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Photocatalytic benzylic C–H bond oxidation with a flavin scandium complex†

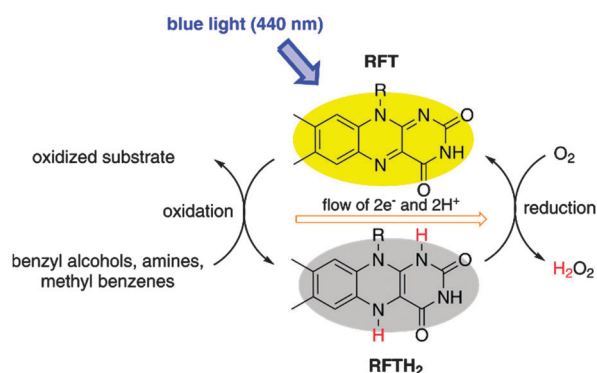Bernd Mühldorf and Robert Wolf*

The enhanced reduction potential of riboflavin tetraacetate co-ordinating to scandium triflate enables the challenging photocatalytic C–H oxidation of electron-deficient alkylbenzenes and benzyl alcohols.

The important role of flavins as photoreceptors and redox cofactors in nature has inspired the use of synthetic flavin analogues as bioinspired photocatalysts.[1] The most prominent example, riboflavin tetraacetate (RFT), catalyses the aerobic photooxidation of benzyl alcohols,[2] benzyl amines,[3] and sulfoxides (Scheme 1).[4,5] A particularly intriguing application of RFT is the photocatalytic C–H bond oxidation of alkyl benzenes to the corresponding aldehydes.[6,7] Spectroscopic studies revealed an initial electron transfer from the aromatic substrate to the singlet excited state $^1RFT^*$ as the basis of this process.[8] However, the limited reduction potential $E^0(^1RFT^*/^2RFT^-) = 1.67$ V vs. SCE exclusively allows the oxidation of very few selected substrates

which feature strongly electron-donating arene substituents. Most other substrates are unsuccessful, because their oxidation potential is too positive.

Fukuzumi *et al.* found that the redox potential of RFT can be modified by metal ion coordination.[9] As shown in Fig. 1, complexes of RFT with Mg^{2+}, Zn^{2+}, Yb^{3+} and Sc^{3+} ions have a significantly more positive reduction potential $E^0(^1RFT^*/^2RFT^-)$ in the excited singlet state. In particular, the Sc^{3+} system‡ appears promising as it features high fluorescence quenching rate constants of $(^1RFT–2Sc^{3+})^*$ in the presence of alkyl- and methoxy-substituted benzenes.[8] This indicates an efficient single electron transfer from the substrate to $(^1RFT–2Sc^{3+})^*$, which is a prerequisite for photocatalytic activity.
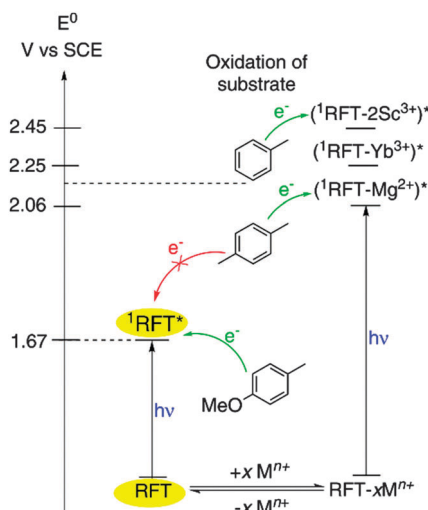
Motivated by these insights, we sought to explore the catalytic properties of RFT/metal salt combinations for challenging benzylic C–H bond oxidations. The reaction of ethylbenzene (**1**) to acetophenone (**2**) was chosen as a benchmark (Scheme 2), because **1** shows a high oxidation peak potential $(E^0_p(\mathbf{1}^{+\bullet}/\mathbf{1}) = 2.14$ vs. SCE) and

Scheme 1 Photocatalytic cycle for the aerobic oxidation of various organic substrates with riboflavin tetraacetate (RFT) and blue light.[5]

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Fig. 1 Enhanced reduction potentials $E^0(^1RFT^*/^2RFT^-)$ of RFT–metal ion complexes (RFT–xM^{n+}).[8,9]

Scheme 2 Photocatalytic oxidation of ethylbenzene.

therefore cannot be oxidised by ^{1}RFT* alone.[8] A screening of various Lewis acids (Table S1, ESI†) and solvents (Table S2†) indicated Sc(OTf)$_3$ in acetonitrile to be the best choice. Irradiation of **1** (0.02 mmol) in CH$_3$CN for 2.5 h with blue light (440 nm) in the presence of RFT (10 mol%) and Sc(OTf)$_3$ (20 mol%) afforded acetophenone **2** in 58% yield. Substrate **1** was completely consumed, and the formation of H$_2$O$_2$ was confirmed by UV-vis spectroscopy (Fig. S1†). Note that **2** is formed in <10% yield in the absence of Sc^{3+}-ions, while Mg(OTf)$_2$ and Zn(OTf)$_2$ gave only very low yields of **2**. The reaction is significantly accelerated by higher Sc^{3+} concentrations (Fig. S2†). In order to reduce the amount of Sc(OTf)$_3$ required, the effect of acids and other additives was investigated (Table S3†). Importantly, **1** is converted nearly four times as fast in the presence of HCl (30 mol%) with the same Sc(OTf)$_3$ concentration (Fig. S3†).

Using this optimized system, we subsequently assessed the substrate scope (Table 1). Toluene is converted to benzaldehyde

in 71% yield, while *p-tert*-butylbenzaldehyde and *p*-chlorobenzaldehyde are obtained in 68% and 84% yield, respectively (entry 1). Benzylethers do not give the corresponding esters, but benzaldehydes (entry 3). Diarylmethylene derivatives (entry 4) and benzyl alcohols (entries 5 and 6) are oxidised with good to excellent yields as well. Triphenylmethane and diphenylacetic acid both yield benzophenone *via* oxidative C–C cleavage.[10] Note that the oxidations of *p*-trifluorobenzyl alcohol and *p*-nitrobenzyl alcohol proceed selectively, but the reaction speed is slow, resulting in an incomplete conversion.

Control experiments confirmed that the reaction does not proceed in the dark, in the absence of RFT or under anaerobic conditions (Table S4,† entries 1–5). When the reaction was carried out in an atmosphere of pure dioxygen, slower bleaching of RFT was observed (Fig. S4†), but the yield of **2** did not improve (Table S4, entry 6). Moreover, a very similar yield (44%) was obtained in deuterated acetonitrile, therefore, a singlet oxygen pathway seems unlikely (Table S4,† entries 7 and 8).[11,12]

The reaction mechanism was probed by UV-vis spectroscopy. Before starting to irradiate a mixture of **1**, RFT, Sc(OTf)$_3$ and HCl in acetonitrile with blue light (440 nm), an absorption band can be identified at λ_{max} = 390 nm both under aerobic conditions (Fig. S5†) and under argon (Fig. 2). This band may be assigned to RFTH$^+$–2Sc^{3+} by comparison with the characteristic spectrum of uncoordinated RFTH$^+$.[13] The IR spectrum of the mixture shows that the C=O stretching bands are shifted to lower frequency compared to those of RFTH$^+$ in the absence of metal ions (Table S5†). This indicates that the scandium(III) ions coordinate to the carbonyl groups in RFTH$^+$–2Sc^{3+}.‡[8]

A possible catalytic cycle is displayed in Scheme 3. In line with previous fluorescence quenching experiments by Fukuzumi *et al.*, we propose that the electron transfer occurs between the

Table 1 Photocatalytic oxidation: scope and limitations^a

Entry	Substrate	Product	No Sc^{3+} yield^b [%]	R	Conv.^{b} [%]	Yield^b [%]
1			0	H	96	71
			5	^{t}Bu	100	68
			8	Me^d	100	62
			0	Cl^d	100	84
			0	CN	56	29
			0	CO$_2$Me	44	15
2			3	Me	100	60
			0	CO$_2$Me	92	49
3^c			0	H	93	90
			5	OMe	100	63
4			4	H	100	93
			6	Ph	89	52
			23	COOH	n.d.	80
5			17	H	100	95
			0	Me	100	81
6^c			7	F	100	88
			12	Cl	100	73
			14	Br	100	84
			0	CF$_3$	63	53
			0	NO$_2$^{d}	66	44

^{a} All reactions were performed with substrate (0.02 mmol), RFT (10 mol%), HCl (37%, 0.8 μL) and Sc(OTf)$_3$ (4.6 mM) in 1 mL MeCN and irradiated with blue light (440 nm, 3 W) for 2.5 h when not indicated otherwise (see footnote d). ^{b} Conversion and yield determined by GC-FID integration. ^{c} No HCl added; n.d. = not determined. ^{d} Irradiation time: 0.5 h (R = Me), 1 h (R = Cl) and 7 h (R = NO$_2$).
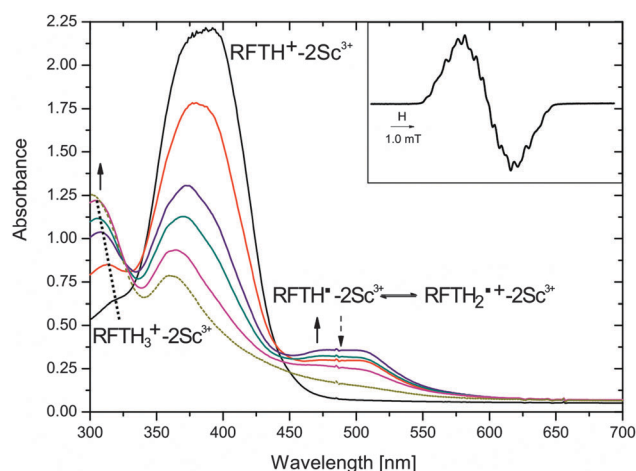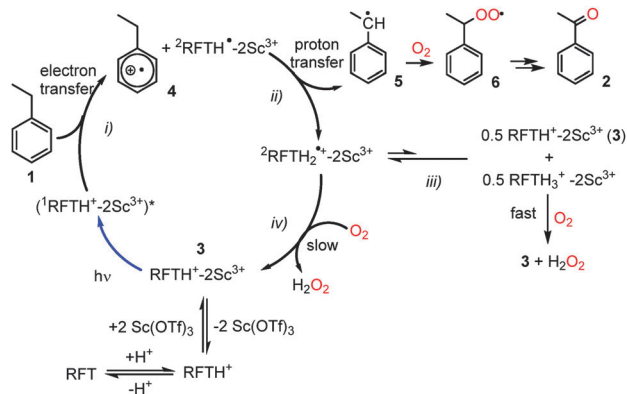

Fig. 2 UV-vis absorption spectra of ethylbenzene (5.8 mM) and RFT (0.14 mM) in the presence of Sc(OTf)$_3$ (0.68 mM) and HCl (2.7 mM) during irradiation with blue light in deaerated MeCN at 298 K under nitrogen (straight: 0 s, 60 s, 120 s, 180 s, 360 s; dashed: 2 h). Inset: ESR-spectrum of ^{2}RFTH$_2$$^{•+}$–2Sc^{3+} generated in the photocatalytic reaction RFT (3.0 mM) with ethylbenzene (20 mM), Sc(OTf)$_3$ (10 mM) and 10 mM HClO$_4$ in deaerated MeCN at 298 K. Parameters obtained by computer simulation: g = 2.0033, a(N^5) = 6.7 G, a(N^{10}) = 4.6 G, a(H^5) = 10.6 G, a(3H^8) = 2.9 G, a(N^{10}–CH$_2$) = 4.3 G; see the ESI† for the labelling scheme.

Scheme 3 Proposed mechanism for the photocatalytic aerobic oxidation of ethylbenzene (**1**) to acetophenone (**2**) with RFT in presence of Sc^{3+}-ions and HCl.

substrate and the photoexcited flavin metal complex (^{1}RFTH$^+$–2Sc^{3+})* in its singlet state (step i).[8] This electron transfer produces the ethylbenzene radical cation **4** and the protonated flavin radical complex ^{2}RFTH$^•$–2Sc^{3+}. It seems likely that the ^{2}RFTH$^•$–2Sc^{3+} complex is then protonated to yield ^{2}RFTH$_2^{•+}$–2Sc^{3+}, while the strongly acidic ethylbenzene radical cation **4** is deprotonated to the benzyl radical **5** (step ii).§[14] ^{2}RFTH$_2^{•+}$–2Sc^{3+} should give rise to broad absorptions at λ_{max} = 400–550 nm similar to those of the uncoordinated dihydroflavin radical cation ^{2}RFTH$_2^{•+}$.[15] Such a broad band is indeed observed in the UV-vis spectrum of the reaction mixture under argon (Fig. 2). In addition, the ESR spectrum of the reaction mixture of **1**, RFT, Sc(OTf)$_3$ and HClO$_4$ obtained while irradiating at 440 nm exhibits a signal at g = 2.0033 (Fig. 2, inset), which is in line with the expected spectrum for RFTH$_2^{•+}$–2Sc^{3+}.[8] The presence of the scandium(III) ions appears to have only a slight effect on the shape of the ESR spectrum. The hyperfine coupling constants obtained by computer simulation are similar to those reported for free ^{2}RFTH$_2^{•+}$.[16] The ESR spectrum of a mixture of **1**, RFT, Sc(OTf)$_3$ and HCl (instead of HClO$_4$, Fig. S6†) is more complicated and thus defied a satisfactory simulation so far. This is presumably due to the formation of an equilibrium between RFTH$_2^{•+}$–2Sc^{3+} and RFTH$^•$–2Sc^{3+} with the weaker acid HCl.

There are at least two conceivable pathways that connect the benzyl radical **5** with the final product **2** (Scheme 3). One possibility is that ^{2}RFTH$_2^{•+}$–2Sc^{3+} recombines with **5** to form a covalent RFT-benzyl radical adduct (not shown in Scheme 3), which rapidly collapses under irradiation in air to product **2** and RFTH$^+$–2Sc^{3+} (**3**).[17] However, this pathway seems less likely based on the UV-vis spectra of the reaction mixture, where characteristic broad absorptions are expected for such an adduct at λ_{max} = 600–630 nm. An alternative pathway is the conversion of **5** into the benzylperoxyl radical **6**, which subsequently transforms into **2** via the benzyl hydroperoxide.[18] As observed for ^{2}RFTH$_2^{•+}$, ^{2}RFTH$_2^{•+}$–2Sc^{3+} may disproportionate into oxidized RFTH$^+$–2Sc^{3+} and the reduced dihydroflavin RFTH$_3^+$–2Sc^{3+} (step iii).[15] The formation of the latter species is supported by the observation of an absorption band at 295 nm that increases over time (see Fig. 2).[15] RFTH$_3^+$–2Sc^{3+} can react

with dioxygen, regenerating **3** while producing H$_2$O$_2$ (Fig. S8†).[16] In addition, RFTH$^+$–2Sc^{3+} (**3**) may also be regenerated by the direct reaction of ^{2}RFTH$_2^{•+}$–2Sc^{3+} with O$_2$ (step iv, Fig. S7†). This process may conceivably be facilitated by Lewis acid coordination.[19]

We presume that the mechanism of the catalytic oxidation of benzyl alcohols (Table S1 (ESI†), entries 5 and 6) is analogous to the one previously suggested by Fukuzumi *et al.* for the oxidation *p*-chlorobenzyl alcohol.[8] The proposed catalytic cycle involves an initial electron transfer from the substrate to (^{1}RFT–2Sc^{3+})*, followed by proton transfer forming the hydroxybenzyl radical (*p*-R-C$_6$H$_4$CHOH$^•$) and the protonated RFT radical anion (^{2}RFTH$^•$–2Sc^{3+})*. Subsequent H atom transfer between these species yields the aldehyde and RFTH$_2$–2Sc^{3+}.

In summary, RFT/scandium triflate is an efficient photocatalytic system for the aerobic oxidation of alkylbenzenes and electron deficient benzyl alcohols. The results show that the well-known effect of Lewis acid coordination on the redox potential of flavins[8,9] can be exploited to improve their photocatalytic properties. An extension of this principle, and an exploration of the effects of other metal ions including redox-active ones, is hand.

Note added after first publication: This article replaces the version published on 03 Feb 2015, which contained errors in the text introduced by the Editorial Office.

Notes and references

‡ No structural information is presently available on the scandium(III) complexes in solution, though it seems likely that these correspond to neutral or cationic complexes or clusters with the general composition [Sc$_x$X$_y$(RFTH$_n$)$_z$]$^{m+}$ (X = OTf or Cl). We choose to designate the species involved in the catalytic mechanism as RFTH$_n^{m+}$–2Sc^{3+} for simplicity.
§ The pK_a of the closely-related RFTH$_2^{+•}$ radical is approximately 2, while the pK_a of a toluene radical cation in MeCN is estimated to −12 to −13.[20]

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