# Technical Production of Aldehydes by Continuous Bleach Oxidation of Alcohols Catalyzed by 4-Hydroxy-TEMPO

Elke Fritz-Langhals*

*Consortium für Elektrochemische Industrie GmbH, a subsidiary of Wacker-Chemie GmbH, Zielstattstrasse 20-22, D-81379 München, Germany*

**Abstract:**
**Aldehydes can be easily prepared from the corresponding alcohols in good to excellent yields by oxidation with technical bleach and catalytic amounts of 4-hydroxy-2,2,6,6-tetramethyl-piperidine-1-oxyl (1b, 4-hydroxy TEMPO, "HOT"). Whereas the well-known batch process performed on lab scale is not suitable for the technical synthesis especially of activated $\beta$-substituted aldehydes, this transformation can be performed continuously in a simple tube reactor. This layout meets all requirements necessary for the process, i.e., turbulent mixing of the biphasic mixture, removal of heat, short contact times, and high output. Thus, a single tube of 3 mm diameter renders about 60 mol of aldehyde per day.**

## Introduction

The oxidation of alcohols to aldehydes or ketones is a fundamental and important transformation in organic chemistry,[1–3] since these compounds having a high reaction potential are formed from readily available substrates. Aldehydes are versatile intermediates, e.g., for the asymmetric synthesis of cyanohydrins,[4,5] hydroxy carboxylic acids,[4,5] and amino acids,[6] for asymmetric aldol reactions,[7] and for Wittig reactions.[8] Aldehydes with additional substituents in $\beta$ or $\gamma$ position[8] are especially useful as building blocks in pharmaceutical syntheses. Therefore, the transformation of alcohols to aldehydes is very interesting to be performed on industrial scale.

Some industrially employed methods for the synthesis of aldehydes from the corresponding alcohols are known. Gas-phase dehydrogenation[9] is frequently employed in industry but is restricted to volatile and thermally stable substrates. The reaction conditions have to be matched specifically to each substrate. The oxidation with chromium (VI) oxides, for example, pyridinium dichromate[10] or pyridinium chlo-

**Scheme 1.** Oxidations of alcohols to aldehydes catalyzed by TEMPO (1)
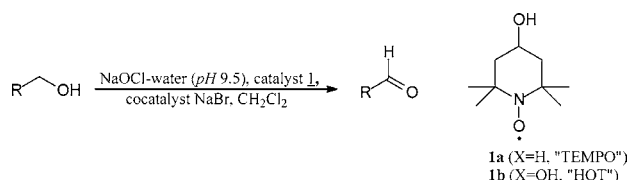


rochromate,[11] is also well-established. The handling of chromium(VI), however, is crucial due to its toxicity and the risk of product contamination. Moreover, the selectivity with functionalized substrates is only modest in many cases.

Mild and selective oxidation reagents have been developed, for example, activated DMSO,[12] Dess Martin periodinane[13] or IBX,[14,15] and palladium catalyzed air oxidations.[16] Their applicability, however, is restricted to transformations on the lab scale. Therefore, there is still a demand for mild and selective reagents in modern synthetic chemistry which are especially prone to industrial application. Catalytic methods would be most advantageous.

Oxidation of alcohols employing nitroxyl compounds (**1**), in particular TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl, **1a**), as oxidation catalysts seems to be applicable more generally.[17] The catalytic process using sodium hypochlorite (i.e., bleach) or sodium hypobromite as oxidant was first developed by Anelli and co-workers[18–20] (Scheme 1). Further oxidants in combination with TEMPO are described in the recent literature.[21–25] The Anelli protocol using bleach, however, seems to be most attractive because of its high

* Corresponding author. E-mail: elke.fritz-langhals@wacker.com. Telephone: +49-89 74844227. Fax: +49-89-74844242.
(1) Bäckvall, J.-E. *Modern Oxidation Reactions*, 1st ed.; Wiley-VCH: 2004.
(2) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1984.
(3) Hudlicki, M. *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990.
(4) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752–2778.
(5) Blanrue, A.; Wilhelm, R. *Synlett* **2004**, 2621–2623.
(6) Groeger, H. *Chem. Rev.* **2003**, *103*, 2795–2827.
(7) *Comprehensive Asymmetric Catalysis*, Vol. III, Aldol Reactions; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; p 997 ff.
(8) Herradon, B.; Mann, E.; Salgado, A.; Sanchez-Sancho, F. *Recent Res. Dev. Org. Chem.* **2001**, *5*, 49–62.
(9) Review: Mills, P. L.; Harold, M. P.; Lerou, J. J. In *Catalytic Oxidation: Principles and Applications*; Sheldon, R. A., Van Santen, R. A., Eds.; World Scientific: Singapore, Singapore, 1995; pp 291–369 {*Chem. Abstr. 124*, 157110}.

(10) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
(11) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245–258.
(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. Tidwell, T. T. *Synthesis* **1990**, 857–870.
(13) Dess, D. B.; Martin J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
(14) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111–124.
(15) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *117*, 3656–3665.
(16) Reviews: Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816. Stahl, S. S *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353–357.
(17) Reviews: Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499–3548. De Nooy, A. E. J.; Besemer A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.
(18) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
(19) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970–2972.
(20) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212–219.
(21) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441–443.
(22) Kim, S. S.; Jung, H. C. *Synthesis* **2003**, *14*, 2135–2137.
(23) Kashiwagi, Y.; Chiba, S.; Junichi, A. *New J. Chem.* **2003**, *27*, 1545–1549.
(24) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112–4113.
(25) Bolm, C.; Magnus, A.; Hildebrand, J. P. *Org. Lett.* **2000**, *2*, 1173–1175.

**Scheme 2.** Formation of ester 4 in the oxidation of activated alcohols 2





**Figure 1.** Tube reactor for the synthesis of activated aldehydes 3 from alcohols 2.
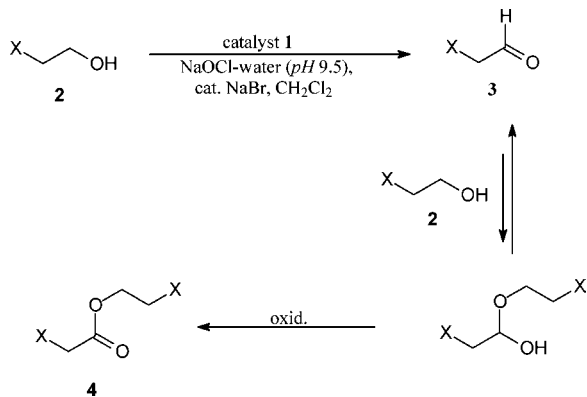
velocity[18] which enables a high output of product most interesting for industrial production. It gives almost quantitative yields of aliphatic, aromatic, and heteroaromatic non-functionalized aldehydes.

Most TEMPO-catalyzed oxidations are carried out in two-phase systems, e.g., dichloromethane/water or ethyl acetate/water. In a typical batch experiment an aqueous sodium hypochlorite solution is adjusted to pH 9.5[26] (e.g., by adding 20% sulfuric acid) and added to the organic phase containing the alcohol to be oxidized and catalytic amounts of the nitroxyl compound.

## Results and Discussion

On a small scale, the TEMPO/bleach process renders functionalized aldehydes in good yields within short reaction times. The only side reaction is the formation of the corresponding carboxylic acid if quantitative conversion of the alcohol is desired. In larger batches, however, a disadvantage of the established procedure is that there are great difficulties to remove the heat of the strongly exothermic oxidation process, particularly in the case of large batches. This lengthens the reaction time of the process, as a result of which secondary reactions, e.g., the reaction of alkali-sensitive groups such as ester groups or further oxidation of the aldehyde to the carboxylic acid, become more prominent. This can be seen in the oxidation of *i*-butyryloxy ethanol (**2a**, X = *i*-butyryloxy), which gives increasing amounts of the side products *i*-butyric acid and *i*-butyryloxy acetic acid. A further side reaction we found also with enlarged reaction times in larger batches is the formation of an ester **4** (Scheme 2). A Tishchenko reaction[27] which proceeds between aldehydes in alkaline medium can be ruled out because the aldehyde does not give ester **4** under the reaction conditions.[28] We suppose intermediate formation of a hemiacetal (which can proceed without acid catalysis) and the further oxidation
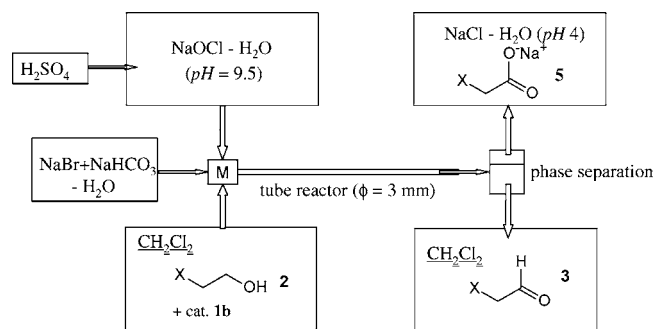
of its hydroxy group to give the corresponding ester **4**. We also found formation of the ester using trichloroisocyanuric acid/TEMPO as an oxidation system according to the protocol described in the literature.[29] The proposed mechanism is also in accordance to literature[30] and our own experiments[28] with mixtures of **2** and **3**. This side reaction is especially prominent in the case of the synthetically interesting $\beta$-functionalized systems, e.g., **3a**, due to the activating character of a $\beta$-electron withdrawing substituent (see also ref 31). In the oxidation of isobutyryloxy ethanol (**2a**, X = *i*-butyryloxy), for example, the yield of aldehyde **3a** is significantly decreased already in 20 g batches; moreover the ester **4a** becomes the major product in a 40 g batch (Scheme 3) due to the prolonged contact time between the starting alcohol **2a** and the formed aldehyde **3a** (see also Chart 1, entry 4). Residence time reactors do not help to solve this problem since remixing of **2** and **3** still takes place.

We found that the aldehydes **3** can be prepared in good yields without impurities of ester by rapidly pumping the components together into a static mixing element (M in Figure 1) and through a cooled tube (Figure 1). The turbulent flow creates a pressure of about 1 atm per meter length of the tube. It is necessary to use titanium for the mixing element and the tube because stainless steel and hastelloy B or C are not resistant to bleach under the conditions. Because the tube volume is low and the transformation is finished at the end of the tube, the reaction can be easily controlled and renders a maximum of safety.

The simple layout meets all requirements necessary for scale-up of the TEMPO/bleach oxidation: intensive, i.e., turbulent mixing, of the biphasic reaction system, removal of heat, and short contact times.[32]

In many cases, especially with cheap alcohols, it is favorable to use bleach in excess in order to guarantee total consumption of the alcohol **2** and to tolerate the formation

(26) At pH > 9.5 the oxidation reaction is much slower. According to our experiments bleach is stable at pH 9.5 at 0 °C, whereas below this pH degradation sets in.

(27) Törmäkangas, O. P.; Koskinen, A. M. P. *Recent Res. Dev. Org. Chem.* **2001**, *5*, 225−255.

(28) (a) A mixture of 10.8 mmol of benzoyloxyacetaldehyde (**3**, X = C$_6$H$_5$-COO) and 13.1 mmol of benzoyloxyethanol (**2**, X = C$_6$H$_5$COO) was oxidized in the presence of 0.5 mmol of HOT with 11.8 mmol of NaOCl pH 9.5 as described in the Experimental Section. Analysis by GC/internal standard: 2.8 mmol of **4** (X = C$_6$H$_5$COO), 7.0 mmol of **3** (X = C$_6$H$_5$-

COO), 3.5 mmol of **2** (X = C$_6$H$_5$COO). (b) 21.6 mmol of **3** (X = C$_6$H$_5$-COO) were oxidized with 13.0 mmol of NaOCl pH 9.5 according to (a) Analysis by GC/internal standard: 9.0 mmol of **3** (X = C$_6$H$_5$COO), no ester **4** detected.

(29) Jenny, C.-J.; Lohri, B.; Schlageter, M. (Hoffmann-La Roche AG, Basel) EP 0775684 1996.

(30) Conversion of aldehydes into esters using trichloroisocyanuric acid: Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamashiro, G. S.; Hilberath, L. A. *Synth. Commun.* **1996**, *26*, 2633−2639.
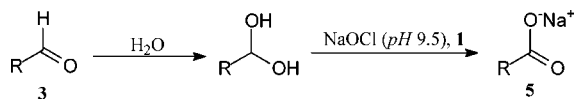
(31) Klausener, A. In *Methoden der Organischen Chemie* (ed. Houben-Weyl); Thieme: Stuttgart 1991; E14, A1, pp 591, 592.

(32) Fritz-Langhals, E.; Petersen, H.; Stohrer, J. *EP 1302456* (16.4.2003) {Chem. Abstr. *138*, 303933}.

**Scheme 3.** Yield of aldehyde 3a and ester 4a as a function of batch size
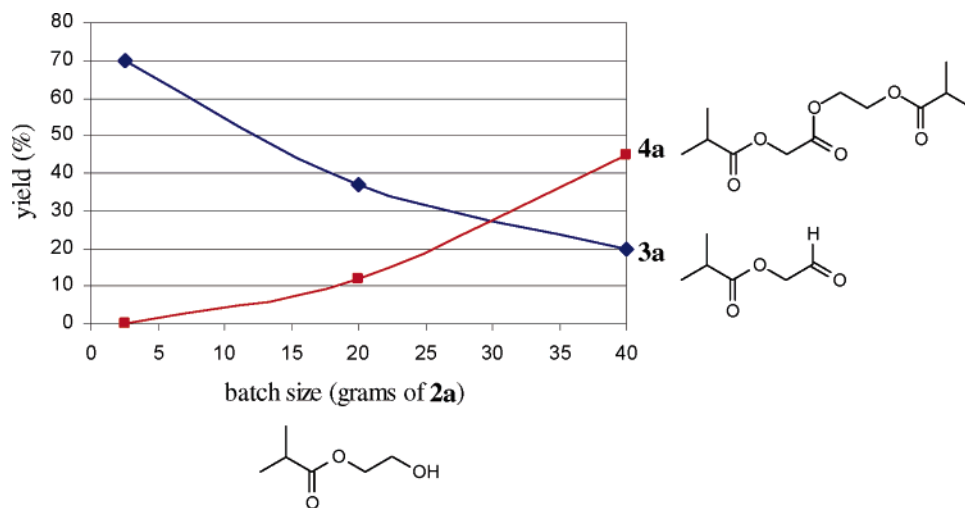


**Scheme 4.** Formation of carboxylates 5 in the oxidation of hydrophilic substrates



of **5** by overoxidation because the separation of the aldehyde from the alcohol may be difficult, whereas the carboxylic acid can be separated easily by $NaHCO_3$ treatment of the organic phase. This is important because many functionalized aldehydes are too unstable for distillation. In the tube reactor the $NaHCO_3$ is applied together with the cocatalyst sodium bromide as a third dosage (see Scheme 4). Formation of carboxylic acid **5** preferably takes place with hydrophilic substrates and aldehydes which form hydrates (Scheme 4).

The pH of the aqueous phase may drop during the oxidation process as carboxylic acid is formed. The dosage of $NaHCO_3$ can be adjusted so that the solution coming out of the tube is neutral and the aldehyde is thus stable.

The tube reactor renders a high output of aldehyde. With a single tube (3 mm internal $\phi$), an output of about 60 mol aldehyde per day is reached.

Chart 1 shows some examples of the prepared aldehydes (**3**). The yields in the tube reactor (method A) resemble the yields in small batches (20 mmol **2**, method B). In larger batches the yield of aldehyde drops as can be seen in Chart 1, entry 4, due to formation of ester and increasing amounts of hydrolysis products. Bleach was used in excess to reach a complete conversion. The purity of the products in the organic phase is 98% or even higher, because the carboxylic acids are separated in the aqueous phase.

The yields are generally high in the synthesis of nonactivated aldehydes (Chart 1, entries 11−15), but they also markedly depend on batch size. This can be seen in the synthesis of 2,2-dimethyl propanal (Chart 1, entry 11). The drop of yield, however, is visible only with comparably large batches. Therefore, the tube reactor is also favored for the technical production of nonfunctionalized aldehydes.

**Kinetic Measurements.** Kinetic experiments were performed for the oxidation of 2-butoxy ethanol (**2b**) to 2-butoxy

acetaldehyde (**3b**) to determine the required contact times and therefore the required length of the reaction tube. The reaction was quenched at definite times by addition of sodium thiosulfate to the reaction mixture and subsequent determination of the conversion rate. The experiments resulted in a half reaction time $\tau_{1/2}$ in the range of 2 to 3 s for this $\beta$-functionalized system under the prerequisite of intensive mixing (Figure 2).[33] With linear velocities of 2.8 m/s for the applied 3 mm tube the optimal length is about 5 m. Competition experiments revealed that purely aliphatic alcohols (e.g., 1-octanol) react even faster by a factor of approximately 3. The velocities in the oxidation of benzylic alcohols exceed 2-butoxyethanol by a factor of about 30. The results contradict the indication of Annelli[18] who stated half reaction times of at least 50 s for the oxidation of 1-nonanol to nonanal.

The use of the cheap HOT (**1b**) instead of TEMPO (**1a**) is strongly favored especially in technical scale oxidations. HOT undergoes side reactions during the oxidation process as outlined in Scheme 5. The products **6a**, **6b**, and **6c** were identified by GC/MS analysis in transformations **2→3** and in a blank experiment (see Experimental Section).[34] The amount of each is below 0.5% in respect to the produced aldehyde. The presence of a nitro compound (**6c**) should be taken into account in safety considerations for very large batches in cases of distillative workup.

The degradation of HOT, however, is of no importance within the very short reaction times. For the oxidation of some secondary alcohols which proceeds much slower than the oxidation of primary alcohols,[17] more stable TEMPO derivatives have to be used.[36]

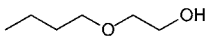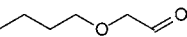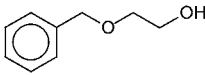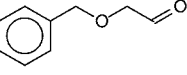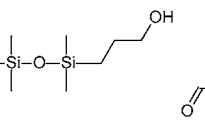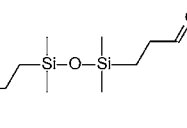(33) Experiments in microreactors are in progress.
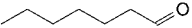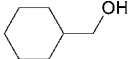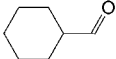(34) The isomers **6b\*** of **6b** and **6c\***of **6c** cannot be ruled out.
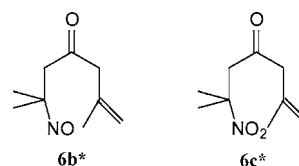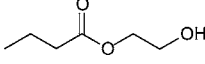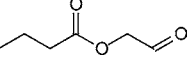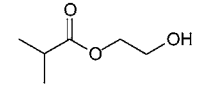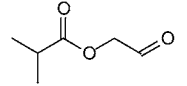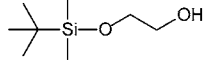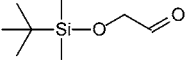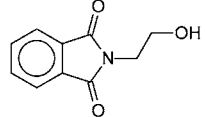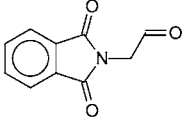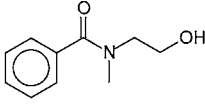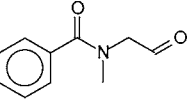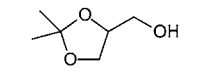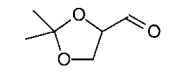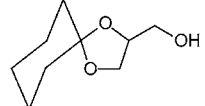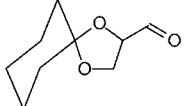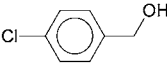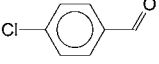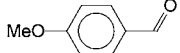


(35) Zakrzewski, J. *J. Prakt. Chem.* **1985**, *327*, 1011−1014.
(36) Work in progress.

**Chart 1.** List of synthesized aldehydes 3 (method A: tube reactor; method B: batch, cat. 1b, sodium bromide; method C: batch, cat. 1a, bromine; method C was used in kinetic experiments)

| Entry | alcohol | product | method (mmol 2) | yield 3 (%)[a] |
|-------|---------|---------|-----------------|----------------|
| 1 | | | A | 77 |
| | | | B (20) | 75 |
| | | | C (10) | 78 |
| 2 | | | B (20) | 71 (5) |
| 3 | | | B (20) | 68 (1) |
| 4 | | | A | 60 |
| | | | B (20) | 69 (7) |
| | | | B (20) | 69 (3) |
| | | | B (150) | 37 (0)[b] |
| | | | B (300) | 20 (0)[c] |
| | | | B (20) | 74 |
| 5 | | | B (20) | 98 (2) |
| 6 | | | B (20) | 75 |
| 7 | | | B (20) | 50 |
| 8 | | | B (20) | 27 |
| 9 | | | B (20) | 50 |
| 10 | | | B (20) | 89 (5[d]) |
| 11 | | | B (80) | 90 |
| | | | B (398) | 70 |
| | | | B (2480) | 63 |

| 12 | (n-heptanol) | (heptanal) | B (20) | 99 (<1) |
|----|----|----|----|----|
| 13 | (cyclohexylmethanol) | (cyclohexanecarbaldehyde) | B (20) | 97 (<1) |
| 14 | (4-chlorobenzyl alcohol) | (4-chlorobenzaldehyde) | B (20) | 100 |
| 15 | (4-methoxybenzyl alcohol) | (4-methoxybenzaldehyde) | B (20) | 95 (<2) |

(a) Absolute yields determined by NMR analysis with internal standard; nonconverted alcohol **2** in brackets; no further byproducts are detected in the organic phase in 20 mmol batches; the aqueous phase contents include the corresponding carboxylic acid, and both yields add to 100% within experimental error. (b) 12% Ester **4a**, 4% isobutyric acid in the aqueous phase. (c) 45% Ester **4a**, 8% isobutyric acid in the aqueous phase. (d) *Mono*aldehyde.
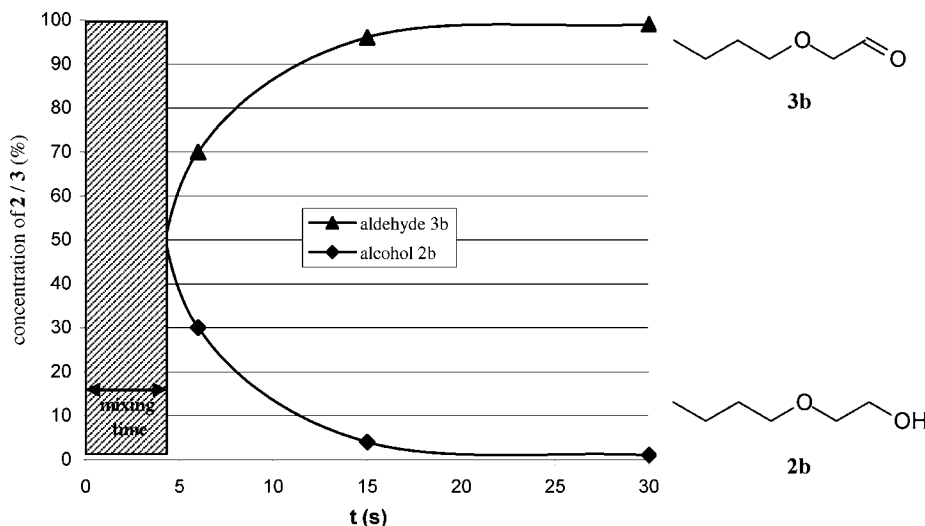


**Figure 2.** Oxidation of 2-butoxyethanol (**2b**) to 2-butoxyacetaldehyde (**3b**) in dichloromethane with 1 M NaOCl (pH 9.5), 5 mol % HOT (**1b**), and 5.5 mol % NaBr.

**Scheme 5.** Degradation of HOT (**1b**) in oxidation reactions[a]
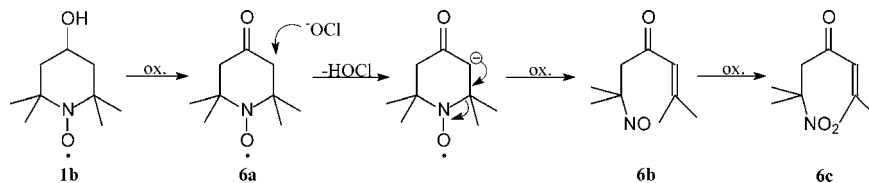


[a] Products were detected by GC/MS analysis; nitroso compound **6b** is additionally identified by its characteristic UV-absorption[35] (green colour, $\lambda_{max} = 663$ nm (acetonitrile), 667 nm (ethyl acetate)).

## Conclusion

TEMPO-catalyzed oxidations can be performed on industrial scale with high output continuously in a tube reactor. This layout is essential for the synthesis of activated $\beta$-substituted aldehydes and also recommended for nonactivated aldehydes.

## Experimental Section

**Synthesis of Aldehydes − Tube Reactor (Method A).** The following solutions were prepared: (1) alcohol **2** (3.74 mol) and 12.9 g (0.075 mol, 2 mol percent) of HOT (**1b**) in 7.3 L of dichloromethane, (2) sodium hypochlorite solution (4.2 l, 13% free chlorine, technical-grade) was adjusted to a pH of 9.5 by means of 20% sulfuric acid, $c_{NaOCl} \cong 1.8$ M, (3) sodium bromide (19.5 g, 19.0 mmol) and sodium hydrogen carbonate (84.0 g, 1.00 mol) in 1 L of water. The solutions 1, 2, and 3 were pumped from reservoirs by means of metering pumps via a static mixing element into a helically wound 20 m titanium tube (internal diameter 3 mm, external diameter 4.1 mm). The pumping rate was 48 L/h for solution 1, 17 L/h for solution 2, and 2.6 L/h for solution 3. The biphasic reaction mixture was collected in a 20 L receiver, and the dichloromethane solution was separated and washed with sodium thiosulfate solution and with water.

**Synthesis of Aldehydes − Batch (Method B).** To a solution alcohol **2** (20.0 mmol) and HOT (**1b**, X = OH) (189 mg, 1.10 mmol) in 40 mL of dichloromethane is added sodium bromide (227 mg, 2.21 mmol) in 1.2 g of water and 5 mL of saturated sodium hydrogen carbonate. The mixture is cooled to −10 °C. Within a period of 10 s, 14.5 mL of a freshly prepared 1.8 M sodium hypochlorite solution (pH adjusted to 9.5 by means of 20% sulfuric acid) are added to the solution which is stirred at 700 rpm. After 3 min, the

phases are separated, and the organic phase is washed with sodium thiosulfate and with water.

The activated aldehydes **3** are stable in solution. They undergo condensation reactions when the dichloromethane solutions are concentrated. Aldehyde **3b** (R = butoxy) was isolated by distillation in vacuo (bp 40 °C/14 mbar, lit.[37] 51−52 °C/20 Torr). Aldehyde **3** with R = phthalimidyl is purified by crystallization from pentane/dichloromethane (mp 116 °C, lit.[38] 114 °C).

**Synthesis of Aldehydes − Batch (Method C).** To a solution of alcohol **2** (10.3 mmol) and TEMPO (**1a**, X = H) (88.7 mg, 0.57 mmol) in 20 mL of dichloromethane is added bromine (91 mg, 1.14 mmol) in 2 mL of dichloromethane. The solution is cooled to −10 °C. Within a period of 3 s, 10 mL of a freshly prepared 1.25 M sodium hypochlorite solution from 11 g technical bleach, 20% sulfuric acid to adjust the pH to 9.5, potassium hydrogen carbonate (1 g), and 6 mL of water are added to the solution and stirred at 700 rpm. After 3 min, the phases are separated, and the organic phase is washed with sodium thiosulfate and with water. **Kinetic measurements.** The reaction is quenched after 6, 15, and 30 s by fast addition of 10 mL of a cooled 10%

sodium thiosulfate solution. The amount of **2** and **3** is measured by $^1$H NMR by means of naphthaline as internal standard.

**Degradation of HOT (1b, X = OH) − Blank Experiment.** 584 mg (3.39 mmol) of HOT (**1b**, X = OH) are dissolved in 40 mL of dichloromethane. Solutions of 234 mg (2.27 mmol) sodium bromide in 3 mL of water and 17.9 g (14.5 mL) of a freshly prepared 1.8 M sodium hypochlorite solution (pH adjusted to 9.5 by means of 20% sulfuric acid) are added separately to the solution and stirred at 700 rpm. The mixture turns green after approximately 20 min. After 1 h the phases are separated. The organic phase is analyzed by GC, GC/MS, UV/vis, and $^1$H NMR spectroscopy.

Compounds identified by GC/MS: 2,2,6,6-tetramethyl-4-piperidone: $m/z$ = 155 (in accordance to database). 4-Oxo-TEMPO (**6a**): $m/z$ = 170 (in accordance to database). **6b/ 6b***: $m/z$ = 170 (M$^+$ + 1; in accordance to lit.[24]). **6c/6c***:[34] $m/z$ = 185 (in accordance to lit.[35] and database).

UV-absorption: $\lambda_{max}$ = 663 nm (acetonitrile), 667 nm (ethyl acetate) in accordance to lit.:[35] nitroso compound **6b** or isomeric nitroso compound **6b***.[34]

$^1$H NMR (CDCl$_3$): $\delta$ = 5.98−6.08 (m, CH=, H$_2$C=).

(37) Shostakovskii, J. *Appl. Chem. USSR (Engl. Transl.)* **1970**, *43*, 1137−1139.
(38) Alvarez, M.; Fernandez, D.; Joule, J. A. *Tetrahedron Lett.* **2001**, *42*, 315−318.