Catalytic selective oxidation of primary and secondary alcohols using nonheme [Iron(III)(Pyridine-Containing Ligand)] complexes

Nicola Panza, Armando di Biase, Silvia Rizzato, Emma Gallo, Giorgio Tseberlidis and Alessandro Caselli*

ABSTRACT:

The selective oxidation of different primary and secondary alcohols to carbonyl compounds by hydrogen peroxide was found to be catalysed in conversion ranging from good to excellent by an iron(III) complex of a pyridine-containing macrocyclic ligand (Pc-L), without the need of any additive. The choice of the counteranion (Cl, Br, OTf) appeared to be of fundamental importance and the best results in terms of selectivity (up to 99%) and conversion (up to 98%) were obtained using the well characterised [Fe(III)(Br)2(Pc-L)]Br complex, 4c. Magnetic moments in solid state, also confirmed in solution (d6-DMSO) by Evans NMR method, were calculated and point out to an iron metal centre in the high spin state of 5/2. The crystal structure shows that the iron(III) centre is coordinated by the four nitrogen atoms of the macrocycle and two bromide anions to form a distorted octahedral coordination environment. The catalytic oxidation of benzyl alcohol in acetonitrile was found occurring with better conversions and selectivities than in other solvents. The reaction proved to be quite general, tolerating aromatic and aliphatic alcohols, although very low yields were obtained for terminal aliphatic alcohols. Preliminary mechanistic studies are in agreement with a catalytic cycle promoted by a high-spin iron complex.
INTRODUCTION

The oxidation of alcohols to the corresponding carbonyl compounds is an important chemical process in industrial synthesis and academic research. Compared to the alcohols, in fact, carbonyl compounds show a wider reactivity as precursors and intermediates for many bioactive compounds.[1] Both laboratory-scale syntheses and industrial oxidation processes in the past heavily relied on the use of highly toxic metal-oxo reagents (i.e. KMnO₄) and metal oxide surfaces.[2] Despite the fact that a large number of oxidation reactions have been reported in the last decades,[3] the demand for more selective, efficient, eco-friendly oxidation methods is still increasing. In light of the rising interest in green chemistry principles, a tremendous effort is devoted to develop environmentally benign catalysts and bioinspired oxidation reactions. Several different strategies and efficient methods have been reported for the selective oxidation of primary and secondary alcohols to aldehydes and ketones.[4] The reagents of choice as green oxidants are by far O₂ and H₂O₂ since they possess the highest oxygen content.[5] For instance, in the last five years, significant advances have been achieved in the oxidation of benzyl alcohols to benzaldehydes, using homogeneous iron(II),[6] iron(III)[7][7a] and copper(II)[7a] complexes, metallacarboranes,[7d] supported nanoparticles,[8] MOF,[9] and substoichiometric organic reagents.[10]

In particular, the use of iron,[11] the most abundant transition metal on earth, and its complexes in organic synthesis, biochemistry and also in industrial application is of particular interest.[12] The impressive boost that this area has received in the last few years is witnessed by several timely reviews.[13]

Natural mononuclear nonheme iron enzymes are involved in metabolically vital oxidative transformations, catalysing a wide range of chemical reactions with high efficiency,[14] and the search of synthetic models mimicking Nature is constantly pursued.[15] In the case of nonheme iron enzymes and their models, key intermediates are high-valent iron-oxo intermediates, such as iron(III)-superoxo, iron(III)-peroxo, iron(III)-hydroperoxo, and iron(IV)- or iron(V)-oxo species.[14a, 16] While iron(III)-superoxo species have been recognised as active oxidants in the C–H bond activation and oxygen atom transfer (OAT) reactions although the intermediates are only able to activate weak C-H bonds in hydrocarbons, the reactivities of nonheme iron(III)–hydroperoxo species are still matter of debate and subject of in depth experimental and theoretical investigations.[17] On the other hand, nonheme iron(IV)-oxo species are competent oxidants capable of abstracting hydrogen atom in C–H bond activation reactions.[15e]

Amongst nonheme catalysts, iron complexes of polyamine and aminopyridine ligands surely occupy a prominent role.[18] In particular, iron(II) complexes of tetradeinate N₄ donor-ligands,
[Fe(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>(PyNMe<sub>3</sub>)]<sup>[19]</sup> have proven to be easily oxidised by H<sub>2</sub>O<sub>2</sub> to yield a hydroperoxo iron(III) species which upon the acid triggered O-O bond cleavage is active in the stereospecific hydroxylation of strong C-H bonds.<sup>[20]</sup>

Our group has been interested since several years in the synthesis and study of the coordination behaviour of a series of pyridine-based 12-membered tetraaza-macrocyclic ligands (Pc-L),<sup>[21]</sup> and we have reported the catalytic activity of their copper(I)<sup>[22]</sup> and silver(I)<sup>[23]</sup> complexes in C-C and C-X bond formation reactions. Last year, we reported the synthesis and characterization of robust [iron(III)(Pyridine-Containing Ligand)] complexes, [Fe(III)(Pc-L)], highly active and selective for the alkene oxidation using hydrogen peroxide as the terminal oxidant, in the absence of any additive.<sup>[24]</sup> Depending on the anion, X<sup>-</sup>, of the iron(III) metal complex employed as a catalyst, we observed the selective formation of epoxide (X = Cl), or a clean dihydroxylation reaction (X = OTf) (Figure 1a). –the rationale for this reversal of selectivity could be traced to the influence of the counteranion on the spin state of the iron centre (low spin for X = Cl, high spin for X = OTf) although a possible role of hidden HOTf in the opening of the epoxide cannot be ruled out. Intrigued by this results, we were interested in further exploring the reactivity of these iron(III)(Pc-L) complexes in other oxidation reactions. We report here our findings in the selective oxidation of alcohols by using H<sub>2</sub>O<sub>2</sub>, in the absence of any acid co-catalyst Figure 1b).

![Figure 1. a) Epoxidation or syn-dihydroxylation reactions catalysed by [FeIII(X)2(Pc-L)]X complexes; b) selective oxidation of primary and secondary alcohols reported in this work.](image)

RESULTS AND DISCUSSION

Preparation of the iron complexes. As we recently reported,<sup>[24]</sup> macrocycle 1 was obtained in a useful overall yield by treatment of N-tritosyl-diethylenetriamine with pyridine-2,6-
diylbis(methylene) dimethanesulfonate, followed by the hydrolysis in HBr of the Ts protecting
groups. The $sp^3$ nitrogen atoms of the bromohydrated salt, $2\cdot$HBr, have been directly benzylated in
the presence of excess of DIPEA (DIPEA = $N,N$-diisopropylethylamine) as a base (see Supporting
Information for details), Scheme 1. Metal complexes 3a-b were obtained by mixing an acetonitrile
solution of the selected ligand with an acetonitrile solution of iron(III) chloride hexahydrate or
iron(III) triflate at room temperature in a 1:1 ligand to metal ratio. Both complexes showed a good
solubility in polar non protic solvents (acetone, CH$_3$CN, etc.).

Better yields of the free base ligand 2 were obtained when using concentrated sulphuric acid followed
by treatment with NaOH in the deprotection step. As already reported,$^{[19a]}$ with this method, less
reproducible yields ranging from 60 to 80% are obtained, but the product can be isolated in high
purity after a simple extraction with organic solvents. Metal complexes 4a-c were isolated using the
same procedure described above, albeit in slightly lower yields. These complexes are characterised
by a lower solubility in non-protic solvents but are highly soluble in water.

The structures of complexes 4a-c were characterised by means of mass and elemental analysis as
detailed in the Supporting Information. Elemental analysis for the iron chloride complex 4a·H$_2$O is
consistent with the presence of a lattice molecule of water, not observed in the case of complexes 4b-c.
Based on the ionization observed, together with our previous findings for complexes 3a,b, we
propose the structure depicted in Scheme 1, with the iron placed in an octahedral environment and
two X groups directly bound to the metal (X = Cl, Br or OTf). Magnetic moments, $\mu_{eff}$, of 4.67 $\mu_B$
and of 5.42 $\mu_B$ were measured by the Evans’ method for complexes 4a·H$_2$O and 4c, respectively.$^{[25]}$
These room temperature magnetic moments in solid state were also confirmed in solution (d$_6$-DMSO)
by Evans NMR method,$^{[26]}$ where $\mu_{eff}$, of 5.37 $\mu_B$ (4a·H$_2$O) and of 5.36 $\mu_B$ (4c) were calculated and
seems to point out to an iron metal centre in the high spin state of 5/2.$^{[27]}$ This values have to be
compared with those of complexes 3a·H$_2$O and 3b, that at room temperature possess lower magnetic
moments, in agreement with a mixture of low spin and high spin states as already reported by us.$^{[24]}$
Detailed EPR studies showed that for complex 3a·H$_2$O both low ($S = 1/2$) and high ($S = 5/2$) spin
iron(III) species are present at RT, while lowering the T, the populated spin state 5/2 increases.
Scheme 1. Synthetic route used to obtain ligands 1 and 2 and their corresponding ferric complexes 3 and 4. Ts = tosyl; Ms = mesyl.

Single crystals suitable for X-ray crystallography were grown by slow evaporation from a water solution of complex 4c. Figure 2 shows the chemical structure of the complex.

Figure 2. Molecular structure of the complex [Fe(III)(Br)₂(Pc-L)]Br (50% probability thermal ellipsoids). The water molecule has been omitted for clarity. Selected bond lengths (Å): Fe – N1 2.102(2), Fe – N2 2.180(2), Fe – N3 2.169(2), Fe – N4 2.188(2), Fe – Br1 2.4219(5), Fe – Br2 2.4353(5). Full crystal structure data of 4c are reported in the Supporting Information.

The iron(III) centre is coordinated by the four nitrogen atoms of the macrocycle and two bromide anions to form a distorted octahedral coordination environment. As shown, the macrocycle ligand L
chelates the metal centre with the four nitrogen atoms in a tetradeinate \textit{cis-\alpha} fashion, leaving two \textit{cis} position free for two bromine.\textsuperscript{[28]} Among the Fe-N distances the Fe-N1 bond length is the shortest one, indicating that the strongest metal-ligand interaction occurs with the pyridinic nitrogen.\textsuperscript{[24]} All the structural parameters are in good agreement with those previously reported in the literature for similar complexes.\textsuperscript{[24, 28]}\textsuperscript{[29]} A comparison with the analogous chloride complex [Fe(III)(Cl)\textsubscript{2}(Pc-L)]Cl (CSD refcode JIKPAX)\textsuperscript{[28b]} reveals similar values of the geometrical parameters (Fe-N bond lengths and N\textsuperscript{ax}-Fe-N\textsuperscript{ax}, N\textsuperscript{eq}-Fe-N\textsuperscript{eq} bond angles: 2.182, 2.182 and 2.161 Å for the amino nitrogens and 2.098 Å for the pyridinic nitrogen, 146.68°, 86.62° in JIKPAX; Fe-N values range from 2.102 to 2.188 Å, see figure 2 caption, N\textsuperscript{ax}-Fe-N\textsuperscript{ax}, N\textsuperscript{eq}-Fe-N\textsuperscript{eq} bond angles: 147.63°, 85.63° for the complex under study).

**Iron-catalysed alcohol oxidations.** At the outset, oxidation of benzyl alcohol 5a by H\textsubscript{2}O\textsubscript{2} served as benchmark for the optimization of the reaction conditions (see Table 1). This reaction has been widely studied in recent years, but good results with high selectivities were obtained mainly with heterogeneous catalysts.\textsuperscript{[8, 30]} The lack of good homogeneous catalysts capable of yielding selectively benzaldehyde in such a reaction prompted us to test our iron(III) complexes 3a-b, choosing as a starting point the conditions very close to what we have already recently reported for the epoxidation/dihydroxylation reaction of alkenes.

Reactions were performed by adding the catalyst and the benzyl alcohol to the solvent and then the oxidant (H\textsubscript{2}O\textsubscript{2}, 30\%) by slow addition with syringe pump or by repeated single additions. The reactions were followed by \textsuperscript{1}H NMR adding CH\textsubscript{2}Br\textsubscript{2} as internal standard;\textsuperscript{[31]} GC (dodecane as internal standard) confirmed conversion of the starting benzyl alcohol and selectivities in 6a and 7a. Results of the optimisation of the reaction conditions are reported in Table S1 in the supporting information. Although complex 3b seems to be much more active as catalyst and higher conversion were always observed, better selectivities were obtained at 0 °C using catalyst 3a\textcdot2H\textsubscript{2}O (5 mol\%) and a 1:1 ratio between the oxidant and the substrate, although under those conditions a very low conversion was observed (see Table S1, Supporting Information). Under those conditions, blank control experiments in the absence of any catalyst gave no conversion of the starting aldehyde.

Oxidations by hydrogen peroxide catalysed by Fenton’s reagent (ferrous ion) have received considerable scrutiny since last century,\textsuperscript{[32]} while the use of ferric salts have been given considerably less attention. However, iron(III) chloride in the absence of a ligand can catalyse the oxidation of benzylic primary aromatic alcohols to aldehydes by using a three-fold excess of H\textsubscript{2}O\textsubscript{2} using water as solvent at room temperature, albeit in very modest yields and with concomitant over-oxidation to benzoic acids.\textsuperscript{[7c]} Martin and Garrone have reported since 2003, that FeBr\textsubscript{3} can catalyse efficiently
the selective oxidation of benzylic alcohols by H₂O₂ under solvent free conditions. A large excess amount of hydrogen peroxide was needed because of its fast decomposition in the presence of the ferric ion. To the best of our knowledge, ferric salts have been since then neglected in such oxidation reaction, until recent reports on the use of Fe(OTs)₃ for the selective oxidation of benzyl alcohol and on the efficient use of Fe(OTf)₃ as the catalyst for the solvent free oxidation of cyclohexane.

We were thus interested in comparing the results of the use of simple iron(III) salts under our conditions (Table 1). All the tested ferric salts catalysed a fast decomposition of H₂O₂, but if a large excess of the oxidant was used, 20-fold excess with respect to the alcohol, a good conversion could be achieved. However, only using FeBr₃ an acceptable selectivity was observed and benzaldehyde was obtained as the major product (83% selectivity, entry 3, Table 1). If the addition of the oxidant was slow enough, its quantity can be reduced and sustainable conversions, 76%, and selectivity, 83%, were obtained also when using a 4:1 H₂O₂/alcohol ratio (entry 4, Table 1). However, it should be pointed out that both FeCl₃ and Fe(OTf)₃ behave very similarly as metal complexes 3a·2H₂O and 3b respectively, despite their lower solubility in the reaction medium (compare for example entry 1, Table 1 with entry 5, Table S1).

Table 1. Oxidation reaction of benzyl alcohol to benzaldehyde with H₂O₂ as oxidant catalysed by ferric salts, [Fe(III)X₃][a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>eq H₂O₂</th>
<th>Conv (%)[b]</th>
<th>6a Select (%)[b]</th>
<th>7a Select (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCl₃</td>
<td>20</td>
<td>98</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Fe(OTf)₃</td>
<td>20</td>
<td>72</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>FeBr₃</td>
<td>20</td>
<td>84</td>
<td>83</td>
<td>5</td>
</tr>
<tr>
<td>4[c]</td>
<td></td>
<td>4</td>
<td>76</td>
<td>83</td>
<td>4</td>
</tr>
</tbody>
</table>

[a] Reactions were performed with [FeIII] (2.5 x 10⁻² mmol) in the CH₃CN (10 mL) at a cat/alcohol ratio of 1:20 at 30 °C; H₂O₂ (30% sol; equiv. as reported) was added in a single addition, unless otherwise stated, [b] Conversions and selectivities were calculated after 24 h by ¹H NMR adding CH₂Br₂ as the internal standard to the crude reaction mixture and confirmed by GC (dodecane as the internal standard, [c] H₂O₂ (30% sol) was added dropwise by a syringe pump in 2 h.
It is known that the presence of free N-H bonds might render polyazamacrocyclic ligands sensitive to strong oxidants and affect the complex stability, but it is also reported that N-alkylation of the ligand can cause a change in the spin state configuration at iron, resulting in a lower catalytic activity.\cite{35} We were thus interested in studying the catalytic activity of our iron(III) complexes 4a-c, that in the solid state were shown to possess a high-spin iron centre. Interestingly, complexes 4a·H$_2$O and 4b, which showed a sluggish solubility in CH$_3$CN compares quite well with their respective salts, and in particular for complex 4a·H$_2$O a slightly better selectivity in benzaldehyde was observed (compare entry 1, Table 2 with entry 1, Table 1). On the other hand, complex 4c, under those conditions was less active and less selective than ferric bromide alone when a 20-fold excess of the oxidant was added (compare entry 7, Table 2 with entry 3, Table 1). Instead, if the oxidant was added in small portions, the catalytic system was much more selective and, for instance, if 1 eq of hydrogen peroxide was added every 15 minutes to the reaction mixture, a reasonable selectivity of 73% with a conversion of 76% in just 3h was observed (entry 10, Table 2). A better selectivity (>98%) was obtained when using complex 4c as catalyst by slowly adding 2 eq of the oxidant by syringe pump in 2 h and allowing the reaction mixture to stir at 30 °C for further 22 h (entry 12, Table 2).

Finally, the best compromise between conversion (up to 96%) and selectivity (90%) was obtained by the slow addition of 4 eq of oxidant and allowing the reaction to stir at 30 °C for 24 h (Entry 14, Table 2).
Table 2. Optimization of [Fe(III)(X)(Pc-L)]X, 4a-c, catalysed alcohol oxidation\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>eq H$_2$O$_2$</th>
<th>time (h)</th>
<th>Conv (%)\textsuperscript{[b]}</th>
<th>6a Select (%)\textsuperscript{[b]}</th>
<th>7a Select (%)\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{[c]}</td>
<td>4a·H$_2$O</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>1</td>
<td>33</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>3\textsuperscript{[c]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>8</td>
<td>2</td>
<td>46</td>
<td>52</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>CH$_3$CN</td>
<td>20</td>
<td>24</td>
<td>86</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>5\textsuperscript{[c]}</td>
<td>4b</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>1</td>
<td>69</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>6\textsuperscript{[c]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>8</td>
<td>2</td>
<td>85</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>CH$_3$CN</td>
<td>20</td>
<td>24</td>
<td>66</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>8\textsuperscript{[c]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>4</td>
<td>1</td>
<td>30</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>9\textsuperscript{[c]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>8</td>
<td>2</td>
<td>60</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>10\textsuperscript{[c]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>12</td>
<td>3</td>
<td>78</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>11\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>2</td>
<td>2</td>
<td>29</td>
<td>93</td>
<td>3</td>
</tr>
<tr>
<td>12\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>2</td>
<td>24</td>
<td>50</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>13\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>4</td>
<td>2</td>
<td>45</td>
<td>87</td>
<td>2</td>
</tr>
<tr>
<td>14\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>4</td>
<td>24</td>
<td>96</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>15\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>8</td>
<td>2</td>
<td>58</td>
<td>88</td>
<td>2</td>
</tr>
<tr>
<td>16\textsuperscript{[d]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>8</td>
<td>24</td>
<td>87</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>17\textsuperscript{[d,e]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>4</td>
<td>24</td>
<td>49</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>18\textsuperscript{[d]}</td>
<td></td>
<td>AcOEt</td>
<td>4</td>
<td>24</td>
<td>55</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>19\textsuperscript{[d]}</td>
<td></td>
<td>acetone</td>
<td>4</td>
<td>24</td>
<td>35</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>20\textsuperscript{[d]}</td>
<td></td>
<td>$t$-amylalcohol</td>
<td>4</td>
<td>24</td>
<td>&lt;10</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>21\textsuperscript{[d]}</td>
<td></td>
<td>water</td>
<td>4</td>
<td>24</td>
<td>98</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>22\textsuperscript{[d,f]}</td>
<td></td>
<td>CH$_3$CN</td>
<td>4</td>
<td>2</td>
<td>76</td>
<td>89</td>
<td>7</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reactions were performed with [Fe\textsuperscript{III}] (2.5 x 10$^{-2}$ mmol) in the solvent (10 mL) at a cat/alcohol ratio of 1:20 at 30 °C; H$_2$O$_2$ (30% sol; equiv. as reported) was added in a single addition, unless otherwise stated. \textsuperscript{[b]} Conversions and selectivities were calculated by $^1$H NMR adding CH$_3$Br$_2$ as the internal standard to the crude reaction mixture and confirmed by GC (dodecane as the internal standard. \textsuperscript{[c]} 1 equiv. of H$_2$O$_2$ was added every 15 min to the reaction mixture, \textsuperscript{[d]} H$_2$O$_2$ (30% sol) was added dropwise by syringe pump in 2 h, \textsuperscript{[e]} Cat/alcohol ratio of 1:40, \textsuperscript{[f]} T = 60 °C.

Under those conditions, even if the catalyst amount was halved (2.5 mol%), a high selectivity in benzaldehyde was maintained (88%, entry 17, Table 2). It should be pointed out that under identical conditions pure FeBr$_3$ was almost inactive (< 24% conversion) and less selective (< 75%).
We next checked the effect of the solvent, and higher selectivities (> 99%) were obtained only in AcOEt (Entry 18, Table 2). The lower conversion observed when using acetone as solvent could be accounted to its ability to trap free hydroxyl radicals that might, in this case, be involved in the reaction.\[36\]

As expected, at higher temperatures, 60 °C, good conversions were observed in just 2 h, and still a reasonable selectivity (89 %) was kept (see Table S2, Supporting Information).

**Reaction scope.** We decided to explore the scope of the reaction by using the optimised conditions (entry 14, Table 2) that gave the best compromise between quantitative conversions while keeping high selectivity. Results are summarised in Table 3, where conversion of the starting alcohol is reported in brackets.

Oxidation of *para* substituted benzyl alcohols proceeded smoothly and high conversions with good selectivities were observed especially with electron withdrawing substituents (products 6b and 6c, Table 3). Slightly lower conversions and selectivities were obtained instead when electron donating substituents were present (products 6d and 6e, Table 3; *vide infra* for a comparative Hammett analysis). Reasonable selectivities were retained also in case of 2-substituted benzyl alcohols, with lower conversions (products 6f and 6g, Table 3).

Benzylic secondary alcohols gave excellent results and products 6h and 6g were obtained in 83% and 71% yield respectively. Given the fact that selectivity in the case of secondary benzyl alcohol oxidation is not an issue, product 6h could be selectively obtained in 71% yield in just 2h by slowly adding the oxidant at 90 °C (see Table S2, Supporting Information).

A lower efficacy in the oxidation of both primary and secondary aliphatic alcohols stands out from data reported in Table 3. As a matter of fact, conversions of both nonyl alcohol, 5k, and 1-penyl-2-propanol, 5l, hardly exceeds 15%, although in both cases reasonable selectivities were observed (67% for product 6k and 99% for 6l). Cyclic secondary alcohols were oxidised more efficiently and ketones 6m-o were obtained in good to excellent selectivities. Interestingly, cyclobutanol, 5p, was mainly converted into cyclobutanone 6p (78% selectivity), but from GC-MS analysis we were able to detect 4-hydroxybutyraldehyde, 8, and γ-butyrolactone as major by-products (see later for mechanistic considerations).

In order to further test the selectivity of our system, several alcohols having both –CH₂OH and C=C units were considered. Since we have already studied the reactivity of alkenes to give epoxide or diols in the presence of Fe(III)Pc-L complexes using hydrogen peroxide as oxidant,\[24\] it was interesting to evaluate the possibility of competitive reactions. When cinnamyl alcohol, 5r, was used as substrate,
we observed a good conversion (60%), but a poor selectivity towards the expected cinnamaldehyde, 6r (17%). Interestingly, the low yield in 6r was accompanied by the formation of benzaldehyde as major byproduct (25%), which is known to occur through a disruptive oxidation of the starting unsaturated alcohol via the formation of epoxides as reaction intermediates. The complete absence of products derived from the epoxidation reaction of the double bond was observed also in the case of 2-cyclohexenol and geraniol.

**Table 3. Scope of alcohol oxidations catalysed by complex 4c.**

[a] Reactions were performed with [Fe(III)] (2.5 x 10^{-2} mmol) in CH3CN (10 mL) at a cat/alcohol/H2O2 ratio of 1:20:80; H2O2 (30% sol) was added by syringe pump in 2 h than allowing the reaction mixture to stir at 30 °C for further 22 h. Conversions of the starting alcohol (in brackets) and selectivities were calculated by GC and GC-MS (dodecane as the internal standard, n.d. = not detected), [b] When the same reaction was repeated at 90 °C a 81% conversion was observed in just 2 h and 6h was obtained with a 88% selectivity, [c] The presence of ring opened product was detected by GC-MS and 8 was obtained as major by-product, [d] Benzaldehyde 6a was obtained as a major product in 25% selectivity.

Finally, we also checked the possibility to selectively oxidise 1,2-diols, whose chemo- and/or regioselective oxidation has still proven to be challenging. When hydrobenzoin was treated under...
our optimised conditions, the diketone 6u was formed with a 46% selectivity, accompanied by the formation of benzaldehyde (18%) as major by product, along with traces of other overoxidation products such as benzoic acid. Dodecane-1,2-diol, 5v, was not efficiently converted into the corresponding hydroxymethyl ketone 6v, which was observed by GC-MS as one of the products formed along with high quantities of undecanal as major byproduct, 6w.

**Discussion of the proposed reaction mechanism.** In order to gain better insights in the reaction mechanism, UV spectra of complex 4c were recorded both in CH$_3$CN (Figure S4a) and in water (Figure S4b) before and after the addition of H$_2$O$_2$. Samples with different concentration of the complex were used to estimate the ε value of the most relevant absorption bands. In CH$_3$CN, two bands at 255 nm and 394 nm respectively accounted to MLCT and solvent interaction, with ε values (L mol$^{-1}$ cm$^{-1}$) of ε$_{255\text{nm}}$= 2719 and ε$_{394\text{nm}}$=1154 whilst in water the only relevant band observed was found at 253 nm with ε$_{253\text{nm}}$= 7087. After addition of small amount of hydrogen peroxide to a 10$^{-4}$ M solution of the complex in acetonitrile, we could observe the disappearance of the band at 394 nm and the formation of an intense band at 272 nm, which may imply a modification in the coordination sphere of the metal and the formation of an iron(III)-hydroperoxo intermediate with long life time (Figure S5a). On the other hand, we were not able to detect any formation of significant bands in the range between 500-700 nm accountable to an iron(IV)-oxo species when the experiment was repeated on a more concentrated solution of the complex (2.5*10$^{-3}$ M) in water, we detected a small band at 540 nm that might be attributed to a possible iron(IV)-oxo intermediate (Figure S5b). This band disappeared upon the addition of more equivalents of hydrogen peroxide, due to the reaction of the oxo complex with hydrogen peroxide itself to yield oxygen and water.

The chemistry of nonheme iron complexes in oxidation reactions has been widely studied and it is commonly accepted that the true active species in such transformation are high-valent iron oxo complexes. The formation of such species derives from the homolytic or heterolytic cleavage of O-O bond in Fe(III)OOH generated by the interaction of iron with hydrogen peroxide. The iron(III) hydroperoxo is known to be itself a sluggish oxidant. The reactivity of these iron complexes is strongly influenced by various condition including the solvent, the substrate and oxidant concentrations and the pH.

In our case, to shed light in the reactivity of our system, we performed a series of experiment in order to assess the different possible reaction path followed by our catalyst. First, we evaluated the influence of EWG and EDG on the reaction kinetics using a series of p-substituted benzyl alcohols under the optimised reaction conditions described above. Plotting the k$_{rel}$ of the reactions (k$_{rel}$ = k$_X$/k$_H$) and the Hammett parameter we obtained a ρ value of −0.42 (Figure 3). The low value of this parameter indicates that the reaction is not strongly influenced by EW and ED ability of the substituents and
that the transition state does not involve a strong electrophilic species. The value is comparable with the synthetic Fe(IV)(O)−porphyrin•+ (ρ = −0.39).\[40\

![Figure 3. Plot of the k_{rel} of the reactions (k_{rel} = k_X/k_H) against the Hammet parameter for the reaction of benzyl alcohols 5a-d catalysed by complex 4c.](image)

The kinetic constant (k_D) for the oxidation of α,α-d² benzyl alcohol was calculated (see Supporting Information) and a C-H kinetic isotope effect (KIE - k_H/k_D) of 3.52 was found. This relatively low value at 30 °C is typical for other oxo species and seems not to involve any tunnelling effect, which might become predominant at lower temperatures. The rate determining step can be considered the αC-H hydrogen atom abstraction of alcohols.\[41\] The high valent iron species responsible for this transformation can be nevertheless formed by two substantial mechanisms: i) a 1e⁻ mechanism in which O-O of iron(III) hydroperoxo undergoes homolytic cleavage to form Fe(IV)(O) + OH or ii) a 2e⁻ mechanism in which the same species undergoes heterolytic cleavage to form Fe(V)(O) and OH⁻ (Scheme 2). In our case, it seems that the bond dissociation energy (BDE) of the αC-H hydrogen atom cannot be neglected. In fact, the conversion of benzylic alcohols (BDE ~80 Kcal/mol) are much higher than the aliphatic ones (BDE ~90+ Kcal/mol).\[41\] This might be more predominant in a 2e⁻ mechanism, where instead a 1e⁻ mechanism would produce a strong hydroxyl radical that would discriminate less between different C-H bonds. Unfortunately, most of the substrates are not mechanism sensitive to this, because for example benzyl alcohol can be oxidised to benzaldehyde by gem-diol formation and dehydration ( typical for hydroxyl radicals) and by oxidation of the carbon radical and proton transfer to the solvent cage (typical of 2e⁻ mechanism).\[41\]
More significant in this respect is the careful observation of the product distribution in the oxidation of cyclobutanol (Scheme 2). In this case in fact, only a single step, 2e⁻ process will lead to the expected ketone 6p leaving the 4-membered ring intact.\textsuperscript{[42]} When we carried out this reaction in our optimised condition, as reported above a 78% selectivity for the cyclobutanone 6p was observed which can be fully consistent with a 2e⁻ process. Nevertheless, some ring-opening products were detected by GC-MS and thus we cannot exclude the participation of different active species in the oxidation reaction.

![Scheme 2](image)

**Scheme 2.** Possible reaction mechanism and product distribution in the oxidation of cyclobutanol.

Finally, we carried out benzyl alcohol oxidation in presence of a radical scavenger (BHT = butyl-hydroxytoluene) and the observed conversion of the substrate was lower and this might be consistent with a radical mechanism (see Table S3, Supporting Information). A similar observation was made also when we performed the reaction in acetone as solvent (see above).\textsuperscript{[36]} Taking in consideration the long reaction time needed for our system to reach a good conversion of the substrate, we cannot exclude the interaction of carbon centre radicals deriving from the hydrogen atom abstraction (HAA) with molecular oxygen to form organic peroxides and hydroperoxides which are known to be slowly converted into alcohol and aldehyde/ketone (Scheme 3).

![Scheme 3](image)

**Scheme 3.** a) Possible formation of organic peroxides/hydroperoxides and b) their decomposition pathways.
This very complex behaviour is not unusual for iron systems in oxidation reaction. The presence of single electron processes is typical for high-spin iron complexes and this might lead to a plethora of possible reaction mechanism. Our catalyst presents two cis-labile positions which might be responsible for this behaviour because once the Fe(III)(OOH) is formed, it can both undergo the well-defined homolytic cleavage to Fe(IV)(O) or it can be coordinated in a $\eta^2$ fashion and undergo heterolytic cleavage to Fe(V)(O)(OH) (Figure 4).

![Two possible coordination geometries (\(\eta^1\) and \(\eta^2\)) of iron-bound OOH species.](image)

The simultaneous occurrence of both 1e- and 2e- processes might also be the reason for the trace presence of brominated products detected by GC-MS analysis (see Supporting information). If a 2e- mechanism reduces iron(IV) to iron(II), we formally produce a free bromide atom which might compete with other species to product formation. In fact, we also observed the formation of brominated acetonitrile when CH$_3$CN was used as the solvent and it is well documented that it could be a promoter for 1e- processes.$^{[36]}$ After 24 h of reaction, the metal complex could only be recovered as a flocculent brown powder that was not active anymore as catalyst in the oxidation reaction. This might be attributed to either the decomplexation of iron or the formation of other inactive dimer species. Finally, an interesting finding was the peculiar reactivity of vicinal diols as substrates: in addition to keto-alcohol and di-keto products, we found the C-C bond cleavage products, which usually are produced by strong oxidizing agents.

**Conclusions**

In summary, the well-defined [Fe(III)(Br)$_2$(Pc-L)]Br complex, 4c, served as an excellent catalyst for primary and secondary alcohols oxidation to carbonyl compounds using hydrogen peroxide as the sole terminal oxidant under mild reaction conditions. In particular, aromatic benzyl alcohols were converted to benzaldehydes in good to excellent selectivities (up to 99%) and conversions (up to 98%). The effect of different anions coordinated to the iron centre were investigated and the non-innocent behaviour of the bromine atom was shown. Characterisation of the most active catalyst precursor was performed by several different techniques and by resolution of the X-ray structure. UV-Vis studies were performed to monitor the changes of the pre-catalyst in presence of the oxidant.
and the formation of a long life iron(III)-hydroperoxo intermediate could be inferred. Hammett correlation with different \( p \)-substituted benzyl alcohols pointed out to the C-H abstraction as the rate determining step. However, a quite low KIE at 30 °C and the observation that “radical clock” cyclobutanone as a substrate are consistent with the occurrence of both 1e\(^-\) and 2e\(^-\) oxidation processes.

**EXPERIMENTAL SECTION**

**General experimental details.** All the reactions that involved the use of reagents sensitive to oxygen or to hydrolysis were carried out under an inert atmosphere. The glassware was previously dried in an oven at 110 °C and was set with cycles of vacuum and nitrogen. All chemicals and solvents were commercially available and used as received except where specified. \(^1\)H NMR analyses were performed with 300 or 400 MHz spectrometers at room temperature. The coupling constants (\( J \)) are expressed in hertz (Hz), and the chemical shifts (\( \delta \)) in ppm. Low resolution MS spectra were recorded with instruments equipped with electron ionization (EI), electrospray ionization (ESI)/ion trap (using a syringe pump device to directly inject sample solutions), or fast atom bombardment (FAB) sources. The values are expressed as mass–charge ratio and the relative intensities of the most significant peaks are shown in brackets. Synthesis of the ligands and iron complexes is described in the experimental section. GC experiments were conducted on a Shimadzu GC-2010 Pro instrument using an SBL™-5ms fused silica capillary column (10 m x 0.1 mm x 0.1 \( \mu \)m film thickness, Sigma-Aldrich – Supelco). Detailed instrument parameters and all methods used are reported in the Supporting Information.

**General procedure for the synthesis of Fe(III) complexes.**

To a stirring solution of ligand 2 (0.48 mmol) in acetonitrile (10 mL) at 40°C, the appropriate iron salt was added (0.48 mmol) and the reaction mixture was left stirring for 4 h. An immediate colour change was observed and, in the case of complexes \( 4a \cdot H_2O \) and \( 4c \), the precipitation of a solid was noticed. Complexes \( 4a \cdot H_2O \) and \( 4c \) were collected by filtration and washed with diethyl ether, then dried under vacuum to obtain a yellow and a red powder, respectively. For complex \( 4b \), the solvent was evaporated under vacuum and the residue was washed several times with \( n \)-hexane to yield a brown powder.

**Yields:** \( 4a \cdot H_2O \) 66% \[ \text{iron source: } FeCl_3 \cdot 6H_2O \]

**MS (ESI)**

\[ m/z (\%) = \text{calcd for } C_{11}H_{18}Cl_3FeN_4: 385.01, \text{ found: } 332.06 (100) \ [M^+ - Cl] \]

**Elem. An.**

\( C_{11}H_{26}Cl_3FeN_4O \) Calcd: C 34.18, H 5.22, N 14.50; found: C 34.72, H 4.90, N 14.20
General catalytic procedure

The catalyst (0.025 mmol) and the substrate (0.5 mmol) were dissolved in acetonitrile (10.0 mL) at 30°C. H₂O₂ (30%, 2.0 mmol) was added in 2 hours by using a syringe pump and the mixture was stirred for 24 h. After this period, 1 mL of the reaction mixture was collected, then a standard aliquot of dodecane was added and the solution was diluted to 10 mL and analysed by GC. To selected reactions, the remaining reaction mixture was filtered through a PTFE 0.20 μm filter to remove the catalyst and concentrated in vacuum. The so obtained crudes were analysed by NMR (CH₂Br₂ as internal standard) to identify the products and to confirm the GC values.

Crystal structure determination

Suitable block red crystals of the compound [Fe(III)(Br)₂(Pc-L)]Br·½H₂O for X-ray analysis were isolated by slow evaporation from an aqueous solution of complex 4c at room temperature.

The single crystal X-ray diffraction experiment was performed on a Bruker Smart APEX II CCD diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were collected at 180 K in the ω-scan mode within the range 3.5° < 2θ < 53.0°. The frames were integrated and corrected for Lorentz-polarization effects with the Bruker SAINT software package. The intensity data were then corrected for absorption by using SADABS. No decay correction was applied. The structure was solved by direct methods (SIR-97) and refined by iterative cycles of full-matrix least-squares on F₀² and ΔF synthesis with SHELXL-97 within the WinGX interface. Compound (4c) crystallises in the monoclinic space group P2₁/c (n° 13), Z = 4. All atoms are in general position except for the water oxygen atom, which is located on the 2-fold axes. Hydrogen atoms of the ligand were placed in geometrically calculated positions and then refined using a riding model based on the positions of the parent atoms with Uiso = 1.2 Ueq(C). The hydrogen atom of water molecule (H1W) was located from a difference Fourier map and refined isotropically. A restrain was applied to the
H...H distance in order to obtain a reasonable value for the H-O-H angle. All non-hydrogen atoms were refined with anisotropic displacement parameters.

Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 2016034). A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

ASSOCIATED CONTENT
Supporting Information
Detailed experimental procedures, text, figures and tables reporting NMR spectra of products and characterisation of the iron complexes. General catalytic procedures and chromatograms of selected reactions including general GC methods used, GC-MS spectra of certain reactions. Kinetic studies on p-substituted benzyl alcohols, Hammett plot and KIE determination procedure. Uv-Vis and IR spectra of the complexes. More detailed crystal structure determination for compound 4c and detailed study on its geometry. This material is available free of charge via the Internet.

ACKNOWLEDGEMENT
We thank the MUR-Italy (Ph.D. fellowship to N. P.) for financial support. Margherita Orazi is gratefully acknowledged for precious help in the synthesis of iron(III) complexes.

KEYWORDS
Alcohol oxidation; Hydrogen peroxide; Macrocycles; Nonheme iron complexes; Pyridine containing macrocyclic ligands.

REFERENCES


[25] The complex 4b could not be characterised by this method due to its highly hygroscopic behavior, which made impossible to weight and fill the sample tube.


