

Highly Efficient Catalytic Asymmetric Epoxidation of Allylic Alcohols by an Oxovanadium-Substituted Polyoxometalate with a Regenerative TADDOL-Derived Hydroperoxide

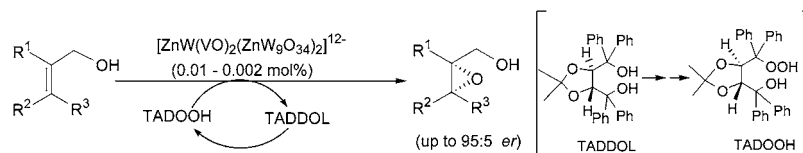
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ABSTRACT



The oxovanadium(IV) sandwich-type POM catalyzes the chemo-, regio-, and stereoselective epoxidation of allylic alcohols by chiral hydroperoxides with very high catalytic efficiency (up to 42 000 TON), a potentially valuable oxidation for the development of sustainable processes. By using the sterically demanding, TADDOL-derived hydroperoxide TADOOH as the chiral oxygen source, enantiomeric ratios (er) of up to 95:5 have been achieved.

Despite the vast array of homogeneously catalyzed reactions that has been developed in the past decades, industrial fine chemical manufacture still heavily depends on classical organic chemistry based on stoichiometric reagents. Large-scale use of homogeneous catalysis not only requires high *selectivity*, but also sufficiently high catalyst *activity* to obtain a process that is economically and environmentally viable.¹ Development of highly active homogeneous catalysts that meet industrial demands is a challenging task. At very low catalyst concentrations and very high substrate-to-catalyst

ratios, the process becomes particularly sensitive to catalyst deactivation by traces of impurities, which adversely affects the robustness of the catalytic system. Unquestionably, there is a need for highly persistent homogeneous catalysts.

Polyoxometalates (POMs), in particular their transition-metal-substituted derivatives, have been extensively used as oxidation catalysts in view of their resistance toward oxidation, ease of preparation, and compatibility with various oxygen sources.^{2,3} We found earlier the “sandwich-type” POMs, viz. $[\text{ZnWM}_2(\text{ZnW}_9\text{O}_{34})_2]^{9-}$, may be used as oxida-

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(1) (a) Tucker, C. E.; De Vries, J. G. *Top. Catal.* **2002**, *19*, 111–118. (b) Blaser, H. U. *Adv. Synth. Catal.* **2002**, *344*, 17–31.

(2) For reviews, see: (a) Mizuno, N.; Misono, M. *Chem. Rev.* **1998**, *98*, 199–218. (b) Hill, C. L.; Prosser-McCarthy, C. M. *Coord. Chem. Rev.* **1995**, *143*, 407–455. (c) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171–198. (d) Neumann, R. *Prog. Inorg. Chem.* **1998**, *47*, 317–370. (e) Finke, R. G. In *Polyoxometalate Chemistry*; Pope, M. T., Müller, A., Eds; Kluwer Academic Publisher: Dordrecht, The Netherlands, 2001; pp 363–390.

tion catalysts in the presence of aqueous H₂O₂ because they resist both oxidative and hydrolytic degradation.^{3c} The good performance of these POM catalysts with aqueous H₂O₂,^{3g,h} notably their tolerance of water, prompted us to use sandwich POMs as epoxidation catalysts in combination with organic hydroperoxides, which are often superior to those by H₂O₂ in regard to selectivity.⁴ Unfortunately, catalytic hydroperoxide oxidations are not well-suited for the manufacture of fine chemicals in multipurpose plant equipment because of the low process efficiency due to catalyst deactivation by adventitious water.⁵ We report our unprecedented results on the use of [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ as a highly active catalyst for the selective epoxidation of allylic alcohols by hydroperoxides.⁶ Stimulated by the high enantioselectivity that we have obtained recently in the asymmetric Weitz–Scheffer epoxidation of α,β enones by enantiopure hydroperoxides,⁷ notably the sterically demanding TADDOL-derived hydroperoxide TADOOH,^{7b} we also present here the first POM-catalyzed asymmetric epoxidation of allylic alcohols by TADOOH.

First an extensive screening of various transition-metal-substituted sandwich-type POMs, namely [ZnWM₂(ZnW₉O₃₄)₂]^{q-} or M-POM (M = OV^{IV}, Mn^{II}, Ru^{III}, Fe^{III}, Zn^{II}, Pd^{II}, and Pt^{II}, q = 10–12), was conducted with racemic hydroperoxides. The reactions were carried out in a 1,2-dichloroethane solution of the POMs, obtained by extraction from an aqueous solution of their alkali metal derivatives, through the addition of Aliquat 336 as a lipophilic quaternary ammonium salt. No meticulous precautions were taken to exclude water, other than brief drying over Na₂SO₄ (see Supporting Information).

Mesitylol (1a) was chosen as model substrate, which is an established probe for the assessment of the chemoselectivity (epoxidation versus allylic oxidation)^{8a,b} and diastereoselectivity (*threo* versus *erythro* epoxidation) in metal-

catalyzed oxidations,^{8c} and the racemic [1-(4-chlorophenyl)]ethyl hydroperoxide (4a) as oxygen donor (Table 1). This

Table 1. Catalytic Oxidation of Mesitylol (1a) by the Various Transition-Metal-Substituted Polyoxometalates with the Racemic Hydroperoxide 4a

entry	M	temp ^b (°C)	convn ^a (%)	mb ^a (%)	selectivity ^a	
					2a:3a	diastereo (<i>threo</i> : <i>erythro</i>)
1	OV(IV)	20	>95	>95	>95:5	91:9
2	OV(IV)	50 ^c	>95	>95	>95:5	91:9
3	Mn(II)	50	85	85	90:10	90:10
4	Ru(III)	50	94	70	70:30	90:10
5	Fe(III)	50	18	95	90:10	94:6
6	Zn(II)	50	8	90	85:15	95:5
7	Pd(II)	50	18	92	93:7	92:8
8	Pt(II)	50	12	95	88:12	95:5

^a Conversions (allylic alcohol), material balances, and product ratios were determined by ¹H NMR analysis of the crude reaction mixture, ca. 5% error of the stated value. ^b For entries 3–8, 0.02 mol % of catalyst loading was employed; no conversion was observed at 20 °C. ^c Reaction time was 6 h.

screening revealed that the oxovanadium(IV)-substituted POM, namely [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ or O=V(IV)-POM, was the most reactive and selective catalyst for the epoxidation of allylic alcohols (Table 1). High yields were obtained within 24 h at 20 °C (entry 1) or within 6 h at 50 °C (entry 2), with only 0.01 mol % of POM catalyst.

Although the sandwich-type POM [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ has been known for some time,⁹ apparently it had hitherto not been used for catalytic epoxidations. Our results on the epoxidation of a variety of substituted allylic alcohols **1** by the racemic (1-phenyl)ethyl hydroperoxide (**4b**) with the O=V(IV)-POM catalyst are collected in Table 2. As is evident, the secondary allylic alcohol **1a** (entry 1) afforded the epoxy alcohol in high diastereoselectivity (*threo*:*erythro* 91:09). The usual undesirable allylic oxidation (CH insertion) was not observed, which manifests the high chemoselectivity of this reaction. With *tert*-butyl hydroperoxide (Table 2, entry 2) instead of (1-phenyl)ethyl hydroperoxide (**4b**), a lower conversion (65%) was obtained under identical reaction conditions. 2-Cyclohexen-1-ol (**1b**) was found to be less reactive than the acyclic allylic alcohols and gave selectively the *cis*-epoxy alcohol **2b** (entry 3), but a higher (50 °C) temperature was necessary for complete conversion of the allylic substrate. Significant in regard to regioselectivity is 1-methylgeraniol (**1c**) with two types of double bonds, which gave only the 3,4 epoxide in excellent yield and high diastereoselectivity (entry 4). Similarly, the primary allylic

(9) The synthesis and X-ray structure of oxovanadium(IV) POM is known; see: Tourné, C. M.; Tourné, G. F.; Zonnevillie, F. J. *Chem. Soc., Dalton Trans.* **1991**, 143–155.

(3) For leading examples in catalysis, see: (a) Hill, C. L.; Brown, R. B. *J. Am. Chem. Soc.* **1986**, *108*, 536–538. (b) Mansuy, D.; Bartoli, J. F.; Battioni, P.; Lyon, D. K.; Finke, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7222–7226. (c) Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1995**, *117*, 5066–5074. (d) Bösing, M.; Nöh, A.; Loose, I.; Krebs, B. *J. Am. Chem. Soc.* **1998**, *120*, 7252–7259. (e) Mizuno, N.; Nozaki, C.; Kiyoto, I.; Misono, M. *J. Am. Chem. Soc.* **1998**, *120*, 9267–9272. (f) Weiner, H.; Finke, R. G. *J. Am. Chem. Soc.* **1999**, *121*, 9831–9842. (g) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *Synlett* **2002**, *12*, 2011–2014. (h) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *J. Org. Chem.* In press.

(4) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; pp 48–62.

(5) For example, even in the presence of molecular sieves, the Sharpless–Katsuki epoxidation still requires 5–10 mol % of Ti catalyst to protect the latter from adventitious water; see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; pp 231–280.

(6) Hydroperoxides such as *tert*-butyl hydroperoxide are known to serve as the oxygen source for POM-catalyzed oxidations; however, these epoxidations are of limited success in view of the low reactivity and, in most cases, undesirable radical-type reactions, see: (a) Faraj, M.; Hill, C. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1487–1489. (b) Neumann, R.; Khenkin, A. M. *Inorg. Chem.* **1995**, *34*, 5753–5760.

(7) (a) Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 5654–5655. (b) Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187–207.

(8) (a) Adam, W.; Hajra, S.; Herderich M.; Saha-Möller, C. R. *Org. Lett.* **2000**, *2*, 2773–2776. (b) Adam, W.; Herold, M.; Hill, C. L.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2002**, 941–946. (c) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703–710.

Table 2. Catalytic Epoxidation^a of Allylic Alcohols by [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ with the Racemic (1-Phenyl)ethyl Hydroperoxide (**4b**)

entry	allylic alcohol	epoxy alcohol	convn ^b (%)	yield ^c 2 (%)	dr ^b (<i>threo:erythro</i>)
1			> 95	91	91: 9
2 ^d			65	89 ^e	87:13
3			> 95 (50 °C)	86	> 95: 5 (<i>cis:trans</i>)
4			> 95	94	91: 9
5			> 95	94	—

^a All reactions were carried out in 1,2-dichloroethane at 20 °C (except for entry 3) for 24 h with the particular allylic alcohol **1** (0.50 mmol), 1.1 equiv of (1-phenyl)ethyl hydroperoxide (used in all reactions unless otherwise stated), and 0.01 mol % of [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻; in all cases no enone (allylic oxidation) was detected. ^b Determined by ¹H 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 *tert*-Butyl hydroperoxide was used as the oxygen source. ^e Based on 100% conversion of allylic alcohol.

alcohol **1d** (entry 5) was selectively oxidized to the corresponding epoxy alcohol **2d** in quantitative yield. In addition, it was noted that under identical conditions, the unfunctionalized cyclohexene (convn 13% within 24 h) was much less reactive than the allylic alcohols (data not shown in Table 2).

These successful results with the racemic hydroperoxide prompted us to employ enantiomerically pure hydroperoxides in the oxovanadium(IV)-POM-catalyzed epoxidation of allylic alcohols, to assess the suitability of this catalyst system for asymmetric oxygen transfer. A screening of diverse chiral hydroperoxides under a variety of experimental conditions disclosed that the sterically demanding TADDOL-derived hydroperoxide TADDOOH was especially effective for the intended purpose, as representative results show in Table 3.¹⁰ The epoxidation of the primary allylic alcohol **1d** by TADDOOH at 0 °C led to the (*2R,3R*) epoxy alcohol **2d** in high (er 95:5) enantioselectivity (Table 3, entry 1). Since the reactivity was low (40% convn after 48 h) at 0 °C, the reaction was carried out at 20 °C and complete consumption of the allylic substrate was obtained within 30 h, to afford the epoxide **2d** quantitatively with an er value of 91:9 (entry 2).

Significant for our aim to develop a robust catalytic epoxidation system with hydroperoxides, similar catalytic activity and identical enantioselectivity (entry 3) was achieved even at the very low catalyst loading of only 0.002 mol %. This illustrates unequivocally the high efficiency (42 000

(10) Only primary allylic alcohols were used 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.; 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.

Table 3. Catalytic Enantioselective Epoxidation^a of the Primary Allylic Alcohols **1** by [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ with TADDOOH

entry	allylic alcohol 1	time (h)	convn ^b (%)	yield ^c 2 (%)	er ^d	config ^e
1		48 (0 °C)	40	90 ^f	95: 5	(<i>2R, 3R</i>)-(-)
2		30	> 95	94	91: 9	
3 ^a		48	90	82	90:10	
4		6 (50 °C)	> 95	92	85:15	
5		30	> 95	92	92: 8	(<i>2R, 3R</i>)-(+)
6		24	90	86	85:15	(<i>2R, 3R</i>)-(+)
7		48	> 95	88	75:25	(<i>2R, 3R</i>)-(+)
8		36	95	93	72:28	(<i>2R</i>)-(+)
9		24	> 95	96	59:41 ^d	(<i>2R, 3R</i>)-(+)

^a Unless otherwise specified, all reactions were carried out in 1,2-dichloroethane at 20 °C with the particular allylic alcohol **1** (0.50 mmol), 1.1 equiv of TADDOOH, and 0.01 mol % of [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻, except for entry 3, for which 0.002 mol % of catalyst loading was used. ^b Determined by ¹H 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), except entry 9, for which GC-MS analysis on a chiral β-TG column was employed. ^e Assigned by direct comparison of the specific rotation, determined on a polarimeter, with the literature value. ^f Based on 100% conversion of allylic alcohol.

TON!) of the oxovanadium(IV)-substituted POM in the enantioselective epoxidation of allylic alcohols. The catalyst loading in terms of vanadium concentration is 2–3 orders of magnitude lower than those commonly employed in vanadium-catalyzed epoxidations of allylic alcohols by hydroperoxides.^{11,15} As expected, at elevated temperature (50 °C), the enhanced catalytic activity (>95% convn in 6 h) was accompanied by a somewhat lower (er 85:15) enantioselectivity (entry 4).

In contrast to TADDOOH, the enantiomerically pure (*S*)-(-)-(1-phenyl)ethyl hydroperoxide¹² gave substantially lower (er 56:44) asymmetric induction with the substrate **1d**, catalyzed by O=V(IV)-POM (not shown in Table 3). An

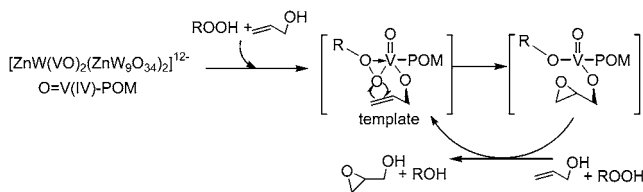
(11) (a) Villa, A. L.; De Vos, D. E.; Verpoort, F.; Sels, B. F.; Jacobs, P. A. *J. Catal.* **2001**, *198*, 223–231. (b) Haanepen, M. J.; Van Hooff, J. H. C. *Appl. Catal. A* **1997**, *152*, 183–201. (c) Haanepen, M. J.; Elemans-Mehring, A. M.; Van Hooff, J. H. C. *Appl. Catal. A* **1997**, *152*, 203–219.

(12) (*S*)-(-)-(1-Phenyl)ethyl hydroperoxide was prepared by enzymatic kinetic resolution according to the literature procedure: Adam, W.; Hoch, U.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. *J. Am. Chem. Soc.* **1995**, *117*, 11898–11901.

(13) The resulting TADDOL was recovered in >95% yield by silica gel chromatography without loss of optical purity, from which TADDOOH may be easily regenerated, see ref 7b.

(14) In contrast, our recent studies on the sandwich-type POM-catalyzed epoxidation of allylic alcohols with H₂O₂ as oxygen source revealed that the substituting transition metals are not directly involved in the oxygen-transfer process, see refs 3g and 3h.

Scheme 1. A Proposed Catalytic Cycle



additional advantage of the TADOOH, besides the high enantioselectivity, is the fact that this chiral hydroperoxide may be regenerated from the resulting TADDOL without loss of optical purity.¹³

In view of these advantages, the TADOOH was used as the chiral oxygen source for the asymmetric epoxidation of a variety of allylic alcohols under the optimized conditions (20 °C, 0.01 mol % of catalyst). Quite generally, the similarly *cis*-disubstituted allylic alcohols **1e** and **1f** (entries 5 and 6) were epoxidized in about as high enantioselectivities and yields as substrate **1d** (entry 2), but for the *p*-anisyl derivative **1e**, the enantiomeric ratio dropped slightly to 85:15 (entry 6) from 92:8 (entry 5). The epoxidation of the monosubstituted allylic alcohols **1g** and **1h** afforded the corresponding epoxides in moderate enantioselectivities (entries 7 and 8), but in high yield. Geraniol (**1i**) was regioselectively epoxidized exclusively to the 2,3 epoxide in excellent yield, albeit in poor enantioselectivity (entry 9).

Of mechanistic relevance is the fact that the reactivity and chemoselectivity (epoxidation versus allylic oxidation) of the sandwich-type POM-catalyzed oxidation of the allylic alcohol **1a** with the hydroperoxide **4a** depend decisively on the redox-type substituting transition metal in the central ring of the sandwich POM (Table 1). This indicates that the transition metal is directly involved in the oxygen-transfer process.¹⁴ Moreover, the reactivity pattern of the oxovanadium(IV) POM in the present study parallels that of earlier studies on the catalytic epoxidation of allylic alcohols by oxovanadium complexes,¹⁵ i.e., allylic alcohols react faster than unfunctionalized alkenes and geraniol shows a high regioselective preference for the allylic double bond. In this context, our more recent studies are of interest, in which for the asymmetric epoxidation of allylic alcohols by TADOOH *er* values of up to 86:14 have been achieved; instead of the sandwich oxovanadium(IV) POM, the VO(O^{*i*}Pr)₃ catalyst was used in the presence of an achiral hydroxamic acid ligand.¹⁶

(15) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137. (b) Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 1990–1992. (c) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63–73.

(16) Vogl, N. Diplomarbeit, University of Würzburg, Germany, 2002.

(17) It would be too speculative at this time to propose a definite structure for the vanadium(V)-centered POM template to rationalize the stereochemical course of the epoxidation.

On the basis of the present experimental facts, a catalytic cycle is proposed, with the vanadium metal as reaction center in the POM, which accounts adequately for the high reactivity and selectivity displayed by the oxovanadium(IV)-substituted POM (Scheme 1). In the proposed catalytic cycle, the oxygen transfer takes place in a vanadium(V) template, formed from the hydroperoxide and allylic alcohol. Clearly, such a relatively rigid metal template plays a pivotal role in steering the stereochemical course of the attacking chiral hydroperoxide, since the restricted freedom of motion through the POM ligand ensures the pertinent steric interactions between the chiral hydroperoxide, the allylic alcohol, and the POM ligand.¹⁷

To substantiate this hypothesis, an unfunctionalized alkene, namely 1-phenylcyclohexene, was epoxidized by TADOOH with oxovanadium(IV) POM as catalyst under identical reactions as for the allylic alcohols **1**. Besides the poor reactivity, the enantioselectivity was essentially negligible (see Scheme S1 in the Supporting Information). Furthermore, we found that related transition-metal-substituted POMs, for example, Mn(II)-POM, which cannot react through a similar peroxy-type template, afforded racemic epoxide in poor **2:3** product selectivity when the allylic alcohol **1g** was oxidized by TADOOH (see Table S1 in the Supporting Information).

In summary, the oxovanadium(IV)-substituted sandwich-type POM [ZnW(VO)₂(ZnW₉O₃₄)₂]¹²⁻ derives its remarkable reactivity and selectivity in the catalytic epoxidation of allylic alcohols from its resistance toward deterioration by hydroperoxides. For the first time, a POM-catalyzed asymmetric epoxidation of allylic alcohols has been accomplished, and that in high enantioselectivity (*er* values up to 95:5), by the sterically demanding TADDOL-derived hydroperoxide TADOOH as regenerative chiral oxygen source. The high selectivities of this unprecedented oxygen-transfer process have been rationalized in terms of a vanadium(V) template. We anticipate that the efficiency (up to 42 000 TON) and accessibility of the oxovanadium(IV) POM catalyst should contribute to the development of sustainable oxidation processes.

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Supporting Information Available: Experimental details and data on the reactivity and selectivity of the Mn(II)-POM (Table S1) and the epoxidation of 1-phenylcyclohexene (Scheme S1). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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