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Hot Paper

A Sustainable Ruthenium(III) Chloride Catalyzed Alcohol Oxidation

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Dedicated to Prof. Dr. Otto J. Scherer on the occasion of his 90th birthday.

Systematic optimization of the ruthenium-catalyzed oxidation of alcohols with *tert*-butyl hydroperoxide (TBHP) as the oxidizing agent was carried out. This resulted in the development of a sustainable protocol with a water/*tert*-butanol mixture as the solvent and an optimum use of the oxidizing agent by continuous addition with a syringe pump. The protocol is applicable for a broad variety of substrates. High yields of ketones and aldehydes are accessible.

Introduction

Due to their particular reactivity, ketones and aldehydes are important starting materials for chemical synthesis. Aromatic aldehydes and ketones are accessible by the electrophilic substitution of arenes. For an industrial synthesis of aliphatic aldehydes, the Rhône-Poulenc process has been developed.[1] Aside to this, aliphatic carbonyl compounds are mainly generated by the oxidation of alcohols or the hydrogenation of carboxylic acid derivatives. However, aldehydes are in particular prone to consecutive transformations under both, oxidation and hydrogenation conditions. Due to this, highly selective reactions for the oxidation of primary alcohols to aldehydes have been developed in the past. Most of them use environmentally questionable and expensive oxidizing agents such as chromates,[2] hypervalent iodine derivatives[3] or NaOCl (with TEMPO)[4] in stoichiometric amounts. Obviously, there still is a demand for methods for the oxidation of alcohols by using sustainable and cheap oxidizing agents.

In 1987, W. P. Griffith and S. V. Ley made an important step into this direction.[5] The Griffith-Ley oxidation of alcohols takes advantage of the property of ruthenium to be able to stabilize the oxidation states +VII and +VIII in the presence of strong σ- and π-donors.[6,7,8] Griffith and Ley used perruthenate(VII) (RuO_4^-) as a catalyst, which is less toxic and less aggressive than ruthenium tetroxide (RuO_4), allowing for more selective oxidations still under rather mild reaction conditions. In their initial publication,[5] they reported the use of two perruthenate(VII) compounds: *n*-tetrapropylammonium and *n*-tetrabutylammonium perruthenate(VII). $^nPr_4N(RuO_4)$, in particular, is readily accessible from $RuCl_3 \cdot (H_2O)$, $NaBrO_3$, and $^nPr_4N(OH)$.[9] This method allows the selective oxidation of a wide range of alcohols to the corresponding carbonyl compounds in organic solvents at low reaction temperatures. It leaves intact labile functionalities such as esters, (silyl)ethers, epoxides or double bonds. *N*-Methylmorpholine-*N*-oxide is mainly used as oxidizing agent. The addition of powdered 4 Å molecular sieve increases the efficiency of the system considerably.

However, the oxidation of alcohols is not only possible with ruthenium catalysts in high oxidation states, but also with compounds in which the ruthenium center is in a lower oxidation state. As early as 1976, K. B. Sharpless investigated the use of various low-valent ruthenium compounds for the oxidation of a wide range of alcohols.[10] Rather simple, commercially available ruthenium compounds such as $RuCl_2(PPh_3)_3$ or $RuCl_3 \cdot (H_2O)$ were used as catalysts, and *N*-methylmorpholine-N-oxide was identified as the most active oxidizing agent. Polar organic solvents (for example DMF, acetone, or HMPT) have to be used because of the limited solubility of the ruthenium catalysts in other organic solvents.

In 2020 we published the use of a bispyrazolylruthenium(II) complex for the selective oxidation of secondary and primary alcohols allowing to apply non-polar organic solvents (*n*-heptane), which facilitates catalyst separation and product isolation.[11] Here, the cheaper trimethylamine *N*-oxide (TMAO) is used as the oxidizing agent. This catalyst was originally developed for the transfer hydrogenation of aldehydes and ketones.[12,13,14] Parallel to this, we investigated the optimization of the $RuCl_3 \cdot (H_2O)$ catalyzed alcohol oxidation and succeeded in establishing a protocol for the efficient oxidation of a series of fatty alcohols,[15] which for example find application in fragrance industries.

Although it is possible to use cheap $RuCl_3 \cdot (H_2O)$ as the catalyst in rather low amounts, this system is still not perfect in the sense of sustainability. In particular the cost of the oxidizing agent TMAO, the very unpleasantly smelling gaseous side-product trimethylamine and the fact that the reaction requires

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dried organic solvents gave an impetus to look closer for alternatives.

Results and Discussion

Catalyst Development

We started the development of the catalytic system for the oxidation of secondary alcohols by investigating a series of oxidizing agents with cyclohexanol as the model substrate. Table 1 compares the performance of TBHP (*tert*-butyl hydroperoxide) with urea$\cdot H_2O_2$ and Me_3NO (TMAO). The reactions were carried out at 60 °C in dry DMF with 0.5 mol% of $RuCl_3\cdot(H_2O)$ and the outcome was analyzed by gas chromatography. This corresponds to the reaction conditions recently developed in our group for the oxidation of alcohols with TMAO.[11,15] Aqueous H_2O_2 was not investigated, since it did not show any activity for this type of reaction in the past.

The reaction conditions used here were intended to provide an overview of oxidant activity with respect to the ruthenium-catalyzed oxidation of alcohols. Obviously, there are pronounced differences in the activity of the oxidants. Although, being less active than TMAO, TBHP showed some promising activity in these first experiments.

Based on this result, a comprehensive modification of the conditions for the application of TBHP as the oxidizing agent in the oxidation of cyclohexanol was carried out. First, different solvents were investigated for their influence on the product yield. The number of possible organic solvents is limited by the poor solubility of $RuCl_3\cdot(H_2O)$. Solubility studies with purely organic solvents showed sufficient solubility of $RuCl_3\cdot(H_2O)$ in DMF, acetone, and chloroform. Acetone was not used due to its low boiling point, which does not allow higher reaction temperatures. DMF and chloroform were excluded due to sustainability reasons. Since TBHP is commercially available as an aqueous solution, we looked for combinations of water and an organic solvent and finally found *tert*-butanol to be suitable for this reaction (Table 2).

Table 1. Oxidation of cyclohexanol to cyclohexanone; variation of the oxidizing agent.[a]

Oxidizing agent	Yield [%] after	
	15 min	3 h
Me_3NO	95	96
urea$\cdot H_2O_2$	<1	<1
TBHP	3	18

[a] Cyclohexanol (1.0 mmol), $RuCl_3\cdot(H_2O)$ (0.5 mol-%) as a stock solution in DMF, oxidizing agent (2.0 equivalents), DMF (1.0 mL), 60 °C.

Table 2. Oxidation of cyclohexanol in a 1:1 mixture of water and *tert*-butanol.[a]

Yield [%] after						
15 min	30 min	1 h	2 h	4 h	6 h	8 h
52	57	58	65	66	67	68

[a] Cyclohexanol (1.0 mmol), $RuCl_3\cdot(H_2O)$ (0.5 mol-%) as a stock solution in water, aqueous TBHP (2.0 equivalents), water/^{t}BuOH (1.0 mL, 1:1 v:v), 60 °C.

The outcome of this study was rather unexpected, since water has a largely negative effect on the performance of the ruthenium-catalyzed alcohol oxidation when TMAO is used. Nevertheless, the application of an aqueous *tert*-butanol solution represents a major step in the development of an environmentally friendly oxidation system. Both components of the solvent mixture are non-toxic, non-water hazardous, inexpensive, and can easily be separated from the desired target products by distillation or extraction. In addition, the joint use of water and a fully miscible organic component allows the solvent mixture to be adaptable to the polarity requirements of the substrates used. Consequently, the focus was laid on the further development of the water/*tert*-butanol system. While the activity of hydrogen peroxide can be enhanced by the addition of acids,[16,17,18] there is neither a positive nor a negative influence on the water/*tert*-butanol system by the addition of various acids (1–10 mol-% of *p*-$CH_3C_6H_4SO_3H$, CF_3COOH, H_2SO_4, HCl, H_3PO_4).

Next, the order of the addition of the different components was investigated in detail. In all the reactions described above, the solvent was introduced before the oxidizing agent and the catalyst were added while heating the reaction vial to reaction temperature. The reaction was started by finally adding the substrate. Hereby some gas evolution can be observed once TBHP (2.0 equivalents) and $RuCl_3\cdot(H_2O)$ are in the mixture, indicating degradation of the oxidizing agent by the catalyst. This was proved by increasing the time between the addition of the catalyst and the addition of the substrate: Waiting just 5 min for the addition of the substrate limited the yield of cyclohexanone to 40 %. Furthermore, there is no increase of yield between 15 min and 2 h in this case. It therefore was decided to add the catalyst as the last component to the reaction mixture. By doing so, some fluctuation of the yields that was observed before could be eliminated.

By knowing that there are at least two competing reactions occurring in parallel, the catalytic degradation of the oxidizing agent and the catalytic oxidation of cyclohexanol, it became important to evaluate the influence of the reaction temperature in more detail (Table 3, Figure 1).

The data presented in Table 3 and Figure 1 further confirm the statements given above. At temperatures of 60 °C and above, there is almost no further conversion of the alcohol after 15 min, which is a strong hint, that either the catalyst gets deactivated or the oxidizing agent is decomposed during this period. The yields at 80 °C are lower than at 60 °C, a further argument for a deactivation process. At temperatures of 50 °C and below, the yields still increase with time, at lower temperatures even up to 24 h. In this temperature regime, cyclohexanol oxidation as expected increases with temperature (see yields after 15 min). The highest yields are observed between room temperature and 40 °C.

Table 3. Oxidation of cyclohexanol to cyclohexanone at different temperatures.[a]

T [°C]	yield [%] after							
	15 min	30 min	1 h	2 h	4 h	6 h	8 h	24 h
r.t.	41	45	52	60	65	70	71	77
40	51	56	63	68	72	74	75	79
50	56	61	66	66	70	69	72	72
60	69	72	72	72	73	72	72	71
80	69	68	67	68	69	67	68	70

[a] Cyclohexanol (1.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, aqueous TBHP (2.0 equivalents), water/tBuOH (1.0 mL, 1 : 1 v:v), temperature as indicated.

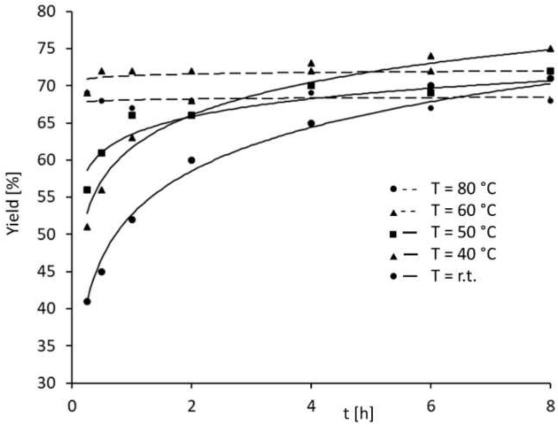

Figure 1. Oxidation of cyclohexanol to cyclohexanone at different reaction temperatures; conditions as in Table 3.

From a chemical point of view, the degradation of the oxidizing agent resulting in the formation of dioxygen is more likely under the given reaction conditions than the deactivation of the catalyst. In an aqueous environment, Ru^{3+} and related catalytically active species (generated from $RuCl_3 \cdot (H_2O)$) should be sufficiently stable to prevent the reaction from ceasing completely. To prove this hypothesis, some variations of the reaction conditions were studied. First, the amount of TBHP was increased (Table 4) while still running the reaction at room temperature.

As expected, the yields increase with increasing amounts of TBHP, which already makes a deactivation of the catalyst rather unlikely. However, even with 4.0 equivalents of TBHB it is not possible to reach 100 % of conversion (Figure 2).

In addition to a variation of the temperature, a lowering of the amount of catalyst was investigated (from 0.5 mol-% to 0.3 and 0.1 mol-%, respectively). However, this leads to a significant drop in yields. For this reason, the amount of catalyst was kept constantly at 0.5 mol-% in the following experiments.

To finally rule out a deactivation of the catalyst, experiments were started with 2.0 equivalents of TBHP and one additional equivalent of TBHP was added to the reaction mixture at the beginning or later in the reaction course (Table 5, Figure 3).

If the limitation of conversion that was observed in the previous experiments is due to catalyst deactivation, a later addition of fresh TBHP should have no or a rather small influence on the yields. If, on the other hand, this limitation is due to a rapid decomposition of the oxidizing agent, a later addition of fresh TBHP should result in a significant increase in product yield. This is exactly what is observed (Table 5, Figure 3).

In addition to varying the timing of the addition of additional TBHP, the amount of fresh oxidant needed to be added to achieve a nearly quantitative conversion of cyclo-

Table 4. Oxidation of cyclohexanol to cyclohexanone in the presence different amounts of TBHP.[a]

Equivalents of TBHP	yield [%] after 15 min	30 min	1 h	2 h	4 h	6 h	8 h	24 h
2	41	45	52	60	65	70	71	77
3	49	55	60	66	71	73	76	80
4	57	64	70	75	80	82	83	86

[a] Cyclohexanol (1 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, aqueous TBHP as indicated, water/tBuOH (1.0 mL, 1 : 1 v:v), r.t..

Table 5. Oxidation of cyclohexanol to cyclohexanone by addition of a second equivalent of TBHP at the beginning of the reaction and after 60 min and 360 min, respectively.[a]

TBHP after	yield [%] after 15 min	30 min	1 h	2 h	4 h	6 h	8 h	24 h
0 min	49	55	60	66	71	73	76	80
120 min	47	50	56	61	90	92	96	99
360 min	49	52	58	63	67	71	95	98

[a] Cyclohexanol (1.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, TBHP (2.0 equivalents at the beginning, 1.0 equivalents at the indicated time), water/^{t}BuOH (1.0 mL, 1 : 1 v:v), r.t..

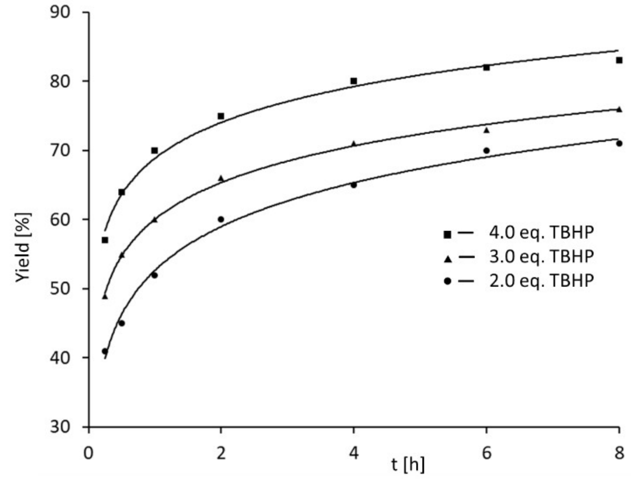

Figure 2. Oxidation of cyclohexanol to cyclohexanone in the presence of different amounts of TBHP; conditions as in Table 4.

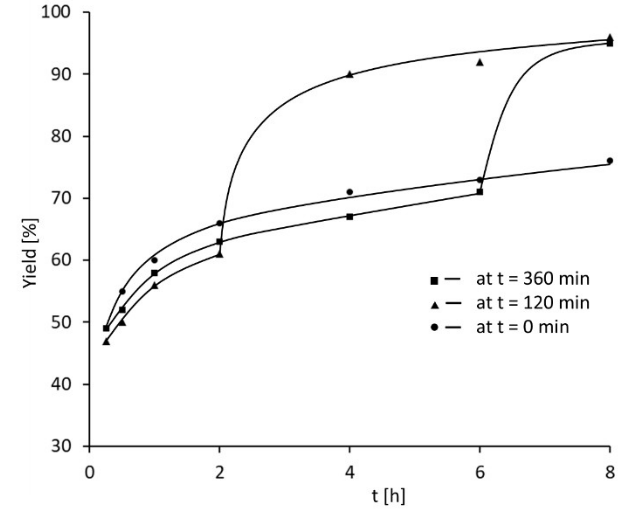

Figure 3. Oxidation of cyclohexanol to cyclohexanone with 2.0 equivalents of TBHP and a time-shifted addition of a 3rd equivalent of TBHP; conditions as in Table 5.

hexanol was investigated. For this purpose, two equivalents of TBHP were added at the beginning before additional oxidant was added in variable amounts (0.5–1.0 equivalents) after two hours. The yields decrease slightly with decreasing amounts of fresh oxidant. However, an almost complete conversion of cyclohexanol can even be recorded with 0.5 equivalents of additional TBHP.

In two further experiments, the reaction was started with 2.0 and 1.0 equivalents of TBHP, respectively. One further equivalent of TBHP was added after two hours. The results are summarized in Table 6 and Figure 4.

It obviously is possible to reach about 50% of conversion with 1.0 equivalents of TBHP after 120 min. The addition of a second equivalent at this time allows for nearly complete conversion, while this is not possible by the addition of the second equivalent directly at the beginning of the reaction (see also Table 4 and Figure 2). This confirms the dependence of the product yields on the decomposition of the oxidizing agent.

To overcome this problem and decrease decomposition, the concentration of TBHP should be kept as low as possible. In the following, the oxidizing agent was therefore added continuously using a syringe pump. In a first experiment, two equivalents of TBHP were added to the reaction mixture at a flow rate of $0.25\ \mathrm{mL \cdot h^{-1}}$, which in turn corresponds to an addition time of approximately 3.3 hours. Due to the experimental setup, the amount of the substrate cyclohexanol had to be increased from 1.0 to 3.0 mmol when working with a syringe pump. During the first hour, a nearly linear increase of the yield of cyclohexanone up to about 60% was observed, which indicates that the oxidant is primarily applied to oxidize the substrate and is only deactivated to a small extent. After 3 h, complete conversion was achieved, no more substrate was detected. At this point, the addition of the oxidizing agent was not completed. It therefore can be assumed that the actual amount of TBHP required for complete oxidation is less than two equivalents.

Therefore, the amount of TBHP was further decreased to 1.1 equivalents. By preserving a flow rate of $0.25\ \mathrm{mL \cdot h^{-1}}$, the addition time reduces to about 1.8 h. Figure 5 graphically summarizes a comparison between the continuous addition of 1.1 equivalents of TBHP, the addition of 1.0 equiv. at the beginning and 1.0 equivalents after 120 min, and the addition of 3.0 equivalents at the beginning. Obviously, continuous addition provides the best results

Substrate Scope

After the implementation of a sustainable system for the ruthenium catalyzed alcohol oxidation with cyclohexanol as the

Table 6. Oxidation of cyclohexanol to cyclohexanone with 2.0 or 1.0 equivalents of TBHP at the beginning and the addition of further 1.0 equivalents after 120 min.[a]

TBHP	yield [%] after							
at t = 0	15 min	30 min	1 h	2 h	4 h	6 h	8 h	24 h
2.0	47	50	56	61	90	92	96	99
1.0	41	45	47	50	87	92	94	97

[a] Cyclohexanol (1.0 mmol), $\mathrm{RuCl_3 \cdot (H_2O)}$ (0.5 mol-%) as a stock solution in water, TBHP (amount at the beginning as indicated, 1.0 further equivalents after 2 h), water/^{t}BuOH (1.0 mL, 1:1 v:v), r.t..

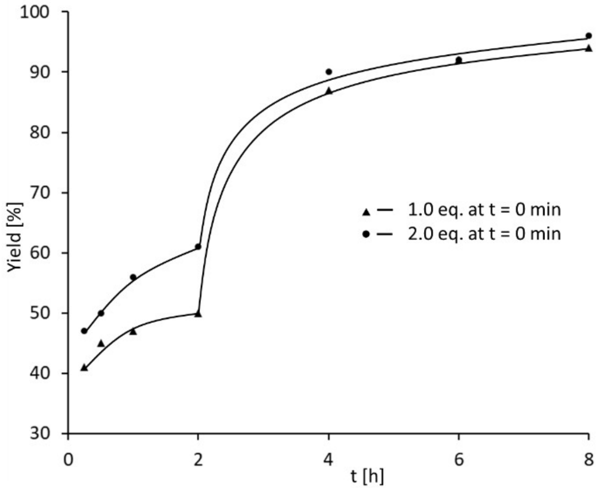

Figure 4. Oxidation of cyclohexanol to cyclohexanone with two or one equivalents of TBHP at the beginning and the addition of a further equivalents after 120 min; conditions as in Table 6.

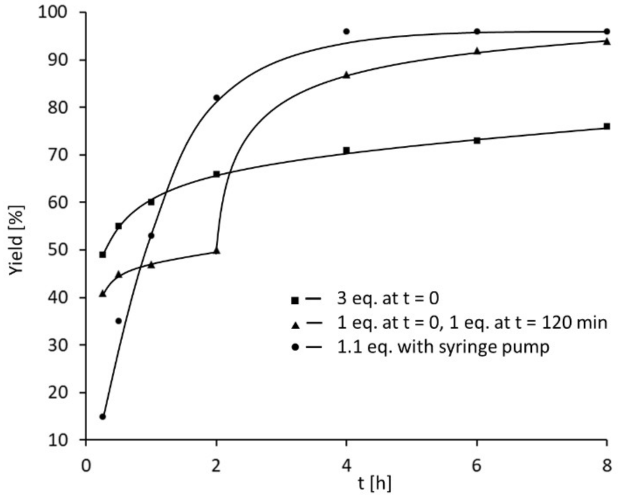

Figure 5. Oxidation of cyclohexanol to cyclohexanone with three different strategies of TBHP addition. Cyclohexanol (3.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, TBHP (as indicated in the inset), water/^{t}BuOH (1.0 mL, 1 : 1 v:v), r.t..

model substrate, the substrate scope of this strategy was worked out using a series of secondary and primary alcohols.

Initially, 2-phenylethanol and some of its derivatives were investigated with a particular focus on the influence of the substituents at the phenyl ring on the outcome of the reactions. The substrates were converted into the corresponding acetophenon derivatives under the reaction conditions optimized in the previous section. The corresponding data are summarized in Table 7 and Figure 6.

Table 7. Oxidation of various 1-phenylethanol derivatives to the corresponding carbonyl compounds.[a]

Subst.	Yield [%] after						
R	15 min	30 min	1 h	2 h	3 h	4 h	5 h
H	3	7	33	81	99	99	99
4-Cl	1	4	22	70	96	98	98
4-CH_3	2	4	26	80	99	99	99
4-OCH_3	1	2	18	48	82	98	99
2-Cl	1	5	13	32	49	54	56
2-CH_3	4	10	22	44	62	67	70

[a] Substrate (3.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, TBHP (1.1 eq., continuous addition at 0.25 $mL \cdot h^{-1}$), water/^{t}BuOH (1.0 mL, 1 : 1 v:v), r.t..

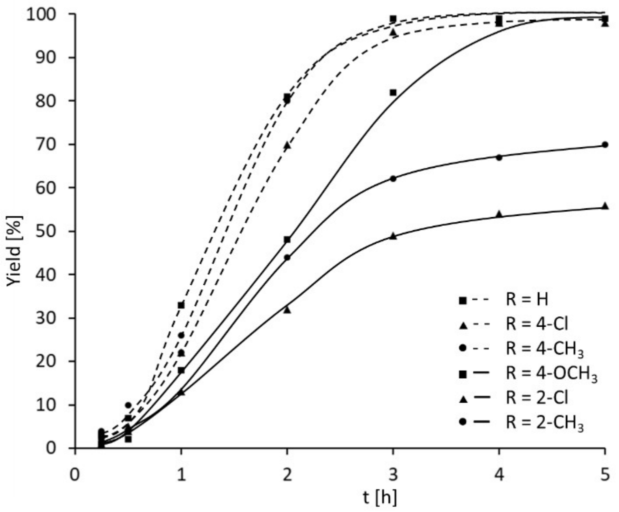

Figure 6. Oxidation of various 1-phenylethanol derivatives to the corresponding carbonyl compounds; conditions as in Table 7.

Obviously, steric effects dominate the rates of conversion. They are modulated by electronic effects. The *ortho*-substituted derivatives 2-chloro- and 2-methyl-1-phenylethanol are converted much slower than the *para*-substituted derivatives. Here, quantitative conversion is not feasible under the given reaction conditions, which means that the decomposition of TBHP seems to proceed at a rate that is comparable to the alcohol oxidation. To overcome this problem, an even slower addition of TBHP, an increase of the catalyst concentration or a variation of the reaction temperature might be suitable. The *para*-substituted derivatives and 1-phenylethanol are converted rather rapidly (comparable to cyclohexanol) mostly reaching quantitative conversion after 5 h. In addition, some electronic influence can be worked out. While 1-phenylethanol and 4-methyl-1-phenylethanol are converted rapidly with almost the same rate, the two derivatives possessing substituents with a +M effect are converted slower, in particular 4-methoxy-1-phenylethanol. 4-Methoxy-1-phenylethanol is an interesting case: Although its rate of conversion is comparable to that of 2-methyl-1-phenylethanol at the beginning of the reaction (up to approx. 2 h), almost quantitative yields of acetophenone are accessible, while the conversion of 2-methyl-1-phenylethanol stops at approx. 70 %. This speaks for some influence of the substrate on the parallel occurring decomposition of TBHP. 4-Methoxy-1-phenylethanol seems to be able to decrease the rate of the decomposition of TBHP, resulting in a longer-lasting and desired oxidation of the substrate.

1-(2-Naphtylethanol) was investigated as another secondary alcohol possessing an aromatic substituent. Here, a largely negative effect of the enlarged aromatic system was observed, since complete conversion could not be achieved. 70% yield of 2-acetylnaphthaline was accessible after 5 h of reaction. Again, it seems that the decomposition rate of TBHP is in the range of the rate of the oxidation reaction.

Cyclopentanol and cyclooctanol are secondary aliphatic alcohols and thus structurally rather similar to the model substrate cyclohexanol. Oxidation of these alcohols under the optimized reaction conditions gave cyclopentanone and cyclooctanone in 64 and 95% yield, respectively, after 3 h. As a result – presumably again due to the deactivation of TBHP – no complete conversion of cyclopentanol can be realized even after 24 h. The smaller ring seems to be harder to get oxidized, which can be attributed to the reduced intramolecular flexibility of the ring systems. The oxidation of an alcohol to a ketone leads to a change of the hybridization of the oxidized carbon atom from sp^3 to sp^2 resulting in a widening of the bond angles.[19] This is more difficult for the smaller five-membered ring.

Trans-1,4-cyclohexanediol was used to broaden the substrate spectrum to diols. Chelating diols such as 1,2-ethandiol have turned out not to be suitable substrates for this reaction. They are not converted to the corresponding carbonyl compounds at all, probably due to a chelating coordination to the catalyst (see discussion below). Complete oxidation of *trans*-1,4-cyclohexanediol would result in 1,4-cyclohexanedione with 4-hydroxycyclohexanone as an intermediate. The continuous addition of 2.2 equivalents of TBHP at a flow rate of $0.25\ mL \cdot h^{-1}$ (0.5 mol-% of $RuCl_3 \cdot (H_2O)$, 1.0 mL of water/^{t}BuOH) results in the formation of 65% of 4-hydroxycyclohexanone and 15% of 1,4-cyclohexanedione after 2 h at 60 °C. In the following 22 h, the yield of the intermediate decreases to 59% and the yield of 1,4-cyclohexanedione increases to 36%, as expected for a consecutive reaction.

2-Hexanol and 3-hexanol served as model substrates for the oxidation of secondary linear alcohols. From the obtained data it is clear that the new developed oxidation system seems to benefit from a cyclic substrate structure. The yields of the aliphatic hexanone derivatives increase considerably slower than the yields of cyclohexanone under identical conditions (continuous addition of 1.1 equivalents of TBHP). This allows for a stronger impact of the parallel TBHP deactivation and results in just 70–75 yields of the ketones after 5 h. As expected, there is not very much difference in the behavior of 2-hexanol and 3-hexanol. An explanation of the reduced reactivity of these linear substrates might be in the increase of flexibility of these molecules compared to cyclic aliphatic systems hindering the coordination to the ruthenium site to some extent.

Aldehydes are valuable substrates for a broad variety of chemical reactions.[20,21,22,23,24] Therefore, the new developed the oxidation system was also tested for primary alcohols with 1-octanol as the model alcohol. It however has to be mentioned at this point, that aldehydes are prone to consecutive oxidation reactions leading for example to the corresponding carboxylic acids.[23,24] As a deviation from the developed reaction conditions, the oxidation of 1-octanol was not carried out in the established water/*tert*-butanol mixture, but in pure *tert*-butanol to avoid a two-phase mixture. $RuCl_3 \cdot (H_2O)$ and TBHP were still added as aqueous solutions. In contrast to the substrates discussed before, conversion and yields do not match for the oxidation of 1-octanol (Table 8).

There is a clear difference of 20–30% between the conversions and the obtained yields, indicating the formation of by-products during the reaction. Examination of the recorded GC-FID data proves that these differences are not due to only one, but due to a larger number of by-products. Lowering the reaction temperature to 0 °C did result in a pronounced decrease of the reaction rate but the ratio of octanal formation vs. 1-octanol conversion did not change very much. Since 1,2-ethandiol cannot be oxidized with this system, the in-situ protection of octanal by acetal formation was investigated by addition of 1.0 or 1.5 equivalents of the diol to the reaction mixture. The conversion of 1-octanol is reduced drastically in these cases. However, side product formation also seems to be lowered. This result again speaks for a chelating coordination of the diol to the ruthenium site and in consequence for a pronounced lowering of its catalytic activity.

Figure 7 summarizes the products of the alcohol oxidation discussed in this manuscript and demonstrates the suitability of the newly developed TBHP-based oxidation system for a variety of substrates.

Conclusions

Starting from a cyclohexanol conversion of approx. 18% after 3 h in a catalytic mixture based on DMF as the solvent, a systematic optimization of the $RuCl_3 \cdot (H_2O)$ catalyzed alcohol oxidation with *tert*-butyl hydroperoxide as the oxidizing agent led a highly sustainable protocol. Hereby a water/*tert*-butanol mixture is applied and the consumption of TBHP is reduced to a minimum by continuous addition of the oxidizing agent with a syringe pump. This strategy avoids the decomposition of TBHP as long as the oxidation reaction is faster than the decomposition of the oxidizing agent. The protocol was optimized for cyclohexanol as the model substrate. It however is applicable for a broad variety of other substrates resulting in good yields of ketones and aldehydes. Nevertheless, there is still space for improvement! Conversions and yields of a series of substrates can for sure be further improved by individually tuning the

Table 8. Oxidation of 1-octanol to 1-octanal.[a]

at t	30 min	1 h	1.5 h	2 h	3 h	4 h	5 h
Yield [%]	9	24	31	35	48	47	54
Conversion [%]	20	40	53	58	75	77	80

[a] 1-Octanol (3.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, TBHP (1.1 eq., continuous addition at $0.25\ mL \cdot h^{-1}$), cyclohexanone (100 μL) as internal standard, ^{t}BuOH (3.0 mL), r.t..

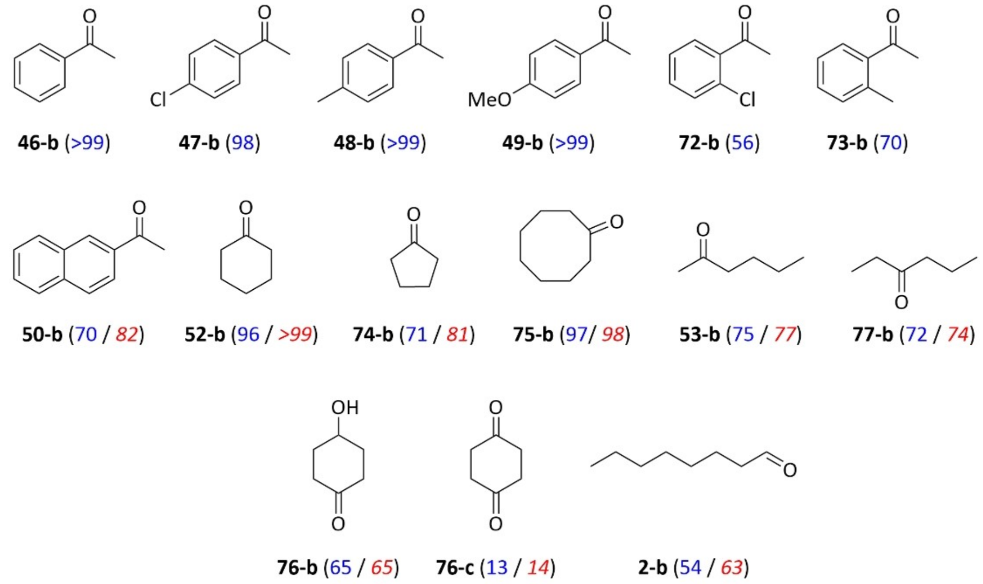

Figure 7. Overview of the oxidation products obtained using the TBHP-based oxidation system; yields after 5 h (blue) and 24 h (red); substrate (3.0 mmol), $RuCl_3 \cdot (H_2O)$ (0.5 mol-%) as a stock solution in water, TBHP (1.1 eq., continuous addition at 0.25 mL·h^{-1}), variations in the water/^{t}BuOH ratio and the reaction temperature as discussed above.

reaction conditions, for example by increasing the catalyst concentration, by the addition of more than 1.1 equivalents of TBHP or by optimizing the flow rate of the TBHP addition.

Experimental Section

The catalytic oxidation of alcohols was carried out in rolling rim tubes from VWR International (Radnor; USA) with a diameter of 2 cm and a capacity of 20 mL. The reaction tubes were equipped with a Teflon-covered magnetic stir bar before the solvent was added using syringes and cannulas from B. Braun. The substrate, internal standard and, if necessary, oxidant were then added by weighing in, in the case of solid components, or by volumetric measurement using a pipette from Eppendorf SE in the case of liquid components. The catalyst was added in the form of a stock solution of defined concentration using a pipette from Eppendorf SE before the reaction vessel was sealed with a Teflon-coated septum cap from VWR International. The reaction vessel was placed in an aluminium block tempered to reaction temperature. In the case of continuous oxidant addition, the oxidant was added by means of a syringe pump type "LA 30" from Bruno Kummer GmbH using syringes and cannulas from the B. Braun. After fixed time intervals, samples were taken using syringes and cannulas from B. Braun to study the catalytic activity. 0.05–0.1 mL of the reaction solution was filtered over a bed of magnesium sulphate and alumina and was eluted with a solvent adapted to the substrate. The resulting samples were analysed by gas chromatography or NMR spectroscopy.

Supporting Information

A Supporting Information for this manuscript is available.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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