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Research Article

Vanadium-Containing Chloroperoxidase-Catalyzed Versatile Valorization of Phenols and Phenolic Acids

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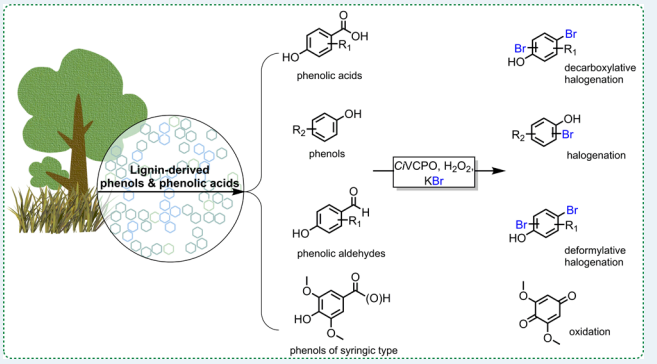
ABSTRACT: The downstream product transformation of lignin depolymerization is of great interest in the production of high-value aromatic chemicals. However, this transformation is often impeded by chemical oxidation under harsh reaction conditions. In this study, we demonstrate that hypohalites generated in situ by the vanadium-containing chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) can halogenate various electron-rich and electron-poor phenol and phenolic acid substrates. Specifically, *Ci*VCPO enabled decarboxylative halogenation, deformylative halogenation, halogenation, and direct oxidation reactions. The versatile transformation routes for the valorization of phenolic compounds showed up to 99% conversion and 99% selectivity, with a turnover number of 60,700 and a turnover frequency of 60 s^{-1} for *Ci*VCPO. This study potentially expands the biocatalytic toolbox for lignin valorization.



KEYWORDS: *vanadium-containing chloroperoxidase, lignin valorization, decarboxylation, halogenation, biocatalysis*

INTRODUCTION

Looking ahead to the future of the biobased chemical industry, there is growing interest in converting plant-derived raw materials into chemical building blocks.[1−4] Specifically, lignocellulose, which consists of cellulose, hemicellulose, and lignin, is widely recognized as a sustainable feedstock for biorefineries.[5,6] In a typical biorefinery process, lignocellulose is separated via an energy-intensive process into its structural components with a primary focus on cellulose production.[7,8] However, further depolymerization of the remaining lignin and its effective utilization present significant challenges.[9] Consequently, there is a high demand for lignin processing methods. Lignin can be polymerized into a considerable number of phenolic acids and phenols using various chemical and biochemical methods.[9−11] Various phenolic acids, such as *p*-hydroxy benzoic acid, *p*-coumaric acid, vanillic acid, gallic acid, and cinnamic acid, can be obtained. The abundance of the phenolic acid product is influenced by the catalytic methods and the lignin compositions.

While these obtained feedstocks are versatile compounds for direct use in chemical processing, their value can be substantially increased through further conversion into high-value-added chemicals.[10] To unlock this potential, the utilization of existing catalysts and the development of novel catalytic methods are essential. In the past decades, biocatalysis has been continuously investigated for the conversion of biobased wastes into value-added products.[12] A variety of enzymes and bacteria involved in reactions such as hydroxylation, esterification, amination, halogenation, decarboxylation, and dearomatization have been demonstrated under mild reaction conditions as compared to the chemical counterparts (Scheme 1A).[13−22] More recently, combining engineered methyltransferase and ammonia lyase in an engineered *Escherichia coli* strain,[23] a methylation−hydroamination of lignin-derived phenolic substrates was established to generate L-veratrylglycine, a key precursor to L-DOPA. Overall, the converted products of lignin-derived compounds are of significant interest to the pharmaceutical, polymer, food, and chemical industries. However, decarboxylation and halogenation reactions have been underexplored for lignin-derived monomer valorization. In nature, various enzymes have been shown to catalyze decarboxylation[24,25] and halogenation[26] reactions. Accordingly, the decarboxylation of lignin-derived phenolic acids produces valuable phenols, and the halogenation of phenols can yield bioactive compounds that are particularly intriguing for pharmaceuticals and agrochemicals. Despite notable progress in understanding the

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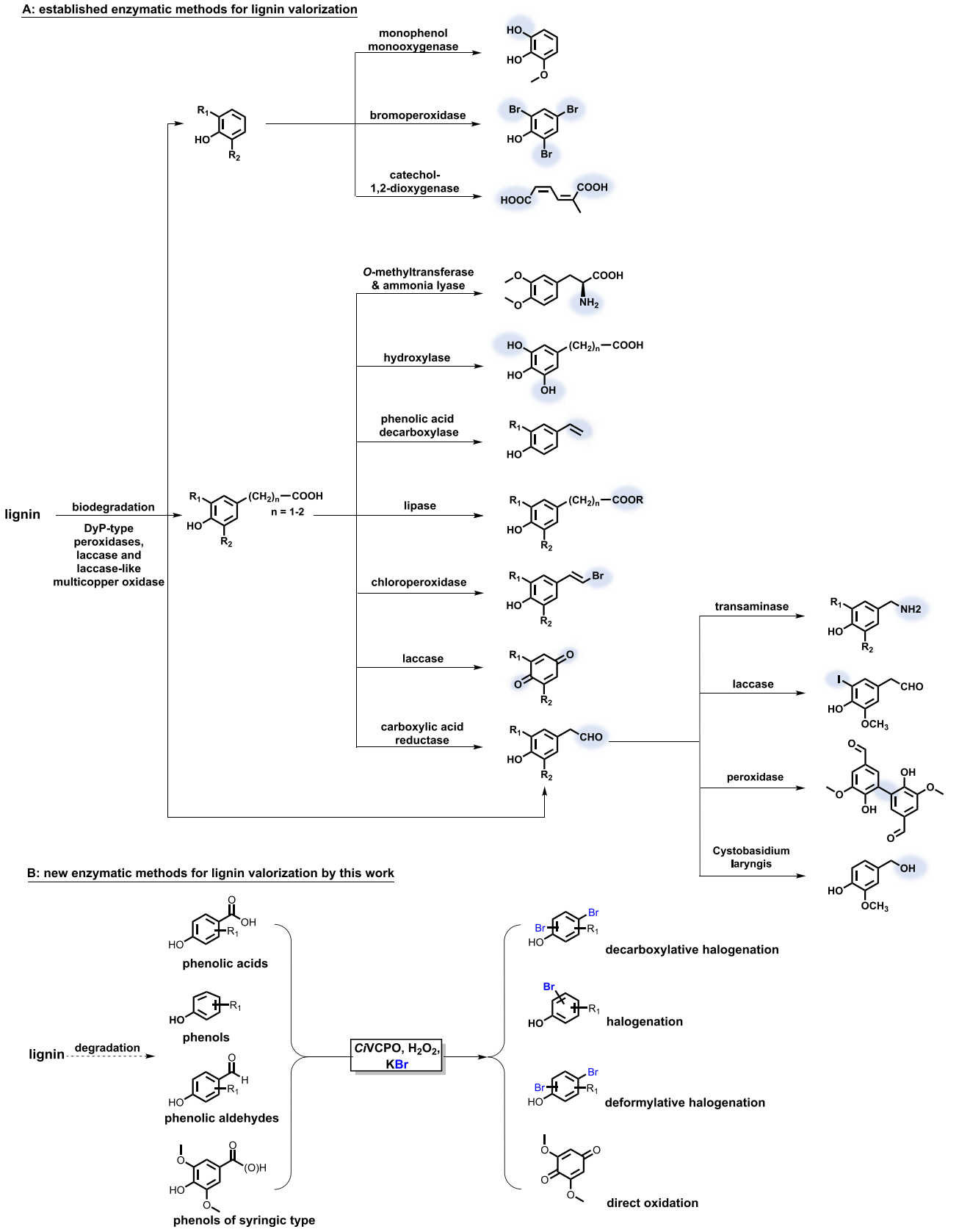
Scheme 1. Biocatalytic Methods for the Valorization of Lignin-Derived Phenolic Compounds[a]



[a](A) Established pathways using enzymes or bacteria and (B) the envisioned chemoenzymatic valorization of lignin-derived monomers in various transformations using a single vanadium-containing chloroperoxidase.

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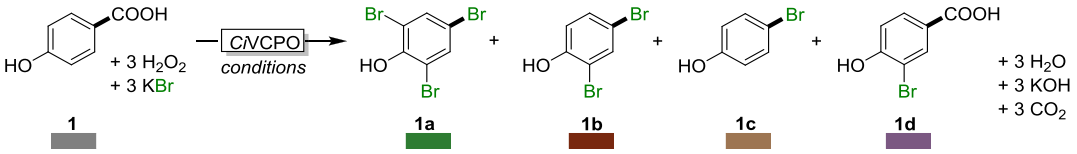
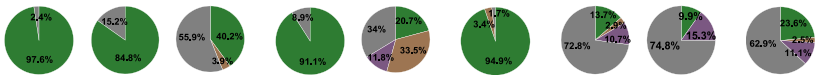
Table 1. Reaction Parameters Influencing the Efficiency of the Chemoenzymatic Decarboxylative Halogenation of *p*-Hydroxy Benzoic Acid[a]



Entry	1	2	3	4	5	6	7	8	9
cosolvent	acetone	acetone	acetone	acetone	acetone	DMSO	CH_3CN	methanol	ethanol
pH	3.5	4.5	5	3.5	3.5	3.5	3.5	3.5	3.5
KBr [mM]	100	100	100	100	12.5	100	100	100	100
Enzyme [nM]	250	250	250	150	250	250	250	250	250
TTN	39040	33920	16080	60733	8296	37960	5460	3960	9400
1a [mM]	9.7	8.5	4.0	9.1	2.1	9.5	1.4	1.0	2.4
Conv. [%]	97.6	84.8	40.2	91.1	20.7	94.9	13.7	9.9	23.6
Product distribution									

[a]Reaction conditions: [**1**] = 10 mM, citrate buffer (100 mM, pH 3.5−5), [*Ci*VCPO] = 150−250 nM, [KBr] = 12.5−100 mM, [H_2O_2] = 100 mM, 30 °C, 20% cosolvent, 3 h, 1 mL reaction scale. TTN (total turnover number) = ([**1a**]/[*Ci*VCPO]). The concentration was determined by HPLC at 3 h.

biosynthesis mechanisms involving decarboxylation or halogenation, the use of isolated enzymes to catalyze these reactions is still limited compared with other extensively studied reactions. One typical challenge of this scenario lies in the high substrate specificity of decarboxylases[27,28] or halogenases.[29−31] Therefore, the development of innovative biocatalytic techniques and the broadening of enzyme substrate scopes offer significant potential for enhancing the value of phenolic compounds that can be derived from lignin depolymerization.

We have recently developed a chemoenzymatic Hunsdiecker-type reaction that enables the bromodecarboxylation of α,β-unsaturated carboxylic acids.[32] The vanadium-containing chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) is a highly robust catalyst that can tolerate high concentrations of H_2O_2 and various organic solvents.[33−35] *Ci*VCPO efficiently oxidizes halides to hypohalites by using only H_2O_2 as an oxidant. Following this oxidation, the resulting hypohalites diffuse out of the enzyme channel.[36] This process potentially overcomes limitations on the substrate scope, as the overall chemoenzymatic reaction occurs outside of the enzyme pocket. *Ci*VCPO's exceptional catalytic performance has encouraged us to investigate its potential as a (bio)catalyst for establishing new pathways of the valorization of feedstocks derived from lignin degradation under mild conditions (Scheme 1B). We envision that the chemoenzymatic process would allow *Ci*VCPO to serve as a versatile catalyst (e.g., one enzyme for quadruple reactions) due to the diverse patterns of monomeric phenolic compounds that can be derived from lignin depolymerization.

RESULTS AND DISCUSSION

We started our investigations using *p*-hydroxy benzoic acid (**1**) as a model substrate, which can be obtained via catalytic hydrogenolysis[37] or hydrothermal pretreatment[38] of wood. In accordance with the reported pH spectrum of *Ci*VCPO,[39] a clear preference for acidic reaction media was observed under reaction conditions (Table 1), presumably originating from a combination of increasing affinity of the enzyme for the halide and the increasing Nernst potential of the Br^-/OBr^- redox couple. At pH 3.5, we observed that in 3 h almost complete conversion (97.6%) of the starting material into 1,3,5-tribromophenol (**1a**), a compound as fungicide, wood preservative, and a precursor to prepare flame retardants. Reducing the molar surplus of KBr to 42% (mol × mol^{-1}; i.e., ca. 0.25 equiv with respect to the tribromination reaction) resulted in incomplete conversion of the starting material as well as broader distribution of mono- and dibrominated products (Table S1). Among the cosolvents tested, acetone and DMSO excelled, whereas ethanol and acetonitrile gave only mediocre results in terms of low conversion and a significant amount of brominated substrate (Table 1). Negative controls in the absence of H_2O_2, KBr, *Ci*VCPO or in the presence of free Na_3VO_4 did not give noticeable conversion under otherwise identical reaction conditions (Table S2).

A typical time course for the reaction conditions in Table 1 (entry 1) is shown in Figure 1 (with HPLC chromatograms shown in Figure S1). Already after 30 min reaction time, the initial starting material was converted at more than 90% into the desired tribromophenol product corresponding to a

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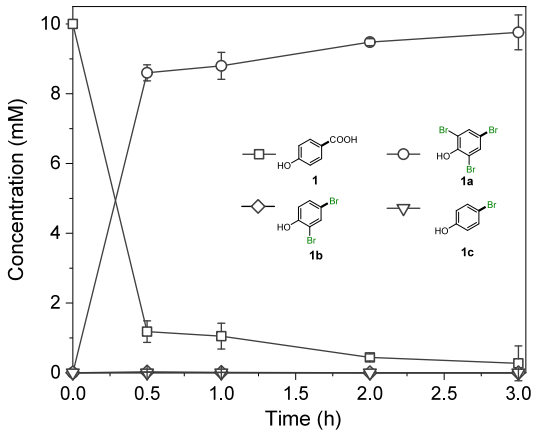
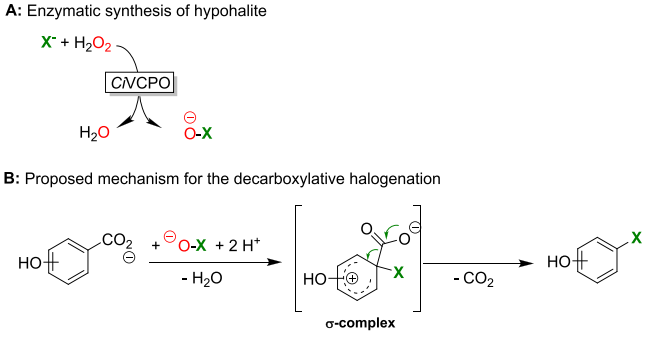


Figure 1. Time course of the *Ci*VCPO-initiated transformation of **1** to **1a**. Reaction conditions: [**1**] = 10 mM, citrate buffer (100 mM, pH 3.5), [*Ci*VCPO] = 250 nM, [KBr] = 100 mM, [H_2O_2] = 100 mM, 30 °C, 20% acetone, 3 h, 1 mL reaction scale. The concentration was determined by HPLC at 3 h. Duplicate experiments were performed.

turnover number and turnover frequency for the biocatalyst of 60,700 and 60 s^{-1}, respectively. Interestingly, in this experiment, only trace amounts of the partially halogenated products were observed (Figure S1). Apparently, for *p*-hydroxy benzoic acid, the decarboxylative bromination step was not overall rate limiting in the chemical part of the overall reaction. It is worth mentioning that substituting *p*-hydroxy benzoic acid by one of the putative intermediate bromination products under otherwise identical conditions mostly led to full conversion into tribromophenol (Table S3).

Vanadium-containing haloperoxidases catalyze the H_2O_2-driven oxidation of halides into their corresponding hypohalites (Scheme 2A).[33,35,40−44] As pointed out by Wever and Barnett,[36] the oxidative hypohalite product diffuses out of the enzyme active site. Therefore, an influence of the biocatalyst on the (regio)selectivity of the following chemical halogenation reaction was expected, as shown in the model reaction with substrate **1**.

Scheme 2. Mechanism of Enzymatic Generation of Hypohalite (A) and Proposed Mechanisms for the Chemoenzymatic Decarboxylation Reactions (B)



The observed decarboxylation reaction of phenolic acids can be explained straightforwardly via the σ-complex originating from the electrophilic attack of the hypohalite to the carboxylate-bearing arene atom (Scheme 2B). In this complex, rearomatization can be attained via decarboxylation. This mechanism may also explain the apparent faster decarboxylative halogenation as compared to the "regular" aromatic substitution, as observed in Figure S1. Especially under acidic conditions, proton elimination may be considered to be less favorable than the CO_2 extrusion. Along with our previous discovery,[32] the chemoenzymatic Hunsdiecker-type reaction has proven a powerful strategy in converting the lignin-derived compounds into high-value added chemicals.

Next, we investigated the substrate scope of the proposed decarboxylative halogenation reactions. All substrates are potential monomers from the degradation of lignin with various substitution patterns.[10] First, *o*-, *m*-, and *p*-hydroxy benzoic acids were readily converted in the reaction scheme, already suggesting a wide substrate scope (Figure 2 and Figures S2−S14). The 4-hydroxy-3-nitrobenzoic acid (Figure 2, substrate **5**), a nitrated product from nitric acid-mediated treatment of lignin,[45] was also investigated. The electron-withdrawing nitro group accelerated the decarboxylative bromination reaction, whereas electron-donating substituents (such as methoxy, Figure 2, substrate **4** or an additional phenolic OH, Figure 2, substrate **6**) considerably slowed down the reaction rate. Protecting the carboxylate group (e.g., as methyl ester) prevented the decarboxylation reaction but apparently did not impair the bromination reaction (Figure 2, substrates **7** and **8**).

Interestingly, also, formyl-substituted phenols were converted (Figure 2, substrates **9** and **10**). The previously observed preference of electron-poor phenols was observed as well. Even more interestingly, however, also, deformylative bromination was observed here. At first glance, this may be explained by the oxidation of the benzaldehyde group by hypohalites. However, in none of these experiments were indications for benzoic acid found. Further analysis of the reaction mixture revealed that in these cases, formic acid was formed as a byproduct (Figures S15 and S16). Following the suggestion by Larrosa and co-workers[46] in the case of the deformylative halogenation reaction, we suggest a nucleophilic attack of the hypohalites to the aldehyde carbonyl group (Scheme 3), followed by a concerted intramolecular substitution of formate by the halogen atom, resulting in the observed halogenated starting material and formic acid.

Next, we investigated the conversion of some alkyl-substituted phenols as they also represent a significant fraction of the lignin refining process (Figure 3 and Figures S17−S36).[10] Quite expectedly, halogenation occurred preferentially in the *o*- or *p*-position to the phenolic OH group. In the presence of another directing group (such as OCH_3), also, some further bromination in the *o*-position to the methoxy group (*meta* with respect to OH) was observed. This halogenation reaction also leads to new compounds such as **13b**, as proved by its crystal structure (Table S4).

It is worth noting that in the presence of further +M substituents (i.e., additional methoxy substituents, the so-called phenolic derivatives of syringic type[19]), "thorough oxidation" to the corresponding quinones was observed (Figure 3, substrates **16**−**19**). The observed exclusive formation of 2,6-dimethoxy-l,4-benzoquinone is expected to follow the oxygen-based radical oxidation as documented with lignin peroxidase[47] and horseradish peroxidase.[48]

Finally, we performed a preparative-scale reaction of the bromo-decarboxylative valorization of *p*-hydroxybenzoic acid (Figures S37−S40). In a 100 mL reaction scale (1.38 g of the substrate, 100 mmol), the desired 2,4,6-tribromophenol (**1a**) continuously precipitated upon complete transformation of the substrate in 12 h. The downstream process was exploited by

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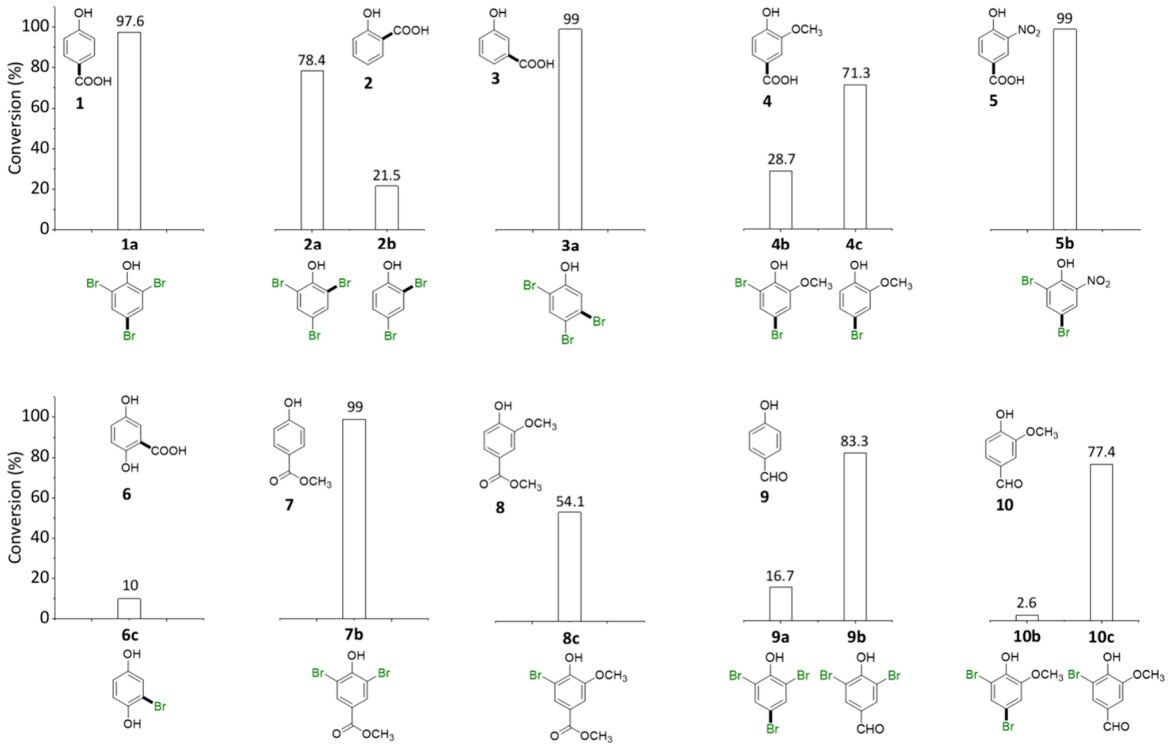
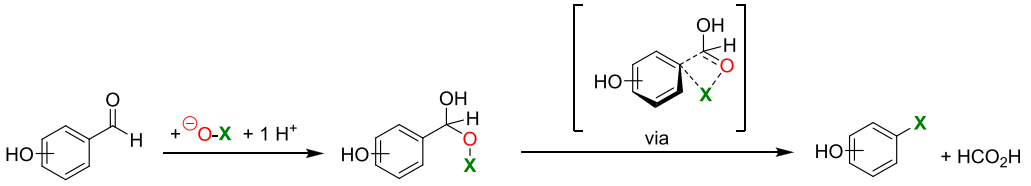


Figure 2. Substrate scope of the decarboxylation reactions with varied substituents on the arene. Reaction conditions, unless otherwise specified: [substrates] = 10 mM, citrate buffer (100 mM, pH 3.5), [*Ci*VCPO] = 250 or 400 nM for substrate **3**, [KBr] = 100 mM, [H_2O_2] = 100 mM, 30 °C, 20% acetone, 3 h, 1 mL reaction scale. The conversion was determined by GC−MS at 3 h.

Scheme 3. Mechanism of Enzymatic Deformylation Reactions Enabled by *Ci*VCPO



multiple precipitation of the reaction mixture at 4 °C, which was followed by the simple centrifugation. In this way, the overall downstream process yielded 3.17 g of the product (95.8% isolated yield) with an *E*-factor of 38.3 (Table S5). The *E*-factor analysis[49] of the preparative-scale reaction reveals that far more than 90% of the wastes generated have been caused by the solvents (aqueous buffer and acetone) used in this reaction. Therefore, further increase of the reagent payload (e.g., through a fed-batch strategy) will further reduce the waste generation and advance the current method toward a more sustainable approach for lignin valorization.

CONCLUSIONS

To summarize our studies, we used vanadium-containing chloroperoxidase to develop new catalytic approaches for the valorization of phenolic compounds that can be obtained from lignin depolymerization. A range of new substrates were converted, which also leads to the production of various valuable chemicals in very high turnover numbers and turnover frequencies under mild conditions. Compared to the use of stoichiometric hypohalites such as hypochlorites (hypobromites are not commercially available) or even organic precursors such as *N*-halo succinimides (NXSs), the proposed method for the derivatization of phenols and phenolic acids appears advantageous. The vanadium-containing chloroperoxidase can be combined with other enzymes via in vitro cascades, or in synthetic metabolic pathways to access a variety of halogenated products, thus expanding the biocatalytic toolbox for lignin valorization.

EXPERIMENTAL SECTION

Enzymes. The vanadium-containing chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) was prepared in-house, and the detailed procedures are included in the Supporting Information.

Enzymatic Reactions. In a typical procedure of the decarboxylative bromination, to a 2 mL glass vial were added *p*-hydroxybenzoic acid (**1**) (10 mM), H_2O_2 (100 mM), KBr (100 mM), *Ci*VCPO (250 nM), cosolvent acetone (20% v/v), and citrate buffer (100 mM, pH 3.5), and the reaction volume was adjusted to 1 mL using citrate buffer. The above concentration means the final concentration of each component. The reaction mixture was placed in a thermal shaker at 30 °C and 800 rpm for 3 h. During the intervals, the mixture was subjected to HPLC or GC−MS analysis to determine the conversion or product concentration. For the halogenation, deformylative bromination, and oxidation

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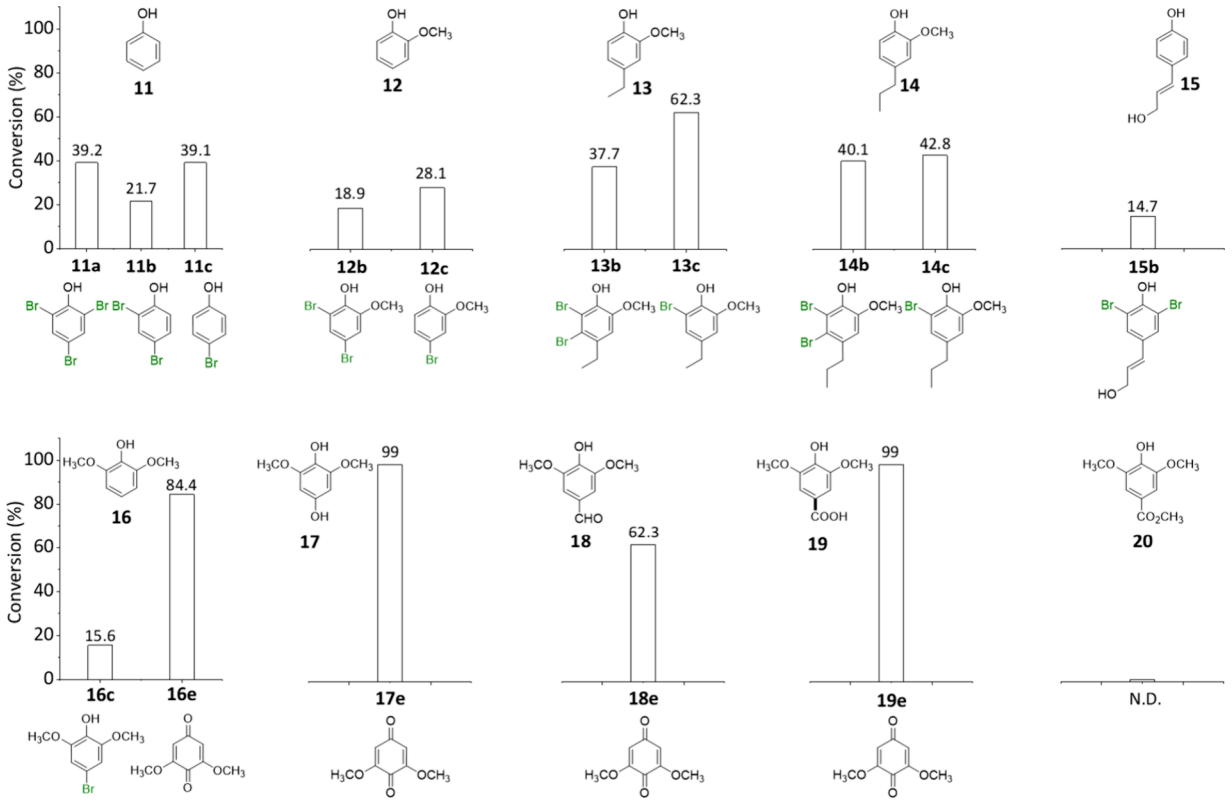

Figure 3. Chemoenzymatic conversion of phenols. Conditions: citrate buffer (100 mM, pH 3.5), [*Ci*VCPO] = 250 or 400 nM for substrate **11**, [KBr] = 100 mM, [H_2O_2] = 100 mM, 30 °C, 20% acetone, 3 h, 1 mL reaction scale. The conversion was determined by GC−MS at 3 h.

reactions catalyzed by *Ci*VCPO, similar reaction products were adopted, as described in the decarboxylative reactions.

Preparative-Scale Synthesis. The reaction using *p*-hydroxybenzoic acid (**1**) was performed in 100 mL. To a reaction mixture, 1.38 g (100 mM) of the *p*-hydroxybenzoic acid, H_2O_2 (1 M), KBr (1 M), *Ci*VCPO (3 μM), cosolvent acetone (20% v/v), and citrate buffer (100 mM, pH 3.5) were added. After stirring at 30 °C and 800 rpm for 12 h, the products (**1a**) were collected by precipitation and centrifugation at 4 °C. The product was dried at 50 °C for 5 h, and 3.17 g of white solid was obtained (95.8% isolated yield).

Crystallography. The crystal of **13b** was measured by keeping the sample at 100.01(10) K during data collection. Using Olex2, the structure was solved with the unknown structure solution program and refined with the unknown refinement package.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c05333.

Preparation of the enzymes, enzymatic procedures, analytical data, and additional results (PDF)

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Author Contributions

H.L., Y.H., Y.M., and J.Z. performed the experimental work and analyzed the results. P.D., C.C., Y.W., and W.L. participated in the planning and analysis of the experiments. H.L., F.H., and W.Z. conceived and designed the experiments. H.L., F.H., and W.Z. cowrote the manuscript. All authors participated in the writing of the manuscript.

Notes

The authors declare no competing financial interest.

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