Journal of Catalysis 331 (2015) 147–153

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Iron-catalyzed oxidation of unreactive C—H bonds: Utilizing bio-inspired axial ligand modification to increase catalyst stability

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ARTICLE INFO

Article history:
Received 12 June 2015
Revised 30 July 2015
Accepted 26 August 2015

Keywords:
Oxidation catalysis
Iron
C—H activation
Cyclohexane
Bio-inspired

ABSTRACT

Three different bio-inspired Fe(II) complexes are applied as powerful catalysts for the oxidation of unreactive C—H bonds under ambient conditions. Cyclohexane as the main model substrate is oxidized to cyclohexanol, cyclohexyl hydroperoxide, and cyclohexanone. Alcohol + cyclohexyl hydroperoxide to ketone ratios ((A + H)/K) of up to 26 are obtained with comparatively high turnovers of up to 43. Bio-inspired modification of the Fe(II) complexes in the axial positions is used to increase catalyst stability toward hydrogen peroxide, leading to an increase in turnovers of up to 34%. Several parameters for the catalytic oxidation are investigated, e.g., the amount and type of oxidant, reaction temperature, and the relative catalyst concentration. Among others, 9,10-dihydroantracene and 2,3-dimethylbutane are used as substrates for the catalytic C—H bond oxidation.

1. Introduction

Remarkable advances were made in the oxidation of light alkanes with molecular iron catalysts in recent years, with many catalysts being inspired by the iron active sites in soluble methane monooxygenase (sMMO) and cytochrome P450 (cyt-P450) [1–13]. Adapting nature's ability to selectively convert unreactive alkanes has been in the focus of academic research for several years [1,14,15]. Examples of homogeneously catalyzed formation of methanol from methane were described by Shilov and Periana, using Pt-, Hg-, Tl-, and Pb-containing compounds among others as catalytically active metals [16–19]. More recently, iron-based coordination complexes were used as "bio-inspired" catalysts, taking advantage of the bio-catalytic role of iron and its low price and low toxicity [5,8,14,20–23]. The use of iron in oxidation catalysis is historically best known from Fenton's reagent, where simple iron(II) salts catalytically decompose hydrogen peroxide [24–26]. The resulting highly reactive hydroxyl radicals unselectively oxidize hydrocarbons, leading to a 1:1 mixture of the respective alcohols and ketones as oxidation products [26,27]. In contrast to that, natural iron-porphyrins and derived bio-inspired iron catalysts can selectively produce the alcohol via a metal-centered non-radical mechanism, as it has been first demonstrated by Groves [28,29]. Furthermore, a radical-chain autooxidative pathway can lead to alkyl hydroperoxides as major oxidation product, which can be selectively reduced to the desired alcohol, e.g., by the addition of phosphines [18].

Cyclohexane ($D_{C-H} \approx 99.3$ kcal/mol [30], compared to $D_{C-H} \approx 104.9$ kcal/mol for methane [31]) has become the most prominent model substrate in the literature for the Fe(II)-catalyzed C—H oxidation in homogeneous solution [2,21,32]. However, even when defined iron coordination compounds are used as catalysts, two main issues remain unsolved [2,21,26,32]: First, in many cases large amounts of the ketone cyclohexanone are formed, sometimes even exclusively. Second, the number of turnovers per catalyst molecule is often very low. So far the catalyst performance can be optimized either to a higher selectivity – as described by the alcohol to ketone ratio (A/K) – or to a larger number of turnovers [33]. Examples of good selectivity were given by Que (A/K = 19) and Costas (A/K = 12); however, in both cases the number of turnovers was moderate, being 2.3 and 6.5, respectively [33,34]. Di Stefano and Costas provided examples with the relatively large turnover number of 64 on the cost of selectivity (A/K = 0.1 and 3.4, respectively) [33,35]. Combining

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http://dx.doi.org/10.1016/j.jcat.2015.08.026
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both a large turnover number and a high A/K ratio still poses a challenge in the field of iron-catalyzed oxidation of cyclohexane.

Recently, the Fe(II) complex **1** bearing a tetradentate bis (pyridyl-*N*-heterocyclic carbene) ligand (NCCN) in the equatorial plane (Fig. 1) has been reported by our group as a highly active catalyst for olefin epoxidation and aromatic hydroxylation, including investigations on electronic fine-tuning [36–39].

In this work, compound **1** is applied as catalyst to the oxidation of unreactive C—H bonds (e.g., cyclohexane). Bio-inspired modification of the axial ligands in analogy to cyt-P450 is a potentially powerful tool for influencing the catalyst performance, as seen in the crucial role of the apical thiolate in cyt-P450 for the O—O bond splitting of dioxygen [1,40–43]. Encouraged by this, two irreversibly axially monosubstituted derivatives of **1** are introduced as active catalysts for C—H bond oxidation in this article. The influence of the substitution on the catalyst performance is investigated with a main focus on catalyst stability and product selectivity. Crucial parameters such as the amount of oxidant, the relative catalyst concentration, and the reaction temperature are varied in order to increase the turnovers while studying the selectivity of product formation.

2. Experimental section

2.1. General remarks

Caution: Hydrogen peroxide as well as organic peroxides are potentially explosive if highly concentrated and exposed to heat or mechanical impact. All chemicals were purchased from commercial suppliers and used without further purification with the exception of the iron source $FeBr_2$, which was purified by extraction with THF under standard Schlenk conditions to give $[FeBr_2(THF)_2]$. Complexes **1** and **2** were synthesized according to the literature [38,39,44]. Liquid NMR spectra were recorded on a Bruker Avance DPX 400 and a Bruker Ultrashield 500 Plus with cryo unit. Chemical shifts are given in parts per million (ppm) and the spectra were referenced by using the residual solvent shifts as internal standards (MeCN-d_3, ^{1}H NMR δ 1.94, ^{13}C NMR δ 1.32). A Thermo Scientific LCQ/Fleet spectrometer by Thermo Fisher Scientific was used to collect MS-ESI data and elemental analyses were obtained from the microanalytical laboratory of TUM. IR spectra were acquired on a Bruker Vertex-70 FT-IR spectrometer with a Platinum ATR unit at room temperature using a solid sample of bulk material. GC-FID measurements were performed on a Varian CP-3800 equipped with an Optima 5-Amin capillary column by Macherey-Nagel (1.50 μm; 30 m × 0.32 mm), using *p*-xylene as external standard.

2.2. Single crystal X-ray diffraction

Single crystals of **3** suitable for X-ray diffraction were obtained by slow diffusion of diethyl ether into an acetonitrile solution of **3**.

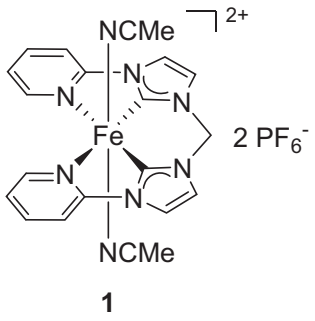

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Fig. 1. Fe(II) catalyst **1** bearing an bis(pyridyl-*N*-heterocyclic carbene) ligand in its equatorial plane and two axial acetonitrile ligands [38].

The intense yellow compound crystallizes in the monoclinic crystal system in space group $P2_1/c$ (No. 14) with the cell parameters a = 19.4664(8) Å, b = 10.7818(4) Å, c = 15.7930(6) Å, β = 108.113(2)°.

2.3. Synthesis of [Fe(NCCN)(MeCN)(CN^{t}Bu)](PF$_6$)$_2$ (**3**)

Complex **1** (1.37 mmol, 1.00 g) was dissolved in 70 mL acetonitrile. *tert*-Butyl isocyanide (2.05 mmol, 232 μL) was added under vigorous stirring and the resulting mixture was stirred at room temperature for 30 min. Diethyl ether (600 mL) was added, giving a yellow suspension. Filtration yielded a yellow powder, which was washed three times with diethyl ether and dried under high vacuum (0.85 g of **3**, 80% yield). ^{1}H NMR (400.13 MHz, MeCN-d_3): δ 9.26 (d, J = 5.3 Hz, 2H, *o*-H_{py}), 8.31 (t, J = 7.4 Hz, 2H, H_{py}), 8.21 (d, J = 2.1 Hz, 2H, H_{NHC}), 8.00 (d, J = 8.2 Hz, 2H, H_{py}), 7.76 (d, J = 2.1 Hz, 2H, H_{NHC}), 7.69 (t, J = 6.3 Hz, 2H, H_{py}), 6.77 (dd, J = 12.4, 45.5 Hz, 2H, CH_2), 0.87 (s, 9H, C(CH_3)$_3$). ^{13}C{^{1}H} NMR (125.83 MHz, MeCN-d_3): δ 209.1 ($NC_{NHC}N$), 154.3, 153.4 (*o*-C_{py}), 142.2 (C_{py}), 131.1, 125.7 (C_{NHC}), 124.3 (C_{py}), 119.7 (C_{NHC}), 113.3 (C_{py}), 64.7 (NCH_2N), 59.5 ($C(CH_3)_3$), 30.2 ($C(CH_3)_3$). IR: 2139 cm^{-1} (C≡N^{t}Bu). MS-ESI (*m*/*z*): [**3** – PF$_6$]$^+$ calcd., 627.13; found, 626.38; [**3** – MeCN – PF$_6$]$^+$ calcd., 586.10; found, 585.48. Anal. calcd. for $C_{24}H_{26}F_{12}FeN_8P_2$: C, 37.33; H, 3.39; N, 14.51. Found: C, 36.95; H, 3.13; N, 14.21.

2.4. Experimental procedure for the catalytic oxidation of cyclohexane

For the catalytic oxidation of cyclohexane under standard conditions (0.50 mol% relative catalyst concentration), 1.00 mL of a 2.80 mM stock solution of **1**, **2**, or **3** in acetonitrile was added to a mixture of 61.5 μL (569 μmol) of cyclohexane and 2.00 mL acetonitrile under air. The catalytic reaction was started by the addition of 272 μL of an acetonitrile solution containing the respective amount of hydrogen peroxide (50% aqueous solution) or the respective organic peroxide used as oxidant. For other catalyst concentrations, the amount taken from the stock solution and the amount of acetonitrile used for dilution were adjusted accordingly, giving the same reaction volume for each reaction. For each data point, after the respective reaction time an aliquot of 1.00 mL from the reaction solution was taken and added to 1.00 mL of a saturated solution of triphenylphosphine in acetonitrile. The resulting mixture was filtered through a short plug of silica. For GC analysis, two individual samples were prepared by combining 400 μL of the filtered solution with 400 μL of the solution containing the external standard (*p*-xylene in acetonitrile). Double injections before and after the reduction with triphenylphosphine were performed for selected data points to identify cyclohexyl hydroperoxide, as it has been introduced originally by Shul'pin et al. [18,45]. In case of substrates other than cyclohexane, ^{1}H NMR was used for quantification of the respective products and the catalytic reaction was carried out in acetonitrile-d_3. Nitromethane was added as external standard after the reaction was finished (δ 4.30, 3H, CH_3). The following signals were used for the quantification of the respective substrates: 9,10-dihydroanthracene δ 3.90 (4H, 2 × CH_2), xanthene δ 4.06 (2H, CH_2), triphenylmethane δ 5.61 (1H, Ph_3CH), 2,3-dimethyl-2-butanol δ 1.07 (1H, C(CH_3)$_2$OH).

3. Results and discussion

3.1. Preparation of the catalysts

The syntheses of the iron(II) complexes **1** and **2** have been reported previously by our group [38,39,44]. Here, the mono(isocyanide) derivative **3**, obtained by addition of *tert*-butyl isocyanide

(CN^tBu) to a solution of **1** in acetonitrile at room temperature, is described (Scheme 1).

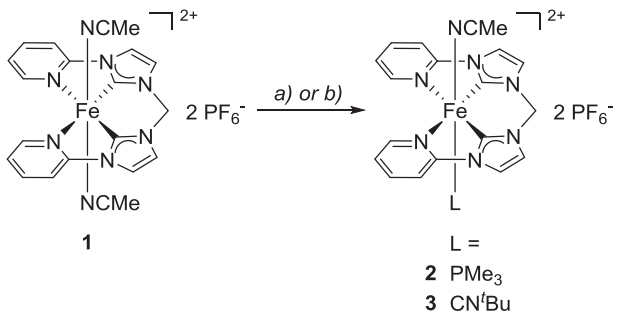
Within 30 min, the color of the solution changes from orange to yellow, and after precipitation **3** can be collected as a yellow powder in 80% yield. The substitution by CN^tBu is irreversible, and **3** is air and moisture stable both as a solid and in acetonitrile solution. ^1H NMR spectroscopy of **3** reveals a signal pattern similar to **2**, which also is substituted in only one of the axial positions. The signal of the methylene bridge in the equatorial tetradentate ligand of **3** appears as a doublet of doublets at 6.77 ppm, which is also the case for **2** [39]. In contrast, for the methylene bridge of **1** only a singlet is observed, since for **1** the equatorial plane is a plane of symmetry [38]. Infrared (IR) absorption spectroscopy shows the isocyanide stretching resonance band at 2139 cm^{-1}, which matches the value observed by Smith et al. [46] for an Fe NHC complex with CN^tBu ligands.

In addition, the molecular structure of **3** was determined by single crystal X-ray diffraction, confirming the octahedral coordination of the iron atom with CN^tBu and acetonitrile in the axial positions (Fig. 2).

With respect to the X-ray data of **1** [38], the changes in geometry of the equatorial plane in **3** are negligible. The axial CN^tBu coordinates to the iron atom in 1.852(5) Å distance and the isocyanide bond (C18—N7) has a length of 1.155(5) Å. Both values are in accord with values previously reported for CN^tBu-coordinated Fe NHC complexes [46]. Compared to **1** (1.9151(1) Å), the Fe1—N8 bond to the trans-positioned acetonitrile in **3** (1.963(4) Å) is slightly elongated.

3.2. Catalytic oxidation of cyclohexane

Cyclohexane is a well-established model substrate in the homogeneous iron-catalyzed oxidation of light hydrocarbons, with cyclohexanol, cyclohexanone, and cyclohexyl hydroperoxide as the main oxidation products [21,47]. Cyclohexyl hydroperoxide can be converted quantitatively to cyclohexanol by reduction with triphenylphosphine, a method often applied to ensure the precise quantification of the oxidation products by gas chromatography [18,45]. The presence of cyclohexyl hydroperoxide is verified by additional GC injections of the samples before the treatment with triphenylphosphine. The alcohol to ketone ratio (A/K) is regarded as an indicator for catalyst selectivity, reflecting the combined conversion of cyclohexane either to directly the alcohol or to cyclohexyl hydroperoxide, which subsequently is reduced to the alcohol [21]. Thus, the A/K ratio is in fact a (alcohol + hydroperoxide)/ketone ratio, (A + H)/K, and this nomenclature is used in the following discussion. Complexes **1**–**3** were applied as catalysts



Scheme 1. Iron(II) NHC complex **1** and its transformation to the monosubstituted derivatives **2** and **3**, having one accessible coordination site, which is occupied by a labile acetonitrile ligand. **1**–**3** are used as catalysts for the iron-catalyzed C—H bond oxidation. Complexes **1** and **2** have been reported previously by our group [38,39]. Conditions: (*a*) 1 equiv. PMe_3, acetonitrile, 30 min, r.t.; (*b*) 1.5 equiv. CN^tBu, acetonitrile, 30 min, r.t.

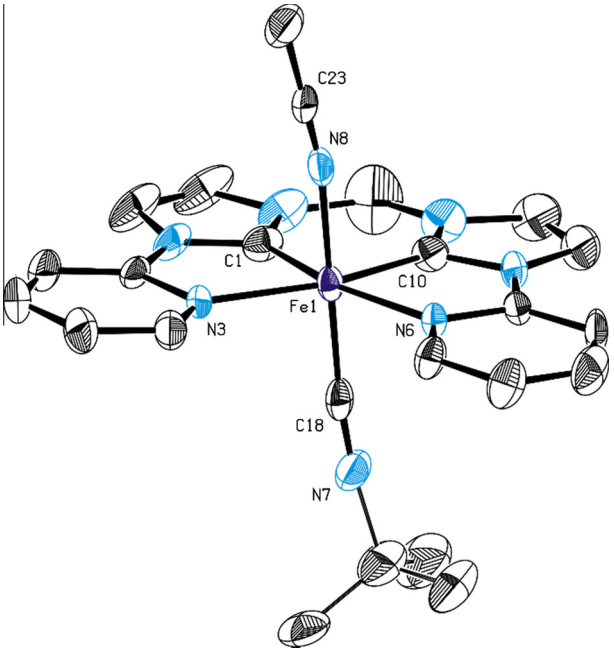
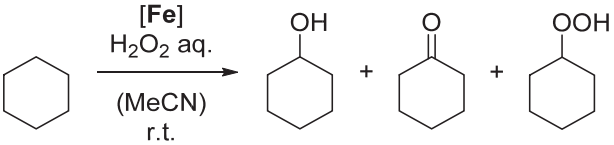


Fig. 2. ORTEP style representation of the dicationic fragment of complex **3**. Ellipsoids are shown at a 50% probability level. Hydrogen atoms, PF_6^- anions, and disordered isocyanide are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Fe1—C1 1.837(4), Fe1—C10 1.839(4), Fe1—N3 2.092(3), Fe1—N6 2.094(3), Fe1—C18 1.852(5), C18—N7 1.155(5), Fe1—N8 1.963(4), C18—Fe1—N8 174.03(16), N3—Fe1—N6 115.17(12).

for the oxidation of cyclohexane with hydrogen peroxide as the oxidizing agent (Scheme 2).

For an initial evaluation of the catalytic oxidation, the relative catalyst concentration was set to 0.5 mol% and one equivalent of both cyclohexane and hydrogen peroxide was used. All three complexes were able to convert cyclohexane with 10–12 turnovers per molecule catalyst to a mixture of cyclohexyl hydroperoxide, cyclohexanol, and cyclohexanone. Based on the reports on aromatic hydroxylation and olefin epoxidation with **1** as catalyst, it is known that the relative amount of hydrogen peroxide influences the catalytic reaction significantly [36,37]. On the one hand, unproductive decomposition of hydrogen peroxide can occur upon reaction with Fe(II) compounds, well-known from Fenton's reagent [24,25]. On the other hand, the stability of Fe(II) coordination compounds in the presence of hydrogen peroxide is a key issue in oxidation catalysis [21,37,48–52]. Consequently, the amount of H_2O_2 used as oxidant in the catalytic oxidation of cyclohexane by **1**–**3** was varied from 1 to 5 equivalents (Fig. 3).

Based on the data shown in Fig. 3, the axial substitution and the applied hydrogen peroxide amount have significant impact on stability and selectivity of the catalysts. The turnovers per catalyst molecule peak for 2 equiv. hydrogen peroxide in case of **1** and **2** (21 and 25 turnovers, respectively) and 3 equiv. in case of **3** (32 turnovers). Compared to the use of one equiv. H_2O_2 the turnovers



Scheme 2. Catalytic oxidation of cyclohexane to form cyclohexanol and cyclohexanone as well as cyclohexyl hydroperoxide. Complexes **1**–**3** are used as catalysts [**Fe**] and aqueous hydrogen peroxide (50%) as the oxidant in an acetonitrile solution at room temperature.

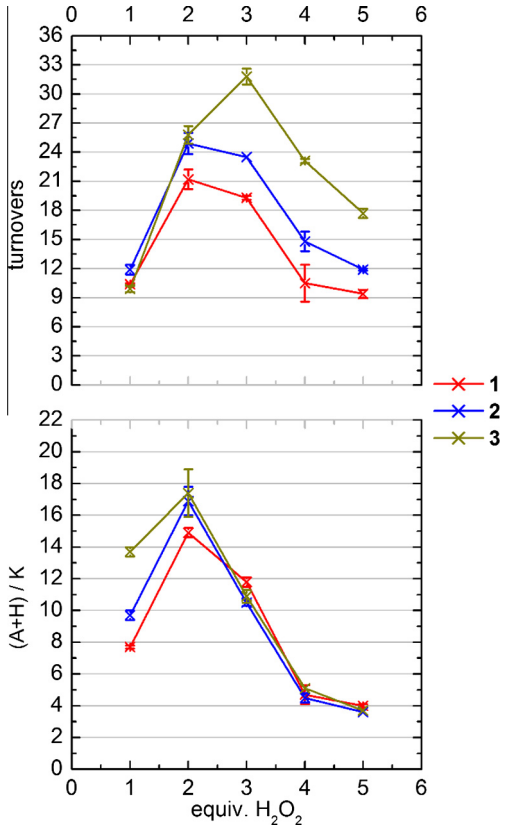


Fig. 3. Dependence of turnovers (top) and selectivity (bottom; (A + H)/K) on the amount of hydrogen peroxide used relative to cyclohexane for complexes **1** (red line), **2** (blue line), and **3** (yellow line). Reaction conditions: Cyclohexane (0.569 mmol), aqueous H_2O_2 (50 wt%, 1–5 equiv.), catalyst (**1**, **2**, or **3**, 2.486 μmol, 0.5 mol%), acetonitrile (3.0 mL), r.t., 24 h. Turnovers determined by GC, turnovers are combined turnovers for cyclohexyl hydroperoxide, alcohol, and ketone formation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

are doubled for **1** and **2** and tripled for **3**. A further increase of the amount of hydrogen peroxide results in reduced turnovers for all three complexes. This is in agreement with previously reported results for **1** as epoxidation catalyst [37]. The data show that the irreversible substitution of one of the axial acetonitrile ligands leads to a higher stability of the catalyst toward hydrogen peroxide. Also, the nature of the axial substituent has significant influence on the stability of the catalyst, as 28% more turnovers were observed for π-acceptor-ligated **3** than for σ-donor-ligated **2**. A larger amount of hydrogen peroxide is also beneficial for the selectivity, as the (A + H)/K ratio increases as shown in Fig. 3. However, for all three complexes the (A + H)/K ratio is highest for 2 equiv. hydrogen peroxide. An increase to 3 equiv. results in lower (A + H)/K ratios. The (A + H)/K ratios of 15 (**1**) and 17 (**2** and **3**) are not influenced as significantly as the turnovers are by variation of the axial ligand, yet a slightly higher performance of the monosubstituted derivatives **2** and **3** is observed. It is evident from Fig. 3, that for **3** the number of turnovers (best for 3 equiv. H_2O_2) and the (A + H)/K ratio (best for 2 equiv. H_2O_2) cannot be maximized at the same time. In contrast, **1** and **2** gave the best results for both turnovers and (A + H)/K ratio when 2 equiv. of hydrogen peroxide were used. With respect to the amount of hydrogen peroxide that is consumed for product formation, the increased amount of hydrogen peroxide in case of **3** lowers the efficiency of hydrogen peroxide conversion from 13.0% (2 equiv. H_2O_2) to 10.7% (3 equiv. H_2O_2). For **1** and **2**, with 2 equiv. H_2O_2 10.5% and 12.5% of hydrogen peroxide are converted to the alkane oxidation products, respectively.

As mentioned above, cyclohexyl hydroperoxide is formed as an oxidation product. It is detected as cyclohexanol in the gas chromatogram as a result from the reduction with triphenylphosphine. Hence, additional GC analysis is required before treatment of the sample with triphenylphosphine. Comparison of the (A + H)/K ratios before and after the reduction allows identification of cyclohexyl hydroperoxide, as it will decompose unselectively to both alcohol and ketone upon injection in the GC [45]. For all three complexes **1**–**3**, the (A + H)/K ratio was determined as 3 when analyzing the samples without addition of triphenylphosphine, which is significantly smaller compared to the values obtained after reduction. Thus, formation of cyclohexyl hydroperoxide upon the catalytic reaction is indicated with a share of roughly 80%, rendering cyclohexyl hydroperoxide the major oxidation product. However, as described by Shul'pin, for a precise quantitative analysis the reduction with triphenylphosphine is necessary prior to GC injection. The decomposition of cyclohexyl hydroperoxide upon injection is neither well-defined nor necessarily quantitative [45]. Therefore, all values discussed in this article are determined after reduction.

The observation of cyclohexyl hydroperoxide indicates a radical-chain autooxidative pathway that is responsible for at least a part of the overall product formation. Hence, 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT) is added as radical trap to the catalytic reaction in order to verify a radical pathway. With BHT being present, the overall turnovers are significantly lower (below 10 for **1**–**3** after 24 h with 2 equiv. hydrogen peroxide as oxidant). Also, the (A + H)/K ratio is lowered and most importantly the difference in the (A + H)/K ratio when analyzed before and after treatment with triphenylphosphine is almost diminished ((A + H)/K = 7–8 with addition of triphenylphosphine and 4–5 without addition of triphenylphosphine). Compared to the values obtained in the absence of the radical trap these data indicate a decrease in cyclohexyl hydroperoxide formation under the presence of BHT, which clearly underlines the role of a radical-chain autooxidative pathway that leads to the formation of cyclohexyl hydroperoxide.

The reaction was monitored over a period of 24 h for **1**–**3** with 2 equiv. hydrogen peroxide and additionally for 29 h with 3 equiv. hydrogen peroxide for **3** (see Fig. 4).

These experiments show that the activity of the catalysts differs significantly, depending on the axial substituent. In all cases the turnover frequency (TOF) was determined by a linear fit at the steepest slope (see SI for graphical representations of all TOFs discussed in this article). Complex **1** (Fig. 4 left, red) reacts comparably fast with a TOF of 47 h^{-1} and reaches the maximum turnovers within approximately 7 h reaction time. No induction period is observed; the catalytic conversion starts immediately after addition of the oxidant to a solution of substrate and catalyst. Introduction of trimethylphosphine as axial ligand to form compound **2** results in a slower catalytic reaction (Fig. 4 left, blue). The TOF is 8 h^{-1} without an induction period being observed. This stands in clear contrast to the reaction kinetics of **3**, where a considerably slower conversion of the substrate revealed an induction period of approximately 1 h for both 2 equiv. (Fig. 4 left, yellow) and 3 equiv. (Fig. 4 left, black) of hydrogen peroxide. After the induction period the TOF for **3** is 4 h^{-1} in both cases, showing clearly that the conversion is significantly slower after introduction of the isocyanide ligand in the axial position. The long induction period for **3** can be explained by the π-acceptor properties of CN^tBu, which disfavors the dissociation of the acetonitrile ligand in trans position. A larger amount of oxidant has no impact on the TOF but on the number of turnovers of **3**. In order to overcome the induction period, the catalytic reaction was performed at elevated temperatures and the time-dependent turnovers at a reaction temperature of 40 °C were recorded and compared to

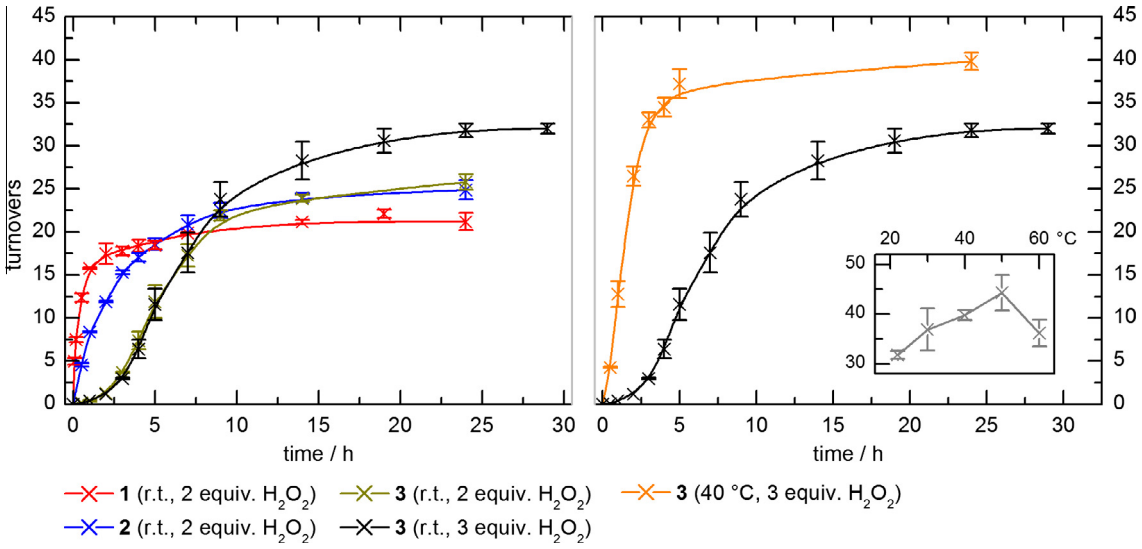


Fig. 4. Kinetic plots for the oxidation of cyclohexane (569 μmol) with complexes **1**–**3** at a relative catalyst concentration of 0.5 mol% (2.486 μmol). The turnovers are presented as combined turnovers for cyclohexyl hydroperoxide, cyclohexanol, and cyclohexanone (determined by GC). *Left*: Time-dependent turnovers at r.t. with 2 equiv. H_2O_2 for **1** (red), **2** (blue), and **3** (dark yellow) as well as for **3** with 3 equiv. H_2O_2 at r.t. (black). *Right*: Time-dependent turnovers for **3** with 3 equiv. H_2O_2 at r.t. (black) and 40 °C (orange). *Inset*: Number of turnovers after 24 h for **3** with 3 equiv. H_2O_2 at various temperatures. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the respective values at r.t. (Fig. 4, right). The reaction is accelerated significantly and the induction period is shortened as dissociation of the acetonitrile ligand is facilitated at higher temperatures. Compared to the reaction at r.t., with 15 h^{-1} the TOF is four times larger. Moreover, the turnovers within 24 h increase by 25% from 32 to 40 at the expense of selectivity, as the (A + H)/K ratio slightly decreases. A further increase in temperature to 50 °C results in an even larger number of turnovers of 44 (compare Fig. 4, inset). Concurrently, the decrease in selectivity becomes more severe with an (A + H)/K ratio of only 7. Raising the temperature to 60 °C is no longer beneficial as the number of turnovers drops, which can be attributed to an accelerated decomposition of H_2O_2 and to a decreased catalyst stability at elevated temperatures.

In addition to evaluating the impact of the amount of hydrogen peroxide and to the collection of time-dependent data, the influence of the relative catalyst concentration was investigated. Starting with 0.50 mol% catalyst, the amount was lowered to 0.25 and 0.10 mol% as well as increased to 1.00 and 2.00 mol% (Table 1).

The trends observed for the variation of catalyst amount are the same for all three complexes. An increase of the relative catalyst concentrations from 0.50 mol% to 1.00 or 2.00 mol% results in decreased turnovers. Interestingly, the number of turnovers is approximately reduced to half when the amount of catalyst is doubled, e.g., for **1** the turnovers are reduced from 21 (0.50 mol %) to 12 (1.00 mol%) and finally to 5 (2.00 mol%). This implies that the overall yield of cyclohexyl hydroperoxide, cyclohexanol, and cyclohexanone remains approximately constant. The observation can be understood in the context of the main challenges in the field of iron(II) catalyzed hydrocarbon oxidation: As mentioned above, unproductive decomposition of hydrogen peroxide by iron(II) compounds competes with the productive conversion of the substrate to the desired product [21,37,48–51]. Certainly for this side-reaction not only the amount of hydrogen peroxide is a relevant factor, but also the relative catalyst concentration is crucial. While a minimum amount of catalyst is required for the catalytic oxidation to take place, at a certain catalyst concentration the unproductive side reactions become dominant. In order to identify an ideal catalyst concentration for the maximization of turnovers, the catalyst amount was also lowered from 0.50 mol% to 0.25 and 0.10 mol% (Table 1). The number of turnovers clearly peaks at 0.25 mol% for all three complexes, being 32 (complex **1**), 39 (complex **2**), and 43 (complex **3**). Compared to the values obtained for 0.50 mol% this is a significant increase of 50–65% depending on the catalyst. Moreover, the selectivity rises from an (A + H)/K ratio of 15–17 to 19–20. Although the selectivity still increases, it is no longer beneficial to lower the catalyst concentration further to 0.10 mol%, as the turnovers then decrease significantly. Control experiments were conducted without catalyst and with $FeSO_4$ as the catalyst (Table 1). In both cases no significant amount of oxidation products was detected, corresponding to less than 1 turnover in case of $FeSO_4$ as the catalyst.

Table 1
Dependence of turnovers and selectivity on the relative catalyst concentrations of complexes **1**–**3** in the oxidation of cyclohexane.

Relative cat. conc.	Turnovers			(A + H)/K		
	1	**2**	**3**	**1**	**2**	**3**
0.10 mol%	26	26	24	26	22	26
0.25 mol%	32	39	43	19	20	19
0.50 mol%	21	25	26	15	17	17
1.00 mol%	12	13	14	9	10	13
2.00 mol%	5	7	8	4	7	11
–[a]		<1			–[c]	
$FeSO_4$[b]		<1			–[c]	

Reaction conditions: Cyclohexane (0.569 mmol), aqueous H_2O_2 (50 wt%, 1.138 mmol), acetonitrile (3.0 mL), r.t., 24 h. Turnovers determined by GC, turnovers are combined turnovers for cyclohexyl hydroperoxide, alcohol and ketone formation.
[a] No catalyst used.
[b] $FeSO_4 \times 7H_2O$ used as catalyst in a 1:1 mixture of acetonitrile and H_2O.
[c] (A + H)/K not determined in GC.

Beside hydrogen peroxide other common peroxides were applied as oxidants (Table 2), i.e., *tert*-butyl hydroperoxide (TBHP), *p*-cymene hydroperoxide (CHP), and *m*-chloroperoxybenzoic acid (*m*CPBA).

In all cases the use of alkyl peroxides as oxidants gives poorer results compared to hydrogen peroxide for both the number of turnovers and the (A + H)/K ratio. Within the alkyl peroxides TBHP yields the largest turnovers, with values between 6 and 10. CHP performs slightly worse and *m*CPBA results in very low turnovers

of 2–4. As indicated by the (A + H)/K ratios, the selectivity is strongly reduced by the use of alkyl peroxides with (A + H)/K ratios as low as 1. A possible reason for the severe difference between hydrogen peroxide and alkyl peroxides is the lifetime of iron(III) peroxides, which are typically understood as key intermediates in the reaction of iron(II) complexes with hydrogen peroxide [22,52]. As shown for a variety of systems, iron(III) alkyl peroxides FeOOR are more reactive than iron(III) hydroperoxides FeOOH and therefore more prone to fast and unproductive decomposition [22,37,53]. This is attributed to the weaker O—O bond of the alkyl peroxide ligands [52,54]. Based on the given data hydrogen peroxide is the most suitable oxidant for the catalytic oxidation of cyclohexane by **1**–**3**.

3.3. Additional substrates in C—H bond oxidation

Beside cyclohexane, additional substrates were subjected to C—H bond oxidation (Table 3). The substrates were selected based on previously reported investigations on Fe-based C—H bond oxidation [20,30,55]. Based on the data obtained for cyclohexane, **3** was chosen as catalyst (0.5 mol%) together with 3 equiv. H_2O_2 as the oxidant (cyclohexane after 24 h: 32 turnovers, (A + H)/K ratio of 17).

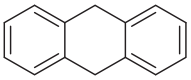
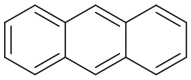
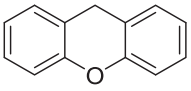
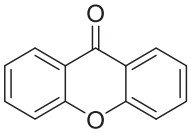
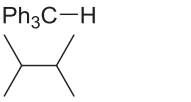
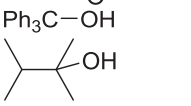
9,10-Dihydroanthracene and xanthene were used as substrates with a C—H bond that can be oxidized comparatively easily ($D_{C-H} \approx 75$–77 kcal/mol) [22]. Despite the fact that the C—H bond dissociation energies of both substrates are almost equal, the number of turnovers for 9,10-dihydroantracene is with 144 significantly larger than for xanthene (87 turnovers). This can be explained by the higher thermodynamic stability of anthracene compared to xanthone. Also, anthracene precipitates from the reaction solution upon formation due to its low solubility in acetonitrile, thus generating an additional driving force for the conversion of 9,10-dihydroanthracene. The selective formation of anthracene without over-oxidation to anthraquinone indicates H-atom abstraction as a key-step in the substrate oxidation [22]. Triphenylmethane ($D_{C-H} \approx 81.0$ kcal/mol) [30] as commonly used substrate in C—H oxidation catalysis is oxidized successfully by **3** with 54 turnovers. As expected from the C—H bond dissociation energy, the number of turnovers is lower compared to the substrates that form aromatic products upon oxidation, but is still larger than observed for cyclohexane under these reaction conditions. With a C—H bond dissociation energy close to cyclohexane, also 2,3-dimethylbutane (2,3-DMB; $D_{C-H} \approx 96.5$ kcal/mol) [30] was exposed to the oxidizing conditions with **3** as catalyst. 2,3-DMB contains both primary and tertiary C—H bonds, thus being an interesting benchmark substrate for the selectivity of **3**. Tracked by ^{1}H NMR, selectively the tertiary alcohol 2,3-dimethyl-2-butanol was obtained as oxidation product (Table 3). **3** converts 2,3-DMB with 28 turnovers, which is close to the value observed for the oxidation of cyclohexane. The selective formation of the tertiary alcohol confirms H-atom abstraction as it already has been indicated by the formation of anthracene from 9,10-dihydroanthracene, thus favoring thermodynamic product formation.

Table 2
Dependence of turnovers and selectivity on the oxidant for complexes **1**–**3** as catalysts for the oxidation of cyclohexane.

Oxidant	Turnovers			(A + H)/K		
	1	**2**	**3**	**1**	**2**	**3**
H_2O_2 aq.	21	25	26	15	17	17
TBHP aq.	10	6	7	1	2	2
CHP	7	7	5	1	2	2
*m*CPBA	2	3	4	5	3	2

Reaction conditions: Cyclohexane (0.569 mmol), oxidant (1.138 mmol), catalyst (**1**, **2**, or **3**, 2.486 μmol, 0.5 mol%), acetonitrile (3.0 mL), r.t., 24 h. Turnovers determined by GC, turnovers are combined turnovers for cyclohexyl hydroperoxide, alcohol and ketone formation. H_2O_2 (50% in H_2O); TBHP = *tert*-butyl hydroperoxide (70% in H_2O); CHP = *p*-cymene hydroperoxide (80% in *p*-cymene); *m*CPBA = *meta*-chloroperoxybenzoic acid.

Table 3
Substrates and the respective main products obtained by catalytic C—H bond oxidation with **3** as the catalyst within 24 h reaction time.

Substrate	Oxidation product	Turnovers
		144
		87
		54
		28[a]

Reaction conditions: Substrate (0.190 mmol), aqueous H_2O_2 (50 wt%, 0.569 mmol, 3 equiv.), **3** (0.949 μmol, 0.5 mol%), acetonitrile-d_3 (1.0 mL), r.t., 24 h. Turnovers based on the substrate determined by ^{1}H NMR.
[a] Turnovers based on the main product.

4. Conclusion

Three Fe(II) complexes **1**–**3** were applied as catalysts in the oxidation of unreactive C—H bonds, with cyclohexane being the main model substrate. All compounds are capable of oxidizing cyclohexane under ambient conditions with a high selectivity toward cyclohexanol and cyclohexyl hydroperoxide ((A + H)/K ratio up to 26), with the latter being easily reduced to the alcohol by addition of triphenylphosphine. Additionally, **1**–**3** show good stabilities toward oxidizing conditions, as indicated by the comparatively large number of turnovers for Fe(II)-catalyzed oxidation of cyclohexane (up to 43). The best results for a combination of good turnovers and a high (A + H)/K ratio were achieved at room temperature with a relative catalyst concentration of 0.25 mol% and 2 equiv. H_2O_2 (relative to the substrate) (**1**: 32 turnovers, (A + H)/K = 19; **2**: 39 turnovers, (A + H)/K = 20; **3**: 43 turnovers, (A + H)/K = 19). By using the double injection technique – as introduced by Shul'pin – it was shown, that cyclohexyl hydroperoxide is formed as the major oxidation product. Compared to recent examples (e.g., 78.6 turnovers, (A + H)/K = 1.2 [56]; 27.9 turnovers, (A + H)/K = 8.9 [57]) that follow the same work-up procedure, compounds **1**–**3** show good selectivity and stability.

While the selectivity is not influenced significantly by axial ligand exchange of **1**, the stability to hydrogen peroxide is increased remarkably and therefore the turnovers rose by 34% in case of **3** compared to **1**. Furthermore, selectivity and stability could not be optimized at the same time. Selectivity increases constantly with a lower relative catalyst concentration, while the number of turnovers – the representative value for the catalyst stability – peaks at 0.25 mol%. However, in case of **3** a higher reaction temperature or a larger amount of hydrogen peroxide results in more turnovers but decreasing selectivity. Oxidants other than H_2O_2 do not result in larger turnovers or better selectivity. Beside cyclohexane, additional substrates could be oxidized successfully, attributing the catalyst system a broad applicability as C—H oxidation catalysts. Selective formation of the H-atom abstraction product anthracene and the secondary alcohol as oxidation product from 2,3-DMB highlight the suitability of **3** as mild, selective, and yet powerful oxidation catalyst.

Acknowledgment

SH and AR gratefully acknowledge support by the Technische Universität München graduate school.

Appendix A. Supplementary material

Spectroscopic data and X-ray data for **3** in CIF format as well as linear fits for TOF determination. Crystallographic data for structure **3** have also been deposited with the Cambridge Crystallographic Data Centre (CCDC 1061411). These coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2015.08.026.

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