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An Improved Protocol for the RuO_4-Catalyzed Dihydroxylation of Olefins

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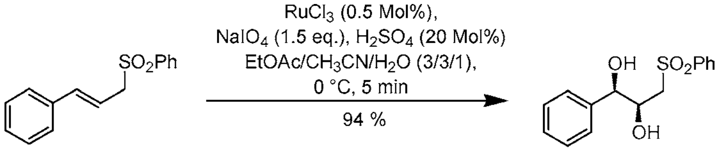
ABSTRACT



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Dihydroxylation under ruthenium catalysis provides an easy access to *syn*-diols, although overoxidation is a common side reaction. Furthermore, the high catalyst loadings offset the lower price of ruthenium compared to osmium. In this paper, we present an improved protocol for the RuO_4-catalyzed *syn*-dihydroxylation using only 0.5 mol % catalyst under acidic conditions. A variety of olefins can be hydroxylated in good to excellent yields with only minor formation of side products.

Transition-metal-catalyzed oxidations of C,C-double bonds have been a major topic in chemical research for more than 30 years.[1] As a result, they have become one of the most commonly used transformations in organic synthesis. Among these reactions, the osmium-catalyzed dihydroxylation in its asymmetric version represents a benchmark when it comes to generality and selectivity.[2] Despite its success, some problems still need to be solved. The oxidation is limited to electron-rich or mono-, di-, and in some cases, trisubstituted olefins.[3] Furthermore, the osmium catalyst is toxic and very expensive. Alternative oxidants have been described for this reaction; however, RuO_4, as a dihydroxylation catalyst, is most promising.[4] In 1954, Djerassi introduced RuO_4 in organic chemistry.[5] Since then, it has mainly been used for the degradation of unsaturated organic compounds.[6] However, in ethyl acetate/acetonitrile/water a very fast dihydroxylation of olefins using 7 mol % of RuO_4 was observed.[4] Longer reaction times resulted in the formation of fission products.

During the course of our studies on the stability of ruthenate esters, we became interested in the RuO_4-catalyzed dihydroxylation reaction. The hydrolysis of these cyclic esters plays a key role in our attempts to develop new oxidation reactions. Based on literature results and our own investigations, we envisioned the intermediate ruthenates to be responsible for the oxidative fragmentation. Three different scenarios could lead to the formation of fission products. First, an electrocyclic C,C-bond cleavage in either **III** or **V**

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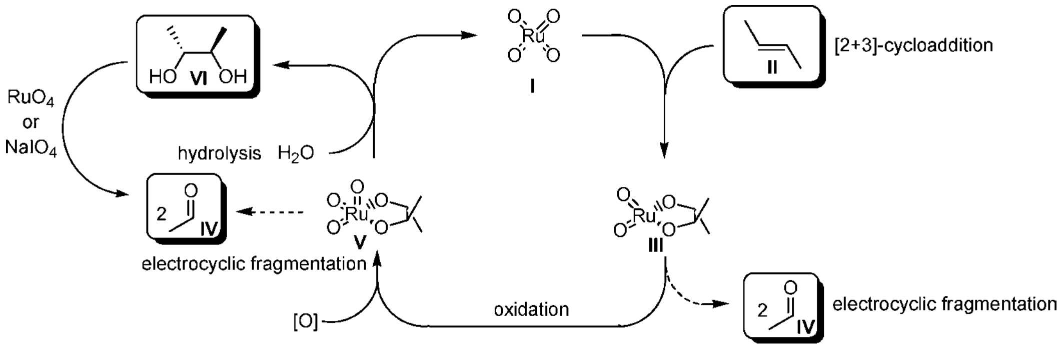
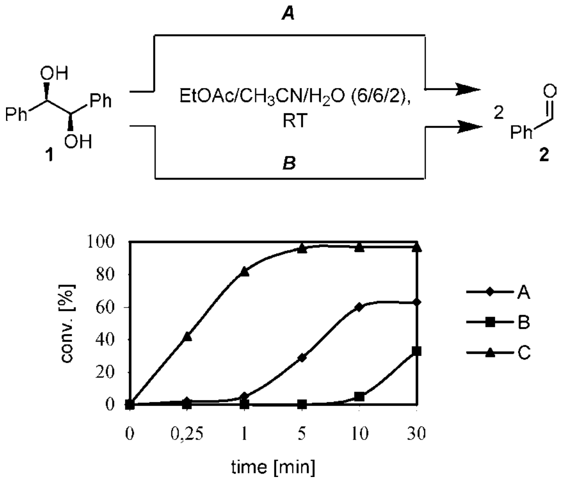


Figure 1. Proposed mechanism for formation of fission products.

could account for the formation of aldehyde **IV**. Second, RuO_4 **I** itself could react with the *vic*-diol **VI** in a condensation followed by an electrocyclic fragmentation. Finally, the reoxidant $NaIO_4$ itself could act as a cleavage reagent (Figure 1).

The latter two cases were simulated in a control experiment. Hydrobenzoin (**1**) was treated under the standard reaction conditions[4] with either $RuCl_3/NaIO_4$ (path **A**) or $NaIO_4$ (path **B**, Scheme 1). The rate in the dihydroxylation of *trans*-stilbene is shown for comparison.

Scheme 1. RuO_4 and $NaIO_4$-Mediated Glycol Cleavage of Hydrobenzoin **1**[a]



[a] Key: (A) $RuCl_3$ (3.5 mol %)/$NaIO_4$; (B) $NaIO_4$; (C) dihydroxylation of *trans*-stilbene with $RuCl_3$ (3.5 mol %)/$NaIO_4$

After an induction period of about 3 min, the formation of fission products in the presence of $RuCl_3$ was observed, whereas the reaction in the absence of $RuCl_3$ started after almost 10 min. However, both reactions were slow on the time scale of the dihydoxylation, which occurred in seconds to minutes. Scheme 1 visualizes the difference in reaction rates for both RuO_4- (**A**) and $NaIO_4$-assisted (**B**) glycol cleavage. Importantly, both conversions stopped after some time indicating that a further oxidation of the resulting aldehyde **2** to benzoic acid is faster than the glycol cleavage. Carboxylic acids are known to inhibit the catalyst activity probably due to a stabilization of the intermediate ruthenium species.[7] The difference in the reaction rates confirms the hypothesis of ruthenate ester **III** and **V** being responsible for the formation of fission products. Apparently, the electrocyclic fragmentation of both **III** and **V** is too fast compared to the hydrolysis. Thus, we sought a method to speed up the hydrolysis of the metallo esters.

Different approaches toward a faster hydrolysis of ruthenate ester **V** were investigated in detail. An intense solvent screening confirmed a mixture of ethyl acetate/acetonitrile/water (3/3/1) to be the optimum for the reaction. Higher temperatures favor the formation of fission products. Since a variation in these reaction parameters did not show an improvement in the selectivity, the influence of additives known to assist an ester hydrolysis was investigated. In contrast to osmium-catalyzed oxidations, the addition of base or methane sulfonamide[3] did not improve the selectivity for the dihydroxylated product. However, addition of a catalytic amount of acid accelerated the reaction. Because of this acceleration, we were able to lower the catalyst concentration to 0.5 mol % (from originally 7 mol %).[4,8] Different protic acids were used in a preliminary screening (Table 1). Whereas carboxylic acids had a minor influence on both selectivity and yield, the addition of 5 mol % sulfuric acid improved the conversion significantly while maintaining the selectivity.

A strong influence of the concentration on the conversion was observed in the dihydroxylation of methyl cinnamate (**3**) under conditions listed in Table 1 (Figure 2). A linear dependence between conversion and concentration of acid was observed. However, with regard to scope and limitation, a further increase of the amount of acid did not seem appropriate. Therefore, further optimizations were performed using 20 mol % sulfuric acid.

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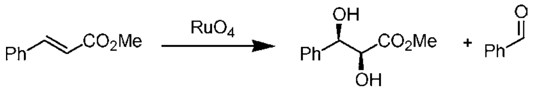
Table 1. Effect of Acid on the Dihydroxylation



3 4 2

acid[a]	**4**/**2**[b]	yield[c] (%)
–	74:26	47
HOAc	70:30	46
TFA	79:21	52
H_2SO_4	79:21	71
HCl	77:23	53
$MeSO_3H$	78:22	63
p-TosOH	76:23	61

[a] All reactions were performed within 5 min on a 2 mmol scale in a solvent mixture of ethyl acetate (12 mL)/acetonitrile (12 mL)/water (4 mL) at room temperature using 0.5 mol % $RuCl_3$ (as a 0.1 M solution in water) and 5 mol % acid (as a 1 M solution in water). [b] Determined by GC integration of the crude product. [c] Isolated yield of diol **4**.

An alternative way of lowering the pH value without adding more acid is a reduction of the total amount of solvent. Thus, increasing the substrate concentration from originally 0.07 to 0.14 M by dividing the solvent amount by a factor of 2 resulted in a fast and clean reaction. The influence of added acid was reinvestigated at this point. The oxidation of olefin **3** in the absence of acid led to the formation of fission product **2** and only minor amounts of diol **4**.

Having in hand the optimized conditions, we turned our attention to a first investigation on scope and limitation (Table 2).

The acidic conditions are compatible with a variety of functional groups. Esters **3**, **7**, and **15** are not hydrolyzed. The conversion of azide **5** is highly attractive since the concomitant reduction would lead to amino alcohols. However, due to the acidic conditions some limitations exist. Silyl ethers are cleaved in the presence of sulfuric acid, whereas the corresponding acetates are not hydrolyzed. Highly substituted and electron-poor substrates do not give satisfying conversions. Hence, to oxidize these substrates a further intense screening of acids is required.[7]

The mechanistic rationale shown in Scheme 2 can be used in order to explain the experimental observations. Hence, protonation of ruthenate ester **V** would lead to a highly electrophilic intermediate reacting with water as the nucleophile.

The present paper describes the beneficial influence of protic acids in ruthenium-catalyzed dihydroxylations of

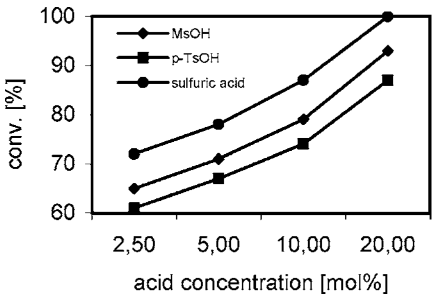
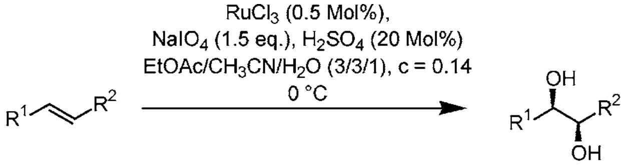
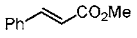
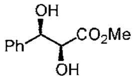
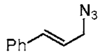
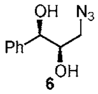
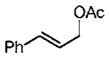
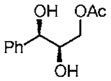
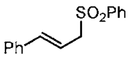
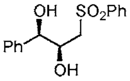
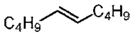
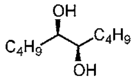
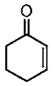
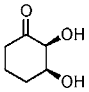
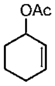
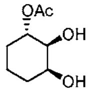


Figure 2. Effect of acid concentration on the conversion.

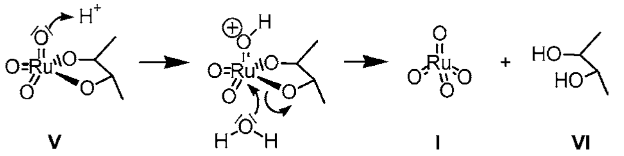
Table 2. Dihydroxylation of Olefins



substrate[a]	product	time [min]	yield [%][b]
 3	 4	2	84
 5	 6	2	65
 7	 8	3	78
 9	 10	5	94
 11	 12	2	91
 13	 14	5	69
 15	 16 *ds*: 94 %[c]	3	75

[a] All reactions were run on a 2 mmol scale in a solvent mixture of ethyl acetate (6 mL)/acetonitrile (6 mL)/water (2 mL) at 0 °C using 0.5 mol % $RuCl_3$ (as a 0.1 M solution in water) and 20 mol % sulfuric acid (as a 2 N solution in water). [b] Isolated yield. [c] Determined by GC integration.

Scheme 2. Acid-Accelerated Hydrolysis: A Mechanistic Proposal



olefins. In the presence of 20 mol % sulfuric acid, we were able to decrease the amount of catalyst from originally 7 mol % to only 0.5 mol % without loss of activity.[9] The reaction is very fast and clean. A variety of olefins were oxidized in good to excellent isolated yields. This reaction represents an efficient less toxic alternative to the dihydroxylation using osmium or manganese reagents. We are currently working toward an extensive investigation on scope and limitation as well as an asymmetric version of this reaction.

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Supporting Information Available: Experimental procedures and analytical data including NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] **General Procedure.** $NaIO_4$ (642 mg, 3 mmol) was stirred in 1.5 mL of H_2O and 2 N H_2SO_4 (400 μL, 0.4 mmol). After all solids were dissolved, the solution was cooled to 0 °C. A 0.1 M solution of $RuCl_3$ (100 μL, 0.01 mmol) was added, and the mixture was stirred until the color turned bright yellow. Ethyl acetate (6 mL) and acetonitrile (6 mL) were added. Stirring was continued for a further 5 min. The olefin (2 mmol) was added, and the slurry was stirred until all starting material was consumed. The mixture was poured onto 15 mL of saturated $NaHCO_3$ solution and 20 mL of saturated $Na_2S_2O_3$ solution. Phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). After the combined organic layer was dried over Na_2SO_4 and the solvent evaporated in a vacuum, the crude product was purified by flash chromatography.