Sol-Gel Entrapped TPAP: An Off-the-Shelf Catalyst Set for the Clean Oxidation of Alcohols

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Abstract: Whether in supercritical CO\textsubscript{2} or in organic solvent and using O\textsubscript{2} or aqueous H\textsubscript{2}O\textsubscript{2} as primary oxidants, the series of sol-gel entrapped TPAP hybrid silica gels is a versatile class of oxidation catalysts suitable for the highly selective conversion of alcohols to carbonyls. These materials are generally more stable and active than traditional polymer-supported analogues. This report summarizes recent findings showing the large potential of this technology for synthetic chemistry.

1. INTRODUCTION

Ruthenium is an highly selective and versatile metal catalyst for the oxidation of alcohols [1]. In particular, the VII species tetra-n-propylammonium perruthenate (TPAP) either dissolved in solution or immobilized on polymer support is a very efficient and selective catalyst for the aerial oxidation of primary, secondary, benzyl and alkyl alcohols in non-aqueous media, including dense-phase carbon dioxide. Most functional groups such as carbon-carbon double bond, epoxy, indole, acetal, remain unaffected in the TPAP/O\textsubscript{2} conversion of alcohols which eventually are transformed into valued carbonyls [2]. However, after reaction the spent catalyst is isolated as a black colloidal suspension of RuO\textsubscript{2} which cannot be recycled. This limits the commercial application of expensive TPAP-based catalysis only to those industrial processes where an extremely high degree of selectivity is needed such as in the pharmaceutical industry. In such cases, a solid heterogenized version of the catalyst is used to avoid product contamination and speed up product isolation from reactants [3]. In general, heterogenization of TPAP on commercial supports (Fig. 1) adds significant financial value [4].

For catalysis to achieve its full potential in the fine chemicals and pharmaceutical industries, where only about 10% of all productions currently use catalysis, heterogenous processes are to be developed in which reduction of waste, increased selectivity and shortened synthetic routes go along with process robustness and catalyst stability.

Remarkably, in the last few years a number of selective and clean catalytic processes for alcohols oxidations have been developed that are being increasingly adopted by industry [5]. Among these, the series of sol-gel entrapped TPAP catalysts are versatile mediators suitable for the selective oxidation of alcohols to carbonyls with oxygen or aqueous H\textsubscript{2}O\textsubscript{2} as terminal oxidants. These materials and related oxidative processes are of urgent commercial interest to drugs, perfumery and fragrance manufacturers commercializing highly pure products (devoid of organic solvents and metals) to prevent drug contamination and alteration of olfactory test screenings. In general, the selectivity and the activity of entrapped TPAP materials are higher than for homogeneous perruthenate, i.e., the solid surface in these hybrid organic-inorganic catalysts participates actively in the reaction mechanism. Reactions can be carried out in conventional organic solvent with O\textsubscript{2} [6] or with H\textsubscript{2}O\textsubscript{2} [7] or aerobically in dense phase carbon dioxide [8] affording in all cases high yields of aldehydes or ketones with pronounced selectivity.

We summarize here the achievements in each of these reaction media, and discuss how the versatility of the sol-gel entrapment process allows active site optimization affording a true off-the-shelf catalytic series suitable for application in diverse environments.

2. AEROBIC OXIDATION IN ORGANIC SOLVENT

Sol-gel nanohybrid silica particles organically modified and doped with TPAP are highly efficient catalysts for the selective oxidation of alcohols to carbonyls with O\textsubscript{2} at low pressure (1 bar) in toluene [6]. The materials are easily prepared by a one-step sol-gel process and their catalytic per-
formance can be optimised tailoring the conditions of their synthesis by hydrolytic co-polycondensation of tetramethoxysilane (TMOS) and alkyltrimethoxysilanes R-Si(OMe)$_3$ in the presence of TPAP. Eventually, leach-proof heterogeneous catalysts are obtained that are up to 6 times more active than unsupported perruthenate (Fig. 2).

The best performing catalysts require both an high degree of surface hydrophobicity as well as high amounts of water and co-solvent in the sol-gel polycondensation. The alcoholic oxidation is carried out by the oxygen in the coordination sphere of the metal center which leads to carbonyl products by an intramolecular hydride abstraction from the α-carbon (a primary KIE indicates that such abstraction is the rate determining step of the overall process) [9]. We invoked a ternary complex involving perruthenate, alcohol and oxygen which explains in a single mechanistic picture the overall kinetics. Indeed, high concentration of both oxygen and alcohol show a clear inhibitory effect resulting from a decrease in concentration of the catalytically effective 1:1:1 ternary complex.

3. AEROBIC OXIDATION IN scCO$_2$

Alkyl-modified silica gels doped with TPAP are good catalyst in the catalytic aerobic oxidation of alcohols in supercritical CO$_2$ [10]. The structure-activity relationship for these ORMOSILs shows that the best performing catalysts require both a high degree of surface hydrophobicity as well as high amounts of water in the sol-gel polycondensation process. Later on, the FluoRuGel series of hybrid fluorinated silica glasses doped with TPAP was introduced with marked stabilization and activity enhancement of perruthenate upon its confinement in the sol-gel fluorinated silica matrix [8].

The oxoruthenate catalyst is entrapped in a porous sol-gel fluorinated matrix. Dense phase carbon dioxide dissolving both O$_2$ and the alcohol substrate upon contact with the powdered CO$_2$-philic sol-gel material rapidly spills the reactants into the cages where the oxidative dehydrogenation takes place, and then it extracts the carbonyl product.

In general, the activity and stability of these materials are subtly dictated by structure, depending on the degree of fluorination and on the length of the fluoroalkyl chain linked to the silica network of the matrix. While both homogeneous TPAP and also ORMOSIL-entrapped TPAP in scCO$_2$ show the typical perruthenate-mediated oxidation kinetics consisting of a fast initial stage up to 40-50% conversions, followed by a slower oxidation stage mediated by less reactive RuO$_2$, the reaction mediated by FluoRuGel shows an initial induction stage followed by a faster linear stage up to complete conversion of the substrate (Fig. 3). This points to improved catalysis by TPAP entrapped in the fluoroalkyl-modified silica matrix: i.e., to a different chemistry of the entrapped dopant obtained by changing the properties of the sol-gel cage. We made the hypothesis that the partly positive carbon in highly dipolar -CF$_3$ groups that concentrate at the cage’s surface further attracts the entrapped RuO$_4^-$ adding to the effect of the large N(CH$_2$CH$_2$CH$_3$)$_4^+$ cation (whose use in combination with perruthenate was indeed introduced to promote selectivity by mitigation of the strong oxidation power of RuO$_4^-$ alone) [11].

Finally, the general concept of supported ionic liquid catalysis in supercritical phase (sc-Silc) has been first successfully applied to the aerobic oxidation of alcohols by using perruthenate-based materials [12]. The methodology combines the advantages of ionic liquids as solvent booster; dense phase carbon dioxide as reaction (and extraction) solvent, and immobilized metal catalyst for easy product separation and catalyst recycle. The hybrid mesostructured silica gel co-incapsulating the ionic liquid imidazolium and the aerobic catalyst perruthenate prepared by co-polymerization of TEOS and imidazolium-modified organosilane, is the most active perruthenate-based catalyst in the oxidative dehydrogenation of alcohols in scCO$_2$. Its activity was substantially

**Fig. (2).** Oxidation kinetics in the aerobic conversion of benzyl alcohol in toluene mediated by 10 mol% ORMOSIL-entrapped TPAP (A-Me$_3$, ■) and unsupported (○). [Reproduced from Ref. 6, with permission].

![Oxidation kinetics in the aerobic conversion of benzyl alcohol](image-url)
higher compared to a simple ORMOSIL-entrapped per-
ruthenate, while site isolation of the entrapped Ru centers
prevents catalyst degradation and renders these silica gels
ideal candidates for practical use in commercial alcohols
oxidation.

The system indeed meets industry requirement for het-
ergeneous conversions in scCO<sub>2</sub> (the catalyst is highly se-
lective, stable, easily obtained with high catalytic loads and
in any desired shape). Similarly, no conventional solvent is
used to extract the product out of the IL, and the same leach-
proof entrapped IL has broad application achieving what is
required for practical use of ionic liquids.

4. OXIDATION WITH H<sub>2</sub>O<sub>2</sub> IN ORGANIC SOLVENT

Even though molecular oxygen is the most environmen-
tally and economically convenient primary oxidant, its use in
association with TPAP suffers the disadvantage of requiring
high reaction temperatures (T>70°C) in order to reoxidize
the spent catalyst to the native species. Complementing thus
the aerobic processes discussed above, unmodified SiO<sub>2</sub> gels
doped with TPAP are effective catalysts for the oxidation of
alcohols by hydrogen peroxide at room temperature, pro-
vided that the oxidant H<sub>2</sub>O<sub>2</sub> solution is added slowly (Fig. 4)
[7].

Two processes are involved: the oxidation of the alcohol
and H<sub>2</sub>O<sub>2</sub> decomposition. Hence, quick addition of the H<sub>2</sub>O<sub>2</sub>
solution to the reaction mixture containing the substrate and
the catalyst leads to very low alcohol conversion (3-4%),
with peroxide decomposition being the main reaction. Con-
versely, when the H<sub>2</sub>O<sub>2</sub> solution is added slowly by means of a
syringe-pump, the alcohol conversion increases up to be-
come almost quantitative. In other words, when the concen-
tration of peroxide is kept low during the whole process the
alcohol is smoothly oxidised and decomposition of H<sub>2</sub>O<sub>2</sub> to
water and O<sub>2</sub> is minimised.

Even the selectivity of the oxidative process is affected
by the pace of hydrogen peroxide addition. Hence, when
alcohol conversions are lower than 50%, benzaldehyde is the
only product detected. At conversion higher than 50%, the
alcohol overoxidation becomes significant and benzoic acid
is detected along with benzaldehyde. However, the overoxi-
dation can be completely eliminated by sequestering the wa-
ter formed along with the aldehyde in the first oxidative step.
Eventually, almost quantitative alcohol conversion and an
excellent aldehyde selectivity are obtained.

The method is general and can be applied to widely dif-
ferent substrates (Table 1) because contrary to crystalline
catalytic materials such as zeolites (including zeolite X [13]
and MCM-41 [14] doped with perruthenate, which are shape
selective), sol-gel silica glasses are amorphous materials
showing a distribution of inner porosities which allows their
application to the conversion of largely different substrates.

### Table 1. Alcohol Conversions and Carbonyl Yields in the Oxidation at 25 °C of Various Substrates in Ether With Hydrogen Peroxide Added at the
Velocity of 0.15 mL/h Catalysed by Silica-Entrapped TPAP in the Presence of 3Å Molecular Sieves

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Alcohol Conv. (%)</th>
<th>Carbonyl Yield (%)</th>
<th>Carboxylic Acid Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl alcohol</td>
<td>94.3</td>
<td>94.3</td>
<td>0</td>
</tr>
<tr>
<td>(±)-1-Phenylethanol</td>
<td>63.3</td>
<td>63.0</td>
<td>0</td>
</tr>
<tr>
<td>1-octanol</td>
<td>71.6</td>
<td>41.7</td>
<td>29.9</td>
</tr>
<tr>
<td>(±)-2-octanol</td>
<td>58.9</td>
<td>58.9</td>
<td>0</td>
</tr>
</tbody>
</table>

[reproduced from Ref. 7, with permission]
5. STABILIZATION OF ENTRAPPED TPAP

Catalyst recycle experiments recovering the catalyst from scCO$_2$ medium and washing it with various organic solvents show (Fig. 5) that after only 10 TONs performed in the course of the first experiment, the catalyst retains only 10-40% of the initial efficiency in the second experiment (first recycle) [9]. Such efficiency decay continues with further recycling and after a total of five runs (four recycle) the catalyst becomes inactive. The rate of catalyst degradation depends on the nature of the solvent used for recovering and washing the material. In DCM, which is a good solvent for unsupported TPAP, the inactivation takes place very quickly and already after the first recycle the catalyst is almost inactive. On the other hand, in diethyl ether and even more in hexane, where unsupported TPAP does not dissolve at all, the efficiency decay is noticeably slower.

These observations corroborate the hypothesis of a TPAP inactivation caused by self-aggregation of Ru derivatives induced by the solvent. In fact, when the catalyst is recovered and washed with CH$_2$Cl$_2$, a fast development of chlorine gas bubbles occurs which is revealed by a pungent smell of chlorine during drying of the wet catalyst. To the contrary, use of chemically inert compressed carbon dioxide as unique trapping medium leaves the un-inactivated catalyst the cage’s surface of the entrapping matrix takes active part in the chemical reaction occurring at the interface by dictating the accessibility of the active center to the external reactants.

Fine chemicals companies in Europe and in the US have an expensive manufacturing base and the business is suffering from 25% excess capacity [16]. Moreover, all companies have very similar technology offerings whereas suppliers having specialized niche capabilities often report shortfalls in capacity. Production of active molecules over selective sol-gel catalysts would differentiate production and offer superior products capable to satisfy top market demand.

Indeed, a number of new heterogenous silica-based sol-gel catalysts for the fine chemicals industry have been lately introduced ranging from Rhodia’s immobilized Co(salen) cobalt catalyst [17] for hydrolytic kinetic resolution through Aveca’s catalytic asymmetric cyanoxydrol (CACHy) catalysts [18] and SiliCycle’s SiliaCat TEMPO [19] for selective oxidations. Sol-gel entrapped catalysts are then not only prevented from becoming impurities but also lead to improved turnover numbers. Also, they can be easily adapted to continuous processes.

All these economic and technical drivers are likely to make the production of fine chemicals over sol-gel entrapped catalysts a central technology of the fine chemicals industry [20]. Entrapped perruthenate will be a most useful aerobic catalyst useful in the preparation of a large variety of important carbonyl compounds.

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REFERENCES

[3] For example, manufacturer Aldrich commercializes perruthenate supported on silica gel (572578), (polystyrene-supported (511587) and bound to polymeric FibreCat (590223). Codes are from the company’s catalog accessible at: www.sigmaaldrich.com/catalog.
[4] For instance, prices in Eur/g from above catalog of 100 g of supported perruthenate are: 1415 on silica; 2420 on resin; and 2900 on with H$_2$O$_2$ at room temperature; alkyl-modified organosilica works best in the aerobic oxidation in toluene; organo-fluorosilica or supported-ionic liquids are suited for oxidative dehydrogenation in scCO$_2$.
FibreCat. These materials generally have loadings in the range 0.2-0.4 mmol/g. Hence, 100 g contain up to 40 mmol of perruthenate which (as potassium salt) are commercialized at 930 Eur.


[18] These sol-gel catalyst-immobilizing technologies originally developed by ICI Synetix (now Johnson Matthey after its purchase in 2002).
