Supporting Information

Halogenase-Inspired Oxidative Chlorination Using Flavin Photocatalysis

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Supporting Information

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**General Information**

**Chemicals:**

RFT was prepared according to a known literature procedure.\textsuperscript{1} All other chemicals were obtained commercially (Sigma Aldrich, VWR or TCI) or synthesized according to known literature procedures; 4,\textsuperscript{2} 8,\textsuperscript{3} and 17,\textsuperscript{4} Compounds 12 and 21 were synthesized using a scaled up reaction of peracetic acid described in the general procedure for reactions with peracetic acid.

**Photochemical set-up, LEDs:** Photocatalytic reactions were performed with 455 nm LEDs (OSRAM Oslon SSL 80 royal-blue LEDs, $\lambda_{em} = 455$ nm ($\pm$ 15 nm), 3.5 V, 700 mA). Reaction vials (5 mL crimp cap vials, no cap) were illuminated from the bottom with LEDs and cooled or heated from the side using custom made aluminum cooling block connected to a thermostat. A magnetic stirrer is placed below the LED array.

![Figure S1 Photochemical set-up.](image)

**General Procedure for the photocatalytic chlorination**

In a vial 0.02 mmol of the respective substrate, together with 10 mol\% (0.002 mmol) RFT, 0.2 mmol (10 eq.) HCl, 0.2 mmol (10 eq.) HOAc (or TFA) and 0.12 mmol (6 eq.) $p$-methoxy benzylalcohol were dissolved in 2 mL of dry acetonitrile. The reaction mixture was irradiated under stirring for 2.5 h using the set-up depicted in Figure S1. After the irradiation the internal standard (0.01 mmol $n$-pentadecane) was added to the reaction and the reaction was immediately quenched.
with sat. Na$_2$CO$_3$-solution and brine. The mixture was extracted with ethyl acetate and subjected to GC-FID analysis.

**GC-FID measurements**

The GC oven temperature program was adjusted as follows: The initial temperature of 60 °C was kept for 3 minutes, the temperature was increased at a rate of 20 °C/min until the final temperature (290 °C) was reached and kept for 2 minutes; internal standard: $n$-pentadecane.

For substrates with lower boiling points a slightly different method was applied: The initial temperature of 60 °C was kept for 3 minutes, the temperature was increased at a rate of 25 °C/min until the final temperature (160 °C) was reached and kept for 5 minutes; internal standard: $n$-pentadecane.

GC was calibrated using a six-point calibration; the calibration curve for $o$-chloroanisole is shown as an example. Authentic samples of each compound were used for calibration.

![Exemplary calibration curve for $o$-chloroanisole.](image)

**Figure S2** Exemplary calibration curve for $o$-chloroanisole.
Control reactions

Control reactions were performed using equal amounts of the respective compounds as described in the general procedure. Work-up and analysis was done accordingly. No chlorination product was observed, when any of the components was omitted or the reaction was kept in the dark (entry 9). As described in the manuscript an unproductive background reaction occurred with protonated RFT.

Table S1 Control reactions.

| entry | condition          | conversion/% | yield /% |
|-------|--------------------|--------------|----------|
| 1     | RFTA, anisole      | 17           | 0        |
| 2     | RFTA, anisole, HCl | 100          | 0        |
| 3     | RFTA, anisole, HCl, HOAc | 100      | 0        |
| 4     | RFTA, anisole, pMBA| 24           | 0        |
| 5     | RFTA, anisole, pMBA, HOAc | 100      | 0        |
| 6     | RFTA, anisole, pMBA, HCl | 100   | 0        |
| 7     | anisole, HCl       | 0            | 0        |
| 8     | anisole, HOAc, HCl | 0            | 0        |
| 9     | no light           | 28           | 0        |
Reactions with peracetic acid

Peracetic acid can be used as a stoichiometric oxidant in oxidative chlorination. Table S2 shows the yields of oxidative chlorination obtained for the substrates described in the manuscript. The results were obtained using the following procedure.

General procedure for the reaction with peracetic acid

In a vial 0.02 mmol of the respective substrate, 10 eq. HCl and 0.024 mmol (1.2 eq) peracetic acid were dissolved in 2.5 mL MeCN. The reaction mixture was stirred for 2.5 h at r.t.. Afterwards the internal standard (0.01 mmol \( n \)-pentadecane) was added to the reaction and the reaction was immediately quenched with sat. Na\(_2\)CO\(_3\)-solution and brine. The mixture was extracted with ethyl acetate and subjected to GC-FID analysis.

For all substrates except for the electron poor compound 15 the corresponding chlorinated product was obtained. This observation proves that peracetic acid induces oxidative chlorination. However, for most substrates the use of peracetic acid employed directly will lead to an undesired double chlorination. The high reactivity of peracetic acid leads to overchlorination if used as a reagent directly, but is beneficial for the use as a mediator generated slowly in small amount as in the flavin photocatalysis.
Table S2 Oxidative chlorination using peracetic acid as the stoichiometric oxidant.

![Chemical structure showing oxidative chlorination using peracetic acid as the oxidant.]

| Entry | Substrate | Yield/\%[^a] | Double chlorination/\%[^a] |
|-------|-----------|-------------|---------------------------|
| 1     | PhN       | 50 (p:o 0:100) | 32                        |
| 2     | PhN       | 68 (p:o 5:1) | --                        |
| 3     | PhNPh     | >99         | 0                         |
| 4     | PhOMe     | 65 (p:o 15:1) | 13                        |
| 5[^b] | PhOPh     | 46          | 48[^b]                    |
| 6     | MeOMe     | 82          | 0                         |
| 7     | PhOCF₃    | --          | --                        |
| 8[^b] | PhN       | 64 (p:o 1:11) | 25                        |
| 9     | PhO       | 64          | 8                         |
| 10[^b]| PhO       | 84          | 18[^b]                    |

[^a]: obtained by GC-FID analysis using n-petadecane as the internal standard. [^b]: calibration factor for the monochlorinated product was used for estimation.

**Optimization of the reaction conditions**

As described in the manuscript Table S3 summarized the results of the screening of different routes for the generation of peracetic acid (entries 1-6) and the variation of the peracid (entries 7-11). The most efficient generation of peracetic acid was achieved by a combination of acetic acid and hydrochloric acid (entry 1), even though acetic anhydride and acetyl chloride showed formation of
chloroanisol, but in significantly lower yields. Triflic acid yielded the best results when a combination of hydrochloric acid and TEACl was used as the chloride source (entry 8).

Table S3 Variation of the peracid and chloride source.

| entry | system | conv. /% | yield /% |
|-------|--------|----------|----------|
| 1     | HOAc (10 eq.), HCl (10 eq.) | 100 | 66 |
| 2     | HOAc (10 eq.), KCl | 97 | 0 |
| 3     | HOAc (10 eq.), TEACl (10 eq.), 20 mol% H2SO4 | 100 | 34 |
| 4     | Ac2O (10 eq.), HCl (10 eq.) | 86 | 28 |
| 5     | acetyl chloride (10 eq.) | 100 | 17 |
| 6     | acetyl chloride (10 eq.), HCl (5 eq.) | 85 | 15 |
| 7     | TFA (10 eq.), HCl (10 eq.) | 65 | 27 |
| 8     | TFA (10 eq.), HCl (5 eq.), TEACl (5 eq.) | 100 | 57 |
| 9     | TFA (10 eq.), KCl | 100 | 30 |
| 10    | HCOOH (10 eq.), HCl (10 eq.) | 86 | 42 |
| 11    | HCOOH (10 eq.), TEACl (10 eq.) | 40 | 0 |

Table S4 shows the temperature dependence of the reaction.

Table S4 Temperature dependence of the reaction.

| entry | temperature | yield / %a | conv. anisole / % |
|-------|-------------|-------------|-------------------|
| 1     | 25 °C       | 28          | 98                |
| 2     | 35 °C       | 35          | 64                |
| 3     | 45 °C       | 66          | 100               |
| 4     | 45 °C (5 mol% RFTA) | 46 | 62 |
| 5     | 60 °C       | 0           | 16                |

Table S5 shows the screening of solvents known to lead to an efficient photooxidation of pMBA and hence formation of H2O2. Except for MeCN, none of the investigated solvents led to formation of the chlorinated product. Even though water is reported to be beneficial for the oxidation of pMBA, it prevents productive formation of peracetic acid as it shifts the equilibrium (equ. 1) to the side of acetic acid.

\[
\text{HOAc} + \text{H}_2\text{O}_2 \rightleftharpoons \text{HOOAc} + \text{H}_2\text{O}
\] (equ. 1)
Table S5 Solvent screening at 45 °C.\textsuperscript{a}

| entry | solvent                | yield/ %\textsuperscript{b} | conv. anisole / %\textsuperscript{b} |
|-------|------------------------|-------------------------------|--------------------------------------|
| 1     | MeOH                   | 0                             | 9                                    |
| 2     | MeOH/MeCN 1:1          | 0                             | 64                                   |
| 3     | DMSO                   | 0                             | 10                                   |
| 4     | MeCN/H\textsubscript{2}O 2:1 | 0                             | 56                                   |
| 5     | MeCN, dry              | 66                            | 95                                   |

\textsuperscript{a} average over 2 reactions \textsuperscript{b} yields determined by GC-FID analysis

**UV/VIS spectroscopy**

The UV-Vis measurements with online irradiation were performed on a self-made apparatus using a fluorescence cuvette in a fluorescence cuvette holder, LED (Cree-XP, royal blue, 455 nm) placed perpendicular to the optical pathway of the Agilent 8453 UV-Vis Spectrometer. The measurement was performed in 10 mm Hellma fluorescence quartz cuvettes (117.100F-QS).

First, we monitored the change of the absorption bands of RFT in the presence of HCl in MeCN (Figure S4). The formation of an absorption band is observed at $\lambda_{\text{max}} = 390$ nm, which is assigned to the protonated species RFTH$^+$.\textsuperscript{[5]} We irradiated a degassed mixture of RFT and pMBA in MeCN in the presence of HCl and HOAc (Figure S5). The absorption band at $\lambda_{\text{max}} = 390$ nm decreases under irradiation, whereas the formation of a distinct broad band at $\lambda_{\text{max}} = 460$-530 nm is observed. This broad band is characteristic for $^2$RFTH$_2$+$^\bullet$, which is generated by protonation of the reduced flavin species $^2$RFTH$^\bullet$ under acid conditions.\textsuperscript{[5]}
Figure S4 Electronic absorption spectra of RFT (0.1 mM, blue) in the presence of HCl in MeCN at 298 K.

Figure S5 Electronic absorption spectra of pMBA (6.7 mM) and RFT (0.1 mM) in the presence of HCl while irradiating with blue light in MeCN at 298 K. The spectra were measured over 6 min recording one spectra every 10 s.
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