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RuO_4-Catalyzed Ketohydroxylation of Olefins

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Abstract: A new mild method for the oxidation of a variety of olefins to α-hydroxy ketones is described. Using the concept of a nucleophilic reoxidant, different olefins were ketohydroxylated with high regioselectivity in good to excellent yields.

Alkenes are useful starting materials for a variety of transformations in organic synthesis.[1] The formation of olefins with both defined stereochemistry and substitution pattern can be achieved by the classical olefination of carbonyl compounds or by metal-catalyzed cross-coupling[2] or metathesis reactions[3] established over the past few years. Further elaborations often imply the addition of heteroatoms across the π-bond. Among these, oxidation reactions belong to the most important transformations. The most likely pericyclic nature of the stereoinducing step in both asymmetric dihydroxylation[4] and epoxidation[5] is responsible for a direct translation of the π-bond geometry to the relative stereochemistry of the newly formed chiral centers. Despite the great success of these two oxidation reactions it is surprising to find that the direct oxidation of double bonds to α-hydroxy ketones has rarely been investigated.[6]

Development of RuO_4-Catalyzed Ketohydroxylation. Highly oxidized transition metals are the focus of our current research. RuO_4 (**I**) is isoelectronic to OsO_4, and hence, during the course of the reaction with olefins, ruthenate esters **III** and **V** are formed.[7] A concomitant hydrolysis (i.e., the nucleophilic attack of water at the metal center) of these cyclic esters leads to *syn*-diols. We envisioned these compounds to be more than just reactive intermediates. Our working model is based upon the idea to use a reagent capable of functioning as both a nucleophile and reoxidant (Figure 1). It could open a new mechanistic pathway leading to α-hydroxy-ketones **VI**. The reaction would combine the advantages of the [2 + 3]-cycloaddition (stereoinducing step) of **I** toward an olefin **II** and, after the nucleophilic addition, of the intrinsic peroxide substructure in metallo ester **V** (Figure 1). Since the stereocenter in **V** has already been established, the oxidative fragmentation should not corrupt the stereochemical outcome of the reaction. However, the mechanism of the fragmentation remains unclear. Apart from a β-hydride elimination pathway from **V** and subsequent reaction of the resulting Ru−H species with the liberated acyloin anion, an internal deprotonation of the carbinol carbon by the alkoxide substructure could lead to the formation of **I**, SO_4^{2-} and ketol **VI**.

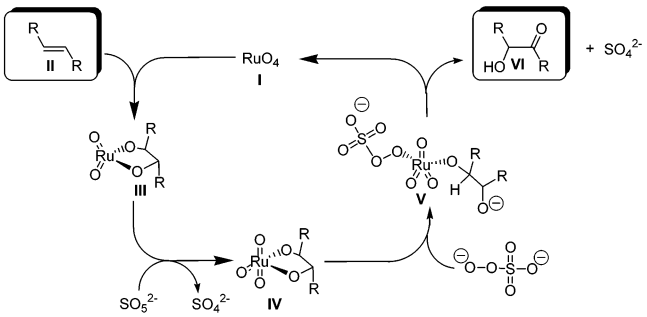

FIGURE 1. Proposed mechanism of Ru-catalyzed ketohydroxylation.

Different reoxidants that would match our criteria of a "nucleophilic reoxidant" have been investigated. Some representative results are listed in Table 1. Neither of the common oxidation systems gave significant conversion or high chemoselectivity. However, Oxone under strictly buffered conditions turned out to be the reoxidant of choice (Table 1).

The combination of Oxone and $RuCl_3$ in the presence of $NaHCO_3$ (5 equiv) has been used for the oxidative cleavage of double bonds.[8,9] To force the reaction into our desired direction we increased the amount of Oxone to 5 equiv in combination with a decrease in the amount of water. Thus, we suppressed a competing hydrolysis of the ruthenate ester and favored the postulated nucleophilic addition of SO_5^{2-}. A dramatic influence of base on

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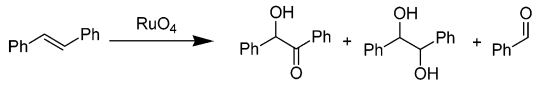
TABLE 1. Development of the Ketohydroxylation; Part I, Influence of Reoxidant



1 2 3 4

reoxidant[a]	time	conversion [%][b]	2 [%][c]	3 [%][c]	4 [%][c]
t-BuOOH, Et_4NOH	1 d	30	17	5	78
H_2O_2, Et_4NOH	1 d	12	nd	nd	nd
NaOCl	60 min	60	15	10	75
Oxone, $NaHCO_3$[d]	10 min	80	66	23	11

[a] All reactions were performed on a 2 mmol scale in a solvent mixture of ethyl acetate (12 mL)/acetonitrile (12 mL)/water (2 mL) at room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water) and 5 equiv of reoxidant. [b] Determined by GC integration. [c] Percentage refers to the amount of product in the mixture. [d] 1.5 equiv of $NaHCO_3$ was used.

TABLE 2. Development of the Ketohydroxylation; Part II, Influence of Base Concentration

$NaHCO_3$[a] [equiv]	time [min]	conversion [%][b]	2 [%][c]	3 [%][c]	4 [%][c]
1	30	38	62	5	33
2.5	10	96	98	0	2
5	60	86	21	6	73

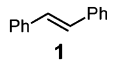
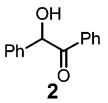
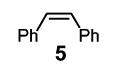
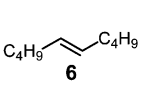
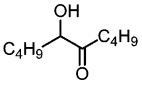
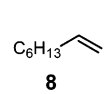
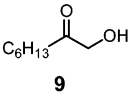
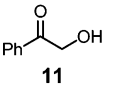
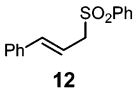
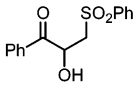
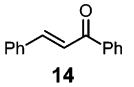
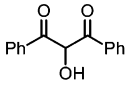
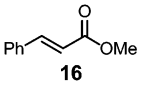
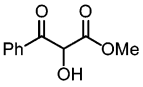
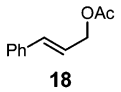
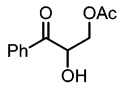
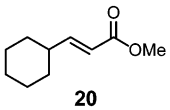
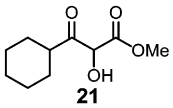
[a] All reactions were performed under the conditions listed in Table 1 employing 5 equiv of Oxone. [b] Determined by GC integration. [c] Percentage refers to the amount of product in the mixture.

the course of the reaction was observed. When we increased the amount of $NaHCO_3$, the oxidative cleavage is strongly favored (Table 2); different reasons could account for this finding. The $NaHCO_3$ could function as a buffer, thus maintaining the pH throughout the reaction slightly acidic. UV-spectroscopic analysis proved the formation of RuO_4 under the given reaction conditions. However, the identification of the catalytically active species and the influence of the pH on the course of the reaction awaits further investigations. With the optimum conditions in hand we were able to selectively ketohydroxylate *trans*-stilbene **1** to ketol **2** in 94% isolated yield.

Scope and Limitations. We turned our attention toward an intense screening of scope and limitations. We were pleased to find that a variety of olefins are ketohydroxylated in high yields and high regioselectivity. Scission products or *syn*-diols are formed in minor amounts (less than 10%) and can easily be removed by column chromatography. Moreover, the formation of these side products can be further reduced by variation of the amount of water and base. Although the reaction medium is slightly acidic, esters are not hydrolyzed. Furthermore, the reaction times for the full conversion of *trans*-olefin **1** and the corresponding *cis*-isomer **5** into ketol **2** were the same, indicating that in contrast to the osmylation reactions the RuO_4-catalyzed [2 + 3]-cycloaddition is very fast independent of the olefin geometry. In general electron-rich substrates are ketohydroxylated much faster than electron-poor starting materials. The results are summarized in Table 3.

With respect to a future development of an asymmetric version it is important to note that enantiopure ketol **2** did not epimerize under the reaction conditions. The enantiomeric excess was checked before and after 12 h of stirring at room temperature, and no decrease in the enantiomeric excess was observed. The results of these experiments and a detailed investigation regarding the reaction scope, functional group tolerance, and diastereoselectivity will be published separately soon.

TABLE 3. Ketohydroxylation of Olefins

substrate[a]	product	time [min]	yield [%][b]
 1	 2	10	94
 5		10	91
 6	 7	10	87
 8	 9	10	64
 10	 11	10	66
 12	 13	20	84
 14	 15	60	54
 16	 17	30	76
 18	 19	30	51
 20	 21	30	82

[a] All reaction were performed under the conditions listed in Table 1 employing 5 equiv of Oxone and 2.5 equiv of $NaHCO_3$. [b] Isolated yield.

The high regioselectivity in the oxidation of nonsymmetrical olefins is remarkable. We were not able to detect any regioisomeric products from the crude mixture. Different explanations can be used to rationalize the regiochemistry; however, the mechanism remains unclear at this point of our research and awaits further investigation. Apart from the one-step mechanism involving a nucleophilic addition of SO_5^{2-} to the metal center (Figure 1) an alternative mechanistic scenario could involve a two-step process of *syn*-dihydroxylation and concomitant mono oxidation of the resulting diol. To get a first insight into the mechanism and the role of our reoxidant, we performed two separate control experiments in which *trans*-stilbene (**1**) and hydrobenzoin (**3**) were treated with RuO_4 under the reaction conditions mentioned above (Scheme 1).

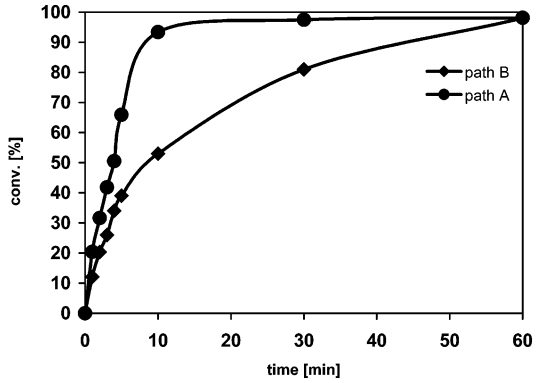
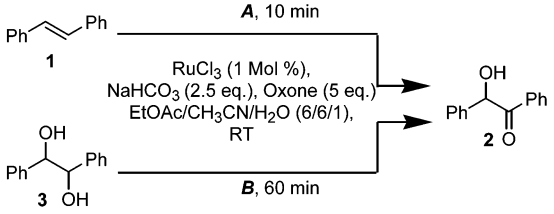


FIGURE 2. Conversion−time graph for oxidation of **1** (path A) and **3** (path B).

SCHEME 1. Oxidation of Hydrobenzoin 3 and *trans*-Stilbene 1



If the overall oxidation occurs in two steps, the reaction of hydrobenzoin (**3**) as part of the process should be faster than the transformation of *trans*-stilbene (**1**). This option can be ruled out, because the ketohydroxylation of **1** is significantly faster than the mono oxidation of **3**.

In summary, we developed a new direct and mild ketohydroxylation of olefins under Ru(VIII)-catalysis. First results indicate that the products are obtained in one step without formation of an intermediate *syn*-diol. A variety of olefins can be oxidized regioselectively to α-hydroxy-ketones in good to excellent yields. Further investigation on the scope and limitations, the diastereoselectivity, and the mechanism awaits further investigations. On the basis of these results the development of an asymmetric version should be possible.

Experimental Section

General Remarks. Petroleum ether refers to that fraction boiling in the range 35−60 °C. HPLC-grade acetonitrile was purchased commercially, and ethyl acetate was purified by distillation over $CaCl_2$ prior to use. $RuCl_3$ was obtained commercially . A stock solution was prepared calculating with $RuCl_3$-$(H_2O)_2$ and dissolving the catalyst (2.44 g, 10 mmol) in 100 mL of water (0.1 M). The deep brown solution can be stored on the bench for weeks without loss of activity. Literature-known compounds **2**,[10] **7**,[6g] **9**,[11] **11**,[12] **15**,[13] **17**,[14] and **19**[15] were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data and comparison of these data with the literature reports.

General Procedure for Ketohydroxylation. A 100-mL round-bottomed flask equipped with magnetic stirring bar and overpressure valve was charged with $NaHCO_3$ (420 mg, 5 mmol). A 0.1 M aqueous solution of $RuCl_3$ (200 μL, 0.02 mmol) was added, and the suspension was diluted with 2 mL of H_2O, 12 mL of CH_3CN, and 12 mL of ethyl acetate. Oxone (6.1 g, 10 mmol) was added in one portion to the resulting brownish suspension (**gas evolution**). When the color turned bright yellow, the olefin (2 mmol) was added in one portion. The reaction was followed by TLC. After complete conversion the mixture was poured onto 30 mL of saturated $NaHCO_3$ and 30 mL of saturated Na_2SO_3 solution. Phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). After drying of the combined organic layer over Na_2SO_4 and evaporation of the solvent in a vacuum, the oily crude product was purified by flash chromatography.

2-Hydroxy-1-phenyl-3-(phenylsulfonyl)propan-1-one (13). Yellow solid; mp 78 °C; R_f (pentane/ethyl acetate (5:1)) 0.59; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, 4*H*), 6.56−7.67 (m, 6*H*), 5.60 (dd, J = 9.7, 1.6 Hz, 1*H*), 3.57 (dd, J = 14.8, 1.6 Hz, 1*H*), 3.29 (dd, J = 14.8, 9.7 Hz, 1*H*), 2.95 (s, 1*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 236.3, 197.4, 139.6, 134.9, 134.2, 132.3, 129.4, 129.1, 128.5, 68.7, 61.2; MS (GC−MS) *m*/*z* 141 (4) [$C_6H_5SO_2$], 122 (84), 105 (100) [C_6H_5CO], 77 (65), 51 (34); IR (KBr) ν 3451 (br), 3064 (m), 1694 (s), 1692 (s), 1310 (s), 1151 (m), 1024 (m), 737 (m); HRMS calcd for [$C_{15}H_{14}O_4S$ + H] 291.0691, found 291.0697. Anal. Calcd for $C_{15}H_{14}O_4S$ (290.06): C, 62.05; H, 4.86. Found: C, 62.12; H, 4.82.

3-Cyclohexyl-2-hydroxy-3-oxo-propionic Acid Methyl Ester (21). Colorless oil; R_f (pentane/ethyl acetate (3:1)) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1*H*), 3.78 (s, 3*H*), 2.77 (m, 1*H*), 1.61−1.83 (m, 5*H*), 1.22−1.45 (m, 5*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 169.0, 76.3, 53.2, 46.6, 29.3, 27.7, 25.6; MS (GC−MS) *m*/*z* 201 (71) [M^+ + H], 183 (28) [M^+ + H − H_2O], 83 (71) [$C_6H_{11}^+$], 55 (100); IR (film) ν 3448 (br), 2933 (s), 2856 (s), 1749 (s), 1717 (s), 1450 (m), 1242 (m); HRMS calcd for [$C_{10}H_{16}O_4$ + H] 201.1127, found 201.1125. Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C, 59.98; H, 8.05. Found: C, 59.92; H, 8.11.

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Supporting Information Available: Text giving detailed experimental procedures, including analytical and spectroscopic data for compounds **2**,[10] **7**,[6g] **9**,[11] **11**,[12] **15**,[13] **17**,[14] **19**[15]. This material is available free of charge via the Internet at http://pubs.acs.org.

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