Photocatalysis

C-H Photooxygenation of Alkyl Benzenes Catalyzed by Riboflavin Tetraacetate and a Non-Heme Iron Catalyst

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Dedicated to Professor Henri Brunner on the occasion of his 80th birthday

Abstract: A mixture of the photocatalyst riboflavin tetraacetate (RFT) and the biomimetic non-heme iron complex [Fe(TPA)- $(MeCN)_2$](ClO₄)₂ (TPA = tris(2-pyridylmethyl)amine) efficiently catalyzes the visible-light-driven aerobic oxidation of alkyl benzenes to ketones and carboxylic acids. An RFT-catalyzed photocycle and the independent action of the iron complex as a catalyst for H_2O_2 disproportionation and alkyl benzene oxygenation ensure high yields and selectivities.

he photocatalytic oxygenation of alkyl benzenes using dioxygen and visible light is an atom-economic and benign alternative to classical oxidation methods.^[1] Only a few photocatalysts are suitable for such transformations.^[2–5] Organic dyes, such as 1,4-dicyanonapthalene, the 10-phenyl-9-methylacridinium ion, and the 3-cyano-1-methylquinolinium ion, as well as iron porphyrins and manganese porphyrinoids catalyze the photooxygenation of toluene derivatives and related substrates.^[3,4] Several heterogeneous catalysts have also been reported.^[5]

The vitamin B_2 derivative riboflavin tetraacetate (RFT) is a promising and versatile catalyst for the visible-light-driven photooxidation of benzyl alcohols,^[6] benzyl amines,^[7] and sulfides.^[8] Moreover, a derivative of RFT was very recently applied for [2+2] cycloadditions.^[9] However, the C-H oxygenation of alkyl benzenes is difficult to achieve using RFT alone.^[10] The additive Sc(OTf)₃ enables the oxygenation of alkyl benzenes with electron-withdrawing substituents, but this Sc(OTf)₃/RFT system performs poorly for various other benzylic substrates.^[11,12] We herein report that a dual catalyst system consisting of RFT and the tris(2-pyridylmethyl)amine complex [Fe(TPA)(MeCN)₂](ClO₄)₂ (4)^[13] efficiently catalyzes the challenging photooxygenation of alkyl benzenes. The catalytic activity of 4 for H_2O_2 disproportionation and alkyl benzene oxygenation appears to be key for the high efficiency of this catalyst combination.

The formation of hydrogen peroxide as a by-product is a major drawback of the previously established RFT-catalyzed photocycle (Scheme 1, step i).^[14] H_2O_2 degrades RFT under irradiation. As a result, the corresponding ketones and benzyl alcohols are obtained as product mixtures in poor

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Scheme 1. Proposed dual catalysis mechanism for the oxidation of benzylic substrates exemplified for the oxidation of 4-ethylanisole (1) to 4-acetylanisole (2) and 4-methoxy- α -methylbenzyl alcohol (3).

yields owing to rapid photocatalyst bleaching (see the Supporting Information, Chapters S2 and S3).^[10,15] We wondered whether this problem could be solved by adding a metal complex that catalyzes H₂O₂ disproportionation or utilizes photochemically generated H₂O₂ as an oxidant. In this context, it is worth mentioning that a photobiocatalytic tandem catalyst system developed by Hollmann et al. enables impressive stereospecific visible-light-driven sulfoxidations. alkene epoxidations, and C-H hydroxylations.^[16] This system uses a catalyst combination of flavin mononucleotide and a peroxidase enzyme and EDTA as a sacrificial electron donor. Feringa et al. reported that bioinspired iron complexes with tetra- and pentadentate nitrogen donor ligands catalyze the oxidation of ethylbenzene and 4-ethylanisole with H_2O_2 (Scheme 1, step ii), albeit with low yields and selectivities.^[17] Moreover, the ability of such iron complexes to catalyze H_2O_2 disproportionation (Scheme 1, step iii) is well-known.^[18] Lower H₂O₂ concentrations should improve the photostability of RFT, allowing the flavin-mediated oxidation of the benzyl alcohol to the ketone (Scheme 1, step iv) to proceed.^[14,15]

We initially studied the effect of adding selected biomimetic iron complexes to the benchmark oxidation reaction of 4-ethylanisole (1) to 4-acetylanisole (2) and 4-methoxy- α methylbenzyl alcohol (3; Figure 1 and Chapters S2 and S4). In line with previous results by König et al., the photooxygenation of 1 with RFT gave unsatisfactory yields for 2 (30%) and



[a] All reactions were performed with substrate (0.02 mmol), RFT (10 mol%), iron catalyst (8 mol%) in 1.5 mL MeCN/H₂O (1/1, v/v) and irradiated with blue light (440 nm, 3 W) for 60 min. Conversion and yield were determined by GC-FID integration.



Figure 1. Reaction-time profiles for the aerobic oxygenation of 1 (0.02 mmol) to **2** (\blacktriangle) and **3** (\blacklozenge) catalyzed by RFT (10 mol%) in the presence of an iron complex [8 mol%; **4** (red), **5** (blue), or **6** (green)] in MeCN/H₂O (1:1, v/v) under irradiation with blue light (440 nm); lines are visual guides only.

3 (12%) in the absence of a cocatalyst.^[10] In contrast, ketone **2** was obtained exclusively in high yield (80%) when a mixture of RFT (10 mol%) and **4** (8 mol%) was employed. In the initial stages of the reaction, ketone **2** and benzyl alcohol **3** are formed simultaneously (Figure 1), but **3** is subsequently converted into **2** by an RFT-catalyzed process (Scheme 1, step iv).^[14] The related non-heme iron complexes **5**^[19] and **6**^[20] gave a reaction profile similar to that of **4**, but the reactions took longer to reach completion (Figure 1). Other non-heme iron complexes and binary iron salts such as Fe(ClO₄)_x (x = 2 or 3) turned out to be less effective (Chapters S2 and S4).

RFT/4 was the most expedient catalyst combination; hence we subsequently investigated its substrate scope (Table 1). Esters are selectively obtained from benzyl ethers in very good yields (entry 1). Xanthene affords xanthen-9-one in an excellent yield of 96% (entry 2). Similarly, the oxidation



Entry	Substrate	Product	R,n,X	t [h]	Yield [%] ^[c]
1 ^[d]	R	R COMe	H OMe	24 3.0	79 84
2 ^[d]			O S	1.5 0.1	96 99
3			-	2.5	66
4 ^[f]		€ C C C C C C C C C C C C C C	1 2	2.0 2.0	70 70
5	PhPh	Ph Ph	_	2.5	48
6	Ph Ph	0	_	1.5	76
7	R	R	OMe Br ^[e] H ^[e]	2.5 2.5 1.0	80 72 74
8	R	R OH	OMe Cl ^[e] Br ^[e]	8 5 5	80 60 62
9	OH R	R	H Me	2.5 2.5	81 68
10	OH R	R	F Cl Br NO_2 CO_2Me CF_3	2.5 1.0 2.5 16 4.5 8	74 74 72 71 83 60

[a] Unless noted otherwise, the reactions were performed with substrate (0.02 mmol), RFT (10 mol%), [Fe(TPA) (MeCN)₂](ClO₄)₂ (**4**, 2 mol%) in 1.5 mL MeCN/H₂O (1:1, v/v) and irradiated with blue light (440 nm, 3 W). [b] Results of analogous experiments using MnO₂ and Fe(ClO₄)₃ as the cocatalysts are given in the Supporting Information, Chapter S2). [c] Conversion and yield determined by GC-FID. [d] In MeCN, **4** (8 mol%). [e] In MeCN, HClO₄ (30 mol%) as an additive. [f] **4** (8 mol%).

of thioxanthene is fast and proceeds quantitatively. Remarkably, overoxidation was not observed although the oxidation of sulfides to sulfoxides is known to proceed by an RFTcatalyzed singlet oxygen pathway in the absence of a cocatalyst.^[8] Isochroman, indane, and tetrahydronaphthalene are converted into the corresponding ketones in good yields (entries 3 and 4). The photocatalytic oxygenation of tolane gives benzil in a moderate yield of 48% (entry 5) whereas *trans*-stilbene affords benzaldehyde in 76% yield (entry 6). *para*-Substituted ethylbenzenes afford the corresponding GDCh

acetophenones in good yields when $HClO_4$ (30 mol%) is added to the reaction mixture (entry 7). Toluene derivatives are first rapidly converted into aldehydes and subsequently into the corresponding carboxylic acids (entry 8) through an iron-catalyzed aerobic oxidation process (Chapter S4). Benzyl alcohols with strongly electron-withdrawing para substituents ($R = NO_2$, CO_2Me , CF_3) are also converted into the corresponding aldehydes with high efficiency (entries 9 and 10). For synthetic applications, an efficient separation of the catalysts from the product is highly desirable. As shown by UV/Vis spectroscopy, both catalyst components can be easily removed by adsorption on basic alumina, whereas <1% of the product are lost in this operation (Chapter S4). The oxygenation of 1 does not proceed in the dark, in the absence of RFT, or under an N₂ atmosphere (Chapter S2). The presence of water is crucial for a high reaction rate (Chapter S4). Product yield and substrate conversion are unaffected when the reaction is carried out in an atmosphere of pure dioxygen, and the yield of 2 was 60% in CD₃CN/D₂O (1:1, v/v; Chapters S2 and S4). A singlet oxygen pathway thus appears to be unlikely.^[21]

Whereas RFT/4 efficiently catalyzes the photooxygenation of alkyl benzenes, RFT alone shows only modest catalytic activity (Chapter S2). Insights into the striking effect of the iron cocatalyst were gained from spectroscopic investigations and monitoring the reaction progress. Fluorescence emission quenching experiments revealed enhanced quenching of the excited singlet state, ¹RFT*, in the presence of various metal complexes or metal salts (Chapter S2). However, there seems to be no correlation between the magnitude of the Stern-Volmer constants and the catalyst activity, which indicates that the observed emission quenching is probably unproductive. An ESI-MS spectrum of RFT/4 (Chapter S4) showed signals corresponding to $[Fe(TPA)(MeCN)]^{2+}$ (m/z 193.5) and RFTH⁺ (m/z 545.2). Additional signals were apparent at m/z 445.1, 889.5, and 989.5, which may indicate the formation of an adduct between RFT and 4 (Chapter S4). Nonetheless, the UV/Vis and IR spectra of the catalyst mixture correspond to a superposition of the individual spectra of 4 and RFT, which suggests that the partial complex formation observed by ESI-MS, if at all present at the lower catalytic concentrations, does not affect the ground state of the photocatalyst.

Whereas a direct interaction between RFT and the cocatalyst thus does not seem to be responsible for the improved catalytic activity, metal-catalyzed H₂O₂ disproportionation is important. The rapid photobleaching of RFT observed in the absence of a cocatalyst is effectively diminished by the addition of complex 4 (Chapter S4). Compared to using RTF alone, the yields of 2(30%) and 3(12%) improved to 60% and 8%, respectively, with manganese dioxide as the cocatalyst instead of 4 (Chapters S2 and S4). MnO₂ has no oxygenation activity; therefore, this increase must be attributed to its activity as an H₂O₂ disproportionation catalyst. The efficiencies of the RFT/4 and RFT/MnO₂ combinations can be directly compared when the concentrations of the cocatalysts are adjusted such that the bleaching rates of RFT are the same (Figure 2a). Even when only 0.5 mol% of 4 are used, the combined yield of 2



Figure 2. a) Reaction-time profiles of the photooxygenation of 1 (0.02 mmol) to **2** and **3** catalyzed by RFT/MO₂ (**■**, black) or RFT/**4** (**●**, red) with RFT (8 mol%) and MnO₂ (20 mg) or **4** (0.5 mol%); the combined yield is defined as the sum of the molar yields of **2** and **3** divided by the molar amount of converted starting material **1**; the relative concentration of RFT was determined by the change in the absorbance A at λ_{max} = 443 nm (inset). b) Reaction-time profile of the photooxygenation of **1** (0.02 mmol) to **2** and **3** catalyzed by RFT/**4** in the absence of additional H₂O₂ (**▲**, blue) and with addition of **1** equiv H₂O₂ (**■**, black) before starting to irradiate at 440 nm; catalyst loadings: RFT (8 mol%), **4** (8 mol%); the inset shows a magnification of the reaction-time profile; lines are visual guides only.

and **3** is still substantially higher for RFT/4 than for RFT/ MnO₂. RFT/MnO₂ also performed significantly worse than RFT/4 in the oxygenation of related alkyl benzenes (Chapter S2). Assuming that MnO₂ and **4** are efficient H_2O_2 disproportionation catalysts under these conditions, it seems likely that the higher yields of **2** obtained with RFT/4 are due to the additional oxygenation activity of the iron complex (Scheme 1, step ii).

An additional monitoring study further supports the relevance of the oxygenation activity of the iron complex (Figure 2b). In the presence of RFT and 4, the formation of 2 and 3 is initially slow (<2% yield after two minutes). Subsequently, the reaction rate starts to increase rapidly. By contrast, a high initial rate was observed when H_2O_2 (1 equiv) was added immediately before starting the irradiation. In this

case, **2** (35%) has already been formed in substantial yield after the first two minutes. This change in the reaction kinetics is likely due to the ability of the iron catalyst to enable the oxygenation of **1** independently from RFT as soon as H_2O_2 is present in the reaction solution. A plausible mechanism is based on the well-investigated reaction between **4** and H_2O_2 .^[22] Spectroscopic and kinetic studies have shown that the addition of H_2O_2 to solutions of **4** in acetonitrile gives rise to a low-spin hydroperoxido iron(III) complex, $[Fe^{III}(TPA)-(OOH)]^{2+}$, which has been proposed to be converted into the putative iron(V) oxidant $[Fe^V(TPA)(O)(OH)]^{2+}$ in the next step.^[22,23]

In conclusion, the combination of the photocatalyst riboflavin tetraacetate with the bioinspired complex [Fe- $(TPA)(MeCN)_2](ClO_4)_2$ (4) affords a readily accessible, inexpensive, and efficient catalyst system for the visible-lightdriven aerobic C-H bond oxidation of alkyl benzenes. The reactivity of the iron complex with photocatalytically generated H₂O₂ is key to ensuring high conversions and selectivities. Our experiments have indicated that 4 acts as an H₂O₂ disproportionation catalyst and an oxygenation catalyst at the same time. Other recently reported dual photooxygenation catalyst systems rely on the direct photocatalytic generation of reactive transition-metal oxo species.^[24] Unlike the complementary enzyme-based photobiocatalytic tandem catalyst system reported by Hollmann and co-workers, the present system uses a transition-metal cocatalyst; a sacrificial electron donor is not required.^[16] The application of a wider range of cocatalysts and an extension to other useful substrate classes are currently under investigation.

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- M. Hudlicky, Oxidations in Organic Chemistry, ACS Monograph No. 186, American Chemical Society, Washington, 1990.
- For reviews on photocatalytic oxygenations, see: a) S. Fukuzumi, *Dalton Trans.* 2015, 44, 6696; b) S. Fukuzumi, K. Ohkubo, *Chem. Sci.* 2013, 4, 561.
- [3] For selected examples of using organic photosensitizers, see: a) J. Jung, K. Ohkubo, D. P. Goldberg, S. Fukuzumi, J. Phys. Chem. A 2014, 118, 6223; b) G. Pandey, S. Pal, R. Laha, Angew. Chem. Int. Ed. 2013, 52, 5146; Angew. Chem. 2013, 125, 5250; c) S. Fukuzumi, K. Doi, A. Itoh, T. Suenobu, K. Ohkubo, Y. Yamada, K. D. Karlin, Proc. Natl. Acad. Sci. USA 2012, 109, 15572; d) S. Fukuzumi, J. Yuasa, N. Satoh, T. Suenobu, J. Am. Chem. Soc. 2004, 126, 7585; e) K. Ohkubo, S. Fukuzumi, Org. Lett. 2000, 2, 3647.

- [4] For selected examples of using photosensitizers based on porphyrin or porphyrinoid complexes, see: a) H. M. Neu, J. Jung, R. A. Baglia, M. A. Siegler, K. Ohkubo, S. Fukuzumi, D. P. Goldberg, J. Am. Chem. Soc. 2015, 137, 4614; b) J. Rosenthal, T. D. Luckett, J. M. Hodgkiss, D. G. Nocera, J. Am. Chem. Soc. 2006, 128, 6546; c) L. Weber, R. Hommel, J. Behling, G. Haufe, H. Hennig, J. Am. Chem. Soc. 1994, 116, 2400.
- [5] a) H. Yuzawa, H. Yoshida, *Top. Catal.* **2014**, *57*, 984; b) M. Carraro, M. Gardan, G. Scorrano, E. Drioli, E. Fontananova, M. Bonchio, *Chem. Commun.* **2006**, 4533.
- [6] a) R. Cibulka, R. Vasold, B. König, *Chem. Eur. J.* 2004, *10*, 6223;
 b) B. König, S. Kümmel, R. Cibulka in *Chemical Photocatalysis* (Ed.: B. König), De Gruyter, Berlin, 2013, pp. 45 66.
- [7] R. Lechner, B. König, Synthesis 2010, 1712.
- [8] J. Dad'ová, E. Svobodová, M. Sikorski, B. König, R. Cibulka, *ChemCatChem* 2012, 4, 620.
- [9] V. Mojr, E. Svobodová, K. Straková, T. Neveselý, J. Chudoba, H. Dvořáková, R. Cibulka, *Chem. Commun.* 2015, 51, 12036.
- [10] R. Lechner, S. Kümmel, B. König, *Photochem. Photobiol. Sci.* 2010, 9, 1367.
- [11] a) S. Fukuzumi, K. Yasui, T. Suenobu, K. Ohkubo, M. Fujitsuka,
 O. Ito, J. Phys. Chem. A 2001, 105, 10501; b) S. Fukuzumi, S. Kuroda, T. Tanaka, J. Am. Chem. Soc. 1985, 107, 3020.
- [12] B. Mühldorf, R. Wolf, Chem. Commun. 2015, 51, 8425.
- [13] P. D. Oldenburg, A. A. Shteinman, L. Que, Jr., J. Am. Chem. Soc. 2005, 127, 15672.
- [14] a) U. Megerle, M. Wenninger, R.-J. Kutta, R. Lechner, B. König,
 B. Dick, E. Riedle, *Phys. Chem. Chem. Phys.* 2011, *13*, 8869;
 b) C. Feldmeier, H. Bartling, K. Magerl, R. M. Gschwind, *Angew. Chem. Int. Ed.* 2015, *54*, 1347; *Angew. Chem.* 2015, *127*, 1363.
- [15] See the Supporting Information for further experimental details.
- [16] a) E. Churakova, M. Kluge, R. Ullrich, I. Arends, M. Hofrichter, F. Hollmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10716; *Angew. Chem.* **2011**, *123*, 10904; b) D. I. Perez, M. M. Grau, I. W. C. E. Arends, F. Hollmann, *Chem. Commun.* **2009**, 6848.
- [17] M. Klopstra, R. Hage, R. M. Kellogg, B. L. Feringa, *Tetrahedron Lett.* 2003, 44, 4581.
- [18] a) J. Paschke, M. Kirsch, H.-G. Korth, H. de Groot, R. Sustmann, J. Am. Chem. Soc. 2001, 123, 11099; b) A. Ghosh, D. A. Mitchell,
 A. Chanda, A. D. Ryabov, D. L. Popescu, E. C. Upham, G. J.
 Collins, T. J. Collins, J. Am. Chem. Soc. 2008, 130, 15116.
- [19] I. Prat, A. Company, T. Corona, T. Parella, X. Ribas, M. Costas, *Inorg. Chem.* 2013, 52, 9229.
- [20] G. J. P. Britovsek, J. England, A. J. P. White, *Inorg. Chem.* 2005, 44, 8125.
- [21] E. Sikorska, I. Khmelinskii, A. Komasa, J. Koput, L. F. V. Ferreira, J. R. Herance, J. L. Bourdelande, S. L. Williams, D. R. Worrall, M. Insińska-Rak et al., *Chem. Phys.* 2005, *314*, 239.
- [22] For a review, see: W. N. Oloo, L. Que, Jr., Acc. Chem. Res. 2015, 48, 2612.
- [23] a) K. Chen, L. Que, Jr., J. Am. Chem. Soc. 2001, 123, 6327; b) K.
 Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., J. Am. Chem.
 Soc. 2002, 124, 3026; c) A. Mairata i Payeras, R. Y. N. Ho, M.
 Fujita, L. Que, Jr., Chem. Eur. J. 2004, 10, 4944.
- [24] a) X. Wu, X. Yang, Y.-M. Lee, W. Nam, L. Sun, *Chem. Commun.* 2015, *51*, 4013; b) A. Company, G. Sabenya, M. González-Béjar, L. Gómez, M. Clémancey, G. Blondin, A. J. Jasniewski, M. Puri, W. R. Browne, J.-M. Latour et al., *J. Am. Chem. Soc.* 2014, *136*, 4624; c) W. Iali, P.-H. Lanoe, S. Torelli, D. Jouvenot, F. Loiseau, C. Lebrun, O. Hamelin, S. Menage, *Angew. Chem. Int. Ed.* 2015, *54*, 8415; *Angew. Chem.* 2015, *127*, 8535.

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