A new chiral diiron catalyst for enantioselective epoxidation†

Caroline Marchi-Delapierre, Adeline Jorge-Robin, Aurore Thibon and Stéphane Ménage*

Received (in Cambridge, UK) 8th November 2006, Accepted 24th November 2006
First published as an Advance Article on the web 19th December 2006
DOI: 10.1039/b616172c

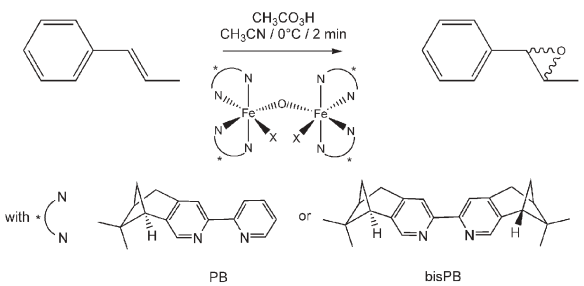
The dinuclear chiral complex $Fe_2O(bisPB)_4(X)_2(ClO_4)_4$ (X = H_2O or CH_3CN) catalyzes with high efficiency (up to 850 TON) and moderate enantioselectivity (63%) the epoxidation of electron deficient alkenes at 0 °C by a peracid.

μ-Oxo diferric complexes have received much attention as they represent structural mimics of the active center of methane monooxygenase and related enzymes.[1,2] These enzymes are very attractive as they catalyze unique selective chemical transformations such as methane oxidation using dioxygen or a peroxide.[3,4] These unique functions have prompted chemists to design new bio-inspired diiron catalysts for hydroxylation, epoxidation and sulfoxidation reactions. Among them, diiron complexes with polypyridine/nitrogen ligands afford these selective transformations leading to a better understanding of the enzymatic reactions.[5–7]

So far, only one diiron complex designed in our laboratory, $[Fe_2O(PB)_4(H_2O)_2](ClO_4)_4$ **1** (PB = 4,5-pinene-2,2′-bipyridine), has been reported to provide an enantioselective catalysis for oxidation. In this system, sulfides were oxidized by H_2O_2 into sulfoxides with moderate enantiomeric excesses (ee up to 40%).[8] The major drawback of this catalytic system was that total conversion could not be reached, as generally observed with such an oxidant, with one exception.[9] The evidence of high conversion for alkene epoxidation by peracetic acid for $Fe_2O(phen)_4(H_2O)_2(ClO_4)_4$ (phen = 1,10-phenanthroline),[10] known to be a good catalyst for selective cyclohexane oxidation with H_2O_2,[11] has led us to test our chiral complex for enantioselective epoxidation. $[Fe_2O(phen)_4(H_2O)_2](ClO_4)_4$ catalyzes the oxidation of a wide range of alkenes, including terminal alkenes, combining low catalyst loading, fast reaction time and enhanced reaction performance at high substrate concentration. Under the catalytic conditions reported by Stack *et al.*,[10] complex **1** was able to provide an encouraging ee value of 10% but with a poor epoxide yield (16%) for the oxidation of *trans*-β-methylstyrene by peracetic acid. Based on this positive result, a new chiral version of the diiron μ-oxo complex was designed by the introduction of a second chiral (−)-pinene group on the ligand PB, namely bisPB.[12] Here, we describe the first example of a non-heme chiral diiron complex catalyzing enantioselective conversion of alkenes into epoxides.

Mixing 25 μl of a 0.275 M aqueous solution of $Fe(ClO_4)_3{\cdot}6H_2O$ with 225 μl CH_3CN followed by the addition of two equivalents of solid bisPB ligand at room temperature led to the build up of a brown–green color after 15 min. Accordingly, its UV visible spectrum displayed three resonances at 600 nm (ε = 170 M^{-1} cm^{-1}), 440 sh (1800), 370 (10 600), characteristic for μ-oxo diiron complexes.[13] Only a few resonances were observed between 0 and 40 ppm in the ^1H NMR spectrum of the solution in CD_3CN, indicating the presence of the expected μ-oxo dinuclear unit.[11] Accordingly, this solution was found to be EPR silent, as expected for a dinuclear ferric unit with a large spin coupling. Positive mode ESI/MS revealed the exclusive formation of the complex $[Fe_2O(bisPB)_4(H_2O)_2](ClO_4)_4$ **2**. Three observed peaks at *m*/*z* 1803 (10%), 852 (100%), 535 (30%) have been attributed to the fragments $[Fe_2O(bisPB)_4(ClO_4)_3]^+$, $[Fe_2O(bisPB)_4(ClO_4)_2]^{2+}$, $[Fe_2O(bisPB)_4(ClO_4)]^{3+}$, respectively, whose isotopic patterns were in agreement with theoretical ones. This solution of complex **2** was used for catalytic experiments.

When **2** (0.2% equiv. *vs.* substrate) was added to commercial 32% peracetic acid (1.15 equiv.) efficient and rapid epoxidation of styrene (0.9 M) occurred with a high conversion yield after 2 min (see Scheme 1 and Table 1). Styrene was readily transformed into styrene oxide (entry 2, 60% yield based on substrate) but benzaldehyde and phenylacetaldehyde were also detected (19 and 8% yield, respectively). ^1H NMR confirmed also the presence of benzoic acid, issued of the overoxidation of benzaldehyde. The generation of these three by-products was not related to the decomposition of the styrene oxide since the latter was not reactive under the reported catalytic conditions. No epoxidation occurred in the absence of catalyst and only traces of products were observed in the presence of $Fe(ClO_4)_3{\cdot}6H_2O$. Furthermore, the use of other oxidants such as alkyl peroxides, hydrogen peroxide or *m*-chloroperbenzoic acid did not lead to epoxide formation. It should be noted that the addition of a second amount of substrate and oxidant did not produce any new products attesting that under these conditions the catalyst was inactivated or destroyed. The selectivity for 4-bromostyrene epoxide reached 82% when 4-bromostyrene was used as the substrate (entry 3 *vs.* 2, Table 1) and ranged between 49 and 78% for other unsymmetrical



Scheme 1 Catalytic epoxidation of *trans*-β-methylstyrene by complex **1** or **2**.

Laboratoire de Chimie et Biochimie des Centres Redox Biologiques; Université Joseph Fourier; CNRS, UMR 5047; CEA DSV/DRDC/CB, Grenoble, France. E-mail: smenage@cea.fr

† Electronic supplementary information (ESI) available: Chromatograms of reaction mixtures. See DOI: 10.1039/b616172c

Table 1 Epoxidation of alkenes with **2** and peracetic acid[a]

	Substrate	Conv. (%)	Yield[d] of epoxide (%)	Select. (%)	ee[d] (%)
1	*trans*-2-Heptene[b]	97	100	100	9
2	Styrene[c]	84	60	73	15 (*R*)
3	4-Bromostyrene[c]	100	82	82	28
4	2-Bromostyrene[c]	87	67	78	15
5	*trans*-β-Methylstyrene[c]	86	48	56	24 (1*R*,2*R*)
6	*cis*-β-Methylstyrene[b]	100	74	74	15
7	*trans*-β-Methylcinnamate[c]	70	35	49	63
8	*trans*-β-Isopropylcinnamate[b]	nd	nd	nd	19
9	*trans*-Chalcone[b]	92	66	72	56 (2*S*,3*R*)
10	*trans*-Stilbene[b]	67	67	100	0
11	(*R*)-(−)-Carvone[b]	86	86	100	19 (de)

[a] *Reaction conditions*: alkene (0.9 M) in CH_3CN[b] or CH_2Cl_2,[c] catalyst 0.2 mol% and 32% peracetic acid (1.15 equiv.) added at 0 °C at once; time of reaction, 2 min. [d] Yields determined by GC using benzophenone as internal reference. Averaged over three separate runs. Errors ±5%. Enantiomeric excess determined by HPLC or GC using WELKO-2 or Lipodex E columns respectively. Error ±3%. In parentheses, the absolute configuration of the major enantiomer.

substituted styryl alkenes (Table 1). More remarkably, total conversion and excellent selectivity were observed for non-aromatic olefins such as *trans*-2-heptene (entry 1).

The efficiency of **2** is quite significant since in the case of the epoxidation of *trans*-β-methylstyrene, 850 catalytic cycles could be measured with 0.1% catalyst loading (TON frequency corresponding to 425 min^{-1}).

Complex **2** is the first example of an enantioselective epoxidation catalyzed by a non heme μ-oxo-diferric unit. Under these conditions, the ee values were identical whatever the temperature and the reaction time. No enantiomeric excess could be measured in the absence of the catalyst or the presence of the chiral ligand alone. All unsymmetrical alkenes were oxidized into their epoxides with enantiomeric excesses ranging from 9 to 63% (Table 1) whereas the catalyzed oxidation of the symmetrical *trans*-stilbene led to a racemic mixture (entry 10). The introduction of a bromide in *para* position of the styrene led to a higher ee value compared to the styrene case (entry 3 *vs.* 2). The introduction of electron withdrawing groups in the β position of the styrene moiety led to a greater enantioselectivity up to 63% (entries 7 and 9 *vs.* entries 2 and 5). The replacement of the methyl group of *trans*-β-methylcinnamate by an isopropyl substituent caused a large decrease of the ee value (entry 7 *vs.* 8), indicating the importance of the bulkiness of the substituent on this position. The absence of a phenyl ring into the olefin led to smaller ee values, suggesting the possible involvement of π-stacking interactions between the pyridyl rings of the chiral ligand and the substrate (entries 1 and 11 *vs.* 7 and 9).

The importance of the dinuclearity of the iron catalyst has been assessed. Two related complexes $[Fe_2O(bisPB)_4Cl_2]Cl_2$ **3** and $[Fe(bisPB)_2Cl_2]Cl$ **4**, have been synthesized from two different procedures (low labile chloro ligands has been chosen to favor the mononuclear species).‡ Both complexes were able to catalyze the epoxidation of *trans*-β-methylstyrene in dichloromethane but with a lower rate than complex **2** (the reaction time was extended to 30 min) but with lower yield in epoxide (21 and 16% for **3** and **4**, respectively). A remarkable decrease of the ee was observed in the case of the mononuclear species **4** (from 24% for **2** to 9%) whereas it is conserved for **3** (20%).

The nature of the active oxidant has been probed by intramolecular competitive reaction. The catalytic oxidation of (*R*)-(−)-carvone, containing two double bonds, led to the unique formation of the monoepoxide on the terminal double bond with a low diastereomeric excess (19%). This regioselectivity supports the electrophilic nature of the oxidant. Furthermore, complex **2** oxidizes efficiently *trans*- and *cis*-β-methylstyrene or -stilbene with total retention of configuration (entries 5 and 6). The observed stereoselectivity of the epoxidation excludes the presence of a long-lived free substrate radical during the oxygen transfer.[14] Finally, labeling experiments have been undertaken in order to discriminate between metal or oxidant based oxidizing species.[15] The introduction of up to 1000 equiv. of $H_2{}^{18}O$ or $^{18}O_2$ into the reaction medium led to the absence of labeled epoxide. Taken altogether, including the specificity of the epoxidation for peracetic acid, a concerted oxygen transfer between the activated bound peracid and the substrate is proposed.

In this paper, we have demonstrated for the first time the ability of a non-heme diferric complex to catalyze stereoselective, high enantioselective epoxidation by peracetic acid with high conversion yield (TON up to 850). The requirement for dinuclearity of the catalyst has been also demonstrated. Its easy preparation and high efficiency may represent a good alternative for asymmetric oxidations of terminal and electron deficient alkenes. Improvement of this catalytic system will require a better understanding of the parameters controlling the reaction. We are aware that the catalyst may exist as a mixture of diastereomers, formed by the combination of the C_2 chiral ligands and the two possible isomers of the metal center (Δ or Λ). Further experiments will address this issue in order to discriminate between the control of the enantioselectivity by the chiral ligands alone or by the chirality of the metal center itself.

We thank to Prof. Marc Fontecave for fruitful discussions during the manuscript preparation.

Notes and references

‡ The dinuclear unit has been obtained from the reaction of $Fe_2OCl_6(NEt_4)_2$ with 4 equivalents of bisPB in MeOH. The solid obtained was characterized by positive mode ESI-MS revealing only one fragment (m/z = 787 corresponding to the dinuclear chloro fragment $[Fe_2O(bisPB)_4Cl_2]^{2+}$. The UV-vis spectrum of the dinuclear unit displayed two absorptions at 530 and 310 nm, in agreement with the presence of the oxo bridge. The mononuclear unit was synthesized using anhydrous $FeCl_3$ in dichloromethane. The UV-vis spectrum of the solid obtained *via* slow evaporation reveals no CT bands in the visible region. Its ESI-MS spectrum displays only one fragment at m/z 814 attributed to $[Fe(bisPB)_2Cl_2]^+$.

1 M. H. Baik, M. Newcomb, R. A. Friesner and S. J. Lippard, *Chem. Rev.*, 2003, **103**, 2385.
2 B. J. Wallar and J. D. Lipscomb, *Chem. Rev.*, 1996, **96**, 2625.
3 Y. Jin and J. D. Lipscomb, *J. Biol. Inorg. Chem.*, 2001, **6**, 717.
4 J. Green and H. Dalton, *J. Biol. Chem.*, 1989, **264**, 17698.
5 M. Costas, K. Chen and L. Que, *Coord. Chem. Rev.*, 2000, **200**, 517.
6 M. Fontecave, S. Ménage and C. Duboc-Toia, *Coord. Chem. Rev.*, 1998, **180**, 1555.
7 M. Kodera, M. Itoh, K. Kano, T. Funabiki and M. Reglier, *Angew. Chem., Int. Ed.*, 2005, **44**, 7104.
8 Y. Mekmouche, H. Hummel, R. Y. N. Ho, L. Que, V. Schunemann, F. Thomas, A. X. Trautwein, C. Lebrun, K. Gorgy, J. C. Lepretre, M. N. Collomb, A. Deronzier, M. Fontecave and S. Ménage, *Chem.–Eur. J.*, 2002, **8**, 1196.
9 M. C. White, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 7194.

10 G. Dubois, A. Murphy and T. D. P. Stack, *Org. Lett.*, 2003, **5**, 2469.
11 S. Ménage, J. M. Vincent, C. Lambeaux, G. Chottard, A. Grand and M. Fontecave, *Inorg. Chem.*, 1993, **32**, 4766.
12 N. C. Fletcher, F. R. Keene, M. Ziegler, H. Stoeckli-Evans, H. Viebrock and A. von Zelewsky, *Helv. Chim. Acta*, 1996, **79**, 1192.
13 R. E. Norman, R. C. Holz, S. Menage, C. J. O'Connor, J. H. Zhang and L. Que, *Inorg. Chem.*, 1990, **29**, 4629.
14 M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Guler, T. Ishida and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 948.
15 K. Chen and L. Que, *J. Am. Chem. Soc.*, 2001, **123**, 6327.

