Supporting information

Fast Colorimetric Screening for Visible Light Photocatalytic Oxidation and Reduction Reactions

M. Poznik[a] and B. König[a]

[a.] Faculty of Chemistry and Pharmacy, University of Regensburg, 93040 Regensburg, Germany.
E-Mail: burkhard.koenig@ur.de; Fax: +49 943 1717; Tel: +49 943 4576.

Content

General methods and materials

All compounds and solvents were purchased from Sigma-Aldrich or Acros and used as delivered. UV-Vis clear flat bottom polystyrene and polypropylene 96 well microtiter plates were purchased from Grenier bio-one. In reactions with solvents, polypropylene microtiter plates were used. In all experiment was used deionised MiliQ water. Buffered solutions were prepared according to known literature.[1]

NMR-Spectroscopy: NMR-spectra were recorded on a Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz, T = 295 K) using the solvent residual peak as internal reference ($CDCl_3$: δ H 7.26). The chemical shifts are reported in δ [ppm] relative to internal standards (solvent residual peak). The spectra were analyzed by first order, the coupling constants *J* are given in Hertz [Hz]. Integration is determined as the relative number of atoms. Error of reported values: chemical shift: 0.01 ppm for ^{1}H-NMR, 0.1 ppm for ^{13}C-NMR and 0.1 Hz for coupling constants. The solvent used is reported for each spectrum.

GC chromatography: Performed using capillary column (length: 30 m; diam. 0.25 mm; film: 0.25 μ) with helium gas as carrier. Quantitative analysis was performed with an FID detector.

Spectroscopy: Absorption spectroscopy using microtiter plates was carried out by a plate reader OMEGA Fluorostar.

Indicators

KI-starch

The redox indicator consists of a solution of KI (0.1 mM) and starch (1 mg/mL) in MiliQ water with acetic acid (5 μL/mL). KI and starch were prepared as stock solutions in tenfold concentration and used for preparing the indicator prior to the

measurement. The starch stock solution was boiled for 10 min to allow starch dissolving and used after cooling. If not stated differently, addition of 100 μL of indicator solution was used in each well to determine the amount of produced hydrogen peroxide. Indicator response was measured as the difference of the optical densities at the absorption maxima (570 nm) of the formed complex between measured sample and blank (Fig S1). As a blank experiment, we used a sample with the same volume of solvent, while omitting the catalyst or the substrate. The read out for each well was obtained as the average of three measurements (every 20 s) five minutes after the addition of the indicator. The given values for each reaction are the average of at least three separate measurements (wells).

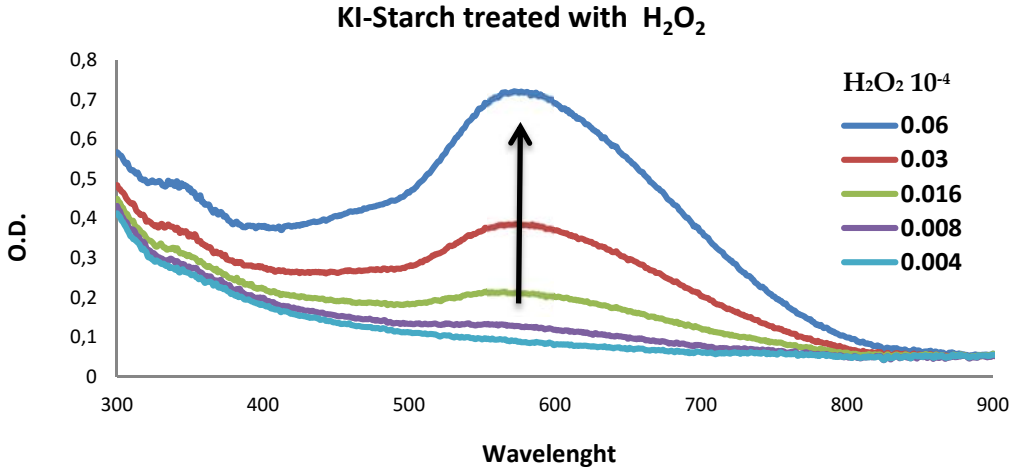


Figure S1: Recorded spectra of the KI-starch indicator after addition of hydrogen peroxide.

Indicator response to changing pH was measured using a series of citrate and phosphate buffers and a constant concentration of hydrogen peroxide (0.001 %) (Fig. S2, left).

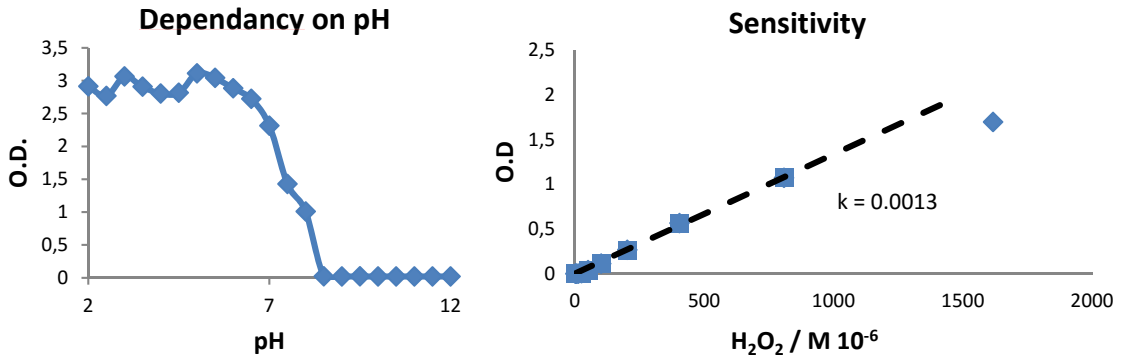
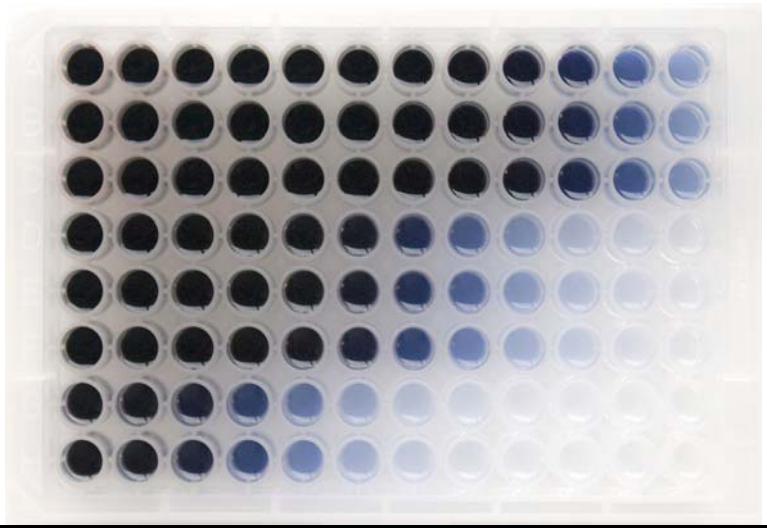


Figure S2: KI-starch indicator tested in a microtiter plate reader for different pH (**left**) and different concentrations of H_2O_2 (**right**).

The sensitivity was measured in pure MiliQ water with changing concentration of hydrogen peroxide (Fig. S2, right). All presented data were measured under conditions where the optical density of the indicator response did not exceed 1, hence Lambert-Beer law can be applied and calibration can be used (Fig. S2, right).[§]



	1	2	3	4	5	6	7	8	9	10	11	12
A	1%	0.5%	0.3%	0.1%	0.06%	0.03%	0.02%	0.008%	0.004%	0.002%	0.001%	0.0005%
B	1%	0.5%	0.3%	0.1%	0.06%	0.03%	0.02%	0.008%	0.004%	0.002%	0.001%	0.0005%
C	1%	0.5%	0.3%	0.1%	0.06%	0.03%	0.02%	0.008%	0.004%	0.002%	0.001%	0.0005%
D	0.1%	0.05%	0.03%	0.01%	0.006%	0.003%	0.002%	0.0008%	0.0004%	0.0002%	0.0001%	0.00005%
E	0.1%	0.05%	0.03%	0.01%	0.006%	0.003%	0.002%	0.0008%	0.0004%	0.0002%	0.0001%	0.00005%
F	0.1%	0.05%	0.03%	0.01%	0.006%	0.003%	0.002%	0.0008%	0.0004%	0.0002%	0.0001%	0.00005%
G	0.01%	0.005%	0.003%	0.001%	0.0006%	0.0003%	0.0002%	0.0001%	0.00004%	0.00002%	0.00001%	0.000005%
H	0.01%	0.005%	0.003%	0.001%	0.0006%	0.0003%	0.0002%	0.0001%	0.00004%	0.00002%	0.00001%	0.000005%

Figure S3: Example of a microtiter plate experiment using a gradient of hydrogen peroxide after 1 hour.

Indication in water : solvent mixtures

Response of the KI-Starch indicator to the presence of 0.01 % hydrogen peroxide in different aq. solutions of commonly used solvents was examined (Fg. S4, left). As the ideal ratio, 80% of water in solvent was selected. Therefore, all reactions, which were performed in organic solvents, were in 50 µL scale and for evaluation 200 µL of indicator solution was used to obtain the desired water content. For these solvent mixtures we measured linear dependencies on the hydrogen peroxide content (Fig. S4, right).

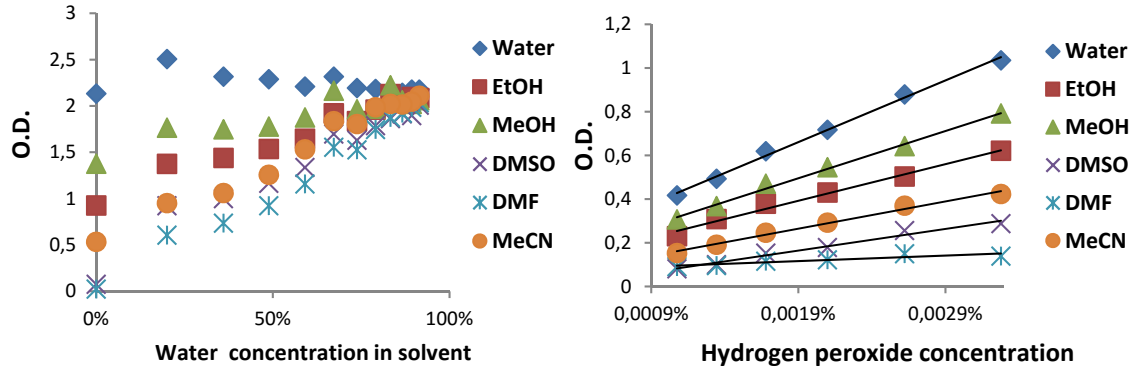


Figure S4: Response of the KI-starch indicator on hydrogen peroxide in different solvent : water mixtures (left) and in water : solvent (80:20) mixtures for changing hydrogen peroxide concentration (right).

From the slope of the linear regression, an empirical solvent constant $\mathbf{a}_{(solvent)}$, which was used for calculation of the correct amount of produced hydrogen peroxide in different solvents, was derived (Tab. S1). This constant resembles the calibration of the indicator response in different solvent normalized for water.

	Water	EtOH	MeOH	DMSO	DMF	MeCN
Slope	1181	454	875	281	433	773
$a_{(solvet)}$	**1.00**	**2.60**	**1.35**	**4.20**	**2.73**	**1.53**

Table S1: Derived established solvent constants for the KI-Starch indicator.

pH Indicators

All pH indicators were used as a solutions (0.1 mM) in a mixture of ethanol : water (1:10). 50 µL of the indicator solution was always used per well. Response was

measured as a change in optical density at the maxima of the respective indicator (phenolphtalein (555 nm), bromcresol green (615 nm), bromthymol blue (615 nm), methyl orange (507 nm)). All indicators were examined on the microtiter plate using buffered solutions (Fig. S5).

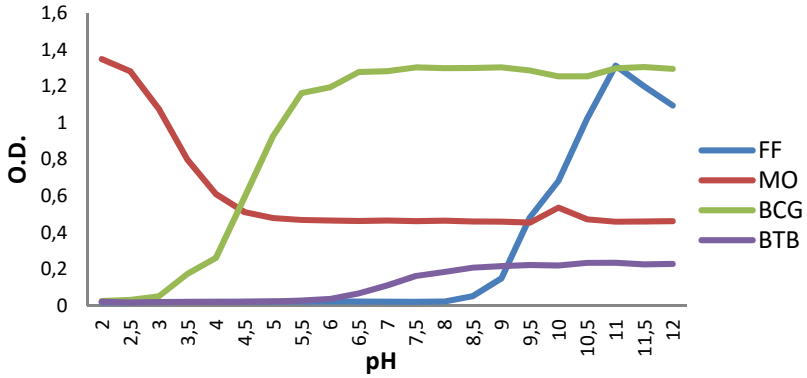


Figure S5: Different pH indicators (200 µL volume in well, 0.05 mM): Phenolphtalein (FF), Bromcresol green (BCG), Bromthymol blue (BTB), Methyl orange (MO).

Reactor

Construction

The reactor consists of two parts (Fig. S6). A hollow aluminum block at the bottom provides water cooling. It is manufactured to precisely hold the microtiter plate in the way that the metal is in contact with the flat bottom of the wells providing maximum cooling efficiency. Irradiation was carried out by a custom made 96 LED array positioned above the microtiter plate. Every well was irradiated by blue LED Superflux (LT-1229) at 20 mA. For experiments where oxygen has to be excluded, a PMMA box with appropriate connection and insulation was built, and the whole reactor was placed inside it (Fig. S6, right).

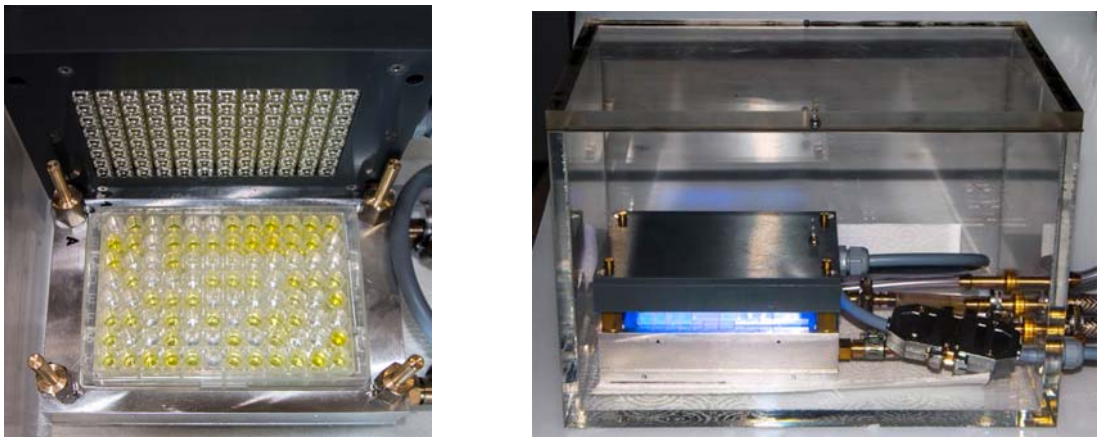


Figure S6: Experimental setup for microtiter plate irradiation.

Homogeneity of irradiation and error of the measurement

To test if the conditions are homogenous in the reactor an established reaction was performed in each well of the microtiter plate and evaluated by addition of KI-starch indicator (Fig. S7). Solution of benzyl alcohol (10 mM) and RFTA (0.1 mM) was prepared in aq. solution of DMSO (4 %) and 100 μL pipetted in each of 96 wells. The microtiter plate was irradiated for 15 min and the conversion evaluated with KI-starch indicator.

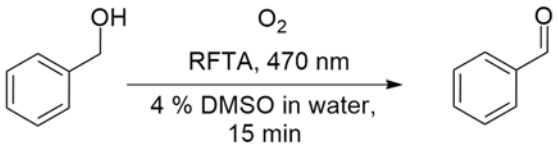


Figure S7: Oxidation of benzyl alcohol to aldehyde using RFTA.

Standard deviation was calculated for each well (Fig. S8). Error of the measurement in microtiter plate using KI-starch indicator was determined to be 10 %. Slight difference in irradiation intensity is observed with increase intensity towards the center of the plate. This was taken into account in designing the experiments and duplicate reactions were placed in edge and inner wells.

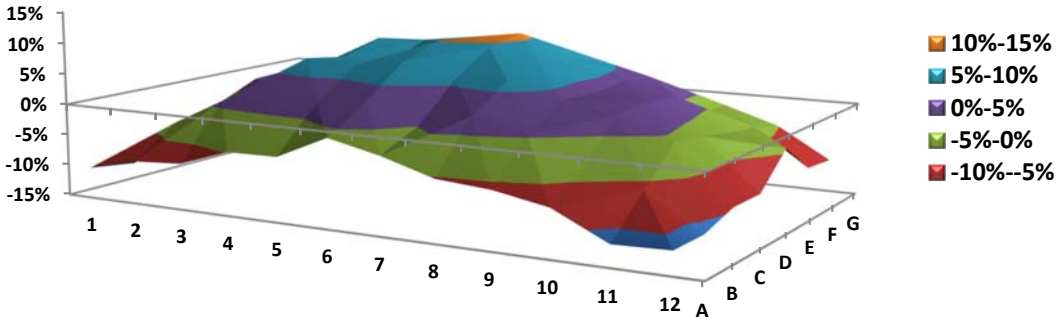


Figure S8: Relative deviation for each well from the average.

Exclusion of oxygen

A PMMA-box was equipped with an outlet, which was connected to a vacuum line and nitrogen source through a three-way valve. Exclusion of oxygen was performed by decreasing the pressure inside the box to 750 mbar followed by flushing it with pure nitrogen. The effectiveness of the process was evaluated by performing a photocatalytic transformation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde with **RFTA** (Fig. S9).

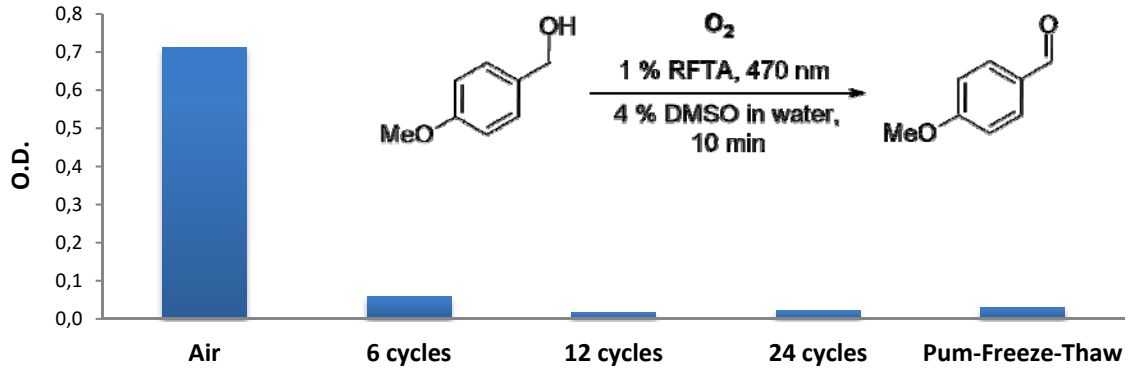


Figure S9: Response of the KI-starch indicator towards the oxidation of 4-methoxybenzyl alcohol performed under different oxygen exclusion technique.

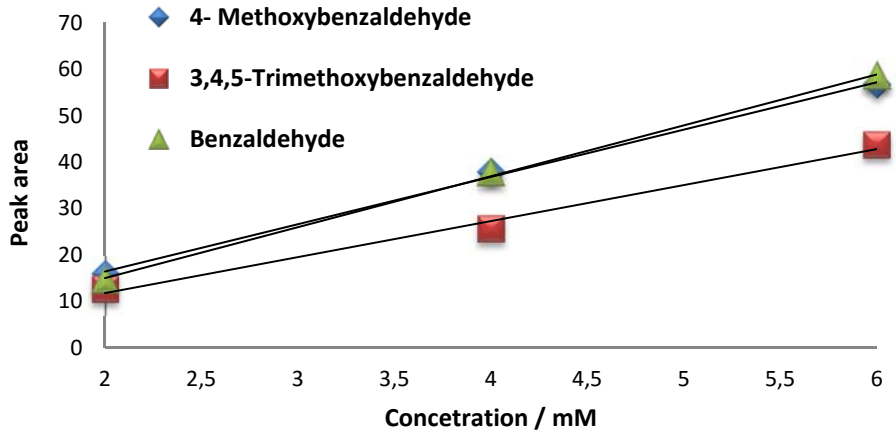
Oxygen is required for completion of the catalytic cycle and the effect of the vacuum-nitrogen cycles on the conversion was examined (Fig. S9). Results were compared to one reaction carried out in a vial where exclusion of the oxygen was achieved by pump-freeze-thaw technique, but the evaluation was done similarly in a microtiter plate using 100 μL of its solution. 12 cycles provide sufficient

exclusion of the oxygen for the reaction not to occur and this procedure was used in all later reaction performed in absence of air.

Oxidation of benzyl alcohols and amines

Substrates (benzyl alcohols and amines) were prepared as stock solutions (4.16 mM) in MiliQ water and **RFTA** in DMSO (0.1 mM). Prior to the measurement 960 µL of the substrate and 40 µL of **RFTA** were mixed and 100 µL aliquots were pipetted into each well to obtain the required concentration of the substrate (4 mM) and photocatalyst (4 µM, 0.1 mol. %). After irradiation for 10 min 100 µL of KI-starch indicator was added in each well. The response was evaluated according to the procedure described above. Every microtiter plate experiment is the average of 8 measurements done in separate wells. As a blank reaction, a solution without substrate was used. The relative reactivity was calculated from the optical readout, which was normalized for the substrate with highest response.

GC Analysis



	Slope
MBA	10.175
3MBA	7.75
BA	10.95

Figure S10: GC calibration for products of the transformation.

Three selected substrates were compared: benzyl alcohol (**BA**), 4-methoxybenzyl alcohol (**MBA**) and 3,4,5-trimethoxybenzyl alcohol (**3MBA**). GC calibration was

performed in the range of the reaction concentration for the expected products of the oxidation (Fig. S10). Measurements were performed in a similar manner as for the screening with a difference that solutions from 4 wells were combined, filtered and used for GC evaluation. Reaction conditions were altered to higher concentrations: substrate (10 mM), **RFTA** (0.01 mM), solvent (water with 4 % DMSO), loading (100 µL in well), irradiation time (20 min). The irradiation time should not exceed 20 min, because the generated amount of hydrogen peroxide is too high for reliable detection via colourimetric screening.

Irradiation with fluorescent 55 W light bulb

The effect of different irradiation sources was determined by experiments with benzylamines and alcohols. A simple white fluorescent light bulb (55 W) suspended above the microtiter plate was used for irradiation. The conditions were similar as in the previous screening using the LED reactor, but longer irradiation times were used due to lower light intensity (30 min). The reactions were evaluated in the same way as before and results compared with the ones obtained when irradiated with 96 LED array (Figure S11).

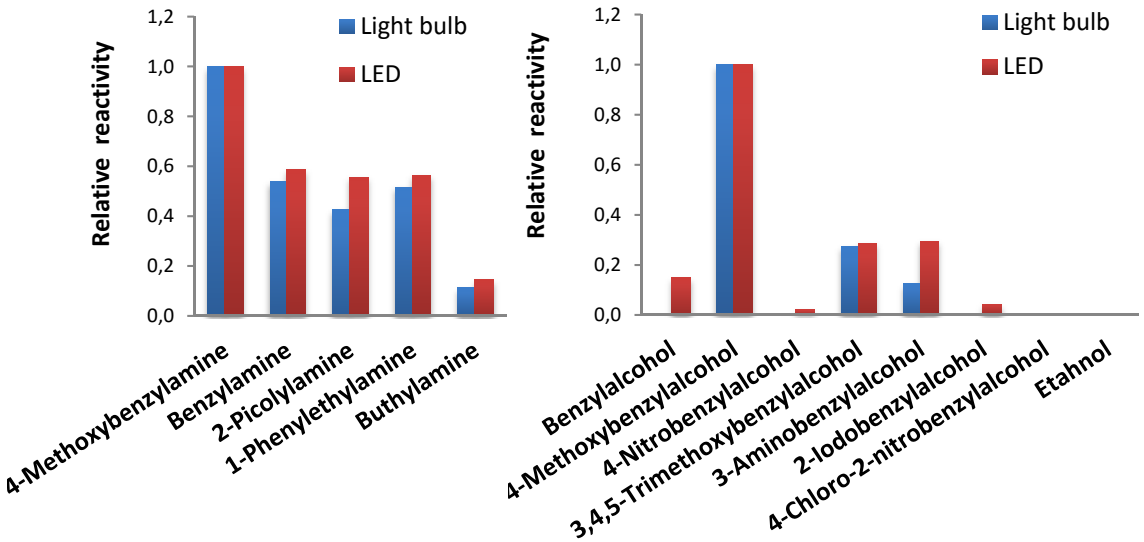


Figure S11: Comparison of screening outcome using 96 LEDs (15 min) and 55W fluorescent light bulb.

Hydroxylation of boronic acids

Amine screening

All stock solutions were prepared and measurements were performed in MeCN. Each measurement comprised one well filled with a solution (50μL) of one dye (0.01 mM, 0.2 mol. %) and amine (5 mM). The array was irradiated for 5 min at 470 nm at room temperature. Then 200 μL KI-starch indicator solution was added and the response evaluated as previously. As blank, a measurement without added amine was used. The blank experiment was performed for every catalyst independently. The given value is the average of three measurements. The relative reactivity of amines was evaluated as the optical response of the indicator normalized to the value of the best performing amine. This represents the relative amount of released superoxide for the different amines.

Solvent screening

Each measurement comprised two wells filled with a solution (65 μL) of one dye (**ACR**: 0.008 mM, 0.2 mol. % or **RFTA** 0.08mM, 2 mol. %) and triethylamine (5 mM) with and without phenylboronic acid (4 mM) in 6 different solvents. The microtiter plate was irradiated for 5 min at 470 nm at room temperature. Next, 200 μL of indicator solution was added and the indicator response evaluated as described before. A measurement without boronic acid was used as blank experiment. Difference in colorimetric response of blank (only amine) and sample (amine and boronic acid) was calculated for each case. These values for different solvents were then corrected by the above described solvent constant $\mathbf{a}_{(solvent)}$ (Table S1) in order to be able to compare them between each other. The values represent the amount of superoxide consumed by the boronic acid and were used for calculation of relative reactivities.

Substrate screening

Each measurement comprised two wells filled with a solution (50 µL) of one dye (**ACR**: 0.008 mM, 0.2 mol. % or **RFTA** 0.08mM, 2 mol. %) and triethylamine (5 mM) with and without boronic acid (4 mM, 9 boronic acids) in acetonitrile. The microtiter plate was irradiated for 5 min at 470 nm at room temperature. Next, 200 µL of indicator solution was added. The evaluation of the relative reactivity was done in the same way as for the solvents.

Isolated compounds

General procedure

Tris(2,2′-bipyridyl)dichlororuthenium(II) hexahydrate (**Ru(bpy)$_3$**) (0.01 mmol, 0.02 eq.), octylboronic acid (0.5 mmol, 1.0 eq.) and DIPEA (1.0 mmol, 2.0 eq.) were dissolved in DMF (5 mL), placed in a crimp cap vial, flushed with nitrogen for 5 times and irradiated with 455 nm (high power LED) under stirring at room temperature for 16 h. Subsequently the reaction mixture was quenched with cold hydrochloric acid (5 ml, 10 %), and extracted with diethyl ether (3 × 10 mL). The organic layers were combined, washed with brine (5 ml) and dried over $MgSO_4$. Solids were filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (PE:EA, 9:1 → 7:3) to obtain 50 mg (77 %) of octanol as colorless liquid.

			Product / mg (%)		
	Amine	**Solvent**	Octanol	Phenol	3-Fluorophenol
Ru	DIPEA	DMF	50 (70 %)	35 (74 %)	53 (93 %)
RFTA	TEA	MeCN	55 (80 %)	22 (47 %)	27 (66 %)
Acr	TEA	MeCN	40 (62 %)	17 (36 %)	52 (91 %)

Table S2: Conditions and yields of reactions for each catalyst and substrate.

NMR

1-Octanol:

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.7 Hz, 2H), 2.21 (bs, 1H), 1.62 – 1.44 (m, 2H), 1.40 – 1.18 (m, 10H), 0.95 – 0.78 (m, 3H).

Phenol:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 2H), 7.00 – 6.90 (m, 1H), 6.90 – 6.79 (m, 2H), 5.20 (bs, 1H).

3-Fluorophenol:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.10 (m, 2H), 6.70 – 6.52 (m, 3H), 5.22 (bs, 1H).

Stability of the dyes

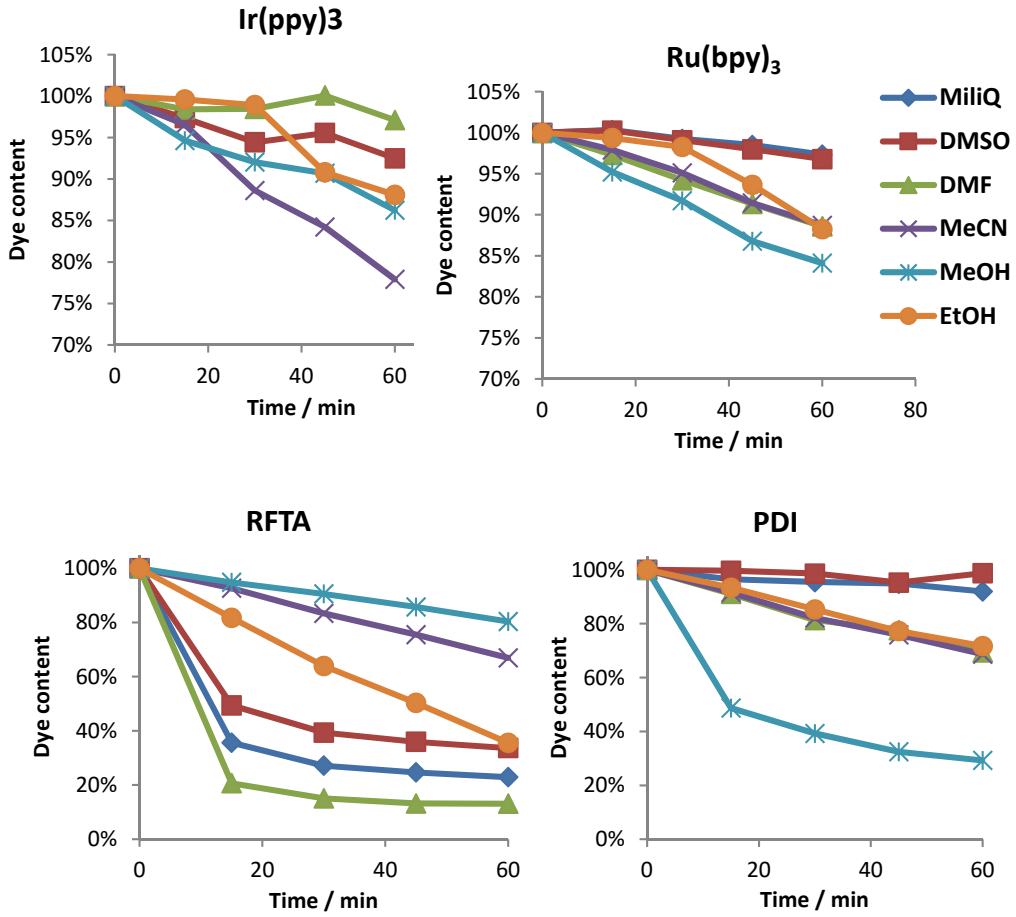


Figure S12: Examples of recorded data for photo-stability experiments. Irradiation with the 470 nm LED setup was performed in a microtiter plate in presence of air at 20 °C. Concentration of each dye is 0.1 mM.

Each well of the microtiter plate (polypropylene) contained 220 μL of the dye solution (0.1 mM) in a different solvent. The full absorption spectra (200–800 nm) were recorded for each well prior to irradiation (470 nm) and then every 15 min over one hour. The dye content was derived from the optical density at the absorption maxima and its relative decrease through time was as assigned to bleaching (Fig. S12). The slope of the linear bleaching of the dye over time was ascribed as relative stability of the dye in %/h (Tab. S3).

If the dye was too unstable, the fitting was performed on the linear part of the bleaching curve, which often exhibited complete bleaching in 1 h. For every solvent and dye the average of two measurements from two separate wells was used.

In the case of measurements done in nitrogen atmosphere only the measurement before and after 30 min irradiation was performed and the bleaching after 1 hour was calculated accordingly.

Measurements performed in the presence of acid or base were performed in the same condition with the difference that each solvent was a 10 mM solution of either trifluoroacetic acid or sodium hydroxide (in DMSO, DMF and MeCN concentration might be lower due to solubility). If potassium *tert*-butoxide was used as base, most of the dyes are unstable in aprotic solvents and show a strong color change.

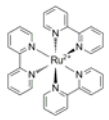
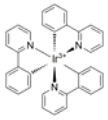
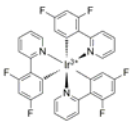
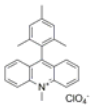
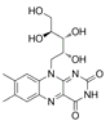
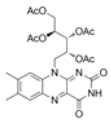
Abs. maxima	 450 nm			 375 nm			 300 nm			 420 nm			 440 nm			 445 nm			 490 nm		
Water	96	97	61				94	100		92	95	34	0	0	0	0	0	0			
DMSO	9	95	98	97	94	100	99	100	100	76	80		0	0		0	0		100	97	
MeCN	86	88	82	89	98	100	94	94	98	0	0	92	0	0	100	0	0	66	75	70	0
DMF	78	88	64	75	77	83	96	99	86	81	90	46	0	0	0	0	67	12	88	69	68
MeOH	61	84	70	68	87	83	83	86	92	76	82	0	0	0	24	0	80	14	38	37	27
EtOH	73	88	55	71	87	93	90	92	108	75	79	0	0	0	70	0	36	38	78	71	66
									Nitrogen												
Water	98	97	49				90	88		93	87	48	0	0	0	0	0	2			
DMSO	100	100	100	100	100	100	100	63	99	59	39		0	0		0	0		0	82	
MeCN	93	81	59	92	94	100	88	78	98	0	0	100	0	0	62	0	0	76	11	66	100
DMF	59	53	30	84	92	77	87	89	100	50	10	85	0	0	62	0	0	0	81	79	78
MeOH	86	70	21	52	80	88	98	73	91	15	0	0	0	0	23	0	43	19	0	0	0
EtOH	83	81	19	83	92	92	84	95	100	36	36	0	0	0	83	0	0	59	81	53	82

Table S3: Relative photo stability of the dyes (under 470 nm irradiation in microtiter plate) provided as the rate (1-(% bleached)/h) which resembles amount of remained dye after 1 h irradiation at concentration 0.1 mM (220 µL in well). Photo stability was measured in the presence of air (up) and its absence in nitrogen atmosphere (down) as well as under acidic (red) and basic (blue) conditions.

It is important to notice that absorption coefficients vary drastically at 470 nm and expected stability at different wavelength might differ (Fig. S13).

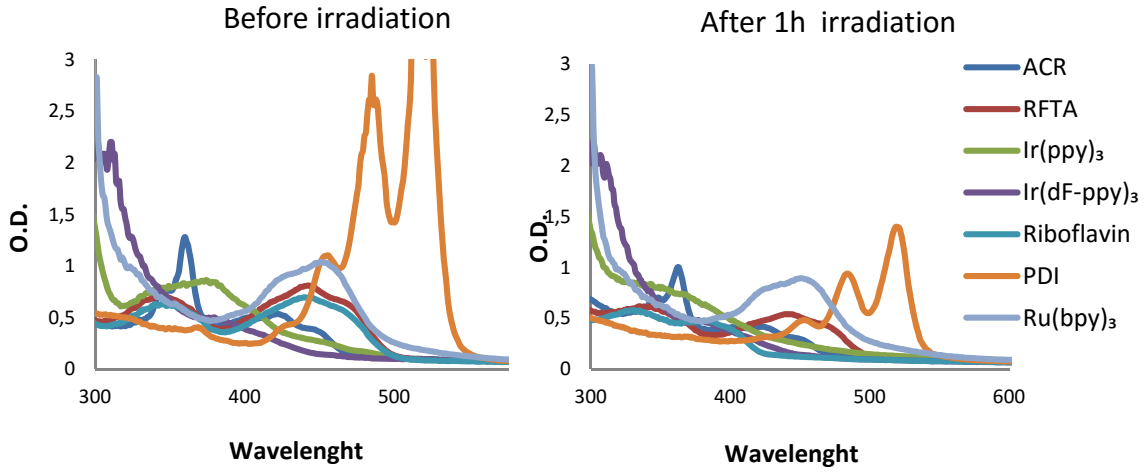


Figure S13: Recorded spectra during the experiment in acetonitrile before and after irradiation.

Aryl radical generation using PDI

Stock solutions of DIPEA (4 mM), dye (0.2) mM and substrate (4 mM) were prepared fresh in DMF prior to each measurement. In a well, DIPEA (12.5 µL) and substrate (12.5 µL) were pipetted, followed by the respective dye (25 µL). Two sets of blank measurements were performed: omitting either the dye or the catalyst.

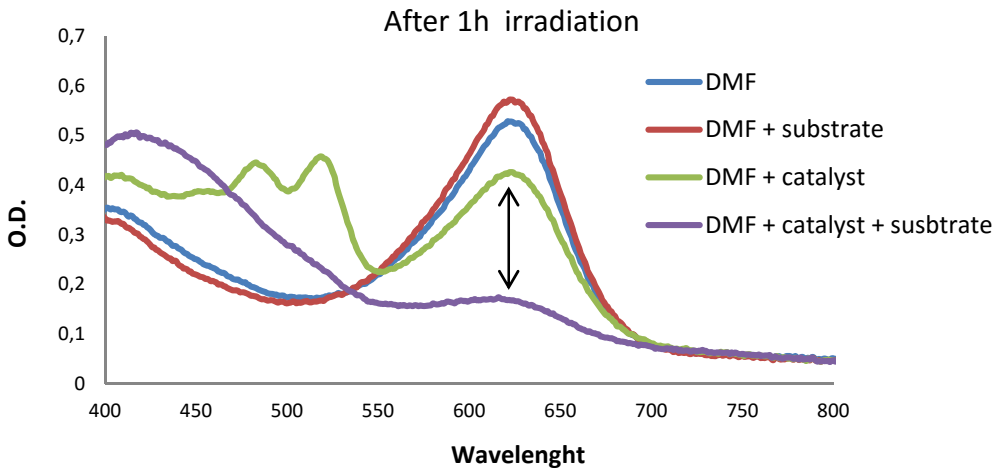


Figure S14: Example of spectra recorded for experiment performed with PDI and 4-bromoacetophenone after irradiation for 1 h and addition of BCG indicator.

The microtiter plate was placed in the reactor inside the gas-tight box, which was flushed with nitrogen (as described above) and irradiated for 1 h at 470 nm. Next, a solution of bromocresol green (**BCG**) (50 µL, 0.1 mM, 1:10 EtOH : H_2O) was added to each well and the full absorption spectra were recorded (250–850 nm) (Fig. S14). For each sample the optical density at the maxima of the absorption of BCG (617 nm) was corrected to baseline by subtracting the O.D. value measured at 800 nm to obtain the absolute response of the indicator. Samples were investigated in pairs and the resulting average was used for calculations. The ratio between the substrate containing the sample and the blank with only the catalyst was subtracted from one, which resembles the relative reactivity of the substrate (Table S4). The values indicate the relative amount of released protons by the different substrates, hence their ability to react.

	$-E^0_{ArX/ArX^{\bullet-}}$ (V vs SCE)[a]	PDI	Ir(ppy)$_3$	Ru(bpy)$_3$
2-Chloronitrobenzene	0.99	0%	13%	24%
9-Bromoanthracene	1.7	80%	74%	72%
4'-Bromoacetophenone	1.84	63%	79%	7%
4-Chloroacetophenone	1.9	24%	2%	0%
4'-Bromobenzonitirle	1.94	48%	28%	0%
4-Chlorobenzonitrile	2.08	36%	18%	8%
4-Bromoanisole	–	13%	20%	0%
2-Bromonaphthalen	2.21	6%	5%	0%
3-Brompyridin	2.23	10%	16%	0%
Bromooctadecane	–	0%	5%	0%

Table S4: Relative reactivity values obtained for different aryl halides with their redox potentials. [a] Reported values.[2]

The relative reactivity was compared with the published redox potential of the aryl halides. An important aspect of the measurement to observe a high contrast between reacting and non-reacting substrates is to optimize the amine concentration and the irradiation time.‡ In our case it was 1eq of DIPEA and 1h of irradiation.

	PDI	Ir(ppy)$_3$	Ru(bpy)$_3$
4'-Bromoacetophenone	53%	67%	0%
9-Bromoanthracene	68%	55%	54%
2-Chloro-4-(trifluoromethyl)pyrimidine	0%	24%	5%
6-Chloropurine	23%	0%	0%
5-Bromouracil	17%	19%	18%
2-Chloropyrazine	44%	49%	0%
3-Bromothiophene	9%	6%	1%
2-Brombenzophenon	49%	63%	11%
5-Bromo-1-methylindol	14%	10%	7%
5-Bromonicotinamide	47%	24%	4%

Table S5: Relative reactivity values obtained for extended substrate scope.

Screening of heterocycles and benzophenone was performed in a similar fashion (Fig. S15, Table S5).

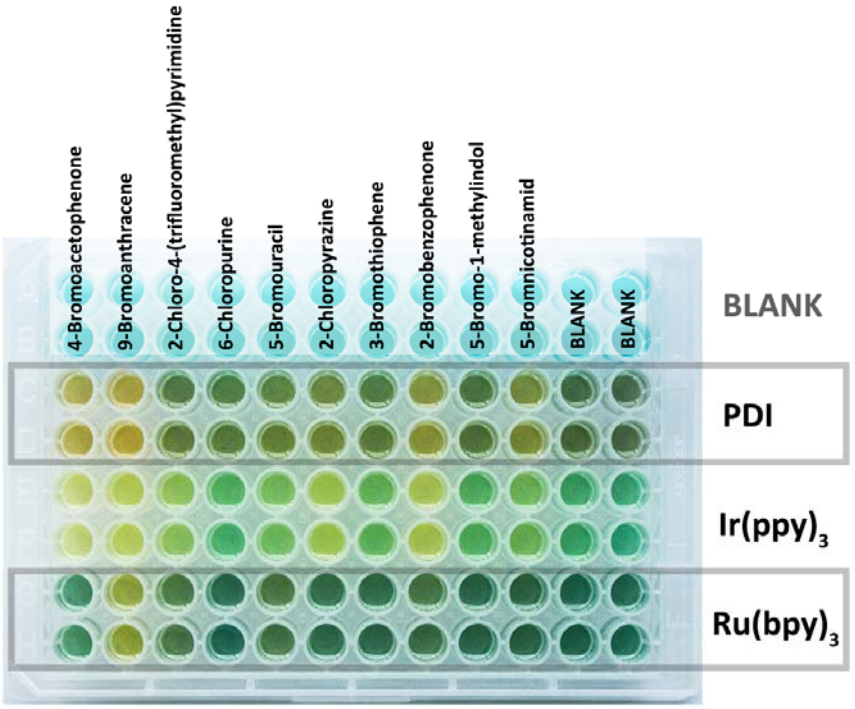


Figure S15: Picture of a microtiter plate experiment after irradiation and addition of **BCG** indicator. Yellow color indicates increased acidity and hence reaction conversion producing acid.

UV analysis of the conversion

9-Bromoanthracene and anthracene have a distinct UV/Vis absorptions that were used to monitor the reaction with all three catalyst (Fig. S16) confirming the expected transformation.

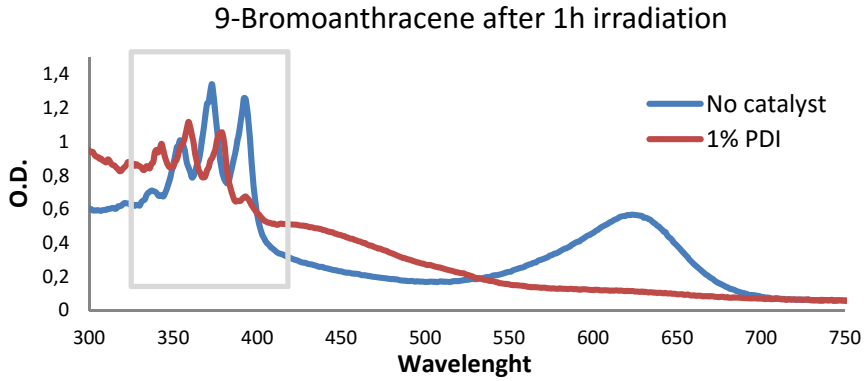


Figure S16: Recorded spectra of 9-bromoanthracene after 1 h irradiation in the presence and absence of the catalyst.

GC analysis

Three point calibrations were performed for all measured substrates and products (Fig. S17).

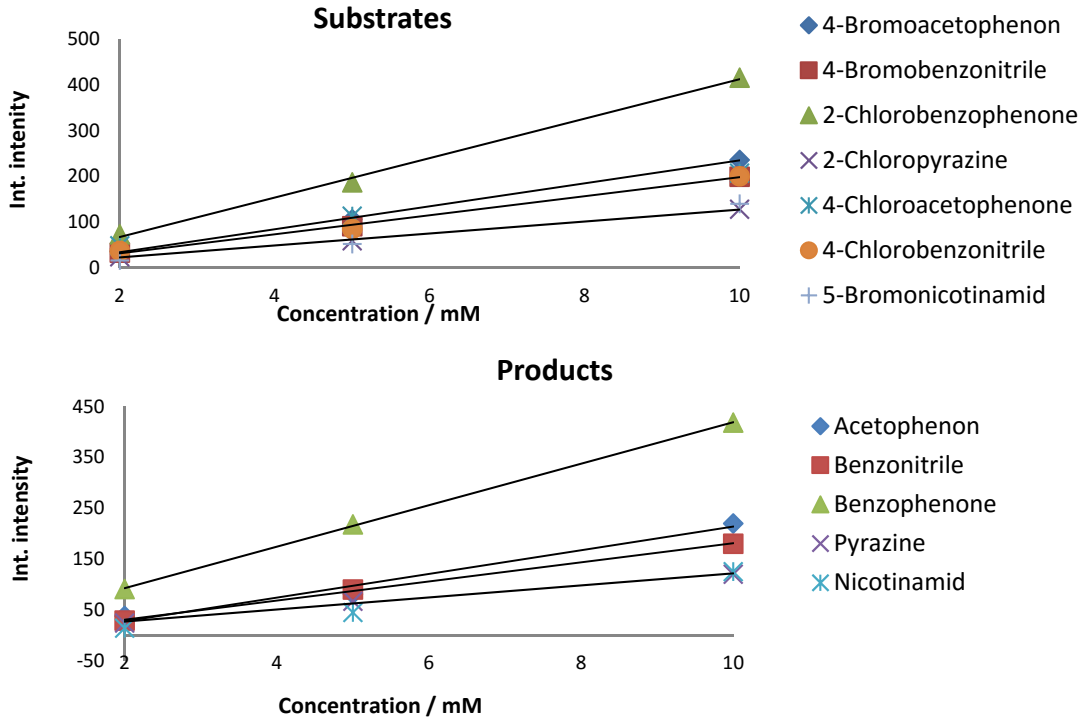


Figure S17: GC calibration for substrates and products.

All the GC measurements were performed in crimp-cap vials flushed with nitrogen and irradiated for 16 or 24 h. As shown above, the **PDI** dye is more prone to bleach. Therefore 10 mol% was used in contrary to 1 mol% in case of **Ru(bpy)$_3$** an **Ir(ppy)$_3$**. Reactions were performed in DMF with one substrate (20 mM) and DIPEA (10 eq., 200 mM) and irradiation was provided by high power LED (455 nm) for each crimp-cap vial. Samples were analyzed by GC, and yields and conversion were calculated using the calibration (Table S6).

	Conversion			Yield		
	PDI	**$Ir(ppy)_3$**	**$Ru(bpy)_3$**	**PDI**	**$Ir(ppy)_3$**	**$Ru(bpy)_3$**
4-Bromoacetophenon	59%	84%	0%	86%	8%	6%
4-Chloroacetophenone	0%	89%	2%	1%	4%	0%
4-Bromobenzonitrile	28%	100%	0%	35%	81%	2%
4-Chlorobenzonitrile	14%	100%	0%	26%	92%	0%
2-Chloropyrazine	0%	65%	0%	17%	50%	0%
2-Bromobenzophenone	78%	100%	4%	41%	28%	8%
5-Bromnicotinamid	93%	100%	1%	49%	53%	2%

Table S6: Obtained conversions and yields via GC analysis.

Screening of commercially available drugs

Screening of the drugs was performed in the similar manner as for the aryl halides. The major difference is that they often bear an amine or acidic residue, which has to be taken into account for a correct readout of the assay. This was addressed by calculating the relative difference between the absorption at BCG maxima (617 nm) in plain DMF with only DIPEA and with the substrate. This represents the response due to the varying p*K*a of the compounds. The relative colorimetric change in DMF was then subtracted from the one with catalyst after irradiation (Figure S18). If the obtained relative change in color of the indicator was positive, acidification occurs upon irradiation in the presence of the catalyst. Values greater than 10 % were considered as a positive result (•) (Tables S7). All drugs were compared with the reactivity of 9-bromoanthracene under identical reaction conditions.

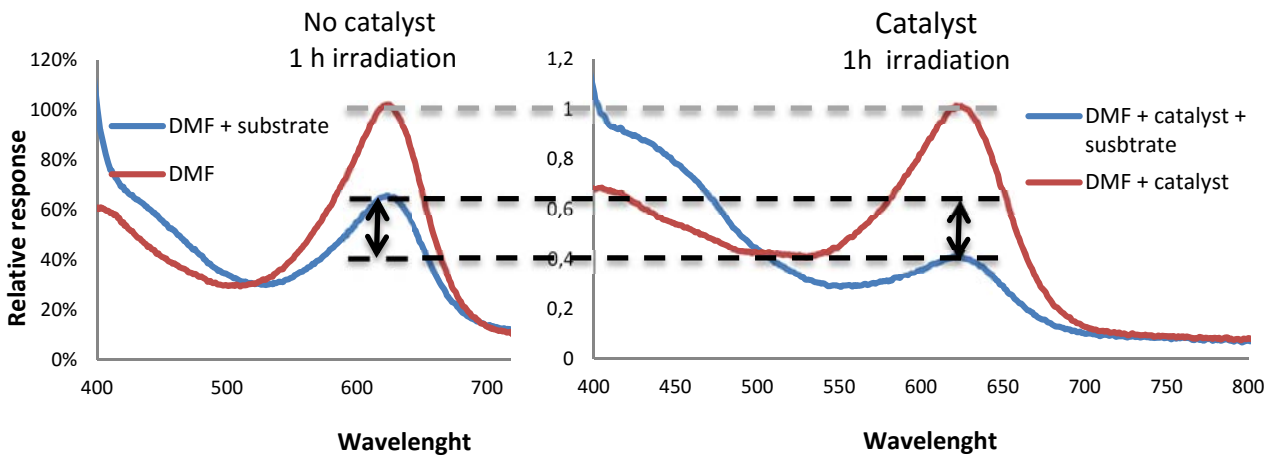


Figure S18: Illustration of colorimetric response evaluation for hydrochlorothiazide using $Ru(bpy)_3$ as catalyst.

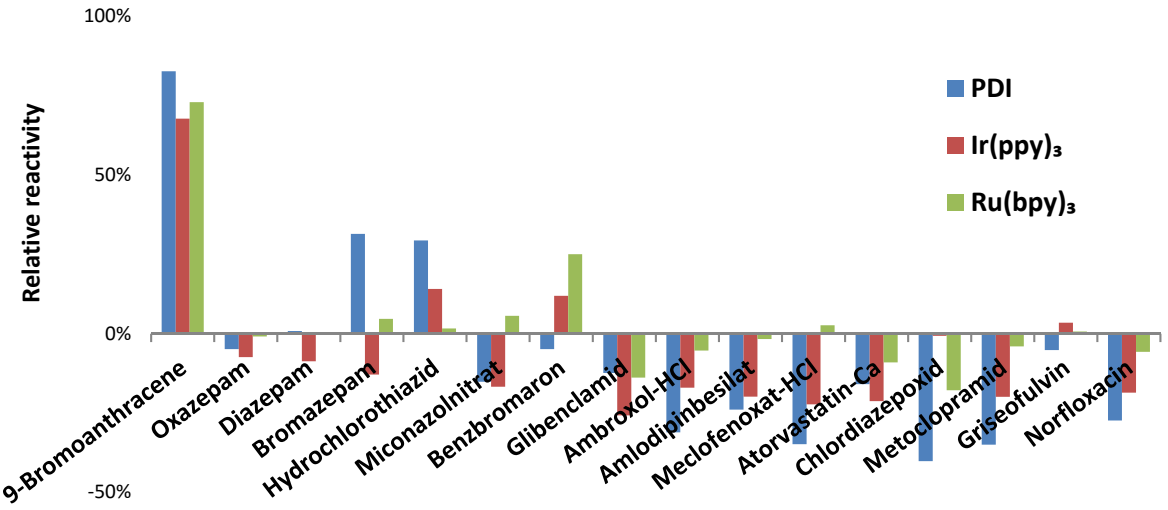
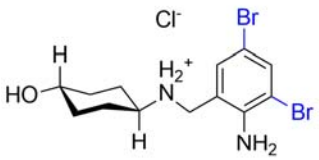


Figure S19: Relative reactivity of the selected drugs compared with reactivity of 9-bromoanthracene.

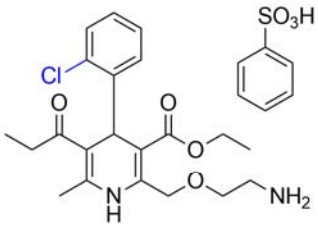
	PDI	$Ir(ppy)_3$	$Ru(bpy)_3$
9-Bromoanthracene	83%	68%	73%
Oxazepam	-5%	-7%	-1%
Diazepam	1%	-9%	0%
Bromazepam	31%	-13%	5%
Hydrochlorothiazide	29%	14%	2%
Miconazole	-15%	-17%	6%
Benzbromarone	-5%	12%	25%
Glibenclamid	-12%	-26%	-14%
Ambroxol-HCl	-31%	-17%	-5%
Amlodipinbesilat	-24%	-20%	-2%
Meclofenoxat-HCl	-35%	-22%	3%
Atorvastatin-Ca	-16%	-21%	-9%
Chlordiazepoxid	-40%	-1%	-18%
Metoclopramid	-35%	-20%	-4%
Griseofulvin	-5%	3%	1%
Norfloxacin	-27%	-19%	-6%

Table S7: Relative reactivity of the selected drugs compared with reactivity of 9-bromoanthracene.

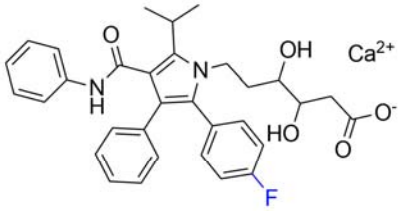
List of used commercial drugs



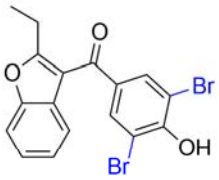
Ambroxol-HCl



Amlopidinbesilat



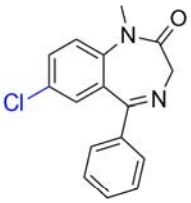
Atorvastatin-Ca



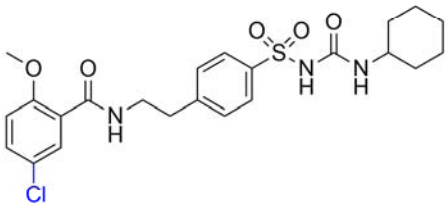
Benzbromarone

Bromazepam

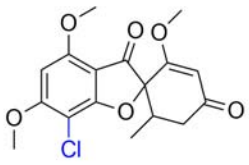
Chlorodiazepoxid



Diazepam

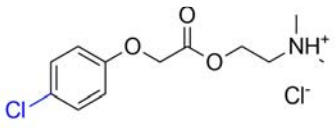


Glibenclamide

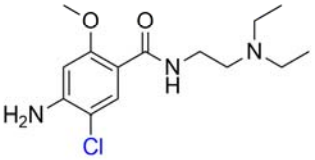


Griseofulvin

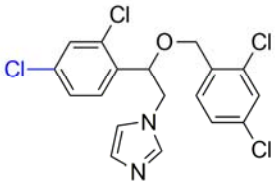
Hydrochlorothiazide



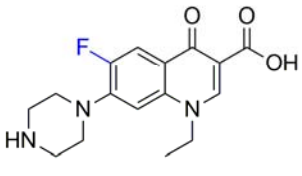
Meclofenoxate-HCl



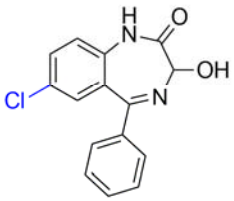
Metoclopramide



Miconazole



Norfloxacin



Oxazepam

Synthetic procedure for the dehalogenation of selected drugs

Benzbromarone

Tris(2,2′-bipyridyl)ruthenium(II) chloride (**Ru(bpy)$_3$**) (0.5 mg, 0.006 mmol), benzbromarone (24 mg, 0.6 mmol) and DIPEA (93 μL, 73 mg, 6 mmol) were dissolved in DMF (5 mL), placed into a crimp cap vial, flushed with nitrogen 5 times and irradiated with 455 nm (high power LED) under stirring at room temperature for 48 h. Subsequently, the reaction mixture was quenched with water (12 mL) and extracted with ethyl acetate (3 × 3 mL). The organic layers were combined, washed with brine (1 mL) and dried over $MgSO_4$. Solids were filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (PE:EA, 9:1 to 7:3) to obtain 14 mg (80 %) of the mixture of mono and non-brominated product in 1:1 ratio (according to NMR).

Obtained mixed NMR spectra correspond to the reported values.[3]

Monobrominated: MS (ESI(+)): m/z = 345.0126 [MH^+]

Debrominated: MS (ESI(+)): m/z = 267.1022 [MH^+]

Hydrochlorothiazide

Tris[2-phenylpyridinato-C2,N]iridium(III) (**Ir(ppy)$_3$**) (0.8 mg, 0.012 mmol), hydrochlorothiazide (36 mg, 1 mmol) and DIPEA (200 μL, 157 mg, 12 mmol) were dissolved in DMF (5 mL), closed in crimp cap vial, flushed with nitrogen 5 times and irradiated with 455 nm (high power LED) under stirring at room temperature for 4 days. Subsequently, the reaction mixture was quenched with water (12 mL) and extracted with ethyl acetate (3 × 3 mL). The organic layers were combined, washed with brine (1 ml) and dried over $MgSO_4$. Solids were filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (PE : EA, 2:1 to 0:1) to obtain 12 mg (38 %) of the dechlorinated hydrochlorothiazide.

In the case of **PDI** (10 mol. %) 15 mg (50 %) of product were obtained.

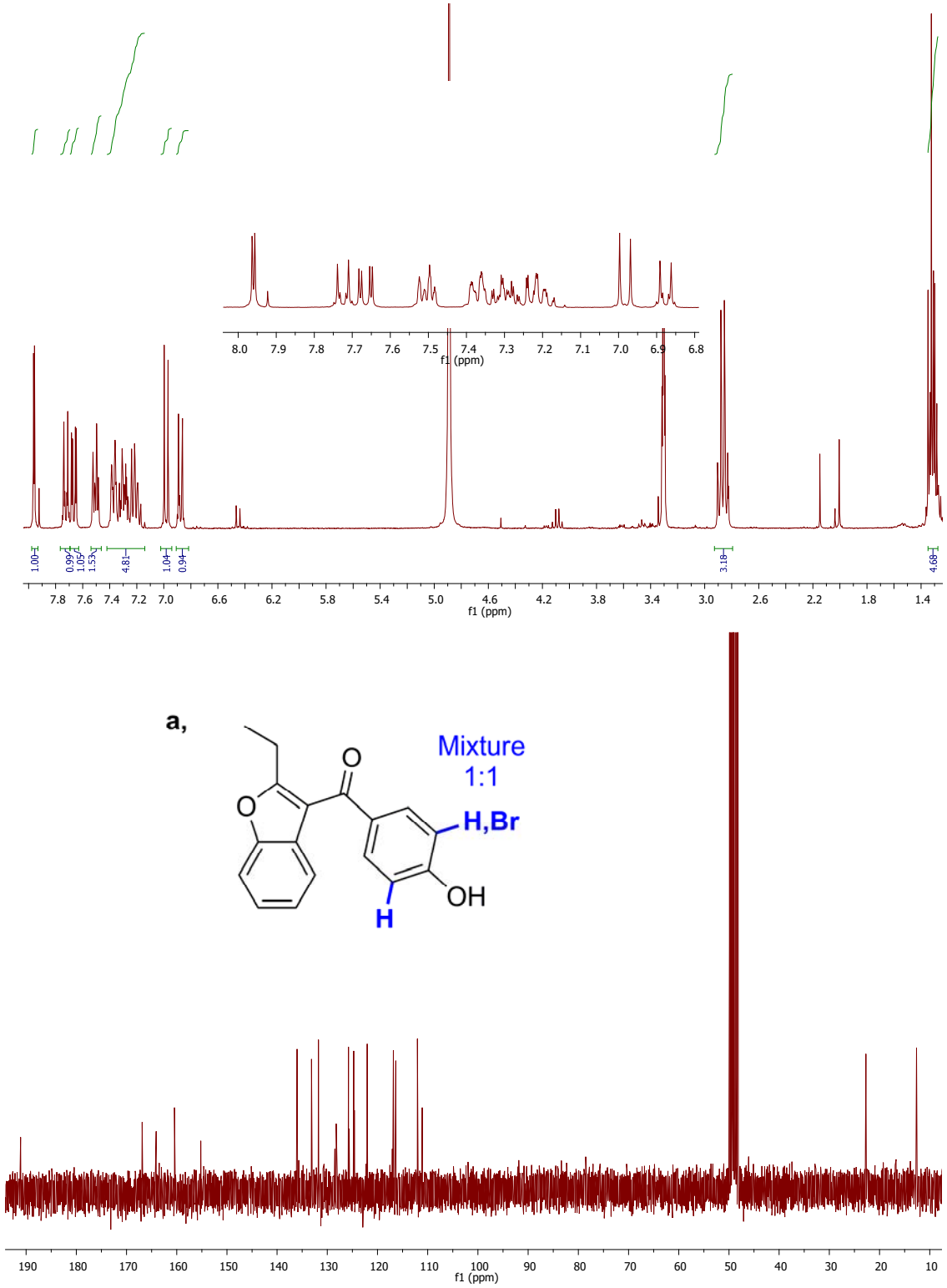
^{1}H NMR (400 MHz, MeOD) δ 8.04 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.9, 2.2 Hz, 1H), 6.85 (d, J = 8.9 Hz, 1H), 4.77 (s, 2H).

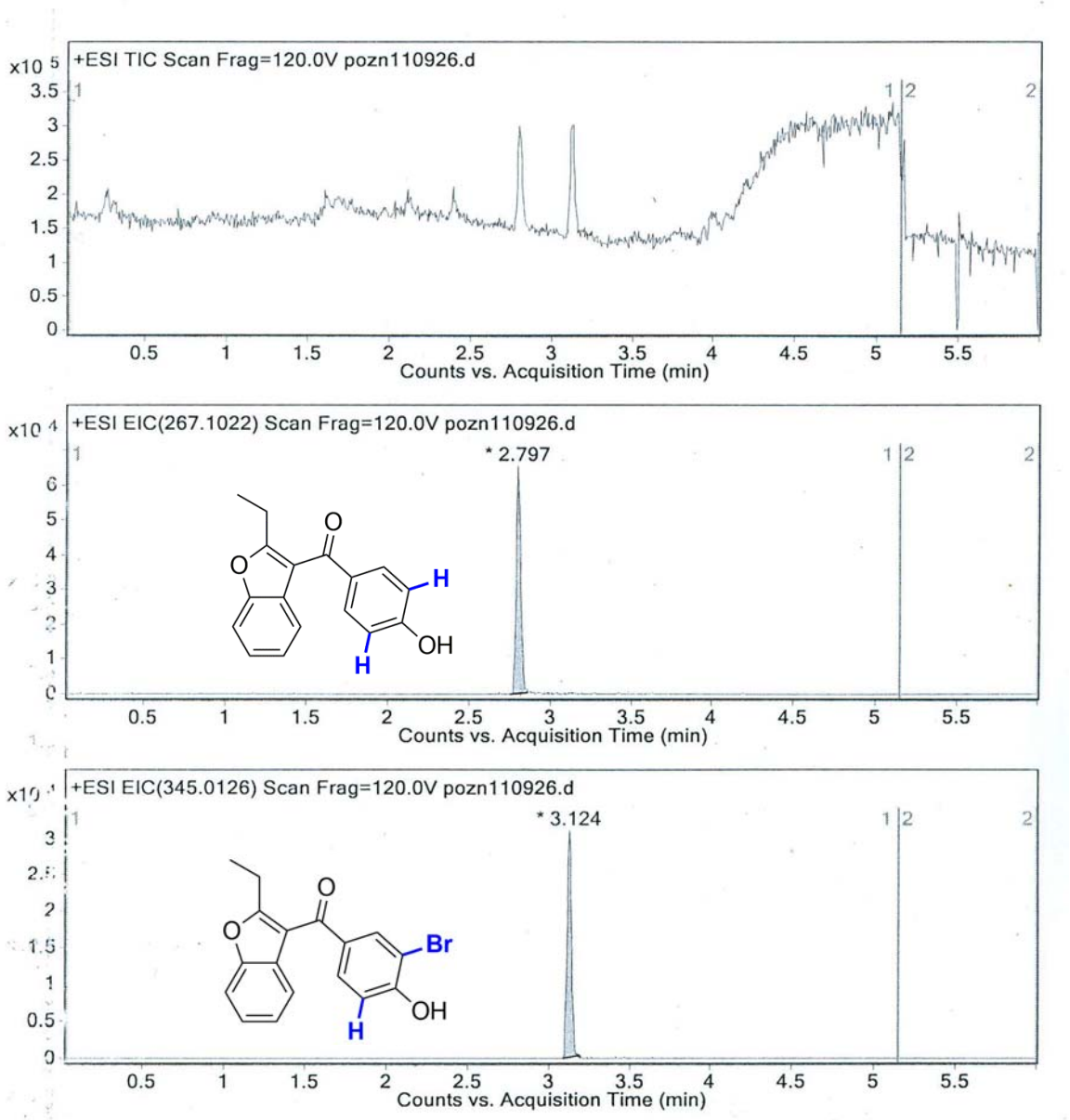
^{13}C NMR (101 MHz, MeOD) δ 147.87, 130.85, 130.10, 123.10, 120.68, 115.74, 54.42.

MS (ESI(+)): m/z = 264.011 [MH^+]

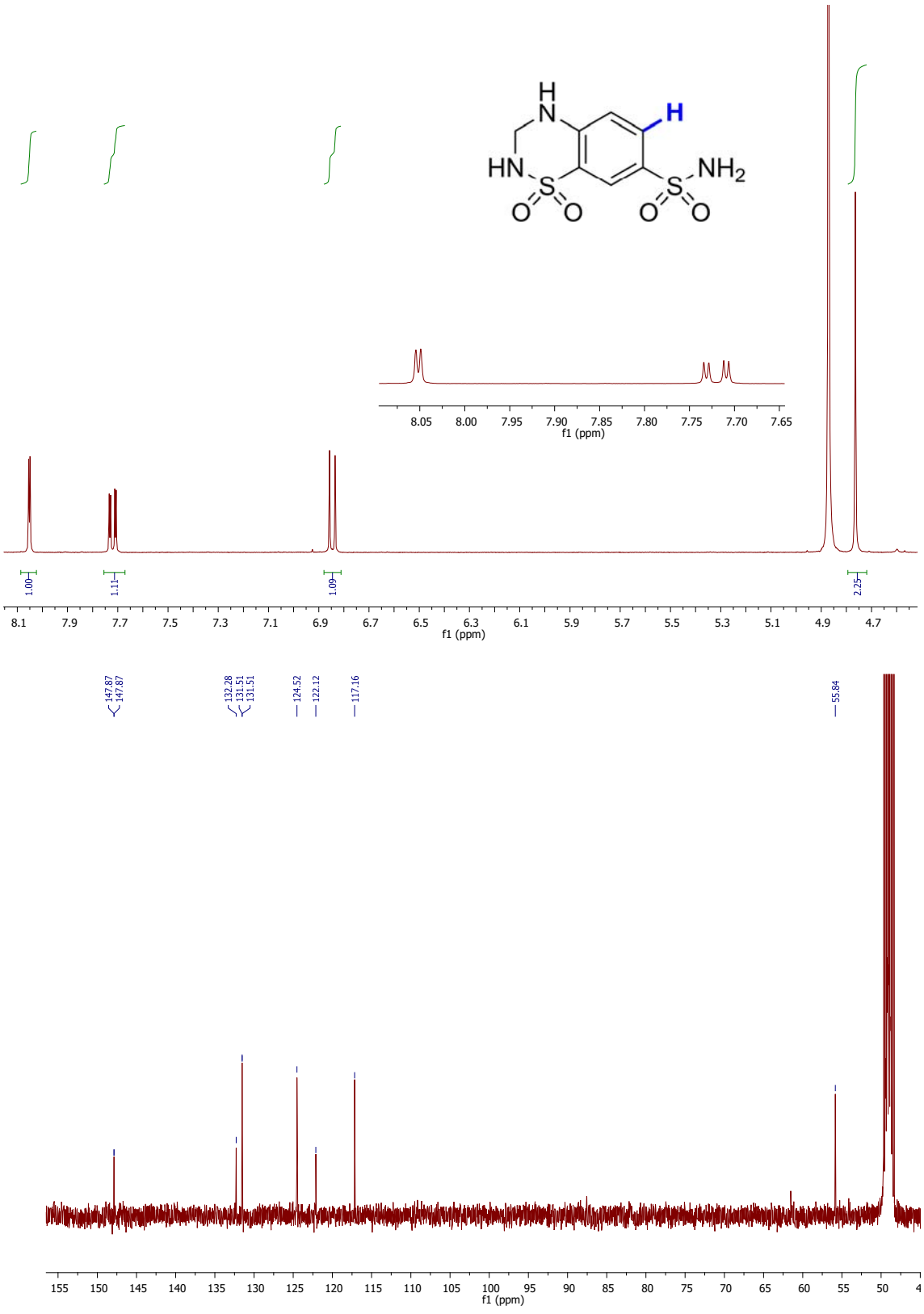
The measured NMR resonance signals correspond to the reported values.[4]

Characterization of reduced benzobromarone




+ESI TIC Scan Frag=120.0V pozn110926.d
x10 5
Counts vs. Acquisition Time (min)
+ESI EIC(267.1022) Scan Frag=120.0V pozn110926.d
* 2.797
O
O
H
H
OH
Counts vs. Acquisition Time (min)
+ESI EIC(345.0126) Scan Frag=120.0V pozn110926.d
* 3.124
O
O
Br
H
OH
Counts vs. Acquisition Time (min)

Characterization of reduced hydrochlorothiazide



References

§ The calibration can strongly depend on the type and quality of the starch and the indicator preparation. Therefore, is advised to prepare fresh indicator solution for every series of experiments to obtain comparable results.

‡ DMF might contain amines. Therefore, amine-free DMF or pre-optimization of the correct concentration of added amine and irradiation time is required to achieve highest resolution.

[1] W. R. Carmody, *J. Chem. Educ.* **1963**, *40*, A386.

[2] C. Costentin, M. Robert, J.-M. Savéant, *J. Am. Chem. Soc.* **2004**, *126*, 16051-16057.

[3] a, M. F. Wempe, B. Quade, P. Jutabha, T. Iwen, M. Frick, P. J. Rice, S. Wakui, H. Endou, *Nucleosides, Nucleotides Nucleic Acids* **2011**, *30*, 1312-1323; b, M. F. Wempe, P. Jutabha, B. Quade, T. J. Iwen, M. M. Frick, I. R. Ross, P. J. Rice, N. Anzai, H. Endou, *J. Med. Chem.* **2011**, *54*, 2701-2713.

[4] Y. Monguchi, A. Kume, K. Hattori, T. Maegawa, H. Sajiki, *Tetrahedron* **2006**, *62*, 7926-7933.