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

Gopinathan Anilkumar,[a] Bianca Bitterlich,[a] Feyissa Gadissa Gelalcha,[a] Man Kin Tse[ab] and Matthias Beller*[ab]

Received (in Cambridge, UK) 22nd August 2006, Accepted 28th September 2006
First published as an Advance Article on the web 27th October 2006
DOI: 10.1039/b612048b

A new, environmentally benign and practical epoxidation method was developed using inexpensive and efficient Fe catalysts. $FeCl_3 \cdot 6H_2O$ 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 H_2O_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.[1–3] 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.[4] 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.[5]

With respect to the oxidants[6] commonly used, molecular oxygen[7] and H_2O_2[8] are the reagents of choice. The latter is more convenient to use and produces only water as the by-product. Thus, a combination of H_2O_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 H_2O_2 in combination with simple non-heme manganese[9] or iron[10] is limited, since H_2O_2 is well-known to decompose vigorously in the presence of these metals.[11] Consequently, iron-catalyzed epoxidation using non-heme complexes and H_2O_2 are scant in the literature.[12] For example, the Jacobsen's Fe-mep catalyst[13] is known to epoxidize aliphatic olefins in the presence of acetic acid.[14] However, to the best of our knowledge there is no Fe catalyst known which allows for a general epoxidation under neutral conditions.[12c]

In this context, we were interested in exploring the possibility of Fe-catalyzed epoxidation using H_2O_2, since iron and H_2O_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[15–18] 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.[19]

A screening of different iron sources of Fe^{2+} and Fe^{3+} in the presence of acid or base revealed that complete conversion was observed only in the case of $FeCl_3 \cdot 6H_2O$. Hence, our further investigations focused on this iron source. While studying various nitrogen ligands, it was observed that simply pyridine-2,6-dicarboxylic acid (H_2pydic) is sufficient to form an active Fe epoxidation catalyst! Advantageously, the *in situ* formation of the active complex with H_2pydic and Fe occurs at rt. The combination of $FeCl_3 \cdot 6H_2O$, H_2pydic, 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 H_2pydic 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.[20] 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.[21] 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 (H_2O_2)

[a]*Leibniz-Institut für Katalyse, Albert-Einstein Straße 29a, Rostock, D-18059, Germany*
[b]*Center for Life Science Automation, Friedrich-Barnewitz-Straße 8, D-Rostock, 18119, Germany. E-mail: matthias.beller@catalysis.de; Fax: +49 381-1281-5000; Tel: +49 381-1281-113*
† Electronic supplementary information (ESI) available: Base effect of Fe-catalyzed epoxidation of *trans*-stilbene. See DOI: 10.1039/b612048b

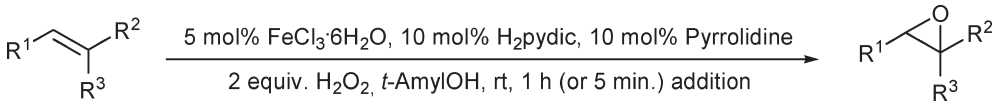
over a period of one hour using a syringe pump. Even an addition of hydrogen peroxide within 5 minutes showed no decrease in reactivity and selectivity for *trans*-stilbene.

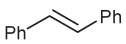
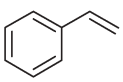
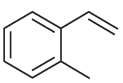
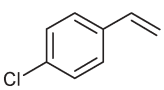
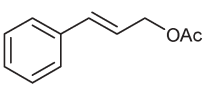
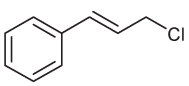
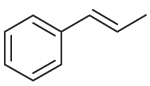
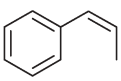
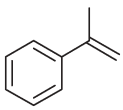
Next, different substrates were tested in these optimized reaction conditions (Table 1). Styrene, generally known as a difficult substrate for epoxidation, afforded excellent yield and selectivity of styrene oxide (Table 1, entries 3–4). The reaction also performed well for *ortho*- and electron donating/withdrawing substituted styrenes (Table 1, entries 5–8). Cinnamyl acetate, cinnamyl chloride, and *cis*- as well as *trans*-β-methyl styrene gave good to excellent yields (Table 1, entries 9–13). In the case of α-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,[22] non-heme dioxygenases, such as TauD,[23] TfdA[24] and NDO,[25] which contain carboxylate and histidine on their coordination sphere, may give us some insights.[26]

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_2O_2. 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. (%)[a,b]	Yield (%)[b]	Selectivity (%)[c]
1		100	97	97
2		98[d]	96[d]	98[d]
3		94	93	99
4		88[d]	69[d]	78[d]
5		100	97	97
6		88[d]	87[d]	99[d]
7		100	77	77
8		100[d]	79[d]	79[d]
9		71	69	97
10		77	63	82
11		100	95	95
12		75	56[e]	75
13		93	64	69
14		77	65	84

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (114 μL, 1.0 mmol) in *tert*-amyl alcohol (886 μL) was added over a period of 1 h (or 5 min) at rt by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Selectivity refers to the ratio of yield to conversion as percentage. [d] The oxidant was added over a period of 5 min. [e] 19% *trans*-β-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.

We thank the State of Mecklenburg-Western Pommerania, the Federal Ministry of Education and Research (BMBF) and the Deutsche Forschungsgemeinschaft (SPP 1118 and Leibniz-prize) for financial support. Dr D. Michalik, Mrs C. Mewes, Mrs A. Lehmann, Mrs C. Fisher and Mrs S. Buchholz (LIKAT) are acknowledged for their technical and analytical support.

Notes and references

1 (*a*) M. J. Nelson and S. Seitz, in *Active Oxygen in Biochemistry*, ed. J. S. Valentine, C. S. Foote, A. Greenberg and J. F. Leibman, Chapman and Hill, Glasgow, 1995, pp. 276; (*b*) O. Hayaishi, in *Molecular Mechanism Of Oxygen Activation*, ed. O. Hayaishi, Academic Press, New York, 1974, pp. 1.

2 J. T. Groves, R. C. Haushalter, M. Nakamura, T. E. Nemo and B. J. Evans, *J. Am. Chem. Soc.*, 1981, **103**, 2884.

3 (*a*) C. Colas and P. R. O. Mantellano, *Chem. Rev.*, 2003, **103**, 2305; (*b*) P. R. O. Montellano, *Acc. Chem. Res.*, 1998, **31**, 543; (*c*) M. Sono, M. P. Roach, E. D. Coulter and J. H. Dawson, *Chem. Rev.*, 1996, **96**, 2841.

4 (*a*) For a recent review on catalytic enantioselective epoxidation using chiral metalloporphyrins, see: E. Rose, B. Andrioletti, S. Zrig and M. Q. Etheve, *Chem. Soc. Rev.*, 2005, **34**, 573. (*b*) For an excellent review on metalloporphyrin-catalyzed oxidation reactions, see: B. Meunier, *Chem. Rev.*, 1992, **92**, 1411.

5 (*a*) K. A. Jørgensen, in *Transition Metals For Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 1998, vol. 2, pp. 157; (*b*) K. Furuhashi, in *Chirality In Industry*, ed. A. N. Collins, G. N. Sheldrake and J. Crosby, John Wiley, England, 1992, pp. 167; (*c*) U. Sundermeier, C. Döbler and M. Beller, in *Modern Oxidation Methods*, ed. J. E. Bäckvall, Wiley-VCH, Weinheim, 2004, pp. 1.

6 For a list of common oxidants, their active oxygen contents and waste products, see: H. Adolfsson, in *Modern Oxidation Methods*, ed. J. E. Bäckvall, Wiley-VCH, Weinheim, 2004, pp. 22.

7 For a recent review on transition metal catalyzed oxidation of organic substrates with molecular oxygen, see: T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329; for use of molecular oxygen or air in oxidation reactions, see: (*a*) U. Sundermeier, C. Döbler, G. M. Mehltretter, W. Baumann and M. Beller, *Chirality*, 2003, **15**, 127; (*b*) C. Döbler, G. M. Mehltretter, U. Sundermeier and M. Beller, *J. Organomet. Chem.*, 2001, **621**, 70; (*c*) C. Döbler, G. M. Mehltretter, U. Sundermeier and M. Beller, *J. Am. Chem. Soc.*, 2000, **122**, 10289; (*d*) G. M. Mehltretter, C. Döbler, U. Sundermeier and M. Beller, *Tetrahedron Lett.*, 2000, **41**, 8083; (*e*) C. Döbler, G. M. Mehltretter and M. Beller, *Angew. Chem.*, 1999, **111**, 3211 (*Angew. Chem., Int. Ed.*, 1999, **38**, 3026).

8 For excellent reviews on metal catalyzed epoxidation using H_2O_2, see: (*a*) B. S. Lane and K. Burgess, *Chem. Rev.*, 2003, **103**, 2457; (*b*) G. Grigoropoulou, J. H. Clark and J. A. Elings, *Green Chem.*, 2003, **5**, 1; (*c*) I. W. C. E. Arends and R. A. Sheldon, *Top. Catal.*, 2002, **19**, 133.

9 For a catalytic epoxidation using H_2O_2 and $MnSO_4$, see: B. S. Lane and K. Burgess, *J. Am. Chem. Soc.*, 2001, **123**, 2933.

10 For alkane oxygenation with H_2O_2 catalyzed by $FeCl_3$, see: (*a*) G. B. Shulpin, C. C. Golfeto, G. Suss-Fink, L. S. Shulpina and D. Mandelli, *Tetrahedron Lett.*, 2005, **46**, 4563; (*b*) D. H. R. Barton and B. Hu, *Pure Appl. Chem.*, 1997, **69**, 1941; (*c*) D. H. R. Barton and D. K. Taylor, *Pure Appl. Chem.*, 1996, **68**, 497.

11 (*a*) W. Nam, R. Ho and J. S. Valentine, *J. Am. Chem. Soc.*, 1991, **113**, 7052; (*b*) T. G. Traylor, S. Tsuchiya, Y. S. Byun and C. Kim, *J. Am. Chem. Soc.*, 1993, **115**, 2775; (*c*) D. Dolphin, T. G. Traylor and L. Y. Xie, *Acc. Chem. Res.*, 1997, **30**, 251.

12 (*a*) For an iron(II) tpa complex (tpa = tris-(2-pyridylmethyl)amine) catalyzed epoxidation of olefins by *in situ* formation of peracetic acid from H_2O_2 and HOAc applied to a few substrates affording a mixture of epoxides and diols, see: M. Fujita and L. Que, Jr., *Adv. Synth. Catal.*, 2004, **346**, 190. (*b*) for epoxidation of cyclooctene by H_2O_2 catalyzed by iron complexes yielding a mixture of epoxide and diol, see: K. Chen, M. Costas, J. Kim, A. T. Tipton and L. Que, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 3026. (*c*) for oxidation of olefins by activation of H_2O_2 with anhydrous $FeCl_3$ yielding a mixture of epoxide, dimer and aldehydes, see: H. Sugimoto and D. T. Sawyer, *J. Org. Chem.*, 1985, **50**, 1786. (*d*) H. Sugimoto, L. Spencer and D. T. Sawyer, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, **84**, 1731.

13 mep = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-ethane 1,2-diamine, see: M. C. White, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 7194.

14 Stack's Fe-phenanthroline system also epoxidizes olefins with CH_3CO_3H, see: G. Dubois, A. Murphy and T. D. P. Stack, *Org. Lett.*, 2003, **5**, 2469.

15 (*a*) M. K. Tse, S. Bhor, M. Klawonn, C. Döbler and M. Beller, *Tetrahedron Lett.*, 2003, **44**, 7479; (*b*) S. Bhor, M. K. Tse, M. Klawonn, C. Döbler, W. Mägerlein and M. Beller, *Adv. Synth. Catal.*, 2004, **346**, 263; (*c*) M. Klawonn, M. K. Tse, S. Bhor, C. Döbler and M. Beller, *J. Mol. Catal. A: Chem.*, 2004, **218**, 13.

16 M. K. Tse, C. Döbler, S. Bhor, M. Klawonn, W. Mägerlein, H. Hugl and M. Beller, *Angew. Chem.*, 2004, **116**, 5367 (*Angew. Chem., Int. Ed.*, 2004, **43**, 5255).

17 M. K. Tse, M. Klawonn, S. Bhor, C. Döbler, G. Anilkumar, H. Hugl, W. Mägerlein and M. Beller, *Org. Lett.*, 2005, **7**, 987.

18 (*a*) S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt and M. Beller, *Org. Lett.*, 2005, **7**, 3393; (*b*) G. Anilkumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich and M. Beller, *Tetrahedron: Asymmetry*, 2005, **16**, 3536.

19 Typically, iron complexes were generated by heating an iron source, ligand and co-ligand (pyridine-2,6-dicarboxylic acid) in various solvents at 65 °C for 1 h. After cooling to room temperature, commercially available 30% H_2O_2 was added using a syringe pump.

20 For the effect of pyridine on the reactivity and selectivity of epoxide formation from alkenes using H_2O_2 and MTO, see: (*a*) J. Rudolph, K. L. Reddy, J. P. Chiang and K. B. Sharpless, *J. Am. Chem. Soc.*, 1997, **119**, 6189; (*b*) W. D. Wang and J. H. Espenson, *J. Am. Chem. Soc.*, 1998, **120**, 11335; (*c*) For the effect of additives, see: G. B. Shulpin, *J. Mol. Catal. A: Chem.*, 2002, **189**, 39.

21 P. Laine, A. Gourdon and J. P. Launay, *Inorg. Chem.*, 1995, **34**, 5129.

22 For the structure of some iron-dipicolinic acid complexes, see ref. 21; P. Laine, A. Gourdon and J. P. Launay, *Inorg. Chem.*, 1995, **34**, 5156.

23 J. M. Elkins, M. J. Ryle, I. J. Clifton, J. C. Dunning Hotopp, J. S. Lloyd, N. I. Burzlaff, J. E. Baldwin, R. P. Hausinger and P. L. Roach, *Biochemistry*, 2002, **41**, 5185.

24 E. L. Hegg, A. K. Whiting, R. E. Saari, J. McCracken, R. P. Hausinger and L. Que, Jr., *Biochemistry*, 1999, **38**, 16714.

25 A. Karlsson, J. V. Parales, R. E. Parales, D. T. Gibson, H. Eklund and S. Ramaswamy, *Science*, 2003, **299**, 1039.

26 (*a*) For a recent report on biomimetic approach to oxidation catalysis, see: A. Berkessel, *Pure Appl. Chem.*, 2005, **77**, 1277(*b*) L. Que, Jr. and R. Y. N. Ho, *Chem. Rev.*, 2004, **104**, 2607; (*c*) M. Coastas, M. P. Mehn, M. P. Jensen and L. Que, Jr., *Chem. Rev.*, 2004, **104**, 939.