Organic Process Research & Development **2004**, *8,* 524–531

Self-Assembled $Na_{12}[WZn_3(ZnW_9O_{34})_2]$ as an Industrially Attractive Multi-Purpose Catalyst for Oxidations with Aqueous Hydrogen Peroxide

Peter T. Witte and Paul L. Alsters*

DSM Pharma Chemicals, Advanced Synthesis, Catalysis, and Development, P.O. Box 18, NL-6160 MD Geleen, The Netherlands

Walther Jary, Ruth Müllner, and Peter Pöchlauer

DSM Pharma Chemicals, P.O. Box 296, A-4021 Linz, Austria

Dorit Sloboda-Rozner and Ronny Neumann

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel 76100

Abstract:

Eleven W-based catalyst systems for alkene epoxidation with aqueous H_2O_2 were compared under identical conditions and at equal level of 0.1 mol % W-atoms. Of these, those based on a combination of H_2WO_4 and a methyltrioctylammonium phase transfer catalyst turned out to be most active in particular systems that contain a source of phosphate. Evidence is presented that under our conditions the actual epoxidizing species in H_2WO_4-based catalyst systems without phosphate source is mononuclear $[WO(OH)(O_2)_2]^-$ rather than binuclear $[\{WO(O_2)_2\}_2O]^{2-}$ that is usually thought to be active. For large-scale applications, however, the polyoxometalate $Na_{12}[WZn_3(ZnW_9O_{34})_2]$ (NaZnPOM) in combination with a suitable phase transfer catalyst such as methyltrioctylammonium chloride is preferred over H_2WO_4-based catalysts. This preference results from the fact that use of H_2WO_4 requires a catalyst activation step that is troublesome on a large scale, whereas epoxidations catalyzed by NaZnPOM start without induction period on addition of H_2O_2. Optimizations of epoxidations catalyzed by QCl/NaZnPOM or QCl/H_2WO_4 have shown that the optimum Q/W ratio depends on the alkene that is epoxidized and differs from that expected from catalyst stoichiometry. An attractive feature of NaZnPOM from the viewpoint of industrial applicability is that epoxidations and other reactions with H_2O_2 are efficiently catalyzed by a readily available aqueous solution of NaZnPOM prepared through self-assembly. A 1 mol scale example is provided of an epoxidation catalyzed by a combination of self-assembled NaZnPOM and Luviquat mono CP as a multifunctional cocatalyst with emulsifying, buffering, and phase-transferring properties.

Introduction

Many catalytic methods are currently available for the liquid-phase oxidation of alkenes with hydrogen peroxide.[1] Among these, methods based on tungsten catalysts are particularly attractive for industrial use. Not only are W-based catalyst systems using a readily available, inexpensive transition metal, but in most cases they also do not require organic ligands that negatively influence catalyst availability, stability, and cost price.[2] In addition, tungsten is poorly active for unproductive H_2O_2 decomposition, which necessitates the use of an excess of aqueous H_2O_2 that lowers the efficiency of the process by increasing reagent costs and by reducing the space−time yield as a result of diluted reaction mixtures.

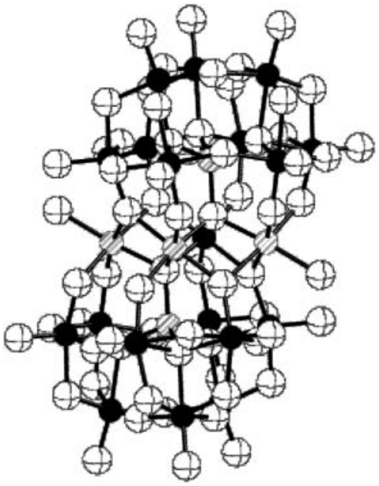

Figure 1. **Structure of the $[WZn_3(H_2O)_2(ZnW_9O_{34})_2]^{12-}$ ($ZnPOM^{12-}$) Sandwich-type polytungstate anion.**

We have recently reported the use of the readily available Sandwich polyoxometalate $[WZn_3(ZnW_9O_{34})_2]^{12-}$ (ZnPOM,$^{12-}$ Figure 1) as a catalyst for various oxidative transformations with H_2O_2, such as epoxidation,[3,4] heteroatom oxidation, and alcohol oxidation.[5]

---

* To whom correspondence should be addressed. Telephone: ++31 46 4761348. Fax: ++31 46 4767604. E-mail: paul.alsters@dsm.com.

(1) For a recent review on metal-catalyzed epoxidations, see: Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457−2474.

(2) Sanderson, W. R. *Pure Appl. Chem.* **2000**, *72*, 1289−1304.

(3) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *Synlett* **2002**, *12*, 2011−2014.

(4) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *J. Org. Chem.* **2003**, *68*, 1721−1728.

10.1021/op034184o CCC: $27.50

In the latter case, we demonstrated that not only isolated, solid $Na_{12}[WZn_3(ZnW_9O_{34})_2]$ (NaZnPOM) can be used to that end, but that also an aqueous solution of NaZnPOM, obtained by self-assembly, is effective for alcohol oxidation.[6] This strongly adds to the industrial attractiveness of NaZnPOM as an oxidation catalyst, since the self-assembly is very easily carried out by simple mixing of readily available, cheap inorganic components in water according to:[7]

$$19\ Na_2WO_4 + 5\ Zn(NO_3)_2 + 16\ HNO_3 \rightarrow Na_{12}[WZn_3(ZnW_9O_{34})_2] + 26\ NaNO_3 + 8H_2O \quad (1)$$

It has also been demonstrated that such "self-assembled catalyst solutions" can be recycled by simple phase separation from the organic phase, e.g. the corresponding carbonyl compound derived from a liquid alcohol that can be oxidized efficiently by an aqueous H_2O_2 + NaZnPOM catalyst solution without the need for an additional organic solvent.[6]

In this contribution we address in greater detail the feasibility of NaZnPOM, in particular in the form of a self-assembled solution, as a catalyst for oxidations with aqueous H_2O_2 on a large scale. To that end, first the properties and performance of NaZnPOM are compared with other W-based epoxidation catalyst systems, with an emphasis on process items of relevance for industrial-scale application of these systems. This comparison is restricted to the epoxidation of cyclooctene as a typical example that reflects main processing issues, without being interested in this particular transformation per se. Second, the use of a self-assembled NaZnPOM catalyst solution for the preparation of epoxides from two representative classes of alkenes is illustrated, with geraniol representing a highly reactive allylic alcohol and 3-carene representing a much less reactive olefin. The Experimental Section provides detailed descriptions for the preparation of aqueous solutions of NaZnPOM through self-assembly and for the use of these catalyst solutions in preparative-scale epoxidations (up to 1 mol for 3-carene).

Results and Discussion

Comparison of W-Based Catalyst Systems in the Epoxidation of Cyclooctene. We have compared 11 different W-catalyst systems with respect to their properties and performance in the epoxidation of cyclooctene with H_2O_2. This alkene has been chosen because it generally affords only one well-defined product, i.e., cyclooctene oxide, without complications arising from undesirable epoxide hydrolysis or allylic oxidation.[8] The choice of the olefin that is epoxidized is considered to be less relevant for this research on catalyst comparison because several issues related to large-scale processing that will be dealt with below are expected not to be dependent on the actual nature of the transformation.

Catalyst Preparation. The catalyst systems were either added as an *isolated* tungsten compound, or prepared *in situ* without isolation. The eleven different catalyst systems that have been studied are ($Q^+ = [MeNOc_3]^+$; Oc = *n*-octyl; C_5H_5N = pyridine):

- 12 $[MeNOc_3]Cl$ + aqueous NaZnPOM, i.e., QZnPOM *in situ*
- $[MeNOc_3]_{12}[WZn_3(ZnW_9O_{34})_2]$, i.e., QZnPOM *isolated*
- 3 $[C_5H_5N(CH_2)_{15}Me]Cl + H_3[PO_4(WO_3)_{12}]$, i.e., Ishii *in situ*
- $[C_5H_5N(CH_2)_{15}Me]_3[PO_4(WO_3)_{12}]$, i.e., Ishii *isolated*
- 3 $[MeNOc_3]Cl + H_3PO_4 + 4\ H_2WO_4$, i.e., Venturello *in situ*
- $[MeNOc_3]_3[PO_4\{WO(O_2)_2\}_4]$, i.e., Venturello *isolated*
- 2 $[MeNOc_3]Cl + 2\ H_2WO_4$, i.e., Prandi *in situ*
- $[MeNOc_3]_2[\{WO(O_2)_2\}_2O]$, i.e., Prandi *isolated*
- $[MeNOc_3]_{12}[WZnMn_2(ZnW_9O_{34})_2]$, i.e., QMnPOM *isolated*
- $[MeNOc_3]HSO_4 + 2\ Na_2WO_4 + PO(OH)_2CH_2NH_2$ i.e., Noyori *in situ*
- $[MeNOc_3]HSO_4 + 2\ H_2WO_4 + PO(OH)_2CH_2NH_2$ i.e., Noyori-plus *in situ*

The *isolated* catalysts can be divided into nonperoxo and peroxo systems. Nonperoxo systems, i.e., QZnPOM,[3,4] QMnPOM,[9] and Ishii,[10] are simply prepared from the required quaternary ammonium chloride and polytungstate species, as indicated above for their corresponding *in situ* preparation. The *isolated* peroxo catalysts, i.e., Venturello[11] and Prandi,[12] are prepared by dissolving H_2WO_4 in a large excess of aqueous H_2O_2 at 60 °C, followed by addition of QCl and (for the Venturello system) H_3PO_4. The Noyori system[13,14] has only been used with *in situ* generation of the catalyst.[15] The *in situ* QZnPOM was prepared by extraction of $ZnPOM^{12-}$ from an aqueous solution of NaZnPOM into the required organic solvent using QCl, with aqueous NaZnPOM being prepared through self-assembly according

---

[5] Sloboda-Rozner, D.; Witte, P.; Alsters, P. L.; Neumann, R. *Adv. Synth. Catal.* submitted.

[6] Sloboda-Rozner, D.; Alsters, P. L.; Neumann, R. *J. Am. Chem. Soc.* **2003**, *125*, 5280−5281.

[7] Tourné, C. M.; Tourné, G. F.; Zonnevijlle, F. *J. Chem. Soc., Dalton Trans.* **1991**, 143−151.

[8] Appleton, A. J.; Evans, S.; Lindsay Smith, J. R. *J. Chem. Soc. Perkin Trans. 2* **1996**, 281−285.

[9] Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1995**, *117*, 5066−5074.

[10] Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3587−3593.

[11] Venturello, C.; D'Aloisio, R. *J. Org. Chem.* **1988**, *53*, 1553−1557.

[12] Prandi, J.; Kagan, H. B.; Mimoun, H. *Tetrahedron Lett.* **1986**, *27*, 2617−2620. The original Prandi system uses $[BnPPh_3]Cl$ instead of $[MeNOc_3]Cl$ as the phase transfer catalyst.

[13] Satu, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310−8311.

[14] Satu, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905−915.

[15] The Noyori catalyst is not known in isolated form. In the presence of H_2O_2, both the aqueous as well as the organic layer is yellow-colored, which indicates that a yellow peroxo tungsten species is divided over both layers, thus hampering its isolation.

to eq 1.[7] The other *in situ* catalysts were obtained from the catalyst system components in the stoichiometry shown above.

Catalyst Activation and Induction Period. Initial experiments on cyclooctene epoxidation revealed an induction period of about half an hour in the conversion/time profile for the *isolated* Ishii and Prandi catalysts. This induction period was even observed at 60 °C. Consequently, subsequent experiments aiming at comparing catalyst activities were carried out by adding cyclooctene as the final reagent after these catalyst systems were activated for 1 h at 60 °C by stirring them under two-phase organic solvent/aqueous H_2O_2 conditions. Such a catalyst activation procedure before cyclooctene addition was also carried out for the corresponding *in situ* catalysts, but is was not required for QZnPOM, QMnPOM, and the *isolated* Venturello catalyst. For epoxidations with *in situ* catalyst systems, the occurrence of an induction period can be explained by time required for formation of the active W-peroxo species from the individual components of the catalyst system.[16,17] The occurrence of an induction period with the *isolated* Ishii and Prandi catalysts might also be related to Brégeault's observation that catalytic activity in W-catalyzed epoxidations is very low when H_2O_2 is added as the final reagent to systems in which the W-catalyst resides in the organic phase (as is the case in our experiments).[18] The absence of an induction period in case of QZnPOM, QMnPOM, and *isolated* Venturello indicates that the active W-peroxo species is rapidly formed from the POM precursors on contact with H_2O_2,[19] and that the peroxo-type Venturello species corresponds to the active epoxidizing species.[11] It should also be noted that the catalyst loading under our conditions (0.1 mol % W, corresponding to ([W] < 0.01 mol/L) is much lower than that commonly employed in W-catalyzed epoxidations (typically 2−5 mol % W). Aubry has shown that under such diluted, acidic conditions ([W] = 0.01 mol/L) tungstate interacts with H_2O_2 to a *mononuclear*, protonated $[WO(OH)(O_2)_2]^-$ species rather than to the *dinuclear* Prandi-type anion $[\{WO(O_2)_2\}_2O]^{2-}$ that is present under more concentrated ([W] = 1 mol/L) acidic conditions.[20] Accordingly, the induction period with the *isolated* Prandi system might be caused by generation of the mononuclear peroxotungstate species from its dinuclear precursor by hydrolysis (eq 2):

$$[\{WO(O_2)_2\}_2O]^{2-} + H_2O \rightarrow 2\,[WO(OH)(O_2)_2]^- \tag{2}$$

This hypothesis implies that the mononuclear species is much more active than the dinuclear peroxo-tungstate, since otherwise no induction period would be observed when starting with the *isolated*, dinuclear Prandi catalyst. This implication is supported by the catalyst activity comparisons that will be discussed below.

Catalyst Activity. From the viewpoint of industrial applicability, catalyst activity is one of the more important distinguishing factors that determines which catalyst system is preferred. Unfortunately, available literature data on catalyst activity of the above 11 systems cannot be compared readily because both reaction conditions as well as the amounts of these catalysts used in the experiments differ greatly.[21] Therefore, we decided to compare these catalysts under identical reaction conditions and at a constant catalyst concentration of 0.1 mol % W-atoms relative to cyclooctene.[22] As is evident from the greatly varying amount of W-atoms in the molecular formulas of the catalyst systems, expressing the catalyst concentration in mol % W is more relevant from an industrial applicability point of view than using mol % catalyst. Keeping the latter at a constant level would result in greatly varying weight percentages of the catalysts. At 0.1 mol % W, catalyst concentrations expressed in wt % relative to the alkene are very similar because the molecular weight of the catalysts is largely determined by the number of W-atoms in the molecular formula, and for practical industrial use comparing catalysts at a similar wt % level is preferred.

The catalyst activity experiments were carried out at 0.1 mol % W level by stirring a two-phase mixture of a 5 mol/L solution of cyclooctene in toluene and 1.5 mol equiv of H_2O_2 as a 50 wt % aqueous solution at 800 rpm,[23] with the temperature being varied from 20 to 60 °C. Conversion/time profiles are shown in Figure 2. The highest activities are observed for the *in situ* Venturello, Prandi, and Noyori-plus systems. The *in situ* Venturello, Prandi, and Ishii systems are all more active than the corresponding *isolated* systems. We attribute the higher *in situ* activity to residual acidity present in the *in situ* systems compared to the *isolated* systems (eqs 3−5):[24]

$$3\,[C_5H_5N(CH_2)_{15}Me]Cl + H_3[PO_4(WO_3)_{12}] \rightarrow [C_5H_5N(CH_2)_{15}Me]_3[PO_4(WO_3)_{12}] + 3\,HCl \tag{3a}$$

$$\text{Ishii } \textit{in situ} \rightarrow \text{Ishii } \textit{isolated} + 3\,HCl \tag{3b}$$

$$3\,QCl + H_3PO_4 + 4\,H_2WO_4 + 8\,H_2O_2 \rightarrow Q_3[PO_4\{WO(O_2)_2\}_4] + 12\,H_2O + 3\,HCl \tag{4a}$$

$$\text{Venturello } \textit{in situ} + 8\,H_2O_2 \rightarrow \text{Venturello } \textit{isolated} + 12\,H_2O + 3\,HCl \tag{4b}$$

$$2\,QCl + 2\,H_2WO_4 + 4\,H_2O_2 \rightarrow Q_2[\{WO(O_2)_2\}_2O] + 5\,H_2O + 2\,HCl \tag{5a}$$

$$\text{Prandi } \textit{in situ} + 4\,H_2O_2 \rightarrow \text{Prandi } \textit{isolated} + 5\,H_2O + 2\,HCl \tag{5b}$$

The importance of the acidic nature of the W-catalyst precursor species in the *in situ* experiments is illustrated by the fact that for *in situ* Venturello- and Prandi-catalyzed

---

[16] Tungstic acid dissolves only slowly in warm aqueous H_2O_2 with concomitant formation of a peroxo W-species.

[17] The $[PO_4(WO_3)_{12}]^{3-}$ anion in the Ishii system is known to react with H_2O_2 to Venturello type $[PO_4\{WO(O_2)_2\}_4]^{3-}$, see ref 18.

[18] Aubry, C.; Chottard, G.; Platzer, N.; Brégeault, J. M.; Thouvenot, R.; Chauveau, F.; Huet, C.; Ledon, H. *Inorg. Chem.* **1991**, *30*, 4409−4415.

[19] Peroxo W-species derived from $[WZn_3(ZnW_9O_{34})_2]^{12-}$ are known to form rapidly on contact with H_2O_2, as shown by ^{183}W NMR, see refs 5 and 7.

[20] Nardello, V.; Marko, J.; Vermeersch, G.; Aubry, J. M. *Inorg. Chem.* **1998**, *37*, 5418−5423.

[21] Not only catalyst loadings and temperatures vary greatly among different authors, but also H_2O_2/alkene ratios. Thus, some authors that use an excess of alkene measure yields based on H_2O_2 rather than on the substrate.

[22] Brégeault has also compared the epoxidation efficiency of various W-catalysts at constant W/alkene ratio, which was much higher (2 mol % W) than in our experiments (0.1 mol % W), see ref 18.

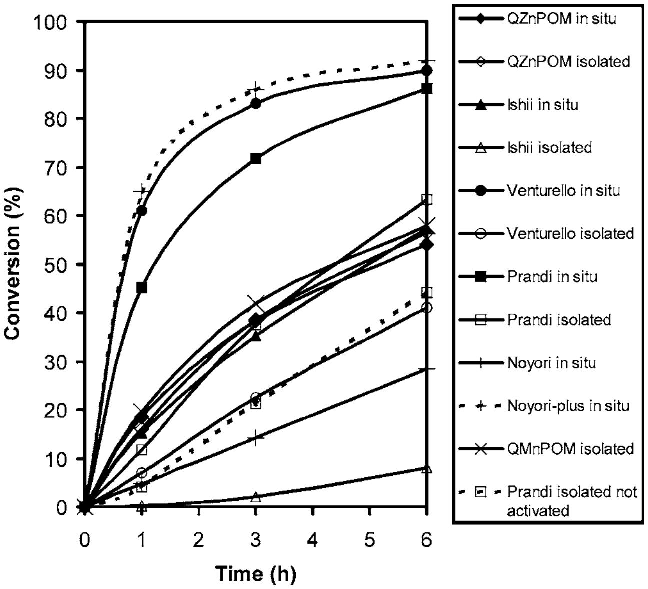

Figure 2. **Conversion/time profiles for the epoxidation of cyclooctene with 1.5 equiv of 50% H_2O_2 catalyzed by various W-based catalyst systems (0.1 mol % W) at 60 °C in toluene. The dotted □-□-□ labeled line shows the induction period of about 30 min that occurs when the *isolated* Prandi system is not activated by stirring for 1 h at 60 °C in the presence of H_2O_2. Similar induction periods in the absence of such catalyst activation were observed for the other *isolated* and *in situ* catalysts, except for QZnPOM QMnPOM, and *isolated* Venturello. The dotted +-+-+- labeled line refers to the *in situ* Noyori system with H_2WO_4 instead of Na_2WO_4 as the tungstate source.**

cyclooctene epoxidation negligible activities are observed on substitution of H_2WO_4 with Na_2WO_4, which generates NaOH on formation of a peroxotungstate species with H_2O_2.[25] In this respect, it is remarkable that the Noyori system, which is also based on Na_2WO_4, does show appreciable activity. This is probably a result of the acidic HSO_4^- anion in the phase transfer catalyst. In line with the strong activity increase on using H_2WO_4 instead of Na_2WO_4 as the tungstate source in the Venturello and Prandi systems, the performance of the Noyori system also improved significantly when using H_2WO_4 instead of Na_2WO_4. Of all tested catalysts, the H_2WO_4-based Noyori system was found to be the most active; hence, we named it the "Noyori-plus" system. It should be noted that the reported solvent-free cyclooctene epoxidation catalyzed by the original Na_2WO_4-based Noyori system was carried out at 90 °C with 0.2 mol % loading of Na_2WO_4. We conclude that the large, sometimes dramatic (*in situ* Venturello, Prandi) difference between H_2WO_4 and Na_2WO_4 as tungstate source in W-catalyzed epoxidations systems has been largely ignored in the literature.

Nearly identical activities are observed for *isolated* QMnPOM and *in situ* or *isolated* QZnPOM. As is evident from eq 1, HNO_3 required for the *in situ* preparation of QZnPOM is completely neutralized,[26] and the absence of any residual acidity in the preparation of *in situ* QZnPOM is in line with the observed identical activities of *in situ* and *isolated* QZnPOM. From the above it follows that activity differences between otherwise identical (*in situ* or *isolated*; H_2WO_4 or Na_2WO_4) catalyst systems can be rationalized qualitatively by simple recognition of acidity differences.[27] Similar to that in all the other systems, the activity of the POM catalysts probably increases by adding some additional acid. The somewhat lower activity of the POM systems compared to the *in situ* Venturello, Prandi, and Noyori-plus systems that appears from Figure 2 has to be judged against such acidity differences, with POM solutions having a near-neutral pH,[26] and the *in situ* Venturello, Prandi, and Noyori-plus systems reacting acidic. In addition, the activity measurements under identical reaction conditions and at a constant catalyst concentration of 0.1 mol % W-atoms reveal substantial differences between chemically distinct catalyst systems, with the highest activities being observed for the *in situ* Venturello, Prandi, and Noyori-plus systems. It is surprising that the Prandi and Venturello systems have a comparable activity, since Hill has found that Prandi's dinuclear $[\{WO(O_2)_2\}_2O]^{2-}$ species is at least 2 orders of magnitude *less* reactive in alkene epoxidation than Venturello's tetranuclear $[PO_4\{WO(O_2)_2\}_4]^{3-}$ complex.[28] This finding suggests that the actual epoxidizing species in the Prandi system is *not* dinuclear $[\{WO(O_2)_2\}_2O]^{2-}$. This conclusion is in line with the observation of an induction period for the *isolated* Prandi system, which was explained above by generation of *mononuclear* $[WO(OH)(O_2)_2]^-$ as the active epoxidizing species from binuclear $[\{WO(O_2)_2\}_2O]^{2-}$ through eq 2.

Optimization of the Prandi and QZnPOM Systems. Conversion/time profiles have also been measured for the *isolated* Prandi and QZnPOM systems under conditions identical to those described above, but without organic solvent or in 1,2-dichloroethane (DCE) instead of toluene as the solvent. Substitution of toluene with DCE was found to have a slightly beneficial effect on the activity at lower temperatures (20 and 40 °C), but at 60 °C activities were almost identical. Conversion/time values for *isolated* QZnPOM-catalyzed epoxidation of cyclooctene in toluene, DCE, or under solvent-free conditions at 20 and 60 °C are listed in Table 1. In terms of space−time yield the reaction proceeds most efficiently without any organic solvent, but

---

(23) Conversion/time profiles at varying stirring rates were independent of the rate of stirring above 200 rpm.

(24) Ishii also attributes the higher activity of the *in situ* Ishii system compared to the *isolated* catalyst to the higher acidity as a result of HCl evolution, see ref 10. A rate-enhancing effect of acidity in Venturello-type epoxidations has also been reported: Wang, M. L.; Huang, T. H.; Wu, W. T. *Ind. Eng. Chem. Res.* **2002**, *41*, 518−523.

(25) Remarkably, not only the pH but also the nature of the acid influences the activity of tungstate-based catalyst systems in epoxidations with H_2O_2. Thus, the lack of activity of Na_2WO_4 compared to that of H_2WO_4 cannot be compensated by addition of 2 mol equiv of HCl to the Na_2WO_4 catalyst. The Na_2WO_4/2HCl system is still not active, probably because another peroxo-W species is formed in contact with H_2O_2 rather than from H_2WO_4, as evidenced by different pH values and different color intensities of the Na_2WO_4/2HCl/H_2O_2 *vs* H_2WO_4/H_2O_2 systems. Note from ref 24 that HCl does have a positive effect on the Ishii system.

(26) The pH of an aqueous solution of NaZnPOM prepared according to eq 1 is 7.5.

(27) Even although many reactivity differences between the various catalyst systems can be understood qualitatively from differences in acidity, a simple reasoning based on acidity alone cannot account for all the differences, as has been pointed out in ref 25.

(28) Duncan, D. C.; Chambers, C.; Hecht, E.; Hill, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 681−691.

Table 1. **Conversion (%) after 6 h for the epoxidation of cyclooctene with 1.5 equiv of 50% H_2O_2 catalyzed by *isolated* QZnPOM (0.1 mol % W) at 20 and 60 °C without solvent, in toluene, or in DCE**

temperature (°C)	no solvent	toluene	DCE
20	16	10	24
60	54	56	54

Table 2. **Conversion (%) after 3 h for the epoxidation of cyclooctene with 1.5 equiv of 50% H_2O_2 catalyzed by NaZnPOM or *in situ* Prandi (0.1 mol % W) at 60 °C in toluene with different ratios of QCl/W**

	QCl/W ratio (mol/mol)											
catalyst	0	0.1	0.2	0.3	0.4	0.5	0.6	0.8	1	2	4	10
NaZnPOM	5	32	40	43		29			20	16	5	4
Prandi	1		89		89	89	94	87	76	27	5	5

such solvent-free epoxidations are evidently limited to substrates that are liquid at the reaction temperature.

Table 2 lists conversions after 3 h for the *in situ* Prandi system (QCl + H_2WO_4) and for QCl + NaZnPOM,[29] but with varying Q/W ratios. These 3-h conversions reflect the activities of the systems as observed from full conversion/time profiles similar to those of Figure 2, which have been measured in each case. Compared to the activity with Q/W = 1 (as used in the Prandi experiments for Figure 2), the activity of the Prandi system increases somewhat when less than the stoichiometric amount of QCl is used (with a 1/1 Q/W ratio being expected from the formation of $Q_2[W_2O_{11}]$ as the active species). When no QCl is added or when Q/W ≥ 2, the activity drops dramatically.

Optimization of the Q/W ratio for QZnPOM-catalyzed epoxidations has been carried out by adding varying amounts of QCl to an aqueous solution of NaZnPOM. In this case too, the highest activity is obtained with Q/W being less than the stoichiometric ratio (i.e. Q/W = 12/19 from Q_{12}-$[Zn_5W_{19}O_{68}]$), and leaving out QCl or increasing Q/W significantly above the stoichiometric ratio negatively affects the activity of the system. For both the Prandi as well as the QZnPOM system, the optimum Q/W ratio in terms of *maximum rate* (~0.6 for the Prandi system; ~0.3 for the QZnPOM system) is about half of the value expected from the catalyst stoichiometry. As will be discussed below, high Q/W ratios might be preferred in order to increase the *selectivity* of QZnPOM-catalyzed epoxidations.

NaZnPOM-Catalyzed Epoxidations of Geraniol. Even though *in situ* H_2WO_4-based catalyst systems are most active in terms of turnover frequency per mol W, the use of NaZnPOM in combination with a phase transfer catalyst (QZnPOM) is preferred for larger-scale use because ready-to-use stock solutions of NaZnPOM are easily made through eq 1, and epoxidations catalyzed by NaZnPOM do not require a catalyst activation step with H_2O_2 at elevated temperature that is considered troublesome on a large scale. As has been pointed out earlier, epoxidations with QZnPOM start without an induction period on addition of H_2O_2. Especially on production scale, this is considered to be advantageous since the occurrence of an induction period in highly exothermic reactions such as epoxidations might lead to uncontrollable processing caused by nonequilibrated heat transfer (nonisothermal conditions) that causes an increase of temperature, with the risk of a run-away. We therefore explored the scope of *in situ* NaZnPOM as a catalyst for the epoxidation of other alkenes besides cyclooctene.

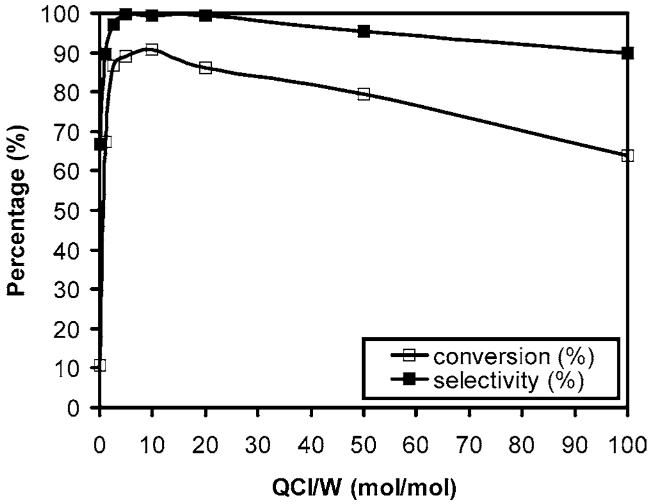

Figure 3. **Conversion and selectivity after 4 h *vs* QCl/W ratio in the epoxidation of geraniol with 1.06 equiv of 50% H_2O_2 catalyzed by *in situ* NaZnPOM (0.0005 mol %; 0.01 mol % W) at 60 °C in toluene.**

Although we found earlier that QZnPOM is an efficient catalyst for the epoxidation of allylic alcohols with aqueous H_2O_2,[3,4] we decided to study allylic alcohol epoxidation in greater detail using an aqueous, self-assembled NaZnPOM solution rather than *isolated* QZnPOM as the catalyst. To that end, geraniol was used as a typical allylic alcohol substrate, which undergoes regioselective 2,3-epoxidation with QZnPOM catalysis.[3,4] It was found that, under optimal conditions, the NaZnPOM catalyst loading can be drastically reduced compared to that in our earlier experiments with QZnPOM, which employed 0.1 mol % QZnPOM. As with cyclooctene, epoxidation of geraniol with NaZnPOM and QCl showed an optimum in the Q/W ratio. These Q/W optimization experiments were carried out with a NaZnPOM catalyst loading of only 0.0005 mol % NaZnPOM (0.01 mol % W) at 60 °C in a concentrated toluene solution. Some toluene (only 0.57 mL/mL of geraniol) was found to be beneficial to the selectivity, since in its absence (no solvent) a monophasic system is formed in the presence of 50% aqueous H_2O_2, and under such monophasic conditions the epoxide selectivity is low because of extensive hydrolysis. Figure 3 shows that both conversion and selectivity, measured after 4 h, reach an optimum at a Q/W ratio of about 10. It appears from these results that QCl lowers the Lewis-acidity of the POM catalyst, thus increasing selectivity by preventing POM-catalyzed epoxide hydrolysis. Note that the optimum Q/W value is much higher for geraniol than for cyclooctene.[30]

---

(29) For these experiments, isolated, crystalline NaZnPOM was used (prepared according to ref 7).

As can be judged from the foregoing, (self-assembled) NaZnPOM is an extremely efficient catalyst for allylic alcohol epoxidation with aqueous H_2O_2. Translated to 10 m^3 reactor production scale, 4.35 m^3 geraniol can be epoxidized with >90% yield for 2,3-geranyl oxide within 4 h in 2.5 m^3 toluene using 1.5 m^3 50% H_2O_2 and only 0.74 kg of NaZnPOM synthesized through self-assembly. This corresponds to a turnover frequency (TOF) of 43385 h^{-1}, a turnover number (TON) of 173538, and a space−time yield 95 $kg \cdot m^{-3} \cdot h^{-1}$ in such a 10 m^3 reactor. Both the TOF as well as the TON are much higher than the best values recently reported for allylic alcohol epoxidation with a tungsten catalyst, i.e. TOF = 594 h^{-1} and TON = 4200 obtained with Prandi-type $K_2[\{WO(O_2)_2\}_2O]$ as the catalyst.[31,32]

Preparative NaZnPOM-Catalyzed Epoxidation of 3-Carene. 3-Carene presents a typical example of an alkene that is devoid of a reactivity-boosting allylic alcohol group and that affords an epoxide sensitive to acid- or base-catalyzed decompositions.[33,34] As expected, efficient epoxidation by self-assembled, *in situ* QZnPOM requires much higher catalyst loadings than with cyclooctene, which is much more reactive.[2] To obtain reasonably good results for 3-carene epoxidation catalyzed by *in situ* QZnPOM, it was required to add some phosphate buffer (pH = 7.0), which suppressed epoxide hydrolysis. Still, only a 60% nonisolated yield was obtained at 65% conversion with 5 mol % W after 21 h at 60 °C. We decided to look for an alternative to QCl as the phase transfer agent to improve the results. We were intrigued by hexadecyl(2-hydroxyethyl)dimethylammonium dihydrogenphosphate (Luviquat mono CP) as a potential bifunctional phase transfer catalyst for NaZnPOM-catalyzed epoxidations, with the ammonium cation providing solubility in the organic phase and the $H_2PO_4^-$ anion providing pH buffering capacity to the system, thus preventing epoxide hydrolysis.[35] Luviquat mono CP finds extensive application in hair and skin care product formulations.[36] Accordingly, it is readily available on a large scale, inexpensive, and biocompatible. These properties add positively to its relevance for large-scale applications, even though the use of this compound as a phase transfer catalyst seems to have been overlooked in the chemical literature.

We were, therefore, pleased to find that 3-carene is epoxidized in high yield on a 1 mol scale by the combined Luviquat mono CP/*in situ* NaZnPOM catalyst system. At a catalyst loading of 4.4 mol % Luviquat mono CP and 5 mol % W (0.26 mol % NaZnPOM; 6.7 wt % W relative to 3-carene), the reaction was completed within a few hours with 1.5 equiv of H_2O_2 at 60 °C in toluene as the solvent. A remarkable property of this system is that during the reaction a very stable emulsion is present that requires a turbine stirrer to ensure efficient mixing during H_2O_2 addition, but at the end of the reaction this emulsion separates readily into an aqueous and organic layer within a few minutes (Figure 4). This greatly facilitates the workup procedure (see Experimental Section). No problems arising from foam formation were encountered during the workup. 3-Carene oxide was isolated after distillation in 78% yield (the nonisolated yield was near-quantitative).

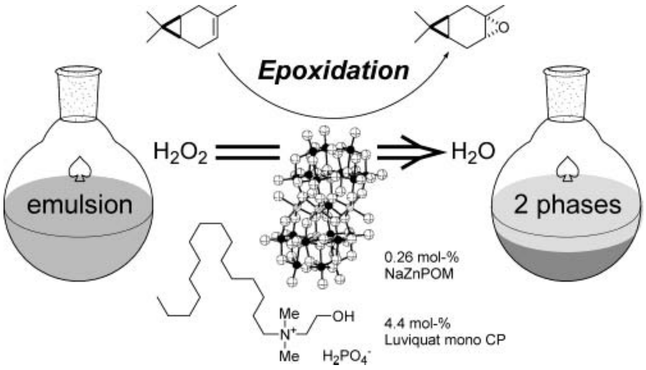

Figure 4. **Epoxidation of 3-carene with H_2O_2 catalyzed by the mixed *in situ* NaZnPOM/Luviquat mono CP system, accelerating the reaction through formation of a stable emulsion that easily separates into an aqueous and organic phase at full conversion.**

Conclusions

The present study has shown that, when compared under identical conditions and at equal level of 0.1 mol % W-atoms, *in situ* catalyst systems based on H_2WO_4 (Venturello, Prandi, and Noyori-plus) have the highest activity of the 11 W-catalyst systems tested for the epoxidation of cyclooctene with H_2O_2. H_2WO_4-based systems that also contain a phosphate source (Venturello, Noyori-plus) are somewhat faster than the simple Prandi system without phosphate. Acid liberated on formation of *in situ* catalysts was found to have a pronounced rate-enhancing effect. The acid effect is also thought to be responsible for the negligible or strongly reduced activity observed when H_2WO_4 is replaced with Na_2WO_4 in Venturello, Prandi, and Noyori systems. For all catalysts, except QZnPOM, QMnPOM, and *isolated* Venturello, a significant induction period was observed before the epoxidation starts efficiently. The fact that this induction period was, surprisingly, also present for the *isolated*, peroxo-type Prandi catalyst indicates that the active epoxidizing species is not the same as the binuclear peroxo $[\{WO(O_2)_2\}_2O]^{2-}$ species added through the catalyst. Evidence has been presented that under these conditions with a very low W-catalyst concentration the actual epoxidizing species in the Prandi system might be mononuclear $[WO(OH)(O_2)_2]^-$ formed by hydrolysis of binuclear $[\{WO(O_2)_2\}_2O]^{2-}$ under the acidic reaction conditions. Optimization experiments of

---

(30) It should be noted that the Q/W optimization experiments for cyclooctene were carried out with crystalline, *isolated* NaZnPOM, rather than with a self-assembled NaZnPOM solution, used for optimizing the Q/W ratio for the epoxidation of geraniol. The self-assembled solutions contain, besides NaZnPOM, substantial amounts of $NaNO_3$ (see eq 1). Nitrate might compete with the POM anion in transfer to the organic layer $[MeNOc]^+$, thus necessitating the use of more QCl.

(31) Kamata, K.; Yamaguchi, K.; Hikichi, S.; Mizuno, N. *Adv. Synth. Catal.* **2003**, *345*, 1193−1196.

(32) When expressed per mol W rather than per mol W-catalyst, the corresponding values for NaZnPOM are: TOF = 2283 h^{-1}; TON = 9134, and those for $K_2[\{WO(O_2)_2\}_2O]$ correspond to: TOF = 297 h^{-1}; TON = 2100.

(33) Arata, K.; Bledsoe, J. O.; Tanabe, K. *J. Org. Chem.* **1978**, *43*, 1660−1664.

(34) Villa de P., A. L.; Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *J. Org. Chem.* **1999**, *64*, 7267−7270.

(35) In addition, phosphate might influence catalyst performance through interaction with the polyoxotungstate, analogous to the Venturello system.

(36) See: http://www.basf.com/businesses/consumer/cosmeticingredients/html/mquaternary.html.

epoxidations catalyzed by QCl/NaZnPOM or QCl/H_2WO_4 have shown that the optimum Q/W ratio does not correspond to that expected from catalyst stoichiometry. In addition, the optimum Q/W ratio depends on the alkene that is epoxidized. For large-scale applications, the use of NaZnPOM in combination with a suitable phase transfer catalyst is preferred over H_2WO_4-based catalysts, since the latter require a catalyst activation step that is not readily carried out on a large scale.[37] In contrast, NaZnPOM-catalyzed epoxidations start without an induction period on addition of H_2O_2, thus avoiding nonisothermal processing conditions. It has been shown that a readily available aqueous solution of NaZnPOM prepared through self-assembly is effective for catalyzing epoxidations and other reactions with H_2O_2.[5,6] The 1 mol-scale epoxidation of 3-carene catalyzed by self-assembled NaZnPOM has been demonstrated. This reaction was found to proceed very efficiently with Luviquat mono CP as a multifunctional cocatalyst with emulsifying, buffering, and phase transferring properties. MZnPOM (M = Na, Q) gain further in attractiveness as catalysts for industrial applications because they can be efficiently recycled, thus also allowing higher catalyst loadings. Results on this will be published soon.

Experimental Section

General Information. Solvents and chemicals (including cyclooctene oxide, used as reference material for GC analysis) were commercial products used without purification. GC spectra were measured on an HP6890 spectrometer, using a cross-linked 5% PH ME siloxane column.

Comparison of W-Based Catalyst Systems in the Epoxidation of Cyclooctene. The following describes three procedures, taking into account the need to prepare the *in situ* catalysts or the need to activate catalysts that show a pronounced induction period, which was not observed in each of the following procedures. In these experiments, mass balances >95% were found by GC analysis.

Procedure A: QZnPOM *isolated*, QZnPOM *in situ*, QMnPOM *isolated*, Venturello *isolated*: A 50-mL flask was charged with catalyst (25 μmol W = 1.32 μmol POM[38] or 6.25 μmol Venturello[39]) and (when appropriate) solvent (toluene or DCE; 5 mL). The flask was immersed in a bath with the desired temperature (20, 40, or 60 °C) and stirred at 800 rpm. Subsequently were added *n*-dodecane (internal standard; 227 μL, 1 mmol), cyclooctene (3.25 mL, 25 mmol), and 50% aqueous H_2O_2 (2.1 mL, 37 mmol). Samples (25 μL) were taken after 1, 3, and 6 h. The samples were diluted with toluene (1 mL) before GC analysis.

Procedure B: Ishii *isolated*, Prandi *isolated*: A 50-mL flask was charged with catalyst (25 μmol W = 2.1 μmol Ishii; 12.5 μmol Prandi)[40] and (when appropriate) solvent (toluene or DCE; 5 mL). After addition of 50% aqueous H_2O_2 (2.1 mL, 37 mmol), the flask was stirred at 800 rpm for 1 h in a bath of 60 °C. The bath was brought to the desired temperature (20, 40, or 60 °C). Subsequently were added *n*-dodecane (internal standard; 227 μL, 1 mmol) and cyclooctene (3.25 mL, 25 mmol). Samples (25 μL) were taken after 1, 3, and 6 h. The samples were diluted with toluene (1 mL) before GC analysis.

Procedure C: Ishii *in situ*, Venturello *in situ*, Prandi *in situ*, Noyori *in situ*, Noyori-plus *in situ*: A 50-mL flask was charged with W-catalyst precursor (25 μmol W = 6.6 mg, 2.1 μmol $H_3[PO_4(WO_3)_{12}]\cdot xH_2O$ ($x \approx 15$) for Ishii; 6.2 mg, 25 μmol H_2WO_4 for Venturello, Prandi, and Noyori-plus; 8.2 mg, 25 μmol $Na_2WO_4\cdot 2H_2O$ for Noyori), the appropriate P-source (39 μL, 6.25 μmol aqueous 0.16 mol/L H_3PO_4 for Venturello; 1.4 mg, 13 μmol $PO(OH)_2CH_2NH_2$ for Noyori and Noyori-plus), and 50% aqueous H_2O_2 (2.1 mL, 37 mmol). The flask was stirred at 800 rpm for 1 h in a bath of 60 °C. The bath was brought to the desired temperature (20, 40, or 60 °C). A solution of the phase transfer catalyst (2.2 mg, 6.1 μmol $[C_5H_5N(CH_2)_{15}Me]Cl\cdot H_2O$ for Ishii; 7.6 mg, 19 μmol QCl for Venturello; 10.1 mg, 25 μmol QCl for Prandi; 5.8 mg, 13 μmol $QHSO_4$ for Noyori) in the solvent (toluene or DCE; 5 mL) was added.[41] Subsequently were added *n*-dodecane (internal standard; 227 μL, 1 mmol) and cyclooctene (3.25 mL, 25 mmol). Samples (25 μL) were taken after 1, 3, and 6 h. The samples were diluted with toluene (1 mL) before GC analysis.

Optimization of the Q/W ratio for NaZnPOM was carried out by dissolving NaZnPOM (1.5 mg, 5 μmol W = 0.26 μmol POM) in aqueous 50% H_2O_2 (420 μL, 7.5 mmol), followed by subsequent addition of a solution of QCl (different amounts) in toluene (1 mL), and *n*-dodecane (internal standard; 45.4 μL, 0.2 mmol). Finally, the mixture was warmed to 60 °C, and cyclooctene (651 μL, 5 mmol) was added. The amounts of QCl (in mg) per 1 mL of toluene solution were: 0, 0.2, 0.4, 0.6, 1, 2, 4, 8, and 20.

Optimization of the Q/W ratio for *in situ* Prandi was carried out by stirring H_2WO_4 (1.3 mg, 5 μmol) in aqueous 50% H_2O_2 (420 μL, 7.5 mmol) for 1 h at 60 °C. Subsequently, to the clear solution were added a solution of QCl (different amounts) in toluene (1 mL), *n*-dodecane (internal standard; 45.4 μL, 0.2 mmol), and cyclooctene (651 μL, 5 mmol). The amounts of QCl (in mg) per 1 mL of toluene solution were: 0, 0.4, 0.8, 1, 1.2, 1.6, 2, 4, 8, and 20.

Epoxidation of Geraniol Catalyzed by Self-Assembled NaZnPOM. Generation of the self-assembled NaZnPOM stock solution: $Na_2WO_4\cdot 2H_2O$ (16.5 g, 50 mmol) was dissolved in water (45 mL) at 85 °C. At this temperature, aqueous 65% HNO_3 (3.3 mL, 48 mmol) was added. The yellow solid that was formed dissolved almost immediately, and the reaction mixture was heated to 95 °C. A solution of $Zn(NO_3)_2\cdot 6H_2O$ (3.91 g, 13 mmol) in water (15 mL) was added dropwise in 4 h to the well-stirred solution. The slightly turbid mixture was added with stirring to water (300

---

[37] Obviously, use of *isolated* peroxo-type catalysts (Venturello, Prandi) is not feasible on a large scale.

[38] A W-catalyst stock solution (92 μL; 0.27 mol W/L) of *isolated* QZnPOM or QMnPOM (0.014 mol/L) in toluene was added. See ref 4 for the preparation of stock solutions.

[39] A W-catalyst stock solution (92 μL; 0.27 mol W/L) of *isolated* Venturello (0.068 mol/L) in toluene was added. See ref 11 for the preparation of stock solutions.

[40] A W-catalyst stock solution (92 μL; 0.27 mol W/L) of *isolated* Prandi (0.135 mol/L) in toluene was added. Ishii *isolated* was added as a solid (7.9 mg, 2.1 μmol).

[41] In reactions without solvent, the phase transfer catalyst was added as a solution in the required amount of cyclooctene.

mL) at room temperature, and more water was added until a total weight of 500 g was reached. Concentration stock solution: 0.1 mmol W/g.

Optimization of the Q/W ratio in the epoxidation of geraniol: A solution of QCl (different amounts) in toluene (5 mL) was mixed with NaZnPOM stock solution (50 mg, 5 μmol W) at room temperature, and geraniol (8.7 mL, 50 mmol) was added. The mixture was warmed to 60 °C, and aqueous 50% H_2O_2 (3 mL, 53 mmol) was added. The mixture was stirred at 60 °C. After 4 and 20 h, a sample (50 μL) of the reaction mixture was taken and diluted with diethyl ether (1 mL) before GC analysis. The amounts of QCl (in mg) per 5 mL of toluene solution were: 0, 2, 5, 10, 20, 40, 100, and 200. Product identification of 2,3-epoxy geraniol was confirmed by isolation and subsequent NMR analysis.[42]

One Molar Scale Epoxidation of 3-Carene Catalyzed by Self-Assembled NaZnPOM. The slightly turbid mixture obtained after addition of $Zn(NO_3)_2 \cdot 6H_2O$ (3.91 g, 13 mmol) to the $Na_2WO_4 \cdot 2H_2O$ (16.5 g, 50 mmol)/HNO_3 mixture as described above for preparing the NaZnPOM stock solution was added at 20 °C with stirring at 500 rpm to a mixture of toluene (200 mL), 3-carene (159 mL, 1 mol), and aqueous 30% Luviquat mono CP (60 mL, 44 mmol) in a 1-L jacketed glass reactor (diameter: 12 cm) equipped with a turbine stirrer (6 blades; diameter: 6 cm). A white emulsion formed, which was warmed to 60 °C. To this mixture a small portion of aqueous 50% H_2O_2 (5 mL, 0.1 mol) was added in one minute, followed by dropwise addition of the remaining 50% H_2O_2 (80 mL, 1.4 mol) in 3.5 h. During the addition, the temperature was kept between 60 and 65 °C. After complete addition, the mixture was stirred for 5 h at 60 °C. GC analysis showed a near quantitative yield of 3-carene oxide. After cooling to room temperature, the turbid yellow organic layer was separated, and the clear water layer was washed with toluene (200 mL). The organic layers were combined, dried with Na_2SO_4 (50 g), filtered, and tested for peroxide content ($>$25 mg/L) with peroxide test paper. The peroxide content was reduced to 10 mg/L by stirring the yellow solution with solid Na_2SO_3 (50 g) for 1 h. After filtration and removal of the solvent by rotary evaporation, 3-carene oxide was isolated by distillation (bp = 36 °C at 0.88 mbar). Yield: 118 g (78%). Product identification of 3-carene oxide was confirmed by subsequent NMR analysis.[43]

Acknowledgment

The research was supported by the European Commission (G1RD-CT-2000-00347). We thank Dominique Callant (DSM Pharma Chemicals) for very useful suggestions on reactor and stirring equipment.

Received for review December 4, 2003.

OP034184O

---

(42) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004−4006.

(43) Karim, A.; Fdil, N.; Romane, A.; Allaoud, S.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A* **1996**, *108*, 15−21.