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Recent developments in the aerobic oxidation of alcohols

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1. Introduction

The oxidation of alcohols to their corresponding aldehydes and ketones is of significant importance in organic chemistry, both for fundamental research and industrial manufacturing.[1–3] The world-wide annual production of carbonyl compounds is over 10^7 tonnes and many of these compounds are produced from the oxidation of alcohols.[4]

The oxidation of alcohols is traditionally carried out with stoichiometric amounts of oxidants such as chromium reagents,[5–9] permanganates,[10,11] ruthenium (VIII) oxide,[12,13] TPAP/NMO (tetra-*N*-propylammonium perruthenate/*N*-methyl-morpholine-*N*-oxide),[14,15] activated dimethyl sulfoxide (DMSO) reagents,[16] or Dess–Martin periodinane reagent.[17] Unfortunately, these methods often require one or more equivalents of these relatively expensive oxidizing agents. Some of these processes also generate equal amounts of metal waste. Furthermore, oxidation reactions are usually carried out in halogenated organic solvents, typically chlorinated hydrocarbons, which are environmentally undesirable. Therefore, developing green, selective and efficient aerobic catalysts for the oxidation of alcohols, that can use air or pure dioxygen (O_2) as oxidants, is of paramount importance for both economic and environmental reasons (Scheme 1). These green processes produce water as the only by-product. Due to the obvious advantages of using air or dioxygen as the ultimate and stoichiometric oxidant, considerable effort has been invested in the last few years to develop novel catalysts for the aerobic oxidation of alcohols to their corresponding aldehydes and ketones. This topic has been discussed in various books and reviews, but with restrictions to specific catalytic systems.[18] The aim of this report is to give an

Keywords: Alcohol; Aerobic oxidation; Homogeneous catalysis; Heterogeneous catalysis.

Abbreviations: ARP-Pd, palladium nanoparticles dispersed on an amphiphilic resin; convn., conversion; DABCO, 1,4-diazabicyclo-[2,2,2]octane; DMF, dimethylformamide; dba, dibenzylideneacetone; DMSO, dimethyl sulfoxide; FAU, faujasite zeolite; GO, galactose oxidase; HAP, hydroxyapatite; MTBE, methyl *tert*-butyl ether; MS3Å, 3 Å molecular sieves; nbd, norbornyldiene; NaX, faujasite zeolite-X in sodium form; NMO, *N*-methyl-morpholine-*N*-oxide; Phen, 1,10-phenanthroline; PhenS*, bathophenanthroline disulfonate; PIPO, polyamine immobilized piperidinyl oxyl; PSP, polymer supported perruthenate; sel., selectivity; TEMPO, 2,2′,6,6′-tetramethylpiperidine-*N*-oxyl; TMAO, trimethylamine-*N*-oxide; TOF, turn over frequency; TON, turn over number; TPAP, tetra-propylammonium perruthenate; XPS, X-ray photoelectron spectroscopy.

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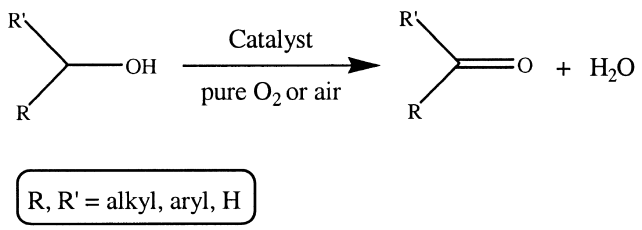


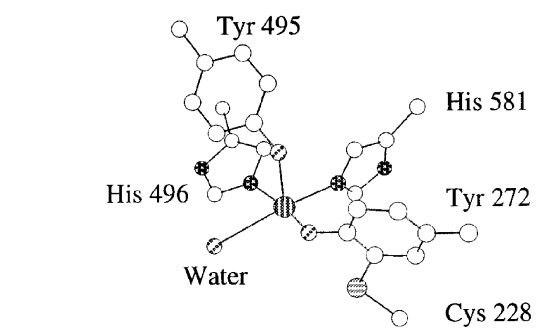
Scheme 1. Catalytic aerobic oxidation of alcohols.

overview of the recent developments in this rapidly growing area, covering both homogeneous and heterogeneous catalytic systems. The mechanistic features of some catalytic systems will be briefly discussed herein.

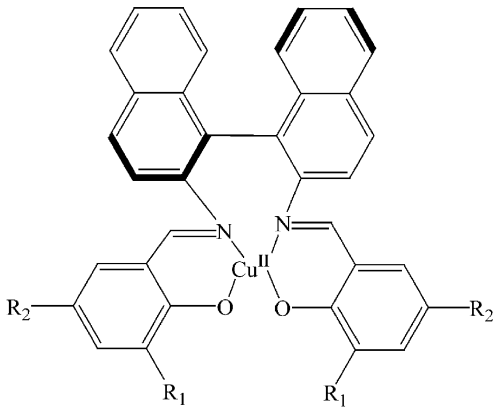
2. Homogeneous catalysis

There are several advantages to using homogeneous catalysis, including high activity and selectivity (especially enantioselectivity) since the reactants and catalysts co-exist in the same phase.

Homogeneous catalysts often have structures similar to the active sites of natural enzymes. A typical example in the study of the aerobic oxidation of alcohols is the biomimetic chemistry of the copper(II)-containing metalloprotein galactose oxidase (GO), which selectively catalyzes the aerobic oxidation of primary alcohols to aldehydes with the formation of 1 equiv. of hydrogen peroxide (Eq. 1) under very mild conditions.[19,20] The active centre of GO is a single copper(II) ion coordinated with a tyrosinate anion, a (thioether-modified) tyrosyl radical and two histidine residues, as shown in Scheme 2.[21,22] The mechanism of the oxidation of primary alcohols by GO has been thoroughly studied and defined. Initially, the alcohol coordinates to the Cu(II) ion, and then the O-coordinated alkoxide ligand undergoes H-abstraction from the α-carbon atom of the alkoxide by the coordinated tyrosyl radical. This is considered to be the rate-determining step, leading to the generation of a bound ketyl radical anion and tyrosine. The ketyl radical ligand is then intramolecularly converted to the aldehyde through one-electron oxidation with concomitant formation of a Cu(I) species. Re-oxidation of the latter by dioxygen regenerates the active Cu(II)-tyrosyl form of the enzyme and H_2O_2, and the process is thus stoichiometric in dioxygen.[23] A great number of model compounds containing Cu(II)-phenoxyl, having a structure around the Cu(II) ion similar to that in GO, have been synthesized and characterized by measuring their catalytic properties for the aerobic oxidation of alcohols.[24] Scheme 3 presents a typical model compound. Recently, Stack and co-workers have published a review paper with the title 'Biomimetic modeling of copper oxidase reactivity'.[18c] Therefore, discussion of the synthesis and catalysis of copper(II)-phenoxyl modeling complexes is abbreviated in this report. However, it is necessary to point out that the catalytic activity of the synthesized Cu(II) model complexes is still low and is mostly limited to activated (e.g., benzylic and allylic) primary alcohols.[24] Furthermore, base is required.



Scheme 2. Copper active site of GOase at pH 7.0.[22]



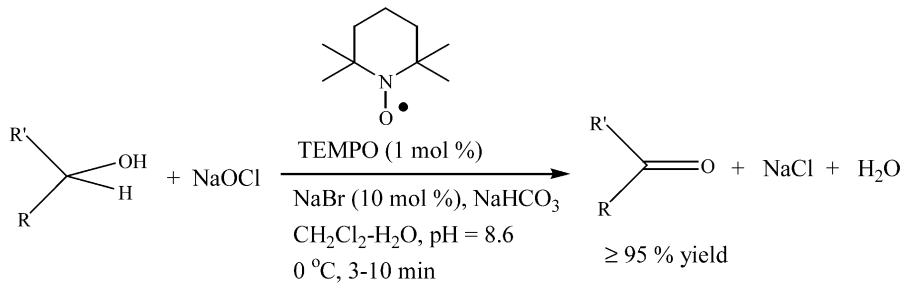
Scheme 3. A typical copper(II)-phenoxyl complex with a structure similar to GO, where R_1=SPh and R_2=*tert*-butyl.[24a]

$$RCH_2OH + O_2 \xrightarrow{[GO]} RCHO + H_2O_2 \quad (1)$$

The mechanistic studies involving the GO enzyme clearly indicate that the dioxygen molecule is actually activated by the Cu(I) species. Therefore, it was anticipated that Cu(I)-containing complexes could be useful as aerobic oxidation catalysts. Markó and co-workers successfully demonstrated that a CuCl/1,10-phenanthroline (Phen) complex is able to catalytically oxidize activated primary alcohols to aldehydes in the presence of appropriate solvents, additives and base (usually K_2CO_3).[25] However, both saturated primary and secondary aliphatic alcohols, for example, unactivated alcohols, proved to be poor substrates. The conversions were only modest even though a larger amount of CuCl/Phen catalyst (20 mol%) was employed.[25]

2.1. M/TEMPO Complexes

Nitroxyl radicals are well-established catalysts for oxidation processes. They are increasingly applied on both industrial and laboratory scales for the oxidation of alcohols.[26,27] Typically, the oxidation reactions are carried out in the presence of 1 mol% of 2,2′,6,6′-tetramethylpiperidine-*N*-oxyl (also known as TEMPO) and a stoichiometric amount of sodium hypochlorite (bleach) as shown in Eq. 2.[28] The oxoammonium cation, which is formed via the oxidation of TEMPO with hypochlorite, is the active oxidant. Oxidation of alcohols gives the corresponding carbonyl compounds and the reduced form of TEMPO (e.g., the hydroxylamine,



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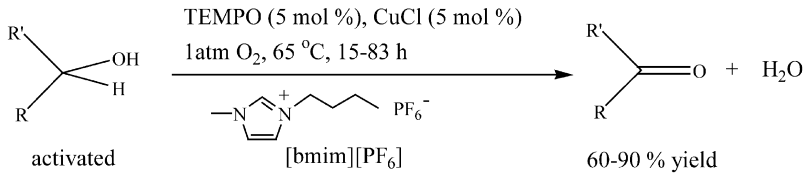


(3)

or TEMPOH). The latter is then re-oxidized by hypochlorite to regenerate the oxoammonium cation. Sodium bromide (10 mol%) is usually exploited as a co-catalyst, as the re-oxidation of TEMPOH is more favorable with hypobromite, and the hypobromite is steadily produced via oxidation of the sodium bromite with hypochlorite.[28]

In 1984, Semmelhack et al. first reported that the CuCl/TEMPO catalytic system can catalyze the aerobic oxidation of activated primary alcohols using dioxygen as a stoichiometric oxidant.[29] A turn over frequency (TOF) of up to 9.6 h^{-1} was reached in the oxidation of *p*-methoxybenzyl alcohol at room temperature. The catalytic properties are significantly enhanced if the reaction is conducted at high temperature with a co-catalyst, in both biphasic and ionic liquid conditions.[30,31] For instance, a CuCl/TEMPO catalytic system aerobically oxidizes both activated primary and secondary alcohols to the corresponding aldehydes and ketones in the ionic liquid [bmim][PF_6], for example, Eq. 3.[31] The product was isolated by a simple extraction with organic solvent, and the ionic liquid can be recycled or re-used. However, the oxidation of unactivated aliphatic and cyclic alcohols is slower and incomplete. No oxidation is observed when the solubility of alcohols in the ionic solvent is poor.[31] Very recently, Sheldon and co-workers reported that [Cu(II)-(2,2′-bipyridine)]/TEMPO systems selectively catalyze the aerobic oxidation of primary alcohols to aldehydes at room temperature with a base as co-catalyst.[32] However, these catalysts are completely inert to secondary alcohols.

Recently, the catalytic properties of TEMPO-based aerobic oxidation catalysts have been found to be significantly enhanced if Cu(I)Cl is replaced by other transition metal compounds. For example, Sheldon and co-workers reported that a $Ru(PPh_3)_3Cl_2$/TEMPO system can smoothly oxidize both activated and unactivated alcohols to the corresponding aldehydes and ketones with a selectivity of over 99% in a reasonable length of time (2.5–7 h), for example, Eq. 4 and entries 1–5 in Table 1.[33] Interestingly, primary alcohols were found to be more active than secondary alcohols in this catalytic system: in a competitive oxidation of 1-octanol and

Table 1. Selected aerobic oxidation results with $Ru(PPh_3)_3Cl_2$/TEMPO and Mn(II)-Co(II)/TEMPO catalytic systems[32,35]

Entry	Substrate	Product	Time (h)	Temperature (°C)	Convn. (%)[a]
1[b]	Benzyl alcohol	Benzaldehyde	2.5	100	>99 (90)
2[c]	2-Octanol	2-Octanone	7	100	98 (90)
3[d]	1-Octanol	Octanal	7	100	85
4[c]	Cyclooctanol	Cyclooctanone	7	100	92
5[c]	2-Adamantanol	2-Adamantanone	6	100	98
6[d]	2-Octanol/1-octanol	2-Octanone/octanal	7	100	10/80
7[e]	Benzyl alcohol	Benzaldehyde	10	20	(98)
8	1-Heptanol	Heptanal	6	40	(97)
9	2-Nonanol	2-Nonanone	5	40	(100)
10	Cyclohexanol	Cyclohexanone	9	20	(96)
11	2-Adamantanol	2-Adamantanone	6	20	(97)

Reaction conditions for entries 1–6 (Ref. 32): 15 mmol of substrate, $Ru(PPh_3)_3Cl_2$/TEMPO mole ratio 1:3, 30 mL PhCl, 10 mL min^{-1} O_2/N_2 (8:92; v/v), p=10 bar, T=100 °C.

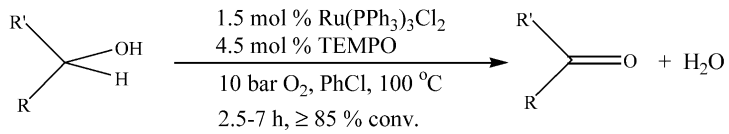
[a] Conversions based on GC results (selectivity >99% in all cases); numbers in parentheses are isolated yields.

[b] Ru(II)=0.075 mmol.

[c] Ru(II)=0.15 mmol.

[d] Ru(II)=0.30 mmol, 1 atm of dioxygen.
Reaction conditions for entries 7–11 (Ref. 35): 12.5 mmol alcohol, 1.25 mmol TEMPO, 0.25 mmol $Mn(NO_3)_2$, 0.25 mmol $Co(NO_3)_2$ in AcOH (12.5 mL) and 1 atm of dioxygen.

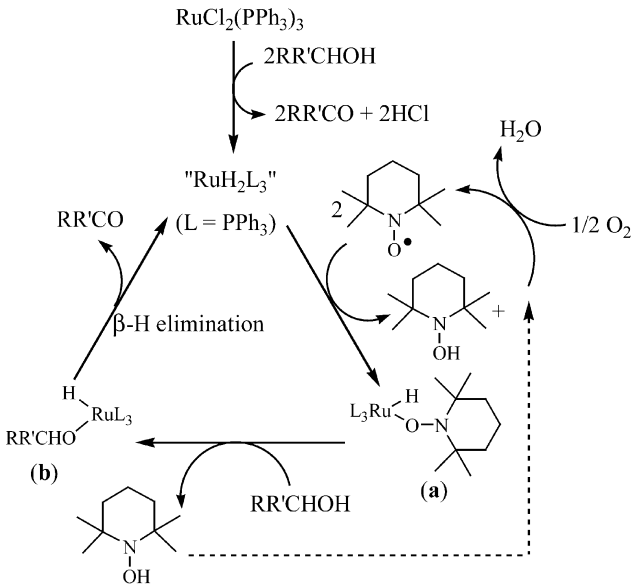
[e] 1 atm of air.



(4)

2-octanol, the conversion for 1-octanol was 80%, while it was only 10% for 2-octanol (entry 6, Table 1). However, these oxidations must be carried out at relatively high pressure (10 bar) and temperature (100 °C), and an intrinsically oxidatively unstable triphenylphosphine ligand is required. Furthermore, alcohols containing additional heteroatoms, that is, S, N and O, are inert due to their coordination to, and poisoning of, the ruthenium ion leading to the deactivation of catalyst.

Mechanistic studies suggest that the formation of ruthenium hydride ($RuH_2(PPh_3)_3$) is the key intermediate for the aerobic oxidation of alcohols with the $Ru(PPh_3)_3Cl_2$/TEMPO catalyst (Scheme 4):[33d] initially, the alcohol substrate is dehydrogenated by the $Ru(PPh_3)_3Cl_2$, giving the corresponding carbonyl compound and a ruthenium hydride. The latter then reacts with 2 equiv. of TEMPO to produce TEMPOH and complex, (a) in Scheme 4, which contains a hydride and a piperidinyloxyl ligand. The latter is displaced by an alcohol to form another TEMPOH molecule and an alkoxy ruthenium hydride, (b) in Scheme 4. The alkoxy ruthenium hydride then undergoes β-hydride elimination, releasing the carbonyl compound and regenerating the ruthenium hydride. TEMPO is regenerated via rapid oxidation of TEMPOH by dioxygen with concomitant formation of water by-product.



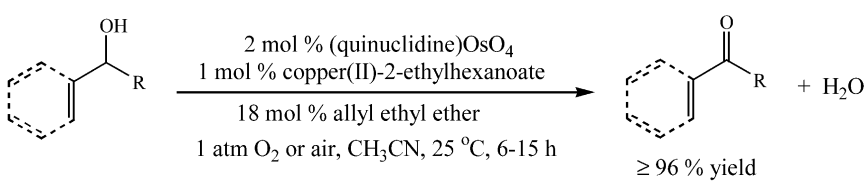
Scheme 4. Suggested mechanism for the $Ru(PPh_3)_3Cl_2$/TEMPO-catalyzed aerobic oxidation of alcohols.[33d]

Hydroquinone can also be used in oxidations of this type, replacing TEMPO. Ishii and co-workers reported that $Ru(PPh_3)_3Cl_2$ is an active catalyst in the presence of hydroquinone and K_2CO_3.[34] The $Ru(PPh_3)_3Cl_2$/hydroquinone/K_2CO_3 system can efficiently convert a variety of alcohols to the corresponding aldehydes and ketones at 60 °C and 1 atm of dioxygen.[34] For instance, the oxidation of 1-decanol proceeds smoothly with catalytic amounts of $Ru(PPh_3)_3Cl_2$ (20 mol%), hydroquinone (20 mol%), and K_2CO_3 (3 mol%) in trifluorotoluene solvent under 1 atm of dioxygen at 60 °C for 20 h. The conversion is 90% with over 99% selectivity for decanal production.

Minisci and co-workers reported that the aerobic oxidation of both activated and unactivated alcohols can be performed under relatively mild conditions, such as in 1 atm of dioxygen or even 1 atm of air at temperatures of 20–40 °C, if copper is replaced by a bimetallic salt, such as Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates.[35] Some of their oxidation results are given in entries 7–11 of Table 1. Benzyl alcohol was oxidized to benzaldehyde with an isolated yield of 98% in 10 h at 20 °C in 1 atm of dioxygen (Table 1, entry 7). A primary aliphatic alcohol, 1-heptanol, was oxidized to heptanal in an isolated yield of 97% in 6 h at 40 °C (Table 1, entry 8). Unactivated secondary alcohols were oxidized to their corresponding ketones (Table 1, entries 9–11). For example, the oxidation of cyclohexanol gave an isolated yield of 96% of cyclohexanone in 9 h at 20 °C (Table 1, entry 10). However, acetic acid had to be used as solvent as non-acidic media, such as acetonitrile, resulted in almost no oxidation. It should be noted that relatively large amounts of somewhat expensive TEMPO (10 mmol%) are necessary for these oxidation reactions.

2.2. OsO_4-Copper catalysts

Other efficient bimetallic systems include OsO_4–Cu(I), OsO_4–Cu(II), Mo(VI)–Cu(II), and Mo(VI)–Fe(II).[36] Osborn and co-workers reported that OsO_4–CuCl is an efficient catalytic system for the aerobic oxidation of primary allylic and benzylic alcohols to the corresponding aldehydes in the presence of pyridine base and molecular sieves.[36a,b] Activation of OsO_4 with quinuclidine and copper(II)-2-ethylhexanoate was found to significantly improve both reactivity and selectivity in the aerobic



(5)

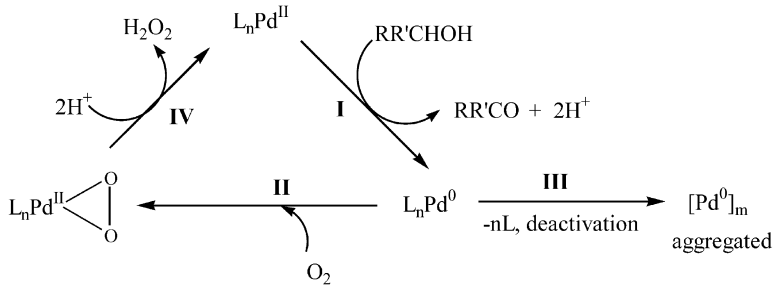
oxidation of alcohols.[36c] Both allylic and benzylic alcohols oxidized completely in acetonitrile solvent within 6–15 h at room temperature (e.g., Eq. 5), and the products were easily isolated. A $K_2[OsO_2(OH)_4]$/1,4-diazabicyclo[2,2,2]octane (DABCO) system has also been investigated for potential application in the aerobic oxidation of alcohols.[37]

2.3. Pd(II) Catalysts

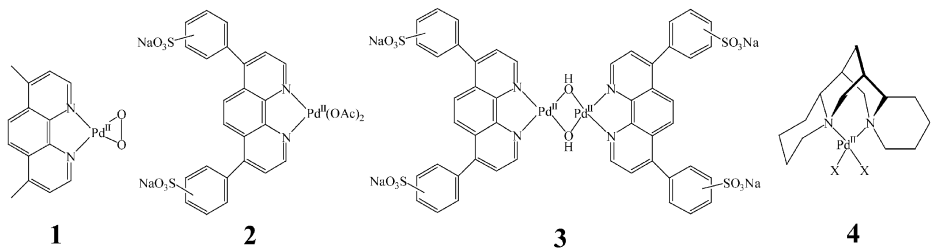
The Wacker process, that is, Pd/Cu-catalyzed aerobic oxidation of ethylene to acetaldehyde (Eq. 6), was developed more than 40 years ago,[38] but the use of palladium as catalyst for the aerobic oxidation of alcohols was first reported by Schwartz in 1977.[39] Since then, considerable research has resulted in the development of more selective and efficient Pd(II)-containing catalytic systems.[33,40–50] For example, a catalytic system of $Pd(OAc)_2$/dimethyl sulfoxide (DMSO) was found to effectively and selectively oxidize allylic and benzylic alcohols to the corresponding aldehydes and ketones.[42] The reaction rates and yields are further improved by adding appropriate bases such as Na_2CO_3. The success of DMSO as the solvent suggested several mechanistic possibilities, including the prospect that DMSO itself participates in the redox process. DMSO is a stoichiometric oxidant in a variety of chemical and biological oxidation reactions, yielding dimethyl sulfide as by-product.[16] However, Stahl and co-workers have recently proposed an oxidation mechanism excluding the involvement of DMSO in the redox process (Scheme 5).[45] The Pd(II)-catalyzed aerobic oxidation of alcohols likely proceeds through a reduction of Pd(II) to Pd(0) by the alcohol. Pd(0) then reacts with dioxygen to produce a palladium peroxo intermediate (step II). The role of DMSO as a solvent corresponds to its ability to coordinate palladium(0), preventing the formation of aggregated palladium metal (step III).[45b] This oxidation mechanism is supported by several facts:[45a,b] successful separation of a structurally characterized peroxopalladium(II) species (e.g., **1** in Scheme 6) in reacting bathocuproine–palladium(0) complex with dioxygen; a first order dependence on dioxygen pressure; a substantial negative entropy of activation, $\Delta S^{\neq} = -180\ \mathrm{J\ K^{-1}\ mol^{-1}}$. The exclusion of DMSO in the redox process is also supported by the success of a $Pd(OAc)_2$/pyridine (Py) catalyst system, in which the Py ligand plays a similar role as DMSO in preventing the Pd(0) aggregation.[45c]

$$H_2C = CH_2 + 1/2O_2 \xrightarrow{\text{Pd/Cu cat.}} CH_3CHO \qquad (6)$$

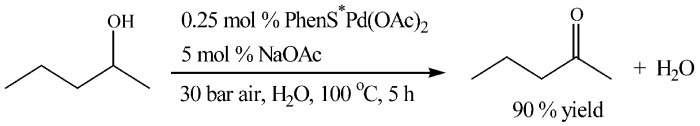
Sheldon et al. have created a novel, active and cleaner/greener catalytic system, in which the aerobic oxidation of alcohols can be carried out in water using a water-soluble bathophenanthroline disulfonate palladium complex ($PhenS^*Pd(OAc)_2$, **2** in Scheme 6 and Eq. 7) as catalyst in the presence of a small amount of sodium acetate at 100 °C under high air pressure.[46] Small secondary aliphatic and cyclic alcohols, with relatively high water solubility, are very active and are easily oxidized to the corresponding ketones using this system. For instance, 2-pentanol was completely converted to 2-pentanone in 5 h with a TOF of 80 h^{-1} (Eq. 7). Surprisingly, benzylic alcohols reacted more slowly than expected, even accounting for their low solubility in water. Lower activity was also found in the oxidation of allylic alcohols, due to the competing coordination of the olefinic double bonds to the palladium. These results are very different from the systems discussed above. For alcohols containing terminal olefinic double bonds, at a distance from the alcohol moieties, Wacker-type reactions strongly dominate. This is in contrast to the catalytic system with DMSO as solvent.[42] Furthermore, due to the use of high temperature (100 °C) and high pressure (30 bar) reaction conditions for the aqueous reactions, the formed aldehydes further oxidize to the corresponding carboxylic acids. As such, radical scavengers, such as TEMPO, are required to prevent the over-oxidation. As with many procedures, alcohols containing other functionalities, for example, N, S and multiple O atoms which are able to coordinate strongly to the palladium, were shown to be inert



Scheme 5. Oxidation mechanism for the aerobic oxidation of alcohols in $Pd(OAc)_2$/DMSO system.[45a,b]



Scheme 6. Some Pd(II) complexes.

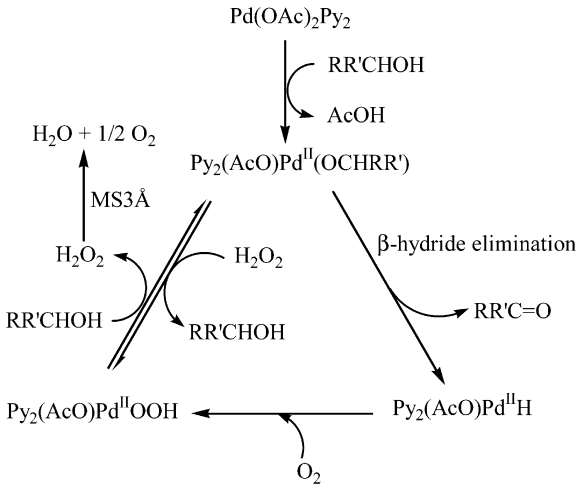


(7)

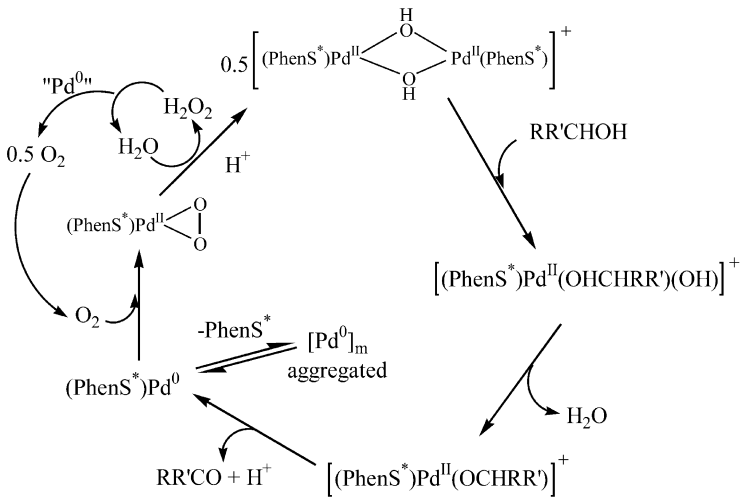
in this PhenS*Pd(OAc)$_2$ catalyst system, and alcohols with low solubilities in water were less efficient. Interestingly, the ability to recycle the catalyst solution has been demonstrated using 2-hexanol as the substrate.[46]

Mechanistic studies suggested the oxidation mechanism shown in Scheme 7,[46] which is similar to that proposed by Stahl for the Pd(OAc)$_2$/DMSO catalytic system.[45] The starting complex is believed to be a dihydroxy-bridged palladium dimer (e.g., **3** in Scheme 6) that is in equilibrium with 2 equiv. of a palladium monomer, [(PhenS*)-Pd(II)OH]$^+$. After alcohol coordination, the bridged-palladium dimer decomposes. The alcohol-coordinated Pd(II) complex undergoes a water elimination, affording a palladium alkoxide, [(PhenS*)Pd(II)OCHRR′]$^+$. The palladium alkoxy intermediate then undergoes β-elimination, the rate-determining step, affording a carbonyl compound, (PhenS*)Pd(0), and a proton. The results of mechanistic studies on the Pd(OAc)$_2$/DMSO and PhenS*Pd(OAc)$_2$/NaOAc/H$_2$O systems (e.g., Schemes 5 and 7) clearly suggest the key factor to developing more efficient and stable Pd(II)-based catalysts for the aerobic oxidation of alcohols, namely, accelerating the re-oxidation rate of palladium(0) with dioxygen and suppressing the aggregation of palladium(0), which leads to deactivation.

The Pd(II)-catalyzed aerobic oxidation of alcohols seems to be very sensitive to the nature of organic ligands and reaction media. Uemura and co-workers have demonstrated that the Pd(OAc)$_2$/pyridine/MS3Å catalytic system is more than 10 times as efficient as the Pd(OAc)$_2$/DMSO catalytic system in the aerobic oxidation of alcohols using toluene as solvent at 80 °C under anhydrous conditions.[43] Using these conditions, a variety of primary and secondary (both activated and unactivated) alcohols may be oxidized to the corresponding aldehydes and ketones with high yields. Interestingly, air can be used instead of dioxygen (with a resulting longer reaction time). The use of other palladium compounds, such as PdCl$_2$, PdCl$_2$(MeCN)$_2$, Pd(OCOCF$_3$)$_2$, Pd(PPh$_3$)$_4$, or Pd(dba)$_2$ (dba=dibenzylideneacetone), was found to be ineffective, and lower yields were observed using other solvents or bases. However, there are some limitations to using the Pd(OAc)$_2$/pyridine/MS3Å system, including lower activity in the oxidation of 1-dimethylamino-2-propanol, 1-methoxy-1-phenyl-2-ethanol or 1-phenyl-1-propynol, etc. and dominant olefin oxidation over alcohol oxidation in the presence of trace amounts of water. This difference in reactivity was attributed to an alternative mechanism as shown in Scheme 8. In contrast to the Pd(OAc)$_2$/DMSO and PhenS*Pd(OAc)$_2$ systems, the valence state of the palladium(II) ion does not change in the catalytic cycle. The reaction starts by binding the alcohol to the Pd(II)-pyridine complex, giving the Pd(II)-alkoxide. The latter then undergoes β-hydride elimination, affording



Scheme 8. Suggested aerobic oxidation mechanism for Pd(OAc)$_2$/-pyridine/MS3Å system.[43]



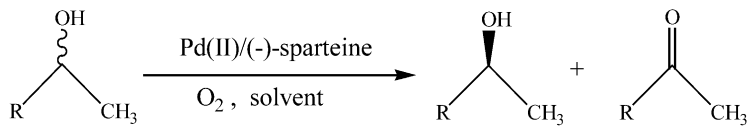
Scheme 7. Reaction cycle proposed for PhenS*Pd(OAc)$_2$-catalyzed alcohol oxidation.[46]

the corresponding Pd(II)-hydride species. This active hydride species reacts with dioxygen, forming Pd(II)-hydroperoxide. The Pd(II)-alkoxide complex is regenerated via ligand exchange of Pd(II)-hydroperoxide with alcohol, releasing H_2O_2 as by-product.[43] The in situ formation of H_2O_2 has been demonstrated: its decomposition into water and dioxygen is promoted by molecular sieves. The removal of H_2O_2 by the use of molecular sieves accelerates the oxidation of alcohols as its competition with the alcohol for binding to the palladium(II) ion is eliminated. The mechanism is also supported by an dioxygen uptake experiment.[43b] However, it is worth pointing out that, in the absence of molecular sieves, the $Pd(OAc)_2$/pyridine-catalyzed aerobic alcohol oxidation can proceed via a different mechanism.[45c]

The successes of the Pd(II)-catalyzed aerobic oxidation of alcohols using bidentate nitrogen ligands inspired research into the oxidative kinetic resolution of alcohols. In early 2001, the successful application of Pd(II) catalysts to the oxidative kinetic resolution of secondary alcohols (Eq. 8) using Pd(II) salts and a natural diamine, that is, (−)-sparteine, was reported by two independent teams led by Sigman[48] and Stoltz.[49] In these reactions, the Pd(II)-sparteine complex (e.g., **4** in Scheme 6) is formed in situ from 5 mol% of either $Pd(OAc)_2$, or a soluble $PdCl_2$ source such as $Pd(MeCN)_2Cl_2$ or $Pd(nbd)Cl_2$ (nbd=norbornyldiene), and 20 mol% of (−)-sparteine. The choice of solvent, counter ion for the Pd(II) ion, and base significantly influences both the reaction rates and the enantioselectivities.

The isolation of enantiomerically enriched alcohols with over 50% total yield can be achieved by the oxidative kinetic resolution as the ketones are recyclable, as demonstrated by Stoltz and Ferreira.[49a] For example, in the oxidative kinetic resolution of (±)-2-naphthylethanol, the first cycle gave a 44% yield of (−)-2-naphthylethanol in 99% ee. After isolation of the enantiomerically enriched alcohol, the ketone was reduced back to the racemic alcohol by treatment with $NaBH_4$ (99% yield). A second oxidative kinetic resolution cycle gave a 24% yield in 99% ee (Eq. 9).

Additionally, Pd(II)/(−)-sparteine-catalyzed oxidative kinetic resolution has been employed in the enantioselective synthesis of two pharmaceuticals, (*S*)-fluoxetine–HCl and (*R*)-tomoxetine–HCl.[50] Furthermore, the $PdCl_2$/(−)-sparteine catalytic system has also been employed in the desymmetrization of *meso* diols. For example, desymmetrization of 1,3-*meso*-diol (Eq. 10) provided the enantiomerically enriched hydroxy-ketone product in 69% yield and 82% ee (59% yield, 93% ee after recrystallization).[48a]



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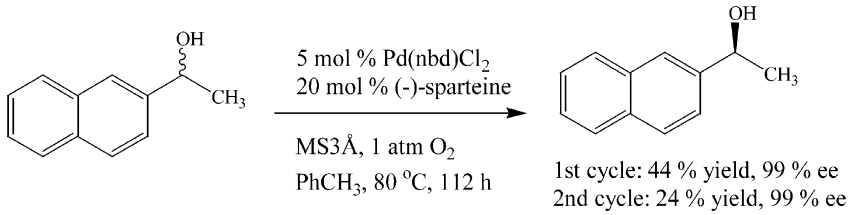

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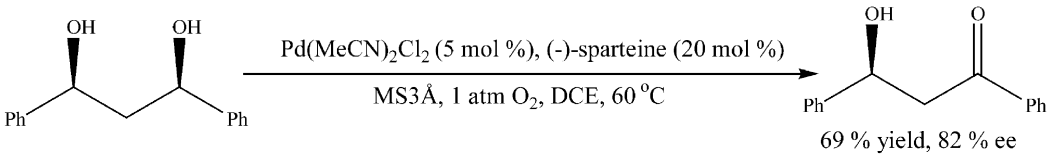

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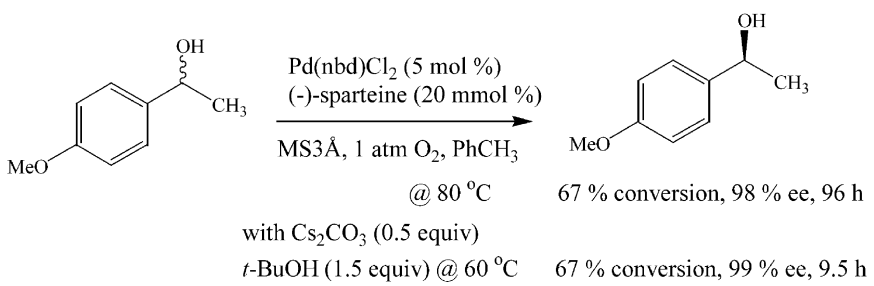


(11)

Very recently, Stoltz and co-workers reported that the addition of Cs_2CO_3/*t*-BuOH can dramatically accelerate the palladium-catalyzed aerobic oxidative kinetic resolution while maintaining enantioselectivity.[49b] A typical example is given in Eq. 11: with similar conversion, the required reaction time for this oxidative kinetic resolution decreases from 96 to 9.5 h by the addition of Cs_2CO_3/*t*-BuOH.

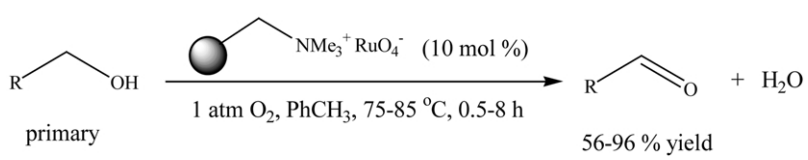
3. Heterogeneous catalysis

Heterogeneous catalysis has several advantages over homogeneous processes, including simple product isolation as well as catalyst separation and recycling.

It has been known for a long time that the aerobic oxidation of alcohols to the corresponding aldehydes and ketones can be performed in aqueous media using platinum, palladium and other noble metals as catalysts under mild conditions (20–80 °C and atmospheric pressure).[51–53] Considerable advances have been made in this area over the last 20 years. These catalytic reactions proceed in an environmentally-friendly solvent (water), replace expensive stoichiometric oxidants[5–17] with dioxygen, and produce water as the only by-product. Such heterogeneous oxidations proceed via an oxidative dehydrogenation mechanism, in which the substrates are adsorbed and dehydrogenated on the metal surfaces. The adsorbed hydrogen atoms are then oxidized to water by oxygen. This field is maturing rapidly with research led by Heyns,[51] Kuster,[52] van Bekkum,[53] Mallat,[54] Gallezot,[55] and Kimura.[56] However, severe deactivation of the catalysts is often found in the noble metal-catalyzed aerobic oxidation processes, causing serious concern and limitations for process development. Several causes of deactivation have been defined: metal oxidation and leaching, blocking of active sites by the strong absorption of side-products, and the aggregation of fine metal-crystals. Several recent reviews, including one in 2000 regarding the aerobic oxidation of alcohols over noble metal catalysts, have already been published,[57–60] therefore, no detailed discussion of this field will be covered in this review. However, it is worth pointing out that supported noble metals have been found to be excellent catalysts for the selective oxidation of alcohols to the corresponding aldehydes and ketones with high yields, using dioxygen as an oxidant in a supercritical CO_2 fluid medium.[61,62] Bimetals and metallic nanoparticles also act as efficient catalysts for the aerobic oxidation of alcohols.[63,64] For example, it was reported that the polystyrene–poly(ethylene glycol) resin-supported nanopalladium (~9 nm) displays high efficiency and selectivity in the aerobic oxidation of a variety of alcohols, and this has been attributed to the huge external surface area of nanomaterials.[64] The catalytic activity of palladium nanoparticles dispersed on an amphiphilic resin (ARP-Pd) was examined for the catalytic aerobic oxidation of alcohols in refluxing water.[64] Benzyl alcohol was oxidized to benzaldehyde almost quantitatively in 90 min under 1 atm of dioxygen using 1 mol% palladium as ARP-Pd. Secondary activated alcohols, such as 1-phenylethanol, diphenylmethanol, and 1-hydroxyindane undergo aerobic oxidation in water giving acetophenone, benzophenone, and indanone in 99, 85, and 95% yield, respectively. However, in the oxidation of unactivated alcohols, longer reaction times and larger amounts of Pd catalyst (20 mol%) are required, and over-oxidation products are obtained in the oxidation of saturated aliphatic primary alcohols. The experimental results from the oxidation of cyclooctanol indicate that the supported palladium nanoparticles can be recycled without losing catalytic activity.

3.1. Supported TPAP

In combination with *N*-methyl-morpholine-*N*-oxide (NMO), tetra-*N*-propylammonium perruthenate (TPAP) is an efficient reagent for the conversion of primary and secondary alcohols to the corresponding aldehydes and ketones.[14,15] TPAP alone is an active catalyst for the oxidation of alcohols at room temperature if the water formed can be removed in situ by adding activated molecular sieves to the reaction system.[65,66b] However, it is difficult to remove the expensive and relatively large amount (10 mol%) of TPAP catalyst and side products.[66] Ley and co-workers tried to solve these problems by grafting perruthenate onto the polymer of Amberlyst A-26 (Fluka) through strong ionic interactions.[66a,c] Results of alcohol oxidation reactions indicated that both activated and unactivated primary alcohols are aerobically oxidized to the corresponding aldehydes over polymer-supported perruthenate (PSP) catalyst in toluene at a temperature of 75–85 °C under 1 atm of dioxygen, similar to the conditions employed for homogeneous catalysis.[65] The yields of aldehydes were 56–96% within 0.5–8 h (Eq. 12).[66c] Interestingly, the PSP catalyst displays significant selectivity for the oxidation of primary over secondary alcohols:[66c] using a 1:1 mixture of benzyl alcohol and 1-phenylethanol at 75 °C for 3 h, benzaldehyde was the only oxidation product. No oxidation product of 1-phenylethanol was found under these reaction conditions. Similar results were obtained in the competitive oxidation of 1-octanol versus 2-octanol. Indeed, 83% of 1-octanol was oxidized to octanal, while only 13% of 2-octanol was converted to 2-octanone within 6 h at 85 °C.[66c] However, it is worth pointing out that relatively large amounts of catalyst (10 mol%) are required (Eq. 12). These results demonstrate that the PSP catalyst could provide a practical synthetic alternative for the oxidation of alcohols. However, it is still quite difficult to recycle the PSP reagent, possibly due to oxidative degradation of the



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polymer support. The use of inorganic materials, such as SiO_2 and molecular sieves, as supports could potentially overcome these problems.[67]

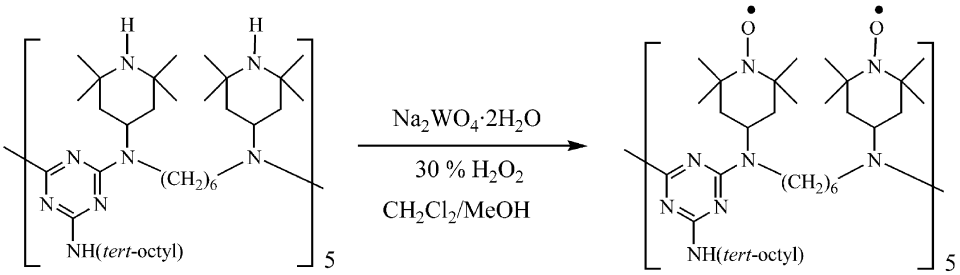
Mesoporous silica molecular sieves, MCM-41 for example, have multiple silanol groups (SiOH) on their internal and external surfaces. These silanol groups can potentially provide active sites to immobilize catalytically active species. Ley and co-workers have successfully immobilized perruthenates to the channels of MCM-41 molecular sieves through strong ionic interactions.[67] A MCM-41-supported propylamine-tethered triethylammonium perruthenate catalyst with a loading of 1.1 wt% Ru was found to be most active.[67] It quantitatively oxidizes various benzylic alcohols to the corresponding aldehydes in 0.5–3 h at 80 °C under 1 atm of dioxygen. No over-oxidation products were found with these supported-catalysts. Furthermore, experimental results indicated that no deactivation and no leaching were found after 12-recycle runs. However, these MCM-41-supported catalysts are much less active than the homogeneous TPAP catalytic system,[65] and neither cyclohexanol nor cyclohexenol was oxidized to the corresponding ketones. The use of NMO or TMAO (trimethylamine *N*-oxide) in place of dioxygen, gives good yields of oxidized products although contamination of the products by ruthenium species and organic impurities was observed.[67]

TPAP-incorporated silica gels have been prepared by directly adding TPAP to the sol–gel polymerization processes for silica gels.[68] It has been demonstrated that the TPAP/gel catalysts are stable under operational conditions, and that the leaching of ruthenium into the organic solvent is negligible. Results from catalysis studies indicated that the nature of the gel supports significantly affects the oxidation activity of the resultant catalysts. It was found that the catalyst made with TPAP and pure methyltrimethoxysilan, called ormosil-doped TPAP, was about 30 times more active than the catalyst prepared with TPAP and pure tetramethoxysilane.[68] The ormosil-doped TPAP catalyst is quite active toward the aerobic oxidation of benzyl alcohol. However, its activity towards other alcohols is quite low. For instance, in the oxidation of 1-octanol a TOF of only 1 h^{-1} was observed.[68] Recently, potassium perruthenate-impregnated zeolite X was reported.[69] Experiments to oxidize alcohols indicated that this zeolite-supported perruthenate catalyst displays interesting shape-selective ability on the substrates of benzyl alcohol and 1-pyrenemethanol, although the reactivity was quite low under the reported conditions.[69] Benzyl alcohol, being smaller than the open channels of zeolite X, was selectively oxidized to benzaldehyde, while 1-pyrenemethanol, which is too large to enter the channels of zeolite X, was inert under the same conditions.[69]

3.2. Supported TEMPO/M

3.2.1. Polymer-supported TEMPO/M. As we have described in the homogeneous catalysis section of this review, nitroxyl radicals are well-established catalysts for the oxidation of alcohols. Indeed, the protocol introduced by Anelli et al., involving TEMPO and bleach, is very useful, especially for large scale oxidations (Eq. 2);[28] a few polymer-bound nitroxyl radical systems have been used as oxidation catalysts, based on the Anelli protocol. These studies have encouraged efforts to develop efficient and green heterogeneous systems, which allow simple catalyst separation and recycling. One of the most advanced polymer-immobilized TEMPO derivative catalysts reported so far was developed by Sheldon and co-workers.[70–72] Polyamine-immobilized piperidinyl oxyl, PIPO, was prepared from a commercially available oligomeric sterically hindered amine, known as Chimassorb 944. Nitroxyl species were formed by treating Chimassorb 944 with hydrogen peroxide and a catalytic amount of $Na_2WO_4 \cdot 2H_2O$ (Eq. 13).

PIPO-catalyzed oxidations of alcohols can be either homogeneous or heterogeneous depending on the nature of the solvents used.[70–72] PIPO is soluble in dichloromethane, thus the catalysis is homogeneous if dichloromethane is adopted as solvent. Both activated and unactivated alcohols are oxidized to the corresponding aldehydes and ketones in PIPO/CH_2Cl_2/NaOCl/KBr systems, akin to the conventional TEMPO-bleach



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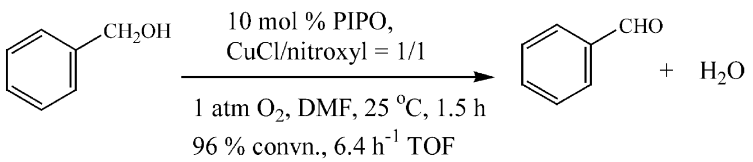


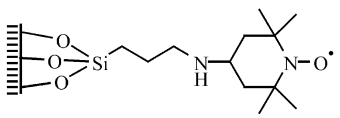
(14)

homogeneous oxidation system in which CH_2Cl_2 is the solvent and KBr is a co-catalyst (Eq. 2).[28]

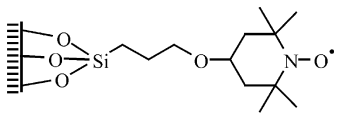
Besides sodium hypochlorite, dioxygen can also be used as the oxidant in PIPO-catalyzed oxidations. For example, PIPO/CuCl catalyzes the aerobic oxidation of benzyl alcohol to benzaldehyde with a TOF of 6.4 h^{-1} in dimethylformamide (DMF) solvent (Eq. 14).[71] This reactivity is comparable to the homogeneous TEMPO/CuCl system, in which a TOF of 4.7 h^{-1} was observed.[29] The PIPO/CuCl system also catalyzes the aerobic oxidation of alcohols under solvent-free conditions, but this is limited to activated benzylic and allylic alcohols as for the homogeneous TEMPO/CuCl catalytic system.[29] However, in contrast to the homogeneous system of TEMPO/$Ru(PPh_3)_3Cl_2$,[32] the PIPO/$Ru(PPh_3)_3Cl_2$ in chlorobenzene does not catalyze the aerobic oxidation of alcohol. This is believed to be due to coordination of ruthenium to the polyamine.[70]

3.2.2. Silica-supported TEMPO/M. There have been reports of silica-supported nitroxyl radicals as catalysts for the oxidation of alcohols.[73–75] For instance, TEMPO can be grafted to silica surfaces through reductive amination, affording SiO_2-amine-TEMPO (**5** in Scheme 9).[74] According to Anelli's protocol,[28] various alcohols were successfully oxidized in high yield to give the corresponding aldehydes and ketones using the SiO_2-amine-TEMPO system as catalyst.[74] Furthermore, the silica-supported catalyst exhibits behavior similar to that of the unsupported TEMPO catalyst, such as in the selective oxidation of the primary alcohols within mixtures of primary and secondary alcohols. Recycling experiments showed that the silica-bound TEMPO derivative was stable under the reaction conditions, thus allowing it to be recovered without significant loss of catalytic activity.[74]

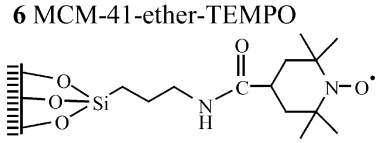
TEMPO derivatives have also been immobilized on the internal surfaces of mesoporous silica of MCM-41 through both ether and amide linkages, for example, MCM-41-ether-TEMPO (**6**) and MCM-41-amide-TEMPO (**7**), as shown in Scheme 9.[76] α-Methyl glucoside was oxidized to 1-*O*-methyl glucuronate with over 95% selectivity using the MCM-41 supported TEMPOs/NaOCl catalytic systems, and no obvious difference was found between the MCM-41-ether-TEMPO and MCM-41-amide-TEMPO catalysts.



5 SiO_2-amine-TEMPO



6 MCM-41-ether-TEMPO



7 MCM-41-amide-TEMPO

Scheme 9. Silica supported TEMPO derivatives.[74,76]

Aerobic oxidation results for benzyl alcohol over the MCM-41-ether-TEMPO/CuCl catalytic system are given in Table 2, along with controlled CuCl and unsupported TEMPO/CuCl results for comparison.[76a] The MCM-41-ether-TEMPO/CuCl catalytic system was much more active than CuCl alone (Table 2, entries 2 and 3). However, in comparison to the homogeneous TEMPO/CuCl system, the MCM-41-ether-TEMPO/CuCl system gave relatively low oxidation activity, although the selectivity for aldehydes is similar (Table 2, entries 3 and 4). In the oxidation of benzyl alcohol, for example, a conversion of 35% in 48 h (Table 2, entry 3) was found, corresponding to an average TOF of ~0.5 h^{-1},[76a] which is much lower than that of the homogeneous TEMPO/CuCl system (4.7 h^{-1} TOF, Table 2, entry 4)[29] and the PIPO/CuCl system (6.4 h^{-1} TOF, Eq. 14).[71] According to the proposal by Semmelhack et al.[29] the re-oxidation step involves disproportionation, which requires two TEMPO molecules to be in close proximity. The loading in the immobilized TEMPO system is probably not optimal for this reaction step. No over-oxidation to benzoic acid was found in the MCM-41-ether-TEMPO/CuCl system, which can be attributed to the low water content in the reaction mixture (only stoichiometric amounts of water are produced in the reaction), leading to a low concentration of the hydrated aldehyde. The latter is the intermediate in the production of carboxylic acid.

Table 2. Benzyl alcohol aerobic oxidation using MCM-41 supported TEMPO/CuCl catalyst[76a]

Entry	Catalyst	Convn. (%)	Sel. (%)[a]
1	None	0	—
2	CuCl	1.2	50
3	MCM-41-TEMPO/CuCl	35	>99
4	TEMPO/CuCl[b]	94	>99

Reaction conditions: 10 mmol benzyl alcohol, 0.25 mmol CuCl and 0.25 g MCM-41-ether-TEMPO in 25 mL DMF, reaction mixture was analyzed by GC after 48 h at room temperature and 1 atm of dioxygen.

[a] Selectivity to benzaldehyde.

[b] 10 mmol benzyl alcohol, 0.5 mmol TEMPO and 0.5 mol CuCl in 25 mL DMF, 4 h.[29]

3.3. Supported Pd(II) complexes

As we have already discussed in Section 2.3, Pd(II) complexes are important homogeneous catalysts in the aerobic oxidation of alcohols. However, there are very few reports concerning the synthesis of supported-Pd(II) complexes and their use as aerobic oxidation catalysts. Based on the success in developing the $Pd(OAc)_2$/pyridine/MS3Å catalytic systems for the aerobic oxidation of alcohols using dioxygen oxidant,[43] Uemura and co-workers synthesized a $Pd(OAc)_2$-pyridine complex on the surface of hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$) to give a heterogeneous palladium catalyst, denoted as Pd(II)-hydrotalcite.[77–79] The Pd(II)-hydrotalcite catalyst efficiently catalyzes the aerobic oxidation of benzyl alcohol to benzaldehyde in the presence of pyridine as co-catalyst (Eq. 15).[78] Unactivated secondary

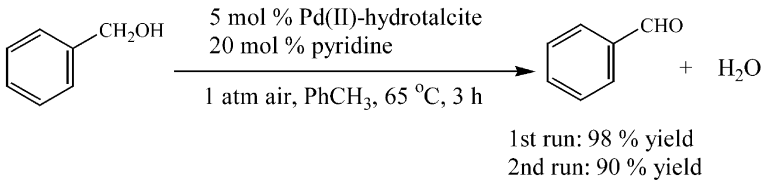


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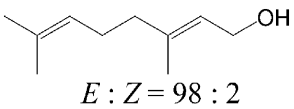
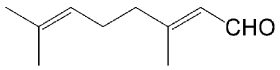
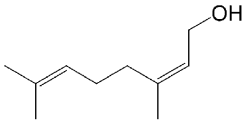
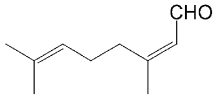
Table 3. Catalytic oxidation of geraniol and nerol using Pd(II)-hydrotalcite and $Pd(OAc)_2$/pyridine/MS3Å[77]

Entry	Substrate	Product	Pd(II)-hydrotalcite[a]		$Pd(OAc)_2$/pyridine/MS3Å[b]	
			Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	 $E:Z=98:2$		4.5	91 (98) *E*:*Z*=95:5	15	56 (76) *E*:*Z*=63:37
2	 $E:Z=2:98$		4.5	89 (100) *E*:*Z*=6:94	15	39 (71) *E*:*Z*=31:69

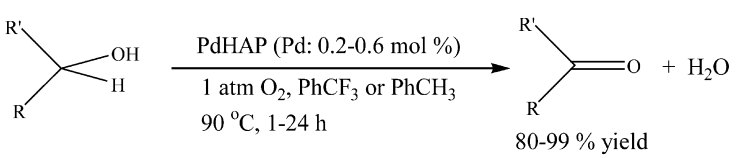
Reaction conditions: alcohol (1.0 mmol), pyridine (5.0 mmol), 1 atm of dioxygen, 80 °C.
[a] Pd(II)-hydrotalcite (300 mg, 0.05 mmol Pd).
[b] Pd(OAc) (0.05 mmol), MS3Å (500 mg).
[c] The value in parentheses is the conversion of alcohol in%. *E*:*Z* ratio was determined by ^{1}H NMR spectroscopy.

aliphatic alcohols were also oxidized, although an excess amount of pyridine was required.

Interesting results were found in the oxidation of alkenic alcohols using the Pd(II)-hydrotalcite catalyst;[77] these are summarized in Table 3. The Pd(II)-hydrotalcite system smoothly catalyzed the aerobic oxidation of geraniol to the corresponding aldehyde in 91% isolated yield in 4.5 h without geometrical isomerization (*E*:*Z*=95:5), while the reaction is incomplete even after long reaction times (76% conversion in 15 h) using the homogeneous $Pd(OAc)_2$/pyridine/MS3Å catalytic system. Furthermore, the *E*:*Z* ratio was significantly disturbed (*E*:*Z*=63:37), entry 1 in Table 3, under the $Pd(OAc)_2$/pyridine/MS3Å conditions. Similar results were found in the oxidation of nerol. The Pd(II)-hydrotalcite catalyst gives a yield of 89% with *E*:*Z*=6:94 (entry 2, Table 3), while both yield and selectivity were low using the $Pd(OAc)_2$/pyridine/MS3Å system (39% yield, *E*:*Z*=31:69). Although the reason for the high activity and selectivity of the Pd(II)-hydrotalcite catalyst is not yet clear (inhibition of strong complexation between Pd(II) and olefin due to the steric bulk of hydrotalcite surface may be a reason for the very low geometric isomerization observed in the heterogeneous system), this catalyst has shown its usefulness for the oxidation of unsaturated alcohols. However, it is still unclear how the Pd(II) complex is bound to the hydrotalcite surface, and how to overcome the leaching of the immobilized catalyst, especially in the presence of an excess amount of pyridine co-catalyst. In the oxidation of benzyl alcohol, the yield decreased from 98% with fresh catalyst (first run) to about 90% in the second run (Eq. 15, the catalyst was separated and washed after the first run, and then re-used for the second run).[78] The oxidation of alcohols to aldehydes or ketones using $PdCl_2(PhCN)_2$-exchanged hydroxyapatites (PdHAP) has been reported recently.[80] PdHAP exhibits high activity for benzylic and allylic alcohols, giving the corresponding carbonyl compounds in excellent yields.[80] Aliphatic and heterocyclic alcohols are also smoothly oxidized to the corresponding ketones and aldehydes (Eq. 16). Furthermore, a turn over number (TON) up to 236,000 was reached in a solvent-free oxidation of 1-phenylethanol to acetophenone in 24 h at 160 °C under 1 atm of dioxygen. In addition, no leaching of palladium occurred, allowing the re-use of catalyst without loss of catalytic activity and selectivity.

3.4. Polyoxometalate catalysts

Polyoxometalate catalysts have attracted much attention because of their strong acidity and rich redox properties.[81] However, polyoxometalate-catalyzed aerobic oxidation of alcohols was not reported until 1991 when Neumann and Levin discovered that benzyl alcohol is smoothly oxidized to benzaldehyde with 100% selectivity by a Keggin-type



(16)

polyoxometalate salt, $Na_5PV_2Mo_{10}O_{40}$, supported on activated carbon at 100 °C under 1 atm of air.[82] Substituted benzyl alcohols such as 4-bromobenzyl-, 4-nitrobenzyl-, 4-methoxy- and 4-methylbenzyl alcohols are also oxidized to their corresponding aldehydes in good yields (93–98%). However, unactivated secondary alcohols were only moderately reactive, and saturated primary alcohols were found to be inert under these reaction conditions. Interestingly, further studies indicated that the non-supported $PV_2Mo_{10}O_{40}^{5-}$ and silica or alumina supported $PV_2Mo_{10}O_{40}^{5-}$ were catalytically inactive.[83] These results suggest that activated carbon is not an inert support, but instead plays an integral part in the catalytic cycle. Indeed, it is known that there are multiple oxygen-containing groups present on the surface of activated carbon.[84] The intermediate or promoter, formed by these groups and $PV_2Mo_{10}O_{40}^{5-}$, could play a key role in the oxidation. This speculation was confirmed by using catalytic systems of $Na_5PV_2Mo_{10}O_{40}$ and quinones.[83] Experimental results indicate that the $Na_5PV_2Mo_{10}O_{40}$ is active for the aerobic oxidation of benzylic and allylic alcohols in the presence of quinines, which could be promoters. Furthermore, $H_5PV_2Mo_{10}O_{40}$ alone was active for the oxidation of benzylic alcohol if the reaction was conducted at 100 °C under 2 atm of dioxygen using polyethylene glycol as solvent.[85] PVMo-based polyoxometalates were also found to be efficient catalysts in the aerobic oxidation of 2-butyl-5-hydroxymethylimidazole to 2-butyl-5-formyl-imidazole under high pressure and temperature conditions.[86]

Using DMSO as solvent, the $H_5PV_2Mo_{10}O_{40}$ catalyst was found to be active for the oxidation of aliphatic alcohols, such as cyclooctanol, 3-octanol, etc.[87] Mechanistic studies revealed that DMSO is in fact the oxygen donor.[87] The catalytic properties of $H_5PV_2Mo_{10}O_{40}$ are significantly enhanced (over 100 times in most cases) if TEMPO is employed as co-catalyst.[88] Table 4 gives some catalytic results for $H_5PV_2Mo_{10}O_{40}$ catalyst with and without TEMPO. The catalytic activity of the $H_5PV_2Mo_{10}O_{40}$/TEMPO system is comparable to that of the $Ru(PPh_3)_3Cl_2$/TEMPO system as we have discussed in section 2.1.

The catalytic activities of polyoxometalates can be improved by introducing other substitution patterns. For example, $Q_4PSb^{v}(O)Mo_{11}O_{39}$ and $Q_3PSb^{v}(Br)Mo_{11}O_{39}$, where Q^+=tetra-*n*-butylammonium cation, are much more active than $Q_5PV_2Mo_{10}O_{40}$ in the aerobic oxidation of alcohols.[89] Recently, Neumann et al. reported that ruthenium and osmium-containing polyoxometalates, $[M(DMSO)_3Mo_7O_{24}]^{4-}$ (M=Ru(II) or Os(II)), are very active catalysts for the aerobic oxidation of alcohols.[90] Benzylic alcohols are efficiently and selectively oxidized to the corresponding benzaldehyde derivatives at 120 °C with 0.2 mol% catalyst in the absence of solvent. Although the use of toluene as solvent gave good yields of products, the reactions were about 20–50% slower than when no solvent was used. Secondary allylic alcohols were also oxidized effectively to the corresponding β-unsaturated ketones, generally with over 90% selectivity. However, primary aliphatic allylic alcohols were less active with only about 50% selectivity for β-unsaturated aldehydes. Lower activities were also found in the oxidation of unactivated alcohols.

Table 4. Selected aerobic oxidation results for $H_5PV_2Mo_{10}O_{40}$/TEMPO catalyst[87]

Entry	Substrate	Product	Time (h)	Convn. (%)[a]
1	Benzyl alcohol	Benzaldehyde	6	>99
2	Benzyl alcohol (no TEMPO)	Benzaldehyde	6	8.4
3	1-Octanol	Octanal	18	98
4	1-Octanol (no TEMPO)	Octanal	18	0.2
5	*cis*-2-Hexen-1-ol	2-Hexenal	10	>99
6	*cis*-2-Hexen-1-ol (no TEMPO)	2-Hexenal	10	1.1

Reaction conditions: 1 mmol of substrate, 0.01 mmol of $H_5PV_2Mo_{10}O_{40}$, 0.03 mmol of TEMPO, 0.15 mL of acetone. 2 atm of dioxygen at room temperature, T=100 °C.

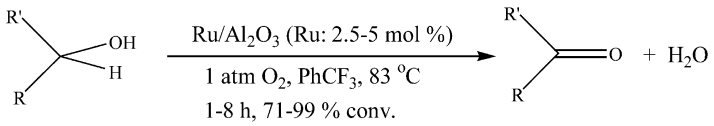
[a] Conversions based on GC results.

Ru(III)-substituted polyoxometalate is also an efficient oxidation catalyst. Mizuno et al. reported that a monoruthenium(III) substituted silicotungstate, $[(C_4H_9)_4N]_4H[SiW_{11}Ru^{III}(H_2O)O_{39}]\cdot 2H_2O$, synthesized by the reaction of the lacunary polyoxometalate $[SiW_{11}O_{39}]^{8-}$ with Ru^{3+}, is an efficient catalyst for the aerobic oxidation of various alkanes and alcohols in 1 atm of dioxygen.[91] Very high TONs (over 1000) were achieved in the aerobic oxidation of secondary alkanes, such as adamantane and cyclohexane, and alcohols in the absence of co-catalysts or reductants. However, the selectivity was lower in the oxidation of primary alcohols due to over-oxidation, forming carboxylic acids. Furthermore, a relatively long reaction period, 48–120 h, lead to low TOFs and reduced the practicality of these systems.

3.5. Supported Ru(III) catalysts

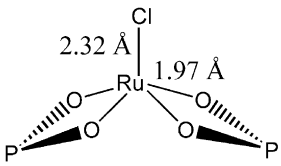
The catalytic activity of Ru(III) was significantly improved by using Al_2O_3 as support in an dioxygen atmosphere.[92] The Ru/Al_2O_3 catalyst shows high catalytic activities in the oxidation of both activated and unactivated alcohols under 1 atm of dioxygen, and all primary and secondary benzylic alcohols were quantitatively converted into the corresponding benzaldehydes and ketones, respectively. Also, enals and enones were prepared from the corresponding primary and secondary allylic alcohols, with no hydrogen transfer or isomerization of double bonds, and unactivated alcohols were oxidized smoothly (Eq. 17).[92] However, over-oxidation of unactivated primary alcohols to the carboxylic acids was found, but this can be overcome by the addition of a small amount of hydroquinone. The Ru/Al_2O_3 catalyst efficiently catalyzes the oxidation of unactivated 2-octanol and activated 1-phenylethanol under solvent-free conditions. Thus, solvent-free oxidation of 2-octanol and 1-phenylethanol gave TOFs of 300 and 340 h^{-1}, and TONs of 950 and 980, respectively, albeit at relatively high temperature (150 °C). These oxidations can be performed in air, instead of dioxygen, without influencing the conversion or selectivity. However, it is still not clear either how the Ru species resides on the Al_2O_3 support, or what kind of interaction prevents Ru from leaching during reactions. The ability to recycle this catalyst was demonstrated through the oxidation of benzyl alcohol at 83 °C.

Another Ru(III)-containing heterogeneous catalyst that has been reported is ruthenium-exchanged hydroxyapatite



(17)

(RuHAP), prepared by ion exchange of hydroxyapatite (HAP) powder with aqueous $RuCl_3$ solution at 25 °C for 24 h.[93] The presence and chemical environment of the Ru(III) species on the surface of HAP have been fully characterized and defined by elemental analysis, X-ray photoelectron spectroscopy (XPS), and X-ray absorption techniques (Scheme 10). Various alcohols are efficiently oxidized to the corresponding aldehydes and ketones using RuHAP as catalyst at 80 °C under 1 atm of dioxygen. Benzylic and allylic compounds show especially high reactivity for oxidative dehydrogenation. Interestingly, 1-octanol was oxidized to 1-octanal without any over-oxidation products being observed. Primary alcohols are more reactive than secondary alcohols with the RuHAP catalyst: in a competitive oxidation where equimolar 1-octanol and 4-octanol were mixed as substrates, octanal was obtained with 95% selectivity; in the intramolecular competitive oxidation of 1,7-octanediol, 7-hydroxyoctanal was obtained with 80% chemoselectivity. Furthermore, the RuHAP catalyst is active in the oxidation of various heterocyclic alcohols containing nitrogen and sulfur atoms. For example, 2-pyridinemethanol and 2-thiophenemethanol were oxidized to the corresponding aldehydes in good yields. These substrates were inert to the $Ru(PPh_3)_3Cl_2$ and Pd(II) catalytic systems as we have discussed in the homogeneous catalysis sections.

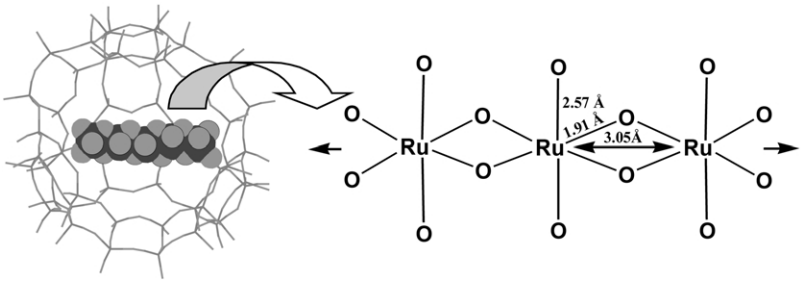


Scheme 10. Proposed environment of Ru^{3+} on hydroxyapatite.[93]

3.6. Functionalized zeolites

Zeolites form a major subclass of microporous materials.[94] Microporous zeolitic materials have several special features: very high surface area, well-defined pores/cages, polarity-controlled frameworks, tunable acid sites, molecular sieve and ion exchange capabilities. These unique advantages make them one of the most widely used catalysts in the petrochemical industry. Zeolites can be functionalized as acid catalysts by generating acidic sites in the framework, with the opportunity to tailor strength and concentration for particular applications.[94] Zeolites can be functionalized as redox catalysts by introducing various transition metals into their frameworks,[95] or confining nanometer-sized transition metal compounds into their pores/cages. The latter was named a ship-in-a-bottle (or host–guest) system,[96–99] in which the zeolitic frameworks serve only as an inert support. One of the most interesting zeolites is faujasite (FAU) zeolite, in which ~13 Å supercages are tetrahedrally connected via open channels of diameter ~7.4 Å.[94] This specific structure allows physical trapping of molecules of size ~1 nm into its supercages. The guest molecules, once encapsulated, do not diffuse out during various chemical processes unless the zeolitic frameworks are destroyed.[96–99] Furthermore, the catalytic properties of these ship-in-a-bottle systems mainly depend on the properties of the guest molecules. Various transition-metalloporphyrins have been synthesized inside the supercages of faujasite zeolites using the build-bottle-around-ship strategy.[97–99] These zeolite-confined metalloporphyrins display rich catalysis-chemistry such as oxidation,[97] hydrogenation[98] and hydroxylation.[99] It is well known that a variety of transition-metal oxides, such as RuO_2, MnO_2, CrO_3, etc.[1] act as oxidants or catalysts in the oxidative dehydrogenation of alcohols to carbonyl compounds. For example, for the oxidation of cinnamyl alcohol, hydrated RuO_2 was found to be more efficient than MnO_2.[100] Recently, microporous manganese oxide was found active for the aerobic oxidation of alcohols and its reactivity was accelerated in the presence of Brønsted acids.[101]

Cognizant of the oxidative ability of RuO_2, and the ability of the faujasite zeolite to promote catalytic reactions, Zhan and co-workers have synthesized nanometer-sized RuO_2 clusters (~1 nm) in the supercages of faujasite zeolite,[102,103] using an organic-template-free approach:[104,105] the system was named RuO_2-FAU. Ru K-edge X-ray adsorption experiments indicate that RuO_2-FAU has a two-dimensional chain structure, similar to amorphous hydrous RuO_2, in which the RuO_6 units are connected together by two shared oxygen atoms (Scheme 11).[102,106] RuO_2-FAU is a green, selective and efficient catalyst for the aerobic oxidation of alcohols. It catalytically and aerobically oxidizes a variety of alcohols using air as the sole oxidant under very mild conditions (e.g., 80 °C and 1 atm). Table 5 gives some of the aerobic oxidation results for benzyl alcohol.[102] No oxidation product was detected from GC analysis using unmodified faujasite zeolite (NaX) as catalyst, indicating that the unmodified faujasite zeolite itself is inert under the experimental conditions (Table 5, entry 1). Using pure hydrous RuO_2 as a catalyst and toluene as solvent, benzyl alcohol was converted to benzaldehyde in 16% in 1.5 h at 80 °C (Table 5, entry 2). However, benzyl alcohol was completely and selectively converted to benzaldehyde in 1.5 h when RuO_2-FAU was used as catalyst under the same reaction conditions (Table 5, entry 3), indicating that the FAU-confined RuO_2 nanocluster is much more active than bulk RuO_2. Furthermore, aerobic oxidation with this system can be carried out without using an organic solvent. For example, neat benzyl alcohol was selectively oxidized to benzaldehyde with a conversion of 22% in 20 h at 80 °C and 1 atm of air (Table 5, entry 4). The RuO_2-FAU catalyst in toluene is active in the aerobic oxidation of benzyl alcohol even at ambient temperature without the need for any co-catalysts or reductants (Table 5, entry 5).



Scheme 11. The 2D-chain structure of nano-RuO_2 in the faujasite zeolite.

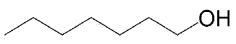
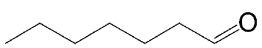
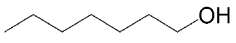
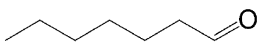
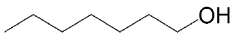
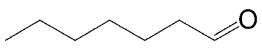
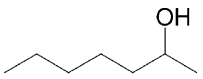
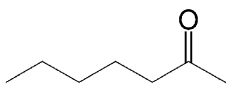
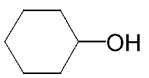
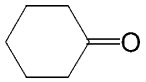
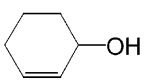
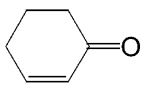
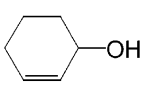
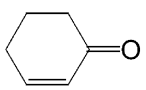
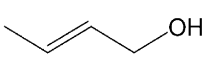
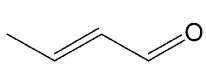
Table 5. RuO_2-FAU catalyzed aerobic oxidation of benzyl alcohol[102]

Entry	Catalyst	Time (h)	Conditions	Convn. (%)	TON
1[a,b]	NaX	4	80 °C, air	0	0
2[b]	RuO_2	1.5	80 °C, air	16	2
3[b]	RuO_2-FAU	1.5	80 °C, air	100	13
4[c]	RuO_2-FAU	20	80 °C, air	22	28
5[d]	RuO_2-FAU	24	RT, O_2	58	7

[a] Unmodified faujasite zeolite (0.1 g) was used as 'catalyst'.
[b] 0.078 mmol RuO_2 (or 0.1 g RuO_2-FAU, for example, 0.078 mmol Ru), 1 mmol alcohol, 3 mL toluene.
[c] 30 mmol alcohol, 0.3 g RuO_2-FAU.
[d] 10 mL toluene. All reactions were conducted at ambient pressure and benzaldehyde was the only oxidation product.

The RuO_2-FAU catalyst is active in the oxidation of various alcohols, including unactivated alcohols (Table 6), which are rarely oxidized by RuO_2 or RuO_2/dioxygen.[100] For example, *n*-heptanol was selectively oxidized to *n*-heptaldehyde with 44% conversion in 4 h (Table 6, entry 1). The oxidation was essentially complete in 20 h with over 99% selectivity for *n*-heptaldehyde (Table 6, entry 2). No over-oxidation product was detected by GC analysis. In comparison with unactivated primary aliphatic alcohols, secondary acyclic aliphatic alcohols are more reactive with the RuO_2-FAU catalyst: 69% of 2-heptanol was oxidized to 2-heptanone in 4 h (Table 6, entry 4). This trend is very different from that observed in the monomeric ruthenium catalysts, such as $Ru(PPh_3)_3Cl_2$,[32] Ru/Al_2O_3[92] and RuHAP.[93] Unfortunately, only 17% of cyclohexanol was oxidized to cyclohexanone under the RuO_2-FAU conditions (Table 6, entry 5). This is further confirmed by a competitive reaction, in which heptanol is found to be about 3 times more reactive than cyclohexanol.[102] This result agrees very well with the individual reactions (Table 6, entries 1 and 5). The oxidation of alcohols using RuO_2-FAU is significantly promoted in 1 atm of dioxygen (Table 6, entries 1 and 3). Furthermore, allylic alcohols are oxidized easily: 68% of 2-cyclohexenol was selectively oxidized to 2-cyclohexenone in 4 h (Table 6, entry 6). This oxidation was complete in 8 h (Table 6, entry 7). 2-Buten-1-ol was selectively converted to 2-butenal in 95% yield after 4 h. The physically trapped nano-RuO_2 in FAU is very stable during the oxidation processes, allowing the catalyst to be recycled without losing activity and selectivity.[102] The shape-selectivity of zeolites, derived from their well-defined pores/cages, was observed in the RuO_2-FAU-catalyzed

Table 6. RuO_2-FAU catalyzed aerobic oxidation of alcohols[102]

Entry	Time (h)	Substrate	Product	Convn. (%)
1	4			44
2	20			93
3	4[a]			98
4	4			69
5	4			17
6	4			68
7	8			100
8	4			95

Reaction conditions: 0.1 g nanoRuO_2-FAU (0.078 mmol Ru); 1 mmol alcohol; 3 mL toluene; 80 °C and 1 atm of air.
[a] 1 atm of dioxygen. For all reactions, aldehydes or ketones are the only oxidation product.

competitive aerobic oxidation of benzyl alcohol over 9-hydroxyfluorene.[102] Similar phenomena were observed in the $KRuO_4$ impregnated NaX system.[69]

4. Conclusion

The environmental and economic significance of the aerobic oxidation of alcohols to the corresponding carbonyls is continuing to inspire research to develop novel, green and efficient oxidation catalysts. In homogeneous catalysis, TEMPO-based systems are the most important and widely investigated catalysts for the aerobic oxidation of alcohols. The development of supported TEMPOs could potentially provide a solution to re-use the expensive TEMPO-based catalysts, even though the catalytic abilities of heterogenized TEMPO catalysts are still much lower than their homogeneous counterparts. Progress has been made in the development of polyoxometalate-based catalytic systems, and the catalytic abilities of these systems are significantly improved by the introduction of various catalytically active species as building units. The unique Pd(II)/Pd(0) catalytic cycle and the rich redox chemistry of ruthenium compounds have enabled tremendous development in the aerobic oxidation of alcohols. In the Pd(II)-catalytic system, mechanistic studies reveal that the prevention of Pd(0) aggregation and the promotion of Pd(0) re-oxidation to Pd(II) with dioxygen are key factors in improving the performance of Pd(II) catalysts. In preliminary studies, the supported Pd(II) complexes and Pd nanoparticle have already displayed useful chemistry. A variety of ruthenium compounds, for example, Ru(II, III, and IV), have shown very significant reactivity and diversity for the catalytic aerobic oxidation of alcohols. Due to significant advances in product and catalyst separation, heterogeneous catalysis has gained increasing attention in the last few years. The availability of various supports with differing physical properties and porosities, for example, hydroxyapatite, microporous zeolite, and mesoporous silica, allows chemists to design and create many catalytic systems and to explore and understand their oxidation mechanisms. Porous supports with well-defined cages and channels provide a nano-reactor environment, which can introduce shape-selectivity for substrates, products, and transition states.

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