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# The *TEMPO*/Copper Catalyzed Oxidation of Primary Alcohols to Aldehydes Using Oxygen as Stoichiometric Oxidant

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**Summary.** A catalytic system for the selective oxidation of primary alcohols to aldehydes under very mild conditions was developed. 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. Compared to existing Cu/*TEMPO* oxidation methods we substantially lowered the amount of copper necessary and discovered that the reaction is dependent on *pH*. The catalytic system was also tested with polymer-bound *TEMPO* and new insights into the currently discussed mechanism were derived.

**Keywords.** *TEMPO*; Nitroxyl radical; Copper; 2,2′-Bipyridine; Immobilized catalyst.

## Introduction

The selective oxidation of primary alcohols to aldehydes is one of the most important functional group transformations in organic synthesis and industrial fine chemical production. Classical methods are based on chromium reagents, manganese dioxide, silver oxide, *N*-chlorosuccinimide [1], dimethyl sulfoxide activated by oxalyl chloride [2], and periodanes [3, 4]. These methods are generally only useful on a laboratory scale because of the toxicity or corrositivity of the reagents, and because of the amount of chemical waste, which is produced due to the stoichiometric nature of these reactions. Modern oxidation methods work on a catalytic basis, using clean stoichiometric oxidants, like oxygen or hydrogen peroxide. In addition, nitroxyl radicals like 2,2,6,6-tetramethylpiperidin-1-oxyl (*TEMPO*) and its derivatives in combination with copper ions, turned out to be efficient and selective catalysts in the oxidation of alcohols to the corresponding carbonyl compounds. The first copper/nitroxyl radical catalyzed oxidation has been reported by *Semmelhack et al.* in 1984 [5], who managed to oxidize allylic and benzylic

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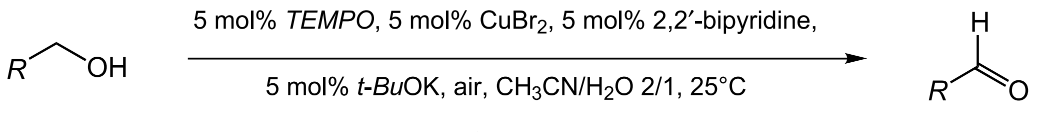
alcohols at room temperature in *DMF*. More recently, several copper/*TEMPO* catalytic systems have been published: *Knochel et al.* have used a mixture of chlorobenzene/perfluorooctane as biphasic solvent system in combination with perfluoroalkylated bipyridines as copper complexing agents [6, 7]. *Ansari* and *Gree* as well as *Jiang* and *Ragauskas* have reported *TEMPO* catalyzed alcohol oxidations in ionic liquids [8]. *Minisci et al.* have reported a highly efficient method for the oxidation of alcohols using *TEMPO* in combination with Co/Mn or Cu/Mn nitrates using acetic acid as the solvent. This reaction was carried out under ambient pressure and temperature [9]. In most recent works *Sheldon et al.* have investigated the mechanism of the original *Semmelhack* procedure [10] and developed a new catalytic system using $CuBr_2$/*TEMPO* in combination with 2,2′-bipyridine as complexing agent [11, 12]. Herein, we want to report fundamental improvements of the catalytic system developed by *Sheldon et al.* as well as new insights into the reaction mechanism.

## Results and Discussion

### *Catalytic System*

The *Sheldon* procedure, as shown in Scheme 1, is carried out in an acetonitrile/water solvent mixture under ambient conditions. Although the reaction is very environmentally friendly and safe, it has some drawbacks concerning its industrial use, especially in terms of catalyst concentrations (5 mol% catalysts and co-catalysts) and high cost of co-catalysts (*e.g.* potassium *tert.*-butoxide). We now improved the catalytic system using benzyl alcohol as a substrate example. It turned out that under the given reaction conditions a copper salt has not necessarily to be used. It can be substituted by elemental, fine powdered copper, which is oxidized *in situ* to Cu(II) and is then chelated by 2,2′-bipyridine (*bipy*) by stirring copper powder and *bipy* for 30 min before adding the other reagents. The reported differences in reactivity of various copper salts [11], which are due to the counter-ion, are circumvented in this way. In addition, we discovered that the amount of *TEMPO* has a much higher influence on the reaction time than the amount of copper catalyst. Thus, it was possible to lower the amount of copper to 0.5 mol% and *bipy* concentrations to 2.5 mol% maintaining reasonable reaction times (Fig. 1). By means of ICP analysis of the reaction mixture it turned out that only 0.22 mol% copper are active. Lowering the amount of copper was one of our main goals, because it is highly toxic for microorganisms and might cause problems in industrial waste water treatment.

Upon replacing the costly potassium *tert.*-butoxide with NaOH, it turned out that the reaction is *pH*-controlled. The reaction completely stopped at *pH* = 8 and the optimum *pH* was determined to be 13–13.5. By carrying out the reaction in this



**Scheme 1**

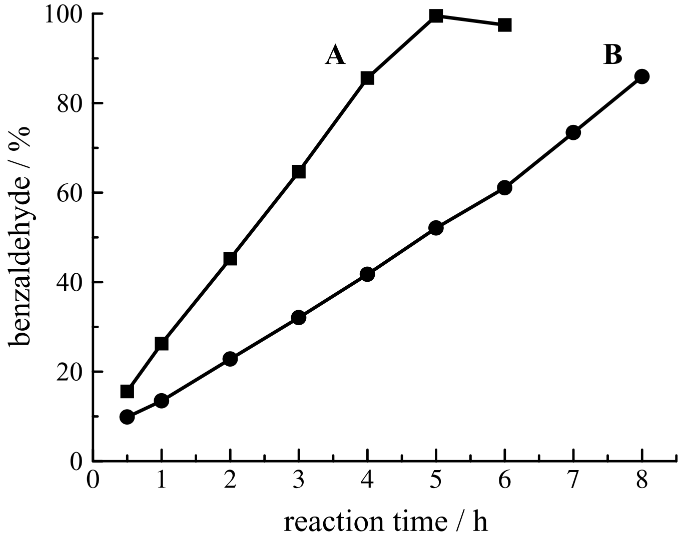


**Fig. 1.** Effects of *TEMPO* concentration on the Cu/*TEMPO* catalyzed oxidation of benzyl alcohol; reaction conditions: 2.5 mol% 2,2′-bipyridine, 0.5 mol% Cu, *pH* 13.5, 25°C, $O_2$ atmosphere (**A**) 5 mol% *TEMPO* (**B**) 2.5 mol% *TEMPO*

*pH* range maintained by constantly adding small amounts of NaOH, the influence of the *TEMPO* concentration on the catalytic system was shown to be essential. Thus, by halving the amount of *TEMPO*, the reaction time approximately doubled (Fig. 1).

Furthermore, the commercially available immobilized *TEMPO* derivative (*TEMPO*-4-oxymethyl)polystyrene [13, 14] was tested in a scale-up experiment

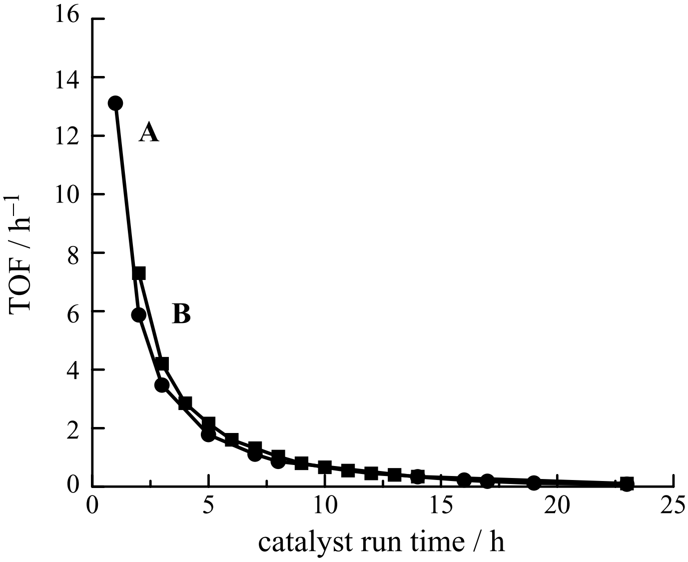


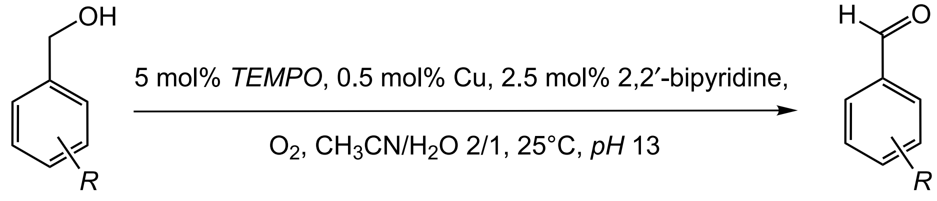
**Fig. 2.** Deactivation of polymer bound *TEMPO* in the oxidation of benzyl alcohol; reaction conditions: 5 mol% *TEMPO* (2.5 mmol *TEMPO*/g (*TEMPO*-4-oxymethyl)polystyrene), 2.5 mol% Cu, 5 mol% 2,2′-bipyridine, *pH* 13, 25°C, $O_2$ (0.3 $dm^3$/min) (**A**) run 1 (**B**) run 2

under the same reaction conditions. After separation of the reaction mixture, the polymer bound catalyst was washed with a small amount of solvent and reused for the next experiment. In this way immobilized *TEMPO* was reused four times and did not show any significant loss in activity or selectivity. However, during the course of such a reaction it was observed that conversion rates dropped rather quickly with reaction time, due to a deactivation of the catalyst. A turnover frequency (TOF) *vs.* catalyst run time plot according to Ref. [15] showed that after 5 h and approximately 50% conversion the catalyst activity was already very low (Fig. 2). Thus, experiments were aborted at 80–85% and the immobilized *TEMPO* was reused for the next run.

### *Substrate Scope*

After having obtained promising results with benzyl alcohol, a substrate screening was carried out using various substituted benzylic alcohols (Scheme 2, Table 1).

Unfortunately, it turned out that substrates, whose aldehydes are likely to form hydrates under the given reaction conditions [16], are overoxidized to the acid by about 50%. Substrates with electron donating groups, like methyl- or methoxybenzyl alcohols, are selectively oxidized to the aldehyde if substituted in *ortho*- or



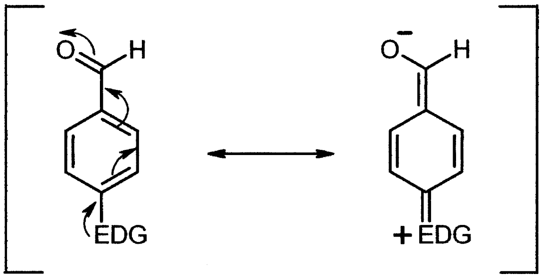
*R* = *o*-$NO_2$, *o*-Cl, *o-Me*, *o-OMe*, *m*-$NO_2$, *m*-Cl, *m-Me*, *m*-O*Me*, *p*-$NO_2$, *p*-Cl, *p-Me*, *p*-O*Me*

**Scheme 2**

**Table 1.** Substrate screening of benzylic alcohols

| Run | Substrate | Reaction time/h | Conversion/% | Selectivity/% |
|---|---|---|---|---|
| 1 | 2-Nitrobenzyl alcohol | 23 | 92 | 41 |
| 2[a] | 3-Nitrobenzyl alcohol | 8 | 71 | 42 |
| 3[a] | 4-Nitrobenzyl alcohol | 8 | 82 | 45 |
| 4 | 2-Chlorbenzyl alcohol | 23 | >99 | 49 |
| 5[b] | 3-Chlorbenzyl alcohol | 4 | 99 | 56 |
| 6 | 4-Chlorbenzyl alcohol | 8 | >99 | 64 |
| 7 | 2-Methylbenzyl alcohol | 30 | 91 | >99 |
| 8[a] | 3-Methylbenzyl alcohol | 8 | 67 | 53 |
| 9 | 4-Methylbenzyl alcohol | 23 | 98 | 97 |
| 10 | 2-Methoxybenzyl alcohol | 23 | >99 | 97 |
| 11 | 3-Methoxybenzyl alcohol | 8 | 90 | 68 |
| 12[a] | 4-Methoxybenzyl alcohol | 8 | 69 | >99 |

[a] Reactions were discontinued, although not finished; [b] 35 mmol alcohol, 7 mol% *TEMPO*, 3.5 mol% 2,2′-bipyridine, 0.7 mol% Cu



**Scheme 3**

**Table 2.** Substrate screening of aliphatic and allylic alcohols

| Run | Substrate | Reaction time/h | Conversion/% |
|---|---|---|---|
| 1 | Citronellol | 29 | 74[a] |
| 2 | 1-Octanol | 7 | 39[a] |
| 3 | 2-Octanol | 29 | traces |
| 4 | Phenylethanol | 29 | traces |
| 5 | Geraniol | 5 | 99[b] |

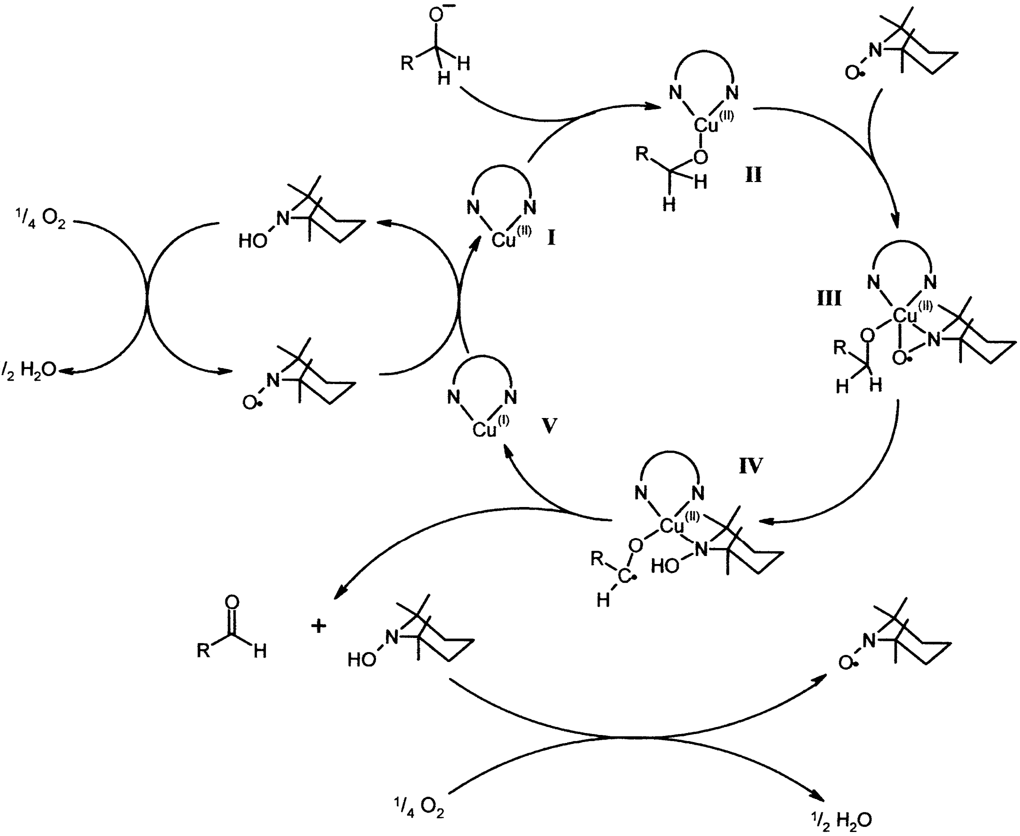
[a] Selectivity >99%, no further conversion with longer reaction times; [b] selectivity 97%, *de* 67% (*E*)-citral

*para*-position. For the corresponding aldehydes a resonance structure as shown in Scheme 3 can be formulated and accordingly these compounds are stabilized against a hydroxide ion attack and subsequent hydrate formation.

Another substrate screening was carried out on different aliphatic and allylic alcohols. However, when using standard reaction conditions as described above only very low conversions were observed. Thus, we decided to raise the amount of copper to 2.5 mol% and the amount of *bipy* to 5 mol%. In case of 1-octanol the reaction stopped at a conversion of 39%, which is remarkably lower than the results obtained with citronellol and geraniol. The already known selectivity for primary over secondary alcohols [12] was also proven, because only traces of 2-octanol were oxidized to the corresponding ketone. It was not possible to completely oxidize citronellol even when using long reaction times. On the contrary, geraniol was completely and highly selectively oxidized within 5 h under the same reaction conditions (Table 2). Accordingly, an allylic or benzylic activation of the alcohol seems to be a prerequisite for a fast and complete conversion when using a copper/ *TEMPO* system under these conditions.

## *Mechanistic Aspects*

The first mechanism for the copper/*TEMPO* catalyzed oxidation of aldehydes proposed by *Semmelhack et al.* [5] involves the oxoammonium ion, which is generated by oxidation or disproportionation of *TEMPO* [17]. In the *Semmelhack* mechanism the hydrogen abstraction of the $\alpha$-hydrogen during the oxidation takes place *via* an ionic transition state. Later on *Sheldon et al.* [10, 11] have proposed a mechanism based on radical mediated $\alpha$-hydrogen abstraction in the transition



Scheme 4

state (Scheme 4). Following this mechanism, Cu(II) forms a complex with a bidentate nitrogen ligand like 2,2′-bipyridine (**I**) and then a deprotonated alcohol forms an alkoxy species with this complex (**II**). The next step is the coordination of *TEMPO* to copper in an $\eta^2$ manner (**III**). Such complexes of copper(II) halides with $\eta^2$ coordinated *TEMPO* have been reported by *Rey et al.* and were proven by X-ray diffraction [18, 19]. Abstraction of the $\alpha$-proton by *TEMPO* then results in a radical species **IV**, which breaks up into the corresponding aldehyde, *TEMPO*H, and a copper(I) species **V** after intramolecular one-electron transfer. This is proposed to be the rate determining step of the reaction. The second role of *TEMPO* is to reoxidize Cu(I) to Cu(II) and then the catalytic cycle is closed by regeneration of *TEMPO*H by oxygen.

The results obtained in our experiments are clearly in favor of the latter radical mechanism. Stoichiometric oxidations of simple aliphatic alcohols by the separately synthetisized oxoammonium salt of *TEMPO* are known [17]. For example, 1-octanol and 2-octanol are oxidized smoothly to the corresponding aldehyde and ketone at ambient temperature and in good yields. In our case, however, these two substrates showed almost no reactivity or did not react at all. On the contrary, allylic and benzylic alcohols reacted readily using our method, because these compounds are able to stabilize the radical transition state **IV** of Scheme 4. Furthermore, according to literature [20–22] oxoammonium ions of various nitroxyl radicals including *TEMPO* are rather unstable in aqueous solutions of alkali hydroxides. These compounds are reduced to the nitroxyl radical with simultaneous formation of hydrogen peroxide. This fact is in conflict with our findings that the optimum *pH* for high reaction rates is 13. Another reason to favor the radical mechanism is the difference in reactivity of substituted benzyl alcohols (Table 1). Abstraction of the $\alpha$-proton *via* an ionic transition state should be much faster if the benzylic alcohols are substituted with electron withdrawing groups. Our results show approximately equal reactivity regardless of the substitution of the benzylic alcohol. This is due to the fact that radical species can be stabilized by electron withdrawing as well as electron donating substituents. *Neumann et al.* [23], who used *TEMPO* under acidic conditions, suggested that the reoxidation of *TEMPO*H to *TEMPO* is the rate determining step. This proposal was restricted by *Sheldon et al.*, who showed, that reoxidation of *TEMPO*H is much faster at alkaline *pH* than under neutral or acidic conditions [10], and thus the reoxidation step may only be rate determining at low *pH* values. A radical transition state can also explain the formation of (*Z*)-citral in the oxidation of (*E*)-geraniol (67% *de* (*E*)-citral was observed after the reaction was finished). According to literature [24] rotational barriers for allyl radicals range between 10 and 67 kJ/mol. Thus, it is likely that a diastereomerization during the transition state takes place under our conditions.

The presence of water is crucial for the catalytic cycle. In the absence of water a conversion equal to the amount of *TEMPO* catalyst added was observed. In our opinion the most important effect of water and the hydroxide ion is the formation of a hydroxo-complex together with Cu(II) and *bipy*, which has been first reported by *Wagner-Jauregg et al.* [25]. Usually, Cu(II) forms a 3:1 complex $[\mathrm{Cu}\ bipy_3]^{2+}$ with excess of *bipy*, but in this case the copper ion sphere is completely shielded against a coordination with *TEMPO* or the alcohol. It has been shown by *Ojima* [26] that under aqueous alkaline conditions this complex reacts to the hydroxo-complex $[\mathrm{Cu}\ [\mathrm{OH}]_2\ bipy]$ and in this case the hydroxo-groups should be readily replaced by the deprotonated alcohol or *TEMPO* (compare **II** and **III** in Scheme 4).

## Conclusions

The initial reaction conditions for the Cu/*TEMPO* catalyzed oxidation of alcohols to aldehydes developed by *Sheldon et al.* were fundamentally revised. The most important improvement is the replacement of copper halogenide salts by elemental copper powder, which is oxidized *in situ* to Cu(II) under the given reaction conditions. In addition, the environmentally toxic copper catalyst was reduced to 0.5 mol%, and it was determined that only 0.22 mol% copper actively catalyzes the reaction. The discovery that the reaction is controlled by *pH* gives a further edge in terms of dosage of co-catalyst like the costly potassium *tert.*-butoxide, which can be substituted by NaOH. A substrate screening showed that the catalytic system is very useful for the oxidation of allyl and benzyl alcohols. However, if the benzyl alcohols tend to form hydrates under the given reaction conditions, overoxidation to the corresponding acids will take place. Immobilized *TEMPO* was successfully used along with Cu(0) and *bipy* in the oxidation of benzyl alcohol on a larger scale. Our results rather imply a radical reaction mechanism, as proposed by *Sheldon et al.*, than a mechanism involving the oxoammonium ion. In particular, higher reactivity of allyl and benzyl alcohols connected to the stabilization of the intermediary formed radical species and the observed diastereomerization of allyl alcohols favor the *Sheldon* radical mechanism.

## Experimental

All chemicals were obtained from commercial suppliers and were used without further purification. Reaction products were identified and quantified by GC analysis using a Hewlett Packard 5890 series II gas chromatograph with FID detection equipped with a DB-1 column (30 m × 0.53 mm) or by HPLC analysis using a Hewlett Packard 1050 LC system with UV detection (210 nm) equipped with a Zorbax Eclipse-XDB C8 column (4.6 × 150 mm). Compounds were identified by comparison of the retention times with commercially available references and quantified using nitrobenzene as internal standard, or by external calibration.

### *Typical Oxidation Procedure*

The oxidation of the alcohols was carried out under $O_2$ in a 100 $cm^3$ double jacketed vessel, thermostated at 25°C and equipped with a magnetic stirrer, thermometer, and *pH*-electrode. Cu powder (16 mg, 0.25 mmol) were suspended in 60 $cm^3$ $CH_3CN/H_2O$ 2/1, 195.5 mg 2,2′-bipyridine (1.25 mmol) were added, and the reaction mixture was stirred for 30 min whereby it turned deep red. Then 390 mg *TEMPO* (2.5 mmol) and 200 $mm^3$ NaOH 40% were added and the reaction was started by addition of 50 mmol alcohol. During the reaction the *pH*-value was kept between 12.5 and 13.5 by addition of small amounts of NaOH 40%. Samples to monitor the progress of the reaction were taken out regularly, acidified with acetic acid, and extracted with $CH_2Cl_2$ followed by derivatization with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (*BSTFA*) if necessary.

### *Oxidation Procedure Using Immobilized TEMPO*

The oxidation was carried out in a 500 $cm^3$ double jacketed vessel (*Schmizo*), thermostated at 25°C, and equipped with reflux condenser, KPG stirrer, gas tube with frit por. 1, and *pH*-electrode. (*TEMPO*-4-oxymethyl)polystyrene (7.5 g, 2.5 mmol *TEMPO*/g), 596 mg Cu (9.34 mmol), and 2.93 g 2,2′-bipyridine (18.76 mmol) were suspended in 500 $cm^3$ $CH_3CN/H_2O$ 2/1 and stirred for 45 min. Then 40.6 g benzylalcohol (375 mmol) were added and $O_2$ was bubbled through the reaction mixture (0.3 $dm^3$/min). During the reaction the *pH*-value was kept between 12.5 and 13.5 by addition of small amounts of NaOH 40%. Samples to monitor the progress of the reaction were taken out regularly, acidified with acetic acid, and extracted with $CH_2Cl_2$ followed by derivatization with *BSTFA*. Reactions were stopped at a conversion between 80% and 90% and the reaction mixture was removed. (*TEMPO*-4-oxymethyl)polystyrene was washed with 300 $cm^3$ $CH_3CN/H_2O$ 2/1 and reused for succeeding experiments.

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