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The effect of phenolates in the (salen)Mn-catalyzed epoxidation reactions

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Abstract—By addition of 2,4,6-tri-*tert*-butylphenolate in the Mn(salen) catalyzed epoxidation of *cis*-alkenes with iodosobenzene, essentially pure *trans*-epoxides can be obtained.

The development of the (salen)Mn-catalyzed epoxidation reaction,[1] especially as a procedure for asymmetric epoxidation of alkenes, has provided a useful tool for the formation of chiral centers with carbon–oxygen bonds.[2–5] The highest enantiomeric selectivities have been obtained for *cis*-1,2-disubstituted alkenes but the epoxidation of tri- and tetrasubstituted alkenes is also highly enantioselective.[6,7] Recently, it was found that optically active (salen)Cr complexes catalyze the epoxidation of *trans*-alkenes with high enantioselectivity.[8] The enantioselectivity in (salen)Mn catalyzed systems is generally low for this substrate class.[5,9] However, some time ago, Jacobsen and co-workers found an alternative enantioselective route to *trans*-epoxides. They reported that the addition of chiral quaternary ammonium salts, derived from naturally occurring cinchona alkaloids, promoted a dramatic increase in the preference for *trans*-epoxide formation starting from conjugated *cis*-alkenes.[10] Somewhat later, we found that the addition of 2,4,6-tri-*tert*-butylphenol and base to the catalytic system could induce highly enantio- and diastereoselective formation of *trans*-stilbene oxide from *cis*-stilbene.[11]

A number of research groups have since shown that both the counterion and oxidant have a considerable influence on the diastereoselectivity of the manganese(salen)-catalyzed epoxidation.[12–16] Since, Mn^{V} oxo species are possible intermediates both in Mn(salen)-catalyzed epoxidation and in the water oxidizing system in photosystem II (PS II),[17–19] an understanding of the mechanism of epoxidation could also have bearing on the mechanism for water oxidation in PS II.

There are several potential reasons for the influence of counterions and oxidants in epoxidation. One is that the manganese(V) oxo species, which is formed from the reaction of the oxidant, for example, iodosobenzene, with the $\mathrm{Mn}^{\mathrm{III}}$-salen precatalyst, is not the sole epoxidation catalyst, but that another competing mechanism also operates. This is suggested by the fact that the product pattern can vary with factors such as temperature and solvent. One such differing pathway could be direct epoxidation by the oxidant coordinated to the $\mathrm{Mn}^{\mathrm{III–V}}$, which simply acts as a Lewis acid. General catalysis of epoxidation by Lewis acids has in fact been observed earlier by Valentine and co-workers.[20,21] More recently, evidence for salen catalyzed epoxidation and related reactions going both via Mn^{V} oxo species and an Mn-activated oxidant has been reported.[12–16] In a related study of sulfimidation of sulfides, Ohta and Katsuki were able to show that both a Mn^{V} imido complex and the precursor $\mathrm{Mn}^{\mathrm{III}}$ complex with coordinated phenyliodosylimide are responsible for imidation at sulfur.[22]

It has also been noted that with non-coordinating counterions, such as triflate, in Mn(salen)(triflate) complexes, fairly specific *cis*-epoxidation occurred, while with coordinating counterions such as chloride, mixed *cis*- and *trans*-epoxidation was observed. This could be explained

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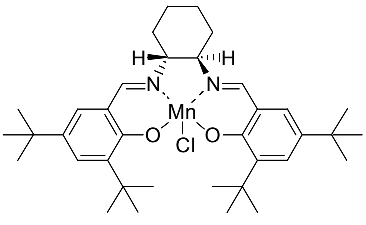
by reactions of a Mn^{V} oxo species via different spin states since coordinating and non-coordinating counterions could affect the relative energies of these different states.[12–16,23–27] However, it could also be explained in terms of formation of Mn(salen) oxo complexes with both Mn^{V} and $\mathrm{Mn}^{\mathrm{IV}}$. The latter species would be expected to react unselectively via radicals. In fact, quite some time ago, Groves and Stern showed that epoxidation catalyzed by a manganese–porphyrin complex probably proceeded via a manganese(V) species at low temperature and a manganese(IV) species at room temperature, based on observations of both different Mn species and different product patterns at high and low temperatures.[28] Mass spectrometric evidence for the presence of both Mn^{V} oxo and $\mathrm{Mn}^{\mathrm{IV}}$ species, produced from $\mathrm{Mn}^{\mathrm{III}}$ salen complexes and iodosobenzene has been presented by Feichtinger and Plattner and Adam et al.[29,30] This supports the idea that the primary Mn^{V} oxo complexes can give rise to $\mathrm{Mn}^{\mathrm{IV}}$ species during the epoxidation reactions.[31] A recent Hammett study also supports this conclusion.[32]

Since phenolate ions are readily oxidized by high valent manganese species and we have seen a number of examples, where we have been unable to oxidize phenolate manganese complexes beyond the $\mathrm{Mn}^{\mathrm{IV}}$ state,[33] we decided to study in some detail the effects of phenolates added as ligands to the presumed (salen)Mn^{V} oxo intermediates in epoxidation with (salen)Mn-catalysts.



(*R*,*R*)-**1**

Our initial studies focused on the epoxidation of *cis*-stilbene, using (*R*,*R*)-**1** as the catalyst. Whereas very high cis-selectivity and high enantioselectivity have been observed under optimal conditions, see for example, Ref. 34 the use of iodosobenzene as oxidant and either benzene[11] or dichloromethane[12–14] as solvent has been shown to give cis/trans ratios below 0.5. When a two phase system with hypochlorite as oxidant was used, and phenol was added, it had a substantial influence on the cis/trans ratio, 2,4,6-tri-*tert*-butylphenol giving the highest yield of trans-product.[11] This phenol was therefore also used in the present study.[35] It was found that the phenol itself had no effect (Table 1, entries 1 and 2). Since, the aqueous hypochlorite solution is strongly basic, it seemed reasonable that the formation of the deprotonated form of 2,4,6-tri-*tert*-butylphenol, which is an excellent single electron donor, is required. The effect of added bases was therefore studied. As anticipated, the trans-selectivity of the reaction was significantly increased when the phenolate was generated by the addition of base, for example, *t*-BuOK, *n*-BuLi or aqueous potassium hydroxide (Table 1, entries 3–5). It should be noted that with both *n*-BuLi and *t*-BuOK as base, the phenolate had to be generated prior to the addition of alkene and catalyst. As the trans-product selectivity was increased, also the enantioselectivity of the formed *trans*-epoxide was improved. The best result was obtained with *n*-BuLi as base (Table 1, entry 4), while the use of triethylamine as base effectively inhibited the catalytic activity (Table 1, entry 6). The effect of the weaker base pyridine was also similar.

Table 1. Epoxidation results with 2,4,6-tri-*tert*-butylphenol and base in benzene using PhIO as the oxidant

Entry[a]	Base[b]	Conv. [%]	cis:trans [%][c]	ee [%][d]
1[e]	—	100	25:75	75
2	—	100	26:76	80
3[f]	*t*-BuOK	100	4:96	86
4	*n*-BuLi	100	10:90	89
5	2 M KOH	75	7:93	87
6	Et_3N	0	—	—

[a] 1 mmol of *cis*-stilbene, 2 equiv PhIO, benzene, 0.5 equiv of 2,4,6-tri-*tert*-butylphenol, 4 mol% of (*R*,*R*)-**1**.
[b] 0.5 equiv.
[c] *cis*/*trans* epoxide ratio.
[d] ee of *trans*-stilbene oxide.
[e] No 2,4,6-tri-*tert*-butylphenol added.
[f] 8 mol% of (*R*,*R*)-**1**.

The catalytic activity was generally low and the reproducibility of the experiments was not always satisfactory when *t*-BuOK was used as base, perhaps because deprotonation is slow due to poor solubility in benzene. It was found that excess *t*-BuOK deactivated the catalyst but under optimized conditions, including a doubling of the catalyst concentration, the reaction proceeded with full conversion and excellent trans-selectivity with this base also. The relatively poor yield with hydroxide as base can probably also be explained by solubility problems. In contrast, no such problems should be associated with *n*-BuLi, with which the deprotonation was efficient and instantaneous. This base was therefore preferred.

The influence of the structure of the added phenols was also studied. In the reaction in the presence of the electron poor *p*-nitrophenol, the trans-selectivity was decreased, while the enantioselectivity was increased (Table 2, entries 1 and 2). A possible reason is that *p*-nitrophenolate could act as a fairly loosely coordinated

Table 2. Epoxidation results with added phenols and *n*-BuLi in benzene using PhIO as the oxidant

Entry[a]	Phenol[b]	Conv. [%]	cis:trans [%][c]	ee [%][d]
1	*p*-NO_2–	100	39:61	82
2	—	100	25:75	75
3	*p*-Me–	89	23:77	89
4	*p*-MeO–	61	14:86	90
5	2,6-Di-*t*-Bu–	47	8:92	86
6	2,4,6-Tri-*t*-Bu–	100	10:90	89
7	*p*-Octyl–	71	8:92	88

[a] 1 mmol of *cis*-stilbene, 4 mol% of (*R*,*R*)-**1**, benzene, 2 equiv of PhIO.
[b] 0.6 equiv phenol to *cis*-stilbene + 0.5 equiv of *n*-BuLi.
[c] *cis*/*trans* epoxide ratio.
[d] ee of *trans*-stilbene oxide.