

## Silica-Supported TEMPO Catalysts: Synthesis and Application in the Anelli Oxidation of Alcohols

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The application of silica-supported TEMPO as a recyclable catalyst in the Anelli oxidation of alcohols is reported. The catalyst is easily obtained in a one-step reductive amination procedure starting from a commercially available aminopropyl-functionalized silica. Details of the synthesis of the supported catalyst and its analysis by MAS NMR are presented. Various alcohol oxidations according to the Anelli protocol have been carried out and the stability of the applied silica-supported TEMPO has been studied.

### Introduction

Carbonyl groups are among the most important functional groups in organic synthesis, and their introduction by oxidation chemistry starting from alcohols is a process of major importance. Early protocols for this transformation relied on the use of stoichiometric oxidants such as chromium(VI) reagents<sup>1</sup> or DMSO.<sup>2</sup> With the goal to improve synthetic efficiency and to avoid potential environmental hazards, new methods have been developed over the past decades which circumvent the use of toxic reagents.<sup>3</sup> Alcohol oxidations with the Dess–Martin reagent<sup>4</sup> and catalyses by TPAP<sup>5</sup> are two of the best-known examples for new oxidation strategies.<sup>6</sup>

An alternative approach involves the use of oxoammonium ions as oxidants.<sup>7</sup> Such compounds can either be applied in stoichiometric quantities<sup>8</sup> or as catalysts in combination with a terminal oxidant. In the latter case, stable free nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **1**) and its derivatives are common catalysts. TEMPO is easily oxidized to oxoammonium ion **2** which itself is reduced to hydroxylamine **3** within alcohol oxidation. A stoichiometric amount of terminal oxidant allows closure of a catalytic cycle by

reoxidation of hydroxylamine **3** to oxoammonium ion **2**. The redox relationship between these three compounds is shown in Scheme 1.

Numerous terminal oxidants have successfully been employed in TEMPO-catalyzed oxidations, and the list includes reagents such as bleach,<sup>9</sup> sodium chlorite,<sup>10</sup> sodium bromite,<sup>11</sup> *tert*-butyl hypochlorite,<sup>12</sup> Oxone,<sup>13</sup> MCP-BA,<sup>14</sup> *N*-chlorosuccinimide,<sup>15</sup> [bis(acetoxy)iodo]benzene,<sup>16</sup> hydrogen peroxide in combination with methyltrioxorhe-

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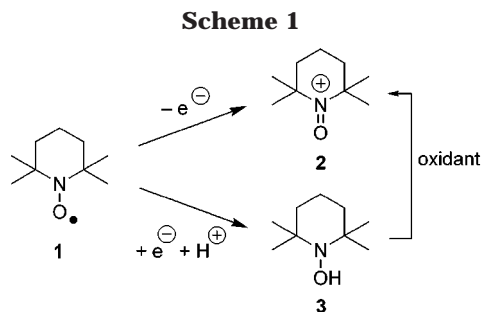
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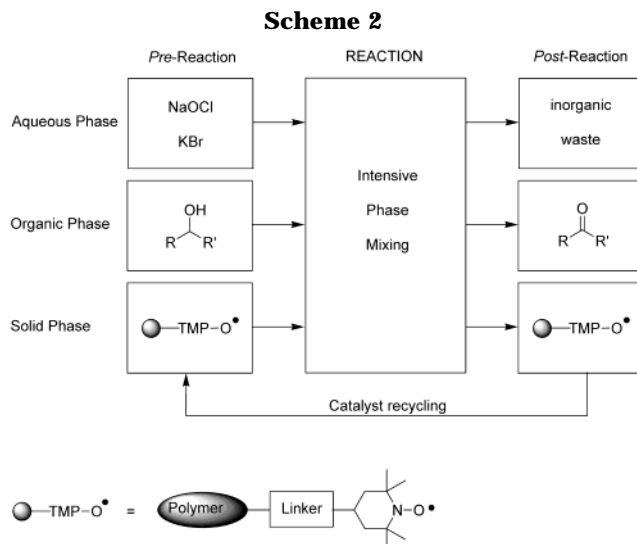
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nium(VII),<sup>17</sup> various peroxides in the presence of a silver cocatalyst,<sup>18</sup> or oxygen in combination with a high-valent metal salt.<sup>19</sup> Furthermore, electrochemical methods<sup>20</sup> for catalyst regeneration are known.

One of the most important protocols in this area was introduced by Anelli and co-workers as early as 1987. It involves the use of nontoxic reagents and is a metal-free catalytic route to carbonyl compounds. According to the original protocol,<sup>9a</sup> a TEMPO-type nitroxyl radical is used as catalyst in combination with potassium bromide as cocatalyst and a solution of buffered bleach as the terminal oxidant.

Besides its high catalytic efficiency, Anelli's oxidation protocol is known for its mild reaction conditions and pronounced selectivities. Thus, primary hydroxyl groups are oxidized with high preference over secondary ones and over-oxidations of the resulting aldehydes can usually be avoided by simply adjusting the amount of oxidant.<sup>21</sup> As a consequence of the mild reaction conditions, even substrates which possess labile protecting groups or stereogenic centers in the  $\alpha$ -position to the hydroxyl group can efficiently be oxidized.<sup>9c</sup> For example, the Anelli oxidation has been applied in the synthesis of  $\alpha$ -alkoxy aldehydes,<sup>22</sup>  $\alpha$ -amino aldehydes,<sup>22,23</sup> and various amino acid derivatives.<sup>24</sup> Even on larger scale the method proved reliable as illustrated by examples from the patent literature. At BASF K ukenh ohner and Goetz<sup>25</sup> and at



Degussa Drauz and co-workers<sup>26</sup> used Anelli's protocol in oxidations of 2,3-disubstituted benzyl alcohols and hydroxyproline derivatives, respectively.

The broad applicability of the Anelli oxidation attracted the interest of various research groups with the aim of finding further improvements for the original method. In particular the use of polymer-supported catalysts seemed desirable, since they enable both catalyst recycling and simplified workup of the reaction mixture.<sup>27</sup> After the oxidation the carbonyl compounds could easily be obtained from the organic phase by a simple phase separation step as they are usually formed in high yields without significant amounts of byproducts.<sup>28</sup> Scheme 2 illustrates this approach schematically.

Previous to our work,<sup>29</sup> various polymer-supported nitroxyl radicals had already been synthesized based on organic<sup>30</sup> as well as inorganic supports.<sup>31</sup> Some of them were applied as catalysts in oxidation reactions,<sup>30a-d,31b,c</sup>

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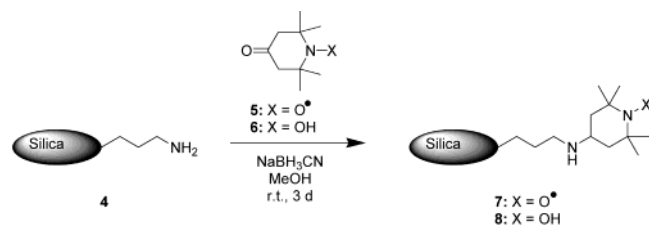
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Scheme 3



but to the best of our knowledge none of them has been used in oxidations according to the Anelli protocol. The work most closely resembling this approach was carried out by Heeres and co-workers,<sup>31c</sup> who used a silica-supported TEMPO catalyst and bleach as terminal oxidant. However, in contrast to the Anelli protocol, the reactions were carried out in the *absence* of an organic solvent, and under these reaction conditions an efficient catalyst recycling proved impossible.<sup>32,33</sup>

## Results and Discussion

**Synthesis and Characterization of Silica-Supported TEMPO Catalysts.** Since various inorganic supports have been described to be stable even under harsh reaction conditions,<sup>27a</sup> we focused our initial investigation on the use of a TEMPO catalyst bound onto silica. Its synthesis is summarized in Scheme 3. This route was chosen for several reasons. Aminopropyl-functionalized silica is commercially available and has a relatively high degree of functionalization ( $df \approx 1$  mmol/g). Oxo-derivatives of TEMPO can easily be attached in one step by reductive amination. Furthermore, Hall and Waterton demonstrated that analogous covalently attached TEMPO derivatives on aminopropyl-functionalized silica-based support (controlled-pore glasses) had a high stability and were only released from the inorganic support under conditions which did also cause dissolution of the silica surface.<sup>31a</sup>

Our first aims were to optimize the attachment procedure and to determine how much 4-oxo-TEMPO (**5**) was required in order to achieve the highest possible degree of functionalization of **7**. Therefore, a number of reductive aminations were carried out varying the amounts of **5** between 0.5 and 10.0 equiv with respect to the aminopropyl-groups on the silica. After the reactions, the solids were washed extensively with methanol in a Soxhlet apparatus to remove adsorbed excess of 4-oxo-TEMPO from the surface. The carbon contents of the supported catalysts were then determined by microanalyses, and the final  $df$ -values were calculated on the basis of the carbon content increase with respect to the nonmodified support (Table 1).

According to the distributors information, the selected support had a degree of functionalization of approximately 1 mmol/g. TEMPO attachment to all amino-

Table 1. Syntheses of Silica-Supported TEMPO Catalysts<sup>a</sup>

entry	carbonyl component	amount of carbonyl component, equiv <sup>b</sup>	catalyst	$df$ -value <sup>c</sup> [ $\mu$ mol/g]
1	<b>5</b>	10.0	<b>7</b>	510
2	<b>5</b>	5.0	<b>7</b>	480
3	<b>5</b>	2.55	<b>7</b>	550
4	<b>5</b>	1.25	<b>7</b>	480
5 <sup>d</sup>	<b>5</b>	1.25	<b>7</b>	380
6	<b>5</b>	0.75	<b>7</b>	220
7	<b>5</b>	0.50	<b>7</b>	170
8	<b>6</b>	9.6	<b>8</b>	500
9	<b>6</b>	2.5	<b>8</b>	500

<sup>a</sup> According to the representative procedure; see Experimental Section. <sup>b</sup> With respect to the amino groups of the aminopropyl-functionalized silica ( $df \approx 1$  mmol/g according to the distributor's information). <sup>c</sup> Calculated on the basis of the increase of carbon content in comparison to the unmodified support. <sup>d</sup> A second fraction of silica gel was converted under identical conditions as in entry 4.

groups would result in a final  $df$ -value of 870  $\mu$ mol/g. However, only a maximum value of approximately 500  $\mu$ mol/g was reached, even when a large excess of **5** was applied (Table 1). This value corresponds to 54% conversion of the amino groups on the silica, and it can already be obtained from reactions with 1.25 equiv of 4-oxo-TEMPO. Presumably this incomplete functionalization is due to a lack of accessibility of the amino groups on the support. If the attachment sites have partially been encapsulated during the process of silica formation they might not be available for the reaction with the sterically demanding TEMPO derivative **5**. Use of less than 1.25 equiv of 4-oxo-TEMPO led to a significant decrease in the final  $df$ -value (Table 1, entries 5 and 6). Even though the results varied slightly from run to run (entries 4 and 5), an amount of 1.25 equiv of **5** was considered to be optimal.

Although the covalent nature of such newly formed carbon nitrogen bond had already been shown,<sup>31a</sup> further unequivocal proof appeared desirable and MAS NMR-experiments were taken into consideration. As pointed out by Brunel and co-workers,<sup>32a</sup> such investigations are hampered by the paramagnetic properties of the free radical in silica-supported TEMPO itself. Therefore, the same attachment reaction was carried out using the aminopropyl-functionalized silica and hydroxylamine (4-oxo-TMP-OH, **6**) giving **8** as a product which could readily be analyzed by this technique. The <sup>13</sup>C-MAS NMR spectra of the unmodified support **4** and the silica-attached hydroxylamine **8** are presented in Figure 1.

The chemical shifts for the carbon atoms of **4** (Figure 1, top) are consistent with those presented by Brunel and co-workers.<sup>32a</sup> The signals at 9, 24, and 43 ppm can be attributed to the three carbon atoms of the silica-attached aminopropyl group. Unfortunately, several <sup>13</sup>C-MAS NMR signals of **8** (Figure 1, bottom) overlap. Nevertheless, the effect of the formation of the secondary amine through attachment of the piperidine ring can be seen. The signal corresponding to the methylene group directly attached to the nitrogen is shifted from 43 to 51 ppm, which provides further evidence for the proposed amino-linked covalent attachment of the TEMPO derivative onto the silica surface.

**Oxidation of Alcohols.** As described in our earlier report<sup>29</sup> the silica-supported TEMPO catalysts can efficiently be applied in the oxidation of various alcohols. Following a typical protocol for the Anelli oxidation

(32) After our first communication (ref 29) several other polymer-supported TEMPO catalysts have been described. (a) Silica-supported: Brunel, D.; Lentz, P.; Sutra, P.; Deroide, B.; Fajula, F.; Nagy, J. B. *Stud. Surf. Sci. Catal.* **1999**, *125*, 237–244. (b) MCM-41-supported: Verhoef, M. J.; Peters, J. A.; van Bekkum, H. *Stud. Surf. Sci. Catal.* **1999**, *125*, 465–472. (c) Sol-gel: Ciriminna, R.; Blum, J.; Avnir, D.; Pagliaro, M. *Chem. Commun.* **2000**, 1441–1442. (d) Oligomeric tri(alkyl amino)triazines: Dijkstra, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271–272.

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Table 2. Oxidation of Alcohols on a 4 Mmol-Scale in the Presence of 7<sup>a</sup>

entry	alcohol	product	yield [%]
1	benzyl alcohol	benzaldehyde	75
2	4-nitrobenzyl alcohol	4-nitrobenzaldehyde	69
3	2-bromobenzyl alcohol	2-bromobenzaldehyde	99
4	4-methoxybenzyl alcohol	4-methoxybenzaldehyde	44
5	1-phenylethanol	acetophenone	99
6	1-phenyl-1-propanol	propiophenone	99
7	1,2,3,4-tetrahydro-1-naphthol	1-tetralone	95
8	1-nonanol	nonanale	85
9	2-nonanol	2-nonanone	97
10	cyclohexanol	cyclohexanone	76
11	4- <i>tert</i> -butylcyclohexanol	4- <i>tert</i> -butylcyclohexanone	96

<sup>a</sup> All reactions were carried out according to the general procedure; see Experimental Section.

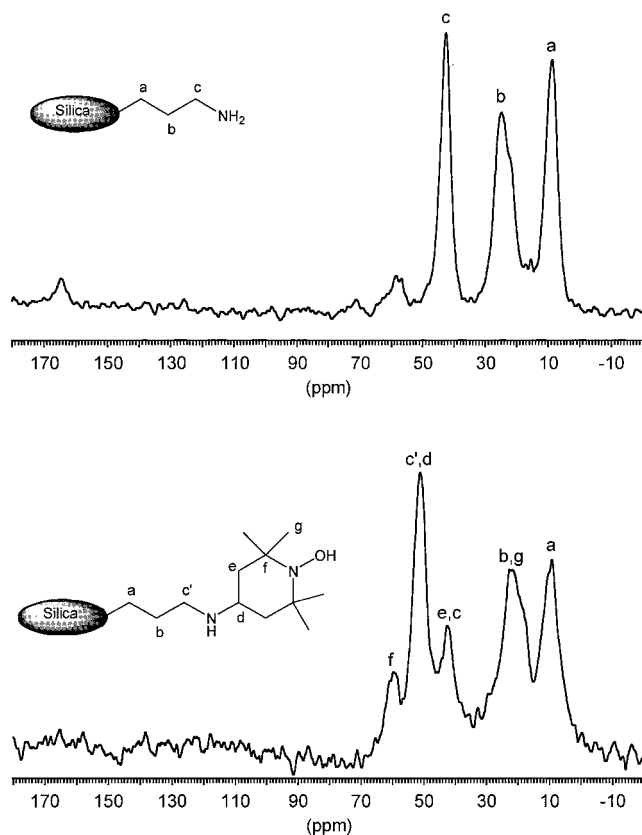


Figure 1. MAS-NMR spectra of aminopropyl-functionalized silica **4** and silica-supported TMP-OH **8**.

primary as well as secondary alcohols were oxidized to aldehydes and ketones, respectively. Even though extended reaction times were required for the immobilized catalyst, the high selectivity toward the oxidation of primary alcohols in the presence of secondary ones was verified, and due to the very mild reaction conditions stereogenic centers were not affected.<sup>29</sup>

Since most of the oxidations reported in our previous publication were only carried out on an analytical scale, we now intended to demonstrate the synthetic utility of the developed protocol. For this reason we applied the supported catalysts in the Anelli oxidation of various alcohols on a 4 mmol-scale. The results are summarized in Table 2.

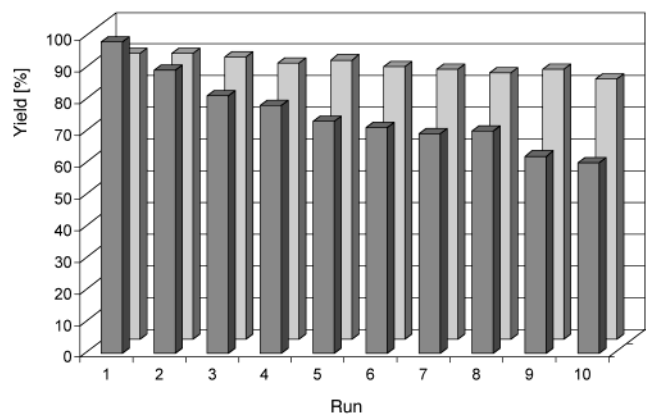
All reactions were carried out under standard reaction conditions as described in the Experimental Section. Both catalysts the silica-supported nitroxyl radical **7** and the corresponding hydroxylamine **8** were equally effective. The introduced protocol is applicable for a large variety of substrates affording the corresponding carbonyl com-

pounds in good to excellent yields. It is possible to oxidize benzylic as well as aliphatic alcohols. After a reaction time of 1 h, full conversion of both primary and secondary alcohols is achieved. For some substrates minor modifications of the given protocol are recommended. For example, in the case of primary alcohols, an excess of oxidant and an extended reaction time can cause over-oxidation to the carboxylic acids as indicated by slightly reduced yields. Activated aromatic alcohols such as 4-methoxybenzyl alcohol tend to form side products, and their oxidation remains critical. The low yield of the oxidation product (Table 2, entry 4) corresponds to the result published for the reaction with the unsupported TEMPO-catalyst.<sup>9a</sup> Other than cyclohexanol, all secondary alcohols are transferred to the corresponding ketones in almost quantitative yield. In the case of cyclohexanone the moderate yield of only 76% is attributed to the high volatility of this compound.

**Catalyst Recycling and Stability.** Our first results concerning catalyst recycling appeared to be very promising. When the reaction time was set to 30 min, which proved to be sufficient for most primary alcohols, comparably high yields of the carbonyl compounds were obtained in 10 subsequent runs using the same catalyst. This result was remarkable because Heeres and co-workers had reported a significant loss of activity for a recycled analogous catalyst in reactions which were performed in the absence of an organic solvent.<sup>31c</sup> In their case, the yield in the third run was reduced by half compared to the previous one even though the reaction time was drastically increased from 3 to 24 h.<sup>31c</sup> This observation caused us to further investigate the catalyst stability of our own system. We therefore carried out oxidations of 1-nonanol in 10 subsequent runs with a reaction time of only 15 min and expected an incomplete conversion and, in the case of absolute catalyst stability, a constant yield in all runs. Figure 2 illustrates the results of this study.

Whereas the product yield remained high in the 30 min runs, a decrease in yield was observed in the ones with the shortened reaction time. This effect was attributed to a partial catalyst degradation, which was compensated for by prolonging the reaction time. It was assumed that the high density of active sites on the silica surface led to interactions between neighboring functional groups which then resulted in an oxoammonium ion-mediated cleavage of amino-bonds and partial destruction of the supported catalyst.<sup>35</sup>

(34) 3-Aminopropyl-functionalized silica gel was purchased at Aldrich (36,425-8). According to the distributor's information the degree of functionalization is approximately 1 mmol/g.



**Figure 2.** Yields obtained in the Anelli oxidation of 1-nonanol to give nonanal in the presence of silica-supported catalyst **8** after 15 and 30 min (front and back rows, respectively) reaction time.

**Table 3. Physical Data of the Supported TEMPO Catalysts**

entry	polymer	df-value <sup>a</sup> [ $\mu\text{mol/g}$ ]	specific surface [ $\text{m}^2/\text{g}$ ]	surface concn [ $\mu\text{mol}/\text{m}^2$ ]
1	silica <sup>34</sup>	500	350 <sup>b</sup>	1.4
2	Trisoperl <sup>36</sup>	38	70.7 <sup>c</sup>	0.5

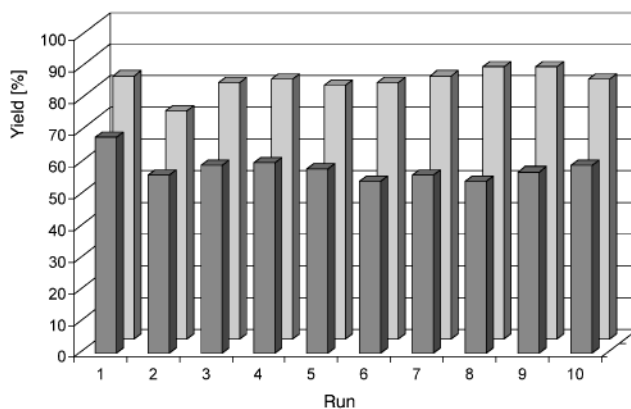
<sup>a</sup> Calculated on the basis of the increase of carbon content in comparison to the unmodified support. <sup>b</sup> Determined by BET analysis. <sup>c</sup> According to the distributor's information.

To verify this hypothesis, a related aminopropyl-functionalized porous glass (Trisoperl)<sup>36</sup> having a lower surface concentration of functional groups was used as alternative support for the TEMPO unit. Since now the catalytically active sites on this polymer surface were further apart, an enhanced catalyst stability was expected. For comparison the physical data of both supported TEMPO catalysts are presented in Table 3.

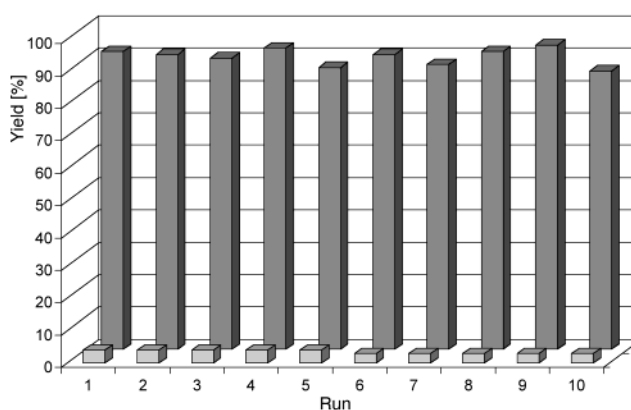
Also with the Trisoperl-TEMPO catalyst the oxidation of 1-nonanol was carried out according to the Anelli protocol in 10 subsequent runs. The yields of the corresponding aldehyde after 15 and 30 min reaction time are presented in Figure 3.

To our delight, we found that even in the 15 min reaction time sequence the catalytic performance of the new Trisoperl-based system was very good. With the exception of the first repetitive run, the yields remained constant at about  $57 \pm 3\%$  over a range of 10 reaction/recovery cycles. This increased stability of the porous glass-supported TEMPO catalyst provided evidence for the assumption of the necessity of sufficient site separation on the polymer surface.

The high selectivity toward the oxidation of primary alcohols in the presence of secondary ones is a main characteristic of the Anelli oxidation, and in a final experiment we intended to ensure that this selectivity



**Figure 3.** Yields obtained in the Anelli oxidation of 1-nonanol to give nonanal in the presence of the porous glass-supported catalyst after 15 and 30 min (front and back rows, respectively) reaction time.



**Figure 4.** Yields obtained in the competitive Anelli oxidation of benzyl alcohol and 1-phenylethanol to give benzaldehyde (back) and acetophenone (front), respectively, in the presence of the silica-supported catalyst **8**.

was not effected by the catalyst recycling. For this reason, the same silica-supported catalyst was applied in 10 subsequent runs for the oxidation of a mixture of benzyl alcohol and 1-phenylethanol. The results obtained in these experiments are summarized in Figure 4.

In each of the 10 runs benzaldehyde was obtained in excellent yield, whereas the conversion of 1-phenylethanol remained low. These results demonstrate that silica-supported TEMPO catalysts retain their pronounced selectivity even after numerous reaction/recovery cycles and furthermore confirm that the oxidation involves an oxammonium ion-mediated reaction pathway in all runs.<sup>37</sup>

## Conclusions

We have developed silica-based polymer-supported TEMPO catalysts for Anelli oxidations of alcohols to the corresponding carbonyl compounds. The catalysts can be recycled, and their applicability has been demonstrated by performing sequential catalytic oxidations. A separation of the functional groups on the polymer surface proved beneficial for the catalyst stability and led to the introduction of a porous glass-supported TEMPO catalyst. The general observations made in this study estab-

(35) (a) For an oxoammonium ion-mediated cleavage of amino-bonds, see: Bobbitt, J. M.; Flores, C. L. *Heterocycles* **1988**, *27*, 509–533. (b) Such neighboring effects have already been studied in the case of a polystyrene-supported TEMPO catalyst by Endo and co-workers (ref 30a). Filtration experiments performed by Sheldon and co-workers revealed that if TEMPO derivatives were liberated by the degradation of **7**, they had to be catalytically inactive in alcohol oxidations because no catalytic activity was found in the filtrate (ref 33).

(36) 3-Aminopropyl-functionalized porous glass Trisoperl (PMGK N 23/94, amino-111) was purchased at Schuller GmbH, Tröbach 2, D-96523 Steinach. According to the distributor's information the degree of functionalization is 0.147 mmol/g and the specific surface is 70.69  $\text{m}^2/\text{g}$ .

(37) The high selectivity is one of the main characteristics of the Anelli oxidation. See also ref 21.

lished guidelines for further catalyst development and optimization.

### Experimental Section

**General.** All reactions were carried out in glass tubes which were equipped with a ceramic filter plate and a stopcock allowing easy separation of the solid-supported material and liquid reaction mixtures. A cooling mantle enabled tempering of the reaction vessels.

All reagents were purchased from commercial suppliers, unless otherwise specified, and used without further purification. Dichloromethane was distilled before use. Methanol was treated with sodium, heated to reflux for several hours, and distilled. 4-Oxo-2,2,6,6-piperidine-1-oxyl (**5**)<sup>38</sup> and 1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine (**6**)<sup>39</sup> were prepared according to known procedures. All microanalyses were conducted at the Institute of Organic Chemistry at the RWTH Aachen. Products obtained in oxidation experiments were analyzed via GC and <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

**Representative Procedure for the Synthesis of Silica-Supported TEMPO (7) and TMP-OH (8).** Aminopropyl-functionalized silica gel (2 g, 2 mmol)<sup>34</sup> was placed in the reaction vessel, and the required amount (1.0–20.0 mmol; see Table 1) of 4-oxo-TEMPO (**5**) or 4-oxo-TMP-OH (**6**) dissolved in dry methanol (10 mL) was added, followed by 1.25 g of NaBH<sub>3</sub>CN (20.0 mmol). The reaction mixture was then shaken for 3 days at ambient temperature. The solution was removed by filtration, and the remaining solid was sequentially washed five times with methanol, water, and methanol (10 mL each). The solid was finally extracted with methanol in a Soxhlet apparatus for 3 d, to remove traces of surface adsorbed TEMPO derivatives. The degree of functionalization was determined by microanalysis after drying in vacuo.

(38) Rosen, G. M. *J. Med. Chem.* **1974**, *17*, 358–360.

(39) Paleos, C. M.; Dais, P. *J. Chem. Soc., Chem. Commun.* **1977**, 345–346.

**Synthesis of Porous Glass-Supported TMP-OH.** Aminopropyl-functionalized porous glass (Trisoperl, 1.0 g, 0.15 mmol)<sup>36</sup> was treated with a solution of 255 mg (1.5 mmol) of 4-oxo-TMP-OH (**6**) in methanol (5 mL) followed by the addition of 94 mg (1.5 mmol) of NaBH<sub>3</sub>CN. The reaction and the workup were carried out according to the procedure for the synthesis of silica-supported TEMPO catalysts described above. For the Trisoperl-catalyst a final df-value of 38 μmol/g was obtained.

**Representative Procedure for the Oxidation of Alcohols.** In the reaction vessel 46 mg of silica-supported TEMPO (23 μmol of TEMPO according to microanalysis) was placed. A solution of the alcohol (4.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and an aqueous solution (0.8 mL) of KBr (0.5 M) were then added. After the reaction mixture was cooled to 0 °C, an aqueous solution of NaOCl (13.5 mL, diluted to a final concentration of 0.37 M and buffered by the addition of NaHCO<sub>3</sub> to a pH of 9.1) was added. The reaction mixture was vigorously shaken for 60 min. After filtration, the organic layer was removed, and the aqueous phase was extracted once with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over MgSO<sub>4</sub>, the solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent.

Repetitive reaction/recovery experiments were carried out on an analytical scale as previously described.<sup>29</sup>

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