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L-Proline derived mimics of the non-haem iron active site catalyse allylic oxidation in acetonitrile solutions

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ABSTRACT

Non-haem iron complexes are important reagents for the oxidative functionalisation of C–H bonds. Peptidomimetic ligands derived from L-proline, pyridine-2,6-dimethanol and pyridine-2,6-dicarboxylic acid have been combined with iron(II) triflate and hydrogen peroxide in acetonitrile. The resulting complexes convert cyclohexene into the allylic oxidation products, 2-cyclohexen-1-ol, 2-cyclohexen-1-one and 2-cyclohexenyl hydroperoxide in high turnover yields. A mechanism for product formation is proposed, in which the hydroperoxy radical ($HOO^{\cdot}$) is the active oxidant.

The development of efficient, selective and environmentally benign methods for the functionalisation of C–H bonds is an area of considerable current interest.[1–3] Iron has emerged as a key player in this field due to its availability, affordability and capacity to promote a range of oxidative chemistry.[1,4] The ability of iron complexes to drive oxidative transformations has long been apparent in nature, where haem and non-haem iron enzymes catalyse reactions including oxidative cyclisation, desaturation, hydroxylation, epoxidation and dihydroxylation.[5,6]

Inspired by the biological example, chemists have used the non-haem iron active site **1** as the starting point for the design of effective iron-centred oxidation catalysts.[5–12] Amongst the most effective of these biomimetic systems in the context of C–H activation are those based upon neutral, multidentate amine ligands such as *tris*(2-pyridylmethyl)amine (TPA),[9] pyridine-substituted 1,4,7-triazacyclononane (TACN)[10] and 2-({2-[1-(pyridin-2-ylmethyl) pyrrolidin-2-yl]pyrrolidin-1-yl}methyl)pyridine (PDP).[12]

We have previously utilised ligands **2**–**5** (Fig. 1) in combination with iron(II) acetate, hydrogen peroxide and methanol as the solvent to convert alkenes into oxidised products in low to moderate yields.[13–17] Here we report that the reactivity of these ligands is significantly enhanced when used with iron(II) triflate in acetonitrile solution: this change of iron salt and solvent renders a substantial increase in the overall efficiency of oxidative turnover. Alcohol **4** is tetradentate, so binding to iron should leave two coordination sites available for oxidant binding, an arrangement that mirrors oxygen binding at the non-haem iron active site.[5,18] Ligands **5** and **6** are designed to bind iron in a pentadentate manner, leaving one vacant site to be occupied by the oxidant. Klein Gebbink and co-workers have observed this coordination geometry crystallographically in complexes of diester **7**.[19,20]

The combination of iron(II), ligand and hydrogen peroxide can generate a number of possible oxidation products from cyclohexene **8**, via two general pathways (Scheme 1): biomimetic oxidation reactions mediated by an iron–ligand complex to form the *cis*-diol **9** and/or epoxide **10** via high-valent iron-oxo intermediates (Path A);[21–23] or competing reactions via radical mechanisms affording the allylic oxidation products, alcohol **11**, ketone **12** and hydroperoxide **13** (Path B).[24]

Ligands **4**–**6** have limited solubility in acetonitrile, so iron complexes were prepared by combining the ligands with iron(II) triflate [$Fe(OTf)_2{\cdot}(CH_3CN)_2$] in anhydrous methanol and removing the solvent in vacuo. The resulting complexes were then dissolved in acetonitrile, in which they were readily soluble. Oxidative turnover reactions were carried out by introducing the substrate, cyclohexene (1000 equiv, used in excess to minimise over-oxidation of initial oxidation products and protect the catalyst from oxidative degradation) followed by slow addition of hydrogen peroxide (10 equiv of a 30% aqueous solution, added over 30 min). The reaction was stirred at room temperature overnight

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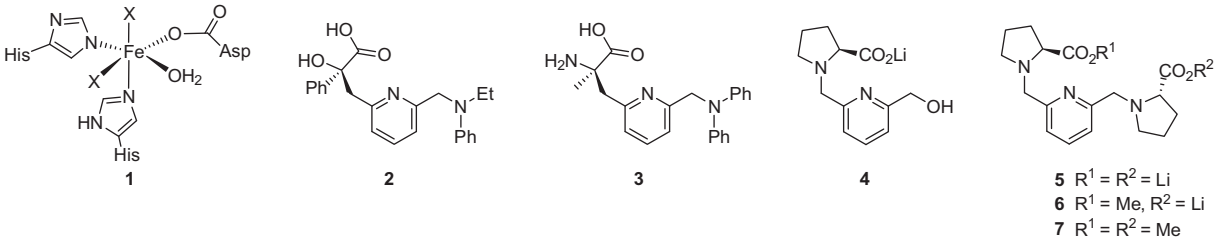
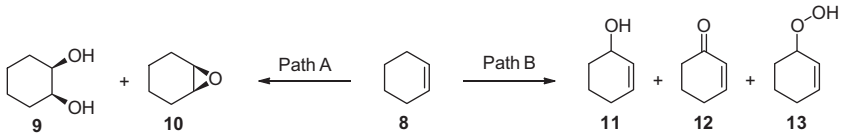


Figure 1. Generalized non-haem iron active site **1** (X = solvent or substrate-derived ligand) and ligand architectures **2**–**7** designed to mimic non-haem iron oxidase structure and function.



Scheme 1. Potential oxidation products from turnover of cyclohexene **8**: Path A is biomimetic oxidation to give *cis*-cyclohexane-1,2-diol **9** and/or cyclohexene oxide **10**. Path B is Fenton-type reactivity to allylic oxidation products alcohol **11**, ketone **12** and hydroperoxide **13**.

under argon (to exclude molecular oxygen).[25] Reaction products were isolated from the mixture and analysed by gas chromatography (Table 1).[26]

Ligands **4**–**6** all combine with iron(II) triflate to convert cyclohexene into oxidised products (alcohol **11**, ketone **12** and hydroperoxide **13**) at levels well above the ligand-free combination of iron(II) triflate and hydrogen peroxide. Neither diol **9** nor epoxide **10** were observed under these conditions. Overall levels of product formation with ligands **4** and **5** were considerably higher than previously achieved using iron(II) acetate and methanol: under those conditions, ligand **4** gave an overall yield of 31% (**9**:**11**:**12**, 2%:7%:22%), while with ligand **5** the overall yield was 52% (**9**:**11**:**12**, 4%:6%:42%).[16]

The allylic oxidation of cyclohexene to similar product combinations of **11**, **12** and **13** has previously been achieved using hydrogen peroxide or molecular oxygen with various transition metal catalysts including vanadium–pyrazine,[27] manganese–TACN,[28] copper–cyclam,[29] cobalt–salen[30] and iron–porphyrin[31] complexes. Several iron-based catalysts have also been shown to form similar combinations of the corresponding hydroperoxide, alcohol and ketone products from cyclohexane.[32,33] These reactions are generally thought to be mediated by hydroxy (·OH) and/or hydroperoxy (·OOH) radicals.

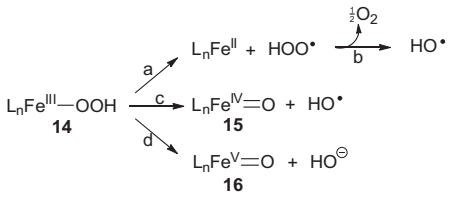
In the non-haem iron context, an iron complex (L_nFe^{II}) and peroxide oxidant first form an iron-peroxo intermediate (L_nFe^{III}–OOH, **14**).[34] Klein Gebbink and coworkers have observed the corresponding iron(III)–alkylperoxo complex (LnFe^{III}–OOR) formed transiently from diester **7**, iron(II) and *tert*-butyl hydroperoxide.[20] The iron(III)-peroxo intermediate **14** can break down via four different pathways giving rise to five possible oxidants (Scheme 2): the iron–hydroperoxy intermediate L_nFe^{III}–OOH **14**; the hydroperoxy radical ·OOH; the hydroxy radical ·OH; an iron(IV)-oxo species L_nFe^{IV}=O (**15**); or an iron(V)-oxo species L_nFe^{V}=O (**16**).[34] The nature of L_n dictates which of these pathways predominates, and thus controls the overall outcome of the reaction.

With cyclohexene as substrate, iron–hydroperoxy **14**, iron(IV)-oxo **15** and iron(V)-oxo **16** species should all react to some extent with the π system of the alkene to give diol and/or epoxide products. Diol **9** and epoxide **10** were not observed in reactions of **4**(Fe)–**6**(Fe) with cyclohexene **8** in acetonitrile, indicating that **14**, **15** and **16** are not active oxidants in this system. Instead it seems that L_nFe–OOH **14** breaks down via homolysis of the Fe–O bond (Scheme 2, path a). But which of the hydroperoxy radical (·OOH) and hydroxy radical (·OH) is the active oxidant? Both these species are capable of abstracting the relatively weak allylic C–H in cyclohexene [ΔH_{DBE}(C–H) = 351 kJmol^{-1}, compared to ΔH_{DBE}(HOO–H) = 367 kJmol^{-1} and ΔH_{DBE}(HO–H) = 497 kJmol^{-1}].[35,36] The hydroxy radical can drive the corresponding reaction with cyclohexane [ΔH_{DBE}(C–H) = 400 kJmol^{-1}] whereas the hydroperoxy radical cannot. Subjecting cyclohexane to reaction with **4**(Fe) or **5**(Fe) and hydrogen peroxide under analogous conditions affords cyclohexanol and cyclohexanone at levels equal to or below those observed in control experiments without ligand [hydrogen peroxide/iron(II) triflate; data not shown]. Thus we propose that the hydroperoxy radical ·OOH is the primary oxidant in these systems: in acetonitrile solution, the iron(II) triflate complexes of ligands **4**–**6** catalyse the formation of hydroperoxy radicals from hydrogen peroxide, and these reactive species drive the turnover of

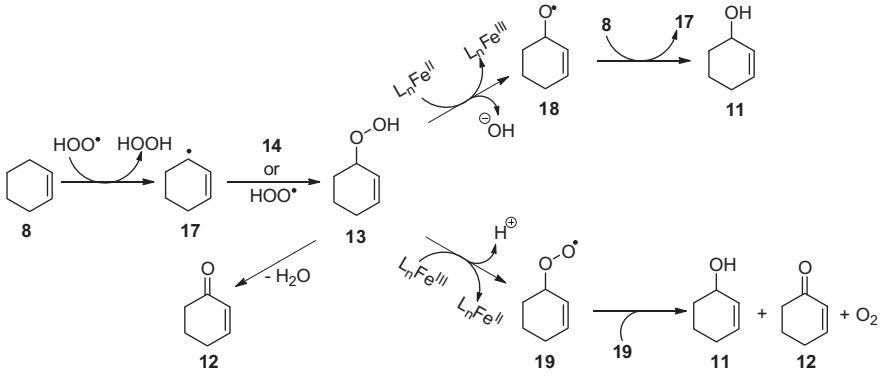
Table 1
Oxidation of cyclohexene by iron triflate complexes of ligands **4**–**6** in acetonitrile

Entry	Ligand[a,b]	**11**[c,d] (%)	**12**[c,d] (%)	**13**[c,d] (%)	Total yield (%)
1	**4**	16	21	49	86
2	**5**	17	29	52	98
3	**6**	33	45	0	78
4[e]	—	15	9	10	34

[a] Initial ratio catalyst:H_2O_2:substrate = 1:10:1000. See Supplementary data for more details.
[b] Catalyst prepared in situ from ligand and iron(II) triflate in methanol; methanol was then removed, the complex dissolved in acetonitrile, and the reaction run in acetonitrile.
[c] Percentage yield relative to H_2O_2, the limiting reagent. Turnover number (μmol product produced per μmol catalyst) can be derived by dividing these percentage yields by 10. Percentage conversion of alkene = percentage yield/100.
[d] Values shown are the averages of three repetitions.
[e] Control experiments using only iron(II) salt and H_2O_2 (i.e. no ligand).



Scheme 2. Potential breakdown pathways for the L_nFe^{III} intermediate **14**, which give rise to five potential oxidants in non-haem iron systems.[34]



Scheme 3. Potential routes for formation of **11**, **12** and **13** from cyclohexene **8**: Abstraction of H· from **8** by the hydroperoxy radical ·OOH would give **17**, which could be converted into hydroperoxide **13** by either a second hydroperoxy radical or complex **14**. Redox conversion of **13** into **11** and **12** could proceed via intermediates **18** and **19**, with the iron complex functioning to decompose the hydroperoxide as observed by Gray and co-workers with porphyrin and salen complexes of iron.[37,38] Alternatively ketone **12** may also arise from **13** via elimination of water.[39,40]

cyclohexene to the alcohol **11**, ketone **12** and hydroperoxide **13** products observed, via intermediates **17**–**19** (Scheme 3).

In conclusion, the iron(II) triflate complexes of non-haem ligands **4**–**6** catalyse high levels of oxidative turnover of cyclohexene **8** into the alcohol **11**, ketone **12** and hydroperoxide **13** in acetonitrile solutions. We propose that the hydroperoxy radical ·OOH is the primary oxidant and that hydroperoxide **13** is a common intermediate in the formation of **11** and **12**. Further work (including kinetic studies, spectroscopic characterisation of intermediates and experiments with $H_2{}^{18}O_2$) is required to confirm this proposal and to fully elucidate the mechanism of these transformations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.095. These data include MOL files and InChiKeys of the most important compounds described in this article.

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26. Samples were analysed on a Hewlett-Packard 5890 Series II gas chromatograph using an HP-1 ms column (30 m × 0.25 mm ID, 0.25 μm; S/N US2469051H) and a Hewlett-Packard 5890A gas chromatograph with a BP-20 column (25 m × 0.22 mm ID, 0.25 μm), each equipped with a split/splitless capillary inlet and a flame ionisation detector (FID) and controlled using ChemStation software. Products were identified unambiguously by comparison and spiking with authentic samples.
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