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Efficient Aerobic Ruthenium-Catalyzed Oxidation of Secondary Alcohols by the Use of a Hybrid Electron Transfer Catalyst

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Biomimetic aerobic oxidation of secondary alcohols has been performed using hybrid catalyst 1 and Shvo's catalyst 2. This combination allows mild reaction conditions and low catalytic loading, due to the efficiency of intramolecular electron transfer. By this method a wide range of different alcohols have been converted into their corresponding ketones. Oxidation of benzylic as well as aliphatic, electron-rich, electron-deficient and sterically hindered alcohols could be oxidized in excellent yield and selectivity. Oxidation of (*S*)-1-phenylethanol showed that no racemization occurred during the course of the reaction, indicating that the hydride **2b** adds to the quinone much faster than it re-adds to the ketone product. The kinetic deuterium isotope effect of the oxidation was determined by the use of 1-phenylethanol (**3a**) and 1-deuterio-1-phenylethanol (**3a-d1**) in parallel and competitive manner, which gave the same isotope effect within experimental error ($k_H/k_D \approx 2.8$). This indicates that there is no strong coordination of the substrate to the catalyst.

Introduction

Selective oxidation of alcohols to carbonyl compounds with environmentally benign oxidants is of great importance, and numerous approaches have been explored successfully.[1,2] However, the development of cleaner and cheaper catalytic systems for the aerobic oxidation of alcohols is still highly attractive and challenging. In nature these oxidations involve selective electron-transfer processes, enabling them to occur under very mild reaction conditions. However, both in the pharmaceutical industry and in academic laboratories, the classic oxidation methods employing stoichiometric amounts of inorganic oxidants are still widely used.[3] Due to the increased demand for environmentally benign oxidation processes in organic chemistry, especially in large-scale synthesis, there is a growing interest to mimic biological transformations.[4] In the biomimetic approach one would employ a substrate-selective redox catalyst for the oxidation and then transfer the electrons of the reduced form of the redox catalyst to O_2 or H_2O_2. Reoxidation of the substrate-selective catalyst by direct interaction with molecular oxygen can occur[5,6] but is often difficult due to unfavored electron transfer between the catalyst and O_2. By mimicking nature's respiratory chain, and employing several coupled redox catalysts as electron transfer mediators (ETMs), this obstacle can be overcome.[4a]

During the past decade our group has designed and developed coupled catalytic electron-transfer systems used in allylic oxidation,[7] dihydroxylation of olefins,[8] Pd-catalyzed oxidative ene-allene carbocyclization,[9] 1,4-oxidation of conjugated dienes,[7,10] and Ru-catalyzed oxidation of alcohols[11] and amines.[12] However, efficient oxidation of secondary alcohols was found to require a high loading of 2,6-dimethoxy-1,4-benzoquinone (20 mol-%), which serves as an electron transfer mediator (ETM). There is a demand to make these reactions more efficient, and particular emphasis has been put on facilitating electron transfer from the alcohol to molecular oxygen.

Our research group has recently been able to significantly increase the efficiency of these reactions by covalently linking two ETMs into one catalyst, thus enhancing the rate of the electron transfer.[13] These new hybrid catalysts consist of a Schiff base unit with pendant hydroquinone groups and have been used to facilitate electron transfer in aerobic oxidations.[13a,13c] In this paper, we report on the use of hybrid catalyst **1** in the ruthenium-catalyzed oxidation of secondary alcohols, involving **2a** and **2b** (Scheme 1).

Results and Discussion

In our previous work on selective alcohol oxidation we employed a triple catalytic system with a low-valent ruthenium complex as the dehydrogenating catalyst.[11c] In the optimized version, this method required 20 mol-% loading

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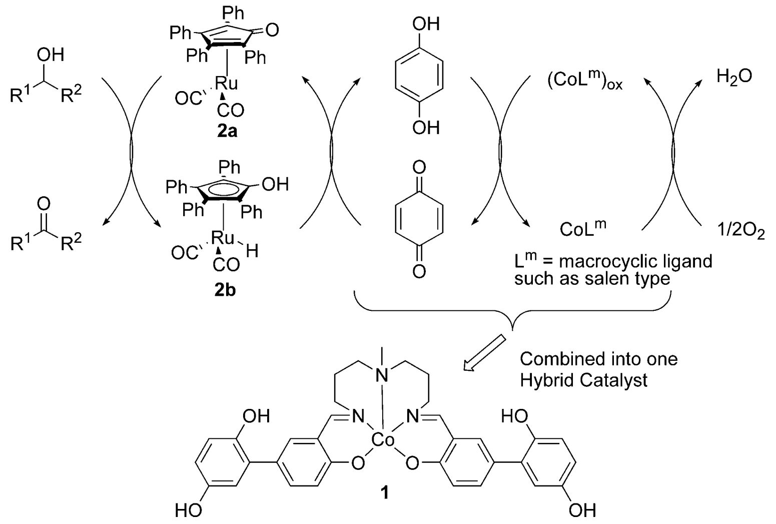
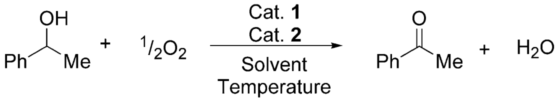
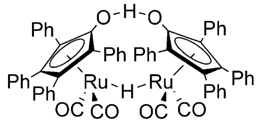


Scheme 1. In biomimetic aerobic oxidation the use of ETMs allows for low-energy electron transfer from substrate to molecular oxygen. Merging of two ETMs facilitates the electron transfer.

of 2,6-dimethoxy-1,4-benzoquinone as electron-transfer mediator and a temperature of 100 °C. The aim of the present work was to replace the separate hydroquinone and Schiff-base Co(salmdpt) by the hybrid catalyst **1** in aerobic oxidation of secondary alcohols. As in the previous study we chose binuclear ruthenium complex **2**[14] as the substrate-selective catalyst. We expected that with the new hybrid catalyst **1** the efficiency of intramolecular electron

Table 1. Ruthenium-catalyzed aerobic oxidation of 1-phenyletanol.[a]





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Entry	Catalyst [mol-%]	Solvent, temp.	Atmosphere	Time [h]	Conversion [%][b]
1	**2** (0.1%) **1** (1.0%)	neat, 65 °C	air	20	100
2	**2** (0.05%) **1** (1.0%)	neat, 65 °C	air	20	90
3	**2** (0.1%) **1** (1.0%)	neat, 75 °C	air	22	100
4	**2** (0.5%) **1** (1.0%)	neat, 75 °C	air	9	100
5	**2** (1.0%) **1** (3.0%)	toluene, 100 °C	air	20	62
6	**2** (1.0%) **1** (3.0%)	*o*-xylene, 100 °C	air	20	66
7	**2** (1.0%) **1** (3.0%)	sulfolane, 100 °C	air	20	86
8	**2** (0.5%) **1** (1.0%)	MeCN, 75 °C	air	10	100
9	**2** (0.1%) **1** (1.0%)	MeCN, 75 °C	air	20	85
10	**2** (1.0%) **1** (2%)	MeCN, 75 °C	O_2 5% in N_2	16	91
11	**2** (1.0%) **1** (2%)	MeCN, 75 °C	O_2	10	82

[a] All reactions were carried out on 2 mmol scale in 1 mL of solvent with the Shvo catalyst **2** and hybrid catalyst **1**. [b] . Conversions were determined by GC after filtration through a silica plug.

transfer would enable much lower catalytic loadings and milder reaction conditions.

Initially, the reaction was performed under solvent-free conditions, with promising results (Table 1, Entries 1–4). Solvent-free reactions have many advantages, such as reduction of waste and easy isolation of products. There are, however, some major drawbacks. Only substrates with low enough melting points can be used. The reaction also seems to be highly dependent on the solubility of the catalysts. Oxidation of aliphatic alcohols, such as cyclohexanol and 2-octanol, under solvent-free conditions gave very poor results, probably due to the low solubility of catalyst **2** in aliphatic alcohols.

To make the reaction more general, solvents were therefore included. A suitable solvent should be inert under the reaction conditions (i.e. no alcohols or ketones), be resistant to peroxide formation and other oxidative processes (i.e. no ethers or sulfoxides), have a high enough boiling point, and should dissolve both catalysts. Non-polar solvents, such as toluene or *o*-xylene, where the solubility of hybrid catalyst **1** is low, gave poor results (Table 1, Entries 5–6). Sulfolane dissolves catalyst **1** very well but not catalyst **2** and therefore poor results were obtained in that solvent (Table 1, Entry 7). Finally good results were obtained using acetonitrile, where both catalysts **1** and **2** are highly soluble (Table 1, Entries 8–11). Acetonitrile was thus chosen for further studies.

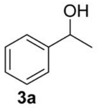
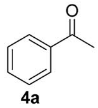
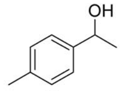
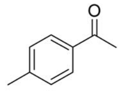
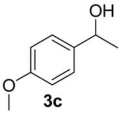
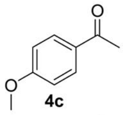
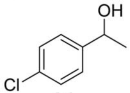
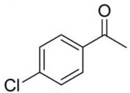
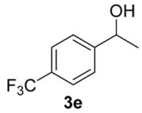
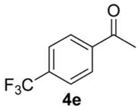
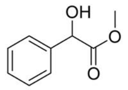
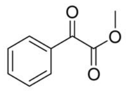
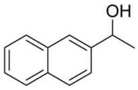
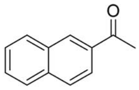
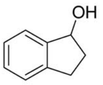
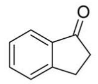
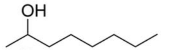
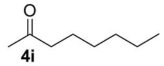
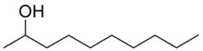
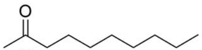
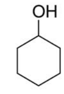
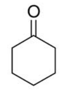
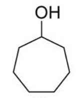
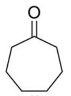
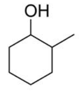
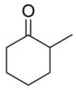
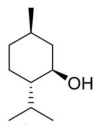
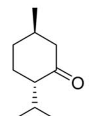
Some important advantages with the present system over the previous system[11c] are that the catalytic reaction tolerates a wider range of O_2 concentrations and does not require large amounts of additional quinone. In the previous method[11c] it was necessary to have a large excess of 2,6-dimethoxy-1,4-benzoquinone present to prevent the catalytic system from being deactivated. The hydroquinone and excess of quinone had to be removed by washing with NaOH, which is not suitable for base-sensitive products.

The new hybrid system can be run under neat O_2 without rapid deactivation, but is preferentially run under air. The oxidations were also performed at lower and higher oxygen concentrations using 5% O_2 in N_2, (Table 1, Entry 10) and under neat oxygen atmosphere (Entry 11). The conversion (monitored by GC) to the corresponding ketone was still high in both cases (> 80%), but the reactions were slower and never reached full conversion. One explanation of the lower conversions under these conditions could be that there is a less efficient reoxidation of catalyst **2** when the reaction is run under 5% O_2 in N_2, and a slight degradation of catalyst **2** when performing the reaction under neat oxygen.

Substrate Scope

To study the scope of the reaction, a variety of substrates were tested under the reaction conditions described above for the aerobic oxidation (from Entry 8, Table 1). From the results with the benzylic substrates (Table 2, Entries 1–8), we found that electron-donating groups such as a methoxy

Table 2. Ruthenium-catalyzed aerobic oxidation of secondary alcohols.

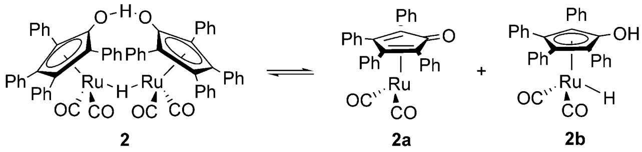
Entry	Substrate	Reaction time (h)	Product	Yield (%)
1	 **3a**	10	 **4a**	92
2	 **3b**	10	 **4b**	94
3	 **3c**	9	 **4c**	96
4	 **3d**	11	 **4d**	89
5	 **3e**	13	 **4e**	87
6	 **3f**	15	 **4f**	84
7	 **3g**	14	 **4g**	94
8	 **3h**	17	 **4h**	92
9	 **3i**	10	 **4i**	93
10	 **3j**	10	 **4j**	89
11	 **3k**	10	 **4k**	91
12	 **3l**	10	 **4l**	90
13	 **3m**	14	 **4m**	87
14	 **3n**	15	 **4n**	82

[a] The reactions were carried out on a 2 mmol scale with **2** (0.5 mol-%), hybrid catalyst **1** (1 mol-%) in MeCN (1 mL) at 75 °C under air. [b] Isolated yield of pure product.

group in the *para*-position, has a beneficial effect, while an electron-withdrawing group such as trifluoromethyl, leads to a slightly slower reaction. Sterically hindered alcohols such as menthol (Entry 14) were efficiently oxidized to ketones using this new ruthenium-catalyzed aerobic process. Also more resistant substrates, such as cyclic and linear aliphatic alcohols, can be oxidized with the current system in good to excellent yields. (Table 2, Entries 9–14). The previous system required 100 °C with 20 mol-% of the 2,6-dimethoxy-1,4-benzoquinone, with reaction times ranging from 1–3 h. These new aerobic oxidations are quite efficient and in most cases complete within 9–14 h at 75 °C. However, in the present system 1 mol-% of hybrid catalyst is employed, which is a much lower catalytic loading than the previous system. The loading of Ru-catalyst **2** is 0.5 mol-% in both the previous and present system.

Mechanistic Considerations

The ruthenium-catalyzed aerobic oxidation of alcohols with **2** as catalyst involves a highly efficient dehydrogenation step. Catalyst **2** is known to dissociate into **2a** and **2b** (Scheme 2). The former can act as a dehydrogenation species for alcohols, and the latter can hydrogenate ketones, C–C double bonds, and other unsaturated compounds. The principle for the biomimetic aerobic oxidation of alcohols with the coupled catalytic system is shown in Scheme 1. The dehydrogenation of the alcohol with **2a** produces the ketone and **2b**. This reaction is known to be reversible, and in the absence of a stoichiometric oxidant, re-addition of hydrogen to the ketone leads to racemization of enantiomerically enriched alcohols. Re-oxidation of **2b** to **2a** occurs by transfer of hydrogen from **2b** to the benzoquione moiety of the oxidized form of hybrid catalyst **1**, thus forming **2a** and the reduced hydroquinone form of **1**, which in turn is reoxidized by molecular oxygen.



Scheme 2. The Shvo catalyst **2** and its proposed dissociation.

To gain some insight into the mechanism the kinetic deuterium isotope effect of the oxidation was determined by the use of 1-phenylethanol (**3a**) and 1-deuterio-1-phenylethanol (**3a-d$_1$**), with the conditions described above in Table 2. The oxidations of **3a** and **3a-d$_1$** were run in two parallel reactions and the conversion of each reaction was determined by GC. This gave a primary kinetic isotope effect $k_H/k_D = 2.83 \pm 0.30$, determined from initial rates (Figure 1). The isotope effect was also determined in a competitive experiment, by the use of a 1:1 mixture of **3a** and one with **3a-d$_1$** (see Supporting Information). The decay of both substrates were monitored by GC/MS giving a primary kinetic isotope effect $k_H/k_D = 2.89 \pm 0.40$, which is within experimental error the same deuterium isotope effect as that determined in the parallel experiment. This shows that there is no strong coordination of the substrate to the catalyst.[15]

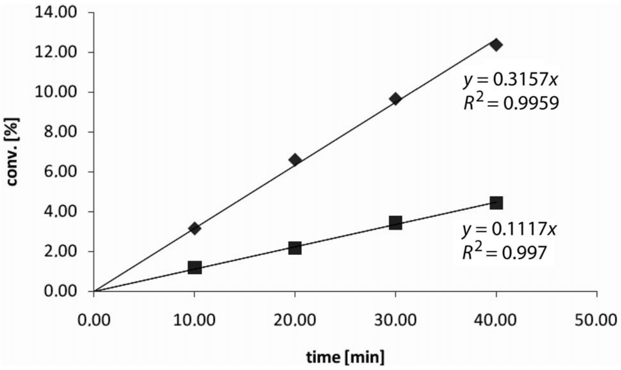


Figure 1. Reaction profiles as a function of time using ruthenium-catalyzed aerobic oxidation system measured in a non-competitive manner. Filled diamonds: 1-phenylethanol (**3a**), filled squares: 1-deuterio-1-phenylethanol (**3a-d$_1$**) $k_H/k_D = 2.83$.

To obtain information about the relative rates between dehydrogenation of the alcohol **3a**, hydrogenation of the product ketone **4a**, and hydrogenation of benzoquinone in the hybrid catalyst **1** (**Q-1**) an experiment was performed using enantiomerically pure (*S*)-1-phenylethanol [(*S*)-**3a**] in the oxidation described above in Table 2. An interesting question is whether racemization of (*S*)-**3a** occurs during the oxidation, i.e. if the reversible reduction of ketone **4a** by **2b** (k_{-1}) is faster than reaction of **2b** with **Q-1** (k_2); see Equations (1) and (2).

$$\mathbf{3a} + \mathbf{2a} \; \overset{k_1}{\underset{k_{-1}}{\rightleftarrows}} \; \mathbf{4a} + \mathbf{2b} \qquad (1)$$

$$\mathbf{2b} + \mathbf{Q\text{-}1} \xrightarrow{k_2} \mathbf{2a} + \mathbf{HQ\text{-}1} \qquad (2)$$

Monitoring by chiral GC showed that no racemization of (*S*)-**3a** [i.e. no formation of the (*R*)-enantiomer] occurred during the course of the reaction. This shows that the hydride **2b** adds to the quinone much faster than it adds to ketone **4a**. (k_2[Q-**1**] > k_{-1}[**4a**]). Thus the quinone unit of the hybrid catalyst reacts very fast with the hydride **2b** and hence $k_2 >> k_{-1}$. The present data do not allow any conclusions concerning the relative rates of dehydrogenation (k_1[**3a**][**2a**]) and hydrogen transfer to the quinone in **1** (k_2[**2b**][**Q-1**]). The observed isotope effect of $k_H/k_D \approx 2.8$ is consistent with a rate-determining dehydrogenation since it has been previously shown that the isotope effect for dehydrogenation of 1-(*p*-fluorophenyl)ethanol by **2a** is 2.57.[16]

Decreased catalytic loading of hybrid catalyst **1** led to a significant drop in reaction rate and product yield, which suggests that Equation (2) becomes rate-determining at very low concentrations of **1**. Very low concentrations of **1** are deleterious because efficient reoxidation of **2b** into **2a** seems to be necessary to avoid decomposition of catalyst **2** into inactive ruthenium species. We could also see that the rate of the reaction was heavily dependent on the solubility of both catalysts. Control experiments further showed that no aerobic oxidation took place according to GC within 24 h if one of the components of the catalytic system was removed.

Conclusions

We have developed an efficient catalytic process for the biomimetic aerobic oxidation of secondary alcohols that tolerates a wide range of substrates. The oxidation of benzylic alcohols as well as aliphatic alcohols can be performed. Electron-rich, electron-deficient and sterically hindered alcohols can be oxidized to the corresponding ketones in high yield and selectivity by this methodology. The deuterium isotope effect was determined by the use of 1-deuterio-1-phenylethanol. Due to the efficiency of intramolecular electron transfer, hybrid catalyst **1** allows for a lower catalytic loading and milder reaction conditions compared to the use of the separate quinone and Co(salmdpt) triple catalytic system.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were obtained with a 400 MHz spectrometer using $[D_1]$chloroform (δ = 7.26 ppm ^{1}H, 77 ppm ^{13}C) as internal standard and were in good agreement with the data previously reported in the literature.[9d] Analytical gas chromatography was performed with a Varian 3800 GC with a FID detector, connected to a Varian computing integrator. A 30-m CP-CHIRASIL-DEX CB fused silica column was used. Ruthenium catalyst **2** was prepared according to a literature procedure.[17] The hybrid catalysts **1** was prepared according to a new method developed in our laboratory.[13b] Compound **3a-d$_1$** was prepared according to a literature procedure.[18] All other reagents are commercially available and were used without further purification. Column chromatography was performed with DAVISIL LC60A silica gel and analytical TLC was performed on Merck precoated silica 60-F$_{254}$ plates. Solvents for extraction and chromatography were of analytical grade.

General Procedure for Ruthenium-Catalyzed Aerobic Oxidation of Secondary Alcohols 3a–e. Oxidation of 3a to 4a: Ruthenium complex **2** (11 mg, 0.01 mmol) and hybrid catalyst **1** (12.5 mg, 0.02 mmol) were mixed and stirred in acetonitrile (1 mL). Compound **3a** (244 mg, 2 mmol) was added to the resulting solution whilst stirring at 75 °C in a closed vessel under air atmosphere with an oxygen replacement balloon connected to the reaction vessel via a 5 cm long syringe (diameter 1.2 mm). After the appropriate reaction time, the mixture was cooled to room temperature, the solvent was removed by rotary evaporation and then purified by flash chromatography (pentane/diethyl ether, 9:1). All the products obtained, shown in Table 2, are known compounds and were characterized by comparison with spectroscopic data from the literature.

General Procedure for the Kinetic Experiments: Ruthenium complex **2** (11 mg, 0.01 mmol) and hybrid catalyst **1** (12.5 mg, 0.02 mmol) were mixed and stirred in acetonitrile (1 mL). Compound **3a** (244 mg, 2 mmol) was added to the resulting solution whilst stirring at 75 °C in air with an oxygen replacement balloon. Aliquots were taken every 10 min for the first 40 min. The aliquots were passed through a pad of silica using EtOAc as eluent, which quenched the reaction by removal of the catalyst. Reactions were run in a parallel as well in a competitive manner. The resulting solutions were analyzed by GC (CP Chirasil DEXCB) in the case of the parallel experiments. Samples from the competitive runs were analyzed by GC/MS.

Supporting Information (see also the footnote on the first page of this article): Kinetic plots and reaction profiles.

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