Recent Advances in Metal-, Organo- and Biocatalysed One-Pot Tandem Reactions Under Environmentally Responsible Conditions

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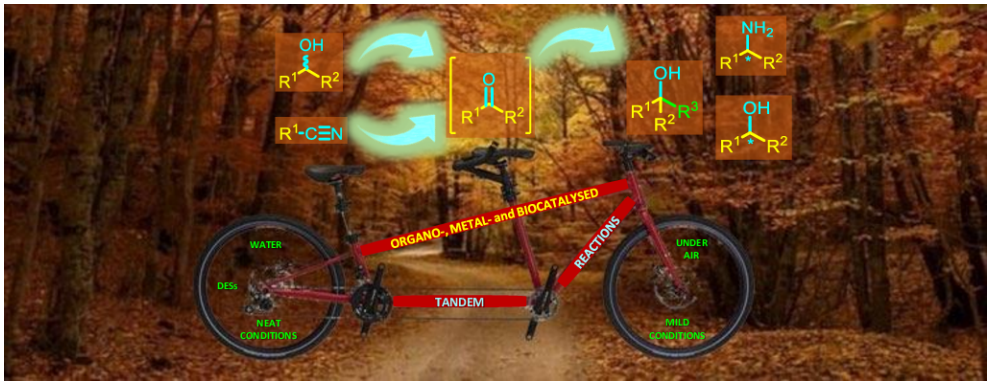
Abstract

Due to their handedness and wide scope, transition-metal-, organo- and biocatalysed tandem processes have become routine and highly sought-after methodologies because they dramatically increase synthetic efficiency, while decreasing the number of laboratory operations, the quantities of chemicals and solvents used, producing in a simpler way highly complex organic molecules with the desired selectivity. In this *Current Opinion*, recent examples of the use of metal-, organo- and biocatalysed tandem processes, run under environmentally responsible conditions (e.g., use of water, bio-based solvents or without additional solvents), are showcased, highlighting practical and valuable aspects.

Keywords

Deep Eutectic Solvents; Metal-catalysis; Organo-catalysis; Biocatalysis; Sustainable synthesis.

Graphical abstract



1. Introduction

The environmental impact associated with chemical transformations has been pressing the researchers to design new environmentally responsible and cost-effective synthetic procedures in accordance to the Twelve Principles of Green Chemistry [1] and to improve and/or modify existing processes to achieve a similar goal. One of the most easily accessible manifolds affecting the footprint of a chemical process concerns the nature of the reaction medium. For this reason, considerable efforts are being made in using benign reaction media in place of often toxic, volatile organic compounds (VOCs) in many domains of chemical synthesis.

The conventional preparation of a complex molecule, however, generally requires multiple synthetic operations that include stages of purification and extraction for each individual step. Not only this lowers the synthetic efficiency, but also generates very large amounts of chemical waste, with long reaction times and energy-consuming pathways [2]. Thus, running the synthesis of a target molecule in a single reaction vessel ('one-pot') and with the single steps run in 'tandem' represents an effective and forward-looking approach worth pursuing. This also allows to work with unstable reaction intermediates, as no isolation of reactive or transition species is required, overall simplifying practical aspects [3–5]. Many highly efficient and sustainable one-pot two-step sequential processes are today already available in non-conventional solvents [6–11]. This brief *Opinion* showcases in two Sections recent studies published, in particular since 2020 (with background references), in which metal-, organo- and biocatalysed processes are run in tandem with other relevant chemical transformations under mild and environmentally responsible conditions aimed at forging new carbon-carbon or carbon-heteroatom bonds, highlighting chemo-, regio- and stereoselective aspects. Special emphasis will be given to those processes carried out without additional solvents, in water or buffer mixtures, in green (e.g., cyclopentyl methyl ether, CPME) [12] or bio-based solvents like the so-called Deep Eutectic Solvents (DESs). The latter are binary or ternary combination of safe and inexpensive components comprising Lewis or Brønsted acids and bases, which are strongly associated with each other via hydrogen bond interactions to form a eutectic mixture with a melting point far below that of an ideal liquid mixture [13,14]. DESs show tuneable and attractive physicochemical properties from an environmental point of view such as negligible vapour pressures, high thermal stability, nonflammability, easy recycling, and low

toxicity. As for the last point, new guidelines have recently been published for DESs toxicity monitoring [15].

2. Metal- and/or Organo-catalysed tandem processes using green solvents or green conditions

Nowadays, metal- and/or organo-catalysed tandem reactions run in environmentally friendly or nature-inspired solvents are at the forefront of the sustainability agenda of several scientific communities that have started to reorganize strategic, industrially or biologically relevant chemical processes [16,17]. Recent advances in this field are briefly reviewed.

Blangetti, Prandi and co-workers have recently reported the synthesis of a functionalised benzofuran carboxamide derivative **4** (71%), *en route* to (+)-(*R*)-concentricolide (an anti-HIV agent), by exploiting a tandem Sonogashira coupling annulation in CPME of a salicylamide derivative **2** with TMS-acetylene **3**, the former being obtained through an *ortho*-Fries (A*o*F) rearrangement of **1**, triggered by lithium 2,2,6,6-tetramethylpiperidide (LiTMP) at room temperature (RT) and under aerobic conditions (Figure 1a) [18]. Free amine TMP could be recycled after acidic quenching of the reaction mixture, followed by treatment with NaOH, extraction with EtOAc, and evaporation of the solvent under reduced pressure.

S-Trityl-L-cysteine and related analogues (**7a**,**b**), which are selective inhibitors of human mitotic kinesin Eg5, have straightforwardly been prepared by means of telescoped, one-pot processes, using water as the sole reaction medium. Overall, the process consists in the preliminary synthesis of a tertiary alcohol (triphenylmethanol) (**6**) via a nucleophilic addition of PhLi to a suspension of methyl benzoate (**5**) in water under aerobic conditions, followed by the reaction with L-cysteine·HCl or cysteamine·HCl in the presence of trifluoroacetic acid. Products **7a**,**b** were isolated by filtration in good yield (80–84%) and purity with no need of column chromatography (Figure 1b) [19].

Primary benzylic alcohols **8** could be directly converted into secondary benzylic alcohols **10** (up to 94% yield) or nitroalkenes **11** (up to 80% yield), through the corresponding carbonyl derivatives **9**, by means of one-pot two-step transformations in

which oxidation processes have been combined either with main group-mediated nucleophilic additions or with nitroaldol (Henry) reactions, respectively, carried out in water or in a D-fructose/urea low melting mixture under mild conditions [40 °C with the assistance of ultrasound]. In both processes, a key role is played by the $CuCl_2$/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine(TMEDA)/2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) system, with air being the terminal oxidant (Figure 1c) [20*].

The synthesis of highly-substituted and non-simmetric tertiary alcohols **13**, **16** has also been achieved (a) by exploiting a double chemoselective addition of different organolithium/Grignard reagents to aromatic nitriles **12**, working under neat conditions in air at RT (**13**: up to 84% yield) (Figure 1d) [21*], and (b) via tandem protocols that combine the 2-azaadamantane *N*-oxyl (AZADO)/NaClO organocatalytic/oxidation of secondary alcohols **14** to ketones **15** with the chemoselective addition of several organolithium reagents to **15**, at RT under air and in aqueous media, with improved selectivities than when using VOCs under inert atmosphere (**16**: up to 95% yield) (Figure 1e) [22].

Regioselective and straightforward access to 2-(hetero)aryl THF **20** or THP derivatives **21** (up to 95% yield) has been enabled by ligandless, telescoped, one-pot Mizoroki-Heck (M-H) cross-coupling/reduction processes, run in a choline chloride (ChCl)/glycerol (Gly) eutectic mixture and under aerobic conditions, upon reacting 2,3-dihydrofuran (**17**) or 3,4-dihydro-2*H*-pyran (**18**) with several electron-rich or electron-deficient (hetero)aryl halides **19**. Key intermediates to pharmacologically relevant inhibitors of Kv1.2 channel have also been targeted (Figure 1f) [23*]. The recycle of the solvent/catalyst was, in this case, ineffective even if performed soon after the M-H reaction (that is, before the final reduction step), most probably because of the increased viscosity of the reaction medium and the precipitation of Pd-black.

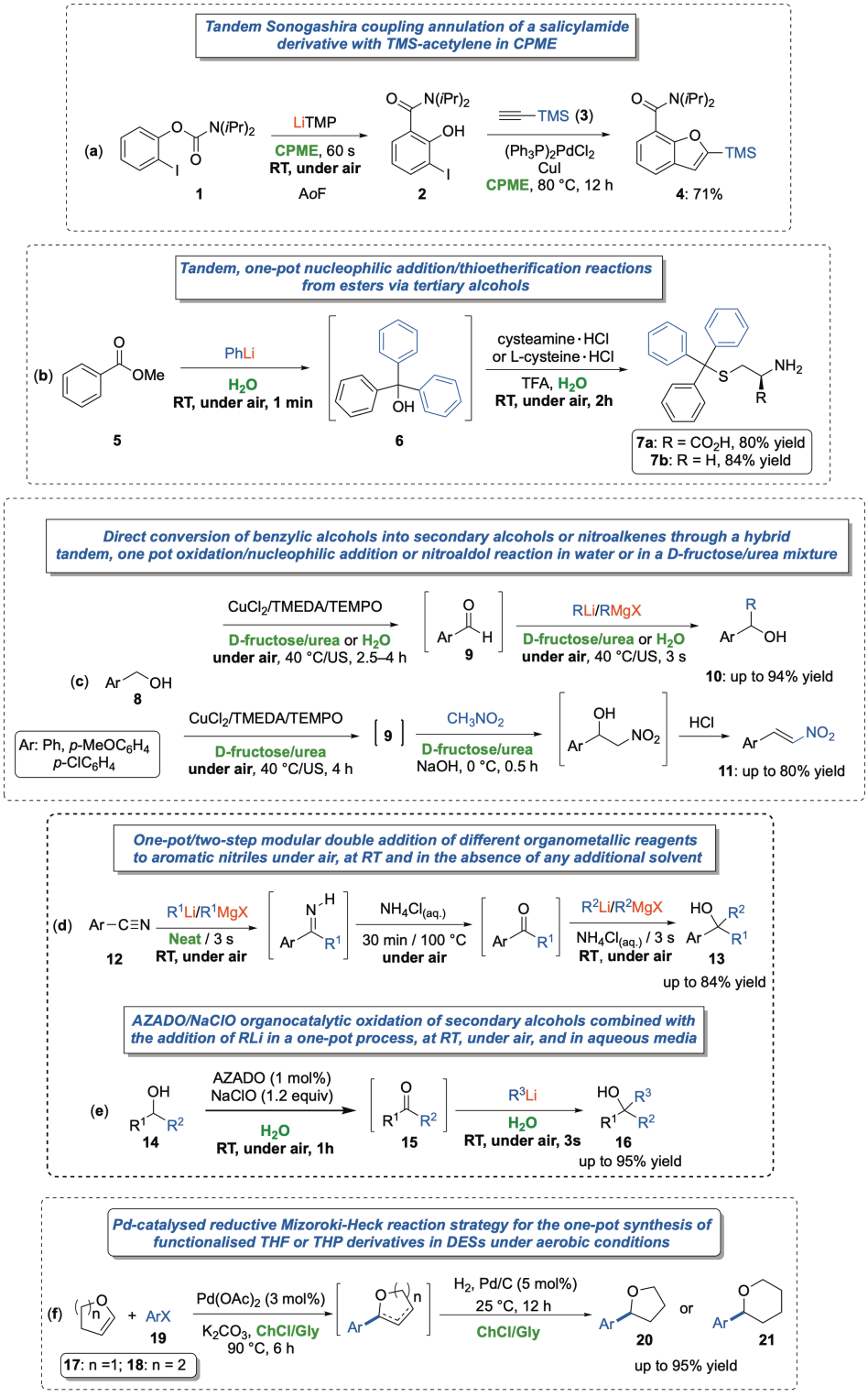


Figure 1. Selected metal- and organo-catalysed one-pot tandem processes using green solvents and/or green conditions (**a**–**f**). ChCl = choline chloride; Gly = glycerol; AZADO = 2-azaadamantane *N*-oxyl; LiTMP = lithium 2,2,6,6-tetramethylpiperidide; CPME = cyclopentyl methyl ether; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TFA = trifluoroacetic acid; US = ultrasound; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl; RT = room temperature.

3. Biocatalysed tandem processes in non-conventional media

There is an increasing interest in the development of tandem chemoenzymatic processes for the synthesis of chiral compounds, fine chemicals and Active Pharmaceutical Ingredients (APIs) that combine the versatility of traditional chemical catalysis with the unbeatable selectivity brought about by an enzyme [24–30]. In principle, the catalysts involved in these processes remain prone to conflicts because of the preference of many chemical catalysts for hydrophobic solvents and of many enzymes for water mixtures. In this context, environmentally friendly reaction media like ionic liquids, DESs, supercritical CO_2, used as solvents, co-solvents or performance additives, have offered a great help not only in overcoming barriers associated with the solvent compatibility, but also in solving issues related to the low solubility of many substrates in aqueous media, and in improving or reverting the stereoselectivity of reactions [31–37]. Revolutionary advances have recently been made with several *ad hoc* protocols set up for biotransformations catalysed by both isolated enzymes and whole cells, also interfaced with metal- or organocatalytic processes, for the synthesis of enantiomerically enriched alcohols and amines [38–40].

The development of efficient catalytic technologies for processing renewable sources of raw materials represents one of the primary objectives for many researchers. Bio-based furfural, 5-hydroxymethylfurfural (HMF) and 2,5-bis(hydroxymethyl)furan (BHMF) are key building blocks to produce bioactive compounds, value-added intermediates, polymers, and fuels [41,42]. Recent studies have disclosed green processes for simultaneous biomass fractionation and furfural production. The acidic eutectic mixture ChCl/glycolic acid/water, for example, straightforwardly converted either a C_6/C_5 (glucose/xylose) sugar mixture or birch sawdust to furfural (**22**) and HMF (**23**), without any additional catalyst. Up to 10 equiv of water revealed to be beneficial to obtain **22** in 62% yield from the sugar mixture, and in 37.5% from birch sawdust, whereas HMF yields remained lower (14%), probably due to HMF-DES interactions. DES could successfully be recycled for three runs after extraction of products with methyl isobutyl ketone (Figure 2a) [43].

A hybrid process for selective valorisation of D-fructose (**24**) to BHMF (**25**) was set up by He, Ma and co-workers by bridging chemo- and biocatalysis in a betaine (Bet)/benzenesulfonic acid DES. The tandem transformation consisted of a preliminary

fast dehydration of **24** to **23** (62.3% yield, 120 °C, 2 min) followed by a mild bioreduction of **23** to **25** with the recombinant *Escherichia Coli* DCF containing both reductase and formate dehydrogenase (99.6% yield, 40 °C, pH 7.5, 48 h) (Figure 2b) [44*].

An important HMF derivative, that is 5-hydroxymethyl-2-furfurylamine (HMFA) (**26**), an intermediate widely used in the synthesis of drugs and as a curing agent in epoxy resins, could be prepared by a tandem chemoenzymatic approach based on a preliminary dehydration of **24** to **23** followed by a biological amination of HMF to HMFA, the latter being catalysed by a double-mutated *Aspergillus terreus* ω-transaminase as the biocatalyst, working in a DES (Bet/formic acid)/water mixture, reaching the yield of 0.46 g HMFA per kg D-fructose (Figure 2c) [45].

He and co-workers set up an effective one-pot chemo- and biocatalytic cascade process for converting corncob-valorized furfural (**22**) into furfuryl alcohol (**27**) (97.7% yield at pH 7.5 and 40 °C) using immobilized DES Bet/lactic acid on silica gel as a heterogeneous catalyst and newly constructed recombinant *E. coli* KF2021 whole-cells harboring formate dehydrogenase and reductase (Figure 2d) [46].

Furoic acid (**28**), which is an important bio-based furan chemical, was obtained in 42.51% yield by means of a hybrid strategy first converting easily available and renewable bulrushes (*Phragmites communis*) into **22** (47.64% yield; 180 °C, 30 min) in an aqueous ChCl-based DES with citric acid. Then, a dehydrogenase biocatalyst (recombinant *E. coli* HMFOMUT whole-cells) was used to valorize **22** into **28** under mild conditions. DES mixture could be recycled, although furfural concentration decreased significantly from 51.82% to 37.84% on going from the 2nd to the 5th round (Figure 2e) [47].

The chemistry of polar organometallic compounds has also been successfully combined with biocatalytic organic transformations run in aqueous media under aerobic conditions at RT. Densely functionalised tertiary alcohols **31** have been prepared in up to 96% yield by exploiting one-pot tandem processes based on a preliminary oxidation of secondary alcohols **29** to **30** [promoted by the laccase from *Trametes*

versicolor/TEMPO system, in the presence of O_2 as the terminal oxidant, in citrate buffer or bulk water] followed by the chemoselective and fast addition (reaction time: 3 s) of aromatic and aliphatic organolithium and Grignard reagents to transiently-formed ketones **30**. Higher conversion efficiency have been achieved in the presence of CPME in the second step (Figure 3a) [48*].

The synthesis of stilbene derivatives **37**,**38** was developed by García-Álvarez, González-Sabín and co-workers by combining a tandem decarboxylation of *p*-hydroxycinnamic acid derivatives **32**,**33**, catalysed by *Bs*PAD (phenolic acid decarboxylase from *Bacillus subtilis*), either with a Ru-catalysed (Grubbs-II) metathesis of transiently-formed styrene-type olefin **34** or with a Pd-catalysed Heck coupling process of transient olefin intermediate **35** with iodobenzene (**36**) performed in a DES-water medium (Figure 3b). The inhibitory activity detected in the Heck coupling reaction on the Pd catalyst was circumvented by using an immobilized biocatalyst or aqueous micellar solutions, with the target biaryl derivatives being isolated in moderate to good overall yields [49]. The heterogeneous immobilized biocatalyst could be efficiently recycled up to four times in water, though it completely lost its activity after just one cycle in the DES mixture, most probably because of the high concentration of choline chloride in the reaction medium that partially released the enzyme from the carrier. Of note, the decarboxylation of **33** by *Bs*PAD, coupled with a Pd-catalysed Heck-cross-coupling reaction of **35** with **36**, *en route* to olefin **38**, has also been performed by exploiting a fully integrated two-step continuous (more than 16 h) flow process in a DES-water medium. When working in flow, the latter mixture allowed to overcome solvent compatibility problems, while increasing the substrate concentration up to 20 mM [50].

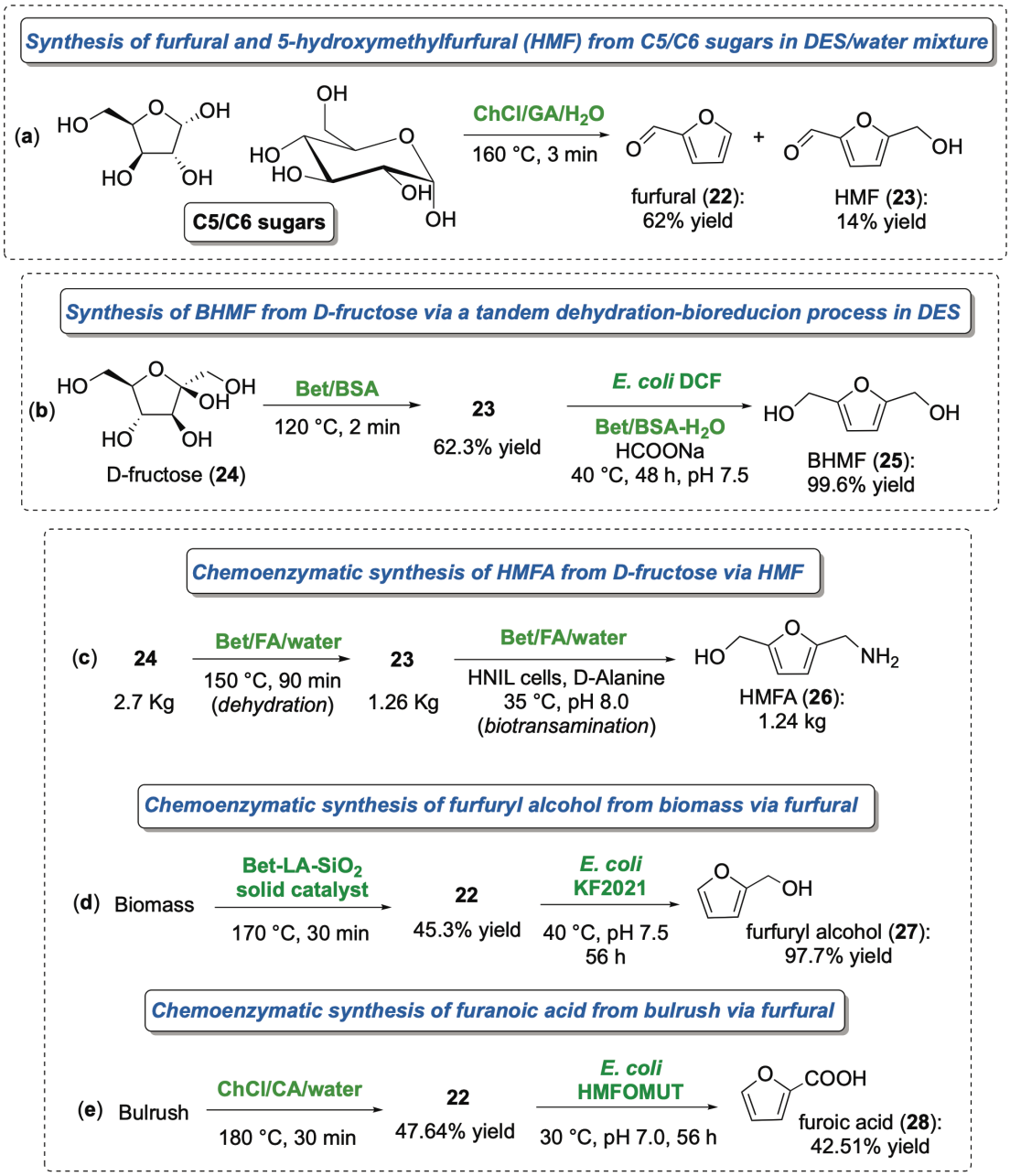


Figure 2. Selected biocatalysed one-pot tandem processes using green solvents (**a**–**e**). ChCl = choline chloride; GA = glycolic acid; Bet = betaine; BSA = benzenesulfonic acid; FA = formic acid; LA = lactic acid; CA = citric acid.

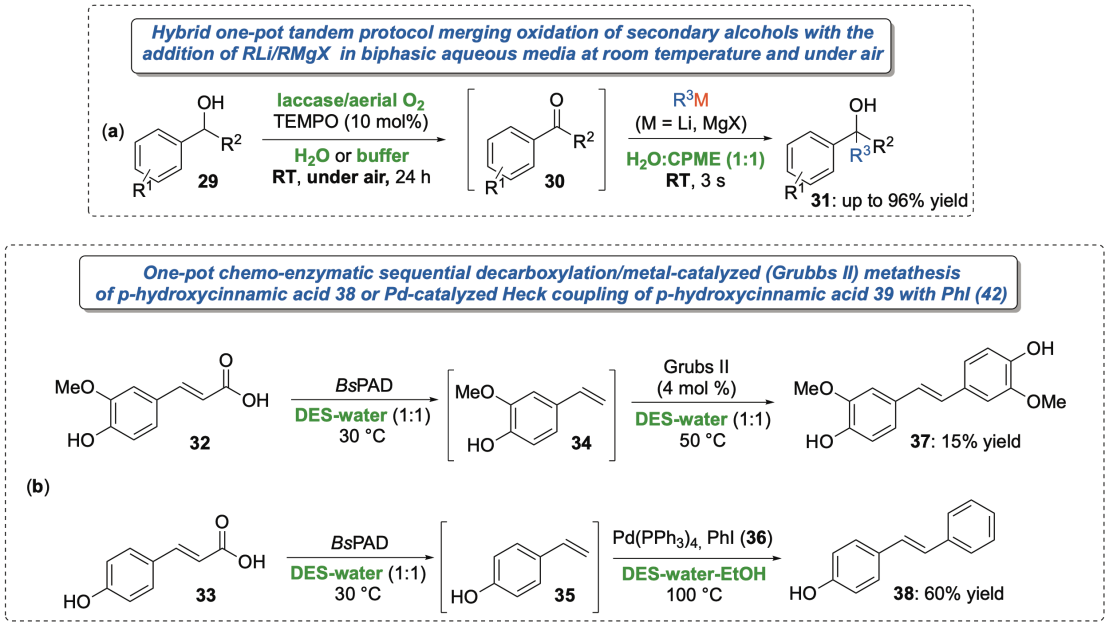


Figure 3. Selected biocatalysed one-pot tandem processes using green solvents (**a**,**b**). DES = Deep Eutectic Solvent; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl; CPME = cyclopentyl methyl ether; *Bs*PAD = phenolic acid decarboxylase from *Bacillus subtilis*.

4. Conclusions and opportunities

In this last decade, efforts have been made to design sustainable multistep, one-pot processes and simplified work-up procedures aimed at reducing the environmental impact of solvents, while minimizing time consumption and chemical waste. In this *Current Opinion*, recent organo-, metal- and biocatalysed tandem transformations run in bio-based/green solvents, water or under neat conditions have been highlighted. In particular, the use of s-block organometallic reagents in combination with organo- or biocatalysts, under aerobic and mild conditions, working in protic DESs or water, is well established, and thus worth pursuing. Future directions should focus on scalable strategies based on earth-crust abundant metals as chemocatalysts [51] jointly with engineered recombinant biocatalysts in order to set up more efficient and *ad hoc* designed multistep stereoselective chemoenzymatic processes [52**] in DES mixtures or water amenable of industrial applicability.

Conflict of interest statement

Nothing declared.

Acknowledgements

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References and recommended reading

* of special interest

* * of outstanding interest

[1] Anastas PT, Warner JC: **Green Chemistry Theory and Practice**, Oxford University Press, Oxford, UK (1998).

[2] Hayashi Y: **Pot economy and one-pot synthesis**. *Chem. Sci.* 2016, **7**:866–880.

[3] Gu Y: **Multicomponent reactions in unconventional solvents: state of the art**. *Green Chem.* 2012, **14**:2091–2128.

[4] Nicolau KC, Chen JS: **The art of total synthesis through cascade reactions**. *Chem. Soc. Rev.* 2009, **38**:2993–3009.

[5] Jiang Y, McNamee RY, Smith PJ, Sozanschi A, Tong Z, Anderson EA: **Advances in polycyclization cascades in natural product synthesis**. *Chem. Soc. Rev.* 2021, **50**:58–71.

[6] Nemati F, Hosseini MM, Kiani H: **Glycerol as a green solvent for efficient, one-pot and catalyst free synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives**. *J. Saudi Chem. Soc.* 2016, **20**:503–508.

[7] Wu H, Wang L: **Expedient green-chemistry approaches for a one-pot synthesis of two series of novel 1,5-benzodiazepines via domino reactions**. *New J. Chem.* 2020, **44**:10428–10440.

[8] Min J, Hai-Feng L, Xiao-Qing W, Yan-Bing D Bin G: **An efficient one-pot, two-step synthesis of cyclobuxophyllinine M from cyclovirobuxine D in aqueous media**. *Lett. Org. Chem.* 2008, **5**:140–141.

[9] Yu S, Hu K, Gong J, Qi L, Zhu J, Zhang Y, Cheng T, Chen J: **Palladium-catalyzed tandem addition/cyclization in aqueous medium: Synthesis of 2-arylindoles.** *Org. Biom. Chem*. 2017, **15**:4300–4307.

[10] Mishra PK, Verma AK: **Metal-free regioselective tandem synthesis of diversely substituted benzimidazo-fused polyheterocycles in aqueous medium**. *Green Chem.* 2016, **18**:6367–6372.

[11] Suriyakala, T, Chinnaraj A, Senthilkumar V, Nasar, MK, Ravindran G. **Regioselective synthesis and antibacterial studies of α,β-unsaturated ketone substituted cyclohexanol via tandem Michael addition-aldol addition-cyclization sequence under solvent-free conditions**. *Asian J. Chem.* 2022, **34**:2646–2650.

[12] Azzena U, Carraro M, Pisano L, Monticelli S, Bartolotta R, Pace V: **Cyclopentyl Methyl Ether: An Elective Ecofriendly Ethereal Solvent in Classical and Modern Organic Chemistry**. *ChemSusChem* 2019, **12**:40–70.

[13] Hansen BB, Spittle S, Chen B, Poe D, Zhang Y, Klein JM, Horton A, Adhikari L, Zelovich T, Doherty BW, Gurkan B, Maginn EJ, Ragauskas A, Dadmun M, Zawodzinski TA, Baker GA, Tuckerman ME, Savinell RF, Sangoro JR: **Deep Eutectic Solvents: A Review of Fundamentals and Applications**. *Chem. Rev.* 2021, **121**:1232–1285.

[14] Martins MAR, Pinho SP, Coutinho JAP: **Insights into the Nature of Eutectic and Deep Eutectic Mixtures**. *J. Solut. Chem.* 2019, **48**:962–982.

[15] Torregrosa-Crespo J, Marset X, Guillena G, Ramòn DJ, Martìnez-Espinosa RM: **New guidelines for testing "Deep eutectic solvents" toxicity and their effects on the environment and living beings**. *Sci. Total Environ.* 2020, **704**:135382.

[16] Cortes-Clerget M, Yu J, Kincaid JRA, Walde P, Gallou F, Lipshutz BH: **Water as the reaction medium in organic chemistry: from our worst enemy to our best friend**. *Chem. Sci.* 2021, **12**:4237–4266.

[17] Marset X, Guillena G: **Deep eutectic solvents as à-la-carte medium for transition-metal-catalyzed organic processes**. *Molecules* 2022, **27**: 8445.

[18] Ghinato S, De Nardi F, Bolzoni P, Antenucci A, Blangetti M, Prandi C: **Chemo- and regioselective anionic fries rearrangement promoted by lithium amides under aerobic conditions in sustainable reaction media**. *Chem. Eur. J.* 2022, **28**:e202201154.

[19] Quivelli AF, D'Addato G, Vitale P, Perna FM, García-Álvarez J, Capriati V: **Expeditious and practical synthesis of tertiary alcohols from esters enabled by highly polarized organometallic compounds under aerobic conditions in deep eutectic solvents or bulk water**. *Tetrahedron* 2021, **81**:131898.

[20*] Cicco L, Roggio M, López-Aguilar M, Ramos-Martín M, Perna FM, García-Álvarez J, Vitale P, Capriati V: **Selective aerobic oxidation of alcohols in low melting**

mixtures and water and use for telescoped one-pot hybrid reactions. *ChemistryOpen* 2022, **11**:e202200160.

The bio-based D-fructose-urea mixture and water are effective reaction media to promote the direct conversion of benzylic alcohols into secondary alcohols or nitroalkenes via a hybrid process combining a one-pot $CuCl_2$/TEMPO/TMEDA-catalyzed aerobic oxidation either with a chemoselective nucleophilic addition of main group organometallics or a nitroaldol reaction to transient aldehydes, respectively.

[21*] Elorriaga D, Carrillo-Hermosilla F, Parra-Cadenas B, Antiñolo A, García-Álvarez J: **Aerobic/room-temperature-compatible *s*-block organometallic chemistry in neat conditions: a missing synthetic tool for the selective conversion of nitriles into asymmetric alcohols**. *ChemSusChem,* 2022*,* **15**:e202201348.

The selective and straightforward double addition of organolithium/organomagnesium reagents to nitriles, *en route* to non-simmetric tertiary alcohols, takes place in the presence of air/moisture at RT, when working in the absence of any additional organic solvent. The whole process can be scaled up, is compatible with a variety of functional groups, and proceeds well competitively with protonolysis, and with no side reactions (e.g., Li/halogen exchange, *ortho*-lithiations or benzylic metalations).

[22] Elorriaga D, Rodríguez-Álvarez MJ, Ríos-Lombardía N, Morís F, Presa Soto A, González-Sabín J, Hevia E, García-Álvarez J: **Combination of organocatalytic oxidation of alcohols and organolithium chemistry (RLi) in aqueous media, at room temperature and under aerobic conditions.** *Chem. Commun.* 2020, **56**: 8932–8935

[23*] Dilauro G, Cicco L, Vitale P, Perna FM, Capriati V: **Ligand-free Pd-catalyzed reductive Mizoroki-Heck reaction strategy for the one-pot synthesis of functionalized oxygen heterocycles in deep eutectic solvent**. *Eur. J. Org. Chem.* 2022, e202200814.

Functionalised 2-(hetero)aryl THF and THP derivatives can straightforwardly and regioselectively be prepared in up to 95% yield, by assembling a ligand-free Mizoroki-Heck cross-coupling reaction between the corresponding unsaturated precursors and several (hetero)aryl halides with a reduction process in a ChCl/Gly eutectic mixture, working under aerobic conditions and without any halfway isolation/purification step.

[24] Grabner B, Schweiger AK, Gavric K, Kourist R, Gruber-Woelfler H: **A chemo-enzymatic tandem reaction in a mixture of deep eutectic solvent and water in continuous flow**. *React. Chem. Eng.* 2020, **5**:263–269.

[25] Gröger H, Hummel W: **Combining the 'two worlds' of chemocatalysis and biocatalysis towards multi-step one-pot processes in aqueous media**. *Current Opin. Chem. Biol.* 2014, **19**:171–179.

[26] Bornscheuer UT: **Biocatalysis: Successfully crossing Boundaries**. *Angew. Chem. Int. Ed.* 2016, **55**:4372–4373.

[27] Schmidt S, Castiglione K, Kourist R: **Overcoming the incompatibility challenge in chemoenzymatic and multi-catalytic cascade reactions**. *Chem. Eur. J.* 2018, **24**:1755–1768.

[28] Ríos-Lombardía N, García-Álvarez J, González-Sabín J: **One-pot combination of metal- and bio-catalysis in water for the synthesis of chiral molecules**. *Catalysts* 2018, **8**:75.

[29] Rodrigues JAR, Moran PJS, Conceiçao GJA, Fardelone LC: **Recent advances in the biocatalytic asymmetric reduction of acetophenones and α,β-unsaturated carbonyl compounds**. *Food Technol. Biotechnol.* 2004, **42**:295–303.

[30] Pscheidt B, Glieder A: **Yeast cell factories for fine chemical and API production**. *Microb. Cell Fact Eng.* 2008, **7**:25.

[31] Kourist R, González-Sabín J: **Non-conventional media as strategy to overcome the solvent dilemma in chemoenzymatic tandem catalysis**. *ChemCatChem.* 2020, **12**:1903–1912.

[32] Paris J, Ríos-Lombardía N, Morís F, Gröger H, González-Sabín J: **Novel insights into the combination of metal- and biocatalysis**. *ChemCatChem.* 2018, **10**:4417–4423.

[33] Gotor-Fernández V, Paul CE: **Biotransformations in Deep Eutectic Solvents** in *Sustainable Catalysis in Ionic Liquids*. Edited by Lozano P, Ed. (Boca Raton: CRC Press) 2018, 137–172.

[34] Gotor-Fernández V, Paul CE: **Deep eutectic solvents for redox biocatalysis**. *J. Biotechnol.* 2019, **29**:24–35.

[35] Guajardo N, Müller CR, Schrebler R, Carlesi C, Domínguez de María P: **Deep eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations**. *ChemCatChem* 2016, **8**:1020–1027.

[36] Maugeri Z, Domínguez de María P: **Whole-cell biocatalysis in deep-eutectic-solvents/aqueous mixtures**. *ChemCatChem* 2014, **6**:1535–1537.

[37] Vitale P, Abbinante VM, Perna FM, Salomone A, Cardellicchio C, Capriati V: **Unveiling the hidden performance of whole cells in the asymmetric bioreduction of aryl-containing ketones in aqueous deep eutectic solvents**. *Adv. Synth. Catal.* 2017, **359**:1049–1057.

[38] Goldberg K, Schroer K, Lütz S, Liese A: **Biocatalytic ketone reduction-a powerful tool for the production of chiral alcohols-part II: whole-cell reductions**. *Appl. Microbiol. Biotechnol.* 2007, **76**:249–255.

[39] Liardo E, Ríos-Lombardía N, Morís F, Rebolledo F, González-Sabín J: **Hybrid organo- and biocatalytic process for the asymmetric transformation of alcohols into amines in aqueous medium**. *ACS Catal.* 2017, **7**:4768–4774.

[40] Paris J, Telzerow A, Ríos-Lombardía N, Steiner K, Schwab H, Morís F, Gröger H, González-Sabín J: **Enantioselective one-pot synthesis of biaryl-substituted amines by combining palladium and enzyme catalysis in deep eutectic solvents**. *ACS Sustainable Chem. Eng.* 2019, **7**:5486–5493.

[41] Thoma C, Konnerth J, Sailer-Kronlachner W, Solt P, Rosenau T, van Herwijnen HWG: **Current situation of the challenging scale-up development of hydroxymethylfurfural production**. *ChemSusChem* 2020, **13**:3544–3564.

[42] Kabbour M, Luque R: **Biomass, Biofuels, Biochemicals** (Eds.: S. Saravanamurugan, A. Pandey, H. Li, A. Riisager), Elsevier, pp. 283–297 (2020).

[43] Rusanen A, Lappalainen K, Kärkkäinen J, Lassi U: **Furfural and 5-hydroxymethylfurfural production from sugar mixture using Deep Eutectic Solvent/MIBK system**. *ChemistryOpen* 2021, **10**:1004−1012.

[44*] Li Q, Ren JQ, Di JH, Ma C, He Y: **A hybrid process for valorization of D-fructose to 2,5-bis(hydroxymethyl)furan by bridging chemocatalysis and biocatalysis in a betaine: benzenesulfonic acid system**. *ACS Sustainable Chem. Eng.* 2022, **10**:12165−12176.

In this study, an efficient hybrid process was designed for the valorization of D-fructose into 2,5-bis(hydroxymethyl)furan (BHMF), which is a versatile building blocks for the production of drugs, bioactive and several value-added compounds. This newly tandem transformation relies on a quick dehydration process, promoted by the betaine/benzenesulfonic acid eutectic mixture, of D-fructose to 5-hydroxymethylfurfural (62.3% yield; 120 °C, 2 min), the latter then undergoing, in the same pot, a mild bioreduction carried out by recombinant *Escherichia coli* DCF, working at 40 °C and pH 7.5, to produce BHMF in over 99% yield after 48 h.

[45] Gao R, Li Q, Di J, Li Q, He Y-C, Ma C: **Improved 5-hydroxymethyl-2-furfurylamine production from D-fructose-derived 5-hydroxymethylfurfural by a robust double mutant *Aspergillus terreus* ω-transaminase biocatalyst in a betaine-formic acid medium**. *Ind. Crops Prod.* 2023, **193**:116199.

[46] Li Q, Ma C, Di J, Ni J, He Y-C: **Catalytic valorization of biomass for furfuryl alcohol by novel deep eutectic solvent-silica chemocatalyst and newly constructed reductase biocatalyst**. *Bioresour. Technol.* 2022, **347**:126376.

[47] Yang D, Zhao N, Tang S, Zhu X, Ma C, Fan B, Liang J, Yu B, Yang L, He Y-C: **A hybrid strategy for efficient valorization of bulrush into furoic acid in water-ChCl-based deep eutectic solvent**. *Ind. Crops Prod.* 2022, **177**:114434.

[48**] Ramos-Martín M, Lecuna R, Cicco L, Vitale P, Capriati V, Ríos-Lombardía N, González-Sabín J, Presta Soto A, García-Álvarez J: **A one-pot two-step synthesis of tertiary alcohols combining the biocatalytic laccase/TEMPO oxidation system with organolithium reagents in aerobic aqueous media at room temperature**. *Chem. Commun.* 2021, **57**:13534–13537.

This work describes how densely-substituted tertiary alcohols can be synthesized with excellent conversions (up to 96%) and a broad substrate scope by adopting a hybrid, one-pot tandem protocol based on a biocatalytic oxidation of secondary alcohols (promoted by the laccase/TEMPO system) with a fast (3 s reaction time) nucleophilic addition of polar organometallic reagents to the *in situ* formed ketones, under aerobic conditions at room temperature. Besides avoiding typical Schlenk-type conditions, this protocol minimizes undesired and frequently occurring decomposition processes when working in VOCs at low temperature and under an inert atmosphere.

[49] Ríos-Lombardía N, Rodríguez-Álvarez MJ, Morís F, Kourist R, Natalia Comino N, López-Gallego F, González-Sabín J, García-Álvarez J: **DESign of sustainable one-pot chemoenzymatic organic transformations in deep eutectic solvents for the synthesis of 1,2-disubstituted aromatic olefins**. *Front. Chem.* 2020, **8**:139.

[50] Grabner B, Schweiger AK, Gavric K, Kourist R, Gruber-Woelfler H: **A chemo-enzymatic tandem reaction in a mixture of deep eutectic solvents and water in continuous flow**. *React. Chem. Eng.* 2020, **5**:263–269.

[51] Kaushik M, Moores A: **New trends in sustainable nanocatalysis: emerging use of earth abundant metals.** *Curr. Opin. Green Sustain. Chem.* 2017, **7**:39–45.

[52**] Gröger H, Gallou F, Lipshutz BH: Where chemocatalysis meets biocatalysis: in water. *Chem. Rev.* 2022, https://doi.org/10.1021/acs.chemrev.2c00416.
This review discusses challenges and strategies for overcoming the compatibility between biocatalysis and chemocatalysis when using water as the reaction medium, highlighting latest achievements aimed at solving practical, synthetic problems.