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Halofunctionalization of alkenes by vanadium chloroperoxidase from *Curvularia inaequalis*†

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The vanadium-dependent chloroperoxidase from *Curvularia inaequalis* is a stable and efficient biocatalyst for the hydroxyhalogenation of a broad range of alkenes into halohydrins. Up to 1 200 000 TON with 69 s^{-1} TOF were observed for the biocatalyst. A bienzymatic cascade to yield epoxides as reaction products is presented.

Vic-Halohydrins are valuable building blocks *e.g.* in natural product synthesis.[1] Two functional groups endow the organic chemist with handles for further transformations such as conversion into epoxides and other fuctionalities.[2] To attain *vic*-halohydrins, halohydroxylation of olefins appears to be the most direct approach next to ring-opening of epoxides by nucleophilic attack.[3]

Treatment of olefins with elementary halogens in water provides halohydrins. This approach, however, is hampered by the high reactivity of the reagents leading to side products and the corrosive reaction conditions.[4] Also the formation of significant inorganic wastes renders this approach questionable from an environmental point of view. Therefore, *N*-halo compounds such as *N*-halosuccinimide represent the most commonly used reagents, or sodium periodate, despite the fact of low atom efficiency causing large amounts of waste products.[5] More recently, transition metal catalysts (including W and V) have received increasing interest for the conversion of alkenes to halohydrins using H_2O_2 and inorganic halide as reagents.[6] In addition, oxone has been successfully applied as oxidant using NH_4Cl as halogen source.[7]

Finally, biocatalysis also in principle enables the conversion of alkenes to halohydrins using so-called haloperoxidases (E.C. 1.11.1.8, 1.11.1.10 and 1.11.1.18). These enzymes generate reactive hypohalites from the corresponding halides and hydrogen peroxide. This has been reported for example using the heme-dependent chloroperoxidase from *Caldariomyces fumago* (*Cfu*CPO).[8] However, the poor stability of heme-dependent haloperoxidases against H_2O_2 limits the broad applicability of this enzyme class and make control over the *in situ* concentration of H_2O_2 inevitable.[9] In fact, the catalytic performance (in terms of turnover numbers, TON) reported for *Cfu*CPO is too low to be of preparative value (generally a few thousand turnovers can be estimated from the publications).[8c,10] Vanadium-dependent haloperoxidases are principally more robust against H_2O_2 and therefore maybe more practical catalysts.[11]

The vanadium chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) for example excels by its superb stability against H_2O_2 as well as demanding environmental conditions such as cosolvents and temperature.[12] It was successfully applied for the catalytic halogenation of phenols[13] as well as to mediate the (Aza-) Achmatowicz reaction.[14]

Therefore, we became interested in evaluating *Ci*VCPO as catalyst for the halogenation of alkenes striving for more robust reactions than reported for the heme-dependent halogenases (Scheme 1).

In a first set of experiments we investigated the halohydroxylation of styrene. As starting point we chose the optimised reaction conditions determined previously.[13,14] Full conversion was achieved after 4 hours with high selectivity towards *vic*-bromohydrin (>90%) with only trace amount of side products (epoxide, ketone derivatives) detectable (Table 1, entry 2). The regio chemistry of the hydroxybromination reaction exclusively followed Markovnikov's rule. In accordance with the suspected chemo-enzymatic reaction mechanism, no enantioselectivity was observed. When the enzyme was omitted from the reaction, no product formation was observed (Table 1, entry 3), which confirms the proposed chemoenzymatic cascade. Likewise, no conversion was observed in the absence of H_2O_2 or KBr (data not shown).

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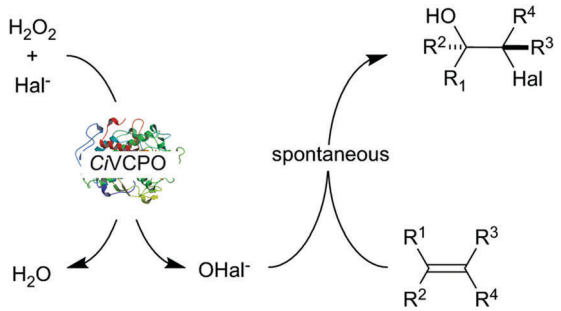
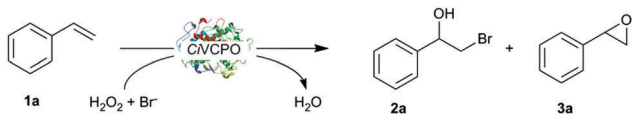


Scheme 1 Chemoenzymatic oxidation of alkenes using the vanadium chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) as hypohalite generation catalyst. Here, the most popular chemo-enzymatic mechanism is shown wherein the enzyme forms the hypohalite *in situ* followed by spontaneous reaction of the latter with an alkene. It should, however be mentioned that also some indications for a direct enzymatic halohydroxylation within the enzyme active site exist.[11]

Table 1 Characterisation of the reaction conditions for the chemoenzymatic bromohydroxylation of styrene



Entry	pH[a]	Solvent	KBr[b]	H_2O_2[b]	Conversion[c] (%)	Yield **2a**[d] (%)	Yield **3a**[d] (%)
1	3	H_2O	160	170	10	8	n.d.
2	5	H_2O	160	170	Full	90	2
3[e]	5	H_2O	160	170	0	0	0
4[f]	Water	H_2O	160	170	Full	41	55
5[f]	7	H_2O	160	170	Full	40	52
6	9	H_2O	160	170	13	4	8
7	5	H_2O	20	170	45	40	0
8	5	H_2O/EtOH (2 : 1)	160	170	50	25	7
9[g]	5	H_2O	160	110	Full	90	2

[a] Buffers used: acetate (pH 3), citrate (pH 5) and Britton–Robinson (pH 7 and 9). [b] Concentration units (mM). [c] Determined by ^{1}H NMR. [d] NMR yield determined from the crude reaction mixture. [e] Control reaction in the absence of *Ci*VCPO. [f] 20 hours reaction time. [g] Portion-wise addition of H_2O_2.

When using ethanol a cosolvent, also very significant amounts (13%) of (2-bromo-1-ethoxyethyl)benzene were obtained (Table 1, entry 8). We attribute this to the competition of water and ethanol as nucleophiles.

Adding the oxidant (H_2O_2) portion-wise proved to be more efficient than a single addition at the beginning of the reaction (Table 1, entries 2 *vs.* 9). This can be attributed to a the well-known formation of singlet oxygen ($^1O_2$) from hypohalites and H_2O_2, which in our case represents an undesired side reaction consuming H_2O_2.[15]

Varying the pH value of the reaction medium had the most significant effect on the reaction (Fig. S1, ESI†). Consistent with previous observations, highest *Ci*VCPO activity was observed at slightly acidic to neutral conditions. Even in the absence of buffer, essentially the same results were observed as using BR (Britton–Robinson) buffer (Table 1, entries 4 and 5). Raising or lowering the pH value lead to dramatic activity decreases. Under acidic reaction conditions the bromohydrin was the predominant/sole product of the reaction. The relative epoxide yield increased with increasing pH. This is consistent with the well-known base-catalysed ring-closure of halohydrins.

To obtain further insights into the kinetics of the hydroxybromination reaction, we followed the time course of the chemoenzymatic conversion of (water soluble) sodium styrene-4-sulfonate **1g** (Fig. 1). Following a very short lag-phase, the product accumulation proceeded linearly until approx. 75% conversion and then considerably slowed down. After 5–6 h, full conversion was obtained. It is worth emphasising the excellent catalytic performance of the biocatalyst here: Over 6.5 h *Ci*VCPO performed 400 000 catalytic turnovers corresponding to an average turnover frequency of more than 15 s^{-1} (over 6.5 h). Within the first 2 h, this value was even higher (69 s^{-1}). Raising the concentration of **1g** from 40 mM to 160 mM (while concomitantly increasing the concentration of KBr as well as the buffer strength to avoid pH shifts, *vide infra*) resulted in 80% of the desired product **2g**. Hence *Ci*VCPO performed at least 1 280 000 catalytic cycles. These values underline the robustness and efficiency of the biocatalyst.

Applying the optimised reaction conditions (Table 1, entry 9) we advanced to evaluate the product scope of the chemo enzymatic hydroxyhalogenation reaction. As shown in Fig. 2 both aromatic and aliphatic alkenes were converted into the corresponding halohydrins. Styrene was transformed into the corresponding bromohydrin **2a** and chlorohydrin **2b** with 81% and 77% yield, respectively. α- and β-methylstyrene were converted in satisfactory yields. The (*E*)/(*Z*) configuration of the latter influenced the product conformation leading to the *anti*-bromohydrin

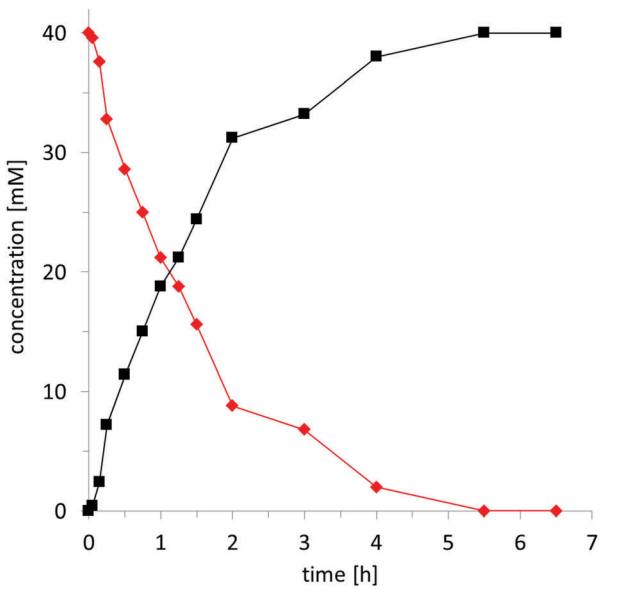


Fig. 1 Time course of the chemoenzymatic oxidation of alkene **1g** (◆) to **2g** (■). General conditions: aqueous medium (D_2O, 0.1 M citrate pH 5), *c*(**1g**) = 40 mM, *c*(KBr) = 160 mM, *c*(H_2O_2) = 170 mM, *c*(*Ci*VCPO) = 100 nM, *T* = 25 °C. The concentration of substrate and product was determined by ^{1}H NMR (see ESI†).

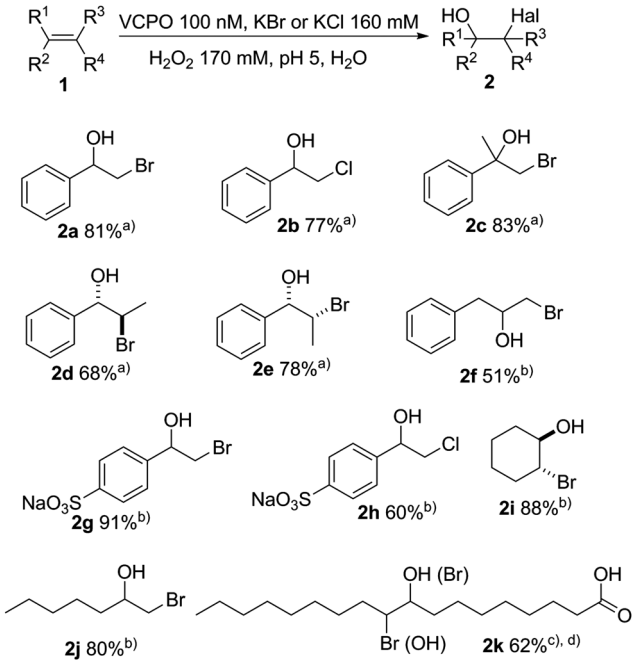


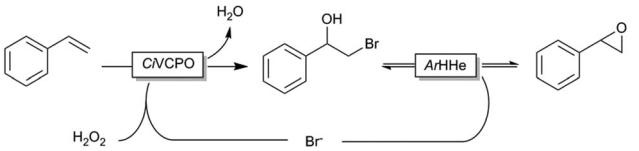
Fig. 2 Preliminary substrate scope of the chemoenzymatic hydroxyl halogenation scheme. Reaction condition: c(*Ci*VCPO) = 100 nM, c(alkene) = 40 mM, c(KX) = 160 mM, $c(H_2O_2)$ = 170 mM, citrate buffer (0.1 M, pH 5), T = 25 °C, t = 20 h. (a) Isolated yield; (b) ^{1}H NMR yield. (c) Ethanol as co-solvent; (d) yield of two regioisomers (see ESI†).

2d in case of the (*E*)-starting material and *syn*-bromohydrin **2e** from the (*Z*)-substrate. Allylbenzene **1f** shows lower reactivity, yielding 51% bromohydrin **2f** at 63% conversion. Exchanging bromide by chloride generally lead to a slight reduction in yields with the exception of 4-styrenesulfonic acid **1h** where next to the desired chlorohydrin **2h** also approx. 10% of 4-formylbenzenesulfonate were observed (Fig. 2).

Likewise, aliphatic alkenes were also converted smoothly: 2-bromocyclohexan-1-ol **2i** and 1-bromoheptan-2-ol **2j** were obtained in good yields (88% and 80%, respectively). Due to its hydrophobicity, oleic acid required some cosolvent to enhance its solubility enabling an 62% yield of the bromohydrin **2k**. The lower yield is due to the 10(9)-bromo-9(10)-ethoxyoctadecanoic acid formation as side product as ethanol competed as nucleophile (Fig. 2).

Preparative scale (1.1 gram) reactions of some selected alkenes were performed. For example styrene **1a** was converted almost quantitatively albeit at lower selectivity than shown in Fig. 2. After 24h the desired bromohydrin was isolated in only 50% yield whereas styrene oxide accumulated to overall 30%. We attribute this to the prolonged reaction time and an alkaline shift of the reaction pH value favouring the ring-closure reaction. Future experiments with pH control are likely to circumvent this current limitation.

Nevertheless, we became interested in the further transformation of the halohydrins into epoxides. The pH optimum of *Ci*VCPO within the acidic range does not allow for efficient concurrent hydroxyhalogenation and ring closure. This may be circumvented by a two-step procedure wherein the halohydrin



Scheme 2 Envisioned cascade for the direct transformation of alkenes (*e.g.* styrene) into epoxides by combining the *Ci*VCPO-initiated halohydrin formation to ring-closure catalysed by a halohydrin dehalogenase (*e.g.* from *Agrobacterium radiobacter*, *Ar*HHe).

formation reaction is performed first at acidic pH followed by a base treatment to pH 10 with NaOH. This method proved to be successful for most products with the exception of the halohydrin obtained from oleic acid (**2k**). Here, intensive foaming (of the carboxylate) interfered with product isolation, which could be avoided by substituting NaOH with trimethylamine. Also, it is worth mentioning here that the previously mentioned 10(9)-bromo-9(10)-ethoxyoctadecanoic acid was also retained here (approx. 30% yield).

Even though this two-step procedure was efficient for the production of epoxides, we envision a more elegant (and less wasteful) approach. For this, we evaluated a bienzymatic cascade reaction comprising *Ci*VCPO-initiated halohydrin formation followed by halohydrin dehalogenase (HHe)-catalysed ring-closure (Scheme 2). Such a cascade would, in principle, also allow for catalytic use of the halides. For this, we recombinantly expressed the HHe from *Agrobacterium radiobacter*. Particularly, its poor enantioselectivity appeared attractive in this case as a more enantioselective version would lead to kinetic resolution of the racemic bromohydrin and consequently in decreased yields of the desired epoxide.[16]

A reaction employing 20 mM styrene **1a** in the presence of 5 mM KBr indeed gave 6.6 mM of the desired epoxide and 1.8 mM of the bromohydrin indicating the principal feasibility of the reaction shown in Scheme 2, despite the reduced activity of biocatalysts at pH 7 (Fig. S2, ESI†).

The present study underlines the synthetic potential of the vanadium-dependent chloroperoxidase from *Curvularia inaequalis*. Its high robustness and activity enabled efficient halohydroxylation of various alkenes to the corresponding halohydrins on preparative scale. Despite the promising first results, a range of issues will have to be overcome to render this method truly practical. First, efficient *in situ* H_2O_2 generation systems[17] will be applied to this reaction in order to circumvent the undesired $^1O_2$ formation reaction. Also the envisioned bienzymatic cascade forming epoxides from alkenes (while using catalytic amounts of halides) will need further improvements such as the application of *Ci*VCPO mutants with engineered pH optima,[18] reaction engineering approaches utilizing spatially separated reaction compartments and immobilized enzymes.[19]

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