Reviews

Industrial Oxidations with Organocatalyst TEMPO and Its Derivatives

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Abstract:

The radical TEMPO and its derivatives find a variety of industrial applications as highly selective oxidation catalysts for the production of pharmaceuticals, flavors and fragrances, agrochemicals, and a variety of other specialty chemicals. Reviewing recent notable examples, we show how and why homogeneous and heterogeneous TEMPO-mediated oxidations are becoming part of a central toolbox in industrial organic synthesis applicable for the conversion of alcohols into aldehydes, ketones, and carboxylic acids.

1. Introduction

The stable tetraalkylnitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)[1] is a well-known oxidation catalyst, whose numerous applications in organic synthesis, including oxidation of alcohols, sulfides, and organometallic compounds have been recently reviewed.[2] Of particular synthetic interest is the oxidation of alcohols to carbonyl compounds. In general, reactions can be carried out either in organic solvent or in biphasic reaction systems affording aldehydes or ketones or in water where soluble hydroxylated substrates such as sugars are selectively oxidized to glucuronates.[3] In the former case, typically the oxoammonium cation formed by oxidation of TEMPO with hypochlorite at 0−4 °C under slightly basic conditions selectively oxidizes a variety of alcohols (Scheme 1, Anelli−Montanari process).

Instead of hypochlorite, a variety of different primary oxidants can be used to generate the oxoammonium ion including a mild electric potential (0.7 V versus Ag/AgCl);[3] O_2 along with active metal catalysts (Ru^{2+}, Mn^{2+}/Co^{2+} and Cu^+)[4] and several other oxidants.

The fast conversion protocol using bleach is most attractive and enables a high output of product giving almost quantitative yields of aliphatic, aromatic, and heteroaromatic aldehydes of crucial importance in the fine chemicals industry.[5] Such

Scheme 1. Bielectronic oxidation mechanism of TEMPO-mediated oxidations
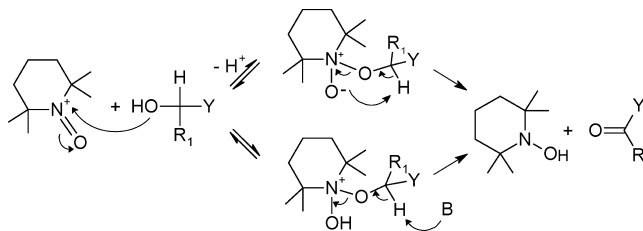
aldehydes in fact are either used as fragrances, drugs, or food additives or act as versatile precursors in a number of processes, including the synthesis of cyanohydrins, hydroxycarboxylic acids, amino acids, and esters. Selected examples of industrial oxidative processes based on TEMPO include Novartis aerobic process with Cu^+/O_2 developed by Semmelack in the early 1980s to synthesise retinal from retinol; the continuous process developed by Wacker Chemie to synthesize aldehydes with additional substituents in the β or γ position; and Pfizer's synthesis of bisnoraldehyde (an intermediate to progesterone) from bisnoralcohol using bleach and 4-hydroxy-TEMPO in a two-phase reaction medium.

TEMPO itself, however, is an expensive chemical, and in order to find wider application in industry its 80−100 $/kg spot price should decrease to ∼$20/kg.[6] Therefore, industry generally employs nitroxyl derivatives functionalized in the 4 position such as 4-hydroxy-TEMPO or 4-acetamido-TEMPO obtained from the cheap ($3/kg) precursor triacetoneamine, a readily available chemical manufactured in large amounts as a light stabilizer for plastics. Although TEMPO is usually applied in small quantities (0.1−10 mol %), clearly it must be recovered from homogeneous reaction mixtures and thus separated from the product. Costly azeotropic distillation can only be applied to the most volatile nitroxyl compounds such as TEMPO; hence, recovery is preferably carried out by selective absorption onto a hydrophobic resin such as Amberlite or hydrophobized silica gel.[7]

Alternatively, heterogenization of the radical on a solid support has attracted great attention, and several materials derivatized with the TEMPO moiety are commercially available

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(1) Montanari, F.; Quici, S.; Henry-Riyad, H.; Tidwell, T. T. 2,2,6,6-Tetramethylpiperidin-1-oxyl. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, 2005.
(2) Vogler, T.; Studer, A. *Synthesis* **2008**, *13*, 1979.
(3) de Nooy, A. E. J.; van Bekkum, H.; Besemer, A. *Synthesis* **1996**, 1153.
(4) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051.
(5) See also: Bäckvall, J. E., Ed. *Modern Oxidation Methods*; Wiley-VCH: Weinheim, 2004.

(6) Personal information to M.P. from W. Kesber (ChemConserve).
(7) Stable nitroxyl radicals are hydrophobic and are separated from a reaction mixture by means of hydrophobic interactions. Thornton, J.; Besemer, A.; Schraven, B. WO/2002/059064, 2002.

Scheme 2. Steroidal intermediate BNA is today obtained by 4-hydroxy-TEMPO-mediated oxidation of bisnoralcohol
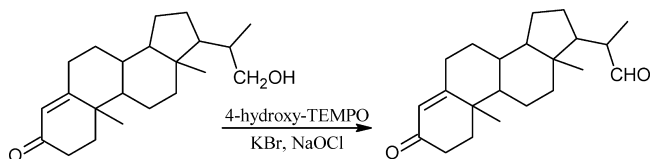
for solid-state oxidative synthesis.[8] In the following, we review some of the most notable examples of both industrial homogeneous and heterogeneous TEMPO-mediated oxidation processes highlighting the scope and limitation of a powerful synthetic toolbox applicable at industrial scale for the conversion of alcohols to carbonyls and carboxylates.

2. Batch Processes

2.1. Bisnoraldehyde. The first industrial example rendering the economic and environmental potential of the methodology was developed in the mid 1990s by Pharmacia and Upjohn aiming to synthesize the steroidal intermediate bisnoraldehyde (BNA) from bisnoralcohol, an important precursor used to produce bulk pharmaceutical steroids such as progesterone and corticosteroids. The new route to BNA from waste soya bean residues is based on the oxidation of bisnoralcohol with bleach and 4-hydroxy-TEMPO (Scheme 2).[9]

The catalytic route to BNA has many economic, health, and environmental benefits. In fact it: (i) avoids using heavy metal based oxidants such as hexavalent chromium salts and complexes, manganese oxides, or lead salts; (ii) does not produce noxious emissions unlike oxidations which use activated dimethylsulfoxide; (iii) increases utilization of soya sterol feedstock from 15% to 100%; (iv) produces nontoxic aqueous process waste streams and recoverable organic solvent waste streams. As a result, the new process (v) eliminates a conversion with a recycled inventory of 227,000 L of carcinogenic ethylene dichloride, and (vi) produces the same product amount as the previous route with 89% less nonrecoverable organic solvent waste and 79% less aqueous waste.

2.2. HIV Protease Inhibitor Proline Derivative and 5-HT2B Receptor Antagonist. The multikilogram production of the proline derivative **1** (a key intermediate of a HIV protease inhibitor) has been recently developed at Pfizer. The synthesis proceeds via a ketone fluorination with Deoxo-Fluor (Scheme 3).[10]

The requisite ketone for fluorination is prepared via oxidation of the enantiomerically pure **2**, using NaClO and catalytic TEMPO. The process, which has been scaled up, afforded the production of 7.5 kg of **1** after 10 steps, in 4.5% overall molar yield and high purity.

Similarly, Eli Lilly synthesizes 2-cyclohexylacetaldehyde on a 20 kg scale by oxidizing 2-cyclohexylethanol by the

Scheme 3. Multikilogram production of the proline derivative 1, a key intermediate of a HIV protease inhibitor developed by Pfizer [reproduced from ref 10 with permission]
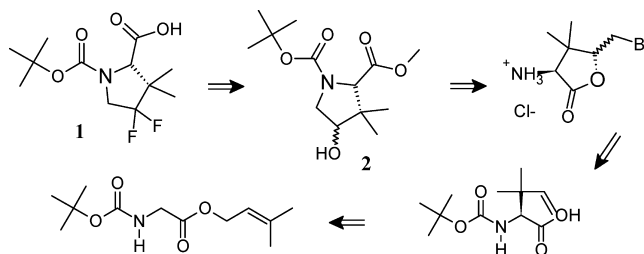
Anelli−Montanari protocol (Scheme 4) affording the product as stable sodium bisulfite adduct in 83% yield.[11]

The aldehyde is then used as precursor of a tryptamine and further used as key synthon for the synthesis of the important 5-HT2B receptor antagonist.

2.3. Aerobic Reactions. The fine chemicals manufacturer DSM employs the aerobic process developed by Neumann and co-workers[12] for the synthesis of an undisclosed set of carbonyl compounds. The method makes use of 1 mol % polyoxometalate heteropolyacid $H_5PV_2Mo_{10}O_{40}$, belonging to the class of phosphonomolybdates, and 3 mol % TEMPO as cocatalysts at 100 °C and under 2 bar O_2 (Scheme 5).

The oxoammonium cation is generated by one-electron oxidation of TEMPO by $H_5PV_2Mo_{10}O_{40}$. Oxidation of the alcohol by the oxoammonium cation affords the hydroxylamine TEMPOH followed by rate-limiting oxidation of the latter by a second equivalent of the heteropolyacid. The reduced form, $H_5PV_2Mo_{10}O_{40}$ is rapidly reoxidized by oxygen. It is also interesting from an industrial point of view that this reaction was found not to be dependent on the oxygen pressure, meaning that it could work also in oxygen or air without the need of pressure vessels.

Scientists at the same company (DSM) also improved the Cu^+/TEMPO aerobic oxidation protocol of primary alcohols to aldehydes. The catalytic system is based on TEMPO and Cu(II), which is generated *in situ* by oxidation of elemental copper and chelated by means of 2,2′-bipyridine.[13] Compared to existing Cu^+/TEMPO oxidation methods the amount of copper necessary has been considerably lowered, and the catalytic system was shown to work also with polymer-bound TEMPO.

2.4. Heterogenized Co-oxidant: Sugar Oxidation. Evonik (former Degussa), the world's leading manufacturer of TEMPO precursor TAA, employs an elegant methodology developed by Hölderich and co-workers to selectively oxidise sugars' primary hydroxy groups to carboxylic acid using organic nitrosonium salt in aqueous solution.[14] The oxidant is generated on supported silver catalysts, which promote disproportionation

(8) For instance, by the U.S. chemicals supplier, Aldrich, which sells both TEMPO supported over polymeric organic resin and over a silica gel.

(9) Hewitt, B. D. Conversion of bisnoralcohol to bisnoraldehyde. (Upjohn Co., U.S.A.). WO 016698 1995. See also the URL: http://epa.gov/greenchemistry/pubs/docs/award_entries_and_recipients1996.pdf.

(10) Rossi, F.; Corcella, F.; Caldarelli, F. S.; Heidempergher, F.; Marchionni, C.; Auguadro, M.; Cattaneo, M.; Ceriani, L.; Visentin, G.; Ventrella, G.; Pinciroli, V.; Ramella, G.; Candiani, I.; Bedeschi, A.; Tomasi, A.; Kline, B. J.; Martinez, C. A.; Yazbeck, D.; Kucera, D. J. *Org. Process Res. Dev.* **2008**, *12*, 322.

(11) Borghese, A.; Merschaert, A. Challenges in an Ever Changing Climate. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K., Braish, T., Eds.; CRC Press: Boca Raton, FL, 2007; Chapter 6, Vol. 2.

(12) Ben-Daniel, R.; Alsters, P.; Neumann, R. *J. Org. Chem.* **2001**, *66*, 8650.

(13) Geiβlmeir, D.; Jary, W. G.; Falk, H. *Monatsh. Chem./Chem. Mon.* **2005**, *136*, 1591.

(14) Kochkar, H.; Lassalle, L.; Morawietz, M.; Hölderich, W. F. *J. Catal.* **2000**, *194*, 343.

Scheme 4. Eli Lilly synthesizes 2-cyclohexylaldehyde on a 20 kg scale by oxidizing 2-cyclohexylethanol with the Anelli−Montanari protocol
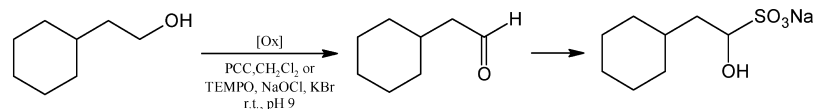
Scheme 5. Co-catalytic oxidation process developed by Neumann and co-workers is commercially employed by DSM [reproduced from ref 12 with permission]
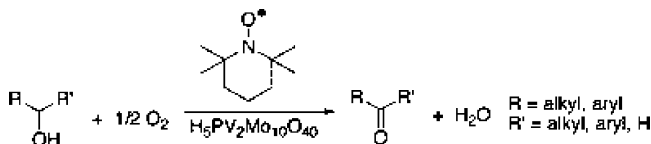
of TEMPO in a batch reactor at room temperature and peroxides as primary co-oxidant. For example, by carrying out the oxidation reaction at pH 9.5 using a silver carbonate-Celite catalyst, 99 mol % selectivity to methyl-α-D-glucopyranosiduronic acid was obtained at 90% conversion of the pyranoside. Adding carbonates to the silver catalyst increases the electron charge deficiency on silver and accelerates the nucleophilic attack of hydroxyls and/or TEMPO, resulting in increased efficiency.

2.5. One-Pot Oxidation of Alcohols to Aldehydes or Acids. The chemical manufacturer Fujisama (Japan) developed a straightforward, one-pot process for the conversion of alcohols to the corresponding acids using TEMPO.[15] Alcohols dissolved in acetonitrile or in ethyl acetate are first converted to the corresponding aldehydes under slightly basic conditions (pH 8−10) adding NaOCl dropwise to the mixture over 30 min at pH of 8−10 in the presence of TEMPO; and then the formed aldehydes are converted to acids by dropwise addition of $NaClO_2$ under acidic conditions (pH 5). No side reactions between $NaClO_2$ and NaOCl take place, and many alcohols are cleanly and quantitatively converted to acids in quantitative yield (Table 1).

Arkema, in its turn, has developed Oxynitrox S100 an oligomeric catalyst whose structure contains several TEMPO moieties (Figure 1).[16] The high molecular weight (between 2000 and 3000 g/mol) allows easy recovery of the end products by simple distillation.
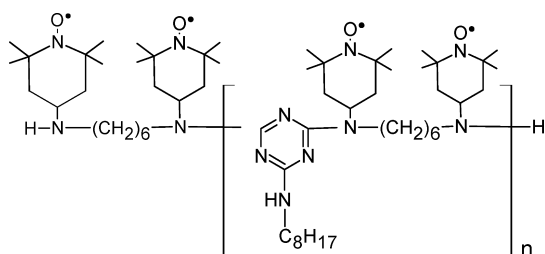
Figure 1. Structure of Arkema's catalyst Oxynitrox S100.

This commercially available catalyst was developed for application in the Anelli−Montanari process in biphasic medium and can be successfully employed for the oxidation with NaOBr of aliphatic, benzylic, cycloaliphatic, or unsaturated alcohols, with good yields and selectivities.[17] The degree of oxidation of the final product can be controlled by the amount of sodium hypochlorite: when using 1−1.3 equiv of NaOCl, the primary alcohol is converted into the corresponding aldehyde, but using 2 equiv of NaOCl affords the corresponding carboxylic acid.

Finally, Tanielyan and co-workers have extended the Anelli−Montanari protocol replacing potassium bromide with the more benign Borax, $Na_2B_4O_7$.[18] Furthermore, the new process does not require any organic solvents, thereby eliminating the methylene chloride solvent of the former process. In the absence of any organic solvents the reactant alcohol comprises about 38% of the total reaction volume as compared with only about 2.5% when the classic reaction is run in dichloromethane. This has positive cost, environmental, and process safety implications. A further advantage to the use of the solvent-free reaction is the fact that the product can be isolated by phase separation from the aqueous solution with considerable energy savings since no solvent needs to be removed. This modified process was used for the selective oxidation of a number of primary and secondary alcohols, giving the corresponding aldehydes or ketones in very good to excellent yields. Again, the level of oxidation can be controlled by varying the temperature and amount of oxidant. Of relevance to this report is the fact that the assignee of the patent is a food company (The Nutrasweet Company).

3. Continuous Processes

Continuous TEMPO-mediated oxidations are used for producing aldehydes in good yields using a method developed by Fritz Langhals at Wacker Chemie.[19] The reaction is performed continuously in a tube reactor with technical bleach and catalytic amounts of 4-hydroxy TEMPO. This lay-out meets all requirements necessary for the process, i.e. turbulent mixing of the biphasic mixture, removal of heat generated by the strongly exothermic reaction, short contact times, and high output. Typically, a single tube of titanium (stainless steel is not resistant to bleach) with a 3 mm diameter renders about 60 mol of activated β-substituted aldehyde per day.

The continuous process furthermore resolves the main disadvantage of the established batch procedure in the case of large batches where difficulties to remove the heat of the strongly exothermic oxidation process lengthen the reaction time, giving place to secondary reactions such as the reaction of alkali-sensitive groups such as ester groups or further oxidation of the aldehyde.

(15) Zanka, A. *Chem. Pharm. Bull.* **2003**, *51*, 888.

(16) Gillet, J.-P.; et al. EP Patent 1140807, 1999.

(17) For an account on the catalyst performance: Couturier, J.-L.; Grimaldi, S. *Spec. Chem. Mag.* **2006**, *12*, 32–33.
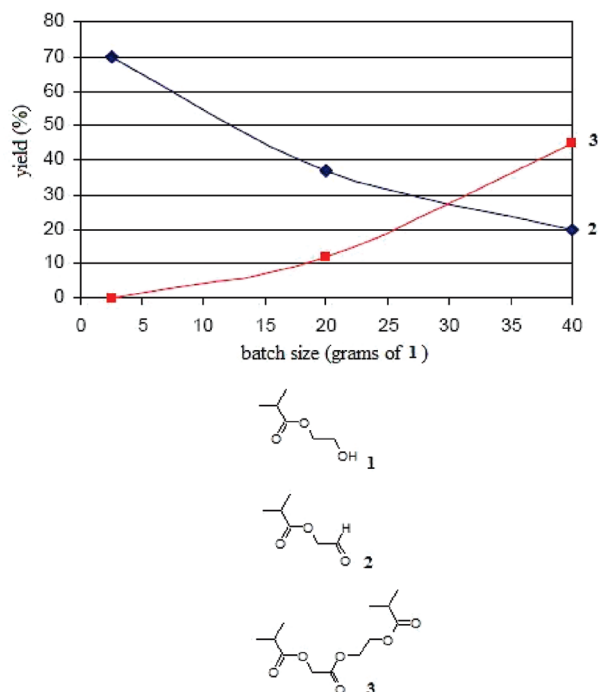
(18) Prakash, I.;Tanielyan, S. K.; Augustine, R. L.; Furlong, K. E.; Scherm, R. C.; Jackson, H. E. Bromine free TEMPO based catalyst system for oxidation of primary and secondary alcohols using NaOCl as an oxidant. U.S. Patent 6,825,384, 2004.

(19) A single tube of 3 mm diameter renders about 60 mol aldehyde per day: Fritz-Langhals, E. *Org. Process Res. Dev.* **2005**, *9*, 577.
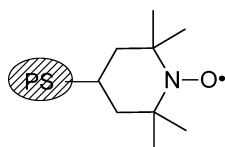
Figure 2. Yield of aldehyde 3a and ester 4a as a function of batch size [reproduced from ref 19 with permission].

Figure 3. Merrifield resin functionalized with the TEMPO moiety to a solid-supported free radical catalyst.

For example, in the oxidation of isobutyryloxy ethanol **1**, the yield of aldehyde **2** is significantly decreased already in 20 g batches, and the ester **3** becomes the major product in a 40 g batch (Figure 2) due to the prolonged contact time between the starting alcohol **1** and the formed aldehyde **2**. To obtain the aldehyde in good yields without impurities of ester it is enough to rapidly pump the reactants together into a static mixing element and then through the cooled titanium tube. Finally, whereas the degradation of 4-hydroxy-TEMPO is of minor importance within the very short reaction times typical of the oxidation of primary alcohols, for the much *slower* oxidation of secondary alcohols, more stable and expensive TEMPO is required (Figure 3).

4. Polymers: Aldehyde and Carboxy Functional Polysiloxanes

Aldehyde functional polysiloxanes are selectively synthesized at Wacker Chemie in high yield and purity by oxidation of the corresponding carbinols with technical bleach and catalytic amounts of TEMPO.[20] The same oxidation method is successfully used for the preparation of the corresponding carboxylic acids. Carbinols, such as **3** in Scheme 6, are oxidized according the Anelli−Montanari protocol at ambient temperature under almost neutral or weakly alkaline conditions. The reaction is very fast, having a reaction half-life ($\tau_{1/2}$) of about 4 s.

Polysiloxanes (silicones) are highly hydrophobic, inert polymers, displaying good water repellency and weather

resistance, whereas the polysiloxane chain flexibility gives place to the macroscopic properties of smoothness and lubricity. These polymers, however, have poor adhesive properties, due to their limited interaction with most materials, and thus require the introduction of functional groups for this purpose. Aldehyde functionalities are very reactive toward amino and hydroxy groups. As a result, polymers **1** can bind to cellulose or protein surfaces.

Carboxy functional polysiloxanes **2** are also able to bind to surfaces because of the carboxy groups' high polarity. They can undergo cross-linking reactions, e.g. with epoxides. Wacker Chemie thus also makes disiloxane dicarboxylic acids in high purity and quantitatively from the corresponding diols by simply using 2.4 equiv of bleach with TEMPO at buffered neutral pH. The free carboxylic acids are eventually isolated from the organic phase after acidification; and the polysiloxane α,ω-carboxylic acids are eventually synthesized by further redistribution of the dimeric compounds.

5. Heterogeneous Catalysts

Several heterogeneous catalysts are commercially available from leading chemical suppliers. In general, these catalysts are purchased in the required amounts by the pharmaceutical and fine chemicals companies for specific productions. Here the industrial applications are as different and as numerous as the number of fragrances commercially obtained by alcohol oxidation can be (a few examples of aldehydes used: 1-decanal, 3,7-dimethyl-6-octenal, *trans*-2-hexanal, etc.). Needless to say, in the highly competitive market of specialty chemicals, companies acquiring the catalysts do not reveal in which manufacturing process the materials get employed (see DSM above). For example, the catalyst Silia*Cat* TEMPO is sold by SiliCycle to several pharmaceutical customers. Yet, the company is not informed of the application sought.

5.1. SiliaCat TEMPO. Silia*Cat* TEMPO (a trademark of SiliCycle) is a new oxidizing catalyst made using a sol−gel encapsulation in an organically modified silica matrix. Said encapsulation confers enhanced reactivity and properties compared to simple silica-supported TEMPO (Scheme 7).[21]

Like all silica-based reactants, Silia*Cat* TEMPO is solvent-independent, as organosilica neither shrinks nor swells nor dissolves in any solvent. However, with the use of the ORMOSIL catalyst a number of valuable organic compounds such as (benzyl, allylic, aliphatic) aldehydes or α-hydroxy- and aminohydroxy acids are easily synthesised with greater yields and selectivity compared to classical reaction protocols. Comparative experiments indeed have clearly shown the superior performance of Silia*Cat* TEMPO compared to either homogeneously or heterogeneously catalyzed oxidations mediated by TEMPO.[21]

For example, in the oxidation of benzyl alcohol the TOF of Silia*Cat* TEMPO is 3 times higher than that of commercial silica-supported TEMPO, pointing to the large enhancement in activity of the radicals upon sol−gel encapsulation in an organosilica matrix. In addition, the employment of Silia*Cat* TEMPO uniquely affords benzaldehyde with complete selectivity (i.e., no traces of benzoic acid), due to the lack of hydrophilicity of the organosilica matrix which impedes access

Table 1. One-pot TEMPO-catalyzed oxidation of primary alcohols to acids

| Entry	Substrate	Product	Solvent	Yield (%)[a]
1			CH_3CN	98
2			AcOEt	92
3			AcOEt	93
4			AcOEt	100
5			CH_3CN	99
6			CH_3CN	95
7			AcOEt / CH_3CN	16 (65)[b] / 17 (70)[b]
8			AcOEt	24 (55)[c]
9			AcOEt	84

[a] Isolated yield. [b] Yields in parentheses refer to percent of aldehyde. [c] Yield in parentheses refers to percent of 2-chloro-5-methoxybenzoic acid. [Reproduced from ref 15 with permission.]

Scheme 6. Carbinols, e.g. 3, which are readily available on an industrial scale, for example by termination of α,ω-dihydroxypolysiloxanes with the 2,2-dimethyl[1,2]oxasilolane 4, and are oxidized according the Anelli−Montanari protocol at ambient temperature under almost neutral or weakly alkaline conditions [adapted from ref 20 with permission]
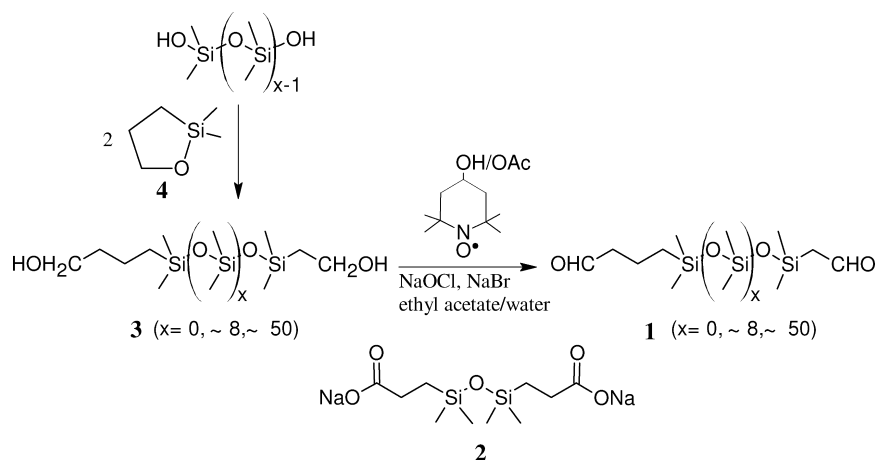
Scheme 7. Silia*Cat* TEMPO is made with innovative technology, which comprises the sol−gel synthesis of organically modified hybrid organic−inorganic silica
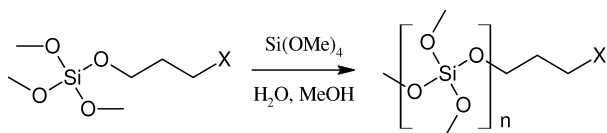
of any hydrated aldehyde to the entrapped radical. Finally, the superior performance of Silia*Cat* TEMPO compared to silica-supported TEMPO in terms of stability is due to the sol−gel entrapment phenomenon which, opposed to traditional surface heterogenization methods where the active species are left unprotected at the external surface of the doped material, chemically and physically stabilizes the radical species *within* the sol−gel cages. Thanks to all these advantages, the catalyst can be used in various nitroxide-mediated oxidations for the

production of pharmaceuticals, flavours and fragrances, cosmetics, and agrochemicals. Silia*Cat* TEMPO is commercially available either in bulk or in SPE and Flash cartridge formats, suitable for batch and continuous selective oxidation of delicate substrates, respectively.

5.2. Polymer-Supported TEMPO. PS-TEMPO, a polymer-supported TEMPO material (Figure 3), is commercialized as a recyclable, active, and selective catalyst for the oxidation of alcohols by companies such as Aldrich or Novabiochem (Merck). The material, 4-(polystyrylmethyloxy)-2,2,6,6-tetra-methylpiperidin-1-yloxy free radical, typically sold with a 1.0

(20) Fritz-Langhals, E. Aldehyde and Carboxy Functional Polysiloxanes. In *Silicon Based Polymers. Advances in Synthesis and Supramolecular Organization*; Ganachaud, F., Boileau, S., Boury, B., Eds.; Springer: New York, 2008.

(21) Michaud, A.; Gingras, G.; Morin, M.; Bland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M. *Org. Process Res. Dev.* **2007**, *11*, 766.

Scheme 8. Preparations of immobilised TEMPO [reproduced from ref 24 with permission]
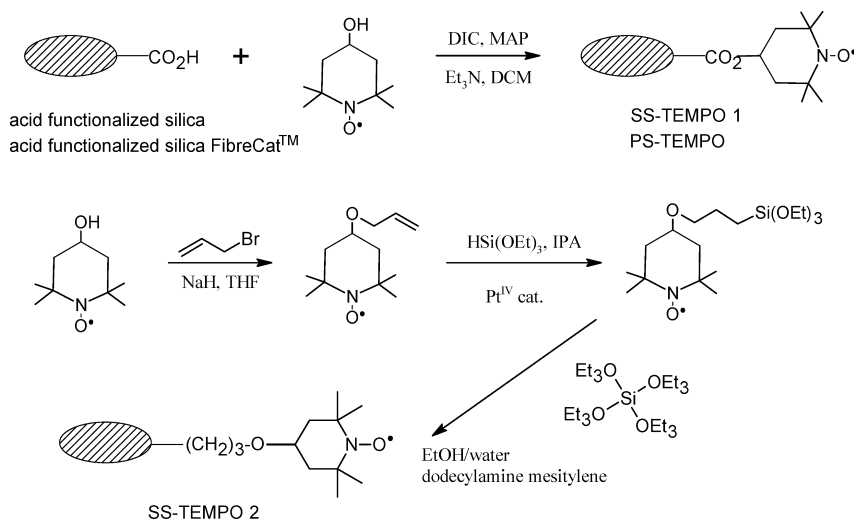
Scheme 9. Aerobic oxidation with co-catalysts Mn^{2+}, Co^{2+} and immobilised TEMPO affords high yields of all alcohols
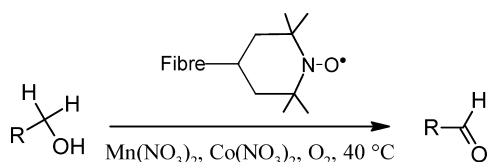
mmol/g loading, is a Merrifield resin obtained by reacting the resin with the TEMPO-Na.[22]

These oxoammonium resins are metal-free, versatile, and highly reactive oxidation reagents suitable for the oxidation of alcohols to aldehydes or to acids.[23] However, in contrast to functionalized silicas, which are easy to weigh and handle since silica does not carry a static charge and is always free-flowing, resins are not ideally suited for scalability as they rapidly swell in organic solvents and have poor thermal and mechanical stability.

5.3. FibreCat TEMPO. The fine chemical manufacturer Johnson Matthey commercializes FibreCat TEMPO, the nitroxyl radical version of its trademarked FibreCat catalyst line. A study comparing the performance of FibreCat TEMPO along with that of two synthetic silica-entrapped catalysts obtained by sol−gel polycondensation (Scheme 8) clearly concluded that the FibreCat catalyst shows superior behaviour.[24]

FibreCat TEMPO is truly heterogeneous and can selectively be applied for the conversion of unreactive aliphatic primary alcohols into aldehydes using bleach or, with Co(II) and Mn(II) as cocatalysts, molecular oxygen and air as terminal oxidants (Scheme 9).

The intrinsic activity and selectivity of TEMPO for primary alcohols to aldehydes are retained, while the heterogenisation of TEMPO allows a much simpler purification of the oxidation products and offers the chance to recover and reuse the catalyst as shown by 20 consecutive reaction runs in the oxidation of 1-octanol to give octanal performed on small scale (48 mmol)

in which the catalyst (400 mg of FibreCat-TEMPO), after 15 min of reaction, was recovered by filtration, washed, and reused without any reactivation process and without significant loss of activity/selectivity.

6. Outlook and Conclusions

TEMPO-mediated oxidations of alcohols are eventually finding widespread application in the fine chemicals industry for the synthesis of aldehydes and ketones or carboxylic acids. Following the discovery in the mid 1980s of the fast two-phase process using bleach as primary oxidant at low temperature,[25] a number of alternative terminal oxidants have been identified and suitable selective processes developed. As these processes replace older stoichiometric oxidations with either highly toxic chromium (VI) and Mn(II) oxides or milder organic reagents, such as activated DMSO, Dess−Martin periodinane, or IBX, one easily understands the economic and environmental advantages afforded by the employment of this versatile reactant discovered by Lebedev and co-workers in 1960.

The examples described in this account do not cover all of the processes that are being employed in industry. An alternative class of catalysts developed by Ciba, for instance, is made of convenient macrocyclic tetrafunctional nitroxyl radical obtained by oxidation of commercial amine Chimassorb 966 which is an excellent oxidation cocatalyst in combination with Mn(II) and Co(II) under oxygen atmosphere at ambient pressure.[26] By the same token, as chemical process technology advances, a number of innovative methods are being developed such as in the case of the continuous production of aldehydes by feeding aqueous bleach and organic TEMPO/substrate/solvent solutions through the inlets of a spinning tube-in-tube reactor with residence times as short as 1−2 min which eliminates the need for slow addition of the bleach reagent to control the exothermic oxidation.[27]

Selected exemples of homogeneous and heterogeneous reactions in this report, however, show the scope of a methodol-

(22) Hodges, J.; Harikrishnan, L. S.; Ault-Justus, S. *J. Comb. Chem.* **2000**, *2*, 88.
(23) Weik, S.; Nicholson, G.; Jung, G.; Rademann, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1436.
(24) Gilhespy, M.; Lok, M.; Baucherel, X. *Catal. Today* **2006**, *117*, 114.

(25) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
(26) Minisci, F.; Recupero, F.; Rodinò, M.; Sala, M.; Schneider, A. *Org. Process Res. Dev* **2003**, *7*, 794.

ogy that has opened the route to a number of different oxidation processes suitable for the selective oxidation of alcohols in the fine chemicals and pharmaceutical industry, affording products that range from steroids to silicon polymers and from glucuronic acids to aromatic aldehydes. Given the broad versatility of the methodology and the recent commercial availability of powerful solid catalysts functionalized with nitroxyl radicals, it may be envisaged that several new commercial processes will be implemented in the near future.

Acknowledgment

Note Added after ASAP: There was an error in information for Scheme 4 in the version published on the Web May 18, 2009. The version published June 8, 2009 and the print version are correct.

(27) Hampton, P. D.; Whealon, M. D.; Roberts, L. M.; Yaeger, A. A.; Boydso, R. *Org. Process Res. Dev* **2008**, *12*, 946.