Metal-Catalyzed Oxidations with Pinane Hydroperoxide: A Mechanistic Probe To Distinguish between Oxometal and Peroxometal Pathways

H. E. B. Lempers, A. Ripollès i Garcia, and R. A. Sheldon*

Delft University of Technology, Department of Organic Chemistry and Catalysis, Julianalaan 136, 2628 BL Delft, The Netherlands

The relative reactivities of *tert*-butyl hydroperoxide (TBHP) and pinane hydroperoxide (PHP) in metal (Cr, Mo, Ru, Se, V, and Zr)-catalyzed oxidations were compared. When these oxidations involve rate-limiting oxygen transfer from a peroxometal species to the substrate huge differences between TBHP and PHP were observed, e.g., molybdenum-catalyzed epoxidation of cyclohexene with TBHP gave a 98% yield while PHP gave 0%. When the reaction involves reaction of an oxometal species with the substrate as the rate-limiting step, little or no difference is observed, e.g., the selenium-catalyzed allylic oxidation of β-pinene gave a 96% and 99% yield with TBHP and PHP, respectively. Small but significant differences are observed when reoxidation of the catalyst by the hydroperoxide to the active oxometal species is the rate-limiting step; e.g., the chromium-catalyzed oxidation of carveol gave carvone in 89% and 24% yield with TBHP and PHP, respectively. Hence, the effect of RO_2H structure on rate is dependent on the rate-limiting step.

Introduction

Metal-catalyzed oxidations with alkyl hydroperoxides can be divided into two categories on the basis of the key intermediate involved in the oxygen-transfer step: peroxometal or oxometal (Scheme 1).[1]

Molybdenum-[2] and vanadium-catalyzed[3] epoxidations with alkyl hydroperoxides have been extensively studied, and there is general agreement that these reactions involve an alkylperoxometal (Mo^{VI} or V^{V}) complex as the active oxidant.[3g,4] The molybdenum-catalyzed epoxidation of propylene with *tert*-butyl hydroperoxide (TBHP) or ethylbenzene hydroperoxide is used industrially for

Scheme 1. Peroxometal vs Oxometal Pathways
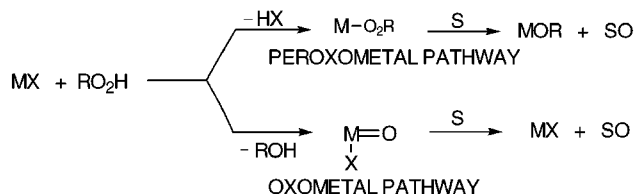
the manufacture of propylene oxide.[5] Catalytic oxidations with selenium,[6] ruthenium,[7] osmium,[8] and chromium,[9] on the other hand, are generally believed to involve oxometal species as the active oxidant.

We became interested in the use of pinane hydroperoxide (PHP) as an oxidant on the basis of its commercial availability from the autoxidation of pinane.[10] Catalytic reduction to pinanol and subsequent pyrolysis affords linalool, which has applications in flavors and fragrances and vitamin E synthesis.[10] We were interested, therefore, to see if the active oxygen in PHP could be utilized in a catalytic oxidation rather than "sacrificed" in catalytic reduction. An obvious application was in the catalytic epoxidation of olefins, and we were particularly interested in the epoxidation of styrene, as the product is of interest as a precursor to the flavor chemical, 2-phenylethanol.

Results and Discussion

Our attempts to epoxidize styrene with PHP in the presence of $Mo(CO)_6$ as catalyst afforded no epoxide. We

* To whome correspondence should be addressed.

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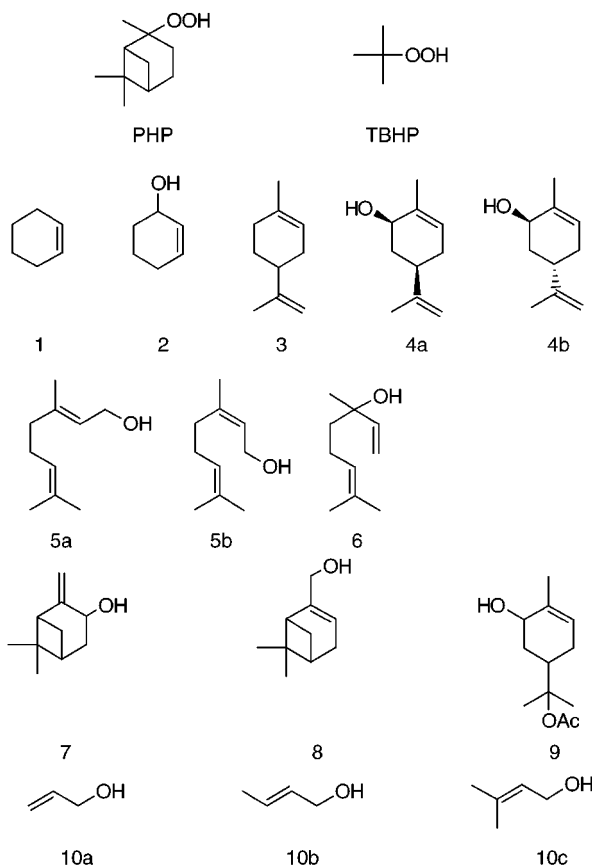
Figure 1. Substrates used in the Mo-, V-, and Zr-catalyzed epoxidation.

Table 1. Molybdenum- and Vanadium-Catalyzed Epoxidation[a] of Olefins and Their Corresponding Allylic Alcohols

substrate	catalyst	oxidant	conversion (%)	selectivity (%)
1	Mo	TBHP	89	96
1	Mo	PHP	0	
1	V	TBHP	66	34
1	V	PHP	6	7
2	Mo	TBHP	96	100
2	Mo	PHP	7	0
2	V	TBHP	89	98
2	V	PHP	61	100
3	Mo	TBHP	81	84[b]
3	Mo	PHP	4	0
3	V	TBHP	60	70[b]
3	V	PHP	10	0
4a/4b	Mo	TBHP	100	90[c]
4a/4b	Mo	PHP	8	0
4a/4b	V	TBHP	100	80[c]
4a/4b	V	PHP	100	85[c]

[a] For experimental details see the Experimental Section. [b] A small amount of isopropenyl epoxidized product was observed. [c] α,β-Unsaturated ketone (carvone) was formed as byproduct.

next turned our attention to the more reactive olefins **1** and **3** (Figure 1). Surprisingly, although we observed smooth molybdenum-catalyzed epoxidation of these olefins with TBHP (89% and 84% yield with **1** and **3**, respectively, Table 1) under standard conditions,[4b,11] no epoxidation was observed with PHP.

We tentatively concluded that the lack of reactivity of PHP is due to steric hindrance toward approach of the
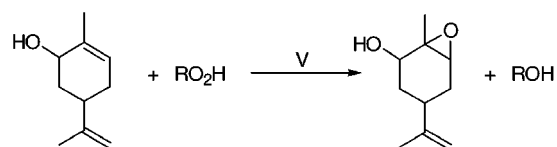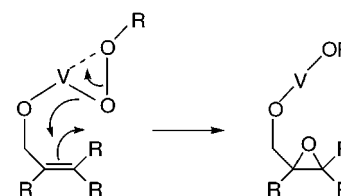
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Figure 2. Vanadium-catalyzed epoxidation of carveol.

Scheme 2. Vanadium-Catalyzed Intramolecular Oxygen Transfer

olefin substrate to the O—O bond of the putative alkyl-peroxomolybdenum(VI) intermediate.[11] This was confirmed in a systematic study[11] of the effect of the size of alkyl substituents in the alkyl hydroperoxide on the pseudo first-order rate constant of molybdenum catalyzed epoxidations. For example, epoxidation of cyclohexene gave the highest rate with TBHP. Successive substitution of the methyl groups in TBHP by higher alkyl groups resulted in a steadily decreasing reaction rate. Substitution of all three methyls by three ethyls resulted in a 99% decrease in rate compared to TBHP, and a further increase in steric bulk of the alkyl group as in PHP resulted in a complete loss of epoxidation activity.

Similarly, epoxidation of **1** and **3** with TBHP in the presence of VO(acac)$_2$ as catalyst at 80 °C afforded epoxides in yields comparable to those reported in the literature,[12] while with PHP no epoxidation was observed. We next turned our attention to allylic alcohols as substrates. It is well established[13] that vanadium(V) is ca. 100 times more active than molybdenum(VI) in the epoxidation of allylic alcohols. This is due to the different complexing ability of vanadium(V) and molybdenum(VI) to the hydroxyl group of the allylic alcohol. Complexation of the hydroxyl group with vanadium(V) provides for a facile intramolecular oxygen transfer from a coordinated alkylperoxo moiety to the double bond of the coordinated allylic alcohol (Scheme 2 and Figure 2).[2k,14]

As expected, molybdenum- and vanadium-catalyzed epoxidations of **2** and carveol (**4a/4b**) with TBHP proceeded smoothly, high conversions and epoxide selectivities being observed in 5 h at 80 °C. The vanadium-catalyzed reaction was much faster than with molybdenum (25 min and 5 h for complete conversion, respectively), consistent with previous studies of allylic alcohols.[2k] In contrast, no epoxidation of **2** or **4a/4b** was observed with PHP in the presence of molybdenum as catalyst (Table 1). On the other hand, with vanadium as catalyst, high conversions and epoxide selectivities, comparable to those obtained with TBHP, were observed with PHP as the oxidant. These results can be rationalized by assuming that efficient coordination of the hydroxyl group of the alkylperoxovanadium(V) intermediate (Scheme 2) brings the double bond into close proximity of the peroxo group,

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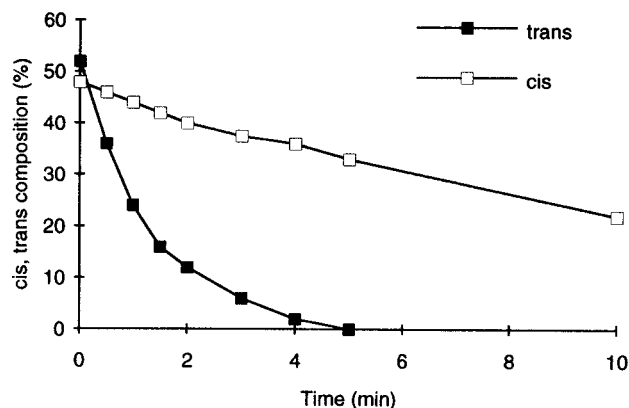
Figure 3. Conversion of *cis-* and *trans-*carveol in the vanadium-catalyzed epoxidation with TBHP.

Table 2. Vanadium-Catalyzed Epoxidation[a] of Carveol with TBHP and PHP as Oxidant

substrate	oxidant	enone (%)	epoxy alcohol (%)	$k_e(trans)/k_e(cis)$[b]
4a	TBHP	20	80	
4b	TBHP	0	100	6.4
4a	PHP	36	64	
4b	PHP	4	96	5.9

[a] For experimental details see the Experimental Section. [b] $k_{trans}/k_{cis} = (k_e + k_o)_{trans}/(k_e + k_o)_{cis}$, with $(k_e/k_e + k_o)$ = fraction of alcohol giving epoxide and $(k_o/k_o + k_e)$ = fraction of alcohol giving ketone.

thus facilitating intramolecular transfer, even with the bulky PHP. The lack of epoxidation observed with molybdenum/PHP suggests that, in this case, epoxidation proceeds intermolecularly and is subject to the same steric limitations as with the unfunctionalized olefins. The commercial sample of carveol consisted of a mixture of cis (**4a**) and trans (**4b**) isomers. When we monitored the course of the vanadium-catalyzed epoxidation of this mixture with TBHP we noted that one isomer reacted much faster than the other (Figure 3).

Subsequent experiments with pure **4a** and **4b** prepared by LiAlH₄ reduction of carvone[15] and acid-catalyzed rearrangement of α-pinene oxide,[16] respectively, revealed that the trans isomer was more active. This agrees well with results observed in the vanadium-catalyzed epoxidation of 5-methylcyclohex-2-en-1-ol[17] in which the trans isomer was epoxidized 34 times faster than the cis isomer. Furthermore, competing oxidative dehydrogenation of the alcohol group, to afford the corresponding unsaturated ketone, was observed with the less reactive cis isomer (**4a**) (see Table 2). This is also in agreement with results observed with 5-*tert*-butylcyclohexen-2-en-1-ol where the less reactive cis isomer afforded 91% of the unsaturated ketone.[17] Competition experiments at 80 °C in which a mixture of **4a** and **4b** was allowed to react with TBHP or PHP in the presence of VO(acac)₂ revealed that k_e(trans)/k_e(cis) was similar (6.4 vs 5.9, respectively) even though reaction with TBHP was three times faster than with PHP.

Hence, although a bulky hydroperoxide gives a lower overall rate, the relative rates of cis and trans isomers do not change appreciably. This is most likely caused

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Table 3. Vanadium- and Zirconium-Catalyzed Epoxidation[a] of Some Terpene-Based Allylic Alcohols with TBHP and PHP as Oxidant

substrate	oxidant	conversion (%)	selectivity[b] (%)
5a	TBHP	100	95
5a	PHP	78	97
5b	TBHP	100	98
5b	PHP	70	100
6	TBHP	96	99
6	PHP	13	95
7	TBHP	38	92
7	PHP	36	94
8	TBHP	100	95
8	PHP	75	96
9	TBHP	100	94
9	PHP	100	97
4a/4b[c]	TBHP	73	86[d]
4a/4b[c]	PHP	51	86[d]
4a/4b[e]	TBHP	46	67[d]
4a/4b[e]	PHP	22	63[d]

[a] For experimental details see the Experimental Section. [b] Selectivity to 2,3-epoxy 1-ol. [c] Room-temperature experiment. [d] The rest is the α,β-unsaturated ketone (carvone). [e] Zr(propoxide)₄ as catalyst, room-temperature experiment.

Table 4. Vanadium-Catalyzed Epoxidation[a] of Allylic Alcohols that Have Different Electronic Properties with TBHP and PHP as Oxidant

substrate	oxidant	conversion[b] (%)
10a	TBHP	100
10a	PHP	0
10b	TBHP	99
10b	PHP	57
10c	TBHP	99
10c	PHP	88

[a] For experimental details see the Experimental Section. [b] Selectivies >95% to the epoxide.

by equally increased steric constraints of **4a** and **4b** with the pinane group in the alkylperoxovanadium(V) intermediate. Similarly, we compared the vanadium-catalyzed epoxidations of a variety of allylic alcohols with TBHP and PHP. **5a**, **5b**, and **6** (Table 3) were epoxidized smoothly with TBHP/VO(acac)₂, exhibiting a high regioselectivity for the α,β-double bond, i.e., the allylic alcohol moiety, in all cases.

Epoxidation of **5a** and **5b** with PHP was slower than with TBHP but still afforded very high epoxide selectivities. In contrast, the less reactive **6**, which contains a monosubstituted double bond compared to the trisubstituted double bonds of **5a** and **5b**, showed a more dramatic decrease in rate with PHP compared to TBHP. This difference can be due to both electronic and steric effects in the substrate (the alcohol group in **6** is more sterically hindered than those in **5a** and **5b**). In the vanadium-catalyzed epoxidations of the equally sterically demanding allylic alcohols (**10a**–**c**, Table 4) electronic effects were shown to dramatically influence the relative rates with TBHP and PHP.

With the least electron-rich olefin (**10a**) 100% conversion was observed with TBHP while virtually no reaction occurred with PHP. The most electron-rich olefin (**10c**), on the other hand, gave similar results with TBHP and PHP while the olefin with intermediate reactivity (**10b**) gave substantially lower conversion with PHP. Similar results were obtained[11] in the molybdenum-catalyzed epoxidation of 1-octene and cyclohexene. Epoxidation of the more reactive cyclohexene was less influenced by increasing size of the alkyl hydroperoxide than that of 1-octene. Vanadium-catalyzed epoxidation of the rela-

Scheme 3. Selenium-Catalyzed Allylic Oxidation
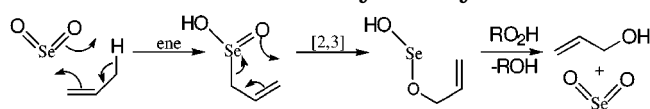
tively reactive allylic alcohols (**7**−**9**, Table 3) afforded results similar to those observed with **4b**, i.e., TBHP and PHP exhibited similar reactivities. Hence, a general conclusion from these studies of allylic alcohols containing double bonds of varying reactivity is that the steric limitations imposed by the use of PHP compared to TBHP become much more important with decreasing reactivity of the double bond.

With both the intermolecular molybdenum-/vanadium-catalyzed epoxidation as with the intramolecular vanadium-catalyzed epoxidation of allylic alcohols steric interactions are observed when the bulky PHP is applied as oxidant, which is reflected in a decrease in reaction rate. This decrease is, however, less pronounced in the case of the intramolecular vanadium-catalyzed epoxidation due to the coordination of the substrate as well as the oxidant to the vanadium catalyst (see Table 1). Steric effects could also be important in the equilibrium formation of the alkylperoxometal intermediate leading to a decrease in rate with PHP compared to TBHP.

We also performed epoxidations with TBHP and PHP in the presence of zirconium[18] as the catalyst (Table 3). Both **4a** and **4b** were epoxidized at room temperature using TBHP and PHP, although PHP was considerably less active. These results were compared with vanadium-catalyzed epoxidation of **4a/4b** at room temperature, which showed that vanadium is more active than zirconium as catalyst. Furthermore, the relative decrease in reactivity going from TBHP to PHP was less when vanadium was used as catalyst. These results can be explained by a less effective coordination of the hydroxyl group in **4a/4b** to the zirconium compared to vanadium.

It is generally believed that the selenium dioxide-catalyzed allylic oxidation of olefins with TBHP involves initial ene reaction of SeO$_2$ with the olefin followed by a sigmatropic [2,3] rearrangement (Scheme 3).[19a−d] The resulting Se(II) is reoxidized by the TBHP.

Hence, the selenium-catalyzed allylic oxidations with RO$_2$H involve an oxometal pathway, and assuming that reaction of oxoselenium(IV) with the olefin is the rate-limiting step, the rate should not be significantly influenced by the structure of RO$_2$H. This was indeed observed: using 2 mol % and 1.5 equiv of RO$_2$H at room-temperature, PHP was as active (substrates **11** and **12**, Figure 4) or even more active (substrates **13**−**15**) than TBHP in allylic oxidations (see Table 5).

A slower reaction with PHP compared to TBHP was observed only in the case of α-methylstyrene. The reactivity order for allylic C−H groups is CH$_2$ > CH$_3$ > CH.[19e] Thus, β-pinene was selectively oxidized at the allylic CH$_2$ group to give pinocarveol (96−99% yield) together with trace amounts of pinocarvone. **13** and **15** also gave the product derived from oxidation of the allylic CH$_2$ group. The major byproducts were the α,β-unsatur-

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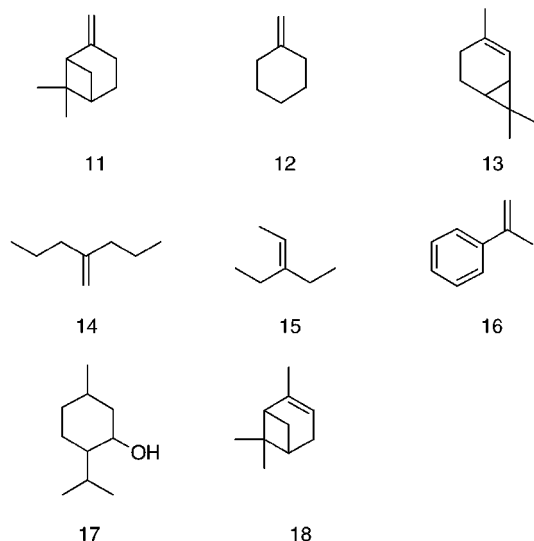

Figure 4. Substrates used in the Se-, Os-, Ru-, Cr-, and V-catalyzed oxidation.

Table 5. Se, Os, Ru, Cr and V-Catalyzed Oxidations with Either TBHP or PHP as Oxidant

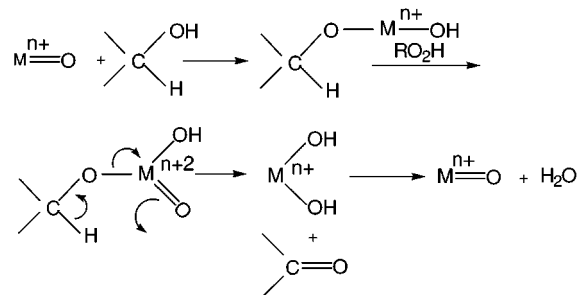| substrate	catalyst	oxidant	conversion (%)	selectivity[a] (%)
11	Se	TBHP	100	96
11	Se	PHP	100	99
12	Se	TBHP	100	87
12	Se	PHP	100	89
13	Se	TBHP	68	92
13	Se	PHP	91	95
14	Se	TBHP	33	84
14	Se	PHP	51	75
15	Se	TBHP	58	80
15	Se	PHP	84	81
16	Se	TBHP	90	86
16	Se	PHP	38	84
16	Os	TBHP	95	60 (19)
16	Os	PHP	76	48 (10)
18	Os	TBHP	82	16 (17)
18	Os	PHP	43	n.d. (44)
1	Os	TBHP	100	78
1	Os	PHP	73	65
4a/4b	Ru	TBHP	57[b]	72
4a/4b	Ru	PHP	33[c]	75
17	Ru	TBHP	81	54
17	Ru	PHP	85	55
5a	Ru	TBHP	83	52
5a	Ru	PHP	32	58
4a/4b	Cr	TBHP	96[d]	93
4a/4b	Cr	PHP	24[e]	98
17	V	TBHP	67	65
17	V	PHP	25	75

[a] To α,β-unsaturated alcohol for the selenium-catalyzed reactions (α,β-unsaturated ketone being the major byproduct), to the diol for the osmium-catalyzed reactions (between brackets the selectivity to ketol). For ruthenium- and chromium-catalyzed reaction the selectivity is toward ketone/aldehyde, with major byproducts coming from double-bond cleavage. [b] 21% trans/36% cis. [c] 13% trans/20% cis. [d] 46% trans/50% cis. [e] 9% trans/15% cis.

ated ketone, resulting from further oxidation, and in the case of **13**, small amounts of rearranged products were also observed. Similar results were observed with **12**, **14**, and **16**: high selectivities to the allylic alcohol with minor amounts of the corresponding α,β-unsaturated ketones.

Another example of a metal-catalyzed oxidation with RO$_2$H that involves an oxometal pathway is the OsO$_4$-catalyzed dihydroxylation of olefins.[20a−c] Two major pathways, with several variations, have been proposed

Scheme 4. Osmium-Catalyzed Dihydroxylations

Stepwise [2 + 2] pathway

Concerted [3 + 2] pathway

Scheme 5[a]

[a] M = Cr, Ru, or V.
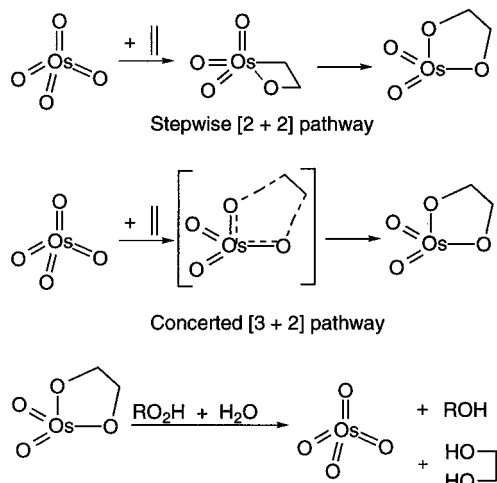
for the dihydroxylation process: a concerted [3 + 2] cycloaddition[21] and a formal [2 + 2] cycloaddition[22] leading to an osmaoxetane intermediate, which in turn rearranges to the primary product, the cyclic osmate ester.[23] Reaction of the latter with RO_2H/H_2O affords the diol product with regeneration of OsO_4 (Scheme 4).

We found that the OsO_4-catalyzed dihydroxylation of **16**,[20d] **1**, and **18** gave a faster reaction with TBHP than with PHP, the final conversion being reached in 6 and 24 h, respectively (Table 5). The slower reaction with PHP is consistent with the observation that the reoxidation of the relatively substitution-inert osmium(VI) ester to a substitution labile osmium(VIII), and not reaction of oxoosmium(VIII) with the olefin, is the rate-limiting step.[20f] This step would be expected to be slower with the more sterically demanding PHP than with TBHP. The diol derived from **16** is sensitive toward further oxidation, and substantial amounts of acetophenone were observed. Dihydroxylation of **1** gave, with both oxidants, in addition to cyclohexanediol also considerable amounts of glycol ether, formed from the diol and the solvent, *tert*-butyl alcohol. OsO_4-catalyzed di-

hydroxylation of the sterically hindered **18** with TBHP afforded only small amounts of diol as reported earlier for this substrate.[20g] The major (by)products were the ketol (32%) and glycol ether (10%). The longer reaction times needed with PHP resulted in a higher selectivity to the ketol at the expense of the diol. Because we were primarily interested in a comparison of TBHP and PHP we did not investigate possible improvements in the oxidations with PHP, e.g., by increasing the reaction temperature and/or addition of pyridine to enhance the formation of the osmate ester.[20h]

Ruthenium[21] and chromium[9] also catalyze various oxidative transformations with TBHP via the intermediate formation of high-valent oxometal species as the active oxidants (Scheme 5).

We examined the $RuCl_3$-catalyzed oxidation of **17**, **4a/4b**, and **5a** and the $Cr(acac)_3$-catalyzed oxidation of **4a/4b** (Table 5) to the corresponding carbonyl compounds with TBHP and PHP. The reactions with TBHP were generally faster than with PHP. By analogy with the results obtained in OsO_4-catalyzed dihydroxylations (see above) this suggests that the rate-limiting step in the ruthenium- and chromium-catalyzed oxidation of alcohols may involve reaction of a metal alkoxide with RO_2H resulting in formation of the carbonyl compound with simultaneous reoxidation of the ruthenium or chromium.

Vanadium can react via a peroxometal or an oxometal mechanism depending on the substrate. It catalyzes epoxidations via a peroxometal mechanism (see above) and alcohol oxidations via an oxometal mechanism.[17b] Vanadium-catalyzed oxidation of **17** showed a faster reaction using TBHP compared to PHP which can be rationalized by assuming that reoxidation of the vanadium(III) alkoxide by the alkyl hydroperoxide is rate-limiting (Scheme 5).

Conclusions

In conclusion, we have shown that PHP is a valuable mechanistic probe for distinguishing between alternative pathways in metal-catalyzed oxidations with alkyl hydroperoxides. When the reaction involves rate-limiting intermolecular oxygen transfer from a peroxometal species to the substrate, e.g., in Mo- and V-catalyzed epoxidations, the bulky PHP is unreactive. The steric constraints are less of a problem, however, when coordination of the substrate, e.g., in V-catalyzed epoxidation of allylic alcohols, provides for an intramolecular oxygen transfer. When the reaction involves reaction of an oxometal species with the substrate as the rate-limiting step virtually no difference is observed. Small differences in reactivity are observed when reoxidation of the catalyst

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by RO_2H to the active oxometal species is the rate-limiting step.

Experimental Section

General Methods. Unless otherwise stated, all starting materials were obtained from commercial suppliers and used without further purification. Pinane hydroperoxide was obtained from Quest International as a 44% solution in pinane and was used without further purification.

Gas chromatography was either performed on a CP wax 52 CB (50 m × 0.53 mm, df = 2) or on a CP Sil 5 CB (50 m × 0.53 mm, df = 2) column. GC−MS data were obtained on a VG 70 Se mass spectrometer coupled to a Sil 5 (25 m × 0.25 mm, df = 0.4) column.

Anhydrous *tert*-Butyl Hydroperoxide. A mixture of 100 g of aqueous 70% TBHP and 210 g of chlorobenzene was shaken in a separatory funnel. The organic layer was separated and dried over Na_2SO_4, after which the solution was further dried and stored over activated 3 Å molecular sieves at 4 °C. The peroxide concentration was determined by iodometric titration.

Catalytic Experiments (Mo, V, Zr, Cr, and Ru). A mixture of 10 mmol of substrate, 10 mmol of oxidant (25% TBHP in chlorobenzene or 44% PHP in pinane), 1 g of bromobenzene or 1 g of 1,4-dichlorobenzene as internal standard, and 0.1 mmol of molybdenum hexacarbonyl or vanadyl acetylacetonate in 10 mL of chlorobenzene was heated at 80 °C for 5 h. The zirconium-catalyzed epoxidations were carried out at room temperature using 0.1 mmol of zirconium propoxide as catalyst. The ruthenium-catalyzed reactions were performed by adding 0.05 mmol of $RuCl_3$ in 1 mL of *tert*-butyl alcohol to the reaction mixture. The reaction mixture was stirred for 24 h at room temperature. The epoxidations of limonene and cyclohexene were performed under a nitrogen atmosphere. Samples were taken at regular time intervals and analyzed by GC using an internal standard.

Catalytic Experiments (Se). A mixture of 15 mmol of alkyl hydroperoxide, 1 g of chlorobenzene or bromobenzene, 0.2 mmol of SeO_2, and 0.3 mmol of acetic acid was stirred in 10 mL of CH_2Cl_2 for 30 min, after which 10 mmol of substrate was added. The reaction mixture was stirred at room temperature and was followed by GC.

Catalytic Experiments (Os). A mixture of 20 mL of *tert*-butyl alcohol, 0.75 mL of 20% aqueous tetraethylammonium hydroxide, 10 mmol of olefin, and 16 mmol of alkyl hydroperoxide was cooled to 0 °C. A solution of 40 mg of 2.5% OsO_4 in *tert*-butyl alcohol (substrate/Os = 1900) was added, and the reaction mixture was stirred at 0 °C for 4 h, after which it was allowed to warm to room temperature, and stirring was continued at room temperature overnight.

Supporting Information Available: ^{1}H, ^{13}C NMR and MS data of the products (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.