Decarboxylative Halogenation of Indoles by Vanadium Haloperoxidases

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Abstract:

Halogenated heteroarenes are key building blocks across numerous chemical industries. Here, we report that vanadium haloperoxidases can produce 3-haloindoles through decarboxylative halogenation of 3-carboxyindoles. This biocatalytic method is applicable to decarboxylative chlorination, bromination, and iodination in moderate to high yields and with excellent chemoselectivity.

Main Text:

Organohalides have demonstrated an unrivaled utility as precursors for organometallic reagent preparation, cross-coupling reactions, and radical-mediated transformations in organic chemistry.[1] The synthetic applicability of organohalides and their increasing prevalence in drug discovery[2] make the selective synthesis of these building blocks from readily available starting materials a remarkably attractive area for synthetic exploration. To achieve this goal, carboxylic acids have emerged as valuable functional group targets for chemoselective interconversion to organohalides because of their ubiquity across commodity chemicals, materials, and pharmaceuticals. Despite the numerous advancements made in this area, decarboxylative halogenation methods often still require air- and moisture-sensitive reagents and/or forcing conditions that lead to overhalogenation events (Figure 1, a).[3] Moreover, there is only a single catalytic system capable of

halogenation generality[4], leaving new methods for decarboxylative halogenation to be desired.

More recently, these challenges have been addressed using enzyme catalyst platforms to achieve selective decarboxylative halogenation on various synthetic scaffolds. This strategy has been highlighted in reports of the decarboxylative bromination of cinnamic acids by Hollmann[5] and in the context of a decarboxylative bromooxidation of 3-carboxyindoles by our laboratory[6], all of which demonstrate that the vanadium chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO)[7] is a viable biocatalyst for decarboxylative bromination. Our previous studies into decarboxylative bromooxidation revealed that the reaction proceeds in a tandem process through the initial formation of a 3-bromoindole that undergoes an ensuing oxidation to the corresponding 3-bromooxindole. While this method was found to be robust towards the synthesis of a wide range of 3-bromooxindoles, it left the selective generation of the 3-bromoindoles elusive. Moreover, while all biocatalytic decarboxylative halogenations reported to date are notable, they are currently limited to bromination, leaving room for extension into alternative halogenation types. This series of limitations motivated us to develop a biocatalytic decarboxylative halogenation protocol for selective production of 3-haloindoles with halogenation generality (Figure 1, b).

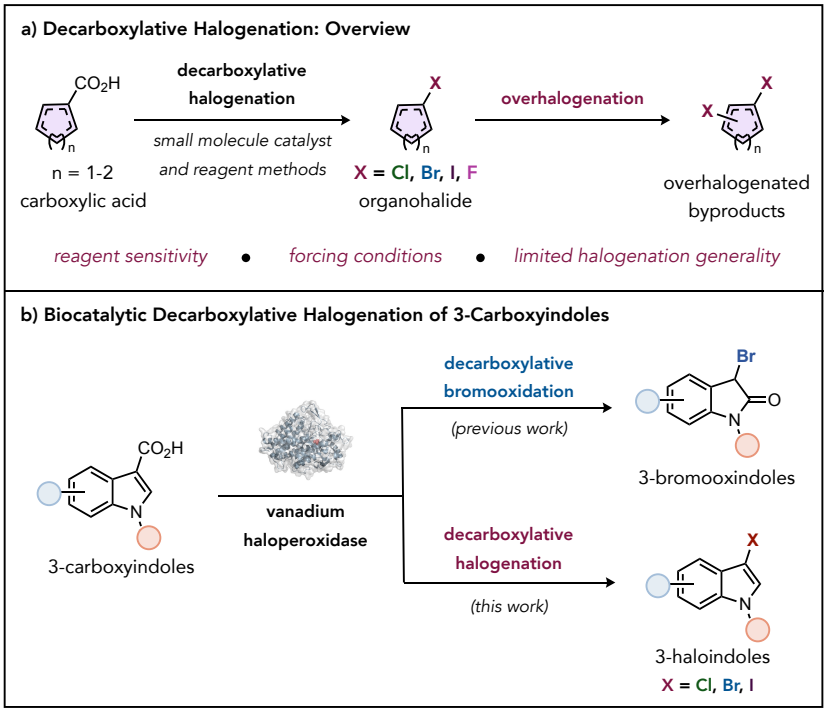
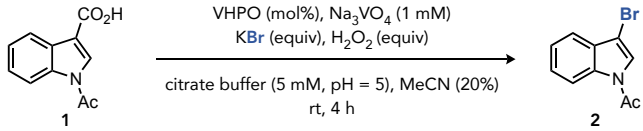


Figure 1. Chemical and Biocatalytic Strategies for Decarboxylative Halogenation of (Hetero)aryl Carboxylic Acids

At the outset of reaction development, we hypothesized that starting with a 3-carboxyindole containing an electron withdrawing group on the nitrogen atom would allow for selective decarboxylative halogenation of 3-carboxyindoles by discouraging the oxidation event observed in our previous studies.[6] We began our investigation with the conversion of 1-acetyl-1*H*-indole-3-carboxylic acid (**1**) to 1-(3-bromo-1*H*-indol-yl)ethan-1-one (**2**) using *Ci*VCPO as biocatalyst. We were pleased to find that the reaction proceeded in 71% yield using 0.00125 mol% enzyme loading and 2.2 equivalents each of potassium bromide (KBr) and hydrogen peroxide (H_2O_2) in citrate buffer (5 mM, pH = 5) with 20% loading (v/v) of acetonitrile (MeCN) as co-solvent (Table 1, Entry 1). Under the same reaction conditions, vanadium bromoperoxidases from *Corallina officinalis* (*Co*VBPO)[8], *Corallina pilulifera* (*Cp*VBPO)[9], and *Acaryochloris marina* (*Am*VBPO)[10] were tested but

resulted in no detectable product formation (Table 1, Entries 2-4). When control reactions were performed to confirm the necessity of all reaction components (Table 1, Entries 5-8), only a minor background reaction (5% yield) was observed when excluding Na_3VO_4.[11] Ultimately, the yield of **2** was further optimized to 89% by changing the enzyme loading to 0.00375 mol% and the KBr and H_2O_2 loadings to 6.6 and 4.4 equivalents, respectively (Table 1, Entry 9). The optimized reaction conditions were amenable to a preparative, 0.3 mmol scale reaction, producing **2** in 85% yield after extending the reaction time to 24 hours (Table 2, **2**).

Table 1. Decarboxylative Halogenation Optimization



Entry	Enzyme	KBr	H_2O_2	Yield (%)
1	0.00125 mol% *Ci*VCPO	2.2 equiv	2.2 equiv	71
2	0.00125 mol% *Co*VBPO	2.2 equiv	2.2 equiv	0
3	0.00125 mol% *Cp*VBPO	2.2 equiv	2.2 equiv	0
4	0.00125 mol% *Am*VBPO	2.2 equiv	2.2 equiv	0
5	**no enzyme** (w/ Na_3VO_4)	2.2 equiv	2.2 equiv	0
6	0.00125 mol% *Ci*VCPO (**no Na_3VO_4**)	2.2 equiv	2.2 equiv	5
7	0.00125 mol% *Ci*VCPO	**0.0 equiv**	2.2 equiv	0
8	0.00125 mol% *Ci*VCPO	2.2 equiv	**0.0 equiv**	0
9	0.00375 mol% *Ci*VCPO	6.6 equiv	4.4 equiv	89

Reaction conditions: **1** (4.0 µmol, 0.8 mg), VHPO (0.00125-0.00375 mol%), Na_3VO_4 (1 mM), KBr (2.2-6.6 equiv), H_2O_2 (2.2-4.4 equiv), citrate buffer (5 mM, pH = 5), MeCN (200 µL), 1 mL total reaction volume. Yields determined by HPLC based on a calibration curve. See the Supporting Information for details.

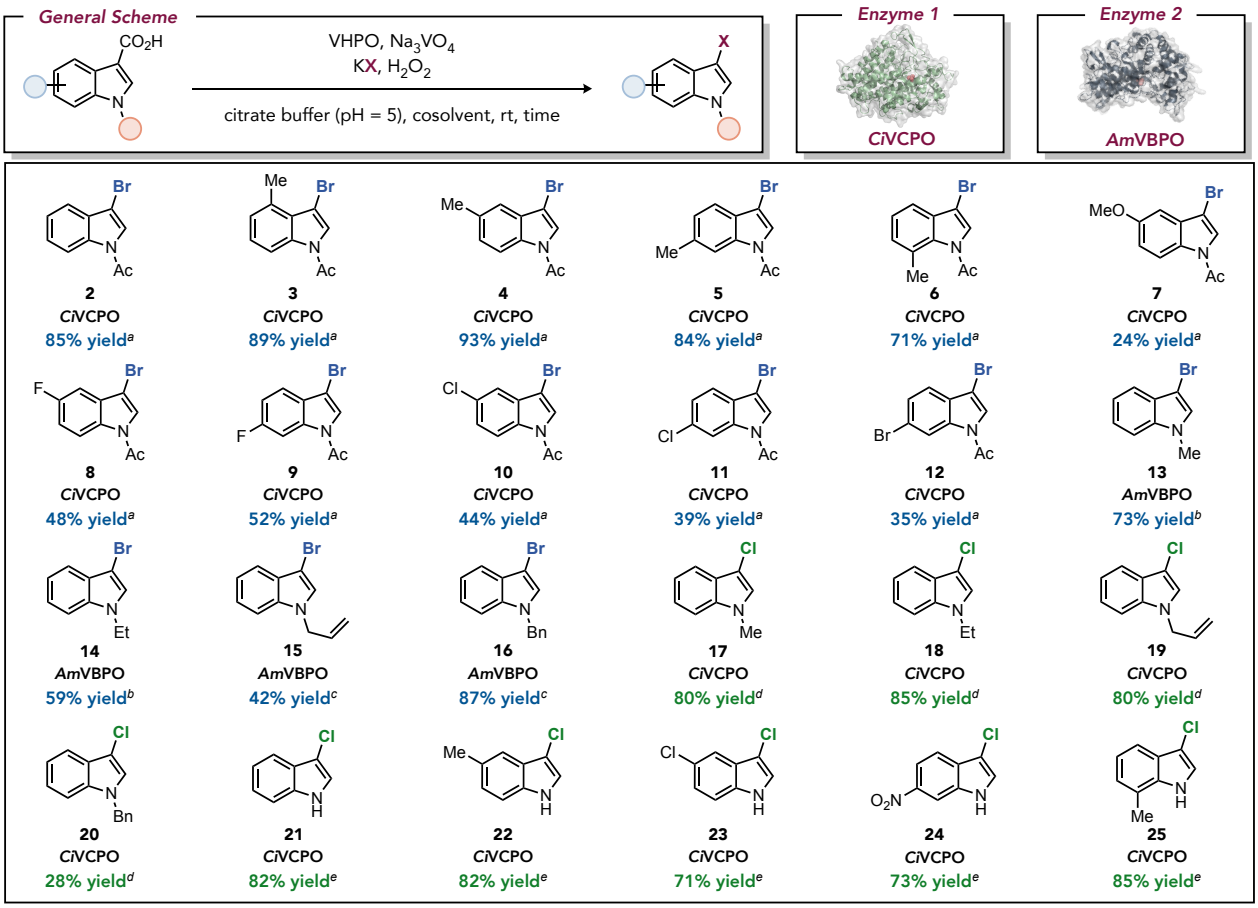
With the model substrate fully optimized, we next turned to interrogation of the scope of substituted N-acetylindoles. The reaction conditions were compatible with indoles bearing methyl substituents on the 4-, 5-, 6-, and 7-positions, with yields ranging from 71-93% (Table 2, **3-6**). Introduction of a methoxy group in the 5-position dramatically decreased the yield to 24% as the result of indistinguishable byproduct formation (Table 2, **7**). Halogen-substituted (fluoro-, chloro-, bromo-) N-acetylindoles were also tolerated in moderate yields from 35-52% (Table 2, **8-12**).

After investigating N-acetylindoles, we turned our attention to the decarboxylative bromination of N-alkyl indoles with the goal of providing a complementary method to our previously reported bromooxidation of these substrates.[6] We began with the conversion of 1-methyl-1*H*-indole-3-carboxylic acid to 3-bromo-1-methyl-1*H*-indole (**13**). Critical to the success of this optimization was the use of 0.00625 mol% *Am*VBPO with KBr (2.0 equiv) and H_2O_2 (3.0 equiv) in a biphasic mixture of citrate buffer (10 mM, pH = 5) and EtOAc (30% v/v) at room temperature for 7 hours, affording the corresponding 3-bromoindole in 73% yield (Table 2, **13**). This system was readily applied to the preparation of additional N-alkylindoles, producing the brominated N-ethyl, N-allyl, and N-benzyl indoles in 42-87% yield (Table 2, **14-16**).

To access halogenation generality, decarboxylative chlorination was next explored by switching to potassium chloride (KCl) as the halogen salt additive. This allowed decarboxylative chlorination to be performed on a series of N-alkyl substrates by using *Ci*VCPO (0.00375 mol%) with KCl (4.0 equiv) and H_2O_2 (4.0 equiv) shaken at room temperature for 16 hours in a mixture of citrate buffer (100 mM, pH = 5) and EtOAc (30% v/v), resulting in the formation of the chlorinated N-methyl, N-ethyl, and N-allyl indoles in 80-85% yield (Table 2, **17-19**). A diminished yield (28%) was achieved with the N-benzyl-substituted 3-carboxyindole (Table 2, **20**). We currently attribute this to less favorable

protein binding compared to *Am*VBPO in our decarboxylative bromination of the same substrate (Table 2, **16**). Collectively, these findings demonstrate generality in the biphasic system for decarboxylative halogenation on N-alkylindoles. The decarboxylative chlorination procedure could also be applied to free N-H indoles by changing the organic cosolvent to DMF and reducing the reaction time to 2 hours. Using this protocol, 3- chloro-1*H*-indole (**21**) was synthesized in 82% yield (Table 2, **21**). The extension to 3-carboxyindoles bearing electron donating and electron withdrawing substituents on the 5-, 6-, and 7-position was achieved in 71-85% yield (Table 2, **22-25**).

Table 2. Substrate Scope



All reactions are 0.3 mmol substrate with yields determined by isolation. [a]*Ci*VCPO (0.00375 mol%), Na_3VO_4 (1 mM), KBr (6.6 equiv), H_2O_2 (4.4 equiv), citrate buffer (5 mM, pH = 5), MeCN (20%), rt, 24 h. [b]*Am*VBPO (0.00625 mol%),

Na_3VO_4 (1 mM), KBr (2.0 equiv), H_2O_2 (3.0 equiv), citrate buffer (10 mM, pH = 5), EtOAc (30%), rt, 7 h. [c]*Am*VBPO (0.00625 mol%), Na_3VO_4 (1 mM), KBr (2.0 equiv), H_2O_2 (3.0 equiv), citrate buffer (10 mM, pH = 5), EtOAc (30%), rt, 24 h. [d]*Ci*VCPO (0.00375 mol%), Na_3VO_4 (1 mM), KCl (4.0 equiv), H_2O_2 (4.0 equiv), citrate buffer (100 mM, pH = 5), EtOAc (30%), rt, 16 h. [e]*Ci*VCPO (0.00375 mol%), Na_3VO_4 (1 mM), KCl (4.0 equiv), H_2O_2 (4.0 equiv), citrate buffer (100 mM, pH = 5), DMF (30%), rt, 2 h

Upon complete optimization of the decarboxylative bromination and chlorination protocols, scalability was next examined. Decarboxylative bromination and chlorination were both achieved on gram scale to produce 3-bromo-N-acetylindole **2** in 80% yield and 6-nitro-3-chloroindole **24** in 71% yield, respectively. As a final demonstration of the generality of this enzymatic decarboxylative halogenation protocol, we were pleased to find that decarboxylative iodination could be readily achieved by changing the halide salt additive to potassium iodide (KI), which allowed for the conversion of N-benzyl-3-carboxyindole **27** to 3-iodo-N-benzylindole **28** in 76% yield.

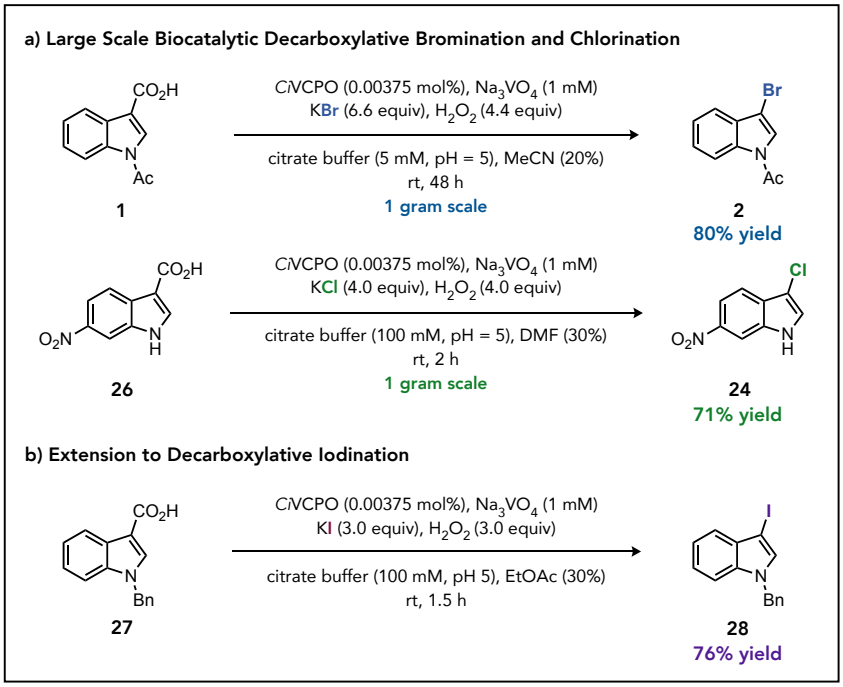


Figure 2. Reaction Scale-Up and Decarboxylative Iodination

In summary, we have reported a biocatalytic protocol for decarboxylative halogenation of 3-carboxyindoles. This enzymatic platform can perform the desired reaction with halogenation generality in the form of decarboxylative chlorination, bromination, and iodination. These studies provide a synthetically useful starting point for further development of biocatalytic decarboxylative halogenation reactions and extend the synthetic utility of VHPOs in chemical synthesis.

Acknowledgements:

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Conflicts of interest:

There are no conflicts to declare.

Notes and references:

1 (a) F.A. Carey, R.J. Sundberg, Advanced Organic Chemistry, Part B: Reaction and Synthesis, 5th Ed., Springer: New York, NY, USA, 2007, 217-223.; (b) K.C. Nicolaou, D.J. Edmonds, P.G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134.; (c) N. Kambe, T. Iwasaki, J. Terao, *Chem. Soc. Rev.*, 2011, **40**, 4937.

2 B. Gál, C. Bucher, N.Z. Burns, *Mar. Drugs*, 2016, **14**, 206.

3 A. Varenikov, E. Shapiro, M. Gandelman, *Chem. Rev.*, 2021, **121**, 412.

4 T.Q. Chen, P.S. Pedersen, N.W. Dow, R. Fayad, C.E. Hauke, M.C. Rosko, E.O. Danilov, D.C. Blakemore, A.-M. Dechert-Schmitt, T. Knauber, F.N. Castellano, D.W.C. MacMillan, *J. Am. Chem. Soc.*, 2022, **144**, 8296.

5 (a) H. Li, S.H.H. Younes, S. Chen, P. Duan, C. Cui, R. Wever, W. Zhang, F. Hollmann, *ACS Catal.*, 2022, **12**, 4554.; (b) C. Zippilli, M.J. Bartolome, T. Hilberath, L. Botta, F. Hollmann, *ChemBioChem*, 2022, **23**, No. e202200367.

6 C.E. Wells, L.P.T. Ramos, L.J. Harstad, L.Z. Hessefort, H.J. Lee, M. Sharma, K.F. Biegasiewicz, *ACS Catal.*, 2023, **13**, 4622.

7 J.W.P.M. van Schijndel, E.G.M. Vollenbroek, R. Wever, *Biochim. Biophys. Acta, Protein Struct. Mol. Enzymol.*, 1993, **1161**, 249.

8 H. Yu, J.W. Whittaker, *Biochem. Biophys. Res. Commun.*, 1989, **160**, 87.

9 N. Itoh, Y. Izumi, H. Yamada, *J. Biol. Chem.*, 1986, **261**, 5194.

10 A. Frank, C.J. Seel, M. Groll, T. Gulder, *ChemBioChem*, 2016, **17**, 2028.

11 The mechanistic features of this background reaction are currently under investigation in our laboratory.