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Catalytic transformation of alcohols to carboxylic acid salts and H_2 using water as the oxygen atom source

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The oxidation of alcohols to carboxylic acids is an important industrial reaction used in the synthesis of bulk and fine chemicals. Most current processes are performed by making use of either stoichiometric amounts of toxic oxidizing agents or the use of pressurized dioxygen. Here, we describe an alternative dehydrogenative pathway effected by water and base with the concomitant generation of hydrogen gas. A homogeneous ruthenium complex catalyses the transformation of primary alcohols to carboxylic acid salts at low catalyst loadings (0.2 mol%) in basic aqueous solution. A consequence of this finding could be a safer and cleaner process for the synthesis of carboxylic acids and their derivatives at both laboratory and industrial scales.

Selective catalytic oxidation of alcohols is an important process for the synthesis of intermediates and chemicals of industrial interest[1–9]. Traditionally, chlorinated solvents and stoichiometric oxidants are often used to accomplish this transformation[1]. However, recent reports present catalytic systems that operate with water as the solvent and use molecular oxygen as an oxidant. The role of O_2 during oxidation in water is not always straightforward, with a recent computational report suggesting that the oxygen incorporated into the substrate originates from water[7]. Within these examples, direct catalytic oxidation of primary alcohols to carboxylic acids or their salts is rare[7,8]. Acids are still produced from primary alcohols in one step by the use of toxic strong oxidants such as iodate or chlorite with catalytic ruthenium and chromium oxides, resulting in copious waste[10]. Even recent literature examples of primary alcohol oxidation to acids involve expensive and non-atom-economic stoichiometric reagents[11]. According to Fernandez and Tojo[10], 40% of all oxidations to carboxylic acids are carried out by a two-step procedure via the aldehyde, leading them to conclude that 'the transformation of primary alcohols to carboxylic acids is [undoubtedly not a mature technology]'.

Recently, Grützmacher and co-workers reported a homogeneous rhodium-catalysed oxidation of alcohol to an acid salt[12–14] that occurs under mild conditions at high pH and is driven by a sacrificial hydrogen acceptor ketone as an oxidant[12]. A variant of the reaction includes O_2 oxidation with dimethylsulphoxide (DMSO) acting as a sacrificial oxygen acceptor[13]. Oxidation accomplished with O_2 might be problematic at the higher pressures that are usually used on large scales in order to increase the effective concentration of the oxidant. Concurrently, the use of sacrificial substrates such as olefins and DMSO limits the latest systems. A potentially attractive approach towards the oxidation of alcohols to acid salts is to consider water as the oxygen donor with concomitant emission of dihydrogen gas. This approach would limit the possible intermediacy of radicals, could be accomplished under an inert atmosphere, and may serve as a clean source of hydrogen. A marginally catalytic heterogeneous copper system for conversion of amino alcohols to acids in water under nitrogen pressure at 160 °C (maximum of six turnovers) has been reported in the patent literature[15]. Reaction of primary alcohols with NaOH to form carboxylic acid salts at a very high temperature (320 °C) in a high-pressure reactor has also been reported[16].

Earlier, our group reported a number of ruthenium complexes that catalyse the dehydrogenative homocoupling of alcohols to form esters, and the dehydrogenative coupling of alcohols with amines to give amides (Fig. 1)[17–22]. Hydrogen gas is produced as the only by-product of this reaction. The suggested mechanism involves metal–ligand cooperation in both substrate O–H bond activation and dihydrogen generation[23–25]. Complex **1** was also used in a water-splitting study, proving that both O_2 and H_2 can be generated at a single metal centre, and showing a new mode of O–O bond formation[26].

We were interested in seeing whether water could play the role of both an oxygen donor and reaction medium in a catalytic coupling

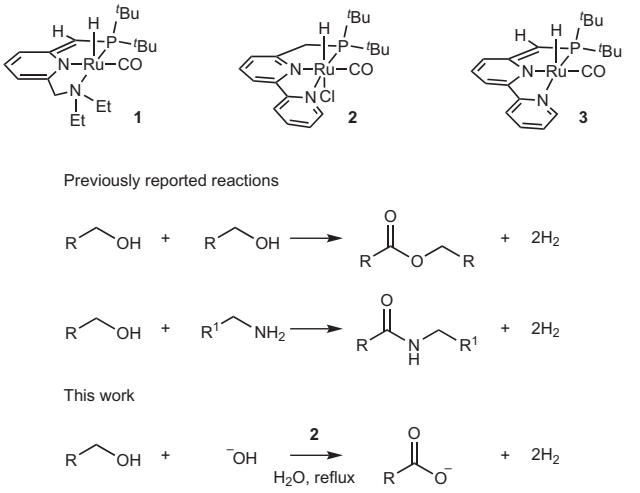

Figure 1 | Complexes utilized in dehydrogenation reactions with liberation of dihydrogen.

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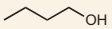
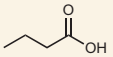
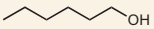
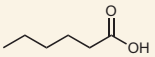
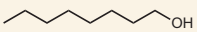
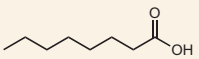
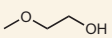
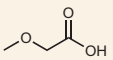
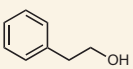
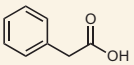
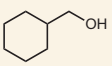
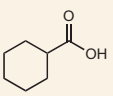
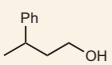
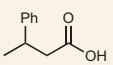
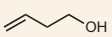
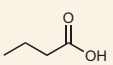
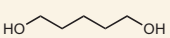
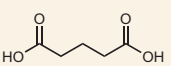
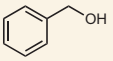
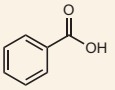
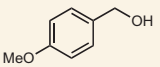
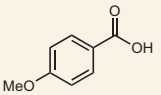
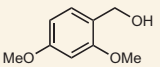
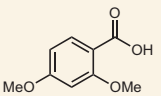
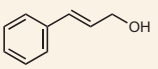
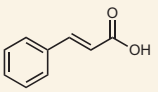
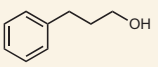
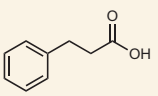
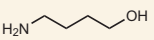
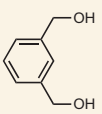
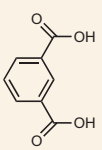
Table 1 | Transformation of alcohols to acids and dihydrogen using water as oxygen source.

Entry	Alcohol	Product	Yield (%)*
1	 **4a**	 **5a**	84
2	 **4b**	 **5b**	88
3	 **4c**	 **5c**	78
4	 **4d**	 **5d**	73
5	 **4e**	 **5e**	78
6	 **4f**	 **5f**	80
7	 **4g**	 **5g**	74
8	 **4h**	 **5a**	63
9	 **4i**	 **5i**	61 (+14% lactone)
10	 **4j**	 **5j**	91
11	 **4k**	 **5k**	89
12	 **4l**	 **5l**	83
13	 **4m**	 **5m**	68 (% conversion to three products) **5m**:**6**:**7** = 5:7:2
		 **6**	
		 **7**	
14	 **4n**	**8**	85 (by NMR)
15	 **4o**	 **5o**	Quantitative

Entries 1 and 3–12. 0.02 mmol **2**, 500 equiv. alcohol, 550 equiv. NaOH, 2 ml water, 18 h reflux under argon. Entries 2, and 13–15: 1 mg **2**, 500 equiv. substrate, 550 equiv. NaOH, 2 ml water, 18 h reflux under argon.
*Carboxylic acids were obtained by acid treatment of the salts.

between alcohols and water under mild reaction conditions and in the absence of any other oxidant. Gratifyingly, we found that coupling of various alcohols and water at basic pH, catalysed by the bipyridine-based ruthenium complex **2**, gave high turnovers and high yields of the desired salts of carboxylic acids and resulted in hydrogen gas evolution (Fig. 1).

Our system shows high turnovers and selectivity for both aromatic and aliphatic alcohols. Sheldon's important system for the palladium-catalysed aerobic oxidation of primary alcohols[8] displays retardation of the reaction rate as hexanoic acid salt is formed, but the catalytic reaction reported here does not suffer from this drawback. The oxygen atom incorporated into the final product originates from the water solvent. The intermediacy of esters was ruled out in the reaction. To the best of our knowledge, this is the first reported example of homogeneously catalysed transformation of alcohols to carboxylic acids using no oxidant or hydrogen acceptor, with liberation of hydrogen gas.

Results and discussion

Catalytic experiments. A typical catalytic reaction was carried out in a vigorously refluxing mixture of water (2 ml), alcohol (10 mmol) and complex **2** (BIPY-PNN)Ru(H)(Cl)(CO)[19] at a loading of 0.2 mol% under an atmosphere of argon gas open to a bubbler. A slight excess of NaOH (11 mmol) was used to deprotonate complex **2** to form the actual catalyst **3**, and to convert the formed acids to their carboxylic salts. After 18 h of reaction time, the corresponding acid salts were obtained in good yields and converted to carboxylic acids by acid treatment.

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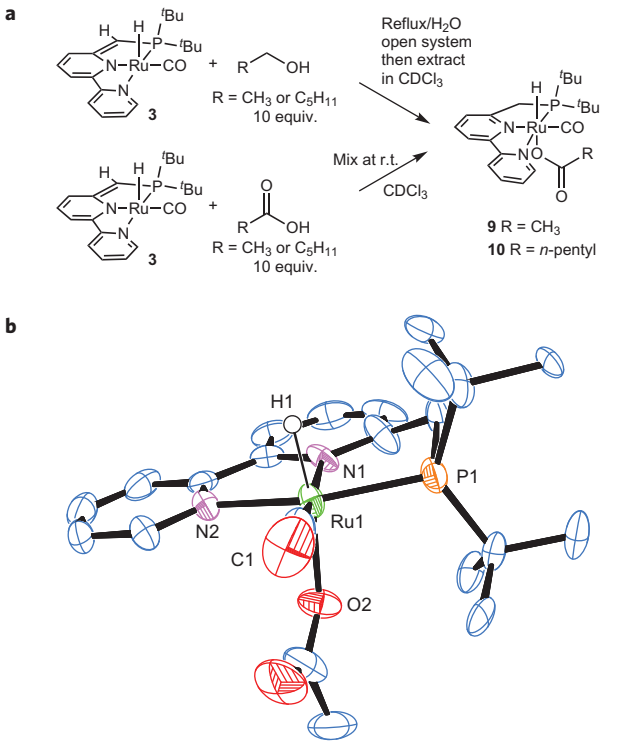

Figure 2 | Formation of a carboxylic acid-addition complex. a, Treatment of ruthenium complex **3** with aqueous alcohol followed by reflux or treatment with carboxylic acid at room temperature both lead to formation of carboxylic acid-addition complexes **9** and **10**. **b**, X-ray structure of **9** (50% probability level, CCDC 905640). Hydrogen atoms (except Ru-H) are omitted for clarity. Selected bond lengths (Å): Ru1-P1, 2.2719(13); Ru1-C1, 1.828(5); Ru1-N1, 2.092(4); Ru1-N2, 2.117(4); Ru1-O2, 2.200(3); Ru1-H1, 1.55(5). Selected angles (deg): C1-Ru1-N1, 173.8(2); N1-Ru1-N2, 76.82(14); N2-Ru1-P1, 160.33(11).

Table 1 shows the isolated yields of the carboxylic acid products obtained after acid treatment of the carboxylic acid salts. The scope of the water-mediated alcohol dehydrogenation reaction allowed for the transformation of aliphatic, non-activated alcohols in isolated yields close to those obtained for activated benzylic substrates. The benzylic position was also not compromised when the alcohol functionality was found on the β carbon (entries 5 and 7), arguing against a radical or rearrangement mechanism. Diol (entry 9) resulted in lactone by-products, but the major product was still the dicarboxylic acid. A diol that cannot undergo lactonization was found to give dicarboxylic acid exclusively (entry 15). Carbon–carbon double bonds were not preserved during catalysis (entries 8 and 13), suggesting that **3** is, in this case undesirably, a competent hydrogenation catalyst in aqueous solution able to utilize the H_2 evolved. Interestingly, aldol products were absent from the reaction mixture despite the high pH, suggesting that the aldehydes that formed were short-lived intermediate species and were present in small amounts. However, an alternative explanation could be that the formed aldehyde is still bound to the metal centre when OH^- attack on the carbonyl carbon occurs (see mechanistic discussion below; Fig. 3). Regardless, the only species detected in the oxidations of most of the substrates in Table 1 were the product acid and unreacted starting material.

Labelling study and experiments without base. We found the presence of dioxygen to be detrimental to the catalyst (resulting in decomposition and thus lower conversions), and labelling experiments unambiguously show that the incorporated oxygen atom originates from water and not from adventitious dioxygen. Thus, water enriched with $^{18}OH_2$ (0.4 ml) mixed with 9.2 mg (0.23 mmol) of $Na^{16}OH$ and 19.1 μl (0.21 mmol) of 1-butanol gave, after stirring, a mixture that was ~90% ^{18}O-labelled. Subsequent catalysis by 5 mol% of **2** utilizing this mixture gave butyric acid, which was shown by electro-spray ionization/mass spectrometry (ESI/MS) to be ~90% ^{18}O-labelled at both positions. An experiment in which 2 ml of water was added to the dearomatized catalyst **3** under catalytic conditions but without any base, and with 10 equiv. of either 1-hexanol or ethanol, gave a new complex. The ^1H NMR spectrum had a number of minor impurities, but it revealed that most ethanol/hexanol remained unreacted and that exactly the same major complex was obtained following the addition of acetic acid or hexanoic acid (depending on the substrate tested) to **3** in $CDCl_3$ (Fig. 2a). A crystal structure of one of the products, complex **9**, was also obtained (Fig. 2b).

In all non-base experiments, no trace of ester was observed, with the remainder of the organic species being unreacted alcohol. However, small amounts of free acid were observed. The same result was obtained when using the Lewis base tributylamine instead of NaOH. A control experiment also confirmed that hydrolysis of the ester hexyl hexanoate cannot occur under base-free catalytic conditions in the presence of catalyst **3**. These stoichiometric experiments discount the intermediacy of the ester in acid synthesis and highlight an important role of the base, which scavenges the formed acid and allows the catalyst to reform.

In line with previous reports[17–21] and the current results, we suggest the mechanism presented in Fig. 3 for the transformation of primary alcohol to carboxylic acid salt.

Discussion of the proposed mechanism. Dearomatized complex **3** is formed *in situ* by deprotonation of **2** in basic solvent. The first step probably involves the reversible addition of water, as it has a greater immediate concentration, to give complex **11**, which was separately prepared by the addition of water to **3** and spectroscopically

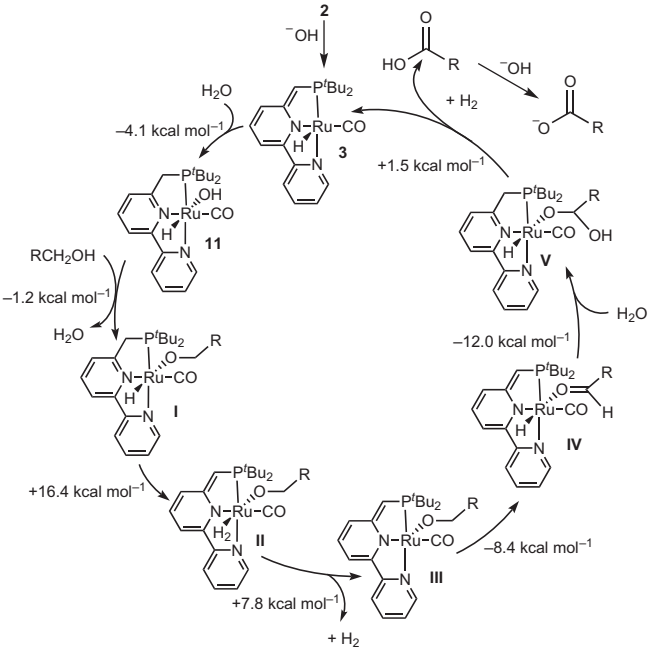

Figure 3 | Proposed mechanism for formation of carboxylate from alcohol catalysed by ruthenium complex 3. DFT calculations were performed to calculate the enthalpy change (ΔH_{298}) for each transformation for the oxidation of ethanol ($R = CH_3$). The use of basic reaction conditions results in sequestration of the product acid as the carboxylate salt, and allows catalyst turnover.

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characterized (see Supplementary Information). Alcohol addition product **I** can be formed either via regeneration of **3** and addition of an ROH moiety (that is, formation of **11** as a side equilibrium), or via substitution of RO^- for HO^-. The next step may involve hydrogen transfer from the ligand arm (intermediate **II**) and subsequent H_2 evolution to form complex **III**. Subsequently, hydride elimination from the coordinated RO^- occurs to form a dearomatized complex with an associated aldehyde complex **IV**. The aldehyde can dissociate and react with another equivalent of complex **3**, or alternatively intermediate **IV** can react with water to give coordinated gem–diolate complex **V**. Loss of H_2 from the gem–diolate complex leads to the carboxylic acid product and regenerates the catalyst; this last step may happen without metal catalysis[13]. Addition of carboxylic acid across the dearomatized complex can be argued to be highly thermodynamically favourable, leading to **9** in preference over **11** and **I**. Thus, one of the most important roles for the stoichiometric base equivalent may be to trap the product as a salt, allowing for regeneration of the active catalyst. The liberation of H_2 during the experiment was qualitatively analysed by gas chromatography. In aqueous basic solutions, complex **11** was seen after heating the alcohol and complex **3** inside a closed NMR tube, suggesting it is the resting state of the complex during catalysis in a large excess of water; production of carboxylic acid salts was not seen inside a closed system.

To interrogate the plausibility of the mechanism outlined in Fig. 3, we calculated, by density functional theory (DFT), the minimized energy structures of all the intermediates presented in the figure. According to calculations performed by the groups of Hall[23] and Yoshizawa[24] on our original water-splitting system[26], one of the most endergonic steps of the process is the transfer of a proton from the methylene arm of the ligand to the hydride located on the metal centre. According to the reports of Yoshizawa and Hall, where the barrier for H_2 release is suggested to be exaggerated, this is also the rate-determining step of the water-splitting reaction. A high barrier is also suggested from previous computational studies carried out in our group[25,26]. As well as calculating the enthalpies of all the proposed intermediates of the system, which show that the proposed catalytic cycle is plausible, we looked at the step of hydrogen transfer in particular, which may very well be the rate-determining step for the catalytic cycle. The results and the change in enthalpies with respect to **3** are presented in Fig. 3. The transfer of hydrogen from the methylene arm to the metal centre has a barrier of $\sim$28.3 kcal mol^{-1}. From the Eyring equation, the expected highest barrier value to account for the turn over numbers (TONs) observed would have an upper limit of $\sim$26 kcal mol^{-1}, which compares well with the calculated value (see DFT section of the Supplementary Information for further discussion).

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Author contributions

E.B. made the initial discovery, carried out catalytic experiments and wrote the manuscript. E.K carried out catalytic experiments, stoichiometric experiments, DFT calculations, synthesis and crystallization of complex **10**, and wrote the manuscript. G.L. performed the X-ray structural study of complex **10**. D.M. designed and directed the project and wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.M.

Competing financial interests

The authors declare no competing financial interests.

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