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Enzymatic Bromocyclization of α- and γ-Allenols by Chloroperoxidase from *Curvularia inaequalis*

Janne M. Naapuri,[a] Philip K. Wagner,[a, b] Frank Hollmann,[c] and Jan Deska*[a]

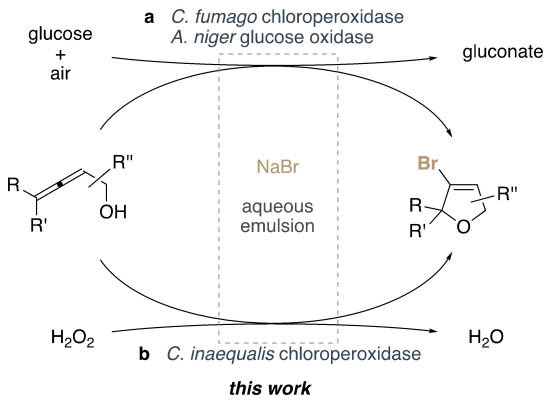
Vanadate-dependent chloroperoxidase from *Curvularia inaequalis* catalyzes 5-*endo*-*trig* bromocyclizations of α-allenols to produce valuable halofunctionalized furans as versatile synthetic building blocks. In contrast to other haloperoxidases, also the more challenging 5-*exo*-*trig* halocyclizations of γ-allenols succeed with this system even though the scope still remains more narrow. Benefitting from the vanadate chloroperoxidase's high resiliency towards oxidative conditions, cyclization-inducing reactive hypohalite species are generated in situ from bromide salts and hydrogen peroxide. Crucial requirements for high conversions are aqueous biphasic emulsions as reaction media, stabilized by either cationic or non-ionic surfactants.

Introduction

Accessing organic halides is an essential part of organic synthesis as they are a critical intermediary structure for many carbon–carbon and carbon–heteroatom coupling processes, as well as a defining feature on a range of natural and pharmaceutical compounds.[1] Halogenations have been traditionally carried out using rather corrosive and harmful molecular halogens.[1c] More recently, the use of X_2 has largely been bypassed by organic halogenating agents such as *N*-halosuccinimides, though their synthesis often still involves the elemental dihalogens. As an alternative strategy, a moderated in situ generation of hypohalites from halide salts and hydrogen peroxide has emerged as a mild and sustainable approach, emulating the mode of action of Nature's haloperoxidases.[2] While biomimetic catalyst systems including transition metals[2b,c] and chalcogens[2d,e] have been developed, biocatalysis using haloperoxidases offers unsurmountable efficiency,[3] alongside other benefits attributed to enzyme catalysis including environmental friendliness and mild operating conditions.[4]

Allenes represent a versatile and appealing class of building blocks, able to participate in a unique reaction scope due to their cumulene structure.[5] Specifically, allenes with a nucleophilic functionalization incorporated in their structure have attracted attention due to their potential for cycloisomerization reactions yielding heterocyclic compounds.[6] Among these methods, halogenative cyclizations of allenes have been found a robust form of synthesis of *O*-heterocycles carrying useful halide handles for further valorization.[7]

We recently reported on a hydroxyallene halocyclization mediated by a heme-dependent chloroperoxidase from *Caldariomyces fumago* (*Cf*CPO).[8] Though an efficient and mild catalyst for the process, the heme-haloperoxidase suffers from a vulnerability to elevated hydrogen peroxide concentrations, leading to oxidation and degradation of the porphyrin-moiety active site.[9] Several strategies for controlled in situ generation of hydrogen peroxide have been developed to circumvent this,[10] and in our research, the H_2O_2 was introduced as a by-product of *Aspergillus niger* glucose oxidase (GOx)-mediated oxidation of glucose (Scheme 1a). Contrastingly, vanadate-dependent haloperoxidases have been found very resilient towards outside factors, and exhibit far higher tolerance towards oxidants than the hemoenzymes.[11] In recent years, especially fungal vanadate-chloroperoxidase from *Curvularia*



Scheme 1. Possible routes in enzymatic halocyclization of allenic alcohols.

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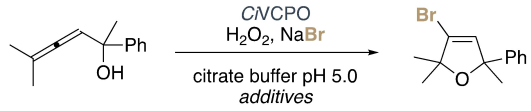
inaequalis (*Ci*VCPO) has gained attention and has been involved in several biocatalytic halogenation and oxidation processes.[12] We became interested in implementing the vanadate-haloperoxidase into the halocyclizations of allenic alcohols, as the higher resiliency could aid with potential compatibility issues in some processes, while also simplifying the reaction scheme and increasing atom-efficiency as no sacrificial agent is needed for the peroxide generation. Here, electrophilic hypohalite-species are generated from simple halide salts and hydrogen peroxide by the vanadium-dependent enzyme, triggering halogenation and subsequent cyclization of suitable nucleophilic functionalization carrying allenes, while just water is released as a by-product in the process (Scheme 1b).

Results and Discussion

As in our earlier research on halocyclizations mediated by heme-haloperoxidases the choice of reaction media was found to be crucial for product selectivity,[8] we began our current study by evaluating the effects of various solvent systems on the *Ci*VCPO catalyzed 5-*endo-trig* bromocyclization of model substrate α-allenol **1a**.[13] Though the desired reactivity was observed in initial attempts using purely aquatic medium with sodium bromide and hydrogen peroxide as stoichiometric reagents at room temperature, the conversion rate was disappointingly low (Table 1, entry 1). The dihydrofuran **2a** production was somewhat improved through enhanced solubility using varying co-solvents (Table 1, entries 2–5). In heme-peroxidase biocatalysis, colloidal biphasic media stabilized by detergents was found beneficial for the desired halocyclization reactivity by facilitating transfer between the phases. As the vanadate-enzyme has been shown to tolerate and benefit from emulsified conditions before,[14] we also examined the *Ci*VCPO-catalyzed biotransformation in the presence of surfactant additives. Gratifyingly, introducing non- ionic detergents Brij L23 or Tween 85 into a 1:1 mixture of hexane and aquatic buffer provided a jump in **2a** production to over 70% yields (Table 1, entries 6 and 7). The efficiency was further improved by stabilizing the emulsion with the cationic surfactant CTAB, resulting in an excellent yield of 86% (Table 1, entry 8).

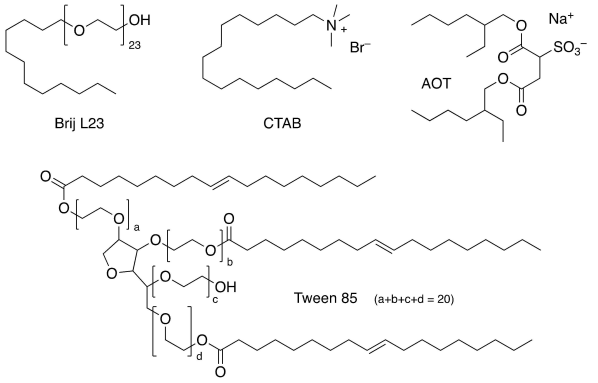
Table 1. Solvent and additive screening for the bromocyclization with *Ci*VCPO.



1a **2a**

Entry[a]	Additives	Conversion [%]	Yield [%]
1	none	29	9
2	*t*BuOH (5% v/v)	50	17
3	MeCN (5% v/v)	54	14
4	acetone (5% v/v)	32	18
5	hexane (5% v/v)	62	16
6	hexane (50% v/v), Brij L23	93	72
7	hexane (50% v/v), Tween 85	>99	74
8	hexane (50% v/v), CTAB	>99	86
9	hexane (50% v/v), AOT	95	49

[a] Conditions: allenol **1a** (0.1 mmol), NaBr (0.3 mmol), H_2O_2 (0.3 mmol), pH 5.0 citrate buffer/solvent additive (4 ml), surfactant additive (0.1 mmol), *Ci*VCPO (0.06 nM), 24 h reaction time.



Examining the kinetic profile of the biotransformation shows full conversion within 18 h, with the enzyme performing 1,400,000 catalytic cycles during the complete process with a turnover frequency of 38 s^{-1} over the first 6 h (Figure 1).

An anionic emulsifier in AOT could also be used for the bromination (Table 1, entry 9), but the product selectivity fell below that achieved with the cationic ammonium bromide. Though the arbitrary initial protocol with CTAB additive gave excellent results, further investigations were done to probe the

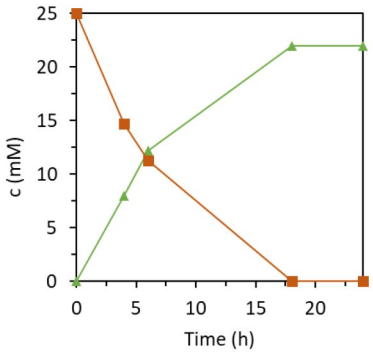


Figure 1. Representative time course of the bromocyclization of **1a** catalyzed by *Ci*VCPO. (▲) = c(bromodihydrofuran **2a**), (■) = c(allenol **1a**). Conditions: allenol **1a** (25 mM), *Ci*VCPO (0.015 nM), NaBr (75 mM), H_2O_2 (75 mM), CTAB (250 mM), 1:1 mixture of *n*-hexane and citrate buffer (pH 5.0). Yields determined by NMR spectroscopy using dimethyl sulfone as internal standard.

reaction conditions, starting with the effect of pH. Predictably, pH 5.0 was found optimal for the biohalogenation (Figure 2), as it is known to be the pH where the enzyme *Ci*VCPO performs most efficiently.[11,12] The production of bromofuran **2a** however falls off fairly quickly when deviating from this pH. As the cationic surfactant CTAB also provides bromide counterions for the reaction, we looked into effects of different initial bromide concentrations. Whether the required bromide ions come to the reaction as a sodium salt or with the ammonium detergent does not have a significant effect on the overall yield (Figure 3). The bromide concentration, however, has a slight impact on the halocyclization of **1a**, with around four equivalents leading to highest yields. Optimal conditions for this substrate were determined to be four equivalents of CTAB as the only bromide source, but the balance could be tipped towards the sodium salt for higher atom-efficiency without a significant reduction on the yields. Interestingly, reducing the hydrogen peroxide amount from three equivalents had a dramatic effect on the dihydrofuran **2a** production (Figure 3). One reason for the high requirement for H_2O_2 in the process could be its consumption in a competing formation of singlet oxygen from reaction with generated hypobromite, a known side process in haloperoxidase-mediated biocatalysis.[11b,14] A noticeable drop in yield is also seen when peroxide is added in amounts higher than three equivalents. This could be due to slight deactivation of the enzyme in elevated hydrogen peroxide concentrations, resulting in slower conversion rates.

The optimized *Ci*VCPO-catalyzed enzymatic bromocyclization protocol was then extended to a broader range of structurally related allene substrates to gauge the limitations of the method (Scheme 2). The model compound **2a** was isolated in an excellent 88% yield, indicating a good agreement between the NMR spectroscopic analysis used to monitor the reaction condition screening and the isolated yields. The similarly *gem*-dimethylated allenols **1b** and **1c** were also cyclized into dihydrofurans **2b** and **2c** in good yields, although the product selectivity fell from that achieved for the more densely substituted **1a**, possibly due to side reactions arising from having a potentially labile allylic C–H bond. The biocatalytic bromination could be used to furnish interesting spirocyclic bromocompounds as well, as the bis-*spiro*-dihydrofuran **2d** was obtained in high efficiency. The substitution pattern on the allene structure is known to have a significant effect on the reactivity towards halocyclizations.[7a] However, moving from geminally alkylated to terminally monoarylated allene **1e** also furnished desired **2e** in similarly great yields. The experiment also demonstrates the stereochemical integrity during the biohalogenation, as the 98% diastereopurity of the

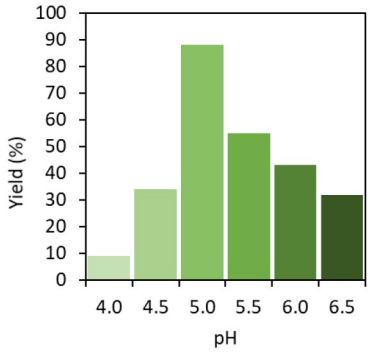


Figure 2. Effect of pH on the bromocyclization of **1a** catalyzed by *Ci*VCPO. Conditions: allenol **1a** (25 mM), *Ci*VCPO (0.015 nM), NaBr (75 mM), H_2O_2 (75 mM), CTAB (250 mM), 1:1 mixture of *n*-hexane and citrate buffer. Yields determined by NMR spectroscopy using dimethyl sulfone as internal standard.

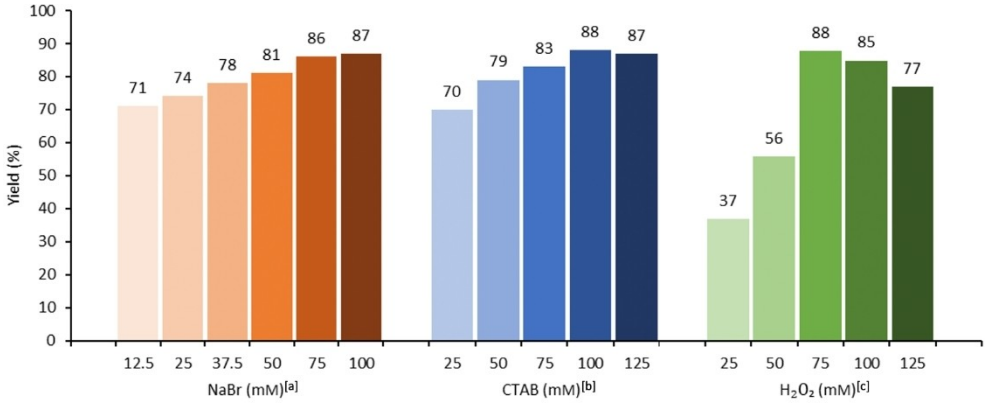
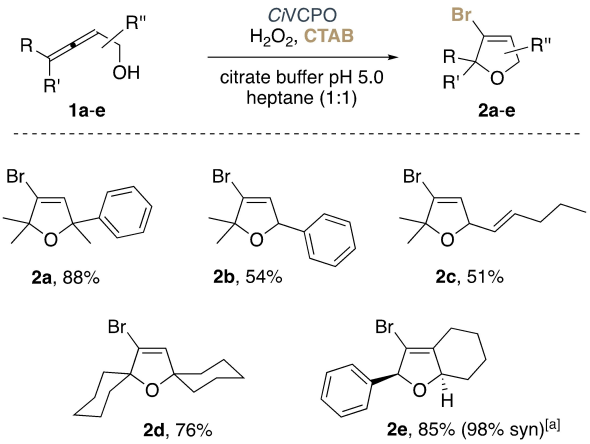


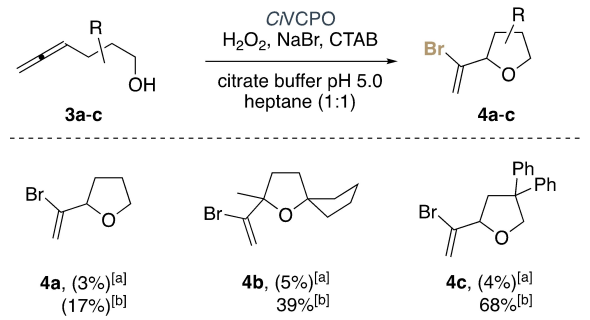
Figure 3. Optimization of *Ci*VCPO driven bromocyclization of allenic alcohol **1a** in micellar reaction medium consisting of 1:1 mixture of pH 5.0 citrate buffer and *n*-hexane. Yields determined by NMR spectroscopy using dimethyl sulfone as internal standard. Conditions: c(allenol **1a**) = 25 mM, c(*Ci*VCPO) = 0.015 nM, 18 h reaction time, [a] c(CTAB) = 25 mM, c(H_2O_2) = 75 mM, c(NaBr) = brown columns, [b] c(CTAB) = blue columns, c(H_2O_2) = 75 mM, c(NaBr) = 0 mM, [c] c(CTAB) = 100 mM, c(H_2O_2) = green columns, c(NaBr) = 0 mM.



Scheme 2. Substrate scope for *Ci*VCPO catalyzed endo-bromocyclization of α-allenic alcohols. [a] The allenic substrate **1e** is 98% *syn*.

axially chiral *syn*-**1e** was quantitively transferred to the centrochiral *O*-heterocycle *syn*-**2e**.

As the cycloisomerisation of α-hydroxyallenes was proceeding robustly in the biocatalytic process, we became interested in attempting far less researched 5-*exo*-*trig* bromocyclizations of γ-allenic alcohols **3a–c**. While the Baldwin rules, a set of guidelines to predict the favorability of cyclization reactions based on the accessibility of relevant frontier orbitals, classifies 5-*exo*-*trig* ring closures as generally more likely than corresponding *endo* cyclizations, the particular orbital geometries of allenes (and other cumulenes) provide a different reactivity profile and do not render *exo* versus *endo* mutually exclusive. As such, the known methods for 5-*exo*-*trig* ring closure events transforming γ-allenols to bromotetrahydrofurans **4** include Pd[15] and Au[16] catalysis, while analogous iodocyclizations have been performed using iodine or *N*-iodosuccinimide.[17] Disappointingly, adopting the same optimized *Ci*VCPO protocol for bromocyclization of allenes **3a–c** only furnished trace amounts of the desired tetrahydrofurans **4a–c** (Scheme 3), while mostly unreacted substrates could be recovered. It would seem that, due to the longer alkyl chain between the nucleophilic functionalization and the π-system, the reaction rate is low



Scheme 3. Substrate scope for *Ci*VCPO catalyzed *exo*-bromocyclization of γ-allenols. Conditions: c(allenol) = 25 mM, c(CTAB) = 100 nM, [a] c(*Ci*VCPO) = 0.025 nM, $c(H_2O_2)$ = 75 mM, c(NaBr) = 0 mM, [b] c(*Ci*VCPO) = 0.0625 nM, $c(H_2O_2)$ = 500 mM, c(NaBr) = 500 mM. Parentheses indicate yields determined by NMR spectroscopy using dimethyl sulfone as internal standard.

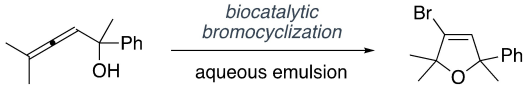
enough to be suppressed by competing side-processes, such as the *Ci*VCPO mediated singlet oxygen production. The problem could gratifyingly be overcome by increasing the initial hydrogen peroxide and bromide concentrations to excessive levels, resulting in full conversions of the allenes **3a–c** (Scheme 3). While **4a**, produced from reaction of unsubstituted allenol **3a**, could not be isolated, NMR spectroscopic analysis indicated low product selectivity of about 17%. Incorporating substituents that would favor intramolecular cyclizations through increased bulkiness on the alkyl chain, however, gave encouraging results, as **4b** was obtained in mediocre 39% yield and **4c** in good 68% yield. While these transformations inconveniently require high amounts of the reactants, the results underline the benefits of implementing the vanadate-dependent chloroperoxidase in this type of processes over the heme-haloperoxidases, as the vanadium-dependent-enzyme, through its high tolerance towards oxidative conditions of peroxide, singlet oxygen and hypohalites, is able to catalyze the reaction even in the high initial concentration of 500 mM H_2O_2 in the 1:1 heptane/buffer emulsion stabilized by cationic CTAB.

The greater operational stability of *Ci*VCPO also enables improvements of the environmental impact in the biocatalysis, as through lowered dilution, the mass balance between generated waste and desired product, an important aspect of green chemistry,[18] is considerably enhanced compared to a process mediated by a heme-dependent haloperoxidase (Table 2).

Conclusion

The highly robust vanadium-dependent chloroperoxidase from *Curvularia inaequalis* is able to efficiently mediate 5-*endo*-*trig* bromocyclizations of α-hydroxyallenes, furnishing bromodihydrofurans as attractive building blocks for further transformations. A colloidal medium stabilized by cationic surfactant CTAB was found optimal for the process, facilitating increased reaction rates and product selectivities. While the optimized conditions included a significant excess of the detergent, the wide screening established more atom-economical optional conditions. In addition, the biocatalytic halogenation was extended to 5-*exo*-*trig* cyclizations of γ-allenols. While requiring a fair excess of reagents to overcome competing reactions, the

Table 2. Comparative estimation of mass balances between waste and product **2a** in biocatalytic bromocyclizations using either *Ci*VCPO or *Cf*CPO.



*Ci*VCPO process ($g\,g^{-1}_{product}$)		*Cf*CPO process ($g\,g^{-1}_{product}$)	
medium ($heptane/H_2O$/citrate buffer)	145.4	medium ($hexane/H_2O$/citrate buffer)	370.9
chemicals (H_2O_2/CTAB/catalyst)	7.1	chemicals (NaBr, glucose/Brij/catalyst)	8.3
total	152.5	total	379.2

method could deliver desired tetrahydrofurans in good yields. Taking advantage of the vanadate-dependent enzyme's high tolerance towards harsh oxidative conditions in the process perfectly underlines the advantages over heme-counterparts.

Experimental Section

Commercially available reagents were used without further purification. Chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) was produced heterologously through a previously reported procedure and used as 21 μM solution in Tris buffer.[19] Synthesized compounds were purified by column chromatography over silica gel (Merck Millipore 60, 40–60 μm, 240–400 mesh) or by distillation. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance NEO 400 spectrometer (^{1}H 400.13 MHz, ^{13}C 100.62 MHz). The chemical shifts are reported in parts per million (ppm) related to non-deuterated chloroform signal (^{1}H NMR: $\delta = 7.26$; ^{13}C NMR: $\delta = 77.16$). Quantitative ^{1}H NMR spectra were recorded using delay time D = 30 s and 30° pulse, and are reported relative to the dimethyl sulfone internal standard signal ($\delta = 3.00$, s, 6 H).

Representative procedure for endo-trig bromocyclization of α-allenols: A cylindrical vial was charged with CTAB (400 μmol) in an aqueous citrate buffer solution (2 mL, 0.1 M, pH 5.0). 5-Methyl-2-phenylhexa-3,4-dien-2-ol **1a** (100 μmol) in *n*-heptane (2 mL) was added to form an emulsion with vigorous stirring. Hydrogen peroxide (300 μmol, 50 wt% in water) and chloroperoxidase from *Curvularia inaequalis* (0.1 nmol, 21 μM in pH 5.0 Tris-base buffer) were added to the emulsion. The mixture was stirred vigorously at room temperature for 24 h. Acetonitrile (3 mL) was added to enable phase separation. The mixture was extracted with *n*-pentane (3× 10 mL). The combined organic layers were concentrated under reduced pressure. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether 20:1) provided 3-bromo-2,2,5-trimethyl-5-phenyl-2,5-dihydrofuran **2a** as a colorless oil (88 μmol, 88% yield).

Representative procedure for *exo*-trig bromocyclization of γ-allenols: A cylindrical vial was charged with CTAB (400 μmol) in an aqueous citrate buffer solution (2 mL, 0.1 M, pH 5.0). Sodium bromide (2 mmol) was added to the mixture. 2,2-diphenylhexa-4,5-dien-1-ol **3c** (100 μmol) in *n*-heptane (2 mL) was added to form an emulsion with vigorous stirring. Hydrogen peroxide (2 mmol, 50 wt% in water) and chloroperoxidase from *Curvularia inaequalis* (0.25 nmol, 21 μM in pH 5.0 Tris-base buffer) were added to the emulsion. The mixture was stirred vigorously at room temperature for 24 h. Acetonitrile (3 mL) was added to enable phase separation. The mixture was extracted with n-pentane (3×10 mL). The combined organic layers were concentrated under reduced pressure. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether 10:1) provided 2-(1-bromovinyl)-4,4-diphenyltetrahydrofuran **4c** as a colorless oil (68 μmol, 68% yield).

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: allenes · cyclization · halogenation · haloperoxidase · heterocycles

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