Chapter 7

Recent Advances in Sustainable Organocatalysis

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Abstract

The recent advances on green and sustainable organocatalysis are revised in this chapter. An important focus on one of the 12 principles of green chemistry, organocatalysis pursues to reduce energy consumption as well as to optimize the use of different resources, targeting to become a sustainable strategy in organic chemical transformations. In last decades, several experimental methodologies have been performed to make organocatalysis an even greener and sustainable alternative to stoichiometric approaches as well as non-catalytic conditions by the use of benign and friendlier reaction media. In this line, several approaches using water as preferential solvent, alternative solvents such as ionic liquids including chiral ones, deep eutectic solvents, polyethylene glycol (PEG), supercritical fluids and organic carbonates or solvent-free methodologies have been reported. In this chapter, we mainly focus on the recent remarkable advancements in organocatalysis using green and sustainable protocols.

Keywords: water, solvent-free, heterogeneous organocatalysis, alternative solvents, sustainable organocatalysis

1. Introduction

Aqueous reactions can combine the unique physical properties exhibited by water and other desirable advantages from the point of view of environmental concerns, safety and low cost. For many cases, the application of water is limited due to the reduced solubility and stability of diverse organic substrates in aqueous media as well as the problems associated with possible contamination of water phase with organic substrates and the need of efficient purification steps.

Alternatively, the strategy to use solvent-free organocatalysed reactions has also been explored. In these cases, a large excess of reagent, which acts as reaction media avoiding the additional use of auxiliary solvents is tested. Alternative solvents such as ionic liquids (ILs); acyclic and cyclic carbonate and polycarbonate solvents (e.g. dimethylcarbonate and polyethylenoglycol derivatives); fluorinated solvents and supercritical carbon dioxide have been largely explored for catalytic processes. In this context, the large number of examples is centred in the application of ionic liquids including chiral ones as efficient reaction media for several organic transformations. Taking advantage of physical, chemical and thermal properties of ionic liquids as well as the possibility to tune their properties according to the adequate cation-anion combinations, it is possible to develop designer solvents for organocatalytic reactions. Also, the high capacities to solubilize and stabilize different organic, inorganic and polymeric materials as well as the reusable and recyclable behaviour are relevant parameters to justify the large application of ionic liquids in synthesis and catalysis. Recent advances showed the potential use of supercritical carbon dioxide as unique solvent or in combination with ionic liquids for efficient reaction-extraction processes. Supported catalytic processes as efficient, greener and recyclable methodologies for some organocatalytic processes have been also described. The organocatalysts including chiral ones can be incorporated in solid supports improving their stability and catalytic activity as well as the possibility to reuse and recycle several times without significant decrease in their performance. The use of alternative techniques such as microwave irradiation and ultra-sons (sonication) instead of the traditional synthetic protocols will be also reviewed. One of the most important challenges of synthetic chemistry is related with the combination of efficiency, reduced costs and environmental impact in the production of relevant molecules, particularly for the preparation of chiral compounds. The creation of chiral centres can be achieved by several methodologies such as by using chiral auxiliaries, readily obtained by chemical manipulation of chiral natural and non-natural compounds by asymmetric catalysis including biocatalysis.

2. Organocatalytic reactions in water

Traditionally, the majority of organic reactions have been performed in organic solvents, mainly due to the fact that most organic compounds are not very water-soluble. In addition, many reagents used in organic synthesis are destroyed by water. This fact is contradictory to what happens in nature, where reactions promoted by enzymes and antibodies take place in aqueous media. Despite their utility in solubilising substrates and reagents, organic solvents are toxic and volatile. Water has a few obvious advantages over organic solvents [1–4]; it is relatively abundant, non-toxic, non-flammable and inexpensive. In addition, it has a large temperature window in which it remains in the liquid state and high heat capacity, making it a good and safe heat sink for exothermic reactions, particularly important when they are carried out on a large scale. Water also has a large dielectric constant, high surface tension, hydrogen bonding capacity and optimum oxygen solubility. Since the solvent is usually present in large excess, it can play an important role in the reaction. Initially, it was thought that the presence of water was only detrimental to organic reactions [5]; it brought insolubility

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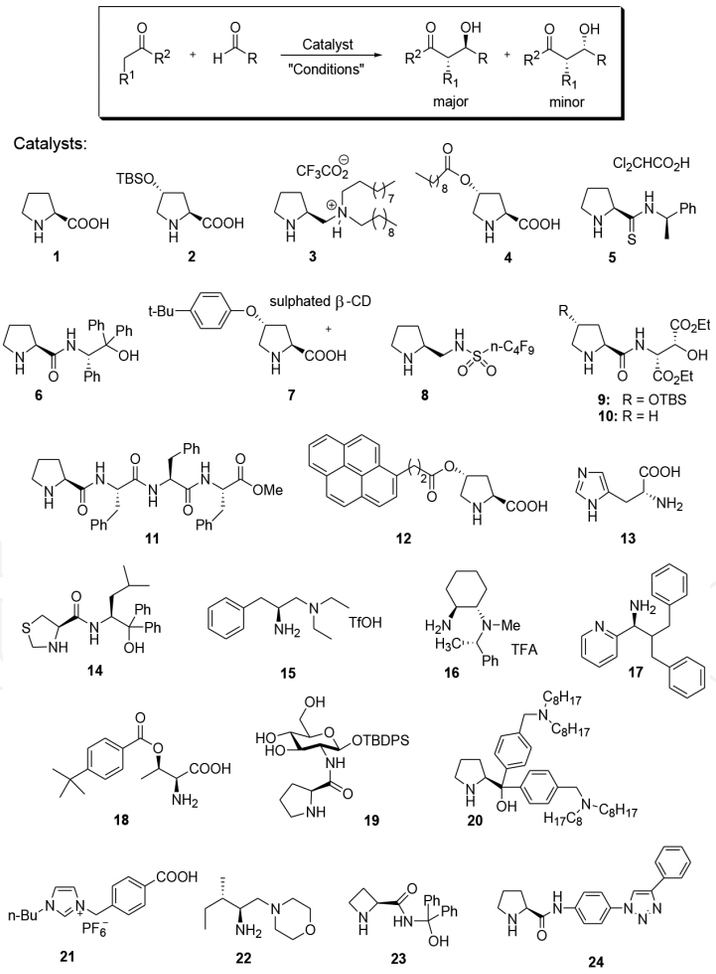
problems, and it could react with functional groups from different substrates, slowing them down and causing low yields. Due to its capacity to form hydrogen bonds, water could disrupt H-bonding in transition states, i.e. those formed between catalyst and substrate molecules, deteriorating catalytic activity and stereocontrol. Pioneering studies by Breslow showed that Diels-Alder reactions were accelerated in water [6]. This fact was a surprise, since Diels-Alder reactions are relatively insensitive to solvent polarity. He determined that the acceleration was due to the fact that in the presence of water, the less polar reagents would be drawn together in hydrophobic hydration, resulting in a more favourable overall entropy. The increase in concentration led to rate enhancements. In 2005, Sharpless showed that many uni- and bimolecular reactions were accelerated when carried out in vigorously stirred aqueous media [7]. Reactions which took place as an emulsion displaying rate acceleration, he described as taking place 'on water'. It would later be observed that under the right conditions the benefits of water may be not only to rate acceleration but also to increased selectivity (vide infra). The effect of water on organocatalytic reactions was investigated even when the first examples of this type of catalysis were studied, i.e. in the direct proline-catalysed aldol reaction (**Scheme 1**). This reaction, in which two unmodified carbonyl compounds react to give a β-hydroxy



Scheme 1. The direct aldol reaction and a selection of catalysts which perform well in aqueous media.

carbonyl product, is used by aldolase enzymes for the biosynthesis of carbohydrates, keto acids and some amino acids. In organic synthesis, the organocatalytic direct aldol version is catalysed by chiral amines via *in situ* formation of imines and then enamines, in a mechanism similar to that used by aldolase Type I enzymes and antibodies. This C-C bond-forming reaction is extremely useful and it may be used for the stereoselective assembly of complex polyols. Nowadays, the use of water as a solvent for few asymmetric organocatalytic reactions was already described, but studies on the aldol reaction predominate by far in the literature [8–10].

2.1. The direct aldol reaction

The capability of proline (1) to promote asymmetric direct intra-molecular aldol reactions was shown in the Hajos-Parrish-Eder-Sauer-Wiechert cyclisation in 1971. However, despite the utility of this reaction for the synthesis of steroids, it would be only 30 years later that the broad applicability of this catalyst would be discovered and the first inter-molecular version of the direct aldol was described by List and Barbas [11]. High yields and stereoselectivities can be obtained with proline catalysis in organic solvents, but addition of water to the reaction mixture lowers the yields and stereoselectivities, not only in these examples but also in other studies reported in subsequent years. In the asymmetric direct aldol reaction, the chemo-, regio-, diastereo- and enantioselectivity should be controlled. Side reactions are possible, which reduce the yield: aldol condensation, aldol reaction and condensation of the aldehyde acceptor and also oxazolidinone formation between the catalyst and the aldehyde. Excess ketone is often used to prevent aldehyde homodimerisation and catalyst kill events. Another inherent problem is that aldol reactions are very difficult to achieve under stoichiometric conditions, since the equilibrium constants for many direct ketone-aldehyde aldol reactions are just barely on the side of the products. Pihko and co-workers were the first to observe significant rate enhancements, yield and stereoselectivity increases in the proline-catalysed aldol reaction when small amounts of water (1–10 equiv.) were added to a DMF solution of acetone or 4-thianone and various aromatic aldehydes [12]. The effect obtained was such that the reaction could be performed with equimolar quantities of reagents. The beneficial role of water was attributed to a suppression of the competing reaction which leads to oxazolidinone formation. The first direct aldol reactions performed solely in water were later described independently by Hayashi [13] and Barbas [14] in 2006. To achieve their aim, these authors developed novel organocatalysts derived from proline containing hydrophobic groups. In these reactions, aldehyde and ketone substrate molecules aggregate excluding water, thus generating a two-phase system. Hayashi's catalyst, 4-siloxyproline 2 (**Scheme 1**) operates in the organic phase where enamine formation takes place. A reaction in this heterogeneous system was defined by Hayashi as a '*direct aldol reaction in the presence of water*' as opposed to a system in which the reactants are dissolved in water, which he labelled '*reactions in water*'. In these reactions, water is not an inert second phase, but it influences the stereoselectivity and yield, although an explanation for the effect obtained was not presented. Barbas and co-workers performed the direct cross-aldol reaction of cyclohexanone (2 equiv.) with 4-nitrobenzaldehyde in pure water, obtaining the *anti*-aldol product in 94% *ee*. Catalyst loading could be as low as 1 mol% with protonated diamine 3. This catalyst is a water soluble quaternary

ammonium salt with long hydrophobic chains, and it probably worked at the water-organic interface of the emulsion formed, in a similar way than organic surfactants.

In an emulsion, hydrophobic catalysts also reduce the contacts between the transition state and bulky water. Catalysts 2 and 3 were less efficient in reactions with non-activated aldehydes showing lower yields and *ees* of products. Hayashi also developed catalyst 4 for cross-aldol reactions of aldehydes in water [15]. In the presence of 5 equiv. of aliphatic aldehyde, products were isolated in moderate to high yields, high *drs* and *ees* (89–99%).

The concepts applied in the development of catalysts 2–4 would also be used for catalyst design in subsequent years (**Scheme 1**). Proline analogues obtained through derivatisation of the carboxyl or the amino groups and 4-hydroxyproline derivatives have predominated. These reactions are usually *anti*-selective while the use of acyclic amino acids and analogues usually promote *syn*-selective reactions.

Due to space limitations, in the examples the highlighted solvent was usually pure water without the addition of any organic co-solvents, although in some cases one of the carbonyl components was used in excess and could play the role of a solvent too.

Gryko studied in more detail hydrophobic aggregation processes [16]. The use of different salting-in and salting-out conditions in the reaction between cyclic ketones and aromatic aldehydes catalysed by protonated thioamide 5 showed that both the reaction rate and stereochemistry were affected by the rate of hydrophobic aggregation. Around this time, Singh described a very efficient prolinamide (6) for *anti*-aldol reactions between ketones and aldehydes in brine [17]. As little as 0.5 mol% provided very high *ees* even in reactions of acetone. The efficiency of this catalyst was ascribed to its capability to activate the acceptor aldehyde through the formation of hydrogen bonds via the amine and hydroxyl groups and also to a salting-out effect. Armstrong emphasized product recovery and developed protected hydroxyproline 7 which, when used in water with a sulphated β-cyclodextrin, allowed the formation of *anti*-aldol products from equimolar amounts of cyclohexanone and aryl aldehydes. The products could be obtained in quantitative yields after a simple filtration [18]. Catalyst recovery and recycling was possible with Wang's fluorous proline sulphonamide 8, developed for aldol reactions between ketones or aldehydes with aromatic aldehydes on water. The catalyst was recovered by fluorous extraction and reused up to seven cycles [19].

In 2008, Gong developed highly reactive prolinamide 9, showing that only 1 mol% was enough to catalyse the direct aldol between a wide range of aromatic aldehydes and 2 equiv. of cyclic or linear ketones in water to afford products in high yields and *ees* (91–99%) [20]. For direct aldol reactions of hydroxyacetone and fluoroacetone with electron-poor aromatic aldehydes, the related prolinamide 10 (20–30 mol%) was developed [21]. However, for hydroxyacetone products (with 84–96% *ees*), THF/water mixtures (2:1) were required. Chiral 1,4-diols, which are disfavoured products in aldol reactions catalysed by aldolases or L-proline, were obtained as the major products. This regioselectivity was possible only when water is presented. Similarly, fluoroacetone would only react when water was added to the THF solution. Theoretical studies revealed that water forms hydrogen bonds with the amide oxygen of the prolinamide and the hydroxyl of hydroxyacetone, which influence the regioselectivity by

micro-solvation. Previously, the same group had used small proline-based peptides, e.g. catalyst 11, which also worked well provided water was presented [22]. Contrary to what is observed with cyclohexanone, the aldol reactions of cyclopentanone are more difficult, and often the *drs* obtained are low. As little as 2 mol% of catalyst 12, developed by Gruttadauria in 2008, catalysed reactions with aromatic aldehydes, giving *ees* in the range 93–99% [23]. The solvent was pure water, but 5 equiv. of ketone were used. In the same year, Zhao achieved the direct cross-aldol reaction between ketones and β, γ-unsaturated ketoesters with 2 [24]. Two chiral centres, one quaternary, were assembled in 98 to more than 99% *ee* when cyclohexanone was the selected substrate. The reaction was faster and the yield and stereoselectivities were higher in water. Other ketones provided lower *ees*, but *dr* remained very high (≥19:1). Cross-reactions of aldehydes are particularly problematic to achieve because of the formation of various side products, in particular the self-aldolisation is very difficult to control. When secondary amines are used, anti-products are obtained. The first cross-aldol reaction in which α-branched aldehydes were reacted as the ene component was reported by Mahrwald in 2009 [25]. Under D-histidine (13) catalysis, *syn* β-hydroxyaldehydes were obtained in high yields and very high *ees*. Electron-rich aldehydes reacted in water exclusively as the ene component and electron-poor aldehydes as the carbonyl component, allowing for the formation of quaternary carbon centres. Aldol methodologies were applied for the first time to total synthesis of pantolactone and lyxose. Also in 2009, Singh developed highly reactive L-cysteine-derived 14, which promoted even aldol reactions of acetone (a problematic substrate) in brine, in quantities as low as 1 mol%, with several aromatic aldehydes affording 70–86% yields, 96–99% *ees* [26].

Despite all these developments, during the next five years the organocatalytic direct aldol reaction still continued to attract considerable attention and catalysts with novel backbones were reported. Luo used primary-tertiary diamine Brønsted acid 15 to obtain the otherwise difficult to get *syn* aldol products, isolated after borohydride reduction [27]. Good results were reported with linear and branched aldehydes. Glycoaldehyde donors were also used, but in DMF, although it was observed for the first time for these substrates that addition of water caused large improvements in *ee*.

In an early study on the cross-aldol reaction of ketones catalysed by proline, Garden and co-workers explored the effect of water [28]. They found that when excess acetone was reacted neat with isatins, which may be viewed as a type of activated ketones, addition of small amounts of water gave large enhancements in yields and *ees*. In 2010, Singh showed that cross-aldol reaction between cyclohexanone and five substituted isatins is possible in water in the presence of primary-tertiary diamine Brønsted acid 16 [29]. The *syn* products, which are potential anti-convulsants, were obtained in excellent *drs* and high *ees* in either DMF or water. The majority of catalysts tried during this period were based on amino acids. Nugent used a different template to obtain 2-pycolylamine 17 [30]. It performed very well affording 89–99% *ees* in reactions between cyclic ketones, including *N*-Boc-piperidone and aromatic aldehydes, in water or brine, in the presence of 2,4-dinitrobenzenesulphonic acid. Simple O-acylation of threonine provided novel surfactant organocatalysts, e.g. 18 [31]. When tested by Fu on reactions between cyclic or aliphatic ketones and aromatic aldehydes, high yields and

stereoselectivities were described. Even unprotected hydroxyacetone could be reacted in water with nitrobenzaldehydes to provide very good results too. The catalyst could be recovered and reused without loss of performance when tried on a large-scale reaction (25 mmol aldehyde). In the same year, Caputo showed that D-glucosamine could be used successfully as a catalyst template when coupled with L-proline, e.g. in 19, to promote the direct aldol reaction between cyclohexanone and substituted benzaldehydes in brine [32]. Catalytic loading could be as low as 2 mol% to provide very high *ees* (82–99%). Ni, Headley and co-workers were the first to achieve successfully the direct asymmetric cross-aldol reaction of acetaldehyde (10 equiv.), a difficult substrate prone to undergo side reactions with various aromatic aldehydes in aqueous media [33]. To catalyse the reaction, a diaryl prolinol containing dioctylamino groups (20) (5 mol%) was used, with ionic liquid 21 (10 mol%) as co-catalyst. The products were isolated in high yields and *ees* after borohydride reduction. Also, in 2013 the catalyst loading in cross-aldol reactions of ketones in water was lowered to a new minimum value: from 5 to 1 mol%. This was possible with new primary-tertiary diamine catalyst 22 developed by Chimni for reactions of isatins [34]. In 2014, Wang developed azetidine-2-carboxamides 23 as catalysts [35], which were tested on aldol reactions between acetone and benzaldehydes in brine. The yields varied in the range of 38–88%, being lower with more demanding substrates (67–96% *ees*). In the same year, Dash developed a novel approach to obtain tubuvaline precursors based on a prolinamide 24 catalysed aldol reaction of thiazole carbaldehydes with ketones 'on water' [36]. Tubuvalin is the core structure of a family of tetrapeptides, the tubulysins, which are the most potent anti-cancer agents known so far. The best results obtained with methyl isopropyl ketones donors were when 20 mol% catalyst was used together with two acid additives, formic acid and 2,4,6-trifluorobenzoic acid. The formation of a branched product competed, but when the reaction was performed in water, the linear aldol product was obtained with >99:1 regioselectivity and 92% *ee*. The authors reasoned that the facial linear selectivity was due to the preferential formation of the least substituted enamine, since the more substituted one is thermodynamically less favourable due to greater steric congestion. In this system, the reactants and the catalyst remain undissolved during the reaction. When a soluble ketone, acetone, was reacted, the product was racemic, but an enantioselective reaction was possible when the catalyst was changed to proline with *R*-BINOL as co-catalyst.

2.2. The Mannich reaction

The asymmetric Mannich reaction is one of the most important methods for the synthesis of enantioenriched molecules containing a stereogenic carbon-nitrogen bond. Of lately, there have been several reports on Mannich reactions performed in organic solvents to which small amounts of water were added [1, 37]. Reported methods using water as unique reaction media are few, probably because this is more difficult to achieve due to the inherent susceptibility of the imine substrates to hydrolysis [1]. Enamine catalysis was used in all cases. The first reaction performed solely in water was described by Ibrahim and Córdova in 2006 [38]. They showed that 10 mol% of TMS-protected prolinol **25** catalysed the Mannich reaction between aldehydes (3 equiv.) and glyoxylate imines, to afford *anti*-products in moderate yields but very high stereoselectivities (97–99% *ee*).

In 2007, a three-component Mannich reaction of O-benzyl hydroxyacetone, *p*-anisidine and aliphatic or aromatic aldehydes, taking place solely in water, was described by Lu [39]. The reaction was promoted by primary amino acid, derived from L-threonine, and also led to the formation of *O*-protected *anti*-1,2-amino alcohols in good to excellent yields and high *ees*. Amedjkouh and Brandberg described an interesting example of autocatalysis based on a direct Mannich reaction when cyclohexanone was reacted with *N*-PMP-protected glyoxylate imine [40]. The product was found to act as a catalyst for its own replication and the *ees* obtained in aqueous solutions (pH 7) were much better than those obtained in organic solvents. The major product was *syn*-configured. Teo, Lau and Wu found that 5–10 mol% of a TBDPS-protected L-serine could catalyse the three-component Mannich reaction between ketones, aldehydes and *p*-anisidine in water. In this example, *syn*-products were obtained with aliphatic aldehydes, but *anti*-products were produced from cyclic ketones [41]. Protected hydroxyl proline was found by Hayashi to promote *syn*-selective Mannich reactions between linear aldehydes and glyoxylate imines. The reactions were more favourable in basic solutions made with sodium bicarbonate and the products could be obtained in good yields and high stereoselectivities [42]. For the three-component reaction of dimethoxyacetaldehyde with cyclohexanone and *p*-anisidine, siloxy-tetrazole hybrid catalyst afforded the product in 95% *ee*. In 2011, this group reported an asymmetric Mannich reaction between imines formed *in situ* from aliphatic and aromatic aldehydes and amidesulphones, catalysed by prolinol 25. In these *anti*-selective reactions performed in basic solutions, β-amino aldehydes were obtained with excellent *ees* [43]. Tao's isosteviol-proline conjugates were used in water to promote three-component Mannich reactions between cyclohexanone, aromatic amines and aromatic aldehydes [44]. *Syn* Mannich products were obtained in high *drs* and *ees*. More recently, in 2013, Šebesta and co-workers developed a Mannich reaction between ethyl *N*-PMP-iminoglyoxylate and cyclohexanone which afforded β-aminoketones in a high yield of 70% and high stereoselectivity [45]. The best catalyst reported for this reaction was proline sulphonamide, which also promoted a Mannich-type cyclisation domino reaction between ethyl *N*-PMP-iminoglyoxylate and 5-hydroxypentanal. The aldehyde is available commercially as a water solution, in which it is present predominantly in the cyclic hemiacetal form, tetrahydro-2*H*-pyran-2,6-diol. The desired tetrahydropyridine was obtained in excellent *dr* (>95:5) and 96% *ee* but a low yield (20%) compared to reactions in organic solvents.

2.3. The Diels-Alder reaction

The Diels-Alder reaction was one of the first organocatalytic asymmetric reactions to be studied in pure water [46]. In 2002, Northrup and MacMillan reported that linear and cyclic enones reacted with cyclopentadiene in the presence of the chiral amine salt of oxazolidinone 26, to give bicyclic adducts in good yields and high stereoselectivities (**Scheme 2**) [47]. The reaction presumably proceeds via the formation of an intermediate iminium, a process which lowers the energy of the HOMO, facilitating the cycloaddition. When R^2 was bulky, e.g. *i*-Pr, the yield dropped considerably, and the product was racemic as a result of steric inhibition to iminium formation. In reactions of ethyl vinyl ketone and acyclic dienes, yields and *ees* were even higher and the endo selectivity was greater than 100:1 in all cases. In 2005, Lemay and

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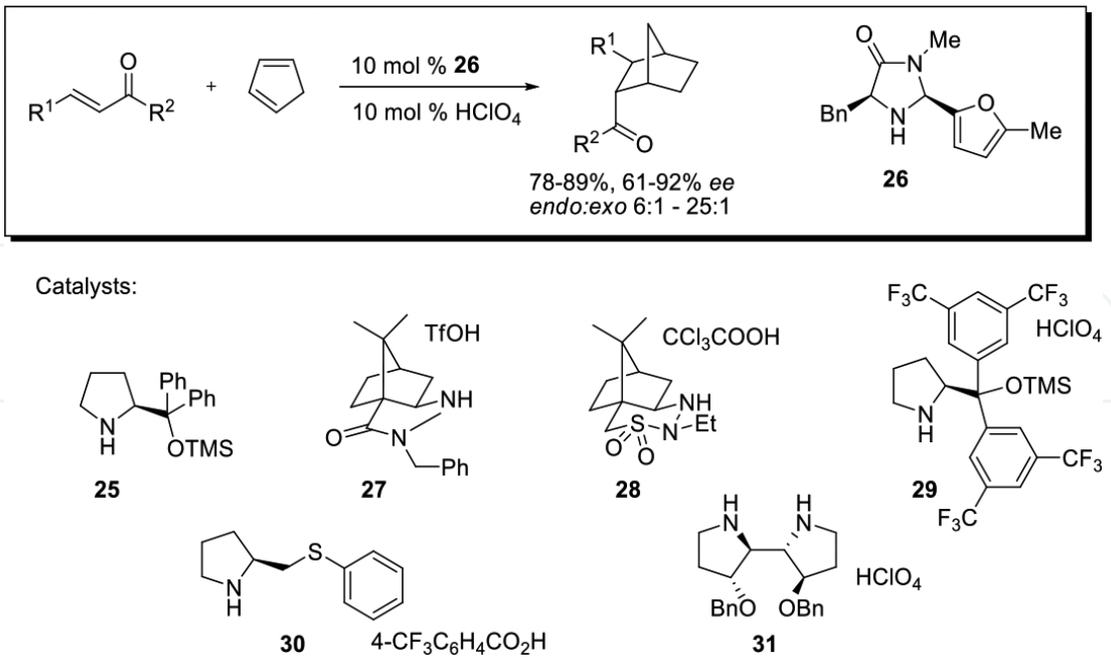
Ogilvie showed that aldehydes can also be used as dienophiles [48]. Protonated cyclic hydrazide 27 afforded high yields (71–96%) and *ees* (69–94%) of products in reactions of linear enals with cyclopentadiene. The diastereoselectivity was low, with either *endo* or *exo* isomers predominating according to the structure, the enal. Later, Lee described the use of camphor sulfonyl hydrazines like 28 to promote Diels-Alder reactions between aldehydes and cyclopentadiene in brine [49]. In the presence of trichloroacetic acid, high yields of predominantly endo products were obtained in high *ees*. The *dr* was once again low (1:0.9–1:2.5 *exo*/*endo*). In 2008, Hayashi and co-workers widened the scope of the organocatalytic aqueous Diels-Alder reaction of enals showing that a low loading of 5 mol% of TMS-protected pyrrolidine salt 29 provided high *drs* and *ees* of product with a variety of cyclic and acyclic dienes with cyclopentadiene or linear dienes [50]. Water accelerated the reaction and increased *ees* but in brine the results were worse, as a result of a detrimental salting-out effect. In this case, the reaction was *exo*-selective and pyrrolidine salt 29 afforded better *drs* than the camphor-based catalysts previously developed (62:38 to 85:15). In 2009, Xu's pyrrolidine-based catalyst 30 allowed for the first time Diels-Alder reactions of cyclohexenones with nitroolefins [51]. Water was found to provide both rate acceleration and higher *ees* with respect to organic solvents and eventually the reactions could also be performed in brine and in seawater. When the catalyst (20 mol%) was used in conjunction with 4-trifluoromethylbenzoic acid, high yields (55–99%) and *ees* (83–96%) were reported for a variety of substrates. The *exo*/*endo* ratio was higher than 25:1 for all the products. The dienamine obtained via reaction of the catalyst with the ketone and the Diels-Alder adduct resulting from the cycloaddition prior to enamine hydrolysis in the reaction of cyclohexenone with β-nitrostyrene could be detected by ESI-MS analysis. In 2010, Zhang and co-workers developed C_2-symmetric bipyrrolidine 31 for Diels-Alder



Scheme 2. The first organocatalytic asymmetric Diels-Alder reaction performed in water and other catalysts for cycloadditions in aqueous media.

reactions of enals with cyclopentadiene in water [52]. High yields of products and *ees* could be obtained but in this *exo* selective reaction *dr* was also low (0.8-1:2.2-1). The catalyst could be recycled up to five cycles without losses in stereoselectivity, but after the 4th cycle the yield dropped. In 2011, Merino showed that 1,3-dipolar cycloaddition reactions could be performed in water to afford cyclic nitrones [53].

The reaction promoted by 28 was initially developed as a one-pot procedure involving addition of aldehydes to nitroolefins, followed by *in situ* reductive cyclisation. The nitrones were obtained in good yields and more than 99% *ee*. The addition reaction was then performed on 5-hexenal. The resulting alkenyl nitrones underwent spontaneous intra-molecular 1,3-dipolar cycloaddition reactions leading to tricyclic derivatives containing four chiral in high yields and excellent *ees* simply by pH adjustment to 6 and stirring a few hours at room temperature. It is important to mention that in all cases only one enantiomer was reported in the literature.

3. Organocatalytic reaction in alternative solvents

In previous years, the search of alternative solvents as sustainable reaction media for asymmetric organocatalysis have been reported [54]. In particular, ionic liquids including chiral ones: polyethylene glycol (PEG) derivatives, organic carbonates and supercritical fluids are the major examples of alternative solvents already tested with comparable or even better performances than conventional organic solvents [55].

3.1. Ionic liquids and chiral ionic liquids

Ionic liquids as organic salts with low melting point (lower than 100°C) have emerged as environmentally benign alternative media to classic organic solvents [56]. Some peculiar properties of ILs such as their almost negligible vapour pressure, high thermal stability, high ionic conductivity, large electrochemical window, insolubility in supercritical CO_2 ($scCO_2$) and significant dissolution performance of a large range of organic molecules and transition metal complexes are very attractive for application in organic synthesis and catalytic processes. In general, the physical and structural properties of the ILs are dependent on the suitable combination of cation/anion structures.

The possibility to use different ILs as efficient and recyclable reaction media is one important parameter for applications in organocatalysis. Additionally, the organocatalyst can be dissolved and stabilized into IL allowing to preserve its catalytic activity for several cycles [57]. In 2002, two independent reports [58, 59] showed the possibility to use ILs as alternative solvent for asymmetric aldol reaction between acetone and some aromatic aldehydes in the presence of (S)-proline (1–30 mol%) as organocatalyst. The best results (94% yield and 89% *ee*) were obtained using 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6] as IL and the organocatalyst could be reused four times without significant decrease in the yield and enantioselectivities. After these first reports, other research groups have used ILs as reaction media for different organocatalytic reactions such as Michael reaction [60]; Mannich reaction

[61]; Diels- Alder [62]; alfa-amination [63] and alfa-aminoxylation [64], among others [65]. Normally, the ILs are mainly based on alkylmethylimidazolium cation combined with BF_4, PF_6, TfO and NTf_2 anions. According some limitations related to loss of catalyst during the recovery of the product and recycle of the IL media, different approaches reported an efficient linkage of the catalyst (e.g. proline) to cationic or anionic unit from IL structure [66]. The novel class of ILs-supported catalyst have been described in the literature allowing a significant improvement of stability and recycling of the catalyst [67]. It is possible to use chiral ILs by simple incorporation of chiral organocatalyst into original cation/anion scaffold or alternatively using natural chiral cations/anions based on aminoacids (protic chiral ILs and chiral ILs based on aminoacids as anions) [68].

Chiral ionic liquids (CILs) have been recognized as having potential application for chiral discrimination, including in asymmetric synthesis and resolution of racemates [69]. A transfer of chirality in these solvents should be expected; however, only a few number of chiral ILs have been reported to date [70]. The initial report from Seddon and co-workers [71] showed the preparation of CIL [bmim][Lactate] for application in catalysis. Then, a number of new chiral ILs have been synthesized and employed as chiral additives in order to induce moderate enantioselectivity in some reactions such as in Aldol reaction, photo-isomerisation, the Baylis-Hillman reaction and Michael additions [72]. Recently, several chiral ILs have been reported based on introduction of chiral units in the organic cation or anion by efficient synthetic methods. In parallel, many examples have described the use of natural chiral sources such as aminoacids or commercially available chiral compounds such as chiral carboxylic or sulphonic acids [73]. A larger number of reported chiral ionic liquids derive their chirality from the cationic moiety. Taking advantage of the readily available chiral precursors such as amines, aminoalcohols and amino acids, it is possible to incorporate them in cationic structures.

In this context, Bica and co-workers [74] reported the synthesis and application of basic chiral ILs based on (S)-proline incorporating alkylpyrrolidinium cations and NTf_2 as anions. The authors designed these CILs in order to replace trifluoroacetic acid in enamine-based organocatalysis for asymmetric C-C bond reactions. In the case of asymmetric aldol reaction of 4-nitrobenzaldehyde and acetone, moderate to high yields and enantioselectivites (up to 80% *ee*) were obtained as a novel strategy for acid-free organocatalytic process. Then, González et al. [75] developed CILs based on chiral α-amino amides particularly derived from (S)-valine, (S)-phenylalanine and (S)-leucine for application as solvents or additives for direct enantioselective aldol reaction. Moderate to good yields and enantioselectivities for aldol reaction between p-nitrobenzaldehyde and acetone were obtained using these CILs or [bmim][NTf_2] as additives. A transfer of chirality from the chiral reaction media has been observed as well as the participation of match interactions of the chiral medium with both enantiomers of proline. The catalytic system was recovered by simple filtration, and their reuse and recycle is possible at least four times with only a slight reduction in activity. Zlotin and co-workers [76] reported a novel recyclable prolinamide-derived ionic-liquid-supported organocatalyst of asymmetric cross-aldol reactions in aqueous medium. In particular, they used aromatic aldehydes reacting with cyclic or linear ketones to give chiral aldol adducts in moderate to high yields and good *dr* (anti/syn

up to 96:4) and *ee* (81–99%) values. The catalyst was recycled more than 10 times without any reduction of catalytic efficiency. Chauan et al. [77] published an efficient method for the enantioselective Diels-Alder reaction between cyclopentadiene and crotonaldehyde (94% conversion of product with exo/endo (1/1.1) and 90% *ee* of endo product) catalysed by recoverable MacMillan catalyst tailored with imidazolium ionic liquid at room temperature. In this conditions, IL-supported MacMillan catalyst is used as catalyst in the presence of trifluoroacetic acid (5 mol%) as co-catalyst, and it is reported that the catalyst can be reused up to five cycles without any significant decrease in conversions and *ee*'s values. De Nino et al. [78] described a novel chiral organocatalyst based on (5S)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone hydrochloride for enantioselective Diels-Alder reactions in good yields with good to excellent enantioselectivities. This catalyst can be recovered and recycled for further transformations at least six times with the retention of its catalysis and enantioselectivity. In addition, only 6 mol% of catalyst and a slight excess of donor aldehyde (1.5 equiv.) are required, without additional organic solvent for final purification step. Recently, Kragl and collaborators [79] reported a novel strategy for the embedding of quinine-based organocatalysts in polymer ionic liquids-based hydrogels for application in asymmetric nitroaldol (Henry) reaction. Using this organocatalyst encapsulated into polymer IL, it is possible to recover and reuse the catalyst four times without any loss of enantioselectivity (up to 91% *ee*) and significant catalytic leaching (<0.01%).

3.2. Polyethylene glycol and deep eutectic solvents (DESs)

Polyethylene glycol as alternative media for asymmetric aldol reaction was first reported in 2004 by the Chandrasekar group [80]. The authors tested different aldehydes and ketones with comparable yields and enantioselectivities than conventional organic solvents. Also, PEG400 and Proline as catalyst were recycled at least 10 times without any decrease in the activity. In 2011, Verma et al. [81] described PEG-embedded thiourea dioxide (PEG.TUD) as an useful and recyclable host-guest complex organocatalyst for the synthesis of 3, 4-dihydropyrimidones via Biginelli condensation in order to afford the desired pure product in high yields. It is interesting to know that these results are in contrary to unreactive PEG-thiourea complexes (PEG.TU) for similar reaction condition processes. Despite the potential use of PEG derivatives as biocompatible alternative reaction media for organocatalysis, only few examples in the literature have been reported.

Deep eutectic solvents were first introduced by Abbott and co-workers [82] to describe the formation of a liquid eutectic mixture (mp 12°C) starting from two solid materials with high melting points: choline chloride (ChCl, mp 133°C) and urea (mp 302°C) in a molar ratio of 1:2. DES are generally formed by suitable combinations of two or three safe and inexpensive components which are able to engage in hydrogen-bond interactions with each other to form an eutectic mixture with a melting point lower than either of the individual components. The application of DES as alternative solvent for catalysis is very promising mainly because no purification is required; their physicochemical properties can be easily tuned according to specific reaction requirements, and they offer convenient methods of product isolation simply

based on organic phase extraction or even precipitation upon addition of water, which can be subsequently removed, thereby restoring a reusable DES [83]. In recent years, DES have been applied in the fields of biotransformations, metal-catalysed reactions, organometallic chemistry and also in organocatalysis. Benaglia and co-workers [84] published three distinct stereoselective reactions (addition reactions: isobutyraldehyde to β-nitrostyrene; E-3-methyl-3-nitroethylacrylate to benzylacetone and 4-hydroxycoumarin to benzaldehyde) catalysed by a chiral primary amine through different activation methods. For these reactions, they tested three different DES (choline chloride: urea, 1:2; choline chloride: fructose; water, 1:1:1; choline chloride: glycerol, 1:2) in order to obtain the desired chiral products in high yields and enantioselectivities. Also, the use of these unconventional and biorenewable reaction media based on DES allowed the recovery and the recycling of the chiral catalyst.

3.3. Supercritical fluids and organic carbonates

The use of supercritical carbon dioxide (*sc*CO_2) as an alternative medium for organocatalytic reactions is very promising from the 'green chemistry' viewpoint [85]. CO_2 in the supercritical state (critical point 31.1°C, 73.8 bar) is characterized by higher diffusion rates and a unique capability of dispersing poorly soluble reagents, thus enhancing the reaction scope, rates and selectivity. In 2014, Zlotin and co-workers [86] reported the first enantioselective organocatalytic reaction in the *sc*CO_2 medium, in particular asymmetric Michael addition of diphenylphosphite to α-nitroalkenes in the presence of tertiary amine-squaramide-derived bi-functional organocatalysts. The reaction products, chiral β-nitrophosphonates, are precursors of β-amino phosphonic acid derivatives that occur in nature and possess valuable biological activities. In the reported reaction conditions (100 bar, 35°C), α-nitroalkenes enantioselectively accept diphenylphosphite in the presence of bi-functional organocatalysts bearing the tertiary amino group and the squaramide fragment to give corresponding β-nitrophosphonates in high yields and enantioselectivities (up to 94% *ee*). The use of *sc*CO_2 is crucial for reaction as well as product isolation by efficient extraction and further catalyst recovery. Recently, the same group discovered the application of supercritical fluids (*sc*CO_2 and scCHF_3) as an alternative media for asymmetric Michael domino-reactions catalysed by bi-functional tertiary chiral amines [87]. In the optimized conditions, o-N-nitrosylaminophenyl α,β-unsaturated ketones react with α-nitroalkenes in order to give functionalized chiral tetrahydroquinolenes in moderate to high yields and excellent diastereo- (*dr* > 99:1) and enantioselectivities (*ee* > 98%).

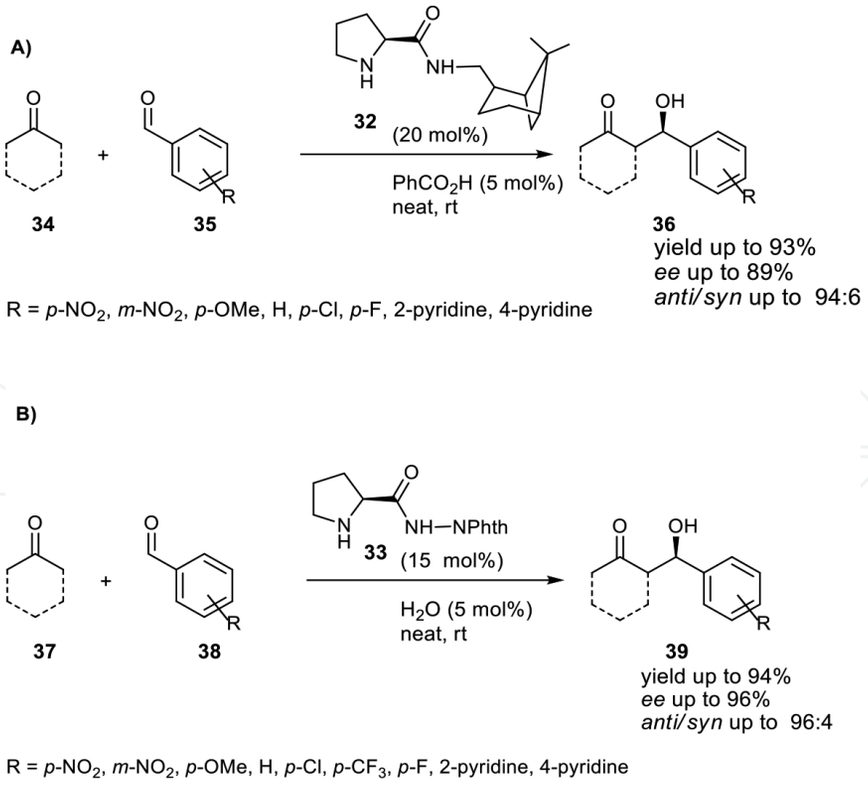
Organic carbonates have been claimed as alternative low cost and biodegradable solvents for application in organocatalytic reactions [88]. North et al. [89] reported ethylene and propylene carbonate as an alternative solvent in asymmetric aldol reactions catalysed by (S)-proline. Using cyclic and acyclic ketones reacting with aromatic aldehydes, the desired chiral aldol products were obtained in good yields and high stereoselectivities. Additionally, an appropriate combination between propylene carbonate and the proline enantiomer was observed allowing a considerable improvement in the stereoselectivity of aldol product [90]. The same authors also reported the use of cyclic carbonates as solvents for α-hydrazination of aldehydes and ketones by diazodicarboxylates using (S)-proline as organocatalyst [91].

4. Organocatalytic reaction under solvent-free conditions

On the road to sustainability, organic chemistry has been changing and the application of catalytic processes has contributed to a more efficient use of energy, less waste and the exploration of raw materials [92]. Indeed, sustainability is a growing concern in the twenty-first century, and consequently the use of solvent-free reactions in organic chemistry is gaining importance, with a foremost impact in the environmental protection as well as on human health. Organic reactions in the absence of conventional organic solvents have become highly attractive. Consequently, over the last years, the number of reactions under solvent-free conditions has grown.

4.1. Aldol reactions

The solvent-free enantioselective organocatalysed reactions have been reviewed [93] and this chapter focuses on the most recent advances. Kumar and co-workers have recently reported two new prolinamide catalysts 32 and 33 for direct stereoselective organocatalytic and direct aldol reaction of aldehydes and ketones to produce the corresponding β-hydroxy carbonyl compounds under neat conditions [94, 95]. Catalyst based on myrtanyl-prolinamide that was synthesized in two steps from *N*-Boc-L-proline and *cis*-myrtanylamine using standard peptide coupling conditions followed by Boc group removal. The authors also explored the D-proline version of catalyst 32; however, similar results were found and only



Scheme 3. Two approaches of solvent-free enantioselective aldol reactions.

this catalyst was further explored. The best catalytic conditions comprised the use of 20 mol % of catalyst and 5 mol% of benzoic acid as an additive. Several other additives were investigated such as acetic acid, formic acid, phenol, CSA, TFA and *p*-TSA. The protocol revealed to be highly effective for the preparation of several aldol adducts with high yields and high stereoselectivities under solvent-free conditions (**Scheme 3A**) [94]. Furthermore, the same authors reported the use of catalysts 33 for asymmetric direct aldol reaction, compatible with solvent-free conditions [95]. The phthalimido-prolinamide was prepared in a similar procedure, in two steps from *N*-Boc-proline and *N*-aminophthalimide. The enantioselective aldol reaction catalysed by 33 was performed using various ketones 37 and aldehydes 38 (**Scheme 3**), and proved to be effective with 15 mol% of catalyst under neat conditions. The use of 5 mol% of water accelerated the reaction and the α-hydroxy carbonyl product 39 could be attained in high yields and high stereoselectivities. Proline-containing catalysts under solvent-free conditions have also been explored by Juaristi and co-workers. They reported the use of four (*S*)-proline-containing dipeptidic organocatalysts bound to MBHA (4-methylbenzhydrylamine) resin in the asymmetric aldol reaction between cyclohexanone and several aldehydes [96]. The authors have explored different spacers (linker between the proline moiety and the resin) with different lengths in order to investigate the influence in catalytic activity in the case of spacial position of the catalyst attached to resin. Preliminary studies with all catalysts pointed 40a (10 mol%) as the best catalyst for the aldol reaction of 41 with 42 to afford 94% of isomer anti-**43** with 74:26 (*anti*/*syn*) and 77:23 (*er*). However, the conditions were optimized and the presence of benzoic acid and water as additive showed considerable improvement of the yield of 56 to 99% as well as higher stereoselectivity. Concerning the four catalysts 40a–**d**, under the optimized conditions, organocatalyst 40c gave best results. Although the results obtained were very similar for all the catalysts tested. The authors concluded that the spacer length of the bound catalyst had a slight influence on the catalytic activity, and that 40b and 40c showed an improved stereoselectivity. Furthermore, organocatalyst 40c can be reused at least for five consecutive cycles. A limitation of these catalysts is that they are not effective for less electrophilic aldehydes. Then, Jurasti and Machuca also reported the use of a dipeptidic organocatalyst in the asymmetric aldol reaction between 41 and several aldehydes under solvent-free conditions and mechanochemical activation in a ball mill [97]. Previous studies suggested that the catalysis by dipeptides and prolinamides is operative [98]. The authors proposed that the pyrrolidine moiety in catalyst activates the ketone through formation of a chiral enamine intermediate, and the aldehyde is activated by the formation of a strong hydrogen bond, via amide NH. Furthermore, they proposed that a non-covalent π-π interaction between aromatic rings of the catalyst and the aldehydes leading to a rigid transition state and inducing a higher stereoselectivity in the condensation reaction. Thus, the authors decided to explore the catalyst containing a naphthyl substituent in order to obtain further data to support the proposed non-covalent π-π interaction between the aromatic ring of catalyst and aldehyde units. The fact that the reaction is carried under solvent-free conditions and with the use of HSBM (high speed ball milling) allowed reduction of the molecular motion. Thus, this dipeptide catalyst was prepared via condensation of *N*-Cbz-(*S*)-proline and the hydrochloric salt of the methyl ester of (*S*)-naphthylalanine and subsequent *N*-deprotection via hydrogenation under Pd/C. Several ar-

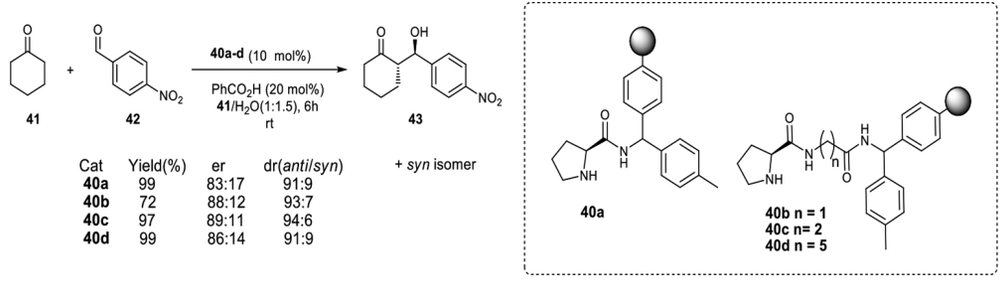
omatic aldehydes were tested and the reaction was carried in a ball mill. Higher stereoselectivities and higher yields (except for aldehyde possessing *m*-Cl group) were obtained with aldehydes possessing electron-withdrawing groups on the aromatic ring. Best stereoselectivity was reported for aldehydes possessing a *p*-metoxy and *per*-fluorinated aromatic ring (99:1, *anti*/*syn*) and *er* (99:1). The results obtained supported the proposed transition state in which a π-stacking between naphthyl ring of the catalyst and electron poor aromatic aldehyde furnishes a more rigid transition state and therefore a higher stereoselective aldol reaction.

Additionally, the same group has further used solvent-free conditions and evaluated the use of three (*S*)-proline containing dipeptides as organocatalysts in asymmetric aldol reactions of cyclohexanone (41) p-nitrobenzaldehyde (42) and under ball-milling conditions [99]. The authors have used three different protocols: solvent-free under HSBM activation; neat conditions with conventional stirring; and in solution phase. The HSBM was the best strategy since shorter reaction times were needed and higher stereoselectivities were observed. Some catalysts led to comparable yields and stereoselectivity [98% yield, 90:10 (*anti*/*syn*) and 90:10 *er*]. Thus, the authors concluded that the presence of a second stereogenic centre in the α,β-dipeptide organocatalysts did not result in a higher stereoselectivity comparing with examples with one stereogenic centre. Asymmetric aldol reactions under solvent-free conditions have been further explored by Nájera and Gómez-Bengoa [100] comparing with examples with one stereogenic centre (**Scheme 4**).

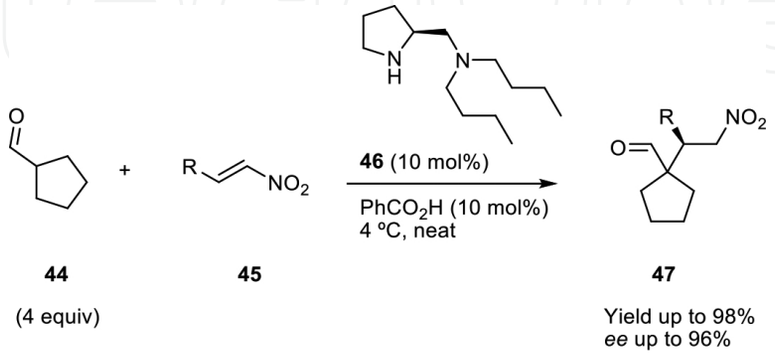
4.2. Michael addition reactions

Asymmetric organocatalysed reactions under solvent-free conditions have been extended to Michael addition reactions. Recently, Bolm and co-workers developed an efficient, solvent-free protocol for Michael addition reactions of α-nitrocyclohexanone to nitroalkenes using thiourea derivatives as catalysts [101]. These reactions have been carried out in sustainable conditions, using planetary ball mill, with low catalyst loading and short reaction times, leading to high yields (up to 97%) and high enantioselectivities (*er* up to 98:2). In a previous study, the authors have developed the use of natural amino acid-derived bi-functional thioureas as bi-functional organocatalysts in the asymmetric Michael addition reaction [102]. On the follow-up of this work, the authors investigated mechanochemical effects induced by ball milling on the aforementioned thiourea-catalysed asymmetric Michael addition reactions of α-nitrocyclohexanone to nitroalkenes to provide desired products. The reaction conditions were optimized such as the catalyst loading. The reaction proceeded with high stereoselectivity even with 1 mol% of catalyst; however, the yield was lower (57%) and thus 2.5 mol% of catalyst was used. Thiourea-organocatalysts have also been explored by Hestericová and Šebesta as hydrogen-bonding organocatalysts for the Michael addition reaction to nitrostyrene under solvent-free conditions [103]. Thus, different thioureas have been used involving aminoalcohols, Cinchona alkaloid, binaphthyl diamine, bis(thiourea) and also squaramides. The authors have performed comparative reactions in a ball mill and in solution. In terms of yields, both reactions proceeded well; however, a large variation of yields was obtained (19–95%) under solvent-free conditions. The use of an additive such as benzoic

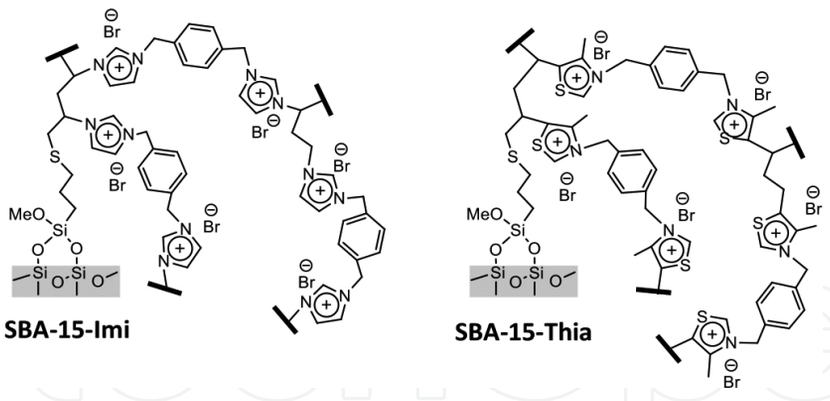
acid or mandelic acid (20 mol%) improved the yield from 50 to 80% and 95%, respectively, in the case of the reaction carried in the ball mill. Concerning enantioselectivities, the best results were obtained with thiourea catalysts as well as with Cinchona-containing catalyst, which increased the enantiomer ratio up to 10:90. A pyrrolidine-diaminomethylenelononitrile organocatalyst was developed by Miura and co-workers for the Michael addition of carbonyl compounds to nitroalkenes under solvent-free conditions [104]. The novel organocatalyst promotes the asymmetric conjugate addition of cyclohexanone to nitroalkene to afford the corresponding adduct in high yield with up to 99% *ee*, under solvent-free conditions. The novel organocatalyst based on the skeleton of DMM (diaminomethylenemalononitrile) efficiently catalysed the reaction employing low amounts of catalyst and in a short reaction time under mild conditions, affording high enantioselectivity. The authors proposed that the DMM skeleton can act as an efficient double hydrogen bond donor for Michael additions to nitroalkenes under solvent-free conditions. A highly efficient and simple asymmetric organocatalytic Michael addition of α,β-disubstituted aldehydes 44 to nitroolefins 45 under solvent-free conditions was developed by Ni and co-workers [105]. The authors have developed a chiral pyrrolide-based diamine 46, that in combination with benzoic acid, proved to be very effective in order to prepare the adduct 47 in high yields and high enentioselectivities (up to 96% *ee*) with a wide range of Michael acceptors (**Scheme 5**).



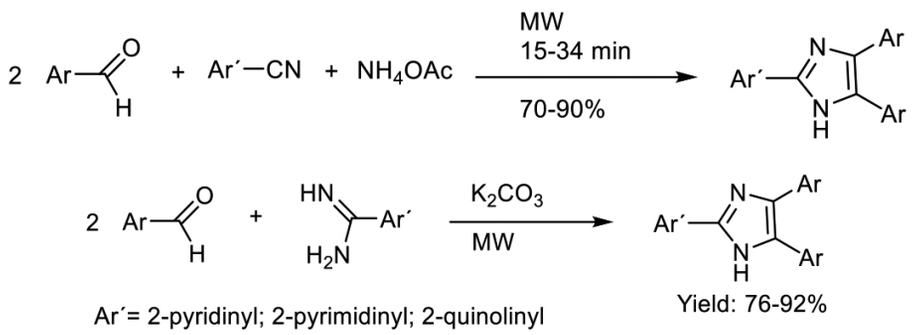
Scheme 4. Solvent-free approach using (S)-proline containing dipeptides as organocatalysts in asymmetric aldol reactions.



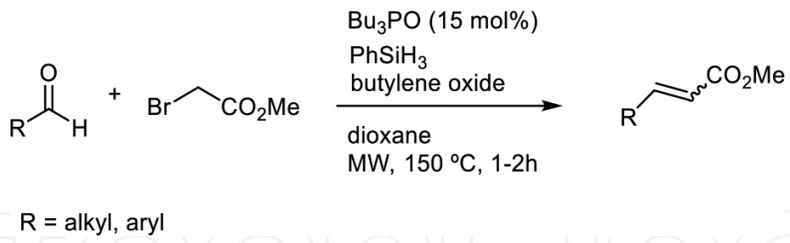
Scheme 5. Highly efficient and simple asymmetric organocatalytic Michael addition of α, β-disubstituted aldehydes to nitroolefins under solvent-free conditions.



Scheme 6. SBA-15 mesoporous silica functionalized with imidazolium (SBA-15-Imi) and thiazolium groups (SBA-15-Thia).



Scheme 7. Multi-component synthesis of 2-(2′-azaaryl)imidazoles under microwave irradiation.



Scheme 8. Microwave-assisted catalytic Wittig reaction.

The organocatalytic Michael reaction of ketones with γ-monohalonitrodienes was reported by the Xu group using chiral prolinethiol ether as organocatalyst for the synthesis of functionalized monohaloalkenes, under solvent-free conditions [106]. After optimisation of the reaction conditions, the reaction scope was examined and several substitutions on the aromatic ring were investigated (for X = Br), and several groups were well tolerated (e.g. *p*-Cl and *p*-CF_3), as well as several ketones. Furthermore, the enantioselectivity of the reaction was not much affected by the substituents on the cyclic ketone. The authors highlighted that the reactions proceeded on the sterically less hindered carbon, which is opposite to the other acyclic ketones. They propose that the balance between steric effects and stability of the

enamine derived from the catalyst and ketones might favour the formation of the terminal Michael adduct. Different substituents on the γ-position of the nitryl scaffold demonstrated that nucleophiles possessing substituents can be used to form the desired adducts in high diastereoselectivities and high to excellent enantioselectivities. The method represents a novel approach for accessing highly functionalized monohaloalkenes with α,β stereocentres of up to >99% *ee*. In 2015, Jurasti and co-workers reported the organocatalysed Michael addition reaction under solvent-free conditions of ketones to nitro-olefins [107]. The authors synthesized several organocatalysts derived from chiral (*S*)-proline containing a thiohydantoin moiety. The prepared thiohydantoins were evaluated as organocatalysts in asymmetric Michael addition under solvent-free conditions, using cyclohexanone and β-nitrostyrene as models.

4.3. Mannich reaction

Organocatalysed Mannich reactions have also been recently explored under solvent-free conditions. Fioravanti and co-workers have reported the synthesis of trifluoromethyl *syn*- or *anti*-amino alcohols by one-pot solvent-free Mannich-type reactions under temperature control [108]. On the basis of their previous results [109], these authors explored a one-pot solvent-free approach [110]. Thus, a L-proline catalysed Mannich-type reaction was investigated to prepare nitrogen-containing organofluorine compounds. On the expectation that the presence of a stereocentre in the α-position to the electrophilic site of not isolated (R,E)-aldimines could influence the diastereoselective reaction outcome, the authors started from the chiral amines(*R*)-1-phenylethylamine and (*R*)-1-(*p*-methoxyphenyl) ethylamine. The results reported demonstrated that at room temperature a mixture of *syn*/*anti* was always formed, while changing the temperature only *syn* or *anti* isomers were formed at 40 and 0°C, respectively. The products were detected by ^{19}F NMR experiments of the crude mixtures. Moreover, the chiral stereocentre on the benzyl moiety strongly affected the stereoselectivity of the reaction. The absolute configurations of the created chiral centres were determined. The protocol developed by Fioravanti and co-workers consists on a highly diastereoselective one-pot solvent-free synthesis of fluorinated *syn*- or *anti*-amino alcohols by an environmental friendly approach. Under solvent-free conditions, the authors highlight the presence of a resident stereocentre in the α-position to the imine carbon that leads to the facial stereoselective control of nucleophilic attack, suggesting that the proline is able to control only the *syn* or *anti* diastereoselectivity. A theoretical study was developed by Parasuk and co-workers about the factors that influence stereoselectivity in proline-catalysed Mannich reactions [111].

5. Organocatalytic reaction using heterogeneous systems

The immobilisation of homogeneous organocatalysts using several supports has been quite explored in previous years since in general their heterogenisation allows more stable and efficient catalyst. These parameters are aligned to the demands of sustainability and economical scalability issues. Several supports have been used: mesoporous silica [112, 113], biopolymers as chitosan [114, 115], synthetic polymers as polystyrene and polyacrylamide [116],

carbon nitrides [117], metal organic frameworks (MOFs) [118], dendrimers [119], graphene [120] and magnetic nanoparticles [121–123].

5.1. Recent approaches in heterogeneous organocatalysts

Corma and Garcia have reported silica-bound organocatalysts as heterogeneous, recoverable and recyclable catalysts in several organic transformations [112]. Heterogeneous organocatalysts based on organically modified hybrid mesoporous silica (mainly MCM-41 and SBA-15) and their efficiency in several organic transformations have been also reviewed by Rostamnia [113]. These types of supports are very stable, biocompatible and can be functionalized with a wide range of functional groups. In general, their resultant-supported organocatalyst is more stereoselective, chemoselective and efficient than the homogeneous analogous. The organic moieties supported include: amines (primary, secondary and tertiary), sulphonic acids, acid-based bi-functionalized systems, ephedrine, proline, urea, thiourea and guanidine and fluorinated alcohol [114]. Kadib [114] and Mahé et al. [115] summarized the field of organocatalytic reactions promoted by chitosan used as an insoluble organocatalyst or as a support for organocatalysts. Chitosan is ranked as the second most abundant polysaccharide after cellulose and it is obtained from deacetylation of chitin, which is exclusively extracted from industrial marine discharge. Chitin is constituted by *N*-acetyl-d-glucosamine monomers connected through β (1–>4) linkages. The presence of amino groups on the polymer backbone enables the covalent linkage of different functional groups to its skeleton. Several organocatalysts based on pyridine, proline, ionic liquids and quaternary ammonium have been supported. These chitosan derivatives showed reactivity similar to their homogeneous analogous, nevertheless the introduction of cooperative acid-based interactions enhances significantly their reactivity. Carbon nitride, for simplicity C_3N_4, mainly composed of C and N, is one of the oldest reported polymers and has many advantages when compared with traditional heterogeneous catalysts, it is abundant and cheap, metal free, tunable electronic structure and has good thermal and chemical stabilities. The group of Antonietti [117] has emphasized the recent breakthroughs in their modification and their applications as sustainable catalysts in several reactions, such as photochemical splitting of water, mild and selective oxidation and hydrogenation reactions, and in photodegradation of pollutants.

In the previous years, dendrimers have also attracted the attention of the scientific community as they combine the advantages of homogeneous catalysts, showing fast kinetic behaviour, and heterogeneous catalaysts, since they can be easily separated from the reaction mixture by precipitation, membrane or nanofiltration methods. Wang et al. described the recent advances for metallodendritic catalysts and dendritic organocatalysts [119]. Magnetic nanoparticles are another interesting supports for heterogenisation of organocatalysts since it allows their recovery with sustainable techniques of magnetic separation. Magnetite, also known as ferrite (Fe_3O_4), has a very active surface suitable for functionalisation or adsorption of several metal- and organic-based catalysts. In general, these heterogeneous catalysts are highly stable and can operate under mild conditions, using environmentally benign solvents or even water, with good performances and recyclabilities [121–123]. They have been applied in a wide range of reactions, such as Mannich-type reactions, C-C, C-S and C-O

coupling reactions, alkylation, oxidation, reductions and asymmetric synthesis. Mrówczyński et al. summarized their use as supports for organocatalysts [122], their use in asymmetric catalysis has been reviewed by Dalpozzo [123] and their application in catalysis, green chemistry and pharmaceuticals reactions are described by Gawande et al. [121]. Bartók reports the advancements of heterogeneous asymmetric direct aldol reactions using organocatalysts based on hydroxyproline, prolinamide and peptides immobilized by covalent or ionic bonding and by adsorption on different supports [124]. In order to allow the application of organocatalysts in industry, their scale-up using continuous flow technology has attracted much attention in recent years. Three very interested reviews in this field were published recently [125–127]. Puglisi et al. [126] and Atodiresei et al. [127] reported several types of asymmetric organocatalysed reactions in continuous flow and highlighted their advantages over batch reactors. Heterogeneous-supported organocatalysts are focused on both reviews. This field is still in its infancy since the examples known are applicable mostly for particular substrates and with some problems of catalyst deactivation. However, in general these processes improve the efficiency of the organic transformations by reducing the amount of catalyst loading and reactions times. Very recently, Munirathinam et al. [125] reviewed the main achievements that has been in this area but focusing on a broader range of supported catalysts including acid, base, organomettalic, peptidic, enzymatic, ionic liquids and metal nanoparticles by using the three main approaches to incorporate them into the catalytic micro-reactors: (i) packed-bed, (ii) monolithic and (iii) inner wall-functionalized. The application of these catalytic micro-reactors on several reactions and their advantages over classical batch reactors were also presented.

5.2. Some examples of heterogeneous organocatalysts in solvent-free conditions

SBA-15 mesoporous silica functionalized with mercaptopropyl groups were used for the covalent immobilisation of multi-layered ionic-liquid-like phases containing imidazolium or thiazolium active sites [128]. These new hybrid materials were used for the etherification of 1-phenylethanol under solvent-free conditions at 160°C under different gas phase (oxygen, air, nitrogen and argon). The best catalytic performances were obtained for the material bearing thiazolium groups under oxygen, and this hybrid material also showed higher catalytic activity (92% of conversion and 75% of selectivity, under O_2, 160°C, 7 h) when compared with its homogeneous analogous catalyst (92% of conversion and 72% of selectivity in the same reaction conditions). For example, the heterogeneous catalyst was recycled seven times, without loss of activity, for the etherification of 1-phenylethanol. Other two alcohols were also tested: benzyl alcohol and diphenylmethanol. García-Suárez et al. [129] have tested for the first time the catalytic activity of a Bio-IL [Chol][Pro] (choline-proline) in the Michael addition reaction and supported this catalyst on different heat-treated mesoporous carbon materials by simple physical adsorption in organic media, reporting also the catalytic activity of the heterogeneous systems. The coupling of cyclohexanone and β-nitrostyrene to produce 2-(2-nitro-1-phenylethyl)cyclohexanone was selected to evaluate the catalytic activity of the catalysts, under solvent-free and at room temperature conditions. Excellent conversions and high diasteroselectivities were obtained for the heterogeneous catalysts based on commercially available mesoporous carbon beads

heated at 1500°C and 2000°C. These results are similar to those obtained for the homogeneous catalyst. The stability of the supported Bio-IL is strongly influenced by the textural and surface chemical properties of the supports tested.

Recently, the group of Wang [130] described a new method for the hollow-structured phenylene-bridged periodic mesoporous organosilica (PMO) spheres using hematite (α-Fe_2O_3) nanoparticles as a hard template. These materials were functionalized with MacMillan catalyst (H-PhPMO-Mac) by a co-condensation process and a 'click chemistry' post-modification and by grafting. For comparison, analogous materials were prepared in the absence of hematite. Their catalytic activity was tested in asymmetric Diels-Alder reaction using water as solvent. The model reaction tested was the Diels-Alder cycloaddition of 1,3-cyclopentadiene with trans-cinnamaldehyde. The catalyst H-PhPMO-Mac has shown higher catalytic activity (98% yield, 81% enantiomeric excess (*ee*) for endo and 81% *ee* for exo) in water than its non-hollow analogous and it can be reused for seven runs without a significant loss of activity. For the homogeneous catalyst in the same conditions, lower yield of product (80%) and higher *ee* for endo (93%) and exo (91%) were obtained. The materials functionalized with the catalyst by grafting exhibit lower catalytic efficiency. Colloidal graphene oxide was synthesized through a modified Hummer's method, avoiding additional hazardous treatments, and its activity as base catalyst for the condensation of several substituted benzaldehydes with acetophenone (aldol reaction) and with active methylene compound malononitrile (Knoevenagel reaction) at room temperature and under solvent-free conditions was tested [131]. The heterogeneous organocatalyst showed high reactivity in 8 h toward Knoevenagel condensation with 97% of conversion and 99% of product selectivity. It can also be reused for five cycles without any loss of activity (**Scheme 6**).

The same group reported for the first time the incorporation of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) into the network of a nanoporous-conjugated polymer (NCP) prepared through the Sonogashira-Hagihara coupling reaction of rigid building blocks of DMAP monomer and a structural linker [132]. A nanoporous structure, mainly with mesoporous, with highly concentrated and homogeneously distributed DMAP catalytic sites was obtained and its activity in the acylation of alcohols studied. This catalyst has shown excellent catalytic performance for the conversion of several aliphatic alcohols and phenols into the corresponding ester products, at room temperature and with dry dichloromethane as solvent (if necessary), with yields higher than 90%. This heterogeneous catalyst can be reused for 14 cycles without significant loss of activity and run for 536 h under continuous-flow conditions, which shows its potential as robust heterogeneous catalyst for industrial use [132]. Guan et al. prepared bi-functionalized SBA-15 and Al-SBA-15 mesoporous materials with different matches of acid and base by immobilisation of different organic amines, 3-aminopropyltriethoxysilane and 3-(triethoxysilyl)propylcarbamoyl)pyrrolidine, through a post-synthesis method. The materials were tested in a Knoevenagel reaction, tandem deacetalisation-Knoevenagel reaction, one-pot deacetalisation-Henry reaction, aldol reaction and nitroaldol reaction. In these systems, there is a synergic effect between the acid and base which favoured different reactions. For example, weak acid matching weak base favoured the Knoevenagel reaction and nitroaldol reaction, while moderately strong acid matching weak

base showed good results for one-pot deacetalisation-Knoevenagel reaction, one-pot deacetalisation-Henry reaction and aldol reaction [133]. A bi-functional catalyst was prepared by covalent immobilisation of trans-4-hydroxy-L-proline on graphene oxide via a succinate spacer and its catalytic performance tested for the solvent-free ketene forming reaction of benzaldehyde and acetone [134]. The results demonstrated that it behaves as an efficient, recoverable and recyclable catalyst (for five cycles). The effect of different solvents on its performance was also studied.

A new approach to obtain chiral metal organic frameworks as heterogeneous asymmetric photocatalysts through the cooperative combination of stereoselective organocatalyst L-or D-pyrrolidin-2-ylimidazole (PYI) and a triphenylamine photoredox group into a single framework was developed by Duan, He and co-authors [135]. Two enantiomeric MOFs of Zn were prepared and applied to prompt the light-driven α-alkylation of aliphatic aldehydes with high catalytic efficiency and enantioselectivity. For comparison, lanthanide-based MOFsHo-TCA (H3TCA = 4, 4′,4′′- tricarboxyltrihexylamine and MOF-150, assembled from 4,4′,4″-nitrilotribenzoic acid, were studied and the results suggested that both photosensitizer triphenylamine and the chiral organocatalyst were necessary for the light-driven reaction. However, the corresponding MOF obtained by mixing the chiral moiety has shown lower enantioselectivity. Two chiral porous MOFs functionalized with carboxylic acid groups were reported for the first time by Liu et al. [136]. One of them was able to encapsulate S)-2-(dimethylaminomethyl) pyrrolidine by combining the carboxylic acids and chiral amines *in situ* through acid-base interactions. This organocatalyst revealed to be an efficient and recyclable heterogeneous catalyst for the asymmetric direct aldol reactions of both acetone and cyclohexanone with nitro-substituted aromatic aldehydes, in a ketone/water mixture at room temperature. The results indicated a significant enhancement of stereoselectivity by comparison with its homogeneous organocatalyst. The yield/*ee* values for the three consecutive runs were 73/74, 72/73 and 70/73%, respectively. Krishnan et al. [137] described for the first time the use of polystyrene-supported poly(amidoamine) (PAMAM) dendrimers of first, second and third generations as highly efficient and heterogeneous basic organocatalyst in Knoevenagel condensations of carbonyl compounds with active methylene compounds. The third generation catalyst gave the better results. The reactions of several carbonyl compounds proceeds very well in ethanol for short periods of times, at 30°C or 50°C, with product yield in the range of 95–100%. The catalyst can be recycled up to 10 times with only a decrease in the product yield from 100 to 97% and an increase of time reaction from 15 to 20 min for the reaction of benzaldehyde with malonitrile at 30°C. This catalyst is also environmentally friendly, once the use of aromatic and halogenated solvents and complicated purification processes is avoided.

6. Organocatalytic reactions using sustainable synthetic protocols

Over the past two decades, many efforts have been made both in industry and academia to develop synthetic organic protocols using more efficient methodologies with the aim to protect the environment and prevent waste. With that goal in mind, sustainable mechanochemical processes such as high-speed ball [138–140] microwave (MW) [138, 141, 142] or ultrasound

[143] are being increasingly used in the synthetic organic chemistry [144]. Employing this unconventional energy inputs, it is conceivable to offer innovative and highly appropriate alternatives to traditional synthetic processes [145, 146]. The use of microwave or ultrasound in organocatalytic processes have been previously reviewed by others [147, 148].

MW irradiation offers several advantages over conventional heating, such as instantaneous and rapid heating (deep-inside heating), high temperature homogeneity and selective heating [138, 142, 148, 149]. The observed enhancement of the reaction rate is in part associated with the rapid heating caused by MW irradiation relative to the same reaction using conventional heating. Beyond the controversial debate around the existence or not of non-thermal microwave effects, we must have to accept that MW chemistry is an effective, safe, rapid and highly reproducible way to perform chemical reactions that recently were translated to continuous flow processes [149, 150]. Also, the possibility to performing the MW and ultrasound reactions in the absence of a solvent is a major advantage [151]. An example is the Michael addiction of diethyl malonate to several enones catalysed by (*S*)-proline (15 mol%) under solvent-free conditions. The Michael adducts were obtained in short reaction times with good yields and moderate to excellent enantioselectivities (40–99% *ee*) [152]. In another procedure, pyranones were prepared under microwave irradiation and solvent-free conditions in ball-milling through a oxa-Diels-Alder reaction between α,β-unsaturated ketones and aldehydes. Enantioselectivities up to *e.r*. 63:37 were observed with chiral pyrrolidine-based organocatalysts [153]. Also under solvent-free conditions, Qaroush and collaborators reported a microwave-assisted preparation of [6]-oligourea based on an isocyanate-free method utilising propylene carbonate as a green carbonylating agent and 1,6-hexamethylene diamine under catalysis of 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD). Whereas dynamic mode microwave-assisted synthesis gave 79% yields of [6]-oligourea, almost quantitative yields were obtained using the fixed mode, within 20 min, at 10 W and with the same catalyst loading [154]. The imidazole ring is a very important motif since this ring is the key constituent of a range of bioactive compounds [155]. Multicomponent approaches between aromatic aldehydes and heteroaryl nitriles under solvent-free and microwave-irradiation conditions led to highly substituted 2-(2'-aza-aryl)imidazoles. *Anti*-1,2-diarylethylbenzamides could also be obtained in an efficient six-component approach between aldehydes and ammonium acetate [156]. The syntheses were finished within short periods (15–34 min) with good to excellent chemical yields and stereoselectivity. An interesting mechanistic approach was proposed by the authors for these two reaction processes [156] (**Scheme 7**).

Recently, the same authors describe an efficient three-component domino [3+1+1] heterocyclisation to 2-(2′-aza-aryl)imidazoles promoted by K_2CO_3 under microwave irradiation conditions [157]. This one-pot operation makes use of mild conditions and short reaction times of 20–32 min and excellent atom economy. An interesting mechanism involving a umpolung process has been proposed for the formation of the 2-(2′aza-aryl)imidazoles [157]. Catalytic amounts (10 mol%) of bis-arylureas and bis-thioureas promote the Friedel-Crafts alkylation between nitroolefins and aromatic and heteroaromatic N-containing derivatives [158]. Best results are noticed on running the reactions in the absence of solvent. When applied to indoles, this protocol provides the corresponding Michael adducts in good to excellent yields and with

high selectivity. *L*-Proline is actually one of the most studied catalysts in organic catalytic transformations [159], in particular involving Michael additions [160], and as expected quite applied also in transformations using unconventional energy inputs. The *L*-proline catalysed Michael addition of aldehydes and ketones to *trans*-nitrostyrene using microwave irradiation was investigated by Russo et al. [161]. High yields, short reaction times and comparable diastereo- and enantioselectivity were obtained under simple and more environmentally benign conditions such as the use of ethanol as solvent and only a slight excess of the carbonyl compound. Omara et al. [162] using microwave-assisted technique and *L*-proline catalysed the Michael addition reaction of aldehyde to α-styrene using the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)inide ([bmim]NTf_2) as reaction medium. The Michael product was obtained in excellent yield (96.5%) and 36.9% *ee* with 10 mol% catalyst loading, 5.0 min reaction time and 2.0 substrate equivalent ratio. Other amines where some natural alkaloids are included are also used as catalyst in organic Michael additions. A quadruple cascade Michael/Henry condensation/Michael/aldol condensation reaction allows an efficient asymmetric synthesis of tri-substituted cyclohexene carbaldehydes employing acetaldehyde and nitroalkenes as substrates. Moderate to good yields (25–45%) and high enantioselectivities (*ee* = 89–99%) were obtained [163]. Enders et al. performed the reaction between acetaldehyde and nitrostyrene in dioxane at room temperature using (*S*)-diphenylprolinol TMS-ether (20 mol%) as a catalyst. This procedure has the disadvantage of needing 14 days to complete affording the aldehyde with a moderate yield, high enantioselectivity and a good diastereomeric ratio. In an attempt to try to improve the results, the authors observed that the presence of water accelerates the reaction substantially and also tested the reaction under microwave irradiation [164]. *L*-Proline and proline analogues were used as catalyst for the α-amination of di-substituted aldehydes with azodicarboxylates under microwave conditions. It could be observed that enantioselectivity and yield could be significantly increased by the use of microwave irradiation. Although the catalyst loading is slightly high, this is an interesting protocol that allows the α-amination of branched aldehydes. An extensive study was performed by the authors changing several parameters as the temperature, solvent and reaction time [165]. Chiral squaramides have proven to be very effective hydrogen-bonding organocatalysts with application in several asymmetric transformations [166]. Sánchez-Roselló and co-workers applied chiral squaramides in intra-molecular aza-Michael reactions under microwave irradiation with conjugated *N*-acyl pyrazoles as ester-type Michael acceptors. This protocol was especially efficient in the formation of piperidine derivatives and the authors evaluate the synthesis of different 6-memberering heterocycles [167].

Chiral tetrahydroisoquinoline-based guanidines were prepared by Naicker and collaborators [168] using a microwave-assisted synthesis. The prepared catalyst was applied as chiral catalysts to promote the asymmetric 1,4-addition of β-keto esters or malonates to nitroolefins in up to 97% *ee*. α-Spirolactones and α-spirolactams can be obtained in an overall transformation involving an olefin cross-metathesis followed by an intra-molecular organocatalytic Michael-induced spirocyclisation under microwave irradiation. The Hoveyda-Grubbs catalyst can be used on the metathesis reaction and also as a spirocyclisation *N*-heterocyclic carbene catalyst [169]. Thiazolium derive *N*-heterocyclic carbene (NHC)-catalysed

Stetter reaction of acetyl anions to various α, β-unsaturated acceptors under microwave irradiation. This procedure involving microwave heating significantly increased the chemical efficiency by the substantial reduction of reaction time [169].

The aldol reaction is one of the most important carbon-carbon bond formation reactions widely employed in synthetic organic chemistry. Proline has also an important role as organocatalyst on this reaction. Liao and co-workers [170] developed a microwave-based procedure to promoted direct aldol condensation using polystyrene-supported amine catalyst. Microwave greatly shorten the reaction times to only 20 min and improved the yield significantly. This procedure has the advantage of recovering the catalyst by simple filtration and can be reused for at least four times without significant loss of reactivity. The synthesis of heterocycles can be achieved under mild conditions using microwave irradiation. Gangwar et al. [171] using oxalic acid as catalyst reported the preparation of 3,4-dihydropyrimidin-2(1H)-one derivatives by Biginelli reaction between aromatic aldehydes, ethylacetoacetate or methylacetoacetate and urea under microwave irradiation for 2–5 min. The oxalic acid was used in very low quantity (2 mol%). The antioxidant properties were evaluated and the compounds having −OH group on benzene ring were found to have higher activity. A new, efficient and convenient approach to the synthesis of new extended angular fused aza-heterocycles including dibenzacridine and naphth[2,3-a:2',3'-j] acridine units with good luminescent properties is described [172]. The multicomponent reactions (MCRs) were conducted by reacting readily available and inexpensive starting materials using thiosalicylic acid as a catalyst under microwave irradiation. A total of 14 examples were examined, and a broad substrate scope and high overall yields (72–89%) were revealed. 1,2,3-Triazoles are an interesting class of heterocyclic unit widely used in the discovery and modulation of drug candidates. The copper-free cycloaddition reaction of azidophenyl arylselenides with β-ketoesters under catalysis of diethylamine and microwave irradiation allowed the synthesis of high-functionalized-1,2,3-triazole in good to excellent yield. With microwave irradiation it was possible to reduce the reaction time from hours to few minutes [173]. The proposed mechanism involves [3 + 2] cycloaddition reaction between the azide group and the enamine followed by elimination of the diethylamine catalyst. A very interesting MW-assisted formation of polysubstituted salicylaldehydes from propargyl vinyl ethers using imidazole as catalyst was developed by Tejedor et al. [174]. A diverse array of salicylaldehydes from simple aromatic monocyclic to complex fused polycyclic systems was obtained in moderate to high yields (38–72%). Using this procedure, it was possible to achieve the benzophenone-derived natural product morintrifolin B in a five-step synthesis. The authors proved that the reaction is scalable and instrumentally simple to perform, highly regioselective and takes place under symmetry-breaking conditions. Symmetrically substituted propargyl vinyl ethers afforded asymmetrically substituted salicylaldehydes. Some protocols are being developed for the microwave-assisted catalytic Wittig reaction. Recently, Hoffmann, Werner and Deshmukh [175–177] address this subject and a very extensive study was carried out to find the scope and limitations of this reaction. Among the several catalysts tested, epoxides proved to be suitable masked bases for this reaction. Phosphine oxides $Bu_3P = O$ proved to be the most promising catalyst that can be reduced *in situ* with silanes to generate Bu_3P as the actual catalyst. Good isolated yields and excellent *E*/*Z* selectivities were achieved. In respect to the halide compo-

nent, 2-bromoacetonitrile proved to be particularly suitable, giving the desired product in yields of up to 88%. Using chiral bis-phosphines enantiomerically enriched alkene with a *er* of 81:19 were obtained (**Scheme 8**).

In another approach, McNulty and collaborators [178] have shown that it is possible to achieve high (*E*)-olefin selectivity employing phosphonium salts in water as the solvent and with weak bases, including secondary amine catalysis under MW irradiation. Extension of this procedure for the preparation of stilbenes under physiological conditions is also described. A very simple work up of the reaction involves filtration or aqueous organic partition which allows easy separation of water-soluble phosphine oxides. Taking advantage of the higher temperature achieved via either microwave (vessels heated to 190°C over 5 min) or conventional heating (5–40 min at 190°C), the decarboxylation of L-histidine and other L-amino acids were achieved with R-carvone as catalyst [179]. The use of carvone can be of advantage as any unrecovered R-carvone catalysts can hydrolyse at high-temperature to carvacrol. Ultrasound is considered an environmentally clean technology, which is based on the application of sound energy. With this technology it is possible to speed dissolution by breaking intermolecular interaction and provide the energy for certain chemical reactions to proceed. This can lead to an increased yield and selectivity of the products avoiding adverse reactions conditions that use long reaction times and high temperatures [180]. Mangilal et al. reported [169, 181] the regioselective ring opening of *trans* spiro-epoxyoxindoles with aniline derivatives, from the less hindered end, to obtain β-hydroxy-β-amino esters, in water under sonication. From the several organocatalysts used, quinine combined with urea-hydrogen peroxide (UHP) was proved to be the best for the diastereoselective epoxidation of (*E*)-3-ylidene-indolin-2-one derivatives to afford *trans* spiro-epoxyindoles. Azizi et al. [182] made use of ultrasound in water or polyethylene glycol to assist the rapid and sustainable catalyst-free synthesis of thiourea from the condensation between aliphatic aines and carbon disulphide. The traditional mechanical shaking method required prolonged reaction times, whereas sonicated reactions were completed within 5 min of ultrasonic irradiation. Unsymmetrical and symmetrical thiourea can be achieved with a very simple work up involving simply filtration of the precipitated thiourea or extraction with ethyl acetate for the liquid products. The reaction products were obtained in high purity and moderate to high yields (50–80%) with PEG offering a slightly higher yields and did not require further purification. This procedure has the advantaged over the traditional ones which resort to the use of the more dangerous thiophosgene and isothiocyanates.

Warfarin is one of the most effective anticoagulants used as a racemate. However, the (S)-form proved to be more active to its mirror image [183]. Warfarin can be achieved by the asymmetric Michael addition catalysed by organic primary amines and under ultrasound. The conjugate addition of the enolate from the 4-hydroycoumarin to an α,β-unsaturated ketone, with catalysis of (*S*,*S*)-diphenylethylenediamine afforded warfarin in 98% yield. A series of warfarin analogues were achieved in good to excellent yields (73–98%) and with good enantioselectivities (up to 76%) [184].

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References

[1] N. Mase, C. F. Barbas III. In water, on water, and by water: mimicking nature's aldolases with organocatalysis and water. Org. Biomol. Chem. 2010; 8:4043–4050.

[2] M. Raj, V. K. Singh. Organocatalytic reactions in water. Chem. Commun. 2009; 44:6687–6703.

[3] J. G. Hernández, E. Juaristi. Recent efforts directed to the development of more sustainable asymmetric organocatalysis. Chem. Commun. 2012; 48:5396–5409.

[4] B. H. Lipshutz, S. Ghorai. Transitioning organic synthesis from organic solvents to water. What's your E factor? Green Chem. 2014; 16:3660–3679.

[5] U. M. Lindström. Stereoselective organic reactions in water. Chem. Rev. 2002; 102:2751–2772.

[6] R. Breslow. Hydrophobic effects on simple organic reactions in water. Acc. Chem. Res. 1991; 24:159–164.

[7] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless. "On water": unique reactivity of organic compounds in aqueous suspension. Angew. Chem. Int. Ed. 2005; 44:3275–3279.

[8] B. M. Trost, C. S. Brindle. The direct catalytic asymmetric aldol reaction. Chem. Soc. Rev. 2010; 39:1600–1632.

[9] J. Mlynarski, S. Bas. Catalytic asymmetric aldol reactions in aqueous media – a 5 year update. Chem. Soc. Rev. 2014; 43:577–587.

[10] S. Bhowmick, A. Mondal, A. Ghosh, K. C. Bhowmick. Water: the most versatile and nature's friendly media in asymmetric organocatalyzed direct aldol reactions. Tetrahedron Asymmetry 2015; 26:1215–1244.

[11] B. List, R. A. Lerner, C. F. Barbas III. Proline-catalyzed direct asymmetric aldol reaction. J. Am. Chem. Soc. 2000; 122:2395–2396.

[12] A. I. Nyberg, A. Usano, P. M. Pihko. Proline-catalyzed ketone-aldehyde aldol reactions are accelerated by water. Synlett 2004; 11:1891–1896.

[13] Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji. Highly diastereo- and enantioselective direct aldol reactions in water. Angew. Chem. Int. Ed. 2006; 45:958–961.

[14] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III. Organocatalytic direct aldol reactions in water. J. Am. Chem. Soc. 2006; 128:734–735.

[15] Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji. Combined proline-surfactant organocatalyst for the highly diastereo- and enantioselective aqueous direct cross-aldol reaction of aldehydes. Angew. Chem. Int. Ed. 2006; 45:5527–5529.

[16] D. Gryko, W. J. Saletra. Organocatalytic asymmetric aldol reaction in the presence of water. Org. Biomol. Chem. 2007; 5:2148–2153.

[17] V. Maya, M. Raj, V. K. Singh. Highly enantioselective organocatalytic direct aldol reaction in an aqueous medium. Org. Lett. 2007; 9:2593–2595.

[18] J. F. Zhao, L. He, J. Jiang, J. Tang, L. F. Cun, L. Z. Gong. Organo-catalyzed highly diastereo- and enantio-selective direct aldol reactions in water. Tetrahedron Lett. 2008; 49:3372–3375.

[19] X. H. Chen, S. W. Luo, Z. Tang, L. F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong. Organocatalyzed highly enantioselective direct aldol reactions of aldehyde with hydroxyacetone and fluoroacetone in aqueous media: the use of water to control regioselectivity. Chem. Eur. J. 2007; 13:689–701.

[20] J. Huang, X. Zhang, D. W. Armstrong. Highly efficient asymmetric direct stoichiometric aldol reactions on/in water. Angew. Chem. Int. Ed. 2007; 46:9073–9077.

[21] L. Zu, H. Xie, H. Li, J. Wang, W. Wang. Highly enantioselective aldol reactions catalyzed by a recyclable fluorous (S) pyrrolidine sulfonamide on water. Org. Lett. 2008; 10:1211–1214.

[22] Z. Tang, Z. H. Yang, L. F. Cun, L. Z. Gong, A. Q. Mi, Y. Z. Jiang. Small peptides catalyze highly enantioselective direct aldol reactions of aldehydes with

hydroxyacetone: unprecedented regiocontrol in aqueous media. Org. Lett. 2004; 24:2285–2287.

[23] F. Giacalone, M. Gruttadauria, P. L. Meo, R. Noto. New simple hydrophobic proline derivatives as highly active and stereoselective catalysts for the direct asymmetric aldol reaction in aqueous medium. Adv. Synth. Catal. 2008; 350:2747–2760.

[24] C. Zheng, Y. Wu, X. Wang, G. Zhao. Highly enantioselective organocatalyzed construction of quaternary carbon centers via cross-aldol reaction of ketones in water. Adv. Synth. Catal. 2008; 250:2690–2694.

[25] M. Markert, U. Scheffler, R. Mahrwald. Asymmetric histidine-catalyzed cross-aldol reactions of enolizble aldehydes: access to defined configured quaternary stereogenic centers. J. Am. Chem. 2009; 131:16642–16643.

[26] M. R. Vishnumaya, V. K. Singh. Highly efficient small organic molecules for enantioselective direct aldol reaction in organic and aqueous media. J. Org. Chem. 2009; 74:4289–4297.

[27] J. Li, N. Fu, X. Li, S. Luo, J. P. Cheng. Chiral primary-tertiary diamine-Brønsted acid salt catalyzed syn-selective cross-aldol reaction of aldehydes. J. Org. Chem. 2010; 75:4501–4507.

[28] G. Angelici, R. J. Corrêa, S. J. Garden, C. Tomasini. Water influences the enantioselectivity in the proline or prolinamide-catalyzed aldol addition of acetone to isatins. Tetrahedron Lett. 2009; 50:814–817.

[29] M. Raj, N. Veerasamy, V. K. Singh. Highly enantioselective synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles, potential anticonvulsants. Tetrahedron Lett. 2010; 51:2157–2159.

[30] T. C. Nugent, M. N. Umar, A. Bibi. Picolylamine as an organocatalyst template for highly diastereo- and enantioselective aqueous aldol reactions. Org. Biomol. Chem. 2010; 8:4085–4089.

[31] C. Wu, X. Fu, S. A. Li. Highly efficient, large-scale, asymmetric direct aldol reaction employing simple threonine derivatives as recoverable organocatalysts in the presence of water. Eur. J. Org. Chem. 2011; 7:1291–1299.

[32] M. De Nisco, S. Pedatella, S. Bektas, A. Nucci, R. Caputo. D-Glucosamine in a chimeric prolinamide organocatalyst for direct asymmetric aldol addition. Carb. Res. 2012; 356:273–277.

[33] Y. Qiao, Q. Chen, S. Lin, B. Ni, A. D. Headley. Organocatalytic direct asymmetric crossed-aldol reactions of acetaldehyde in aqueous media. J. Org. Chem. 2013; 78:2693–2697.

[34] A. Kumar, S. S. Chimni. Organocatalyzed direct asymmetric aldol reaction of isatins in water: low catalyst loading in command. Tetrahedron. 2013; 69:5197–5204.

[35] X. Song, A. X. Liu, S. S. Liu, W. C. Gao, M. C. Wang, J. Chang. Enantiopure azetidine-2-carboxamides as organocatalysts for direct asymmetric aldol reactions in aqueous and organic media. Tetrahedron. 2014; 70:1464–1470.

[36] S. Paladhi, J. Das, M. Samanta, J. Dash. Asymmetric aldol reaction of thiazole-carbaldehydes: regio- and stereoselective synthesis of tubuvalin analogues. Adv. Synth. Catal. 2014; 356:3370–3376.

[37] H. Y. Bae, C. E. Song. Unprecedented hydrophobic amplification in noncovalent organocatalysis "on water": hydrophobic chiral squaramide catalyzed Michael addition of malonates to nitroalkenes. ACS Catal. 2015; 5:3613–3619.

[38] X. H. Cai, B. Xie. Recent advances on organocatalysed asymmetric Mannich reactions. Arkivoc. 2013; i:264–293.

[39] I. Ibrahem, A. Córdova. Direct catalytic asymmetric anti-selective Mannich-type reactions. Chem. Commun. 2006; 16:1760–1762.

[40] L. Cheng, X. Wu, Y. Lu. Direct asymmetric three-component anti-selective Mannich reactions in a purely aqueous system. Org. Biomol. Chem. 2007; 5:1018–1020.

[41] M. Amedjkouh, M. Brandberg. Asymmetric autocatalytic Mannich reaction in the presence of water and its implication in prebiotic chemistry. Chem. Commun. 2008; 26:3043–3045.

[42] Y.-C. Teo, J.-J. Lau, M.-C. Wu. Direct asymmetric three-component Mannich reactions catalyzed by a siloxy serine organocatalyst in water. Tetrahedron Asymmetry. 2008; 19:186–190.

[43] Y. Hayashi, T. Urushima, S. Aratake, T. Okano, K. Obi. Organic solvent-free, enantio- and diastereoselective, direct Mannich reaction in the presence of water. Org. Lett. 2008; 10:21–24.

[44] T. Urushima, H. Ishikawa, Y. Hayashi. Asymmetric Mannich reaction of imines derived from aliphatic and aromatic aldehydes catalyzed by diarylprolinol silyl ether. Chem. Eur. J. 2011; 17:8273–8276.

[45] Y.-J. An, C.-C. Wang, Z.-P. Liu, J.-C. Tao. Isosteviol-proline conjugates as highly efficient amphiphilic organocatalysts for asymmetric three-component Mannich reactions in the presence of water. Helv. Chim. Acta. 2012; 95:43–51.

[46] E. Veverkova, L. Liptakova, M. Veverka, R. Šebesta. Asymmetric Mannich reactions catalyzed by proline and 4-hydroxyproline derived organocatalysts in the presence of water. Tetrahedron Asymmetry. 2013; 24:548–552.

[47] S. Moulay, A. Touati. Cycloaddition reactions in aqueous systems: a two-decade trend endeavor. C. R. Chimie. 2010; 13:1474–1511.

[48] A. B. Northrup, D. W. C. MacMillan. The first general enantioselective catalytic Diels-Alder reaction with simple α,β-unsaturated ketones. J. Am. Chem. Soc. 2002; 124:2458–2460.

[49] M. Lemay, W. W. Ogilvie. Aqueous enantioselective organocatalytic Diels-Alder reactions employing hydrazide catalysts. A new scaffold for organic acceleration. Org. Lett. 2005; 7:4141–4144.

[50] H. He, B.-J. Pei, H.-H. Chou, T. Tian, W.-H. Chan, A. W. M. Lee. Camphor sulfonyl hydrazines (CaSH) as organocatalysts in enantioselective Diels-Alder reactions. Org. Lett. 2008; 10:2421–2424.

[51] Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa. Asymmetric Diels–Alder reactions of α,β-unsaturated aldehydes catalyzed by a diarylprolinol silyl ether salt in the presence of water. Angew. Chem. Int. Ed. 2008; 47:6634–6637.

[52] D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu. In situ enamine activation in aqueous salt solutions: highly efficient asymmetric organocatalytic Diels–Alder reaction of cyclohexenones with nitroolefins. Angew. Chem. Int. Ed. 2009; 48:3821–3824.

[53] Y. Ma, S. Jin, Y. Kan, Y. J. Zhang, W. Zhang. Highly active asymmetric Diels–Alder reactions catalyzed by C2-symmetric bipyrrolidines: catalyst recycling in water medium and insight into the catalytic mode. Tetrahedron 2010; 66:3849–3854.

[54] E. Neggish. Catalysis with d-block transition metals for green organic synthesis and a sustainable world. J. Synth. Org. Chem. Jpn. 2011; 69:1201.

[55] J. G. Hernandez, E. Juaristi. Recent efforts directed to the development of more sustainable asymmetric organocatalysis. Chem. Commun. 2012, 48, 5396–5409.

[56] R. Rogers, K. R. Seddon (Eds.). Ionic Liquids: Industrial Applications for Green Chemistry. American Chemical Society: Washington, 2002.

[57] J. P. Hallett, T. Welton. Room-temperature ionic liquids: solvents for synthesis and catalysis. Chem. Rev. 2011; 111:3508–3576.

[58] P. Kotrusz, I. Kmentova, B. Gotov, S. Toma, E. Solcaniova. Proline-catalysed asymmetric aldol reaction in the room temperature ionic liquid [bmim]PF_6. Chem. Commun. 2002; 21:2510–2511.

[59] T.-P. Loh, L.-C. Feng, H.-Y. Yang, J.-Y. Yang. L-Proline in an ionic liquid as an efficient and reusable catalyst for direct asymmetric aldol reactions. Tetrahedron Lett. 2002; 43:8741–8743.

[60] D. Sarkar, R. Bhattarai, A. D. Headley, B. Ni. A novel recyclable organocatalytic system for the highly asymmetric Michael addition of aldehydes to nitroolefins in water. Synthesis. 2011; 12:1993–1997.

[61] F.-F. Yong, Y.-C. Teo. Recyclabe siloxy serine organocatalyst for the direct asymmetric reactions in ionic liquids. Synth. Commun. 2011; 41:1293–1300.

[62] A. De Nino, O. Bortolini, L. Maiuolo, A. Garofalo, B. Russo, G. Sindona. A sustainable procedure for highly enantioselective organocatalyzed Diels–Alder cycloadditions in homogeneous ionic liquid/water phase. Tetrahedron Lett. 2011; 52:1415–1417.

[63] X. Ding, H.-L. Jiang, C.-J. Zhu, Y.-X. Cheng. Direct asymmetric α-amination of aldehydes with azodicarboxylates in ionic liquids catalyzed by imidazolium ion-tagged proline organocatalyst. Tetrahedron Lett. 2010; 51:6105–6107.

[64] H.-M. Guo, H.-Y. Niu, M.-X. Xue, Q.-X. Guo, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, J.-J. Wang. L-Proline in an ionic liquid as an efficient and reusable catalyst for direct asymmetric α-aminoxylation of aldehydes and ketones. Green Chem. 2006; 8:682–684.

[65] O. V. Maltsev, A. S. Kucherenko, A. L. Chimishkyan, S. G. Zlotin. α,α-Diarylprolinol-derived chiral ionic liquids: recoverable organocatalysts for the domino reaction between α,β-enals and N-protected hydroxylamines. Tetrahedron Asymmetry. 2010; 21:2659–2670.

[66] L. Zhou, L. Wang. Chiral ionic liquid containing L-proline unit as a highly efficient and recyclable asymmetric organocatalyst for aldol reaction. Chem. Lett. 2007; 36:628–629.

[67] W. Miao, T. H. Chan. Ionic-liquid-supported organocatalyst: efficient and recyclable ionic-liquid-anchored proline for asymmetric aldol reaction. Adv. Synth. Catal. 2006; 348:1711–1718.

[68] M. L. Patil, H. Sasai. Recent developments on chiral ionic liquids: design, synthesis and applications. Chem. Rec. 2008; 8:98–108.

[69] K. Zalewska, L. C. Branco. Organocatalysis with chiral ionic liquids. Mini-Rev. Org. Chem. 2014, 11:141–153.

[70] C. Baudequin, D. Brégeon, J. Levillain, F. Guillen, J.-C. Plaquevent, A.-C. Gaumont. Chiral ionic liquids, a renewal for the chemistry of chiral solvents? Design, synthesis and applications for chiral recognition and asymmetric synthesis. Tetrahedron Asymmetry. 2005; 16:3921–3945.

[71] M. J. Earle, P. B. McCormac, K. R. Seddon. Diels–Alder reactions in ionic liquids. A safe recyclable alternative to lithium perchlorate–diethyl ether mixtures. Green Chem. 1999; 1:23–25.

[72] L. C. Branco, P. M. P. Gois, N. M. T. Lourenço, V. B. Kurteva, C. A. M. Afonso. Simple transformation of crystalline chiral natural anions to liquid medium and their use to induce chirality. Chem. Commun. 2006; 22:2371–2372.

[73] S. Luo, L. Zhang, J. P. Cheng. Functionalized chiral ionic liquids: a new type of asymmetric organocatalysts and nonclassical chiral ligands. Chem. Asian J. 2009; 4:1184–1195.

[74] M. Vasiloiu, D. Rainer, P. Gaertner, C. Reichel, C. Shroeder, K. Bica. Basic chiral ionic liquids: a novel strategy for acid-free organocatalysis. Catalysis Today 2011; 200:80–86.

[75] L. González, J. Escorihuela, B. Altava, M. I. Burguete, Santiago V. Luis. Chiral room temperature ionic liquids as enantioselective promoters for the asymmetric aldol reaction. Eur. J. Org. Chem. 2014; 24:5356–5363.

[76] A. S. Kucherenko, V. V. Gerasimchuk, V. G. Lisnyak, Y. V. Nelyubina, S. G. Zlotin. Prolinamide-derived ionic-liquid-supported organocatalyst for asymmetric mono- and bis-aldol reactions in the presence of water. Eur. J. Org. Chem. 2015; 25:5649–5654.

[77] M. S. Chauhan, P. Kumar, S. Singh. Synthesis of MacMillan catalyst tailored with ionic liquid as a recoverable catalyst for asymmetric Diels-Alder reaction. RSC Adv. 2015; 5:52636–52641.

[78] A. De Nino, L. Maiuolo, P. Merino, M. Nardi, A. Procopio, D. Roca-Lopez, B. Russo, V. Algieri. Efficient organocatalyst supported on a simple ionic liquid as a recoverable system for the asymmetric diels–alder reaction in the presence of water. ChemCatChem. 2015; 7:830–835.

[79] J. Großeheilmann, J. Bandomir, U. Kragl. Preparation of poly(ionic liquid)s-supported recyclable organocatalysts for the asymmetric nitroaldol (Henry) reaction. Chem. Eur. J. 2015; 52:18957–18960.

[80] S. Chandrasekhar, C. Narsihmulu, N. R. Reddy, S. S. Sultana. Asymmetric aldol reactions in poly (ethylene glycol) catalyzed by l-proline. Tetrahedron Lett. 2004; 45:4581–4582

[81] S. Verma, S. L. Jain, B. Sain. PEG-embedded thiourea dioxide (PEG.TUD) as a novel organocatalyst for the highly efficient synthesis of 3,4-dihydropyrimidinones. Tetrahedron Lett. 2010; 51:6897–6900.

[82] E. L. Smith, A. P. Abbott, K. S. Ryder. Deep eutectic solvents (DESs) and their applications. Chem. Rev. 2014; 114:11060–11082.

[83] Q. Zhang, K. O. Vigier, S. Royera, F. Jérôme. Deep eutectic solvents: syntheses, properties and application. Chem. Soc. Rev. 2012; 41:7108–7714.

[84] E. Massolo, S. Palmieri, M. Benaglia, V. Capriati, F. M. Perna. Stereoselective organocatalysed reactions in deep eutectic solvents: highly tunable and biorenewable reaction media for sustainable organic synthesis. Green Chem. 2016; 18:792–797.

[85] W. Leitner. Supercritical carbon dioxide as a green reaction medium for catalysis. Acc. Chem. Res. 2002; 35:746–756.

[86] I. V. Kuchurov, A. G. Nigmatov, E. V. Kryuchkova, A. A. Kostenko, A. S. Kucherenko, S. G. Zlotin. Stereodivergent Michael addition of diphenylphosphite to α-nitroalkenes in the presence of squaramide-derived tertiary amines: an enantioselective organocatalytic reaction in supercritical carbon dioxide. Green Chem. 2014; 16:1521–1526.

[87] E. V. Filatova, O. V. Turova, I. V. Kuchurov, A. A. Kostenko, A. G. Nigmatov, S. G. Zlotin. Asymmetric catalytic synthesis of functionalized tetrahydroquinolines in supercritical fluids. J. Supercritical Fluids. 2016; 109:35–42.

[88] B. Schaffner, F. Schaffner, S. P. Verevkin, A. Borner. Organic carbonates as solvents in synthesis and catalysis. Chem. Rev. 2010; 110:4554–4581.

[89] M. North, F. Pizzato, P. Villuendas. Organocatalytic, asymmetric aldol reactions with a sustainable catalyst in a green solvent. ChemSusChem. 2009; 2:862–865.

[90] M. North, P. Villuendas. A chiral solvent effect in asymmetric organocatalysis. Org. Lett. 2010; 12:2378–2381.

[91] C. Beattie, M. North, P. Villuendas. Proline-catalysed amination reactions in cyclic carbonate solvents. Molecules. 2011; 16:3420–3432.

[92] R. A. Sheldon, I. Arends, U. Hanefeld. Green Chemistry and Catalysis. Wiley-VCH, Weinheim, 2007.

[93] A. Banon-Caballero, G. Guillena, C. Najera. Solvent-free enantioselective organocatalyzed aldol reactions. Mini-Rev. Org. Chem. 2014; 11:118–128.

[94] T. P. Kumar, R. C. Shekhar, K. S. Sunder, R. Vadaparthi. Myrtanyl-prolinamide: a new chiral organocatalyst for stereoselective aldol reactions. Tetrahedron Asymmetry. 2014; 26:543–547.

[95] T. P. Kumar, N. C. Vavle, V. Patro, K. Haribabu. Phthalimido-prolinamide: a new chiral catalyst for solvent free enantioselective aldol reactions. Tetrahedron-Asymmetry. 2014; 25:457–461.

[96] E. Machuca, G. Granados, B. Hinojosa, E. Juaristi. Synthesis and evaluation of (S)-proline-containing dipeptidic organocatalysts bound to MBHA resin in asymmetric aldol reactions. Tetrahedron Lett. 2014; 56:6047–6051.

[97] E. Machuca, E. Juaristi. Organocatalytic activity of α,α-dipeptide derivatives of (S)-proline in the asymmetric aldol reaction in absence of solvent. Evidence for non-covalent π–π interactions in the transition state. Tetrahedron Lett. 2014; 56:1144–1148.

[98] J. G. Hernández, V. García-López, E. Jurasti. Solvent-free asymmetric aldol reaction organocatalyzed by (S)-proline-containing thiodipeptides under ball-milling conditions. Tetrahedron. 2012; 68:92–97.

[99] E. Machuca, Y. Rojas, E. Jurasti. Synthesis and evaluation of (S)-proline-containing α,β-dipeptides as organocatalysts in solvent-free asymmetric aldol reactions under ball-milling conditions. Asian J. Org. Chem. 2015; 4:46–53.

[100] P. Vizcaíno-Milla, J. M. Sansano, C. Nájera, B. Fiser, E. Gómez-Bengoa. Pyrimidine-derived prolinamides as recoverable bifunctional organocatalysts for enantioselective inter- and intramolecular aldol reactions under solvent-free conditions. Eur. J. Org. Chem. 2015; 12:2614–2621.

[101] M. Jörres, S. Mersmann, G. Raabe, C. Bolm. Organocatalytic solvent-free hydrogen bonding-mediated asymmetric Michael additions under ball milling conditions. Green Chem. 2013; 15:612–616.

[102] M. Jörres, I. Schiffers, I. Atodiresei, C. Bolm. Asymmetric Michael additions of α-nitrocyclohexanone to aryl nitroalkenes catalyzed by natural amino acid-derived bifunctional thioureas. Org. Lett. 2012; 14:4518–4521.

[103] M. Hestericová, R. Šebesta. Higher enantioselectivities in thiourea-catalyzed Michael additions under solvent-free conditions. Tetrahedron. 2014; 70:901–905.

[104] K. Nakashima, S.-I. Hirashima, M. Kawada, Y. Koseki, N. Tada, A. Itoh, T. Miura. Pyrrolidine-diaminomethylenemalononitrile organocatalyst for Michael additions of carbonyl compounds to nitroalkenes under solvent-free conditions. Tetrahedron Lett. 2014; 55:2703–2706.

[105] J. He, Q. Chen, B. Ni. Highly efficient asymmetric organocatalytic Michael addition of α,α-disubstituted aldehydes to nitroolefins under solvent-free conditions. Tetrahedron Lett. 2014; 55:3030–3032.

[106] A.-B. Xia, C. Wu, D.-Q. Xu, Y.-F. Wang, X.-H. Du, Z.-B. Li, Z.-Y. Xu. Prolinethiol ether catalysis in an asymmetric Michael reaction: solvent-free synthesis of functionalized monohaloalkenes. J. Org. Chem. 2013; 78:1254–1259.

[107] A. Vega-PeÇaloza, O. Sánchez-Antonio, C. G. Ávila-Ortiz, M. Escudero-Casao, E. Juaristi. An alternative synthesis of chiral (S)-proline derivatives that contain a thiohydantoin moiety and their application as organocatalysts in the asymmetric Michael addition reaction under solvent-free conditions. Asian J. Org. 2014; 3:487–496.

[108] S. Fioravanti, L. Parise, A. Pelagalli, L. Pellacani, L. Trulli. Trifluoromethyl syn- or anti-γ-amino alcohols by one-pot solvent-free Mannich-type reactions under temperature control. RSC Adv. 2015; 5:29312–29318.

[109] A. Kumar, M. K. Gupta, M. Kumar. L-Proline catalysed multicomponent synthesis of 3-amino alkylated indolesvia a Mannich-type reaction under solvent-free conditions. Green Chem. 2012; 14:290–295.

[110] M. S. Singh, S. Chowdhury. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. RSC Adv. 2012; 2:4547–4592.

[111] W. Parasuk, V. Parasuk. Factors that influence stereoselectivity in proline-catalyzed Mannich reactions. Asian J. Org. Chem. 2013; 2:85–90.

[112] A. Corma, H. Garcia. Silica-bound homogenous catalysts as recoverable and reusable catalysts in organic synthesis. Adv. Synth. Cat. 2006; 348:1391–1412.

[113] S. Rostamnia, E. Doustkhah. Nanoporous silica-supported organocatalyst: a heterogeneous and green hybrid catalyst for organic transformations. RSC Adv. 2014; 4:28238–28248.

[114] A. El Kadib. Chitosan as a sustainable organocatalyst: a concise overview. ChemSusChem. 2015; 8:217–244.

[115] O. Mahé, J.-F. Brière, I. Dez. Chitosan: an upgraded polysaccharide waste for organocatalysis. Eur. J. Org. Chem. 2015; 12:2559–2578.

[116] M. Benaglia, A. Puglisi, F. Cozzi. Polymer-supported organic catalysts. Chem. Rev. 2003, 103:3401–3429.

[117] Y. Wang, X. Wang, M. Antonietti. Polymeric graphitic carbon nitride as a heterogeneous organocatalyst: from photochemistry to multipurpose catalysis to sustainable chemistry. Angew. Chem. Int. Ed. 2012; 51:68–89.

[118] B. Li, M. Chrzanowski, Y. Zhang, S. Ma. Applications of metal-organic frameworks featuring multi-functional sites. Coord. Chem. Rev. 2016; 307:106–129.

[119] D. Wang, D. Astruc. Dendritic catalysis-basic concepts and recent trends. Coord. Chem. Rev. 2013; 257:2317–2334.

[120] X. Fan, F. Zhang. Multiple roles of graphene in heterogeneous catalysis. Chem. Soc. Rev. 2015; 44:3023–3035.

[121] M. B. Gawande, P. S. Branco, R. S. Varma. Nano-magnetite (Fe_3O_4) as a support for recyclable catalysts in the development of sustainable methodologies. Chem. Soc. Rev. 2013; 42:3371–3393.

[122] R. Mrówczyński, A. Nan, J. Liebscher. Magnetic nanoparticle-supported organocatalysts – an efficient way of recycling and reuse. RSC Adv. 2014; 4:5927–5952.

[123] R. Dalpozzo. Magnetic nanoparticle supports for asymmetric catalysts. Green Chem. 2015; 17:3671–3686.

[124] M. Bartók. Advances in immobilized organocatalysts for the heterogeneous asymmetric direct aldol reactions advances in immobilized organocatalysts for the heterogeneous asymmetric direct aldol reactions. Cat. Rev. Sci. Eng. 2015; 57:192–255.

[125] R. Munirathinam, J. Huskens, W. Verboom. Supported catalysis in continuous-flow microreactors. Adv. Synth. Cat. 2015; 357:1093–1123.

[126] A. Puglisi, M. Benaglia, V. Chiroli. Stereoselective organic reactions promoted by immobilized chiral catalysts in continuous flow systems. Green Chem. 2013; 15:1790–1813.

[127] I. Atodiresei, C. Vila, M. Rueping. Asymmetric organocatalysis in continuous flow: opportunities for impacting industrial catalysis. ACS Catal. 2015; 5:1972–1985.

[128] L. A. Bivona, F. Quertinmont, H. A. Beejapur, F. Giacalone, M. Buaki-Sogo, M. Gruttadauria, C. Aprile. Thiazolium-based catalysts for the etherification of benzylic alcohols under solvent-free conditions. Adv. Synth. Cat. 2015; 357:800–810.

[129] E. J. García-Suárez, P. Moriel, C. Menéndez-Vázquez, M. A. Montes-Morán, A. B. García. Carbons supported bio-ionic liquids: stability and catalytic activity. Microporous Mesoporous Mater. 2011; 144:205–208.

[130] J. Y. Shi, C. A. Wang, Z. J. Li, Q. Wang, Y. Zhang, W. Wang. Heterogeneous organocatalysis at work: functionalization of hollow periodic mesoporous organosilica spheres with MacMillan catalyst. Chem. Eur. J. 2011; 17:6206–6213.

[131] S. M. Islam, A. S. Roy, R. C. Dey, S. Paul. Graphene based material as a base catalyst for solvent free Aldol condensation and Knoevenagel reaction at room temperature. J. Mol. Catal. A Chem. 2014; 394:66–73.

[132] Y. Zhang, Y. Zhang, L. Sun, X. Du, J. Y. Shi, W. D. Wang, W. Wang. 4-(N,N-dimethylamino)pyridine-embedded nanoporous conjugated polymer as a highly active heterogeneous organocatalyst. Chem. Eur. J. 2012; 18:6328–6334.

[133] J. Guan, B. Liu, X. Yang, J. Hu, C. Wang, Q. Kan. Immobilization of proline onto Al-SBA-15 for C–C bond-forming reactions. ACS Sustain. Chem. Eng. 2014; 2:925–933.

[134] W. Zhang, Z. Li, H. Gu, Y. Li, G. Zhang, F. Zhang, X. Fan. L-Proline Covalently Anchored on Graphene Oxide as an Effective Bifunctional Catalyst for Ketene Forming Reaction. Chem. Eng. Sci. 2015; 135:187–192.

[135] P. Wu, C. He, J. Wang, X. Peng, X. Li, Y. An, C. Duan. Photoactive chiral metal–organic frameworks for light-driven asymmetric α-alkylation of aldehydes. J. Am. Chem. Soc. 2012; 134:14991–14999.

[136] Y. Liu, X. Xi, C. Ye, T. Gong, Z. Yang, Y. Cui. Chiral metal-organic frameworks bearing free carboxylic acids for organocatalyst encapsulation. Angew. Chem. Int. Ed. 2014; 53:13821–13825.

[137] G. R. Krishnan, K. Sreekumar. First example of organocatalysis by polystyrene-supported PAMAM dendrimers: highly efficient and reusable catalyst for knoevenagel condensations. Eur. J. Org. Chem. 2008; 28:4763–4768.

[138] R. B. N. Baig, R. S. Varma. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. Chem. Soc. Rev. 2012; 41:1559–1584.

[139] M. O. M'hamed. Ball milling for heterocyclic compounds synthesis in green chemistry: a review. Synth. Comm. 2015; 45:2511–2528.

[140] R. M. Claramunt, C. Lopez, D. Sanz, J. Elguero. Mechano heterocyclic chemistry: grinding and ball mills. In *Advances in Hetercyclic Chemistry*. San Diego, USA: Elsevier Academic Press Inc., 2014; 117–143.

[141] V. Polshettiwar, R. S. Varma. Microwave-assisted organic synthesis and transformations using benign reaction media. Acc. Chem. Res. 2008; 41:629–639.

[142] V. Polshettiwar, R. S. Varma. Aqueous microwave chemistry: a clean and green synthetic tool for rapid drug discovery. Chem. Soc. Rev. 2008; 37:1546–1557.

[143] G. Cravotto, E. Borretto, M. Oliverio, A. Procopio, A. Penoni. Organic reactions in water or biphasic aqueous systems under sonochemical conditions. A review on catalytic effects. Cat. Comm. 2015; 63:2–9.

[144] N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso, A. F. Trindade. More sustainable approaches for the synthesis of N-based heterocycles. Chem. Rev. 2009; 109:2703–2802.

[145] M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol, P. Machado. Solvent-free heterocyclic synthesis. Chem. Rev. 2009; 109:4140–4182.

[146] S. Toma, R. Sebesta, M. Meciarova. Organocatalytic reactions under unusual conditions. Curr. Org. Chem. 2011; 15:2257–2281.

[147] A. Bruckmann, A. Krebs, C. Bolm. Organocatalytic reactions: effects of ball milling, microwave and ultrasound irradiation. Green Chem. 2008; 10:1131–1141.

[148] A. M. Balu, D. Dallinger, D. Obermayer, J. M. Campelo, A. A. Romero, D. Carmona, F. Balas, K. Yohida, P. L. Gai, C. Vargas. Insights into the microwave-assisted preparation of supported iron oxide nanoparticles on silica-type mesoporous materials. Green Chem. 2012; 14:393–402.

[149] D. Obermayer, T. N. Glasnov, C. O. Kappe. Microwave-assisted and continuous flow multistep synthesis of 4-(pyrazol-1-yl)carboxanilides. J. Org. Chem. 2011; 76:6657–6669.

[150] T. N. Glasnov, C. Kappe. The microwave-to-flow paradigm: translating high-temperature batch microwave chemistry to scalable continuous-flow processes. Chem. Eur. J. 2011; 17:11956–11968.

[151] M. B. Gawande, V. D. B. Bonifacio, R. Luque, P. S. Branco, R. S. Varma. Solvent-free and catalysts-free chemistry: a benign pathway to sustainability. ChemSusChem. 2014; 7:24–44.

[152] A. Procopio, A. De Nino, M. Nardi, M. Oliverio, R. Paonessa, R. Pasceri. A new microwave-assisted organocatalytic solvent-free synthesis of optically enriched Michael adducts. Synlett. 2010; 12:1849–1853.

[153] M. Mojzesová, M. Mečiarová, R. Marti, R. Šebesta. Organocatalytic oxa-Diels-Alder reaction of α, β-unsaturated ketones under non-classical conditions. New J. Chem. 2015; 39: 2573–2579.

[154] A. K. Qaroush, A. S. Al-Hamayda, Y. K. Khashman, S. I. Vagin, C. Troll, B. Rieger. Highly efficient isocyanate-free microwave-assisted synthesis of [6]-oligourea. Cat. Sci. Tech. 2013; 2:2221–2226.

[155] B. Narasimhan, D. Sharma, P. Kumar. Biological importance of imidazole nucleus in the new millennium. Med. Chem. Res. 2011; 20:1119–1140.

[156] B. Jiang, X. Wang, F. Shi, S.-J. Tu, T. Ai, A. Ballew, G. Li. Microwave enabled umpolung mechanism based rapid and efficient four- and six-component formations of 2-(2′-azaaryl)imidazoles and anti-1,2-diarylethylbenzamides. J. Org. Chem. 2009; 74:9486–9489.

[157] X.-J. Zhang, W. Fan, L.-P. Fu, B. Jiang, S.-J. Tu. Domino [3+1+1] heterocyclization providing an efficient umpolung strategy for synthesis of 2-(2'azaaryl)imidazoles. Res. Chem. Inter. 2015; 41:773–783.

[158] G. Dessolea, R. P. Herrera, A. Ricci. H-Bonding organocatalysed Friedel-crafts alkylation of aromatic and heteroaromatic systems with nitroolefins. Synlett. 2004; 13:2374–2378.

[159] H. Kotsuki, H. Ikishima, A. Okuyama. Organocatalytic asymmetric synthesis using proline and related molecules (Part 1). Heterocycles. 2009; 75:493–529.

[160] F. Vetica, R. M. Figueiredo, M. Orsini, D. Tofani, T. Gasperi. Recent advances in organocatalytic cascade reactions toward the formation of quaternary stereocenters. Synthesis. 2015; 47:2139–2184.

[161] A. Russo, N. E. Leadbeater, A. Lattanzi. A convenient methodology for nitro-Michael addition of carbonyl compounds catalyzed by L-proline using microwave heating. Lett. Org. Chem. 2010; 7:98–102.

[162] E. M. Omara, M. B. A. R. Rahman, E. Abdulmalek, B. A. Tejo, B. Ni, A. D. Headley. Optimization of microwave-assisted Michael addition reaction catalyzed by L-proline

in ionic liquid medium using response surface methodology. Synth. Commun. 2014; 44:381–398.

[163] D. Enders, R. Krull, W. Bettray. Microwave-assisted organocatalytic quadruple domino reactions of acetaldehyde and nitroalkenes. Synthesis. 2010; 4:567–572.

[164] T. Baumann, M. Baechle, C. Hartmann, S. Braese. Thermal effects in the organocatalytic asymmetric alpha-amination of disubstituted aldehydes with azodicarboxylates: a high-temperature organocatalysis. Eur. J. Org. Chem. 2008; 13:2207–2212.

[165] J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen. Squaramides: bridging from molecular recognition to bifunctional organocatalysis. Chem. Eur. J. 2011; 17:6890–6899.

[166] M. Sanchez-Rosello, C. Mulet, M. Guerola, C. del Pozo, S. Fustero. Microwave-assisted tandem organocatalytic peptide-coupling intramolecular aza-Michael reaction: alpha, beta-unsaturated N-acyl pyrazoles as Michael acceptors. Chem. Eur. J. 2014; 20:15697–15701.

[167] T. Naicker, P. I. Arvidsson, H. G. Kruger, G. E. M. Maguire, T. Govender. Microwave-assisted synthesis of guanidine organocatalysts bearing a tetrahydroisoquinoline framework and their evaluation in Michael addition reactions. Eur. J. Org. Chem. 2012; 17:3331–3337.

[168] T. Boddaert, Y. Coquerel, J. Rodriguez. Organocatalytic activity of N-heterocyclic carbenes in the Michael addition of 1,3-dicarbonyl compounds: application to a stereoselective spirocyclization sequence. Adv. Synth. Cat. 2009; 351:1744–1748.

[169] O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Massi, S. Pacifico. Thiazolium-catalyzed intermolecular Stetter reaction of linear and cyclic alkyl alpha-diketones. Org. Biomol. Chem. 2011; 9:8437–8444.

[170] F. X. Liao, Y. G. Wang, Q. Zhu. Catalytic microwave-promoted direct aldol condensation using resin-bound secondary amine. Synth. Commun. 2014; 44:161–169.

[171] N. Gangwar, V. K. Kasana. 3,4-Dihydropyrimidin-2(1H)-one derivatives: organocatalysed microwave assisted synthesis and evaluation of their antioxidant activity. Med. Chem. Res. 2012; 21:4506–4511.

[172] G. Zhang, N. Ma, B. Jiang, F. Shi, S.-J. Tu. Thiosalicylic acid catalyzed multicomponent reactions: microwave-assisted synthesis of new extended angular fused azaheterocycles. Synthesis. 2010; 23:3993–3998.

[173] N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixao. Synthesis of arylselanyl-1H-1,2,3-triazole-4-carboxylates by organocatalytic cycloaddition of azidophenyl arylselenides with beta-keto-esters. Tetrahedron. 2012; 68:10456–10463.

[174] D. Tejedor, L. Cotos, D. Marquez-Arce, M. Odriozola-Gimeno, M. Torrent-Sucarrat, F. P. Cossio, F. Garcia-Tellado. Microwave-assisted organocatalyzed rearrangement of propargyl vinyl ethers to salicylaldehyde derivatives: an experimental and theoretical study. Chem. Eur. J. 2015; 21:18280–18289.

[175] M. Hoffmann, S. Deshmukh, T. Werner. Scope and limitation of the microwave-assisted catalytic wittig reaction. Eur. J. Org. Chem. 2015; 20:4532–4543.

[176] T. Werner, M. Hoffmann, S. Deshmukh. First enantioselective catalytic wittig reaction. Eur. J. Org. Chem. 2014; 30:6630–6633.

[177] T. Werner, M. Hoffmann, S. Deshmukh. First microwave-assisted catalytic wittig reaction. Eur. J. Org. Chem. 2014; 30:6873–6876.

[178] J. McNulty, D. McLeod, P. Das, C. Zepeda-Velazquez. Wittig reactions of trialkylphosphine-derived ylides: new directions and applications in organic synthesis. Phosphorus Sulfur Silicon Related Elements. 2015; 190:619–632.

[179] D. M. Jackson, R. L. Ashley, C. B. Brownfield, D. R. Morrison, R. W. Morrison. Rapid conventional and microwave-assisted decarboxylation of L-histidine and other amino acids via organocatalysis with R-carvone under superheated conditions. Synth. Commun. 2015; 45:2691–2700.

[180] T. J. Mason. Ultrasound in synthetic organic chemistry. Chem. Soc. Rev. 1997; 26:443–451.

[181] C. Mangilal, P. Anang, S. Ratnesh, A. N. Vipin. Quinine as an organocatalytic dual activator for the diastereoselective synthesis of spiro-epoxyoxindoles. Tetrahedron Lett. 2013; 54:7119–7123.

[182] N. Azizi, A. Rahimzadeh-Oskooee, Z. Yadollahy, A. G. Ourimi. Ultrasound-assisted rapid sustainable synthesis of substituted thiourea. Monatsh. Chem. 2014; 145:1675–1680.

[183] D. Fishelovitch, C. Hazan, S. Shaik, H. J. Wolfson, R. Nussinov. Structural dynamics of the cooperative binding of organic molecules in the human cytochrome P4503A4. J. Am. Chem. Soc. 2007; 129:1602–1611.

[184] M. Rogozinska-Szymczak, J. Mlynarski. Asymmetric synthesis of warfarin and its analogues on water. Tetrahedron Asymmetry. 2014; 25:813–820.