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# Epoxidation of Alkenes with $H_2O_2$ Catalyzed by Dititanium-Containing 19-Tungstodiarsenate(III): Experimental and Theoretical Studies

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**Keywords:** Polyoxometalates / Titanium / Epoxidation / Density functional calculations / Hydrogen peroxide

Epoxidation of a range of alkenes with aqueous $H_2O_2$ easily proceeds in the presence of the dititanium-containing 19-tungstodiarsenate(III) $[Ti_2(OH)_2As_2W_{19}O_{67}(H_2O)]^{8-}$ (**1**), which contains five-coordinate Ti atoms. The results of product and kinetics studies support a mechanism that involves a reversible interaction between $H_2O_2$ and the Ti–OH group of **1** to produce a titanium hydroperoxo complex followed by electrophilic oxygen atom transfer from the hydroperoxo ligand to the alkene substrate in the rate-limiting step. The effect of the alkene substrate nature has been investigated at the DFT level. A clear correlation between the energy of $\pi_{C=C}$ orbitals in the alkene and the turnover frequency values has been found, thereby indicating that the higher nucleophilicity of the alkene, the higher the reactivity. ONIOM (ONIOM = our own *n*-layered integrated molecular orbital and molecular mechanics) calculations have been employed to evaluate the role of steric effects of alkene substituents. The calculations show that the steric bulk can play a secondary role and tunes the activity in specific cases such as *trans*-stilbene.

## Introduction

Alkene epoxidation is one of the basic reactions in industrial organic synthesis.[1] Epoxides are among the most versatile synthetic intermediates for a wide variety of valuable products, and much effort is devoted to the development of new active and selective epoxidation catalysts. Aqueous hydrogen peroxide has attracted great attention as an oxidant because it is clean, inexpensive, safe, readily available and gives water as the only byproduct.[2] Titanium-containing heterogeneous catalysts are highly efficient in a range of selective oxidations with hydrogen peroxide.[3] The microporous titanium-silicalite TS-1 developed in the early 1980s by the Enichem group is currently employed in three industrial oxidation processes, including epoxidation of propene.[4] TS-1 possesses a unique ability to activate $H_2O_2$ and oxidize small organic substrates ($<0.6$ nm) by means of heterolytic oxidation mechanisms.[3a,3c] Numerous attempts to create a mesoporous Ti catalyst that would display catalytic properties of TS-1 but could be used in the oxidation of bulk organic molecules have failed. To date, the reasons for that are not completely understood and remain under debate.

Soluble compounds are widely used in mechanistic studies as tractable models that allow probing interactions at the molecular level.[5] Studies on hydrolytically stable and well-characterized titanium compounds could shed light on the mechanisms of $H_2O_2$ activation by Ti centres. Titanium-substituted polyoxometalates (POMs for short) are inorganic metal–oxide-like structures that are thermodynamically stable to oxidation and hydrolysis under appropriate pH conditions. POMs are useful molecular models for studying mechanisms of $H_2O_2$-based liquid-phase selective oxidations.[6]

Kholdeeva et al. have demonstrated that the catalytic performance of tetra-*n*-butyl ammonium (TBA) salt of Ti-monosubstituted Keggin-type heteropolytungstate, $(TBA)_4[PTi(OH)W_{11}O_{39}]$ (Ti-POM), in the oxidation of alkenes, thioethers and alkylphenols with $H_2O_2$ is very similar to that of hydrophilic mesoporous titanium-silicate catalysts.[6,7] It has been established that hexacoordinate isolated Ti centres catalyze $H_2O_2$-based oxidations predominantly through homolytic mechanisms but are not capable of a heterolytic oxygen atom transfer.[6]

Recently, the "sandwich"-type dititanium 19-tungstodiarsenate(III) $[Ti_2(OH)_2As_2W_{19}O_{67}(H_2O)]^{8-}$ (**1**) (the structure is shown in Figure 1) has been synthesized and comprehensively characterized.[8] Polyanion **1** comprises two (*B*-$\alpha$-$As^{III}W_9O_{33}$) Keggin moieties linked through two square-pyramidal $[Ti(OH)]^{3+}$ groups and an octahedral $[WO(H_2O)]^{4+}$ fragment. The unprecedented arrangement of

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the two TiOH groups in **1** allows neither intra- nor intermolecular Ti–O–Ti bond formation. Following our interest in Ti-containing soluble probes and taking into account the unusual coordination environment of Ti in polyanion **1**, we assessed the catalytic properties of TBA salts of **1** in the selective oxidation of a few model organic substrates using $H_2O_2$ as oxidant.[9] The stability of **1** under turnover conditions was confirmed by means of IR, UV/Vis and cyclic voltammetry (CV) techniques.[8,9]

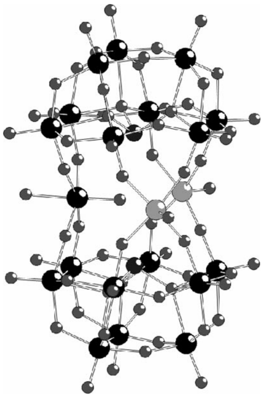


Figure 1. Ball-and-stick representation of polyanion **1**.

Previously, we have found that the composition of counterions of **1** strongly affects the cyclohexene oxidation products.[9] A POM with two counterprotons, $TBA_{5.5}K_{0.5}H_2$-**1**, favoured subsequent transformation of cyclohexene to epoxide, diol, α-ketol and further oxidation products, right up to adipic acid. At the same time, TBA salt prepared at a higher pH (ca. 2.7) contained a lower amount of counterprotons, $TBA_{5.5}Na_{1.5}K_{0.5}H_{0.5}$-**1**, and produced cyclohexene epoxide with high selectivity based on both substrate and oxidant.

In this work, we have further explored the catalytic properties of the low-protonated salt $TBA_{5.5}Na_{1.5}K_{0.5}H_{0.5}$-**1** and studied homogeneous epoxidation of a range of alkenes with aqueous $H_2O_2$. The results of the product and kinetics studies are presented and compared with the results of the theoretical calculations.

## Results and Discussion

### Product Studies

We have found that the selectivity of alkene oxidation with $H_2O_2$ in the presence of catalytic amounts of **1** strongly depends on the alkene structure. Benzaldehyde predominated among the oxidation products of styrene, whereas α-pinene produced mainly campholenic aldehyde. The other alkenes studied gave epoxides as the main products with good to high selectivity. The results of the catalytic runs are presented in Table 1.

Table 1. Alkene epoxidation with $H_2O_2$ catalyzed by **1**.[a]

| | Substrate conversion [%] | Epoxide selectivity[b] [%] |
|---|---|---|
| *trans*-Stilbene | 14 | 70[c] |
| *cis*-Stilbene | 19 | 80[c] |
| 1-Octene | 49 | 90 |
| Cyclohexene | 74 | 94 |
| Cyclooctene | 70 | 95 |
| Limonene | 76 | 75[d] |

[a] Reaction conditions: [S] = 0.1 M, [$H_2O_2$] = 0.1 M, [**1**] = $2\times10^{-3}$ M, 50 °C, MeCN, 5 h. [b] GC yield based on substrate consumed. [c] Benzaldehyde was the main byproduct. [d] Only 1,2-epoxide formed.

Cyclohexene is a test substrate that is useful for the distinction between homo- and heterolytic oxidation mechanisms. Importantly, the selectivity towards cyclohexene epoxide achieved 94% and no allylic oxidation products, 2-cyclohexene-1-ol and 2-cyclohexene-1-one, which are typical of homolytic oxidation mechanisms, were found even at the early stages of the reaction. This allowed us to suggest a heterolytic oxidation mechanism.

Epoxidation of *cis*-stilbene proceeded stereospecifically, thus indicating a concerted mechanism of oxygen atom transfer. This implies that no formation of any intermediate radical species capable of transformation to the thermodynamically more stable *trans*-epoxide occurs during the reaction course.

In contrast to the epoxidation reaction catalyzed by another sandwich POM, $\{[(WZnMn_2)(H_2O)_2][(ZnW_9O_{34})_2]\}^{12-}$ (**2**),[10] the reactivity of alkenes was not strongly affected by the steric bulk of the substrate. With **1**, the oxidation rate was just slightly higher for *cis*-stilbene than for the *trans* isomer. α-Pinene was more reactive than cyclohexene in the presence of **1**, whereas in the presence of **2** this substrate was not active at all and cyclohexene was more reactive than 1-methylcyclohexene.

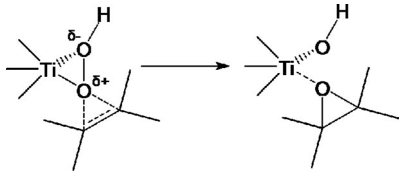
As one can judge from the turnover frequency (TOF) values given in Table 2, the alkene oxidation rate correlated with nucleophilicity of the C=C double bond and increased in the order: 1-octene < cyclooctene < cyclohexene < limonene. Accordingly, epoxidation of limonene proceeded regioselectively and gave exclusively *endo* epoxide, whereas the terminal C=C bond remained intact. All these facts strongly support the mechanism of the electrophilic oxygen atom transfer shown in Scheme 1.

Table 2. Turnover frequencies (TOFs) for alkene oxidation with $H_2O_2$, and NBO orbital energies of $\pi_{C=C}$.

| Substrate | $TOF_{Ti}$[a] [$h^{-1}$] | $\pi_{C=C}$ [eV] |
|---|---|---|
| *trans*-Stilbene | 0.7 | –7.00 |
| *cis*-Stilbene | 0.9 | –7.02 |
| 1-Octene | 1.6 | –6.99 |
| Cyclooctene | 3.7 | –6.73 |
| Cyclohexene | 3.7 | –6.73 |
| Limonene | 6.0 | –6.67 (–6.82)[b] |

[a] Reaction conditions as in Table 1. [b] The energy of the terminal C=C double bond is given in parentheses.

Note that Neumann et al. observed different reaction selectivity for **2** in limonene epoxidation in which both epoxides were formed in equal amounts.[10]



Scheme 1. Proposed mechanism of electrophilic oxygen atom transfer.

### Kinetics Studies

By using cyclooctene as the model substrate, we have studied the kinetics of epoxidation with $H_2O_2$ in the presence of **1**. The reaction rate was not affected by light and by the presence of molecular oxygen, thereby indicating that neither photochemical nor autoxidation processes are involved.

Typical kinetic curves of alkene consumption and epoxide accumulation are shown in Figure 2. The kinetic curves revealed no induction period.

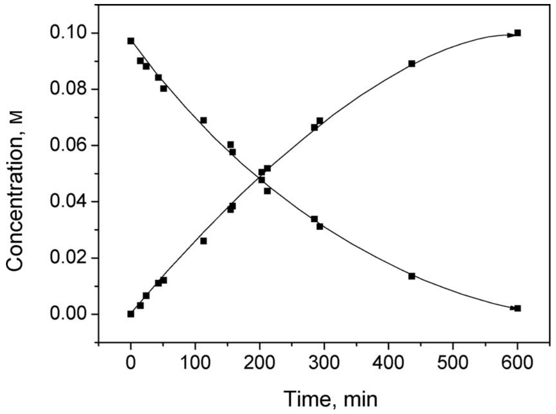


Figure 2. Kinetic curves for cyclooctene consumption and epoxide accumulation in the presence of $H_2O_2$ and **1** ([S] = 0.1 м, [$H_2O_2$] = 0.1 м, [**1**] = $2\times10^{-3}$ м, 50 °C, MeCN).

The reaction was found to be first order in substrate (Figure 3, a) and catalyst (Figure 3, b). The order in the oxidant changed from 1 to 0 with increasing $H_2O_2$ concentration (Figure 4, a).

Such kinetic behaviour implies Michaelis–Menten-type kinetics and allows one to suggest a two-step mechanism in which the first step is a reversible interaction between $H_2O_2$ and the Ti–OH group to produce a titanium hydroperoxo complex [Equation (1)] and the second step is oxygen atom transfer from the peroxo species to the alkene substrate [Equation (2)].

$$\mathrm{TiOH} + \mathrm{H_2O_2} \xrightleftharpoons{K} \text{'TiOOH'} \qquad (1)$$

$$\text{'TiOOH'} + \mathrm{S} \xrightarrow{k_0} \mathrm{TiOH} + \mathrm{SO} \qquad (2)$$

If we assume that the second step is rate limiting, the reaction rate law can be described by Equation (3), which is consistent with the experimental data.

$$W = K\cdot k_0\cdot\frac{[\mathbf{1}]\cdot[\mathrm{S}]\cdot[\mathrm{H_2O_2}]}{1+K\cdot[\mathrm{H_2O_2}]} \qquad (3)$$

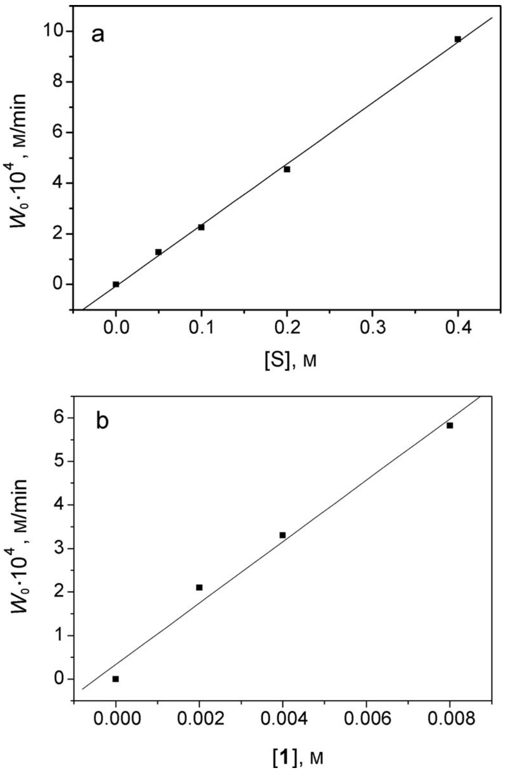


Figure 3. Plots of the initial rate of cyclooctene oxidation versus (a) concentration of cyclooctene ([**1**] = $2\times10^{-3}$ м, [$H_2O_2$] = 0.1 м, 50 °C) and (b) concentration of catalyst ([S] = 0.1 м, [$H_2O_2$] = 0.1 м, 50 °C).

By using the plot $1/W_0 = 1/k_0K[\mathbf{1}][H_2O_2][S] + 1/k_0[\mathbf{1}][S]$ (the dependence is shown in Figure 4, b), we estimated the values of $K$ and $k_0$: $K = (3.50\pm0.56)$ м$^{-1}$ and $k_0 = (0.067\pm0.008)$ м$^{-1}$ s$^{-1}$.

When one employs POMs in oxidations with $H_2O_2$, the critical issue is the stability of the catalyst under turnover conditions because many POMs tend to produce low-nuclearity species upon interaction with $H_2O_2$. The question of the stability of **1** under the turnover conditions, in which typically 100-fold excess amounts of the oxidant were employed, was addressed in our previous work.[8,9] It has been established that the IR spectra of the initial POM and the POM separated after the catalytic oxidation runs are very similar. In agreement, the catalytic performance in the second run of cyclohexene oxidation was very close to what was observed in the first run. The stability of **1** towards excess amounts of $H_2O_2$ was also confirmed by UV/Vis and CV studies.[8] The lack of an induction period in the kinetic curves and the first reaction order in the concentration of the catalyst established in the present work also provide evidence in favour of the stability of **1** under turnover conditions.

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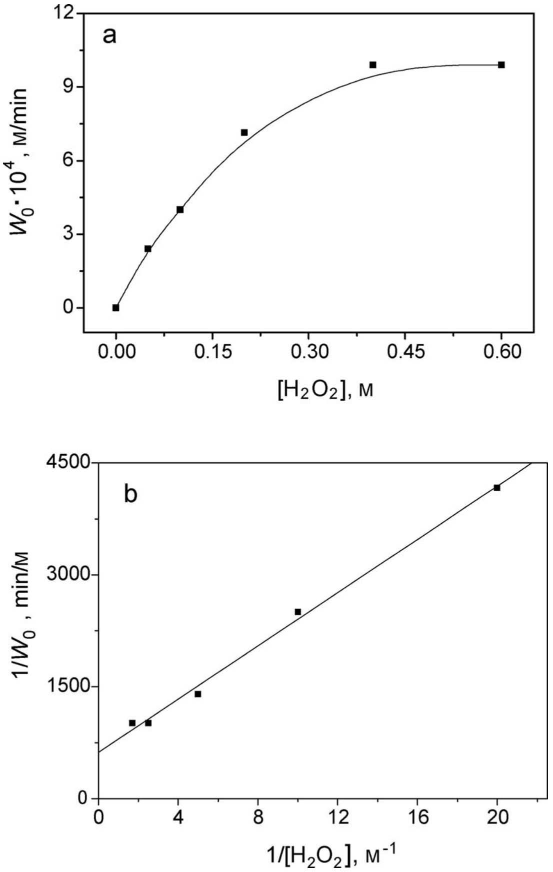

Figure 4. (a) Plot of the initial rate of cyclooctene oxidation versus concentration of $H_2O_2$ ([S] = 0.1 M, [**1**] = $4 \times 10^{-3}$ M, 50 °C, MeCN) and (b) plot of $1/W_0$ versus $1/[H_2O_2]$.

## Theoretical Studies on the Alkene Substrate Effect

In a previous contribution,[11] we have theoretically analyzed in detail alkene epoxidation with $H_2O_2$ catalyzed by nonprotonated model anion **1** by means of DFT methods. The results agree well with the proposed two-step mechanism, in which the Ti centres are responsible for the catalytic activity. Using ethene as the simplest model substrate, calculations showed that first the Ti–OH groups in **1** activate hydrogen peroxide, and second, the oxygen is transferred from the hydroperoxo Ti–OOH intermediate to the alkene, the latter step being the rate-limiting step. Moreover, we showed that the heterolytic mechanism is energetically favoured over the homolytic one; and that the alkene molecule acts as a nucleophile. Thus, our previous calculations are in qualitative agreement with these new experimental data. Here, we analyze the effect of the alkene substrate nature on the catalytic performance and compare it with the experimental data.

According to the reactivity model for the oxygen transfer to the alkenes in peroxo and hydroperoxo species, the peroxide ligands act as electrophiles and the alkene as a nucleophile.[12] For **1**, the nucleophilic character of the alkene attack was manifested through net natural population analysis (NPA) electron-density transfer from the alkene to the hydroperoxo anion in the corresponding transition state.[11] Thus, we expect that, in the absence of steric effects, the more electron-rich the alkene, the faster the epoxidation. The energy levels of $\pi_{C=C}$ orbitals in the alkene substrates could be used to elucidate the range of reactivity for a given metal complex. The experimentally determined TOF values provide us with a measure of the activity as a function of the alkene type. Table 2 collects the experimental TOF values and the energy of localized natural bond orbital (NBO) $\pi_{C=C}$ orbitals. We can observe a nice correlation between both values: the higher the $\pi_{C=C}$ energy level, the more active the process. Hence, the low TOF values found for *trans*-stilbene, *cis*-stilbene and 1-octene can be associated to the relatively low nucleophilicity of the double bond. The largest TOF values were observed for alkenes with the highest $\pi_{C=C}$ energy levels. It is worth mentioning that for limonene the $\pi_{C=C}$ orbital of the *endo* carbon–carbon double bond is higher in energy (–6.67 eV) than the corresponding orbital of the terminal C=C bond (–6.82 eV), and the former is the one that is selectively epoxidized. These findings further support the electrophilic nature of the oxygen transfer to alkene in the Ti-substituted POM. Moreover, the correlation between the activity and alkene electronic structure further indicates that oxygen transfer is the rate-limiting step and suggests that the steric effect of the alkene substituents has a minor influence on the mechanism, as mentioned above.

The only exception to the correlation corresponds to the stilbene isomers; the *cis* isomer is slightly more active than the *trans* isomer, but it has a slightly lower-energy $\pi_{C=C}$ orbital. It is possible to understand this small discrepancy with regards to the geometry of the transition state for ethene insertion.[11] The ethene substrate attacks the hydroperoxo moiety in a *spiro* orientation (i.e., perpendicular to the TiOO plane). Thus, the *cis*-stilbene can accommodate the two phenyl substituents far away from the POM structure, thereby minimizing the steric repulsion. On the other hand, one of the substituents of the *trans*-stilbene has to face the POM structure, thus probably inducing a repulsive steric interaction and slightly decreasing its reactivity. To account for the steric effects of the phenyl substituents of the *trans*-stilbene substrate, and due to the size of the molecular system, we performed additional hybrid quantum mechanics/molecular mechanics (ONIOM) calculations on the oxygen-transfer step for the realistic alkene substrate. Upon introduction of the steric effects, we observed that the energy barrier is raised by about 6 kcal mol$^{-1}$ with respect to the ethene. Within this methodological partition, there is no charge transfer from the phenyl substituents to the double bond, thereby resulting in very similar nucleophilicities for the ethene and the model *trans*-stilbene, and consequently, the energy difference should be attributed to the steric effects.[13] Moreover, if we look at the computed structure of the transition state (see Figure 5, front and top views), we can observe how one of the phenyl substituents is far away from the POM, whereas the other lies on the same side to generate a destabilizing interaction. Although the molecular mechanics treatment of this interaction is probably overestimated,[14,15] it describes qualitatively the steric contact between the catalyst and the *trans*-stilbene substrate. Hence, in light of experimental and computational evidence, we can conclude that the steric bulk of the substrate does not determine the activity of **1**, but in some cases can tune it. However, we should emphasize that the steric repulsion strongly depends on the specific POM structure. For example, Mizuno and co-workers found that the rate for the epoxidation with $H_2O_2$ by $[TBA]_4[\gamma\text{-}1,2\text{-}H_2SiV_2W_{10}O_{40}]$ of *cis*-2-octene is over 300 times faster than that of *trans*.[16] Note that we computed the same value of the $\pi_{C=C}$ orbital energy for both alkenes, thus indicating similar nucleophilicities.

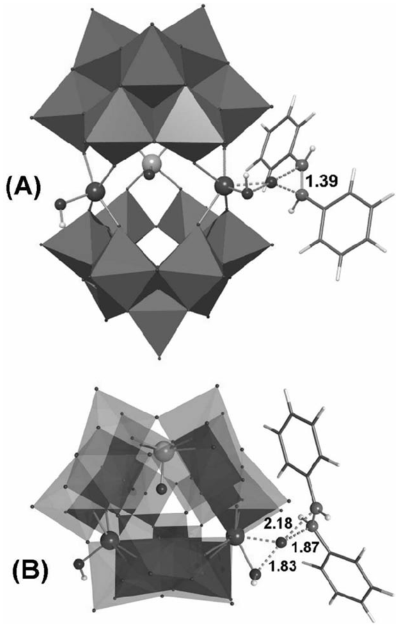

Figure 5. Computed transition-state structures for oxygen transfer to *trans*-stilbene substrate. (A) Front view and (B) top view.

## Conclusion

Epoxidation of a range of alkenes easily proceeds with aqueous $H_2O_2$ as oxidant and the dititanium-containing 19-tungstodiarsenate(III) (**1**) as catalyst. Both the kinetic study and theoretical calculations support a mechanism that involves the interaction between $H_2O_2$ and the Ti–OH group of **1** to produce a titanium hydroperoxo complex followed by electrophilic oxygen atom transfer from the peroxo species to the alkene substrate. The reaction follows Michaelis–Menten-type kinetics, thereby suggesting that the first step is reversible and the second step, the oxygen transfer, is the rate-limiting step. This is further supported by the correlation between the alkene nucleophilicity and turnover frequency values, which indicate that the reaction rate is decided during oxygen transfer to the alkene.

When looking at the effects of the nature of the alkene substrate, the correlation between alkene nucleophlicity and activity also indicates that the electronic properties of the alkene, and not the steric bulk, are the key factors that govern the activity. However, a closer inspection of the results along with the performance of ONIOM calculations revealed that steric interaction can play a secondary role in specific cases, such as *trans*-stilbene.

## Experimental Section

**Materials and Catalysts:** Acetonitrile, alkene substrates and corresponding epoxides were purchased from Aldrich. $H_2O_2$ (30 wt.-% in water) was titrated iodometrically prior to use. The tetra-*n*-butylammonium (TBA) salt $TBA_{5.5}Na_{1.5}K_{0.5}H_{0.5}$-**1** was synthesized as described elsewhere.[9]

**Catalytic Oxidations:** The catalytic oxidations were carried out in temperature-controlled glass vessels equipped with a magnetic stirrer at 50 °C in MeCN. Samples were taken during the reaction course by a syringe, and the reaction products were identified by GC–MS and GC using reference compounds. Substrate conversions and product yields were quantified by GC using biphenyl or dodecane as internal standards. The TOF values were determined from the initial rates of substrate consumption.

**Kinetic Measurements:** The reaction was initiated by injection of the oxidant (0.05–0.6 M) into a solution of cyclooctene (0.05–0.4 M) and catalyst **1** (0.002–0.008 M) in MeCN(1 mL). The oxidant-to-catalyst ratio did not exceed 150. Previously it had been proven that **1** is stable under such reaction conditions.[8,9] The dependence of the reaction rate on the $H_2O_2$ concentration was studied at a fixed concentration of water (1.56 M) to standardize the reaction conditions. Aliquots were taken from the reaction mixture by a syringe, and alkene consumption was determined by GC using internal standard. The initial-rate method was employed to determine the reaction orders.

**Instrumentation:** GC analyses were performed with a Tsvet-500 gas chromatograph equipped with a flame ionization detector and an Agilent DB-5MS quartz capillary column (30 m × 0.25 mm). GC–MS analyses were carried out with an Agilent 6890 gas chromatograph (quartz capillary column 30 m × 0.25 mm/HP-5ms) equipped with an Agilent MSD 5973 quadrupole mass-selective detector.

**Computational Details:** All reported calculations were performed with the Gaussian 03 package[17] and NBO program (version 3.0).[18] Full quantum mechanics calculations on the series of free alkene substrates were performed within the framework of density functional theory (DFT) using the hybrid exchange-correlation B3LYP[19] functional. The 6-31G(d,p) basis set[20] was used for the C and H atoms of the alkene substrates. The hybrid quantum mechanics/molecular mechanics (QM/MM) calculations were performed using the ONIOM method[21] as implemented in the Gaussian 03 series of programs.[17] The MM region was that constituted by the phenyl substituents of the alkene. Molecular mechanics calculations used the UFF force field.[22] The QM level used the B3LYP functional. For Ti, W and As atoms, the LANL2DZ pseudopotential was used.[23] The 6-31G(d,p) basis set[20] was used for the C and H atoms, as well as for the O atoms of hydrogen peroxide and those directly bound to Ti. For the rest of atoms, we employed a 6-31G basis set.[20] For the transition-state search, we used as a starting point that which was calculated at the full DFT level for ethene, checking that the obtained geometrical parameters of the reaction centre were closely related. The natural bond orbital (NBO) method[18] was used to analyze the resultant wave function in terms of optimally chosen localized orbitals that corresponded to a Lewis structure representation of chemical bonding.

**Supporting Information** (see footnote on the first page of this article): Cartesian coordinates and absolute total energy.

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