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# Role of Intermolecular Interactions in Oxygen Transfer Catalyzed by Silsesquioxane Trisilanolate Vanadium(V)

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The polyhedral oligomeric silsesquioxane trisilanolate vanadium(V) complex **1** efficiently catalyzes oxidations at room temperature using cumyl hydroperoxide as the terminal oxidant. Sulfoxidations and *N*-oxidations have been carried out yielding the corresponding products in good yields. The addition of a Lewis base as a coligand can markedly affect reactivity, stability, and chemo- and stereo-selectivity. A proposal for the intermolecular activation, using Gutmann analysis supported by MP2/TZVP calculations, is presented.

## Introduction

The activation of peroxides by metal complexes has been the focus of intense research efforts because of its relevance to biochemical processes and its application in industrial oxidation processes.[1] Several complexes, inspired by natural metalloenzymes, have shown interesting catalytic properties.[2] Typically, a ligand is used to stabilize the metal, to increase its reactivity, and to direct the stereochemistry of the reaction.[3] A less explored alternative is the use of an extra ligand (coligand) able to bind the metal in addition to the ligand and thereby capable of tuning the catalytic properties of the complex.[4] This approach does not only offer the opportunity to module the catalytic systems with a defined reactivity and selectivity profile but also allows for a better understanding of the basic principles behind metal activation in synthetic and biological systems. In fact, intermolecular interactions can either stabilize transition states by charge redistribution or by the action on unstable intermediates. However, in a first approximation, the presence of a coligand (usually a Lewis base, LB) will decrease the catalyst (a Lewis acid) reactivity or even completely inhibit it.[5]

Several $d^0$ metal ions, such as Ti(IV), V(V), Mo(VI), and Re(VII), have shown the possibility to expand their coordination sphere in the presence of other ligands.[5,6] In some cases, this phenomenon results in a variation of the catalytic activity. As an example, earlier we investigated the oxygen transfer to organic sulfur compounds catalyzed by Ti(IV) complexes, noticing that the coordination of a sulfoxide to the metal was responsible for a switch in the reactivity of the peroxometal functionality from electrophilic to nucleophilic.[6] Herein, we provide experimental evidence of a remarkable activation of a vanadium complex by intermolecular interactions. We also propose an activation mechanism, based on charge redistribution on the active peroxometal complex, which accounts for these results.

## Experimental Section

**Materials.** All chemicals were used as provided without further purifications. Vanadium oxytriisopropoxide, methyl *p*-tolyl sulfide, dibenzylamine, triethylamine ($Et_3N$), and (*S*,*R*,*R*)-(+)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a]dinaphthalen-4-yl)bis(1-phenylethyl) amine were purchased from Aldrich. *N*,*N*-Dimethylhexylamine-*N*-oxide (DMENO)

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and a cumene hydroperoxide (CHP) 80% solution in cumene were purchased from Fluka, and isobutyltrisilanol-POSSH$_3$ (isobutyl-POSSH$_3$; POSS = polyhedral oligomeric silsesquioxane trisilanolate) was purchased from Hybrid Catalysis (Eindhoven, NL). ***Caution!*** *HMPA is highly toxic and suspected of being a carcinogen.*

**General Remarks.** $^1$H and $^{13}$C NMR spectra were recorded at 301 K on Bruker AC-300 and Bruker AC-250 instruments. $^{51}$V NMR spectra were obtained on a Bruker AC-300 instrument with a broadband probe and using VOCl$_3$ as an external standard. ESI-MS experiments were performed in a LC/MSD Trap-SL and XCT by flow injection analysis using *n*-hexane as a mobile phase. The V(V)−POSS complex was always handled and stored under an inert atmosphere. All of the product data are in agreement with what has been reported in the literature.

**Synthesis of Vanadium(V) Oxyisobutyl-POSS (1).** ($i$-PrO)$_3$VO (300 $\mu$L, 1.29 mmol), dissolved in 1.70 mL of benzene, was added at room temperature to a solution of isobutyltrisilanol-POSSH$_3$ (1.025 g, 1.29 mmol) in 20 mL of benzene, under vigorous stirring. The mixture was stirred for 1.5 h until reaction completion. Filtration through a fine sintered glass funnel, and solvent removal in vacuo, led to the isolation of 900 mg of VO−isobutyl-POSS (**1**) as a white amorphous foam. The product characterization is in agreement with literature data.[7] $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.93−1.81 (m, 7H, CHMe$_2$), 0.99 (d, 18H, $J$ = 6.6 Hz, CH$_3$), 0.95 (d, 24H, $J$ = 6.6 Hz, CH$_3$), 0.69 (d, 6H, $J$ = 7.0 Hz, CH$_2$), 0.60 (d, 8H, $J$ = 7.0 Hz, CH$_2$). $^{13}$C NMR (250 MHz, CDCl$_3$): $\delta$ 26.0 (CH$_3$), 26.0 (CH$_3$), 25.9 (CH$_3$), 24.2 (CH$_2$), 24.1 (CH$_2$), 24.1 (CH$_2$), 23.4 (CH), 23.0 (CH), 22.7 (CH). $^{51}$V NMR (300 MHz, CDCl$_3$): $\delta$ −694.95. ESI-MS: 855.3 (M + H$^+$). Calcd: 855.2. HRMS-ESI: 855.2520 (855.2166 calcd).

**Typical Procedure for Oxidation of Methyl *p*-Tolyl Sulfide (2).** An NMR tube was charged with a solution of complex **1** in CDCl$_3$ (0.6 × 10$^{-3}$ mmol, 0.51 mg), the internal standard (1,2-dichloroethane; DCE), cumyl hydroperoxide (0.06 mmol, 11.4 mg), and methyl *p*-tolyl sulfide **2** (0.06 mmol, 8.3 mg). The Lewis bases (**3**, **5**, **6**, **7**, **8**, **9**, and **14**) were added to a final volume of 0.6 mL. Concentrations of sulfide **2**, sulfoxide **3**, and sulfone **4** were determined by integration of the methyl group signals: *p*-Tol-S-Me (2.31 ppm), *p*-Tol-SO-Me (2.69 ppm), and *p*-Tol-SO$_2$-Me (3.02 ppm) with respect to the internal standard, DCE (3.73 ppm). The final yield was determined after complete oxidant consumption (iodometric test) via $^1$H NMR. Enantiomeric excess was determined by HPLC on a column [REGIS (*R*,*R*)-DACH DNB, isopropanol/hexane 40:60, and a flow rate of 1.0 mL/min].

**Typical Procedure for the Oxidation of Triethylamine (10).** An NMR tube was charged with a solution of complex **1** in CDCl$_3$ (3.0 × 10$^{-3}$ mmol, 2.6 mg), the internal standard (DCE), CHP (0.3 mmol, 114 mg), and triethylamine **10** (0.3 mmol, 29 mg), and eventually **9** (0.015 mmol, 2.18 mg), with a final volume of 0.6 mL. Concentrations of triethylamine **10** and the corresponding *N*-oxide **11** were determined by integration of the methyl group signals: ($\mathit{Me}$CH$_2$)$_3$N (0.95 ppm) and ($\mathit{Me}$CH$_2$)$_3$NO (1.26 ppm) with respect to the internal standard, DCE (3.73 ppm). The final yield is determined via $^1$H NMR after complete oxidant consumption (iodometric test). Yield: 99%; in the presence of **9**, 98%.

**Typical Procedure for the Oxidation of Dibenzylamine (12).** An NMR tube was charged with a solution of complex **1** in CDCl$_3$ (6.0 × 10$^{-3}$ mmol, 5.1 mg), the internal standard (DCE), CHP (0.24 mmol, 45.7 mg), dibenzylamine **12** (0.06 mmol, 1.2 mg), and eventually DMENO 9 (0.03 mmol, 4.3 mg), with a final volume of 0.6 mL. Concentrations of dibenzylamine **12** and the corresponding nitrone **13** were determined by integration of the methylene signals: (Ph$\mathit{CH_2}$)$_2$NH (4.02 ppm) and (Ph$\mathit{CH_2}$)N$^+$O$^-$=(CHPh) (5.03 ppm) with respect to the internal standard, DCE (3.73 ppm). The final yield is determined via $^1$H NMR after complete oxidant consumption (iodometric test). Yield: 66%; in the presence of **9**, 90%.

## Results and Discussion

Our interest in the possible effect of extra ligands in catalysis came during the course of our studies on oxygen transfer reactions catalyzed by vanadium(V) silsesquioxane complex **1**. Oxidation mediated by vanadium compounds has been revitalized by vanadium-dependent enzymes, haloperoxidases, producing an ever growing number of studies on biomimetic complexes.[8] The main interest has been directed toward oxidations of sulfides,[9] halides,[9,10] and allylic alcohols.[11] In the oxidation pathway followed by these complexes, it has been largely accepted that the mechanism begins with an electrophilic activation of the peroxide followed by a nucleophilic attack by the substrate on the $\eta^2$-coordinated peroxide.[12]

Vanadium POSS complexes,[13] originally synthesized by Feher in 1991,[7] had found application as photooxidation catalysts.[7,14] Their use in homogeneous solution has been

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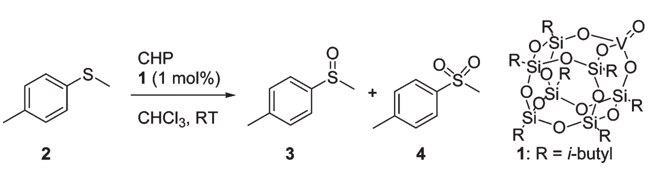
**Scheme 1.** V(V)-Catalyzed Oxidation of Methyl *p*-Tolyl Sulfide **2**



held back because of the instability of the complex in the presence of hydroxylic reagents (e.g., hydroperoxides, alcohols, or water).[7] During the course of our studies on vanadium silsesquioxane **1**, we checked the stability of **1** toward alkyl hydroperoxides, and we found that the complex was able to activate CHP and oxidize methyl *p*-tolyl sulfide **2** to the corresponding sulfoxide **3** (Scheme 1).

The obtained data demonstrate a high catalytic activity of complex **1** itself, with quantitative conversion of the oxidant and minor formation of sulfone **4** (Table 1, entry 1).[15,16]

We further noticed that the presence of a molecule able to act as a coligand in solution distinctively enhanced the catalytic activity of **1**. To shed more light onto this intriguing coligand effect, the sulfoxidation reaction in the presence of different coligands of increasing basic strength (**3**, **5**−**9**, Figure 1) was carried out (Table 1).[17]

Vanadium silsesquioxane **1** was prepared and characterized following a literature procedure, and it was used in solution at millimolar concentration, where it is present as a monomer.[7] Different coligands have been chosen for the different electronic and steric properties and have been tested in the range between 0.001 and 0.150 M (Table 1), which translates from equimolar to a 150-fold excess with respect to catalyst **1**. As shown in Table 1, the addition of the coligand to the reaction mixtures clearly results in increased reactivity and in a variation in the sulfone/sulfoxide ratio. The effect correlates with the electron richness of the coligand, as shown by the correlation with their electrostatic potential surfaces.[18] The more electron-rich the coligand is (**8** or **9**), the more enhanced is the reactivity and the lower the excess that is required for maximizing the acceleration. As an example, the *N*-oxide **9** is able to increase the reaction rate 24 times already at a **1**/**9** = 1:1 ratio (Table 1, entry 7). The less electron-donating coligands (**3**, **5**) produce a small effect on the catalytic properties of complex **1** even when they are present in a large excess (Table 1, entries 2 and 3). On the other hand, the basic but more hindered **6** requires larger excesses to afford significant accelerations, in agreement with a less favorable coordination to the metal center (Table 1, entry 4), as showed in the $[\mathbf{6}]_0$ versus reactivity profile shown in Figure 2.

In order to further evaluate the catalytic activity of **1** in oxygen transfer processes, we examined the oxidation of triethylamine **10** to the corresponding *N*-oxide **11** (Figure 3).[19]

The reaction displays a sigmoid profile (Figure 3, plain dots profile), suggesting that the initially formed *N*-oxide **11** coordinates to the metal center, increasing the catalytic activity of the system, in a typical autocatalytic process. As a confirmation, the addition of 5 equiv of **9** to the starting mixture results in an increase of the reaction rate from the beginning and in comparable yields (Figure 3, empty dots profile).

We then tested the activity of the catalyst in the oxidation of dibenzylamine **12** to the corresponding nitrone **13**.[20] Secondary amine oxidations with peroxo oxidants are known to occur via the corresponding hydroxylamine intermediate, which is then further oxidized with the loss of one water molecule to the nitrone. The reaction, which was carried out in chloroform using **1** (10%) as a catalyst, furnished nitrone **13** in a 66% yield (Figure 4).

Instead, the addition of **9** (5 equiv with respect to the catalyst) resulted in a final, much higher yield (90%). In this case, the coordination of the coligand to the metal center seems to increase the catalyst stability toward the hydrolytic effect of water formed during the reaction (10 equiv). Indeed, the addition of only 1 equiv of water, with respect to the catalyst, at the beginning of the reaction, resulted in a lower yield (51%) using only **1**. On the contrary, yields remained unvaried using **1** in the presence of **9** (90%).

A confirmation of the coordination of the coligands to the catalyst derives from spectroscopic data (Figure 5).

The addition of 1 equiv of *N*-oxide **9** in a 1 mM solution of the vanadium catalyst **1** resulted in the formation of two distinct signals in $^{51}$V NMR corresponding to the two different species (**1**, $^{51}$V = −690.9 ppm; **1·9** $^{51}$V = −605.9 ppm). The addition of a further equivalent shifts the equilibrium toward the new complex.

Definitive proof of the coordination of the coligand to the catalysts during the oxidation process and in particular during the oxygen transfer step came from the use of a chiral, enantiopure coligand, the phosphoric amide (*S*,*R*,*R*)-**14**. This coligand has been used to activate the catalyst and control the stereochemistry of the oxidation of methyl *p*-tolyl sulfide **2** (Scheme 2).[21] The final sulfoxide (*S*)-**3** was recovered in quantitative yield and with ee = 14%.

The unexpected stability of catalyst **1** under turnover conditions (presence of hydroxylic species such as CHP and cumyl alcohol) has been investigated as well. The stability of **1** and **1·9** at the end of the sulfoxidation of methyl *p*-tolyl sulfide **2** and in the presence of a large excess of CHP (up to 100 equivalents) has been monitored via $^{51}$V NMR. In both cases, the two species remained unaltered.[22] On the contrary, a new peak at −686.7 ppm appears either upon standing after the end of the reaction or when a large excess of cumyl alcohol is added to a solution of fresh catalyst **1**.[23] This peak has been assigned to the vanadium oxotricumyloxide **15**, which has been independently synthesized and characterized. Reactivity of **15** in sulfoxidations has been explored, and it was determined to be higher than **1** without a Lewis base (initial rate $R_0$(**15**) = 0.126 mmol/s vs

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(16) Independent kinetic experiments demonstrate that the reaction proceeds with *first-order* reactivity in sulfide **2**, cumyl hydroperoxide (**CHP**), catalyst **1**, and Lewis base **6**. Saturation behavior is observed for Lewis bases **8** and **9**. No sulfoxide inhibition is observed.[22]

(17) No deoxygenated coligands have been observed at the end of the reaction. This to confirm that they are not acting as oxo-atom donors.

(18) A correlation among reactivity and electrostatic potential surfaces of the co-ligand has been found.[22] See: Hunter, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310–5324.

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(21) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940–947. Phosphoric amide **14** can also be generated in situ using the **CHP**/**1** oxidation protocol starting from the corresponding phosporamidite.

(22) See the Supporting Information.

(23) Reactions carried out in $CHCl_3$ at 28 °C using $[\mathbf{2}]_0 = [\mathbf{CHP}]_0 = 0.1$ M and 1 mol % of **15** furnished the sulfoxide **3** in 80% yield, and the time required for a 50% decrease of the initial concentration of **2** is 990 s.

**Table 1.** Oxidation of Methyl *p*-Tolyl Sulfide **2** by CHP Catalyzed by **1** (1%) in the Presence of Coligands **3**, **5**−**9** in Chloroform[a]

| entry | coligand | $t_{1/2}$, s (equiv. coligand)[b,c] | [**3**/**4**] (equiv. coligand)[b] |
|---|---|---|---|
| 1 | none | 6000 | 98:2 |
| 2 | **3** | 5580 (5), 5010 (150) | 98:2 (5), 98:2 (150) |
| 3 | **5** | 6060 (5), 4730 (150) | 96:4 (5), 95:5 (150) |
| 4 | **6** | 3100 (1), 3042 (5), 2200 (40), 1430 (80), 456 (150) | 97:3 (1), 93:7 (5), 81:19 (40), 73:27 (80), 68:32 (150) |
| 5 | **7** | 3525 (1), 2031 (5), 1280 (40), 570 (80), 476 (150) | 95:5 (1), 96:4 (5), 94:6 (40), 91:9 (80), 82:18 (150) |
| 6 | **8** | 628 (1), 290 (5), 217 (40), 235 (80), 230 (150) | 93:7 (1), 95:5 (5), 93:7 (40), 92:8 (80), 82:18 (150) |
| 7 | **9** | 361 (0.5), 250 (1), 233 (5), 195 (40), 200 (80), 200 (150) | 85:15 (0.5), 88:12 (1), 87:13 (5), 85:15 (40), 84:16 (80), 84:16 (150) |

[a] Reactions were carried out in $CHCl_3$ at 28 °C using $[\mathbf{2}]_0 = [\mathrm{CHP}]_0 = 0.1$ M and 1% mol of **1**. Quantitative yields based on the oxidant were obtained in all of the reactions. Yields and **3**/**4** ratios were determined by $^1$H NMR in the presence of DCE as an internal standard in the crude reaction mixture after total oxidant consumption (iodometric test). [b] Coligand equivalents with respect to **1**. [c] Time required for a 50% decrease of the initial concentration of **2**.

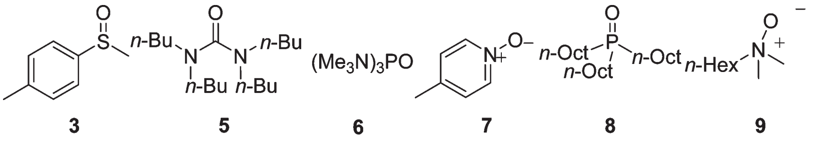

**Figure 1.** Lewis Bases **3**, **5**−**9** used as coligands.

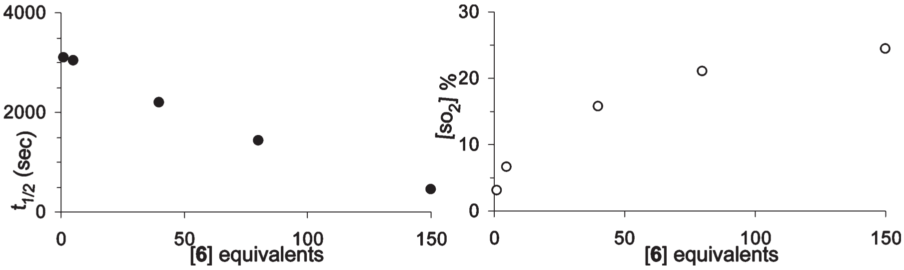

**Figure 2.** Variation of the half-time of methyl-*p*-tolyl sulfide **2** consuption (left, ●) and of the final concentration of methyl-*p*-tolyl sulfone **4** (right, ○) using $[\mathbf{2}]_0 = [\mathrm{CHP}]_0 = 0.1$ M and 1 mol % of **1** and **6** (HMPA; 1−150 equiv with respect to **1**) as the coligand.

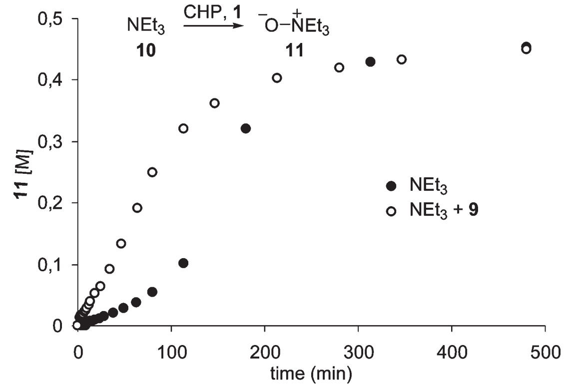

**Figure 3.** Plot of triethylamine-*N*-oxide **11** formation vs time (min) in the oxidation of triethylamine **10** (0.5 M) by CHP (0.5 M) in $CDCl_3$ at 28 °C, catalyzed by **1** (1%) in the presence (○) or in the absence (●) of **9** (5%).

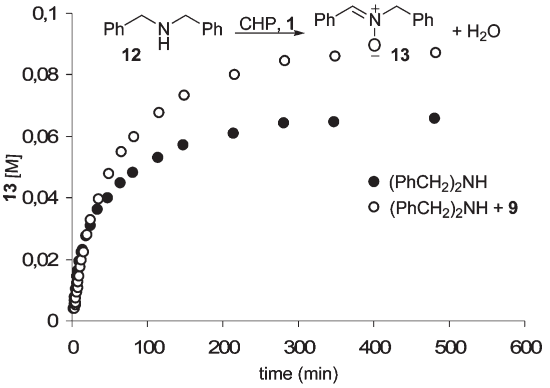

**Figure 4.** Plot of nitrone **13** formation vs time (min) in the oxidation of dibenzylamine **12** (0.1 M) by CHP (0.4 M) in $CDCl_3$ at 28 °C, catalyzed by **1** (0.01 M) in the presence (○) or in the absence (●) of **9** (0.05 M).

$R_0(\mathbf{1}) = 0.019$ mmol/s), confirming that **15** is not the active catalyst in the process.[24] Furthermore, even if catalyst **15** forms during the course of the reaction, at a concentration lower than that detectable via $^{51}$V NMR, its quantity should increase along the reaction, determining a deviation from the first-order reactivity in **1**, which is not observed.[16]

In order to explain the reasons for the LB's activation, we recalled the extensively studied chemistry developed by Denmark in which a similar activation is observed, even if the Lewis acid (silicon or selenium) is directly incorporated in the reactant.[25] In Denmark's studies, the presence of a LB is responsible for changing the electronic properties of the incorporated Lewis acid not only by enhancing its reactivity but also by selectively determining the stereochemistry of the reaction. The switch in reactivity is due to an electronic redistribution, which formally results in a more electropositive metal and in an increased electron density in the atoms attached to the silicon (or selenium), what is recalled as Gutmann analysis.[26]

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[24] $^{51}$V NMR spectra.

[25] (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789. (c) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801–3804. (d) Denmark, S. E.; Beutner, G. L. *Angew. Chem.* **2008**, *120*, 1584–1663; *Angew. Chem., Int. Ed.* **2008**, *47*, 1560−1638.

[26] M. J. Frisch et al. *Gaussian 03*, revision D.02.

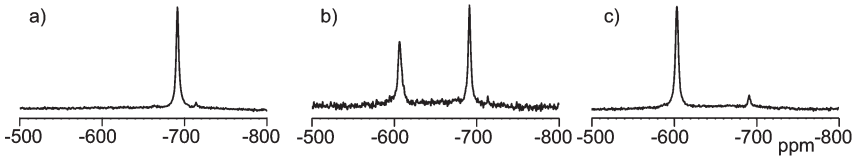
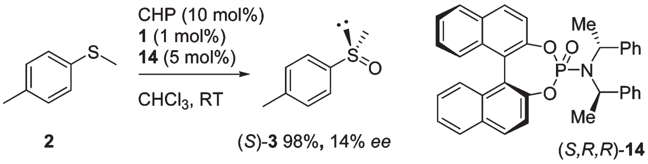


**Figure 5.** $^{51}$V NMR spectra of **1** (0.01 M) in $CDCl_3$ at 28 °C (a), in the presence of 1 equiv of **9** (b) and in the presence of 2 equiv of **9** (c).

**Scheme 2.** Vanadium-Catalyzed Oxidation of Methyl *p*-Tolyl Sulfide **2** Using (*S*,*R*,*R*)-**14** as a Cocatalyst[a]



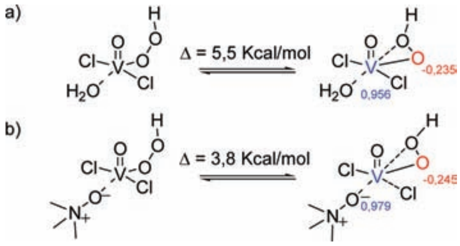
[a] $[\mathbf{2}]_0 = 0.1$ M, $[\mathbf{1}] = 0.001$ M, $[\mathbf{14}] = 0.005$ M, and $[\mathbf{CHP}] = 0.010$ M.[15]

In order to find the origin of the observed different reactivities, the faster reaction rates, and the increased sulfone formation in the presence of Lewis bases, we have to look at the changes in charge redistribution due to the coligand complexation. We believe that, in our case, the mechanism for which the coligand is accelerating the reaction is the stabilization of the $\eta^2$ peroxometal intermediate responsible for the oxygen transfer process. In analogy to what has been shown for other metals, the presence of a coligand coordinated to the metal center should increase the electron density at the coordinated peroxide and decrease the density at the metal, thus stabilizing the $\eta^2$ intermediate.[25]

In order to verify this hypothesis, calculations have been carried at the second-order Møller-Plesset perturbation (MP2) level using the TZVP basis set over model systems (Scheme 3).[25]

As shown, shifting from a poor donor (water; Scheme 3a) to a stronger donor (trimethylamine-*N*-oxide; Scheme 3b) results in a relative stabilization of the $\eta^2$ reactive peroxo species. Moreover, the Mulliken charge analysis supports the increase of the electron density of the oxygen involved in the process when an electron-rich atom is coordinated. This also explains the higher nucleophilic character of oxygen, responsible for the increased sulfone/sulfoxide ratio observed with the more active coligands.

**Scheme 3.** Calculated Energies (MP2/TZVP) for the Formation of the $\eta^2$ Complex in the Presence of Water (a) and Trimethylamine-*N*-oxide (b) as Coligands[a]



[a] The Mulliken electronic charge of the reactive oxygen (red) and metal (blue) are shown for the $\eta^2$ complex.

## Conclusions

In summary, we found that vanadium-POSS **1** is an effective catalyst in the oxygen transfer reactions to heteroatoms like sulfur and nitrogen using CHP as a primary oxidant. Furthermore, the presence of Lewis bases as coligands can markedly affect the reactivity in oxidation transfer. The reactivity can be finely tuned using the different electronic, steric, and stereochemical characteristics of the coligand. This approach will allow for the use of a large variety of coligands via combinatorial methods for the development of tailor-made catalysts.

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**Supporting Information Available:** Typical procedure for the oxidations, tests of stability of complex **1**, and data of the MP2 calculations. This material is available free of charge via the Internet at http://pubs.acs.org.