

SiliaCat TEMPO: An Effective and Useful Oxidizing Catalyst

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Abstract:

Organosilica-based SiliaCat TEMPO can efficiently replace homogeneous TEMPO and its derivatives in the oxidation of a wide variety of alcohols to valued carbonyls (or carboxylic acids), affording advantages in addition to the ease of removal of the catalyst from products by a simple filtration.

Introduction

Stable dialkylnitroxyl radicals belonging to the family of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) selectively catalyze the oxidation of alcohols to carbonyls with single oxygen donors such as hypochlorite and organic peracids.¹ The reaction, typically using a TEMPO/hypochlorite system, involves the intermediate formation of the corresponding oxoammonium cation as a highly active (1 mol %), selective and versatile oxidant.² Reactions indeed can be carried out in organic solvent or in biphasic reaction systems with different primary oxidants, including a mild electric potential (0.7 V vs Ag/AgCl), capable of oxidizing the radicals to oxoammonium cations.

Accordingly, TEMPO-mediated oxidations are increasingly used in the fine-chemicals industry for the synthesis of valued aldehydes and ketones,³ for instance, in continuous processes (removing the heat generated by the strongly exothermic reaction) for the production of valued activated β -substituted aldehydes in a tube reactor with bleach as primary oxidant (a single tube of 3-mm diameter renders about 60 mol of aldehyde per day).⁴ An analogous eloquent example demonstrating the potential of the method is the oxidation of bisnoralcohol to bisnoraldehyde (an intermediate to progesterone and corticosteroids) with bleach and 4-hydroxy-TEMPO in two-phase reaction medium.⁵ Such a route

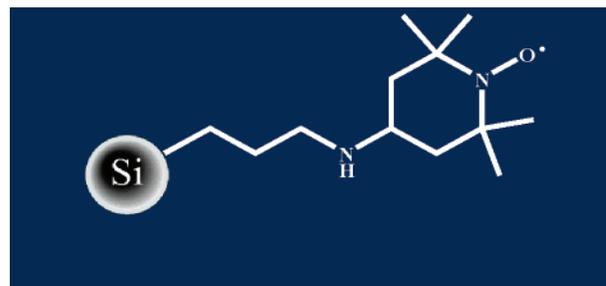


Figure 1. Silica-supported TEMPO.

has the selectivity required for high-quality bulk pharmaceutical manufacture and eliminates a process with an inventory of 227,000 L of ethylene dichloride (a known carcinogen) that needs up to 19,000 L of EDC input annually. Overall, the same product amount as in the previous route is now obtained with 89% less nonrecoverable organic solvent waste and 79% less aqueous waste.

TEMPO-like radicals, however, are expensive, and in order to find wider application in industry the price of TEMPO should be around 20 USD/kg (from the current 80–100 USD/kg).⁶ The precursor triacetoneamine (TAA, from which TEMPO is industrially obtained) is readily available in large amounts (ca. 3 USD/kg) which explains the great efforts devoted to develop a synthetic process capable of conveniently reducing the carbonyl function of TAA, in place of its current reduction with borohydride.

Alternatively, heterogenization of the nitroxyl radical over a solid support has attracted great attention.⁷ The use of solid supported reagents is an excellent way to expedite organic synthesis by simplifying the purification process.⁸ Standard purification procedures including chromatography, liquid–liquid extraction, and crystallization are time-consuming and can be difficult to scale up. In general, both polymer-supported and silica-functionalized TEMPO show poor chemical stability. Nonetheless, both the latter classes of materials are commercially available⁹ for solid-state oxidative

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- (1) de Nooy, A. E. J.; van Bekkum, H.; Besemer, A. *Synthesis* **1996**, 1153.
- (2) Alternatively, in conjunction with ruthenium and copper they catalyze aerobic oxidations of alcohols where the role of TEMPO is to facilitate regeneration of the active catalyst (Ru and Cu). For a recent discussion on the topic, see: Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, 346, 1051.
- (3) For example, the Dutch company DSM licensed the process based on POM/O₂ as primary oxidant (described by Ben-Daniel, R.; Alsters, P.; Neumann, R. *J. Org. Chem.* **2001**, 66, 8650). For years Novartis has been using the Cu⁺/O₂ developed by Semmelack in the early 1980s to synthesize retinal from retinol, and Wacker Chemie uses continuous oxidation with bleach as the primary oxidant to synthesize aldehydes with additional substituents in the β or γ position.
- (4) Fritz-Langhals, E. *Org. Process Res. Dev.* **2005**, 9, 577.

(5) For this technology, the pharmaceutical manufacturer Pharmacia&Upjohn was awarded the 1996 Presidential Green Chemistry Challenge Award. See at: http://epa.gov/greenchemistry/pubs/docs/award_entries_and_recipients1996.pdf.

(6) Personal information (to M.P.) from ChemConserve Ltd.

(7) Approaches include heterogenization over organic and inorganic polymeric supports. An overview is given in ref 2.

(8) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2002.

(9) For instance, by the United States chemicals supplier Aldrich which commercializes TEMPO supported over both polymeric organic resin and silica gel.

Table 1. Comparison between SiliaCat TEMPO and silica-supported TEMPO in benzyl alcohol oxidation^a

material	loading on N mmol/g	loading on C mmol/g	surface area m ² /g	pore size nm	yield % (equiv) ^b
FR14115TEM30B silica-supported TEMPO	0.63	0.62	500	4–6	36.0 (1.2) ^c
					44.1 (1.2)
					76.1 (2.4)
					55.7 (1.2) ^d
					85.2 (2.4)
AM1-217-TEMPO SiliaCat TEMPO	0.24	1.37	456	–	100 (2.4) ^d

^a Reaction conditions: 0.1 equiv of SiliaCat/TEMPO, CH₂Cl₂, aq NaOCl (10% w/w); 0.01 equiv of KBr, pH 9.1, 1 h, 0 °C. ^b Determined by GC. ^c Equivalents of NaOCl. ^d Equivalents of fresh NaOCl.

syntheses in which no contamination of the product and high selectivity are required.¹⁰ We now describe the sol–gel entrapped catalytic system SiliaCat TEMPO, a proprietary class of organosilica-entrapped radicals suitable for the selective oxidation of delicate substrates into valued carbonyl and carboxylic acid derivatives. Using benzyl alcohol as substrate in the Anelli–Montanari production of benzaldehyde we show by comparison the superior performance of SiliaCat TEMPO compared to traditional silica-supported TEMPO.

SiliaCat TEMPO: Preparation and Performance

SiliaCat TEMPO is a useful, new oxidizing catalyst now made using an innovative methodology that confers different reactivity and properties compared to the silica-supported TEMPO (Figure 1).¹¹

The main differences between SiliaCat/TEMPO and silica-entrapped TEMPO are the encapsulation process and the material's chemical structure (organically modified silica for the SiliaCat class of materials and inorganic silica for the latter).

The SiliaCat TEMPO preparation employs an optimized version of a reductive amination protocol described elsewhere¹¹ in which the carbonyl function of 4-oxo-TEMPO, a derivative of TAA, is reacted with the -NH₂ function of an aminopropyltrialkoxysilane in order to copolymerize the resulting functionalized silane with suitable organosilanes such as methyltriethoxysilane (MTES). Eventually, the nitroxyl radical molecules are homogeneously entrapped within the internal huge porosity of the leach-proof organoceramic matrix with high catalyst loading and surface areas up to several hundreds m² g⁻¹ (Table 1).

Performance of the SiliaCat TEMPO. The SiliaCat TEMPO is a highly efficient and selective catalyst compared to homogeneous phase TEMPO. A number of valuable organic compounds such as (benzyl, allylic, aliphatic) aldehydes¹² or α -hydroxy-¹³ and aminohydroxy¹⁴ acids are easily synthesized with greater yields and selectivity, compared to those resulting from classical reactions.

Hence, the conversion of readily available alkenes to valued aminohydroxy acids can be achieved in only two steps, by ruthenium-catalyzed dihydroxylation to *vic*-diols followed by oxidation over SiliaCat TEMPO to reduce the presence of degradation product (oxidation of the secondary alcohol).¹³ Similarly, the conversion of amino diols to aminohydroxy acids by oxidation of the primary hydroxy group (which is useful for the synthesis of commercially available antibiotics such as chloramphenicol) can be easily achieved in only one step over SiliaCat TEMPO, compared to the classical method that requires previous protection of the amine and of the secondary hydroxy group.¹⁴

Comparative Tests. We have already reported the superior performance of organosilica-entrapped TEMPO compared to silica-supported TEMPO in terms of both selective activity and stability.¹² On the basis of detailed structural analysis, we have explained the origins of such enhanced selectivity in these organocatalytic oxidations mediated by sol–gel entrapped TEMPO.¹⁵ Table 1 shows the yields of benzaldehyde after 1 h of the reaction afforded by SiliaCat TEMPO (AM1-217-TEMPO) and by a commercial sample of silica-supported TEMPO (FR14115TEM30B), both marketed by SiliCycle. The reaction is the oxidation of benzyl alcohol to benzaldehyde in dichloromethane with aqueous bleach as the primary oxidant at 0 °C and pH 9.1 (acidified bleach solution further buffered with sodium hydrogencarbonate).¹⁶ A catalytic amount (0.01 eq) of KBr was used to enhance the reaction rates.

Once again, the SiliaCat TEMPO catalyst clearly shows better performance with complete conversion of substrate into benzaldehyde. Employment of fresh NaOCl (10% w/w) affords higher yields due to the well-known degradation of hypochlorite with time.

(10) Solid oxidation catalysts are indeed “philosophers’ stones”: Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485.

(11) Pagliaro, M.; Avnir, D.; Blum, J.; Deganello, G. (SiliCycle Inc.). U.S. Patent 6,797,773 B1, 2004.

(12) Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159.

(13) Gancitano, P.; Ciriminna, R.; Testa, M. L.; Fidalgo, A.; Ilharco, L. M.; Pagliaro, M. *Org. Biomol. Chem.* **2005**, *3*, 389.

(14) Testa, M. L.; Ciriminna, R.; Hajji, C.; Zaballos Garcia, E.; Ciclosi, M.; Sepulveda Arques, J.; Pagliaro, M. *Adv. Synth. Catal.* **2004**, *346*, 655.

(15) Fidalgo, A.; Ciriminna, R.; Ilharco, L. M.; Pagliaro, M. *Chem. Mater.* **2005**, *17*, 6686.

(16) Chlorinated solvent DCM of course is far from being a “green” solvent, and the reason for employing DCM here is due to customer requirements. SiliaCat TEMPO performs equally well in aliphatic solvents as described in the case of another heterogenized TEMPO catalyst: Dijkstra, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271.

Furthermore, the TOF of *SiliaCat* TEMPO is remarkably 3 times higher than that of silica-supported TEMPO as the catalyst loading in the former sample is 0.24 mmol g⁻¹ compared to the load (0.63 mmol g⁻¹) of the SiO₂-based material, pointing to the large enhancement in activity of the radicals upon sol–gel encapsulation in an organosilica matrix. In addition, the employment of *SiliaCat*TEMPO uniquely affords benzaldehyde with complete selectivity (i.e., no traces of benzoic acid). This striking selectivity is due to the lack of hydrophilicity of the organosilica matrix which impedes access of the hydrated aldehyde (*gem*-diol) to the entrapped radical and has been recently observed also in similar TEMPO-mediated electrochemical oxidation of benzyl alcohol.¹⁷

Stability. Stable chemical activity is of crucial importance in all practical applications of solid oxidation catalysts. As mentioned above, we reported the superior performance of *SiliaCat* TEMPO compared to that of silica-supported TEMPO also in terms of stability by investigating the activity of both materials in the Montanari–Anelli oxidation of 1-nonanol for several consecutive runs.¹² The largely enhanced stability was ascribed to the sol–gel entrapment phenomenon which, opposed to traditional surface heterogenization methods where the active species are left unprotected at the external surface of the doped material, chemically and physically stabilizes the radical species *within* the sol–gel cages. Indeed, the rapid deactivation of silica-supported TEMPO is due to interactions between neighboring functional groups which results in an oxoammonium ion-mediated cleavage of amino bonds and partial destruction of the supported catalyst,¹⁸ a phenomenon that in the sol–gel entrapped material is intrinsically prevented.

Scaleability. One-mole scale experiments show consistent results with analogous high yields and selectivity. Functionalized silicas indeed provide superior performance in many applications due to high purity and consistent and accurate loading. Such silica gels are easy to weigh and handle since silica does not carry a static charge and is always free flowing. It does not require extensive washing for high recoveries and will not stick to glassware, making these materials ideally suited for scaleability from the microgram to the multiton scale.

(17) Palmisano, G.; Ciriminna, R.; Pagliaro, M. *Adv. Synth. Catal.* **2006**, *348*, 2033.

(18) Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154.

(19) Pagliaro, M.; Ciriminna, R.; Wong Chi Man, M.; Campestrini, S. *J. Phys. Chem. B* **2006**, *110*, 1976.

(20) Pagliaro, M.; Ciriminna, R.; Palmisano, G. *Chem. Soc. Rev.* Published online <http://dx.doi.org/10.1039/b611171h>.

(21) Reetz, M. T.; Tielmann, P.; Wiesenhöfer, W.; Könen, W.; Zonta, A. *Adv. Synth. Catal.* **2003**, *345*, 717.

Conclusion

SiliaCat TEMPO is an effective and useful oxidizing catalyst that presents unique advantages: excellent yield and selectivity in various reactions, reduction in the synthesis steps, stability, and recyclability. The system allows easy product isolation from the catalyst and thus the replacement of current industrial processes that use stoichiometric (at least) amounts of inorganic (Cr, Mn, Co, etc.) or organic oxidants (DMSO). Indeed, such sol–gel hybrid organic–inorganic materials meet all the industry requirements for oxidation catalysts including versatility (as the low volumes of products of the fine-chemicals industry require catalysts applicable to the conversion of several structurally different alcoholic substrates in different reaction media).

In general, silica-based reactants are solvent independent (aqueous, organic, and biphasic systems), show high thermal and mechanical stability, and demonstrate no swelling and no static charge. Organosilica-entrapped catalysts share all these properties, in addition to sol–gel entrapment, with important physical¹⁹ and chemical²⁰ consequences in terms of enhanced selectivity and stability (most silica xerogels are suitable for use in microwave synthesizers, working well with overhead stirring). Moreover, since silica sol–gels are chemical sponges, diffusion in and out of the polymer is fast, thus ensuring high reaction rates. Finally, organosilica neither shrinks nor swells in any solvent because it is organically modified (an attribute that is exploited with commercial silica gels that are chemically “endcapped” with this aim) and will not dissolve in any solvent. Because they do not swell, silica gels can be packed into a variety of flow-through formats such as HPLC columns and flash and SPE cartridges.

To the best of our knowledge, it is the first example of ORMOSIL-entrapped catalyst made commercially available after organosilica-entrapped lipases that were developed in the mid 1990s.²¹ *SiliaCat* TEMPO is commercially available either in bulk, or in SPE and Flash cartridge formats, suitable for flow-through applications.

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