

Heterogeneously Catalyzed Alcohol Oxidation for the Fine Chemical Industry

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ABSTRACT: A number of new, heterogeneously catalyzed processes to selectively oxidize alcohols into carbonyl or carboxyl compounds have been introduced in the past decade. This study summarizes selected methods suitable for scale-up and convenient adoption by fine chemical and pharmaceutical industries to replace conventional oxidative routes based on homogeneous catalysis or on stoichiometric oxidation with inorganic and organic oxidants.

INTRODUCTION

The selective oxidation of alcohols to aldehyde, ketone, or acid products is a reaction of primary relevance in synthetic organic chemistry and, accordingly, in the fine chemicals and pharmaceutical industries.¹ Unfortunately, for decades, both industrial and laboratory scale oxidation processes were carried out in toxic organic solvents using toxic and hazardous oxidants, such as chromates, permanganates, and organic peroxides.

In the last 15 years, intense research efforts have been devoted to developing new environmentally acceptable catalytic methods capable of replacing conventional stoichiometric processes with catalytic conversions using metal or organo-catalysts coupled to clean oxidants, such as O₂ or H₂O₂.²

Such efforts have been widely successful, especially for homogeneously catalyzed processes. Suffice it to mention the oxidative dehydrogenation of 1-phenylethanol dissolved in toluene on the 100 kilogram scale catalyzed by Pd(OAc)₂/pyridine at 100 °C in solution using a safe O₂/N₂ mixture in a 7 L reactor to give acetophenone in 99.5% yield.³ For comparison, the batch reaction carried out on the same scale would require over 1000 L of solvent. The same team has advanced the aerobic route for the oxidation of primary alcohols based on TEMPO (the stable radical 2,2,6,6-tetramethylpiperidinyloxy) along with Cu(I) inexpensive salt, *N*-methylimidazole, and bipyridine⁴ to such a level (broader scope and functional group tolerance than Pd-catalyzed aerobic oxidation) that the latter homogeneous protocol is now employed in the pharmaceutical industry.

Treaties⁵ and reviews² are regularly published, and conferences⁶ periodically organized on the topic of alcohol selective oxidation, and research continues to flourish. For example, *N*-doped graphene was recently found to be an excellent catalyst for aerobic benzyl alcohol oxidation to benzaldehyde;⁷ whereas silica-entrapped nanostructured Bi₂WO₆ (SiliaSun) or Bi₂WO₆ alone can be used as excellent photocatalytic mediators for the highly selective oxidation of glycerol⁸ or benzylic alcohols⁹, respectively, under visible light with oxygen at ambient pressure and temperature.

Yet, writing at the end of the first decade of the 2000s,¹⁰ Arends and Sheldon were surprised to find that mainstream undergraduate organic chemistry textbooks¹¹ continued to recommend classical oxidation methods using stoichiometric amounts of highly toxic inorganic oxidants, such as chromium(VI), Ru(IV), and Mn(VII) reagents, or less toxic but certainly non-green organic oxidants such as DMSO (Swern oxidation) and hypervalent iodine (Dess–Martin periodinane).

Efficient heterogeneously catalyzed processes are indeed especially important from the viewpoint of practical applications, as they require no further product purification or consequent disposal cost of harmful waste. Furthermore, advanced solid catalysts can be adapted to continuous processes, which will form a central technology of forthcoming synthetic organic chemistry.¹²

In this study, therefore, we focus on the emerging uses of heterogeneously catalyzed processes viable for large scale applications.¹³

Several main methods have emerged, namely, oxidation processes using (i) TEMPO and its derivatives with either hypochlorite¹⁴ or O₂ (combined with copper, cobalt, or iron cocatalysts)¹⁵ as the primary oxidant or (ii) numerous supported transition metal catalysts,¹⁶ including palladium and gold on various supports, both in supercritical CO₂ and in conventional organic solvents.

In this study, we identify the main advantages and limitations of selected practical methods published in the past decade as well as the challenges required to conclusively end the era of industrial alcohol oxidation carried out with toxic reagents in toxic organic solvents.

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OXIDATION OVER SUPPORTED METAL CATALYSTS

Supported Pd is a well-known aerobic oxidation catalyst suitable for the selective oxidation of alcohols, even though many commercial palladium catalysts suffer from poor stability.¹⁶ In 2007, Lee and co-workers reported that palladium supported over mesoporous alumina is a highly active and stable catalyst for the aerobic oxidation of cinnamyl and crotyl alcohols to their respective aldehydes at 60 °C in toluene.¹⁷

The active sites are the Pd(II) atomic centers of a metastable surface PdO (Figure 1). Catalyst deactivation is due to the

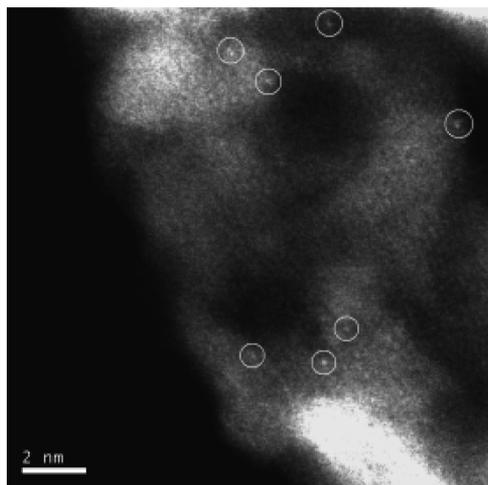


Figure 1. Active sites comprised of Pd(II) atomic centers of metastable surface PdO (circled in the scanning high-resolution high-angle annular dark-field TEM image) in a 0.03 wt % Pd/Al₂O₃ catalyst [Reproduced with permission from ref 17, Copyright 2007 John Wiley and Sons].

reduction reaction Pd(II) → Pd(0), with the exposed metallic Pd(0) sites catalyzing aldehyde decarbonylation, leading to rapid formation of adsorbed CO/alkylidynes and related self-poisoning.¹⁸

This insight allowed the team to develop a more active and stable heterogeneous Pd catalyst by replacing conventional alumina with mesoporous alumina to entrap and stabilize the active palladium centers. The new catalyst was 10 times more active with respect to palladium(II) supported on conventional γ -Al₂O₃. The catalyst, however, was not commercialized.¹⁹

Similarly, the exceptionally active alloyed PdAu (a Pd-rich shell surrounding a Au-rich core) catalyst supported on TiO₂, introduced by Hutchings and co-workers in 2006 for the solvent-free aerobic oxidation of primary alcohols (at 100–160 °C under 1–10 bar O₂),²⁰ has to the best of our knowledge thus far not found a practical application.

These outcomes might be linked to the serious safety hazards posed by the highly exothermic oxidative dehydrogenation reaction with pure O₂ in the presence of easily flammable organic solvents, especially if the reaction is performed on a large-scale in a batch reactor as is almost invariably found in fine chemical manufacturing.²¹ As described by Muldoon and co-workers, on an industrial scale, even air is too dangerous;¹⁵ the use of O₂ at concentrations <10% to achieve conditions in which combustion cannot take place requires the application of high pressure (>10 bar). Hence, Muldoon concludes that “the best way to make such pressurised systems scalable is to use a continuous flow system”.¹⁵

In further detail, two approaches have indeed been developed to overcome the safety issue of aerobic alcohol oxidation mediated by transition metals. The first makes use of supercritical carbon dioxide (scCO₂) as an environmentally friendly and safe, but technically cumbersome, alternative solvent. The other employs flow microreactor technology as a means to control the exotherm and prevent the formation of explosive mixtures.

The former approach has been independently developed by the groups of Poliakoff²² and Tsang²³ in the U.K., Neumann in Israel,²⁴ Baiker in Switzerland,²⁵ and Campestrini with some of us in Italy²⁶, among others. In scCO₂, the oxidation is highly selective (as rapid desorption of lesser hydrophilic aldehyde prevents overoxidation of the alcohol substrate to acid). Most supported catalysts remain stable with no metal leaching in the supercritical fluid phase, whereas modification of the catalyst surface hydrophobicity/hydrophilicity balance leads to a significant increase in the reaction turnover and selectivity.²⁷

The second widely explored approach has been to carry out the oxidative dehydrogenation reaction under continuous flow conditions. Good yields and high carbonyl selectivity can be obtained with numerous supported catalysts, including Ru/Al₂O₃,²⁸ Fe₂O₃/SiO₂,²⁹ and Pd, over numerous supports, including palladium double entrapped first in a metal organic framework (MOF) and then within silica.³⁰

Alternatively, the safety issue posed by the use of O₂ can be overcome altogether using safe and clean aqueous H₂O₂ as primary oxidant.³¹ Hydrogen peroxide alone, however, is a poorly selective oxidant. Remarkably, Cao and co-workers in China discovered in 2009 that a commercially available gold catalyst (Au/TiO₂) could be used for green and selective synthesis of carbonyls (and of acids in the case of primary aliphatic alcohols) by simply carrying out the reaction with aqueous H₂O₂ at 90 °C.³²

No base is employed, and thus no purification of the carbonyl or carboxylic acid product is required. The method is similar to the use of H₂O₂ in association with sol-gel entrapped tetra-*n*-propylammonium perruthenate (TPAP) in the catalytic oxidation of alcohols to carbonyls at room temperature.³³ However, the reaction over supported gold is considerably faster and can be easily scaled up. Showing the practical relevance of the new process, Cao's team adapted the optimized reaction conditions (0.01 molar amount of 1 wt % of Au catalyst and 3 molar amount of 5 wt % of aqueous H₂O₂ at 90 °C for 2.5 h) to convert 1-hexanol to 1-hexanoic acid with 93% yield on a hectogram scale.³²

OXIDATION MEDIATED BY TEMPO

Alcohol oxidation mediated by TEMPO or its derivatives are today routinely employed in the fine chemical industry.¹⁴ The organocatalyst has limited toxicity and, being easily synthesized from triacetoneamine (namely, via condensation of ammonia with acetone),³⁴ is nowadays widely available at low cost.

Two main processes for the oxidation of alcohols to carbonyls are employed, namely, the Anelli–Montanari biphasic reaction with TEMPO/dichloromethane/hypochlorite at 0–4 °C³⁵ and aerobic oxidation with oxygen (typically in the presence of Cu⁺).¹⁵

When the reaction with NaOCl (and bromide in a catalytic amount) is carried out with soluble alcohols, such as carbohydrates in water, valued carboxylic acids, such as glucuronates, are rather obtained.³⁶ In each case, the highly active (1 mol %) and selective bielectronic oxidant is the

corresponding oxoammonium cation formed and continuously regenerated by the primary oxidant.

Scale-up of TEMPO-mediated oxidation processes is generally easily accomplished.¹⁴ In the United States, Stahl even conducts laboratory classes aimed at organic chemistry undergraduates in which the selective oxidation of a primary alcohol to the corresponding aldehyde, using (bpy)/NMI/Cu(I)/TEMPO in acetonitrile with air as the only oxidant, is demonstrated on a semi-industrial scale.³⁷

The TEMPO radical moiety has been successfully supported over a number of different solid supports, including polymeric resin beads,³⁸ carboxylic acid functionalized polymer fibers (FibreCat TEMPO),³⁹ organically modified silica (SiliaCat TEMPO),⁴⁰ and TEMPO polymer grafted onto silica.⁴¹

FibreCat TEMPO is particularly stable in the consecutive oxidation of alcohols with bleach.³⁹ The open structure of the FibreCat polymer (polypropylene or polyethylene fibers functionalized with monomers, such as carboxylic acid, obtained by graft copolymerization), allows for the achievement of high catalytic loading (up to 2 mmol g⁻¹ of nitroxyl radical), whereas the fibrous nature of the catalyst, moderately swelling in organic solvent, provides better functional group accessibility when compared to polystyrene beads in which the substrate slowly diffuses through the beads.³⁹

Obviously, the lack of swelling of the solid catalyst will further ease catalyst and product separation. Comprised of TEMPO moieties encapsulated within the huge internal porosity of the organosilica SiliaCat matrix (several hundred m² g⁻¹),⁴² the catalyst shows superior performance with respect to both homogeneous and silica-entrapped TEMPO. For example, when compared to TEMPO dissolved in solution, the sol-gel hybrid catalyst affords a number of valuable organic compounds, such as benzyl-, allylic-, and aliphatic-aldehydes⁴⁰ or α -hydroxy⁴³ and aminohydroxy⁴⁴ acids with greater yields and selectivity.

Along with Bolm, we investigated the performance of SiliaCat TEMPO compared to silica-supported TEMPO in terms of stability in the Montanari–Anelli oxidation of 1-nonanol.⁴⁵ The organosilica catalyst retained its activity in numerous consecutive runs, whereas the silica-functionalized catalyst rapidly deactivated.

Such enhanced stability is due to both the sol-gel encapsulation within the inner sol-gel cage (Figure 2), which protects and stabilizes the delicate nitroxyl radical from quenching interactions between neighboring functional groups,⁴⁶ as well as to the organic modification of the silica

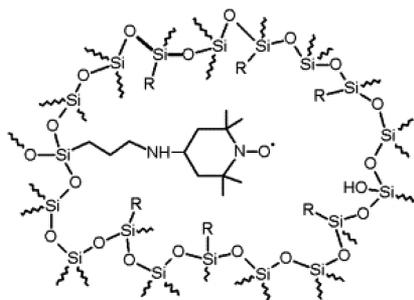


Figure 2. Chemical structure of SiliaCat TEMPO. This sol-gel catalyst typically has 0.8 mmol g⁻¹ loading and a large (600 m² g⁻¹) surface area.

matrix, which greatly stabilizes the silica structure in the alkaline environment of the Anelli–Montanari reaction.

An even more active silica-based TEMPO catalyst has been developed by Hearn, Saito, and co-workers, who grafted via RAFT polymerization a TEMPO polymer (poly(2,2,6,6-tetramethylpiperidine methacrylate) subsequently treated with 3-chloroperoxybenzoic acid) onto silica.⁴¹ The high catalyst loading (up to 1.6 mmol g⁻¹) ensures exceptionally high activity in the Montanari–Anelli oxidation of benzyl alcohol and linear aliphatic alcohols, even though secondary alcohols could barely be oxidized due to the remarkable substrate specificity of the catalytic material.

Getting back to SiliaCat TEMPO, the open mesoporous structure of the organosilica amorphous matrix ensures fast diffusion in and out of the hybrid silica. This, coupled to the pronounced physical and mechanical stability of the glassy organosilica matrix, makes the SiliaCat catalyst ideally suited for fast continuous oxidative conversions by exploiting the rapid heat and mass transfer of reactions in continuous-flow microreactors.

For example, it is enough to carry out the Montanari–Anelli reaction under flow at room temperature at a flow rate between 50 and 500 μ L/min to observe full conversion of benzyl alcohol to pure benzaldehyde in only 0.3 min.⁴⁷ For comparison, under batch conditions, the conversion of the same amount of benzyl alcohol requires 1 h to achieve a maximum 97% conversion at 0 °C (entry 3 in Table 1).

Furthermore, the reaction under flow can be performed at room temperature and does not require the use of corroding KBr as a cocatalyst. As a further comparison, the same reaction under flow over resin-immobilized TEMPO requires cooling at 0 °C and the use of cocatalyst KBr.⁴⁸ Similarly, the aerobic oxidation of benzyl alcohol under flow over Ru(OH)_x/Al₂O₃ requires residence times of \sim 1 h due to the very low turnover frequency of this Ru catalyst (2 mol substrate mol Ru⁻¹ h⁻¹).⁴⁹

The high stability of the sol-gel hybrid catalyst observed under batch conditions is retained under continuous-flow, whereas the much shorter reaction time (a 1 h batch process with 97% yield is successfully replaced with a <1 min process affording 100% conversion with complete selectivity) makes the process particularly suitable for scale-up. Under flow, one column packed with SiliaCat TEMPO particles (0.8 mmol g⁻¹) remains completely stable for several hours, affording constant conversion of the alcohol substrate without noticeable reduction in activity.

The same catalyst is being considered for new applications for forthcoming biomass-based processes. For example, Domínguez de María and co-workers in Germany recently used SiliaCat TEMPO to selectively oxidize the hydroxymethyl group of HMF to afford 2,5-diformylfuran.⁵⁰ In this case, yields were slightly lower than those observed with TEMPO in solution, but the heterogeneous catalysts were reusable without reduction in catalytic activity (Figure 3).

The authors concluded that a heterogeneous flow-integrated process for producing valued dialdehyde 2,5-diformylfuran over SiliaCat TEMPO may be easily envisaged.⁵⁰

■ CONCLUSIONS AND PERSPECTIVES

Cost-effective and clean selective oxidation of alcohols over solid catalysts is a key enabling technology capable of streamlining a wide range of organic transformations in the fine chemical and pharmaceutical industries.² When a reaction is complete using one of the leach-proof catalysts described in

Table 1. Applications in Flow Chemistry for Benzyl Alcohol Oxidation over SiliaCat TEMPO [Reproduced with Permission from Ref 47, Copyright 2013 Elsevier].

entry	catalyst	T (°C)	flow (μL/min)	volume reactor (mL)	residence time ^a (min)	conv/select ^b (%)
1	SiliaCat TEMPO	20	50	0.7	3.2	100/100
2	SiliaCat TEMPO	20	100	0.7	1.6	100/100
			250		0.6	
			500		0.3	
3	SiliaCat TEMPO (0.1 mol %)	0	batch		60	97/100

^aThe residence time was calculated in the function of the catalyst density and pore volume. ^bConversion/selectivity determined by GC–MS analysis.

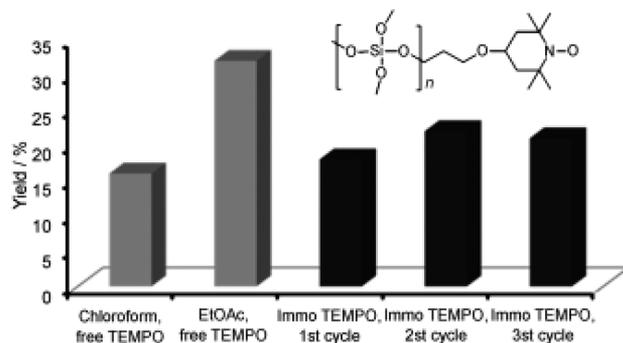


Figure 3. Performance of SiliaCat TEMPO-catalyzed oxidation of HMF to yield 2,5-diformylfuran with NaOCl as the primary oxidant. The biphasic reaction is carried out in EtOAc for 1 h at room temperature [Reproduced with permission from ref 50, Copyright 2013 John Wiley and Sons].

this study, the product can be obtained by simple evaporation of the solvent, or the solution comprising the carbonyl/carboxyl compound can be used directly in another conversion.

At least two classes of reliable, versatile, and cost-effective heterogeneously catalyzed methods are currently available. The first makes use of fiber-functionalized FibreCat TEMPO and organosilica-entrapped TEMPO with NaOCl as the primary oxidant. The second relies on gold-based catalysis with aqueous H₂O₂ as the terminal oxidant. Both are suitable for scale-up to the large scale required by industrial processes.

The polyolefin and the organosilica matrix of the former catalysts present unique advantages in terms of thermal, mechanical, and chemical stability. Furthermore, functionalized organosilica of huge mesoporosity, narrow particle size distribution, and consistently high loading, not swelling in an aqueous, organic, and biphasic system, can be successfully applied in continuous conversions, selectively affording high yields of valued carbonyls at an unprecedented high rate.

Evaluating the feasibility of gold-based syntheses in the fine chemical industry, Cao recently suggested⁵¹ that, contrary to supported nanoparticles (NPs) of platinum-group metals (PGMs: Pd, Pt, Ru, Rh, and Ir), which are essential to a wide variety of commercially important processes,⁵² gold is considerably more abundant (2700 tonnes of gold mined in 2012, against an overall 432 tonnes for PGMs). Furthermore, in general, supported gold NPs exhibit reactivity that is far superior to that of traditional PGM catalysts.

In addition, whereas expensive and ever scarcer PGMs are “Class 1 metals: metals of significant safety concern”,⁵³ gold nanoparticles are generally nontoxic,⁵⁴ which, also considering that gold catalysts are cheaper than palladium catalysts, opens up interesting new possibilities in industrial alcohol oxidation with aqueous H₂O₂ over titania-supported gold³² or over

organosilica-entrapped gold nanoparticles⁵⁵ under batch conditions or, even better, continuously in a flow microreactor.

As the fine and specialty chemical industry and its main customer, the pharmaceutical industry, move toward green and sustainable chemistry,⁵⁶ this study will hopefully contribute to accelerating the end of the obsolescent industrial oxidation era where carbonyls and carboxylic acids obtained from alcohols were synthesized using large amounts of toxic oxidants and toxic organic solvent.

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Notes

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