A New Catalytic Route for the Oxidative Halogenation of Cyclic Enol Ethers using Tungstate Exchanged on Takovite

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Abstract: An efficient and benign method for the regio- and stereoselective synthesis of halohydrins and β-halo ethers from dihydropyrans, dihydrofurans and anhydro sugars in the presence of a halide salt and hydrogen peroxide is presented with tungstate-exchanged takovite as oxidation catalyst.

Keywords: cyclic enol ethers; heterogeneous catalysis; hydrogen peroxide; layered double hydroxide; oxidative halogenation; tungstate

Introduction

Halogen-based oxidants such as elemental halogens, organic and inorganic hypohalites, hypervalent iodine(III) and (V) reagents, dihalo-5,5′-dimethylhydantoins and *N*-halosuccinimides are often used for the selective halogenation of unsaturated hydrocarbons.[1,2] In particular, the stereo- and regioselective halogenation of alkenes such as vinyl ethers finds wide application in organic synthesis. However, most of the aforementioned reagents are either highly toxic or expensive and produce stoichiometric amounts of waste.

Today's increased environmental awareness prompts chemists to search for clean and sustainable synthesis methodologies. *In situ* formation of reactive halogen compounds is one of the most promising approaches to overcome the safety and waste handling problems. Electrochemical haloalkoxylation and halohydroxylation of alkenes using common halide salts have been employed for the synthesis of various halogenated products.[3] However, taking into account the costs and the apparatus needed with electrochemistry, reactive halides are better generated gradually in a chemical way. For instance, a reductive halogenation using $NaBrO_3$ or H_5IO_6 in the presence of $NaHSO_3$ has been published for the production of iodohydrins and bromohydrins.[4] The oxidative variant of *in situ* reactive halogen production has been recently looked at more frequently. One promising example of oxidative halogenation is illustrated in nature, where haloperoxidases use H_2O_2 to oxidize a halide to the halonium species, which in turn halogenates unsaturated hydrocarbons.[5] Instead of using enzymes, man-made analogues offer almost comparable activities with improved long-term stabilities and this for an acceptable price. Recently, tungstate exchanged on naturally occurring minerals such as hydrotalcite- and takovite-like materials has been demonstrated to be an excellent mimic for haloperoxidases.[6] Not only is the catalytic activity of the W-based catalyst close to that of the crude enzyme mixture; the solid catalyst also shows an excellent stability against oxidation in contrast to the majority of the biocatalysts. Hydrotalcite and takovite-like minerals, generally denoted as layered double hydroxides, have been frequently applied as catalyst support in other chemical transformations such as epoxidation, amine and thiol oxidation, hydroperoxidation and reductions.[7]

The catalytic oxyhalogenation cycle using the tungstate exchanged takovites has been fully elucidated and appears to be similar to that of the vanadium-containing haloperoxidases (VHPO).[5,6] The mechanism behind the oxidative halogenation is illustrated in Scheme 1. A key step is the oxidation of the halide to the hypohalite anion by tungstate-activated peroxides at the surface of the takovite mineral. The hypohalite anion equilibrates with its conjugate acid and the corresponding dihalide, the ratio depending on the pH, the halide concentration and the solvent. Subsequently, the hypohalous acid rapidly reacts with the substrate producing halogenated hydrocarbons. Crucial in this process is the availability of protons during the reaction as one proton is consumed per cycle. In order to exclude corrosive conditions and to ensure product and catalyst stability, the protons are best delivered from weak acids

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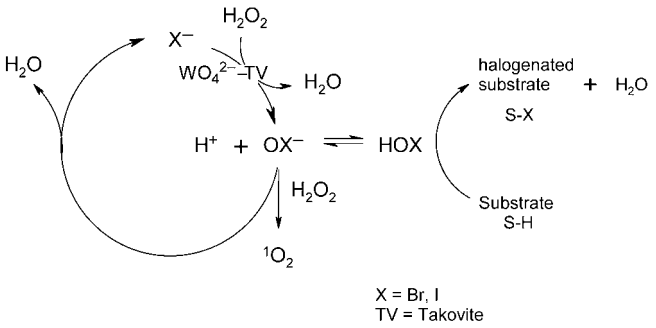
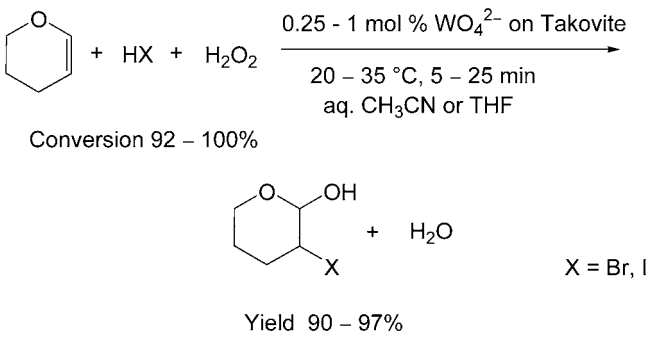


Scheme 1.



Scheme 2.

such as NH_4^+. If the oxidative halogenation is not buffered properly, the equilibrium shifts toward hypohalite anions which rapidly react with H_2O_2 to form dioxygen in its singlet state and water. Obviously, this unproductive decomposition of H_2O_2 should be avoided as much as possible.

Herein, we report on the oxidative halogenation of cyclic enol ethers into halo alcohols and ethers with ammonium halide salts and hydrogen peroxide using tungstate anions exchanged on a synthetic takovite-like mineral as catalyst.

Results and Discussion

Initially, we studied the catalyzed oxidative bromination of 2,3-dihydro-4*H*-pyran (DHP) in aqueous solvent conditions. As can be deduced from Table 1, the experiments resulted in an efficient procedure for the transformation of the alkene to the expected bromohydrin in excellent yield (Scheme 2, 90–97%).

Several general features are apparent in the reaction with DHP (Table 1). First, the composition of the aqueous organic solvent mixture plays an important role in the bromohydrin selectivity (compare entries 1 and 2). When the bromination is carried out in one liquid phase, e.g., by using water and CH_3CN in a volume ratio of 2 to 3, the bromohydrin is formed in 29% yield, whereas in a two liquid phase system, e.g., with 20 vol % CH_3CN in H_2O, a yield as high as 63% was detected. The yield improvement is the result of increased bromohydrin selectivity rather than rate acceleration. The increase in selectivity likely results from the protective role of the organic phase taking into account the instability of the brominated tetrahydropyran. The nature of the organic solvent is not crucial as acetonitrile can be replaced by similarly polar solvents such as methyltetrahydrofuran, tetrahydrofuran and dioxane without considerably affecting the catalytic results (compare for instance entry 3 with 4). Although not always necessary, small amounts of ethyl acetate, toluene, dichloromethane or benzonitrile may be added in order to ensure the protection of the bromohydrin. Increased polarity differences between the two phases may be of interest in case of bromohydroxylation of more polar substrates such as dihydrofurans.

Further improvement of the bromination procedure focussed on the yield based on oxidant efficiency. The bromohydroxylation proceeds more efficiently with respect to the oxidant consumption in presence of an appropriate NH_4Br concentration. For instance, when using the same amount of hydrogen peroxide, the olefinic substrate was completely converted in the presence of 0.8 M NH_4Br, whereas the conversion was only 66% with 0.4 M NH_4Br (entries 2 and 3). The more efficient use of the oxidant is due to an increased $HOBr/BrO^-$ ratio, so that bromination is preferred over singlet oxygen formation (Scheme 1). Interestingly, even with the high initial Br^- concentration, hardly any dibromide is formed. Replacement of NH_4Br by HBr as source of Br^- and H^+ appeared to be unsuccessful as the reaction was completely non-selective (entry 16). The by-products in this reaction were not further investigated.

Variation in the total amount of H_2O_2 revealed that 1.2–1.4 equivalents of oxidant, i.e., 5–6 aliquots of H_2O_2 (22 mmol) are sufficient to fully convert the pyran selectively into the desired bromohydrin (entries 3, 5–9). The time between consecutive additions of aliquots of H_2O_2 seems to be crucial. It was indeed established that the catalytic bromination system efficiently deals with up to 22 mM of oxidant per 2 mM of W catalyst every 2.5 minutes at room temperature (entries 12 and 13). According to this most efficient procedure the catalyst runs with a maximum of 275 cycles per hour at room temperature of which 85% produces the desired brominated compound. Faster addition of the oxidant leads to a pressure build-up in the reaction vessel as a result of the competitive decomposition of H_2O_2. The loss of oxidant is clearly reflected in the moderate yields, as obtained in entries 10 and 11 (58% and 84%, respectively). Despite the lower oxidant efficiency, the oxidative bromination remains selective, hence showing that the highly reactive singlet oxygen does not influence the product outcome in the case of cyclic enol ether bromination.

The oxidative bromination system is not only selective and efficient; it also shows a high productivity. In entry

Table 1. Oxidative hydrohalogenation (Br or I) of 2,3-dihydro-4*H*-pyran under various conditions catalyzed by WO_4^{2-} exchanged on takovite.

Entry	[DHP], mM	[WO_4^{2-}], mM	[NH_4Br], mM	[H_2O_2], mM	Time [min]	Selectivity [%][a]	Conversion [%]	Productivity [mmol product·g^{-1}·h^{-1}]
1[b]	90	1.0	400	176	40	29	100	20
2	90	1.0	400	176	40	96	66	43
3	90	1.0	800	176	40	92	100	61
4[c]	90	1.0	800	176	40	94	100	63
5	90	1.0	800	132	30	97	100	87
6	90	1.0	800	110	25	97	92	96
7	90	1.0	800	66	15	96	51	88
8	90	1.0	800	44	10	100	35	95
9	90	1.0	800	22	5	95	14	70
10	90	2.0	800	110	7.5	98	59	104
11	90	2.0	800	110	10	99	84	112
12	90	2.0	800	110	12	99	97	104
13	90	2.0	800	110	25	96	96	50
14	180	2.0	800	220	25	93	99	93
15	360	4.0	800	440	25	93	96	96
16[d]	360	4.0	330	440	25	–[e]	100	–
17[f]	360	4.0	400	440	10	93	99	246
18[g]	360	1.0	400	506	23	99	97	450

Standard reaction conditions: 2 mL CH_3CN, 8 mL H_2O, 2,3-dihydro-4*H*-pyran, NH_4Br, WO_4^{2-} on takovite, H_2O_2 (aqueous 35 wt %) in portions of 0.22 mmol, ambient conditions, 1000 rpm stirring.
[a] 3-Bromo-2-hydroxy product.
[b] In 6 mL CH_3CN and 4 mL H_2O.
[c] In 2 mL THF and 8 mL H_2O.
[d] HBr instead of NH_4Br.
[e] Completely non-selective.
[f] At 35 °C.
[g] NH_4I instead of NH_4Br at 35 °C.

15 for instance, DHP (0.36 M) is almost quantitatively converted into the 3-bromo-2-hydroxytetrahydropyran in the presence of the heterogeneous W catalyst (4 mM) at ambient temperature using only 1.2 equivalents of oxidant. This result corresponds to a productivity of almost 100 mmol bromohydrin per gram of catalyst and per hour. The production can rise to 250 mmol·g^{-1}·h^{-1} (or 45 g·g^{-1}·h^{-1}) by raising the reaction temperature by 10 °C (entry 17).

According to a similar procedure, iodohydrin is synthesized in yields up to 96% by replacing NH_4Br for NH_4I. The lower reduction potential of iodide in comparison with that of bromide allows lower catalyst concentrations. In the optimal conditions 450 mmol or 94 g of 2-hydroxy-3-iodotetrahydropyran were produced at 35 °C using 1 g of catalyst within one hour reaction time (entry 18).

Reactions with iodide are easy to follow in contrast to reactions with bromide. After addition of H_2O_2 to the reaction mixture containing iodide, the reaction immediately turns yellow-brown due to I_2 accumulation. The reaction mixture fades to colourless within a couple of minutes as the iodination of DHP proceeds. At this time a new shot of H_2O_2 may be added. Reaction completeness is evidenced by a stable yellow-brown coloration of the suspension as a result of the slight molar excess of the iodide salt initially available with respect to the substrate. When new substrate is added to the coloured solution, the solution turns colourless again, thus showing that reactions can be carried out with high atom efficiency in the halogen.

When the oxidative bromination was carried out in methanol the alkene was selectively transformed into the 3-bromo-2-methoxy ether (Scheme 3). Although the bromination in methanol requires somewhat more oxidant in order to ensure full conversion, the bromomethoxylation yields and productivities remain excellent (Table 2). For instance, DHP (0.36 M) on treatment with NH_4Br (0.40 M) and 1.7 equivalents H_2O_2 in methanol in the presence of 4 mM WO_4^{2-} exchanged on synthetic takovite gave the 3-bromo-2-methoxy adduct in almost quantitative yield (entry 2, 98%) corresponding to a productivity of 62 mmol 3-bromo-2-methoxy ether per hour and per gram catalyst. Again, the productivity can be doubled by increasing the reaction temperature by 10 °C (entry 3, 130 mmol·g^{-1}·h^{-1}). A similar iodomethoxylation using NH_4I gives the corresponding product in almost quantitative yields (entry 4, 96%).

Table 3 shows the general applicability of the halogenation using various alcohols including primary, secon-

Table 2. Oxidative methoxy(iodination)bromination of 2,3-dihydro-4*H*-pyran at various conditions catalyzed by WO_4^{2-} exchanged on takovite.

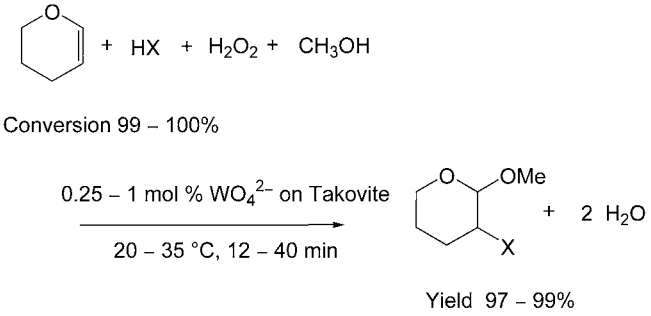
Entry	[DHP], mM	[WO_4^{2-}], mM	[NH_4Br], mM	[H_2O_2], mM	Time [min]	Selectivity [%][a]	Conversion [%]	Productivity [mmol product·g^{-1}·h^{-1}]
1	90	2.0	400	154	35	93	100	35
2	360	4.0	400	616	42	98	99	62
3[b]	360	4.0	400	616	20	99	100	130
4[c]	360	1.0	400	550	25	97	99	415

Standard reaction conditions: 10 mL CH_3OH, 2,3-dihydro-4*H*-pyran, NH_4Br, WO_4^{2-} on Takovite, H_2O_2 (aqueous 35 wt %) in portions of 0.22 mmol, ambient conditions, 1000 rpm stirring.
[a] 3-Bromo-2-methoxy product.
[b] At 35 °C.
[c] With NH_4I instead of NH_4Br at 35 °C.

Table 3. Synthesis of various 2-alkoxy-3-bromo adducts of 2,3-dihydro-4*H*-pyran.

Entry	ROH	Selectivity [%]	Conversion [%]	Productivity [mmol·g^{-1}·h^{-1}]	*trans*/*cis*[a]
1	MeOH	99	100	65	8.5 (9)[b]
2	EtOH	99	99	64	10
3	*n*-PrOH	84	97	52	11
4	*n*-BuOH	85	92[c]	48	12
5	$CH_2(OCH_3)CH_2OH$	95	100	61	10
6	CF_3CH_2OH	73	55	26	12
7	*i*-PrOH	94	100	63	12
8	*i*-BuOH	91	84[c]	49	13
9[d]	*i*-BuOH	92	97[c]	57	13
10	*t*-BuOH	10	40[c]	3	–
11	1,2-Propanediol	94	67	41	9 (4[e])

Standard reaction conditions: 10 mL CH_3OH, 3.6 mmol 2,3-dihydro-4*H*-pyran, 4 mmol NH_4Br, 3,6 mM WO_4^{2-} on Takovite (80 mg), 1.7 equivs. H_2O_2 (aqueous 35 wt%) in portions of 0.22 mmol every 1.5 minutes, ambient conditions , 1000 rpm stirring.
[a] Stereochemistry: molar ratio of *trans*/*cis* isomer calculated based on the GC areas.
[b] Molar ratio calculated based on ^1H NMR.
[c] NH_4Br not completely solubilized.
[d] 2.0 equivs. instead of 1.7 equivs. H_2O_2 (aqueous 35 wt %).
[e] Regiochemistry: ratio of the 2-OH-*n*-propoxy *vs.* 2-OH-isopropoxy ethers.



Scheme 3.

dary and tertiary alcohols. Whereas tertiary alcohols are difficult to introduce in the final product (entry 10), the reactions proceed remarkably well with the other alcohols as long as these alcohols solubilize an appropriate amount of ammonium bromide, such as for methanol, ethanol and isopropyl alcohol (entries 1–2, 7). The limited solubility of the bromide salt is the reason for the moderate conversions obtained in *n*-butanol and isobutyl alcohol (entries 4 and 8). As incomplete conversions were anticipated, more oxidant was added to drive the reactions to completion without losing selectivity (compare entry 8 with 9). In this way, the 3-bromo-2-*i*-butoxy ether is synthesized with 92% selectivity at 89% yield.

Apart from brominated ethers, some bromohydrins are formed. Hence, despite their low concentration, water molecules may act as competitive nucleophiles, especially when the bromination is carried out in the presence of sterically encumbered alcohols (compare entries 1 and 2 with 7 and 8). When a primary and secondary alcohol are present in the same molecule such as in 1,2-propanediol, the 3-bromo ether derived from the pri-

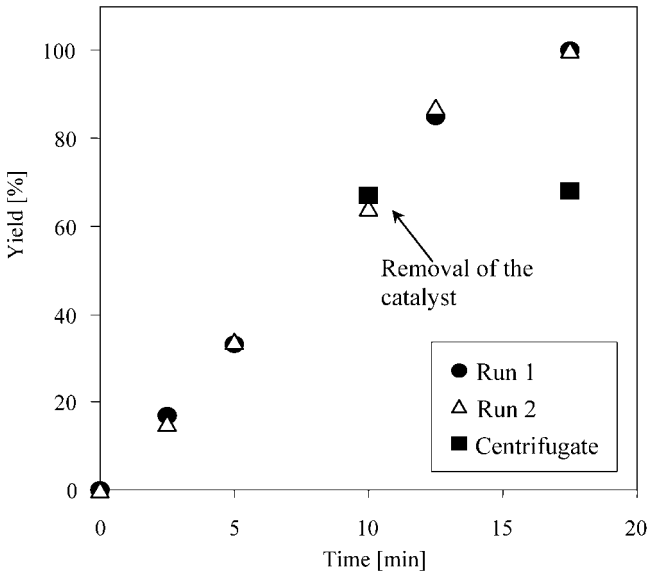


Figure 1. Filtrate test for the bromoethoxylation of DHP in ethanol. Reaction conditions of Table 2.

mary alcohol is preferably formed (entry 11). Ethanol captures the bromonium intermediate more efficiently than trifluoroethanol (entry 6). Here, the low nucleophilicity of trifluoroethanol likely results in a slow reaction with the bromonium intermediate.

Whereas a wide variety of solvent nucleophiles can be incorporated in the product, several attempts to introduce Cl^-, F^-, or N_3^- in the final product by means of addition of their respective ammonium or sodium salts failed.

In order to demonstrate the stability of the catalyst, reactions were subjected to the classic filtrate tests (Figure 1). For instance, in the case of the bromoethoxylation of DHP, a first experiment was performed according to the standard procedure (see entry 1, Table 2) except that only 88 mM H_2O_2 were added instead of 154 mM. Analysis of the reaction mixture shows a 3-bromo-2-ethoxylated ether yield of 68%. Subsequently, the solid catalyst was removed by centrifugation and the centrifugate was contacted 3 times with 22 mM H_2O_2 every 2.5 minutes. Analysis of the reaction solution revealed that no active tungsten was found as the yield of the bromoethoxylated product was unaltered. Moreover, when the removed catalyst was reused in the classic conditions of entry 1 (run 2), similar results were obtained as with a fresh catalyst (run 1) pointing to a real recyclability of the catalyst.

In order to explore the scope of the reactions several substituted and non-substituted cyclic enol ethers (**1**–**7**) were selected including the glycals **6a, 6b** and **7** (Table 4). Halogenation forms one of the major routes toward the stereoselective functionalization of glycals and is reported in literature with *N*-bromoacetamide, *N*-bromosuccinimide, *N*-iodosuccinimide and Br_2.[8] Halohydrins, for instance, are easily dehalogenated or transformed, e.g., into the epoxides, the stereoselectivity of which is highly dependent on the dehydrohalogenation procedure applied.[8f] As an example, the dehydrohalogenation of glucal iodohydrin with NaH in THF at 5 °C selectively leads to the β-epoxide. Note that the stereoisomeric α-epoxide is typically formed *via* direct epoxidation procedures.[9]

As can be seen from Table 4, the W-catalyzed oxidative halogenation method appears to be quite general for the production of 3-iodo- and 3-bromo-2-hydroxylated and alkoxylated cyclic ethers **8**–**41**. The addition to the cyclic enol ethers clearly occurs completely regioselectively in a Markovnikov fashion. This regiocontrol of the halonium attack on the β-carbon has been rationalized by the stabilizing effect of the oxygen atom.

Steric effects play an important role in the stereochemistry of the products. As can be extracted from Table 3, formation of the *cis* isomer appears to be more pronounced in the case of smaller alcohol nucleophiles. For instance, in the reaction with DHP in methanol, the *trans* to *cis* molar ratio of the 2-methoxy-3-bromo products **10** and **11** is 8.5, whereas it is 13 when the nucleophile is isobutyl alcohol (entries 1 and 8, Table 3).

Substituents on the substrate direct the stereoselectivity more strongly than the nature of the alcoholic nucleophile. In the bromomethoxylation of 2-methoxy-3,4-dihydro-2*H*-pyran **2**, for instance, a considerable amount of *cis* product **15** was analyzed, whereas the *cis* isomer is only a minor by-product for the unsubstituted pyran (compare entry 5 with entry 2, Table 4). A similar *cis*:*trans* isomer distribution of 2:3 was found earlier by Duggan and Hall using *t*-butyl hypobromite in methanol.[2c] The crucial factor in the substituent-dependent stereocontrol is the favourable axial orientation of the 6-methoxy group as a result of the anomeric stabilizing effect. So, while the nucleophilic attack of the alcohol is normally *trans* to the halide in the absence of steric hindrance, the formation of the *cis* product becomes more competitive when an axial substituent is located at the 6 position as a consequence of a 1,3-diaxial constraint in the molecule.

The product stereochemistry is not only directed by steric factors but also by the nature of the activated halide. In the iodination, the stereochemistry of addition is almost exclusively *trans*. However, when the electrophile is Br-based, the stereochemistry remains predominantly *trans*, but with considerable *cis* formation (compare entry 2 with 4, entry 8 with 10). This halide-dependent stereochemistry agrees well with earlier work on haloalkoxylation of dihydropyrans and has been rationalized in terms of either a bridged halonium with the charge located at the halide or a carbocation-like intermediate bearing the charge at the carbon atom.[1c,2g,10] In the iodonium case, only the bridged intermediate is formed giving *trans* addition almost exclusively. In the bromination the intermediate bridged cation is not as

Table 4. Oxidative iodination and bromination of glycals, dihydropyrans and dihydrofuran.

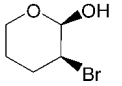
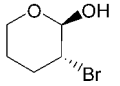
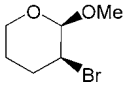
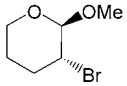
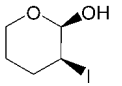
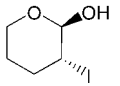
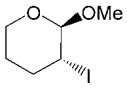
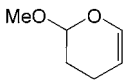
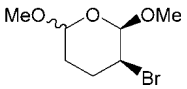
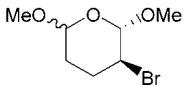
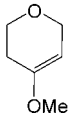
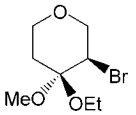
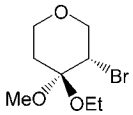
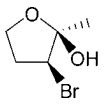
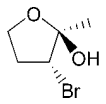
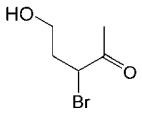
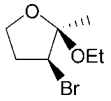
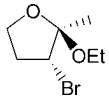
Entry	Olefin	Method[a]	Conversion [%]	Product(s)[b]		Productivity [mmol·g^{-1}·h^{-1}]	Yield [%]	Stereochemistry *cis* : *trans*
1	 **1**	A, CH_3CN	99	 **8**	 **9**	246	97	42 : 58
2	**1**	B	< 99	 **10**	 **11**	175	99	10 : 90
3	**1**	C	97	 **12**	 **13**	518	96	43 : 57
4	**1**	D	97	 **14**		356	94	*trans* only
5	 **2**	B	99	 **15**	 **16**	173	91	40 : 60
6	 **3**	B	100	 **17**	 **18**	171	92	9 : 91
7	 **4**	A[c], THF	100	  **19** **20**	 **21**	262	99	–
8	**4**	B	100	 **22**	 **23**	170	96	12 : 88

Table 4 (cont.)

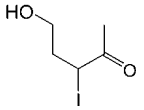
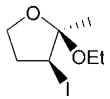
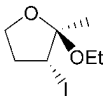
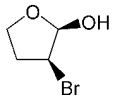
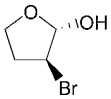
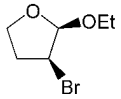
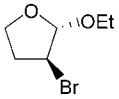
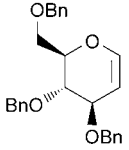
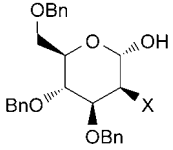
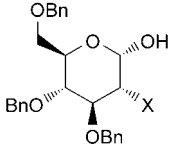
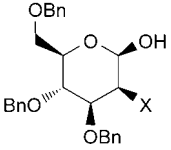
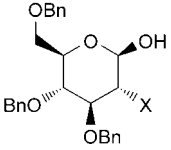
Entry	Olefin	Method[a]	Conversion [%]	Product(s)[b]	Productivity [mmol·g^{-1}·h^{-1}]	Yield [%]	Stereochemistry *cis* : *trans*
9	**4**	C[c]	100	 **24**	513	95	–
10	**4**	D	98		 341	91	6 : 94
11	 **5**	A[c], CH_3THF	99	**25** 	**26**  256	96	14 : 86
12	**5**	B	100	**27** 	**28**  170	96	4 : 96
13	 **6a**	E	[d]	**29**  **31a** X = Br **32a** X = I  **31c** X = Br **32c** X = I	**30**  **31b** X = Br **32b** X = I  **31d** X = Br **32d** X = I	95 (**31**) 96 (**32**)	4 : 2 : 2 : 1 (see note[e]) 6 : 8 : 0 : 1

Table 4 (cont.)

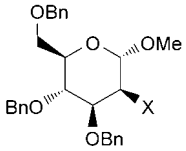
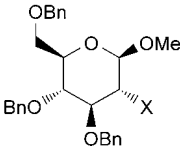
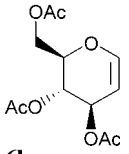
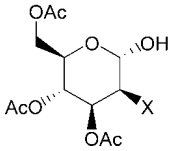
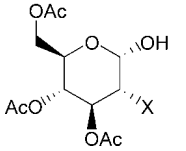
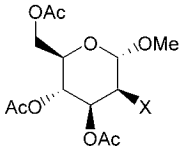
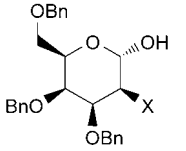
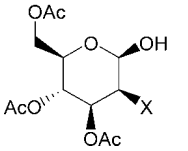
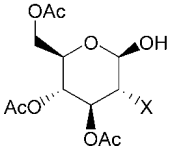
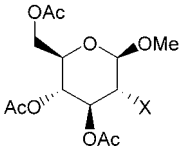
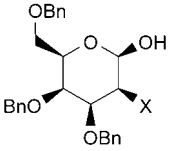
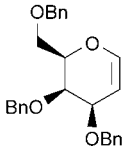
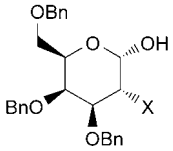
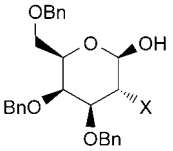
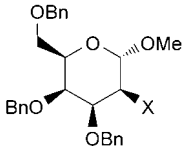
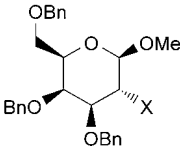
Entry	Olefin	Method[a]	Conversion [%]	Product(s)[b]	Productivity [mmol·g^{-1}·h^{-1}]	Yield [%]	Stereochemistry *cis* : *trans*
14	**6a**	F	[d]	 **33a** X = Br **34a** X = I  **33b** X = Br **34b** X = I		100 (**33**) 85 (**34**)	5 : 4 > 9 : 1
15	 **6b**	E	[d]	 **35a** X = Br **36a** X = I  **35c** X = Br **36c** X = I  **37a** X = Br **38a** X = I  **39a** X = Br **40a** X = I	 **35b** X = Br **36b** X = I  **35d** X = Br **36d** X = I  **37b** X = Br **38b** X = I  **39b** X = Br **40b** X = I	67 (**35**) ~40 (**36**)	5 : 3 : 0 : 1 not determined
16	**6b**	F	[d]			89 (**37**) 66 (**38**)	3 : 1 6 : 1
17	 **7**	E	[d]			97 (**39**) 97 (**40**)	1 : 1 : 0 : 2

Table 4 (cont.)

Entry	Olefin	Method[a]	Conversion [%]	Product(s)[b]	Productivity [mmol·g^{-1}·h^{-1}]	Yield [%]	Stereochemistry *cis* : *trans*
				 **39c** X = Br **40c** X = I	 **39d** X = Br **40d** X = I		5 : 1 : 0 : 1
18	**7**	F	d	 **41a**	 **41b**	81	1 : 1

[a] *Method A:* 2 mL CH_3CN, THF or CH_3THF, 8 mL H_2O, 3.6 mmol substrate, 4 mmol NH_4Br, 1 mol % WO_4^{2-} on takovite (80 mg), 1.2 equivs. H_2O_2 (aqueous 35 wt %) in portions of 0.22 mmol every 30 sec, 35 °C, 1000 rpm stirring.
Method B: 10 mL EtOH or MeOH, 3.6 mmol substrate, 4 mmol NH_4Br, 1 mol % WO_4^{2-} on takovite (80 mg), 1.7 equivs. H_2O_2 (aqueous 35 wt %) in portions of 0.22 mmol every 30 sec, 35 °C, 1000 rpm stirring.
Method C: as method A but with NH_4I and 40 mg WO_4^{2-}-TV (1 mol % W).
Method D: As method B but with NH_4I and 40 mg WO_4^{2-}-TV.
Method E: 3 mL CH_3CN, 0.25 mmol substrate, 1.5 mmol NH_4Br or NH_4I, 1 mol % WO_4^{2-} on takovite (4 mg), 0.37 mmol (20 μL) H_2O_2 (aqueous 35 wt %) every 5 min, R. T. (for benzylated glycals) or 60 °C (for acetylated glycals).
Method F: As method E, but MeOH instead of CH_3CN as solvent.

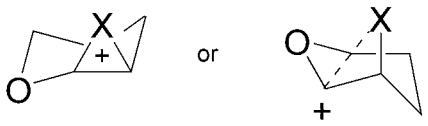
[b] + enantiomeric products.

[c] Additionally with 0.5 mL toluene.

[d] Starting material completely reacted as judged from TLC monitoring of the reaction.

[e] Ratios of all products are reported here, and are estimated from NMR of product mixtures (after acetylation in case of halohydrins), with assignments based on NMR spectra of subsequently isolated pure isomers.[12,14]

stable as with I; some carbocation is formed which affords the *cis* next to the *trans* isomer.



Which of these intermediates are formed, is also strongly related to the nature of the solvent. While the haloalkoxylation in alcohols mainly gives *trans* product, the halohydroxylation in water yields about an equimolar stereoisomeric mixture of *cis* and *trans* products (entries 1 and 3). So, probably due to its better ion solvation power, water exerts a stabilizing effect on the carbocation intermediate leading to an almost equimolar isomer production. By comparison of entry 1 with 3, it is clear that the stabilizing effect of the solvent on the intermediate states exceeds the influence of the halide.

The stereochemical outcome of the haloethoxylation of 2-methyl-4,5-dihydrofuran **4** and 2,3-dihydrofuran **5** in ethanol supports the hypothesis of the existence of two intermediate states. According to the theory, one would expect a larger amount of *cis* isomer in the case of the substituted furan due to the electron-donating effect of the methyl substituent at position 2. The predicted stereochemistry is indeed reflected in the catalytic data showing a *cis*:*trans* ratio of 1:7 for the substituted dihydrofurans **22** and **23**, where it is 1:25 for the unsubstituted dihydrofuran **5** (compare entry 8 with 12).

Whereas the halogenation of 2-methyl-4,5-dihydrofuran predominantly yields cyclic 3-halo-2-alkoxy compounds when performed in alcohol, ring opening appears to be a major pathway in water giving the open-chain α-halo-ω-hydroxy ketones **21** and **24** as the ultimate product (entries 7 and 9). In the case of the iodohydroxylation, the linear α-iodo-methyl ketone **24** was analyzed as the sole product, whereas the cyclic bromohydroxy ethers **19** and **20** appear to be more stable in the bromohydroxylation conditions. A 2:3 molar mixture of bromohydrins (**19** and **20**) and bromomethyl ketone **21** was analyzed by ^{1}H NMR directly after full conversion of the methylfuran.

The methodology was successfully extended to the halofunctionalization of protected glycals, which proceeded in most cases in high yield and with some synthetically useful stereoselectivities (Table 4, entries 13–18). The stereochemical outcomes were consistent with results reported for other methods,[12] and were dependent to some extent on the halide used, the solvent and the presence of ether or ester protecting groups, while the latter factor had a significant effect on the rate of reaction. Reactions of benzylated glucal or galactal proceeded to completion within 1.5 h at ambient temperatures while acetylated glucal required 2.5–5 h at 60 °C, and in some cases did not go to completion.

The higher reactivity of benzylated than acetylated glycals is consistent with the electron-donating and electron-withdrawing characters of the respective protecting groups. The particular role of the C-6 substituent has been discussed previously[8b] in the context of studies on the bromination of benzylated or acetylated glycals, with the postulate that interaction of this with the non-bonding electron pairs on the ring oxygen will affect their stabilizing role on the intermediate carbocation at C-1.

When the reactions were carried out in acetonitrile, bromo- or iodohydrins were formed in excellent yields (entries 13, 15 and 17). In all cases the *manno*-products predominated, i.e., those resulting from top- or β-face addition of the halogen. This selectivity was lowest in the case of benzylated galactal (entry 17), reflecting the influence of the *pseudo*-axial C-4 substituent which presumably alters the conformation of the dihydropyran ring and the orientation of its dipole, thereby influencing the preferred face of attack of the electrophile. With the limited data available it is not possible to draw firm conclusions on the effects of protecting groups on the selectivity in that the reactions of the acetylated glucals were carried out at higher temperatures. However, in formation of bromohydrins (products **31** and **35**) from benzylated and acetylated glucals, respectively, the *manno*:*gluco* ratio changes from 6:3 to 8:1, and the *trans:cis* ratio from 5:4 to 6:3. The selectivity towards the *manno*-configuration is most marked in the reactions using NH_4I (entry 13, products **32**) with a *manno*:*gluco* ratio of 14:1, and a surprisingly high ratio (8:6) of *cis*:*trans*. This suggests that following the favoured β-face addition of the iodonium ion, the oxocarbenium ion is strongly stabilized with assistance from the electron-donating benzyl protecting group on C-6.

When reactions were carried out in the polar, nucleophilic solvent methanol, the methyl-2-deoxy-2-halo glycosides were obtained in good to excellent yields (entries 14, 16 and 18), even in the case of the less reactive acetylated glucal (entry 16). The reactions of benzylated or acetylated glucal using NH_4I (entry 14, products **34** and entry 16, products **38**) were highly stereoselective, yielding predominantly the α-mannosides.

In all of the reactions involving glycals it was established that reaction did not take place or took place very slowly in the absence of the WO_4^{2-} exchanged takovite.

Conclusions

To conclude, we have demonstrated that halohydrins and halo ethers can be generated from cyclic enol ethers *via* the oxidative halogenation with commercial hydrogen peroxide in the presence of a WO_4^{2-} exchanged synthetic takovite under mild conditions. To the best of our knowledge, this is the first report on oxidative halogenation of this type of molecules including the anhydro

sugars using a stable and easily recyclable solid catalyst. Current efforts are focussed on the continued examination of these stereoselective reactions as well as on their application in the synthesis of glycoconjugates and oligosaccharides.

Experimental Section

Preparation of the Tungstate-Exchanged Takovite (WO_4^{2-}-TV)

The synthetic takovite mineral with the formula $Ni_{0.63}Al_{0.37}(OH)_2(NO_3^-)_{0.37}\cdot 0.69\ H_2O$ was prepared by the controlled hydrolysis of the Ni and Al nitrate salts in carbonate-free conditions according to published procedures.[11] The salt solutions were purged with N_2 to avoid uptake of carbonate by the precipitates. Under vigorous stirring, 120 mL of both solutions were combined slowly in an N_2 atmosphere at room temperature at a rate of 60 mL·min^{-1}, while the pH was kept constant at 8.5 by addition of NaOH (1 M). After additional stirring for 12 hours at the same temperature, the suspension was centrifuged and washed with deionized water in 3 cycles, shock-frozen in liquid nitrogen and freeze-dried. For the anion exchange of tungstate, air-dry takovite (1.5 g) was suspended in an aqueous solution of $Na_2WO_4\cdot 2\ H_2O$ (150 mL, 5 mM) at room temperature for 12 h under N_2. The final WO_4^{2-}-TV catalyst was washed and dried as before.

Typical Procedure for the Oxidative Methoxybromination of Cyclic Vinyl Ethers using WO_4^{2-}-TV

To a mixture of WO_4^{2-}-TV (80 mg, 0.04 mmol W) and 3,4-dihydro-2*H*-pyran (**1**; 0.3 g) in methanol containing ammonium bromide (10 mL, 0.4 M) at room temperature, was added in portions of 0.22 mmol hydrogen peroxide (or 20 μL of 35% aqueous solution) every 2.5 minutes until complete conversion of **1**. The catalyst was then removed by filtration or centrifugation and the filtrate partitioned between ice-water and diethyl ether. The organic layer was separated, washed with water and dried over $MgSO_4$. After sampling the dried solution for GC and GC-MS analysis, the solvent was removed under vacuum affording 0.65 g of a pale yellow oil, which was found to be a more or less pure mixture of *cis* and *trans* isomers by ^{1}H and ^{13}C NMR spectroscopy. No further purification of the isomers was attempted.

trans-Isomer (**11**): MS: *m/e* (relative intensities) = 194–196 (5); 163–165 (20); 134–136 (100); 106–108 (45); 87 (28); 55 (67); ^{1}H NMR (300 MHz): δ = 4.51 (1H, d, 2-H, $J_{H2,H3}$ = 4.4 Hz), 3.61/3.97 (2H, m, 6-H), 3.91 (1H, m, 3-H), 3.45 (3H, s, 8-H), 1.49–2.46 (4H, m, 4-H and 5-H); ^{13}C NMR (300 MHz): δ = 102.7(C-2), 63.0(C-6), 56.1(C-8), 49.6(C-3), 30.6(C-4), 23.9(C-5).

cis-Isomer (**10**): MS: *m/e* (relative intensities) = 194–196 (11); 163–165 (24); 134–136 (100); 106–108 (64); 87 (29); 55 (82); ^{1}H NMR (300 MHz): δ_H = 4.61 (1H, d, 2-H, $J_{H2,H3}$ = 2.6 Hz), 3.82/4.11 (2H, m, 6-H), 4.08 (1H, m, 3-H), 3.49 (3H, s, 8-H), 1.63–2.43 (4H, m, 4-H and 5-H); ^{13}C NMR (300 MHz): δ_C = 99.3(C-2), 59.5(C-6), 55.8(C-8), 49.4(C-3), 29.5(C-4), 27.0(C-5).

Typical Procedure for the Oxidative Methoxyhalogenation of Glycals using WO_4^{2-}-TV

Method (a): Benzylated glucal or galactal: To a mixture of WO_4^{2-}-TV (4 mg, 0.002 mmol W) and benzylated glycal **6a** or **7** (100 mg, 0.24 mmol) in acetonitrile or methanol (3–5 mL) containing ammonium bromide or ammonium iodide (1.5–6 equivs.) at room temperature, was added hydrogen peroxide in portions of 0.22 mmol (or 20 μL of 35% aqueous solution) every 5 minutes until complete conversion as judged by TLC. The catalyst was then removed by filtration or centrifugation and the filtrate partitioned between ice-water and diethyl ether. The organic layer was separated, washed with water and dried over $MgSO_4$. After recording ^{1}H and ^{13}C NMR spectra of the mixture of isomers these were separated on a column of silica, eluting with mixtures of ethyl acetate and hexane.

Method (b): Acetylated glucal: To a mixture of WO_4^{2-}-TV (4 mg, 0,002 mmol W) and benzylated glycal **6b** (100 mg, 0.368 mmol) in acetonitrile or methanol (3–5 mL) containing ammonium bromide or ammonium iodide (1.5–6 equivs.) at 60 °C, was added hydrogen peroxide in portions of 0.22 mmol (or 20 μL of 35% aqueous solution) every 5 minutes until complete conversion as judged by TLC. The catalyst was then removed by filtration or centrifugation and the filtrate partitioned between ice-water and diethyl ether. The organic layer was separated, washed with water and dried over $MgSO_4$. After recording ^{1}H and ^{13}C NMR spectra of the mixture of isomers these were separated on a column of silica, eluting with mixtures of ethyl acetate and hexane.

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