Homogeneously catalyzed acceptorless dehydrogenation of alcohols: A progress report

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Abstract

Catalytic dehydrogenation of alcohols represents an attractive approach for future applications as hydrogen storage systems and clean synthesis of fine chemicals. Herein, an overview of recent progress in homogeneously catalyzed acceptorless alcohol dehydrogenation is presented. In Nature, dehydrogenation of alcohols is efficiently catalyzed by multiple metalloenzymes where a non-noble metal–ligand interplay is key to activate and transform a substrate. We highlight the introduction of multifunctional cooperative ligands in the coordination sphere of the metal center in order to improve catalytic activity under photochemical, electrochemical or thermal conditions. Moreover, metal–ligand cooperativity is crucial for an easy transition to first row metal based catalysis, as we have seen in the recent years.
1. Introduction

At the present time, fossil fuels are the main sources of bulk chemicals and energy supplies for quality of life and global economic growth [1]. The utilization of this limited natural feedstock is responsible for two thirds of CO₂ emissions. Consequently, the current sustainable scenario includes severe greenhouse gas emission regulations and the urgent need of an efficient, economically viable and renewable energy storage system. An important step forward was made at the Paris Agreement of 2015 approving the first global climate change settlement establishing the 20–20–20 targets by 2020 (20% increase in energy efficiency, 20% reduction of CO₂ emissions, and 20% renewables) [2]. One year later, the European Commission declared the Clean Mobility Package, a proposal that commits to a transition to low- or zero-emission mobility, among an important decrease of greenhouse gas emissions, 60% by 2050 with respect to original 1990 values [3]. Hence, the challenge to transform the current energy system is extraordinary. In the recent years, hydrogen has been considered as an attractive and clean alternative since it can be converted to electrical energy using the current fuel cell technology and will be able to support the energy transition. Industrial scale and low-emission hydrogen production by methane reforming, coupled with carbon capture and sequestration, is not economically viable for a general and extensive implementation. However, new advances in electrochemical water splitting for the clean production of hydrogen is one of the most promising technologies for generating a renewable energy resource. Drawbacks related with transport and storage of hydrogen remain important obstacles for the broad application of this energy carrier. A possible solution to overcome these issues is the use of renewable, stable and high-density hydrogen storage compounds. Particularly, alcohols from biomass (ethanol and polyols) are mainly considered due to their relatively high hydrogen content. Above all, liquid alcohols can be used directly as transportation fuels employing the already established refueling stations. Here, we review the recent progress in hydrogen production from methanol and bio-relevant alcohols using homogeneous catalysis. This chemical process has the advance of performing transformations at considerable milder conditions than heterogeneous catalysis, and hence it represents a promising approach for future applications. Moreover, this approach allows more easily insight into the detailed mechanisms by which such processes may occur. When dehydrogenation is performed on molecules with a high hydrogen content, the released H₂ is the target product of the reaction. For higher alcohols (with low H₂ wt%), dehydrogenation of an alcohol function to a reactive carbonyl and further functionalization represents a convenient strategy for the clean synthesis of fine chemicals. Examples discussed herein will among others include synthesis of aldehydes, ketones, esters and carboxylic acids from alcohols, or imines and amides via amine/alcohol couplings and heterocycle assembling. The direct conversion of alcohols into fine chemicals and H₂, without the need of a sacrificial oxidant or hydrogen acceptor is a notable example of an atom economic process. Inspiration for the development of artificial catalytic systems can be found in Nature. Dehydrogenase enzymes are outstanding examples of metal–ligand cooperativity and the most efficient biological catalysts for the conversion of alcohols to carbonyl derivatives, protons and electrons (Scheme 1).

Many seminal contributions to the field of acceptorless dehydrogenation of alcohols were carried out decades ago. That is dehydrogenation of an alcohol according to: R-CHOH-R’ → R-C=O-R’ + H₂ (Equation 2, Scheme 2) without the addition of a sacrificial acceptor which would read in simplified form: R-CHOH-R’ + A → R-C=O-R’ + AH₂ (Equation 1, Scheme 2). The reawakening of this field of research over the past 15 years has been enabled mainly by new ligand designs in which chemical cooperativity with a metal center is essential (outer sphere mechanism). In Scheme 2, a and b are presented two operating mechanisms for acceptorless dehydrogenation of alcohols. In early examples, the ligands were not directly involved in the catalyzed reaction, which occurs simply at the metal center (inner sphere mechanism) (Scheme 2a). The introduction of chemically cooperative ligands has allowed the formation of basic and acidic sites in close proximity, favoring substrate binding and activation without modification of the metal oxidation state (Scheme 2b). This Review summarizes the recent achievements that have been made with molecular organometallic complexes as catalysts for the dehydrogenation of alcohols under electrochemical, photochemical or thermal conditions, as continuation of our previous report of 2014 [4]. Mechanistic investigations and structure elucidation of the catalytically active sites in metalloenzymes has given new ideas for artificial metal–ligand cooperative catalysts, with functional groups in the first or second coordination sphere of a first row metal center. This Review also covers recent advances on organometallic-based electrocatalysts for clean energy production in fuel cells (OMFC = Organometallic Fuel Cell) and electrolyzers (OMER = Organometallic Electroreformers) fed by alcohols. In this strategy (equation 3, Scheme 2), the hydrogen acceptor (A in equation 2, Scheme 2) is replaced by an electrode to facilitate the two-electron/one-proton oxidation of a transition metal–hydride intermediate, formed by reaction of an alcohol with a metal complex. The integration of functional ligands in the electrocatalyst structure has demonstrated important advances in this underdeveloped area. We also list the state-of-the-art with heterogeneous catalytic systems for comparison.

In principle, the aim of this area of research is to establish an alcohol fuel (RR’CH-OH) with a high hydrogen content which can be efficiently converted into hydrogen and the corresponding oxidized product by the assistance of a catalyst. Different types of alcohols have been used as substrates in dehydrogenation reactions. Among secondary alcohols, isopropanol has been intensively investigated in preliminary reports. Due to their intrinsic low hydrogen density it has not been considered for H₂ production, but the simple structure allows easy mechanistic studies and prompt feedback for further catalyst design. In general,
dehydrogenation to form ketones is selective and avoids side reactions such as decarbonylation, a frequent catalyst deactivation process. The simplest diol, ethylene glycol, has served as model substrate to study the dehydrogenation of more complex biomass derived alcohols. The main problems related with substrates containing vicinal diols are deactivation of the catalyst by formation of stable metal chelate complexes and polymerization side reactions. Ethanol and glycerol, both derived from biomass, are major emerging sources for sustainable production of hydrogen and chemicals. Although they are high density hydrogen substrates, the main limitation of polyols are the multiple side reactions and consequently low selectivity and low hydrogen yield. In addition, exclusive solubility in aqueous media hinders the catalysis by organometallic compounds. Up to date, very low hydrogen yields have been obtained from glucose in processes catalyzed by homogeneous metal complexes. A possible solution, proposed recently, is a tandem reaction comprising conventional oxidation of the polyol to formic acid followed by dehydrogenation of the later to H₂ and CO₂ by well-known organometallic catalysts. Methanol, with a hydrogen content of 12.5 wt% is considered the most pertinent liquid organic hydrogen carrier (LOHCs). The combined dehydrogenation of methanol and reverse hydrogenation of CO₂ back to the alcohol represents a very relevant research area within sustainable catalysis [5].

2. Catalytic electro-oxidation of alcohols

2.1. Catalytic electro-oxidation of alcohols

The electrochemical oxidation of alcohols has attracted a lot of interest in relation with chemical energy storage. The concepts of
converting chemicals to electrical energy or chemical energy carriers by a fuel cell or an electrolyzer, respectively, are well established. Using dihydrogen gas as an energy carrier is hampered by three main factors: the cost of the fuel cells and electrolyzers, the storage of dihydrogen gas and the large overpotential that is required for electrochemical water splitting. The major part of the overpotential stems from the slow kinetics of the oxygen evolution reaction. Thus, replacing water with an alcohol, allows both to lower the overpotential and to produce valuable chemicals at the same time, provided that the oxidation reaction is selective. See Fig. 1 for a schematic representation of an alcohol FC and an electrolyzer.

Vizza et al. recently noted that this saving of electrical energy does not come for free, but from the chemical energy stored within the alcohol [6]. Photosynthesis-derived bioalcohols like methanol, ethanol, glycerol, other polyols, and sugars are thus the most interesting substrates. To lower the cost of the devices, small amounts of catalyst are impregnated on a relatively cheap conducting support material. Platinum-group metal nanoparticles are often used and exhibit good performance, but also have several intrinsic limitations. The cost of such devices is still largely determined by the high price of the precious metal catalysts. Furthermore, selectivity control is usually poor and catalyst poisoning occurs rather easily, especially with polyols [7]. In fuel cell applications current densities are often below 1 A cm\(^{-2}\) which limits the applicability [8]. Present investigations in this area are directed to reduce metal loadings and increase current densities. The focus of this review is on homogeneous catalytic systems and we only very briefly mention progress made with heterogeneous catalysts in the last decade and refer to the recent literature for detailed reviews.

### 2.2. Heterogeneous catalysts

Recent reviews have been published by Coutanceau and Baranton [9], Andronescu and Bandarenka [10], and Nanda and Isaacs [11]. Recently, Vizza et al. reported Pd nanoparticles on titanium dioxide nanotubes that were able to oxidize basic aqueous solutions of methanol, ethylene glycol, glycerol and 1,2-propanediol with current densities from 1.5 A cm\(^{-2}\) up to 1.95 A cm\(^{-2}\) at an overpotential of 0.9 V vs. RHE at 80 °C [8]. However, the current densities proved to be highly temperature sensitive (510 mA cm\(^{-2}\) at 25 °C) and the polyols produced a mixture of different oxidation products, like glycolate and oxalate from ethylene glycol; glycerate and tartronate from glycerol; or lactate and acetate from 1,2-propanediol (Scheme 3). This selectivity problem could be overcome by the use of Au–Pd core shell nanoparticle [12]. They show very good selectivity in the oxidation of ethyleneglycol and 1,2-propanol to the corresponding monocarboxylates (86–87%; see Scheme 3), but the current densities lie only between 200 mA cm\(^{-2}\) and 400 mA cm\(^{-2}\) at 0.9 V vs. RHE at 60 °C and are significantly lower than with palladium nanoparticles. Higher activities were obtained with rhodium nanoparticles on carbon supports [13]. Ethanol and ethylene glycol were converted into the corresponding acetate and glycolate with current densities between 420 and 490 mA cm\(^{-2}\) at 0.7 V vs. RHE at 60 °C. The substrate scope was later improved to also include methanol [14]. Recently, a catalyst was reported consisting of Pd nanoparticles on nanostructured cobalt oxide grown on a nickel foam, which were treated with phosphorous vapors at high temperature [15]. This catalyst oxidizes ethanol at 150 °C whereby the initial pressure of 7 bar is increased to 12.5 bar during 7 h of electrolysis. Self-pressurizing
catalysts are highly desirable because they reduce (energy) costs for follow-up cascade pressurization of the produced hydrogen gas for further use or storage. Efforts were taken to enhance the reactivity of platinum group catalysts and increase their resistance to catalyst poisoning by modifying the support material [16], finely controlling their shape and size [17], or incorporation of other metals to form binary alloys such as AuPd or PtCu, ternary alloys such as PtMoNiPdAu, or core–shell structures such as Pt(\textsuperscript{Au}@Pd) [18].

Also configurational changes to the cell like new membrane materials [19], employment of gas-diffusion electrodes [20] or membrane-less cell configurations [21] have been explored. Hierarchical porous nitrogen doped carbon on nitride nanosheet networks (\textsuperscript{NC}@\textsuperscript{CuCo\textsubscript{2}N\textsubscript{4}}/CF) proved to be effective catalysts for the oxidation of benzyl alcohol to benzaldehyde alongside water splitting reaction [22]. The catalyst consists of self-supported three-dimensional porous CuCo\textsubscript{2}N\textsubscript{4} nanosheet arrays grown on a carbon fiber (CF) with a conductive nitrogen-doped carbon shell. Remarkably, this catalyst is able to catalyze both hydrogen evolution reaction and oxygen evolution reaction in alkaline media and can therefore be used at both electrodes in a two electrode water electrolyzer which can produce a current density of 10 mA cm\textsuperscript{-2} at 1.62 V.

Recently, heterogeneous and homogeneous catalysts were combined by Rodríguez-Varela et al. who immobilized molecular ruthenium complexes on reduced graphene oxide together with platinum nanoparticles [23]. Their best-performing catalyst for methanol oxidation at room temperature reached a mass current density of ca. 490 mA mg\textsuperscript{-1} at an overpotential of 0.26 V vs. SHE. Platinum nanoparticles, on the same support, without the presence of ruthenium, reached a mass current density of ca. 110 mA mg\textsuperscript{-1} at an overpotential of 0.40 V vs. SHE.

2.3. Molecularly-defined catalysts

Molecular catalysts offer several advantages over heterogeneous catalysts. The metal load can be reduced significantly, since in principle every metal atom is catalytically active [24], whereas only about 20% of the atoms on metal nanoparticles are on its surface [25]. Molecular catalysts possess defined structural conformations and specific ways of interacting with the substrate. Their electronic and steric properties can be controlled more precisely than in heterogeneous catalysts. Rationally designed molecular catalysts usually exhibit higher selectivity and/or higher reactivity than their heterogeneous counterparts.

Molecularly-defined catalysts can be employed in a cell either in homogeneous solution or anchored to a support material that is used as the electrode. Based on their reactivity, molecular catalysts can be divided into two classes: a) Catalysts with non-cooperative ligands that show activity at the metal center only and b) catalysts with cooperative ligands. In the latter case, the ligand does more than tune the steric and electronic properties of the metal, but actively takes part in the substrate transformation, often by temporarily taking up protons or electrons. In addition to classical catalysts that activate substrates by coordination, a growing number of fuel cells and electro-reformers employs redox mediators. These molecules (often organic compounds) act as electron and proton shuttles between the electrode and the substrate or the co-catalyst, thereby reducing the overpotential. An extensive review on redox mediators has recently been published by Anson and Stahl [26].

In the search for electrochemical dihydrogen production catalysts, wet-chemical (de)hydrogenation catalysts are often employed. Especially transfer hydrogenation catalysts are an attractive starting point as they operate close to the thermodynamic potential of alcohol dehydrogenation [27]. In 2018 Grützmacher and Vizza published an extensive review on molecularly-defined catalysts for electrochemical hydrogen gas evolution [28]. Herein, we will discuss only selected results prior to 2018 and focus on reports that have been published afterwards. Additional information can also be found in the reviews of Trincado and Grützmacher [4], Coutanceau and Baranton [9], Andreescu and Bandarenka [10], Nanda and Isaacs [11], and Walde et al. [29].

2.3.1. Precious metal electrocatalyst

A) Metal-based reactivity

Successful electrocatalysts for the oxidation of alcohols have been reported based on many platinum-group metals like iridium [27], rhodium [30], ruthenium [31], and bimetallic complexes based on bimetallic combinations of Ru/Pt, Ru/Pt, Fe/Pt and Fe/Pt [32]. Rhodium is most frequently encountered in combination with porphyrine-derived ligands [30,33]. A membrane electrode assembly of such a catalyst at the anode (Fig. 2) with an established cobalt phthalocyanin catalyst at the cathode allowed Noyori et al. to build an oxygen-breathing fuel cell that uses glucose as fuel [34]. Glucose and sugars are highly interesting substrates as they can easily be obtained in large quantities from renewable resources. This cell represents the first example of a glucose fuel cell with both electrodes comprised of molecularly-defined catalysts. The current density of 0.18 mW cm\textsuperscript{-2} at 0.22 V is lower compared to 1.5 mW cm\textsuperscript{-2} at 0.86 V of a glucose fuel cell with a Pt/Ru nanoparticle catalyst. This lower current density is offset by the metal loading of 0.011 mg cm\textsuperscript{-2}, which is about 270 times lower than the 3 m\textsuperscript{g}Pt/Ru cm\textsuperscript{-2} required for the heterogeneous catalyst.

Waymouth et al. reported the electrooxidation of isopropanol with [Ru\textsuperscript{II}(CNN)(dpbb)] \textsuperscript{2+} (CNN = 2-aminomethyl-6-tolylipyridine; dpbb = 1,4-bis(diphenylphosphino)butane) (Fig. 2, Scheme 4) [37]. This publication represents an early example in the development of an electrocatalyst based on a well-established transfer hydrogenation catalyst [38]. The complex catalyzes the oxidation of isopropanol to acetone in the presence of potassium tert-butoxide. Cyclic voltammetry experiments indicate turnover frequencies of up to 4.8 s\textsuperscript{-1} at an onset potential of around −1 V vs. Fe/Fe\textsuperscript{3+}. Controlled potential electrolysis reaches a Faradaic efficiency of 94 ± 5%. The authors propose a mechanism where the hydride in [Ru\textsuperscript{III}(CNN)(dpbb)] \textsuperscript{2+} is oxidized at the electrode by two electrons with the concomitant release of a proton to an alkoxide base (Scheme 4). This 2e\textsuperscript{-} and one H\textsuperscript{+} transfer occurs at −0.8 V vs. Fe/Fe\textsuperscript{3+} under basic conditions. The authors suggest that the generated empty coordination site at Ru is temporarily occupied by a solvent molecule or electrolyte anion (\textsuperscript{2a}) which is eventually replaced by isopropanol (\textsuperscript{2b}). The coordinated isopropanol becomes deprotonated by a strong base, forming the corresponding isopropoxide [Ru(\textsuperscript{II})(CNN)(dpbb)] \textsuperscript{2c} complex. By fast and reversible elimination of acetone, the hydride complex is regenerated. The authors suggest that all steps except the electrochemical oxidation are reversible. The proposed mechanism does not include active sites at the ligand, although the CNN ligand has been reported to behave non-innocently under certain conditions [37].

B) Cooperative metal – ligand reactivity

Well stabilized transfer hydrogenation cooperative catalysts have been considered as adequate alcohol electrooxidation catalysts. For example, cymene ruthenium complexes \textsuperscript{3} and \textsuperscript{4} (Fig. 2), initially reported by Noyori et al. as catalysts for transfer hydrogenation of ketones by alcohols [39], were employed by Waymouth et al. supported on edge-plane graphite (EPG) electrodes as electrocatalyst for the oxidation of alcohols in aqueous basic solutions [40]. In contrast to previous catalyst \textsuperscript{2} [37], the
ame ligands of both Ru\((p\text{-cymene})\) complexes 3 and 4 act as internal base in the proposed mechanism (Scheme 5). Desorption electrospray ionisation (DESI) combined with electrochemical experiments allowed to propose that the catalytically active species is the oxo complex \([\text{Ru} (=\text{O})(p\text{-cymene})(\text{NH–X})]\) \((3\text{b}, \text{X} = \text{NTsR}; \ 4\text{b}, \text{X} = \text{OR})\). The ruthenium-oxo intermediate dehydrogenates the alcohol and is converted to \([\text{Ru(OH})(p\text{-cymene})(\text{NH}_2\text{–X})]\)

\((3\text{a}/4\text{a})\). The catalytic cycle is turned over by the consecutive oxidation by two electrons and release of two protons at the electrode in basic media. In addition to isopropanol dehydrogenation, the catalyst is active in the dehydrogenation of methanol to formic acid, as deduced from Koutecky-Levich analysis at 750 mV vs. NHE in alkaline media. The best performing catalyst shows a turnover frequency (TOF) of 1 s\(^{-1}\) at an onset potential of 0.560 V vs. SHE for the oxidation of methanol.

Grützmacher and Vizza presented a very versatile rhodium bis-tropolamine complex 5 that could be employed in an organometallic fuel cell (OMFC) \([24,41]\) as well as an organometallic electroreformer (OMER, Fig. 3) \([42]\). The optimal catalyst, \([\text{Rh}(\text{tropol}\text{2NH})(\text{PAr}_3)]\text{OTf} \ (\text{tropol2NH} = \text{bis}(5\text{H}-\text{dibenzo}[a,d]\text{cyclohepten}-5\text{-yl})\text{amin e}; \text{OTf} = \text{OSO}_2\text{CF}_3, \text{Ar} = 4^\text{−}\text{Bu}-\text{C}_6\text{H}_4)\) \((5)\) needs to be activated by one equivalent of base to deprotonate the amine ligand and form \(5\text{a}\). The resulting amide ligand acts as an internal base that promotes the dehydrogenation of alcohols across the rhodium-nitrogen bond to form \(5\text{b}\) and the corresponding aldehyde (Fig. 3, inner circle). Complex \(5\text{a}\) also reacts with water to form \(5\text{c}\), which in turn reacts with the formed aldehyde to another equivalent of \(5\text{b}\) and the corresponding carboxylate (Fig. 3, outer circle). The formed carboxylate can react with the catalyst to form \(5\text{d}\), which inactivates the catalyst. Employed in an oxygen-breathing fuel cell, the catalyst is able to oxidize ethanol to acetate under alkaline conditions \([24]\). Renewable alcohols like 1,2-propanediol, 1,3-propanediol, and 1,4-butanediol could be employed as fuels for the first time in a direct alcohol fuel cell \([41]\). Power densities up to 8.5 mW cm\(^{-2}\) at room temperature and 42.2 mW cm\(^{-2}\) at 80 °C are generated. The alcohols are oxidized to their corresponding mono-carboxylates with selectivity > 74%. Increased selectivity was reached with 1,2-propanediol and ethylene glycol as fuel. If the catalyst is applied in an electrolyzer cell, the same renewable alcohols can be transformed into their corresponding carboxylates with 95–100% selectivity (see Scheme 3) \([42]\). The energy requirement for hydrogen gas production is 19–24 kWh kg\textsubscript{H}_2\(^{\text{−1}}\) and is much lower than the 43–45 kWh kg\textsubscript{H}_2\(^{\text{−1}}\) required for water splitting reaction.

Fig. 2. Overview of molecularly defined catalysts employed in electrochemical alcohol oxidation (1 – 8 and 10). Catalyst 9, derived from catalyst 8 is employed in electrochemical water splitting. For better comparison, potentials reported against Fc/Fc\(^{+}\) are converted to be referenced against SHE according to the literature \([35,36]\).

Scheme 4. Proposed catalytic cycle for electrooxidation of isopropanol by Waymouth et al. (adapted from ref. 37) (RO\(^{−}\) = tBuO\(^{−}\)).
2.3.2. Non-precious metal electrocatalyst

A) Metal-based reactivity

Badalyan and Stahl presented a catalytic system consisting of [Cu(bpy)]OTf2 (bpy = 2,2'-bipyridine) \( \text{[6]} \) in combination with TEMPO to oxidize a variety of benzyl and C1–C3 alcohols in the presence of two equivalents of base [43]. The copper complex activates the alcohol by coordination forming \( 6a \) (Scheme 6). Consequently, \( 6a \) accepts one electron forming \( 6b \), while TEMPO acts as a redox mediator that accepts one proton and one electron. The key step was elucidated to be a concerted 2e−,1 H+ transfer that is similar to a β-hydride elimination, which is typical for platinum-group transition metals. TEMPO has been extensively used as redox mediator but usually requires high overpotentials to regenerate TEMPO from the TEMPOH formed in the reaction [26,43]. The \( \text{(bpy)}\text{Cu(I)/(II)} \) system is able to activate the substrate as well as to regenerate TEMPO (Scheme 6, green cycle). This lowers the overpotential of the reaction to the potential of the Cu(I)/Cu(II) couple, however, two turnovers of the catalyst are necessary for every product molecule. This co-catalytic system reached an electrochemically observed rate constant \( k_{\text{obs}} \) of up to 11.6 s\(^{-1}\) for the oxidation of benzyl alcohol at −0.14 V vs. Fc/Fc\(^+\) in the presence of \( \text{NEt}_3 \).

A nice example for the utilization of well-established oxidation catalyst as an electrocatalyst was presented in 2019 by Das, Nutting, and Stahl [44]. The authors reported the use of complex \( 7 \) \( \text{Na[Fe(III)(TAML)(OH2)]} \) (Fig. 2), a high valent Fe(TAML) species (TAML = tetraamido macrocyclic ligand), as catalyst for the electrochemical oxidation of alcohols to ketones. A key step in this catalysis is the generation of an iron-oxo species \( \text{Na[Fe=O(TAML)]} \) which can also be achieved by chemical oxidants. In this report, the authors were able to generate the iron-oxo species by electrochemical oxidation of a solution of Fe(TAML) in the presence of water, which serves as the oxygen donor. Under bulk electrolysis conditions, ethylbenzene and 1-phenylethanol are oxidized to acetophenone with 79% yield (55% faradaic efficiency) at a potential of 1.25 V vs. Ag/AgCl (ca. 1.45 V vs. NHE [35]). Although this catalyst is a prime example of how a successful non-precious metal catalyst can be employed as an electrocatalyst, the overpotentials for alcohol oxidation are still comparatively high. Moreover, the authors note that the catalyst is not stable under the electrolytic conditions and decomposes.

Fig. 3. Organometallic electroreformer (OMER) and proposed mechanism for the reactions occurring on the anode coated with catalyst 5 on carbon. AEM = anion-exchange membrane.
B) Cooperative ligand reactivity

Bullock, DuBois, Appel et al. successfully employed a series of iron [45], nickel [46], and manganese [47] complexes as hydrogen oxidation catalysts. All catalysts feature non-innocent PR$_2$NR’$_2$ ligands whose pendant amines act as internal bases. Appel et al. employed the nickel catalyst 6 in the electrochemical oxidation of benzyl alcohol in 2015. This represents an early example of a molecularly-defined electrochemical alcohol oxidation catalyst based on a non-precious metal [48]. Electrochemically observed rate constants $k_{obs}$ of up to 3.3 s$^{-1}$ could be achieved. Of the tested substrates, only benzyl alcohol shows high activity, whereas $k_{obs}$ of isopropanol, ethanol and methanol were 0.7 s$^{-1}$, < 0.3 s$^{-1}$ and 0 s$^{-1}$, respectively. Although not used in the oxidation of alcohols, Bullock, Wiedner et al. further optimized the nickel catalyst 8 to yield catalyst 9. The authors were able to increase the turnover frequency by a factor of 100 while reducing the required overpotential by 170 mV [49]. This improvement was achieved by a series of changes to the ligand in combination with a careful choice of solvent. The choice of a high-viscous solvent and long-alkyl chains introduced at the nitrogen atoms of the ligand lead to favorable molecular dynamics which cause the rate increase. The overpotential could be lowered by subsequent introduction of electron-withdrawing groups at the phosphorus atoms of the ligand. Likely, these achievements will influence follow-up work on electrocatalysts with PR$_2$NR’$_2$ ligands for electrochemical alcohol oxidation.

Waymouth et al. employed a known iron (PNN) pincer catalysts 10 for formic acid dehydrogenation [50] in the electrochemical oxidation of isopropanol [51]. During the reaction, the catalyst [(P(N)P)FeH(CO)] (10) [P(N)P = bis[2-(diisopropylphosphino)ethyl]amid e] formally takes up a proton at the amine and a hydride at the iron center to form [(P(NH)P)FeH$_2$(CO)] 10a (Scheme 7). Cyclic voltammetry studies of the starting complex 10 exhibit a chemically irreversible oxidation at ~0.34 V vs. Fc/Fc’, while complex 10a is oxidized reversibly at a lower potential of ~0.74 V vs. Fc/Fc’. Both oxidations are one-electron processes, as found by controlled potential electrolysis. The authors attribute these oxidations to the Fe(II)/Fe(III) couple and explain the different potentials by the increased electron density at the iron center in 10a caused by the σ-donating hydride ligand. The electrochemically or chemically generated Fe(III) complexes are found to decompose rapidly, resulting in free ligand and unidentified Fe species. In the presence of a strong phosphazene base, the oxidation of 10a at ~0.74 V changes from a one-electron to a two-electron process per iron atom. Further studies revealed that deprotonation of the amine only happens after oxidation by one electron. As expected, complex 10a transforms into 10 in presence of excess of base (KORBu) and two equivalents oxidizing agent [CP$_2$Fe(BF$_4$)]. In the presence of isopropanol, 10 reacts to 10a with the concomitant formation of acetone. Running this reaction under electrocatalytic conditions produces acetone from isopropanol with ca. 100% Faradaic efficiency and turnover frequencies of up to 1.7 s$^{-1}$ at ~0.7 V vs. Fc/Fc’. Unfortunately, the complex proves unstable under the catalytic conditions and the maximum turnover number (TON) is 1.9.

In summary, considerable progress has been made in the field of electrochemical alcohol oxidation in the past years. A comparison of the discussed catalysts with their respective benchmark numbers can be found in Table 1. Comparing the catalysts that have been tested in cyclic voltammetry and bulk electrolysis experiments, the high turnover frequencies of base metal catalysts with cooperative ligands 8 and 10 stand out (3.3 s$^{-1}$ and 1.7 s$^{-1}$, respectively). They are in the same order of magnitude than the best performing catalyst 2, who is based on a precious metal with a non-cooperative ligand (4.8 s$^{-1}$). The base metals without coordinating ligands 6 and 7 on the other hand show high overpotentials and a generally lower performance – although no turnover frequencies are reported for 7. Comparing the few examples of catalysts that have been tested in full fuel cells, 1 and 5, the catalysts with the cooperative ligand shows a much higher maximal power density (1: 0.18 mW cm$^{-2}$ at 22 °C; 5: 8.5 mW cm$^{-2}$ at 22 °C). However, this difference might also be attributed to the more challenging substrate use in the glucose fuel cell of catalyst 1.

Molecularly-defined catalysts allow to decrease the load of precious metals or replace them completely at almost the same or even better activity and selectivity. A challenge for the years to come is to improve long-term catalyst stability under electrocatalytic conditions. Furthermore, the substrate scope, especially for non-precious metal catalysts, has to be improved to include feedstock-derived (poly-)alcohols. These substrates require the catalyst to be chemo-specific in addition to the requirements for...
high molecular activities and high current densities at low overpotentials.

3. Photocatalytic dehydrogenation of alcohols/water mixtures

The photocatalytic production of \( \text{H}_2 \) by a water splitting process combined with the oxidation of an organic substrate has been intensively studied in the past years [52]. A process that encompasses the utilization of an alcohol from biomass feedstock (ethanol, sugars) and solar energy represents a new avenue for the sustainable production of hydrogen [53]. In general, photocatalytic conversion of alcohol/water mixtures to hydrogen is typically accomplished under mild conditions. Consequently, the selectivity of the photochemical process is frequently superior to the corresponding electrochemical or thermal dehydrogenations. The utilization of alcohols as sacrificial agents has contributed greatly to

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<th>Cell[a]</th>
<th>Category</th>
<th>Cat</th>
<th>Substrate[b]</th>
<th>TOF [s(^{-1})]</th>
<th>Onset Potential [V vs SHE]</th>
<th>Base[c]</th>
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<td>MeOH, EOH, ( i\text{PrOH}, \text{BuOH} )</td>
<td>3.3</td>
<td>0.08</td>
<td>Et(_3)N</td>
</tr>
<tr>
<td>CV, BE</td>
<td>Non-noble / coop</td>
<td>10</td>
<td>( \text{PrOH} )</td>
<td>1.7</td>
<td>0.08</td>
<td>\text{P}_2\text{-Et}</td>
</tr>
</tbody>
</table>

[b] 1-PE: 1-Phenylethanol, 2-POE: 2-phenoxyethanol, 1,2-P: 1,2-propanediol, 1,3-P: 1,3-propanediol, 1,4-B: 1,4-butanediol.
[c] NaOR: sodium alkoxide of the corresponding substrate, \( \text{P}_2\text{-Et} \): Phosphazene-Base.

Fig. 4. A) Schematic representation of water splitting (i), alcohol (\( \text{C}_x\text{H}_y\text{O}_z \)) photo-oxidation (ii) and photochemical hydrogen evolution from alcohol/water mixtures (iii) over an irradiated co-catalyst/TiO\(_2\) photocatalytic system. B) The solar spectrum. C) Energy comparison of overall water splitting and sugar alcohol reactions. (adapted from reference 52a and 52c).
overcome the thermodynamic and kinetic barriers of the water splitting process. The schematic representation of the general reaction (iii) over an irradiated doped-TiO₂ photocatalyst is depicted in Fig. 4. Upon irradiation with energy (hν) equal or larger than the band gap of the semiconductor (3.0–3.2 eV), an electron from the valence band (VB) is promoted to the conduction band (CB) leading to an electron (e⁻) hole (h⁺) pair. While electrons reduce protons (H⁺) to H₂ in the surface of the photocatalyst, holes oxidize water (water splitting reaction i, Fig. 4A). The photo-oxidation of an alcohol under aerobic conditions reaction (ii, Fig. 4A) occurs by reaction of the alcohol with holes or generated hydroxyl radicals (OH⁻) forming CO₂ and water, while electrons react on the surface of the catalyst with molecular oxygen. In a combined process reaction (iii, Fig. 4A), the alcohol is oxidized by water forming hydrogen. In this scenario, the alcohol reacts irreversibly with the generated oxygen from the water splitting or the photogenerated holes. In this case, electron-hole recombination and back reaction of O₂ and H₂ are effectively inhibited leading to a higher H₂ productivity. A prototypical example is the photochemical hydrogen evolution from aqueous methanol. Since the process is considerable less endergonic, the reaction can be even accomplished at ambient conditions. More sustainable reactants include bioethanol, glycerol or sugars. In Fig. 4C the overall reaction of a biomass alcohol and water to H₂ and CO₂ is presented. The process requires little energy input to overcome activation barriers and in principle the use of low-energy irradiation (visible and IR light) highly abundant in the solar spectrum would be sufficient (Fig. 4B) [54].

In general, TiO₂ semiconductor-based materials are the most widespread photocatalysts for the hydrogen evolving reactions from water/alcohol mixtures. The majority of catalyst modifications include the introduction of noble metal nanoparticles to the surface of the semiconductor to improve the catalytic hydrogen production rate by irradiation with visible light. The metal can improve the lifetime of the electron-hole pair. In other words, it can act as electron scavenger, favoring proton reduction and suppressing electron-hole recombination. On the other hand, the combination with organometallic complexes acting as co-catalyst is also an efficient strategy to endorse the visible light performance of this materials (see Fig. 5) [55].

In heterogeneous systems, metallic or metallic oxide nanoparticles deposited on the surface of the semiconductor are the preferred co-catalysts. Although noble metals (Pd, Pt and Au) are the chosen heterogeneous catalysts in H₂ production under photochemical conditions, efficient examples with first row metals (e.g. Cu) have been reported [56,57]. Photocatalytic hydrogen production from methanol, ethanol, glycerol, and other polyalcohols has been efficiently achieved with this type of heterogeneous systems [58]. For example, Corma et al. have reported the photocatalytic hydrogen production from aqueous ethanol by Au/TiO₂ achieving up to 309 mmol H₂ g⁻¹ h⁻¹ [59]. Reforming of glycerol has been performed with a H₂ evolution rate of 70 mmol g⁻¹ h⁻¹ (entry 1, Table 2) [60]. High catalytic activity has been observed in the photochemical dehydrogenation of glucose by AuPd/TiO₂ (8.8 mmol H₂ gcat⁻¹ h⁻¹) [61]. Likewise, H₂ evolution from cellulose, hemicellulose and lignin has been achieved by CdS QDs in basic aqueous solutions (5 mmol H₂ g⁻¹ h⁻¹). The main limitation is related with their complex structure and more difficult degradation process compared to simple carbohydrates [62].

Several studies have reported the combination of semiconducting materials with metalloenzymes [63], metalloenzyme mimics [64] and metal complexes [65] as active photocatalysts in the hydrogen evolving reaction from water and alcohol mixtures. The schematic representation of a hybrid system that combines a molecular catalyst and a heterogeneous photosensitizer semiconductor is depicted in Fig. 5B. This catalytic model shares common initial mechanistic steps with the heterogeneous catalyst. However, several advantages include defined mechanisms for proton reduction by the structurally defined complex and favored diffusion of the substrate in a homogeneous media [66]. A third category combines a homogeneous catalyst and a molecular (organic or organometallic) photosensitizer (Fig. 5C). A selection of the most efficient catalytic systems of the three categories is listed in Table 2. Metalloenzymes, especially hydrogenases, are very interesting since they are able to interconvert protons and electrons to molecular hydrogen with high efficiency (TOF > 6000 s⁻¹). For example, nickel-iron hydrogenases (active site represented in Scheme 8) and metal complexes as active photocatalysts in the photochemical production of H₂ from aqueous ascorbate achieving TON = 92 (H₂ molecules produced per enzyme) [67]. The authors observed lower efficiency when Ru(bpy)₃²⁺ sensitized enzyme was used instead, justified by multiple electron transfers into the biological system, only possible with QD based systems. Synthetic molecular catalysts of earth-abundant metals resembling structurally and electronically the active site of the hydrogenase enzyme have become very promising catalysts in both, photo- and electrochemical processes. These systems present easily tailored structures and allow a clearer understating of the multi-electron transfer mechanisms occurring within the overall catalytic system. Besides, they might provide anchoring points in coordinated ligands for tethering to the photosensitizer. Gao et al. improved up to five-fold the hydrogen production rate of a [FeFe]-hydrogenase mimic using this strategy [68]. Electrochemical and spectroscopic investigations of the catalytic system based on a dinuclear iron complex bearing a thiolate bridged ligand containing organic chromophores demonstrated photo-induced intramolecular electron transfer during H₂ formation. In general,
replacement of molecular dyes by semiconductors increases the sensitizer photostability, excited state lifetimes and allows multiple electron mechanisms without relevant changes on the structure. For example, Jian et al. reported that the water soluble diiron complex (11) (Scheme 8) exhibited an almost 100-fold increase in the TONs of H₂ generation from aqueous ascorbic acid with CdSe QD compared to the molecular [Ru(bpy)₃]²⁺, used as photosensitizer (entries 2 and 4, Table 2) [69]. An in depth investigation of both systems revealed different quenching mechanisms and considerably faster electron transfer processes for the CdSe system.

The organometallic complex [Ni(P₂PhN₂Ph)₂(CH₃CN)](BF₄)₂ (12) (P₂PhN₂Ph = 1,3,5,7-tetraphenyl-1,5-diaza-3,7-diphosphacyclooctane) (Scheme 8) was originally developed by DuBois et al. as efficient hydrogen evolving electrocatalyst, with turnover frequencies (TOF = 350 s⁻¹), close to the natural enzyme [70]. The same Ni catalyst incorporated in a photo-driven system achieved TONs of up to 200 over a period of only 8 h, which could be extended by continued addition of ascorbic acid and [Ru(bpy)₃]²⁺ (TON = 2'700 in 150 h, TOF = 18 h⁻¹) [71]. Similar catalytic activity (TOF of 19 h⁻¹) was observed using mimics of photosynthetic organelles. This system embraces the electrostatic interaction of the analogue amine nickel catalysts (13) (Scheme 8) and a nanoribbon network formed by the supramolecular assembly of a perylene monoimide [72]. Remarkably high TONs (up to 600'000 mol of H₂ per mole of catalyst after 110 h) and initial TOF values (7'000 h⁻¹) have been obtained in a reaction catalyzed by the nickel salt [Ni(NO₃)₂], either in a homogeneous system (with an organic dye as photosensitizer) or combined with CdSe nanocrystals [73]. The system maintained its catalytic activity for up to 360 h upon irradiation at 520 nm.

### Table 2
Photocatalytic hydrogen production rates from relevant heterogeneous, homogeneous and hybrid catalytic systems.

<table>
<thead>
<tr>
<th>Entry</th>
<th>System</th>
<th>[Cat]</th>
<th>PS</th>
<th>Light source</th>
<th>DH (sacrificial agent)</th>
<th>Max rate (H₂ mmol g⁻¹ h⁻¹)</th>
<th>TOF (h⁻¹)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heterogeneous</td>
<td>TiO₂/rGO/Pt</td>
<td>–</td>
<td>UV–Vis (Hg lamp 450 W)</td>
<td>Glycerol</td>
<td>70.8</td>
<td>5.8</td>
<td>[60]</td>
</tr>
<tr>
<td>2</td>
<td>Homogeneous</td>
<td>11 ([FeFe]H₂ase mimic)</td>
<td>[Ru(bpy)₃]²⁺</td>
<td>Vis (LED 450 nm)</td>
<td>Ascorbic acid</td>
<td>301.2</td>
<td>180</td>
<td>[69]</td>
</tr>
<tr>
<td>3</td>
<td>Hybrid</td>
<td>15 [Co]</td>
<td>[Ru(bpy)₃]²⁺</td>
<td>Vis (LED 469 nm)</td>
<td>Ascorbic acid</td>
<td>319'738</td>
<td>156'000</td>
<td>[76]</td>
</tr>
<tr>
<td>4</td>
<td>Hybrid</td>
<td>11 ([FeFe]H₂ase mimic)</td>
<td>CdSe QDs</td>
<td>Vis (LED 450 nm)</td>
<td>Ascorbic acid</td>
<td>20'840</td>
<td>12'455</td>
<td>[69]</td>
</tr>
<tr>
<td>5</td>
<td>Hybrid</td>
<td>14 [Ni]</td>
<td>CdSe QDs</td>
<td>Vis (LED 520 nm)</td>
<td>Ascorbic acid</td>
<td>7'340</td>
<td>2'280</td>
<td>[75]</td>
</tr>
</tbody>
</table>

### Scheme 8.
Active sites of [FeFe] and [NiFe] hydrogenases. Selected metal complexes (11–17) used in homogeneous or hybrid catalytic systems for the photochemical production of H₂ from aqueous solutions.
Quantum yields (based on two photons per H₂ evolved) of 36% were reached in water and increased to 59% in EtOH/water mixtures. The NiFe hydrogenases active site (dinuclear nickel–iron cluster bearing cyanide, carbonyl and sulfur ligands) has motivated the synthesis and screening of a variety of nickel complexes containing thiolate ligands as potential photocatalysts for hydrogen production [74]. One of the most effective catalytic systems involves CdSe QDs as PS, ascorbic acid as electron donor and the square planar nickel complex 14 (Scheme 8), bearing a redox “non-innocent” pyridinethiolate-N-oxide ligand, which remains active over a period of one week under irradiation achieving TON values >280’000 (entry 5, Table 2) [75].

Several catalysts based on cobalt complexes have been reported for the production of H₂ under homogeneous photocatalytic conditions. Zhan et al. presented a highly active catalytic system that comprised complex [Co(bpy)₂(CN)₂][NO₃] (15) and [Ru(bpy)₃]²⁺ as photosensitizer, producing H₂ with an initial TOF of 1.56 × 10⁸ molₗH₂ mol⁻¹cat⁻¹ h⁻¹ (entry 3, Table 2) from an aqueous solution of ascorbic acid upon irradiation (469 nm) [76]. TON values of up to 7.3 × 10⁵ molₗH₂ mol⁻¹cat⁻¹ were obtained after 18 h. The octahedral bis(glyoximate) Co(III) complex 16 or Co(II) complex 17, containing a tetradeinate macrocyclic ligand, have been used as catalysts coupled with CdTe QDs as photosensitizer [77]. Catalytic activity of complex 17 is superior to the cobalamine complex 16 achieving TON values up to 650 and TOFₖ = 9 min⁻¹. Hydrogen evolution with high TONs (up to 1’960) has been observed using ethanol and benzyl alcohols and a photocatalyst based on the tetranuclear cerium-containing polyoxometalate TBA₆[Ce(CH₃CN)₄][Ce(CH₃CN)₂]x⁴-O[Y-SW₁₀O₃₆] [78]. Upon irradiation with visible light (λ = 400 nm), the complex exhibits an unique Ce³⁺-to-POM(W⁶⁺) charge transfer. The water soluble rhodium complex [Rhᴵᴵᴵ(Cp*)(bpy)(H₂O)][SO₄] (18) (bpy = 2,2'-bipyridine) and the iridium-ruthenium dinuclear complex [Irᴵᴵᴵ(Cp*)(H₂O)]²⁺Ru(III)(bpy)₂(SO₄)²⁻ (19) (bpy = 2,2'-bipyridine) are active catalysts in the photocatalytic hydrogen evolution from aqueous ascorbic acid [79]. Upon irradiation with visible light (λ > 430 nm), the Rh(III) complex undergoes one electron reduction forming a Rh(II) species, followed by disproportionation to a Rh(I) complex and regeneration of the catalysts. Sequential protonation of the Rh(I) leading to a Rh(III) hydride species and proton hydride interaction under acidic media results in the formation of hydrogen. Similar disproportionation reaction and mechanism intermediates were proposed for the iridium catalyst (Scheme 9).

Currently, due to the increased efficiency and tailored design of hybrid and homogeneous catalysts, they have been the focus of recent research. In contrary to heterogeneous catalysts, homogeneous and hybrid systems are less stable and exhibit high activity only in the early stage of the reaction. Moreover, the scope of alcohol substrates used in this chemical approach is very limited.

As shown in the previous examples, photocatalytic hydrogen formation from aqueous solution using alcohol substrates as hole scavengers and water as electron acceptor has focused most of the attention in the last years. Light-driven alcohol splitting into H₂ and a carbonyl product remains still an important challenge. In this regard, promising heterogeneous and homogeneous catalysts have been reported which operate under remarkably mild reaction conditions [80,81]. For example, the dehydrogenation at room temperature and visible light of primary or secondary alcohols to aldehydes and ketones, respectively has been achieved by a photocatalyst based on Ni-modified CdS nanoparticles (Scheme 10A) [82]. The presence of Ni, was essential to achieve high conversion of the alcohol and high selectivity. Recently, Kanai et al. reported the catalyzed splitting of aliphatic secondary alcohols to ketones and hydrogen under similar conditions using a fully homogenous catalytic system (Scheme 10B) [83]. The authors combined an organocatalysts, a photocatalyst and a TM catalyst. The organocatalyst (TFA = thio phosphoric acid), generates a thyl radical (RS⁻) by reaction with a photoexcited acridinium photoredox catalyst (*Mes-Acr). The sulfur radical abstracts a hydrogen atom from an α-C–H bond of the alcohol substrate and the carbon-centered radical. The activated substrate reacts immediately with the Ni(II) salt [Ni(NTf₂)₂ or Ni(BF₄)₂; NTf = trifluoromethanesulfonamide] forming an alkyl Ni(III) species which upon reaction with the reduced photoredox catalyst (*Mes–Acr) undergoes β-hydride elimination leading to the ketone product, upon tautomerization. In Scheme 10B is represented the sequential hydrogen-electron transfer and β-hydride elimination steps interceded by the catalytic set. The synthetic applicability was clearly demonstrated with a variety of secondary alcohol substrates and extended to the cross-dehydrogenative esterification of aldehydes and primary alcohols.

While several advances have been made in the photocatalytic splitting of alcohols in the recent years, some important aspects require further investigations, especially those related with the operating mechanisms in both, homogeneous and heterogeneous catalytic processes. An important progress has been made with
simple aliphatic and aromatic primary and secondary alcohol substrates. Extension of the method to the selective conversion of polyols from biomass in a process driven by sunlight would be highly desirable.

4. Catalytic thermal dehydrogenation of alcohols

Alcohols, which can be obtained from abundantly available sources, are central substrates in organic synthesis as precursors of carbonyl compounds by reaction with stoichiometric equivalents of inorganic and high molecular weight oxidants. In order to increase sustainability and atom efficiency of this process, one of the most investigated approaches involves the acceptorless dehydrogenation of alcohols under thermal conditions, catalyzed by heterogeneous or homogeneous metal catalysts.

Comprehensive reviews have been published regarding alcohol dehydrogenation reactions triggered by heterogeneous catalysts [84]. Although they represent the most convenient choice for large scale applications, due to their easier recovery and reuse, still grieve from numerous drawbacks, including moderate selectivity and lack of detailed kinetic and mechanistic studies. Among them, supported metal nanoparticles display the highest catalytic activities. A remarkable example is the catalyst based on hydrotalcite supported Ag nanoparticles, which achieves total TON > 100,000 and TOF of up to 2,000 h⁻¹ in the dehydrogenation of primary and secondary alcohols to aldehydes and ketones, respectively [85]. Other examples of supported Ni [86], Pd [87], Pt [88], or Ru [89] catalysts have also been reported exhibiting lower activities (TOF < 1,500 h⁻¹). Copper-based catalysts [90] are very active in the methanol steam reforming reaction, although they originate a significant concentration of undesired side products (carbon monoxide) and exhibit low thermal stability and high sensitivity towards air. Homogenous catalysts can overcome some of these disadvantages such as easily elucidation of catalytic mechanisms and fine tuning of catalyst structure–activity relationship. In general, they display higher levels of selectivity compared to the heterogeneous systems. However, the main problems for large scale applications is the separation and recyclability of the catalyst, frequent requirements of additives (base) and the combination of mainly noble metal and sophisticated organic ligands. In the following section is presented an overview latest advances reported in homogenously catalyzed alcohol dehydrogenation reactions.

4.1. Precious metal homogeneous catalysts

Since the pioneering studies on acceptorless alcohol dehydrogenation, homogeneously catalyzed processes under thermal conditions have been mainly achieved by Ru complexes. In early examples, the catalytic entities operated under classical centered mechanisms [91] (Fig. 6a). The observed low selectivity and applicability of these initial catalysts were improved by placing multi-dentate ligands in the catalyst structure to increase stability towards the high temperatures required for the endothermic
process to occur. For example, Garrou et al. [91e] were able to achieve a 5-fold increase in the efficiency of Robinson’s catalyst [Ru(OCOCF₃)₂(CO)(PPh₃)₂] [91a] by replacing mono- by bidentate phosphine ligands. More recently, the concept of metal–ligand cooperativity has been widely established and bifunctional systems represent an elegant class of artificial catalysts with a clear inspiration from the active sites in metalloenzymes [92]. In Fig. 6c are represented two examples of metalloenzyme active sites, lactate racemase and alcohol dehydrogenase, which trigger the reversible dehydrogenation of secondary and primary alcohols by cooperation of basic functional groups adjacent to a metal center. In artificial catalysts, dual activation of an alcohol substrate (concerted or stepwise) by a basic ligand site and acidic metal center has been the key to improve turnover numbers (Fig. 6b). On the other hand, since the formal “oxidative” reactions do not require a typical oxidizing reagent, ligands susceptible to easy degradation can be now safely used. Usual additives are inorganic or organic bases, needed to deprotonate the alcohol (ROH) to the alkoxide (RO⁻) which readily coordinates to the acidic metal. In a classical metal centered mechanism, this step is followed by β-hydride elimination forming a metal hydride and the carbonyl compound. The newly introduced ligands frequently contain basic sites and cooperate in deprotonation/protonation and hydrogen formation steps. This chemical cooperativity has allowed the utilization of the base additive in equimolecular ratio to the catalyst or even suppress its use in some cases.

Since the seminal work of Milstein et al. in the dehydrogenation of secondary alcohols to ketones using the Ru PNP complex 20 (PNP = [2,6-bis-(di-tert-butylphosphinomethyl)pyridine]) [93], multiple ruthenium complexes with functional pincer ligands have been successfully used. For a selection of recent examples, see Scheme 11. For example, Sun et al. reported the complex [RuCl₂(fac-PNN)(PPh₃)] (PNN = N-(2-(diphenylphosphino)ethyl)-5,6,7,8-tetrahydroquinoline-8-amine) as catalyst with base as additive for the acceptorless dehydrogenation of aromatic and aliphatic secondary alcohols to ketones achieving high TON.

Fig. 6. Alcohol dehydrogenation general mechanisms for catalysts with a) classical ancillary ligands. b) Lewis base ligands that show metal–ligand cooperativity and c) Ligand centered or cooperation with a metal in two examples of metalloenzyme active sites. Left: In lactate racemase, dehydrogenation of the secondary alcohol in the chiral substrate (D-/L-lactate) occurs by hydride transfer and deprotonation of the alcohol by the cooperation of a carbon coordinated to a Ni(II) and an adjacent histidine residue. Right: In alcohol dehydrogenase active site, a Zn(II) center coordinates the alcohol and a ligand network in the proximity of the metal allows proton and hydride transfer to the protein surface and NAD⁺, respectively. (Adapted from Ref. [92]).
Yu et al. reported a NNC pincer Ru(II) hydride complex (22), containing a pyrazolyl-indolyl substituted pyridine ligand, as active catalysts in the dehydrogenation of N-heterocycles and secondary alcohols [95]. Although with higher catalyst loadings (0.5 mol%) than in the previous example, a base additive is not needed and the method exhibits a broad substrate scope. The Muthaiah group reported the synthesis of the ruthenium complex 23, introducing phosphaadamantane coordinating groups which confer water solubility to the catalysts and increased stability of phosphine sites towards oxidation. In combination with base, catalyst 23 proved highly efficient in acceptorless dehydrogenation of secondary and primary alcohols to ketones and aldehydes, respectively [96]. The authors used water as solvent, and the selectivity obtained in the conversion of alcohols to aldehydes is remarkable. In general, Ru homogeneous catalysts trigger the dehydrogenative coupling of the resulting aldehydes to carboxylate compounds, under basic aqueous conditions [97]. Examples of selective acceptorless dehydrogenation of primary alcohols to aldehydes under aqueous conditions are scarce. In water has been only previously observed with the C,N-chelated [Cp*Ir(ppy)] (ppy = 6-phenyl-2-hydroxypyridyl) complex [98]. More recently, a water soluble molecular catalyst based on the dinuclear complex [Rh2(µ-OAc)(Cl)2(η2-terpy)]Cl (terpy = 2,2':6',2''-terpyridine) exhibited different selectivity to the acid or aldehyde product in function of the base used. Although the authors proved efficient for obtaining carboxylic acids, aldehydes are only accessible in moderate yields [99]. Bera et al. reported the dinuclear Ru(II) complex 24 bearing a naphthyridine-diamine ligand (Scheme 11) as efficient catalyst for the dehydrogenation of a wide range of primary alcohols to aldehydes (TON up to 98) without significant formation of esters as side products [100]. Kinetic and theoretical studies support a proposed mechanism in which cooperation of both ruthenium centers is essential for the C–H bond activation by b-hydride elimination of a metal-alkoxide intermediate.

Baratta et al. tested a series of stable ruthenium and osmium complexes [MCl2(diphosphine)(L)] (M = Ru, Os; L = bidentate amino ligand) as catalysts in the presence of base in the dehydrogenation of secondary alcohols to form ketones (TON up to 4000, TOF 200 h⁻¹) [101]. The optimal Ru and Os catalysts (25 and 26 in Scheme 11) exhibit similar efficiency in the dehydrogenation reaction. While the Os catalyst 26 generally leads to lower TOFs, it exhibits better activity in the dehydrogenation of specific substrates, such as benzhydrol and sterols. Primary alcohols undergo mainly homocoupling to the corresponding symmetrical esters – likely via Tishchenko-reaction of the corresponding aldehydes as intermediates – with Os complexes bearing PNP, PNN and NNN-pincer ligands as catalysts (TON up to 900) [102]. Esteruelas and Sierra reported the catalyzed dehydrogenation of secondary alcohols to ketones using the Os complex 27 (7 mol%), under base-free conditions [103]. The catalyst also transforms several benzyl alcohols, with electron withdrawing or donating substituents, into the corresponding aldehydes and H2, reducing considerably the Tishchenko side reaction. Acceptorless dehydrogenation of alcohols under base-free conditions has been also achieved with complex 28 [104]. The catalyst was prepared by N–H activation of 3-(2-pyridyl)pyrazol by an Os(IV) dihydride complex forming an Os(II) species which reacts with the dimer [Ir(OMe)(g4-COD)]2 to install the diene iridium fragment (Scheme 12). The resulting heterodinuclear complex 28 catalyzes the efficient dehydrogenation
of secondary alcohols to ketones and of primary alcohols to aldehydes or esters. While aliphatic alcohols undergo ester formation, benzylic and heteroaromatic alcohol substrates are converted to the corresponding aldehydes in good to moderate yields. The proposed mechanism is depicted in **Scheme 12**. Initial activation of the catalysts involves dehydrogenation of the coordinated diene forming a dihydride Ir(III) intermediate A and cyclooctatriene (COT), later detected in the reaction medium. In a second step, proton-hydride interaction of the O–H bond of the alcohol with the dihydride A leads to the alkoxy hydride dihydrogen complex B. Subsequent dissociation of dihydrogen from B to form hydride-alkoxide complex C would be followed by final a β-hydride

**Scheme 12.** Proposed catalytic cycle for the dehydrogenation of secondary or primary alcohols to ketones, aldehydes or esters by complex 28. (Adapted from Ref. [104]).

**Scheme 13.** Selection of recently reported Ru and Os catalysts for the dehydrogenative synthesis of esters from alcohols.

**Homocoupling** (R1 = Alk, Ar)
29 (R, R′=Et )
30 (R = H, R′=Bn)
29 base TON 95, 135 °C

**Dehydrogenative esterification** (R1 = Alk, R2 =Alk, R3 = Alk, Ar)
TON 100, 135 °C

**Heterocoupling**
R1, R2, R3 = Alk, Ar
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C

**Homocoupling** (R1 = Alk)
R1, R2 = Alk, Ar; R3 = H
TON 4040, 135 °C
molecular elimination reaction of the alkoxide ligand to close the catalytic cycle. This result is especially noteworthy since the method allows the synthesis of aldehydes in high yields avoiding decarbonylation and/or the dehydrogenative homocoupling to symmetrical esters. In an early work, Milstein et al. reported the catalytic dehydrogenative homocoupling of two equivalents of a primary alcohol to symmetric esters catalyzed by Ru PNN complex 29 at T > 150 °C (reaction a, Scheme 13) [105]. The same group has developed novel Ru complexes with pyridine-based PNN-type pincer ligands containing a coordinated secondary amine. The resulting complexes are capable of two metal–ligand cooperation modes, by amine–amide and aromatization–dearomatization interconversion. Particularly, complex 30 was able to perform the same reaction at remarkably low temperatures for a dehydrogenation process (<50 °C) with TON (ca. 1000), comparable to previous examples [106]. Since then, other Ru [107], Rh [108] and Ir [109] complexes with structural and electronic modifications on the pincer ligands were developed to improve the applicability and turnover numbers of these catalytic processes (Scheme 13).

The groups of Gauvin and Gusev et al. have studied the pronounced influence that chemical alterations in aliphatic pincer ligand backbones of a series of Ru complexes (33–34) have in the catalytic activity in homocoupling reactions of primary alcohols to symmetrical esters (reaction a, Scheme 13) [110]. More recent reports include the osmium complex [O=HCl(CO)x2-PyCH2NHC2H4NHPBt] (35) employed by Gusev et al. in the same dehydrogenation reaction and the reverse process, ester hydrogenation [111]. Interestingly, the activity of this Os complex in the homocoupling of ethanol to ethyl acetate is superior to the analogous Ru catalyst [TON 8200 (Os) vs. 3′000 (Ru)]. Milstein et al. reported two synthetic approaches for the synthesis of non-symmetrical esters (formed by reaction of the complex with base) [112]. The authors were able to identify a binuclear terpyridine Rh(II) complex as the catalytic active species [99].

The first example of direct conversion of primary alcohols and water mixtures to carboxylates in a dehydrogenative process was successfully accomplished by Milstein et al. using low catalyst loadings of complex 35, the octahedral aromatized precursor of complex 31 [115]. The reaction is applicable to both, aliphatic and benzyl alcohols achieving TON values up to 500. Although 1,2-diols could not be used as substrates, the method could be extended to μ-, γ-diols and amino alcohols. Using water or water-dioxane mixtures and a base additive in stoichiometric ratio to the substrate, a large library of amino acid salts were prepared in good to excellent yields from amino alcohols (Scheme 14) [116]. Two main drawbacks affecting substrate scope are the favored intramolecular amidation of 1,4-aminobutanol to γ-butyro lactam and racemization of chiral substrates due to the strong basic conditions. The deaminated complex 36 is a well-established catalyst for the dehydrogenative coupling of alcohols and amines to amides [117]. When used in the absence of base under anhydrous conditions it promotes the formation of polyamides from the same amino alcohols substrates (Scheme 14) [118]. The avoidance of basic reaction conditions has allowed the application of the method to chiral substrates with full retention of configuration.

Recently, other pincer or NHC Ru [119] and Ir complexes [120] have been used as catalysts in the dehydrogenative coupling of alcohols and water. Prechtl et al. investigated several ruthenium catalysts based on aliphatic pincer PNP-type ligands (Scheme 15) [121]. The dihydrogen complex 37, bearing a "non-cooperative " tertiary amine ligand was active in the conversion of aliphatic and benzylic alcohols. Complexes with a coordinated secondary amine, prone for chemical cooperation in deprotonation – protonation steps, led to lower yields of carboxylate product, suggesting a classic metal center mechanism. Up to date, Beller et al. presented the most efficient catalyst (complex 38-Pr) for the conversion of ethanol/water mixtures to acetic acid (TON 80′000) [122]. The reaction conditions are comparable to methanol reforming catalyzed by the same complex (T < 100 °C, 8 M NaOH) [123].
(95% wet) used directly after fermentation in the catalytic process achieves a TOF \( 3h = 1,686 \text{ h}^{-1} \).

Gauvin et al. found that the related Ru complex \( \text{Ru(DAE)} \) was able to catalyze the conversion of both aliphatic and benzyl alcohols under air. The catalyst could be recovered after reaction and reused up to five times (TON up to 4,000) [97d].

In preliminary studies Grützmacher et al. reported the zerolvent 14e complex \( \text{Ru(trop 2DAE)} \) (Scheme 15) and the neutral \( \text{Ru(trop2DAD)} \) complex \( \text{Ru(DAD)} \). \( \text{Ru(DAD)} \) was formed by protonation of the anionic complex \( \text{Ru(DAD)}^- \) and can be described by two resonance structures with either a Ru(0) (A) or a Ru(II) center (B) (Scheme 16A). Complexes 41-H or 41 can react with an alcohol (methanol or higher alcohol) to form the \([\text{Ru(trop}_2\text{DAE)}]\) complex 39, with a formal uptake of two equivalents of H\(_2\) by the unsaturated ligand backbone. Dehydrogenation of complex 39 under thermal and/or basic conditions releases both equivalents of H\(_2\) to regenerate the diazadiene complex. Both complexes 39 and 41 were active catalysts in the dehydrogenative coupling of methanol and water to H\(_2\) and CO\(_2\) (or carbonate) and two different metal–ligand cooperative mechanisms were proposed for both cases. Recently, the same authors developed a more efficient and generally applicable homogeneous catalyst for the reversible dehydrogenation of alcohols by a simple modification of the cooperative ligand. The insertion of an additional methylene group in the ligand backbone gives trop\(_2\)DAP.
were not included in this work, the utilization of substituted imidazole to cesium benzoate [127]. Although mechanistic investigation of up to 19'600 was obtained in the conversion of benzyl alcohols, the reaction leads to the formation of an anionic square planar Ru (0) complex 42. The process is irreversible and complexes 42-H or 42 can be converted back to 40 by a hydrogen transfer reaction with an alcohol. The reactions under stoichiometric regime of the diamine complex 40 with water or alcohols under diverse conditions generate a series of hydride alkoxide, carboxylate and carbonate complexes, preserving in all cases the hydrogenated 1,3-diaminopropane ligand (Scheme 16B). Complex 42 exhibited lower catalytic activity compared to 40 in both, dehydrogenation or hydrogenation processes which suggested that a catalytic cycle via a metal-centered pathway is more plausible.

Szymczak et al. found that introduction of a functional amide substituent (MesNH) in the terpyridine ligand of complex 43a to confer 43b creates a steric protection and enhances catalyst stability [126]. The modification not only avoids metal aggregation but it also allows accessibility to reactive Ru-hydride intermediates, which results in higher TON and TOF in the dehydrogenative coupling of alcohols and water. Zhang and Peng et al. presented the Ru(II) complex 44 bearing a 2,6-bis( benzimidazol-2-yl)pyridine ligand as active catalysts in the presence of base, forming both aromatic and aliphatic carboxylates from the corresponding primary alcohol and Cs(OH)2H2O in equimolecular ratio. Notable TON values of up to 19'600 were obtained in the conversion of benzyl alcohol to cesium benzoate [127]. Although mechanistic investigation were not included in this work, the utilization of substituted imidazolyl ligands resulted in diminished activity, evidencing the relevance of a “cooperative” NH function on the ligand. The NHC Ru (II) complex 45a catalyzed the conversion of aliphatic and benzylic alcohols to carboxylates in aqueous alkaline media under aerobic conditions (Scheme 15). The reaction scope includes benzyl alcohols with halogen substituents, biologically active alcohols and polymeric substrates [128]. Madsen et al. reported a related catalytic system that encompasses complex 45b (1 mol%), PCY3-HBF4 (equimolecular to catalysts) and 1.2 equivalents of KOH (with respect to the substrate) under anhydrous conditions [129]. TONs up to 88 were achieved and the method was applicable to a wide variety of substituted benzyl, aliphatic and sterically hindered alcohol substrates. Based on theoretical calculations, the authors proposed a classic metal centered mechanism. The carbene complex 45c developed by Mata et al. showed low activity in the dehydrogenative coupling of alcohols and water (TON up to 110) [130]. However, when the molecular catalyst was immobilized on reduced graphene oxide (rGO) the activity was considerably improved. Modifications on the polyaromatic substituents of the carbene ligand have an important influence in the catalytic activity. Reasonably, those that provoke a weaker interaction with the surface and leaching, leading to inactive homogeneous catalysts, were avoided. The authors found that placing a pyrene substituent on the carbene (45c) generated a stable heterogeneous system 45c@rGO, that could be recycled up to ten times without considerable drop in catalytic activity (TONmax up to 4'500). Although the scope of the reaction only includes benzyl alcohols, the reaction conditions involve a weak base (Cs2CO3), CsCO3). In principle, the method could be applied to substrates incompatible with strong alkaline conditions, typically required by other systems. The water soluble rhodium(II) complex 46 was an efficient catalyst for the conversion of alcohols to carboxylic acids or ketones in water via either acceptorless dehydrogenation or in an oxidative process under aerobic conditions [99]. The reactions carried out under air are faster and lead to slightly better yields of carboxylate products (TONmax = 3'450). Since the catalyst is water soluble, it could be easily extracted and recycled from the reaction mixture, being reused up to 19 times without apparent loss of catalytic activity. Yamaguchi et al. presented another remarkable example of a water soluble catalyst (47), containing NHC and α-hydroxypyridine ligands [131]. Complex 47 catalyzed the dehydrogenative coupling reaction without the requirement of a basic additive. Although substrate scope is limited to benzylic alcohols and the TONs are quite low (up to 40), this example signifies one of the rare cases in which the catalyst is stable to acidic conditions and carboxylic acids are obtained directly from the reaction mixture without further acidic work-up.

The dehydrogenation of polyols containing vicinal-diols is a difficult process and scarce efficient catalytic reactions are known. Most of them entail the conversion of C1/C2 mixtures and C3 –C6 alcohol substrates to lactic acid (LA). In Scheme 17 are depicted three catalytic approaches for LA synthesis either from glycerol (Scheme 17a) [132], sorbitol (Scheme 17b) [133] or 1,2-ethanediol/methanol mixtures (Scheme 17c) [134]. Dihydroxyacetone (DHA) and glyceraldehyde (GAL) are common reaction intermediates in all mentioned processes. Crabtree et al. reported the NH Cr complex 48 as catalyst for the conversion of glycerol to lactic acid and one equivalent of hydrogen. The process required strong alkaline conditions and considerably high temperatures (160 °C) to selectively obtain lactic acid (LA) with TONs up to 30'100 (Scheme 17a) [132a]. Moreover, the reaction can be conveniently accomplished using glycerol waste from biofuel, under air and neat conditions. More recently, the authors used the same catalytic system in the conversion of C4–C6 polyols [133]. While all C5 and C6 alcohols gave LA in acceptable yields (40–49%), the method was not applicable to erythritol (C4). In general, these reactions exhibit lower selectivity due to C–C cleavage side reactions leading to complex mixtures of ethylene glycol, methyl, glycolaldehyde and formaldehyde. The complex 49 bearing three NHCs derived from (1,3-dimethylbenzimidazolium) salts (BenIm; Scheme 17c) exhibits excellent selectivity and catalytic activity (TON 40’000, TOF up to 3’660 h–1) in the dehydrogenative coupling of ethyleneglycol and MeOH [134]. The proposed mechanism is shown in Scheme 17c. First, CO dissociates from tris-NHC-Hr(I) complex 49 forming a coordinatively unsaturated r(I) species, which is able to dehydrogenate any of the starting alcohols (ethyleneglycol or methanol) to the corresponding aldehydes resulting in the formation of a r(III) dihydride intermediate. The formed aldehydes undergo a selective aldol condensation to form glyceraldehyde, followed by dehydration to pyruvaldehyde which is converted to LA via intramolecular base-induced disproportionation. The octahedral dihydride complex 49-H2 was isolated as intermediate from the reaction and is also a highly active catalyst. Furthermore, replacing ethyleneglycol by glycerol or sorbitol under the same reaction conditions does not affect the efficiency of the process and excellent yields of LA are obtained (up to 99% conversion, 85% yield).

Since the discovery that metal complexes can efficiently trigger the (reversible) release of molecular hydrogen from alcohols, the utilization of substrates with a high gravimetric hydrogen content has become an intensive area of research. Without question these studies are driven by the need for new methods that employ renewable resources to provide sufficient energy supply worldwide. In this regard, and effective reversible dehydrogenation of methanol/water mixtures to hydrogen and CO2 has centered most of the attention in the development of new efficient homogeneous
catalysts. In 2013, the groups of Beller [123] and Grützmacher [124] established the first examples of efficient and selective homogeneous catalysts \((38\, \text{Ph or iPr})\) and \((41-\text{H})\) for methanol reforming. Under similar reaction conditions \((T < 100\, ^\circ\text{C}, \text{ambient pressure})\), three equivalents of hydrogen are released from aqueous methanol and \(\text{CO}_2\) is trapped as carbonate. Initial mechanistic proposals assumed metal–ligand cooperativity as a key-feature for both systems. Recent reports have presented a clearer visualization of both mechanistic pathways. Up to today PNP Ru pincer complex \(38-\text{iPr}\) is the most efficient catalyst for this transformation, achieving TON values of up to 350'000 with TOF of 4'700 \(h^{-1}\) using a concentrated alkaline solution \((8\, \text{M KOH})\). Initial experimental and computational studies rationalized that the amide complex \(38a\) was the active catalytic species via Noyori-type mechanism \((\text{Scheme 18})\). The amido function in the ligand and the metal center facilitate proton/hydride transfer and \(\text{H}_2\) release steps. Based on DFT calculations, Beller et al. proposed a base \((\text{OH}^-/\text{H}_2\text{O})\) assisted anionic mechanism for the dehydrogenation of methanol by complex \(38a\) \((\text{Scheme 18a})\) [135]. After activation of the \(\text{O–H}\) bond of the substrate by the \(\text{N-Ru}\) in \(38a\), the base can deprotonate the amine moiety from the resulting neutral methoxide complex to generate the anionic complex \(38b\). Formation of this intermediate is also plausible by direct reaction with deprotonated methanol, present in the media. Subsequent rearrangement of the methoxide ligand is followed by a \(\beta\)-hydride transfer to the metal center to form intermediate \(38c\). Successive \(\text{N}\)-protonation of the latter by a solvent molecule generates the hydrogenated complex \(38d-\text{H}\) and formaldehyde. This step is followed by hydrogen formation and release to regenerate complex \(38a\) and complete the catalytic cycle \((\text{Scheme 18a})\). Since the experimental catalytic reactions are performed in protic solvent mixtures \((\text{MeOH}/\text{H}_2\text{O})\), de Bruin et al. performed additional DFT calculations considering the solvation effects and the important influence of solvent assistance on essential proton and hydride transfer steps with the presumed bifunctional catalyst \((\text{Scheme 18b})\) [136]. The calculated high basicity of the amide in the PNP ligand suggest that, in this media, the formed amine should remain protonated along the catalytic cycle and the catalyst resting state is a saturated 18 valence electron octahedral amine Ru(II) species solvated by methanol molecules \((38a-\text{MeOH})\). The rate limiting step for methanol dehydrogenation is \(\beta\)-hydrogen elimination of the methoxide ligand and hydride metal formation. Since only high TON are achieved using high base concentrations, the role of the base is providing high methoxide concentrations for rapid turnover. As in Beller’s proposal, hydrogen formation proceeds by direct protonation of the ruthenium hydride intermediate by a substrate or solvent molecule. The nitrogen in the pincer ligand remains protonated and the cooperative role of the coordinated amine is merely limited to hydrogen bonding interactions with substrate, intermediates or solvent molecules in the second coordination sphere.

The anionic hydride complex \([\text{K(dme)}]_2[\text{Ru(II)(trop-DAD)}]\) \(41-\text{H}\) [124] and the diamine complexes, \(39\) and \(40\) [125] represent the only catalysts that perform the homogeneous quantitative conversion of methanol/water mixtures to \(\text{H}_2\) and \(\text{CO}_2\) without the need
Scheme 18. a) Proposed catalytic cycle for aqueous methanol reforming catalyzed by complex 38-iPr based on calculations. (Adapted from Ref. [135]) b) Proposed mechanism for methanol dehydrogenation taking explicitly solvent molecules into account. (Adapted from [136]) DFT calculated energies (kcal mol$^{-1}$) for methanol dehydrogenation are shown in brackets.

Scheme 19. DFT Calculated pathway for dehydrogenation of methanol to formaldehyde over neutral complex 41 (Adapted from Ref. [137]).
of a base or acid additive. Diazadiene Ru(II) complexes 41-H or the neutral 40 undergo fast transfer hydrogenation reactions with methanol, methanediol, or formic acid leading to the Ru(0) complex 39 and related complexes, bearing the fully hydrogenated ligand DAE (diaminoethane). These processes occur even at room temperature. Since dehydrogenation of complex 39 regenerates complex 41 under the catalytic reaction conditions, an initial mechanism involving the reversible dehydrogenation of the ligand was proposed including both species as intermediates of a single catalytic cycle. Alternatively, they could act as independent catalysts which are in equilibrium but follow two different MERPs. Recently, de Bruin and Grützmacher presented a plausible mechanism on the basis of DFT calculations, considering reaction steps in which new modes of metal–ligand cooperativity are possible [137].

As shown in Scheme 19, complex 41 can be described by two main resonance structures, A (with a Ru(0) coordinated to a neutral diimine moiety) and B (with a Ru(II) coordinated to an enediamide). Theoretical calculations show that methanol interacts with the Ru center either via a Ru(II)-O interaction (41a-CH₃OH) or via a Ru(0)-H-O hydrogen bonding (41b-CH₃OH) (Scheme 19). Note that both complexes are in equilibrium and almost isoenergetic. A third isomer 41c-CH₃OH is energetically slightly less favorable (+7.1 kcal mol⁻¹) but more importantly, it represents an unusual coordination mode of the diazadiene (DAD) moiety which binds through the C=C bond in a π-fashion to the metal. This new coordination mode causes a significant change in the electronic structure of the complex in which the Ru center presents and increased Lewis acidity and the nitrogen atoms in the DAD ligand (N₉₈) have an enhanced Brønsted basicity. In this arrangement the Ru-N moiety cooperates in a synergic manner towards activation of the CH₃OH molecule. Methanol binds via the protic OH group to one nitrogen center of the DAD moiety while the C–H bond binds in an end-on fashion to Ru and concerted proton-hydride transfer is an energetically viable dehydrogenation step (Scheme 19). The dual coordination mode of the DAD unit of the ligand allows similar proton and hydride transfer events for the subsequent methanediol or formic acid reaction intermediates.

Overall, the dehydrogenation of the three hydrogen containing molecules proceeds via a Noyori-type mechanism leading to the hydride amine complex [Ru(H)(tropNH-CH=CH-Ntrop)] 41d'. Hydrogen release from the hydrogenated intermediate 41d intermediate becomes possible directly or via substrate/solvent-assisted MERPs with low activation barriers.

More recently, DFT theoretical calculations tackled the mechanistic pathways of the catalyzed methanol reforming by complex 39 [138]. In this case, the catalyst contains a ligand with a
saturated ethylene bridge and two secondary amines coordinated to Ru(0). Initial stoichiometric experiments with H^+H^+ donors already suggested that this system operates by a classical metal centered mechanism. Based on DFT calculations, initial catalyst activation occurs by proton rearrangement from one coordinated amine to the metal forming the amido hydride Ru(II) complex 39 (Scheme 20a). Activation of the O–H bond in methanol by the Ru–N bond leads to intermediate I which rearranges to II via the activated complex [TS-1]# as the transition state. In Scheme 20b are represented the transitions state structures [TS-1] correspondin- to the C–H activation of methanol, methanediol and formic acid. From there on, the catalytic cycle is comparable to the one shown in Scheme 19 with the unsaturated DAD complex 41. Although in Scheme 20a is presented a simplified view, solvent and substrate molecules assist via interaction through hydrogen bonding in the second coordination sphere (see examples for solvated activated complexes at various transition states in Scheme 20b) to generate a smooth MERP for substrate dehydrogenation and hydrogen release.

In their pioneering studies, Milstein et al. found that the Ru-PNN complex 36 catalyzed the direct dehydrogenative coupling of alcohols and amines to amides and two equivalents of H2 under neutral conditions (TONs of up to 1’000) [117]. The overall transformation represents a new method for the synthesis of organic amides and occurs in three steps: a) dehydrogenation of the primary alcohol to an aldehyde; b) nucleophilic addition of the amine to the aldehyde to form a hemiaminal and c) dehydrogenation of the hemiaminal to the amide product. In their first report a wide range of alcohols and amines were coupled, although with substrate limitations affecting mainly to sterically hindered amines or with low nucleophilicity. From this report to now, very important advances have been achieved. With a careful choice of the catalyst, amine/alcohol substrate combination and reaction conditions, it is possible to control the selectivity of the dehydrogenative C–N coupling. This method has allowed the waste-free synthesis of a myriad of different amides [139] and polyamides [140]. Moreover, it could be extended to the selective formation of imines [141], imides [142], aldimes [143] or hydrazones [144], and large libraries of nitrogen containing heterocycles [145–149].

Due to the low hydrogen density of substrate systems consisting on alcohols-amines mixtures, they were not considered as proper hydrogen storage materials until recently. A mixture formed by ethylenediamine and ethanol in a 1:2 ratio has a hydrogen content of 5.3 wt% and could represent a suitable LOHC if four equivalents of hydrogen are fully released from the substrate system (Scheme 21a). Milstein et al. demonstrated that catalyst 35 (0.1 mol%) is able to perform the quantitative release of hydrogen at ca. 100 °C forming N,N-diacyltelylenediamine selectively, using 1.2 equivalents of KOtBu as additive [150]. The reaction is fully reversible, which is of great relevance for a convenient LOHC. Complete hydrogenation of the amide product to the diamine and ethanol was successfully achieved by applying 70 bar of H2 in a reaction catalyzed by the same complex 35 (0.2 mol%). In the reverse reaction, an excess of base is required, as well slightly high reaction temperatures (115 °C). Since then, other combinations of amine-alcohol mixtures with a high H2 gravimetric content have been explored. For example, a mixture of methanol and ethylenediamine in a 1:1 ratio has a theoretical hydrogen content of 6.5 wt%. Dehydrogenative coupling of this system forming a mixture of ethylene urea, N-(2-aminoethyl)formamide and N,N-(ethane-1,2-diylyl)formamide has been accomplished using catalyst 50 (Scheme 21b) [151]. TON values up to 90 were obtained in the dehydrogenation process using KOtBu (2.2 mol%) in 1,4-dioxane at 150 °C. The reaction is fully reversible and the hydrogenation to ethylenediamine and methanol has been quantitatively achieved by the same catalyst, by applying to the reaction mixture 60 bar of hydrogen gas at 170 °C. Reversible direct amimation reactions of low molecular weight amines and alcohol as a strategy for hydrogen storage has been also studied by Prakash and Olah et al. The dehydrogenative coupling of dimethylethylenediamine/methanol in a 1:2 ratio (5.3 wt%H2) forming a mixture of formamides is catalyzed by complex 38–Ph [152]. Using the resulting reaction mixture, hydrogen can be uploaded in the material by pressurizing the system with H2 (60 bar) at the same reaction temperature (120 °C) and base (K2PO4 (Scheme 15c). Hong et al. reported the related complexes 38–Ph and 38–Ph(BH3) as efficient catalysts for the synthesis of a wide range of urea compounds by using mixtures of methanol and primary or secondary amines. The clear advantage of this last method is the absence of a basic additive [153].

Ethylene glycol (EG) is an inexpensive liquid alcohol produced in large quantities for the industrial synthesis of polyester materials. This alcohol has a gravimetric hydrogen content of 6.4 wt% when 2 equivalent of hydrogen are released per EG molecule. Intermolecular dehydrogenative coupling reactions of ethylene glycol to mixtures of oligoesters or with amines to diamides and H2 have been successfully achieved by Ru complexes [154]. An acridine-based PNP ruthenium complex was the optimal catalyst leading to high hydrogen yields without the need of a base additive. Moreover, the same catalyst performs the full hydrogenation of the reaction mixture back to the diol, using 40 bar of H2 at the same reaction temperature (150 °C) [154a]. Using a similar strategy, when two equivalents of an amine are added to the reaction mixture containing EG, base and the Ru pincer catalyst 30, the process leads to the selective formation of oxalamides (Scheme 21d) [154b]. The overall dehydrogenative coupling encompasses the release of up to 4 equivalents of hydrogen. Once more, the reverse hydrogenation reaction was also accomplished by the same catalytic system in which the starting amines and EG substrates were recovered. The method represents a convenient waste-free synthesis of oxalamides but due to the high molecular weight of the amine substrates, the gravimetric hydrogen content of the overall system is far away of an ideal LOHC (a minimum target of 5.0 wt% has been set by the EU and US governments for an economically viable hydrogen storage system).

4.2. Non-precious metal catalysts

Since the initial studies on alcohol dehydrogenation reactions, molecular complexes of 4d and 5d metals have been the traditional catalysts used in these transformations. However, the high toxicity of certain noble metals made the homogeneous catalysts unsuitable for the synthesis of fine chemicals and pharmaceuticals. In addition, the limited availability and high cost associated with noble metal catalysts make them impossible to use on a scale necessary for global energy delivery [e.g. the worldwide energy consumption in 2017, estimated to 22.3 × 1018 kWh required the production 6.6 × 1014 kg of hydrogen (1 kg H2 = 33.6 kWh)]. Evidently, catalysts with earth-abundant first-row transition metals, mainly manganese, iron, cobalt and nickel offer a possible solution to the problem while avoiding the drawbacks of their heavier congeners and the unpredictable mechanisms in which they operate. First row metal catalysis typically involves one-electron pathways and formation of highly reactive radical species, which are mainly responsible for unselective processes. The utilization of rigid and multidentate ligands can conveniently increase the robustness of the catalyst. On the other hand, the introduction of chemically and/or redox “non-innocent” functional ligands that avoid changes in the oxidation state of the metal will
allow a better control of the selectivity and product distribution. As described in the previous section, a wide range of multidentate functional ligands have been successfully employed with noble metals to reversibly store protons and/or electrons in dehydrogenation reactions [155]. In an early stage of research, the same ligand structures have been effectively coordinated to first row
790 (TOF 16 h/CO (0.1 mol%) achieved, under similar reaction conditions, TONs up to 1'050 [160]. A first dehydrogenation step followed by dehydration-hydration and a final intramolecular hydrogen transfer reaction sequence to the lactate salt was possible by using stoichiometric NaOH in pyrrolidinone/water mixtures. Subsequently, Beller et al. reported the synthesis of several lactones and lactams in moderate to excellent yields by intramolecular dehydrogenative coupling of diols or amino alcohols with catalyst 52 (TONs up to 196) (Scheme 23b) [161]. The interconversion of Fe (II) amide/amine hydride species is proposed in a mechanism that involves two dehydrogenation events interconnected by a lactol intermediate formation (Scheme 24). Gauvin et al. reported the catalyzed dehydrogenative coupling of primary alcohols to symmetrical esters by the amide Mn complex 55 [162]. TONs of up to 340 were obtained under neat and additive-free reaction conditions. The authors found experimentally that complex 55 reacts with a primary alcohol (e.g. BnOH) forming an amine alkoxide intermediate [Mn(OCH₂Ph)(NH–{CH₂CH₂(PPh₂)₂})(CO)₂] through a reversible process and this species undergoes β-hydrogen elimination under thermal conditions forming an amino Mn(II) hydride. DFT calculations confirmed the mechanism, similar to the previously proposed for the isoelectronic PNP Fe(II) and Ru(II) catalysts. The highest energy barrier was found for the hydrogen release from the amine-hydride intermediate to regenerate the active species as in the Fe and Ru cases. However, the main difference resided in the initial proton/hydride transfer to the metal amide which is considerably more energy demanding than in Fe or Ru mechanistic pathways, resulting in a less active catalyst.

Recently, Sortais et al. utilized the air stable PN₃P Mn carbonyl complex 56 in the catalyzed dehydrogenation of secondary alcohols to ketones (Scheme 23c) [163]. Albeit the low TON (up to 18), the reaction is fully reversible and by simply applying 50 bar of H₂ the dehydrogenated product can be fully hydrogenated using the same catalytic system.

Cobalt complexes are excellent hydrogenation catalysts of a myriad of different unsaturated substrates. Remarkable efficiency in the hydrogenation of CO₂ to methanol (TOF = 74'000 h⁻¹) has been achieved with molecular cobalt catalysts. However, few examples of efficient cobalt catalyzed alcohol dehydrogenation reactions are known which typically exhibit inferior catalytic performance compared to iron or manganese catalysts. In 2013, Hanson et al. demonstrated that the efficient hydrogenation...
catalyst $[\text{Co(CH}_2\text{SiMe}_3)(\text{Cy}_2\text{PCH}_2\text{CH}_2\text{N(H)}\text{CH}_2\text{CH}_2\text{PCy}_2)]\text{BArF}_4$ was also able to dehydrogenate secondary alcohols (TON up to 18) [164]. The reaction of this cobalt complex with 1-phenylethanol led to the formation of the diamagnetic cobalt complex 59 (Scheme 23), which showed comparable catalytic activity to the catalyst precursor, pointing to this complex as catalyst resting state in the dehydrogenation reaction [165]. Based on experimental observations, the authors suggested a plausible mechanism involving a Co(I)/(III) catalytic cycle. Another Co catalyst worth to mention is complex 60 [166]. The authors designed a tetradeentate tripodal N,P$_3$ ligand which, upon coordination to cobalt forms an air stable complex able to catalyze the dehydrogenation of secondary alcohols to ketones albeit with similar TON values to the previous example.

Gauvin and Dumeignil screened a number of pincer Fe and Mn complexes as catalysts for the dehydrogenative coupling of primary alcohols and water to carboxylic acids (Scheme 23d).

Scheme 23. Overview of primary and secondary alcohol dehydrogenation and alcohol reforming catalyzed by non-noble metal catalyst.

Scheme 24. Proposed mechanism for synthesis of lactones from diols catalyzed by the PNP Fe complex 51. (Adapted from Ref. [161]) (P = $\text{P}^{\text{iPr}_2}$).
The scope of the method is fairly broad and extensive to fatty alcohols. The PNP-Fe (52 or 53) and PNP-Mn (55) complexes are more active catalyst in the absence of water, simply using a suspension of KOH in toluene at 120 °C [167]. The authors found that in general all Mn catalysts were more efficient than their Fe counterparts, due to their higher stability under the strong alkaline reaction conditions. A few years after their first report on the homogeneous methanol reforming by PNP Ru complexes, Beller et al. presented a PNP Fe catalyst which triggered the reaction efficiently [168]. Complex 52 was able to achieve TON values close to 10'000, with acceptable initial TOF (700 h⁻¹) in a reaction performed at 90 °C under alkaline conditions. As generally accepted for PNP metal complexes, the iron amide 51 formed under the basic reaction conditions is a key-intermediate, able to abstract hydrogen from the substrate (methanol, methanediol or formic acid) and form a Fe hydride species from which hydrogen is evolved. Although the hydroborate complex 52 can also promote the dehydrogenation in the absence of base, catalytic activities are very low (initial TOF = 1.5 h⁻¹) and high concentrations of base are still essential. The catalytic activity can be impressively bolstered (TONs up to 51'000) with the system formed by PNP formate Fe complex 54 and LiBF₄ [169]. This represents the state-of-the-art in the catalytic methanol reforming by a first-row transition metal homogeneous catalyst. The manganese dicarbonyl amine complex 57 is also a catalyst for the dehydrogenation of aqueous methanol under similar reaction conditions used with the iron analog [170]. Although the performance obtained with 57 (TON = 54) is not comparable to the Ru system, a slight improvement in the efficiency of the reaction was achieved with the tricarbonyl complex 58 (TON = 65) [170]. The stability of the Mn catalyst and therefore the catalytic activity could be notably increased (TON up to 20'000) using a mixture of the Mn precursor [MnBr(CO)₂] and free PNP(Pr) ligand in a 1:10 ratio. The Mn catalyst remained active for a period of one month. In Table 3 is presented an overview of selected catalytic systems based on 3d and 4d metal complexes with chemically “innocent” (non-MLC) or “non-innocent” ligands (MLC) active in the dehydrogenation of methanol/water mixture under thermal conditions. The traditional poor performance of noble metal catalysts in this process has been bolstered by the utilization of multidentate functional ligands, dropping considerably the pressure and reaction temperatures needed by heterogeneous catalysts (200–260 °C and > 20 bar). From preliminary reports, molecular Fe and Mn complexes bearing multidentate and functional supporting ligands are giving encouraging results. From all systems with first row transition metals, iron based complexes offer the highest activities in methanol reforming reaction, achieving remarkable TON values although still far from those obtained by ruthenium catalysts. Together with Fe and Ti, Mn represents the most abundantly used metal and therefore signifies an ideal replacement for conventional precious metals. The main problem associated with Mn homogeneous catalysts is their poor stability. In this regard, the design of suitable ligands that offer steric protection towards metal aggregation might offer a possible solution.

In Scheme 25 is summarized the catalyzed dehydrogenation coupling reactions of amines and alcohols to form amides promoted by non-noble metal homogeneous catalysts. The iron amide complex 51 exhibits high catalytic activity in the dehydrogenation of alcohols and secondary amines [171]. TON values up to 600 (TOF 75 h⁻¹) were obtained in the coupling of cyclic secondary amines with methanol, exhibiting a catalytic activity remarkable superior to Ru catalysts. Milstein et al. also reported the catalyzed dehydrogenative N-formylation of amines using methanol as C1-substrate and solvent. In this case, the PNP manganese complex 61 allowed the synthesis of up to 14 different amides with moderate to good yields (55–86%) [172]. The same group reported the reaction of diols and amines to cyclic imides and four equivalent of hydrogen catalyzed by PNN Mn catalyst 62 (5 mol%) activated by KH (10 mol %) [173]. The reaction is mainly applicable to the dehydrogenation-coupling-cyclization of 1,4-butanediol and primary amines to several succinimide compounds. The six-membered glutarimides derived from the corresponding 1,5-pentanediol substrate were obtained in lower yields.

In 2016, Milstein et al. reported the dearomatized Mn PNP pincer complex 63 as selective catalyst for the conversion of mixtures of alcohols and amines to imines, hydrogen and water (Scheme 26a) [174]. This represents the first report on a dehydrogenative coupling and condensation reaction homogeneously catalyzed by Mn complexes. Kirchner et al. also found that the Mn complex 64 was able to promote the selective formation of imines [175]. Under the same reaction conditions, the analogous Fe complex exhibits a completely different selectivity and only secondary amines and water were observed as products from a

### Table 3

Selected heterogeneous and homogeneous metal catalysts for the hydrogen production from aqueous methanol under thermal conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst category</th>
<th>Catalyst</th>
<th>Additive</th>
<th>T (°C)</th>
<th>TON (H₂) [a]</th>
<th>TOF (h⁻¹)[b]</th>
<th>Ref</th>
</tr>
</thead>
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<td>1</td>
<td>Noble/non-MLC</td>
<td>[Ru(H)(μ-PrH₂)₃]</td>
<td>NaOH</td>
<td>150</td>
<td>15</td>
<td>7.5</td>
<td>[91c]</td>
</tr>
<tr>
<td>2</td>
<td>Noble/non-MLC</td>
<td>[Ru(OC)(μ-μ-PrH₂)₃]</td>
<td>AcOH</td>
<td>90</td>
<td>34</td>
<td>0.38</td>
<td>[91b]</td>
</tr>
<tr>
<td>3</td>
<td>Noble/non-MLC</td>
<td>[Ru((μ-μ-Pr)₂Cl]</td>
<td>NaOK</td>
<td>120</td>
<td>21</td>
<td>7</td>
<td>[91d]</td>
</tr>
<tr>
<td>4</td>
<td>Noble/MLC</td>
<td>[41-H(C) = N, C(= O)]; CO₂]</td>
<td>–</td>
<td>90</td>
<td>540</td>
<td>54</td>
<td>[124]</td>
</tr>
<tr>
<td>5</td>
<td>Noble/MLC</td>
<td>[40-H(C) = N, C(= O)]; CO₂]</td>
<td>KOH</td>
<td>91</td>
<td>353409</td>
<td>613</td>
<td>[123]</td>
</tr>
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<td>Non-noble/MLC</td>
<td>[52-H(C) = N, C(= O)]; CO₂]</td>
<td>KOH</td>
<td>91</td>
<td>9334</td>
<td>214</td>
<td>[168]</td>
</tr>
<tr>
<td>8</td>
<td>Non-noble/MLC</td>
<td>[54-H(C) = N, C(= O)]; CO₂]</td>
<td>LiBH₄</td>
<td>77</td>
<td>51000</td>
<td>542</td>
<td>[169]</td>
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<td>9</td>
<td>Non-noble/MLC</td>
<td>[55-H(C) = N, C(= O)]; CO₂]</td>
<td>KOH</td>
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<td>54</td>
<td>11</td>
<td>[170]</td>
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<td>[55-H(C) = N, C(= O)]; CO₂]</td>
<td>KOH</td>
<td>90</td>
<td>20000</td>
<td>28</td>
<td>[170]</td>
</tr>
</tbody>
</table>

[a] TON is referred to hydrogen production. Values from long-term experiments. [b] Average TOF referred to overall reaction time. MLC = metal–ligand cooperation.
Scheme 25. Dehydrogenative coupling of alcohols and amines to form amides catalyzed by non-noble metal complexes.

a) Imine synthesis by dehydrogenation-condensation

\[
\begin{align*}
\text{ROH} + \text{RNH}_2 & \xrightarrow{[\text{Mn}], [\text{Co}] \text{ or } [\text{Fe}]} \text{RN}=\text{N} + \text{H}_2 + \text{H}_2\text{O} \\
\text{63 (3 mol\%), benzene, 135 °C, TON 33} \\
\text{64 (3 mol\%), 3AMS, toluene, 140 °C, TON 31} \\
\text{65 (5 mol\%), Ca}_3\text{N}_2, \text{toluene reflux, TON 18} \\
\text{66 (1 mol\%), } & \text{H[BARF}_{4}\text{](OEt)}_2, \text{toluene, 120 °C, TON 100} \\
\end{align*}
\]

b) Deoxygenation of alcohols with hydrazine

\[
\begin{align*}
\text{ROH} + \text{N}_2\text{H}_4 & \xrightarrow{\text{KOH} \text{Bu}, 115 °C} \text{R} + \text{H}_2 + \text{H}_2\text{O} + \text{N}_2 \\
\text{up to 99% yield} \\
\end{align*}
\]

c) α-Olefination of nitriles with alcohols

\[
\begin{align*}
\text{ROH} + \text{CN} & \xrightarrow{\text{61 (4 mol\%)}} \text{R=CN} + \text{H}_2 + \text{H}_2\text{O} \\
\text{up to 91% yield} \\
\end{align*}
\]

Scheme 26. Synthesis of imines, hydrocarbons and olefins from primary alcohols catalyzed by first row late transition metal catalysts.
hydrogen-borrow tandem reaction. In general, low-valent Mn(I) complexes seem to be the most efficient Mn catalyst up to date in alcohol dehydrogenation reactions. Marsden et al. reported Mn(III) complexes as active catalysts in alcohol dehydrogenation reactions. The salen Mn complex 65 promoted the selective and efficient synthesis of imines from alcohols and amines by the dehydrogenative condensation approach (Scheme 26a) [176]. The observed catalytic activity with the hydrogenated salan Mn(III) complex and further labeled experiments already suggested the participation of the iminic moieties in the dehydrogenation mechanism. DFT calculations corroborated a metal–ligand bifunctional mechanism in which both imine groups from the salen ligand are hydrogenated by the substrate forming a monoanionic amine-amide ligand as the resting state of the catalytic cycle. Dehydrogenation of the alcohol takes place by a stepwise outer-sphere mechanism forming a salan Mn(III) hydride intermediate from which hydrogen is formed by intramolecular interaction with the proton of the amine ligand. This work represents the starting point for the investigation of catalysts with Mn complexes with more common higher oxidation states and the avoidance of carbonyl ligands stabilizing the metal in low oxidation state. Zhang and Hanson et al. [164] used the Co precatalyst 66 whereas Singh et al. [177] introduced the Fe-phthalocyanine complex 67 for the synthesis of imines. Both catalysts perform the dehydrogenation process with considerably better efficiency than Mn complexes (TON up to 100) (Scheme 26). In a related transformation, Milstein et al. reported the catalyzed direct deoxygenation of alcohols via oxidative dehydrogenation/Wolff–Kishner reduction by the hydride PNP Mn complex 61 (Scheme 26b) [178]. The reaction is carried out under mild reaction conditions with a high selectivity for primary alcohols. The only subproducts from the reaction, besides hydrogen, are water and nitrogen gas. The mechanism encompasses an initial hydrogen elimination forming an amido Mn(n) complex which activates the alcohol O–H bond across the Mn-N bond leading to an alkoxo amine complex. A final β-hydride elimination step would regenerate the hydride amine catalysts and release the aldehyde ready for condensing with the hydrazine. Applying the Henbest modification of the Wolff-Kishner reduction using KO2Bu as base in toluene, the overall reaction can be accomplished at T = 115 °C. In a related tandem reaction, catalyzed dehydrogenation of a primary alcohol to the corresponding aldehyde followed by the reaction with the α-methylene group of a nitrile and final dehydration resulted in the α-olefination of the nitrile (Scheme 26c). As in the previous example, the first dehydrogenative step is efficiently catalyzed by the Mn complex 61 (4 mol %) [179]. Since a base additive is not employed, it is proposed that the Knoevenagel condensation is initiated by deprotonation of the nitrile by the amide ligand. The method proved very general and applicable to a series of benzylic, aliphatic and allylic alcohols in addition to various substituted benzyl cyanides.

Recently, synthetic approaches for the preparation of N-heterocyclic compounds by the dehydrogenation and condensation tandem reaction of alcohols and amines have been established using first row metal catalysts (see Scheme 27 for an overview). Since many nitrogen heterocycle syntheses involve the condensation of amines and aldehydes or ketones, introducing the later as intermediate by an initial catalyzed acceptorless dehydrogenation of primary or secondary alcohol substrates encompasses a new atom-economic methodology. For example, the classical Paal-Knorr synthesis of substituted pyrrole compounds, where the 1,4-diketone is reacted with an excess of a primary amine, can be accomplished replacing the dicarbonyl substrate by secondary 1,4-diols in a process catalyzed by the cobalt pincer catalyst 68 (5 mol %) [180]. The optimal reaction conditions involve activation of the catalyst by addition of a hydride reagent (NaBH4) and base (KOrBu). The reaction of the Co(II) precatalyst with superhydride leads to the formation of the paramagnetic species [Co(II)(PNNH)] [181]. The role of the base, although essential, is not clear due to the impossibility of isolation and characterization of the cobalt complexes formed. By comparison with previous metal systems with similar PNN ligands, is proposed deprotonation the coordinated secondary amine or methylene arm in the ligand backbone to provide the required active species for the bifunctional activation of the alcohol. The applicability of the reaction was clearly demonstrated with a variety of 1,4-substituted-1,4-butenediols and several aliphatic and aromatic primary amines, affording the 1,2,5-substituted pyrroles with moderate (for aromatic amines) to excellent yields. (Scheme 27a). The synthesis of pyrroles with a slightly different substituted pattern can be accomplished by reaction of secondary alcohols and 1,2-aminoalcohols (Scheme 27b). Preceded by their work with analogous Ir catalyst [182], Kempe et al. presented a more efficient catalytic system for the dehydrogenative coupling-condensation process that encompassed complex 69 and base (KOrBu) at remarkably mild conditions (80 °C) [183]. More than 20 different 2,3,5-substituted pyrrole products were isolated with good to excellent yields. An extensive number of functionalities can be introduced in the adjacent positions to the heterocyclic nitrogen using a myriad of secondary alcohol and substituted 2-aminoethanol substrates. Although a catalytic mechanism has not been proposed, some insights into the possible active intermediates were suggested by the direct reaction of complex 69 with base in the presence of H2 or an alcohol, as hydrogen donor. Reasonably, the base would deprotonate the acidic amine arm at the ligand backbone and the formed amide complex would trigger the heterolytic splitting of H2 or bifunctional alcohol activation leading to the isolated monovalent hydride complex [Mn(H)(CO)3(PN3P)]. This species was not only observed post-catalysis but also exhibited comparable catalytic activity to the pre-catalyst under identical reaction conditions. As an important remark, the Fe and Co complexes bearing the same functional PN3P ligand proved inactive in the reaction. Benzimidazoles represent another class of relevant nitrogen containing heterocycles. 2-Substituted benzimidazoles are typically obtained from the condensation of o-phenylenediamine and aldehydes. The use of the Co complex 68 [181] and more recently, the Mn complex 70 [184] have allowed the direct utilization of easily accessible primary alcohols instead of the corresponding aldehydes (Scheme 27c). Milstein et al. employed a similar catalytic system to that previously used in the pyrrole synthesis. Although the role of the hydride reagent is essential to achieve quantitative yields, the base additive can be completely suppressed without affecting the efficiency of catalyst 68 [181]. As in the case of pyrrole pre-preparation, the water formed in the condensation step needs to be removed from the media by utilization of 4 Å MS, otherwise the selectivity and isolated yields are considerably reduced. The method presented an acceptable substrate scope in terms of primary alcohols but substituted phenylenediamine substrates were limited to two examples. The authors suggested that the Co(I) intermediate, previously mentioned, was the active catalyst. Moreover, in the absence of amine, the Co(I) species catalyzes the selective dehydrogenation of a primary alcohol to the corresponding aldehyde, proposed as an intermediate of the tandem reaction. Alternatively, the reaction catalyzed by the phosphate-free NNS Mn(I) complex 70 (5 mol %) in the presence of base and under neat conditions allowed the effective preparation of a selection of 1,2-disubstituted benzimidazoles [184]. A relevant contribution to the preparative methods of pyrazines was introduced by Milstein et al. using the acridine PNP Mn complex 71 as catalyst for the dehydrogenative coupling of two β-aminocoholes (Scheme 27d) [185]. The optimal reaction conditions involved the use of the azaboromellallacylic precursor 71 (2 mol%) and potassium hydride (3 mol%) at 150 °C in toluene in either open...
Scheme 27. Overview of catalyzed dehydrogenative coupling of amine/alcohol mixtures and dehydration tandem reactions as synthetic approach for N-heterocycles (a–f) and aminomethylation of aromatic and heteroaromatic compounds (g) by first row metal complexes.
or closed system. The scope of the reaction was limited to 2-substituted β-alcohol and moderate yields of the resulting 2,5-pyrazines are frequently observed due to side reactions forming mixtures of unidentified products. In the same report, the catalytic system could be successfully applied in the coupling of o-phenylene diimine and 1,2-diols forming the corresponding benzofused analogs, quinoxalines. The PN3P hydride Mn complex has been reported as catalyst in the dehydrogenative condensation of 2-aminobenzyl alcohol with secondary alcohols to form substituted quinolones (Scheme 27e) [186]. The catalytic system required high catalyst loading of 64 (5 mol%) and the use of two base additives (KOH/Bu and KOH) with a dual function, to activate the pre-catalyst by deprotonation of the amine ligand and to favor the water elimination step. The reaction was applicable to secondary alcohols with aromatic and heteroaromatic substituents as well as to aliphatic alcohols leading to 2,3,4-substituted quinolones in good to excellent yields. The author explored the applicability of the same catalytic system in the dehydrogenative coupling of diverse primary, secondary alcohols and phenylamidine (Scheme 27f). The three-component reaction resulted in the selective synthesis of up to 14 examples of 1,3,5-substituted pyrimidines with acceptable yields [186]. Independently, Kempe et al. accomplished the same tandem reaction using complex 69 as catalyst [187]. This method presents several advantages over the previous example. The reaction requires lower catalyst loadings of the PN3P Mn(I) complex (2 mol%), only one base additive, still in a stoichiometric ratio, and milder reaction conditions (120 °C). Furthermore, the reaction can be accomplished by coupling three or even four different substrates to have access to a large library of 1,3,4,5-substituted pyrimidines. The four component assembly involved the initial catalyzed β-alkylation reaction of a primary and secondary alcohol. This step is followed by the addition of a different primary alcohol and an amine substrate to conform the tetrasubstituted product. Although moderate isolated yields are generally obtained, the overall reaction represents a remarkably divergent and sustainable process, catalyzed by one of the most abundant metals.

Complex 64 was also presented by Kirchner et al. as efficient catalyst for a selective three-component aminomethylation of aromatic and heteroaromatic compounds (Scheme 27g). The reaction, initially optimized for naphthol, is also applicable to phenols with aliphatic substituents, a series of nitrogen containing heterocycles and a thioene. Additionally, methanol is used as C1-source of the methylene group and only secondary amines can be successfully coupled [188]. Under identical reaction conditions completely different selectivity was observed with the Fe complex bearing the same PNP ligand. In this case, only methylation of the aromatic alcohol was detected. Besides of the inherent different reactivity of iron, another main difference of both catalysts is the presence of dissimilar ancillary ligands in the coordination sphere of the metals. While in the iron species a bromide ligand is coordinated trans to the reactive hydride, the manganese complex contains a carbonyl ligand.

5. Concluding remarks and outlook

In the past years the concept of metal–ligand cooperativity continues to trigger the design of new ligands platforms that enable a higher control on the reaction selectivity of metal homogeneous catalysts. In this regard, DFT studies of the kinetics, mechanisms and thermodynamics of these systems will very valuable for future advances in alcohol dehydrogenation processes. Catalysts based on first row metals coordinated to redox “non-innocent” ligands are not common in alcohol dehydrogenation reactions. As we have seen in other chemical transformations, they have the potential to achieve activity and selectivity comparable to noble metal systems. These types of ligands can act as electron reservoirs and allow the first row metal center to undergo exchange of more than one electron, simulating noble-metal active centers. Alternatively, the redox active ligand can cooperate with the metal in the direct substrate activation. This area of research has been overlooked in dehydrogenation processes and will require more attention in the future.

A new model in alcohol fuel cell research has been introduced using well-defined molecular catalysts on the electrodes to execute the same reactivity than in homogeneous media and produce simultaneously high value chemicals and electrical energy. This scenario defines the concept of “OrganoMetallic Fuel Cells” (OMFCs). The advantage of using a molecular catalyst is based in the early identification of the optimal metal–ligand combination in homogeneous phase catalysis and therefore, an in detail study of the working mechanism. In contrast to the methodology based on metal nanoparticles, in OMFCs every metal atom is catalytically active and thereby reduces considerably the required metal loading of fuel cell electrodes. Since the pioneering studies on OMFCs where an organometallic complex on a conducting support material served as anodic catalyst for the oxidation of several alcohols, a number of molecular metal complexes have been successfully employed, which has validated the method. Electrolysis of water is the obvious way to generate H2 fuel. But again – as the oxygen reduction reaction (ORR) in a fuel cell - the anodic oxygen evolution reaction (OER, H2O → ½ O2 + 2e) is the kinetic blockage and accountable for large over potentials in commonly used electroreforming devices. Because of the lower standard oxidation potentials, the conversion of aqueous solutions of organic fuels can be of advantage. This strategy has been effectively applied in electroreforming devices where the electrochemical oxidation of various simple alcohols or polyols occurs at the anode while hydrogen is produced at the cathode. In this scenario, molecular complexes as active sites in an OrganoMetallic Electro Reformer (OMER) can once more help to significantly lower the metal loadings, substitute noble for earth-abundant metals, and lead to a better understanding of the underpinning reaction mechanisms. In principle, any efficient alcohol dehydrogenation and/or hydrogen oxidation catalyst would represent a candidate to be tested in OMFC or OMER devices. In summary, the approach of manufacturing fine chemicals from easily accessible bio-alcohols, with concomitant release of energy or hydrogen under atmospheric conditions, represents an important challenge which might be achieved by the introduction of new homogeneous catalysts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


