JOC Article

Chiral Hydroperoxides as Oxygen Source in the Catalytic Stereoselective Epoxidation of Allylic Alcohols by Sandwich-Type Polyoxometalates: Control of Enantioselectivity through a Metal-Coordinated Template

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The epoxidation of allylic alcohols is shown to be efficiently and selectively catalyzed by the oxidatively resistant sandwich-type polyoxometalates, POMs, namely $[WZnM_2(ZnW_9O_{34})_2]^{q-}$ [M = OV(IV), Mn(II), Ru(III), Fe(III), Pd(II), Pt(II), Zn(II); $q = 10-12$], with organic hydroperoxides as oxygen source. Conspicuous is the fact that the nature of the transition metal M in the central ring of polyoxometalate affects significantly the reactivity, chemoselectivity, regioselectivity, and stereoselectivity of the allylic alcohol epoxidation. For the first time, it is demonstrated that the oxovanadium(IV)-substituted POM, namely $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$, is a highly chemoselective, regioselective, and also stereoselective catalyst for the clean epoxidation of allylic alcohols. A high enantioselectivity (er values up to 95:5) has been achieved with $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ and the sterically demanding TADOOL-derived hydroperoxide TADOOH as regenerative chiral oxygen source. Thus, a POM-catalyzed asymmetric epoxidation of excellent catalytic efficiency (up to 42 000 TON) has been made available for the development of sustainable oxidation processes. The high reactivity and selectivity of this unprecedented oxygen-transfer process are mechanistically rationalized in terms of a peroxy-type vanadium(V) template.

Introduction

In contrast to the importance of catalytic oxidations for commodity chemicals production, most industrial fine chemicals are still made by classical organic stoichiometric methods. Since fine chemicals are usually manufactured in *liquid-phase* batch processes, there is a particularly large industrial potential for the wide variety of *homogeneously* catalyzed transformations currently available. Industrial application of homogeneous catalysts, however, makes high demands upon both catalyst *selectivity* as well *activity* to obtain economically and environmentally viable processes.[1] Therefore, there is a need for selective, highly persistent homogeneous catalysts that operate at very high catalyst-to-substrate ratios and are not readily deactivated by trace impurities.

In recent years, polyoxometalates (POMs), in particular their transition-metal-substituted derivatives, have received attention as promising oxidation catalysts for the selective oxidation of organic substrates by a variety of oxygen sources.[2,3] We found earlier that "sandwich-type" POMs, viz. $[ZnWM_2(ZnW_9O_{34})_2]^{q-}$, may be used as oxidation catalysts in the presence of aqueous H_2O_2 because they resist both oxidative as well as hydrolytic degradation.[4] This robustness, combined with the low cost and "green" nature of H_2O_2, make sandwich-POM-catalyzed oxidations based on H_2O_2 potentially attractive for large-scale industrial use, in particular when these POMs meet

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the criterion of sufficiently high catalyst activity. A good example of remarkably high catalytic activity in hydrogen-peroxide-mediated oxidations is provided by the disubstituted manganese(II) POM, namely [WZnMn$_2$(II)(ZnW$_9$O$_{34}$)$_2$]$^{12-}$, which displays high selectivity for the epoxidation of alkenes and the oxidation of alcohols to their carbonyl products by 30% H$_2$O$_2$ in a biphasic system.[4a,b] Other isostructural analogues with disubstituted noble metals [Rh(III), Pd(II), Pt(II), and Ru(III)] have also been shown to exhibit activity in alkene and alkane oxidations by H$_2$O$_2$ and *t*-BuOOH.[5] In fact, the ruthenium derivative was effective in the oxidation of adamantane even by molecular oxygen.[6] Very recently, we have demonstrated the efficacy of the oxidatively and solvolytically resistant sandwich-type polyoxometalates for the epoxidation of the chiral allylic alcohols **1** by hydrogen peroxide (30%).[7] High (>95%) chemo-, regio-, and diastereoselectivity have been achieved in the epoxidation of 1,3- or 1,2-allylically strained alcohols. These epoxidations were also efficiently catalyzed by a non-transition-metal-substituted POM, e.g., [WZn$_3$(ZnW$_9$O$_{34}$)$_2$]$^{12-}$.[7]

Despite the wide set of POM-catalyzed transformations, there is to date no report on POM-catalyzed asymmetric oxidations. Conventionally, catalytic asymmetric oxidations are achieved through the combination of chiral metal complexes with achiral oxygen sources. Prominent examples are the Sharpless−Katsuki epoxidation of allylic alcohols[8] and the Jacobsen−Katsuki epoxidation of unfunctionalized alkenes.[9] Chirally modified vanadium complexes have also received considerable scrutiny in asymmetric catalysis.[10] A highly promising asymmetric epoxidation of allylic alcohols was reported by Sharpless as early as 1977, in which enantiomeric ratio (er) values of up to 90:10 have been obtained by the combination of VO(acac)$_2$ and chiral hydroxamic acid, with *tert*-butyl hydroperoxide as oxygen source.[11] Recently, Yamomoto and co-workers achieved a remarkable improvement in the existing vanadium-based asymmetric protocol that allows optically active epoxy alcohols to be obtained with er values of up to 98:2.[12] The disadvantages in all of these vanadium-mediated asymmetric epoxidations are the requirement of a multifold excess of the chiral ligand with respect to the vanadium catalyst (1−10 mol %) and the pronounced "ligand deceleration", which both undoubtedly reduce the catalytic efficiency.[10−12]

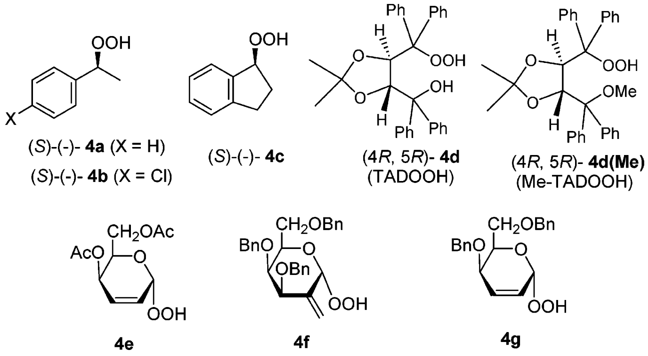

FIGURE 1. Chiral hydroperoxides used as inductors as well as oxygen donors for asymmetric oxidation.

In recent years, alternatively, catalytic enantioselective oxidations have been conducted by combining optically active hydroperoxides **4** (Figure 1; *these organic hydroperoxides are potentially dangerous and should be handled with care*) and achiral metal complexes.[13] An early example on the asymmetric epoxidation of allylic alcohols under titanium catalysis employed optically active sugar-derived (**4e**−**g**)[13a,b] or simple secondary alkyl (**4a**−**c**) hydroperoxides,[13c] which gave er values of 75:25 at best. Very recently, more successful was the VO(O^{i}Pr)$_3$-catalyzed asymmetric epoxidation with the sterically demanding TADDOL-derived hydroperoxide TADOOH (**4d**, = [(4*R*,5*R*)-5-[(hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]diphenylmethanol) in the presence of an achiral hydroxamic acid ligand, which displayed higher (up to 86:14) er values for the epoxy alcohols.[14] In addition, we have utilized such alkyl hydroperoxides in the asymmetric Weitz−Scheffer epoxidation of α,*β* enones and obtained er values of up to 95:5.[13e] Especially high enantioselectivities (er values up to 99:1) have been achieved with TADOOH as chiral oxygen source in the asymmetric Weitz−Scheffer epoxidation, the Baeyer−Villiger oxidation, and in sulfoxidations.[13f]

The good performance of these POM catalysts with aqueous H$_2$O$_2$ prompted us to use sandwich POMs as epoxidation catalysts in combination with organic hydroperoxides, which are often superior to those by H$_2$O$_2$ in regard to selectivity.[15] Furthermore, the successful application of chiral hydroperoxides in asymmetric oxidations encouraged us to employ them as chiral oxygen sources to develop POM-catalyzed asymmetric oxidations. Indeed, in a very recent report, high enantioselectivities (er values up to 95:5) have been accomplished with TADOOH in the catalytic epoxidation of allylic alcohols by the oxovanadium(IV)-disubstituted, sandwich-type

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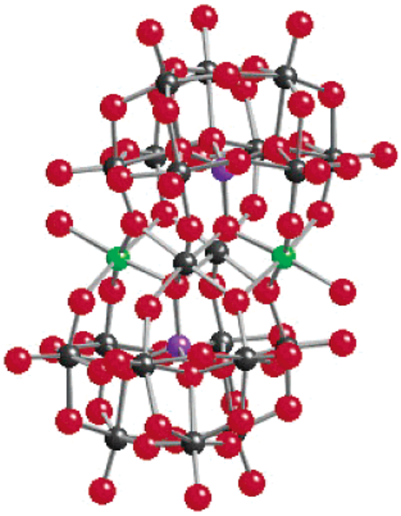

FIGURE 2. Ball-and-stick model of the $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ polyoxometalate.

POM $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ (Figure 2).[16] We report here a detailed study on the use of sandwich-type POMs, in particular $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$, as a highly active catalyst for the asymmetric epoxidation of allylic alcohols by chiral hydroperoxides. In addition, we compare the reactivity of a family of transition-metal-substituted sandwich POMs with hydroperoxides for the epoxidation of allylic alcohols, and show that the reactivity patterns are distinctly different for these sandwich POMs.

Results

An efficient POM-based catalyst was required for the selective epoxidation of allylic alcohols by chiral hydroperoxides as oxygen donor. For this purpose, first an extensive screening of various transition-metal-substituted sandwich-type POMs, namely $[ZnWM_2(ZnW_9O_{34})_2]^{q-}$ (M-POM for convenience; M = OV^{IV}, Mn^{II}, Ru^{III}, Fe^{III}, Zn^{II}, Pd^{II}, and Pt^{II}), was conducted with racemic alkyl hydroperoxides (see Table S1, Supporting Information).[16] The secondary allylic alcohol mesitylol (**1a**) was chosen as model substrate, since it is an established probe for the assessment of the chemoselectivity and diastereoselectivity in metal-catalyzed oxidations,[17] whereas the racemic [1-(4-chlorophenyl)]ethyl hydroperoxide (**4b**) was employed as oxygen donor.

This screening revealed that the oxovanadium(IV)-substituted POM, namely $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ or O=V(IV)-POM for short, was the most reactive and selective catalyst for the epoxidation of allylic alcohols. As shown in Table S1 (Supporting Information), at ambient temperature (ca. 20 °C) and within 24 h, complete conversion (> 95%), excellent chemoselectivity (no enone formation), as well as high diastereoselectivity (threo/erythro = 91:9) were observed in the oxovanadium(IV)-substituted POM-catalyzed epoxidation with only 0.01 mol % catalyst loading (entry 1). At 50 °C, the reactivity was considerably enhanced (>95% conversion in 6 h) without sacrifice of the selectivities (entry 2). By contrast, when other transition-metal-substituted POMs (Mn^{II}, Ru^{III}, Fe^{III}, Zn^{II}, Pd^{II}, Pt^{II}) were employed as catalysts, no reaction occurred at ambient temperature (not shown in Table S1, Supporting Information). Nevertheless, at elevated temperature (50 °C), the M-POMs showed catalytic activity (convn 8−94%), but these oxidations were accompanied by some (up to 30%) undesirable enone formation (entries 3−8). This indicates that in contrast to the aforementioned allylic alcohol epoxidation by H_2O_2,[7] transition-metal-substituted sandwich POMs are essential for reactivity in the epoxidation of allylic alcohols by hydroperoxides. However, the diastereoselectivity is independent of the transition metal in the M-POM catalyst, since nearly the same threo/erythro ratios were observed in all cases (Table S1, entries 1−8, Supporting Information).

Although the sandwich-type POM $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ has been known for some time,[18] its utilization for catalytic oxidations has hitherto apparently not been realized. Thus, with the O=V(IV)-POM as catalyst, the epoxidation of a variety of chiral allylic alcohols 1 with 1,2- and 1,3-allylic strain has been carried out by the racemic (1-phenyl)ethyl hydroperoxide (**4a**) as oxygen donor (Table 1) to assess the chemoselectivity and diastereoselectivity. As is evident from Table 1, the sandwich-type O=V(IV)-POM catalyzes efficiently the epoxidation of the chiral allylic alcohols **1** to the corresponding epoxy alcohols **2** by the alkyl hydroperoxide, most of them in excellent conversions and high yields. The usual undesirable allylic oxidation (C−H bond insertion) to the α,*β*-unsaturated ketone **3** was observed to a minor extent (5−15%) only for cyclic allylic alcohols (Table 1, entries 6 and 7). A control experiment in the absence of substrate showed that no unproductive decomposition of the oxygen source occurred even at a higher temperature (50 °C).

The allylic alcohol **1a** with 1,3-allylic strain (entry 1) afforded the *threo*-epoxy alcohol quantitatively in high diastereoselectivity (91:9). With *tert*-butyl hydroperoxide (entry 2) instead of (1-phenyl)ethyl hydroperoxide (**4a**), a significantly lower conversion (65%) was obtained under identical reaction conditions. A comparatively low reactivity (64% convn) was observed for the allylic alcohols **1b** with 1,2-allylic strain due to the poorer nucleophilicity of the terminal double bond. Mechanistically more significant, the erythro-configured epoxide **2b** was produced in excellent diastereoselectivity (entries 3). This reveals that both 1,2- and 1,3-allylic strain operate in the stereocontrol of the oxygen transfer to the chiral allylic alcohols **1** in the O=V(IV)-POM-catalyzed epoxidation. Consequently, substrate **1c** (entry 4) with both 1,2- and 1,3-allylic strain was epoxidized in low diastereoselectivity because of the opposing sense in the stereochemical differentiation displayed by these two types of allylic strains. Significant in regard to regioselectivity is the finding that 1-methylgeraniol (**1d**) with two distinct double bonds gave only the 3,4-epoxide in excellent yield and high diastereoselectivity (entry 5).

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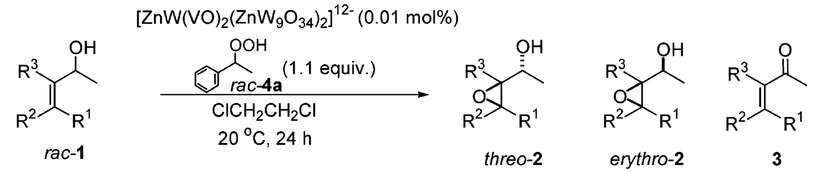
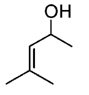
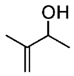
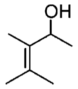
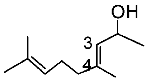
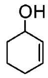
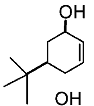
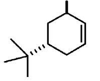
TABLE 1. Diastereoselective Epoxidation[a] of Chiral Allylic Alcohols 1 with Racemic (1-Phenyl)ethyl Hydroperoxide (4a), Catalyzed by the $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$



entry	substrate	convn[b] [%]	yield[b,c] [%]	selectivity[b] chemo (2 : 3)	selectivity[b] diastereo (*threo*:*erythro*)
1	 **1a**	> 95	*93*	> 95 : 5	91 : 9
2		65 (*t*-BuOOH)	90[d]	> 95 : 5	87 : 13
3	 **1b**	64	88[d]	> 95 : 5	6 : 94
4	 **1c**	90	90[d]	> 95 : 5	58 : 42
5	 **1d**	> 95	*94*[e]	> 95 : 5	91 : 9
6	 **1e**	> 95 (50 °C)	*86*	95 : 5	> 95 : 5 (*cis*:*trans*)
7	 *cis*-**1f**	75 (50 °C)	78[d]	85 : 15	92 : 8 (*cis*:*trans*)
8	 *trans*-**1f**	> 95 (50 °C)	88	> 95 : 5	> 95 : 5 (*cis*:*trans*)

[a] All reactions were carried out in 1,2-dichloroethane at ca. 20 °C in the presence of 1.1 equiv of hydroperoxide and 0.01 mol % $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$, unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture, ca. 5% error of the stated values; material balances (mb) > 95%. [c] Isolated material (values in italics) after silica gel chromatography; the diasteromers could not be separated on silica gel chromatography. [d] Based on the conversion of allylic alcohol. [e] Only 3,4-epoxide was observed.

2-Cyclohexen-1-ol (**1e**) was found to be less reactive than the acyclic allylic alcohols and gave selectively the *cis*-epoxy alcohol **2e** (entry 6), but a higher (50 °C) temperature was necessary for complete conversion. In the oxidation of the two conformationally rigid *cis*- and *trans*-5-*tert*-butyl-2-cyclohexenols (**1f**, entries 7 and 8), as much as 15% of enone was formed from the cis isomer (OH pseudoequatorial, α 140°); however, the trans isomer (OH pseudoaxial, α 110°) gave the epoxide exclusively. In both cases, high diastereoselectivities in favor of the *cis*-epoxides were observed.

For the purpose of mechanistic comparison, the catalytic epoxidation of the chiral allylic alcohols **1** has also been conducted with Mn(II)-POM as catalyst instead of the O=V(IV)-POM at elevated temperature (50 °C). It was found that the Mn(II)-POM-catalyzed reactions exhibited substantially poorer selectivities as well as reactivities in all cases, compared to the O=V(IV)-POM (see Table S2, Supporting Information). As for the regioselectivity of the oxidation of geraniol (**1m**) and 1-methylgeraniol (**1d**) by racemic hydroperoxide **4a** as oxygen source, both 2,3/3,4 and 6,7/7,8 epoxides were obtained in a ca. 1:1 ratio, besides significant amounts of enone (Scheme 1).

These unique and highly chemoselective and diastereselective catalytic epoxidations of O=V(IV)-POM encouraged us to employ the enantiomerically pure hydroperoxides **4a**−**d** for asymmetric oxygen transfer. For this purpose, the prochiral allylic alcohol **1g** was chosen as test substrate,[19] the results are displayed in Table 2.

Initially, the reaction was carried out in 1,2-dichloroethane with the enantiopure (*S*)-**4a** at ca. 20 °C, under which conditions the primary allylic alcohol **1g** was selectively oxidized to the corresponding epoxy alcohol **2g** in excellent yield within 24 h, although a poor enantiomeric ratio (56:44) was obtained in favor of the 2*R*,3*R* enantiomer (entry 1). The epoxidations with the structurally related (*S*)-**4b** or the more rigid (*S*)-1-indanyl

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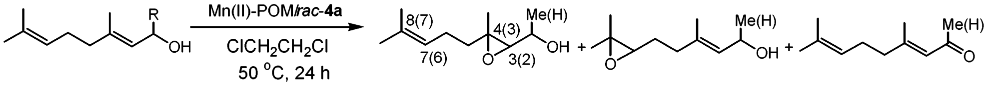
[19] Only primary allylic alcohols were used in this asymmetric study because kinetic resolution of racemic secondary allylic alcohols has been shown to give poor results in metal-catalyzed asymmetric epoxidations, see: (a) Adam, W.; Humpf, H.-U.; Roschmann, K. J.; M.; Saha-Möller, C. R. *J. Org. Chem.* **2001**, *66*, 5796−5800. (b) Adam, W.; Prikhodovski, S.; Roschmann, K. J.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2677−2681.

SCHEME 1. Mn(II)-POM-Catalyzed Epoxidation of 1-Methylgeraniol (1d) and Geraniol (1m) with the Racemic Hydroperoxide 4a as Oxygen Source[a,b]

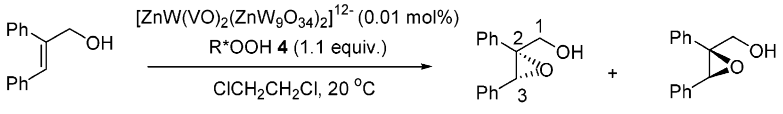


1 **2** **3**

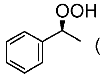
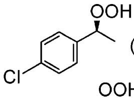
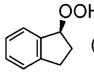
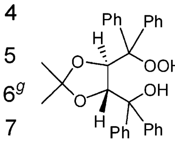
substrate	convn[b] [%]	mb[b] [%]	selectivity[b]	
			regio	chemo
1d (R = Me)	80	70	40:60 (3,4:7,8 **2d**)	91:09 (**2d**:**3d**)
1m (R = H)	60	80	60:40 (2,3:6,7 **2m**)	70:30 (**2m**:**3m**)

[a] Reactions were carried out in the presence of 1.1 equiv of the *rac*-**4a** hydroperoxide and 0.02 mol % of $[ZnWMn(II)_2(ZnW_9O_{34})_2]^{12-}$. [b]Conversions of allylic alcohol, material balances (mb), and product ratios were determined by ^1H NMR analysis of the crude reaction mixture with dimethyl isophthalate as internal standard; ca. 5% error of stated value.

TABLE 2. OV(IV)-POM-Catalyzed Asymmetric Epoxidation of the Primary Allylic Alcohol 1g with a Variety of Chiral Hydroperoxides as Oxygen Source[a]



1g (2*R*,3*R*)-**2g** (2*S*,3*S*)-**2g**

entry	R*OOH	time [h]	convn[b] [%]	yield[c] [%]	er[d] [%]	confign[e]
1	 (*S*)-**4a**	24	> 95	93	56 : 44	(2*R*,3*R*)-(-)
2	 (*S*)-**4b**	24	> 95	90	53 : 47	(2*R*,3*R*)-(-)
3	 (*S*)-**4c**	24	> 95	87	55 : 45	(2*R*,3*R*)-(-)
4	 (4*R*,5*R*)-**4d** TADOOH	48 (0 °C)	40	90[f]	95 : 5	(2*R*,3*R*)-(-)
5		30 (20 °C)	> 95	94	91 : 9	
6[g]		48	90	82	90 : 10	
7		36 (toluene)	95	88	86 : 14	
8		6 (50 °C)	> 95	92	85 : 15	

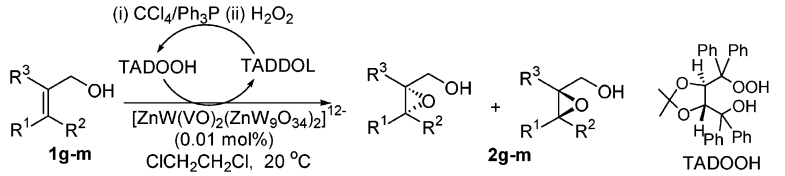
[a] Unless otherwise specified, all reactions were carried out in 1,2-dichloroethane at ca. 20 °C in the presence of 1.1 equiv of hydroperoxide and 0.01 mol % $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$; only epoxide was detected by ^1H NMR analysis of the crude reaction mixture. [b] Determined by ^1H NMR analysis of the crude reaction mixture, ca. 5% error of the stated values; material balance > 95%. [c] Isolated material after silica gel chromatography. [d] Enantiomeric ratio (er), determined by HPLC analysis on a chiral column (Chiralcel OD), ca. 1% error of the stated values. [e] Configuration of the major enantiomer. [f] Based on the conversion of allylic alcohol. [g] 0.002 mol % instead of 0.01 mol % catalyst was used.

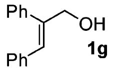
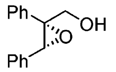
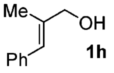
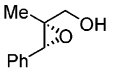
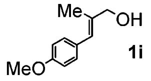
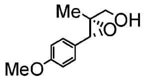
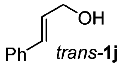
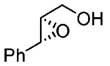
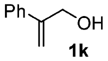
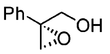
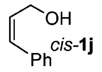
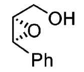
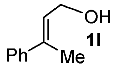
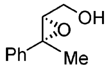
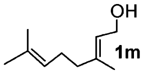
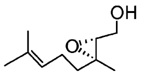
hydroperoxide (**4c**) did not improve the enantioselectivity of this catalytic oxygen transfer (entries 2 and 3).

Gratifyingly, the sterically demanding TADDOL-derived hydroperoxide TADOOH (**4d**) was found to be especially effective for the intended asymmetric oxygen transfer. Thus, the epoxidation of the primary allylic alcohol **1g** by TADOOH at 0 °C led to the (2*R*,3*R*)-configured epoxy alcohol **2g** in high enantioselectivity (er 95:5, entry 4), the highest enantioselectivity obtained so far. In view of the disadvantageously low reactivity at 0 °C, that is, conversion of 40% within 48 h, the reaction was conducted at 20 °C to achieve complete conversion (>95%) within 30 h quantitatively to the epoxide **2g** with an er value of 91:9 (entry 5). Significant for preparative purposes, a similar catalytic activity and identical enantioselectivity (entry 6) was achieved even at the very low catalyst loading of only 0.002 mol %, which illustrates the high efficiency (42 000 TON! The turn-over number is defined as mole epoxide formed per mole catalyst used) of the oxovanadium(IV)-substituted sandwich POM for the enantioselective epoxidation of allylic alcohols.

The use of toluene instead of 1,2-dichloroethane as solvent resulted in a somewhat lower (86:14) enantiomeric ratio (entry 7). Polar solvents such as THF and CH_3CN (data not shown) gave only traces of the epoxide

TABLE 3. O=V(IV)-POM-Catalyzed Asymmetric Epoxidation of Primary Allylic Alcohols with TADOOH as Chiral Oxygen Source[a]



entry	allylic alcohol	epoxy alcohol	time [h]	convn[b] [%]	yield[c] [%]	er[d] [%]	confign[e]
1	 1g		30	> 95	94	91 : 9	(2*R*, 3*R*)-(-)
2	 1h		30	> 95	92	92 : 8	(2*R*, 3*R*)-(+)
3	 1i		24	90	86	85 : 15	(2*R*, 3*R*)-(+)
4	 *trans*-1j		48	> 95	88	75 : 25	(2*R*, 3*R*)-(+)
5	 1k		36	95	93	71 : 29	(2*R*)-(+)
6	 *cis*-1j		48	92	84[i]	62 : 38	(2*R*, 3*S*)-(+)
7	 1l		24	> 95	88	60 : 40	(2*R*, 3*R*)-(+)
8	 1m		24	> 95	96	59 : 41[j]	(2*R*, 3*R*)-(+)

[a] All reactions were carried out in 1,2-dichloroethane at ca. 20 °C in the presence of 1.1 equiv of TADOOH and 0.01 mol % [ZnW(VO)$_2$(ZnW$_9$O$_{34}$)$_2$]$^{12-}$; only epoxide was detected by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture, ca. 5% error of the stated values; material balances >95%. [c] Isolated material after silica gel chromatography. [d] Enantiomeric ratio (er) determined by HPLC analysis on a chiral column (Chiralcel OD), unless otherwise noted; ca. 1% error of the stated values. [e] Configuration of the major enantiomer. [i] 9% of *trans*-epoxide (er 58:42) was obtained as 2*R*,3*R* enantiomer. [j] Determined by GC−MS analysis on a chiral column (β-TG).

product. As expected, the catalytic activity (>95% convn in 6 h) was enhanced at elevated temperature (50 °C), but accompanied by a lower enantioselectivity (er 85:15, entry 8).

Mechanistically significant is the finding that when the hydroxy-protected derivative Me-TADOOH [**4d**(**Me**)] was used instead of TADOOH under the identical conditions for the epoxidation of allylic alcohol **1g**, no reaction was observed even after 48 h (data not shown); both the substrate and oxygen source were completely recovered. From these results, it is concluded that 0.01 mol % of O=V(IV)-POM with TADOOH as chiral oxygen source in 1,2-dichloroethane at 20 °C are so far the best conditions for the catalytic asymmetric epoxidation of allylic alcohols.

Besides the high enantioselectivity, an additional advantage of the TADOOH compared to the other chiral hydroperoxides **4a**−**c** is the fact that it may be regenerated from the resulting TADDOL without loss of optical purity.[20] Thus, the use of TADOOH for the asymmetric epoxidation of differently substituted allylic alcohols **1g**−**m** under the optimized conditions (20 °C, ClCH$_2$CH$_2$Cl, 0.01 mol % catalyst) was studied in detail to assess the influence of substrate structure on the enantioselectivity. The results are shown in Table 3.

Quite generally, the similar cis-disubstituted allylic alcohols **1h** and **1i** (entries 2 and 3) were epoxidized in about as high enantioselectivity and yield as substrate **1g** (entry 1), but the *p*-OMe substitution in the aromatic ring of the derivative **1i** caused the enantioselectivity to drop somewhat to 85:15 (entry 3) from 92:8 (entry 2). The epoxidation of the monosubstituted allylic alcohols *trans*-**1j** and -**1k** afforded the corresponding epoxides in moderate enantioselectivies (entries 4 and 5), but in high yield. For substrate *cis*-**1j,** which is also a poor substrate under Sharpless conditions,[8] as well as for derivative **1l** with two substituents at the position C-3, low enantiomeric ratios were observed (entries 6 and 7). In the case of *cis*-**1j**, additionally 9% of the isomerized *trans*-epoxide was obtained, also in poor enantioselectivity. Analogous to the related 1-methylgeraniol (**1d**), geraniol (**1m**) was regioselectively epoxidized exclusively to the 2,3-epoxide in excellent yield, albeit in poor enantioselectivity (entry 8).

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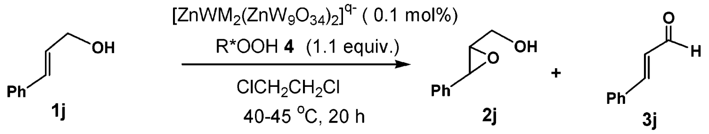
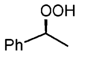
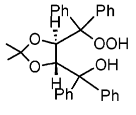
[20] The resulting TADDOL was recovered in >95% yield by silica gel chromatography without loss of optical purity, from which TADOOH may be easily regenerated; see ref 13f.

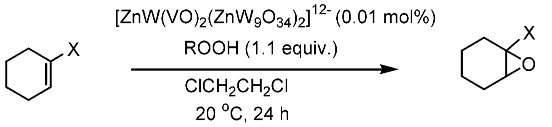
TABLE 4. Enantioselective Oxidation of Cinnamyl Alcohol (1j) Catalyzed by the Mn(II)- and Ru(III)-Substituted Polyoxometalates with Chiral Hydroperoxides 4 as Oxygen Source



entry	R*OOH	$[ZnWM_2(ZnW_9O_{34})_2]^{q-}$	convn[a] [%]	mb[a] [%]	product distribution [%][b]			er [%] [c]	config [d]
					2j	3j	PhCHO	2j	
1	 (*S*)-(-)-**4a**	Mn(II)	> 95	61	56	22	22	50 : 50	
2		Ru(III)	> 95	70	30	30	40	55 : 45	(*2R,3R*)-(+)
3	 TADOOH (**4d**)	Mn(II)	75	77	60	25	15	50 : 50	
4		Ru(III)	45	80	50	28	22	65 : 35	(*2R,3R*)-(+)

[a] Determined by ^1H NMR analysis directly on the crude reaction mixture, ca. 5% error of the stated value. [b] Normalized to 100%. [c] Enantiomeric ratio (er) determined by HPLC ananlysis on a chiral column (Chiralcel OD), ca. 1% error of the stated values. [d] Configuration of the major enantiomer.

SCHEME 2. Epoxidation of Unfunctionalized Cyclohexenes with Hydroperoxides 4 as Oxygen Source, Catalyzed by $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$



X = H *rac*-**4a** convn 13% mb > 95
X = Ph *rac*-**4a** convn 35% mb > 95
TADOOH (**4d**) convn 27% mb > 95 er < 55:45

To substantiate the pivotal role of the vanadium metal in the sandwich POM of this unprecedented asymmetric oxygen transfer, the vanadium-containing α-Keggin type POM, namely $PV_2Mo_{10}O_{40}^{5-}$, was also employed as catalyst. In the epoxidation of the test substrate **1g** with TADOOH under the optimal conditions, catalysis by $PV_2Mo_{10}O_{40}^{5-}$ gave a high enantiomeric ratio of 92:8; however, a very long reaction time (7 d) was required to achieve complete conversion (data not shown in Table 3).

The present results demonstrate that the oxovanadium(IV) sandwich POM is an efficient catalyst for the epoxidation of allylic alcohols. Its efficacy for epoxidation by hydroperoxides was also tested on unfunctionalized cyclohexenes as substrates (Scheme 2). Initial experiments were performed with racemic hydroperoxide **4a** as oxygen source for the optimization of the reaction conditions. The data in Scheme 2 disclose that a significantly lower reactivity (conversion) was observed for the unfunctionalized cyclohexenes than for allylic alcohols under identical reaction conditions. Furthermore, besides the poor reactivity found in the epoxidation of prochiral 1-phenylcyclohexene by the oxovanadium(IV) POM with TADOOH, the enantioselectivity was essentially negligible (Scheme 2).

To gain mechanistic insight into this oxygen-transfer process, the catalytic asymmetric epoxidation of cinnamyl alcohol (*trans*-**1j**) was also conducted with related transition-metal-substituted POMs as catalysts, for example, Mn(II)- and Ru(III)-POM, at elevated temperature (40−45 °C) with chiral hydroperoxides as oxygen source (Table 4).

The data in Table 4 display negligible asymmetric induction and poor chemoselectivity in the Mn(II)-POM-catalyzed epoxidation of **1j** by both enantiopure hydroperoxides (*S*)-(−)-**4a** and TADOOH (**4d**) (entries 1 and 3). In addition, a control experiment revealed that no racemization of the hydroperoxides took place during the reaction, and the unreacted hydroperoxides as well as the resulting alcohols remained enantiopure. Also, low enantiomeric ratios (up to 65:35), as well as poor chemoselectivity, were observed for the Ru(III)-POM (entries 2 and 4). A more pronounced difference in the enantioselectivity values was noted for other allylic alcohols (see Table S3, Supporting Information).

Mechanistic Discussion

Prior to the present studies, the use of hydroperoxides such as *tert*-butyl hydroperoxide as oxygen source for POM-catalyzed oxidations has met with limited success in view of the low reactivity and, in most cases, undesirable radical-type side reactions.[5,21] We now show that several transition-metal-substituted sandwich-type POMs catalyze the epoxidation of allylic alcohols by both achiral and chiral organic hydroperoxides. The preparative utility and synthetic value of the sandwich-type POM-based catalytic systems presented above are indisputable, but mechanistic understanding of the complex oxygen-transfer processes is important for the design of still more effective and selective POM oxidants with general applicability.

In view of the structural composition of these sandwich-type POMs, viz. $[ZnWM_2(ZnW_9O_{34})_2]^{q-}$, the oxygen-transfer reaction may occur either at the substituting metal center (M) or the framework tungsten site (W) of the intact catalyst.[4b] In this regard, our recent study on

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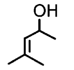
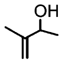
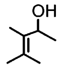
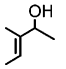
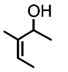
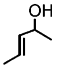
(21) Faraj, M.; Hill, C. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1487−1489.

TABLE 5. Comparison of the Chemoselectivities (Epoxide/Enone) and Diastereoselectivities (Threo/Erythro) for the Epoxidation of the Chiral Allylic Alcohols 1 by the Sandwich-Type Mn(II)-POM with Hydrogen Peroxide versus Hydroperoxide 4b as Oxygen Sources

entry	substrate		Mn(II)-POM/H_2O_2 (30%)[a]		Mn(II)-POM/ROOH (**4b**)[b]	
			chemo	diastereo	chemo	diastereo
1		**1a**	> 95: 5	92: 8	90:10	90:10
2		**1b**	> 95: 5	8:92	55:45	25:75
3		**1c**	> 95: 5	78:22	90:10	78:22
4		**1n**	> 95: 5	13:87	91: 9	55:45
5		**1o**	> 95: 5	45:55	95: 5	65:35
6		**1p**	95: 5	55:45	50:50	60:40

[a] Data from ref 7b. [b] Data from Table S2 (this work, Supporting Information).

the epoxidation of allylic alcohols, catalyzed by sandwich-type POMs but with H_2O_2 instead of hydroperoxides as oxygen source, reveals that the choice of transition metal in these sandwich-type POMs (Mn, Ru, Fe, Pd, Pt, Zn) does not notably affect the reactivity and selectivity.[7] This implies that the substituting transition metals are not directly involved in the oxygen-transfer process; consequently, a peroxotungsten complex was proposed as active oxidant with the allylic alcohol ligated to the tungsten atom through metal−alcoholate bonding (template effect).[7] In contrast, the reactivity and selectivity for the oxidation of the allylic alochol **1a** with the same set of sandwich-type POMs, but with the hydroperoxide **4b** as oxygen source instead of H_2O_2, depend decisively on the substituting transition metal in the central ring of these sandwich POM (Table S1, Supporting Information). This indicates that the transition metal is directly involved in the activation of the hydroperoxides, and therefore, different oxygen-activated species must intervene in the POM-catalyzed epoxidation of chiral allylic alcohols by hydrogen peroxide versus hydroperoxide.[16] To accentuate this point further, the differing chemoselectvities and diastereoselectivities obtained for the Mn(II)-POM catalyst in the oxidation of allylic alcohols with hydrogen peroxide versus hydroperoxide are compared (Table 5): For the Mn(II)-POM/H_2O_2 catalytic system, the epoxidation of allylic alcohols is not only highly chemoselective (only small amounts, if at all, of the enone **3** were observed), but also highly diastereoselective; in contrast, the Mn(II)-POM/ROOH system affords significant amounts of the enone **3** (as much as up to 50%), and for the substrates **1b**,**n** comparatively rather low diastereoselectivities are found (entries 2 and 4). These lines of evidence support the above mechanistic conclusions that the oxygen sources H_2O_2 and ROOH operate through distinct metal-activated complexes: The H_2O_2 is activated by tungsten, whereas the ROOH utilizes the substituting transition metal, in the present case manganese.

In the oxidation of allylic alcohols by hydroperoxide, as mentioned before, the sandwich-type POM with different substituting transition metals in the central ring (OV, Mn, Ru, Fe, Zn, Pd, Pt) exhibited different reactivity patterns (Table S1, Supporting Information). In particular, for the asymmetric epoxidation by enantiomerically pure hydroperoxides as chiral oxygen source, as high as 95:5 enantiomeric ratios have been obtained in O═V(IV)-POM-catalyzed epoxidation of allylic alcohols by TADOOH (Tables 2 and 3), whereas only racemic epoxides [Mn(II)-POM] or poor enantioselectivities [Ru(III)-POM] were observed by other isostructural transition-metal-substituted POMs (Table 4). These drastic differences in reactivity (conversion), chemoselectivity (epoxide versus enone), and enantioselectivity that are displayed by the various transition-metal-substituted POMs convey distinct operating modes for the oxygen-transfer process in these hydroperoxide epoxidations.

In the case of the O═V(IV)-POM, the reactivity pattern of the present work parallels that of earlier studies on the catalytic epoxidations by oxovanadium complexes.[11,14] For instance, analogous to the known catalytic oxidants $VO(acac)_2$/TBHP and $Ti(O^iPr)_4$/TBHP,[22] the high regioselective preference for the allylic double bond in 1-methylgeraniol (Table 1, entry 5) and geraniol (Table 3, entry 8), as well as the remarkable enhancement of reactivity observed for allylic alcohols compared with unfunctionalized cyclohexenes (Scheme 2) make evident the ligation of the allylic hydroxy group in the catalytic species by means of a metal−alkoxide bond. Such binding favors the oxygen transfer to the proximate allylic rather than to the remote unfunctionalized double bond of

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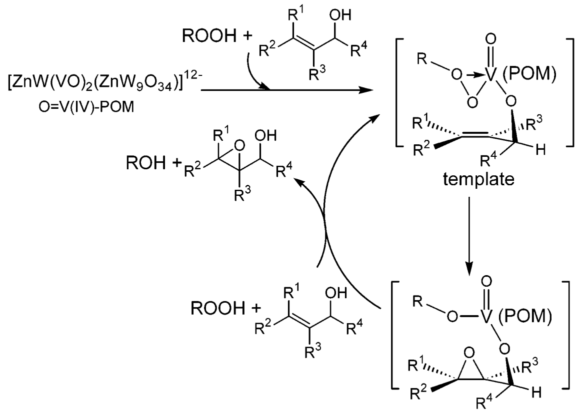
(22) Adam, W.; Mitchell, C. M.; Paredes, R. Smerz, A. K.; Veloza, L. A. *Liebigs Ann./Recueil* **1997**, 1365−1369.

SCHEME 3. Proposed Catalytic Cycle for the Epoxidation of Allylic Alcohols by OV(IV)−POM with Hydroperoxide 4 as Oxygen Source



1-methylgeraniol. These results support template formation in the oxovanadium(IV)-POM-catalyzed epoxidation of allylic alcohols by hydroperoxides.

On the basis of these experimental facts, we propose a catalytic cycle in Scheme 3 that accounts for the high reactivity and selectivity observed in the epoxidation by the oxovanadium(IV)-substituted POM. First, an alkylperoxy V(V) complex is formed after oxidation of vanadium(IV) to vanadium(V), which is widely accepted as oxygen-transfer agent in V(V)-catalyzed epoxidations.[11] Subsequently, a template is formed by ligation of the allylic alcohol to the central vanadium metal in the form of an alcoholate bond. After the oxygen transfer, the template is regenerated through liberation of the epoxy alcohol and the alcohol (ROH) by the allylic alcohol and hydroperoxide (ROOH). The pivotal role of the templating vanadium metal for stereoselective oxygen transfer, as shown in Scheme 3, was unequivocally confirmed when the α-Keggin-type $PV_2Mo_{10}O_{40}^{5-}$ was employed as catalyst. This POM also contains two oxovanadium(IV) centers such as the sandwich-type O=V(IV)-POM employed herein. But despite its lower reactivity, the similar high enantioselectivity for substrate **1g** (er 92:8) as observed for the sandwich-type O=V(IV)-POM substantiates the proposed mechanism that a vanadium metal-coordinated template operates in the oxygen-transfer process.

The important feature pertinent for enantiocontrol in the proposed cycle (Scheme 3) is the template-type aggregation of the allylic alcohol substrate, chiral hydroperoxide, and POM ligand by the central vanadium(V) metal; the POM ligand provides the necessary rigidity in the template for stereoselection control. When such a template effect is lacking, the observed negligible enantioselectivity and poor reactivity are readily rationalized as in the epoxidation of 1-phenylcyclohexene by TADOOH. This substrate cannot coordinate to the vanadium center through a metal−alcoholate bond and poor stereochemical differentiation and enhancement of reactivity apply.

The significant dependence of the enantioselectivity (er ratio) on both chiral hydroperoxide **4** (Table 2) and the allylic alcohol **1** (Table 3) express the pertinent steric interactions between these components in the template.[23] Clearly, the sterically more demanding TADDOL-derived hydroperoxide TADOOH coordinates to the vanadium center to provide a more effective chiral environment for asymmetric induction, and therefore, a higher enantioselectivity is observed. In addition, the significance and importance of the hydroxy functionality are demonstrated in the TADOOH as oxygen source versus its hydroxy-protected Me-TADOOH derivative. The notable absence of reactivity in the case of Me-TADOOH compared to TADOOH (er 92:8, >95% conversion) for the epoxidation of allylic alochol **1g** illustrates that the hydroxy group is essential to effect asymmetric epoxidation. A plausible reason is that the hydroxy group in TADOOH assists oxygen transfer in the transition structure through hydrogen bonding to the metal-activated peroxy functionality, which is prevented in the methyl-ether derivative Me-TADOOH.[14]

At present, we do not have any definitive experimental evidence to account mechanistically in rigorous form the much lower chemo- and enantioselectivities observed with the Mn(II)-POM and Ru(III)-POM compared to the V(IV)-POM. Consequently, we may only speculate: On the basis of the work by Ingold and co-workers,[24] alkyl hydroperoxides tend to undergo homolytic cleavage in the presence of redox-active transition-metal complexes to yield alkoxy and peroxy radicals, as also confirmed by trapping experiments.[25] Thus, hydrogen abstraction from the substrate by intermediary alkoxy radicals and reaction of the resulting radicals with molecular oxygen would explain the significantly lower chemoselectivity, observed in the Mn(II)-POM and Ru(III)-POM-catalyzed oxidations. Furthermore, the peroxy radicals have been generated essentially in racemic form during the hydrogen abstraction and subsequent reaction with molecular oxygen, such that the epoxides are produced in low enantioselectivity.

Conclusions

A series of oxidatively resistant sandwich-type POMs, namely $[WZnM_2(ZnW_9O_{34})_2]^{q-}$ [M = OV(IV), Mn(II), Ru(III), Fe(III), Pd(II), Pt(II), Zn(II); $q = 10-12$] have been shown to catalyze efficiently the epoxidation of allylic alcohols **1** with organic hydroperoxides as oxygen source. In marked contrast to the epoxidation of allylic alcohols catalyzed by the same set of sandwich-type POMs but with H_2O_2 as oxygen source, the transition metal M in the central ring of polyoxometalate significantly affects the reactivity, chemoselectivity, and stereoselectivity of the allylic alcohol epoxidation by hydroperoxide. Evidently, the oxygen sources H_2O_2 and ROOH operate through distinct metal-activated species. Our study conspicuously demonstrates that the oxovanadium(IV)-substituted POM, namely $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$, is uniquely efficient for highly chemoselective, regioselective, and also stereoselective epoxidation of allylic alcohols. Excellent catalyst efficiency (up to 42 000 TON) and high selectivities have been achieved when compared to

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(23) At this time, it would be too speculative to propose a definite structure for the vanadium(V)-centered POM template to rationalize the stereochemical course of the epoxidation.

(24) (a) MacFaul, P. A.; Wayner, D. D. M.; Ingold, K. U. *Acc. Chem. Res.* **1998**, *31*, 159−162. (b) MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M.; Que, L. *J. Am. Chem. Soc.* **1997**, *119*, 10594−10598.

(25) Trapping of such radicals in reactions with TBHP and a high oxidation potential POM is known; see: Khenkin, A. M.; Neumann, R. *J. Am. Chem. Soc.* **2001**, *123*, 6437−6438.

the previously reported methods with POM or other vanadium catalysts;[11,26] the latter are several orders of magnitude less reactive than $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$. By the appropriate choice of the chiral hydroperoxides, a POM-catalyzed asymmetric epoxidation is now available that affords epoxy alcohols in nearly quantitative yields and high enantioselectivities with the regenerative TADDOL-derived hydroperoxide TADOOH (**4d**). The high chemo-, regio-, and stereoselectivity of this unprecedented oxygen-transfer process have been rationalized in terms of a vanadium(V)-coordinated template. The present work not only offers new preparative perspectives for optically active epoxy alcohols, but also provides mechanistic insight into the oxygen-transfer processes mediated by such sandwich-type POMs.

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Supporting Information Available: Experimental details, the screening of various transition-metal-substituted sandwich-type POMs with racemic alkyl hydroperoxide **4b** (Table S1), data on the reactivity and selectivity of the Mn(II)-POM in the epoxidation of a set of chiral allylic alcohols **1** (Table S2), and data on the Ru(III)-POM-mediated asymmetric epoxidations (Table S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) (a) Villa, A. L.; De Vos, D. E.; Verpoort, F.; Sels, B. F.; Jacobs, P. A. *J. Catal.* **2001**, *198*, 223−231. (b) Haanepen, M. J.; Van Hooff, J. H. C. *Appl. Catal. A* **1997**, *152*, 183−201. (c) Haanepen, M. J.; Elemans-Mehring, A. M.; Van Hooff, J. H. C. *Appl. Catal. A* **1997**, *152*, 203-219.