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# Aerobic Oxidations of Alcohols

*Francesca Cardona*[a]* *and Camilla Parmeggiani,*[a,b]

[a]Dipartimento di Chimica “Ugo Schiff”, Via della Lastruccia 13, Polo Scientifico e Tecnologico, Sesto Fiorentino, 50019, Firenze, Italy e-mail: francesca.cardona@unifi.it
[b]Current address: CNR-INO and European Laboratory for Non-linear Spectroscopy (LENS), via N. Carrara 1, Polo Scientifico Sesto Fiorentino, 50019, Firenze, Italy

## INTRODUCTION

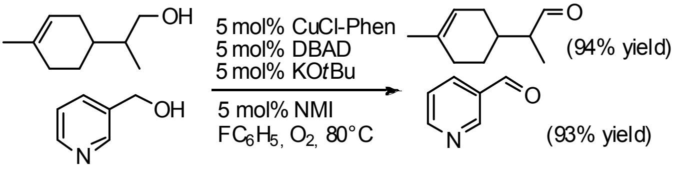
Oxidation reactions are among the most useful and used reactions in the industrial processes. However, at the same time, they are among the most polluting and hazardous processes, often occurring with high E-factor (mass of waste per mass unit of product)[1] and delivering considerable amount of toxic waste, for instance metal salts in oxidations employing stoichiometric Cr(VI) or Mn(VII) derivatives or nitrogen oxides in oxidations carried out with $HNO_3$. In particular, the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds is of fundamental importance in organic synthesis, due to the wide ranging utility of these products as important precursors and intermediates for many drugs, vitamins and fragrances. A recent publication by Pfizer's medicinal chemists[2] showed that the three most popular oxidants used in Pfizer for the oxidation of primary alcohols to the corresponding aldehydes are Dess-Martin periodinane[3] or its precursor IBX, the Swern reagent[4] and TPAP/NMO[5] system. All of these methods still have poor atom efficiencies[6] and significant scale-up issues. As a result, the oxidation of an alcohol to a carbonyl compound, in spite of being a fundamentally important reaction, yet is actually avoided by the pharmaceutical industry.[7] From an environmentally point of view, it is of particular importance the development of methods which use cleaner oxidants and minimize the amount and toxicity of the released waste. Moreover, the use of catalysis, that allows processes to occur under mild conditions in order to save the overall implied energy, is strongly encouraged.[8] In this respect, the recovery and reuse of the catalyst is a further important goal. In this review, we will present an overview of the recent advances made by the international scientific community in this field. Oxygen (or even better air) is among the cheaper and less polluting stoichiometric oxidants, since it produces no waste or water as the sole by-product.[9] The implementation of a catalyst in combination with molecular oxygen represents an emerging alternative process to the traditional procedures.

In the development of transition metal-catalyzed aerobic alcohol oxidations, several challenges exist, as the need of low pressures of $O_2$ especially in flammable organic solvents, mild reaction conditions, low catalyst loadings, and avoidance of costly or toxic additives.

Another main issue is the functional group tolerance and the chemoselectivity of the alcohol transformation when other groups susceptible to oxidation are present. A further goal is the development of methods able to oxidize one class of alcohols in the presence of another. Finally, an ultimate goal is the development of diastereo- and/or enantioselective alcohol oxidations. Many homogeneous and heterogeneous catalytic systems have been developed;[10] this review, that does not pretend to be exhaustive, aims to give an overview on the most significant procedures developed in this extremely investigated field of the research. The most versatile and studied metal catalysts (copper-, ruthenium-, palladium- and gold-based) will be analyzed, highlighting their synthetic potential and always taking in account the previously mentioned synthetic challenges.

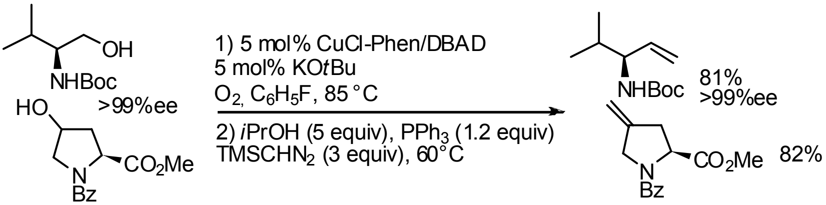
## COPPER-BASED HOMOGENOUS CATALYSTS

Copper seems an appropriate metal for the catalytic oxidation of alcohols with $O_2$ since it is present in Nature as the catalytic centre in a variety of enzymes (e.g. galactose oxidase) that catalyze this conversion. Some catalytically active biomimetic models for these enzymes have been designed and constitute seminal examples in this area.[11] In 1984, Semmelhack reported the first practical Cu-catalyzed aerobic oxidation of alcohols, using Cu in combination with the stable nitroxyl radical TEMPO (2,2,6,6-tetramethyl-1-piperidine-N-oxyl) in DMF as solvent; however, this system was efficient only for activated primary alcohols.[12] Markó and co-workers pioneered much of the catalyst development. In their initial report, a combination of CuCl (5 mol %), phenantroline (5 mol%) and di-*tert*-butylazodicarboxylate, DBAD (5 mol%) allowed oxidation of alcohols with great tolerance of other functional groups.[13] However, this system required the presence of 2 equivalents of a base ($K_2CO_3$) and was not consistent for the oxidation of primary aliphatic alcohols. In these basic conditions, alcohols bearing $\alpha$-stereogenic centres could be oxidized with no racemisation. In these first reports, the active catalyst was postulated to be heterogeneous, and absorbed on the insoluble $K_2CO_3$, since filtration of the mixture gave a solution devoid of any oxidizing ability. Indeed, it appeared that $K_2CO_3$ may also served as a solid support on which the copper catalyst could be anchored. A change of the solvent from toluene to fluorobenzene allowed to use catalytic base,[14] and further investigations led to the discovery that addition of catalytic *N*-methylimidazole dramatically enhanced the activity of the system allowing efficient conversion of primary aliphatic alcohols (Scheme 1).[15]



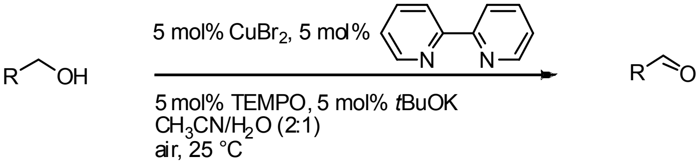
*Scheme 1.* The Cu-catalytic system developed by Markó and co-workers

The use of such system in combination with a diazo reagent and triphenyl phosphine recently allowed a domino one-pot oxidation-olefination process that could be applied to a wide variety of alcohol substrates including aliphatic secondary alcohols. α-Chiral alcohols could be converted into olefins without any detectable racemization (Scheme 2).[16]



*Scheme 2.* Copper-catalyzed tandem oxidation-olefination process

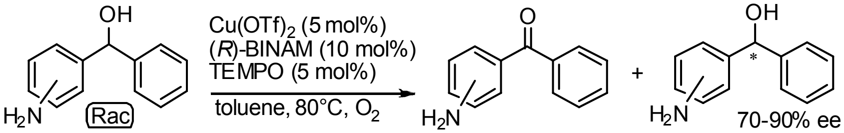
In addition to Markó's work, other groups reported chemoselective oxidations of primary alcohols with Cu in combination with TEMPO. Sheldon and co-workers showed that $CuBr_2$ and TEMPO in the presence of 2,2'-bipyridine as a ligand for Cu led to the oxidation of several primary alcohols with no overoxidation to carboxylic acids. When mixtures of primary and secondary alcohols were reacted in these conditions, only primary alcohols were converted. The advantage of this very mild procedure is that excellent conversions were obtained with air at room temperature (Scheme 3).[17]



*Scheme 3.* The Cu(II)-TEMPO catalyzed aerobic oxidation of primary alcohols by Sheldon et al.

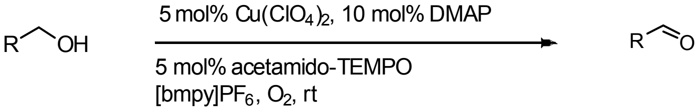
In the presence of an enantiopure bidentate ligand, Seckar and co-workers achieved an efficient non enzymatic kinetic resolution of several secondary benzylic amino alcohols (Scheme 4).[18]

Several other groups reported the use of alternative solvents with the aim of allowing catalyst recycling and simple product purification. In 2002 Ansari and Gree reported a CuCl-TEMPO catalyzed aerobic oxidation of several primary and secondary benzylic and allylic alcohols in the 1-butyl-3-methylimidazolium hexafluorophosphate ($[bmim]PF_6$) ionic liquid.



*Scheme 4.* Oxidative kinetic resolution of secondary benzylic amino alcohols

The authors could recycle the ionic liquid but not the catalyst.[19] Jiang and Ragauskas reported the use of a pyridil based ionic liquid, 1-butyl-4-methylpyridinium hexafluorophosphate ([bmpy]$PF_6$) in a room-temperature aerobic oxidation of primary alcohols catalyzed by a three-component system acetamido-TEMPO/Cu-$(ClO_4)_2$/DMAP, that allowed the recover and reuse of catalyst up to five runs without loss of activity (Scheme 5).[20]



*Scheme 5.* Cu(II)-TEMPO-catalyzed oxidation in ionic liquid

More recently, they reported a similar three component system for the oxidation of primary alcohols to aldehydes under solvent-free conditions, and simply recovered the three catalyst components by addition of a non polar solvent (hexanes) that selectively dissolved the product aldehydes.[21] In case of solid alcohols, PEG-200 (not oxidized in these reaction conditions) was used as solvent.

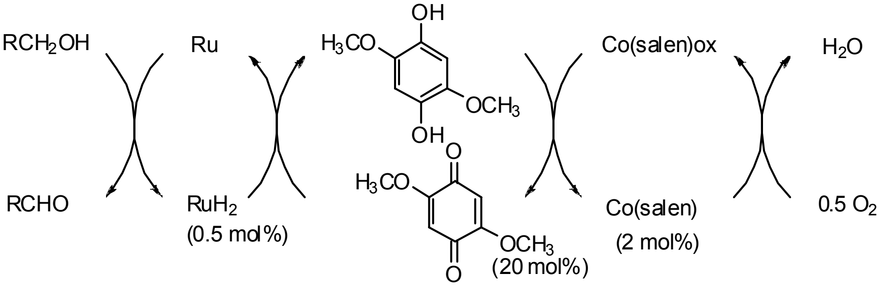
To enhance catalyst recyclability, Knochel and co-workers also used a biphasic solvent system, (chlorobenzene/perfluoroctyl bromide), and a pyridine ligand containing fluorinated ponytails for the CuBr-$Me_2S$-TEMPO catalyzed oxidation of several alcohols, and they could recover and reuse the fluorous layer containing the catalyst up to eight times with little loss of activity.[22] Furthermore, the selective aerobic oxidation of benzyl alcohols to the corresponding benzaldehydes could be achieved using the sole water as solvent without the need of any organic or alternative solvent, employing a multinuclear copper (II) compound in combination with TEMPO at 25-80 °C.[23]

## COPPER-BASED HETEROGENOUS CATALYSTS

In contrast to the great development of homogenous copper-based catalysts, heterogeneous systems are still largely unexplored. One of the few examples is a recyclable Cu-Mn mixed oxide supported on active carbon that was employed in combination with TEMPO as co-catalyst for the aerobic oxidation of several benzylic primary alcohols.[24]

## RUTHENIUM-BASED HOMOGENOUS CATALYSTS

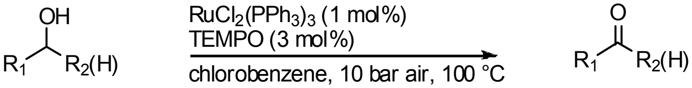
Ruthenium compounds have been extensively studied as catalysts for the aerobic oxidation of alcohols.[25] This metal gives the widest range of oxidation states from +2 to +8, therefore a large variety of oxidative transformations has been developed. The activity of common low valent ruthenium precursors such as $RuCl_2(PPh_3)_3$ can be increased by the use of ionic liquids as solvents.[26] Ruthenium-based compounds have been extensively investigated as catalysts for hydrogen transfer reactions. These systems, in combination with a hydrogen acceptor as co-catalyst and dioxygen as oxidant, can be readily adapted to the aerobic oxidation of alcohols in a multicatalytic process. For example Bäckvall and co-workers, employing a benzoquinone and a cobalt-Schiff's base complex, developed one of the fastest catalytic systems reported for the oxidation of secondary alcohols (Scheme 6).[27]



*Scheme 6.* Bäckvall's multicatalytic system for the aerobic oxidation of alcohols

The sole weakness of this procedure was the requirement of high loading of 2,6-dimethoxy-1,4-benzoquinone (20 mol%) which served as electron transfer mediator (ETM). Recently Bäckvall and co-workers reported, in combination with Ru Shvo's catalyst, a second generation Co hybrid catalyst that comprises cobalt salens and pendant hydroquinone groups, thus avoiding the use of benzoquinone and affording excellent conversions of secondary alcohols.[28] On the other hand, Ishii and co-workers demonstrated that the regeneration of benzoquinone can also be achieved in the absence of the cobalt co-catalyst in $PhCF_3$ as solvent.[29] In these conditions, primary alcohols could be chemoselectively oxidized in the presence of secondary alcohols.

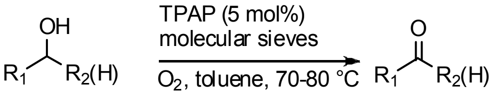
Sheldon and co-workers developed one of the most efficient systems for the aerobic oxidation of non activated primary and secondary alcohols using $RuCl_2(PPh_3)_3$ in combination with TEMPO in PhCl at 100 °C (Scheme 7).[30]



*Scheme 7.* Ruthenium-TEMPO catalyzed oxidation of alcohols

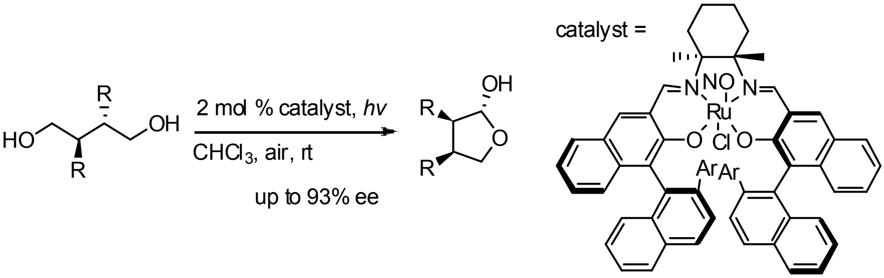
Overoxidation of primary alcohols to carboxylic acids was completely suppressed by catalytic TEMPO, which avoided the autooxidation of aldeydes by efficiently scavenging free radical intermediates. Unfortunately, this system required 10 bar pressure and a number of alcohols containing heteroatoms (O, N, S) still remained unreactive, probably due to their coordination to the ruthenium metal centre and subsequent catalyst inactivation. An oxidative hydrogenation mechanism, analogous to that proposed by Bäckvall and co-workers for the Ru-quinone system, can be envisaged for the Ru/TEMPO system.

High valent perruthenate catalysts, i. e. tetra-*n*-propylammonium perruthenate (TPAP), are excellent air-stable Ru-catalysts, non volatile and soluble in a wide range of organic solvents. In 1997 Markó[31] and Ley[32] simultaneously showed that TPAP is able to perform the aerobic oxidation of alcohols; however, both systems had some drawbacks such as the need for high catalyst loading in a chlorinated solvent[32] or the need for high temperature (70-80 °C) (Scheme 8)[31] and were not effective for the oxidation of primary aliphatic alcohols in contrast to using NMO as the stoichiometric oxidant.[5]



*Scheme 8*. TPAP-catalyzed aerobic oxidation of alcohols

More recently, Katsuki and co-workers have published several papers on Ru-salen catalysts for aerobic alcohol oxidations. They designed an efficient catalyst for the photo-induced chemoselective oxidation of primary alcohols in the presence of secondary alcohols,[33] and upon further derivatization of chiral ligands they could accomplish efficient kinetic resolutions of secondary alcohols[34] and desymmetrization of *meso*-diols (Scheme 9).[35] Moreover, recently, they developed a chemoselective oxidation of primary alcohols using a Ru-salen catalyst that did not need further irradiation conditions.[36]



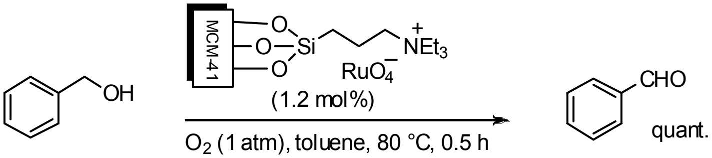
*Scheme 9*. Ru-salen catalyzed oxidative desymmetrization of *meso*-diols

In conclusion, ruthenium has proved to be effective for the homogenous aerobic oxidation of alcohols, but some further work remains to develop general alcohol oxidation catalysts that employ low catalyst loading and perform under mild conditions.

## RUTHENIUM-BASED HETEROGENOUS CATALYSTS

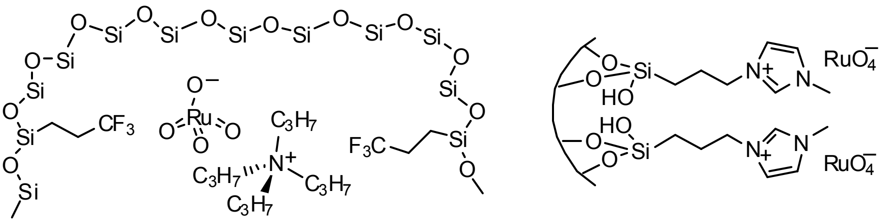
Especially in industrial chemistry, heterogeneous catalytic systems are preferred over homogenous ones due to easy recyclability and separability. However, they usually suffer from low catalytic activity relative to their homogenous counterparts. Much effort has been made to overcome the difficulties involved because reduction of environmental loading due to easy separation and reuse of the catalyst could result.

A pioneering work by Ley and co-workers dates back to 1997 and reports the use of polymer-supported perruthenate (PSP) in the aerobic oxidation of alcohols; however, this catalyst suffered from oxidative degradation of the polymer support.[37] Soon later the same authors found a mesoporous silicate (MCM-41) as an efficient alternative support for TPAP and showed the recyclability of this catalyst up to 12 times (Scheme 10);[38] this material was used in a ten-step linear synthesis of the powerful analgesic natural product epibatidine, which employed only solid supported reagents.[39]



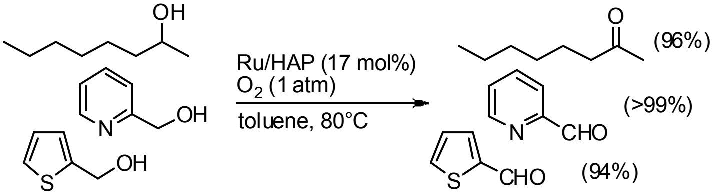
*Scheme 10*. Ley’s modified mesoporous silicate materials MCM-41

The grafting of an organic moiety onto solid surfaces allows the building of organic-inorganic hybrid materials, which are promising supports for catalyst design.[40] For example, organically modified silicates (ORMOSIL) were studied by Pagliaro and Ciriminna for the encapsulation of the TPAP via a sol-gel process (SG-TPAP).[41] However, the first reports did not show a wide substrate scope; in order to broaden the application of the SG-TPAP catalyst, alternative conditions were investigated such as supercritical carbon dioxide ($scCO_2$)[42] and the introduction of ionic moieties[43] or of fluoroalkyl chains[44] into the silica matrix of SG-TPAP. They reported the use of hybrid fluorinated silica glass doped with TPAP (denoted FluoRuGel) as a versatile catalyst for the aerobic oxidation of different alcohols in dense $CO_2$ (Scheme 11).[44,45,46]



*Scheme 11*. TPAP-heterogeneous catalysts developed by Pagliaro and co-workers

Low valent ruthenium species have been also supported on solid matrices. Zeolites impregnated with $RuO_2$ nanoclusters ($RuO_2$-FAU) were found to be effective and selective catalysts for a wide variety of both activated and unactivated alcohols. These materials display a strong shape selectivity due to uniform pore size, and in a competitive experiment benzyl alcohol was reacted in the presence of unreacted 9-hydroxyfluorene.[47] Kaneda and co-workers developed a monomeric ruthenium cation on the surface of hydroxyapatite (Ru/HAP), which gave efficient aerobic oxidations of primary, secondary and functionalized alcohols (Scheme 12). The main disadvantage of this process was the need for a high catalyst loading (17 mol%).[48]

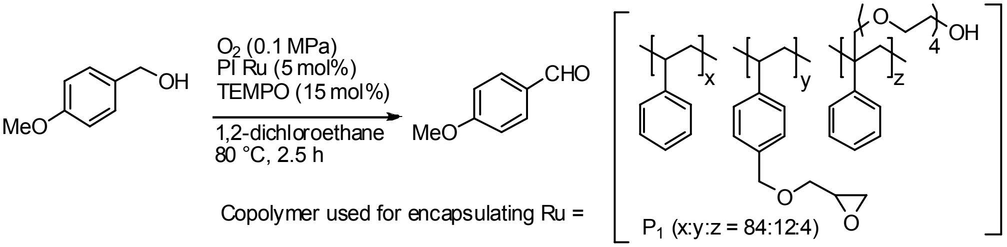


*Scheme 12*. Heterogeneous Ru/HAP catalyst developed by Kaneda and co-workers

Ruthenium supported on alumina ($Ru(OH)_x/Al_2O_3$) was developed by Yamaguchi and Mizuno and demonstrated the ability to oxidize both primary, secondary and activated alcohols in $PhCF_3$ as solvent or even in solvent-free conditions.[49] Recently, the use of superparamagnetic nanoparticles as a supporting material for immobilized metal catalysts was reported. For example, Mizuno and co-workers showed that a ruthenium hydroxide species on magnetite ($Ru(OH)_x/Fe_3O_4$) performed very well in the aerobic oxidation of alcohols, and catalyst/product(s) separation was extremely simple. Indeed, after completion of the oxidation reaction, a permanent magnet was attached to the outside wall of the glass reactor to magnetically "hold" the catalyst, and the reaction solution including the product(s) was separated by simple decantation.[50]

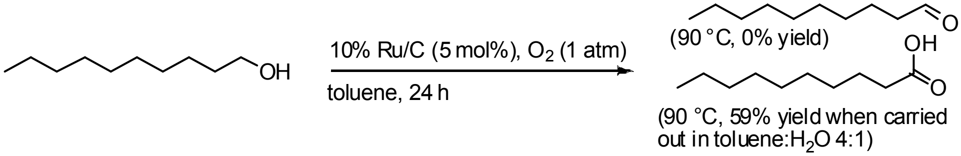
In contrast to the many reports of inorganic supports or organic-inorganic hybrid materials, after the pioneering PSP by Ley and co-workers[37] only a few polymer-supported catalysts for the aerobic oxidation of alcohols were reported. Kobayashi and co-workers developed a polymer incarcerated ruthenium (PI Ru) capable of oxidizing alcohols in aerobic conditions, based on the technique of microencapsulation and cross-linking from a polystyrene-based copolymer and ruthenium chloride hydrate as the metal source. However, this catalyst needed the presence of 15 mol% of TEMPO to show wide applicability to various alcohols (Scheme 13)[51] and leaching of Ru metal was observed in some cases (never exceeding 0.72%), which is typical of polymer supported catalysts, that suffer from low chemical and/or mechanical resistance.

The authors later showed that introduction of inorganic species to organic moieties, thus going back to the creation of organic-inorganic hybrid catalysts generated by the sol-gel approached, allowed the synthesis of an effective heterogenous catalyst which worked well for the aerobic oxidation of alcohols without the need for any additive, avoiding the leaching of Ru.[52]



*Scheme 13*. Polymer Incarcerated (PI) Ruthenium catalyst

The main problem with all these heterogeneous catalysts is that they can be accessed with some difficulties since they are handmade and/or expensive. Much effort has been devoted to develop efficient oxidation methods for alcohols using the readily available carbon-supported metal catalysts.[10] Ruthenium is less expensive than Au, Pd or Pt; however, one of the few reports of Ru/C-catalyzed oxidation methods for alcohols was presented recently by Sajiki and co-workers, who showed that 10% Ru/C as a catalyst in toluene (at 50 °C) under an oxygen atmosphere was able to convert various secondary and primary benzylic alcohols to the corresponding carbonyl compounds and primary aliphatic alcohols to carboxylic acids when water was added as a co-solvent (Scheme 14).[53]

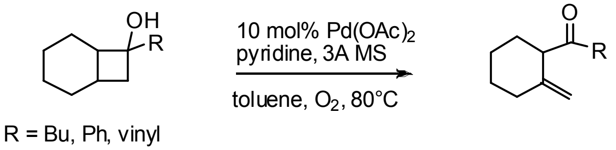


*Scheme 14*. Ru/C-catalyzed aerobic oxidation of alcohols

## PALLADIUM-BASED HOMOGENOUS CATALYSTS

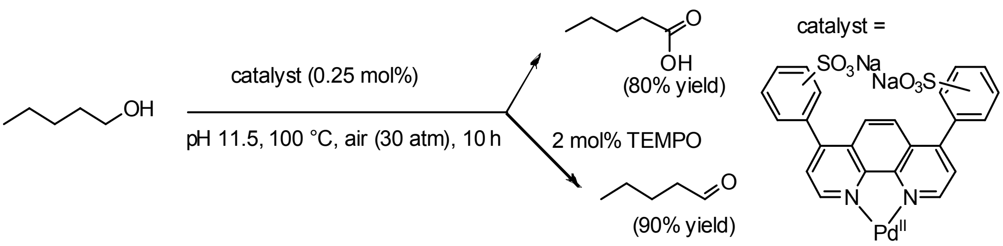
Overall, Pd(II) catalysis represents one of the most mature fields in the aerobic oxidation of alcohols. Much effort has been devoted to finding synthetically useful methods for the palladium-catalyzed aerobic oxidation of alcohols, and some excellent reviews on this topic have appeared.[54] Many mechanistic studies have been undertaken and a generally accepted mechanism for the Pd-catalyzed aerobic oxidations involves the formation of Pd-hydride species.[54b,55,56] The palladium is then reduced to the zerovalent state by the alcohol substrate and is reoxidized to palladium(II) by dioxygen. The transient Pd(0) species is metastable and prone to aggregation to bulk palladium metal (Pd black) with concomitant loss of catalytic activity. One approach to avoid this is to add coordinating ligands, which stabilize the transient Pd(0) species.

The first synthetically useful system was reported in 1998 by Peterson and Larock, who showed that simple $Pd(OAc)_2$ in combination with $NaHCO_3$ as a base in DMSO as solvent catalyzed the aerobic oxidation of primary and secondary allylic and benzylic alcohols to the corresponding aldehydes and ketones, respectively.[57] The replacement of the non-green DMSO by an imidazole-type ionic liquid resulted recently in a higher activity of the Pd-catalyst.[58] However, this method suffered from narrow substrate scope. Uemura and co-workers reported an improved procedure using $Pd(OAc)_2$ (5 mol%) in combination with pyridine and 3Å molecular sieves in toluene at 80°C,[59] that allowed oxidation of primary and secondary aliphatic alcohols in addition to benzylic and allylic ones. When applied to *tert*-cyclobutanols, this reaction proceeded with cleavage of the C-C bond (Scheme 15).[60] This approach could also be employed under fluorous biphasic conditions.[61]



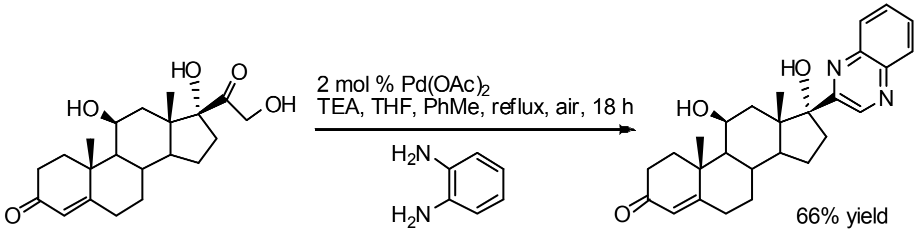
*Scheme 15.* Pd(II)-catalyzed oxidative ring cleavage of *tert*-cyclobutanols under $O_2$ atmosphere

A much more active catalyst is represented by a water-soluble palladium(II) complex of sulfonated bathophenantroline introduced by Sheldon and co-workers.[62] This stable, recyclable catalyst allowed oxidation in a two-phase acqueous-organic medium in 5h at 100 °C/30 bar air with 0.25 mol% catalyst. No organic solvent was required (except for solid alcohols) and the carbonyl product was recovered easily by phase separation. Primary alcohols afforded the corresponding carboxylic acids via further oxidation of the aldehyde intermediate; otherwise, in the presence of 1 mol% of TEMPO, the aldehyde was obtained in high yield (Scheme 16).[62] Pd-neocuproine (in the presence of ethylene carbonate as cosolvent) was found to be even more active and exceptionally tolerant to many functional groups such as C=C bonds, triple bonds, halides, ethers, amines etc, thus showing a broad synthetic utility.[63] However, a more detailed recent investigation of this latter ligand proved that in this case formation of Pd nanoparticles, which are presumably the active catalytic species, occurs (see later for a more detailed discussion).[64]



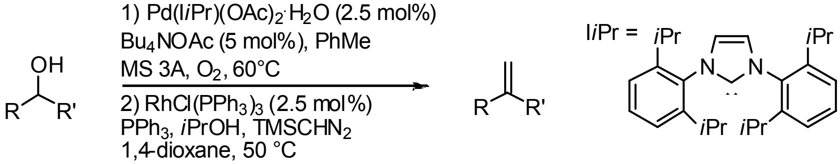
*Scheme 16.* Sheldon's Pd-catalyzed aerobic oxidation of alcohols

One of the main problems associated with homogeneous Pd(II)-catalyzed aerobic oxidations is often represented by Pd black formation. Tsuji and co-workers used substituted pyridines as ligands to prevent formation of Pd black, allowing oxidations to be performed under air and using low catalyst loading.[65] Sigman and co-workers also developed three novel Pd(II)-catalysts for the aerobic oxidations of alcohols,[66] and in a recent publication[67] they reported a comparison study in which they evaluated the substrate scope and the reaction conditions of each of them, concluding that the Pd(OAc)$_2$/TEA system represents the most convenient of the three developed catalytic systems. For example, this catalyst was employed for the direct conversion of α-hydroxy ketones into quinoxalines (Scheme 17).[68]



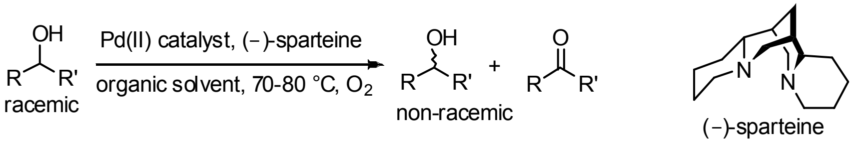
*Scheme 17.* Quinoxaline synthesis via a tandem oxidation process

Another nice example of Pd oxidation catalysis in tandem reactions was shown by Lebel and Paquet, who applied the catalyst developed by Sigman[66b] to the one-pot synthesis of alkenes through a tandem oxidation/olefination process (Scheme 18).[69]



*Scheme 18.* One-pot Pd-catalyzed oxidation and Rh-catalyzed methylenation reaction

In the presence of a chiral diamine, the scope of these oxidations can be expanded to asymmetric catalysis, as for example the oxidative kinetic resolution of racemic secondary alcohols or the oxidative desymmetrization of *meso*-diols. Sigman and Stoltz independently discovered[70] that in the presence of the chiral diamine (−)-sparteine, which plays a dual role of chiral ligand for Pd and exogenous chiral base,[71] the Pd(II)-catalyzed aerobic oxidation of alcohols afforded efficient oxidative kinetic resolution of secondary alcohols, with enantiomeric excesses up to 99.8% (Scheme 19). This methodology was recently applied to the enantioselective total synthesis of various alkaloids,[72] and to the kinetic resolution of key pharmaceutical building blocks, relevant to the enantioselective preparation of Prozac®, Singulair® and the promising hNK-1 receptor antagonist from Merck.[73]



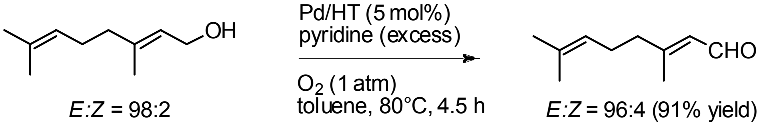
*Scheme 19*. Pd(II)-catalyzed oxidation kinetic resolutions of alcohols

This is an excellent method for the aerobic kinetic resolution of alcohols, leading to remarkably high ee's under optimized conditions; the main limitation of sparteine as a chiral ligand is that only the (−)-enantiomer is available in large quantities, and this will remain a problem until an effective method is found for the preparation of quantities of its enantiomer or a surrogate thereof.[74] However, all the Pd(II)-catalysts reported to date are not widely used on a larger industrial scale. Catalysts with improved stability and activity need to be developed and the research is still very active in this field. A recent study investigated the use of N,O-ligated Pd(II) complexes, which compared well with the previously reported N,N-ligands in the aerobic oxidation of 2-octanol on the gram scale.[75]

## PALLADIUM-BASED HETEROGENEOUS CATALYSTS

Besides the aerobic oxidation of alcohols, palladium catalyzes many oxidative transformations including epoxidation of alkenes, oxidation of terminal alkenes to ketones and other Wacker-type reactions, oxidation of alkanes, hydroxylation of benzenes, and oxidative coupling reactions.[76] Among the transition metals, palladium shows very promising catalytic properties in the form of heterogeneous metal catalysts or nanoparticles. The major problem related to the use of palladium-based catalysts is that palladium agglomeration and formation of palladium black can cause catalyst deactivation in many cases.

Uemura and co-workers attempted heterogenization of their homogenous catalytic system based on $Pd(OAc)_2$, pyridine and 3Å molecular sieves[59] employing hydrotalcite, a naturally produced basic clay mineral, and they found that the Pd/HT system had a higher activity.[77] Especially in the oxidation of geometrically isomerizable allylic alcohols such as geraniol and nerol this catalyst proved to be efficient without any isomerization of the alkenic part (Scheme 20). However, an excess of pyridine instead of the usual 20 mol% was required with such alcohols. Pd/HT was reused at least three times, although a gradual decrease in catalytic activity was observed.

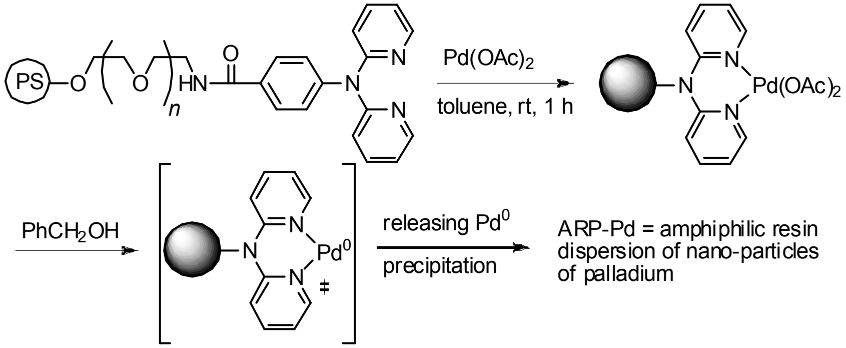


*Scheme 20.* Pd(II)-supported hydrotalcite-catalyzed aerobic oxidation of geraniol

The general routes to nanoclusters/nanoparticles synthesis are based on the chemical reduction of transition metal salts with the appropriate reducing agent in the presence of a stabilizer for the metal. The resulting stabilized metal nanoclusters dispersed in solution can be used as catalysts as such or subsequently heterogeneized on solid supports by different means (e.g surface adsorption, covalent anchoring, embedding by sol-gel techniques). For example, Pd nanoclusters stabilized by *N,N*-dimethylacrylamid-based soluble cross-linked polymers (microgel) were tested as catalysts in the selective oxidation of secondary alcohols to the corresponding ketones with molecular oxygen in water.[78]

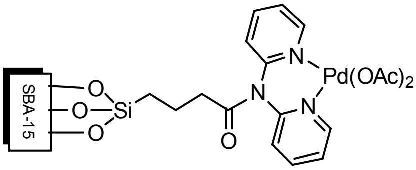
Kaneda and co-workers reported hydroxyapatite–supported palladium nanoclusters (Pd/HAP-0) prepared from stoichiometric HAP with $[PdCl_2(PhCN)_2]$ as a metal source.[79] Fresh Pd/HAP-0 had an induction period of about 10 minutes, in which Pd(II) species were converted into Pd(0) nanoparticles. A wide variety of alcohols, also bearing heteroatoms, were oxidized with this heterogeneous catalyst in trifluorotoluene at 90°C, in water at 110°C or in solvent-free conditions. 1-Phenyl ethanol was oxidized on a quite large scale (30 grams) without any solvent at 160°C.

An amphiphilic resin dispersion of palladium nanoparticles (ARP-Pd) was reported by Uozumi and Nakao, readily prepared by reduction of a PS-PEG resin-supported Pd(II) complex with benzyl alcohol (Scheme 21). This catalyst was applied to the aerobic oxidation of benzylic, allylic and secondary aliphatic alcohols in refluxing water.[80] In the case of primary aliphatic alcohols, the corresponding carboxylic acids were obtained in excellent yields in the presence of $K_2CO_3$.



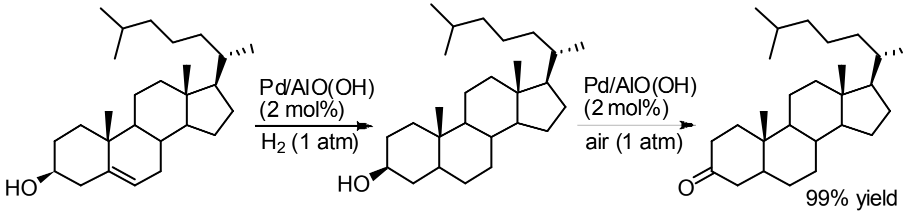
*Scheme 21*. Preparation of amphiphilic resin-dispersion of nanoparticles of palladium (ARP-Pd)

However, organic polymers used as support for Pd nanoclusters are potentially susceptible to oxidative degradation under aerobic oxidative conditions. Besides the already mentioned hydrotalcite and hydroxyapatite minerals, an inorganic alternative for forming a scaffold in which three-dimensional dispersions of nanoparticles can be supported is represented by ordered mesoporous structures (such as MCM-41 and SBA-15) with regular channel and pore diameters in the range of 2 to 30 nm. Karimi and co-workers developed a new type of palladium catalyst immobilized on functionalized SBA-15 and applied it to the oxidation of various alcohols in toluene at 80°C in the presence of $K_2CO_3$ (1 equivalent), which was found to be essential to avoid formation of Pd black.[81] Primary alcohols were converted to the corresponding esters, presumably by previous selective oxidation to carboxylic acids. This example showed that the combination of an organic ligand and ordered mesoporous channels (Scheme 22) resulted in an interesting synergistic effect that led to enhanced reactivity, prevention of the agglomeration of the Pd nanoparticles and generation of a durable catalyst.



*Scheme 22*. Palladium nanoparticles stabilized on mesoporous channels of SBA-15

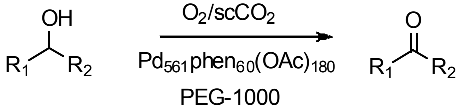
Park and co-workers reported aluminium hydroxide supported-palladium nanoparticles (Pd/AlO(OH)) prepared from [Pd(Ph$_3$)$_4$], tetra(ethylene glycol), 1-butanol, and aluminum tri-*sec*-butoxide.[82] This catalyst displayed dual catalytic activity for both alkene hydrogenation and aerobic oxidation of alcohols. Successful hydrogenation of cholesterol followed by aerobic oxidation to give cholestan-3-one was demonstrated in a one-pot manner (Scheme 23).



*Scheme 23*. Cholesterol hydrogenation followed by aerobic oxidation

However, Pd/AlO(OH) did not catalyze the oxidation or primary aliphatic alcohols such as 1-octanol. Some other examples of palladium-based heterogeneous catalysts obtained by dispersion of the metal on an inorganic support have been recently reported, such as Pd/MgO[83] or $Pd/Al_2O_3$[84] (this latter was found to be selective for the aerobic oxidation of allylic alcohols). Moreover, Wang and co-workers demonstrated that the preparation method of palladium catalyst on aluminum oxide was important for high catalytic performance. Indeed, the activity of $Pd/Al_2O_3$ catalyst prepared by an adsorption method ($Pd/Al_2O_3$-ads) was higher than that prepared by an impregnation method.[85] The authors postulate the formation of Pd nanoparticles, which are probably the true active species, during the course of alcohol oxidation.

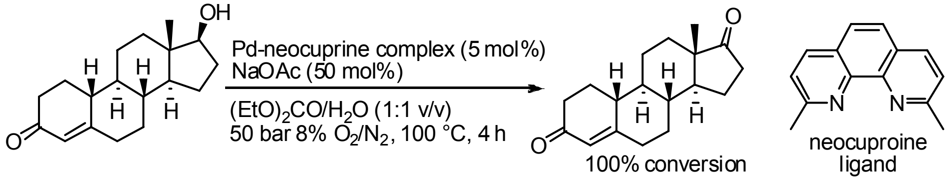
A quite different approach was developed by Leitner and co-workers. They found that the giant palladium cluster, $[Pd_{561}phen_{60}(OAc)_{180}]$, dispersed in poly(ethylene glycol) (PEG), efficiently catalyzes the aerobic oxidation of alcohols in $scCO_2$ (Scheme 24).



*Scheme 24*. Aerobic oxidation of alcohols catalyzed by PEG-stabilized Pd-nanoparticles in $scCO_2$

In this biphasic system, the PEG matrix contains the catalyst (helping in preventing aggregation and deactivation of the catalytically active nanoparticles) while the supercritical carbon dioxide phase dissolves the substrate and the product (thus providing a safe environment for the use of molecular oxygen under essential solvent-free conditions and allowing continuous operation, even with substrates of low volatility).[86] The authors postulate that the high activity and long term stability of the new catalytic system is due to formation of Pd-nanoparticles during the reaction. A variety of alcohols were oxidized in these conditions. Both the catalyst matrix and the mobile phase used in this approach are toxicologically innocuous and environmentally benign materials, thus making this approach particularly appealing for "green" nanoparticle catalysis.

Interestingly, as previously mentioned, Sheldon and co-workers recently demonstrated that, contrarily to the catalytic system based on the bathophenanthroline disulfonate ligand (Scheme 16),[62] their previously described homogeneous catalytic system based on Pd(II) acetate in combination with the more hindered neocuproine ligand[63] actually involves palladium nanoparticles. The susbstrate alcohol acts indeed as the reducing agent and in situ forms Pd-nanoparticles which are the effective catalysts. The catalytic system based on neocuproine-stabilized palladium nanoparticles was applied to the oxidation of nandrolone (Scheme 25).[64]

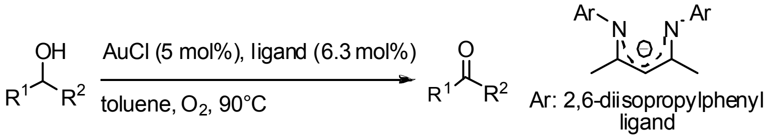


*Scheme 25*. Aerobic oxidation of nandrolone with Pd nanoparticles in acqueous media

Much work has to be done yet in order to investigate in detail the mechanisms involved when nanoparticles are formed in the reaction. Indeed, it is difficult to attribute the actual catalytic activity solely to the ligand bound Pd or to the Pd nanoparticles.

## GOLD-BASED HOMOGENOUS CATALYSTS

The homogeneous oxidation of alcohol catalyzed by gold has rarely been reported. Shi and co-workers,[87] in early evaluations, optimized the aerobic oxidation of primary and secondary benzylic and allylic alcohols using AuCl (5 mol%) and ligand (6.3 mol%) in toluene at 90°C under oxygen atmosphere (Scheme 26).



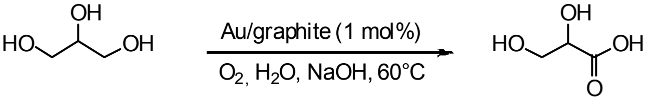
*Scheme 26*. Oxidation of alcohols with gold(I) complexes

Addition of 4Å molecular sieves proved to be beneficial for the reaction. With activated benzyl and allylic alcohols as substrates, both conversions and yields were very high, only aldehydes were produced with excellent selectivity with no overoxidation to carboxylic acids; however, primary aliphatic alcohols were slowly oxidized and formed aldol byproducts. This system was then improved, in terms of sustainability of the process, using water as solvent.[88] Different oxidants, bases and ligands were studied and a final optimized system using 1:1 ratio of gold(I)-neocuproine as catalyst in aqueous basic solution under $O_2$ atmosphere was found. Surprisingly, the oxidation run efficiently only with $NaHCO_3$ as base, NaOH or organic bases, such as $Et_3N$, being inefficient. The limitation of this oxidation procedure is the same as the previous: the narrow substrate scope, being limited to secondary benzyl or allyl alcohols. Moreover, given Sheldon's results with Pd-neocuproine, we cannot exclude that the effective catalysts here are gold nanoparticles formed by gold reduction by the alcohol substrate.

## GOLD-BASED HETEROGENOUS CATALYSTS

Although bulk gold has for a long time being regarded as a poorly active metal, the surprisingly high activity of gold nanoparticles has initiated intensive research into their use for aerobic oxidation reactions. Moreover, the recent findings related to the synergic activity of bimetallic nanocluster catalysis has further expanded the possibilities for the design of new efficient gold-based heterogeneous catalysts.

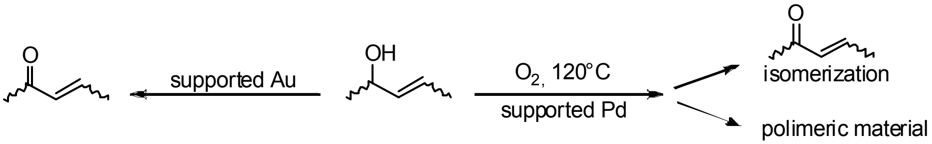
The general procedure for the synthesis of gold nanoparticles is based on reduction of Au salts by a reducing agent or by the support itself in some cases. The first to clearly demonstrate that supported gold nanoparticles can be very effective catalysts for the oxidation of alcohol were Rossi, Prati and co-workers. They employed Au/carbon catalysts, which were effective for a wide range of substrates like diols, glucose and aminoalcohols, and found that the presence of a base was essential for catalysis.[89] Similar Au/$SiO_2$ catalysts were found to be effective with gas-phase reactants and, in this case, no base addition was required.[90] These pioneering studies using Au/carbon catalysts were extended by Hutchings and co-workers[91] who showed that Au supported on graphite could oxidize glycerol to glycerate with 100% selectivity using dioxygen as the oxidant in water with yields approaching to 60%. It was observed that the selectivity to glyceric acid and the glycerol conversion were strongly dependent upon the glycerol/NaOH ratio (Scheme 27).



*Scheme 27.* Oxidation of glycerol using Au/graphite catalysts

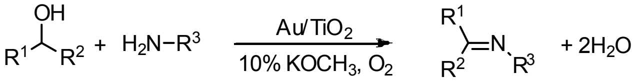
Afterwards, Qiu et al. demonstrated that water has dual promotional functions in the catalytic activity of Au/$TiO_2$ for the selective oxidation of benzyl alcohol: it helps to form microdroplets in a multiphase reaction system and it assists the oxygen adsorption and activation.[92]

One of the most significant advances in the field of alcohol oxidations has been the observations by Corma and co-workers who showed that Au/$CeO_2$ catalyst is active for the selective oxidation of alcohols to aldehydes and ketones and the oxidation of aldehydes to acids.[93] In these studies, the catalysts are active in solvent-free conditions, using $O_2$ as oxidant without the requirement for the addition of NaOH to achieve high activity. Subsequently they showed that for the relevant oxidation of allylic alcohols, gold presented unique selectivity when compared with Pd (Scheme 28).[94]



*Scheme 28.* Aerobic oxidation of allylic alcohols under solvent-free conditions

In many catalytic studies, the support-catalyst interaction is a crucial factor for controlling reactivity.[93,95] Interestingly, Rossi and co-workers have shown that water-dispersed "naked" gold colloidal particles can be very effective catalysts for the oxidation of glucose to gluconic acid.[96] These particles were produced as a colloidal sol by reducing $HAuCl_4$ in the presence of a large excess of glucose acting either as reagent or protector. Christensen, Riisager et al. have made a number of significant advances in the direct oxidation of primary alcohols using supported gold nanocrystals and they have concentrated their efforts on decreasing the amount of base required in these oxidations. They have shown that Au-$MgAl_2O_4$ can catalyze the oxidation of aqueous solutions of ethanol to give acetic acid in high yields.[97] This provides a potential new route to a key commodity chemical that is based on a bio-renewable feedstock using a substantially green technology approach. Recently, they presented the one-pot conversion of alcohols to imines (Scheme 29) by aerobic oxidation with Au/$TiO_2$ followed by condensation with primary amines in methanol.[98]



*Scheme 29.* Au-catalyzed one-pot formation of imines

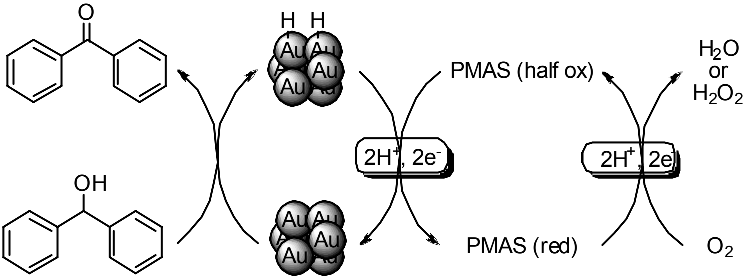
Polymer compounds are attractive because they work as quasi-homogeneous catalysts and provide a large contact area to organic substrates. Examples of these catalysts are represented by the gold-nanocluster stabilized by water-soluble polymer poly(*N*-vinyl-2-pyrrolidone) (Au:PVP),[99] and the microgel-stabilized Au nanoclusters prepared by gold nanoclusters of small size and an appropriate microgel like vinylpyridine with a narrow size.[100] Both catalysts performed very well for the aerobic oxidation of alcohols in water. Kobayashi and co-workers developed, besides PI Ru (Scheme 13), also a polymer-incarcerated gold catalyst (PI Au) for the selective oxidation of alcohols at room temperature and atmospheric pressure of molecular oxygen on air.[101] Aromatic and aliphatic secondary alcohols. also containing S and N heteroatoms, were oxidized to the corresponding carbonyl compounds in good yields and the catalyst could be reused at least 10 times without loss of activity. The same PI Au was used for oxidative esterification of alcohols under ambient conditions[102] and could be applied to triphasic (gas-liquid-solid) reactions by using a microchannel reactor and a capillary column also with molecular oxygen.[103] Recently, Kobayashi et al. included carbon black (CB) to the composition of the PI Au to enhance the stability of gold nanoclusters probably *via* synergistic π-π interactions between the three components which enables they to increase the metal loading amount up to 0.60 mmol $g^{-1}$.[104]

The oxidation of benzyl alcohols was also reported in $scCO_2$ using Au-catalysts supported on $TiO_2$, $Fe_2O_3$ and C.[105] At 100°C and a total gas pressure of 15.0 mPa, benzyl alcohol, $O_2$ and $CO_2$ formed a single homogeneous phase and benzaldheyde was obtained with 99.0% selectivity but only 16.0% conversion using 1% $Au/TiO_2$. Higher conversions were achieved by Kawanami et al. using 2% $Au/TiO_2$, prepared by a deposition-precipitation (DP) method.[106]

Recently, the synergic activity of bimetallic nanoclusters has been presented. Hatchings et al. showed that alloying Pd with Au in supported $Au/TiO_2$ catalysts, that was found the best support in previously studies,[95] the activity for alcohol oxidation was enhanced under solvent-free conditions by a factor of over 25.[107] Then, Zheng and Stucky demonstrated that with the use of low-cost promoting agents (i.e. $K_2CO_3$) instead of Pd and under similar conditions, oxide-supported pure gold nanoparticles could catalyze the oxidation of alcohols even more efficiently; in particular, in contrast to $Au/Pd\text{-}TiO_2$ catalysts which were inactive for the oxidation of 2-octanol, pure supported gold nanoparticles were highly active with the help of a small amount of $K_2CO_3$.[108] Recently, Prati and co-workers reported that Au-Pt nanoparticles supported on the zeolite H-mordenite were able to selectively oxidize glycerol directly to glyceric acid without the use of basic conditions.[109] Also Kobayashi et al. studied the aerobic oxidation of alcohols under ambient condition with gold-platinum bimetallic clusters[110] and in a recent publication they compared the different selectivities using different metal combination catalysts.[111]

Recently, using pyrrolidone-modified SBA-15 supported Au nanoparticles, Xiao, Meng et al. presented a catalytic system which synergistically combined the advantages of both homogeneous catalysts (high activity) and heterogeneous catalysts (good recyclability). This system could oxidized 1-butanol with 50.7% conversion.[112]

Hirao and coworkers reported the first example of catalyst design for the alcohol oxidation reaction using a redox-active polymer as the catalyst support (Scheme 30).[113] They demonstrated that the redox-active PMAS (poly(2-methoxyaniline-5-sulfonic acid)) can work in a multi-catalytic process as both a stabilizer of Au NPs and a redox mediator for aerobic alcohol oxidation in water (Scheme 30). This design concept provides a new type of redox catalyst system for transferring protons and electrons.



*Scheme 30.* Proposed multi-catalytic cycles for the oxidation with Au NPs and PMAS

## CONCLUSIONS

During the last 15 years there has been a considerable increase of interest in the area of metal-catalyzed aerobic alcohol oxidations. In the field of homogeneous alcohol oxidations, the Marko's Cu-(phen), the Sheldon's Pd-(sulfonated bathophenantroline) and the Sigman's Pd($OAc_2$)/TEA systems are the most mature. Ruthenium-based catalysts often suffer from the need for high catalyst loading. A considerable effort has been also made to replace common organic solvents with alternative solvents such as ionic liquids, fluorinated solvents or supercritical $CO_2$ or to perform the oxidation reactions in water. Regarding the chemoselectivity of the reaction, it is interesting to note the complementarity between Cu-based catalysts, who better work with primary alcohols, and gold-based catalysts, who better perform the oxidation of secondary alcohols. Selective methods to obtain aldeydes or carboxylic acids from primary alcohols were also developed. Moreover, elegant examples of efficient kinetic resolutions of racemic secondary alcohols and desymmetrization of meso diols were achieved with Pd-based catalysts in the presence of (−)-sparteine as the chiral ligand. The discovery that Pd and Au nanoparticles are effective catalysts for the oxidation of alcohol moieties has further expanded this research field in the search for new heterogeneous systems, that can allow recovery and reuse of the metal catalyst and the obtainment of pure products. Mechanistically, not much work has been done to elucidate the fine details for many of the metal-catalyzed aerobic alcohol oxidations, except for Pd-catalyzed aerobic alcohol oxidations. Especially for the new heterogeneous procedures involving nanoparticles, the exact nature of the active catalyst has still to be understood. While there has been a tremendous amount of effort applied to the development and improvement of metal-catalyzed aerobic alcohol oxidations, many improvements can be still envisioned. For instance, in order to use these methods in target synthesis, the scope of the individual catalytic systems must be broadened to include more complex alcohols that are synthetically relevant. Moreover, each method should be tested on a larger scale to explore its potential utility in the industrial processes.

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