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Enhancing selectivity in oxidation catalysis with sol–gel nanocomposites

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Valuable organic compounds such as α-hydroxy acids are easily synthesised with relevant selectivity enhancement using a sol–gel hydrophobized nanostructured silica matrix doped with the organocatalyst TEMPO: A materials science based synthetic route which cannot be achieved *via* classical homogeneous synthesis.

Materials science, and sol-gel science and technology in particular,[1] are providing a variety of novel solutions to the requirements of modern organic chemistry where highly selective and stable catalysts are in urgent demand for replacing stoichiometric reagents in many fundamental transformations.[2] Several catalytic processes, therefore, can now be carried out over highly porous, nanostructured silica oxides doped with one (or more) reactive catalytic species, with easy recovery (and recycling) of the precious catalyst at the end of the process.[3]

Our approach to heterogenizing catalytic conversions utilizes doped organically modified silica[4] xerogels (ORMOSILs), developed over the past few years as recyclable catalysts for a variety of conversions,[5] according to processes such as:

$$CH_3Si(OCH_3)_3 + Si(OCH_3)_4 + H_2O \rightarrow [(CH_3)SiO_mH_n]_p + CH_3OH \quad (1)$$

where in the unbalanced eqn. (1), $m < 2$, n is always $\neq 0$ and the value of p approaches Avogadro's number.[6] Here, in addition to describing a convenient catalytic strategy to synthesise fundamental components in several important compounds with potent biological activity such as α-hydroxy acids,[7] we also show that significant improvement in the selectivity of the organocatalyst may be achieved by its entrapment at the inner surface of a microporous hydrophobized sol–gel silica matrix, exploiting the spatial restrictions imposed this entrapment.

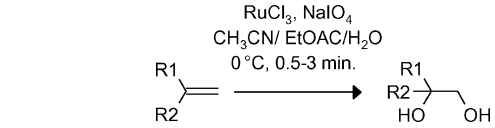
Our two-step oxidation process involves firstly the *syn*-dihydroxylation of a terminal alkene catalyzed by ruthenium, followed by oxidation of the resulting diol with bleach mediated by entrapped TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical).[8]

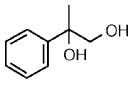
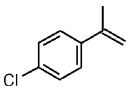
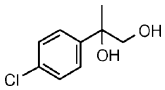
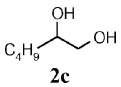
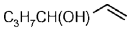
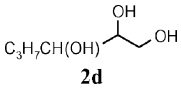
Syn-diols **2a–d** (Table 1) were thus obtained starting from terminal alkenes by using the "flash" RuO_4-catalyzed dihydroxylation protocol in a biphasic solvent system (ethyl acetate : acetonitrile : water = 3 : 3 : 1) in the presence of 7% mol RuO_4 at 0 °C.[9]

A variety of olefins can be selectively oxidised in the presence of diverse oxidisible functional groups. Thus, aliphatic alkenes (1-hexene and 1-hexen-3-ol) were neatly converted into diols **2c** and **2d** with no traces of cleavage products; while with aromatic alkenes the dihydroxylation reaction was even faster and a very short reaction time was crucial to minimise competitive glycol cleavage due to RuO_4-mediated electrocyclic fragmentation.[9b]

In the synthesis of diol **2a**, for example, 4% mol of $RuCl_3$ and 0.5 min were the optimal reaction parameters to obtain the diol in high yield, with longer reaction times or the classical 0.07 equiv. RuO_4 leading to ketone as the sole reaction (fragmentation) product.

Table 1 Dihydroxylation of terminal alkenes



Substrate[a]	Product	Time/min	Diol/ketone[b] (%)
 **1a**	 **2a**	0.5	97/3
 **1b**	 **2b**	0.5	94/6
 **1c**	 **2c**	3	100/0
 **1d**	 **2d**	3	100/0

[a] All reactions were performed on a 1 mmol scale in a solvent mixture of ethyl acetate (3 mL)/acetonitrile (3 mL)/water (1 mL) at 0 °C using 4–7 mol% $RuCl_3$ (see text) and 1.5 equiv. of $NaIO_4$. [b] Calculated by GC-MS.

To synthesize the corresponding α-hydroxy acids, the diols thereby obtained were further oxidised with TEMPO/NaOCl with the idea of exploiting the known selectivity of the nitrosonium ion $TEMPO^+$ for primary alcohols.[10]

Using 10% mol TEMPO dissolved in a 1 : 1 solution of water : acetonitrile cooled to 0 °C and buffered to pH 9.1, the reaction proceeded with good yields in the case of aliphatic diols affording the corresponding α-hydroxy acids (79% in the case of 1,2-hexanediol). The oxidation of the aromatic diol **2a** (Table 2), on the other hand, afforded (±)atrolactic acid in 24% yield, yielding the ketone as the main reaction product (55%).

Such glycol cleavage is due to unselective oxidation of the diol secondary hydroxyl by $TEMPO^+$,[11] which in its turn is favoured by the activated aromatic substrate. Indeed, when a deactived diol such as the *p*-Cl derivative was used as the substrate (**2b**), the cleavage was reduced and the acid : ketone ratio (65 : 20) changed in favour of the acid.

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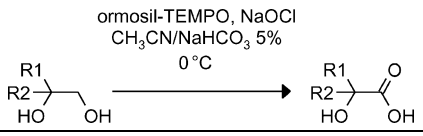
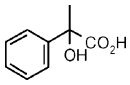
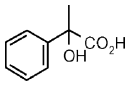
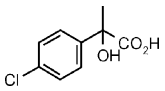
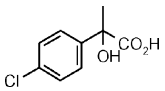
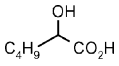
Table 2 TEMPO mediated oxidation of *vic* diols to α-hydroxy acids



Substrate[a]	Product	Product yield[b] (%)	Ketone (%)
2a[c]		24	55
2a		60	40
2b[c]		65	20
2b		80	5
2c		79	0

[a] The reactions were performed on a 1 mmol scale in a solution of water (6 mL)/acetonirile (6 mL) at 0 °C buffered to pH 9.1 using 10 mol% of ORMOSIL-entrapped TEMPO. [b] Isolated yield. [c] The oxidation is carried out under homogeneous conditions.

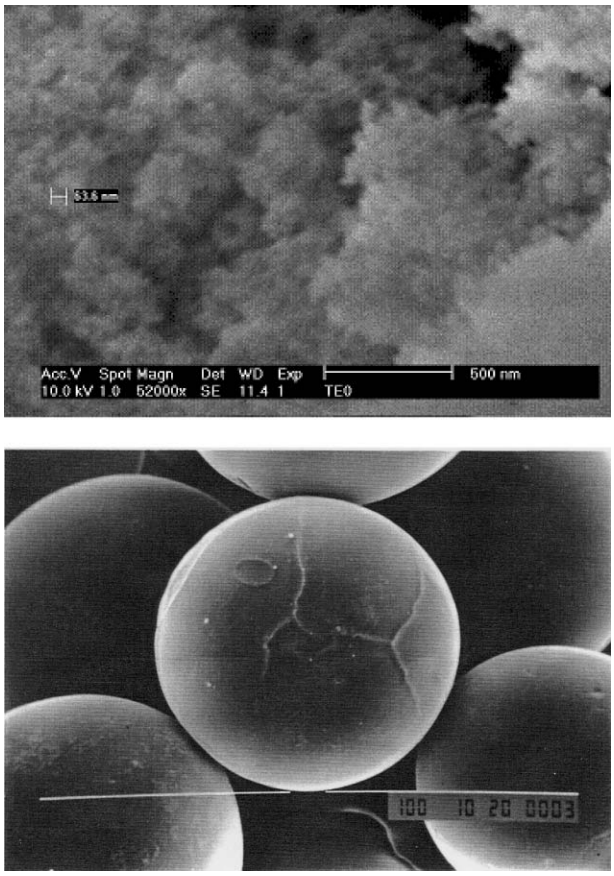


Fig. 1 The SEM photograph (52000×) of ORMOSIL-entrapped TEMPO (*above*) clearly reveals the nanostructured, spongy morphology of the material which is completely different to the non-porous smooth surface of polystyrene beads (*below*, photo courtesy of Prof. Anthony Barrett) commonly used in organic synthesis as catalyst support.

Since the homogeneous TEMPO/bleach reaction protocol applied to the conversion of aromatic diols gives the moderate selectivity reported above, we turned our attention to our newly developed sol–gel entrapped TEMPO catalyst.[12] Indeed, we have recently established that in the oxidative synthesis of (aromatic) amino hydroxy acids from aminodiols catalysed by TEMPO encapsulated in an hydrophobized silica matrix, the heterogeneous oxidation over the sol–gel catalyst results in three-fold selectivity improvement.[13]

In this case too, the heterogenous oxidation of diol **2a** using an entirely (100%) methyl-modified silica xerogel (SiMe100)[14] leads to an inversion of selectivity compared to the homogeneous conversion, with an acid : ketone ratio of 60 : 40. Moreover, diol **2b** is now converted almost entirely (80 : 5) into the corresponding α-hydroxy acid, while conversion of aliphatic substrates such as **3c** proceeds smoothly, also over encapsulated TEMPO, affording high yields of the acid.

As in the case of the oxidation of alcohols[14] and aminohydroxy-alcohols,[13] the ORMOSIL catalysts can also be recycled repeatedly in the oxidation of diols, as consecutive reaction tests show prolonged *intermediate* stability (which truly measures a catalyst's stability), due to the protecting action of the sol–gel ORMOSIL cages towards the entrapped nitroxyl radicals (see below).

These results provide a clear example of enhancement in selectivity upon entrapment of an organocatalyst in the inner porosity of a composite material, which is highly relevant to modern organic chemistry in which solid-phase synthesis is being widely applied (Fig. 1).[15]

The effect of the spatial confinement imposed by the narrow silica pores is to restrict the possible orientations that a reactant can assume on approaching the catalytic center. Moreover, the intra-cage silanol groups, which hinder free tumbling of the substrate molecule, dictate a specific orientational approach to the catalyst through the hydrogen bonds between the substrate (the hydroxylated diol) and the pore/cage surface. As a result of these effects, sol–gel entrapped catalysts generally show higher selectivity in comparison to the catalyst either in solution or surface-bound to a non porous material.

This idea is analogous to Fisher's "key-in-the-lock" mechanism invoked to explain the selectivity of enzymatic reactions and is emerging as a general concept[16] in the theory of heterogeneous catalysis.

In the present case, where the selectivity for primary over secondary hydroxyls is due to steric hindrance associated with the preferential attack of primary alcohols by $TEMPO^+$,[10a] encapsulation of the nitroxyl radical moiety in the restricted environment provided by the cages (15 Å in diameter) further favours the conversion of less hindered primary hydroxyls.

Furthermore, contrary to what happens with catalyst tethering at a material's external pore surface, sol–gel encapsulation ensures effective site isolation and protection. As a consequence, the nitroxyl radical moieties are protected from intermolecular quenching which is known to cause activity degradation in catalysts obtained by supporting TEMPO over commercial silica.[17] In addition, they can be recycled in all seven of the consecutive reaction cycles in which they are used, showing a unique activity *enhancement* upon use which is typical of doped ORMOSILS employed in liquid-phase catalysis.[14]

Organic modification of the silica cages is also required, with the 100% methyl-modified ORMOSIL being significantly more selective than unmodified SiO_2-supported TEMPO.

Indeed, a closer look at the catalyst lamellar shaped cage surface (by DRIFT spectroscopy, Fig. 2)[18] reveals, through the lower relative intensities of the *ν*O–H and *ν*Si–O bands, that the cages are depleted of silanol groups. Besides, adsorbed water is residual, as indicated by the extremely low intensity of the *δ*H–O–H band. These observations point to a low degree of hydrophilicity in the modified ORMOSIL network. The inner

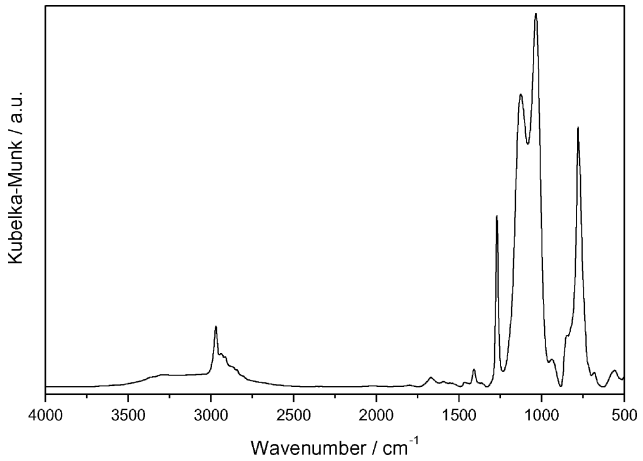


Fig. 2 The DRIFT spectrum of ORMOSIL-entrapped TEMPO clearly reveals that its pores are depleted of silanol groups.

cage surfaces not only contain hydrophobic groups but are also deficient in hydrophilic ones; thus, in the conversion of *vic*-diols, the hydrogen-bonding interaction between the hydrophilic hydroxyl groups in the substrate and the silanol groups at the cage's surface is greatly diminished, while the access to encapsulated TEMPO is spatially restricted by the narrow cages.

Conducting a thorough DRIFT spectral analysis of the catalysts used in the present study, we have recently shown that the presence of the co-precursor MTMS affects the structure and the hydrophilicity/lipophilicity balance (HLB) of the sol–gel catalyst.[19] However, its content does *not* appreciably affect the catalyst's hydrophilicity. In particular, modification with 25% MTMS imparts a significant decrease in the catalyst's hydrophilicity without major structural changes; higher modifier content does not further influence hydrophilicity, but is responsible for a gradual lipophilicity increase and for striking structural changes.

The organically modified silica structure is now made of larger, less strained six-member rings [$(SiO)_6$] (and not by four-member units, $(SiO)_4$) which are able to accommodate the unreactive methyl groups better, with the alkyl organic groups concentrated at the cage surface, diminishing the number of silanols at the surface and, as a consequence, the intra-cage hydrogen bonds which limit the freedom of the dopant molecule.[18,6]

These findings offer a long awaited solution to the "alkyl effect" for which 800–1000% activity enhancements are commonly observed for catalytic species sol–gel entrapped in heavily alkylated ORMOSIL matrices.[20] This also explains why, counter to intuition, the xerogels with the highest limitations to diffusion imposed by the narrow pore network, still posses the highest reactivity. Indeed, a dramatic increase in the activity of ORMOSIL-entrapped catalysts is observed exactly when the transition from four- to six-member rings takes place.

Interestingly, these findings were somewhat anticipated by molecular orbital calculations that clearly predicted how, sol–gel amorphous silica being made of siloxane clusters, large silica clusters with six-membered rings should have "very weak hydrogen bonding between the two Si–O–H groups" and large structural flexibility.[21]

Finally, also of relevance to this report is the fact that the TEMPO moiety has been entrapped by starting from cheap and readily available 4-oxo-TEMPO rather than the expensive radical TEMPO itself, making the use of ORMOSIL-entrapped TEMPO attractive from an economical viewpoint.[22]

In conclusion, the results of the present study further demonstrate the benefits of anchoring the TEMPO catalyst inside nanocages of porous silica for which the surface HLB can be tailored to the requirements of an organic catalytic synthesis, offering a practical alternative to the use of the cyanohydrins currently employed in industrial processes.[8]

Acknowledgements

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Notes and references

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4 Functionalized silica gels are commercial reagents with a rapidly growing market. Doped silica gels offer several technical advantages over well known organic resins being solvent-independent (rigid porous structure and no swelling) and with a high density of functional groups (small volume of gel required). Silica works in all solvents (organic and aqueous), is easy to weigh and handle, mechanically stable and suitable for scale-up. Sigma-Aldrich, for instance, commercializes the silica gels produced by SiliCycle Inc. See also the URL: www.silicycle.com.

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11 That is, the oxidation of the secondary hydroxyl is also mediated by $TEMPO^+$, and due to the action of OCl^-, as shown in: A. Besemer, PhD Thesis, Delft University of Technology, 1994.

12 *General oxidation procedure:* $NaIO_4$ (321 mg, 1.5 mmol) was dissolved under stirring in 1 mL of H_2O. Next, the solution was cooled to 0 °C and a 0.1 M solution of $RuCl_3$ (400 μL, 0.04 mmol) was added and the mixture stirred until the color turned bright yellow. Ethyl acetate (3 mL) and acetonitrile (3 mL) were added, followed by the olefin (1 mmol). The slurry was stirred until all starting material was consumed (0.5 to 3 min, depending on the substrate). The reaction was then quenched adding 5 mL of saturated $Na_2S_2O_3$ solution, and the phases were separated, extracting the aqueous layer with ethyl acetate (3 × 15 mL). After the combined organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure, the crude product was purified by column chromatography on silica gel using a DCM/ethyl acetate as mobile phase. A solution of the diol (1 mmol) in water (6 mL)/acetonitrile (6 mL) was then placed in a

thermostated reaction vessel, with 135 mg of ORMOSIL-supported TEMPO (0.1 mmol of TEMPO, according to microanalysis). After the reaction mixture was cooled to 0 °C, an aqueous solutionof NaOCl (2.5 mL, *ca.* 13% w/w) was added, buffered to a pH of 9.1 by further addition of 5% $NaHCO_3$ (2 mL). The reaction mixture was vigorously shaken until all substrate was consumed (TLC of reaction mixture samples). After filtration, the filtrate was acidified adding 10 mL of a 1 M tartaric acid solution, and the resulting solution extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*, and the crude product was purified by column chromatography on silica gel using a CH_2Cl_2–ethyl acetate mixture as eluent. *General catalyst preparation:* methyltrimethoxysilane (MTMS), 3-aminopropyl-trimethoxysilane (APTMS), tetramethyl-orthosilicate (TMOS), 4-oxo-2,2,6,6-tetramethyl-1-piperidinoloxy free radical (4-oxo TEMPO), and methanol were purchased from Sigma-Aldrich and used without further purification. Ultra pure water (Millipore Type I quality) was used in all the preparations. The chemical entrapment of the TEMPO moiety in the sol–gel silica hybrid materials was performed in two steps: reductive ammination of 4-oxo-TEMPO with APTMS, followed by sol–gel polycondensation of methyltrimethoxysilane (MTMS) and TMOS in the presence of the TEMPO funcionalized alkoxide thereby obtained. The chosen molar ratio was Si : MeOH:H_2O = 1 : 2 : 3 for all of the catalyst preparations. A typical catalytic ORMOSIL doped with TEMPO, such as Si75Me, was obtained by dissolving APTMS (4 mmol) in MeOH (2.6 mL), bringing the pH to 7 with HCl (conc.), and then adding 4-oxo-TEMPO (1 mmol) along with $NaBH_3CN$ (0.5 mmol). After 48 h under fast stirring at room temperature, the $NaBH_3CN$ excess was destroyed by adding HCl (49 mmol) and a precursor mixture made of TMOS (1.750 mL), MTMS (4.370 mL), MeOH (2.730 mL) and H_2O (5.8 mL) was added under fast stirring. The sol gelled slowly and the alcogel obtained was sealed, left to age at room temperature for 24 h and eventually dried at 60 °C for five days. The resulting powder xerogel was washed three times with DCM under reflux and dried again at 60 °C. A typical catalytic load was 0.3 mmol TEMPO g^{-1}.

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22 4-oxo-TEMPO is easily obtained by triacetonamine (TAA), a polymer stabilizer marketed in thousands of tons yearly by large companies such as Degussa at 3 \$ kg^{-1}; whereas the current market price of TEMPO is 80–100 \$ kg^{-1} due to the expensive reduction step (with $NaBH_4$) of the carbonyl group in 4-oxo-TEMPO. In order to be adopted by industry, the price of TEMPO will have to be around 20 \$ kg^{-1}: a requirement clearly met by sol–gel entrapment of 4-oxo-TEMPO. W. Kesber, personal communication, (prices as of March 23, 2005); M. Pagliaro, D. Avnir, J. Blum, G. Deganello, *US Pat.* 6797773 B1, 2004 .