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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.

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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 cisalkenes.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 Mn^{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 Mn^{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 Mnactivated 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 Mn^{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 Mn^{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 Mn^{IV} species, produced from Mn^{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 Mn^{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 Mn^{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.



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 benzene¹¹ 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

 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 ₃ N | 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.

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.

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 | <i>p</i> -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.

ligand, which is not readily oxidized but yields a small amount of the cationic complex. In contrast, all phenolates with electron donating substituents increased both the enantio and the trans-selectivity (Table 2, entries 3– 7). Electronic properties, as well as solubility are probably important factors. Thus p-octylphenolate gave substantially higher trans-selectivity than *p*-methylphenolate although these two phenols should be very similar electronically. The bulky and electron rich 2,4-di-tertbutyl- and 2,4,6-tri-tert-butylphenolates gave transepoxides with fairly high yields and ee (Table 2, entries 5 and 6). However, the conversion was much lower with 2,4-di-tert-butylphenolate, perhaps because it has a free ortho-position and is more readily degraded by oxidation. Reaction in the presence of 2,4,6-tri-tert-butylphenolate is thus superior in that both high transselectivity, high ee and high conversion were obtained. It is easy to explain this as the result of a facile one-electron reduction of an intermediate oxomanganese(V) to an oxomanganese(IV) complex, which will react via diradicals (Scheme 1) and thus be more trans-selective than the oxomanganese(V) species. This is in analogy with observations from manganese porphyrin systems.²

The epoxidations of cis- β -methylstyrene **2** and styrene **3** are recorded in Table 3. The results show that **2** also gives a higher relative yield of the trans isomer in the presence of phenolate. It also suggests that a slightly higher trans/



Scheme 1. Proposed catalytic cycles for epoxidation with iodosobenzene as oxidant.

 Table 3. Epoxidation of 2 and 3 with 2,4,6-tri-*tert*-butylphenol and base in benzene using PhIO as the oxidant

| Alkene | % cis | % trans | ee cis | ee trans |
|-----------------------|-------|---------|-----------------|----------|
| 2 ^a | 36 | 64 | 60 | 67 |
| 2 ^b | 19 | 81 | 75 | 85 |
| 2 ^c | 27 | 73 | 56 | 73 |
| 2 ^d | 9 | 91 | 60 | 86 |
| 3 ^a | _ | _ | 21 ^e | |
| 3 ^b | _ | _ | $10^{\rm e}$ | |

^a 1 mmol of alkene, 4 mol% of (R,R)-1, benzene, no phenol.

^b 1 mmol of alkene, 4 mol% of (R,R)-1, 1 equiv phenol.

^c 1 mmol of alkene, 0.4 mol% of (*R*,*R*)-1, benzene, no phenol.

^d 1 mmol of alkene, 0.4 mol% of (R,R)-1, 1 equiv phenol.

^e ee of styrene epoxide.

cis ratio is obtained with a lower concentration of the catalyst. The ee was fairly high, especially for the transepoxides (Table 3). Finally, styrene itself was epoxidized. Even in the absence of phenolate the ee was very low (20%) and it was decreased to 10% when phenolate was added (Table 3). In principle, the result could be largely due to low face-selectivity in the epoxidation. However, styrene does not appear to be much inferior to cis-alkenes in (salen)Mn-catalyzed epoxidation.³⁴ An alternative explanation is therefore that the Mn-catalyst attacks at the unsubstituted terminus of styrene, to give a benzylic radical intermediate in which rotation of the phenyl group is efficient, leading to extensive racemization. Using deuterium labeled styrene, Jacobsen and co-workers have in fact shown that about 10% transepoxidation takes place using hypochlorite as oxidant, presumably due to a radical pathway.³⁶ Provided that the primary attack, Scheme 1, is enantioselective, *cis*-stilbene and *cis*- β -methylstyrene will give both cis and trans products with ee corresponding to those of the primary attack. For styrene, however, rotation will cause racemization. The results are thus compatible with the mechanism in Scheme 1, with an attack that is highly enantioselective but where ca. 90% of the reaction goes via radical intermediates when a good one-electron donor such as 2,4,6-tri-tert-butylphenolate is present.

The results clearly show the potential of phenolates as tools for increasing the usefulness of the Jacobsen–Katsuki epoxidation reaction. Carried over to the models that we have so far prepared for the water oxidation center in PS II, they also suggest that Mn^V oxo complexes can be readily converted to Mn^{IV} complexes by electron transfer from phenolate ligands.

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- 35. Representative epoxidation procedure: A mixture of 2,4,6tri-*tert*-butylphenol (1 equiv) and *n*-BuLi (1 equiv, 1.4 M in hexane) was stirred in anhydrous benzene under argon for 5 min. (*R*,*R*)-1 (4–8 mol%) and *cis*-stilbene (1 equiv) dissolved in benzene were added together with PhIO (2 equiv) and the mixture was stirred for another 12 h. The catalyst residues were separated on a short silica column. The cis/trans ratio and enantiomeric purity were determined by ¹ H NMR and chiral HPLC on a Chiralcel ODcolumn using a mixture of IPA/IB 90:10. Isolated yield after purification by chromatography on silica: 85% of *trans*-stilbene oxide with 90% ee.
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