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Oxidation Reactions

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] and 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 an 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 an organic solvent in a biphasic reaction medium with water. Previous studies show that dichloromethane cannot easily be substituted because a decrease of selectivity or inhibition of the reaction is observed by using 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 an oxidation agent in nitriles as an 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 in 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 periodinane 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 a catalyst,[5,6] which is a stable nitroxyl radical and readily accessible starting from acetone and ammonia.[7] As an 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 a catalyst for oxidation of alcohols to carbonyl compound was investigated using metal salt additives or different oxidation agents, different TEMPO-derivatives or immobilized TEMPO as a catalyst or different solvent systems.[8–12] Nevertheless, a major disadvantage of the "classical" TEMPO-oxidation using sodium hypochlorite as an 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 despite 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.[15,16,8,17,18,19] 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

[a] *Industrial Organic Chemistry and Biotechnology, Faculty of Chemistry, Bielefeld University, Universitätsstrasse 25, 33615 Bielefeld, Germany*
E-mail: harald.groeger@uni-bielefeld.de
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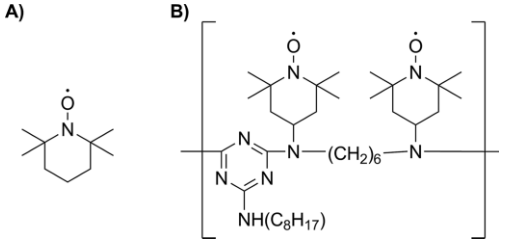
for example PIPO as a polymer-immobilised TEMPO-derivative (Scheme 1),[20,12] which was found to be suitable for catalysing the oxidation of alcohols to aldehydes and/or ketones.[20] PIPO is synthesised from the antioxidant and light-stabiliser Chimassorb 944, which is used as ingredient in different plastics.



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

Since Chimassorb 944 is commercially available and manufactured at large amounts, 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 aldehydes. 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-catalyzed 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-catalyzed 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 for optimization 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-catalyzed oxidation of alcohols to aldehydes, we decided to first optimize 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 an aqueous bleach solution. A major advantage of the use of this pentahydrate is the easy dosage of the oxidation agent. In the case of the 13 % aqueous bleach as an 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 $NaHSO_4$ are used.[21,22] To get a deeper insight into 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 equiv. $NaOCl{\cdot}5H_2O$ and 5 mol-% phase-transfer catalyst or $NaHSO_4$ in DCM at 0 °C for 1 h. As phase-transfer catalyst tetrabutylammonium hydrogensulfate (Bu_4NHSO_4), tetrabutylammonium chloride (Bu_4NCl) and acetylcholine hydrochloride were tested. As an additive, sodium hydrogensulfate ($NaHSO_4$) was tested and additionally, one experiment without phase-transfer catalyst or $NaHSO_4$ was conducted (see Supporting Information). With acetylcholine hydrochloride, Bu_4NCl and without any phase-transfer catalyst the reaction did not proceed. In contrast, when using Bu_4NHSO_4 and $NaHSO_4$ 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.[5,6,8,17,20,23] In particular aliphatic aldehydes tend to overoxidize 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**) to find a generally applicable system for also challenging substrates. Both Bu_4NHSO_4 and $NaHSO_4$ 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, a high conversion exceeding 95 % was achieved, but with $NaHSO_4$ less acid formation of 6 % was observed in contrast to an acid formation of 20 % with Bu_4NHSO_4. In further experiments, the amount of $NaHSO_4$, the amount of TEMPO and the amount of $NaOCl{\cdot}5H_2O$ was varied to find optimal reaction conditions (see Supporting Information). The results show that a change in the amount of $NaHSO_4$ 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 $NaOCl{\cdot}5H_2O$ turned out to be 1.1 equiv. (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

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conditions consisting of 0.25 mol-% TEMPO, 1.1 equiv. $NaOCl{\cdot}5H_2O$ and 5 mol-% $NaHSO_4$ in DCM at 0 °C. The increase in the substrate concentration led to a significant increase in the reaction speed (Supporting 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**).

	***n*-Octan-1-ol (1)**	***n*-Decan-1-ol (4)**
Substrate concentration	1 M	1 M
TEMPO	0.25 mol-%	0.25 mol-%
$NaHSO_4{\cdot}H_2O$	5 mol-%	5 mol-%
$NaOCl{\cdot}5H_2O$	1.1 eq	1.0 eq

Optimization 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 using metal salts as co-catalyst. To identify such a desired alternative reaction medium, we screened several organic solvents for the oxidation of *n*-octan-1-ol (**1**) using the optimized 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, formation of less than 1 % acid **3** 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,[24–26] enabling an alternative access to these nitrile solvents without the need for toxic cyanide and harsh reaction conditions.

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]

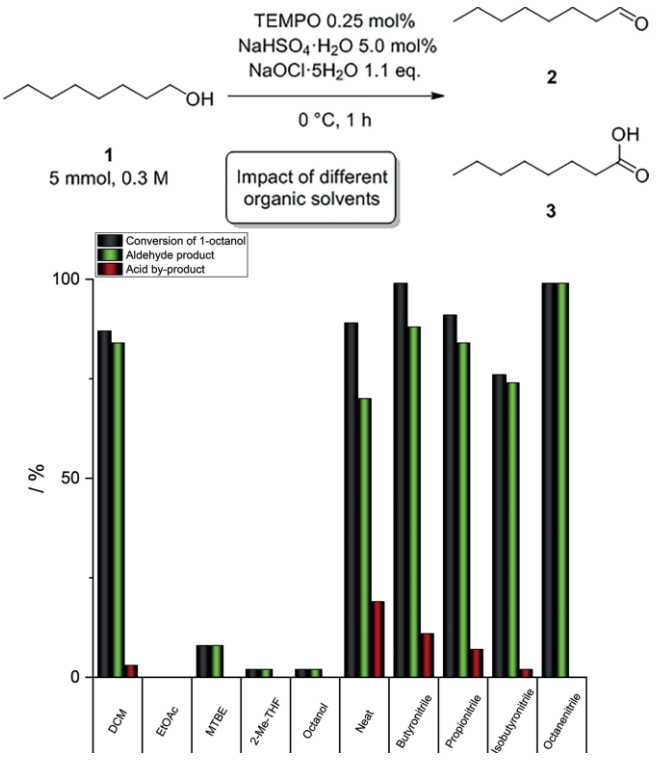

Figure 1. Solvent study of TEMPO-catalyzed oxidation of *n*-octan-1-ol (1) to *n*-octanal (2).

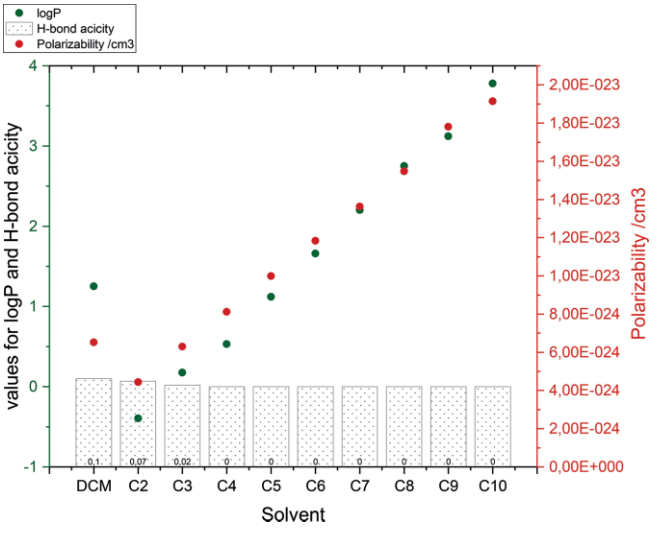

Figure 2. Partition coefficient (log P) (green dots),[28] summation of H-bond-acidity (bars, values are given as numbers in the bars) and polarizability in cm^3 (red dots) of from left to right: DCM, acetonitrile (C2), propionitrile (C3), butyronitrile (C4), pentanenitrile (C5), hexanenitrile (C6), heptanenitrile (C7), octanenitrile (C8), nonanenitrile (C9) and decanenitrile (C10). Y-axis on the left side presents values of log P and H-bond acidity and y-axis on the right represents polarizability.[27]

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

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further investigations. From a synthetic perspective, a replacement of dichloromethane as a solvent for TEMPO-oxidation is of major interest due to the chronical 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 a 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 a 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

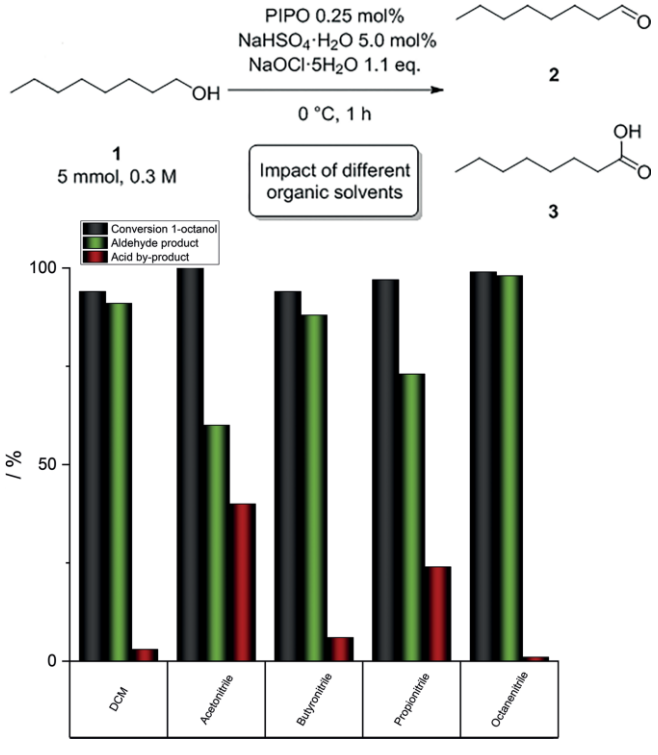
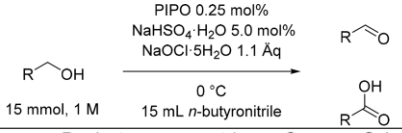


Figure 3. Solvent study for the PIPO-catalyzed oxidation of *n*-octan-1-ol (1) to *n*-octanal (2).

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



Entry	Product	t / min	Conv. /%[a,b]	Sel. /%[c]	Yield /%[d]
1	**2**	15	99	93	90
2	**5**	45	94	96	89
3	**8**	1290[e]	>99	91	95[f]
4	**11**	75[g]	>99	95	58[f]
5	**14**	75	98	>99	95
6	**17**	420	>99	91	75[h]
7	**20**	75	>99	>99	94
8	**23**	25	>99	>99	92
9	**26**	150[i]	95	>99	91
10	**29**	105[i]	95	>99	88

[a] The reactions were quenched by the 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: $c_{aldehyde}/(c_{aldehyde} + c_{side\text{-}products})$. [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.

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the aldehyde **2** was detected (Table 2, entry 1). In addition, *n*-octanal (**2**) was isolated in 90 % yield from the reaction mixture.

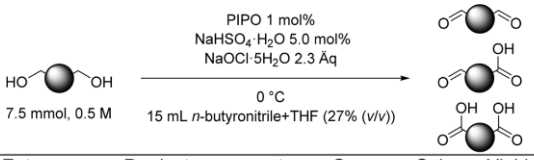
Substrate Scope of PIPO-Catalysed Oxidation in *n*-Butyronitrile as a Solvent

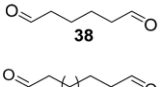
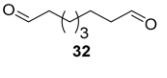
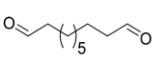
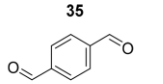
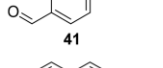
Since this oxidation method using *n*-butyronitrile as solvent, PIPO as catalyst and sodium hypochlorite pentahydrate as an oxidation agent is very simple and as the reaction progress can be easily tracked by GC-analysis, this method was applied for further oxidation experiments using primary and secondary alcohols. In this study, the oxidation of different substrates with different electronic properties was tested 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 optimized 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 because many more side-products can occur, further optimization of our method was conducted later for the oxidation of dialcohols to dialdehydes. The substrate scope was also expanded to secondary alcohols to synthesize 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 an alternative solvent to DCM when utilizing electronically different alcohols as substrates such as, e.g., 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 into 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 synthesizing 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 synthesized 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 because 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 proceeds with a variety of primary alcohols as substrates to synthesize the corresponding aldehydes with high selectivities.

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 oxidized using PIPO as a catalyst, sodium hypochlorite 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 optimization addressing substrate loading and the amount of $NaHSO_4$ and sodium hypochlorite, respectively. We were pleased to find such desired re-

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



Entry	Product	t / min	Conv. /%[a,b]	Sel. /%[c]	Yield /%[d]
1	 **38**	45	96	91	37
2	 **32**	40	>99	90	69
3	 **35**	10	>99	93	56
4	 **41**	45	>99	94	87[e]
5	 **44**	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$_{side\text{-}products}$). [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.

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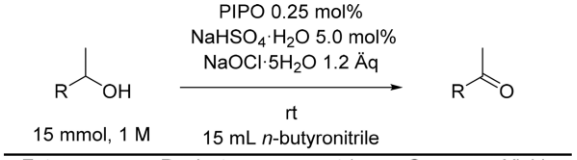
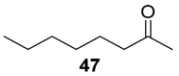
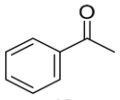
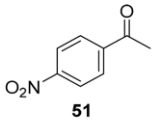
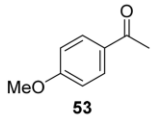
action conditions, leading to the oxidation of *n*-octan-1,8-diol (**31**) to *n*-octanedial (**32**) with >99 % conversion and 90 % selectivity. After purification by automated column chromatography the desired product *n*-octanedial (**32**) was obtained in 69 % isolated yield (Table 3, entry 2). We also applied these optimized 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.

Substrate scope study, part 3: Oxidation of secondary alcohols to ketones. Since we could show that primary mono- as well as dialcohols can be oxidized 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 into the corresponding ketones with quantitative conversions. Also in the 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 with literature results. Kimura et al. also found that nitro-substituted benzyl alcohol is faster converted than methoxy-substituted benzyl alcohol.[21] However, an explanation for this effect is still missing. *n*-Octan-2-ol (**46**) was converted slower than 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 favored.

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



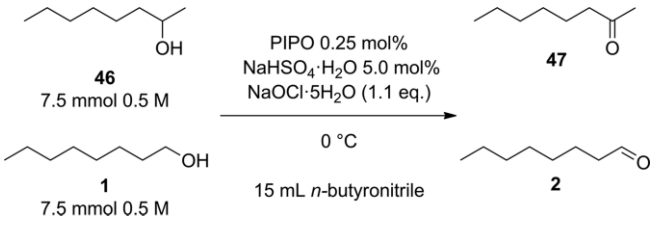
Entry	Product	t / min	Conv. /%[a,b]	Yield /%[b]
1	 **47**	40	>99	22
2	 **49**	70	>99	49
3	 **51**	5	>99	90
4	 **53**	90	>99	65

[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 the 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 than the oxidation of secondary alcohols as shown for the oxidation of a mixture of *n*-nonan-1-ol and *n*-nonan-2-ol.[5] Generally, TEMPO-catalyzed oxidations can proceed in two different ways, following different mechanisms.[32–34] 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 sterically 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). Afterward, 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).

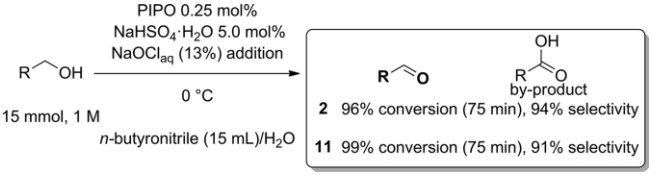


Scheme 2. Oxidation of a mixture of *n*-octan-1-ol (**1**) and *n*-octan-2-ol (**46**).

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 than 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 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 equiv. hypochlorite in aqueous solution. In this experiment, however, we could not obtain full conversion of the alcohol and additionally, 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-type 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 $NaOCl{\cdot}5H_2O$ were purchased by TCI Chemicals (Germany) and used without further purification. NMR spectra were recorded on a Bruker Avance III 500 at a frequence of 500 MHz (^1H). The chemical shift δ is given in ppm and referenced to the corresponding solvent signal ($CDCl_3$ or $(CD_3)_2SO$). 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]

Optimization of the TEMPO-Catalyzed Oxidation of *n*-Octan-1-ol and *n*-Decan-1-ol: Phase-transfer catalyst or $NaHSO_4$ 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, 0.74–1.23 g, 0.9–1.5 equiv.) 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 analyzed by GC chromatography. Further work-up and isolation of the product(s) were not performed. For the substrate *n*-octan-1-ol (**1**) a reaction optimization 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 S3–S4).

Optimization in Terms of Solvent: $NaHSO_4 \cdot H_2O$ (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 equiv.) 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 (Table S5) and in the publication (Figure 1).

Synthesis of Polyamine-Immobilized Piperidinyloxyl Radical (PIPO): PIPO radical was prepared in analogy to Dijksman et al.[20] from Chimassorb 944 (M_n ca. 3,000 g/mol). Chimassorb 944 (10.12 g, 3.5 mmol) was suspended in 15 % aqueous H_2O_2 solution (120 mL) and the reaction mixture was stirred at room temperature for 5 days. The solid was filtered, washed with H_2O (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: $NaHSO_4 \cdot H_2O$ (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 equiv.) 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 study are shown in the Supporting Information (Table S6) and in the publication (Figure 2).

Optimization of the PIPO-Catalyzed Oxidation Reaction of *n*-Octan-1,8-diol: $NaHSO_4 \cdot H_2O$ (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 equiv.) 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 with $MgSO_4$. The organic phase was analyzed by GC chromatography. Further work-up and isolation of the product(s) were 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 S7).

General Protocol for PIPO-Oxidation of Primary Alcohols to Aldehydes: $NaHSO_4 \cdot H_2O$ (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 equiv.) 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 (2 × 5 mL). Organic phases were combined, dried with $MgSO_4$ and the solvent removed in vacuo. The product was analyzed using ^{1}H-NMR spectroscopy in [D_6]DMSO.

***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 equiv.) as oxidation agent. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (t, *J* = 1.6 Hz, 1 H), 2.41 (td, *J* = 1.6, 7.3 Hz, 2 H), 1.51 (p, *J* = 7.2 Hz, 2 H), 1.25 (m, 6 H), 0.86 (t, *J* = 6.9 Hz, 3 H). The ^{1}H-NMR spectrum is in accordance with 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, 1.1 equiv.) as oxidation agent. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (t, *J* = 1.5 Hz, 1 H), 2.41 (td, *J* = 1.5, 7.3 Hz, 2 H), 1.51 (p, *J* = 7.1 Hz, 2 H), 1.25 (m, 6 H), 0.86 (t, *J* = 6.9 Hz, 3 H). The ^{1}H-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, 1.1 equiv.). *n*-Hexanal (**8**) (85 %) was obtained as colorless oil. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (t, *J* = 1.6 Hz, 1 H), 2.41 (td, *J* = 1.6, 2.4 Hz, 2 H), 1.52 (p, *J* = 7.3 Hz, 2 H), 1.26 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3 H). The ^{1}H-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, 1.1 equiv.). Cyclohexancarbaldehyde **11** (0.98 g, 8.7 mmol, 58 %) was obtained as colorless oil. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.55 (s, 1 H), 2.27 (m, 1 H), 1.81 (m, 2 H), 1.65–1.55 (m, 3 H), 1.33–1.18 (m, 5 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) as oxidation agent. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 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 ^{1}H-NMR spectrum is in accordance with 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 equiv.) 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. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.69 (d, *J* = 7.6 Hz, 1 H), 7.75 (m, 4 H), 7.47 (m, 2 H), 6.87 (dd, *J* = 7.8, 16.0 Hz, 1 H). The ^{1}H-NMR spectrum is in accordance with the literature.[35]

4-Nitrobenzaldehyde 20. Yield: 94 % (2.12 g, 14.0 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 equiv.). ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 10.17 (s, 1 H), 8.42 (d, *J* = 8.5 Hz, 2 H), 8.17 (d, *J* = 8.5 Hz, 2 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) as oxidation agent. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 10.14 (s, 1 H), 8.67 (m, 1 H), 8.52 (ddd, *J* = 1.1, 2.4, 8.3 Hz 1 H), 8.33 (d, *J* = 7.7 Hz, 1 H), 7.89 (t, *J* = 7.9 Hz, 1 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) at room temperature instead of 0 °C. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.87 (s, 1 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 3.33 (s, 3 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) as oxidation agent at room temperature instead of 0 °C. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.98 (s, 1 H), 7.52 (m, 2 H), 7.42 (m, 1 H), 7.28 (m, 1 H), 3.83 (s, 3 H). The ^{1}H-NMR spectrum is in accordance with the literature.[35]

General Protocol for PIPO-Oxidation of Dialcohols to Dialdehydes. $NaHSO_4{\cdot}H_2O$ (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 equiv.) 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 r.t. 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 (3 × 30 mL). Organic phases were combined, dried with $MgSO_4$ and the solvent removed in vacuo. The crude product was analyzed using GC analysis and further purified using automated column chromatography. The product was then analyzed using ^{1}H-NMR spectroscopy in $[D_6]$DMSO.

***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 equiv.) 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. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (t, *J* = 1.4 Hz, 2 H), 2.47–2.40 (m, 4 H), 1.55–1.47 (m, 4 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) 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. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (s, 2 H), 2.41 (td, *J* = 7.3, 1.6 Hz, 4 H), 1.56–1.43 (m, 4 H), 1.31–1.19 (m, 4 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) 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. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 9.66 (t, *J* = 1.7 Hz, 2 H), 2.42 (td, *J* = 7.2, 1.7 Hz, 4 H), 1.56–1.47 (m, 4 H), 1.26 (s, 8 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.). The substrate was added neat to a reaction already containing the THF cosolvent. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 10.14 (s, 2 H), 8.12 (s, 4 H). The ^{1}H-NMR spectrum is in accordance with 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 equiv.) 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. ^{1}H NMR (500 MHz; $(CD_3)_2SO$): 10.13 (s, 2 H), 8.43 (d, *J* = 1.9 Hz, 1 H), 8.22 (d, *J* = 7.6 Hz, 2 H), 7.84 (t, *J* = 7.6 Hz, 1 H). The ^{1}H-NMR spectrum is in accordance to the literature.[35]

General Protocol for PIPO-Oxidation of Secondary Alcohols to Ketones. $NaHSO_4{\cdot}H_2O$ (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 equiv.) 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 (2 × 5 mL). Organic phases were combined, dried with $MgSO_4$ and the solvent removed in vacuo. The product was analyzed by ^{1}H-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. ^{1}H NMR (500 MHz; $CDCl_3$): 2.39 (t, *J* = 7.5 Hz, 2 H), 2.10 (s, 3 H), 1.54 (p, *J* = 7.4 Hz, 2 H), 1.26 (m, 6 H), 0.85 (t, *J* = 6.8 Hz, 3 H). The ^{1}H-NMR spectrum is in accordance with 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. ^{1}H NMR (500 MHz; $CDCl_3$): 7.97 (d, *J* = 1.4, 8. Hz, 2 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 2.59 (s, 3 H). The ^{1}H-NMR spectrum is in accordance with 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. ^{1}H NMR (500 MHz; $CDCl_3$): 8.32 (d, *J* = 8.5 Hz, 2 H), 8.12 (d, *J* = 8.5 Hz, 2 H), 2.68 (s, 3 H). The ^{1}H-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. ^{1}H NMR (500 MHz; $CDCl_3$): 7.93 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 3.84 (s, 3 H). The ^{1}H-NMR spectrum is in accordance with the literature.[35]

Oxidation of *n*-Octan-2-ol at 0 °C and 1.1 eq. Sodium Hypochlorite Pentahydrate. $NaHSO_4{\cdot}H_2O$ (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 equiv.) 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 S8).

Oxidation of a Mixture of *n*-Octan-1-ol and *n*-Octan-2-ol. $NaHSO_4$ H_2O (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 equiv.) 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 S9) and in Scheme 2.

Oxidation of Alcohols to Aldehydes Using Aqueous Bleach Solution as Oxidation Agent. $NaHSO_4$•H_2O (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 equiv.) 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 equiv.) was added. The reaction progress was monitored by GC. The results are shown in the Supporting Information (Table S10) and the publication (Scheme 3).

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