



Sol-gel Entrapped Nitroxyl Radicals: Catalysts of Broad Scope

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Sol-gel entrapped TEMPO-like radicals are excellent supported molecular catalysts for the selective and clean alcohol oxidation, including the primary hydroxyl functions of cellulose. Could these materials reach widespread utilization for the syn-

thesis of fine chemicals, bio-based building blocks and even carboxyl cellulose nanofibrils? This study offers a critical perspective.

1. Introduction

About twenty years ago, the fine chemical and pharmaceutical industries started to use the stable nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as organocatalyst to selectively mediate alcohol oxidation,^[1] mostly relying on the Anelli-Montanari reaction protocol performed at 0 °C in a two-phase (CH₂Cl₂/H₂O) system with buffered aqueous NaOCl as primary oxidant, 1 mol% TEMPO and 10 mol% amount of bromide to enhance the reaction rate.^[2] The new method offered a convenient metal-free route replacing older oxidative routes based on stoichiometric (and highly toxic) inorganic and organic oxidants. The carbonyl reaction products are important ingredients of valued drugs, vitamins, fragrances and aromas in which contamination with transition-metal species is subject to stringent limits.^[3]

Subsequent intense research efforts, some of which are reviewed in this study, led to further progress. In 2003, for example, Augustine and industry's partners improved the Anelli-Montanari process by eliminating the organic solvent and replacing KBr with environmentally benign Na₂B₄O₇ (borax).^[4] Under solvent-free conditions, no solvent has to be removed whereas the much higher amount of alcohol substrate compared with about 2.5 % in the classic reaction using dichloromethane, has largely positive cost, environmental and safety implications. A company is using the process to manufacture 3,3-dimethylbutanal, a feedstock for an approved *N*-alkyl derivative of a sweetener.^[5] Similarly, scholars in Japan introduced the advantageous use of high volumetric efficient NaOCl·5H₂O

crystals in place of conventional aqueous NaOCl,^[6] and Chernyshev and co-workers discovered that elemental iodine can replace hypochlorite as primary oxidant (with a catalytic amount of an alkyl-substituted pyridine).^[7]

Concomitantly, aiming at avoiding loss of the valued (and moderately toxic) catalyst, a large research efforts have been devoted to heterogenize the TEMPO moiety by supporting it onto organic, inorganic and hybrid organic-inorganic materials. A review^[8] by Megiel encompasses tens of different examples that span from 1995 Endo's surface derivatization of ultrafine silica and ferrite,^[9] through recent covalent grafting of nitroxyl radicals onto graphene.^[10] Some, including polystyrene-bound TEMPO (PS-TEMPO),^[11] FibreCat TEMPO,^[12] TurboBeads-TEMPO (TEMPO immobilized on the outer surface of Fe₃O₄ magnetic nanoparticles),^[13] and organosilica xerogel SiliaCat TEMPO,^[14] have even been commercialized.

As with any other chemical reactant, all heterogeneous catalysts have their advantages and limitations. Silica- and organosilica-entrapped TEMPO, for example, cannot be used in strongly alkaline media where the silica-based matrix readily dissolves.

Reviewing selected examples of sol-gel encapsulated nitroxyl radical silicas lately emerged as excellent catalysts for tomorrow's clean oxidation processes of direct relevance to the emerging biorefinery, this study offers a critical perspective written from a nanochemistry viewpoint on sol-gel entrapped TEMPO-like radicals. The article is concluded with a practical assessment on the technical and economic feasibility of a widespread adoption of these solid catalysts in the synthesis of fine chemicals and pharmaceutical active ingredients.

As industry lately started to carry out the reaction under flow, increasing reaction yield and avoiding the low temperatures of the conventional NaOCl/KBr process,^[15] the outcomes of this study will hopefully accelerate the introduction of TEMPO-based solid catalysts for waste-free alcohol selective oxidation processes which are ubiquitous in the chemical industry.

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2. Innovative Oxidation Catalysts

2.1 Magnetically recoverable core-shell nanoparticle-supported TEMPO

A major advance in the field of silica-based materials functionalized with TEMPO, was reported by Karimi and Farhangi in 2011.^[16] The team prepared silica-coated Fe₃O₄ core-shell nanoparticles in which the silica layer is functionalized with TEMPO by simply reacting the silica-coated Fe₃O₄ first with (3-aminopropyl)triethoxysilane to give amino-functionalized silica-coated nanomagnets, and subsequently subjecting said amino-propyl-coated nanomagnets to reductive amination with 4-oxo-TEMPO in the presence of NaBH₃CN. The resulting catalyst was successfully employed in the absence of any transition-metal and halide co-catalyst for the metal- and halogen-free aerobic oxidation of a wide range of primary, secondary, allylic, and even sterically hindered alcohols in water at 50 °C with 1 bar O₂ as primary oxidant and 4 mol% *tert*-butylnitrite as nitrite source. After use, the catalyst was quickly separated (in less than 5 s) and effectively recovered by using an appropriate external magnet, thereby minimizing the loss of catalyst during separation. The recovered catalyst was reused for 20 consecutive runs. TEM images of both the fresh and reused catalyst (Figure 1) clearly indicate that no detectable changes of the catalyst occurs during the consecutive reaction cycles.

The same nanobead catalyst was subsequently applied to the oxidative Passerini three-component reaction of alcohol substrates involving the condensation of an isocyanide, an aldehyde or ketone, and a carboxylic acid, followed by the Mumm's rearrangement.^[17] Again, the catalyst could be quickly

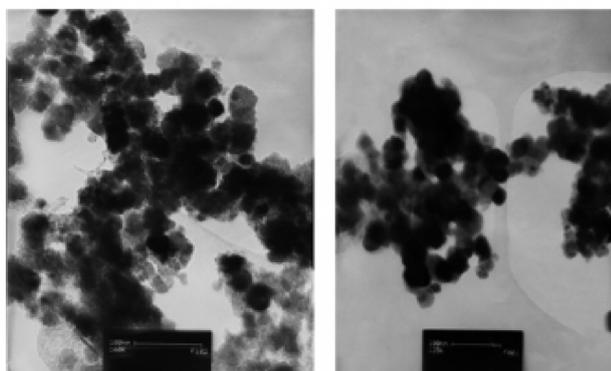
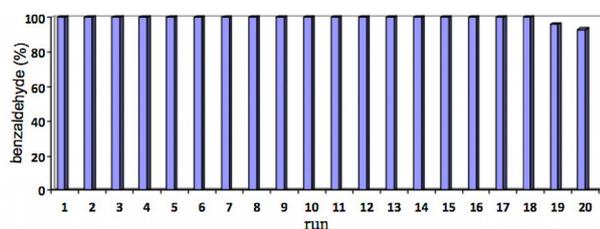


Figure 1. Yields obtained in the aerobic oxidation of benzyl alcohol to afford benzaldehyde in the presence of magnetically core-shell nanoparticle-supported TEMPO catalyst 1 after 4 h (top); and (bottom) TEM images of the catalyst before (left) and after (right) recycling experiments. [Reproduced from Ref. [16], with kind permission.]

recovered and reused in 14 subsequent reaction runs with only slight decrease in activity.

The team went on applying the catalyst first to the selective aerobic oxidation of 5-hydroxymethylfurfural (HMF) to 2,5-diformylfuran (DFF), by carrying out the reaction in pure acetic acid or in toluene in the presence of small quantities of acetic acid and 5 mol% *tert*-butyl nitrite as a co-catalyst, with consistent >99% yield in three subsequent reaction cycles with a decrease to 96% in the fourth run and a drop to 77% yield only in the fifth run. Again, comparison of the TEM images before and after 5 consecutive catalytic cycles showed little or no change in its nanoscale aspect.^[18] HMF is key biorefinery platform chemical easily obtained through dehydration of glucose and fructose, and DFF is an important furan dialdehyde for which synthesis from HMF is an intensely researched topic, as DFF may be used as precursor of functional polymers, pharmaceutical and antifungal agents, and furan-urea resins.^[19]

More recently, the Karimi's catalyst was successfully applied to the green synthesis of cellulose nanofibrils (CNF) in water, by oxidising part of the wood pulp C₆ surface hydroxyls on cellulose microfibril surfaces to carboxylic acid groups. The reaction uses aqueous NaOCl as primary oxidant and a catalytic amount of NaBr as promoter and takes place in water only at the surface of the solid catalyst.^[20] The catalyst was found reusable for 4 successive reaction cycles (Figure 2) with no nitroxyl radical leaching, thereby opening the route to greener and less costly industrial process for the synthesis of CNF, even though the extent and rate of oxidation HMF with the heterogeneous catalyst were slightly lower than those obtained with homogeneous TEMPO. The heterogeneous process smoothly led to fibrillation affording 5 nm nanofibrils of thickness similar to that obtained in the oxidation mediated by TEMPO in solution (Figure 3).

Finally, no iron or silica were found using energy dispersive X-ray analysis in the CNF film product, pointing to effective and complete separation of the catalyst (as usual with an external magnet) from the oxidized pulp fibre.

Started in Japan, production of CNF based on TEMPO-mediated oxidation followed by defibrillation of cellulose fibers is now performed across the world with projected compound annual growth between 2017 and 2021 approaching 30%, and global production capacity rapidly expanding.^[21] In light of practical applications of silica-coated magnetite nanoparticles as carriers of TEMPO-based oxidation catalysts it is relevant to notice here that large-scale continuous production of consistently uniform spherical Fe₃O₄ nanoparticles through a thermal decomposition in a high-temperature continuous flow reactor has been lately achieved.^[22]

CNF is a new, renewable and non-toxic functional material for which exceptional properties (high surface area, large amount of hydroxyl groups, excellent mechanical properties, transparency etc.) enable numerous new applications with several new products containing CNF (for which recently even a quality index for benchmarking of different CNF materials has been proposed)^[23] in the process of being developed. Selected applications include use as rheology modification agent for paint, ink, coating, food, cosmetic and pharmaceutical

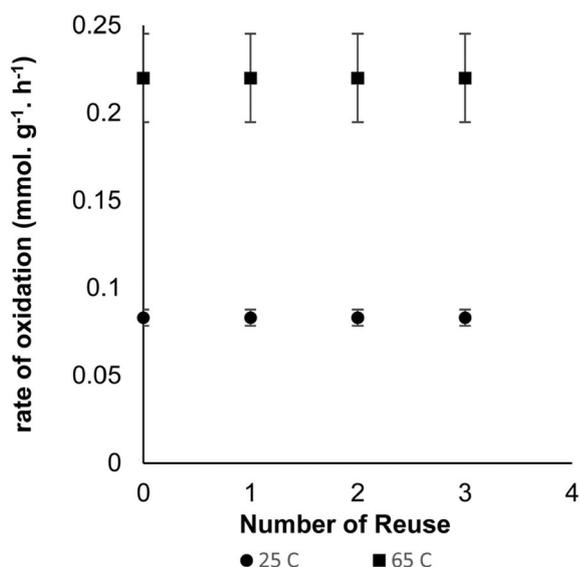
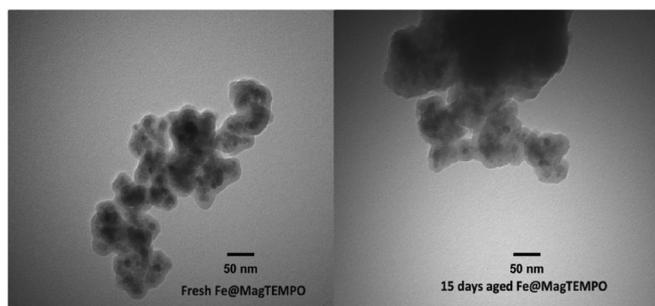


Figure 2. TEM images of fresh magnetically core-shell nanoparticle-supported TEMPO catalyst and 15 days aged catalyst in NaOH solution at pH 10 (top); and (bottom) reusability of the catalyst for oxidation of cellulose pulp: 2 g bleached softwood pulp, 0.2 L water, 0.1 mmol NaBr, 0.175 mg cm⁻³ solid catalyst, 5 mmol g⁻¹ NaClO, NaOH (0.5 M) to maintain pH 10. [Reproduced from Ref. [20], with kind permission.]

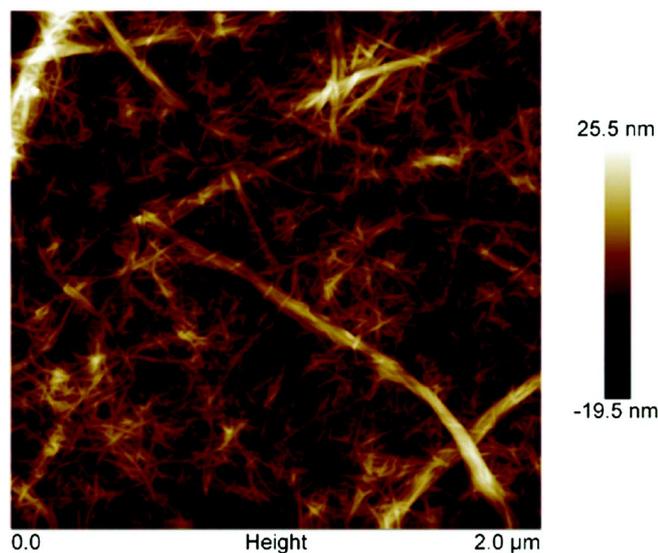


Figure 3. Atomic force microscopy picture of nanofibrillated cellulose obtained by cellulose oxidation over Fe@MagTEMPO. [Reproduced from Ref. [20], with kind permission.]

products, as well as reinforcing agent for lightweight reinforced composites for aeronautic, boat, automotive and textile goods.

2.2 ORMOSIL-entrapped TEMPO

SiliaCat TEMPO is an organically modified silica (ORMOSIL) in which the nitroxyl radicals are homogeneously entrapped within the internal huge mesoporosity of the organic glass obtained through the sol-gel hydrolytic polycondensation of methyltriethoxysilane (MTES) and a trialkoxysilane bearing the TEMPO moiety following reductive amination of 4-oxo-TEMPO and aminopropyltriethoxysilane. The resulting hybrid glass colored in orange is air stable and highly resistant to leaching. The material (Figure 4, top) does not swell in any solvent and

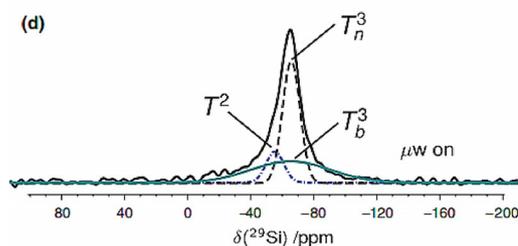
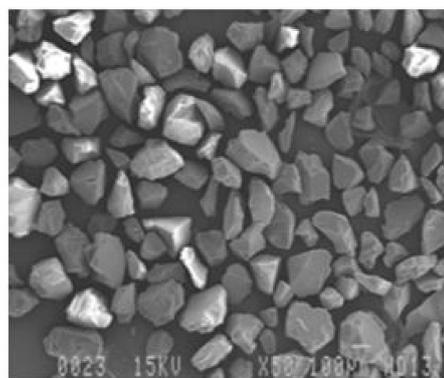


Figure 4. SEM image of SiliaCat TEMPO (top); and deconvolution of the DP MAS ²⁹Si spectrum of SiliaCat TEMPO with microwave irradiation (bottom). [Reproduced from Ref. [24], with kind permission.]

is mechanically and thermally very stable. The direct polarization (DP) ²⁹Si solid-state nuclear magnetic resonance (NMR) signal displays a maximum at -66 ppm (Figure 4, bottom), the chemical shift of RSi(OSi)₃ sites (T₃) with R = CH₃ or (4-TEMPO)aminopropyl groups.^[24] No ²⁹Si signal is observed in the chemical shift range, -110 to -90 ppm, corresponding to (SiO)_nSi(OH)_{4-n} (Q_n) sites, proving that all Si atoms are covalently linked to a carbon atom.

Performed with Fidalgo and Ilharco, the DRIFT (Diffuse reflectance infrared Fourier transform) analysis^[25] shows that the organosilica structure is made of larger, less tensioned six-member rings more able to accommodate the unreactive methyl groups, with the methyl groups concentrating at the cage surface in which they largely diminish the number of silanols thereby decreasing the intracage hydrogen bonds.

Table 1. Anelli-Montanari oxidation of benzyl alcohol to benzaldehyde under flow over SiliaCat TEMPO^[a] [Reproduced from Ref. [26], with kind permission.]

Catalyst	T [°C]	Flow [$\mu\text{L min}^{-1}$]	Reactor volume [mL]	Residence time [min]	Conv./Sel. [%]
SiliaCat TEMPO	20	50/100	0.7	3.2/1.6	100/100
SiliaCat TEMPO	20	250/500	0.7	0.6/0.3	100/100
SiliaCat TEMPO (0.1 mol%)	0	Batch		60	97/100

[a] Modular Asia 220 Syrris flow system; 250 μL glass chip in which the reactant mixtures (a 0.2 M solution of benzyl alcohol in CH_2Cl_2 and a 0.5 M aq NaOCl buffered at pH 9) were premixed at room temperature and then pumped at a flow rate ranging from 50 to 500 $\mu\text{L}/\text{min}$ to achieve the desired residence time (from 3.2 to 0.3 min) in the solid phase reactor.

Under flow the catalyst/substrate ratio for a given fraction of the reaction mixture is much larger than in traditional batch chemistry leading to improved reaction rate. Indeed, in 2013 in collaboration with Drobod and Jina we showed that the use of this material under flow enables the conversion of all benzyl alcohol to pure benzaldehyde with 100% selectivity at room temperature and with a residence time of 0.3 min only, whereas under batch conditions it takes 1 h to achieve maximum 97% conversion, requiring at 0 °C and the concomitant use of 10 mol% of corrosive KBr as co-catalyst (Table 1).^[26]

A few months later, Hermans, Aellig and co-workers independently reported the first application of SiliaCat TEMPO under continuous flow conditions in combination with catalytic amounts of HNO_3 as a NO_x source and O_2 at 5 bar as primary oxidant.^[27]

The gas-liquid feed entered a packed-bed reactor filled with the packed xerogel catalyst microparticles operated at 5 bar to keep a stable segmented flow. Several primary and secondary alcohols were smoothly converted at 55 °C into the corresponding aldehyde or ketone products with very little over-oxidation to the corresponding acids and selectivities close to 90% (Table 2).

Owing to the high reaction rates under the mild conditions requiring only 5 mol% HNO_3 as a co-oxidant, the catalytic process turned out to be extremely selective even in the conversion of alcohol substrates that usually dehydrate under acidic

conditions such as prenol or isoprenol. For comparison, the BASF route to citral, the fundamental building block in the synthesis of vitamin A, involves the synthesis of isoprenal through the aerobic oxidation of isoprenol at 500 °C with O_2 over a Ag/SiO_2 catalyst.^[28]

At the optimized reaction temperature of 55 °C the catalyst showed excellent stability retaining its full activity in the conversion of representative benzyl alcohol over 8 h of time-on-stream (Figure 5, top). Comparison of the EPR (electron paramagnetic resonance) spectra of the fresh catalyst and of the catalyst after 2 h on stream (Figure 5, bottom) clearly showed that the decomposition of the sol-gel entrapped nitroxyl radicals was negligible.^[29]

The team went on to show that renewable substrates such as lactic acid or HMF could be converted into highly valued oxygenate derivatives. In detail (Scheme 1), lactic acid (500 mM) was converted to pyruvic acid with 98% substrate conversion and over 98% selectivity towards pyruvic acid using 5 mol% of HNO_3 with a contact time of only 15 seconds.



Scheme 1. Oxidation of lactic acid to pyruvic acid. [Adapted from Ref. [27], with kind permission.]

Table 2. Aerobic oxidation of different alcohols in dichloroethane mediated by 10 mol% HNO_3 and SiliaCat TEMPO at 55 °C and 5 bar O_2 [Reproduced from Ref. [27], with kind permission.]

Substrate	Product	Residence time ^[a] [min]	Conv. [%]	Sel. [%]
		0.5 ^[b]	98 ^[b]	99
		2	95	99
		2	67	88
		2	93	87
		2	65	70 (80) ^[c]

[a] Contact time not optimized for full conversion. [b] 5 mol% HNO_3 ; [c] Combined selectivity towards isoprenal and prenol.

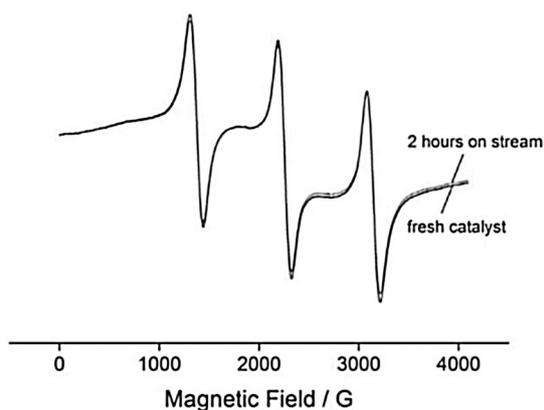
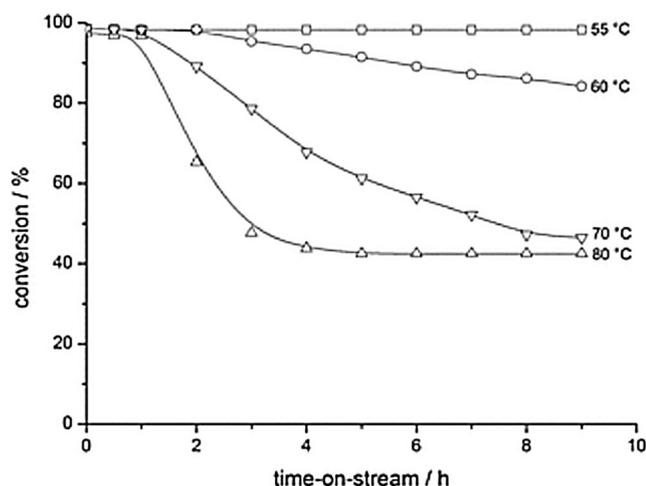


Figure 5. Conversion of benzyl alcohol into benzaldehyde vs. time-on-stream for different temperatures with 5 bar O_2 as primary oxidant, nitric acid = 5 mol%, contact time of 0.5 min (top); EPR spectra of the fresh catalyst and of the used catalyst after 2 h time-on-stream at 55 °C (bottom). [Reproduced from Ref. [27] and Ref. [29], respectively, with kind permission.]

Lactic acid is a key platform chemical of the forthcoming bio-based economy which readily decarboxylates under oxidizing conditions.^[30] Currently commercially obtained through glucose fermentation of glucose or chemically synthesized from tartaric acid, pyruvic acid and its pyruvate salts are increasingly used as precursors for the synthesis of drugs, amino acids and crop protection agents, but as well in cosmetic products and as a dietary supplement and antioxidant.

Under flow, furthermore, HMF was aerobically oxidized to the corresponding 2,5-diformylfuran with a contact time of 2 min only, achieving 98% selectivity towards DFF and 97% substrate conversion (Figure 6). Contrary to the Karimi's catalyst in batch which did not lead to overoxidation of DFF, now it was enough to increase the contact time to further oxidize DFF to 2,5-furandicarboxylic acid (FDCA), namely another valued building block with great potential as a substitute for a wide variety of petrochemicals, such as adipic and terephthalic acid and their polyesters, as well as for levulinic and succinic acid.^[31]

Similar good results in terms of high stability of SiliaCat TEMPO in batch were reported shortly afterwards by Domí-

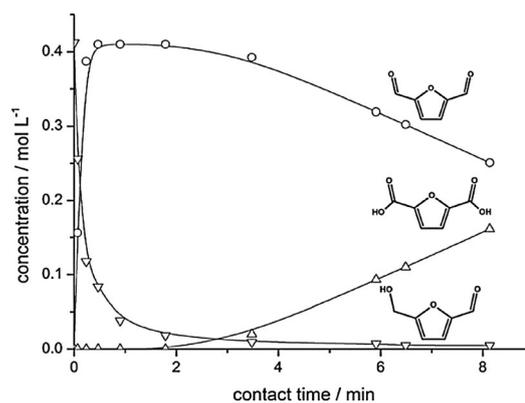


Figure 6. Concentration of HMF and its selective oxidation products vs. time-on-stream at 55 °C with 5 bar O_2 as primary oxidant, nitric acid = 5 mol%, and different contact times. [Reproduced from Ref. [27], with kind permission.]

nguez de María and co-workers in the Anelli-Montanari consecutive oxidation of HMF (Figure 7).^[32] Again, HMF was first oxidized to DFF and then, more slowly to FDCA, leading the team to conclude that a heterogeneously catalyzed process under flow could “be envisaged to provide more sustainable tools for future biomass-based processes”.

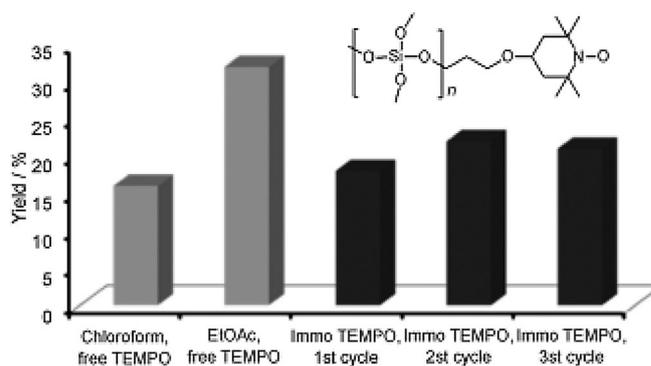


Figure 7. Yield of TEMPO-catalyzed oxidation of HMF to afford DFF after reaction for 1 h at room temperature mediated by TEMPO in solution and by SiliaCat TEMPO in 3 consecutive reaction cycles. with aq. NaOCl and KBr (2 M) as primary oxidant, TEMPO (2 mol%). [Reproduced from Ref. [32], with kind permission.]

A related aerobic route to aldehydes based on SiliaCat TEMPO in batch has been lately developed by Hughes and Muldoon.^[33] The method optimally utilizes air under 40 bar as primary oxidant along with 10 mol% nitric acid as co-oxidant at 60 °C affording, for example, high conversions of 1-phenylethanol dissolved in acetonitrile to acetophenone within 4 h (Figure 8). Even under air balloon conditions, the substrate conversion is significant, with full retention of the selectivity. Under the same conditions—pointing to the profound chemical difference between surface-derivatized and sol-gel encapsulated materials—silica-tethered TEMPO prepared by the reductive amination of the external surface of a silica gel, was almost completely inert (3% yield after 4 h under 40 bar air, and 10% yield in oxygen balloon).

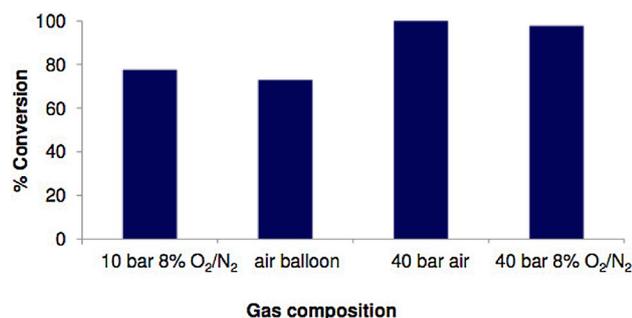


Figure 8. Aerobic oxidation of 1-phenylethanol over SiliaCat TEMPO under various gas compositions. Reaction conditions: 1-phenylethanol (1 mmol), SiliaCat TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (2 mL), gas, 4 h, 60 °C, 500 rpm. [Reproduced from Ref. [33], with kind permission.]

Also aliphatic alcohol substrates, such as 2-octanol, could be smoothly oxidised with O₂ as primary oxidant over SiliaCat TEMPO, though at slower rate than in the case of activated aromatic or allylic substrates.

Again, the catalyst proved to be highly stable without any significant loss in activity in different recycling tests. Recycling was tested by converting 1-phenylethanol to achieve a conversion of 79%, then charging the same reaction mixture with 2-octanol and fresh nitric acid to achieve a 23% conversion to 2-octanone, and finally filtering off the catalyst, rinsing it with acetonitrile and reuse it in a consecutive reaction with fresh substrate and nitric acid. The little loss in activity observed on recycling the catalyst over three consecutive runs, for both 1-phenylethanol and 2-octanol (Figure 9), was ascribed to the inevitable loss of small catalyst amounts during filtration between runs.

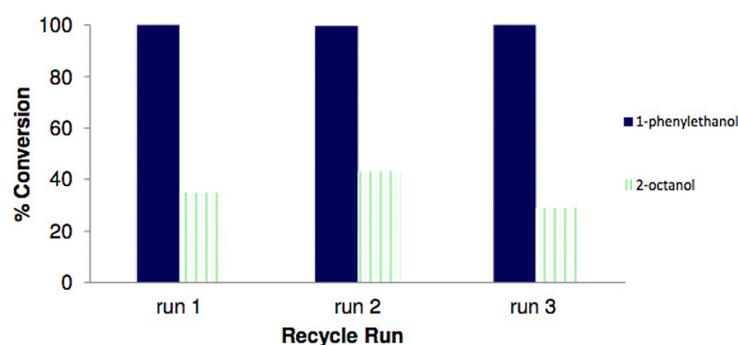


Figure 9. Recycling of SiliaCat TEMPO in the aerobic oxidation of 1-phenylethanol and 2-octanol. Reaction conditions: substrate (1 mmol), SiliaCat TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (2 mL), 40 bar air, 3 h, 60 °C, 500 rpm. [Reproduced from Ref. [33], with kind permission.]

These results offer further evidence of the high chemical stability of the TEMPO moieties encapsulated in the methylsilica cages, wherein the oxoammonium ion-mediated cleavage of amino bonds between neighbouring TEMPO functional groups left unprotected at the outer surface of silica-tethered TEMPO,^[34] is entirely prevented.^[35]

3. Towards Broad Practical Adoption?

As shown above critically reviewing recent catalytic applications of silica-entrapped nitroxyl radicals in various morphologies and compositions, basic chemical research has been successful in demonstrating the feasibility of heterogeneously catalyzed alcohol oxidation using sol-gel entrapped nitroxyl radicals. The catalysts are recyclable, though at different extent depending on the specific process and reaction conditions, and all are of broad synthetic scope. One might therefore ask if the fine and specialty chemical industry will generally switch to alcohol oxidation using solid catalysts and clean primary oxidants.

To answer this question it is relevant to notice that Pollak, one of the world's fine chemical leading industry's experts, in 2011 emphasized how:

"Organic chemical synthesis is a mature science. It did not evolve much beyond the substitution of wood by stainless or glass-lined steel as construction material for chemical reactors, in which chemical reactions developed during the golden years of the dyestuff industry are performed. Except a few niche technologies, the capability to operate a good manufacturing practice (GMP) multipurpose plant is hardly a differentiator any more."^[36]

In this context, any new catalytic material seeking practical use had (and has) to meet the main industry's requirement for the adoption of a new catalyst, namely the possibility to be used as a drop-in solution^[37] in which the solid catalyst is introduced in an existing synthetic process. Now, owing to vastly increased utilization and supply, the price of TEMPO-like radicals in the course of the last decade has significantly diminished. Gone are the days in which "TEMPO and its derivatives are manufactured by a German specialty chemical producer"^[38] and for a long time most nitroxide radical and its derivatives are produced in China.^[39]

It is therefore up to catalyst manufacturers to develop solid catalysts for which performance and cost can justify use of the new solid catalyst through reduced production costs, better performance and multiple reuse. Better performance does not mean only higher TOF (turnover frequency), which allows a true comparison per mole of catalyst employed, but also milder reactions conditions and straightforward catalyst separation from the product. Upon encapsulation in the organosilica ceramic matrix, for example, the TEMPO moiety catalyst becomes more active than in solution.^[35] Coupled to the advantages of flow chemistry, this allows for example to quickly carry out the Anelli-Montanari oxidation at completion at room temperature and without metal corrosive bromide as co-catalyst.^[26]

In brief, the comparison between new heterogeneously catalyzed process and the previous production process will take into account the new: i) TOF, ii) process conditions and iii) number of catalyst recycles. With these figure in their hands, research managers will be able to evaluate the new process and, in case of significant cost reduction of the new production

process, successfully get the top management approval to change.

The recyclable solid catalysts reviewed in this account offer the possibility to easily recover the catalyst and reuse it several times, whereas, in homogeneously catalyzed reactions, volatile TEMPO (but not its less costly derivatives) can be recovered through azeotropic distillation or steam distillation with water under reduced pressure, though at high energy cost (full recovery requires distillation of about 20% of the reaction volume),^[40] or through a four-step more general process involving adjusting the pH of the reaction solution to a value below 4, removal of the organic solvent, redissolution in water and neutralization.^[41]

Getting to flow chemistry technology, progress in the last five years has been dramatic and the “mature science” of organic chemical synthesis is eventually undergoing profound transformation with several multi-ton productions in modular flow reactors now taking place in the industry.^[42] In this case, older catalytic processes under batch are abandoned and batch reactors are replaced by new and much smaller modular flow reactors.

One might therefore ask whether sol–gel entrapped nitroxyl radicals will soon find widespread utilization in heterogeneously catalyzed alcohol oxidation processes performed under flow. Now, the economic advantages of the new process need to be so large to justify new capital investment for the new equipment.^[43]

In general, for heterogeneous catalysts to be actually used in flow reactors, the catalytic materials need to meet two main requirements,^[44] namely broad reaction scope and prolonged stability. Mesoporous and mechanically strong glassy silica-based powdered materials functionalized with TEMPO-like radicals are ideally suited for use in such reactors being easily packed in the tubular reactors in which they retain their structure and morphology for prolonged time owing to their high mechanical and thermal stability. Again, these and related materials will find practical use in alcohol oxidation under flow if lower production costs incurred on switching from homogeneous catalysis in batch to heterogeneous catalysis under flow will enable quick return on investment owing to the improved economics of the continuous oxidation process.

4. Outlook and Conclusion

Paraphrasing Avnir (“from better materials through chemistry, to better chemistry through materials”)^[45] the few selected applications of sol–gel entrapped nitroxyl radical TEMPO as alcohol and cellulose oxidation summarized in this study provide a noticeable example of the dramatic potential of bringing chemistry from solution to the inner nanoscale porosity of advanced sol–gel glasses. The materials can be used in water, organic solvent and biphasic systems, with a host of different primary oxidants to achieve the conversion of widely different alcohol substrates. In batch processes, catalyst separation is easily achieved through filtration and, in the case of Karimi’s magnetic catalyst, even more rapidly (less than 5 s) using a magnet. As the fine chemical industry is undergoing a major

shift from conventional organic synthesis in batch reactors to production under flow in entirely new flow reactors, we have attempted to provide an answer to the question whether these materials will be widely employed in new alcohol oxidation processes under flow. The arguments used to provide a tentative answer are of general value, and can be generalized to other solid catalysts for other ubiquitous processes such as C–C cross coupling reactions.

In conclusion, besides researchers in academy and in industry, colleagues engaged in shaping young interdisciplinary chemists across the world,^[46] might find this work an useful tool in their nanochemistry educational efforts.^[47]

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Conflict of interest

The authors declare no conflict of interest.

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