Effect of Fifth Coordination in Catalytic Epoxidation by a Chiral Manganese Porphyrin

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Abstract: The effect of multifarious organic bases in chiral manganese porphyrin catalyzed enantioselective alkene epoxidation was investigated. For substituted pyridines, the enantioselectivity of *cis*-β-methylstyrene epoxidation follows a linear free energy relationship for pyridines bearing electron-donating groups. Compared to the case of no amine additive, a significant improvement in enantioselectivity from 43% ee to 81% ee for epoxidation of *cis*-β-methylstyrene with a 86.5% stereospecificity were observed when DMAP and $KHSO_5$ were employed as axial ligand and oxidant respectively.

Key words: enantioselective epoxidation, metalloporphyrin, axial ligand, biomimetic oxidation

Heme (iron protoporphyrin) in biochemically functioning proteins such as cytochrome P-450 and hemoglobin are axially co-ordinated by thiolate and imidazole of amino acid residues respectively.[1] Also, the catalytic activity and selectivity of metalloporphyrins and related transition metal complexes in biomimetic oxidation chemistry of cytochrome P-450 is profoundly affected by the fifth coordination.[2] It has been reported that the rate of organic oxidations catalyzed by metalloporphyrins are strongly enhanced by addition of an axial ligand such as pyridine-type bases.[3] For asymmetric epoxidation, addition of axial ligand to catalytic reaction systems is known as a convenient and efficient strategy to enhance enantioselectivity. For instance, high enantioselectivity and good chemical yields were realized in the epoxidation of 2,2-dimethylchromene derivatives using achiral Mn(salen) as a catalyst in the presence of chiral bipyridine *N,N′*-dioxide as ligand.[4] Also, axial ligation is important for effective asymmetry transfer in alkene epoxidation catalyzed by *single-faced* chiral porphyrins as they can act as blocking agents for the unhindered face to force the incoming substrates to interact with the hindered chiral pocket.[5] Although a number of chiral metalloporphyrins for enantioselective epoxidation have been developed during the last two decades,[6] little attention has been paid to the electronic effect of the axial ligands in the catalytic reaction. Recently, Gilheany reported that the use of phosphine oxides as axial ligands enabled oxochrominum salens to stoichiometrically oxidize *trans*-β-methylstyrene with excellent enantioselectivity but this beneficial effect of axial ligation could not be observed in catalytic version.[7] Interestingly, Gross reported a dramatic increase in enantioselectivity from 13% ee to 35% ee in styrene epoxidation with a double-faced chiral iron porphyrin as catalyst by using excess pyridine. However there was no significant improvement in enantioselectivity for the manganese counterpart.[8] We noticed that Halterman's manganese porphyrin catalyst gave satisfactory results in epoxidation of alkenes using Collman's procedure where NaOCl acts as oxidant in the presence of 4-*tert*-butylpyridine as axial ligand.[9] However, there is no account for the necessity of adding 4-*tert*-butylpyridine in order to attain the high enantioselectivity (76% ee for *cis*-β-methylstyrene).[10] Due to the *trans*-relationship of the axial ligand to the oxene moiety, we speculate that enantioselectivity of alkene epoxidation could be substantially varied by employing organic bases with different electronic properties as axial ligand. With the D_4-symmetrical manganese porphyrin (**1**) possessing *two-faced* chirality, we observed a significant improvement in enantioselectivity by proper choice of axial ligand. This axial ligand effect is attributed to electronic modification of the oxidized metal center in the catalytic cycle instead of effect of steric nature.

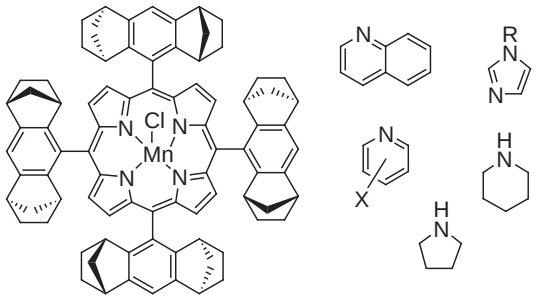

Figure 1 (Por*) MnCl **1**, Organic bases

We are currently interested in utilizing Oxone® ($KHSO_5$) in asymmetric epoxidation due to its environmental friendly results and there is no report describing its successful use with chiral metalloporphyrin catalyst. Therefore, the D_4-symmetrical manganese porphyrin (**1**), Oxone® ($KHSO_5$) and aqueous acetonitrile were employed as catalyst, oxidant and solvent respectively for

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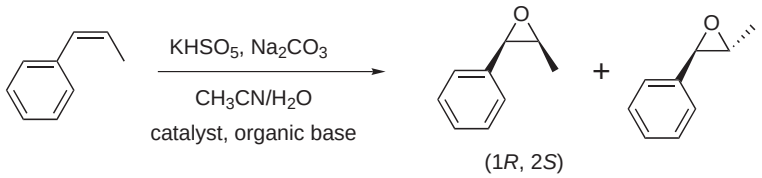
Table 1 Epoxidation of *cis*-β-Methylstyrene with Various Organic Bases as Axial Ligand



(1*R*, 2*S*)

Entry	Organic Base	% ee (*cis*)[a]	Δ % ee (*cis*)[b]	*cis/trans* ratio	Conversion[c] (%)
1	chloride	43	–	21.3	60
2	quinoline	25	–18	18.9	24
3	3-bromopyridine	29	–14	29.6	24
4	4-chloropyridine	31	–11	10.6	28
5	4-cyanopyridine	37	– 6	17.3	22
6	pyridine	38	– 5	8.0	6
7	4-phenylpyridine	61	+18	14.0	50
8	4-*tert*-butylpyridine	65	+22	12.0	18
9	4-methoxypyridine	69	+26	12.8	30
10	piperidine	71	+28	25.2	7
11	1,2-dimethylimidazole	72	+29	10.3	24
12	pyrrolidine	75	+32	18.2	12
13	DMAP	81	+38	6.4	79

[a] Enantiomeric excesses were determined by chiral GC-FID (column: J&W Scientific Cyclodex B, length 30m).
[b] Change in enantiomeric excess using different substituted pyridines compared to the % ee in entry 1.
[c] Conversion is based on the consumption of *cis*-β-methylstyrene after 16 h reaction time.

catalytic epoxidation of *cis*-β-methylstyrene and a series of organic bases was used as axial ligand additives.[11] The results are summarized in Table 1.

The use of heterocycles with sp^3 hybridized *N*-donor such as piperidine and pyrrolidine (entries 8 and 10) provides an improvement in enantioselectivity but resulted in low conversion. 1,2-Dimethylimidazole; which is regarded as an aromatic amine with concentrated π electrons (6π electrons in a five-membered aromatic ring) also provides a substantial improvement in enantioselectivity but the conversion was not satisfactory. Pyridines bearing electron-withdrawing groups 3-Br, 4-Cl and 4-CN displayed obvious negative effect towards enantioselectivity (entries 3–5). It is noteworthy that 4-phenylpyridine, 4-*tert*-butylpyridine and DMAP (4-*N*,*N*-dimethylaminopyridine) form a class of *para*-substituted pyridines that gave significant improvement. Among the organic bases, DMAP shows the best result of catalysis in both conversion and enantioselectivity (entry 13) when compared with organic base free catalysis (entry 1). An increase in the ratio (DMAP/catalyst) from 5 to 12 shows no further improvement in enantioselectivity. In general, organic amines of high basicity tend to give beneficial effect to enantioselectivity for this catalytic system. For the various substituted pyridines (X-C_6H_4N), an attempt has been made to correlate Hammett constants σ and ln(*R*/*S*), where ln(*R*/*S*) is directly proportional to $\Delta\Delta G^{\ddagger}$ (the free energy difference between two diastereomeric transitions states as a result of two facial approaches of *cis*-β-methylstyrene towards the high valent manganese intermediate). The broken line of the Hammett plot shown in Figure 1 indicates the dependence of $\Delta\Delta G^{\ddagger}$ for the facial selectivity on the electronic nature of the substituted pyridines.

Intriguingly, a linear free energy relationship ($\rho = -1.08$, $r^2 = 0.99$) is established for the electron donating region ranging from 4-NMe_2, 4-OMe, 4-*t*-Bu to 4-Ph and represented by the solid line. The linearity of the correlations implies that the changes in enantioselectivity are due to the electronic character of the catalysts, which can be explained on the basis of the work by Jacobsen.[12] Compared to chloride anion, the action of DMAP can lead to a prominent increase in $\Delta\Delta G^{\ddagger}$ by 0.76 $kcalmol^{-1}$. However, that the straight line cannot be extended to the electron-withdrawing region may imply a switch of mechanism when using pyridines bearing electron withdrawing group. Catalytically active intermediate without coordination of

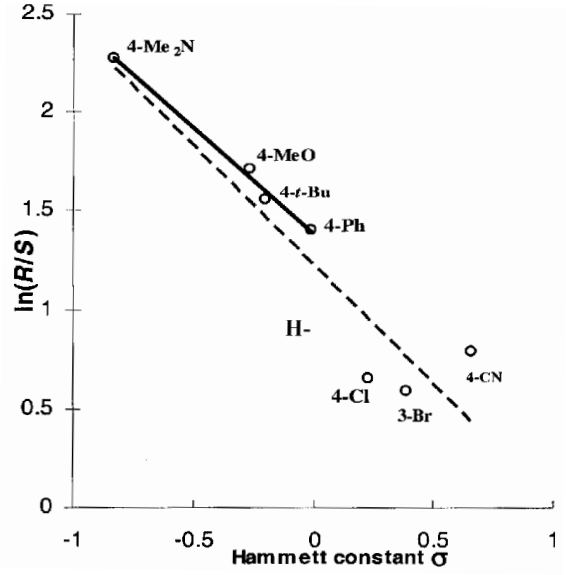
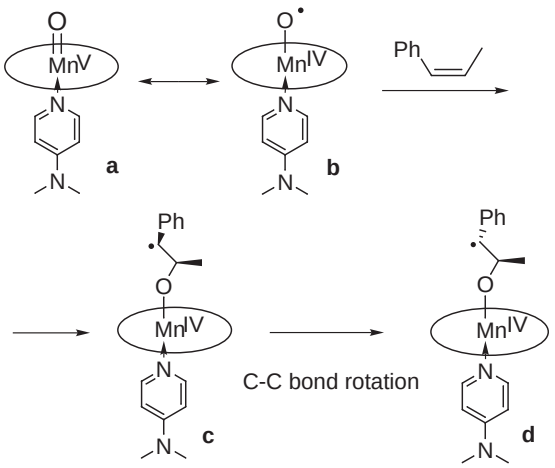


Figure 2 Plot of ln(R/S) against Hammett constant σ for epoxidation of cis-β-methylstyrene using various substituted pyridines as axial ligand



Scheme 1 Plausible reaction intermediates accounting for the considerable loss of stereospecificity in catalytic epoxidation of *cis*-β-methylstyrene by (Por*)MnCl with DMAP.

electron deficient pyridine may involve in catalytic cycle for their weaker donating power. This may be one of the reasons for the deviation from linearity. It seems that an increase in electrophilicity of the metal-oxo moiety can lead to better enantioselectivity. Previous ab initio calculation suggested that replacement of chloride ion by pyridine can lead to an increase of Mn=O length from 1.41 Å to 2.08 Å.[13] Since the π-donating effect of DMAP is much stronger than that of pyridine, it significantly weakens the d_π-p_π interaction of Mn=O resulting in a radial like canonical structure **b** as depicted in Figure 2. Consequently, the ligated oxygen atom is transferred to the alkene substrate forming the intermediate **c** (Scheme 1). This allows C-C bond rotation of the partially oxidized *cis*-β-methylstyrene molecule before epoxide formation. This model can explain the comparatively high stereospecificity in the case of electron withdrawing pyridines such as 3-bromopyridine and 4-cyanopyridine. Therefore, it is reasonable to observe that good enantioselectivity and comparatively high stereospecificity were observed in the case of pyrrolidone and piperidine, having strong σ-donation but no π-interaction.

For *cis*-β-methylstyrene, 81% ee was obtained by using Collman's procedure[5b] indicated that the use of DMAP as axial ligand can result in positive effect towards enantioselectivity. With NaOCl or $KHSO_5$, 70% ee of the epoxides was obtained in the case of 1,2-dihydronapthalene, and this is comparable to the result obtained by using a combination of the ruthenium analogue Ru(Por*)(CO) and 2,6-dichloropyridine *N*-oxide as reported by Berkessel and Frauenkron.[14] Unfortunately, there is only slight improvement for monosubstituted alkene (53% ee compared to 52% ee in enantioselectivity for styrene compared to that obtained by using 4-*tert*-butylpyridine although higher yield and shorter reaction time were attained). Nevertheless, we have demonstrated the convenience of using easily available organic bases to manipulate stereochemical control in alkene epoxidation catalyzed by a double-faced chiral manganese porphyrin. This report also highlights the dependence of enantioselectivity on the electronic nature of axial ligand and the first successful use of Oxone® in metalloporphyrin-catalyzed asymmetric epoxidation.

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References

(1) (a) Casella, L.; Colonna, S. In *Metalloporphyrins Catalyzed Oxidations*; Montanari, F.; Casella, L., Eds.; Kluwer Academic Publishers: New York, **1994**. (b) Auclair, K.; Moenne-Loccoz, P.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 4877.
(2) Jitsukawa, K.; Shiozaki, H.; Masuda, H. *Tetrahedron Lett.* **2002**, *43*, 1491.
(3) Collman, J. P.; Brauman, J. I.; Hampton, P. D.; Tanka, H.; Bohle, D. S.; Hembre, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 7980.
(4) Miura, K.; Katsuki, T. *Synlett* **1999**, 783.
(5) (a) Knoishi, K.; Oda, K.-I.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 1313. (b) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, *115*, 3834.
(6) Collman, J. P.; Lee, V. J.; Zhang, X.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404.
(7) Daly, A. D.; Renehan, M. F.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 663.
(8) Gross, Z.; Ini, S. *J. Org. Chem.* **1997**, *62*, 5514.
(9) Halterman, R. L.; Jan, S.-T. *J. Org. Chem.* **1991**, *113*, 6865.
(10) Halterman, R. L.; Jan, S.-T.; Abdulwali, A. H.; Standlee, D. J. *Tetrahedron* **1997**, *53*, 11277.

(11) General procedure for catalytic oxidation: Oxone (8 mmol), $NaHCO_3$ (3.5 mmol), were dissolved in 4 mL deionized water with stirring. *cis*-β-Methylstyrene (8 mmol), catalyst 1 (0.0016 mmol), and axial ligand (0.008 mmol) were dissolved in acetonitrile (4 mL). The organic mixture was added to the aqueous mixture and the whole mixture was stirred overnight. The product mixture was extracted with diethyl ether four times and the combined extract was evaporated with a rotary evaporator. The product was analyzed by HP-6890 gas chromatography equipped with with a column, J&W Scientific cyclodex B column of 30 m length, 0.250 mm internal diameter, 0.25 μm film thickness.
(12) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.
(13) (a) Jørgensen, K. A.; Swanstrøm, P. *Acta Chem. Scand.* **1988**, *43*, 822. (b) Gunter, M. J.; Turner, R. *J. Mol. Catal.* **1991**, *66*, 121.
(14) Berkessel, A.; Frauenkron, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2265.