

# An efficient biomimetic Fe-catalyzed epoxidation of olefins using hydrogen peroxide†

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A new, environmentally benign and practical epoxidation method was developed using inexpensive and efficient Fe catalysts.  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in combination with commercially available pyridine-2,6-dicarboxylic acid and amines showed excellent reactivity and selectivity towards aromatic olefins and moderate reactivity towards 1,3-cyclooctadiene utilizing  $\text{H}_2\text{O}_2$  as the terminal oxidant.

Nature utilizes iron-proteins such as hemoglobin, myoglobin, and cytochrome oxygenases for vital biochemical processes such as transport of oxygen and electron transfer reactions in plants, animals and microorganisms.<sup>1–3</sup> Understanding such mechanisms may lead to new insights in biocatalysis and drug design as well as the development of new industrial catalysts.

Following nature's path, numerous reports on biomimetic oxidation of olefins using metalloporphyrins are known at present; a major problem curtailing these catalysts for use in industry is their difficult multi-step synthesis.<sup>4</sup> Among the various oxidation methods, epoxidation of olefins continues to be an important field of research in industry and academia due to the formation of two C–O bonds in one reaction and the facile opening of the epoxide ring to useful synthons.<sup>5</sup>

With respect to the oxidants<sup>6</sup> commonly used, molecular oxygen<sup>7</sup> and  $\text{H}_2\text{O}_2$ <sup>8</sup> are the reagents of choice. The latter is more convenient to use and produces only water as the by-product. Thus, a combination of  $\text{H}_2\text{O}_2$  with a catalytic amount of cheap and relatively non-toxic metals such as Mn or Fe would be an ideal system for large scale production in industry. However, the use of  $\text{H}_2\text{O}_2$  in combination with simple non-heme manganese<sup>9</sup> or iron<sup>10</sup> is limited, since  $\text{H}_2\text{O}_2$  is well-known to decompose vigorously in the presence of these metals.<sup>11</sup> Consequently, iron-catalyzed epoxidation using non-heme complexes and  $\text{H}_2\text{O}_2$  are scant in the literature.<sup>12</sup> For example, the Jacobsen's Fe-mep catalyst<sup>13</sup> is known to epoxidize aliphatic olefins in the presence of acetic acid.<sup>14</sup> However, to the best of our knowledge there is no Fe catalyst known which allows for a general epoxidation under neutral conditions.<sup>12c</sup>

In this context, we were interested in exploring the possibility of Fe-catalyzed epoxidation using  $\text{H}_2\text{O}_2$ , since iron and  $\text{H}_2\text{O}_2$  are cheap, environmentally benign and reactive. As a starting point of

our work on Fe catalysts, we tried to extrapolate our previously developed Ru reaction protocols<sup>15–18</sup> with Fe. Not surprisingly, initial attempts with pre-made Fe complexes resulted in low yield and selectivity. Therefore *in situ* generated iron complexes, which are more easily tuned, were used for the epoxidation of *trans*-stilbene at room temperature.<sup>19</sup>

A screening of different iron sources of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  in the presence of acid or base revealed that complete conversion was observed only in the case of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ . Hence, our further investigations focused on this iron source. While studying various nitrogen ligands, it was observed that simply pyridine-2,6-dicarboxylic acid ( $\text{H}_2\text{pydic}$ ) is sufficient to form an active Fe epoxidation catalyst! Advantageously, the *in situ* formation of the active complex with  $\text{H}_2\text{pydic}$  and Fe occurs at rt. The combination of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{H}_2\text{pydic}$ , and an organic base, such as benzylamine, 4-methylimidazole and pyrrolidine, leads to an active and highly selective epoxidation catalyst (see ESI†).

Unlike the corresponding Ru complexes, the use of disodium pyridine-2,6-dicarboxylate or using  $\text{H}_2\text{pydic}$  with 10 mol% of inorganic base was not effective in the case of Fe. To our delight, the addition of organic bases, such as benzylamine, 4-methylimidazole and pyrrolidine, gave full conversion and almost quantitative yield and selectivity. It is envisaged that one of the roles of the base is to deprotonate the pyridine-2,6-dicarboxylic acid; however reports on the influence of base on the stability of the catalyst and selectivity of the oxidation are known.<sup>20</sup> When the NH group of imidazole was substituted with an alkyl group, the reactivity remained. However, the reactivity dropped significantly when 2-methylimidazole was used (12% conv., 11% yield). In comparison with the reactivity of pyridine (56% conv., 50% yield) and pyrrolidine (100% conv., 97% yield), this effect must be attributed to coordination effects to some extent. This is not the case with 4-methylimidazole, which led to full conversion with excellent yield (97%) of *trans*-stilbene oxide. In order to explain the observed ligand effects, gelicification and redissolution of the ligand or catalyst should be considered, too. Such effects were reported during the deprotonation of the pyridine-2,6-dicarboxylic acid in aqueous alkaline solution due to pH dependent electrostatic interactions and hydrogen bonding between the polar species and water.<sup>21</sup> We have not noticed any such process in our reactions, obviously due to the less polar nature of *tert*-amyl alcohol compared to water. Importantly, the formation of *trans*-stilbene oxide was not observed when pyrrolidine, pyridine-2,6-dicarboxylic acid or the iron source was not used in the reaction. It is remarkable that the epoxidation reaction is quite fast and an optimum yield can be achieved by addition of the oxidant ( $\text{H}_2\text{O}_2$ )

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over a period of one hour using a syringe pump. Even an addition of hydrogen peroxide within 5 minutes showed no decrease in reactivity and selectivity for *trans*-stilbene.

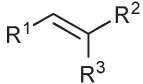
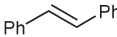
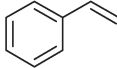
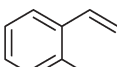
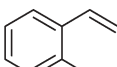
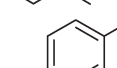
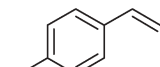
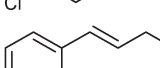
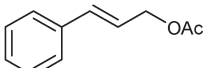
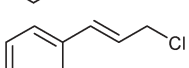
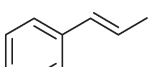
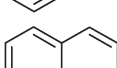
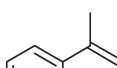

Next, different substrates were tested in these optimized reaction conditions (Table 1). Styrene, generally known as a difficult substrate for epoxidation, afforded excellent yield and selectivity of styrene oxide (Table 1, entries 3–4). The reaction also performed well for *ortho*- and electron donating/withdrawing substituted styrenes (Table 1, entries 5–8). Cinnamyl acetate, cinnamyl chloride, and *cis*- as well as *trans*- $\beta$ -methyl styrene gave good to excellent yields (Table 1, entries 9–13). In the case of  $\alpha$ -methyl styrene, in addition to the epoxide, a small amount of 2-phenylpropanal was also formed, presumably by the iron-promoted rearrangement of the epoxide *via* a stable benzyl carbocation.

To further extend the scope of the reaction 1,3-cyclooctadiene was tested. Here, the corresponding mono-epoxide is obtained in 65% yield with 84% selectivity (Table 1, entry 14). To understand

the mechanism of the reaction in more detail, *trans*-stilbene was subjected to epoxidation using the new protocol in the presence of a radical scavenger (2,6-di-*tert*-butyl-4-methoxyphenol), which afforded the epoxide in very low yield (<10%) suggesting a selective radical pathway occurring as the major process in this reaction. Although to date we have no direct structural evidence of the active catalyst species, and discussions on the nature of the intermediate are so far speculative,<sup>22</sup> non-heme dioxygenases, such as TauD,<sup>23</sup> TfdA<sup>24</sup> and NDO,<sup>25</sup> which contain carboxylate and histidine on their coordination sphere, may give us some insights.<sup>26</sup>

In conclusion, we have developed a new biomimetic, convenient and fast epoxidation protocol using a cheap and environmentally friendly iron source in combination with H<sub>2</sub>O<sub>2</sub>. The system showed excellent reactivity and selectivity towards terminal and 1,2-disubstituted aromatic olefins, and moderate reactivity towards 1,3-dienes. Unlike previous procedures, our protocol is much simpler and demands no pre-made catalyst, acetic acid or freezing reaction temperature. Gratifyingly, all the reagents used in our

**Table 1** Scope and limitations of the reaction

Entry	Substrate	Conv. (%) <sup>a,b</sup>	Yield (%) <sup>b</sup>	Selectivity (%) <sup>c</sup>
1		100	97	97
2		98 <sup>d</sup>	96 <sup>d</sup>	98 <sup>d</sup>
3		94	93	99
4		88 <sup>d</sup>	69 <sup>d</sup>	78 <sup>d</sup>
5		100	97	97
6		88 <sup>d</sup>	87 <sup>d</sup>	99 <sup>d</sup>
7		100	77	77
8		100 <sup>d</sup>	79 <sup>d</sup>	79 <sup>d</sup>
9		71	69	97
10		77	63	82
11		100	95	95
12		75	56 <sup>e</sup>	75
13		93	64	69
14		77	65	84

<sup>a</sup> Reaction conditions: in a 25 mL Schlenk tube, FeCl<sub>3</sub>·6H<sub>2</sub>O (0.025 mmol), H<sub>2</sub>pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol) and dodecane (GC internal standard, 100  $\mu$ L) were added in sequence at rt in air. To this mixture, a solution of 30% H<sub>2</sub>O<sub>2</sub> (114  $\mu$ L, 1.0 mmol) in *tert*-amyl alcohol (886  $\mu$ L) was added over a period of 1 h (or 5 min) at rt by a syringe pump. <sup>b</sup> Conversion and yield were determined by GC analysis. <sup>c</sup> Selectivity refers to the ratio of yield to conversion as percentage. <sup>d</sup> The oxidant was added over a period of 5 min. <sup>e</sup> 19% *trans*- $\beta$ -methylstyrene oxide was observed.

system are simple and commercially available and the reaction can be performed at rt. To the best of our knowledge, the system described here is the simplest and most practical iron-catalyzed epoxidation procedure available for olefins today. Efforts are underway in our group aimed at realizing the asymmetric version of this reaction.

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