Oxidation of Alcohols by Hydrogen Peroxide, Catalyzed by Methyltrioxorhenium (MTO): A Hydride Abstraction

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Primary and secondary alcohols are oxidized using hydrogen peroxide as an oxygen donor and methyltrioxorhenium (MTO) as a catalyst. The methylrhenium di-peroxide, $CH_3Re(O)(\eta_2-O_2)_2(H_2O)$, was the dominant and reactive form of the catalyst. Representative rate constants k/L mol^{-1} s^{-1} are 1.02×10^{-4} for 4-Me-α-methylbenzyl alcohol and 4.9×10^{-5} for 4-Cl-α-methylbenzyl alcohol. There was a kinetic isotope effect of 3.2 for the α C−H bond. When *sec*-phenethyl alcohol was labeled with ^{18}O, 80% of the oxygen was retained in the ketone. Tests for the possible intervention of a free radical intermediate were carried out; the evidence was entirely negative. A mechanism featuring hydride abstraction is proposed, the first time for the H_2O_2/MTO system. Also, a cocatalytic set of reaction conditions has been developed on the synthetic scale, using bromide and MTO as cocatalysts, which cuts the reaction time from hours to minutes.

Introduction

The selective oxidation of C−H bonds has always been a challenging task. Typical of this is the oxidation of alcohols to aldehydes or ketones. Usually only the strongest oxidizing agents, such as $KMnO_4$, Br_2, MnO_2, SeO_2, RuO_4, and acid dichromate can perform this reaction.[1] Only a few of these reagents have been used in a catalytic system; one example is SeO_2.[2] It has recently been shown that methyltrioxorhenium (CH_3ReO_3, or MTO) can catalyze reactions of hydrogen peroxide with alcohols.[3]

Hydrogen peroxide, used with a catalytic amount of MTO, has been shown to oxidize catalytically a variety of substrates besides alcohols, such as sulfides,[4] alkenes,[5,6] amines,[7,8] hydroxylamines,[9] and halides.[10,11] The mechanisms of these oxidations follow a general pathway where the substrate acts as a nucleophile and attacks an electron-poor peroxorhenium oxygen.

The previous study of alcohol oxidations by MTO and H_2O_2 focused on the synthetic aspects of the catalytic system.[3] We were intrigued by these oxidations since the alcohol, unlike other substrates oxidized by this combination, has no center of electron density to act as a nucleophile, nor does it have a site to which an oxygen atom can be easily transferred. Anticipating a new mechanism of oxidation for the catalyst MTO, we undertook a study of the oxidation of alcohols by MTO and hydrogen peroxide.

Experimental Section

Materials. Hydrogen peroxide and HPLC grade solvents were purchased from Fisher. Water was purified by distillation and then filtered by a Milli-Q water purification system. The various alcohols, ketones, and aldehydes were purchased either from Aldrich or Lancaster and used as received. The 10% ^{18}O-labeled water and MTO were purchased from Aldrich. 1-Phenylethanol (1,2,2,2-D$_4$, 98%) was purchased from Cambridge Isotope Laboratories. The methyl (1-phenyl)ethyl ether was made by a standard literature procedure.[12]

The products of alcohol oxidation were identified using various methods. ^{1}H NMR spectra were recorded using Varian VXR 300 MHz NMR or Bruker DRX 400 MHz NMR spectrometers, mass spectra were obtained using a Finnigan TSQ 700 GC−MS, and the UV−vis spectra were determined using Shimadzu 2501 or 3101 spectrophotometers.

Kinetics. The experiments were carried out in 20% water/acetonitrile containing 0.1 M $HClO_4$. This solvent mixture was chosen for solubility reasons and because the kinetics and thermodynamics of the H_2O_2/MTO system are known under these conditions. The reactions were monitored by the absorbance rise in the region of 240−255 nm, due to the formation of the carbonyl product. The reactions were carried out in a quartz cuvette under air, since there was no effect upon saturating the solutions with air or argon. Because of the large molar absorptivities of the products ($\epsilon \sim 1 \times 10^4$ L cm^{-1} mol^{-1}) and the background from hydrogen peroxide and MTO, a 0.01 cm path length cell from Spectrocell was used throughout the study. Reactant stock solutions were made fresh daily. A typical reaction procedure is as follows: 10−50 mM MTO, 200 mM H_2O_2, and 0.10 M $HClO_4$ were mixed together in the cell and allowed to stand for 1−2 min to allow the complete formation of the catalytically active peroxorhenium compounds; 20−50 mM of neat alcohol was added at this point and the solution mixed thoroughly (~25 s). Data acquisition was then started, and the reaction was kept at a constant temperature of 25 °C.

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The reactions were typically monitored until 1−2% of the alcohol had reacted, since over longer periods of time the catalyst is susceptible to decomposition. The absorbance versus time data were analyzed by the initial rate method. To do so, the absorbance traces were first converted to concentrations based on the molar absorptivities of the alcohols and products determined from authentic samples. The concentrations varied linearly with time over the time frame; the data were fit by a linear least-squares analysis using the computer program KaleidaGraph.

Oxygen Labeling. An [18]O isotope labeling experiment was carried out with *sec*-phenethyl alcohol. The 10% labeled alcohol was synthesized by the standard literature preparation[13] from acetophenone mixed with 10% [18]O water and a catalytic amount of acid. After 16 h, the labeled acetophenone was isolated and reduced using sodium borohydride. The resulting alcohol was then purified and stored in a desiccator.

In a typical labeling experiment a reaction solution contained 30 mM of 10% ^{18}O-labeled alcohol, 25−30 mM MTO, and ~200 mM urea hydrogen peroxide (UHP) in acetonitrile. Not all of the UHP was dissolved, but enough was dissolved to ensure that the dominant form of the catalyst was the diperoxorhenium compound, determined by observation of its characteristic 360 nm absorption. UHP was used in these experiments to limit the amount of ^{16}O-bearing water in the reaction solution.

All of the gas chromatography−mass spectrometry experiments were performed using a Finnigan TSQ 700. The system was configured in the electron impact ionization mode. The first quadrupole was used as the analyzer to scan from m/z 35 to m/z 400 at 0.5 s/scan. The second and third quadrupoles were kept in the RF-only mode. Unit mass resolution was achieved using FC43 as calibration and tuning reference. A DB1701 gas column was used for all experiments. This allowed the ketone to flow through the column first, and any tailing of the larger alcohol peak was not a worry. This was a concern lest tailing from the alcohol peak, were it first off the column (as was the case when a DB5 gas column was used), may overlap with the ketone peak. The ratio of labeled to unlabeled compounds was determined by the ratio of mass to charge peaks for both the alcohol and ketone with each injection by taking an average of three mass spectral scans at the maximum of the GC peak and subtracting a background scan. This allowed direct comparison of the starting alcohol labeling and the product ketone, eliminating any variations the instrument might have from day to day. Each data point was the average of three injections, and each reaction was carried out two or three times.

Synthetic Scale Reactions. These reactions were carried out on the 2.5 mmol alcohol scale. A typical procedure is as follows: 4 mol % MTO and 2 equiv of 30% H_2O_2 were combined. The alcohol was then added and the biphasic mixture stirred at 40 ± 2 °C for 1 day. No acid was added, to avoid acid-catalyzed byproducts. Periodically, the NMR spectrum of an aliquot taken from the organic layer was obtained in chloroform-*d* to monitor the progress of the reaction.

Other synthetic scale reactions were carried out using Br⁻ as a cocatalyst with MTO. These reactions were performed with an equal volume of acetonitrile as compared to H_2O_2 and alcohol added, which rendered the reaction mixture homogeneous. The 1.1 equiv of H_2O_2 was added by syringe pump infusion to limit the amount of peroxide decomposition by bromide species in the solution. For these reactions 4.0 mol % of HBr and 0.50

Scheme 1
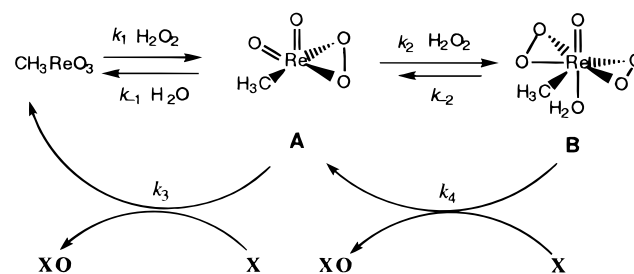
mol % of MTO (relative to the alcohol) were used as the catalysts with addition of hydrogen peroxide over 30−45 min.

Results

The Catalyst. MTO can reversibly coordinate one or two hydrogen peroxides to yield the corresponding mono- and diperoxorhenium complexes **A** and **B,** as shown in Scheme 1. Without a substrate present MTO, **A**, and **B** will reach equilibrium concentrations governed by $[H_2O_2]$ and the values of K_1 $(=k_1/k_{-1})$ and K_2 $(=k_2/k_{-2})$, the equilibrium constants. The same does not hold true during a catalytic reaction cycle where steady-state conditions apply. With the oxidation of a substrate at rates defined by the second-order rate constants k_3 and k_4 and the concentration of substrate, the steady-state concentrations of the various rhenium complexes will be obtained.

With such a number of reactions possible it proved difficult to determine the steady-state concentration of each rhenium complex during the reaction. For example, when the rates of oxidation are faster than the rates of reformation of **A** or **B**, then after a few catalytic cycles the major form of the catalyst will be MTO, with the rate-determining step being the formation of **A**. On the other hand, when the rates of oxidation are slow compared to the formation of **A** or **B**, then the dominant form of the catalyst during the reaction will be **B** at high $[H_2O_2]$. With alcohols the rate of oxidation is much slower than the rate of reformation of the oxidizing species **B** from **A**, leading to a well-behaved catalytic system.

Reaction Kinetics. It has been shown that the initial rate method can be applied to catalytic MTO oxidations.[9] Owing to the long reaction times for alcohol oxidations (typically $t_{1/2} \sim$ 30 h) and the slow decomposition of the catalyst, the initial rate method was employed. For these reactions MTO and H_2O_2 were equilibrated before addition of the alcohol. With the high concentration of H_2O_2 used (0.2−0.3 M), the predominant form of the catalyst will be **B** in accord with the assumption that $[\mathbf{B}] \cong [\text{Re}]_T = [\text{MTO}] + [\mathbf{A}] + [\mathbf{B}]$, which will hold throughout the reaction. This treatment allows the determination of the bimolecular rate constant k_4 for the reaction of **B** with an alcohol as written in eq 1, expressed by the rate law, eq 2, written in terms of initial rates.[14]

$$\mathbf{B} + R_2CHOH \xrightarrow{k_4} \mathbf{A} + R_2CO + H_2O \tag{1}$$

$$v_i = k_4[\mathbf{B}][R_2CHOH]_0 \cong k_4[\text{Re}]_T[R_2CHOH]_0 \tag{2}$$

Based on eqs 1 and 2 a plot was made of the initial rates versus the product $[\text{Re}]_T \times [R_2CHOH]_0$. According to eq 2, the values of v_i should define a straight line that passes through the origin with the slope equal to k_4. The data for 4-Me-α-

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Table 1. Rate Constants and Yields for the Catalytic Oxidation of Alcohols

entry no.	alcohol	$10^5 \times k_4$/L mol^{-1} s^{-1} ^{a}	% yield on synthetic scale^b		% conversion
1	4-Me-α-methylbenzyl alcohol	10.2	84	92	93
2^c	4-MeO-α-methylbenzyl alcohol	8.85			
3	*sec*-phenethyl alcohol	7.7	89	97	98
4	1-phenyl-1-propanol	6.8	69	92	93
5	4-F-α-methylbenzyl alcohol	6.2	91	99	99
6	(R)−(+)−2-methyl-1-phenyl-1-propanol	5.5	64	86	87
7	benzyl alcohol^d	5.3	41 (7)^e	40 (12)	54
			28 (21)	16 (38)	55
8	benzhydrol	5.0	46	48	49
9	4-Cl-α-methylbenzyl alcohol	4.9	84	95	96
10	4-(CF$_3$)-α-methylbenzyl alcohol	4.4	60	85	85
11	1-phenylethanol-1,2,2,2,-D$_4$	2.4			
12	4-Br-α-methylbenzyl alcohol	2.3	58	64	64
13	methyl (1-phenyl)ethyl ether	2.3	22	53	53
14	1-cyclohexylethanol		74	92	93
15	4-phenyl-2-butanol		58	61	64
16	1-phenyl-2-propanol		26	27	30

^{a} Determined in 20% water/acetonitrile, 0.10 M HClO$_4$, at 25 °C. ^{b} Neat alcohol, 2 molar equiv H$_2$O$_2$, 4 mol % MTO, 40 °C. The first column is the yield after 8 h, the second after 24 h, based on NMR integrations. ^{c} 4-MeO gave a number of products, which were not identified; entry 11 was not carried out on a synthetic scale owing to a shortage of the starting material. ^{d} The top entry is with 1 equiv of H$_2$O$_2$; the bottom entry is with 2 equiv. ^{e} The first value refers to benzaldehyde, the parenthetic one to benzoic acid.
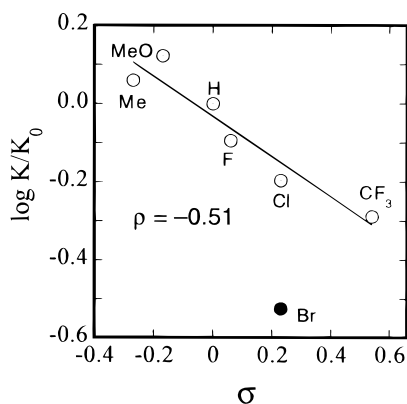

Figure 1. Linear free energy relationship between the rate constant for the oxidation of 4-X-α-methylbenzyl alcohols by MTO and H$_2$O$_2$ and the Hammett σ constant for X.[27] K_0 is defined as X = H. The deviant X = Br point was left out of the ρ calculation. The ρ value of −0.51 describes the effect that electron-donating and -withdrawing groups have on the transition state.

methylbenzyl alcohol are displayed in Figure S-1, Supporting Information. The least-squares slope of the line gives the value $k_4 = 1.02 \times 10^{-4}$ L mol^{-1} s^{-1} (25 °C, in 20% water/acetonitrile, 0.1 M HClO$_4$). The rate constant k_4 determined for each alcohol is listed in Table 1. The spread of rate constants is not large, all being within a factor of 5. Included in this study was the oxidation of methyl (1-phenyl)ethyl ether. This compound has the lowest rate constant of all compounds; it reacts 3.3 times more slowly than the analogous alcohol, *sec*-phenethyl alcohol, entries 3 and 13. The k_4 rate constants could not be determined accurately for some alcohols, but these substrates were also listed to show the widespread applicability of the MTO/H$_2$O$_2$ oxidations.

A linear free energy relationship plot was made of the para-substituted α-methylbenzyl alcohols as shown in Figure 1. From this plot the slope ρ = −0.51 was determined. The negative ρ value implies that electron-donating groups increase the reaction rate, while electron-withdrawing groups decrease the rate. This agrees well with an oxidation mechanism in which the rhenium peroxo-oxygen performs an electrophilic attack on the C−H bond. One of the seven substrates used to make the LFER plot did not react as expected. 4-Bromo-α-methylbenzyl alcohol has a rate constant that is approximately half of the expected value.

The alcohol sample was pure by ^{1}H NMR. We have no explanation for this deviation at this time, but we note that this compound also gave a low product yield (see later).

Isotopic Labeling. A number of reactions were performed using 10% ^{18}O-labeled *sec*-phenethyl alcohol. When it was treated with MTO/UHP, it was found by GC−MS monitoring that $80 \pm 5\%$ of the labeled oxygen remains in the ketone. UHP was used for these experiments to limit the amount of added water, thus minimizing oxygen exchange between the ketone and solvent. When 30% aqueous H$_2$O$_2$ was used, there was significant exchange of the labeled ketone with the solvent oxygens. Even without added acid, when MTO decomposes, it forms perrhenic acid, which will catalyze exchange. With UHP as the oxygen donor the control experiments gave no detectable exchange of the labeled ketone over 24 h. Multiple trials were performed and the reactions were monitored over time to verify that the ketone did not exchange its oxygen during the oxidation experiment. A deuterium kinetic isotope study was performed using 1-phenylethanol (1,1,1,2-D$_4$). As shown in Table 1, entries 3 and 11, the k_H/k_D ratio is 3.2.

Radical Mechanism Possibilities. Another strong oxidizing compound, dimethyldioxirane (DMDO), can also oxidize alcohols.[15] The mechanism of C−H bond activation by DMDO has been investigated by a number of groups.[16−19] The intermediate in DMDO oxidations can be described as a biradical trapped within a solvent cage. Under different conditions the radical nature of this intermediate can be exploited. MTO has been compared to DMDO in the past for alkene oxidations;[6] therefore a radical intermediate for MTO oxidations was examined. We first tested whether O$_2$ affects the reaction rates. For reactions carried out under an air or argon atmosphere, no difference in the rate of the reactions was noted. Another test for radicals was to add freshly distilled BrCCl$_3$.[17] The reaction rate was not changed when 25−50 mM BrCCl$_3$ was added. (No halogenated product was checked for since such a product would rapidly lose HBr to form the ketone.) Other radical trapping agents such

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as Tempo could not be used for this reaction, because the oxidations were performed under acidic conditions. From these negative results we conclude that radical reactions are not significant in the mechanism of these reactions. The basis for this is that BrCCl$_3$ is so reactive toward carbon-centered radicals that they would certainly have trapped any in competition with any radical self-reaction.

Phase-Transfer Reactions. The slow rates of oxidation for the various alcohols necessarily mean that long reaction times are required to reach completion. Recently, it was reported that the oxidation of alcohols occurs with WO$_4{}^{2-}$ and H$_2$O$_2$ under "solvent-free" conditions.[20] That study used neat alcohol and dissolved the catalyst in 30% H$_2$O$_2$ while using a phase-transfer catalyst (PTC) to assist in WO$_4{}^{2-}$ transportation between the phases. Since MTO is soluble in many organic solvents, no PTC would be needed were MTO used under similar reaction conditions.

Synthetic preparations of ketones were carried out on the neat alcohol. Typically 2.5 mmol of the alcohol was used with 5 mmol of hydrogen peroxide as a 30% solution and 4 mol % MTO. The reactions were stirred at 40 °C for 1 day, and then the yields were determined by NMR as found in Table 1. As seen in Table 1 many of the yields are often better than 80%. This is a great improvement over the previous report of alcohol oxidations by MTO/H$_2$O$_2$ (<30% yield, 19 mol % catalyst[3]). The temperature of 40 °C was chosen instead of the previously used 60 °C, to avoid MTO decomposition at higher temperatures.[21] At 40 °C the decomposition of MTO is less, allowing good yields of the product while shortening the reaction times. The reactions were monitored for up to 24 h, but as seen in the table most of the reactions were almost complete after only 8 h. The percent conversion is also listed in the table, demonstrating the low amounts of byproducts in these reactions.

An interesting point is the oxidation of a primary alcohol beyond the aldehyde to the carboxylic acid. When 2 equiv of hydrogen peroxide was used to oxidize benzyl alcohol, not only was benzaldehyde made but a large portion was further oxidized to benzoic acid (21%). When 1 equiv of hydrogen peroxide was used, the product ratio became 40% benzaldehyde, 7% benzoic acid. Most of the α-phenyl alcohols were oxidized in good yields in reference to large-scale reactions. The only two exceptions were the 4-bromo-α-phenylethanol and the 4-methoxy-α-phenylethanol. The reason for the decreased yield for the 4-bromo could be due to the slower rate of reaction than expected as seen in the LFER plot, while the 4-methoxy compound gave a number of products that were not characterized. The non-α-phenyl alcohols varied in amounts of yields from 27% for 1-phenyl-2-propanol to 92% for 1-cyclohexylethanol.

Cocatalysts: MTO and Br. Synthetic scale reactions can be made more environmentally friendly by limiting the number and types of side products. Another goal is for the reactions to be halide-free. We have accomplished this by using nonhalogenated solvents and nonhalogenated oxidizing agents. Now that the oxidation of alcohols by MTO/H$_2$O$_2$ has been defined, we have explored shortening the reaction time by adding bromide as a cocatalyst.

Previously, MTO/H$_2$O$_2$ has been shown to oxidize catalytically Br$^-$ to BrO$^-$,[10] which can form Br$_2$ when in the presence of another Br$^-$ and H$^+$.[22] It is also known that Br$_2$ can oxidize
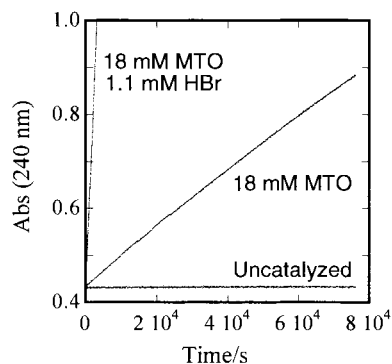

Figure 2. Increase in absorbance at 240 nm accompanying the buildup of the ketone from the reaction of *sec*-phenethyl alcohol and hydrogen peroxide in 20% water/acetonitrile containing 0.10 M HClO$_4$. Without a catalyst the reaction is nonexistent, while adding MTO or HBr and MTO increases the rate of the reaction to different extents.

alcohols.[23] When HBr was added as a cocatalyst for the oxidation of alcohols, the reaction is significantly faster, as seen in Figure 2. This figure demonstrates that the uncatalyzed reaction of the alcohol with hydrogen peroxide is almost nonexistent. When MTO (0.5 molar equiv) is added, the reaction becomes faster. However, if HBr is added as well (2 mol %), the reaction is much faster. Also if the reaction is done on a synthetic scale, 99% of the ketone can be achieved in just minutes, instead of hours without HBr.

There is a competing decomposition of hydrogen peroxide by BrO$^-$ or Br$_2$.[24] Even when hydrogen peroxide is initially added to 5 times excess over the alcohol, it was necessary to add more hydrogen peroxide to oxidize all of the alcohol in this cocatalytic system. If the hydrogen peroxide is added dropwise though, only 10% excess was needed for the reaction to reach completion.

Discussion

Oxidation Mechanism. As stated earlier the oxidation of alcohols by MTO and hydrogen peroxide must proceed by a different mechanism than has been determined for other substrates such as sulfides, alkenes, and hydroxylamines. All of these previous compounds had a center of electron density to which an oxygen atom can be transferred. Scheme 2 best describes the oxidation of alcohols by MTO/H$_2$O$_2$ based on our observations. This mechanism shows the formation of an intermediate in which there are interactions between the peroxorhenium oxygen with both the carbon and the hydrogen of the α C−H bond. This is typically how a hydride abstraction is depicted. The assignment of this mechanism is supported but not defined by the kinetic isotope effect k_H/k_D of 3.2. The electron-poor oxygen performs an electrophilic attack on the electron density of the C−H bond. On the basis of our observations there is no radical intermediate.

This intermediate can then proceed along two pathways in parallel. The major path is followed when the C−H bond is severed, after which the carbocation loses a proton to produce the ketone. This proton could be lost either to the solvent or to the other peroxorhenium oxygen to give a di-hydroxo rhenium product, which rapidly eliminates water to give **A**. The di-hydroxo rhenium species has not been isolated, but is not unreasonable in that MTO oxygens are known to exchange with

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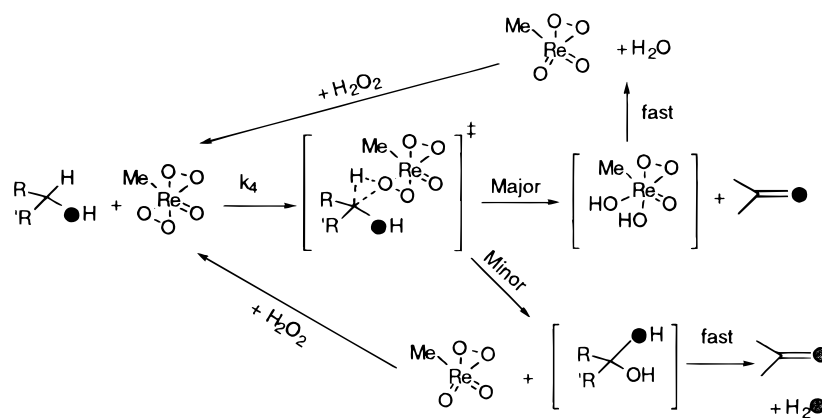(21) Jacob, J.; Espenson, J. H. Unpublished results.
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Scheme 2

those of water, through a similar di-hydroxo rhenium form.[25] This major pathway is further supported by the retention of labeled oxygen in the ketone. These events are depicted in Scheme 2.

The minor pathway is proposed to account for the 20% of labeled oxygen that does not remain in the product and to account for the fact that the methyl ether can be oxidized as well. With the rate constants for the ether and the respective alcohol agreeing within a factor of 4, the mechanism for oxidation of both must be somewhat similar. The difference between the major and minor pathway is where the di-hydroxy group resides when the intermediate breaks apart. Since the active oxidizing form of MTO has capabilities similar to those of DMDO, there appear to be similarities between the rhenium center of MTO and the carbon center of DMDO. The pathway with the di-hydroxo rhenium product is preferred in our mechanism over the carbon gem-diol product, showing that the two centers are not truly identical.

Listed in Table 1 are the substrates oxidized by MTO/H_2O_2 in this study. A LFER plot of the para-substituted α-methyl-benzyl alcohols demonstrates the effect of electronic variations. If an electron-donating group is at the para position, the reaction becomes faster, and vice versa. This also supports a hydride abstraction mechanism. It can also be noticed that steric factors play a role in the rate of the reaction based on the difference in yields for the various non-α-phenyl alcohols. The yields start at 92% for cyclohexylethanol and decrease with additional steric

bulk to 27% for 1-phenyl-2-butanol. A last point of interest is that a primary alcohol (e.g., benzyl alcohol) was oxidized not only to the aldehyde with excess peroxide to the carboxylic acid as well. This second oxidation can be limited by the amount of peroxide added, since the two steps have quite different rate constants, $k_{alc} > k_{ald}$.

Synthetic Considerations. This study has produced a new synthetic scale preparation of ketones from alcohols in good yields. The yields are somewhat dependent on the starting alcohol, with the majority being above 80%. Further, the use of bromide cocatalyst decreased the reaction times by a factor of at least 1000 with decreased reaction temperatures. We feel that this cocatalytic system[26] has great potential.

Supporting Information Available: Figure of kinetic data for oxidation of 4-Me-phenethyl alcohol by hydrogen peroxide, catalyzed by MTO (1 page). Ordering information is given on any current masthead page.

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