Decarboxylative Bromooxidation of Indoles by a Vanadium Haloperoxidase

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Supporting Information Placeholder

ABSTRACT: Halooxindoles are versatile building blocks for the construction of complex oxindole-containing targets of biological importance. Despite their synthetic value, catalytic methods to synthesize 3-halooxindoles from readily available starting materials has remained undisclosed. We recently discovered that the chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) is a viable catalyst for the decarboxylative bromooxidation of 3-carboxyindoles to furnish 3-bromooxindoles with excellent regio- and chemoselectivity. In addition to the development of the synthetic method, this study provides evidence of a bromide recycling mechanism for the indole oxidation event. A discussion of the reaction development, substrate scope, mechanistic insights, and reaction applicability will be discussed herein.

KEYWORDS: *biocatalysis, bromooxidation, oxindole, decarboxylation, vanadium haloperoxidase*

The oxindole core has emerged as a privileged structural motif within numerous biologically active molecules.[1] A particular subclass that has seen increased attention in the last decade has been 3-halooxindoles. While they are present in a select number of natural products and medicinally relevant molecules, including the antifungal cynthichlorine[2] and the vasodilator MaxiPost (BMS-204352),[3] respectively, most of their value can be attributed to their synthetic versatility as ambiphilic building blocks for the rapid construction of more complex oxindole-containing structures. As a result, their synthetic utility has been demonstrated in a wide range of reaction types including direct nucleophilic substitution,[4] [2+1]-cycloaddition[5] and [4+1]-cycloaddition reactions,[6] imine additions,[7] and dehydrogenative coupling reactions (Figure 1, a).[8]

Despite the increasing importance of 3-halooxindoles, their preparation often relies on traditional direct halogenation reactions of the oxindole core with a host of electrophilic halogenating agents.[6d,7b,9,10] More recent methods for accessing 3-halooxindoles have featured controlled mono- and dichlorooxidation of indoles with hypervalent iodine sources,[11] acidolysis of isatin-derived 3-phosphate-substituted oxindole derivatives,[12] and the use of electrophilic halogenating agents with diazoacetamides.[13] While these methods have successfully generated 3-halooxindoles, many suffer from undesirable product formation, a limited substrate scope, and a reliance on air- and moisture-sensitive reagents. One particularly interesting approach to 3-halooxindole synthesis was reported by Prathima and co-workers, whereby deformylative halooxidation of indoles was demonstrated using a combination of sodium chloride (NaCl) or sodium bromide (NaBr) and the oxidizing agent Oxone® in an acetonitrile (MeCN) and water (H_2O) mixture at 50 °C, providing 3-halooxindoles in good yield (Figure 1, b).[14] Despite comparatively mild reaction conditions and the use of environmentally friendly reagents, a necessity for stoichiometric generation of the reactive halogenating agent remains, leaving a general catalytic platform for 3-halooxindole synthesis desired.

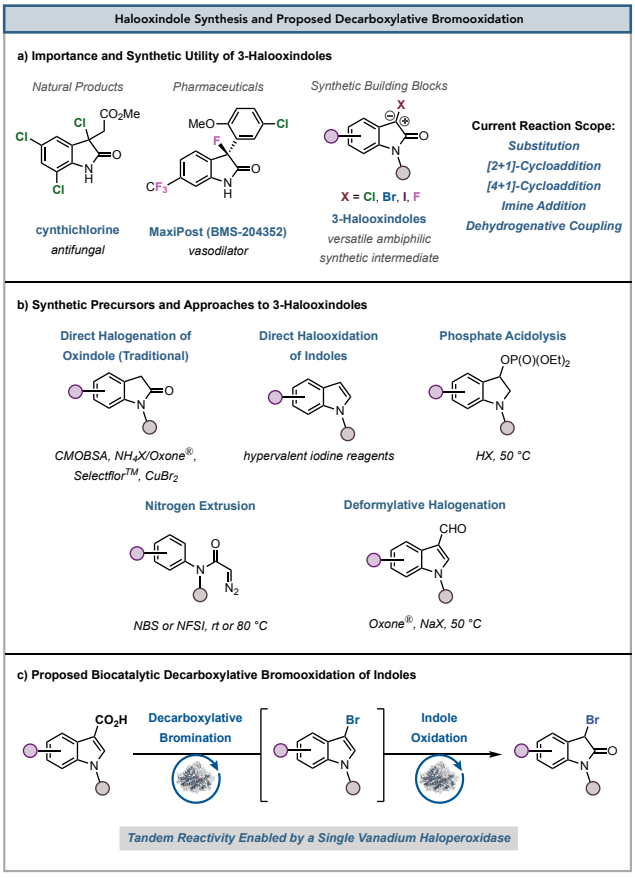
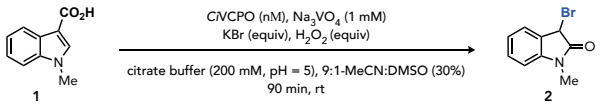


Figure 1. Bromooxindole Synthesis and Proposed Decarboxylative Halooxidation

We envisioned the development of a biocatalytic decarboxylative bromooxidation reaction to prepare 3-bromooxindoles, whereby a single enzyme is responsible for a tandem decarboxylative halogenation and subsequent indole oxidation step (Figure 1, c). The heme-dependent chloroperoxidase from *Caldariomyces fumago* (*Cf*CPO) was initially considered for the proposed reaction, as it is known to perform both decarboxylative halogenation[15] and direct indole oxidation.[16] However, documented difficulties in recombinant expression of *Cf*CPO and its sensitivity to excess quantities of hydrogen peroxide (H_2O_2) loadings discouraged its use.[17] Alternatively, we turned to the vanadium chloroperoxidase from *Curvularia inaequalis* (*Ci*VCPO) due to its emergence as a robust biocatalyst for a number of synthetic transformations[18] and demonstrated superior versatility in toleration of high concentrations of H_2O_2 and organic solvents.[19] While this enzyme was recently explored as an effective catalyst for the chemoenzymatic decarboxylative halogenation of cinnamic acids,[18h,i] its ability to perform this reaction on aromatic substrates has yet to be reported. In addition, there is only a select example of a vanadium haloperoxidase performing a direct oxidation of 3-alkylindole substrates by the vanadium haloperoxidase (VHPO) from *Ascophyllum nodosum*.[20] The successful demonstration of this tandem process would not only provide a robust catalytic platform for 3-halooxindole synthesis, but also serve as a proof-of-concept for application of the VHPO class of enzymes as a multipurpose catalyst system for one-pot chemoenzymatic synthesis. We have recently discovered that *Ci*VCPO is a robust catalyst for the decarboxylative bromooxidation of 3-carboxyindoles. The results of this study will be discussed herein.

Reaction development studies began with the conversion of 1-methyl-1*H*-indole-3-carboxylic acid (**1**) to 3-bromo-1-methylindolin-2-one (**2**). Subjection of **1** to *Ci*VCPO (50 nM), KBr (1.0 equiv), and H_2O_2 (2.0 equiv) in 200 mM citrate buffer (pH = 5) and 30% of a 9:1-MeCN:DMSO cosolvent for 90 minutes provided our desired 3-bromooxindole (**2**) in 87% yield (Table 1, Entry 1). Control reactions were run excluding the addition of enzyme, orthovanadate, KBr, and H_2O_2 in turn, resulting in complete loss of reactivity in all cases (Table 1, Entries 2-5) and demonstrating the necessity of all reaction components. A noticeable improvement in yield to 93% was observed by increasing the KBr loading to 2.0 equivalents (Table 1, Entry 6), but increasing this loading beyond this point led to the production of diminished yields and a complex mixture of products (Figure S2, a). Finally, increasing the H_2O_2 loading up to as much as 8.0 equivalents did not dramatically affect the yield, but higher loadings caused the reaction to become increasingly sluggish (Figure S3, a)

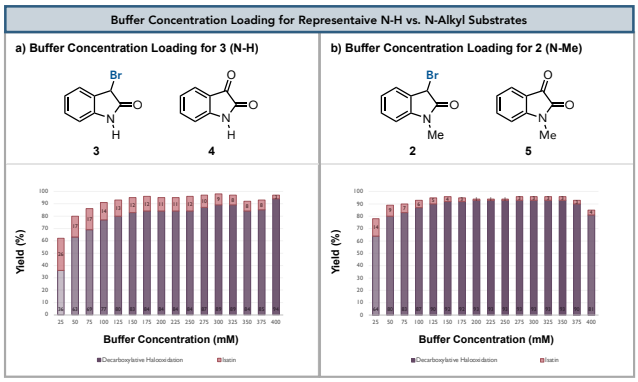
Table 1. Optimization of Decarboxylative Bromooxidation



Entry	Enzyme Loading	KBr (equiv)	H_2O_2 (equiv)	yield (%)
1	50 nM	1.0	2.0	87
2	no enzyme (w/ Na_3VO_4)	1.0	2.0	0
3	50 nM (no Na_3VO_4)	1.0	2.0	0
4	50 nM	no KBr	2.0	0
5	50 nM	1.0	no H_2O_2	0
6	50 nM	2.0	2.0	93

Standard Reaction Conditions: **1** (4.0 µmol, 0.7 mg), *Ci*VCPO (50 nM), Na_3VO_4 (1 mM final concentration), KBr (1.0 equiv), H_2O_2 (2.0 equiv), citrate buffer (200 mM final concentration, pH = 5), 9:1-MeCN:DMSO (300 µL), 1 mL total reaction volume. See the Supporting Information for a detailed experimental procedure and additional optimization studies.

Our initial reaction optimization studies revealed that efficient and selective decarboxylative bromooxidation proceeds using a 30% loading of a 9:1-MeCN:DMSO cosolvent mixture (Figure S4, a). Polar aprotic solvents are also tolerated in place of this mixture (83-90% for DMF, DMSO, dioxane), but polar protic solvents (MeOH, EtOH, *i*PrOH) lead to dramatic decreases in yield (25-70%). We currently attribute this to a combination of substrate solubility and effective buffering capacities of the citrate buffer across the range of buffer and cosolvent mixtures interrogated. This observation was most notable when we examined the generality of our protocol on substrates that were void of an alkyl substituent on the nitrogen atom of the starting material and were noticeably less soluble in our developed 9:1-MeCN:DMSO cosolvent mixture. Starting from an analogous model substrate to **1** without the alkyl substituent on nitrogen, we found that turning to DMF as cosolvent resulted in the highest yield of the bromooxidation product, 3-bromoindolin-2-one (**3**), but also suffered from the production of the corresponding isatin product (**4**) (Figure S4, b). While similar performance trends were observed with various KBr (Figure S2, a) and H_2O_2 (Figure S3, b) loadings, the most critical optimization parameter after cosolvent identity was the citrate buffer concentration used in the reaction. By increasing the concentration to 400 mM, our desired product (**3**) was generated in 94% yield with a decrease in isatin (**4**) formation to as low as 3% (Figure 2, a). Any attempts to increase the buffer loading further led to an apparent salting out of the starting material. With this information in hand, we performed the same analysis for our original model reaction (conversion of **1** to **2**). A different optimal buffer concentration range (200 – 250 mM) was observed for this substrate (Figure 2, b), further supporting the importance of buffer concentration as a critical reaction parameter for optimization of the decarboxylative bromooxidation protocol.



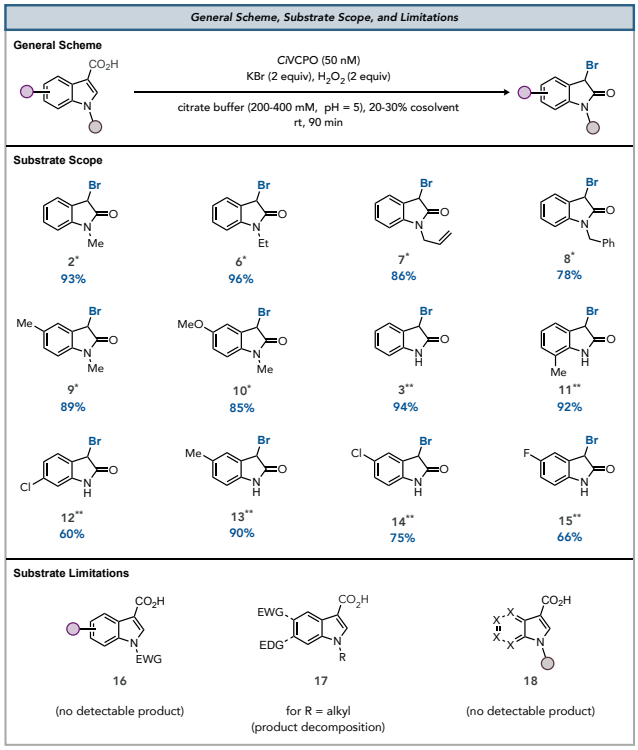
Reaction Conditions: **substrate** (4.0 µmol, 0.7 mg), *Ci*VCPO (50 nM), Na_3VO_4 (1 mM final concentration), KBr (2.0 equiv), H_2O_2 (2.0 equiv), citrate buffer (200 mM final concentration, pH = 5), 1 mL total reaction volume, cosolvent = 9:1-MeCN:DMSO (30%) for (a) and DMF (20%) for (b).

Figure 2. Buffer Concentration Loading for Representative N-H vs. N-Alkyl Substrates

With optimized conditions for both N-alkyl and N-H substrate types in hand, we turned our attention to interrogating the substrate scope for our biocatalytic decarboxylative bromooxidation reaction on a series of commercially available substrates on preparative scale (0.3 mmol). For N-alkyl substrates, we found that the reaction was tolerant of ethyl-, allyl-, and benzyl-substitution on the nitrogen atom (Table 2, **6-8**). Two additional substrates in this class were synthesized to show that substitution on both the nitrogen atom and the aromatic ring is tolerated

(Table 2, **9-10**). This series also demonstrates the excellent regioselectivity and chemoselectivity of the reaction, providing the target 3-bromooxindoles selectively over products with halogenation at alternative or additional sites that would be expected from other bromination methods. Furthermore, this substrate series reveals intriguing biocatalyst selectivity in that *Ci*VCPO has traditionally been used for the direct functionalization of electron-rich arenes and alkenes,[18a,b] but was not observed during our reaction development. For N-H substrates, we were pleased to find that substitution on the 5-, 6-, and 7-position (Table 2, **11-15**) was tolerated in moderate to high yield (60-92%). Throughout our studies, we also discovered some limitations affiliated with reactivity, particularly when using substrates bearing an electron-withdrawing substituent on the nitrogen atom (Table 2, **16**, EWG = Ac, Ts). This resulted in limited to no reactivity, likely because of a decrease in nucleophilicity associated with the carboxyindole starting material. For N-alkyl substrates, the corresponding products with an electron-withdrawing group (EWG) in the 5-position or an electron-donating group (EDG) in the 6-position (Table 2, **17**) suffered from rapid decomposition upon isolation despite showing the desired reactivity in the established protocol. Finally, substrates that contained an additional heteroatom in the indole framework (Table 2, **18**) provided no detectable decarboxylative bromooxidation product.

Table 2. Substrate Scope and Limitations for Bromooxidation



Standard Reaction Conditions: **substrate** (0.3 mmol), *Ci*VCPO (50 nM), Na_3VO_4 (1 mM final concentration), KBr (2.0 equiv), H_2O_2 (2.0 equiv). See the Supporting Information for a detailed experimental procedure and additional optimization studies, *citrate buffer (200 mM final concentration, pH = 5), 9:1-MeCN:DMSO cosolvent (30%), **citrate buffer (400 mM final concentration, pH = 5), DMF cosolvent (20%)

Upon completion of reaction development, we became interested in the mechanistic features of the developed decarboxylative bromooxidation protocol. Throughout our study, we proposed that this tandem reaction process proceeded through intermediacy of a decarboxylative halogenation intermediate. While variable small quantities of these intermediates were detected during the study, we wanted to confirm that this was a plausible key intermediate toward our desired 3-bromooxidation products. To test this, we independently synthesized 3-bromo-1-methyl-1*H*-indole (**19**) and subjected it to our standard decarboxylative bromooxidation protocol (Figure 3, a). This reaction provided desired bromooxindole **2** in 90% yield and the corresponding isatin byproduct (**5**) in 5% yield, suggesting that the decarboxylative bromooxidation likely proceeds through a decarboxylative halogenation intermediate. We then ran a series of control reactions to gain insight into the indole oxidation step (Figure 3, b). Like our previous control reactions, we observed no reactivity upon exclusion of enzyme, vanadate, KBr, and H_2O_2. Interestingly, we discovered that only a catalytic quantity (0.1 equiv) of halide was required for the indole oxidation step, providing our desired bromooxidation product (**2**) in 92% yield with 2% isatin (**5**) formation, suggesting that there is an enzymatic recycling of halide during the indole oxidation event. Finally, to gain insight into byproduct formation, we resubjected the desired bromooxidation product (**3**) to our decarboxylative bromooxidation conditions and observed the formation of the corresponding isatin (**5**) in 6% yield, suggesting that this is likely arising from an undesired hydrolysis/oxidation sequence of **2** after product formation (Figure 3, c).

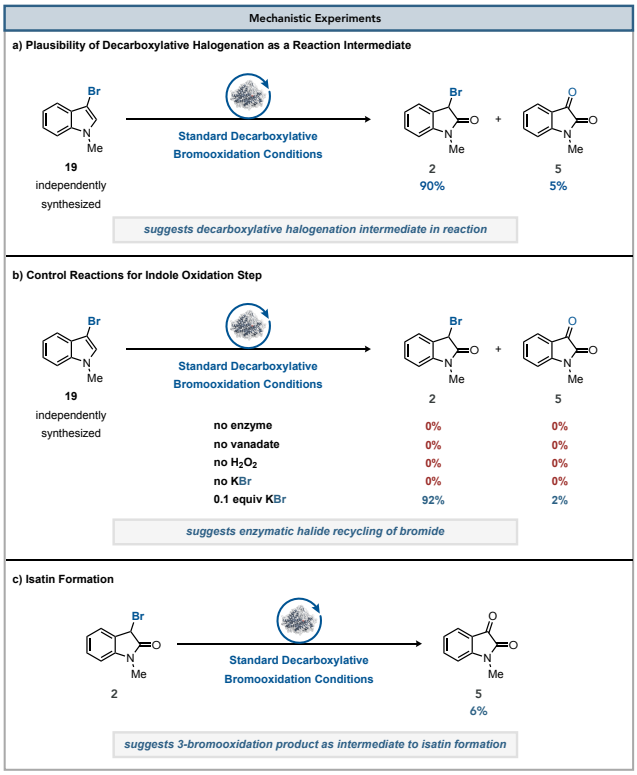


Figure 3. Mechanistic Experiments for Decarboxylative Bromooxidation

Based on the results gathered, we have established a proposed mechanism for our biocatalytic decarboxylative halogenation reaction. In the context of carboxyindole **1**, enzymatic production of hypobromous acid enables a bromination event of **1**, generating the corresponding brominated iminium ion **I**. This intermediate then proceeds through a decarboxylation event, providing bromoindole **19** (Figure 4, a). After an equivalent of bromide is consumed, an additional catalytic quantity

of bromide drives the oxidation step. This begins with VHPO-catalyzed formation of hypobromous acid and subsequent bromination of indole **19** to give dibrominated iminium intermediate **II**. Subsequent trapping of **II** with H_2O would provide the corresponding aminol (**III**), which is primed for an ensuing semi-pinacol rearrangement to give **2** in analogy to Oxone®/KBr indole oxidizing systems.[21] This intermediate exists in solution with its tautomeric equilibrium partner **IV**. Over-extended reaction times or improper buffering conditions lead to a hydrolysis/oxidation sequence of product **2** or **IV**, giving isatin (**5**) as an undesired byproduct. The eliminated bromide from the aminol oxidation event can be recycled by the VHPO for subsequent oxidation events (Figure 4, b). It should also be noted that a singlet oxygen oxidation pathway is also plausible for one or more of the proposed oxidation steps using *Ci*VCPO as catalyst with catalytic halide.[22]

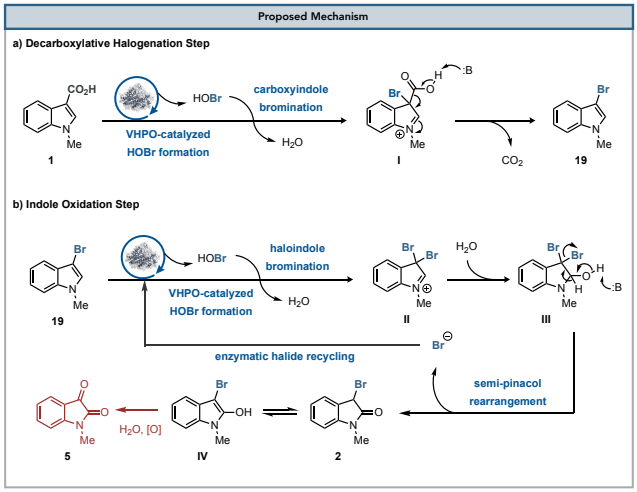


Figure 4. Proposed Mechanism for Biocatalytic Decarboxylative Bromooxidation

To demonstrate the synthetic applicability of our developed decarboxylative bromooxidation protocol, we ran the reaction on 3.0 mmol and observed consistent performance without the need for further development, proceeding in a comparable yield of 93% for the conversion of **1** to **2** (Figure 5, a). We also found that this protocol could be adapted to a biocatalytic deformylative bromooxidation with only slight modification of the reaction contents (Figure 5, b). By changing the cosolvent to exclusively MeCN, the catalyst loading to 100 nM, and the KBr and H_2O_2 loading to 3.3 and 4.0, respectively, 1-methyl-1*H*-indole-3-carbaldehyde (**20**) could be converted to 3-bromooxindole **2** in 96% yield. Finally, to highlight the utility of our 3-bromooxindole products, bromooxindole **2** was used to synthesize the corresponding new reactive intermediate precursor pyridinium bromide salt (**21**) in 75% yield upon treatment with pyridine in EtOAc at elevated temperature.[6d] Bromooxindole **2** was then also used to perform a complexity building reaction in the form of a DBU-catalyzed cyclopropanation with acylcoumarin **22** to generate the corresponding cyclopropane adduct (**23**) in 60% yield (Figure 5, c).[5f]

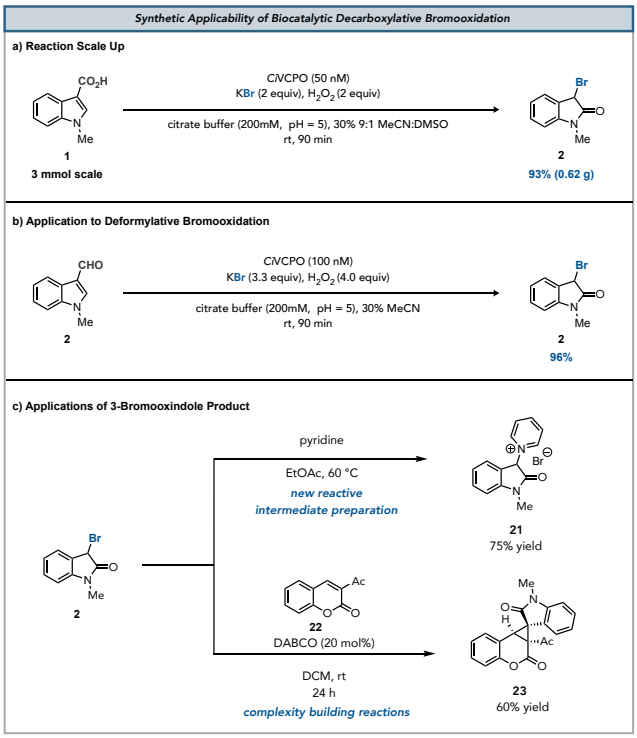


Figure 5. Synthetic Applicability of Biocatalytic Decarboxylative Bromooxidation

In conclusion, we have developed the first biocatalytic decarboxylative bromooxidation of indoles. This methodology has been demonstrated as an effective reaction for the synthesis of 3-bromooxindoles across a range of substrates and the key parameters for reaction development have been identified. We have also discovered a new enzymatic halide recycling process for indole oxidation. Finally, our studies have shown that the reaction is readily scalable, translates to a deformylative bromooxidation, and produces a product that is synthetically useful in new reactive intermediate synthesis and complexity building reactions. These studies not only expand the synthetic utility of VHPOs as catalysts for organic synthesis, but also provide key insights into a new mechanism that can lead to novel reaction development.

ASSOCIATED CONTENT:

Supporting Information is available free of charge at http://pubs.acs.org and contains detailed experimental, supplemental figures, and characterization data.

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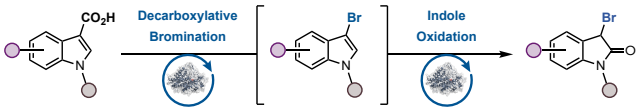
TOC Graphic:



Tandem Reactivity Enabled by a Single Vanadium Haloperoxidase