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A green and sustainable phosphine-free NHC-ruthenium catalyst for selective oxidation of alcohols to carboxylic acids in water†

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In this work, we present a new catalytic system for the selective dehydrogenative oxidation of primary alcohols to carboxylic acids using a phosphine-free NHC-ruthenium catalyst in water under mild reaction conditions. With this catalytic system, a variety of primary alcohols have been converted to carboxylic acids respectively, in aqueous media, without using any additional oxidant; the only side product in this reaction is molecular hydrogen. This novel synthetic protocol is applied for direct oxidation of biologically active monosaccharides and polymers with primary alcohol groups in the side chain. The use of water as a solvent and oxygen donor as well as the absence of any toxic oxidizing agent make this atom economical reaction interesting from an environmental point of view.

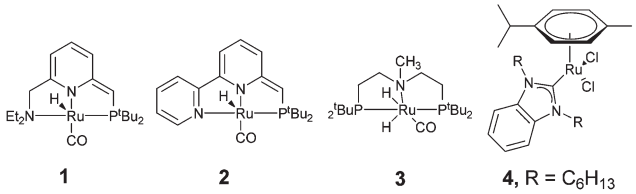
Introduction

Traditionally, many organic fine chemicals and building blocks for polymers are derived from natural resources (fossil feedstock). Due to rapidly increasing environmental concerns, synthetic chemists have paid great attention to the development of clean and green reactions for chemical transformations. Recent developments are focusing on atom-economical, selective and efficient reactions which can be performed under safe and mild conditions with the help of transition metal catalysts in water.

Recent advances in the development of selective fundamental transformation in organic synthesis have led to new processes for the production of biologically active compounds and natural products.[1,2] In particular, the selective oxidation of primary alcohols to carboxylic acids is widely applied as a fundamental transformation process in both basic research and industrial bulk scale production.[3] Traditionally, many oxidizing agents such as stoichiometric Cr^{VI} salts[4] and hypervalent iodine[5] have been used in chlorinated solvents to accomplish this transformation.[6]

However, these reagents show poor atom efficiency and by the use of these oxidants large amounts of heavy-metal by-products are formed causing significant environmental concerns. These catalytic systems are not acceptable. Although several methodologies have been reported for the direct oxidation of primary alcohols to acids, in some cases molecular oxygen acts as an oxidizing agent generating water as a by-product.[7,8] Recently Grützmacher and co-workers presented a rhodium based catalyst for homogeneous catalytic transformation of alcohols to acids under mild conditions at high pH in the presence of cyclohexanone as a hydrogen acceptor.[9] Similarly, the Stark group developed an efficient protocol for direct oxidation of alcohols to carboxylic acids at room temperature in the presence of tetra-*n*-propylammonium perruthenate (TPAP) using *N*-methylmorpholine *N*-oxide (NMO) as a key precursor for stabilizing the aldehyde hydrate intermediate.[10]

In 2005, the Milstein group reported a novel pincer type phosphine based PNN ruthenium catalyst **1**, for the direct synthesis of esters from primary alcohols and of amides from primary alcohols and amines through catalytic dehydrogenation, in the absence of any acid and basic activators (Scheme 1).[11,12]



Scheme 1 NNP and NHC ruthenium complexes.

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†Electronic supplementary information (ESI) available: Experimental procedures, structural proof, and spectral data for all new compounds. See DOI: 10.1039/c5dt01358e

Recently a bipyridyl-based pincer ruthenium hydride complex **2**, was employed for the direct dehydrogenation of alcohols to carboxylic acid salts in an alkaline aqueous medium, where water acts as the oxygen donor and molecular hydrogen being released as the only by-product.[13] Furthermore, the Prechtl group developed a phosphine based pincer type PNP ruthenium complex **3** for catalytic dehydrogenation of primary alcohols to the corresponding carboxylic acids in aqueous medium.[14] Usually, these electron rich phosphine based pincer ruthenium complexes are highly sensitive towards air and difficult to handle in air. To overcome this problem, replacement of the phosphine ligands with N-heterocyclic carbenes (NHCs) was studied.[15] The NHC ligands are strong σ-donors and weak π-acceptors compared to the phosphine ligands which increase the electron density at the metal center, as a result the catalytic activity will increase.[16,17] Moreover, the stable carbon–metal bond shows a unique stability against oxygen, moisture and temperature.[18] Recently, we developed a benzimidazolylidene based NHC ruthenium complex **4**, for the dehydrogenative coupling of primary alcohols to esters and of primary alcohols in the presence of primary amines to the corresponding amides in the absence of any additive and at low catalyst loading.[19] The only by-product during the reaction is molecular hydrogen. The high efficiency of catalyst **4** in the presence of a phosphine ligand was applied for the direct synthesis of polyesters from diols and polyamides from diols and diamines *via* catalytic dehydrogenation.[20] Inspired by the high stability of the NHC complex **4** in water and by the recent developments for the selective oxidation of primary alcohols to carboxylic acids in the presence of water, herein, we report for the first time an efficient simple protocol for direct synthesis of carboxylic acids from primary alcohols in the presence of water using a phosphine free catalyst. The new catalytic system offers a highly atom-economical and environmentally friendly procedure that avoids using additional oxidizing agents, activators and other additives. The only by-product in this conversion is molecular hydrogen. Our catalytic system exhibits high selectivity towards aliphatic and aromatic alcohols irrespective of additional functional groups. Because of the environmental concerns, this novel catalytic system is highly attractive for industrial scale synthesis of chemicals, especially for the synthesis of active pharmaceutical intermediates and natural products.

Experimental section

For experimental details see the ESI.†

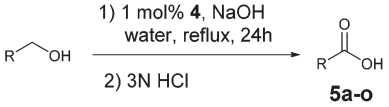
Results and discussion

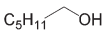
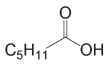
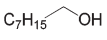
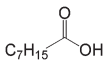
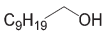
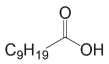
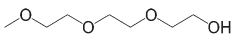
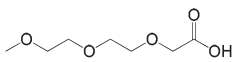
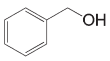
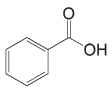
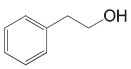
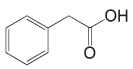
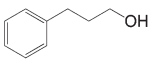
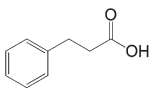
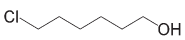
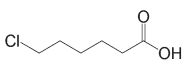
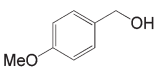
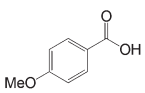
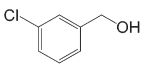
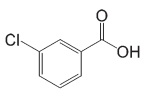
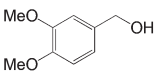
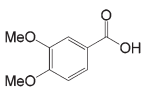
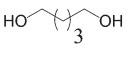
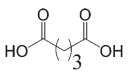
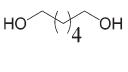
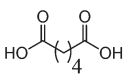
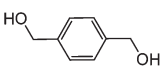
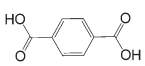
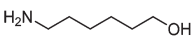
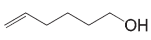
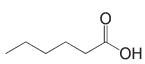
For the initial studies, hexan-1-ol was selected as a test substrate and the reaction was performed in refluxing water under aerobic conditions using catalyst **4**. A model reaction was carried out using 2 mol% loading of catalyst **4**, hexanol (1 mmol) and slight excess of NaOH (1.5 mmol) in refluxing water for 18 h. The dehydrogenation of hexan-1-ol led to sodium hexanoate in 98% yield, hydrogen gas being the only side product. The carboxylic acid salts are further converted to carboxylic acids **5a** by treatment with hydrochloric acid. Under the same reaction conditions, the activity of the ruthenium catalyst **4** was closely studied by the time dependence conversion. It was observed that after 2 h a conversion of 32% was achieved and total conversion after 16 h (ESI chapter 1.5†). An attempt to decrease the catalyst loading to 1 mol%, led to the corresponding carboxylic acid **5a** in 92% yield within 24 h. Using these reaction conditions, our attention shifted to the investigation of electronic influences and steric effects of the substrates on the reaction course. A variety of aliphatic, aromatic and non-activated alcohols were studied (Table 1). Shorter chain aliphatic alcohols gave good yields similar to those of hexan-1-ol (Table 1, entry 1), whereas the yields with longer chain aliphatic alcohols were slightly lower **5b–c** (Table 1, entries 2 and 3). This is probably due to the lack of solubility of these less polar long-chain aliphatic alcohols in water. In contrast, a high conversion was observed in the case of water soluble triethylene glycol monomethyl ether **5d** (Table 1, entry 4). The reaction with aromatic alcohols gave the corresponding carboxylic acids in high yields **5e–g** (Table 1, entries 5–7). Alcohols with methoxy, chloro-substituents were tolerant and converted to the corresponding acids in good yields **5h–k** (Table 1, entries 8–11). However, decreasing yields were observed with diols (Table 1, entries 12–14); lactones were found as side products for alkylidene diols (Table 1, entries 12 and 13). In particular, starting with 6-aminohexan-1-ol the seven membered cyclic lactam **5o** was the major product (Table 1, entry 15). Hex-5-en-1-ol, on the other hand, gave exclusively the hexanoic acid in which the C,C-double bond was hydrogenated by *in situ* formed hydrogen (Table 1, entry 16). Experimental details for these reactions are given in the ESI chapter 1.4.†

To explore the limitations and functional group tolerance of the present catalytic system, we further investigated the dehydrogenation of biologically active alcohols. The reaction of 1,2:3,4-di-*O*-isopropylidene α-D-galactopyranose was carried out using 2 mol% loading of catalyst **4** under reflux in water for 24 h. The free primary hydroxyl group in the galactoside-pyranose was converted to the corresponding uronic acid **6** in 22% yield (Scheme 2). Under similar conditions, methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside was transformed into carboxylic acid **7** in 28% yield (Scheme 2). ^{1}H and ^{13}C NMR spectra of acids **6** and **7** are shown in the ESI.†

The efficiency of the catalytic system was further tested for the conversion of hydroxy functional polymers. Polyglycidol **8** and copolymers with glycidol repeating units offer a broad range of potential applications due to their high functionality, biocompatibility and solubility in aqueous media.[21] We were interested in the catalytic transformation of the hydroxyl groups to carboxylic acids within polyglycidols, which could lead to novel functionalized pH responsive polyethers. The introduction of these kinds of novel functional polymers and

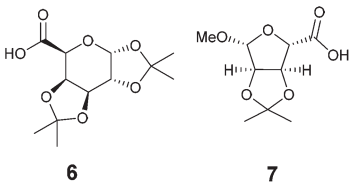
Table 1 Dehydrogenation of primary alcohols to carboxylic acids[a]



Entry	Alcohol	Product		Yield[b]
1			**5a**	92
2			**5b**	76
3			**5c**	52
4			**5d**	88
5			**5e**	91
6			**5f**	90
7			**5g**	87
8			**5h**	81
9			**5i**	83
10			**5j**	79
11			**5k**	84
12			**5l**	63
13			**5m**	59
14			**5n**	45[c]
15			**5o**	62
16			**5a**	73

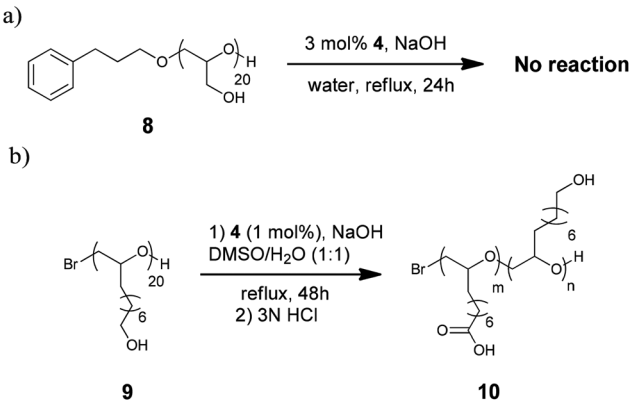
[a] Reaction conditions: 1 mmol of alcohol, 1 mol% catalyst **4**, 1.5 mmol of NaOH, water (2 mL), reflux, 24 h. [b] Isolated yield. [c] 20% DMSO was added.

their derivatives will open a new area of interest and also show significant effects on biomedical applications. Therefore, we applied our standard reaction conditions to polyglycidol **8** by using 3 mol% loading of catalyst **4** and subjected this substrate to dehydrogenation for 24 h (Scheme 3a). No significant conversion was observed.



6 7

Scheme 2 Synthesis of biologically active monosaccharides.



Scheme 3 (a) Functional transformation of polyglycidol **8**. (b) Synthesis of biologically active functional polymers. (For Experimental details see ESI chapter 1.7†).

To overcome this problem, we synthesized a novel functional polyether with hydroxy octyl side chains **9** (Scheme 3b). In the polyether **9** the free hydroxyl groups are far away from the polymer backbone and the possibility of formation of intramolecular H-bonding is greatly diminished. The polymer **9** was synthesized by ring opening polymerization of the epoxy monomer (see the ESI chapter 1.6†) by using tetraalkylammonium salt as the initiator in the presence of triisobutylaluminum (i-Bu_3Al) as the activator.[22] The obtained polymer was further treated with aqueous hydrochloric acid, which leads to polymer **9** in high yield (ESI chapter 1.6†). The hydroxy functional polymer **9** was subjected to catalytic dehydrogenation by using our standard reaction conditions. By applying 3 mol% loading of catalyst **4** under refluxing conditions in water for 48 h, the primary hydroxyl groups are partially converted to carboxylic acid groups. Due to the limited solubility of the hydroxy functional polymer **9** in water only 25% of the hydroxyl groups are converted to carboxylic acids yielding polymer **10** with hydroxyl and carboxylic acid groups. We speculated that the reaction does not occur due to the formation of strong intramolecular H-bonds between the hydroxyl groups and ether oxygen atoms of the main chain. To overcome this problem, we introduced a co-solvent (DMSO) into the reaction medium (ESI chapter 1.7†). Due to the polar effect, the hydroxy functional polymer **9** is soluble in the reaction medium, thus increasing the functional transformation (70% conversion of OH groups) of the hydroxyl groups leading to polyether **10** with hydroxyl and carboxylic acid side groups after acidification with hydrochloric acid (Scheme 3b).

Based on these results and previous studies on catalytic dehydrogenation of primary alcohols by Milstein[13] and Prechtl[14] groups, we propose the reaction mechanism[23,24] presented in ESI chapter 2.2.†

Furthermore, to prove that molecular hydrogen is formed during the reaction we performed an experiment in which the gas phase of two reaction vessels were connected by a cannula. In the first Schlenk tube the catalytic dehydrogenation was performed in the second an olefin and catalyst **4** were dissolved in toluene. We could show that the olefin 1-(chloromethyl)-4-vinylbenzene is converted to 1-(chloromethyl)-4-ethylbenzene (ESI chapter 1.9†).

In order to prove that the oxygen source for the oxidation of primary alcohols to acids is water and not molecular oxygen, experiments with ^{18}O-labeled water were performed. Dehydrogenation of 3-phenylpropanol with 5 mol% of catalyst **4** using $^{18}OH_2$ and $Na^{16}OH$ as bases yields the ^{18}O labelled sodium salt of 3-phenylpropionic acid. In the IR spectrum of the non-labeled sodium salt of 3-phenylpropionic acid asymmetric (ν_{as}) and symmetric (ν_s) carboxylate stretching peaks were detected at 1556.4 and 1420.2 cm^{-1}, while for the ^{18}O labelled sodium salt the corresponding peaks were found at 1537.36 and 1403.9 cm^{-1}, respectively. In the ^{13}C-NMR spectrum, the C═O signal of the unlabeled sodium salt of 3-phenylpropionic acid appeared at δ = 182.7 ppm, while that of the ^{18}O labeled sodium salt showed a signal shifted up field with 54 ppb at δ = 182.6 ppm. Similarly, the electro-spray ionization/mass spectrum (ESI/MS) of the sample prepared in ^{18}O labeled water reveals a major peak at m/z = 199.05 and minor peaks at 197.04 and 195.04 while the sample prepared in ^{16}O labeled water showed only the peak at m/z = 195.04 (ESI chapter 2.3†). Based on the results obtained by NMR, IR spectroscopy and by ESI/MS we conclude that the oxygen incorporated into the carboxylic acids originate from water and not from the molecular oxygen.

To exclude the generation of ruthenium nanoparticles during the catalytic cycle a mercury[17d,25] poisoning test was performed by using 3 mol% loading of catalyst **4**, 1-hexanol as the substrate, NaOH in deuterated water, and mercury (500 equivalents with respect to the ruthenium catalyst). The dehydrogenation of 1-hexanol in the presence of mercury resulted in 56% yield in 18 h. This indicates that the conversion follows the catalytic route and no ruthenium nanoparticles are formed that act as active species in the reaction medium (see ESI chapter 1.8†).

Conclusions

In summary, we have developed a green and efficient novel methodology for the selective oxidation of primary alcohols to the corresponding carboxylic acids in water *via* catalytic dehydrogenation using a phosphine free NHC-ruthenium catalyst. This novel efficient protocol allows a simple and

straightforward synthesis of carboxylic acids irrespective of the electronic nature of the functional groups. It does not generate any toxic heavy metal ions or malodorous by-products; this fact is important with respect to increasing environmental concerns. The only by-product formed during the reaction is molecular hydrogen. Furthermore, the remarkable feature of this new protocol is applied for the synthesis of biologically active monosaccharides. In addition, the present catalytic system shows a significant effect towards the synthesis of biologically active functional polymers that consist of carboxylic acid and primary alcohol functional groups.

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