Use of WO_4^{2-} on Layered Double Hydroxides for Mild Oxidative Bromination and Bromide-Assisted Epoxidation with H_2O_2

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Abstract: Tungstate, exchanged on a (Ni,Al) layered double hydroxide, is applied as a heterogeneous catalyst in the oxidation of bromide with H_2O_2 and the ensuing electrophilic bromination of olefins. The high halogenation activity of the catalyst in essentially neutral conditions mimicks the activity of V-bromoperoxidase enzymes. In water, aromatic and aliphatic olefins are selectively converted to bromohydrins; in methanol, methoxybromides are produced. In appropriate solvent conditions, the bromohydroxylation of geminally di-, tri-, and tetrasubstituted olefins proceeds via dehydrobromination to the epoxide. Evidence for this mechanism is provided by kinetic and labeling experiments. This one-pot alternative for the two-step halohydrin epoxidation process is enabled by the mild pH conditions; bromide is effective in substoichiometric, catalytic amounts. All new catalytic procedures are characterized by a high oxidative stability of the catalyst, high productivity of the catalyst on weight basis, high W turnover frequencies in ambient conditions (up to 50 mol of product per W per h), and high chemo-, regio-, and stereoselectivities.

Introduction

Manufacture of dyes, flame retardants, pharmaceuticals, agrochemicals, and many other products often involves bromination.[1] Classical bromination uses elemental bromine, despite the fact that Br_2 is a pollutant and a safety and health hazard.[2] Perbromide Br_3^- exchanged polymers are safer to handle and are commercially available; nevertheless, their preparation still involves direct contact with Br_2, and like most supported stoichiometric reagents, they lack adequate process productivity.[3] At contrast with Br_2, stoichiometric brominating reagents such as *N*-bromosuccinimide (NBS), *N*-bromoacetamide (NBA), or bromodimethylsulfonium bromide do not produce HBr in bromination of organic molecules, but they are expensive and generate organic waste.[4]

Biohalogenation by bromoperoxidase enzymes follows a quite different strategy.[5] Using H_2O_2 and bromide salts instead of Br_2, "Br^+" is generated in situ by the vanadate catalytic center of the bromoperoxidase (V-BPO); the oxidized "Br^+" is immediately used for halogenation of an organic compound:

$$R{-}H + H_2O_2 + Br^- \rightarrow R{-}Br + H_2O + OH^- \qquad (1)$$

While V-BPOs have some potential in organic synthesis due to their unusual solvent stability, they have several shortcomings as well, e.g. oxidative instability, high purification costs, and strict pH and *T* requirements.[6,7] Enzyme immobilization can to some extent overcome these drawbacks, but it reduces the process productivity.[8]

Attempts to create synthetic V-BPO mimics have mostly focused on d^0 complexes such as V Schiff bases, molybdates, or CH_3ReO_3. Particularly in strong acid, these homogeneous catalysts oxidize halides at appreciable rates, and the oxidized halides have been used for bromination of olefins or aromatics, and for the Br-assisted oxidation of e.g. alcohols.[9] However, catalytic protocols with most V-BPO biomimics still contain major disadvantages, such as the use of chlorinated solvents;[10] more seriously, when milder pH conditions are required, almost stoichiometric amounts of metal must be used to ensure satisfactory activity.[11] Moreover, few groups have till now investigated the potential advantages of heterogeneous catalysts in halide oxidation.[12]

We recently described a new heterogeneous catalyst for halide oxidation, consisting of tungstate, ion-exchanged on a Ni,Al-

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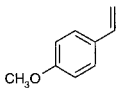
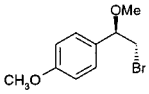
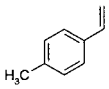
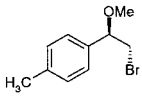
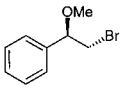
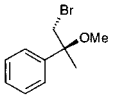
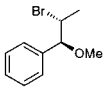
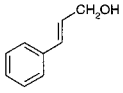
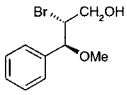
Table 1. LDH-WO_4^{2-} Catalyzed Methoxybromination (MB) and Dibromination (DB)[a]

	Olefin	Eq. H_2O_2	Major product; MS (*m*/*z*) [b]	Yield [c] (%)	Chemoselectivity [d] (%)
1		1.8		151, 244-246	92	MB (97)
2		4.0		135, 228-230	88	MB (92), DB (3)
3		4.5		121	21	MB (94), DB (3)
4		3.5		135, 213-215	96	MB (98) (DB < 1)
5		4.5		121	54	MB (84E), DB (15E) [e]
6		4.5		121	40	MB (75E), DB (19E) [e]

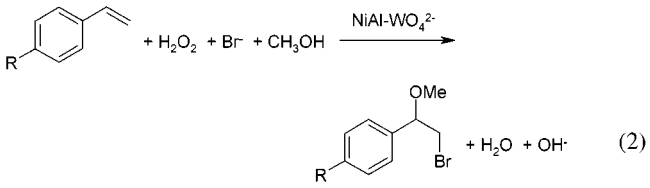
[a] Conditions: 0.8 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.16 M substrate, 0.25 M NH_4Br in MeOH−H_2O (95:5) with H_2O_2. [b] Plus all enantiomers; most prominent peaks in the EI mass spectrum. [c] Yield of methoxybromide (MB) + dibromide (DB), determined after complete consumption of H_2O_2. [d] Only 1-phenyl-1-methoxy-2-bromo methoxybromides were observed. [e] Only erythro (*E*) products in entries 5 and 6.

layered double hydroxide (LDH, or hydrotalcite-type structure).[13] The isomorphic substitution of Ni^{2+} by Al^{3+} in the octahedral layers of the LDH provides a sufficient exchange capacity for efficient tungstate retention. Moreover, the excess positive charge on the surface shields the negative charges of the peroxotungstate and bromide reaction partners,[14] and therefore ensures high halide oxidation rates even in the absence of acid. Since similar charge shielding is operative in the protein mantle of V-BPO, the (Ni,Al)LDH-WO_4^{2-} catalyst can be considered as a functional and structural V-BPO mimic.

In an effort to explore the synthetic scope of the (Ni,Al)-LDH-WO_4^{2-}/NH_4Br/H_2O_2 system, we herein report on the catalytic methoxybromination, dibromination, and bromohydroxylation of olefins. Detailed studies of regio-, stereo-, and chemoselectivity reveal that for most groups of olefins, effective new protocols can be developed. The new catalyst has obvious advantages, such as its fully inorganic and therefore oxidatively stable nature, and more importantly, the decoupling of efficient halide oxidation and low pH. As a consequence of the latter issue, (Ni,Al)LDH-WO_4^{2-} can even be used for the one-pot bromide-assisted epoxidation of olefins. The mechanism of the latter process was investigated, with particular attention for the catalytic role of bromide.

Results and Discussion

1. Bromination of Aromatic Olefins in Methanol. Methoxybromination is a useful approach for introduction of two vicinal functional groups.[15−17] Table 1 gives results for the bromination of styrenes with H_2O_2 and Br^- in methanol using the (Ni,Al)LDH-WO_4^{2-} catalyst. The stoichiometry of the oxidative methoxybromination of a para-substituted styrene is given in eq 2. Note that a hydroxyl anion is produced per incorporated Br atom:



(2)

The increase of the pH could easily be monitored in a semiquantitative way; during a typical bromination, the pH increases from 6 to about 9. In the experiments, typically 2−10 g of brominated products is obtained per g of catalyst, or 40−200 mol of products per mol of exchanged WO_4^{2-}. Substrate conversion is almost complete within 4 to 10 h at 298 K corresponding to a turnover frequency based on brominated product of 20−50 mol·mol^{-1}·h^{-1} (entries 1, 2, and 4). In the absence of the (Ni,Al)LDH-WO_4^{2-} solid, no products are formed.

Apart from the activity, the chemo-, stereo-, and regioselectivities are important aspects of the bromination. In the last column of Table 1, the distribution of the products over dibromides (DB) and methoxybromides (MB) is given. The

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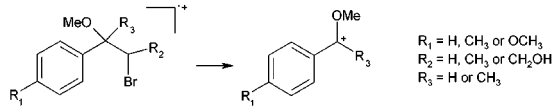
Table 2. Relative Rate Constants k_r for Methoxybromination of 4(3)-X−C_6H_4−CH═CH_2[a]

X	H	NO_2	3-Cl	4-Cl	CH_3	*tert*-butyl	OCH_3
k_r	1.00	0.0016	0.019	0.263	16.6	15.8	1550

[a] Conditions: 0.8 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.2 M NH_4Br and H_2O_2, MeOH, 298 K.

methoxybromide is the major product for all entries, despite the presence of 0.25 M bromide. For instance, 96% MB is obtained in the reaction of α-methylstyrene (entry 4). Only when the styrene has a substituent at the β position is a significant amount of DB produced (entries 5 and 6).

Second, the bromination is stereoselective, implying that the bromide or methanol nucleophiles exclusively add to the brominated intermediate in anti fashion with respect to the first Br atom. With β-substituted styrenes, this results in stereospecificity; for instance, *trans*-β-methylstyrene is brominated to give only the erythro isomers (entry 5). Finally, the attack of the MeOH nucleophile proceeds with Markovnikov-type regioselectivity, leading to a product containing the methoxy group at the α-carbon atom. The regioselectivity of the methoxybromination was determined with the help of GC-MS. The following fragmentation is observed for the major product of all styrenes (see Table 1). Overall, the chemo-, regio-, and



stereoselectivity of the catalytic oxidative bromination of styrenes are similar to those of reactions with slow addition of Br_2 in the same conditions (0.25 M Br^- in MeOH).[16g,17]

The effect of substituents on the styrene bromination rate was investigated using the Hammett equation:

$$\log k_r = \sigma^{(+)}\rho^{(+)} \qquad (3)$$

where the substituent parameter $\sigma^{(+)}$ is positive for electron-withdrawing substituents and vice versa; k_r is the relative reaction rate of a substituted styrene versus that of styrene, and $\rho^{(+)}$ is the slope of the plot. $\rho^{(+)}$ is a reaction-specific parameter that quantifies to what extent the reaction rate is influenced by mesomerically or inductively electron-donating or -withdrawing substituents; thus, $\rho^{(+)}$ is a measure for the charge development in the transition state of the reaction. Electrophilic reactions are accelerated by electron-donating substituents, yielding a ρ value <0, as in the reaction of styrenes with water ($\rho^+ = -3.58$),[18] or with Br_2 in acetic acid ($\rho^+ = -4.8$).[19] As in some cases (e.g. *p*-methoxystyrene) the bromide oxidation may be rate determining rather than the bromination itself, the relative reaction rates k_r were derived from competitive experiments (Table 2).

Figure 1 shows the linear free-energy relationship between $\log k_r$ and σ^+ for the bromination of six differently substituted styrenes by (Ni,Al)LDH-WO_4^{2-}. As expected for electrophilic bromination, the reactivity order for the styrenes was OMe > CH_3 > *tert*-butyl > H > 4-Cl > 3-Cl > NO_2. The slope of the correlation line in Figure 1 gives a ρ^+ value of −3.91 (r^2 = 0.997). The excellent linearity of the Hammett plot with σ^+ indicates that the bromination of the various styrenes operates via a single mechanism. The large negative value of ρ^+ can be

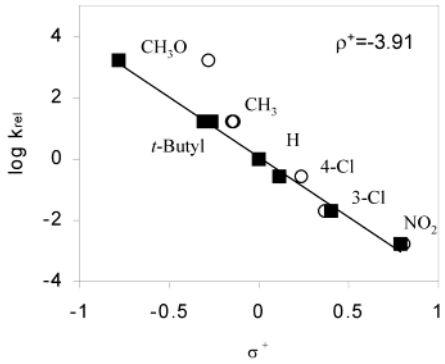
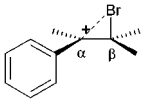


Figure 1. Hammett plot for the relative initial rates of bromomethoxylation of substituted styrenes vs the substituent constants σ^+ (■) and σ (○).

interpreted in terms of a positively charged transition state such as an α-phenylcarbenium ion, with the charge at C_α stabilized by the adjacent phenyl ring. Considerably more scatter is obtained by plotting $\log k_r$ values vs σ ($\rho = -5.15$, $r^2 = 0.952$). The better fit with σ^+ than with σ is consistent with the fact that electron-donating groups stabilize a carbocation transition state largely through resonance. Charge development at C_α is also supported by the Markovnikov-type regioselectivity. However, the complete stereospecificity of the nucleophilic attack proves that the intermediate is not strictly an α-carbenium ion, but rather should be described as an unsymmetrically bridged bromonium ion with weak bonding of the bromine atom to the benzylic carbon atom, as is illustrated for styrene in (3):



An oxidized "Br^+" intermediate may not only react with a double bond, but may also oxidize a new equivalent of H_2O_2 into singlet dioxygen[20] (eq 4). As the lifetime of this reactive form of oxygen is very short in aqueous conditions, it rapidly decays into its ground state.

$$H_2O_2 + OBr^- \rightarrow {}^1O_2 + Br^- + H_2O \qquad (4)$$

The efficiency of the oxidant consumption therefore depends on the reactivity of the substrate. This behavior is indeed reflected in the catalytic results of Table 1. As an example, the highly reactive substrate 4-methoxystyrene can be quantitatively converted with 1.8 equiv of H_2O_2, whereas 4-methylstyrene requires more oxidant for reaction completion (compare entries 1 and 2, Table 1). Only 21% of styrene was brominated even when 4.5 equiv of H_2O_2 was added (entry 5).

2. Bromination of Aliphatic Alkenes in Methanol. In addition to styrenes, linear and cyclic alkenes were used as reactants in the oxidative bromination with (Ni,Al)LDH-WO_4^{2-}. Yields and product selectivities are given in Tables 3 and 4. With 2−5 equiv of H_2O_2, a sufficient amount of "Br^+" is generated to convert the major part of even a nonactivated olefin such as 1-heptene (Table 3, entry 1). In the reaction conditions employed, methoxybromides (MB) are the main products, together with dibromides (DB), but the reaction is generally less chemoselective than with styrenes. For instance, the bromination of 1-heptene results in 46% DB selectivity (Table 3, entry 1) against only 3% DB for styrene (Table 1, entry 3). Methanol attack is favored over bromide addition for substrates

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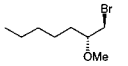
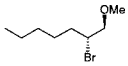
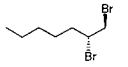
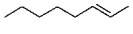
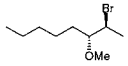
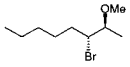
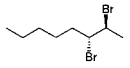
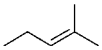
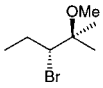
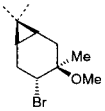
Table 3. LDH-WO_4^{2-} Catalyzed Bromination of Linear and Cyclic Alkenes at 298 K[a]

	Olefin	Eq. H_2O_2	Major product(s); MS (*m/z*) [b]	Yield [c] (%)	Selectivity (%)
1		5.0	 115, 137-139	60	MB (53); DB (46)
			 97, 106-108		
			 97, 177-179		
2		3.5	 115, 151-153	88	MB (53); DB (46)
			 nd [d]		
			 191-193		
3		2.3	 nd [d]	97	MB (76); DB (21)
4		2.7	 nd [d]	91	MB (77); DB (19)
5		3.3	 178-180	95	MB (56); DB (39)
			 147-149; 226-228-230		
6		4.4	 192-194	91	MB (57); DB (43)
			 161-163; 240-242-244		
7		2.5	 127; 166-168; 206-208	93	MB (65); DB (28)
8		2.5	 113; 192-194	92	MB (76); DB (18)
9		2.5	 231-233; 246-248	89	MB (85); DB (8)

[a] Conditions: 0.8 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.16 M substrate, 0.25 M NH_4Br in MeOH−H_2O (95:5) with H_2O_2. [b] Plus all enantiomers; most prominent peaks in the EI mass spectrum. [c] Yield of methoxybromide (MB) + dibromide (DB), determined after complete consumption of H_2O_2. [d] nd = not determined.

with increased steric hindrance. Thus the ratio of DB/MB decreases from 0.75 for cyclohexene to 0.43 and 0.09 for 1-methyl-1-cyclohexene and 3-carene, respectively (Table 3, entries 6, 7, and 9). Analogous effects can be observed for the cyclopentenes (entries 5 and 8) and linear alkenes (entries 2 and 4). With 1,2-di-*tert*-butylethylene, the reaction is fully chemoselective for the methoxybromide (Table 4, entry 9). Such steric effects arise from the considerable size difference between a solvated Br^- anion and methanol.[16g]

For trisubstituted cyclic alkenes such as 1-methyl-1-cyclohexene, the methoxybromination exclusively yields Markovnikov products (Table 3, entries 7, 8, and 9). For linear alkenes, regioselectivity and stereospecificity are summarized in Table 4. Again, Markovnikov's rule correctly predicts the regioselectivities for many substrates, such as mono- or trisubstituted olefins. However, mixed regioselectivities are obtained for the cis and trans disubstituted 2-alkenes.[16g] For instance, starting from *cis*-4-methyl-2-pentene, the 2-methoxy-3-bromo compound is the main methoxybromide, which seemingly contradicts Markovnikov's rule (entry 5). This indicates that steric effects can also play a role, for instance in the attack of the nucleophile to the bridged bromonium intermediate.

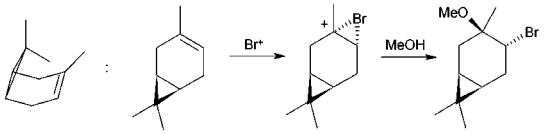
The reactions with alkenes are stereospecific, which is in line with a bridged bromonium ion; thus *cis*-2-hexene gives the threo methoxybromides, while *trans*-2-hexene leads to the corresponding erythro products (Table 4, entries 4 and 6). In the case of 3-carene, the stereoselective syn addition of the methoxy group with respect to the carbon bridge is remarkable (Table 3, entry 9). This is easily explained taking into account the closed-boat conformation of 3-carene.[21] Since the approach of Br^+ to

Table 4. Product Selectivities in the Bromination of Linear and Cyclic Alkenes in MeOH in the Presence of WO_4^{2-} on (Ni,Al)LDH-Cl^-/NH_4Br/H_2O_2[a,b]

	R	R′	DB	MB α-OMe, β-Br	MB α-Br, β-OMe
	$RR'C_\alpha{=}C_\beta H_2$				
1	propyl	H	48	40	12
2	pentyl	H	46	39	15
3	isopropyl	H	48	39	13
	cis-$RHC_\alpha{=}C_\beta HR'$				
4	propyl	CH_3	51T	20T	29T
5	isopropyl	CH_3	56T	10T	34T
	trans-$RHC_\alpha{=}C_\beta HR'$				
6	propyl	CH_3	43E	22E	35E
7	pentyl	CH_3	48E	21E	31E
8	propyl	propyl	53m	47E	
9	*tert*-butyl	*tert*-butyl		100E	
10	$(Me)_2C_\alpha{=}C_\beta HMe$		22	78	
11	$(Me)_2C_\alpha{=}C_\beta HEt$		19	81	
12	$(Me)_2C{=}C(Me)_2$		37	63	

[a] Conditions as in Table 3. [b] In %, determined by GC at conversions <10%. DB = dibromide, MB = methoxybromide, T = threo, E = erythro, m = meso.

the double bond is impeded by the alkyl bridge, Br^+ only adds from the opposite direction, eventually leading to syn addition of MeOH:

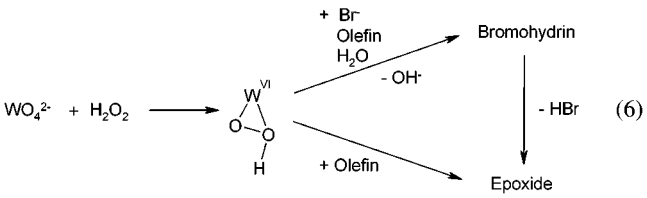


(5)

3. Bromohydroxylation in Aqueous Biphasic Conditions. Bromohydroxylation of olefins leads directly or indirectly to a variety of functionalized compounds of potential interest, e.g., bromohydrins,[22,1b] epoxides,[23] and 1-amido-2-bromo compounds.[24] Yields and product selectivities, obtained in the oxidative bromohydroxylation of various aromatic olefins, linear or cyclic alkenes, and allylic alcohols are given in Table 5. The reactions of Table 5 were performed in the liquid biphasic mode, with a large aqueous phase and a small organic layer, typically containing the olefin and 2-methyltetrahydrofuran (CH_3THF) as a solvent. This protocol results in the highest bromohydrin selectivities, as will be discussed in the next section. With the (Ni,Al)LDH-WO_4^{2-}−H_2O_2−Br^- catalytic system in aqueous biphasic conditions, bromohydrin yields are good to excellent (76−96%, Table 5). Complete conversion of a reactive substrate such as 4-methoxystyrene to its bromohydrin is accomplished with 1.5 equiv of H_2O_2 (entry 1). Such a high oxidant efficiency is not observed for all substrates, and 3−4 equiv of H_2O_2 may be needed, particularly for less reactive molecules such as cinnamyl alcohol or 1-heptene (entries 6 and 7). The productivity of the catalytic system amounts to 170−220 mol of bromohydroxylated product per mol of immobilized WO_4^{2-}, corresponding to 6−10 g of desired product per g of catalyst, within a time span of 8−23 h.

In general, the tendency to dibromide formation is much less pronounced in aqueous solution than in MeOH, despite the higher bromide concentration used in H_2O. Thus, while in MeOH, cyclohexene is converted for 43% into the dibromide adduct, the selectivity for the latter is much lower in aqueous conditions (14%; compare entry 8 of Table 5 with entry 6 in Table 3). Except for the different dibromide yields, there are strong selectivity parallels between the bromohydroxylation with (Ni,Al)LDH-WO_4^{2-}−H_2O_2−Br^- in water and the methoxybromination. Thus, the bromohydroxylation of styrenes and substituted cyclic olefins results in a 100% preference for the Markovnikov product, as indicated by entries 1−6 and 9. A limited anti-Markovnikov reaction is again observed for linear alkenes. For example, bromination of 1-heptene leads to 1-Br-2-OH heptane (78% of bromohydrins formed), but also to the anti-Markovnikov product 1-OH-2-Br heptane (22% of bromohydrins formed) (Table 5, entry 7). Finally, bromination of asymmetric *trans*-alkenes affords the corresponding erythro bromohydrins with negligible formation of the threo isomers, as illustrated for *trans*-β-methylstyrene (entry 4) and cinnamyl alcohol (entry 6)

4. Br-Assisted Epoxidation in Monophasic Aqueous Conditions. During the bromination reactions, we became aware that the (Ni,Al)LDH-WO_4^{2-}−H_2O_2−Br^- system not only effects bromohydroxylation, but also olefin epoxidation, albeit in somewhat different conditions. For α-methylstyrene, bromohydroxylation is the main reaction in biphasic conditions, but epoxidation is favored in a single liquid phase. In principle, two different mechanisms can be envisaged for formation of epoxides with the (Ni,Al)LDH-WO_4^{2-} catalyst. First, the epoxide may be formed from the bromohydrin in an indirect, Br^--assisted epoxidation. In fact, such a mechanism has been proposed for the enzymatic production of steroidal epoxides using the chloroperoxidase of *Caldariomyces fumago*.[25] However, the epoxide may also be formed by direct transfer of an electrophilic O atom to the olefin from the peroxotungstate complex. The latter route is the general mechanism for epoxidation with H_2O_2 catalyzed by d^0 transition metals.[26] The two mechanisms are depicted in (6):



(6)

Evidence in favor of the bromohydrin route is given by the following experiments:

a. Catalytic role of the bromide: To confirm the role of the Br^- anions, the oxidative bromination of 1-methyl-1-cyclohexene with H_2O_2 using LDH-WO_4^{2-} is carried out in the presence and absence of NH_4Br. From the results in Table 6, it is evident that the epoxidation is strongly promoted by bromide anions. Indeed, in the presence of NH_4Br, 90% yield is obtained within 24 h, whereas practically no epoxide is observed in the absence of the bromide salt (compare runs 1 and 2). Nevertheless, run 3 indicates that 1-methyl-1-cyclohexene can be epoxidized directly by LDH-WO_4^{2-} and H_2O_2, but this direct route is at least 25 times slower and the selectivity of the reaction is significantly lower (44% vs 90% with Br^- assistance).[27] Thus, bromide is required for selective epoxidation; as the bromide: olefin ratio is only 1 to 4, the reaction is clearly catalytic in bromide.

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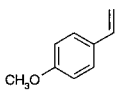
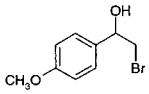
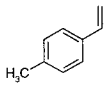
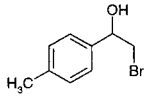
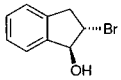
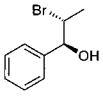
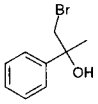
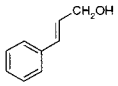
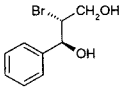
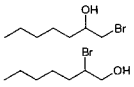
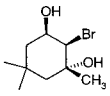
(22) (a) Dalton, D. R.; Dutta, V. P. *J. Chem. Soc. (B)* **1971**, 85. (b) Sisti, A. J.; Meyers, M. *J. Org. Chem.* **1973**, *38*, 4431. (c) Tee, O.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830.
(23) (a) Neidleman, S. L.; Amon, W. F., Jr.; Geigert, J. Cetus Corporation, U.S. Patent 4 247 641, 1981. (b) Vollhardt, K. P. C. *Organic Chemistry*; W. H. Freeman and Company: New York, 1987.
(24) Wohl, R. A. *J. Org. Chem.* **1973**, *38*, 3099.
(25) Neidleman, S. L.; Levine, S. D. *Tetrahedron Lett.* **1968**, *37*, 4057.
(26) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidation of Organic Compounds*; Academic Press: New York, 1981.
(27) Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *Tetrahedron Lett.* **1996**, *37*, 8557.

Table 5. LDH-WO_4^{2-} Catalyzed Hydroxybromination of Olefins, Allylic Alcohols, and Styrenes[a]

Entry	Olefin	Equiv. H_2O_2	Major Product(s); MS (*m*/*z*) [b]	Yield [c] (%)	Selectivity [d] (%)
1		1.5	 137; 151; 212-214; 230-232	95	HB (98) EP (<1)
2		3.0	 121; 196-198; 214-216	94	HB (94) EP (3) DB (1)
3		3.5	 nd [e]	92 [f]	HB (96; t:c = 18) [h] EP (1) DB (3)
4		3.5	 107; 214-216	85	HB (88; E:T = 37) [g, h] EP (6; t:c = 41) [g] DB (5; E:T = 5) [h]
5		3.0	 121; 199-201; 214-216	90	HB (91) EP (8) DB (<1)
6		5.0	 133; 182-184; 230-232	79	HB (86; E:T = 100) [g, h] EP (6; t:c = ∞) [h] DB (7; E:T = 5) [h]
7		3.5	 nd [e]	81 [f]	HB (83) [i] EP (<1) DB (17)
8		2.5	 99; 132-134; 178-180	76	HB (78) EP (8) DB (14)
9		4.0	 nd [e]	83	HB (84) EP (6) Isophorone (9) DB (<1)

[a] Conditions: 0.4 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.09 M substrate, 16 mM·h^{-1} H_2O_2, 0.4 M NH_4Br in H_2O:CH_3THF (4:1 vol %). [b] Including enantiomers; most prominent peaks in the EI mass spectrum. [c] Yield of bromohydrin, determined after complete consumption of H_2O_2. [d] HB = bromohydrin, EP = epoxide, DB = dibromide, E = erythro, T = threo, t = trans, c = cis. [e] Not determined. [f] CH_3CN is used instead of CH_3THF; in the case of indene, the bromohydrins precipitate as a white solid. [g] Only the 1-phenyl-1-hydroxy-2-bromo bromohydrin. [h] Based on GC. [i] Based on ^1H NMR: secondary CH(Br) at 4.15 ppm vs secondary CH(OH) at 3.78 ppm. 1-bromo:2-bromo = 3.5.

Table 6. Effect of NH_4Br on the Epoxidation of 1-Methyl-1-cyclohexene with H_2O_2 Using WO_4^{2-} on (Ni,Al)LDH-Cl^-[a]

	solvent	molar ratio Br:substrate:W:H_2O_2	*t* (h)	epoxide yield (%)
1	CH_3CN:H_2O:^{i}PrOH (8:5:1)	115:460:1:920[b]	20	90[c]
2	CH_3CN:H_2O:^{i}PrOH (8:5:1)	−: 460:1:920[b]	20	0.3
3	MeOH	−: 300:1:900	170	27[d]

[a] WO_4^{2-} on (Ni,Al)LDH-Cl^- (run 1 and 2) and (Mg,Al)LDH-Cl^- (run 3); 298 K. [b] Added dropwise over 18 h. [c] Substrate conversion = 100%. [d] Substrate conversion = 76%. Besides the epoxide, allylic hydroperoxides are formed with 56% selectivity. Data from ref 27.

b. Product distribution: An additional argument in favor of the indirect route is provided by the evolution of the reaction selectivity. A typical plot of the product distribution vs time for the oxidation of 1-methyl-1-cyclohexene with H_2O_2 and Br^- using the (Ni,Al)LDH-WO_4^{2-} catalyst is depicted in Figure 2. The plot shows that the bromohydrin is the initial product; as the reaction proceeds, the epoxide fraction increases at the expense of the bromohydrin. This proves that in the present reaction conditions, the bromohydrin is transformed into the epoxide. Note that the combined selectivities for epoxide and bromohydrin equal 90% throughout the whole experiment.

c. pH effect: As the dehydrobromination of bromohydrins is promoted by bases, it should be possible to stabilize the bromohydrin by adjusting the pH. Therefore, the bromination of 1-methyl-1-cyclohexene was repeated in the conditions of Figure 2, but the pH of the reaction solution was controlled with diluted HBr at about 4−4.5. GC analysis of the reaction solution after complete conversion of the substrate showed 89% bromohydrin yield without epoxide formation, confirming the expected pH effect on the product selectivity. This observation supports the hypothesis of a bromohydrin intermediate in the epoxidation.

d. Solvent-labeled $H_2^{18}O$ experiment: To trace the origin of the oxygen atom in the epoxide, $H_2^{18}O$ was used as a solvent, with $H_2^{16}O_2$ as the oxidant. If an oxygen atom is directly transferred from peroxotungstate to the olefin, the epoxides should only contain ^{16}O, at the condition that there is no isotopic exchange between the peroxo groups and the $H_2^{18}O$ solvent. On the other hand, if the epoxide is obtained by in situ dehydrobromination, the oxygen atom of the epoxide originates in the water solvent, and hence is labeled. Therefore, 0.1 M 1-methyl-1-cyclohexene was reacted with 0.05 M NH_4Br and 0.1 M H_2O_2 (30% in $H_2^{16}O$) in a CH_3CN:water ($H_2^{18}O$ and $H_2^{16}O$) mixture (75:25 vol %) in the presence of LDH-WO_4^{2-}.

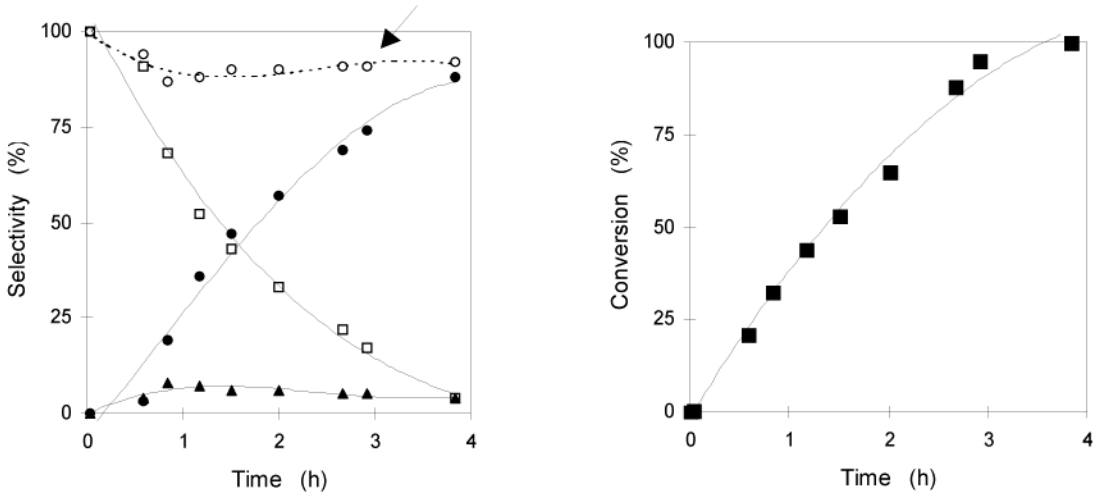
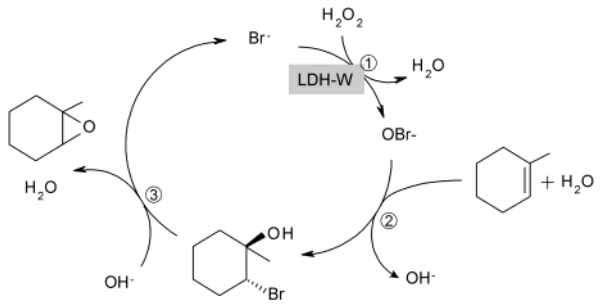


Figure 2. Product distribution (epoxide, ●; bromohydrin, □; dibromide, ▲) and conversion (■) as a function of time for the Br-assisted oxidation of 1-methyl-1-cyclohexene with H_2O_2 and Br^- in the presence of LDH-WO_4^{2-} at 298 K. Conditions: 1.0 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.07 M substrate, 0.16 M H_2O_2 at 50 mM·h^{-1}, 0.25 M NH_4Br in H_2O:CH_3CN (2:3). The dotted line represents the sum of bromohydrin and epoxide selectivity.

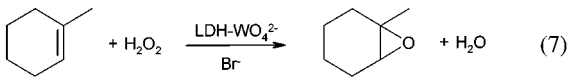
Scheme 1. Proposed Epoxidation Mechanism for (Ni,Al)LDH-WO_4^{2-} (=LDH−W)−Br^-−H_2O_2[a]



[a] Conditions: ① catalytic oxidation of Br^- with H_2O_2 using WO_4^{2-} on the LDH, leading to, e.g., hypobromite; ② Bromination of the olefin in the presence of H_2O with formation of bromohydrin; ③ base-promoted dehydrobromination of the bromohydrin leading to epoxide with recycling of the Br^-.

The isotopic purity of the water is estimated at ∼97% ^{18}O. $H_2{}^{16}O_2$ was added in 10 equal portions over 2 h. After extraction to ether, the products were analyzed by GC-MS. The relative intensities of the 112 and 114 *m*/*z* peaks learn that more than 95% of the epoxide molecules contain a heavy oxygen atom, confirming that the epoxide oxygen atom is supplied by water. This convincingly proves epoxide formation through bromohydrin intermediates.

Bringing together all the information of the aforementioned experiments, one can draw the catalytic cycle of Scheme 1. Via this mechanism, the (Ni,Al)LDH-WO_4^{2-} catalyst allows a one-pot conversion of olefins to epoxides. Note that Br^- anions are recycled from the bromohydrin, making water the only byproduct. Therefore, the net reaction for the epoxidation of e.g., 1-methyl-1-cyclohexene is as follows:



(7)

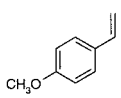
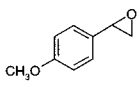
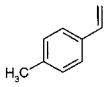
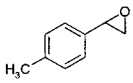
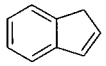
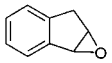
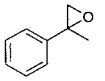
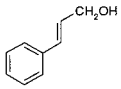
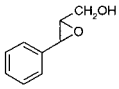
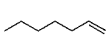
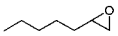
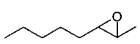
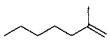
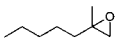
The main differences with the industrial two-step halohydrin process are the controlled catalytic production of "Br^+", which replaces the addition of elemental halogen, and the in situ transformation of the bromohydrin. Thus, isolation of the bromohydrin is no longer needed. The facile transformation of the bromohydrin into the epoxide is possible because of the mild pH range in which the system is active: the initial pH is 6−7, and a final pH of 8−9 is measured in the water suspension. Moreover, each oxidative bromination cycle generates one OH^- anion (eq 1), which may promote the cyclization of the bromohydrin. As alumina has been reported to promote the conversion of bromohydrins into epoxides,[28] the LDH support itself may also play a role in the dehydrobromination process. At contrast with the heterogeneous (Ni,Al)LDH-WO_4^{2-} catalyst, homogeneous VBPO biomimics, such as dissolved vanadates or molybdates, do not allow catalytic Br^--assisted epoxidation. For these homogeneous catalysts the initial step, i.e. the oxidation of the bromide anions, requires strong acidity, and this impedes the conversion of possibly formed bromohydrin into epoxides.

The scope of the Br-assisted epoxidation is investigated in Tables 7 and 8 for a series of aliphatic and alicyclic alkenes, aromatic olefins, and allylic alcohols. To promote selective epoxidation, the reactions were performed in a single liquid phase. In all reactions, substrate conversion is over 99%. The single liquid phase reactions generally require less H_2O_2 than the biphasic reactions to obtain similar conversions, which is due to a more favorable competition between olefin substrate and H_2O_2 for oxidized "Br^+" species. Consequently, fewer oxidation equivalents are lost to singlet dioxygen in the one-phase reactions than in two-phase reactions.

As observed earlier, the solvent composition strongly influences the chemoselectivity of the reaction. As an example, the bromination of α-methylstyrene yields 75% of the corresponding epoxide in the monophasic CH_3CN−H_2O (3:7) mixture, whereas the bromohydrin was obtained almost quantitatively in biphasic H_2O−CH_3THF (compare run 4 in Table 7 with run 5 in Table 5). High epoxide yields are observed for 2-methyl-2-heptene (90%) and 1-methyl-1-cyclohexene (88%) (Table 7, entries 9 and 11). However, the in situ cyclization of the bromohydrin cannot be generalized. For instance, *trans*-2-octene yields only 7% of the corresponding trans epoxide, together with a large amount of the bromohydrin (entry 8). The same holds for, e.g., *p*-methoxystyrene, 1-heptene, and cyclohexene (entries 1, 7, and

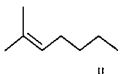
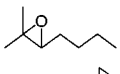
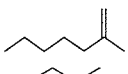
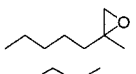
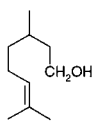
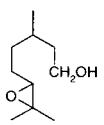
(28) Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* **1983**, *39*, 1765.

Table 7. Br-Assisted Epoxidation of Olefins, Allylic Alcohols, and Styrenes[a]

	Olefin	eq. H_2O_2	Epoxide, MS (*m/z*)	Epoxide yield (%) [b]	Selectivity (%) [c]
1		1.3		121; 150	3	HB (93) EP (3) DB (1)
2		2.5		105; 134	51	HB (39) EP (54) DB (5)
3		3.0		nd [d]	11	HB (82; t:c = 18) EP (11) DB (3)
4		2.5		105; 134	75	HB (22) EP (75) DB (2)
5		2.8		90; 134	56	HB (34; E:T = ∞) [e] EP (56; t:c = 45) DB (8; E:T = 6)
6		4.5		nd [d]	28	HB (65; E:T = 100) [e] EP (28; t:c = ∞) DB (7; E:T = 5)
7		3.5		nd [d]	< 1	HB (83) [f] EP (<1) DB (17)
8		3.0		nd [d]	7	HB (59; E:T = ∞) [g] EP (7; t:c = ∞) DB (34)
9		2.2		nd [d]	90	HB (6) EP (90) DB (2)
10		2.5		98	27	HB (56) EP (28) DB (12)
11		2.0		97; 112	88	HB (4) EP (88) DB (5)

[a] Conditions: 0.4 mM WO_4^{2-} on (Ni,Al)LDH-Cl^-, 0.09 M substrate, 16 mM·h^{-1} H_2O_2, 0.25 M NH_4Br in H_2O:CH_3CN (3:7). [b] Determined after complete consumption of H_2O_2. [c] HB = bromohydrin, EP = epoxide, DB = dibromide, E = erythro, T = threo, c = cis, t = trans. [d] Not determined. [e] Only the 1-phenyl-1-hydroxy-2-bromo bromohydrin. [f] 1-bromo:2-bromo = 3.5. [g] 2-bromo:3-bromo = 1.8.

Table 8. LDH-WO_4^{2-} Catalyzed Bromide-Assisted Epoxidation of Olefins[a]

Entry	Olefin	Equiv. H_2O_2	Product, Yield (%) [b]		Yield of other products (%) [c]
1		1.2		86	nd
2		1.4		88	HB (8); DB (<1)
3		1.8		93	HB (2); DB (3)
4		2.0		90	HB (6); DB (2)
5		1.4		94	HB (2); DB (2); Citral (<1);

[a] Conditions: 0.4 M substrate, 0.1 M NH_4Br, 1.0 mM WO_4^{2-} (on (Ni,Al)LDH-Cl^-), H_2O_2 (0.05 M·h^{-1}) in CH_3CN:H_2O:^{i}PrOH (8:5:1). [b] Product identities have been confirmed by ^1H and ^{13}C NMR. In all cases, olefin conversion was complete. Yields are determined at complete consumption of H_2O_2. [c] HB = bromohydrin; DB = dibromide.

10). Hence, the reaction conditions seem not sufficiently alkaline for the transformation of relatively stable bromohydrins.

That the bromide anion is a true cocatalyst for the epoxidation is demonstrated by the results in Table 8. In these experiments, the epoxidation of geminally disubstituted and various tri- and tetrasubstituted olefins is investigated in the presence of substoichiometric amounts of Br^- (25 mol % Br vs substrate). As can be seen, epoxides are obtained in high yields for all entries, confirming the catalytic role of the bromide anion.

Conclusions

The (Ni,Al)LDH-WO_4^{2-} catalyst allows electrophilic bromination of alkenes in mild and well-controlled conditions. No strong acid is needed for the in situ generation of "Br^+", nor is strong acid generated as a byproduct of the electrophilic bromination. The catalyst is cheap and totally stable toward oxidation. The reactions proceed in environmentally benign, non-chlorinated solvents, or even in water. In general the reactions benefit from the characteristic high reaction selectivity of halonium ions, with complete stereoselectivity; the regioselectivity is Markovnikov-directed, but may be influenced by steric effects in the attack of the nucleophile on the brominated intermediate. Only in the methoxybromination of some aliphatic olefins is the chemoselectivity moderate, due to the formation of a considerable amount of dibromides, but in all other cases, chemo-, regio-, and stereoselectivity are high, e.g. in the methoxybromination of aromatic olefins or in the bromohydroxylation of aromatic or aliphatic olefins.

For the two-electron oxidation of Br^- to "Br^+" species, H_2O_2 is used as an oxidant, with activation of the peroxide on tungstate. The number of H_2O_2 equivalents needed for complete conversion of the olefin is mainly determined by the competition for "Br^+" between olefin and a new molecule of H_2O_2. Obviously, the olefin is a better competitor if its double bond is more electron-rich, and if it is present in the same, single liquid phase as the oxidized "Br^+" species. As the oxidation of a Br^- anion by the peroxotungstates is generally much faster than the spontaneous disproportionation of peroxotungstates, tungstate-only catalyzed H_2O_2 decomposition plays only a negligible role in decreasing the H_2O_2 consumption efficiencies. Efficiencies are lower in the two-liquid-phase mode. Moreover, the observed efficiencies increase when the reaction mixture contains more water, since protic solvents dramatically increase the rates for electrophilic attack of "Br^+" on olefins.[29] Thus, bromohydroxylations proceed more efficiently than methoxybrominations.

The bromide-assisted epoxidation, with the bromohydrin as an intermediate, is a new and unique chemocatalytic reaction. This process became possible because with the WO_4^{2-} on LDH catalyst, halide oxidation no longer requires a strongly acidic pH. Suitable substrates for bromide-assisted epoxidation include geminally di-, tri-, and tetrasubstituted olefins. The reaction is simply switched from bromohydroxylation to epoxidation by the solvent choice, viz. by using a monophasic instead of a biphasic reaction mixture. In typical reaction conditions, monosubstituted and cis and trans disubstituted olefins are not converted into their epoxides, but the bromohydrins can readily be isolated and transformed into the epoxide in an additional base workup.

Bromide-assisted epoxidation is characterized by much higher turnover frequencies than classical W-catalyzed epoxidations. Thus the reactions of Table 8 produce 40 mol of epoxide per mol of W per h at 298 K. At contrast, typical turnover frequencies for W-catalyzed epoxidations are 5−10 mol mol W^{-1} h^{-1}, for reactions performed at 363 K; in optimized conditions and at 363 K, a maximal TOF of 20 mol mol W^{-1} h^{-1} has been observed.[30] Clearly the superior rates of the Br-assisted system in much milder conditions are due to the different mechanism involved. A similar high productivity is characteristic for the methoxybromination and bromohydroxylation procedures.

Experimental Section

1. Catalyst Preparation. The (Ni,Al)-layered double hydroxide with charge balancing chloride anions ((Ni,Al)LDH-Cl^-) is synthesized by coprecipitation under low supersaturation conditions. A 500 mL, three-necked round-bottom flask equipped with a magnetic stirrer is charged with 200 mL of degassed and deionized water and brought to pH 8 with 1 N NaOH. Next 240 mL of a 0.354 M $NiCl_2 \cdot 6H_2O$ and 0.146 M $AlCl_3 \cdot 6H_2O$ aqueous solution is added dropwise over 2 h at 298 K under N_2 atmosphere. During this period, 1 M NaOH solution is added to maintain the pH at 8 ± 0.5. After mixing of the initial salt solutions, the suspension is stirred at 298 K for 18 h in N_2 atmosphere. Finally, the solid is washed with deionized water and freeze-dried. The tungstate is introduced by conventional anion exchange. Typically, 1 g of the (Ni,Al)LDH-Cl^- support is suspended into 100 mL of a 1.875 mM $Na_2WO_4 \cdot 2H_2O$ aqueous solution. The anion exchange is carried out under stirring for 12 h at 298 K in an N_2 atmosphere. The resulting solid is isolated by centrifugation and washed with deionized and degassed water. Lyophilization eventually yields (Ni,Al)LDH-WO_4^{2-}. Bulk chemical elemental analysis shows Ni:Al and W:Al molar ratios of 2.46 and 0.067, respectively. Cell dimensions of the (Ni,Al)LDH-WO_4^{2-} catalyst are obtained from X-ray diffraction, giving $a_0 = 3.046$ nm and $c = 7.80$ nm.

2. Bromination and Br-Assisted Epoxidation. A typical procedure for the methoxybromination of olefins is as follows. A solution of olefin (0.16 M) is prepared in 10 mL of MeOH:H_2O (95:5 vol %) containing 0.25 M NH_4Br at 298 K. (Ni,Al)LDH-WO_4^{2-} (0.8 mM W) is suspended by stirring, and H_2O_2 is added in portions of approximately 0.03 M every 25 min.

The bromohydroxylation of alkenes (0.09 M) is carried out in 20 mL of a CH_3THF:H_2O (4:1 v/v) solvent mixture at 298 K using 0.4 mM (Ni,Al)LDH-WO_4^{2-} and 0.4 M NH_4Br. Hydrogen peroxide (aqueous 15%) is added by means of a syringe pump at a rate of 16 mM·h^{-1}.

The Br-assisted epoxidation of alkenes is performed with alkene (0.09 M), NH_4Br (0.25 M), WO_4^{2-} (0.4 mM) on (Ni,Al)LDH-Cl^-, and H_2O_2 (0.12−0.41 M, added with syringe pump at 16 mM·h^{-1}) in 20 mL of H_2O:CH_3CN (30:70 vol %). In case of substoichiometric amounts of Br^-, the alkenes (0.4 M) are epoxidized in 40 mL of CH_3CN:H_2O:^{i}PrOH (57:36:7 vol %) in the presence of 1.0 mM (Ni,Al)LDH-WO_4^{2-}, 0.1 M NH_4Br, and H_2O_2 (added at a rate of 50 mM·h^{-1}).

3. Product Analysis. The reaction mixture was analyzed by GC on several columns after filtration of the solid catalyst without any workup. Bromination and epoxidation products were identified by comparing retention times with those of authentic samples. Dibromides and methoxybromides were prepared by adding Br_2 at 273 K to an olefin solution in CH_2Cl_2 and MeOH, respectively. Authentic bromohydrins were prepared by adding stoichiometric amounts of NBS to an alkene solution in aqueous dioxane (or CH_3CN) over $CaCO_3$.[31] Epoxides were prepared from the stoichiometric reaction of an olefin with the peracid *m*-chloroperbenzoic acid (mCPBA) in dichloroethane.[32] The identification of the major products was systematically confirmed by GC-MS on the solid-free crude reaction mixture. Reactions were performed in

(29) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, Germany, 1990.

(30) (a) Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1994**, *116*, 5509. (b) Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3587. (c) Duncan, D. C.; Chambers, R. C.; Hecht, E.; Hill, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 681. (d) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905.

(31) Cocker, W.; Grayson, D. H. *Tetrahedron Lett.* **1969**, 4451.

(32) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.

deuterated solvents (CD_3OD and D_2O) to facilitate product assignment in MS. Bromination products were isolated by extraction into diethyl ether and drying in vacuo. The isolated products were identified by their ^1H and ^{13}C NMR spectra (Bruker AMX, 300 MHz) by comparison with the authentic samples.

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Supporting Information Available: Experimental data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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