Halogenase-Inspired Oxidative Chlorination Using Flavin Photocatalysis

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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 O₂ 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 tBuOCl as the source of electrophilic chlorine, nature has developed a more elegant strategy based on the enzymatically catalyzed oxidation of abundant and non-toxic chloride ions in an oxidative chlorination.[2] Halogenases efficiently yield aryl halides from halide ions and aromatic compounds using either O₂ 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.

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: O₂ is used as oxidant avoiding the separate addition of H₂O₂ 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 to yield a reduced FADH₂, which reacts with oxygen to form a peroxy species FAD-OOH that is subsequently attacked by chloride ions to form the “Cl⁻” equivalent HOCl.[8] Our system replaces FAD...
by the cheap dye riboflavin tetraacetate (RFT), which is known to form reduced RFT$^\text{II}$ upon excitation with visible light in the presence of benzyl alcohols (Scheme 1).[7] This allows us to replace the biomolecules FAD and NADH$^\text{II}$ 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 hypohalite. In analogy to the enzymatic system, RFT$^\text{II}$ forms a short-lived flavin-peroxo species RFT-OOH, which should oxidize chloride ions to $\text{OCl}^-$ (Scheme 1). However, in the enzyme the reaction of the flavin peroxide to form hypohalite and the subsequent chlorination of the substrate are catalyzed by the complex enzyme environment. For enzymes such as ReB$^\text{II}$ 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 ($\lambda_{\text{max}} = 455$ nm) in the presence of HCl as the chloride source and $p$-methoxy benzyl alcohol (pMBA) as a replacement for NADH$^\text{II}$ in 2 mL acetonitrile, did not yield any chlorination product of anisole (Scheme 2).

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 $\text{H}_2\text{O}_2$. As it is known that RFT-OOH formed in the photocatalytic oxidation quickly releases one equivalent of $\text{H}_2\text{O}_2$, 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 ($\lambda_{\text{max}} = 455$ nm) to RFT$^*$ and reduced to RFT$^\text{II}$ by oxidation of the benzyl alcohol (pMBA). RFT$^\text{II}$ is re-oxidized by air forming $\text{H}_2\text{O}_2$, 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 chloride 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, $\text{Cl}_2$, $\text{ClOAc}$, $\text{Cl}_2$ and $\text{H}_2\text{OCl}^+$, being involved.[10b,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 $\text{H}_2\text{O}_2$ 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% $\text{H}_2\text{SO}_4$ 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$_4$Cl) 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:0 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 $\text{Ms}$ substituents such as $\text{N,N}$-dimethylamine (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
example in dimethoxybenzene carrying two +M-substituents,
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.[23] Substrates, which are too electron poor, for
example, trifuoromethoxybenzene (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-chlori-
nated 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.

Table 1: Scope of the flavin-catalyzed oxidative chlorination and results obtained by direct addition of
H₂O₂.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conv [%][b]</th>
<th>Yield [%][c,d]</th>
<th>H₂O₂ [%][e]</th>
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<tbody>
<tr>
<td>1</td>
<td>[N₂]</td>
<td>[N₄]</td>
<td>100</td>
<td>96 (p:o 2:1)</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>[N₆]</td>
<td>[N₄]</td>
<td>100</td>
<td>97 (p:o 3:1)</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>[N₈]</td>
<td>[N₈]</td>
<td>96</td>
<td>98 (p:o 1:1)</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>[O₉]</td>
<td>[O₉]</td>
<td>100</td>
<td>66 (p:o 1:1)</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>[O₉]</td>
<td>[O₉]</td>
<td>79</td>
<td>80 (p:o 1:0)</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>[O₁₂]</td>
<td>[O₁₂]</td>
<td>100</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>[O₁₅]</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>–</td>
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<tr>
<td>8</td>
<td>[O₁₆]</td>
<td>[O₁₇]</td>
<td>70</td>
<td>64 (p:o 1:3)</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>[O₂₈]</td>
<td>[O₂₈]</td>
<td>76</td>
<td>63 (p:o 1:5)</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>[O₂₁]</td>
<td>[O₂₁]</td>
<td>49</td>
<td>64</td>
<td>84</td>
</tr>
</tbody>
</table>

[a] Reactions were performed with 0.02 mmol of the substrate, 10 equiv HCl, 10 equiv HOAc, 6 equiv
pMBA 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 H₂O₂,
10 equiv HOAc, and 10 equiv HCl in 2 mL MeCN. [e] With KCl addition. [f] With TFA. [g] di = dichlori-
nation additionally at the para position.

Table 1 also shows the yields of chlorination obtained by adding 6 equiv of
H₂O₂ directly to the reaction mixture instead of being generated by the
photocatalytic process (reaction contained no RFT and pMBA).
Even though the direct addition of H₂O₂ always gave full conversion of
the substrate, the yields were considerably lower for most substrates
than in the photocatalytic system. The slow generation of peroxydioxide
by the flavin-catalyzed process is ben-

In conclusion, visible-light
flavin photocatalysis allows the oxida-
tive chlorination of arenes inspired by FAD-dependent haloo-
genases. The biomolecules FAD
and NADH were replaced by the
cheap organic dye riboflavin tetraa-
cetate 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 per-
acetic 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 amidas, as well as
the α-chlorination of acetonaphenes.

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chlorination photocatalysis

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[10] a) Y. He, C. R. Goldsmith, Synlett 2010, 1377 – 1380; b) Peracetic acid itself has not been extensively used for oxidative chlorination. However, we noticed that a number of oxidative chlorination reactions with hydrogen peroxide were performed in acetic acid as the solvent. We assume also that in these cases an in situ formation of peracetic acid might be responsible for the reactivity; see: c) references in A. Podgórski, M. Zupan, J. Iskra, Angew. Chem. Int. Ed. 2009, 48, 8424 – 8450; Angew. Chem. 2009, 121, 8576 – 8603; d) N. I. Rudakova, Y. G. Erykalov, Russ. J. Gen. Chem. 2005, 75, 748 – 750; e) G. Jerzy, Z. Slawomił, Synth. Commun. 1997, 27, 3291 – 3299.


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