A Fluorescence-Based Screening Protocol for the Identification of Water Oxidation Catalysts

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Efficient catalysts are crucial for the sustainable generation of fuel by splitting water. A versatile screening protocol would simplify the identification of novel and better catalysts by using high throughput experimentation. Herein, such a screening approach for the identification of molecular catalysts for chemical oxidation of water is reported, which is based on oxygen-sensitive fluorescence quenching using an OxoDish. More than 200 reactions were performed revealing several cat-alysts, for example, a dinuclear Fe complex that produced oxygen under the used reaction conditions. Clark electrode measurements confirmed a similar rate in oxygen evolution, making the developed parallel screening approach a robust and versatile tool to screen for molecular water oxidation cata-lysts using chemical oxidants under acidic and neutral condi-tions.

Introduction

The development of efficient processes to generate chemical fuels using sunlight as primary energy source can significantly contribute to the total energy demand and diminish our de-pendence on fossil fuels and nuclear power. The light-driven water splitting reaction to generate molecular hydrogen and oxygen is one of the most promising processes for producing a clean fuel, and catalysis plays a crucial role to facilitate this. For water splitting in a photoelectrochemical (PEC) cell, the two half reactions, water oxidation (anode side) and proton re-duction (cathode side), both require their own specialized cata-lysts. Molecular catalysts can be tailored both structurally and electronically by modifying the ligand and can be studied mechanistically using various spectroscopic techniques, which give them an advantage over heterogeneous systems. Despite the extensive research conducted by the scientific community, only a relatively small number of molecular water oxidation catalysts is known to date.[1] The lack of structure–activity rela-tionships and detailed mechanistic insight makes the rational design of (molecular) water oxidation catalysts that work at low overpotential while displaying a fast catalysis combined with high stability a difficult task.

High throughput screening (HTS) techniques[2] are widely ap-plied in the field of catalysis and facilitate the identification of new and possibly better water oxidation catalysts. A particular difficulty for setting up a HTS system for water oxidation is that the critical observable parameter, the reaction product, is molecular oxygen. Most typical chemical HTS equipment is not suitable for monitoring oxygen-producing reactions or have a high propensity of false positive results (e.g., due to detec-tion of other gasses such as CO_2 when using pressure sensors), which limits the amount of reactions that can be performed tremendously. To speed up the development of water oxida-tion catalysts, there is a need for a reliable and fast lead-find-ing method that allows the evaluation of large numbers of cat-alysts. The leads found should subsequently be analyzed fur-ther and characterized by more standard experiment tech-niques, such as electrochemistry, Clark electrode analysis,[3] headspace analysis using gas chromatography, and/or the use of pressure sensors,[1,4] that are much more laborious and/or expensive to perform. A few combinatorial approaches have been reported to screen a variety of anode materials, mainly metals and metal oxides, for the electrochemical oxidation of methanol and water by making use of indicators,[5] a pH-sensi-tive fluorescent indicator dye,[6] detection of bubble forma-tion,[7] electrochemical techniques,[8] or an oxygen-sensitive fluorescence-quenching assay.[9] Herein, we present a new screening approach based on oxygen-sensitive fluorescence quenching for the chemical oxidation of water that is especial-ly designed for molecular catalysts. For this, the commercially available OxoDishes are used, which are 24-well microplates equipped with optical oxygen sensors integrated at the bottom of each well and which are currently only used to study the growth of algae and bacteria by monitoring the oxygen con-tent. These sensors can be read out using a SensorDish Reader (see Figure 1).[10] The sensor contains an oxygen-sensitive indi-cator dye, which is immobilized in a thin polymer film. The phosphorescence is quenched by the presence of oxygen, and the shortened phosphorescence life time of the dye is thus an indicator for the amount of oxygen present in the solution.

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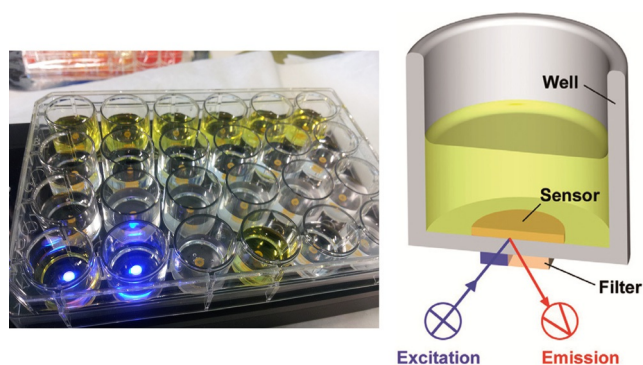
Figure 1. Photograph of the OxoDish on the SDR SensorDish Reader (left) and a schematic representation of an OxoDish well equipped with an optical oxygen sensor integrated at the bottom (right, with permission of Pre-Sens—Precision Sensing GmbH). The sensor is protected by a thin polymer matrix, together forming the sensor spot.

Typically, to screen water oxidation catalysts only one half-reaction of full water splitting (the anode side) is studied and, thus, to complete the catalytic cycle an artificial electron (and proton) acceptor is required that otherwise would be used in the proton reduction at the cathode side. The artificial acceptors, or chemical oxidants, chosen all have their own advantages and disadvantages.[11] In principle, the chemical oxidant also determines 1) the usable pH range, 2) the solvent/buffer, and 3) the oxidation potential that can be used. Although the OxoDish has been extensively used for biological aqueous solutions, no data are available on the suitability and robustness of the OxoDish for the strongly oxidizing reaction conditions used in water oxidation chemistry.

Results and Discussion

Initial experiments were designed to test the three most studied chemical oxidants: cerium ammonium nitrate (CAN), sodium periodate ($NaIO_4$), and ruthenium(III) tris(bipyridine) ($[Ru^{III}(bpy)_3]$). Using these oxidants, a pH domain between 1 and 8 is covered and both one-electron acceptors (CAN, Ru^{III}) and a two-electron acceptor ($NaIO_4$) are included. As is illustrated in Figure 2, the addition of the $NaIO_4$ solutions (blue lines) to the OxoDishwell has no observable influence on the oxygen concentration and shows that the sensor is not affected by the presence of $NaIO_4$. After the addition of a solution of CAN, the oxygen level drops below 100 nmol mL^{-1} and equilibrates back to almost the original value of roughly 250 nmol mL^{-1} after 10 min, where it remains constant. After an overnight experi-
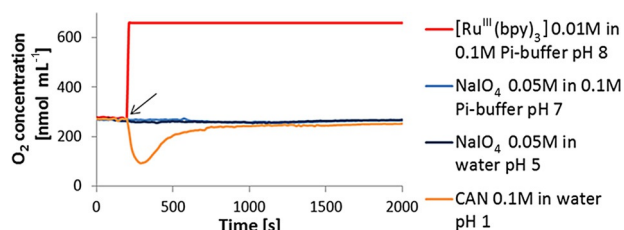
Figure 2. OxoDish response using different chemical oxidants.

ment, the sensor is still intact but sometimes no longer fixed to the bottom, suggesting that the glue is affected. Interestingly, the addition of the freshly prepared $[Ru^{III}(bpy)_3]$ solution to the phosphate buffer of pH 8 already in the OxoDish well results in a maximum signal intensity of >650 nmol mL^{-1}. Clearly, the $[Ru^{III}(bpy)_3]$ dye interferes with the sensor dye of the OxoDish, preventing the detection of the sensor phosphorescence signal by the SensorDish Reader.

Next, the sensitivity of the OxoDish was examined for a pH range between 1 and 7 by using CAN at pH 0.7 and $NaIO_4$ in aqueous (buffered) solutions of pH 4.5 and 7. The initial experiments were performed using N-dimethylimidazolin-2-ylidene iridium(pentamethylcyclopentadienyl)dichloride ($[IrCp*(NHC)Cl_2]$) complex **1**; see Figure 3), which is known to oxidize water using either ceric ammonium nitrate (CAN) or sodium periodate as chemical oxidants.[12] The OxoDish wells were filled with solutions of CAN and $NaIO_4$ (buffered and unbuffered) prepared in double-distilled water. A catalyst solution in water was carefully added while measuring the oxygen levels in solution. Each OxoDish well was filled with 1.2 mL reaction mixture after which the full OxoDish was covered with a seal to prevent gas diffusion. Control experiments, that is, OxoDish wells containing only the buffered chemical oxidant solution showed no increase in oxygen levels whereas reaction wells containing catalyst **1** displayed a continuous increase of the oxygen concentration (Figure 4).

Depending on the catalyst concentration, the oxygen levels increased very rapidly, reaching the maximum detection value within a few data points, or slower, demonstrating that the oxygen production depends on catalyst concentration. The continuous monitoring of oxygen formation makes our methodology ideal for fast lead finding. Thus, in addition to the discovery of a new potential catalyst an estimation of the relative rate is also provided. Further studies using, for example, a Clark electrode, stop-flow kinetics, and electrochemistry can be used to optimize the reaction conditions and study the catalyst in more detail.

To validate the method, four benchmark water oxidation catalysts (WOCs; **1**, **2**, **3**, and **4**), were selected (Table 1). Ru complex **2** showed an extremely fast increase in the oxygen level, and within 15 s (one data point) the solution was saturated with oxygen (Table 1, entry 2); this confirms its very high activity for water oxidation using CAN.[1f] Remarkably, using the two-electron oxidant $NaIO_4$ no oxygen evolution was observed. The complete inactivity of **2** using $NaIO_4$ underlines the need to screen various chemical oxidants to not overlook a potential catalyst lead and to identify which catalysts have an activity that is sensitive to the chemical oxidant.

One of the most promising Fe-based WOCs, reported by Fillol et al., are the iron triflate (OTf) or chloride (Cl) complexes bearing the tetradentate nitrogen ligand N,N′-dimethyl-N,N′-bis(2-pyridylmethyl)-cyclohexane-1,2-diamine (mcp) $[Fe(OTf)_2(mcp)]$ and $[Fe(Cl)_2(mcp)]$ (complexes **3** and **4**, respectively).[13] These catalysts were also identified as active catalysts under the applied reaction conditions (see Table 1, entries 3 and 4); this confirms that 1) all four already known WOC catalysts were positively identified within the OxoDish method and
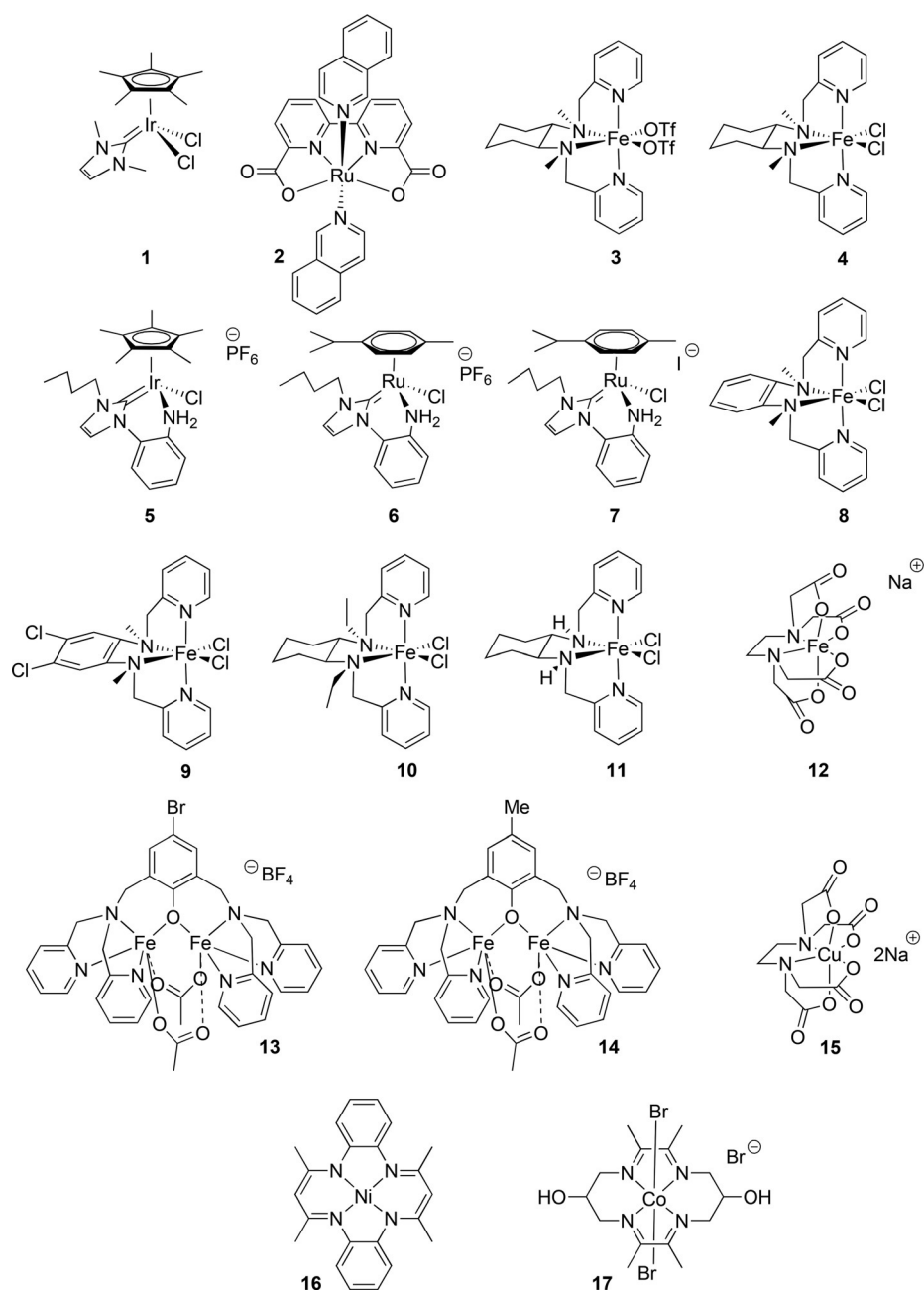
Figure 3. Selection of the evaluated catalysts (full overview in the Supporting Information).

readily available transition-metal catalysts based on first row transition metals are preferred. Therefore, for the remainder of the catalyst screening, we particularly focused on Fe-based water oxidation catalysts due to the use of the inexpensive, readily available metal.

As already described above, the Fe-based catalysts **3** and **4** (entries 7–10) formed oxygen under the applied reaction conditions. The closely related complexes **8**–**11** were also active, particularly when the one-electron oxidant cerium ammonium nitrate was used as chemical oxidant. The catalyst library was extended with other, closely related iron catalysts, and it was found that small changes in the ligand structure completely changed the activity of the catalysts (Figure 5 and also the Supporting Information). Changing the cyclohexyl backbone for an aromatic ring (**4** vs. **8**) resulted in only slightly lower activities, probably due to lower electron density on the Fe center. The small substituent on the two nitrogen atoms had a huge effect on the activity: methyl groups were optimal (**4**), ethyl moieties were tolerated (**10**), but lower activity was observed, and the catalyst with free NH functional groups (**11**) displayed very poor activity. Changing the methylene spacer for an amide linkage completely deactivated the catalyst (**18**). These findings can help to understand the structure–ac-

tivity relationship for this type of ligands, which facilitates the optimization of these catalysts.

In addition to the complexes analogues to benchmark WOCs, also some new leads were found that revealed activity. Under neutral conditions both the Fe–ethylenediaminetetraacetic acid (EDTA) complex **12** and the Cu–EDTA complex **15** demonstrated a low but significant increase in the oxygen concentration, reaching their maximum level after 1 h reaction time. Also, the dinuclear Fe complexes **13** and **14** were active oxygen evolution catalysts when using $NaIO_4$ as the chemical oxidant. Although these complexes are less active as the benchmark Fe complex **3**, the increase in oxygen level, even after almost 2 h reaction time, indicates that the stability is
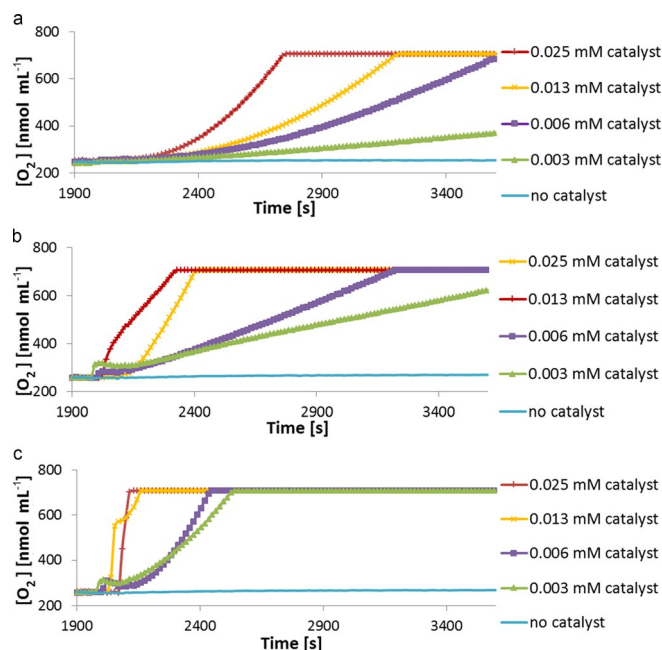
2) both chemical oxidants cerium ammonium nitrate and sodium periodate were appropriate oxidants.

Next, we set out to screen for new WOC catalysts and we performed over 200 reactions in the OxoDish examining various metal complexes (unknown for water oxidation catalysis) using different chemical oxidants and different pH value (Table 2).[14] During screening, oxygen was detected for all tested Ir- and Ru-based complexes (entries 1–6, and the Supporting Information). The relative rate of oxygen evolution allows the comparison of catalyst activity and shows that Ir catalyst **1** and Ru catalyst **2** are among the fastest tested WOC catalysts so far. However, when considering the eventual incorporation into a water splitting device, less expensive and more
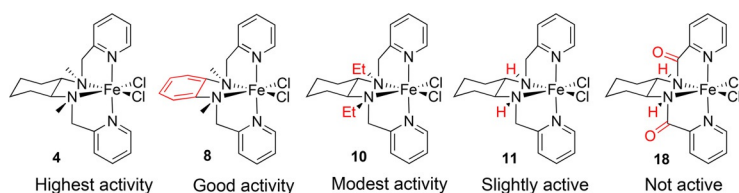
Figure 4. OxoDish response using various concentrations of catalyst **1** under different reaction conditions: a) 0.10 M CAN as chemical oxidant, b) 0.05 M NaIO$_4$ as chemical oxidant, and c) 0.05 M NaIO$_4$ as chemical oxidant in phosphate buffer pH 7.

Table 1. Benchmark water oxidation catalysts evaluated in the OxoDish.

Entry	Complex (metal)	Ratio oxidant[a]/complex	Activity [O$_2$][b] [min] CAN	NaIO$_4$	NaIO$_4$ at pH7
1	**1** (Ir)	1000	17	5	<1
2	**2** (Ru)	1000	<1	–	–
3	**3** (Fe)	1000	13	90	90
4	**4** (Fe)	500	32	75	75

[a] Amount of oxidizing equivalents; the concentration of the chemical oxidant (0.1 M in CAN, 0.05 M in NaIO$_4$) is kept constant in all experiments, only the amount of catalyst is varied. [b] The color indicates the amount of maximum measured O$_2$ concentration: red (high) = >650 nmol mL^{-1}, orange (medium) = 381–650 nmol mL^{-1}, yellow (low) = 270–380 nmol mL^{-1}, no color = <270 nmol mL^{-1}; the number is the time in minutes in which the maximum O$_2$ concentration is reached (smaller number = faster catalysis).

Table 2. Selection of screening results for WOCs in the OxoDish.

Entry	Complex (metal)	Ratio oxidant[a]/complex	Activity [O$_2$][b] [min] CAN	NaIO$_4$	NaIO$_4$ at pH7
1	**1** (Ir)	50	2	<1	<1
2	**1** (Ir)	1000	17	5	<1
3	**5** (Ir)	1000	60	15	4
4	**6** (Ru)	1000	40	–	88
5	**7** (Ru)	1000	32	–	50
6	**2** (Ru)	1000	<1	–	–
7	**3** (Fe)	250	2	63	100
8	**3** (Fe)	1000	13	90	90
9	**4** (Fe)	250	5	60	120
10	**4** (Fe)	500	32	75	75
11	**8** (Fe)	250	8	63	80
12	**9** (Fe)	500	47	–	–
13	**10** (Fe)	500	50	75	–
14	**11** (Fe)	250	27	–	–
15	**12** (Fe)	500	–	–	60
16	**13** (Fe)	50	–	100	100
17	**13** (Fe)	250	–	–	–
18	**14** (Fe)	50	–	–	100
19	**15** (Cu)	500	–	–	60
20	**16** (Ni)	500	–	–	25
21	**17** (Co)	500	–	–	32

[a] Amount of oxidizing equivalents; the concentration of the chemical oxidant (0.1 M in CAN, 0.05 M in NaIO$_4$) is kept constant in all experiments, only the amount of catalyst is varied. [b] The color indicates the amount of maximum measured O$_2$ concentration: red (high) = >650 nmol mL^{-1}; orange (medium) = 381–650 nmol mL^{-1}; yellow (low) = 270–380 nmol mL^{-1}; no color = <270 nmol mL^{-1}. The number is the time in minutes in which the maximum O$_2$ concentration is reached.

Figure 6. OxoDish versus Clark electrode. O$_2$ formation using 0.05 M NaIO$_4$ as chemical oxidant in phosphate buffer pH 7 using complex **13**.
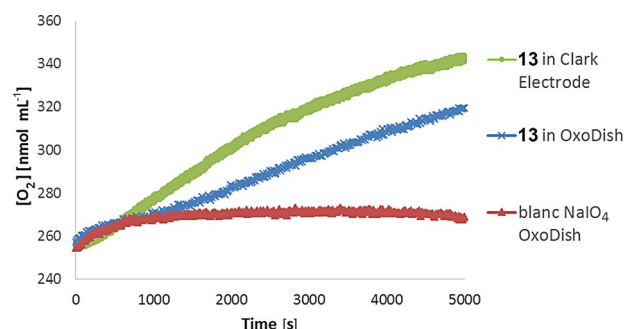
good, which makes these complexes interesting for further optimization. Also, for the Ni complex **16**, and the Co complex **17** a modest increase in the oxygen level was detected. More experiments are required to confirm the water oxidation properties of these complexes. For complex **13**, we confirmed the water oxidation activity by performing Clark electrode experiments that showed similar rates of oxygen formation (see Figure 6). This shows that the OxoDish can even be used to study the rate (and thus kinetics) of the reaction under certain reaction conditions, revealing the versatility of this parallel reaction and analysis tool. All leads found using the screening protocol are currently under further investigation.

Conclusions

We demonstrated in this contribution that the OxoDish provides a robust and versatile tool for the parallel screening of soluble metal complexes for water oxidation activity using chemical oxidants under acidic and neutral conditions. After validation of the

Figure 5. Structure–activity relationships.

protocol using known catalysts, the screening procedure was used to evaluate more than 200 complexes, with main focus on Fe complexes, revealing a few promising leads. Monitoring of the development of the oxygen level with time provided a first indication of the catalyst activity and similar rates were observed when using the Clark electrode. We foresee that the use of fast screening techniques accelerates the development of WOCs, and for this the OxoDish is an easy-to-use and relatively inexpensive methodology.

Experimental Section

Typical OxoDish experiment: a freshly unpacked OxoDish 24-well sensorplate (OD24) was placed on the SensorDish Reader. The wells (3 mL) were filled with aqueous solutions of the chemical oxidant (typical 1 mL of 0.12 M oxidant) and left for roughly 15 min to equilibrate. Next, the solution of catalyst [dissolved in double-distilled water with (if required) some acetonitrile added to dissolve the catalyst; typical 0.2 mL of 0.3 mM catalyst] was gently added to avoid disturbing the sensor response. Control experiments were performed by adding similar solutions without the catalyst (or oxidant). After finishing the additions, the plate was capped with a plastic seal.

OxoDish versus Clark electrode: to test the similarity between the OxoDish and the Clark electrode measurements, the protocol used for the screening was copied for the Clark electrode setup. After calibration of the Clark electrode (using air- and nitrogen-saturated water), the chamber was filled with the $NaIO_4$ solution in phosphate buffer (1.67 mL, 0.06 M, pH 7). After stabilization (5 min), the catalyst solution in water (0.33 mL, 0.5 mM) was added and the chamber was capped.

Data of the full screening are available in the Supporting Information.

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[14] Considering the number of experiments: for us, the number of complexes was the limiting factor. For a typical experiment, the preparation of the solutions and the filling of the plate takes approximately 1 h and analysis also takes 1 h (or less, depending on the catalyst concentration and rate). Thus, three to four plates a day can be analyzed using one OxoDish (72–96 experiments). This number can be increased by running multiple OxoDishes in parallel (integrated option in the software, although at a higher cost because additional SensorDish Readers are required) or use 96-well OxoPlates, which can be read out using a standard fluorescence reader.