Oxidative Chlorination

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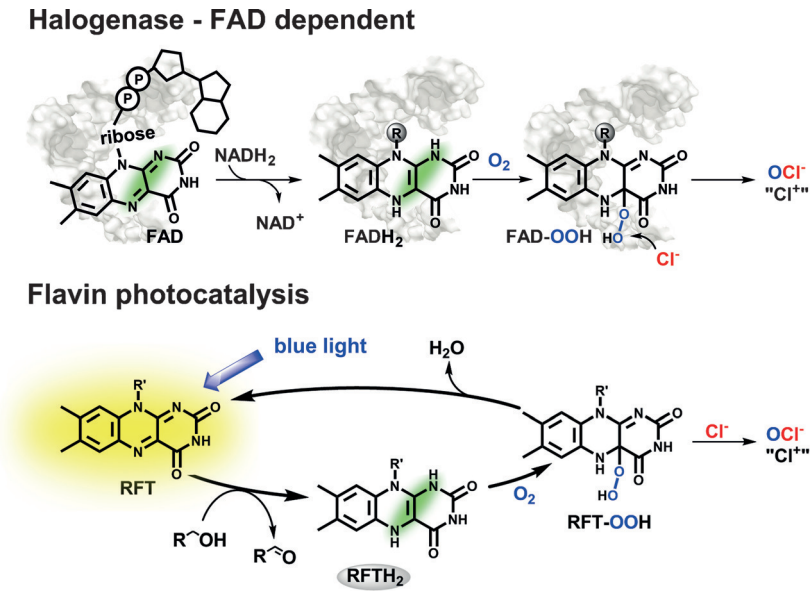
Halogenase-Inspired Oxidative Chlorination Using Flavin Photocatalysis

Thea Hering, Bernd Mühldorf, Robert Wolf, and Burkhard König**

Abstract: *Chlorine gas or electropositive chlorine reagents are used to prepare chlorinated aromatic compounds, which are found in pharmaceuticals, agrochemicals, and polymers, and serve as synthetic precursors for metal-catalyzed cross-couplings. Nature chlorinates with chloride anions, FAD-dependent halogenases, and O_2 as the oxidant. A photocatalytic oxidative chlorination is described based on the organic dye riboflavin tetraacetate mimicking the enzymatic process. The chemical process allows within the suitable arene redox potential window a broader substrate scope compared to the specific activation in the enzymatic binding pocket.*

Chlorinated aromatic compounds are ubiquitous in organic chemistry. They serve as key precursors for metal-catalyzed cross-couplings and are widely employed in natural products, pharmaceuticals, and materials science to tune biological or electronic properties.[1] While traditional chemistry mostly relies on the use of hazardous and toxic chlorine gas or synthetic equivalents such as NCS and *t*BuOCl as the source of electrophilic chlorine, nature has developed a more elegant strategy based on the enzymatically catalyzed oxidation of abundant and nontoxic chloride ions in an oxidative chlorination.[2] Halogenases efficiently yield aryl halides from halide ions and aromatic compounds using either O_2 or hydrogen peroxide (haloperoxidases) as the oxidant.[3] With respect to environmental factors, these are the ideal oxidants as only water is produced as a by-product. For this reason a variety of chemical oxidative halogenations have been developed.[2] However, while great progress has been made in the area of oxidative bromination, oxidative chlorination remains challenging. The few examples known suffer from drastic conditions and low selectivity[2,4] or rely on stronger or metal-based stoichiometric oxidants.[5] Over the last years, halogenases have been successfully isolated and used for the halogenation (mostly bromination) of aromatic compounds.[6] These reactions show high selectivity and have also been scaled up to gram amounts,[6b] but as the enzymes are naturally substrate specific the scope of accessible products is limited, and the isolation and handling of the enzymes is difficult.



Scheme 1. Analogy of the mechanistic model of chloride oxidation by FAD-dependent halogenases (top) and the proposed photocatalytic halogenase mimetic system (bottom); $R' = CH_2(CHOAc)_3CH_2OAc$.

We aimed to develop a biomimetic system inspired by flavin adenine dinucleotide (FAD)-dependent halogenases, which is one of the main families of this enzyme group.[3a] The FAD dependent system combines several advantages: O_2 is used as oxidant avoiding the separate addition of H_2O_2 as required for heme and vanadate dependent haloperoxidases. The cofactor FAD is a purely organic, metal-free catalyst, and simple flavin derivatives are known to act as oxidative photocatalysts.[7] The enzymatic mechanism (Scheme 1) involves the reduction of FAD by $NADH_2$ to yield a reduced $FADH_2$, which reacts with oxygen to form a peroxo species FAD-OOH that is subsequently attacked by chloride ions to form the "Cl^+" equivalent HOCl.[8] Our system replaces FAD

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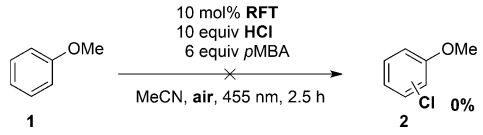
by the cheap dye riboflavin tetraacetate (RFT), which is known to form reduced $RFTH_2$ upon excitation with visible light in the presence of benzyl alcohols (Scheme 1).[7] This allows us to replace the biomolecules FAD and $NADH_2$ and to perform the reactions in organic solvents using a stable and inexpensive catalyst.

A key challenge in developing a photocatalytic halogenase mimetic system is the efficient generation of electrophilic hypochlorite. In analogy to the enzymatic system, $RFTH_2$ forms a short-lived flavin-peroxo species RFT-OOH, which should oxidize chloride ions to OCl^- (Scheme 1). However, in the enzyme the reaction of the flavin peroxide to form hypochlorite and the subsequent chlorination of the substrate are catalyzed by the complex enzyme environment. For enzymes such as RebH the mediation by a lysine residue in the active center is crucial for the reactivity and selectivity of the reaction. Moreover, X-ray studies of halogenases have shown that the substrate and the flavin peroxide (FAD-OOH) are brought in very close proximity (ca. 10 Å) before a reaction takes place.[3a,9] This is also the reason why the simple chemical system, using anisole (**1**) as the substrate, 10 mol% RFT as the photocatalyst under aerobic conditions and irradiation with blue light ($\lambda_{max} = 455$ nm) in the presence of HCl as the chloride source and *p*-methoxy benzyl alcohol (*p*MBA) as a replacement for $NADH_2$ in 2 mL acetonitrile, did not yield any chlorination product of anisole (Scheme 2).



Scheme 2. Test reaction for the chlorination of anisole (**1**) with the photocatalytic system using 20 µmol of **1** in 2 mL acetonitrile.

To chemically mimic the enzymatic system, a mediator is needed, which is sufficiently long lived in order to enable the formation of perchloric acid. During the course of our investigations we discovered that peracetic acid can oxidize chloride ions and is able to perform oxidative chlorination of aromatic compounds (Supporting Information, Table S2).[10] Peracetic acid is highly explosive when isolated, but it can be formed in equilibrium with acetic acid and H_2O_2.[11] As it is known that RFT-OOH formed in the photocatalytic oxidation quickly releases one equivalent of H_2O_2,[7a] we added 10 equiv of acetic acid to the system described above and, to our delight, observed the chlorination of anisole (**1**).

Control reactions showed that all reaction components are essential to observe the chlorination reaction (Supporting Information, Table S1). Based on this we propose an in situ formation of peracetic acid as depicted in Figure 1, which acts as the described mediator and enables the chlorination via the following reaction cycle. In the first step, the photocatalyst RFT is excited by visible light irradiation ($\lambda_{max} = 455$ nm) to RFT* and reduced to $RFTH_2$ by oxidation of the benzylic alcohol (*p*MBA). $RFTH_2$ is re-oxidized by air forming H_2O_2, which does not directly oxidize chloride, but forms peracetic acid (HOOAc) in an equilibrium with acetic acid (HOAc). The hereby in situ generated HOOAc subsequently reacts with chloride to form the electrophilic chlorine species HOCl, which attacks anisole (**1**) in an electrophilic aromatic substitution reaction. However, we cannot exclude other electrophilic chlorine species in equilibrium with HOCl, for example, Cl_2O, ClOAc, Cl_2, and H_2OCl^+, being involved.[4b,12]

With this mechanistic model in hand, we optimized the reaction conditions for the highest formation of peracetic acid (see the Supporting Information). The equilibrium of H_2O_2 and acetic acid is known to be shifted towards the side of peracetic acid by strong acids.[11a] Therefore, hydrochloric acid proved to be the ideal chloride source as it dissolved well in acetonitrile and is a strong acid at the same time. The reaction with triethylammonium chloride (TEACl) and 20 mol% H_2SO_4 also led to product formation, but with a slightly lower yield. No chlorination was observed with any of the tested chloride salts (TEACl, NaCl, KCl, and NH_4Cl) in the absence of added acid. Furthermore, elevated temperatures are known to be beneficial for peracetic acid formation.[11b] An increase of the reaction temperature from 25 °C to 45 °C improved the yield of chloroanisole (**2**) from 28% to 66% (p:o 5:1); a further increase to 60 °C led to decomposition of the photocatalyst (Supporting Information, Table S4). We also varied the peracid and replaced acetic acid by the stronger acids formic acid and triflic acid (Supporting Information, Table S3). Formic acid showed significantly lower yields than acetic acid, while triflic acid with 5 equiv TEACl and 5 equiv HCl gave a comparable yield of the chlorinated anisole. Alternative reagents for the generation of peracetic acid such as acetic anhydride or acetyl chloride enabled product formation, but were less efficient than acetic acid.

The optimized conditions depicted in Scheme 3 were used to investigate the substrate scope. While an enzyme usually has a highly specific binding pocket and thus a narrow substrate scope, but high selectivity, our system does not bind the substrate and should allow a broader substrate scope. The results are summarized in Table 1. The system works excellently for arenes with nitrogen + M substituents such as *N*,*N*-dimethylaniline (entry 1) or amides (entries 2,3). Substrates with an alkoxy group, such as anisole (entry 4) or diphenylether (entry 5), can also be successfully chlorinated in good to moderate yields. When the arene is too electron-rich, as for

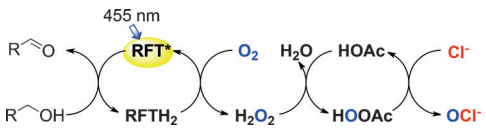
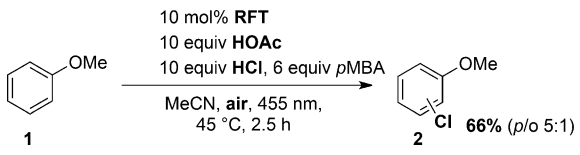
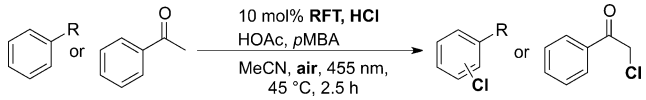


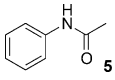
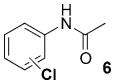
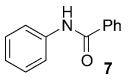
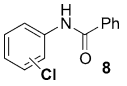
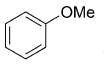
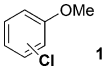
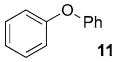
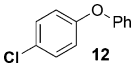
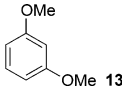
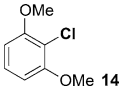
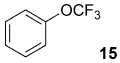
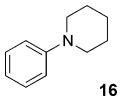
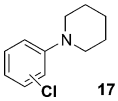
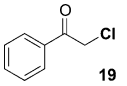
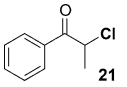
Figure 1. Proposed mechanism of the peracetic acid mediated oxidation of chloride by flavin photocatalysis.



Scheme 3. Oxidative chlorination of anisole (**1**) with the photocatalytic halogenase mimetic system.

Table 1: Scope of the flavin-catalyzed oxidative chlorination and results obtained by direct addition of H_2O_2.[a]



Entry	Substrate	Product	Conv [%][b]	Yield [%][b,c]	H_2O_2[d]
1	 3	 4	100	**96** (o:di 2:1)	14 (o:di 1:0)[g]
2[e]	 5	 6	100	**97** (p:o 3:1)	37 (p:o 1:0)
3[e]	 7	 8	96	**98** (p:o 1:1)	24
4	 9	 10	100	**66** (p:o 1:0)	17
5	 11	 12	79	**80**	55
6	 13	 14	100	**40**	23
7	 15	–	0	–	–
8	 16	 17	70	**64** (p:o 1:3)	68 (p:o 1:5)
9[f]	 18	 19	76	**63**	11
10[f]	 20	 21	49	**64**	84

[a] Reactions were performed with 0.02 mmol of the substrate, 10 equiv HCl, 10 equiv HOAc, 6 equiv *p*MBA and 10 mol% RFT in 2.0 mL MeCN. The reaction mixtures were irradiated for 2.5 h at 45 °C. [b] Determined by GC-FID using an internal standard. [c] Based on conversion. [d] 6 equiv H_2O_2, 10 equiv HOAc, and 10 equiv HCl in 2 mL MeCN. [e] With KCl addition. [f] With TFA. [g] di = dichlorination additionally at the *para* position.

example in dimethoxybenzene carrying two + M-substituents, the yield decreases due to the unselective direct oxidation of the substrate by the photocatalyst (entry 6). The acidic conditions lead to a protonation of RFT observable by UV/VIS measurements (Supporting Information, Tables S4, S5). In its protonated form, RFT is known to have a high oxidative power.[13] Substrates, which are too electron poor, for example, trifluoromethoxybenzene (entry 7), are not attacked by hypochlorite and do not give chlorination products neither in the photocatalytic system nor when peracetic acid is added directly (Supporting Information, Table S2). Acetophenones (entries 9, 10) are mono-chlorinated in the α-position. The reaction proceeds via the enol form and therefore works better when the stronger triflic acid is used instead of acetic acid.[14] It is worth noting that aromatic amines (entries 1, 8) show *ortho* selectivity for the chlorination. This may be explained by the intermediate formation of an *N*-chloramine. This selectivity is not observed with amides (entries 2, 3).

For comparison, Table 1 also shows the yields of chlorination obtained by adding 6 equiv of H_2O_2 directly to the reaction mixture instead of being generated by the photocatalytic process (reaction contained no RFT and *p*MBA). Even though the direct addition of H_2O_2 always gave full conversion of the substrate, the yields were considerably lower for most substrates than in the photocatalytic system. The slow generation of peroxide by the flavin-catalyzed process is beneficial for the reaction as it circumvents the problem of unselective side reactions and over-chlorination often observed for H_2O_2-based systems. The same observation was made for haloperoxidase-catalyzed reactions.[6e]

In conclusion, visible-light flavin photocatalysis allows the oxidative chlorination of arenes inspired by FAD-dependent halogenases. The biomolecules FAD and $NADH_2$ were replaced by the cheap organic dye riboflavin tetraacetate and methoxy benzyl alcohol as the reducing agent. As a result, the reaction can be performed in organic media. Acetic acid was added to the system forming peracetic acid in situ, which acts as a mediator to activate the peroxide for chloride oxidation. Compared to the specific binding pocket of an enzyme, the activation by peracetic acid is a more general strategy and thus allows a broader substrate scope. The developed system allows the chlorination of electron rich arenes, for example, anisole, methylanilines, diphenyl ether, and amides, as well as the α-chlorination of acetophenones.

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[14] Incomplete conversion is observed as the required keto – enol equilibrium slows down the reaction. If the reaction of the substrate and the peracetic acid is not fast enough, a Bayer – Villiger type background reaction of the benzaldehyde consumes the peracid; see: M. Matsumoto, K. Kobayashi, Y. Hotta, *J. Org. Chem.* **1984**, *49*, 4740 – 4741.

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