A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Oxidation of Organic Molecules with a Redox-Active Guanidine Catalyst

Authors: Ute Wild, Florian Schön, and Hans-Jörg Himmel

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201709809
Angew. Chem. 10.1002/ange.201709809

Link to VoR: http://dx.doi.org/10.1002/anie.201709809
http://dx.doi.org/10.1002/ange.201709809

WILEY-VCH

10.1002/anie.201709809

WILEY-VCH

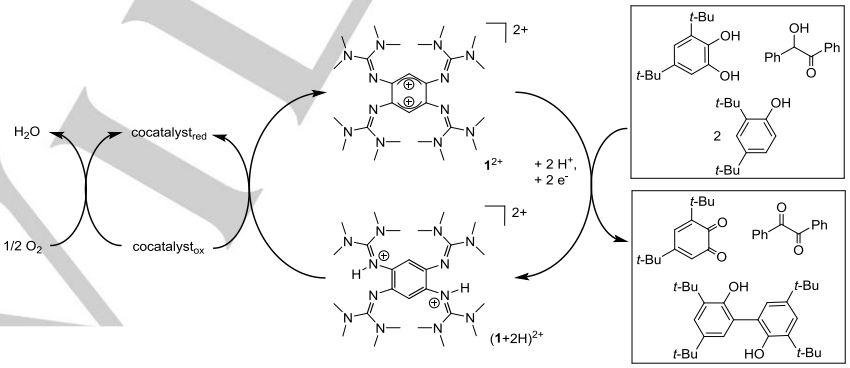
Oxidation of Organic Molecules with a Redox-Active Guanidine Catalyst

Ute Wild, Florian Schön and Hans-Jörg Himmel*

Abstract: *Herein we report the first examples of the use of redox-active guanidines as catalysts in the green oxidation of organic molecules with dioxygen. In one half-reaction, the oxidized state of the redox-active guanidine is converted to the reduced, protonated state, thereby enabling dehydrogenative oxidation of the substrate (3,5-ditertbutylcatechol → o-benzoquinone, benzoin → benzil, and 2,4-ditertbutylphenol → biphenol). In the other half-reaction, efficient re-oxidation of the guanidine to the oxidized state is achieved with dioxygen in the presence of a copper catalyst. The results pave the way for a broader use of redox-active guanidines as oxidation catalysts.*

Catalytic, selective oxidation of organic compounds is one of the top research themes in synthetic chemistry. The use of readily available O_2 as oxidation reagent, generally requiring an oxygen-activating metal catalyst, is particularly attractive. Bäckvall and others established the use of benzoquinones as redox mediators for the oxidation of organic molecules by multistep electron transfer.[1,2] Catalytic oxidation of catechols and *p*-hydroquinone with O_2 was thoroughly investigated, using dinuclear and also mononuclear transition metal complexes (esp. of copper, cobalt and iron) as catalysts.[3,4,5,6,7] Stahl and Hammes-Schiffer et al. disclosed the mechanisms of such reactions and grouped quinones in two families, those with a high redox potential, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and bioinspired *o*-quinones resembling the *o*-quinone cofactor found in amine oxidases and related enzymes, that have lower redox potentials.[7,8] Special *o*-quinones enable aerobic oxidation of amines without the need for a metal cocatalyst.[910] The group of Hirao developed polyanilines as "synthetic metal" catalytic systems.[11]

Redox-active guanidines are up to date unknown as organic oxidation catalysts. Herein, 1,2,4,5-tetrakis(tetramethyl-guanidino)-benzene (**1**, see Scheme 1),[12] being a quite strong electron donor ($E_{1/2}$ = -0.7 V vs. Fc^+/Fc for the redox pair $\mathbf{1}^{2+}$/**1**),[13] is used in the first examples of such reactions. Reduction of the oxidized form, $\mathbf{1}^{2+}$, by proton-coupled electron transfer is favored by the strong Brønsted basicity of guanidines and restoration of the aromatic system. First it is demonstrated that $(\mathbf{1}+2H)^{2+}$ can be efficiently oxidized catalytically with dioxygen to the dication $\mathbf{1}^{2+}$. Then $\mathbf{1}^{2+}$ is applied in (stoichiometric) dehydrogenative oxidation reactions with three organic substrates differing in their nucleophilicity and redox potential (3,5-di-tert-butylcatechol → o-benzoquinone, benzoin → benzil, and 2,4-di-tert-butylphenol → biphenol, see SI). Finally, these half-reactions are combined in a catalytic cycle, using dioxygen as green oxidation reagent and $\mathbf{1}^{2+}$ as organo-catalyst (see Scheme 1). Both involved guanidine species, $\mathbf{1}^{2+}$ and $(\mathbf{1}+2H)^{2+}$, are readily available. In spite of its high nitrogen content, **1** and its twofold-oxidized respectively diprotonated versions, are also thermally stable (neutral **1** melts at ca. 205 °C and sublimes at higher temperature without decomposition). The salt $\mathbf{1}(PF_6)_2$ is prepared by reaction of neutral **1** with $FcPF_6$ (Fc = ferrocene),[14] and the salt $(\mathbf{1}+2H)(PF_6)_2$ by reaction of **1** with $(NH_4)(PF_6)$.[12] Both $\mathbf{1}^{2+}$ and $(\mathbf{1}+2H)^{2+}$ are highly soluble in CH_3CN.



Scheme 1. Catalytic cycle for oxidation of organic molecules with O_2 using the redox-active guanidine 1,2,4,5-tetrakis(tetramethylguanidino)-benzene (**1**) as catalyst (this work). Cocatalyst = Co^{II} or Cu^{II} complexes (best results with $CuCl_2$ / $Cu(H_2O)_6(BF_4)_2$)

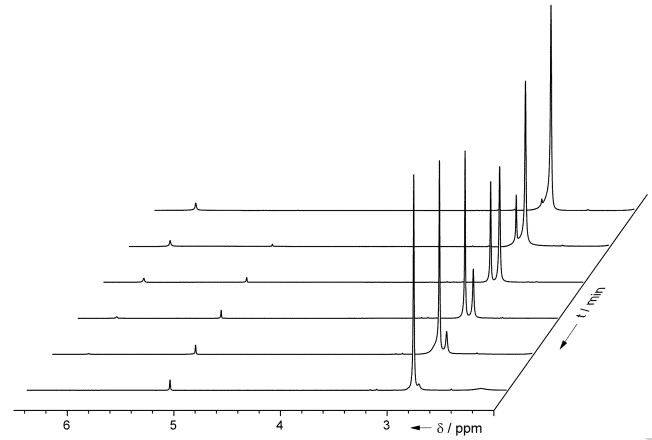
[a] U. Wild, F. Schön, Prof. Dr. H.-J.Himmel
Anorganisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hans-joerg.himmel@aci.uni-heidelberg.de

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201709809

1) Catalytic oxidation of (**1**+2H)$^{2+}$ with O_2. Oxidation of (**1**+2H)$^{2+}$ with dioxygen to give **1**$^{2+}$ requires a cocatalyst. Several cocatalysts are tested (see SI), and conversion followed by NMR spectroscopy at room temperature. In an O_2 atmosphere, the salt (**1**+2H)$(PF_6)_2$ and the cocatalyst (2-5 mol%) are dissolved in acetonitrile (NMR tube experiments). The Co^{II} complex of the dianion of bis[3-(salicylideneimino)propyl]methylamine (salmdptH$_2$), Co(salmdpt),[2,7] an established cocatalyst for catechol-oxidation, enables the reaction (see Figure 1). In the ^{1}H NMR spectra, the signals at δ = 2.78 (methyl protons) and 6.11 ppm due to (**1**+2H)$^{2+}$ disappear completely, and the signals at δ = 2.87 and 5.16 ppm due to **1**$^{2+}$ grow in instead. Due to the tendency of tetrakisguanidine electron donors to donate two electrons simultaneously, O_2 is reduced to water (similar to catechol oxidation). To access the influence of O_2 concentration on the reaction rate, the experiment is repeated in a vial under O_2 atmosphere (vial method). Indeed, the reaction rate considerably increases (see Figure 1 and SI).

a)



b)

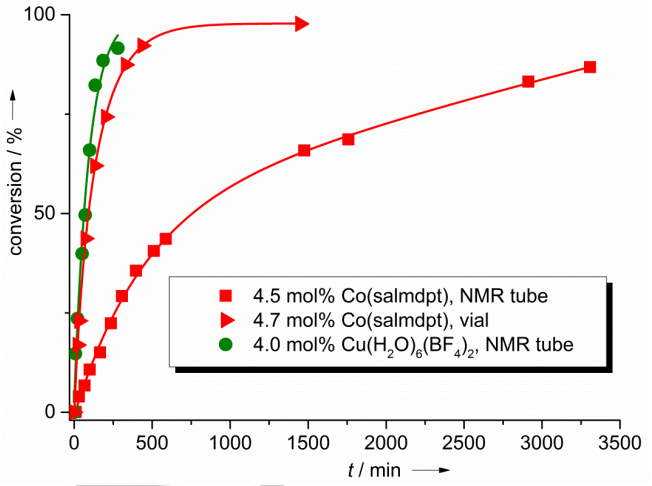


Figure 1. a) ^{1}H NMR spectra for oxidation of (**1**+2H)$^{2+}$ to **1**$^{2+}$ with O_2 and 4.5 mol% Co(salmdpt) as cocatalyst (spectra recorded at 10, 307, 511, 1758, 2913 and 3308 min reaction time), and b) conversion vs. time plot for [Co(salmdpt)] (NMR and vial method, see text) and $Cu(H_2O)_6(BF_4)_2$ catalyzed oxidation.

A cocatalyst screening (see SI) shows that Cu^{II} salts speed up further the reaction. With $Cu(H_2O)_6(BF_4)_2$ (4 mol%), more than 90% conversion is already reached after 280 min at room temperature (see Figure 1). Further optimization shows that a 1:1 mixture of $CuCl_2$ and $Cu(H_2O)_6(BF_4)_2$ as cocatalyst (ca. 3 mol%) gives the best results with 100 mol% conversion in only 22 min (see SI).

2) Stoichiometric dehydrogenative oxidations with **1**$^{2+}$. Next the dication **1**$^{2+}$ is applied in dehydrogenative oxidation of 3,5-ditertbutylcatechol, benzoin and 2,4-ditertbutylphenol (see Scheme 1). In an Ar atmosphere, one of the substrates and **1**$(PF_6)_2$ are dissolved in acetonitrile, and the conversion followed by NMR spectroscopy. Reaction of 3,5-ditertbutylcatechol with **1**$(PF_6)_2$ (0.02 mol/l) at room temperature yields the *o*-benzoquinone product almost quantitatively within 10 min (see Figure 2). The fast rate argues for a concerted pathway. Indeed, quantum chemical calculations find a complex between 3,5-ditertbutylcatechol and **1**$^{2+}$ with two O-H···N bridging interactions (see SI), enabling simultaneous transfer of both hydrogen atoms. The reaction is slowed down at lower concentrations, and can then be monitored by UV/Vis spectroscopy. The benzoquinone absorption near 400 nm can be neglected, since its extinction coefficient (1900 L mol^{-1}cm^{-1})[15] is much lower than that of **1**$(PF_6)_2$ (27610 L mol^{-1}cm^{-1}).[14] The presence of an isosbestic point (at 355 nm) confirms clean conversion (see Figure 2).

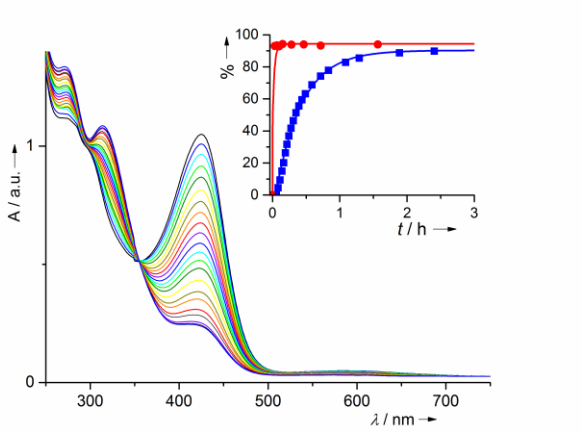


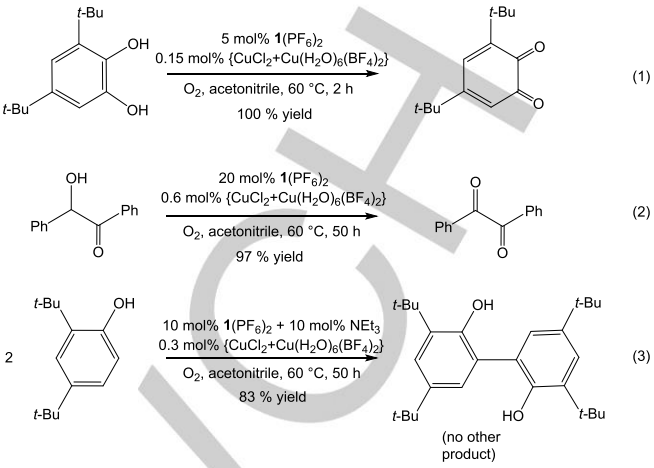
Figure 2. UV/Vis spectra recorded for the reaction between catechol and **1**$(PF_6)_2$ in acetonitrile (band at 425 nm due to **1**$^{2+}$). Inlet: conversion vs. time plots for ca. 0.02 mol/l from NMR (red) and for 3.76·10^{-5} mol/l from UV/Vis spectroscopy (blue).

Oxidation of benzoin to benzil is slower, ca. 85% conversion being reached after 20 h. Keeping the concentration of **1**$^{2+}$ constant at ca. 0.02 mol/l, a benzoin concentration higher than 0.02 mol/l accelerates the reaction, while a decrease of this concentration slows down the reaction (see SI). These results

are in line with those obtained for 3,5-ditertbutylcatechol and also for oxidative coupling of thiols to disulfides and phosphines to diphosphines with $\mathbf{1}^{2+}$.[14] Hence in all reactions the rate increases with increasing concentrations of the two reactants. In our experiments, we deliberately use low concentrations, leading on the one hand to quite long reaction times, but on the other hand maintaining optimal conditions for the NMR spectroscopic monitoring of all reactions. 2,4-Ditertbutylphenol oxidation is still slower under the chosen conditions, presumably due to inhibition by formation of a stable complex between two of the involved species (see below). It selectively leads to the biphenol coupling product. The reaction rate and yield of coupling product can be increased by applying an excess of phenol (see SI). With 6 eq. of phenol, ca. 20% conversion is reached after 45 h. Hence, the rates for dehydrogenative oxidation reactions with $\mathbf{1}^{2+}$ cover a large range.

3) Catalytic reactions. The results of the previous two sections are now combined to elaborate catalytic reactions. As catalysts, $\mathbf{1}(PF_6)_2$ as dehydrogenative oxidation catalyst (with catalyst loadings between 2 and 20 mol%) and $\{CuCl_2+Cu(H_2O)_6(BF_4)_2\}$ (3 mol% with respect to $\mathbf{1}(PF_6)_2$) for dioxygen activation are used. Some Na_2SO_4 is added to remove the water, that otherwise causes broad, perturbing signals in the NMR spectra. Control experiments show that Na_2SO_4 addition has no influence on the reaction. Two series of experiments are carried out. In the first one (termed “NMR method” in the following), the solutions are saturated with O_2 and transferred in an O_2 atmosphere into NMR tubes. Reaction in the NMR tube at a temperature of 60 °C is then followed. In the second series of experiments (termed “vial method” in the following), the O_2 supply is increased by carrying out the reaction in a sealed vial (20 ml) under O_2 atmosphere.

In similarity with the stoichiometric reactions, the catalytic reaction of catechol proceeds fastest and takes only 2 h with the vial method (see Scheme 2). The time for quantitative conversion is reduced to ca. 30 min with 10 mol% of $\mathbf{1}(PF_6)_2$ and to less than 2 h with 5.5 mol% of $\mathbf{1}(PF_6)_2$ by applying the vial method (see Scheme 2 and SI). Using the NMR method, quantitative conversion is achieved within 23 h with 10 mol% of $\mathbf{1}(PF_6)_2$. For benzoin oxidation, the NMR method leads to more than 70% conversion in 50 h with 10 mol% of $\mathbf{1}(PF_6)_2$. With 20 mol% of $\mathbf{1}(PF_6)_2$, the yield increases to more than 80%. Almost quantitative conversion is achieved with the vial method and 20 mol% of $\mathbf{1}(PF_6)_2$. The 2,4-ditertbutylphenol oxidation is not only very selective, leading only to the biphenol product, but also provides the product in quite high yield. The addition of 10 mol% NEt_3 is found to accelerate this particular reaction (in line with previous studies on phenol oxidation [16-23]). The yield of 70% after 50 h obtained with the NMR method (with 10 mol% of $\mathbf{1}(PF_6)_2$ and ca. 10 mol% NEt_3) is increased to more than 80% with the vial method.



Scheme 2. Selected results of catalytic oxidations with $\mathbf{1}(PF_6)_2$ as organo-catalyst and O_2 as oxidation reagent (vial method). Please note that the reaction rates depend on the concentrations (higher concentrations speed up the reactions). In our experiments we deliberately use relatively small concentrations to follow the reactions with NMR spectroscopy (see conversion vs. time plots in the SI).

In all cases, blank tests are run without $\mathbf{1}(PF_6)_2$. Only in the case of benzoin, a significant conversion is observed in these blank tests (ca. 36% conversion with the NMR method and 22% with the vial method after 50 h reaction time, see SI). In additional experiments, the catalyst loadings are varied. If the catalyst loading is reduced, the reaction rate decreases. Nevertheless, with only 2 mol% $\mathbf{1}(PF_6)_2$ and 0.07 mol% $\{CuCl_2+Cu(H_2O)_6(BF_4)_2\}$, still more than 65% 2,4-ditertbutylphenol are converted in 25 h with the vial method. To further clarify the role of copper on the overall reaction mechanism, the copper cocatalyst was added in the stoichiometric reaction between $\mathbf{1}^{2+}$ and 2,4-ditertbutylphenol (see SI). A low product yield of ca. 16 % was obtained after 45 h, much lower than the yield of more than 80% obtained in the catalytic reaction. This result confirms that the copper is mainly responsible for dioxygen activation (Scheme 1).

In summary, the results of this work show that redox-active guanidines are valuable catalysts for the green oxidation of organic molecules with dioxygen. The following points highlight the advantages of redox-active guanidine catalysts.

1) Oxidation of the twofold protonated guanidine, $(\mathbf{1}+2H)^{2+}$, with dioxygen at room temperature to give $\mathbf{1}^{2+}$ is very efficient with simple, commercially available Cu^{II} cocatalysts, enabling quantitative conversion in less than half an hour.

2) The redox-active guanidine used in this work is environmentally benign, readily available and thermally stable, making it an attractive organo-catalyst.

3) The key properties of the redox-active guanidine, its redox potential and its basicity, can easily be tuned, as demonstrated by previous work by our group.[13,24]

We are currently systematically studying the scope of catalytic oxidation reactions with O_2 using redox-active guanidine catalysts.

Acknowledgements

The authors gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft (DFG).

Keywords: oxidation • organocatalysis • guanidines • proton-coupled electron transfer • dioxygen

[1] a) J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558–3576; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506–3523; b) D. Ventura-Espinosa, J. A. Mata, *Eur. J. Inorg. Chem.* **2016**, *17*, 2667–2675.

[2] a) G.-Z. Wang, U. Andreasson, J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.* **1994**, 1037–1038; b) G. Csjernyik, A. H. Éll, L. Fadini, B. Pugin, J.-E. Bäckvall, *J. Org. Chem.* **2002**, *67*, 1657–1662; c) J. S. M. Samec, A. H. Éll, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327–2334; d) Y. Endo, J.-E. Bäckvall, *Chem. Eur. J.* **2011**, *17*, 12596–12601; e) B. P. Babu, Y. Endo, J.-E. Bäckvall, *Chem. Eur.* J. **2012**, *18*, 11524–11527. f) Y. Endo, J.-E. Bäckvall, *Chem. Eur. J.* **2012**, *18*, 13609–13613.

[3] a) K. Selmeczi, M. Réglier, M. Giorgi, G. Speier, *Coord. Chem. Rev.* **2003**, *245*, 191–201; b) L. I. Simándi, T. M. Simándi, Z. May, G. Besenyei, *Coord. Chem. Rev.* **2003**, *245*, 85–93.

[4] L. I. Simándi, T. Barna, G. Argay, T. L. Simándi, *Inorg. Chem.* **1995**, *34*, 6337–6340.

[5] F. Wendt, C. Näther, F. Tuczek, *J. Biol. Inorg. Chem.* **2016**, *21*, 777–792.

[6] S. Tsuruya, S.-i. Yanai, M. Masai, *Inorg. Chem.* **1986**, *25*, 141–146.

[7] C. W. Anson, S. Ghosh, S. Hammes-Schiffer, S. S. Stahl, *J. Am. Chem. Soc.* **2016**, *138*, 4186–4193.

[8] M. T. Huynh, C. W. Anson, A. C. Cavell, S. S. Stahl, S. Hammes-Schiffer, *J. Am. Chem. Soc.* **2016**, *138*, 15903–15910.

[9] Y. Ohshiro, S. Itoh, K. Kurokawa, J. Kato, T. Hirao, T. Agawa, *Tetrahedron Lett.* **1983**, *24*, 3465–3468.

[10] Y. Qin, L. Zhang, J. Lv, S. Luo, J.-P. Cheng, *Org. Lett.* **2015**, *17*, 1469–1472.

[11] a) T. Hirao, M. Higuchi, I. Ikeda, Y. Ohshiro, *J. Chem. Soc., Chem. Commun.* **1993**, 194–195; b) M. Higuchi, I. Ikeda, T. Hirao, *J. Org. Chem.* **1997**, *62*, 1072–1078; c) T. Hirao, S. Fukuhara, *J. Org. Chem.* **1998**, *63*, 7534–7535; d) D. Saio, T. Amaya, T. Hirao, *Adv. Synth. Catal.* **2010**, *352*, 2177–2182.

[12] A. Peters, E. Kaifer, H.-J. Himmel, *Eur. J. Org. Chem.* **2008**, 5907–5914.

[13] B. Eberle, O. Hübner, A. Ziesak, E. Kaifer, H.-J. Himmel, *Chem. Eur. J.* **2015**, *21,* 8578–8590.

[14] U. Wild, S. Federle, A. Wagner, E. Kaifer, H.-J. Himmel, *Chem. Eur. J.* **2016**, *22*, 11971–11976.

[15] A. Rieker, W. Rundel, H. Kessler, Z. Naturforschg. 1969, 24b, 547–562.

[16] K. V. N. Esguerra, Y. Fall, L. Petitjean, J.-P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668.

[17] M. Rolff, J. Schottenheim, G. Peters, F. Tuczek, *Angew. Chem.* **2010**, *122*, 6583–6587; *Angew. Chem. Int. Ed.* **2010**, *49*, 6438–6442.

[18] J. N. Hamann, F. Tuczek, *Chem. Commun.* **2014**, *50*, 2298–2300.

[19] L. Casella, M. Gullotti, R. Radaelli, P. Di Gennaro, *J. Chem. Soc. Chem. Commun.* **1991**, 1611–1612.

[20] M. Rolff, J. Schottenheim, H. Decker, F. Tuczek, *Chem. Soc. Rev.* **2011**, *40*, 4077–4098.

[21] E. Solem, F. Tuczek, H. Decker, *Angew. Chem.* **2016**, *128*, 2934–2938; *Angew. Chem. Int. Ed.* **2016**, *55*, 2884–2888.

[22] D. R. Armstrong, C. Cameron, D. C. Nonhebel, P. G. Perkins, *J. Chem. Soc., Perkin Trans. 2* **1983**, 587–589.

[23] T. Osako, K. Ohkubo, M. Taki, Y. Tachi, S. Fukuzumi, S. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 11027–11033.

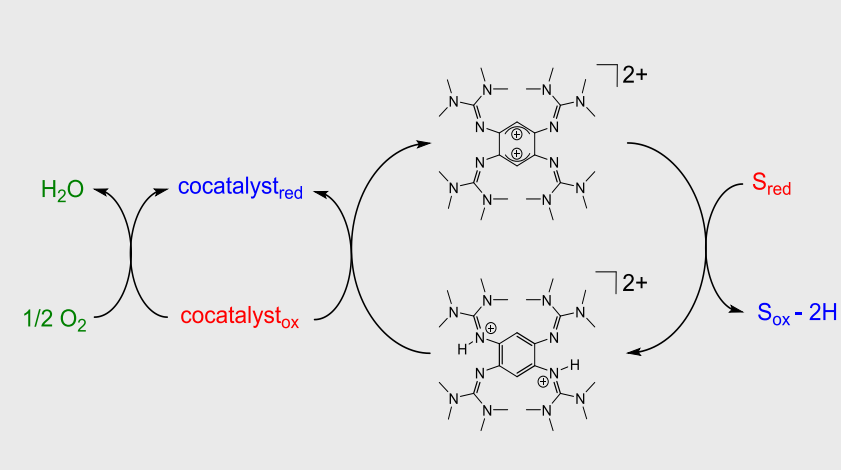
[24] B. Eberle, E. Kaifer, H.-J. Himmel, *Angew. Chem*. **2017**, *129*, 3408–3412; *Angew. Chem. Int. Ed*. **2017**, *56*, 3360–3363.

10.1002/anie.201709809

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



*U. Wild, F. Schön, H.-J. Himmel**

Page No. – Page No.

Oxidation of Organic Molecules with a Redox-Active Guanidine Catalyst

Due to the combination of high Brønsted basicity and electron donor properties, redox-active guanidines are superior organic redox catalysts. Herein we report the first catalytic oxidation reactions with dioxygen.