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Origin of Enantioselectivity in the Jacobsen Epoxidation of Olefins

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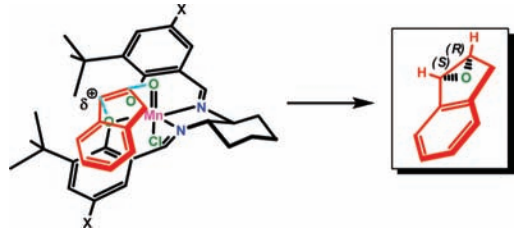
ABSTRACT



It is proposed that facial selectivity in the Jacobsen epoxidation is determined by electrostatic and steric factors with a two-step pathway involving a carbocationic intermediate.

Subsequent to Kochi's seminal discovery[1] that the (salen)Mn(III) catalyst **1**[2] effects the PhIO-mediated epoxidation of olefins, Jacobsen designed several chiral versions which are capable of catalyzing the enantioselective epoxidation of many achiral olefins.[3] The most commonly used Jacobsen catalysts are **2**−**5** (Figure 1). The Jacobsen method is now firmly established in synthetic practice, especially with the inexpensive stoichiometric oxidant NaOCl (common bleach).[4] The reaction has also been studied by Katsuki who has developed a related series of chiral (salen)Mn(III) catalysts such as **6** and **7** in Figure 1.[5]

The Jacobsen epoxidation has been the subject of several detailed reviews.[6] Despite the widespread application and the utility of the reaction, the fundamental basis for its enantioselectivity has remained obscure. There is strong evidence that the effective oxidant is a Mn(V)-oxo species, e.g., **8** (Figure 2), but the mode of oxygen transfer to the olefin has over the years become ever more controversial. Various side-on approaches of the double bond to the oxo subunit and even an end-on approach have all been entertained. These explanations have left generations of students

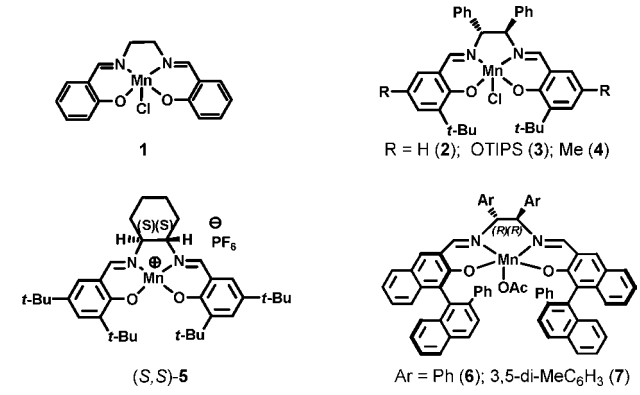


Figure 1. Epoxidation catalysts (Kochi, Jacobsen, Katsuki).

(1) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309–20.

(2) The name "salen" refers to ligands that feature the *N*,*N*′-ethylene-bis(salicylideneamidato) core.

(3) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–3.

(4) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296–8.

(5) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345–8.

(6) For selected reviews on the Jacobsen epoxidation, see: (a) Katsuki, T. *Synlett* **2003**, 281–297. (b) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6* (Organometallics in Process Chemistry), 123–152. (c) Muniz-Fernandez, K.; Bolm, C. Manganese-catalyzed epoxidations. In *Transition Met. Org. Synth.*, 2nd ed.; 2004; Vol. 2, pp 344−356. (d) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563–1602.

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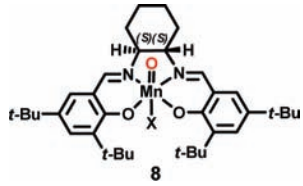

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Figure 2. Mn(V)-oxo species, the presumed epoxidizing agent.

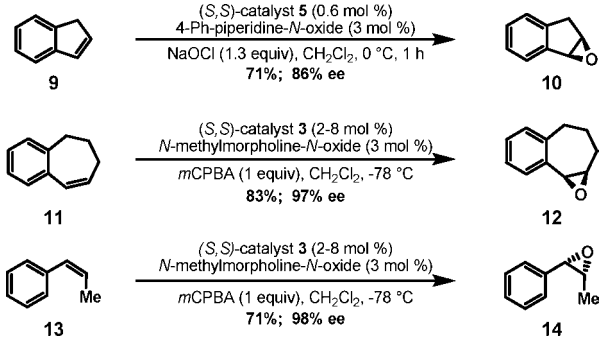
(and not a few of their teachers) with the impression that the factors underlying enantioselectivity may be too complex to unravel. A recent comprehensive review (2005)[6d] ended with the remark: "In conclusion, there is a large scope for increased understanding of the mechanistic possibilities which should lead to further improvements in catalyst design and/or reaction conditions."

This paper presents an analysis of the key features of the Jacobsen epoxidation and the variables that affect enantioselectivity to gain a deeper understanding of the preferred three-dimensional pathway for the reaction. From this approach has come an insight that can explain quite simply the observed π-facial selectivity in Jacobsen epoxidation products of proven absolute configuration. The most relevant experimental observations can be summarized as follows:

(1) Highly enantioselective epoxidation has been observed mainly for double bonds that are conjugated with a π-system, for example, a benzenoid ring or another olefinic linkage.

(2) Conjugated (*Z*)-1,2-disubstituted olefins, especially cyclic olefins, are the substrates most likely to undergo highly enantioselective epoxidation (Scheme 1). Conjugated cyclic trisubstituted olefins are also suitable substrates.[7]

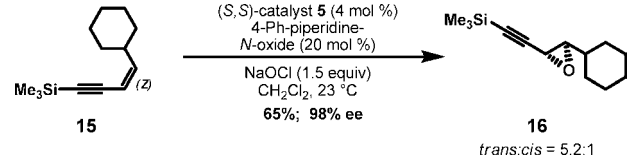
Scheme 1. Epoxidation of Conjugated Cyclic (*Z*)-1,2-Disubstituted Olefins



(3) The epoxidation of conjugated acyclic (*Z*)-1,2-disubstituted olefins is frequently complicated by the formation of *trans*- as well as *cis*-epoxides, indicating a two-step pathway with intervening C−C bond rotation. An example is shown in Scheme 2 (**15**→**16**).[8]

(7) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–80.

Scheme 2. Epoxidation of a Conjugated Acyclic (*Z*)-1,2-Disubstituted Olefin



(4) The occurrence of the two-step pathway may be enhanced by the presence of 25 mol % of various cinchona alkaloid-derived quaternary ammonium salts in benzene or chlorobenzene as solvent with aqueous NaOCl as oxidant.[9] In this system, (*Z*)-stilbene is converted into the corresponding *trans*-epoxide with 95:5 *trans*:*cis* selectivity.

(5) The addition of pyridine *N*-oxides to Jacobsen epoxidation reactions often leads to enhancement of enantioselectivity.

(6) The substitution of an electron-donating group (*O*-alkyl) *para* to the phenolic hydroxyl of the salen ligand enhances enantioselectivity of epoxidation, whereas the presence of a *para* nitro group does the opposite.

(7) The enantioselectivity of the Jacobsen epoxidation depends not only on reaction conditions and medium but also on the nature of the stoichiometric oxidant, for example, PhIO or NaOCl.[6d] The variable course of the Jacobsen epoxidation may arise from multiple factors including: (a) differences in the axial ligand *trans* to the oxo atom of the (salen)Mn(V)-oxo reactant or in solvation; (b) issues arising from electronic spin conservation with the d^2-(salen)Mn(V)-oxo reagent;[10] and (c) differences in coordination number or geometry around the central Mn(V)-oxo subunit (relatively unlikely).

On the basis of the facts summarized above for the Jacobsen epoxidation, it seems reasonable that a mechanistic continuum of pathways is available for the epoxidation of conjugated olefins. Along this continuum, the two bonds of the epoxide are formed to different extents in the transition state—at one end lies a two-step pathway and at the other a completely synchronous formation of the two bonds between oxygen and the olefin. It seems logical that the greater suitability of conjugated olefins for enantioselective Jacobsen epoxidation signals that such substrates generally react by an asynchronous two-step pathway and that substantial positive charge develops on the olefinic substrate during attack by electrophilic oxygen. Delocalization of that positive charge implies that in the case of styrene, for instance, O−CH_2 bond formation would precede O−CH−Ph bond formation, as summarized in the unsymmetrical transition state **17** (Figure 3). The key point to be made is that the

(8) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425–6.

(9) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937−8.

(10) (a) Strassner, T.; Houk, K. N. *Org. Lett.* **1999**, *1*, 419–421. (b) Abashkin, Y. G.; Burt, S. K. *Org. Lett.* **2004**, *6*, 59–62. (c) Linde, C.; Akermark, B.; Norrby, P.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121*, 5083–5084.

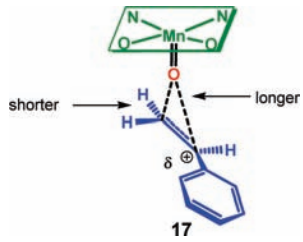


Figure 3. Unsymmetrical transition state for Jacobsen epoxidation.

oxygen transfer process during Jacobsen epoxidation is likely to be asynchronous with positive charge being induced in the π-group attached to the double bond being oxidized. This view of the Jacobsen epoxidation does not appear to be controversial. The electrophilicity of the oxo group in the (salen)Mn(V)-oxo complex was apparent even in the early study by Kochi[1] which showed that cyclohexane is oxidized in acetonitrile by the PhIO−(salen)Mn(III) system to *N*-cyclohexylacetamide, the product expected from a Ritter reaction[11] of the cyclohexyl cation with CH_3CN.

There have been numerous proposals regarding the mode of approach of the olefin substrate to the oxo group of the chiral (salen)Mn(V)-oxo species, some summarized by Katsuki[12] as in **18** and others by Jacobsen[13] as in **19** (Figure 4). The matter has also been discussed even more extensively in review articles without resolution.[6d,14]

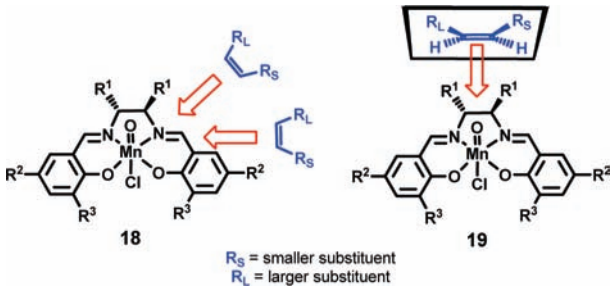


Figure 4. Literature explanations[6,13b] of enantioselective epoxidation.

None of these explanations seem especially plausible when modeled in three dimensions and the basis for enantioselectivity is not at all apparent. This enigma led us to search for a clear and logical way of understanding the origin of enantioselectivity in the Jacobsen epoxidation.

Our argument is based on two assumptions, the first being that electrophilic attack occurs on the π-conjugated olefinic bond to generate an unsymmetrical three-membered transition state **17**. The second assumption is that the two six-membered chelate rings in the chiral (salen)Mn(V) **20** are canted relative to one another as shown in Figure 5. This

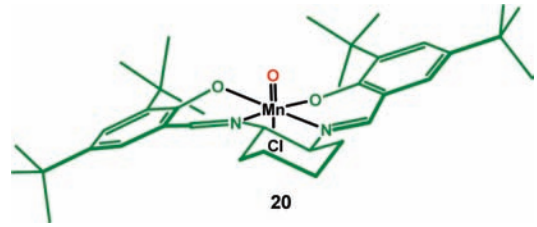


Figure 5. View of the (salen)Mn(V)-oxo complex showing the canted arrangement of the terminal six-membered chelate rings.

dissymmetric arrangement is a consequence of the chirality of the 1,2-diaminocyclohexane subunit. It also ensures that the neighboring *t*-butyl groups *do not clash sterically*.[15]

A geometric consequence of the canted arrangement of the terminal chelate rings is that the *t*-butyl groups *ortho* to the coordinated phenolic oxygens occupy spaces on opposite faces of the N−Mn−N plane. More specifically, with reference to Figure 6 for the (*S*,*S*)-1,2-diaminocyclohexane

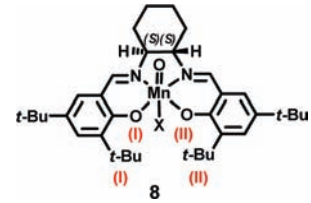


Figure 6. Differentiation of *t*-butyl and phenolic oxygen centers in (salen)Mn(V)-oxo complex **8**.

complex **8**, *t*-butyl group (**I**) lies above that plane and *t*-butyl group (**II**) lies below the plane. Given these assumptions, it seems logical that the pretransition state geometry, taking indene[16] as an exemplary substance, could be stabilized by an attractive electrostatic interaction between the benzylic carbon (δ^+) and the phenoxy oxygen (**II**) (δ^-) with indene approaching the oxidant as shown in Figure 7 (three views shown, **A**−**C**).

The particular orientation of indene in the (salen)Mn(V)-oxo complex **8** that is shown in Figure 7 avoids unfavorable steric repulsion with the *t*-butyl groups (**I**) and (**II**) and takes advantage of stabilizing π-stacking of the indene and aryloxy groups (which occupy parallel planes at a spacing of roughly

(11) Kürti, L.; Czakó, B. Ritter Reaction. In *Strategic Applications of Named Reactions in Organic Synthesis*; Academic Press/Elsevier Science: San Diego, 2005; pp 382−383.

(12) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515–30.

(13) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–4. (b) Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem.−Eur. J.* **1996**, *2*, 974–980.

(14) Linker, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2060–2062.

(15) For earlier proposals of the canted arrangement of the terminal chelate rings of chiral (salen)Mn(V)-oxo complexes, see: Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* **2000**, 1557–1560, and also ref 13b.

(16) For the large-scale Jacobsen epoxidation of indene, see: Larrow, J. F.; Roberts, E.; Verhoeven, T. R.; Ryan, K. M.; Senanayake, C. H.; Reider, P. J.; Jacobsen, E. N. *Org. Synth.* **1999**, *76*, 46–56.

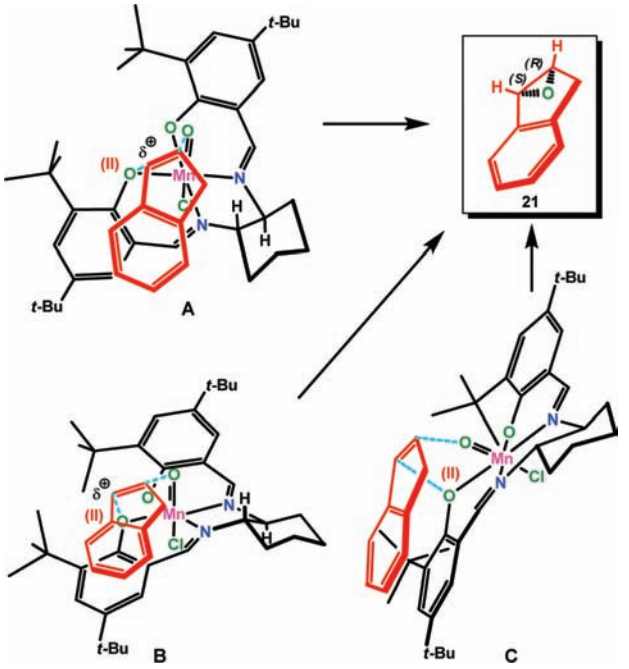


Figure 7. Three different views (A−C) of the favored pathway in the Jacobsen epoxidation of indene.

3.5 Å). The transition state assembly (three views) shown in Figure 7 is slightly reminiscent of a [3 + 2] cycloaddition with regard to the indene double bond, the oxo atom attached to Mn, and the phenoxy oxygen (**II**). Thus, in this model the simultaneous electrophilic attack by the Mn oxo atom on C_2 of indene and the electrostatic attraction between phenoxy oxygen (**II**) and the benzylic carbon (C_1) of the indene double bond leads to a uniquely organized three-dimensional arrangement. The pathway for selective π-facial epoxidation implicit in the model shown in Figure 7 corresponds to the observed absolute configuration for the indene (*S*,*R*)-epoxide **21** that is produced by the (*S*,*S*)-Jacobsen catalyst **5**. This electrostatically guided pathway provides face selection by either a two-step or asynchronous process. Approach of the opposite π-face of indene to the chiral (*S*,*S*)-(salen)Mn(V)-oxo complex is highly disfavored because of severe steric repulsion between the benzenoid ring of indene and the *t*-butyl groups (**I** and **II**).

The stereochemical model outlined above correctly predicts the absolute configuration of the major product in the examples shown in Scheme 1 and Scheme 2. It also is clear from the model why the Jacobsen epoxidation of *trans*-1,2-disubstituted olefins generally is only weakly enantioselective. As can be seen from the illustration in Figure 8 for the case of (*E*)-stilbene, the formation of either the (*R*,*R*)- or (*S*,*S*)-epoxide by a pathway analogous to that summarized

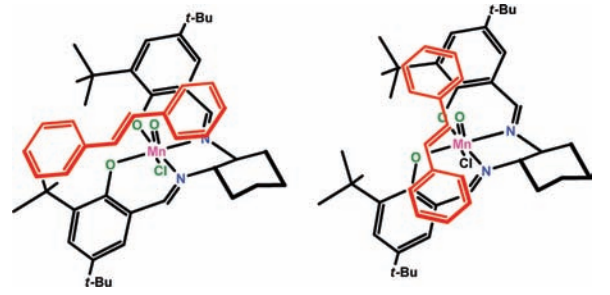


Figure 8. Disfavored pathways for epoxidation of (*E*)-stilbene.

in Figure 7 involves considerable steric repulsion, and so there is no basis for facial selectivity.

The model explains well the *selectivity-enhancing effect of substituents such as methoxy and triisopropylsilyloxy* which *increase* electron density on the phenoxy oxygen and increase the magnitude of the electrostatic attraction between it and the δ^+ terminus of the reacting double bond. The enantioselectivity enhancement by a donor ligand *trans* to the oxo substituent on Mn(V) can be explained similarly. Although it is not possible to evaluate the magnitude of the electrostatic attraction, we point out that it only needs to amount to a few kilocalories/mole to provide the observed stereochemical preference (Scheme 1). Because the model specifies explicitly and clearly the preferred relative orientations of the (salen)Mn(V)-oxo and olefinic reactants, it provides a simple and easy way to remember or predict the absolute stereochemistry of Jacobsen epoxidation. The key ideas expressed herein may also apply to other epoxidations with transition-metal salen complexes.

We close by returning to the influence of Mn spin states on the epoxidation pathway. Calculations of the energies of (salen)Mn(III) and (salen)Mn(V)-oxo complexes suggest that the most stable electronic spin state of d^4-Mn(III) is the quintet state, whereas the most stable spin state for d^2-Mn(V)-oxo is the triplet state.[9] Those data indicate that the concerted conversion of an olefin (singlet) to an epoxide (singlet) is spin-forbidden. It is therefore possible, by this argument, that Jacobsen epoxidations are two-step and that there is a large amount of charge on the olefinic reactant in the transition state. This line of reasoning based on electronic spin conservation in Mn(V)-oxo epoxidations is consistent with the mechanistic model proposed herein, specifically an electrostatically guided two-step process via a delocalized carbocation intermediate.

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