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Selective TEMPO-oxidation of alcohols to aldehydes in alternative organic solvents

Alessa Hinzmann^[a], Michael Stricker^[a], Jasmin Busch^[a], Sylvia Glinski^[a], Keiko Oike^[a], Harald Gröger^{*[a]}

Abstract: The TEMPO-catalyzed oxidation of alcohols to aldehydes has emerged to one of the most widely applied methodologies for such transformations. Advantages are the utilization of sodium hypochlorite, a component of household bleach, as oxidation agent and the use of water as a co-solvent. However, a major drawback of this method is the often occurring strict limitation to use dichloromethane as organic solvent in a biphasic reaction medium with water. Previous studies show that dichloromethane cannot easily be substituted because a decrease of selectivity or an inhibition of the reaction is observed by use of alternative organic solvents. Thus, up to now only a few examples are known in which after a tedious optimization of the reaction dichloromethane could be replaced. In order to overcome the current limitations, we were interested in finding a TEMPO-oxidation method in alternative organic solvents, which is applicable for various alcohol oxidations. As a result, we found a method for N-oxyl radical-catalyzed oxidation using sodium hypochlorite as oxidation agent in nitriles as organic solvent component instead of dichloromethane. Besides the oxidation of aromatic primary alcohols also aliphatic primary alcohols, secondary alcohols as well as dialcohols were successfully converted when using this method, showing high selectivity towards the carbonyl compound and low amounts of the acid side-product.

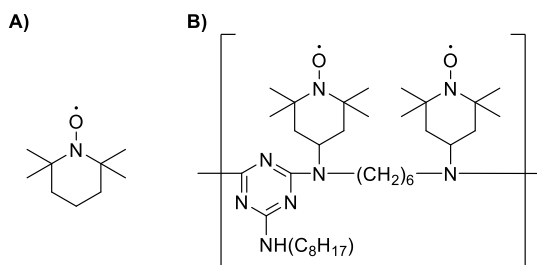
Introduction

Selective oxidation of alcohols to aldehydes is still a major challenge in organic chemistry.^[1] Many methods are known, which are applicable for such transformations. Among them chromium-based oxidations, oxidations using activated dimethyl sulfoxides, oxidations with hypervalent iodine species, ruthenium-based oxidations or 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)-catalyzed oxidations are prominent and widely applied methods.^[1] However, chromium-based oxidation methods are problematic to use, especially in industrial applications due to the high toxicity of chromium salts.^[2] Swern-oxidation of primary alcohols to aldehydes is usually performed at very low temperatures of approx. -80 °C, which makes this method also less favored.^[3] Oxidation methods with hypervalent iodine species

such as the Dess-Martin oxidation is usually performed in halogenated solvents and the Dess-Martin periodane used as oxidation agent is an expensive and explosive compound, which needs to be synthesized beforehand.^[4] Anelli-type TEMPO-catalysed oxidation is a mild method performed at 0 - 15 °C using TEMPO as catalyst,^{[5],[6]} which is a stable nitroxyl radical and readily accessible starting from acetone and ammonia.^[7] As oxidation agent hypochlorite is used in a biphasic reaction medium consisting of water and dichloromethane. Besides the Anelli-type TEMPO-oxidation many other types of this oxidation method were developed. TEMPO as catalyst for oxidation of alcohols to carbonyl compound were investigated using metal salt additives or different oxidation agents, different TEMPO-derivatives or immobilized TEMPO as catalyst or different solvent systems.^{[8],[9],[10],[11],[12]} Nevertheless, a major disadvantage of the "classical" TEMPO-oxidation using sodium hypochlorite as oxidation agent and TEMPO as a catalyst is the strong limitation of the solvent system for selective oxidation of primary alcohols to aldehydes, which consists of a biphasic system of water and dichloromethane (DCM).^{[5],[6],[13],[14]} Many studies were performed to find alternative solvents, but in spite of some examples for replacement no general solvent or solvent type was found to be suitable for the selective TEMPO-catalysed oxidation of primary alcohols to aldehydes.^{[15],[16],[18],[17],[18],[19]} The Sheldon group for example investigated different systems for the selective oxidation of alcohols with aromatic residues to the corresponding aldehydes using alternative solvents like ethyl acetate (EtOAc) or methyl-*tert*-butyl ether (MTBE).^[17] They could show in principle that TEMPO-oxidation can be performed selectively in alternative organic solvents compared to dichloromethane, but no general procedure was found, which was suitable for all substrates. As the authors mentioned, especially the oxidation of aliphatic alcohols such as citronellol to citronellal was challenging in the alternative organic solvents to DCM and led to selectivity problems. However, TEMPO is not the only nitroxyl radical which is active for oxidation reactions, but also for example PIPO as a polymer-immobilised TEMPO-derivative,^{[20],[12]} which was found to be suitable for catalysing the oxidation of alcohols to aldehydes and/or ketones.^[20] PIPO is synthesised from the antioxidant and light-stabiliser Chimassorb 944, which is used as ingredient in different plastics.

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Scheme 1. Structures of **A)** 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and **B)** PIPO.

Since Chimassorb 944 is commercially available and a product manufacture at large amount in industry, the use of PIPO as catalyst is very attractive. In their first report in 2000 about PIPO-catalysed oxidation of alcohols, the Sheldon group studied the reactivity and suitability of this catalyst for different alcohol oxidations.^[20] Within this study they found that a solvent-free approach can be used for aromatic primary alcohols with high selectivity to the aldehyde. They also discovered an approach using *n*-hexane as solvent for the selective oxidation of *n*-octan-1-ol and *n*-hexan-1-ol to the corresponding aldehydes with high selectivity. This study principally shows that PIPO seems to be a more convenient catalyst for nitroxyl radical-catalysed oxidation of primary alcohols in which also other solvents can easier be used. In our study, we were interested in finding a general protocol for the selective nitroxyl radical-catalysed oxidation of primary and secondary alcohols and dialcohols to the corresponding aldehydes, ketones or dialdehydes, based on the use of alternative organic solvents than DCM. Such a method would remove the limitation of the solvent system for TEMPO oxidation. In the following, we report a general working procedure for the synthesis of aldehydes or ketones in alternative organic solvents without the need of optimisation for each alcohol substrate. We present the utilization of aliphatic water-immiscible nitriles as preferred and generally applicable solvent components for the TEMPO as well as PIPO-oxidation. To the best of our knowledge, these solvents have not been tested before for this oxidation method.

Results and Discussion

Optimisation study of TEMPO-catalysed oxidation of *n*-octan-1-ol and *n*-decan-1-ol.

To investigate other solvents being suitable as alternative reaction medium for a selective TEMPO-catalysed oxidation of alcohols to aldehydes, we decided to first optimise the TEMPO-catalysed oxidation of *n*-octan-1-ol (**1**) and *n*-decan-1-ol (**4**) in DCM to obtain a benchmark system which we can use for a solvent screening. As a starting point we chose the TEMPO-catalysed oxidation system described by Kimura *et al.*^[21] In this process, sodium hypochlorite pentahydrate is used as oxidation agent instead of aqueous bleach solution. A major advantage of the use of this pentahydrate is the easy dosage of the oxidation

agent. In case of the 13% aqueous bleach as oxidation agent the amount of hypochlorite usually has to be determined before usage for the oxidation reaction by titration. Kimura *et al.* found that this method based on the use of hypochlorite pentahydrate can be used for the selective oxidation of a variety of primary and secondary alcohols.^[21] Usually, for TEMPO-catalysed oxidation bromide ions were used as a co-catalyst, since the *in situ*-formed hypobromite is even more reactive than hypochlorite and was reported to represent the actual oxidation agent in this process.^{[5],[6]} The Kimura group found, however, that bromide is not necessary when using the pentahydrate as oxidation agent as long as a phase-transfer catalyst or additives like NaHSO₄ are used.^{[21],[22]} To get a deeper insight in the reaction system of Kimura *et al.*, we first investigated the influence of different phase-transfer catalysts and additives. The oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**) was performed with 0.3 M *n*-octan-1-ol (**1**), 1 mol% TEMPO, 1.1 eq. NaOCl·5H₂O and 5 mol% phase-transfer catalyst or NaHSO₄ in DCM at 0 °C for 1 h. As phase-transfer catalyst tetrabutylammonium hydrogensulfate (Bu₄NHSO₄), tetrabutylammonium chloride (Bu₄NCl) and acetylcholine hydrochloride were tested. As additive, sodium hydrogensulfate (NaHSO₄) was tested and in addition one experiment without phase-transfer catalyst or NaHSO₄ was conducted (see Supporting Information). With acetylcholine hydrochloride, Bu₄NCl and without any phase-transfer catalyst the reaction did not proceed. In contrast, when using Bu₄NHSO₄ and NaHSO₄ nearly the same conversion of 85% and acid formation of 4% was observed. Overoxidation through initial oxidation of primary alcohols to aldehydes and subsequent further oxidation to the acids is an often-reported problem in TEMPO-catalysed oxidations.^{[5],[6],[17],[20],[23]} In particular aliphatic aldehydes tend to overoxidise to the acid, which was one major reason for us to first focus on the investigation of the oxidation of the aliphatic alcohols *n*-octan-1-ol (**1**) and *n*-decan-1-ol (**4**) with the goal to find a generally applicable system for also challenging substrates. Both Bu₄NHSO₄ and NaHSO₄ then were used again under the same reaction conditions but with a prolonged reaction time of 2 h. With both phase-transfer catalysts and additive then a high conversion exceeding 95% was achieved, but with NaHSO₄ less acid formation of 6% was observed in contrast to an acid formation of 20% with Bu₄NHSO₄. In further experiments the amount of NaHSO₄, the amount of TEMPO and the amount of NaOCl·5H₂O was varied to find optimal reaction conditions (see Supporting Information). The results show that a change in the amount of NaHSO₄ in the range of 1 mol% to 10 mol% has no relevant effect on the reaction. Thus, we chose 5 mol% as the "standard" amount for further experiments. The optimal catalyst loading was found to be 0.25 mol% and the optimal amount of NaOCl·5H₂O turned out to be 1.1 eq. (both related to the amount of substrate). Using higher amounts of oxidation agent leads to an increased acid formation. As a last parameter the substrate loading was investigated. We increased the substrate concentration from 0.3 M to 1 M and performed the oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**) under the optimised reactions conditions consisting of 0.25 mol% TEMPO, 1.1 eq. NaOCl·5H₂O and 5 mol% NaHSO₄ in DCM at 0 °C. The increase in the substrate concentration led to a significant increase in the reaction speed (Supporting

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Information). Full conversion was obtained after 15 min with 98% selectivity, whereas at a lower substrate concentration of 0.3 M full conversion was reached after 45 min with a selectivity of 96%. We defined selectivity as the ratio of aldehyde concentration to aldehyde and side-products concentrations in the reaction mixture. All optimisation experiments were also carried out for the oxidation of *n*-decan-1-ol (**4**) to *n*-decanal (**5**) (Supporting Information). The optimised reaction conditions for both reactions are summarized in Table 1.

Table 1. Optimized reaction parameters for the oxidation of *n*-octan-1-ol (**1**) and *n*-decan-1-ol (**4**).

	<i>n</i> -octan-1-ol (1)	<i>n</i> -decan-1-ol (4)
Substrate concentration	1 M	1 M
TEMPO	0.25 mol%	0.25 mol%
NaHSO₄·H₂O	5 mol%	5 mol%
NaOCl·5H₂O	1.1 eq	1.0 eq

Optimisation of the solvent component. The usual solvent system for TEMPO-catalysed oxidations consists of aqueous hypochlorite solution and DCM. Although some examples are known in which DCM could be replaced by other solvents,^{[15],[16],[8],[17],[18],[19]} there is still a lack of universal generally applicable oxidation method in solvents other than DCM using nitroxyl radicals as catalyst and hypochlorite as oxidation agent without use of metal salts as co-catalyst. In order to identify such a desired alternative reaction medium, we screened several organic solvents for the oxidation of *n*-octan-1-ol (**1**) using the optimised reaction conditions (Figure 1). It was found, that when using ethyl acetate (EtOAc), methyl *tert*-butyl ether (MTBE) and 2-methyl-tetrahydrofuran (2-Me-THF) as organic solvents nearly no conversion of *n*-octan-1-ol (**1**) was observed. However, we were pleased to find that the oxidation reaction proceeded smoothly when using different types of aliphatic nitriles as an organic solvent. In particular, *n*-octanenitrile and isobutyronitrile turned out to be highly suitable as (nearly) no side-product formation was found in the presence of these solvents. By decreasing the reaction time to 30 min also in *n*-butyronitrile less than 1% acid **3** formation was detected (results not shown). To the best of our knowledge, this is the first solvent study for TEMPO-catalysed oxidation of alcohols in which nitriles except for acetonitrile were tested as alternative solvents to DCM, revealing that such solvents are highly suitable for this type of transformations. Recently our group provided protocols for the biocatalytic access to nitriles using aldoxime dehydratases as biocatalyst,^{[24],[25],[26]} enabling an alternative access to these nitrile solvents without the need for toxic cyanide and harsh reaction conditions.

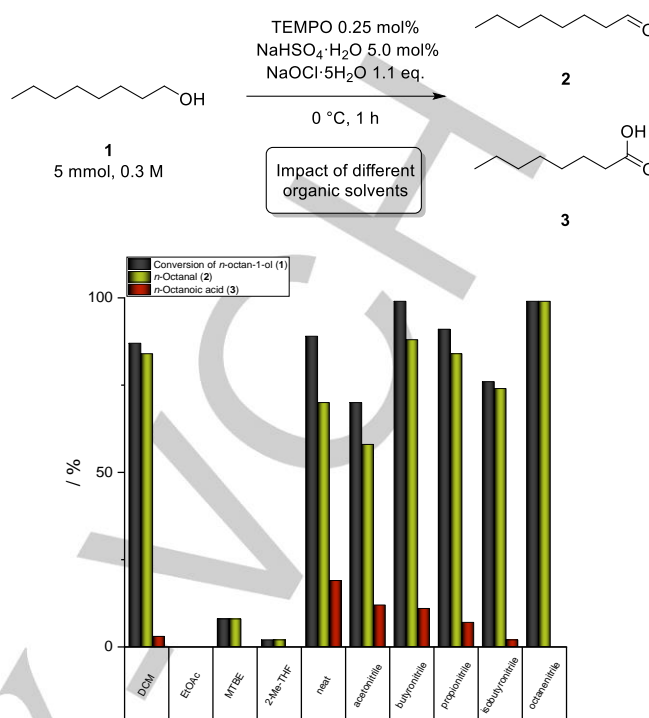


Figure 1. Solvent study of TEMPO-catalyzed oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**).

It is noteworthy that aliphatic nitriles with short and long chain length are suitable solvents for TEMPO-oxidation because as shown in Figure 2 the solvent parameters and properties of long- and short-chain aliphatic nitriles are very different and, thus, complementary to each other.^{[27][28]}

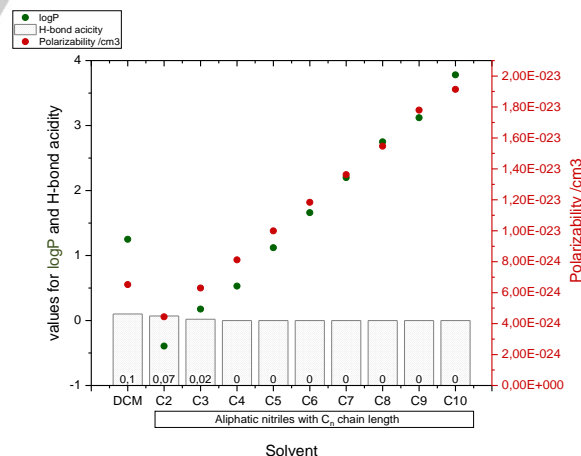


Figure 2. Partition coefficient (logP) (green dots),^[28] summation of H-bond-acidity (bars, values are given as numbers in the bars) and polarizability in cm³ (red dots) of from left to right: DCM, acetonitrile (C2), propionitrile (C3), butyronitrile (C4), pentanenitrile (C5), hexanenitrile (C6), heptanenitrile (C7), octanenitrile (C8), nonanenitrile (C9) and decanenitrile (C10). Y-axis on the left side presents values of logP and H-bond acidity and y-axis on the right represents polarizability.^[27]

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As the solvent properties of dichloromethane and the different nitrile solvents differ, at least in part, strongly from each other it is difficult to explain on this basis the phenomenon that DCM and nitriles are suitable solvents and other solvents usually not. Thus, rationalizing the effect of the solvent needs further investigations. From a synthetic perspective a replacement of dichloromethane as solvent for TEMPO-oxidation is of major interest due to the chronic toxicity and the fact that chlorinated solvents should be substituted in industrial processes.^[29] However, the potential substitution of dichloromethane with aliphatic nitriles needs to be carefully considered. Short-chain aliphatic nitriles, e.g. *n*-butyronitrile,^[30] are acute toxic by exposure, whereas longer-chained aliphatic nitriles, such as *n*-octanenitrile,^[31] are harmful to health. However, short-chain and especially long-chain aliphatic nitriles are not fully characterized in terms of toxicity and environmental impact, making it difficult to evaluate the benefits of replacement of dichloromethane with aliphatic nitriles at the current stage.

Since we could find these promising results for all tested aliphatic nitriles as solvents in these oxidation reactions, we expanded our study to other nitroxyl radicals as catalysts in the oxidation of alcohols to aldehydes and ketones using sodium hypochlorite as oxidation agent and nitriles as solvents.

Transfer of the oxidation conditions for TEMPO to PIPO as a catalyst. As mentioned above, PIPO is a polymeric nitroxyl radical, which is based on Chimassorb 944 that is a stabilizer for plastics and therefore a tons-product and commercially readily available. Since the polymer is insoluble in many solvents, the catalyst can potentially be recycled and easily separated from the reaction mixture.^[20] As described above, for the TEMPO-catalysed oxidation of *n*-octan-1-ol (**1**) nitriles turned out to represent a suitable organic solvent as an alternative for DCM enabling the reaction at high substrate concentration of up to 1 M. These conditions were then transferred to the use of PIPO instead of TEMPO to improve the system further. Initially, a solvent screening (Figure 3) was performed using PIPO and a substrate concentration of 0.3 M of *n*-octan-1-ol (**1**) for a better comparison with the solvent screening which we conducted with TEMPO as a catalyst. These experiments showed that in particular *n*-butyronitrile and *n*-octanenitrile are also suitable solvents for the oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**) when using PIPO as catalyst. In these oxidation reactions only small amounts of acid (<5%) were observed and conversions of >90% of *n*-octan-1-ol (**1**) were reached within a reaction time of 1 h. The same reaction was performed then at 1 M substrate concentration, since this concentration was found to be suitable for the oxidation using TEMPO as catalyst. As an organic solvent *n*-butyronitrile was used because this nitrile solvent can be easily removed *in vacuo*, which simplifies the isolation of the formed aldehyde. In this reaction full conversion of *n*-octan-1-ol (**1**) was reached and a selectivity of 93% towards the aldehyde **2** was detected (Table 2, entry 1). In addition, *n*-octanal (**2**) was isolated in 90% yield from the reaction mixture.

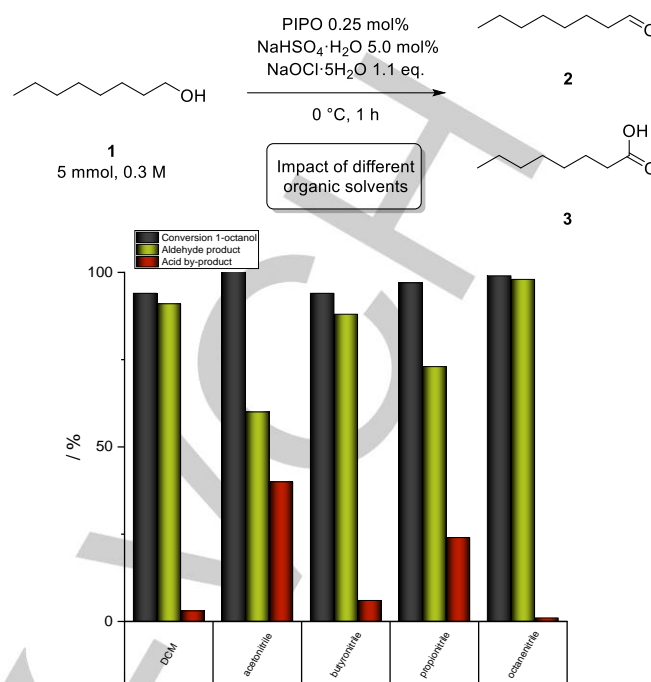


Figure 3. Solvent study for the PIPO-catalyzed oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**).

Substrate scope of PIPO-catalysed oxidation in *n*-butyronitrile as a solvent.

Since this oxidation method using *n*-butyronitrile as solvent, PIPO as catalyst and sodium hypochlorite pentahydrate as oxidation agent is very simple and as the reaction progress can be easily tracked by GC-analysis, this method was applied for further oxidation experiments using primary and secondary alcohols. In this study, the oxidation of different substrates with different electronic properties were tested in order to demonstrate the applicability of this method for the oxidation of a broad range of substrates. We started with the substrate scope of "mono"-alcohols, since the reaction conditions described above were optimised for a mono-alcohol and we expected that our method would be easily applicable also for the preparation of other mono-aldehydes. Taking into account that the synthesis of dialdehydes is much more complicated due to the fact that many more side-products can occur, a further optimisation of our method was conducted later for the oxidation of dialcohols to dialdehydes. The substrate scope was also expanded to secondary alcohols to synthesise ketones, but in this case no side-products due to overoxidation were expected. The results of the substrate scope in terms of mono-primary alcohols, secondary alcohols and dialcohols are shown and discussed in the following sub-chapters.

Substrate scope study, part 1: Oxidation of primary alcohols to aldehydes.

Since we performed detailed studies about the oxidation of *n*-octan-1-ol (**1**) to *n*-octanal (**2**), we became interested in the performance of the PIPO-oxidation in *n*-butyronitrile as alternative solvent to DCM when utilizing electronically different alcohols as substrates such as, e.g.,

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alcohols with aromatic residues (Table 2, entry 5-10). It was found that aromatic primary alcohols with electron-withdrawing groups such as a nitro-group (Table 2, entry 7,8), are very rapidly converted to the corresponding aldehydes with high selectivity at 0 °C reaction temperature. In contrast, when utilizing alcohols substituted with an electron-donating group such as a methoxy-group (Table 2, entry 9,10), the oxidation is much slower even when being performed at room temperature instead of 0 °C. Nevertheless, also in these cases high conversions of 95% were reached and a selectivity of >99% towards the aldehyde was achieved in both cases. When synthesising cinnamaldehyde **17** (Table 2, entry 6), this product needed to be purified by column-chromatography due to undefined side-products found in the GC-chromatogram. However, also for this oxidation a selectivity of 91% was found (calculated by comparison of the aldehyde peak with those of all product peaks detected in the GC-chromatogram). All aliphatic aldehydes were synthesised with high conversions of >90% and selectivities of >90% (Table 2, entry 1-4). In case of the synthesis of cyclohexanecarbaldehyde **11** (Table 2, entry 4), *n*-decanenitrile was used as a solvent instead of *n*-butyronitrile and in case of the preparation of *n*-hexanal (**8**), *n*-octanenitrile was chosen as a solvent component due to the fact that these products are very volatile and *n*-butyronitrile could not be removed from the product. When using *n*-decanenitrile or *n*-octanenitrile as solvent, however, the products cyclohexanecarbaldehyde **11** and *n*-hexanal (**8**) could easily be distilled from the solvent after quenching of the reaction with HCl, phase separation and extraction. These results show that this oxidation method is applicable towards a variety of primary alcohols as substrates to synthesise the corresponding aldehydes with high selectivities.

Table 2. Substrate scope of PIPO-catalyzed oxidation of primary alcohols to aldehydes.

$\text{R-OH} \xrightarrow[\text{15 mL } n\text{-butyronitrile}]{\text{PIPO 0.25 mol\%}, \text{NaHSO}_4 \cdot \text{H}_2\text{O 5.0 mol\%}, \text{NaOCl} \cdot 5\text{H}_2\text{O 1.1 \AA q}, 0^\circ\text{C}}$ R-CHO					
Entry	Product	t / min	Conv. [%] ^[a,b]	Sel. [%] ^[c]	Yield [%] ^[d]
1		15	99	93	90
2		45	94	96	89
3		1290 ^[e]	>99	91	95 ^[f]

4		75 ^[g]	>99	95	58 ^[h]
5		75	98	>99	95
6		420	>99	91	75 ^[h]
7		75	>99	>99	94
8		25	>99	>99	92
9		150 ^[i]	95	>99	91
10		105 ^[i]	95	>99	88

^[a] The reactions were quenched by addition of 2 M HCl (15 mL).

^[b] Conversion of alcohol to the corresponding aldehyde or side-products (e.g. acid) was determined by GC-analysis in comparison to standard-curves. ^[c] Selectivities are defined as: $C_{\text{aldehyde}} / (C_{\text{aldehyde}} + C_{\text{side-products}})$. ^[d] Yields were calculated by isolation of the aldehydes from the reaction mixture by phase-separation after quenching with acid and extraction of the organic phase.

^[e] Reaction was performed in *n*-octanenitrile as solvent. After 12 h reaction time, further reaction at room temperature instead of 0 °C. ^[f] Isolated yield after distillation. ^[g] Reaction was performed in *n*-decanenitrile as solvent. ^[h] Isolated yield after column chromatography. ^[i] Reaction was performed at room temperature.

Substrate scope study, part 2: Oxidation of primary diols to dialdehydes. We were further interested in the challenging oxidation of diols bearing two primary alcohol groups to the corresponding dialdehydes utilizing the same solvent system. Therefore, dialcohols such as various α,ω -*n*-alkanediols (Table 3, entry 1-3) and phenylenedimethanols (Table 3, entry 4, 5) were oxidised using PIPO as a catalyst, sodium hypochlorite

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pentahydrate as oxidation agent and *n*-butyronitrile as organic solvent. Initially, we tried to use the same reaction conditions as for the mono-alcohols, but we could not achieve full conversion and only moderate selectivities were obtained for the oxidation of *n*-octan-1,8-diol (**31**). A major problem was the low solubility of the substrate *n*-octan-1,8-diol (**31**) in *n*-butyronitrile. We could overcome this problem by adding THF (27% v/v) to the reaction solution. This led to full conversion but the selectivity was only in a moderate range (see Supporting Information). Thus, we decided to conduct a reaction optimisation addressing substrate loading and the amount of NaHSO₄ and sodium hypochlorite, respectively. We were pleased to find such desired reaction conditions, leading to the oxidation of *n*-octan-1,8-diol (**31**) to *n*-octanedial (**32**) with >99% conversion and 90% selectivity. After purification by means of automated column chromatography the desired product *n*-octanedial (**32**) was obtained in 69% isolated yield (Table 3, entry 2). We also applied these optimised reaction conditions for the oxidation of *n*-hexan-1,6-diol (**37**) and *n*-decan-1,10-diol (**34**) as two related aliphatic diols, reaching over 90% selectivity and moderate yields (Table 3, entries 1,3). The relatively low yields are due to the instability of the dialdehydes. During the workup oxidation to various acids was observed. Furthermore, this method was successfully applied towards the oxidation of two phenylenedimethanols leading to high selectivity of 94% and high yields (Table 3, entries 4,5), which underlines the generality of *n*-butyronitrile as a suitable solvent system for TEMPO-oxidation even for the challenging dialcohols. However, the oxidation of diols to dialdehydes is rather sensitive in comparison to the oxidation of monoalcohols. Slightly modified conditions in the oxidation of diols using our method can lead to significant changes in conversion and selectivity.

Table 3. Substrate scope of PIPO-catalyzed oxidation of diols to dialdehydes.

<p> </p>						
Entry	Product	t / min	Conv. / % ^[a,b]	Sel. / % ^[c]	Yield / % ^[d]	
1		45	96	91	37	
2		40	>99	90	69	

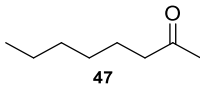
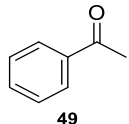
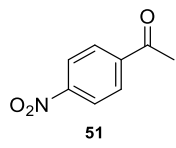
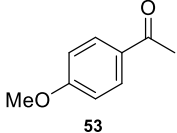
3		10	>99	93	56
4		45	>99	94	87 ^[e]
5		45	>99	91	71

^[a] The reactions were quenched by addition of 1 M HCl (15 mL). ^[b] Conversions are defined as consumption of substrate. ^[c] Selectivities are defined as: GC-Area_{dialdehyde}/(GC-Area_{dialdehyde}+GC-Area_{side-products}). ^[d] Yields were calculated by isolation of the aldehydes from the crude reaction mixture by phase-separation after quenching with acid, extraction of the organic phase and purification via automated column chromatography. ^[e] Yields were calculated by isolation of the aldehydes from the reaction mixture by phase-separation after quenching with acid and extraction of the organic phase.

Substrate scope study, part 3: Oxidation of secondary alcohols to ketones. Since we could show that primary mono- as well as dialcohols can be oxidised by our TEMPO-oxidation method, we were further interested in applying this technique for the oxidation of secondary alcohols to the relating ketones (Table 4). We used the standard oxidation conditions as described for the oxidation for the mono-alcohols with slight modifications. Since we did not expect any side-product formation due to the formation of ketones instead of aldehydes as reaction products, we increased the reaction temperature to room temperature. The results of the four oxidation experiments using secondary alcohols as substrates are shown in Table 4. We were pleased to find that also secondary alcohols were converted to the corresponding ketones with quantitative conversions. Also in case of the secondary alcohols, we found a significantly higher reaction velocity for the nitro-substituted phenylethanol compared to the methoxy-substituted one (Table 4, entry 3, 4). This is in accordance to literature. Kimura *et al.* also found that nitro-substituted benzylalcohol is faster converted than methoxy-substituted benzylalcohol.^[21] However, an explanation for this effect is still missing. *n*-Octan-2-ol (**46**) was converted slower compared to the primary alcohol *n*-octan-1-ol (**1**) with a reaction time of 40 min compared to 15 min for the primary alcohol, although higher reaction temperature was used for the oxidation of the secondary alcohol **46**. This result indicates that the oxidation of primary alcohols is favoured.

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Table 4. Substrate scope of PIPO-catalyzed oxidation of secondary alcohols to ketones.

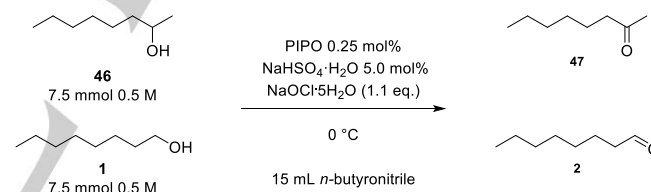
PIPO 0.25 mol% NaHSO ₄ ·H ₂ O 5.0 mol% NaOCl·5H ₂ O 1.2 Äq rt 15 mmol, 1 M 15 mL <i>n</i> -butyronitrile				
Entry	Product	t / min	Conv. [%] ^[a,b]	Yield [%] ^[b]
1		40	>99	22
2		70	>99	49
3		5	>99	90
4		90	>99	65

^[a] The reactions were quenched by addition of 2 M HCl (15 mL). ^[b] Conversions are defined as consumption of substrate. ^[c] Yields were calculated by isolation of the ketones from the crude reaction mixture by phase-separation after quenching with acid and extraction of the organic phase.

Oxidation of a mixture of *n*-octan-1-ol and *n*-octan-2-ol.

In many TEMPO-oxidation studies the chemoselectivity of this oxidation method is addressed.^{[20],[21]} In case of the "classical" TEMPO-catalysed oxidation using bleach as oxidation agent the oxidation of primary alcohols to the aldehyde was found to proceed much faster compared to the oxidation of secondary alcohols as shown for the oxidation of a mixture of 1-nonanol and 2-nonanol.^[5] Generally, TEMPO-catalyzed oxidations can proceed in two different ways, following different mechanisms.^{[32][33][34]} Under acidic conditions a hydride or proton transfer between catalyst and alcohol substrate can occur, while under basic conditions a pre-oxidation complex is formed via an

alkoxide attack on the electrophilic nitrogen of the oxammonium cation. The formation of the pre-oxidation intermediate is slower for secondary alcohols due to steric hindrance, which leads to a faster conversion of primary alcohols compared to secondary alcohols. However, Kimura *et al.* found that the primary and secondary alcohol are oxidized with equal conversions when using sodium hypochlorite pentahydrate as oxidation agent instead of an aqueous solution of hypochlorite.^[21] In detail, the same conversion of *n*-octan-1-ol (**1**) and *n*-octan-2-ol (**46**) in the oxidation reaction of this mixture was observed. Thus, we were interested to gain an insight into the chemoselectivity of our approach for the oxidation of *n*-octan-1-ol (**1**) and *n*-octan-2-ol (**46**). Therefore, we performed the oxidation of *n*-octan-2-ol (**46**) at 0 °C, since this temperature was also used for the oxidation of *n*-octan-1-ol (**1**). We found 40% conversion of *n*-octan-2-ol (**46**) to *n*-octan-2-one (**47**) after 1 min. The reaction proceeds further with a very low reaction velocity leading to 42% conversion of the alcohol **46** after 1 h reaction time. The reason for the high reaction rate at the beginning is not clear yet, but since we could obtain only 42% conversion after 1 h reaction time in case of the secondary alcohol **46**, the overall process efficiency is lower in comparison to the one for the primary alcohol **1** (for which a full conversion after 15 min reaction time was observed; Table 2 entry 1). Afterwards we conducted another oxidation reaction starting from a 1:1-mixture of *n*-octan-1-ol (**1**) and *n*-octan-2-ol (**46**) at 0 °C in *n*-butyronitrile and utilizing sodium hypochlorite pentahydrate as an oxidation agent (Scheme 2).

**Scheme 2.** Oxidation of a mixture of *n*-octan-1-ol (**1**) and *n*-octan-2-ol (**46**).

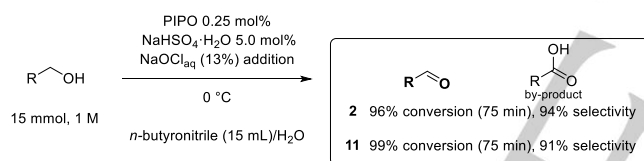
For this process we found a complete conversion of *n*-octan-1-ol (**1**) after 2 min reaction time and a conversion of 61% of *n*-octan-2-ol (**46**) within the same reaction time. When prolonging the reaction time to 1 h, we observed still the same conversion of *n*-octan-2-ol (**46**) with 62%. Thus, this experiment shows that the oxidation of secondary alcohols is slower compared to the oxidation of primary alcohols, indicating that in our method the oxidation follows a basic reaction mechanism. To proof this hypothesis, in principle a simple pH-measurement could be conducted. However, using our method without having an aqueous phase, the pH-value cannot be determined directly. To overcome this problem, we performed one experiment in which we added water to our system, thus making a pH-measurement possible. The pH measurement was performed after 5 min reaction time and after completion of the reaction. While the reaction was proceeding, we could find a basic pH of 8. After completion of the reaction, however, the pH turned out to be neutral. These results support the hypothesis that our system follows a basic reaction mechanism. Interestingly, the group of

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Kimura *et al.* could show that primary and secondary alcohols were converted equally in their reaction system, although they applied very similar reaction conditions.^[21] The major differences between our system and the system of Kimura *et al.* are the choice of organic solvent (*n*-butyronitrile vs. DCM) and nitroxyl radical-derivative as catalyst (PIPO vs. TEMPO).

Oxidation of alcohols to aldehydes using aqueous bleach solution as oxidation agent.

As in the "classical" TEMPO-oxidation method typically a 13% aqueous bleach solution is used as oxidation agent,^[5] we also modified our system by using this oxidation agent. Thus, we used the same conditions as described above with 1 M substrate concentration, an amount of sodium hydrogen sulfate of 5 mol%, 0.25 mol% PIPO, *n*-butyronitrile as an organic solvent and 1.1 eq. hypochlorite in aqueous solution. In this experiment, however, we could not obtain full conversion of the alcohol and in addition we found significant amounts of acid as side-product. By increasing the amount of hypochlorite solution full consumption of the alcohol was detected, but also high amounts of acid were formed. Therefore, we investigated a dosage approach of the hypochlorite solution when conducting the oxidation reaction. We started with 3 mL of 13% sodium hypochlorite solution using 15 mL *n*-butyronitrile phase and added 3 mL after every 15 min reaction time with an overall reaction time 75 min. We tested this method using two aliphatic primary alcohols, namely *n*-octan-1-ol (**1**) and cyclohexylmethanol **16** (Scheme 3).



Scheme 3. Oxidation of *n*-octan-1-ol (**1**) and cyclohexylmethanol **10** to the corresponding aldehydes using 13% bleach solution and *n*-butyronitrile as an organic solvent.

We were pleased to find that the resulting products *n*-octanal (**2**) and cyclohexanecarbaldehyde **11** were formed with conversions of >95% and selectivities of >90%. These results show that this system using *n*-butyronitrile as an organic solvent component is also suitable for the use of bleach solution instead of hypochlorite pentahydrate as an oxidation agent.

Conclusions

In conclusion, we reported a nitroxyl radical-catalysed oxidation method running in nitriles as an organic solvent component, being suitable for the selective synthesis of a broad range of aldehydes, dialdehydes and ketones. Thus, a convenient and easy-to-use method has been developed for the selective oxidation of alcohols and diols to the corresponding aldehydes or ketones, avoiding the need for chlorinated solvents used in the "classical" Anelli oxidation.^{[5],[6]} We also could show that solid sodium hypochlorite

pentahydrate as well as bleach solution can be used as oxidation agent in this system. In this study we investigated the oxidation of 19 different mono- and dialcohols, which were successfully converted into the corresponding carbonyl compounds with high conversion and selectivities at moderate reaction conditions.

Experimental Section

Chemicals were purchased by Sigma Aldrich, VWR Chemicals, Fluka Chemicals, TCI Chemicals, Fluorochem, Alfa Aesar and Carl Roth and were used without further purification. The oxidant NaOCl·5H₂O were purchased by TCI Chemicals (Germany) and used without further purification. NMR spectra were recorded on a Bruker Avance III 500 at a frequency of 500 MHz (¹H). The chemical shift δ is given in ppm and referenced to the corresponding solvent signal (CDCl₃ or (CD₃)₂SO). Reaction progress was monitored by GC analytics. Further information may be found in the Supporting Information. Optimization studies of oxidation of alcohols were performed in analogy to Kimura *et al.* using TEMPO or PIPO as catalyst.^[21]

Optimisation of the TEMPO-catalyzed oxidation of *n*-octan-1-ol and *n*-decan-1-ol. Phase-transfer catalyst or NaHSO₄ as additive (0.1 - 1 mmol, 1 - 10 mol%) was suspended in dichloromethane (15 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (4.5 - 7.5 mmol, - 1.23 g, 0.9 - 1.5 eq) and TEMPO (0.005 - 0.05 mmol, 0.78 - 7.81 mg, 0.1 - 1 mol%) were added. The substrate (5 mmol, 0.3 M) was added under vigorous stirring and the reaction mixture was stirred at 0 °C until completion (GC-control). The reaction was quenched by addition of aqueous HCl solution (15 mL of a 1.2 M solution), the phases were separated. The organic phase was analysed by GC chromatography. Further work-up and isolation of the product(s) was not performed. For the substrate *n*-octan-1-ol (**1**) a reaction optimisation was carried out in terms of phase-transfer catalyst or additive amount, sodium hypochlorite amount, catalyst amount and substrate loading. The results of the optimization studies are shown in the Supporting Information (Tables 3-4).

Optimization in terms of solvent. NaHSO₄·H₂O (0.22 mmol, 31.1 mg, 5 mol%) was suspended in organic solvent (15 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (0.81 g, 5 mmol, 1.1 eq.) and TEMPO (0.0075 mmol, 1.2 mg, 0.25 mol%) were added. *n*-Octan-1-ol (**1**) (0.80 mL, 5 mmol, 0.3 M) was added under vigorous stirring and the reaction mixture was stirred at 0 °C for 1 h. Reaction progress was monitored by GC. The results of the optimization study are shown in the Supporting Information (Tables 5) and in the publication (Figure 1).

Synthesis of Polyamine-immobilized piperidinyloxy radical (PIPO). PIPO radical was prepared in analogy to Dijkstra *et al.*^[20] from Chimassorb 944 (M_n~3,000 g/mol). Chimassorb 944 (10.12 g, 3.5 mmol) was suspended in 15% aqueous H₂O₂-solution (120 mL) and the reaction mixture was stirred at room temperature for 5 days. The solid was filtered, washed with H₂O (500 mL) and dried in high vacuum. PIPO (9.78 g, 3.3 mmol, 94%) was obtained as slightly orange solid.

Transfer of optimized conditions to PIPO as catalyst. NaHSO₄·H₂O (0.22 mmol, 31.1 mg, 5 mol%) was suspended in organic solvent (15 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (0.81 g, 5 mmol, 1.1 eq.) and PIPO (0.005 - 0.01125 mmol, 33.7 mg, 0.25 mol%) were added. The *n*-octan-1-ol (**1**) (0.80 mL, 5 mmol, 0.3 M) was added under vigorous stirring and the reaction mixture was stirred at 0 °C for 1 h. Reaction progress was monitored by GC. The results of the optimization

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study are shown in the Supporting Information (Tables 6) and in the publication (Figure 2).

Optimization of the PIPO-catalyzed oxidation reaction of *n*-octan-1,8-diol. NaHSO₄·H₂O (0.5 - 1 mmol, 69.04 - 138 mg, 5 - 10 mol%) was suspended in *n*-butyronitrile (16 - 20 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (22 - 35 mmol, 3.62 - 5.73 g, 2.2 - 3.5 eq) and PIPO (0.025 - 0.1 mmol, 75 - 300 mg, 0.25 - 1 mol%) were added. The *n*-octan-1,8-diol (**32**) (10 - 20 mmol, 1.46 - 2.92 g, 0.5 - 1 M) was dissolved in THF (0 - 4 mL, 0 - 27% v/v) by gentle warming and added to the reaction mixture. The reaction mixture was stirred at 0 °C until a color change from red to colorless occurred. The reaction was quenched by addition of aqueous HCl solution (50 mL of a 1 M solution), the phases were separated and the organic phase was dried over MgSO₄. The organic phase was analysed by GC chromatography. Further work-up and isolation of the product(s) was not performed. For *n*-octan-1,8-diol (**32**) an optimization study was carried out. The results of the optimization study are shown in the Supporting Information (Table 7).

General protocol for PIPO-oxidation of primary alcohols to aldehydes.

NaHSO₄·H₂O (0.75 mmol, 103.6 mg, 5 mol%) was suspended in *n*-butyronitrile (15 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (16.5 - 22.5 mmol, 2.71 - 3.70 g, 1.1 - 1.5 eq) and PIPO (0.0375 mmol, 112.5 mg, 0.25 mol%) were added. The primary alcohol (15 mmol) was added under vigorous stirring and the reaction mixture was stirred at 0 °C until completion (GC-control). The reaction was quenched by addition of aqueous HCl solution (15 mL of a 2 M solution), the phases were separated and the aqueous phase extracted with *n*-butyronitrile (2x 5 mL). Organic phases were combined, dried over MgSO₄ and the solvent removed *in vacuo*. The product was analysed using ¹H-NMR spectroscopy in DMSO-d₆.

***n*-Octanal (2).** Yield: 90% (1.728 g, 13.5 mmol). (**2**) was obtained from *n*-octan-1-ol (**1**) (2.35 mL, 15 mmol) as colorless oil using sodium hypochlorite pentahydrate (2.70 g, 16.42 mmol, 1 eq.) as oxidation agent. ¹H NMR (500 MHz; (CD₃)₂SO): 9.66 (t, *J* = 1.6 Hz, 1H), 2.41 (td, *J* = 1.6, 7.3, 7.3), 1.51 (p, *J* = 7.2 Hz, 2H), 1.25 (m, 6H), 0.86 (t, *J* = 6.9 Hz, 3H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

***n*-Decanal (5).** Yield: 89% (2.09 g, 13.4 mmol). (**5**) was obtained from *n*-decan-1-ol (**4**) (2.86 mL, 15 mmol) as colorless oil using sodium hypochlorite pentahydrate (2.70 g, 16.42 mmol, 1 eq.) as oxidation agent. ¹H NMR (500 MHz; (CD₃)₂SO): 9.66 (t, *J* = 1.5 Hz, 1H), 2.41 (td, *J* = 1.5, 7.3 Hz, 2H), 1.51 (p, *J* = 7.1 Hz, 2H), 1.25 (m, 6H), 0.86 (t, *J* = 6.9 Hz, 3H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

***n*-Hexanal (8).** Yield: 85% (1.275 g, 12.75 mmol). Synthesis of *n*-hexanal (**8**) from *n*-hexan-1-ol (**7**) (1.88 mL, 15 mmol) was performed in *n*-octanenitrile as solvent instead of *n*-butyronitrile using sodium hypochlorite pentahydrate as oxidation agent (2.70 g, 16.42 mmol, 1 eq.). *n*-Hexanal (**8**) (85 %) was obtained as colorless oil. ¹H NMR (500 MHz; (CD₃)₂SO): 9.66 (t, *J* = 1.6 Hz, 1H), 2.41 (td, *J* = 1.6, 2.4 Hz, 2H), 1.52 (p, *J* = 7.3 Hz, 2H), 1.26 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

Cyclohexancarbaldehyde (11). Yield: 58% (0.98 g, 8.7 mmol). Synthesis of cyclohexancarbaldehyde **11** from cyclohexanemethanol **10** (1.84 mL, 15 mmol) was performed in *n*-decanenitrile as solvent instead of *n*-butyronitrile using sodium hypochlorite pentahydrate as oxidation agent (2.70 g, 16.42 mmol, 1 eq.). Cyclohexancarbaldehyde **11** (0.98 g, 8.7 mmol, 58 %) was obtained as colorless oil. ¹H NMR (500 MHz; (CD₃)₂SO): 9.55 (s, 1H), 2.27 (m, 1H), 1.81 (m, 2H), 1.65-1.55 (m, 3H),

1.33-1.18 (m, 5H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

Benzaldehyde 14. Yield: 95% (1.51 g, 14.23 mmol). **14** was obtained from benzyl alcohol **13** (1.62 g, 15 mmol) as colorless oil using sodium hypochlorite pentahydrate (2.96 g, 18.0 mmol, 1.2 eq.) as oxidation agent. ¹H NMR (500 MHz; (CD₃)₂SO): 10.02 (s, 1H), 7.92 (dd, *J* = 1.4, 8.2 Hz, 2H), 7.71 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 2H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

Cinnamaldehyde (16). Yield: 75% (1.49 g, 11.25 mmol). The oxidation of cinnamyl alcohol **16** (2.01 g, 15 mmol) was performed using sodium hypochlorite pentahydrate (2.96 g, 18.0 mmol, 1.2 eq.) as oxidation agent. Cinnamaldehyde **17** (1.49 g, 11.25 mmol, 75 %) was obtained as yellowish oil after automated column chromatography using cyclohexane and ethyl acetate as solvent (gradient from 10 to 40 % ethyl acetate in cyclohexane), a flow of 75 mL/min on a Biotage® SNAP Ultra 50 g column. ¹H NMR (500 MHz; (CD₃)₂SO): 9.69 (d, *J* = 7.6 Hz, 1H), 7.75 (m, 4H), 7.47 (m, 2H), 6.87 (dd, 1H *J* = 7.8, 16.0 Hz). The ¹H-NMR spectrum is in accordance to the literature.^[35]

4-Nitrobenzaldehyde 20. Yield: 94% (2.12 g, 14.00 mmol). **20** was obtained from 4-nitrobenzyl alcohol **19** (2.30 g, 15 mmol) as a slightly yellowish solid using sodium hypochlorite pentahydrate as oxidation agent (2.96 g, 18.0 mmol, 1.2 eq.). ¹H NMR (500 MHz; (CD₃)₂SO): 10.17 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 2H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

3-Nitrobenzaldehyde 23. Yield: 92% (2.09 g, 13.8 mmol) **23** was obtained from 3-nitrobenzyl alcohol **22** (2.30 g, 15 mmol) as yellowish solid using sodium hypochlorite pentahydrate (2.96 g, 18.0 mmol, 1.2 eq.) as oxidation agent. ¹H NMR (500 MHz; (CD₃)₂SO): 10.14 (s, 1H), 8.67 (m, 1H), 8.52 (ddd, *J* = 1.1, 2.4, 8.3 Hz 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 7.89 (t, *J* = 7.9 Hz, 1H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

4-Methoxybenzaldehyde 26. Yield: 88% (1.79 g, 13.15 mmol). **26** was obtained from 4-methoxybenzyl alcohol **25** (2.07 g, 15 mmol) as slightly yellowish liquid using sodium hypochlorite pentahydrate as oxidation agent (2.96 g, 18.0 mmol, 1.2 eq.) at room temperature instead of 0 °C. ¹H NMR (500 MHz; (CD₃)₂SO): 9.87 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.33 (s, 3H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

3-Methoxybenzaldehyde 29. Yield: 88% (1.79 g, 13.2 mmol). **29** was obtained from 3-methoxybenzyl alcohol **28** (2.07 g, 15 mmol) as slightly yellowish liquid using sodium hypochlorite pentahydrate (2.96 g, 18.0 mmol, 1.2 eq.) as oxidation agent at room temperature instead of 0 °C. ¹H NMR (500 MHz; (CD₃)₂SO): 9.98 (s, 1H), 7.52 (m, 2H), 7.42 (m, 1H), 7.28 (m, 1H), 3.83 (s, 3H). The ¹H-NMR spectrum is in accordance to the literature.^[35]

General protocol for PIPO-oxidation of dialcohols to dialdehydes.

NaHSO₄·H₂O (0.5 mmol, 51.8 mg, 5 mol%) was suspended in *n*-butyronitrile (11 mL) and cooled to 0 °C. Sodium hypochlorite pentahydrate (17.3 mmol, 2.84 g, 2.3 eq) and PIPO (0.38 mmol, 225 mg, 1 mol%) were added. The primary dialcohol (7.5 mmol, 1 M) was dissolved in THF (4 mL, 27% v/v) by gentle warming and added to the reaction mixture after cooling to RT. The reaction mixture was stirred at 0 °C until a color change from red to colorless occurred. The reaction was quenched by addition of aqueous HCl-solution (50 mL of a 1 M solution), the phases were separated and the aqueous phase extracted with ethyl acetate (3x 30 mL). Organic phases were combined, dried over MgSO₄ and the solvent removed *in vacuo*. The crude product was analysed using GC

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analysis and further purified using automated column chromatography. The product was then analysed using ^1H -NMR spectroscopy in DMSO- d_6 .

***n*-Hexanedial (38).** Yield: 37% (316 mg, 2.8 mmol). **38** was obtained from *n*-hexan-1,6-diol (**37**) (886 mg, 7.5 mmol) as colorless liquid using sodium hypochlorite pentahydrate as oxidation agent (2.84 g, 17.3 mmol, 2.2 eq.) after automated column chromatography using cyclohexane and ethyl acetate as solvent (gradient from 5 to 50 % ethyl acetate in cyclohexane), a flow of 75 mL/min on a Biotage® SNAP Ultra 25 g column. ^1H NMR (500 MHz; $(\text{CD}_3)_2\text{SO}$): 9.66 (t, $J = 1.4$ Hz, 2H), 2.47 – 2.40 (m, 4H), 1.55 – 1.47 (m, 4H). The ^1H -NMR spectrum is in accordance to the literature.^[36]

***n*-Octanedial (32).** Yield: 69% (740 mg, 5.2 mmol). **32** was obtained from *n*-octan-1,8-diol (**37**) (1.1 g, 7.5 mmol) as colorless liquid using sodium hypochlorite pentahydrate as oxidation agent (2.84 g, 17.3 mmol, 2.2 eq.) after automated column chromatography using cyclohexane and ethyl acetate as solvent (gradient from 10 to 50 % ethyl acetate in cyclohexane), a flow of 75 mL/min on a Biotage® SNAP Ultra 25 g column. ^1H NMR (500 MHz; $(\text{CD}_3)_2\text{SO}$): 9.66 (s, 2H), 2.41 (td, $J = 7.3, 1.6$ Hz, 4H), 1.56 – 1.43 (m, 4H), 1.31 – 1.19 (m, 4H). The ^1H -NMR spectrum is in accordance to the literature.^[37]

***n*-Decanedial (35).** Yield: 56 % (710 mg, 4.17 mmol). **35** was obtained from *n*-decan-1,10-diol (**34**) (1.3 g, 7.5 mmol) as colorless liquid using sodium hypochlorite pentahydrate as oxidation agent (2.84 g, 17.3 mmol, 2.2 eq.) after automated column chromatography using cyclohexane and ethyl acetate as solvent (gradient from 5 to 50 % ethyl acetate in cyclohexane), a flow of 75 mL/min on a Biotage® SNAP Ultra 25 g column. ^1H NMR (500 MHz; $(\text{CD}_3)_2\text{SO}$): 9.66 (t, $J = 1.7$ Hz, 2H), 2.42 (td, $J = 7.2, 1.7$ Hz, 4H), 1.56 – 1.47 (m, 4H), 1.26 (s, 8H). The ^1H -NMR spectrum is in accordance to the literature.^[38]

Benzene-1,4-dicarboxaldehyde 42. Yield: 87% (876 mg, 6.5 mmol). **42** was obtained from 1,4-benzendimethanol **41** (1.0 g, 7.5 mmol) as colorless solid using sodium hypochlorite pentahydrate as oxidation agent (2.84 g, 17.3 mmol, 2.2 eq.). The substrate was added neat to a reaction already containing the THF co-solvent. ^1H NMR (500 MHz; $(\text{CD}_3)_2\text{SO}$): 10.14 (2H, s), 8.12 (4H, s). The ^1H -NMR spectrum is in accordance to the literature.^[35]

Benzene-1,3-dicarboxaldehyde 45. Yield: 71 % (719 mg, 5.4 mmol) was obtained from 1,4-benzendimethanol **44** (1.0 g, 7.5 mmol) as colorless solid using sodium hypochlorite pentahydrate as oxidation agent (2.84 g, 17.3 mmol, 2.2 eq.) after automated column chromatography using cyclohexane and ethyl acetate as solvent (gradient from 12 to 86 % ethyl acetate in cyclohexane), a flow of 75 mL/min on a Biotage® SNAP Ultra 25 g column. The substrate was added neat to a reaction already containing the THF solvent. ^1H NMR (500 MHz; $(\text{CD}_3)_2\text{SO}$): 10.13 (2H, s), 8.43 (d, $J = 1.9$ Hz 1H), 8.22 (d, $J = 7.6$ Hz, 2H), 7.84 (t, $J = 7.6$ Hz, 1H). The ^1H -NMR spectrum is in accordance to the literature.^[35]

General protocol for PIPO-oxidation of secondary alcohols to ketones. $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ (0.75 mmol, 103.6 mg, 5 mol%) was suspended in *n*-butyronitrile (15 mL) at room temperature. Sodium hypochlorite pentahydrate (22.5 mmol, 3.70 g, 1.5 eq) and PIPO (0.0375 mmol, 112.5 mg, 0.25 mol%) were added. The secondary alcohol (15 mmol) was added under vigorous stirring and the reaction mixture was stirred at room temperature until completion (GC-control). The reaction was quenched by addition of aqueous HCl solution (15 mL of a 2 M solution), the phases were separated and the aqueous phase extracted with *n*-butyronitrile (2x 5 mL). Organic phases were combined, dried over MgSO_4 and the solvent removed *in vacuo*. The product was analysed by ^1H -NMR spectroscopy in CDCl_3 .

2-Octanone (47). Yield: 22% (0.415 g, 3.24 mmol). **47** was obtained from *n*-octan-2-ol (**46**) (2.38 mL, 15 mmol) as colorless liquid. ^1H NMR (500 MHz; CDCl_3): 2.39 (t, $J = 7.5$ Hz, 2H), 2.10 (s, 3H), 1.54 (p, $J = 7.4$ Hz, 2H), 1.26 (m, 6H), 0.85 (t, $J = 6.8$ Hz, 3H). The ^1H -NMR spectrum is in accordance to the literature.^[35]

Acetophenone 49. Yield: 49% (0.899 g, 7.48 mmol) was obtained from 1-phenylethanol (**48**) (1.81 g, 15 mmol) as colorless liquid. ^1H NMR (500 MHz; CDCl_3): 7.97 (d, $J = 1.4, 8$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 2.59 (s, 3H). The ^1H -NMR spectrum is in accordance to the literature.^[35]

4-Nitroacetophenone 51. Yield: 90% (2.23 g, 14 mmol). **51** was obtained from 4-nitro- α -methylbenzyl alcohol (**50**) (2.51 g, 15 mmol) as colorless solid. ^1H NMR (500 MHz; CDCl_3): 8.32 (d, $J = 8.5$ Hz, 2H), 8.12 (d, $J = 8.5$ Hz, 2H), 2.68 (s, 3H). The ^1H -NMR spectrum is in accordance to the literature.^[35]

4-Methoxyacetophenone 53. Yield: 65% (1.46 g, 9.73 mmol). **53** was obtained from 4-methoxy- α -methylbenzyl alcohol (**52**) (2.28 g, 15 mmol) as colorless solid. ^1H NMR (500 MHz; CDCl_3): 7.93 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 3.84 (s, 3H). The ^1H -NMR spectrum is in accordance to the literature.^[35]

Oxidation of *n*-octan-2-ol at 0 °C and 1.1 eq. sodium hypochlorite pentahydrate. $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ (0.75 mmol, 103.6 mg, 5 mol%) was suspended in *n*-butyronitrile (15 mL) at 0 °C. Sodium hypochlorite pentahydrate (16.5 mmol, 2.71 g, 1.1 eq.) and PIPO (0.0375 mmol, 112.5 mg, 0.25 mol%) were added. The secondary alcohol (15 mmol) was added under vigorous stirring and the reaction mixture was stirred at 0 °C. The reaction progress was monitored by GC. The results are shown in the Supporting information (Table 8).

Oxidation of a mixture of *n*-octan-1-ol and *n*-octan-2-ol. $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ (0.75 mmol, 103.6 mg, 5 mol%) was suspended in *n*-butyronitrile (15 mL) at 0 °C. Sodium hypochlorite pentahydrate (16.5 mmol, 2.71 g, 1.1 eq.) and PIPO (0.0375 mmol, 112.5 mg, 0.25 mol%) were added. The alcohol mixture consisting of *n*-octan-1-ol (**1**) (1.18 mL, 7.5 mmol) and *n*-octan-2-ol (**46**) (1.19 mL, 7.5 mmol) (in total 15 mmol) was added under vigorous stirring and the reaction mixture was stirred at 0 °C. The reaction progress was monitored by GC. The results are shown in the Supporting Information (Table 9) and in the publication (Scheme 2).

Oxidation of alcohols to aldehydes using aqueous bleach solution as oxidation agent. $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ (0.75 mmol, 103.6 mg, 5 mol%) was suspended in *n*-butyronitrile (15 mL) at 0 °C. 13% aqueous sodium hypochlorite solution (3 mL, 5 mmol, 0.33 eq.) and PIPO (0.0375 mmol, 112.5 mg, 0.25 mol%) were added. The alcohol (15 mmol) was added under vigorous stirring and the reaction mixture was stirred at 0 °C. Each 15 min reaction time 13% aqueous sodium hypochlorite solution (3 mL, 5 mmol, 0.2 eq.) was added. The reaction progress was monitored by GC. The results are shown in the Supporting Information (Table 10) and the publication (Scheme 3).

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Keywords: TEMPO-Oxidation • Aldehydes • Dialdehydes • Nitriles • Solvents

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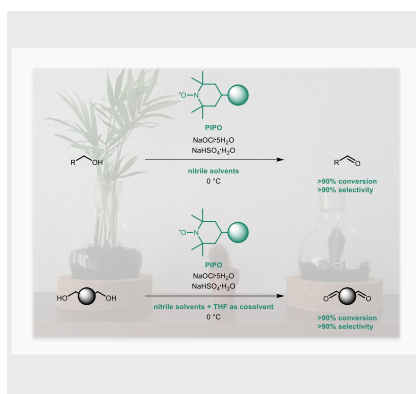
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A nitroxyl radical-catalysed oxidation method for alcohols running in nitriles as an organic solvent component has been developed, which turned out to be suitable for the selective synthesis of a broad range of aldehydes, dialdehydes and ketones. This practical method, for which solid sodium hypochlorite pentahydrate as well as bleach solution can be used, avoids the need for chlorinated solvents as in case of the "classic" Anelli oxidation.



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Selective TEMPO-oxidation of alcohols to aldehydes in alternative organic solvents