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Towards Green Reductions in Bio-Derived Solvents

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The hydrogenation processes, and all the reactions that formally add two hydrogen atoms to an unsaturated bond, are among the most used transformations in the manufacture of bulk and fine chemicals. Although their potential as powerful tool for the sustainable synthesis of organic compounds, hydrogenations, and more generally the reductions, have been typically carried out in volatile organic solvents deriving from petroleum; indeed, all studies and fascinating advances related to the catalysts' activity or the reducing agents' reactivity have been limited to such volatile and often toxic reaction media. In this review, recent advances in the reducing methodologies with an improved degree of sustainability have been described. In particular, a series of examples have been reported to highlight the chance to reduce an organic compound by using a benign solvent deriving from renewable sources, without waiving to the process efficiency and selectivity. Some important key points of green chemistry, such as the easiness of catalyst recovery or the simplicity of product isolation, have been considered in the choice of the described studies.

1. Introduction

The reduction of organic compounds is an effective and useful synthetic strategy that provides a direct way for the formation of C–H, N–H and O–H bonds, pivotal structural elements on which the properties and reactivity of organic compounds are based. The value of such reduction protocols can be perceived by considering the tremendous impact that this transformation had in pharmaceuticals, dyes, pesticides, and fine chemicals production.[1–3]

Among the reactions that formally add a molecule of H_2 to an unsaturated organic substrate, the metal-catalyzed hydrogenation (HY) with gaseous H_2, is undoubtedly the best synthetic strategy in terms of general applicability, efficiency, and selectivity. It can be considered one of the most valuable transformations in bulk and fine chemical industry and is very often based on heterogeneous catalysts.[4]

More challenging HYs, that require chemoselective and/or stereoselective transformations, are typically performed by means of homogeneous catalysts in a family of reactions known as transfer hydrogenations (TH).[5] They are attracting a growing interest because they avoid the use of hazardous molecular H_2, by exploiting the catalytic activity of a transition metal able to promote the transfer of a hydrogen atom, or hydride ion, from a donor molecule to a substrate. The chemo-, regio- and even stereoselectivity reached in such a reaction is often above that achievable by heterogeneous catalysts, or simple reducing agents like conventional boron and aluminum hydrides, as accomplished in the outstanding Noyori asymmetric HY.[6]

When a synthetic strategy is employed in so many areas of chemicals production, it has, inevitably, a dramatic environmental impact even if it is based on a catalytic process. Some important aspects of the reduction methods, catalytic or not, must be considered to diminish their impact on human and environmental health: the toxicity of reagents, the costs and ecological consequences of catalyst manufacture, the recyclability of the catalyst, the energy demand of the reaction, the toxicity of solvents, as well as their recyclability.

Over the past decades, sustainability has become a major issue that has prompted both academic and industrial scientists to develop more environmentally beneficial and atom-efficient chemical processes. Therefore, to fulfil the twelve principles of green chemistry, as stated by Anastas and Kirchoff,[7] an ever-increasing number of new synthetic methods have been proposed. The use in synthetic processes of renewable sources, intended to replace fossil fuels as a source of carbon, is one of the crucial points.

The present Review has the aim of highlighting the most recent advances achieved in the field of reducing synthetic methodologies with a low environmental impact due to the employment of green solvents deriving from renewable sources. The choice has been dictated by considering that solvents employed in chemical transformations represent the 75–80% of the total wastes generated by manufacturing, chemical and pharmaceutical industries.[8] Hence, during the last decades, the request for eco-friendly alternatives that could replace hazardous solvents, has become the subject of intense research, with successful examples including deep eutectic solvents (DESs), alcohols and polyols (such as isopropanol and glycerol), and supercritical CO_2.

As a note, since the meaning of the adjective "green" it is often debated, we used it to indicate solvents characterized by

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at least two or more of the following crucial attributes: 1) have a low toxicity for humans and environment, 2) can be derived from renewable sources, 3) can be easily recycled, 4) are not flammable, 5) have a low volatility.

It is important to note that, regarding the economic convenience of bio-derived solvents use, some major advantages can be easily recognized to date: the utilization of agricultural residues instead of petroleum, the reduced load on waste management system with a resulting decrease in air pollution generation, the reduced cost associated to the workplace safety such as the personal protective equipment.

In addition, some disadvantages cannot be denied: while some of the green solvents are easily available and inexpensive (EtOH, CO_2, etc.), most of the green solvents today available on the market can reach high costs, presumably due to their low demand and/or production processes not yet optimized; the actual scenario needs to be upgraded in a manner to make bio-derived solvents economically viable at least as like the petroleum based solvents.

2. Reductions in Deep Eutectic Solvents

Deep Eutectic Solvents (DESs) are considered to be the direct descendants of ionic liquids (ILs). They have been introduced by Abbott in 2003.[9] The term "Deep Eutectic Solvents" is generally referred to a combination of two or more components, usually a Hydrogen Bond Donor (HBD) and a Hydrogen Bond Acceptor (HBA) that are able to generate a strong hydrogen bond interaction, forming a eutectic mixture with a melting point far below than that of the individual components. The genesis of this interaction leads to a decrease of the lattice energy and towards a stabilization of the system. The basic differences between DESs and ILs reside in the nature of starting materials and the methods of their production. Compared to ILs, the huge advantage of DESs is that they are formed by generally natural, cheap, non-toxic and easily accessible compounds. Furthermore, common components of DESs are naturally occurring biocompatible compounds that are not hazardous if they are released back into nature.[10] Furthermore, DESs are very simple to prepare. There are two principal methods: heating or grinding (process of reduction of the particle size

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Serena Perrone received her second level degree in Biotechnological Science, Industrial-Pharmaceutical course, in 2009 from the University of Salento (Italy). From 2011 to 2012 she joined the group of Professor Matteo Zanda as a PhD visiting student, at the University of Aberdeen (Scotland, UK), working about new melamine-based gemini surfactants as heterocyclic vectors for cell transfection. She obtained her PhD in "Chemical and enzymatic applied synthesis" under the supervision of Professor Luigino Troisi in 2013 from the University of Bari "ALDO MORO" (Italy). In 2013 she returned, as a research fellow, to the University of Salento where she collaborated with Professor Antonio Salomone in the field of organometallic chemistry, including the development of novel catalytic synthetic processes in bio-derived solvents.

She received the C.I.N.M.P.I.S. (National Interuniversity Consortium of Research in Innovative Methodologies and Processes of Synthesis) Award for innovation in organic synthesis in 2015. Currently she is a fixed-term researcher and her current research interests include the development of innovative transition metal-catalyzed methodologies for the preparation of bioactive molecules and heterocycles and the use of nonconventional solvent in organic synthesis.

Antonio Salomone obtained his PhD in 2004 from University of Bari, discussing a thesis on the synthetic utility of functionalized organolithiums in asymmetric synthesis, under the supervision of Prof Saverio Florio. From 2005 to 2009, he applied a postdoctoral position working on the synthesis of chiral organolithiums in the stereoselective synthesis of bioactive molecules. From 2010 to 2015 he worked, as postdoctoral fellow, at University of Bari, leading numerous studies on the kinetic and spectroscopic characterization of labile organometallic intermediates. In 2015 he moved to University of Salento as Assistant Professor working at the Pd-catalyzed carbonylations in the multicomponent synthesis of heterocycles. In 2018 he became Associate Professor in Organic Chemistry at the University of Salento and started his interest in the use of Deep Eutectic Solvents as new reaction media for the development of sustainable synthetic processes. In 2020 he moved to the University of Bari, at the Department of Chemistry. His current research activity is related to the development of green synthetic methodologies, enabled by transition metal catalysis, in Deep Eutectic Solvents.

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through mechanical shredding). The heating method is the most widely used: the components are mixed and heated at temperature between 50 and 80 °C under constant stirring, until a homogeneous liquid is formed. The eutectic liquids are obtained with a yield and an atom economy of 100 % without purification.[11] All these characteristics make DESs relatively inexpensive, bio-friendly and their production does not involve any significant post purification or disposal processes.

In the last years, an explosive growth of publications has focused on the use of DESs as reaction media in the organic synthesis.[12–14] On the other hand, only a few HY reactions have been successfully carried out in this type of solvents.[15] In a recent review, Marset and Guillena, described transition metal-catalyzed organic reactions, including redox processes, in DESs as reaction medium.[16] A first example of HY reaction in DESs was performed in 2006 by König and co-workers. The chlorotris(triphenylphosphine)-rhodium(I) (Wilkinson's catalyst) was employed for the reduction of the methyl ester of α-cinnamic acid (**1**) at 90 °C and under 1 atm of hydrogen, in the eutectic mixture composed by citric acid and *N,N'*-dimethylurea (DMU, Scheme 1).[15]

The reduction proceeds cleanly, rapidly and in quantitative yield in the citric acid/DMU eutectic mixture.

Given the fundamental importance of reductions in organic synthesis and in the preparation of biologically active compounds,[17] in 2012 Ghafuri and co-workers, reported for the first time an efficient, fast and a green procedure for a chemoselective reduction of both functionalized carbonyl
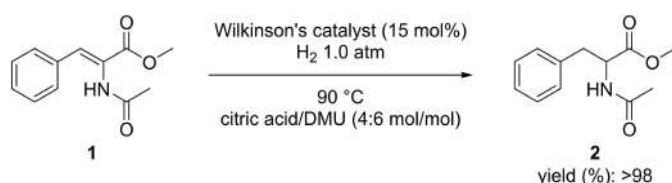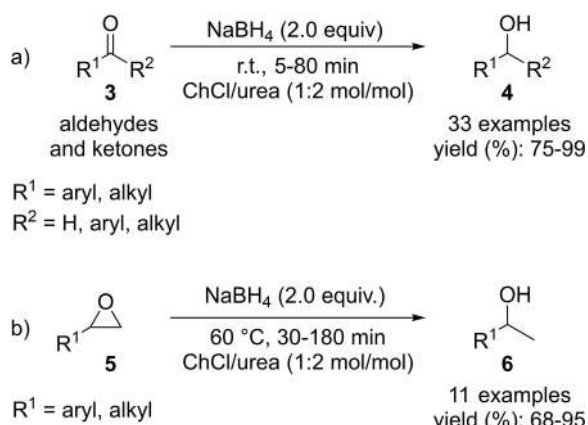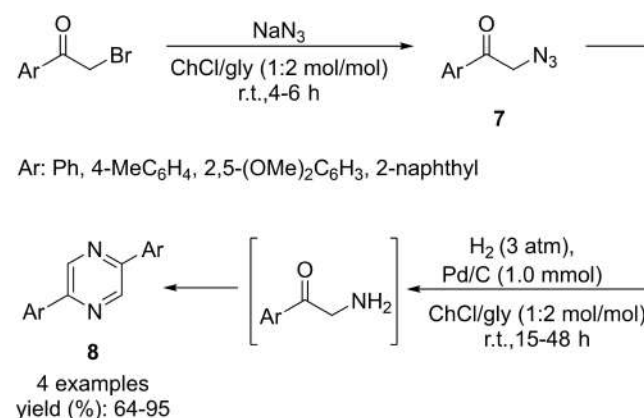
compounds (**3**) and epoxides (**5**) with commercially available sodium borohydride in deep eutectic solvents as a green reaction medium (Scheme 2).[18]

The reductive process is very fast, easy to accomplish and avoids the use of flammable low molecular weight alcohols often used for such a transformation. The substrates (**3** or **5**) were treated with NaBH$_4$ (2.0 equiv.) using the eutectic mixture composed by cholinium chloride (ChCl)/urea (1:2 mol/mol) as the sustainable reaction medium, at room temperature. After a reaction time between 5 and 180 min, the corresponding alcohol was isolated with high yield and purity.

In particular, a large variety of different carbonyl compounds, such as ketones and aldehydes, including saturated, unsaturated, aromatic and heteroaryl aldehydes were subjected to the reduction, affording the corresponding hydroxylated products in good to excellent yield (up to 99 % Scheme 2, a). Furthermore, the reductive protocol was employed for the ring opening of epoxides to afford the corresponding alcohols. The methodology proceeded smoothly with almost all commercially available epoxides, affording high reaction yield (Scheme 2, b). The reactions show good regioselectivity: when epoxides underwent cleavage by NaBH$_4$, in the DES ChCl/urea, the hydride attack preferentially occurs on the less substituted carbon of the epoxide, leading to the secondary alcohol.[18]

In 2019, Vitale and co-workers showed how the biodegradable eutectic mixture ChCl/glycerol (gly), 1:2 mol/mol, represented a sustainable reaction medium to easily prepare both phenacyl azides (**7**) and symmetrical 2,5-diarylpyrazines (**8**), the latter obtained through a reduction process (Scheme 3).[19] Indeed, by a one-pot two-step method, phenacyl azides **7**, synthetized from the corresponding phenacyl halides, were converted into symmetrical 2,5-disubstituted pyrazines **8**: the reaction is supposed to proceed via the formation of an α-amino ketone obtained *in situ* after the catalytic HY of the corresponding azide **7**, by using H$_2$ (3 atm) and Pd/C as the heterogenous catalyst (Scheme 3).[19]

Very recently, Cavallo et al. reported the first example of homogeneously catalyzed TH of commercially available carbonyl compounds in low melting mixtures. These TH


Scheme 1. HY reaction of methyl (Z)-2-acetamido-3-phenylacrylate **1** with Wilkinson's catalyst in citric acid/DMU eutectic mixture. DMU = N,N'-dimethylurea.

Scheme 2. Reduction of a) aldehydes, ketones, and b) epoxides with NaBH$_4$ in ChCl/urea eutectic mixture. ChCl = cholinium chloride.

Scheme 3. Synthesis of 2,5-diarylpyrazines (**8**) by HY of phenacyl azides in ChCl/gly DES. ChCl = cholinium chloride; gly = glycerol.

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processes were mediated by the easily achievable complex {[RuCl$_2$(p-cymene)]$_2$-μ-dppf} (dppf: 1,1'-bis(diphenylphosphino)ferrocene).[20] The reactions were carried out in the eutectic solvent composed by tetrabutylammonium bromide (TBAB)/HCOOH 1:1 mol/mol, employed as both a H$_2$-source and an alternative green reaction medium for the Ru-catalyzed TH. The methodology proceeds smoothly under mild reaction conditions (40–80 °C), in open air without the use of inert gases (Scheme 4).[20]

The reaction required the use of triethylamine as the base and cyclopentyl methyl ether (CPME) as an additive to maintain the system homogeneous under mild conditions. In fact, during the process, the consumption of HCOOH, the liquid component of the DES and the source of protons to generate hydrogen, leads to a heterogeneous system that required the use of a co-solvent (CPME) to make soluble all the species formed during the process.

The TH of aldehydes (**11**) to primary alcohols (**12**) was faster than that of the ketones (**9**), which needed harsher conditions to reach elevated conversion to their corresponding secondary alcohols (**10**). The best chemoselectivity towards the carbonyl moiety reduction was achieved in the presence of aromatic C–Br bonds and isolated C–C double bonds, Scheme 4. Less tolerability was instead attained when nitro- and cyano- groups were present, especially in the case of ketone substrates, most likely because of the higher temperatures employed, as
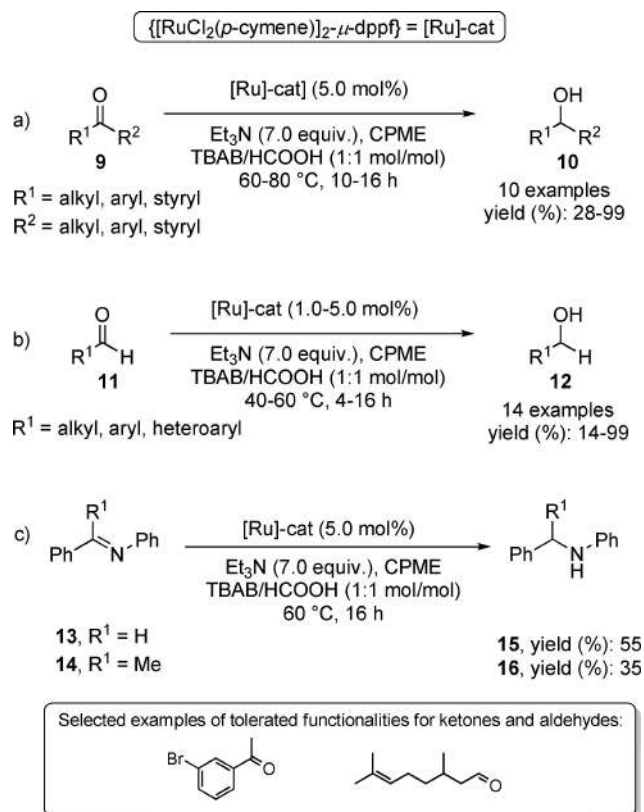
supposed by the authors. Poor chemoselectivity was also observed with α,β-unsaturated carbonyl substrates, due to the concomitant reduction of the conjugated C–C double bond (Scheme 4, a–b).[20] This procedure was also tested with imine derivatives (Scheme 4, c).

The reduction of these substrates proceeded well only with N-benzyl-1-phenylmethanimine **13** to the corresponding amine derivatives (**15**, yield 55%), while the ketimine N-benzyl-1-phenylethan-1-imine **14** showed modest reactivity towards the catalytic system employed (**16** obtained with 35% yield, Scheme 4, c).[20]

Lately, a glycerol-derived DES, composed of a bio-derived ammonium salt as HBA and a glycerol mono-methyl ether as HBD, was selected as the best medium for the efficient preparation of palladium nanoparticles (Pd NPs).[21] Moreover, the corresponding suspension of Pd NPs in glycerol-based DES was applied to perform the catalytic HY, under 1–20 bar of H$_2$, of a variety of alkenes, as well as to carry out the semi-HY of alkynes to alkenes (Scheme 5, a–b). In particular, the semi-HY of alkynes provided a good selectivity towards the formation of the corresponding alkene and only a poor amount of the overreduction product was observed (selectivity alkene/alkane ranging from 100/0 to 87/13 in the optimal reaction conditions).[21] Moreover, Pd NPs were used to carry out some HYs in a mixture of glycerol with choline tosylalaninate.[22]

Regarding the recyclability of Pd NPs/DES in the reduction of alkenes (Scheme 5a), the system has been reused with success in two consecutive HY reactions with a quantitative conversion and in two additional HYs with 61% of conversion. Unfortunately, after the fifth consecutive HY a progressive deactivation of the catalytic system was experienced. The opportunity to regenerate the catalyst, by hydrogen and thermal treatment, or by the addition of solvent, was also examined but without success.

Deep Eutectic Solvents showed to be good solvents also to perform the reduction of nitroalkanes with BH$_3$NH$_3$ (ammonia

Scheme 4. Ru-catalyzed TH for carbonyl compounds and imines reduction in TBAB/HCOOH as non-innocent eutectic mixture. TBAB = tetrabutylammonium bromide; CPME = cyclopentyl methyl ether.
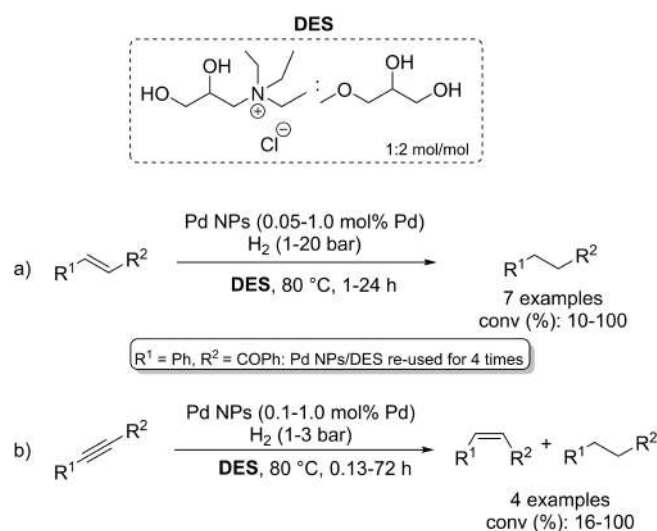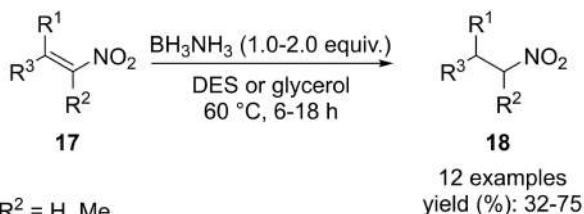
Scheme 5. a) Pd NPs-catalyzed HY of alkenes in DES; b) Pd NPs-catalyzed semi-HY of alkynes in DES.

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borane, AB) as the reducing agent, Scheme 6.[23] AB is receiving increasing attention as relatively inexpensive and useful reducing reagent for developing new green synthetic transformations[24,25] because it generates much less waste compared to other reducing agents, such as the bioinspired Hantzsch ester.[26]

The reduction of nitroolefins (17) using BH_3NH_3 (1.0 equiv.) was carried out in various DESs, under mild reaction conditions (60 °C) to afford the desired nitroalkanes (18) in moderate to good yields (Scheme 6). This highly chemoselective and efficient procedure allowed the direct isolation of the reduction products from the DES medium, without further purifications. The reaction was successfully performed with different aryl- and alkylnitroalkenes. Electron-rich substrates such as methoxy-4-(2-nitrovinyl)benzene or methyl-4-(2-nitrovinyl)benzene reacted much faster than electron-poor ones which needed 2 equivalents of AB to achieve good yields. The best reaction medium was the eutectic mixture composed by betaine/glycolic acid (1:2 mol/mol); this mixture allowed the shortening of the reaction time up to 6 h, a good improvement if compared with the 18 h reaction time required in ChCl/gly (1:2 mol/mol) mixture and in pure glycerol.[23]

The amino group is a central functionality in synthetic chemistry, due to its presence in natural products, pharmaceutical, and many biologically active molecules, as well as in key-intermediates for the synthesis of fine chemicals and dyes.[27] The direct reductive amination of carbonyl compounds still remains one of the most powerful tools for the preparation of molecules that contain such a pivotal functional group. However, most of the widely used reductive amination methods have one or more drawbacks: the harsh reaction conditions, the generally poor yields, the low chemical selectivity, the use of toxic and expensive rare metals, and the generation of toxic by-products.[28–30] In order to reduce the environmental impact of the direct reductive amination procedure, Saberi et al. proposed the synthesis of secondary amines by reductive amination of aldehydes and ketones in the presence of the ChCl/urea (1:2 mol/mol) eutectic mixture as the catalyst and $NaBH_4$ as the reducing agent in MeOH.[31] The methodology requires the use of methanol as a solvent to allow an optimal solubilization of the $NaBH_4$, obtaining high reaction yields (Scheme 7). About the role of ChCl/urea eutectic mixture as catalyst, it is reported that this DES facilitates the reaction through the formation of
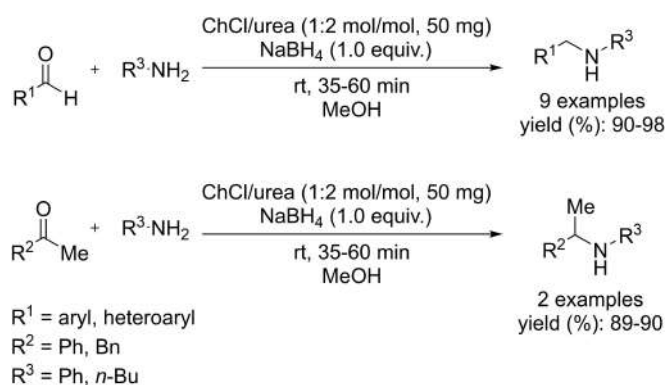

Scheme 7. Reductive amination of carbonyl compounds using ChCl/urea as the catalyst mediated by $NaBH_4$ in MeOH. ChCl = cholinium chloride.
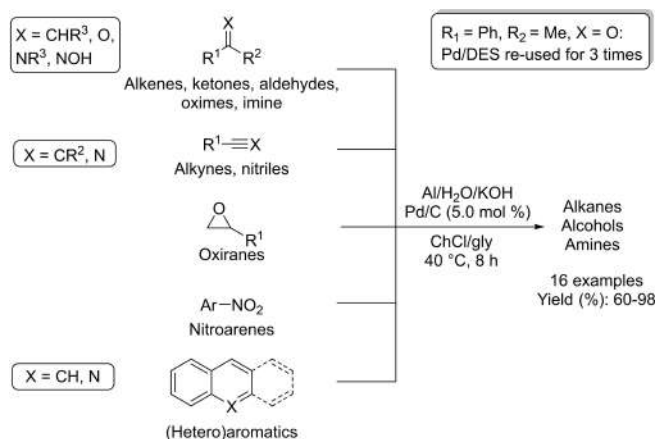
hydrogen bonds with carbonyl and then with imine moieties, resulting in an increased electrophilicity of carbon atom.[31]

The reduction of functional groups by the addition of hydrogen gas under heterogeneous catalysis is one of the most eco-friendly methods for the reduction of organic molecules, because of the ease of catalyst recovery and the elevated atom economy. On the other hand, there are some critical drawbacks, related to the use of gaseous H_2 such as the very broad flammability range of hydrogen gas,[32] the need to use suitable reactors when the process occurs at high pressure and the huge energy demand and large emission of greenhouse gases to produce molecular hydrogen by natural gas reforming.[33]

Based on their research on Pd-catalyzed reactions and sustainable synthetic processes in DESs,[34–43] Messa et al., very recently, described a safe, scalable and sustainable HY reaction of a variety of functional groups. The reactions, enabled by in situ generation of hydrogen from Al powder and small amount of basic water, were catalyzed by the cheap Pd/C catalyst. The reductive process was carried out in ChCl/gly (1:2 mol/mol) eutectic solvent under mild reaction conditions, and a huge number of different organic moieties was reduced (Scheme 8).[44]

The deep eutectic solvent plays a crucial role in the HY process, both by solubilizing the aluminum oxide and allowing the Al metal to be more reactive and by making the process green and safer. Indeed, protocol hazard tests carried out in water (instead of DES) show that the reaction reached a peak of temperature (100 °C) in only 4 seconds after the addition of KOH. Such a violent boiling of the solvent combined with a fast H_2 evolution caused a hazardous and undesirable bumping of the reaction mixture. On the other hand, when the reduction was performed in DES, the temperature of the medium increased very slowly and reached the maximum value (108 °C) after 12 minutes. The insignificant volatility of the DES and its low thermal conductivity ensured a fairly safe reaction.[44]

Furthermore, the optimized reductive protocol was employed to perform the final step of the multigram-scale green synthesis of Benzindopyrine, a sedative and antipsychotic drug, starting from indole. Indeed, the alkyne intermediate 19 was subjected to the system composed of Al/H_2O/KOH in ChCl/gly

Scheme 6. Nitroalkenes reduction promoted by ammonia borane in DESs and glycerol. ChCl = cholinium chloride; gly = glycerol.

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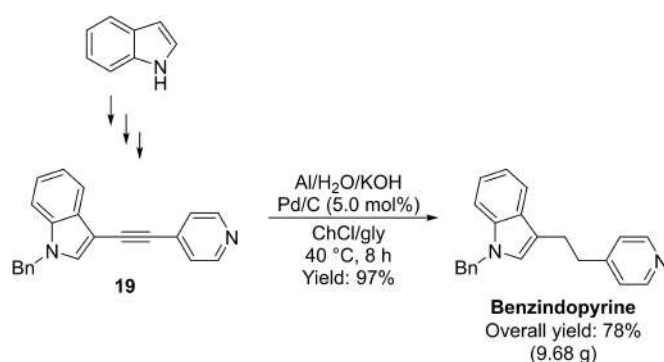**Chemistry
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Scheme 8. Reductive protocol with Al/H$_2$O/KOH and Pd/C carried out in DES ChCl/gly as solvent. ChCl = cholinium chloride; gly = glycerol.

Scheme 10. Catalytic hydrogenolysis in DESs of C-lignin from castor seed coats (castor seed coats/catalyst = 3.3/1 wt:wt). ChCl = cholinium chloride; EG = ethylene glycol; PG = propylene glycol; gly = glycerol.

eutectic mixture at 40 °C for 8 h, in the presence of Pd/C as the catalyst. The methodology proved to be very effective, affording 9.68 g of the pharmacological active target (97% yield), corresponding to a 78% overall yield in four synthetic steps (Scheme 9).
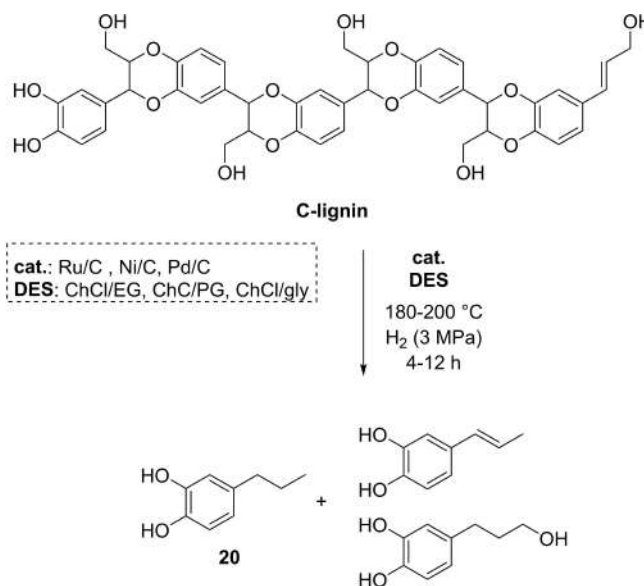
DESs are attractive green solvents also for biocatalytic reductions. Indeed, they can mimic the cell's environment, reproducing metabolites and providing a liquid alternative instead of water and lipids.[45] The use of DESs as bio-friendly solvents for biocatalytic redox reactions, has been widely explored and a plethora of enzymes and microorganisms have been used for the bio-inspired reduction of organic molecules.[46]

Also the catalytic hydrogenolysis of castor seed coats have been investigated in DESs media. Particularly, Song et al. described the hydrogenolysis of castor seed coats by using Ru/C, Ni/C and Pd/C catalysts in the eutectic mixtures ChCl/gly, ChCl/EG (ethylene glycol) and ChCl/PG (propylene glycol) in a 2:1 molar ratio (Scheme 10).

The reduction process, performed in the presence of 3 MPa of H$_2$ at 180–200 °C, enabled the formation of catechol-type monomers through a depolymerization process of C-lignin, a

naturally occurring linear biopolymer contained in castor seed coats. The combination of Pd/C in ChCl/EG and Ru/C in ChCl/PG showed the best performances, leading to a good yield of catechol-type monomers (40.6 mg/g and 56.3 mg/g, respectively) with high selectivity to catechol **20** (Scheme 10).[47]

Finally, some processes involved the use of DES to prepare heterogeneous hydrogenation metallic-catalysts, although these HY reactions are not performed in eutectic mixtures.[48–50]

3. Reductions in Isopropanol

Isopropanol (iPrOH) is an industrially attractive value-added molecule that can be produced by microbes from renewable resources.[51] It is mainly used as a green solvent in organic chemistry due to its very low impact on the environment and on the human health, in accordance with the GSK Solvent Sustainability Guide.[52] iPrOH serves as a chemical intermediate in the production of various esters and amines[53] and is also employed as a disinfectant in pharmaceutical products, or as an anti-freezing agent.[51]

Isopropanol can be chemically produced by reduction of acetone in the presence of excess hydrogen, or from propylene by hydration over an acid catalyst.[53] Currently there are several competitive microbial isopropanol production processes from renewable resources that represents a significant market opportunity. Referring to the biosynthesis of isopropanol by fermentation processes, it can involve natural propanol-producing organisms, or engineered microorganisms expressing the acetone-dependent isopropanol pathway.[51] Therefore, one of the best reported propanol producers is an *E. coli* strain, which was engineered with the acetone-dependent isopropanol path-

Scheme 9. Multigram synthesis of the antipsychotic Benzindopyrine in green media. ChCl = cholinium chloride; gly = glycerol.

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way from *Clostridia.* This organism accumulated 40 g/L isopropanol in a fed batch process.[54]

Isopropanol is among the green solvents of choice widely used in catalytic TH reactions.

Among chemical transformations, TH reactions and high-pressure HY of unsaturated molecules are widely used in organic chemistry.[55–57]

TH reaction, in which hydrogen is transferred from one molecule to another, is nowadays recognized as an efficient reduction method of organic unsaturated substrates, generally ketones, aldehydes and imines (Scheme 11).[57,58] Moreover, it is very helpful to avoid the use of highly flammable $H_{2(g)}$, which requires extra precautions and special high-pressure equipment.[56–58]

Hydrogen transfer is actually an equilibrium reaction between an organic compound (generally an alcohol or an amine) acting as the hydrogen donor (HD) and the substrate to be reduced that acts as the hydrogen acceptor (HA) compound, Scheme 11: the equilibrium can be shifted towards the reaction products through the use of a large excess of HD which acts both as a hydrogen source and as the reaction solvent.

One of the most useful and elegant applications of TH is related to the asymmetric reduction of prochiral ketones and imines, an advantageous method for the preparation of enantiomerically enriched alcohols and amines, respectively, two class of compounds widely used in the pharmaceutical, fragrance, and fine chemicals industries.[59,60]

The synthesis of enantioenriched alcohols is generally carried out using ruthenium-based catalysts and isopropanol/base as the hydride source. In such system, the presence of an organic or inorganic base is generally necessary to activate the catalyst and/or to assist in dissociation of alcohol hydroxylic group. Among the different hydride sources, isopropanol/base combinations are the more attractive because of their stability, easy accessibility, nontoxicity, low relative cost, and environmentally benign nature.[61]

This HY reaction, first developed by Noyori end co-workers,[62,63] was performed in basic isopropanol and employed ruthenium(II) catalysts, containing a chelating enantipure diphosphine ligand and a chelating enantipure diamine ligand.[64–66]

The development of improved catalysts for the asymmetric transfer hydrogenation (ATH) of ketones represents a continuing challenge to synthetic chemists. During the past decade, several catalytic systems have been developed.

In 2012, Wills et al. showed how a tridentate ligand (**21**, Figure 1), based on homochiral 1,2 diamine linked to a triazole group, in conjunction with $Ru_3(CO)_{12}$ as metal source, formed, in isopropanol, an effective catalyst for ATH reactions of ketones.[67]
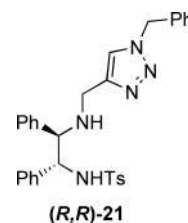
The reductions, performed without base, formed the corresponding alcohols with enantioselectivities of up to 93% and up to 99% conversion. Moreover, a range of *ortho*-substituted acetophenones could be reduced in good enantioselectivity without significant reduction of the ee (up to 99% conversion and 85% ee), a major achievement compared to the usual behaviour of challenging *ortho*-substituted substrates in ATH reactions (Scheme 12).[67]

Isopropanol, as solvent in ATH, plays an important role in the catalytic cycle. Indeed, as a result of an initial fragmentation of $Ru_3(CO)_{12}$ with loss of CO, the ligand **21** may originate an active catalytic bidentate complex **22**; following the insertion of ruthenium into the N–H(Ts) bond, ruthenium hydride **23** could form, which transfers two hydrogen atoms to ketone to produce the corresponding (*R*)-alcohol and to give a tridentate ruthenium complex **24**. The reaction of the complex **24** with isopropanol may then regenerate ruthenium hydride **23** to complete a catalytic cycle (Scheme 13).[67]

In 2014, Karvembu et al. described novel (η^6-*p*-cymene)ruthenium(II) complexes **25**, containing chiral acylthiourea ligands bound to the metal core only via the sulfur donor atom (Scheme 14).[68]
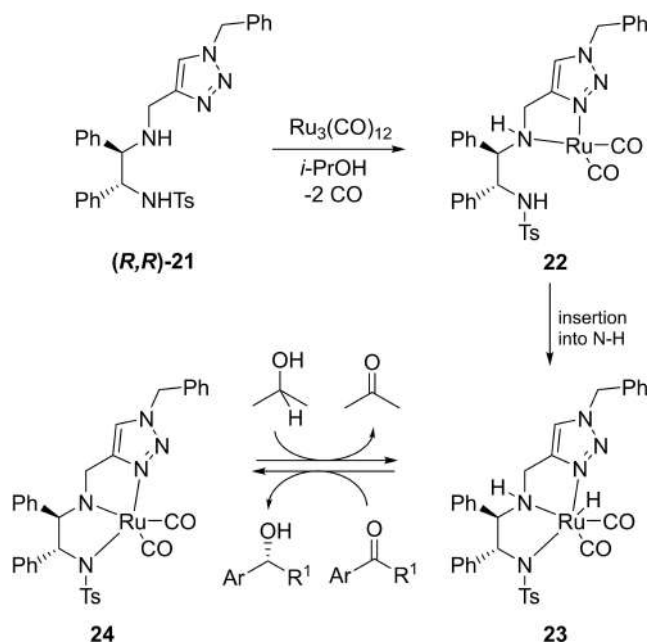
This monodentate coordination was observed for the first time with ruthenium. The Ru(II) complexes **25**, in refluxing isopropanol (82°C) and in the presence of KOH, act as efficient catalysts for the ATH of aromatic ketones to their corresponding chiral alcohols. The optimized substrate:KOH:catalyst ratio was 200:1:1. The reactions proceeded smoothly and all the catalysts examined, after 24 h, showed from moderate to excellent conversions and enantiomeric excesses (Scheme 14).[68]
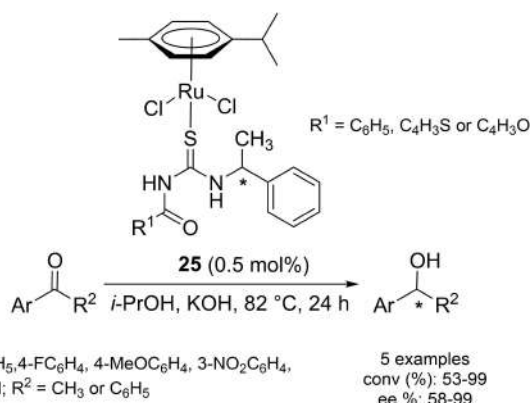

Figure 1. Triazole-containing ligand (*R,R*)-**21** used in ketone ATH.
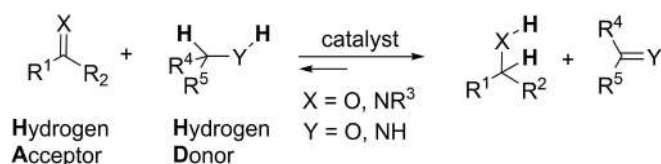
Scheme 11. General equation of the TH reaction.

Scheme 12. ATH reactions of a range of ketones carried out in isopropanol as solvent, using the ligand (*R,R*)-**21**.
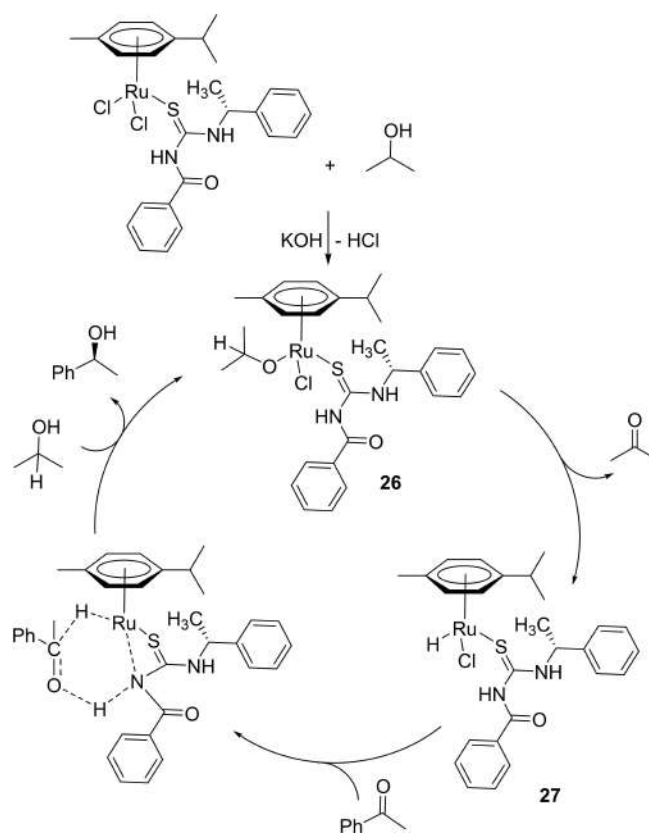
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Scheme 13. Suggested mechanism for ATH of ketones by ligand **21**/Ru₃(CO)₁₂ catalysis in isopropanol as solvent.

Scheme 14. ATH of ketones catalyzed by Ru(II) complexes **25**.

Scheme 15. Suggested mechanism for ATH of ketones in basic isopropanol.
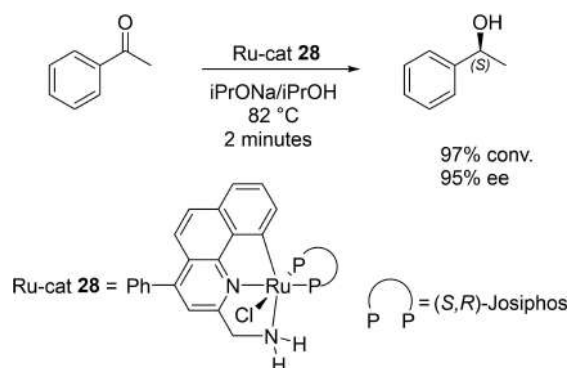
Scheme 16. ATH of ketones in basic isopropanol catalyzed by the pincer Ru-complex **28**.

The ATH of prochiral ketones proceed stepwise via the formation of metal hydride species, confirmed by FTIR and ¹H NMR investigations (Scheme 15). In particular, the reaction between the complex [RuCl₂(η⁶-p-cymene)L] (L=chiral acylthiourea ligand) and basic isopropanol could form an active Ru-alkoxide intermediate **26** that generates an 18-electron Ru-hydride species **27** through intramolecular hydride transfer. The Ru-hydride intermediate, with its Ru—H and N—H units, interacts with the prochiral ketone to form a six membered transition state, according to Noyori's outer-sphere mechanism (Scheme 15).[68]

In 2015, Baratta and co-workers reported a fascinating reducing activity of several pincer Ru-complexes, that were employed in the TH of aromatic and aliphatic ketones in isopropanol.[69] Of note, the Ru-catalyst **28**, (Scheme 16) characterized by a 2-(aminomethyl)pyridine motif and the chiral

diphosphine (S,R)-Josiphos, showed to be useful in the ATH of acetophenone: this prochiral ketone was reduced to (S)-1-phenylethanol with a 97% conversion and 95% ee in only 2 minutes at 82°C and with a substrate/catalyst ratio equal to 10⁴. The high efficiency of such Ru-catalysts probably relies on the presence of the robust ortho-metalated pincer ligand, which most likely retard the catalyst deactivation.

The year before, the same authors described the reducing activity of similar pincer Ru-complexes in the TH of aromatic and heteroaromatic aldehydes to the corresponding primary alchohols.[70]

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Morris and co-workers developed an alternative synthetic strategy to ruthenium catalysis to achieve an efficient catalytic ATH of prochiral ketones, in isopropanol, based on the use of the more sustainable, stable and highly active iron(II)-catalyst **29** (Scheme 17).[71,72]
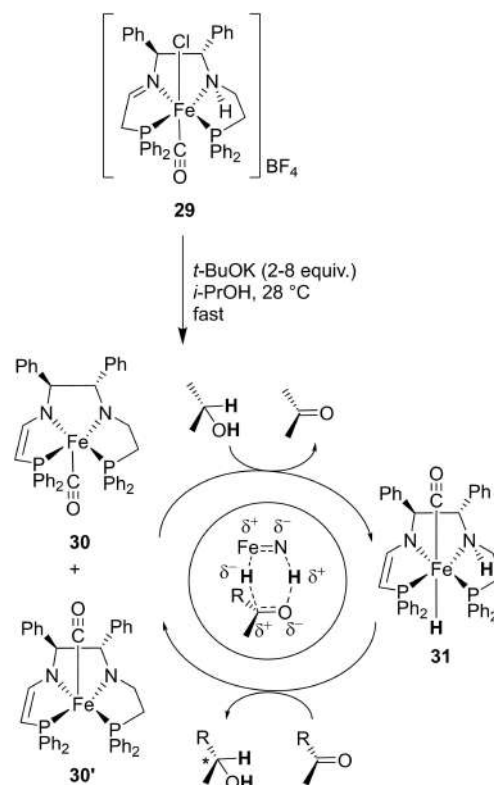
The same iron-based approach was also applied to perform the catalytic ATH of prochiral imines to the enantioenriched amines, typically hydrogenated under higher pressure of hydrogen using iridium di-phosphines catalysts (Scheme 17).[73,74] The asymmetric reduction described is very fast (10 s to 1 h) and represents a convenient approach for an effective generation of chiral alcohols and *N*-protected amines. Particularly, 0.02 mol% loading of the enantiopure (*S,S*) precatalyst **29** allowed the reduction of prochiral ketones to the corresponding (*R*)-alcohols in good to excellent yields (55%–99%) and enantioenrichment (ee at 10 s: 25%–92%). Specifically, the iron complex **29** was active towards a broad range of aryl ketones as well as alkyl ketones, that, from a thermodynamic and kinetic point of view, are less prone to react. The procedure works also with pyridine and furan heterocycles, albeit with a drop in enantioselectivity (ee at 10 s: 25% and 51%, respectively). Moreover, the reduction of polar C=O bond of the *trans*-4-phenyl-3-buten-2-one, initially, led to the formation of the unsaturated alcohol, with relatively low enantioselectivity (40% ee, Scheme 17).[71,72]

Complex **29** was also an effective precatalyst for the ATH of imines activated with the *N*-(diphenylphosphinoyl) group (−P-(O)Ph$_2$), to the corresponding (*R*)-amines, obtained in very high yield (100%) and enantiopurity (ee at 10 s: >99%, Scheme 17).[71,72]

The catalytic mechanism was elucidated by a previous theoretical DFT study and confirmed by NMR analysis: the structures of catalysts **30** and **31** were proposed (Scheme 18).[72] Upon activation with 2 to 8 equiv. of base, these imine-amine iron complexes showed high catalytic activity in the ATH of
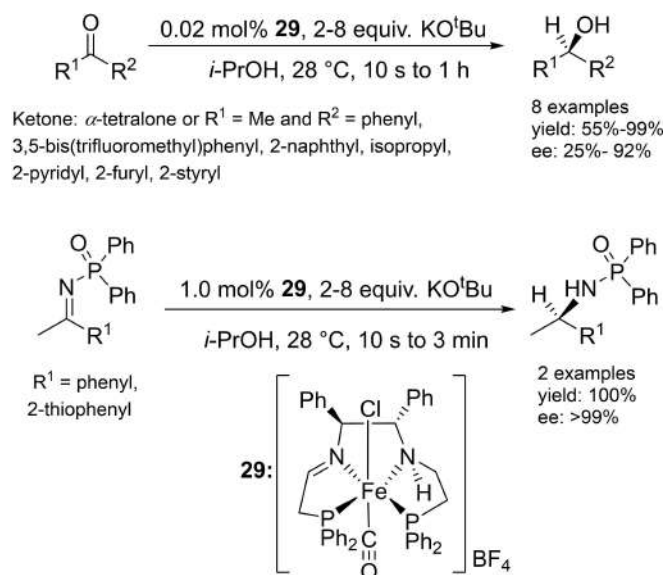
Scheme 18. Proposed mechanism for ATH of ketones mediated by iron-based catalysts containing amine(imine)diphosphine P–NH–N–P ligands.

ketone and imine substrates, transferring hydrogen from the isopropanol solvent with high TOF (turnover frequency), of up to 200 s^{-1} for some ketones.[72] In particular, catalysts **30** and **30′**, isomers likely having the carbonyl on the opposite apex of the square pyramid, were generated as a mixture by reacting the precatalyst **29** with the strong base KO*t*Bu in isopropanol. The hydrogen donor for the catalysts **30** is the solvent; indeed, the reaction of the mixture of isomers **30** with isopropanol led to the formation of the iron hydride amine complex **31**, which makes the iron complex an efficient ATH catalyst of ketones and imines (Scheme 18).[72]

The ATH catalysis proceeds by the outer spere pathway;[75,76] hence the iron hydride amine complex **31** attacks the ketone in the outer sphere and then the hydride amine is regenerated by reaction with isopropanol (Scheme 18).[72]

The same author has also reported a rare example of asymmetric hydrogenation at high pressure (AHHP) using an iron complex.[77] Indeed, in addition to being a highly efficient catalyst for the ATH of ketones, the amine(imine)diphosphine iron complex **29** is able also to catalyse the AHHP of ketone substrates, although with low activity and enantioselectivity.

The same structure of the amine iron hydride intermediate formed by reacting the iron complex **29** with dihydrogen as that obtained by reacting with isopropanol, suggesting a similar reaction mechanism in both AHHP and ATH hydrogenation reactions.[77]

Scheme 17. ATH of prochiral ketones and imines in isopropanol, by the iron catalyst system **29** at 0.02–1 mol% loading.

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With reference AHHP, in 2014 Rodrìguez *at al.* developed novel and efficient ruthenium catalysts, as shown in Figure 2, for the enantioselective reduction of a variety of ketones in isopropanol as solvent.[78]

Particularly, they described a family of amine-tunable ruthenium catalysts, based on chiral bisdihydrobenzooxaphosphole (BIBOP) ligands (complexes 32–34 in Figure 2), as effective catalysts for AHHP of highly challenging ketones, including aryl- and heteroaryl- cyclic ketones (Scheme 19). The reactions, performed in *i*PrOH, under 400 psi of hydrogen, exhibit turnover numbers (TON, molar ratio of converted substrate to catalyst) up to 100,000.[78]

In addition, the opposite sense of enantioselectivity can be obtained by proper selection of the (chiral) diamine ligand with a given chirality of the phosphine. Indeed, the AHHP reactions of cyclic ketones, in the presence of pre-made catalyst 32, provided the heterocycles tetrahydroisoquinolinols 35–36, tetrahydrobenzothiophenol 37, tetrahydrobenzofuranol 38, and tetrahydroindazolol 39 with high (S)-enantioselectivity; with the use of pre-made complex 33, a very interesting and useful inversion of the asymmetric induction was observed, thus obtaining the (R)-enantiomer as the major product (Scheme 19).[78] Analogously, in the case of 1-tetralone as substrate, the (S)-enantiomer 40 was obtained in 99% yield and 98 ee% when using the complex 32 with a very low loading (0.001 mol%), under 400 psi of hydrogen at 25 °C in *i*PrOH; the opposite (R)-enantiomer 40 was achieved in 98% yield and 92 ee% when using the catalyst 33 with same loading and experimental conditions. These catalysts also provided high stereoselectivities of the 1-tetralols 41 (Scheme 19).[78] Interestingly, in the case of use of aryl- and heteroaryl- methyl ketones such as acetophenone, 1-(4-bromophenyl)ethan-1-one and 1-(pyridin-3-yl)ethan-1-one, no inversion of enantioselectivity was observed with the change of the diamine ligand for the catalyst.[78]

Furthermore, the usefulness of the procedure has been demonstrated also in the AHHP of a complex synthetic intermediate towards cholesteryl ester transfer protein (CETP) inhibitors, using the pre-made $RuCl_2$(MeO-BIBOP)(diamine) 34 (Figure 2), with a slightly increased loading (0.02 mol%) under 400 psi of hydrogen on a 0.5 kg scale in 98% yield and >98 ee% in favour of the (R)-isomer 41.[78]

AHHP of ketones with H_2 and *i*PrOH as solvent was also performed with ruthenium catalyst containing chiral tetradentate S_2N_2 ligands (Scheme 20).[79] In particular, based on the works previously reported on the AHHP of ketones with
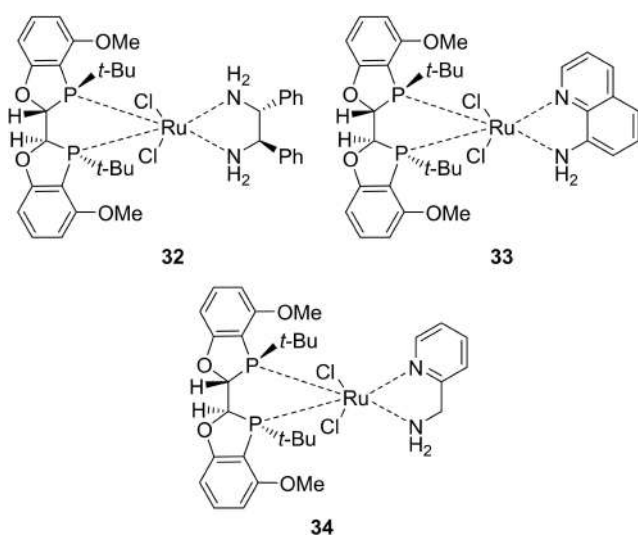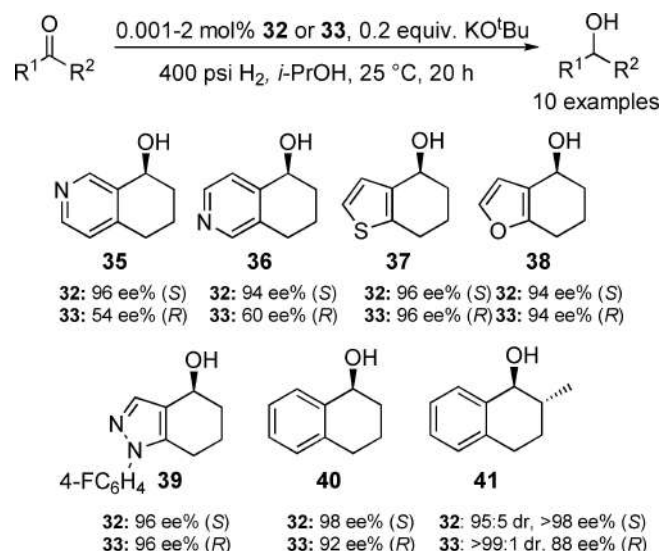

Figure 2. Ammine-tunable Ru-catalysts for ATH of ketones.
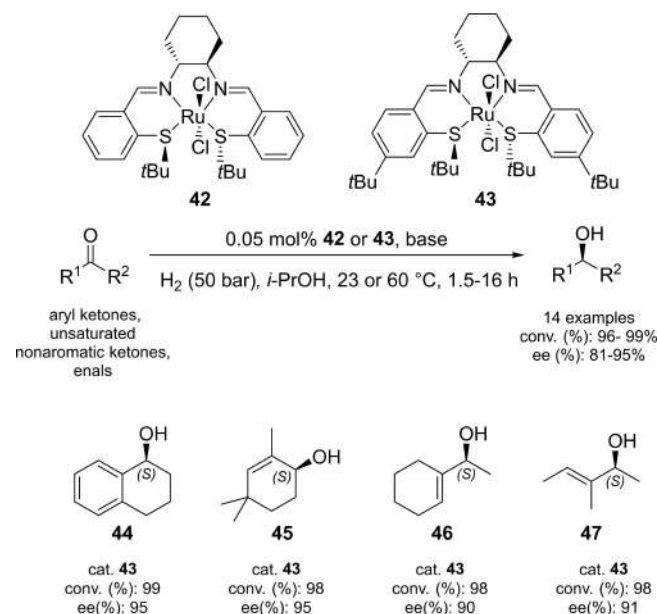

Scheme 19. AHHP of ketones, including aryl- and heteroaryl- cyclic ketones shown, using the ammine-tunable Ru-catalysts 32 or 33 in isopropanol as solvent.

Scheme 20. AHHP of ketones and aldehydes in *i*PrOH as solvent. KOH (5.0 mol%) or tBuOK (0.5 mol%) was used as base. (R,R)-43 gave (S)-product as the major enantiomer.

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[RuCl$_2$(PNNP)] catalysts,[80] where PNNP is a chiral tetradentate ligand with a P$_2$N$_2$ donor, Santoro's and Mezzetti's groups developed catalysts containing tetradentate ligands in which the phosphines are replaced by thioethers (SNNS).[79]

A reaction screening performed on the AHHP of acetophenone identified iPrOH as the solvent and tBuOK or KOH as the bases of choice with a base-to-catalyst ratio of 10:1 and 100:1, respectively. Moreover, as shown for catalysts **42** and **43** in Scheme 20, a bulky tBu on sulfur is necessary to achieve high enantioselectivity, whereas ligands bearing smaller alkyl groups (Cy, iPr, Me) on the sulfur give low ee.
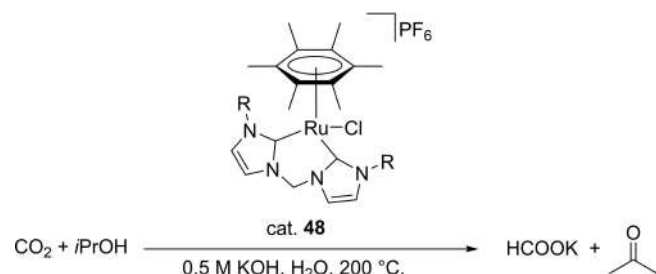
Thus, in the presence of H$_2$ and the base, these phosphorus free, air- and moisture-tolerant Ru(II)/SNNS complexes **42–43** are able to catalyse the AHHP of carbonyl groups of ketones and aldehydes with excellent activity (Ru-loading = 0.05 mol%) and with enantioselectivity of up to 95%, under mild conditions (Scheme 20).

The highest enantioselectivity was observed with α-tetralone and 2,4,4-trimethylcyclohexenone, obtaining the corresponding (S)-alcohol **44–45** with 95% ee for both substrates, Scheme 20. Also other nonaromatic unsaturated ketones, such as 1-(cyclohex-1-en-1-yl)ethan-1-one and (E)-3-methylpent-3-en-2-one, gave the corresponding (S)-alcohol **46–47** with high enantioselectivity (90 and 91% ee, respectively, Scheme 20).[79] Moreover, these Ru/SNNS complexes show excellent chemoselectivity in the reduction of the carbonyl groups of unsaturated ketones and aldehydes, and the ratio of substrate to catalyst can be lowered to 10^6:1 (Ru-loading = 0.0001 mol%), which allows for multimole-scale reactions. All the products were formed quantitatively or nearly so.[79]

Isopropanol was also the solvent of choice to carry out the reduction of CO$_2$ to formate through a hydrogen transfer process (Scheme 21).[81]

The homogeneously catalyzed HY of CO$_2$ to formic acid, is a well-known reaction that was first reported in 1976.[82] This reaction normally involves the reduction of carbon dioxide with pressurized hydrogen.[83]

On the other hand, some reports show that 'Ru^{II}(η^6-arene)' complexes represent valuable catalysts for the TH of CO$_2$ to formic acid. In particular, the '(η^6-arene)Ru(bis-NHC) complex **48** (NHC=N-Heterocyclic carbene), among all the complexes under study, showed to be the most active one in the reduction of carbon dioxide with iPrOH, by the TH methodology (Sc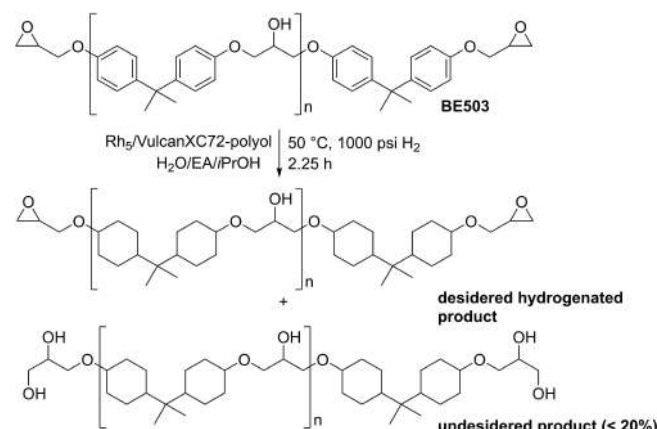heme 21).[81] For the reactions carried out at 110°C, almost negligible activities were obtained for all the catalysts, but the reactions performed at 200°C provided the higher TON value of 874 for the catalyst **48**. The activity of the catalyst is highly dependent on its stability because the complex must stand the severe reaction conditions of the process (200°C).[81]

Bisphenol A type epoxy resins (BPAERs) are currently the subject of numerous research as they are excellent candidates as LED (light emitting diode) packaging materials for their insulating properties, for being durable and transparent. However, these resins are susceptible to yellowing and deteriorating due to the oxidation reaction of aromatic rings to obtain benzoquinone.[84]

Therefore, given their greater resistance to yellowing, hydrogenated BPAERs, characterized by complete HY of aromatic rings preserving the epoxy rings, are actually much investigated as LED packaging materials.[85]

An eco-friendly ternary solvent mixture containing iPrOH [10 wt% H$_2$O, 20 wt% iPrOH and 70% green ethyl acetate (EA)[52]] was recently employed to perform an effective HY of high molecular weight bisphenol A type epoxy resin BE503 (Scheme 22). Particularly, Lai et al. in 2020 were able to carry out the HY of a BE503 with a MW of 1500, under mild reaction conditions. The ternary solvent mixture used was found to accelerate HY of the resin and led to an increased H$_2$ availability, due to higher solubility of BE503 and H$_2$ in iPrOH.[84]

Studying the effect of different reaction parameters and through the modification of operation variables, they menage to maximize the reduction process. Specifically, a 100% HY yield of BE503 aromatic rings, with an epoxy ring opening below the industrially acceptable value 20%, was achieved at 50°C and a H$_2$ pressure of 1000 psi in 2.25 h using Rh$_5$/VulcanXC72-polyol (Scheme 22),[86] a Rh catalyst supported on carbon black VulcanXC72 prepared by the polyol method.[87]

Scheme 21. TH of carbon dioxide with iPrOH. Reactions were carried out at 200°C, 735 psi CO$_2$, 0.5 M KOH in 20 ml of H$_2$O:iPrOH (9:1).

Scheme 22. Hydrogenation of high molecular weight Bisphenol A type epoxy resin BE503.

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## 4. Transfer Hydrogenations of Unsaturated C—O, C—C and N—O Bonds in Other Low Molecular Weight Alcohols

Regarding the green methods for the TH reactions and the synthesis of optically active molecules, also ethanol has been found to be an efficient hydrogen donor.[88]

Ethanol is a renewable resource and has aroused considerable interest as an alternative to fossil fuels and a potential feedstock for the chemical industry, as well as it is an environmental and human-friendly solvent.[89,90]

In 2015, Liu et al. developed an efficient iridium-catalyzed ATH of simple ketones with ethanol as a hydrogen donor, affording chiral alcohols with up to 98% ee.[91] More specifically, with the use of a chiral spiro iridium catalyst (S)-**49**, containing a tridentate ligand consisting of a spiro pyridine aminophosphine group, a variety of aryl-alkyl ketones were hydrogenated to the corresponding chiral (R)-alcohols with high yields (93–99%) and excellent enantioselectivities (90–98% ee, Scheme 23). When the substrate was a dialkyl ketone such as cyclohexyl methyl ketone or tert-butyl methyl ketone, the chiral iridium complex (S)-**49** resulted less efficient for the TH, yielding the corresponding chiral aliphatic alcohols with moderate enantioselectivities (83 and 80 ee, respectively). Moreover, studying this iridium-catalyzed TH in situ, by employing a ReactIR spectrometer, it has been shown how ethanol, used as hydrogen donor, is converted to ethyl acetate, and provided hydride which reduced the substrate to (R)-alcohol.[91]

To reach the goal of more sustainable and cleaner reduction processes, different environmentally friendly solvents, with suitable chemical-physical properties, have been used.

In the last few decades, the use of glycerol as sustainable reaction medium in catalytic and non-catalytic organic synthesis has garnered increased interest. This polyol is a low cost and a renewable raw material deriving, as a by-product, from the transesterification of vegetable oils in biodiesel industry. In particular, the manufacture of biodiesel fuel generates about 10% weight of glycerol as a side-product.[92–94]
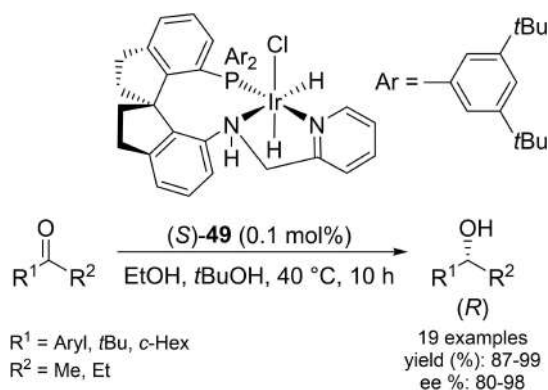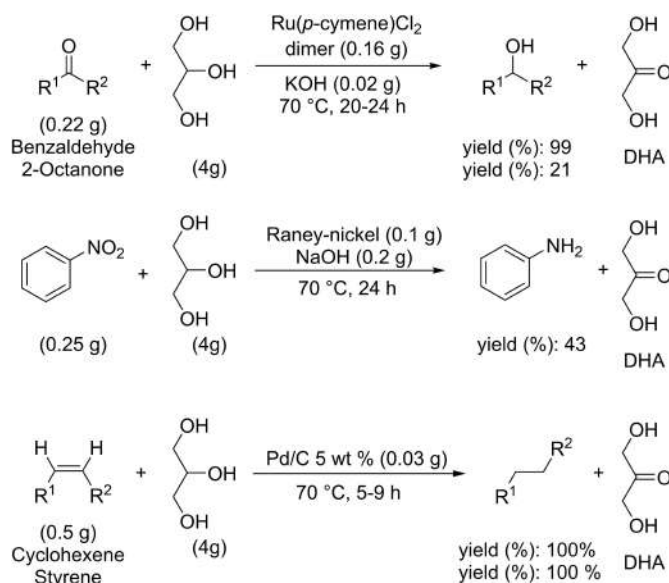
Glycerol represents a versatile and green solvent due to its unique physical and chemical properties: polarity, low toxicity and flammability, non-volatility, biodegradability, and easy recyclability. Moreover, it allows for easy dissolution of a variety of compounds (organic molecules poorly miscible in water, transition metal complexes, enzymes, inorganic salts, acids and bases), and, by using of hydrophobic solvents immiscible with glycerol or by distillation, it enables the easy products separation and catalyst recovery.[92–94]

In the catalytic TH of various unsaturated organic compounds, glycerol fulfils the dual role of both polar solvent and a reactant as hydrogen donor source.[95–97] Compared with isopropanol and ethanol, the high boiling point (290 °C) makes it a suitable solvent for reactions carried out at a high temperature.

In 2009, Wolfson et al., among the first, explored the possibility of using glycerol as an environmentally friendly "donor" solvent in TH reactions of some representative unsaturated organic compounds (benzaldehyde, 2-octanone, cyclohexene, styrene and nitrobenzene, Scheme 24).[95] The reductions, catalyzed by homogeneous or heterogeneous metal catalysts, worked well at 70 °C. For the TH of carbonyl compounds and nitrobenzene, employing Ru(p-cymene)Cl$_2$-dimer and Raney-nickel as the catalyst, respectively, the presence of a base (KOH or NaOH) as co-catalyst was essential to obtain the reduction product (21–99% yields). Moreover, the TH of styrene and cyclohexene worked only in the presence of Pd/C. On the other hand, it was found the glycerol was dehydrogenated to dihydroxyacetone (DHA, Scheme 24).[95]

A more detailed study, carried out by the same authors, on the TH of nitroaromatic derivatives and especially nitrobenzene, in glycerol, revealed that its conversion increased with both the reaction time and temperature. In particular, the best conditions, affording aniline in 95% yield, were reached in the
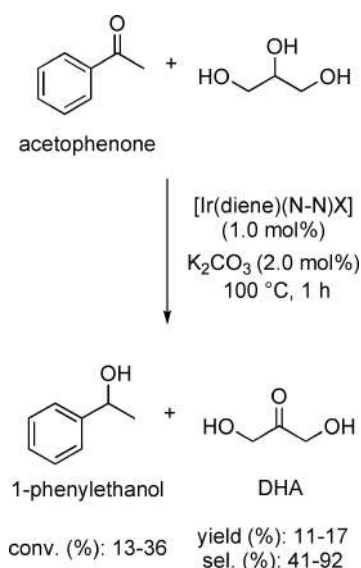

Scheme 23. ATH of ketones in ethanol with a chiral iridium complex as catalyst.

Scheme 24. Catalyzed TH using glycerol as solvent and hydrogen donor. DHA = dihydroxyacetone.

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reaction carried out at 100 °C, after 78 h reaction time, with Raney-nickel catalyst and in the presence of NaOH added as a cocatalyst.[98]

Farnetti et al., in the same year, investigated the hydrogen transfer reaction of acetophenone catalyzed by organoderivatives of iridium metal with the purpose of studying the process of glycerol dehydrogenation.[99]

Both primary and secondary hydroxyl groups of glycerol could be involved in the dehydrogenation process; indeed glycerol oxidation can lead to a variety of compounds such as glyceride, glyceryl acid, tartronic acid, dihydroxyacetone (DHA), just to name a few, depending on whether the oxidation process involves primary or secondary hydroxyl groups.[99] However, the hydrogen transfer reaction from glycerol to acetophenone, performed at 100 °C or higher temperature, in the presence of a base and of organoiridium derivatives of the type Ir(diene)(N−N)X as catalysts, yielded dihydroxyacetone and 1-phenylethanol (Scheme 25). Therefore, as expected from the relative oxidation potentials of secondary vs. primary alcohols,[100] the hydrogen transfer involves only the secondary hydroxyl group, affording, chemoselectively, DHA as the only dehydrogenation product. Interestingly, DHA partially disappears from the reaction mixture with time, owing to further reactions. After 1 h at 100 °C, in the presence of K$_2$CO$_3$ as base, 60 % of the formed DHA in the reaction underwent degradation. This suggests the occurrence of a decomposition process of DHA, promoted by high temperature and basic conditions.[99]

In 2011, Cravotto and co-workers demonstrated that glycerol can be successfully employed as greener and safer alternative to the classic volatile organic solvents in the TH reaction of benzaldehyde to benzylic alcohol, using a Ru(p-cymene)Cl$_2$ dimer as catalyst and in the presence of a combination of two bases (NaOH and KOH).[101] Moreover, by performing the reaction under high-intensity ultrasound (US) the reaction yield increased up to 100 %; indeed, the use of this non-conventional technique, by enhancing heat and mass transfer, allows to solve some drawbacks of this green and renewable solvent such as high viscosity and a low solubility of highly hydrophobic compounds. In addition, the base dispersion in glycerol was improved with a pre-sonication process, resulting in a shorter reaction time (3 h under the reaction optimal conditions, Scheme 26).[101]

The green polyol glycerol was also successfully employed, as solvent and hydrogen donor, in a ruthenium-catalyzed reduction of allylic alcohols, a tandem process involving the initial redox-isomerization of the allylic alcohol, and the subsequent TH of the resulting carbonyl compound (Scheme 27).[102] In particular, the hydrophilic arene-Ru(II) complex [RuCl$_2$(η^6-C$_6$H$_6$)(DAPTA)] (DAPTA = 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane), associated with KOH and glycerol, was able to generate the corresponding saturated alcohols in high yields and from reasonable to long reaction times (Scheme 27). Moreover, the use of this inexpensive and green reaction medium enabled an easy recycling of the catalyst that was re-used, at least, in four consecutive runs.[102]

Furthermore, Gawande et al. developed a highly efficient and recyclable magnetic ferrite-nickel nanoparticles (Fe$_3$O$_4$−Ni MNPs) catalyst for hydrogen-transfer reactions carried out in the environmentally friendly glycerol. In particular, glycerol was
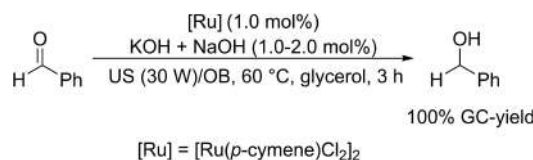
Scheme 26. Hydrogen transfer reduction of acetophenone catalyzed by Ir(diene)(N−N)X complexes, performed in pure glycerol. Diene = 1,5-Hexadiene,1,5-cyclooctadiene; N−N = 2,2′-bipyridine, 1,10-phenanthroline and substituted derivatives; X=Cl, I.

Scheme 25. Hydrogen transfer reduction of acetophenone catalyzed by Ir(diene)(N−N)X complexes, performed in pure glycerol. Diene = 1,5-Hexadiene,1,5-cyclooctadiene; N−N = 2,2′-bipyridine, 1,10-phenanthroline and substituted derivatives; X=Cl, I.
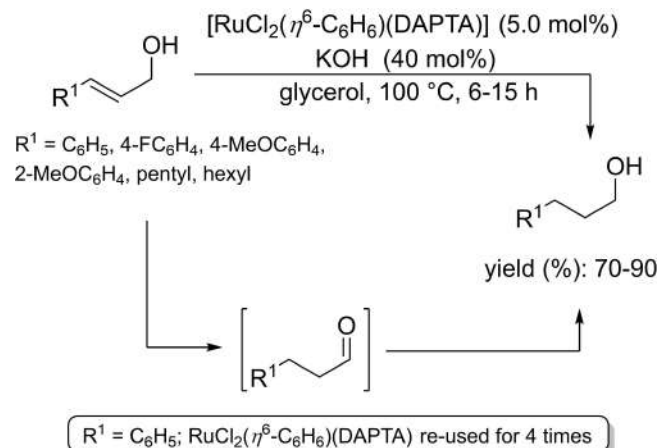
Scheme 27. Ruthenium-catalyzed reduction of allylic alcohols in glycerol. DAPTA = 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane.

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used as solvent as well as hydrogen donor in the reduction of aromatic nitro and carbonyl compounds (Scheme 28).[103]

These hydrogen-transfer reactions over Fe_3O_4–Ni MNPs in glycerol showed excellent regio- and chemo-selectivity affording the corresponding reduction product in good yield (84–94%). In addition, in the reduction of 4-metoxy nitrobenzene, the magnetically recoverable catalyst could be recycled eight times, without any significant loss in catalytic activity and selectivity.[103]

In 2014, Singh and co-workers described half-sandwich complexes of Rh(III) and Ir(III) with (S, S) and (Se, Se) ligands (**50**–**53**, Scheme 29) as successful homogeneous catalysts for the reduction of the carbonyl groups of aldehydes and ketones, using glycerol as solvent and hydrogen source.[104] Considering the four catalysts in Scheme 29, the catalytic efficiencies of Rh complexes **50**–**51** appear to be better than those of Ir complexes **52**–**53**. For instance, when 4′-methoxyacetophenone
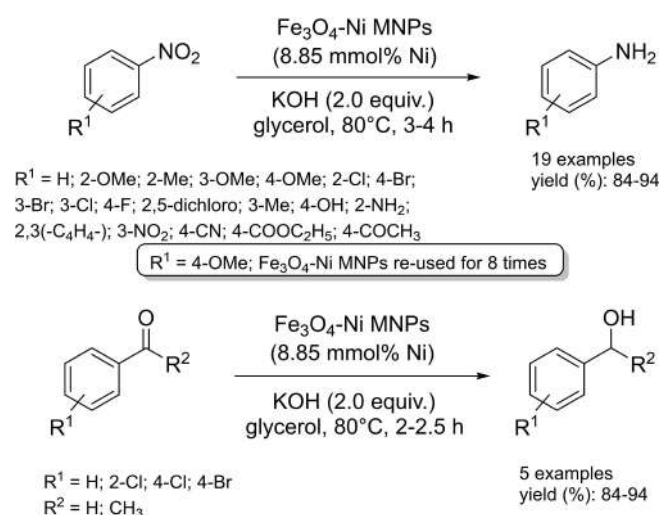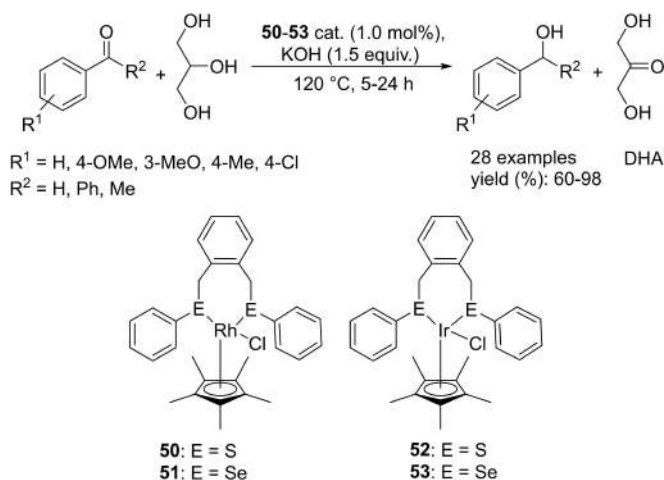
was the substrate for the TH reaction, the reduction product formed in 88% and 92% yield with the use of Rh complexes **50** and **51**, respectively, while the employment of Ir complexes **52**–**53** led to the same product in a lower yield (82% and 85%, respectively). Moreover, the complexes **51** and **53**, with (Se, Se) ligands, were found to be more efficient than the corresponding complexes with (S, S) ligands. In particular, with the use of Rh-catalyst **51** for the TH of benzaldehyde and 3-methoxybenzaldehyde, a reduction product yield of 98% was reached for both reagents.[104]

Ethylene glycol (EG), classified as "green" solvent in the already mentioned GSK Solvent Sustainability Guide,[52] has been employed in reductive protocols, too. EG is an odourless, non-volatile, low toxic liquid, and can be derived from renewable biomass.[105,106] Moreover, the green polyols ethylene glycol and glycerol have proven to act as an efficient hydrogen source and eco-friendly medium also in the transfer semihydrogenation (TSH) of internal alkynes.

In 2021, Moran et al. developed a selective method for the TSH of a wide range of internal aromatic and aliphatic alkynes in ethylene glycol; the corresponding alkenes were obtained with a Z-configuration.[107] The versatility of the procedure, performed with Cu(0) nanoparticles (Cu-NPs) as catalysts, was demonstrated with a variety of structurally and electronically diverse internal alkynes. The reactions proceeded with high chemo- and stereo-selectivity, without further reduction to the alkane for most substrates, and the Z-isomers were isolated in moderate to excellent yields (up to 96%, Scheme 30). Only with the use of pyridinyl derivatives as substrates, the presence of the over-reduced product was observed. The procedure uses ethylene glycol as both green solvent and hydrogen donor, although other polyols (glycerol) and amino alcohols (isoserinol, ethanolamine and diethanolamine) can act as hydrogen sources, affording similar results in longer reaction times. The use of simultaneous MW and US irradiation, enhancing heat and mass transfer, improved the reaction performance providing a reduction in the reaction time (30 min vs. 2 h under conventional conditions, Scheme 30).[107]

Scheme 28. Fe_3O_4-Ni MNPs-catalyzed reduction of nitro arenes and aryl carbonyl compounds performed in glycerol.

5. Hydrogenations in Supercritical Carbon Dioxide (scCO₂)

In the past decade, many research groups have focused their studies on making liquid and supercritical carbon dioxide

Scheme 29. TH of carbonyl compounds using Rh(III) and Ir(III) complexes as catalysts in glycerol.
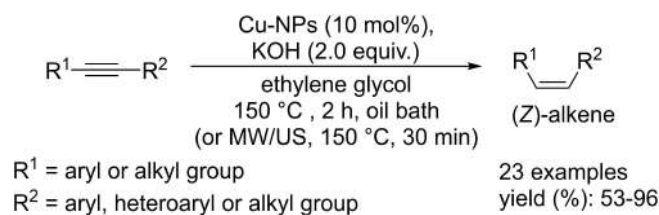
Scheme 30. Cu-NPs-catalyzed TSH of internal alkynes performed in ethylene glycol as eco-friendly solvent.

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(scCO$_2$) as a viable alternative to classical volatile organic solvents.

CO$_2$ is a good solvent for many substances when compressed into its liquid or supercritical fluid state. When critical pressure and temperature are reached (Tc = 31,1 °C, Pc = 73,9 bar), carbon dioxide acquires gas-like viscosities and liquid-like densities.[108] In comparison with conventional organic solvents, scCO$_2$ is an attractive environmentally benign reaction medium, due to its nontoxicity, nonflammability, recyclability.[109]

For these characteristics, scCO$_2$, could be potentially used for the production of consumable products, such as pharmaceutical and nutraceutical goods,[110] as well as already being a well-known solvent for numerous chemical processes such as polymer processing, extractions, modification and production of nanoparticles.[111–113] On the other hand, scCO$_2$ suffers from various drawbacks related to some key physicochemical properties that a good solvents needs to have: in particular, it has as a lower viscosity, surface tension and dielectric constant compared to the mostly employed organic solvents.[114,115]

In 2013, Zhao and co-workers, developed a HY reaction for the reduction of halonitrobenzenes (**54**) to haloanilines (**55**), using supported PEG-stabilized platinum nanoparticles (SPPNs, Scheme 31).

Particularly, Pt-PEG/γ-Al$_2$O$_3$ was employed as a heterogeneous catalyst in scCO$_2$.[116] The combination of this heterogeneous catalyst, with the use of scCO$_2$ as the sustainable solvent, demonstrated high selectivity for the synthesis of haloaniline derivatives. Therefore, a full inhibition of undesired dehalogenated by-products (nitrobenzene, aniline, and condensation products) and a high substrate conversion was achieved. The HY reaction was carried out in a 50 ml Teflon-lined high-pressure stainless-steel batch reactor by treating the halonitrobenzene with 0.02 mol% of Pt-PEG/γ-Al$_2$O$_3$, under 1 MPa of H$_2$ and 8 MPa of CO$_2$ at 60 °C (Scheme 31).[116]

Furthermore, the SPPN catalyst could be also recycled. After the first run the product was simply extracted by scCO$_2$ and the catalyst was reused, without further purification, for four successive cycles with only a slight decrease in conversion and selectivity.

In addition to Pt metal, other metals were used for the reduction of the nitro group on the benzene ring to synthesize the aniline.
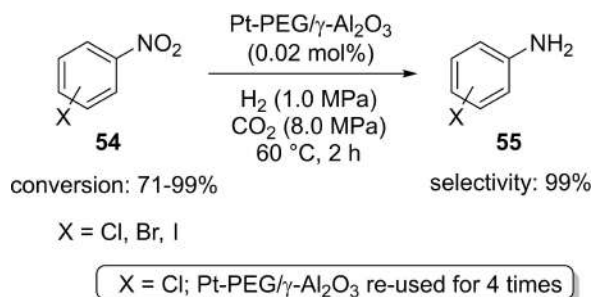
Mateeva and co-workers, demonstrated the efficacy of Ru and Pd-based heterogeneous catalysts for the HY reaction of nitrobenzene to aniline in scCO$_2$.[117,118] The processes proceed with very high conversion (up to 99%) and selectivity (up to 100%), as shown in Scheme 32.

scCO$_2$ was also selected as an eco-friendly solvent in the HY reaction of aldehydes such as 2-furaldehyde (furfural), a methodology that can have some important applications in the field of alternative sources of energy such as the Bio-oil.
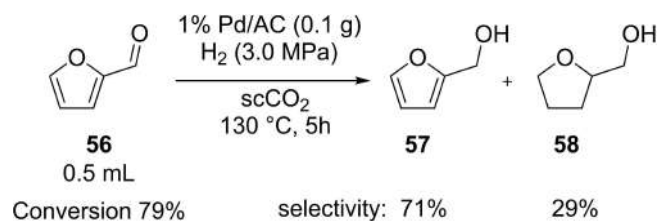
Bio-oil, derived by thermal decomposition of biomass,[119,120] could be a substitute for traditional fossil fuels due to its renewability and sustainability. On the flip side, bio-oil is a complex mixture of different oxygenated compounds, some of which are particularly unwanted as fuel component. Furfural, one of the numerous oxygenated compounds cited above,[121] due to its high reactivity, required to be catalytically hydrodeoxygenated to improve the bio-oil stability, storage capability and water solubility.[122]

In this regard, furfural HY reaction promoted by heterogeneous catalysis in scCO$_2$, was reported by Liu et al.[123] The heterogeneous catalyst, used in the reduction, was prepared by chemical modification of an active carbon surface, employing an oxidation process mediated by nitric acid and subsequently a calcination, at 300 °C under air. These processes led to new oxygenated functional groups such as carbonyl, carboxyl and alcoholic groups on the surface of the active carbon. These groups play a key role for the Pd dispersion on the solid support, that increases with the increasing number of surface oxygen groups.[124]

Furfural (**56**, 0.5 mL) and the Pd-catalyst on modified active carbon (Pd/AC, 0.1 g, 1.0% w/w) were added in stainless steel autoclave equipped with an electrical heating jacket and a magnetic stirrer, under H$_2$ (3.0 MPa) in scCO$_2$ (liquid CO$_2$ compressed at 8.0 MPa). The reaction was carried out at 130 °C for 5 h (Scheme 33).
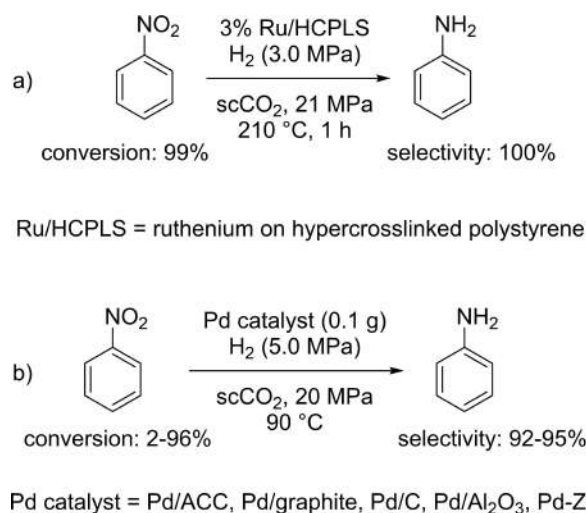
Scheme 32. a) Hydrogenation of nitrobenzene mediated by Ru/HCPLS catalyst in scCO$_2$. b) Synthesis of aniline by reduction of nitrobenzene in scCO$_2$, by the use of various heterogeneous Pd-catalysts.

Scheme 31. Hydrogenation of halonitrobenzenes in scCO$_2$, catalyzed by Pt-PEG/γ-Al$_2$O$_3$ as the heterogeneous catalyst.

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**Scheme 33.** Hydrogenation of furfural (**56**) mediated by Pd on active carbon support in scCO$_2$.

The conversion rate (79%) observed was higher than that obtained in volatile organic solvents such as toluene (60%), with a total selectivity towards furfuryl alcohol (**57**, 71%) and tetrahydrofurfuryl alcohol (**58**, 29%). The high conversion rate of furfural in scCO$_2$ was associated to both an increase of mass-transfer and a higher solubility of H$_2$ in this supercritical fluid.[125]

The combination of scCO$_2$ and transition metal-based catalysts resulted very effective also in reducing other organic molecules deriving from sustainable and renewable sources. Indeed, Yang *at al.* reported, in 2016, the HY of levulinic acid (**59**) to the value-added γ-valerolactone (GVL), by using the homogeneous RuCl$_2$(PPh$_3$)$_3$ catalyst, in scCO$_2$ (Scheme 34).[126] The synthesis of γ-valerolactone through the reduction of levulinic acid is an important reaction in the conversion of biomass to value-added chemicals.[127] GVL is an intermediate to producing fuel and biofuel, valuable chemicals and is used as green reaction media.[128–130]

The reduction of levulinic acid **59**, carried out at 150 °C for 15 min under 4 MPa of H$_2$, was mediated by 1 mol% of RuCl$_2$(PPh$_3$)$_3$ and conducted in a stainless-steel batch reactor using scCO$_2$ as the green solvent (Scheme 34).

The conversion of levulinic acid increased with the increasing of CO$_2$ pressure, reaching 99% at 16 MPa, while the selectivity to GVL changed slightly with CO$_2$ pressure, increasing from 92% (in solvent-free conditions) to 98% (under 16 MPa) in only 15 minutes of reaction time.

It is interesting to note that, at maximum CO$_2$ pressure, the conversion increased up to 100% with time, but in the absence of CO$_2$ was levelled to 70% in 3 h. The authors justify the greater conversion in the presence of high CO$_2$ pressure, with the structural modification of the catalyst mediated by CO. In fact, the presence of H$_2$ in the reaction environment could reduce CO$_2$ to CO, that could then coordinate Ru catalyst to form a more active complex. FTIR and UV-vis studies, combined to a screening of various commercially available Ru complexes
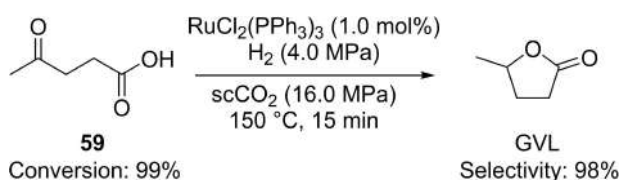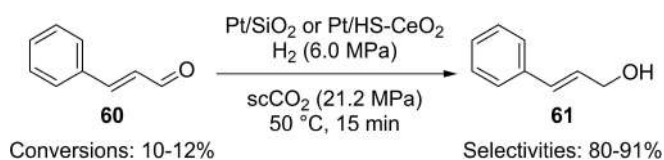
employed for the levulinic acid conversion, in absence of carbon dioxide, suggest the gradually formation of the highly active RuHCl(CO)(PPh$_3$)$_3$ from RuCl$_2$(PPh$_3$)$_3$.[126]

Another type of transition metal-based catalysts for the HY reactions in scCO$_2$, was explored by Volpe and co-workers. In particular, the authors described the selective HY of cinnamaldehyde (**60**) to form cinnamyl alcohol (**61**), under the catalysis of Pt/SiO$_2$ or Pt/HS—CeO$_2$ (high surface ceria, Scheme 35).[131]

At the expense of the low conversions reported, the authors suggested a molecular interaction between scCO$_2$ and the carbonyl group of the substrate, responsible for the higher selectivity than that described in the literature. Indeed, using the identical Pt catalysts and 40 MPa of molecular hydrogen in ethanol as the solvent, the selectivity to cinnamyl alcohol drastically dropped below 50%.[132]

Specifically, the solvent effect mediated by scCO$_2$ on the carbonyl group of cinnamaldehyde could be explained by both a quadrupole/dipole interaction between the solvent and the carbonyl group (due to the enlargement of the quadrupole moment of CO$_2$ in the supercritical region),[133] and by a cooperative hydrogen bond interaction (between one of CO$_2$ oxygen atoms and the electro-deficient hydrogen of aldehyde group or of the side carbon chain), Figure 3.[134] These interactions, which turn more labile the carbonyl bond, are the basis of the greater reduction selectivity towards the aldehydic moiety compared to the olefinic one of the substrate.

To achieve selective HY reactions, the valuable combination of transition metal heterogeneous catalysts and scCO$_2$ was further explored by R. More et al.[135] Specifically, the HY of acetophenone for the synthesis of 1-phenylethanol, using polyurea-based encapsulated metallic and bimetallic catalysts [i.e. Pd encapsulated catalyst (PdEnCat) or a combination of Pd—Ru and Pd—Cu encapsulated catalysts (Pd—RuEnCat and Pd—CuEnCat)], in scCO$_2$, was reported (Scheme 36).[135]

Scheme 35. Pt catalysts for the cinnamaldehyde HY under 6.0 MPa of H$_2$ in scCO$_2$.

Scheme 34. Homogeneous catalytic reduction of levulinic acid (**59**) to GVL in scCO$_2$. GVL = γ-valerolactone.
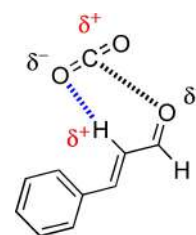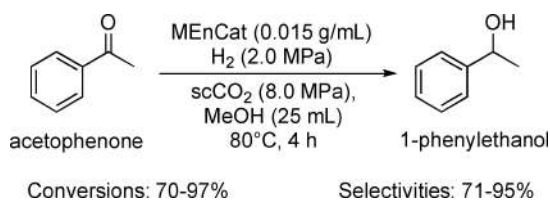

Figure 3. C—H···O hydrogen bond (blue) that acts cooperatively with the CO$_2$-carbonyl interaction in molecules having a hydrogen atom attached to the carbonyl carbon or the α-carbon atom; the C—H acts as the proton donor.

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Scheme 36. Hydrogenation of acetophenone mediated by polyurea-based encapsulated mono- and bimetallic catalyst (MEnCat), under H_2 pressure, in $scCO_2$, using MeOH as a cosolvent. MEnCat=PdEnCat, Pd–CuEnCat, Pd–RuEnCat.

The selective HY of acetophenone to the corresponding alcohol was carried out in a 100 mL high-pressure reactor, equipped with a magnetic stirrer and a process controller. Acetophenone (50 mmol) and catalyst (0.015 g/mL) were added to the reactor system and, subsequently, H_2 gas (2.0 MPa) and $scCO_2$ (8.0 MPa) were flushed in the reactor. The HY was carried out at 80 °C using MeOH as a cosolvent (Scheme 36).[135] The Pd–Ru bimetallic catalyst was found to be the more reactive heterogeneous catalyst but with less selectivity toward 1-phenylethanol. On the other hand, the best compromise between selectivity (85%) and activity (95%), was obtained with the Pd–CuEnCat.

The substrate acetophenone represents an ideal model compound for the synthesis of 1-phenylethanol, an attractive molecule for its pharmaceutical applications, such as anti-inflammatory and analgesic drug,[136] and for its use as a flavouring agent in food industry.[137] However, the HY pathways of acetophenone are very attractive because they could give a variety of products and by-products, through the competitive and/or consecutive reduction of the carbonyl moiety and the aromatic ring (Scheme 37).
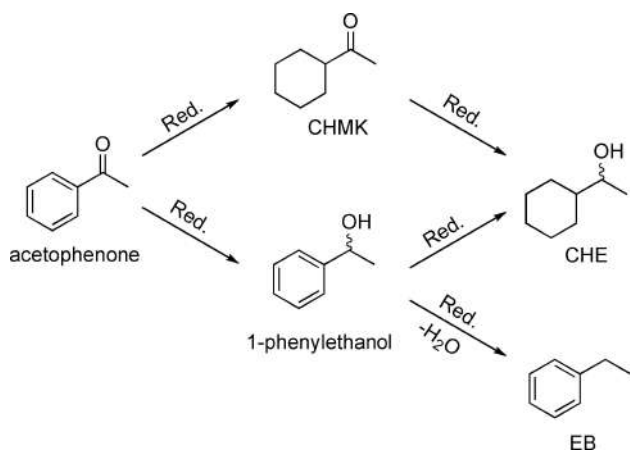
6. Miscellaneous Examples of Eco-Friendly Hydrogenations

Among green solvents, acetic acid can be used as a reaction medium in the HY of organic compounds, too. Gu and co-workers described the ability of platinum nanowires (Pt NWs) to catalyse the heterogeneous HY of nitroaromatic compounds, under a hydrogen atmosphere (1 atm) at 100 °C.[138] In particular, when acetic acid was used as the solvent for the HY reaction, a one-pot reductive amidation of the nitroarene with the carboxylic acid was observed.[139]
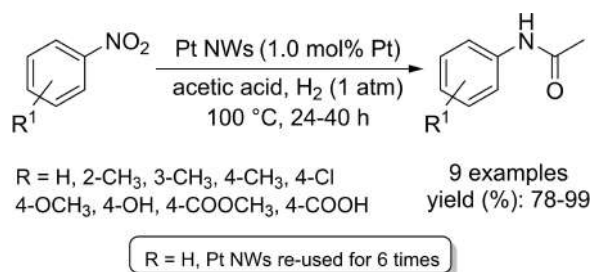
Nitroarenes bearing both electron- donating and withdrawing groups led to the formation of corresponding amides in good to excellent yields (78–99%, Scheme 38) and the catalyst, whose activity remains almost unchanged, can be easily recovered and reused at least six times.

For example, a 99% yield of *N*-phenylacetamide was obtained when acetic acid was employed as both reactant and solvent in the HY of nitrobenzene at 100 °C. The amide formation is the product of a one-pot two-step process: i) HY of the nitro compound to aniline over the Pt NWs and ii) the amidation of the amine with acetic acid over the Pt NWs, under the same reaction conditions. Moreover, the selectivity for the amide product decreases with decreasing temperature: at 40 °C, the main reaction product was represented by the intermediate aniline.[138]
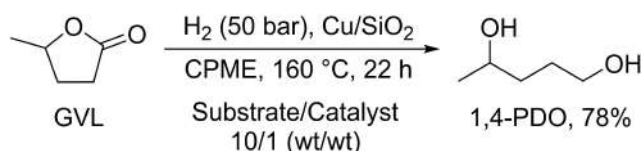
Furthermore, the chemical-physical characteristics of cyclopentyl methyl ether (CPME), such as its high boiling point and low melting point, low peroxide formation rate and minimal toxicity make this solvent a green and sustainable medium in a wide range of chemical transformation.[140,141]

In 2021, CMPE was chosen as medium to carry out the eco-friendly HY of γ-valerolattone (GVL), an ester available from renewable sources.[142] This HY, catalyzed by the nontoxic metal Cu on silica support, was performed at 160 °C and a H_2 pressure of 50 bar affording selectively 1,4-pentandiol (1,4-PDO), a valuable biobased monomer, Scheme 39.[142]

It was found that the outcome of the reaction was strongly influenced by the catalyst surface acidity. In particular, the presence of acidic sites is responsible of the activation of the lactone moiety, whose hydrolysis generally requires harsh reaction conditions. In addition, CPME was able to improve the activity and selectivity of the catalyst: its use as the solvent

Scheme 37. Hydrogenation pathways of acetophenone. CHMK=cyclohexylmethylketone, CHE=1-cyclohexylethanol, EB=ethylbenzene.

Scheme 38. One-pot Pt NWs-catalyzed reductive amidation of nitroarenes with acetic acid employed as both reactant and solvent.

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Scheme 39. Hydrogenation of γ-valerolattone (GVL) to 1,4-pentandiol (1,4-PDO) carried out in the green solvent CPME. CPME=Cyclopentyl methyl ether.
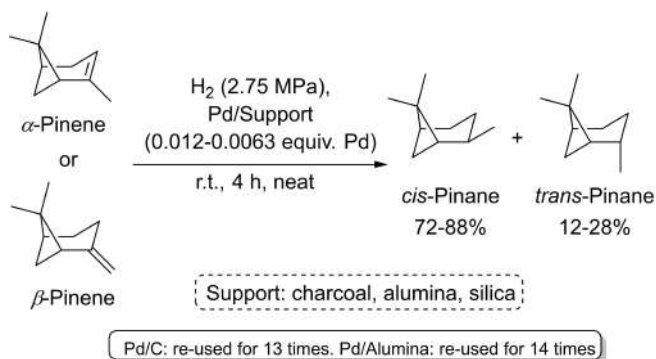
Scheme 40. Solvent-free pinene HY.
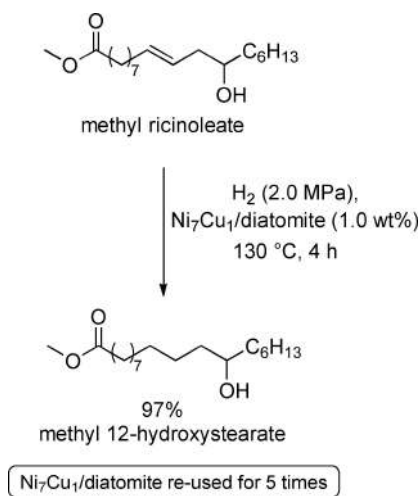
Scheme 41. Solvent-free HY of methyl ricinoleate ester.

together with the fine tuning of the hydrophilic/hydrophobic features of the catalyst support allowed to obtain the diol 1,4-PDO in 78% yield.[142]

CPME has also found successful applications as a (co)solvent in some biotrasformations including biocatalytic AH in which ketones, imines and activated C–C double bonds were selectively reduced to the corresponding optically active compounds.[143]

From a green point of view, solvent-free reactions are more desirable than transformations in any kind of organic solvents. However, these reactions often suffer from some disadvantages related to the viscosity, mass transfer, control of the heat exchange, non-Homogeneity of the reaction medium.

In 2017,[144] an environmentally friendly solvent-free HY of pinenes to afford pinanes, molecules of considerable interest for pharmaceutical, fine chemistry and flavour industry,[145–147] was developed.

In particular, it was performed a comparative study of the solvent-free catalytic HY of both α- and β-pinene isomers, over Pd on various supports (carbon, alumina and silica), Scheme 40.[144] When β-pinene was the substrate, under neat conditions and at room temperature, this heterogenous catalytic reaction was proven to involve an isomerization process of β-pinene to α isomer. Palladium on all three supports worked well affording, after 4 h, pinanes in quantitative yields. Although the HY process could form cis and trans pinane, the reaction shows a high selectivity towards the formation of the cis reduction product (72–88%, Scheme 40).

Moreover, for the recycling process, under solvent-free conditions, the nature of the catalyst support is crucial: Pd/silica was active for only a single cycle, while Pd/C and Pd/alumina were successfully recycled 13 and 14 times, respectively.[144]

More recently, He and co-workers[148] performed a highly efficient solvent-free HY process of methyl ricinoleate ester, deriving from the castor oil, to methyl 12-Hydroxystearate, an important row material widely used in medicine and cosmetics.[149,150]

The HY of the methyl ricinoleate, carried out under 2 MPa H₂ pressure and at 130 °C, proceeded efficiently and selectively leading to methyl 12-Hydroxystearate in 97% yield (Scheme 41). The process was catalyzed by a Cu/Ni supported bimetallic catalyst; in particular, the catalyst Ni₇Cu₁/diatomite (1 wt%) revealed to be the optimum for the selective HY of the C–C double bond in the substrate. Moreover, this heterogeneous Ni/Cu catalyst, which might promote the double bond absorption and activation of hydrogen molecule, can be easily recovered and reused at least for five cycles.[148]

7. Conclusions

This review has described recent advances in the reduction of organic compounds by means of synthetic methodologies with an improved degree of sustainability. Although the reduction of the environmental impact of a chemical process can be pursued in many ways, here the reactions performed in "green" solvents from renewable sources have been highlighted. The reduction of many types of unsaturated bonds can be performed in safe media thus avoiding the use of conventional, and often toxic, organic solvents derived from petroleum. From the low molecular weight alcohols to the ionic deep eutectic solvents, passing through the use of super critical CO₂, plenty of examples demonstrated the opportunity to perform a reductive transformation by using a benign solvent without waiving to the efficiency and selectivity and contextually addressing some important key point of green chemistry: the easiness of catalyst recyclability if deep eutectic solvents are used, the simplicity of

product isolation when employing scCO$_2$, the exiting selectivity when a TH reaction occurs in very safe isopropanol.

In conclusion, we believe that this review has provided a general examination of the potentiality of the sustainable reductions in bio-derived solvents. Although much remains to be learned regarding the physicochemical features that most deeply influence the activity of catalysts, we hope that it will serve to inspire further significant advances in both heterogeneous and homogeneous catalysis in green media, in our opinion the most promising synthetic tools to design a green chemistry future.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: deep eutectic solvent · green solvent · hydrogenation · reduction · transfer hydrogenation

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