence of coupling in completely anhydrous eutectic mixtures. Undoubtedly, hydrophilic DESs always tend to absorb water duration time of exposure in air. Apparently, the water percentage of hydrophilic DES prepared in the air is undertaking a momentous role in the reaction, thus triggering the hydrolysis of organotrifluoroborates to the corresponding boronic acids.

Soon thereafter, Delaye research group demonstrated a sustainable synthesis of biologically active imidazo-fused heterocycles, such as imidazo[1,2-a]pyridine and imidazo[1,2-b]pyridazine, under ligand- or additive-free conditions with 2.5 mol% Pd(OAc)$_2$ in some NADESs as eutectic solvents.[123] Diverse types of NADES such as mannose/DMU, ChCl:gly, gly:glucose, ChCl:glucose and so

on were examined and ChCl:gly (1:2) was found to be the most efficient solvent for coupling. The imidazopyridine scaffolds exist in some marketed drugs such as the gastroprotective, Zolimidine or hypnotic, Zolpidem. Moreover, this important heterocyclic moiety is present in the anticancer drug Ponatinib. Consequently, this promising catalytic synthetic route enabled the researchers to use this strategy for pharmaceutical purposes, particularly the phenylation of heterocyclic scaffolds.

In 2019, a groundbreaking research explained the metalizing of DNA in a multitasking DES for C-C coupling process;[124] a novel dual functionalized Pd−DNA−Fe_3O_4 with an aggregated coil-shaped morphology was designed as an efficient nanobiocatalyst for the Suzuki–Miyaura coupling reaction in the presence of ChCl-EG (1:2; Scheme 3). The results suggested that Pd interacted with phosphate groups and Fe_3O_4 cooperated with the base pairs of DNA. The fiber type morphology of Pd-DNA-Fe_3O_4 with the intermittent appearance of black patches was attributed to the aggregation of Pd and Fe_3O_4 particles with the 2 and 6 wt % amount of Pd and Fe, respectively. The catalyst exhibited outstanding catalytic efficiency in ChCl:EG with 100% conversion and selectivity for the desired C-C coupled product.

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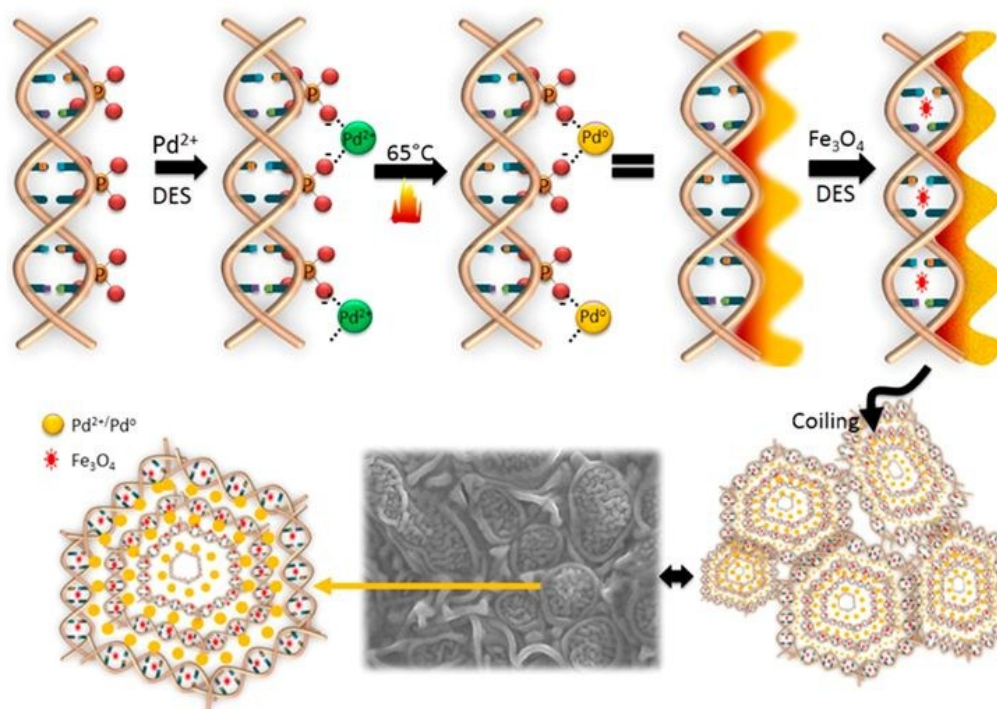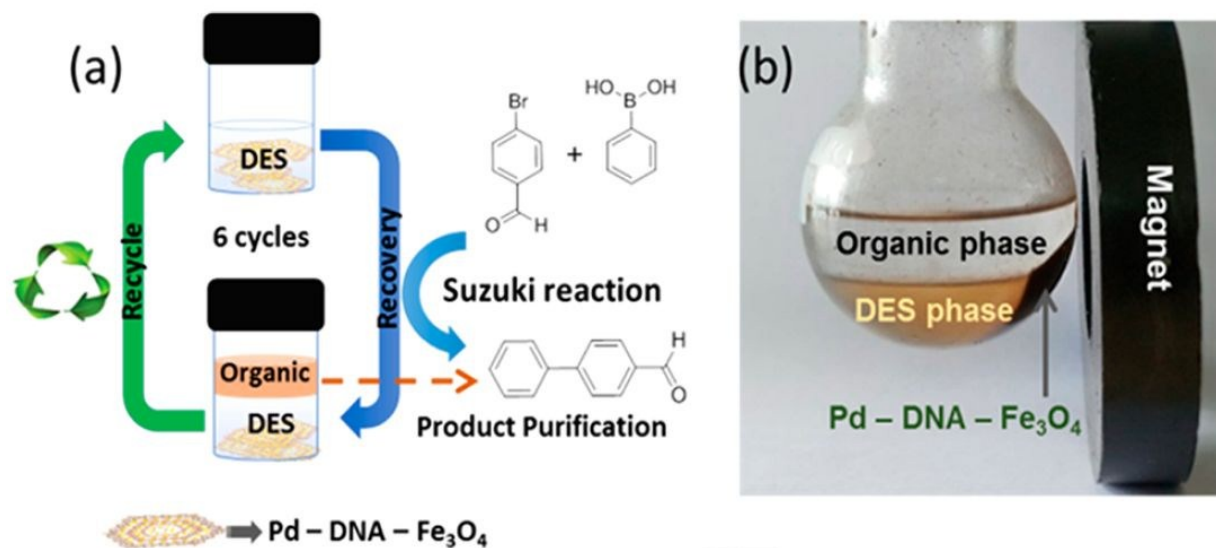
Scheme 3 Stepwise formation of coil type-shape metalized DNA in a ChCl-EG (1:2) DES; (a) recyclability of both, the catalyst and the solvents. (b) Separation of catalyst (Pd-DNA-Fe$_3$O$_4$) by magnetic decantation. Reproduced with permission from ref. 124. Copyright (2019) American Chemical Society.

This effective and recyclable heterogeneous catalyst (up to 6 cycles) without significant loss in the catalytic activity is possibly due to the high-temperature stability of DNA in DES, as illustrated by a TOF value of 214 and a TON value close to 461. Furthermore, DES not only served as a solvent for DNA metallization but also was the reducing agent for the Pd (II) to Pd (0) during the metalization process. The platform could successfully surmount two major drawbacks of time-consuming synthesis procedure and the loss of DNA helicity and is a shining example of the task-specific and multimodal role of this DES solvent. The authors compared the results of some Pd-based catalysts for this reaction in different media such as ILs, xylene and toluene to gain an insight on the efficiency of DES over conventional solvents. As can be seen in Table 1, relatively strong outcomes of DES results in regard to temperature, reaction time, and yield tip the balance in favor of DES as a recyclable greener medium.

Table 1 Comparison of solvent effects on different Pd-catalysts reported in the literature

| Entry	Catalyst	T(^{o}C)	Time (h)	Solvent	Yield (%)	Conv. (%)
1	Pd-biopolymer/CS	130	6	Xylene	-	76
2	Pd-carboxymethyl CS	100	48	Toluene	98/88[a]	-
3	PdCl$_2$	100	24	IL	86	-
4	Pd-DNA-Fe$_3$O$_4$	80	5	DES	92.2	97.6

[a] Two types of catalyst have been used.

DES has been exploited as a versatile medium for enantioselective single-pot direct synthesis of biaryl-substituted amines with the utilization of recently discovered amine transaminases (ATAs) from *Exophiala xenobiotica* (EX-ωTA) as a stable catalyst in DES-buffer mixtures at a percentage of up to 75% (w/w) (Scheme 4).[125] Furthermore, DES was applied to secure a chemoenzymatic tandem biaryl amine formation via cross-coupling sequentially with an enantioselective bioamination catalyzed by the ATA. The metal-catalyzed step at 200 mM loading of substrate occurred due to the solubilization in DESs followed by the subsequent biotransformation at 25 mM. In this progress, four types of choline chloride-based mixtures, such as ChCl:H$_2$O, sorbitol, glycerol and urea were screened with variable water content; reaction in ChCl:gly (1:2) afforded better yield than the other DESs. Similarly, the same research group reported the one-pot synthesis of biaryl alcohols by Pd-catalyzed Suzuki-Miyaura cross-coupling followed by enzymatic reduction.[126]
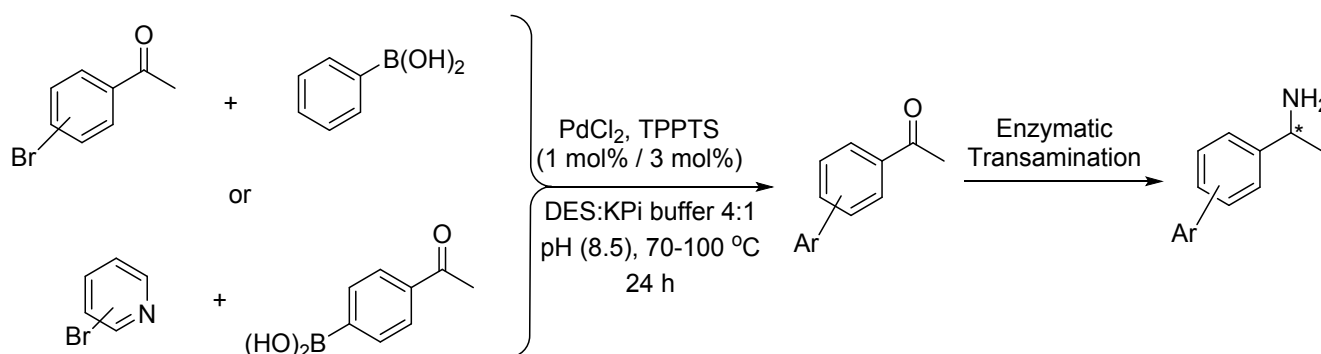
Scheme 4 One-pot synthesis of enantiopure biaryl amines through Pd-catalyzed Suzuki–Miyaura cross-coupling followed by enzymatic transamination in a ChCl:gly (1:2) DES-buffer mixture.

Recently, Heravi, Sedghi, and co-workers identified a new modification of Suzuki–Miyaura cross-coupling reaction using boronic acid as well as *N*-acylsuccinimides as versatile acyl-transfer reagent instead of aryl halides in ChCl:gly (1:2).[127] The 0.03 mol% of this novel Pd NPs supported on β-CD@graphene oxide, as a magnetically reusable heterogeneous catalyst, in the presence of K$_2$CO$_3$ as a base at 90 °C led to the formation of benzophenone derivatives in 5 h with the conversion of 60-89% (Scheme 5). The authors surveyed the effect of several solvents, for example water, ethanol, CH$_3$CN and THF accompanied by three types of DESs (ChCl:urea/EG/gly) for finding the best medium. Whilst, the use of protic solvents like water and EtOH gave inferior results, desired product was obtained only in 32% and 20% yield by using THF and CH$_3$CN, respectively. In contrast, while DESs were used as media, benzophenone derivatives were increasingly achieved.

Scheme 5 Suzuki–Miyaura-type reaction for the synthesis of benzophenones in ChCl:gly (1:2).
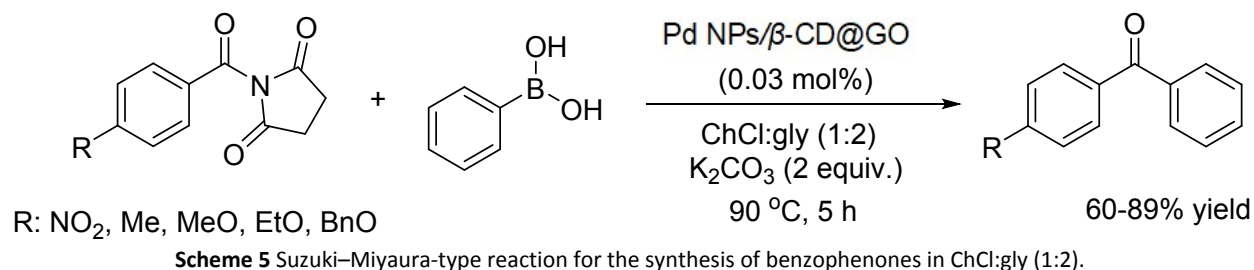
In 2019, Prandi devised a telescopic procedure in DES medium, multiple bond-formation can be accomplished in a one-pot method by reducing the amount of solvent used in a synthetic sequence and minimizing waste production. [128] They examined the competency of DES mixtures for performing one-pot, telescoped ortho-lithiation/Pd-catalyzed Suzuki–Miyaura coupling reactions, which display superiority from efficiency and environmental sustainability point of view. The ensuing ortho-iodo derivative was subjected to an aerial Suzuki–Miyaura cross coupling deploying 10 mol% of Pd(OAc)$_2$ in ChCl:gly admixed with CPME at 100 °C; it afforded ortho-functionalized styryl or (hetero)aryl derivatives in 45 % yield after two steps in one-pot process. The results revealed that DESs can be directly used as an excellent media in this sequential one-pot syntheses wherein reagents were added to a reactor, one at a time, with no need of work-up.
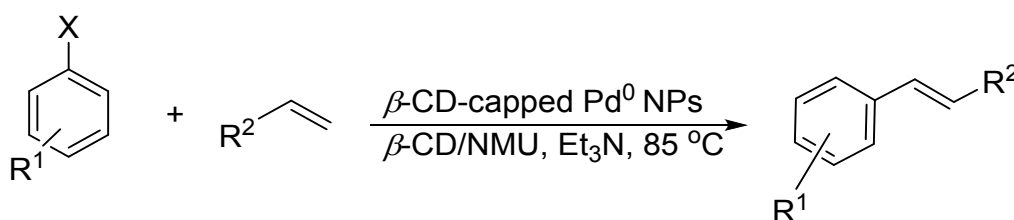
4   Mizoroki-Heck reaction

Mizoroki and Heck independently reported the Pd-catalyzed reaction of alkene derivatives and aryl or alkenyl halides in the presence of a base[129,130] and soon thereafter, this practical cross-coupling reaction was exponentially explored by Heck and other scientific groups, as a versatile and useful class of Pd-catalyzed C-C bond formations.[131–133] For the first time, König research group examined this reaction in two types of DES revealing that D-mannose:DMU (3:7) is a better medium than one obtained from L-carnitine:urea (2:3); aryl iodides and n-butyl acrylate with different Pd sources, such as Pd(OAc)$_2$ or PdCl$_2$(PPh$_3$)$_2$ led to the desired coupling products in good yields. Nonetheless, this green catalytic report suffered from a lack of diversity[134] and the protocol could not be improved using ultrasound as an alternative energy input source. Afterward, PdCl$_2$ in combination with cationic pyridiniophosphine ligands in ChCl:gly (1:2) as DES was used for the reaction between aryl iodides and methyl acrylate to synthesize the corresponding products in reasonable yields.[119]

In 2014, Zhao et al. introduced a deep eutectic or low-melting mixture based on β-CD and N-methylurea (3:7)[135] via a ligand-free Mizoroki-Heck process in the presence of fresh native β-CD-capped Pd^0 nanoparticles. This eco-friendly medium could be prepared in air, with the ability to produce the cross-coupled products in good to excellent yields at a low amount of Pd catalyst loading (0.05 mol%), and via a simple workup (Scheme 6). Additionally, diverse types of bases were examined and the results

indicated the high efficiency of Et$_3$N, while other bases namely KOH, K$_2$CO$_3$ and Na$_2$CO$_3$ being less effective. A broad spectrum of

aryl iodides including electron-poor and electron-rich reagents react with terminal alkene within a short time (~ 2 h) with

satisfactory yields; poor results being obtained for aryl bromides even with a higher amount of catalyst and longer reaction times.

The catalytic system could be reused, however, a decrease in yields in the fifth and sixth recycling runs was observed, due to the

agglomeration of the Pd NPs, thus revealing the effect of the particles size on the catalytic activity of the recycled catalyst.[136]


Scheme 6 Mizoroki-Heck reaction in low-melting β-CD/NMU mixtures.

Very recently, Ramón, Guillena and co-workers reported a mesoionic carbene ligand in Pd-catalyzed Mizoroki-Heck reactions in

AcChCl:urea (1:2) DES;[120] reaction proceeded well with electron-poor aryl iodides and diversely substituted methylacrylates, using

1.5 eq. of NaOAc as a base at 120 ^{o}C and 1 mol% of the catalyst affording good to excellent results. The reaction time was extended

to 16 h for electron-rich reagents, with confirmed the failure for aryl bromides (4'-bromoacetophenone) and aryl chlorides (4'-

chloroacetophenone).

5   C-H bond functionalization reactions

The C-C bond formation through C-H bond activation is one of the most challenging reactions in transition-metal-catalyzed

chemistry.[137] In this context, Farinola *et al.* explored the choline chloride:urea (1:2) medium for a thiophene-aryl direct coupling

reaction via C–H bond activation with Pd$_2$(dba)$_3$ as a catalyst and in the presence of Cs$_2$CO$_3$ (as base), P(o-MeOPh)$_3$ (as ligand),

and pivalic acid as additive (Scheme 7);[138] reaction was performed in non-anhydrous conditions and without exclusion of air. The

authors applied 5-octylthieno[3,4-c]pyrrole-4,6-dione as the C–H activated reagent, in consideration of the interest of this

aromatic moiety in the construction of push–pull molecular and polymeric semiconductors in organic electronics and polymer

solar cells. The addition of small amounts of cyclopentyl methyl ether (CPME) to the DES extends the usefulness of the synthetic

protocol to coupling reactions with diversely functionalized aryl iodides.
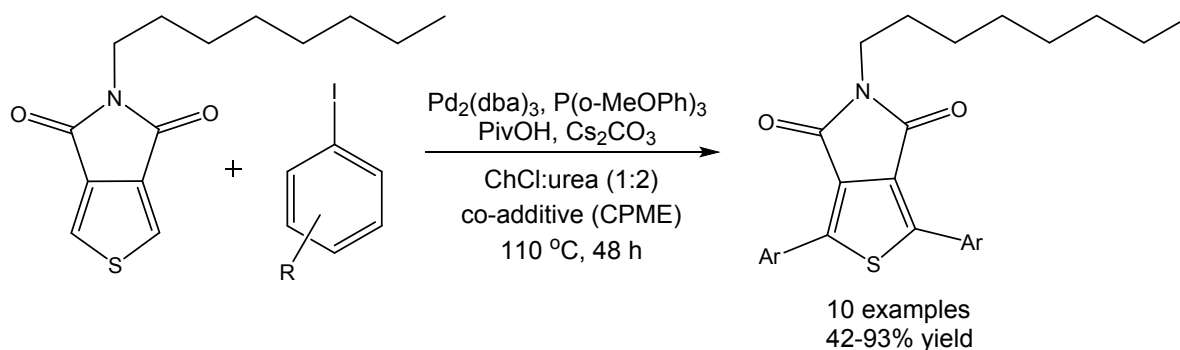
Scheme 7 Direct arylation of 5-octylthieno[3,4-c]pyrrole-4,6-dione in ChCl:urea (1:2)

Subsequently, Heydari and co-workers explicated a reusable heterogeneous catalyst, modified magnetic reduced graphene oxide-supported Pd catalyst, for the regioselective C-5 arylation of imidazoles *via* C-H bond activation pathway for the preparation of C5-arylated imidazoles with several electron-deficient and electron-rich moieties; alkaline DES (K_2CO_3:gly in 1:5 molar ratio) was used under aerobic conditions.[139] The reusability of the catalyst was successfully examined for seven cycles without obvious loss of the reaction yields wherein the heterogeneous character of the catalyst was affirmed by hot filtration and Hg(0) poisoning test. The arylation of benzoxazoles with aromatic aldehydes instead of aryl halide could be catalyzed by $ZnCl_2$:EG (1:4) (Scheme 8)[140] using a diverse range of substrates affording good to excellent yields in short reaction time (4-6 h); the dual role of the DES as a solvent and catalyst was highlighted. Further, the DES medium could be recovered and reused five times without a significant decrease in catalytic activity. The ICP-MS technique was used for the detection of a small amount of DES leaching to the diethyl ether phase during the decantation work-up step, with about 0.08 ppm of Zn being detected in the ethereal phase.
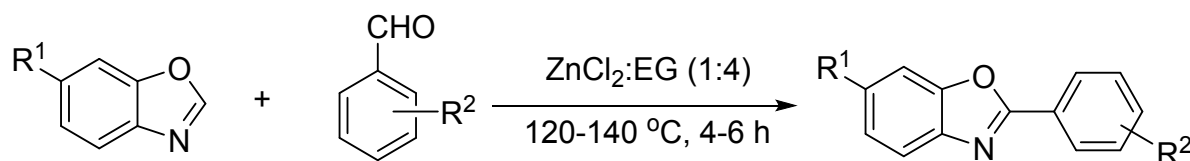
Scheme 8 Arylation of benzoxazoles with aromatic aldehydes in $ZnCl_2$:EG (1:4)

To expand the repertoire of cross-coupling reaction particularly C-H bond functionalization using DESs, Ramón and co-workers reported a recyclable copper-impregnated magnetite catalyst (CuO–Fe_3O_4) in ChCl:EG as medium using air as the only oxidant (Scheme 9);[141] greener protocol was deployed for the synthesis of an array of tetrahydroisoquinolines by direct reaction with a broad range of nucleophiles. The key step is the generation of an iminium intermediate assisted by the lone pair of the nitrogen atom, *via* a single-electron transfer (SET) mechanism. Several DES systems, for example, ChCl:urea, AcChCl:urea, ChCl:gly, Ph_3PMeBr:gly and ChCl:EG were evaluated for this process and ChCl:EG (1:2) emerged as the best medium. The pivotal role of

the DES became obvious from the fact that the reaction did not proceed in the other typical organic solvents, such as water, DMSO, DMF, THF and MeOH. A directly proportional relationship was uncovered between the conductivity of DES medium and the yield attained, which highlighted the tunability of DESs'; DES and the catalyst could be reused up to ten times without any obvious effect on the yield. This sustainable protocol is performed under aerobic conditions where only water is produced as waste. Assorted metal oxides such as CoO, NiO, Ru_2O_3, Rh_2O, PdO, Ag_2O anchored on magnetite were evaluated as catalysts, and none of them gave better results than secured by the copper oxide. Next, various copper salts namely $CuCl_2$ and $Cu(OAc)_2$ were tested, affording moderate to good results, but poorer than the one obtained by the heterogeneous copper oxide anchored on magnetite. Then, the addition of a mixture of CuO and Fe_3O_4 was evaluated, which gave a diminished conversion compared to the anchored catalyst, thereby highlighting a synergic effect between the metal oxide and support in the catalyst. The desired products were achieved with moderate to good yields in spite of long reaction time (3 days).
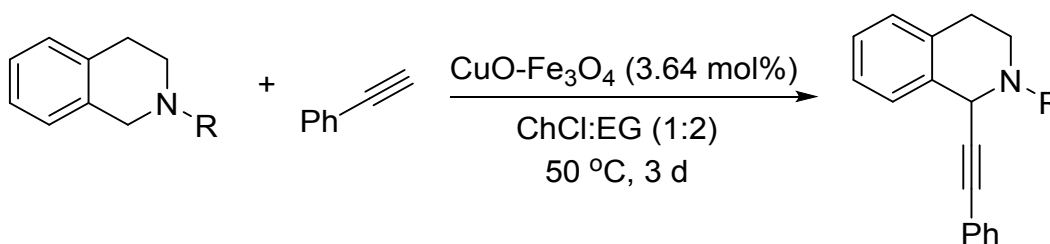
Scheme 9 CuO-Fe_3O_4 catalyzed C-H bond activation in ChCl:EG (1:2)

6   Sonogashira reaction

The advent of Sonogashira cross-coupling reaction, Pd-catalyzed Csp-Csp^2 bond formation between a wide variety of aryl halides and terminal alkynes, and their ever-burgeoning applications in total synthesis, chemical processes and industrial transformations began in 1975.[142] In this remarkable cross-coupling methodology, the acetylene gas or the terminal alkynes react with aryl or alkenyl halides in the presence of the Pd catalysts.[143,144] Nowadays, efficient catalysts based on the other metals such as copper,[145] cobalt,[146] rhodium[147] and gold[148] have been reported for the Sonogashira reaction.

Pd-catalyzed Sonogashira coupling of aryl bromide with phenyl acetylene was shown in mannose:dimethylurea (3:7) DES without copper co-catalyst; nonetheless, only two products were produced in DES medium with $PdCl_2(PPh_3)_2$ as a catalyst.[134] Subsequent, Alonso, Ramón and co-workers utilized the $PdCl_2$ and cationic pyridiniophosphine ligand for the Sonogashira reaction between aryl halides and phenyl acetylene in Ph_3PMeBr:gly (1:2) which led to the desired coupled products in 67–99% yields (Scheme 10).[119] Significantly, Ph_3PMeBr:gly as a medium produced higher yields in comparison to ChCl-based DES system such as ChCl:urea

and ChCl:gly with good to excellent yields for aryl iodides bearing electron-withdrawing, electron-donating groups including heteroaryl iodides. In the case of aryl bromides with electron-poor systems, moderate to good yields could be obtained by increasing the amount of catalyst.
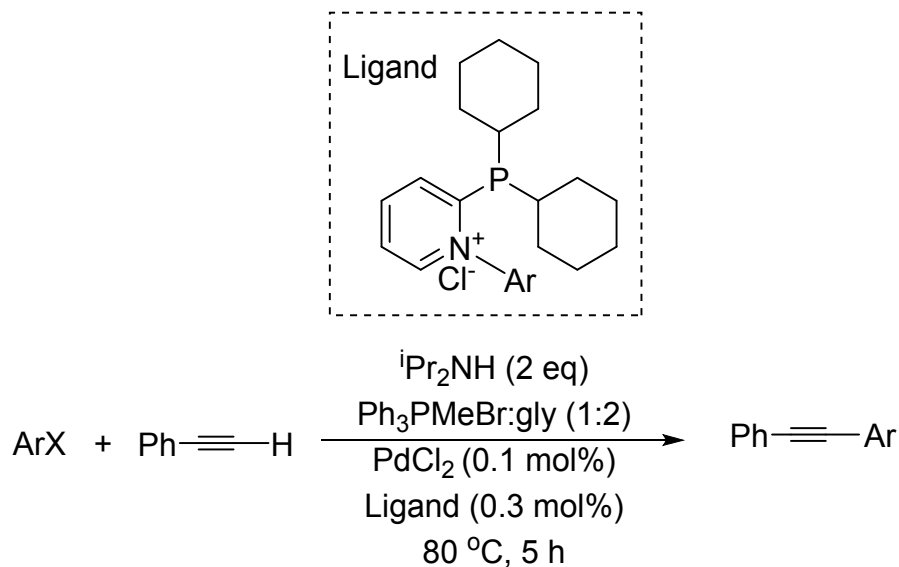
Scheme 10 Palladium-catalyzed Sonogashira reaction in Ph_3PMeBr:gly (1:2)

In 2019, Ramón *et al.* described the copper-free Sonogashira coupling in diverse DESs, and akin to previous results, Ph_3PMeBr:gly was the best medium (Scheme 11)[121] for the reaction catalyzed by a new amino-bipyridine-palladium complex. Although the nitrogen-containing ligands have a lower cost in comparison to phosphines or NHCs ligands, they have been investigated scantily for Pd-catalyzed cross-coupling reactions. Novel ligand was designed not only based on this economic point but on the possible hydrogen bond donor/acceptor character of the complex for various aryl halides and terminal alkynes. For both, the aryl iodides and bromides, appropriate yields were achieved using electron-withdrawing and electron-neutral system with three consecutive cycles for reuse. Although the inactive Pd black precipitate was observed during the sequence of the reactions which impaired its activity, the good catalytic activity was still detected after 3 or 5 runs that confirmed the stabilizing role of the DES on the ensued Pd NPs.[149] The presence of the palladium clusters with an average 1.66±0.33 nm diameter after the completion of the first cycle of the reaction authenticated the presence of Pd NPs in this cross-coupling reactions. The results of the XPS analysis showed that a portion of the initial Pd(II) was reduced to Pd(0).
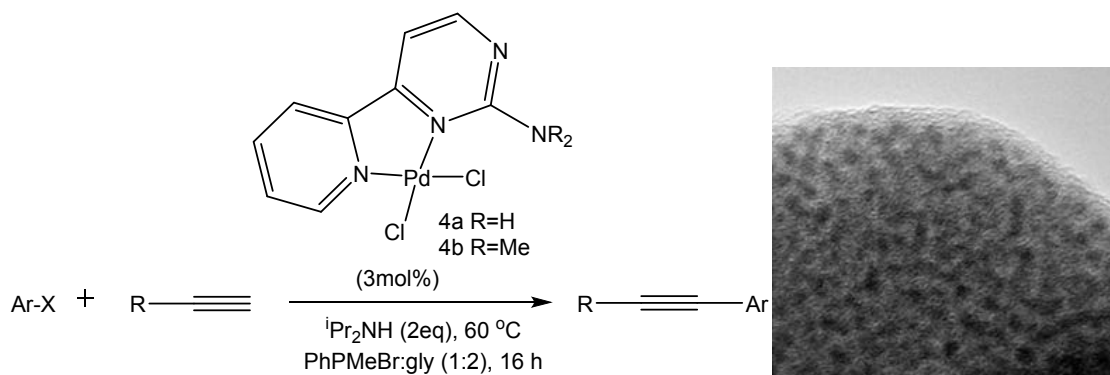
Scheme 11 Sonogashira reaction in Ph₃PMeBr:gly, TEM of catalyst structure at the scale of 2 nm. Reproduced with permission

from ref. 121. Copyright (2019) Wiley-VCH.

In 2019, Ramón, Guillena *et al.* designed a novel σ-donor mesoionic carbene ligand for Pd-catalyzed Sonogashira coupling in AcChCl:urea (1:2) DES with *i*-PrNH₂ as a base; moderate yields were obtained for different aryl iodides with phenylacetylene, however, in the case of 4-bromo- and 4-chloro-acetophenone the desired products were not obtained.[120]

In recent interesting work, Zhu and coworkers reported hydrogen-substituted graphyne (HsGY) comprising alternative phenylene and ethynylene units via Sonogashira polycondensation in DES media by cross-coupling polymerization of 1,3,5-triethynylbenzene and 1,3,5-tribromobenzene (Scheme 12);[150] ethylene glycol, phenol and urea with choline chloride at appropriate molar ratios were used in this polymerization. The results revealed that different DESs' types could absolutely affect the morphologies of the polymer. HsGY in ChCl:EG (1:3) showed the heterogenic massive matrixes containing few holes. HsGY in ChCl:phenol (1:2) encompassed the irregular loose micron rods with a lot of gaps, while in ChCl:urea (1:2) the fibrous morphology was observed.
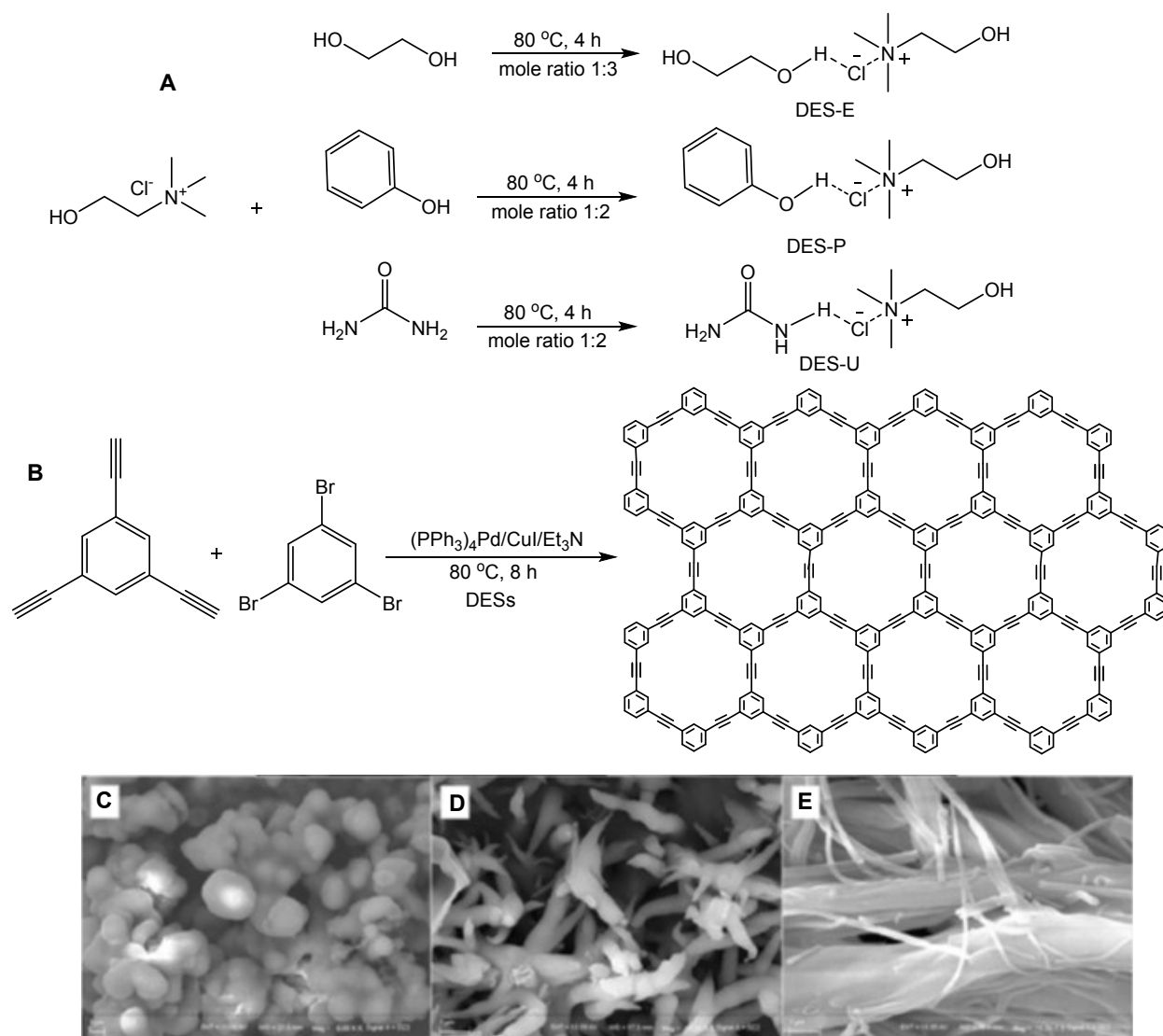
Scheme 12 A: Schematic layout for the synthesis of DESs. B: synthesis of HsGYs. C: SEM of HsGY-from ChCl:EG, D: HsGY-from ChCl:phenol and E: HsGY-from ChCl:urea, at the scale of 1 mm. Reproduced with permission from ref. 150. Copyright (2020) Elsevier.

In 2020, Salomone, Capriati and co-workers exploited the efficiency of commercially available Pd/C in ChCl:glyeutectic mixture for ligand-free Sonogashira reaction.[151] Under the heterogeneous conditions, (hetero)aryl iodides were straightforwardly reacted with not only aromatic alkynes but also aliphatic alkynes thereby affording desired product in 50-99% yields under mild heating (60 °C) and in reasonable reaction time (3 h). Moreover, this catalytic system was efficient towards electron-rich iodides, which are generally known to have poor reactivity in Sonogashira cross coupling; DES as well as the catalyst were reusable up to four times with an E-factor as low as 24.4. To broaden the utilization of DES in cross-coupling reactions, Nawaz Khan *et al*. described an attractive single-pot sequential three-component Sonogashira or Suzuki-Miyaura reaction for the synthesis of highly

functionalized benzo (2, 3)(1, 4)oxazepino(7, 6-b)quinolines in K_2CO_3:EG (1:10).[152] In view of some advantages such as external base-, ligand- and copper-free reaction, good to excellent yields and simple work-up and also low catalyst loading, this Pd-precatalyst synthetic approach could be considered as a straightforward and suitable method for organic process and total synthesis.

7   Hiyama reaction

The Hiyama coupling reaction is a Pd-catalyzed C-C bond formation through organic halides and organosilanes and was discovered in 1988 by Tamejiro Hiyama and Yasuo Hatanaka. An interesting and sustainable peculiarity of the Hiyama reaction is based on the utilization of organosilicon reagents which are non-toxic, eco-friendly, commercially available and stable in air and moisture, and are obtainable at low cost *via* easy preparation procedures.[153] Nevertheless, organosilane reagents are generally less reactive than the corresponding boron counterparts.

In 2018, Guillena and Ramón described Hiyama cross-coupling reactions between organic halides and various types of organosilanes in DESs deploying a highly stable pincer-type Pd complex (Scheme 13);[154] reaction was initially explored between 4-bromoacetophenone and trimethoxyphenylsilane in 20 assorted DESs. Ironically, the reaction failed in most of the DES's, except 70% yield in ChCl:gly (1:2) and 25% yield in ChCl:EG could be obtained. Interestingly, for ChCl:gly (1:2) with 1 mol% catalyst in the presence of K_2CO_3 at 100 °C, moderate to low yields were attained with aryl halides bearing electron-withdrawing groups, electron-neutral aryl halides and electron-rich aryl halides with no sign of homocoupling byproducts. Afterwards, authors examined the vinylation reaction of aryl halides with trimethoxyvinylsilane wherein the high yield reaction could be successfully performed for aryl iodides and bromides bearing electron-withdrawing functional groups, and with moderate yields with aryl iodides with electron-donating groups, including electron-rich heterocycles. Notably, the vinylbenzenes as a reaction products suffer from a second Pd-catalyzed Heck-type reaction with the aryl halide to generate a 1,2-disubstituted ethene derivative and unfortunately, the selectivity to these products could not be regulated. This catalytic system also could be recycled for at least three runs without the need of more catalyst or solvent. Upon completion of the reaction, organics were extracted with 2-MeTHF, a greener VOC solvent (clear two phases facilitating decantation in this reaction with 2-MeTHF is shown in Scheme 13). The recyclability aspects were evaluated using neat glycerol as the solvent, attaining a gradual decrease in the yield after each cycle, nevertheless, the glycerol afforded better yield rather than DES. The ICPMS analysis of 2-MeTHF revealed that by using glycerol the 7.9% of the initial Pd loading was extracted alongside the product, while 16.5% leaching was observed in the case of using DESs as the medium, likely the main reason for the diminishing yield during the recyclability. Importantly, their XPS, HRTEM and mercury test results unveiled that performing this reaction in a eutectic mixture is more likely to occur through the Pd(II)/Pd(IV)

catalytic cycle. Finally, a gram-scale reaction led to biaryl products in high yields and purity by simple liquid-liquid extraction, showing the potent applicability of this synthetic route on a sustainable industrial scale.
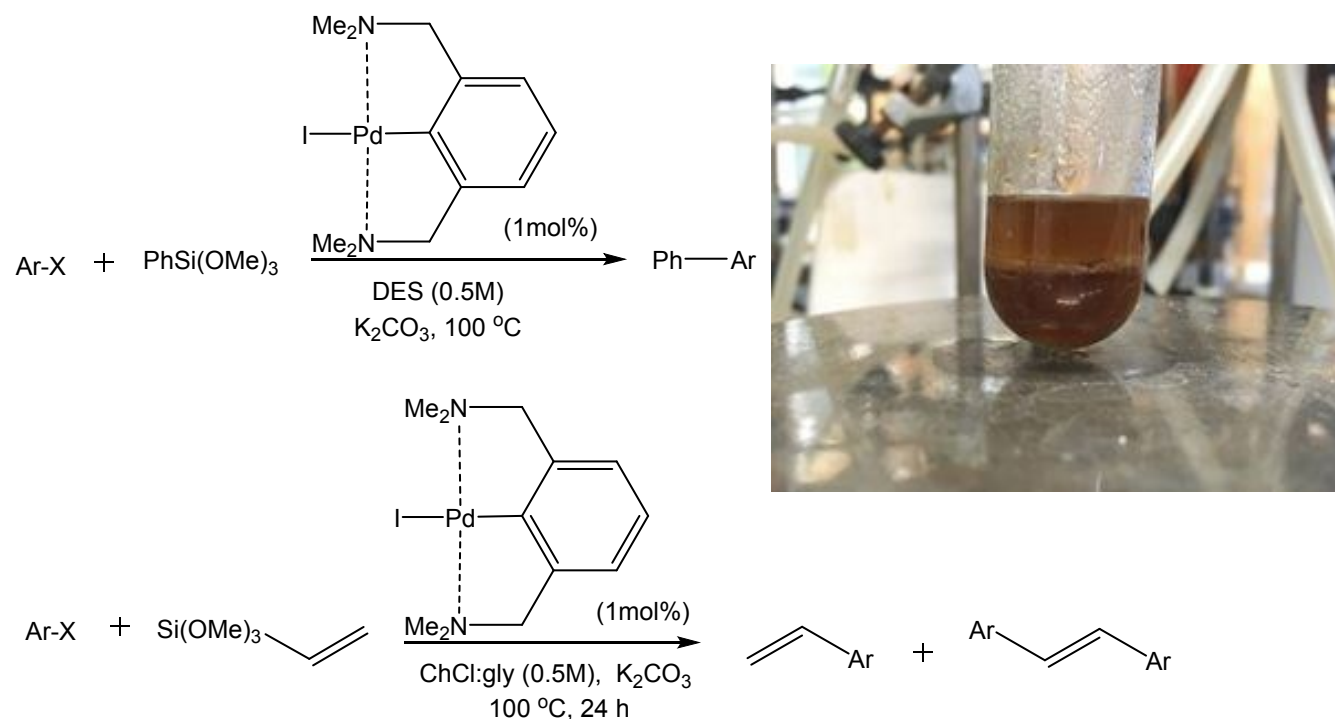
Scheme 13 Hiyama coupling reaction with a robust NCN-Pd pincer catalyst in ChCl:gly (1:2)

The same group in 2019 accomplished the Hiyama cross-coupling reaction with mesoionic *N*-heterocyclic carbene (NHC)-Pd complex in ChCl:gly (1:2, 1 M) in the presence of K_2CO_3, as a base, at 100 °C with good to excellent yields.[120] The approach is tolerant of a wide range of electron-poor, electron-rich aryl bromides as well as heteroaryl bromides as privilege substrates and is adaptable for library synthesis.

A bipyridine Pd complex was developed as a general pre-catalyst for cross-coupling of various activated and deactivated aryl bromides with trimethoxyphenylsilane in ChCl:gly (1:2) with $NaHCO_3$ (2 eq.) at 100 °C;[121] diverse heteroaromatic bromides afforded good results and even, benzyl bromide led to high yields (89%). Importantly, despite mechanistic pathway description of two previous reports, the examinations clarified that in this synthetic route the Pd(0) is the real catalyst, thus authenticating the dynamic behavior of Pd complexes as well as their role as pre-catalyst.

8   Stille reaction

A study published by Stille in 1978, instigated the emergence of neoteric cross-coupling reaction class, and has garnered attention and popularity throughout this field.[155] The Stille cross-coupling synthetic route is a practical and universally applicable procedure

for the formation of new C-C bondsinvolving the Pd-catalyzed coupling of organic electrophiles, often halides or triflates, with organotin substrates. This versatile process fascinates chemists due to the non-sensitivity of most of the organotin reagents to either oxygen or moisture. Stille reactions usually proceed well in aprotic, expensive and relatively toxic solvents namely HMPA, DMF and dioxane. Stille cross-coupling reaction in low-melting mixtures of sugar, urea and inorganic salt with the utilization of $Pd_2(dba)_3$ as a catalyst and triphenylarsine as a ligand has been accomplished (Scheme 14);[156] surprisingly, the reaction with other typical phosphine ligands gave poor results. The procedure was run at 90 °C in various low-melting mixtures or DESs, for instance, sorbitol/DMU/NH_4Cl, lactose/DMU/NH_4Cl, mannose/DMU, mannitol/DMU/NH_4Cl and fructose/urea/NaCl and the yields obtained were dependent on the natures of the organotin substrates and media; Me_4Sn gave the highest yield in mannitol/DMU/NH_4Cl (5:4:1) eutectic mixture, while for vinyl or *tert*-butyltin organometallic substrate, maltose/DMU/NH_4Cl (5:4:1) was the best medium. Stille's biaryl synthesis using both, electron-poor and electron-rich aryl bromides, proceeded in near quantitative yields in diverse sugar-urea-salt melts. The authors speculated that high polarity and nucleophilic character of the media promotes the reaction. Finally, the easy work-up, devoid of typical organic solvents, and the reusability of medium have been considered as efficient and beneficial attributes of this process.

R^1: H, Me, OMe or NO_2
R^2: Me, *t*Bu, vinyl or Ph

89-100% yield
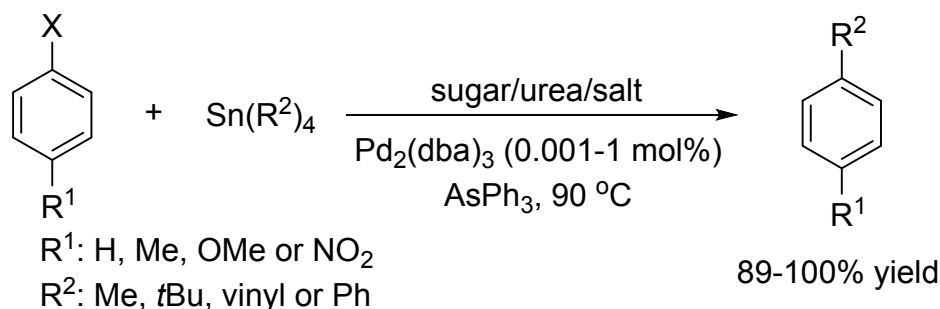
Scheme 14 Stille cross-coupling reaction in DES based on sugar/urea/salt

9 Tsuji–Trost reactions

In view of the growing demand for designing efficient synthetic routes in DESs, chemists have explored Tsuji–Trost reaction; novel type of DESs or LTTMs based on *N,N'*-DMU and β-CD derivatives have been described for this reaction (Scheme 15).[157] Two components of DESs were stirred under N_2 atmosphere for 1 hour in an oil bath at 90 °C, till the medium became transparent fluid which quickly turned to solid after cooling at room temperature. Then, heptane-dissolved allyloctylcarbonate and diethylamine were added to the DESs. The solid catalytic layer changed to liquid after immersion in the oil bath at 90 °C, and the biphasic system was vigorously stirred for 5 minutes. Following cooling, the organic layer was conveniently decanted in aerial

atmosphere and the solid catalytic layer was then reused under N_2 with a new solution of allyloctylcarbonate and diethylamine in heptane. Consequently, this catalytic system exposed two intriguing traits. First, the $Pd(OAc)_2$ as a catalyst dissolved in DMU-β-CD (7:3) is reusable at least 8 times without alteration of its activity and allows the change of reagents under N_2 atmosphere. Second, at ambient temperature, the catalyst species maintained in the medium in the solid-state were protected against degradation thereby facilitating the easy work-up and recycling. Notably, the reusability of the DMU-β-CD phase in the air atmosphere, instead of N_2, was also examined at 90 °C in the presence of a fresh organic layer of allyloctadecylcarbonate when the conversion decreased to 15% and becoming null for the following experiment. The authors asserted that heating in air results in diffusion of O_2 into the DES phase and *tris*-(m-sulfonatophenyl)phosphine trisodium salt (TPPTS) as a ligand was transformed to its oxide. Therefore, the latter was unable to stabilize Pd species which led to a deactivation of the catalyst.
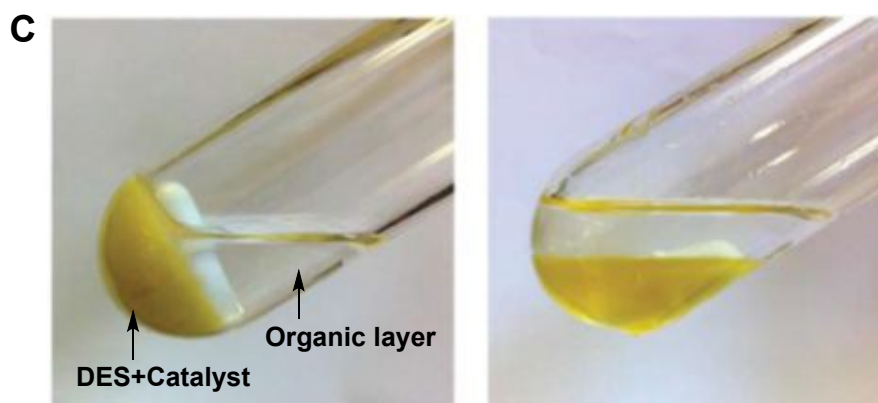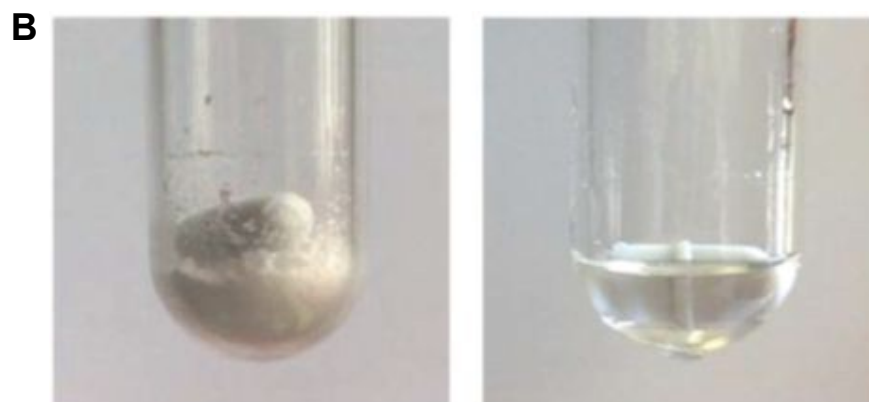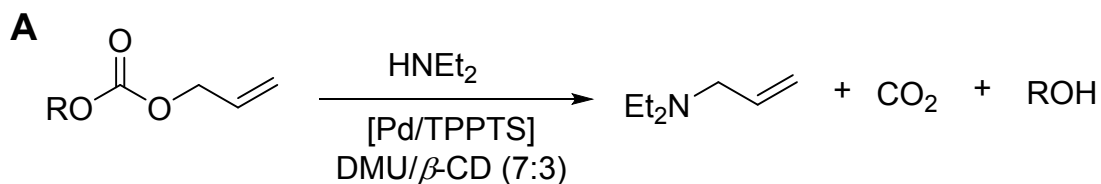
Scheme 15 A: Tsuji–Trost reaction in DES DMU/β-CD (7:3). B: DMU-β-CD (7:3) at room temperature (left) and at 90 °C (right). C: Reaction medium of Tsuji–Trost reaction at room temperature (left) and at 90 °C (right). Reproduced with permission from ref. 157. Copyright (2014) Royal Society of Chemistry.
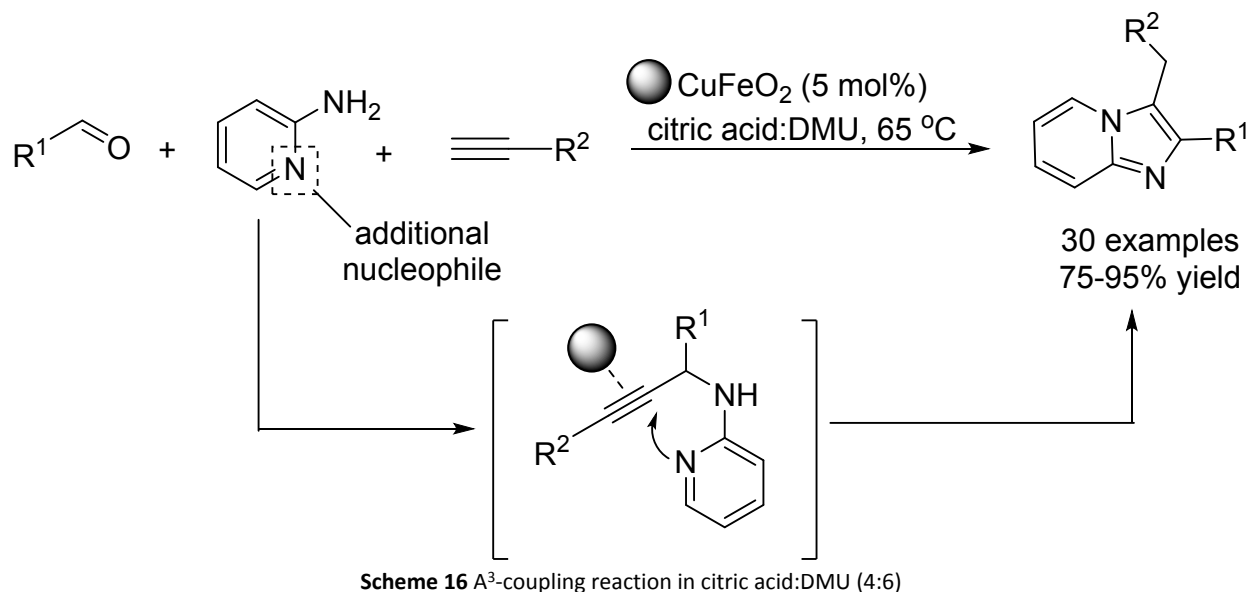
10   A³-coupling reaction

The A³-coupling, a three-component reaction, is an efficient synthetic route for the direct synthesis of propargyl amine *via* amines, aldehydes as well as alkynes. This coupling reaction is generally catalyzed by transition-metal ions, namely Au(I), Au(III), Cu(I), Cu(II), Fe(III) and Zn(II).[158] Mechanistically, the *in situ* reaction of amines with aldehydes lead to the formation of an iminium ion, followed by an attack of the metal-activated alkynes thus producing propargyl amine derivatives, which are remarkable group of building-blocks deployed in numerous organic reactions.

Zhang research group developed a practical method for the efficient access to imidazopyridines *via* a A³-coupling reaction of an aldehyde, an alkyne and 2-aminopyridine, as an amine component, employing a superparamagnetic $CuFeO_2$ nanocatalyst in DES (Scheme 16).[159] The single-phase $CuFeO_2$ magnetic nanoparticles with spherical morphology (diameter of 30–35 nm) were synthesized by the sol-gel process and sequential annealing with an approximately 1:1 molar ratio Cu:Fe. This reaction, moreover, involves a domino A³-coupling and cycloisomerization with the nitrogen atom of the 2-aminopyridine core playing the role of an additional nucleophile. This strategy, exploiting the viable one-pot approach, has been instrumental in gaining access to eminent drugs, namely Alpidem and Zolpidem. This cross-coupling reaction was examined in diverse deep eutectic mixtures, such as mannose-DMU-NH_4Cl, fructose-DMU, tartaric acid-choline chloride, and citric acid-DMU. Apart from the DESs, several typical organic solvents, such as DMF, CH_3CN, toluene, MeOH, including water and PEG 400, were evaluated in this coupling protocol. Almost no reaction occurred in these media and also it was observed that only a trace amount of product was detected in fructose–DMU, mannose–DMU–NH_4Cl and lactose–DMU–NH_4Cl at their minimal melting temperatures. Astoundingly, only citric acid:DMU (4:6) system showed the best result, one possible reason for this is that citric acid–DMU melt simultaneously fulfil a dual role as an acid catalyst and a solvent. The desired products were acquired in good to superior yields with the recyclability of the citric acid/DMU eutectic mixture and the magnetic nanoparticles in six cycles, without appreciable loss of efficiency.

Scheme 16 A^3-coupling reaction in citric acid:DMU (4:6)

In a related study, DES comprising zinc chloride and DMU (2:7) enabled efficient access to propargyl amines through A^3-coupling

reaction of aromatic aldehydes, phenylacetylene derivatives, as well as secondary amines, such as morpholine, piperidine and

diethylamine[160] including aliphatics such as heptanal and cyclopentylacetylene. To optimize the reaction conditions, the effect of

various zinc chloride based-DES and several hydrogen bond donors, such as choline chloride, acetamide, urea, DMU, were

examined for the synthesis of propargyl amine derivatives; DES plays a dual role as a solvent and catalyst, affording a wide range

of propargyl amines, in moderate to good yields.

11   Ullmann reaction

Within the cross-coupling reaction class, the first transition metal-mediated organic transformation, described by Ullmann and

Goldberg has gained widespread attention.[161] There are two different transformations referred to as the Ullmann reaction: (i)

the "classic homocoupling" reaction of aryl halides that delivers symmetrical biphenyls and (ii) the "modified" reaction which

involves Cu-catalyzed coupling of aryl halide and a heteroatomic nucleophile.[162] These reactions have shown great promise,

especially in the medical and biological sectors for the synthesis of various bio-active heterocycles such as biflavanoids,[163] high-

membered heterocyclic rings, drugs, natural products, among others.[143]

Some of the major drawbacks of this process are, for instance, the harsh reaction conditions (elevated temp. ≥ 200 °C) used, the

stoichiometric use of copper salts, and often lower yields. Recently, most of these hurdles have been circumvented via the

development of greener synthetic methodologies, such as the utilization of recyclable heterogeneous catalysts, metal- and ligand-

free conditions, microwave- and ultrasound-assisted synthesis, and the deployment of greener solvents, importantly DESs.[164] It

is needless to state that the choice of an appropriate reaction solvent is of crucial importance for successful synthesis and implementation of DESs, as non-toxic, recyclable and insensitive solvents towards moisture, thus making the century-old Ullmann reaction appropriate test case in the domain of synthetic organic chemistry.

In this context, Shaabani and Afshari illustrated the first accomplishment of Ullmann reaction in DESs for the construction of the C-N bonds via an efficient and recyclable catalytic system encompassing magnetic carboxamide-functionalized graphene oxide complexed with Cu NPs.[107] The preparation of carboxamide ligand was carried out through a one-pot sequential four-component Ugi reaction. The final pre-catalyst with a 0.01 mmol/g loading of Cu NPs had an average particle size range of 349 ±80 nm and 0.8±0.02 for the polydispersity index. Different types of bases and solvents such as DMF, DMSO, water and EtOH, with the focus on diverse DES systems, were examined. Despite relatively good yield in DMSO, DMF and EtOH in this catalytic system produced only low yields. In order to increase the sustainability of the method, authors tried to use water as green solvent, however trace amount of desired product was realized. Significantly, the yield could be improved to 99% when ChCl:gly (1:2) DES and K_2CO_3 were deployed at 110 ^{o}C (0.5-3 h) as an optimum condition. The presence of the synthesized nanocatalyst (0.05 mol%) along with DES set off the synergistic effects to promote the Ullman C-N cross-coupling. The approach is tolerant of a wide range of *N*-heterocycles and primary amines with aryl halides (Br, I) and adaptable for library synthesis. The Ullmann cross-coupling reaction under mild, greener and recyclable conditions (5 run for catalyst and DES) is favored due to the existence of readily available and low-toxic DES producing *N*-aryl amines in good to excellent yields, ranging from 75 to 99% (Scheme 17).
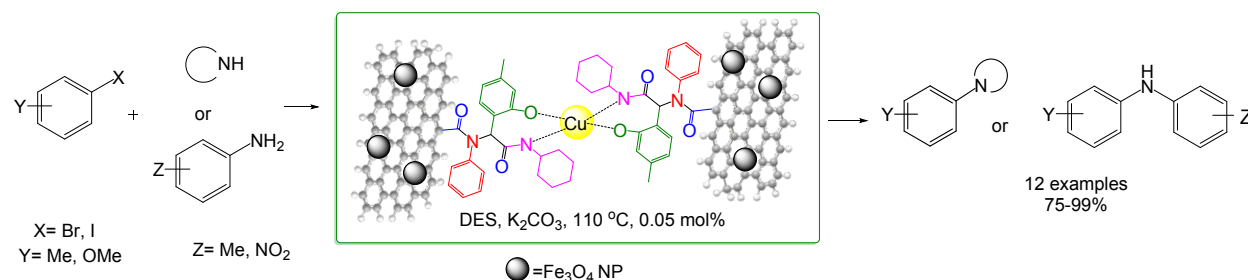
Scheme 17 Synthetic approach to *N*-aryl amines through C-N Ullmann cross-coupling reaction in ChCl:gly with Cu NP-carboxamide-*f*-GO@Fe_3O_4 catalyst

On similar lines, in 2020, Heydari research group utilized Fe_3O_4@creatine-Cu (I) magnetic nanoparticles as a reusable heterogeneous catalyst for *N*- and *O*-arylation in the presence of K_2CO_3:gly (4:1).[165] Both, the aliphatic and aromatic amines as well as phenols were directly coupled with aryl halides, and the desired products ensued in moderate to good yields using 0.04 grams of the catalyst, but 24-hours reaction time could be considered as a drawback for this catalytic system. Besides, the homogenous CuI-catalyzed *N*-arylation of aryl halides (Br, I) with aromatic and aliphatic amines was accomplished in ChCl:gly

(1:2) DES.[166] The reaction proceeded in near quantitative yields under mild conditions (60–100 °C) in air, devoid of any ligands, using CuI loading of 10 mol%, in the presence of the K_2CO_3, for aliphatic primary and secondary amines, or *t*-BuOK, for aromatic amines as the base. In addition to well-known choline-based DESs (ChCl/urea; ChCl/Gly), choline-free DESs platforms (L-proline/L-lactic acid and L-proline/glycerol), termed LTTMs, were also examined with the respective yields of 20 and 91% for the model reaction: bromobenzene and *N,N*-dimethylethylenediamine. Ironically, the choline chloride/water system embodied very low efficiency equal to water entirely (5%). Also, in this experiment, the catalyst, the DES and the base were successfully recycled up to six times with the E-factor as low as 13.8.

Shankarling's group enhanced the metal and ligand-free formation of C-O, C-N and C-S bonds *via* Ullmann cross-coupling reaction through three different reports. The authors applied a similar protocol for the *N*-arylation of aromatic and cyclic amines (80–88%; 15–30 min;),[167] *O*-arylation of ethers (80-96 %; 50 min-7 h; F > Cl > I)[168] and *S*-arylation of ethers (87-98%; 1-4.5 h; KOH (2 eq.)[169] via a 20% v/v loading of ChCl:urea (1:2) DES at 80 °C (Scheme 18). The main reason for the metal-free accomplishment of these reactions is not only due to strong nucleophilic aromatic substitution (S_NAr) mechanistic pathway, but also the utilization of aryl halides with the electron-withdrawing group, such as a nitro group. Authors also investigated different DESs for the synthesis of *O* and *S*-arylated ethers resulting in no net reaction with ChCl:oxalic acid/malonic acid/tartaric acid DESs and poor results with ChCl:gly DES. Besides, the reaction did not proceed over an extended time in choline-free DESs, such as fructose: urea. It could be argued that in all cases the reactions afforded poor yields in the sole presence of ChCl or urea even after prolonged time which highlighted the vital role of the admixed ChCl:urea.
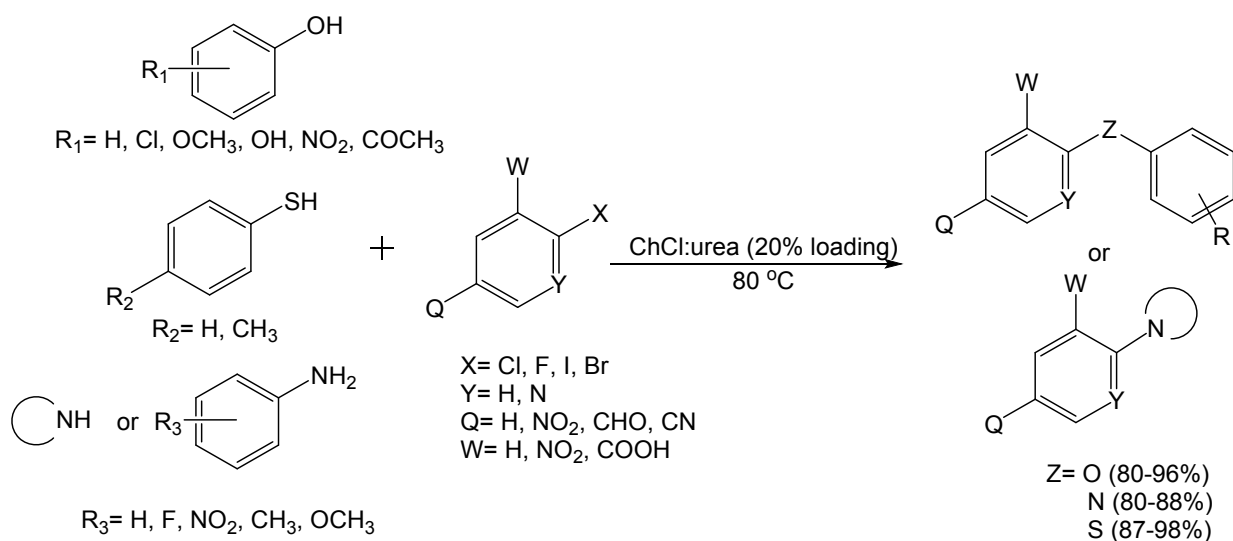
Scheme 18 C-N, C-O and C-S formation in ChCl:urea DES through Ullmann reaction

Very recently, Afshari, Hooshmand and co-workers reported a Pd-catalyzed synthesis of biaryl derivatives from aryl iodides, bromides and chlorides in DES system as a solvent.[170] For this purpose, they benefitted from one-pot pseudo-five component reaction based on the isocyanide and Meldrum's acid for the construction of pseudopeptide ligands on the surface of the multi-wall carbon nanotubes (MWCNTs), which has a high affinity to anchor Pd NPs on its side-walls, with a quantitative content of 9.2 ppm (determined by ICP) and the average size of the 5-10 nm. Two different choline chloride-based DES comprising urea and glycerol were examined. The results revealed that Ullmann homocoupling reaction with both, electron-withdrawing and electron-donating aryl halides could be accomplished in presence of 2 eq. K_2CO_3 and using ChCl:gly (1:2) DES in shorter reaction time (1-1.5 h) at 100 ^{o}C with only 0.02 mol% of catalyst loading; higher yields (80-97 %) were discerned than those performed using typical organic solvents, including DMF and DMSO, under similar conditions. In addition, the intermolecular cross-coupling reaction led to the formation of 5-benzoyl-*N*-cyclohexyl-5,6-dihydrophenanthridine-6-carboxamide in 65% yield.

12   Miscellaneous reactions

In recent years, some outstanding cross-coupling reactions have been reported in DES, which do not fall in the aforementioned category of named reactions and are therefore, discussed in this section. Ramón *et al.* reported a unique jigsaw catalytic system based on ChCl:acetamide (1:2) DES and Pd NPs for the C-S bond formation, from aryl boronic acids and sodium metabisulfite as SO_2 source (Scheme 19).[171] Notably, this reaction could be considered as a combination between Suzuki-Miyaura reaction and Ullmann type reaction due to the presence of the aryl boronic acids in substrates and also the formation of carbon-heteroatom bond in the final products. The functionalization step is compatible *via* three-component reactions with a wide range of reagents such as electrophiles, nucleophiles, or radical scavengers to afford sulfones and aryl sulfides. This procedure is unequivocally sustainable due to the possibility of selecting the appropriate components of the reaction, which engage with another as pieces in a jigsaw culminating in the formation of complex molecules in a one-pot reaction under mild conditions with a TON of 279. The catalytic platform was recyclable for three runs despite the initial loading of only 1 mol% of $PdCl_2$. The TEM of the catalytic system showed Pd clusters of 0.8 nm of average size, with around 14 Pd atoms, of which only around 3 atoms seemingly contributing to the catalytic activity. Within the same context, a novel multicomponent reaction for the expedient access to sulfonamides was introduced using a copper-catalyzed process starting from triarylbismuthines, $Na_2S_2O_5$ and nitro compounds in a new DES based on acetylcholine chloride (AcChCl):acetamide (1:2).[172] Different common DESs were examined including the conventional organic solvents such as water, MeOH and toluene. The reaction did not take place in these media and even though the reaction failed in ChCl:urea (1:2) and chlorocholine chloride:urea (1:2), yields around 50% could be obtained in both, ChCl:acetamide (1:2) and

acetylcholine chloride (AcChCl) : urea (1 : 2). However, when a new DES based on AcChCl:acetamide was applied, desired products were obtained in good to excellent yields.
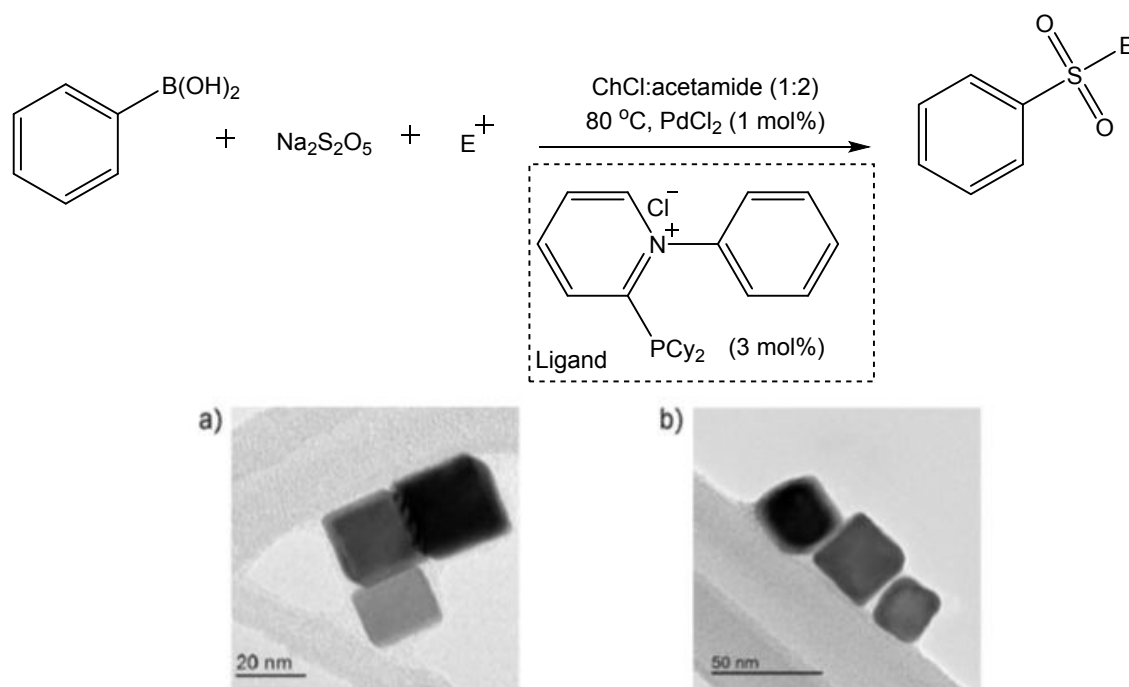
Scheme 19 Pd catalyzed C–S bond formation in ChCl:acetamide (1:2). TEM images corresponding to Pd NPs: a) cubes, b) cubes after reaction. Reproduced with permission from ref. 171. Copyright (2017) Wiley-VCH.

In a vital effort to develop a cross-coupling reaction in DES, Capriati, Salomone and co-workers accomplished a Pd-catalyzed aminocarbonylation of (hetero)aryl iodide in DES (Scheme 20).[173] The Pd(OAc)$_2$ catalyzed reaction of aryl iodides with several amines such as piperidine, 2-aminopyridine, aniline and n-butylamine under a pressure of CO (27 atm) using K$_2$CO$_3$ as a base, straightforwardly led to the desired aminocarbonylated products in excellent yields (up to 98%) in ChCl:urea (1:2) or ChCl:gly (1:2). The reactions proceeded with a fair substrate scope, and a variety of amides could be synthesized in good to excellent yields at 60 °C. Some of the salient advantages of this protocol are, for instance, the facile reaction conditions, no requirement of additional ligands, the high chemoselectivity, and the recyclability of the system (up to 5 consecutive cycles).
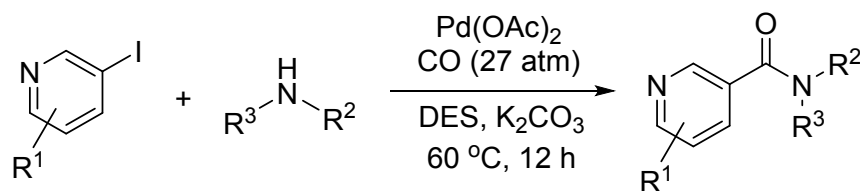
Scheme 20 Synthesis of amides *via* aminocarbonylation of aryl iodides in DES

13   Conclusions

It has been more than 15 years since the first deep eutectic solvent (DES) was developed. It is not an exaggeration to state that it has dramatically revolutionized plentiful aspects of green chemistry. This review covers important achievements related to the appliances of DESs (solvent/catalyst) in various "name-reactions" for carbon-carbon and carbon-heteroatom bond formations with focus on novel catalytic systems developed for these mediums. The superiority of DESs over conventional solvents became apparent through the solubility and stability aspects of chemical conversion, high purity of the formed products, the ready availability of constituents, facile preparation, lower reaction times, selectivity and reusability.

In general, reactions accompanied by the entropy-decreasing transformations are accelerated by pressure and as it is well known, one of the most outstanding features of DESs is their high viscosity which instigated the construction of high-pressure cavities. Cross-coupling reactions have been associated with negative activation volumes and entropy decreases. Therefore, DESs appear to be ideal candidates, as a dual solvent/catalyst for these types of transformations under high pressure and temperature.[107] The formation of cavities is dependent on several factors such as the presence of an extensive hydrogen-bonding network, relatively large ion sizes, and electrostatic forces within the liquid.[100] Based on the hole theory, the viscosity of DESs is attributed to the holes present in the fluid which generate the appropriate ionic motions.[89]

Eco-friendly and environmental benignity is the ideal pursuit for exploiting the neoteric generation of greener solvents. Therefore, the need for the recovery of the DES and catalysts is essential along with green chemistry metrics for producing recyclable, cheaper and eco-friendly methodologies for organic reactions. In the case of organic reactions in DES, since most of the components are soluble in water, addition of water to the reaction mixture dissolves the reaction medium and DES, therefore the organic products either form a separate layer or precipitate can be filtered off. Furthermore, the solvent, catalyst and reaction mixture could be recycled and reused for several runs without significant loss of their efficiency and viscosity, through a simple workup procedure which makes them sustainable candidates for fulfilling some of the green chemistry principles.

Additionally, the DES mediums make a bridge to the realm of sequential cross-coupling reaction/enantioselective synthesis by the accumulation of appropriate and biocompatible mediums to enzyme activity for chemoenzymatic transformations.[174] Moreover, thanks to some critical properties of DESs like extensive hydrogen-bonding network, high solubility and thermal capacity, they could be considered as noteworthy media for some atom-economic synthetic routes[175] such as one-pot, multicomponent, tandem/cascade/sequential or telescopic reactions which accomplishes several steps using reagents and additives that may be add into medium at regular/sequential intervals.

Task specific DESs can be modulated to suit the harsh reaction conditions of cross-couplings thus rendering them as catalytic systems rather than just reaction media. As might be expected, the physicochemical features of DES components directly influence the task-specificity of these mediums. In this context, the breadth of DESs used for assorted cross-coupling reactions along with their physicochemical parameters are summarized in Table 2. As can be concluded, the ChCl:gly (1:2) is perhaps the most frequently used DES system for cross-coupling reactions with a density of 376 Cp; higher than water. Due to the availability and low toxicity of glycerol, this platform is an ideal candidate to be deployed with ChCl to produce an ideal eco-friendly medium for the cross-coupling routes that necessitates high pressure and temperature. As can be seen, except the ChCl:gly, the other utilized DESs showed very high viscosity. Although the reaction rate in diffusion-controlled pathways decreased by increasing the viscosity, in the coupling reaction process which is accompanied by the entropy-decreasing transformation, the highly viscous DESs could elicit better selectivity and higher yield. Besides, the percentage of the absorbed water in the net of the hydrophilic DESs of ChCl:gly (1:2) revealed a momentous role in triggering the hydrolysis of organotrifluoroborates to the corresponding boronic acids in Suzuki–Miyaura reaction[122] which could expand our thinking for future impressive endeavors in designing novel *in situ* coupling systems. It could be argued that the extensive hydrogen networks, basic/acidic feature of DESs, the amount of water content, the reducibility of Pd(II) to Pd(0), oxidation state stability of metals, surface tension and the viscosity of DESs could determine the choice of particular DESs for certain cross coupling reactions. Overall, the studies so far have revealed that when there is a ligand in the medium, the best result is attained using a DES that has hydroxyl groups such as glycerol, glycol, sugars, etc. Although more studies need to be pursued to secure exact answers, it is recommended that the optimization can be offered by DES encompassing hydroxyl groups.

Table 2 DESs use in diverse cross-coupling reactions with their physicochemical parameters*

Cross-coupling reactions	Bond formation types	DES component (molar ratio)	Density (g cm^{-3})	Viscosity (cP)	T_f/T_m (°C)
Suzuki-Miyaura	R-B(OR)$_2$ (sp^2) – R-X (sp^2)	Sorbitol/mannitol/lactose: DMU:NH$_4$Cl (7/5/6:2/4/3:1)			(67) (sorbitol 7:2:1)
		β-CD:NMU (3:7)			
		ChCl:EG (1:2)	1.12	36 (20 °C)	-66
		ChCl:gly (1:2)	1.18	376 (20 °C)	-40
Mizoroki-Heck	Alkene (sp^2) – Ar-X (sp^2)	Mannose:DMU (3:7)			(75)
		ChCl:gly (1:2)	1.18	376 (20 °C)	-40
		β-CD:NMU (3:7)			
		AcChCl:urea (1:2)		2214 (40 °C)	

C-H bond functionalization	Alkene (*sp²*) – Ar-X (*sp²*)	ChCl:urea (1:2)	1.25	750 (25 °C)	12
	Alkene (*sp²*) – Ar-X (*sp²*)	K₂CO₃:gly (1:5)			
	Alkene (*sp²*) – Ar-CHO (*sp²*)	ZnCl₂:EG (1:4)	1.45		-30
	Alkane (*sp³*) – RC≡CH (*sp*)	ChCl:EG (1:2)	1.12	36 (20 °C)	-66
Sonogashira	RC≡CH (*sp*) – R-X (*sp²*)	Mannose:DMU (3:7)			(75)
		Ph₃PMeBr:gly (1:2)	1.31	887 (45 °C)	-4
		AcChCl:urea (1:2)		2214 (40 °C)	
		ChCl:gly (1:2)	1.18	376 (20 °C)	-40
		K₂CO₃:EG (1:10)			
Hiyama	R-SiR₃ (*sp²*) – R-X (*sp²*)	ChCl:gly (1:2)	1.18	376 (20 °C)	-40
Stille	R-SnR₃ (*sp²*) – R-X (*sp²*)	Sorbitol/lactose/mannitol, maltose:DMU:NH₄Cl (7/6/5/5: 2/3/4/4:1)		1732.7 (rt, maltose)	(67) (sorbitol, 7:2:1) 88 (lactose, 5:4:1) 89 (mannitol, 5:4:1)
Tsuji-Trost	π-allyl complex – RNH₂, R₁R₂NH (*sp³*)	*β*-CD:DMU (3:7)			
A³-coupling	Alkene (*sp²*) – RC≡CH (*sp*)	Citric acid:DMU (4:6)		289.6 (rt)	(65)
	Alkene (*sp²*) – RC≡CH (*sp*)	ZnCl₂:DMU (2:7)			
Ullmann	ROH, ArNH₂, R₁R₂NH,	ChCl:gly (1:2)	1.18	376 (20 °C)	-40
	Alkene (*sp²*) – Ar-X (*sp²*)	ChCl:urea (1:2)	1.25	750 (25 °C)	12
		K₂CO₃:gly (4:1)			
Miscellaneous	ArNH₂, R₁R₂NH – Ar-X (*sp²*)	ChCl:gly (1:2)	1.18	376 (20 °C)	-40
	ArNH₂, R₁R₂NH – Ar-X (*sp²*)	ChCl:urea (1:2)	1.25	750 (25 °C)	12
	RS-[M] – Ar-X (*sp²*)	ChCl:acetamide (1:2)			51
	RS-[M] – Ar-X (*sp²*)	AcChCl:acetamide (1:2)		1:09	

* Physicochemical data taken from references 36, 40, 45 and 88

Based on the current state of knowledge, the high strain cavities inside the matrix of the DES with extensive hydrogen-bonding network is responsible for providing the cross-coupling product with high yield in shorter duration, and, also, promotes the coupling reactions efficiency as a co-catalyst. Also, DESs could form more H-bonds between different molecules than ILs and metal salts, thus, they mimic to have more catalytic active sites. Since DESs are not chemically inert and can interfere with the reaction, could influence the cross-coupling reactions in a different way than conventional solvents, acting not only as a solvent but also as a catalyst via the fine tuning of the components. The basic/acidic feature of DES based on utilized components and hydrogen bonding are primary factors for high selectivity and reactivity in the reactions. Although in some cases yields may be lower compared to the conventional solvents, several recycling runs in most of cases afforded consistent yields. In addition, one of the other interesting peculiarities of task-specific, and dual-role playing DES systems in the Pd-based cross-couplings, is their

ability to function as a reducing agent for Pd(II) to Pd(0) during the formation of the catalyst and the reaction pathways.[124] A higher activity and thermal stability of the Pd catalysts in DESs prompted higher yields. In addition, DESs could stabilize the metal catalysts while many of them in water are sensitive to oxidation. Moreover, the high thermal stability and low flammability allows cross-coupling reactions to be performed at high temperatures, which is not possible in volatile solvents.

14   Future trends and prospects

In this section, a perspective view on the opportunity and future trend of DES performance in the cross-coupling domain is advanced. Despite all the aforementioned prolific advances, only a narrow range of DESs have been utilized in cross-coupling reactions which leaves open a gateway to opportunities and challenges in this field. The future prospects could be evolved by utilization of the convenient eco-benign DESs systems that were not envisioned for cross-coupling reactions until now e.g. the DES with chiral components for conduction of the chirality, enantio- or diastereo-selectivity to the products. Since as a metallic DES only zinc-containing DES were investigated, the other metallic-based DESs, especially the copper, palladium and cobalt-based DES could be examined as a dual catalyst/solvent for cross-coupling reactions. Imaginatively, the predominant use of earth-abundant metals that are cheaper and safer should be investigated for cross-coupling reactions, which will open up new avenues. Besides, modern NADES platforms formulated from available natural materials could be developed for the cross-coupling reactions. Since the DES medium has shown great efficiency to combine with enzymes for chemoenzymatic catalytic procedures, it is therefore proposed that the neoteric enzyme/DES systems would be a competent avenue for future biotransformations. Moreover, the employment of a combination of alternative energy outputs, such as microwave and ultrasound or solar and visible light-assisted platforms, along with DESs would be the beginning of a new and more sustainable horizon.

Figure 2 exposes the existing knowledge gap for the other types of known cross-couplings which have not been examined in DES systems, to the best of our knowledge. Examples are, the C-C bond formations through Glaser (by far the oldest acetylenic coupling), Kumada (coupling between a Grignard reagent and an organic halide), Negishi (coupling between organic halides or triflates with organozinc compounds), Fukuyama (coupling between thioester and an organozinc halide), Castro-Stephens [coupling between copper(I) acetylide and an aryl halide in pyridine] and Cadiot-Chodkiewicz [coupling between a terminal alkyne and a haloalkyne catalyzed by a copper(I) salt] reactions, Corey-House synthesis [the reaction of between a lithium diorganylcuprate (R_2CuLi) with an organyl (pseudo)halide (R'X) to form a new alkane], as well as, C-heteroatoms formations such as Buchwald-Hartwig reaction (Pd-catalyzed coupling of amines with aryl halides), Chan-Lam coupling (coupling between of aryl boronic acid and an alcohol or an amine), among others.

Glaser	Kumada	Negishi	Fukuyama	Castro-Stephens
Cadiot-Chodkiewicz	Corey-House	Buchwald-Hartwig	Chan-Lam coupling	Liebeskind–Srogl
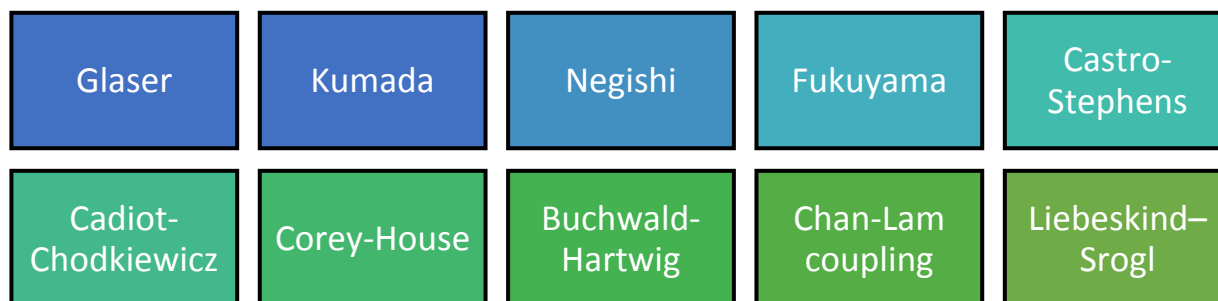
Figure 2 Cross-coupling type name reactions that still need to be explored in DESs platforms

Furthermore, the challenges of utilizing the neoteric derivatives of DES must be the design and development of low viscosity DESs due to their critical role as green media for organic reactions. The reason for this demand is the slower mobility of reagents, catalysts, bases and ligands within the current DES, due to the extensive hydrogen bonding of DES components, large ion sizes or small void volume of discovered DESs. The design of DES compatible ligands for the metallic catalyst would also be an important factor. Since the exact role of the DES as solvent/co-catalyst in cross-coupling reactions is in obscurity, more theoretical calculations need to be undertaken for a better understanding of the catalytic reaction pathways. Additionally, DESs with dual traits of lipophilicity/hydrophilicity (*e.g.* NADES) would be promising candidates for the utilization as solvents in coupling reactions with hydrophilic/hydrophobic components, due to their capability to dissolve all the reactants; increase in the interface interactions between two phases facilitates better contact.

The authors hope that this review will benefit the diverse group of scientists from the various disciplines of materials, chemistry, polymer, pharmaceutical and medicinal chemistry, catalytic systems and total synthesis for the design and development of catalytic pathways in greener medium for the construction of diverse C-C, C-S, C-N, and C-O bonds, as well as, new chemical linkages; any additional stimulation or inspiration for continued development and innovation of the neoteric eutectic solvents for conducting cross-coupling reactions would be an added dividend.

15 Abbreviation

Acethyl choline chloride	AcChCl
Acetonitrile	CH_3CN
Amine transaminases	ATAs
Choline chloride	ChCl
Copper	Cu
β-Cyclodextrin	β-CD

Cyclopentyl methyl ether	CPME
Chitosan	CS
Deep eutectic solvent	DES
Deep eutectic solvent derivatives	DESD
Decomposition temperature	T_{dcp}
Dimethyl sulfoxide	DMSO
Dimethylurea	DMU
Dimethylformamide	DMF
Ethanol	EtOH
Ethylene glycol	EG
Exophiala xenobiotica	EX-Ωta
Freezing point	T_f
Glycerol	gly
High resolution transmission electron microscopy	HRTEM
Hydrogen bond acceptor	HBA
Hydrogen bond donor	HBD
Hexamethylphosphoramide	HMPA
Ionic liquids	ILs
Inductively coupled plasma	ICP
Inductively coupled plasma-mass spectrometry	ICP-MS
Low transition temperature mixtures	LTTMs
Methanol	MeOH
Multi-wall carbon nanotubes	MWCNTs
N-Methyl urea	NMU
Natural deep eutectic solvents	NADES
Nanoparticles	NPs
Poly(ethylene glycol)	PEG
Palladium	Pd
Single-electron transfer	SET
Scanning electron microscopy	SEM
tris-(m-sulfonatophenyl)phosphine trisodium	TPPTS
Tetrahydrofuran	THF
Therapeutic deep eutectic solvents	THEDES

Transmission electron microscopy	TEM
Volatile organic compounds	VOC
X-ray photoelectron spectroscopy	XPS

Conflict of Interest

Authors declare no conflict of interest.

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