A Possible Mechanism for Enantioselectivity in the Chiral Epoxidation of Olefins with [Mn(salen)] Catalysts**

Heiko Jacobsen[b] and Luigi Cavallo*[a]

Abstract: The origin of enantioselectivity in the Jacobsen–Katsuki reaction has been investigated by applying density functional calculations in combination with molecular mechanics methodologies. The calculations suggest that a high enantiomeric excess is connected to three specific features: 1) a chiral diimine bridge, which induces folding of the salen ligand(H_2salen = bis(salicylidene)ethylenediamine), and hence the formation of a chiral pocket; 2) bulky groups at the 3,3′-positions of the salen ligand, which cause a preferential approach from the side of the aromatic rings; and 3) π conjugation of the olefinic double bond, which confers regioselectivity and, consequently, enantioselectivity. In combination with experimental studies, the model also provides a rationale for the decrease in *ee* values when one of these components is missing.

Keywords: asymmetric catalysis · density functional calculations · epoxidations · homogeneous catalysis · molecular modeling

Introduction

Stereoselective oxidation of prochiral olefins using [Mn(salen)]-based catalysts (H_2salen = bis(salicylidene)ethylenediamine) represents one of the most elegant and effective techniques developed for the formation of carbon–oxygen bonds in asymmetric synthesis.[1, 2] The resulting chiral epoxides are usually obtained with enantiomeric excesses higher than 90%. Over the last decade, numerous experimental studies have furnished a detailed knowledge of such catalytic systems.[3–7] It is now possible to control the reaction profile of the [Mn(salen)]-mediated epoxidations by tuning the steric and electronic properties of the ligand system. The two main structural features required to achieve good enantioselectivity are an unsymmetrical diimine bridge derived from a C_2-symmetric diamine, and bulky substituents at the 3,3′-positions of the salen ligand.

Despite the synthetic success of [Mn(salen)] systems, the exact mechanism of this complex reaction still remains unclear.[8] Among the aspects that have to be considered are the mode of oxygen transfer, the possibility of the reaction proceeding on the energy hypersurfaces of triplet or quintet spin states, and the way in which the chiral information is transferred from the catalyst to the olefin during the enantioselective step.

The relevance of different electronic states in the oxidation step has recently attracted some attention in the literature. Results of density functional calculations on suitable simplified models of the real catalytic species have been reported: the geometric and electronic features of [Mn(salen)] complexes,[9] and the elementary steps of the epoxidation reaction[10, 11] were analyzed. According to Svensson and coworkers,[10] the epoxidation occurs on the quintet surface without the formation of a radical intermediate (which instead is predicted to exist on the triplet surface). In contrast, our previous work indicates that the epoxidation most probably occurs on the triplet surface, and that a radical intermediate is indeed involved (which should also be present on the quintet surface).[11] The main difference between these two mechanistic models is the assumption that a free or an occupied coordination site is located *trans* to the oxo group. The coordination chemistry of [Mn(salen)] complexes and the effects of axial ligation have also recently been investigated by electrospray tandem mass spectrometry in combination with hybrid density functional calculations.[12] As already noted by Strassner and Houk,[9] the presence of a *trans* ligand has a significant influence on the coordination geometry of the salen framework, which in turn has implications on the induction of stereoselectivity during the oxidation step.

Seminal ideas about the mechanism of the enantioselective reaction have been proposed by Katsuki and Houk.[4, 13] They

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[a] Dr. L. Cavallo
Dipartimento di Chimica
Università di Napoli Federico II
Complesso Monte S. Angelo
Via Cintia, 80126 Napoli (Italy)
Fax: (+39) 081-674442
E-mail: cavallo@chemistry.unina.it

[b] Dr. H. Jacobsen
Anorganisch-chemisches Institut
Universität Zürich
Winterthurerstrasse 190, 8057 Zürich (Switzerland)

[**] H_2salen = bis(salicylidene)ethylenediamine.

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independently observed that the salen ligand has two sp^3 carbon atoms that link the remaining sp^2 centers, and suggested that the salen ligand might adopt a folded structure. In particular, Houk and co-workers observed that the presence of the two sp^3 C atoms could induce a preference for a *gauche* conformation of the diimine bridge. This feature in turn would cause the salen ligand to fold. The role of the stereogenic C atoms of the linkage is to favor only one of the two possible *gauche* conformations.

Besides these steric influences, electronic factors might also play an important role. Jacobsen clearly showed that enantioselectivity is related to the position of the transition state (TS) along the reaction coordinate, which is affected by subtle electronic effects owing to different substituents at the 5,5′-positions of the salen ligand.[14]

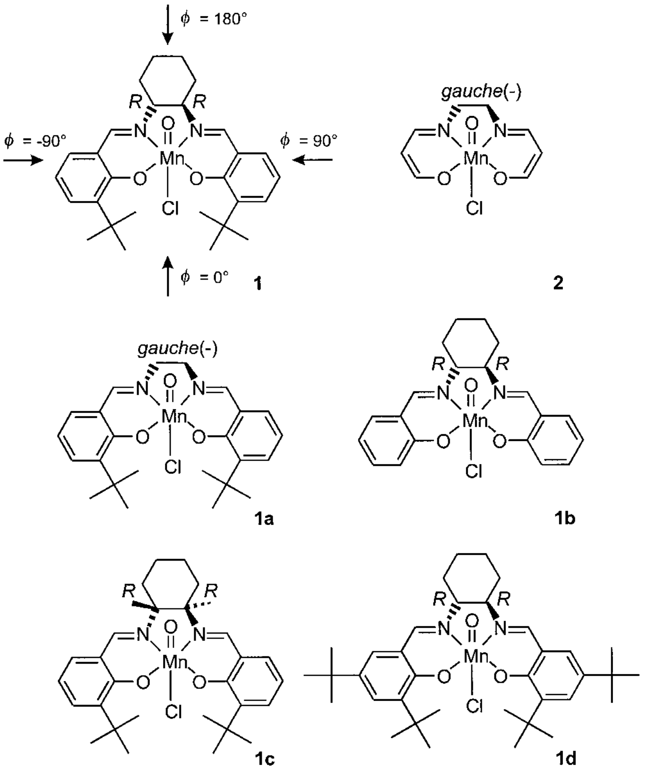
To get a more detailed understanding of some of the ideas mentioned above, we performed combined QM/MM calculations, addressing the issue of chirality transfer. The oxidation of *cis*-β-methylstyrene (CBMS) by the [Mn(salen)] complex **1** has been investigated. Our previous studies[11] support the idea that a stepwise mechanism involving a radical intermediate is favored in the epoxidation reaction. They further suggest that a triplet is the electronic configuration of the system involved in the epoxidation reaction. Under this general framework, it is widely accepted that the configuration of the C atom of the olefin that attacks the Mn=O linkage is established in the first irreversible step leading to the radical intermediate.[15] The present study is then centered on the transition state of the first C–O bond formation leading to an intermediate triplet radical.

Abstract in Italian: *L'origine della enantioselettività nella reazione di Jacobsen – Katsuki è stata studiata mediante un approccio basato sulla teoria del funzionale densità combinata con tecniche di meccanica molecolare. I calcoli effettuati suggeriscono che alti eccessi enantiomerici sono connessi a tre caratteristiche specifiche: 1) un ponte diimminico chirale che induce un ripiegamento del ligando salen, e che porta alla formazione di una tasca reattiva chirale; 2) gruppi ingombranti sulle posizioni 3,3′ del ligando salen, che inducono un approccio preferenziale dal lato degli anelli aromatici; 3) coniugazione π del doppio legame olefinico, che conferisce regioselettività e di conseguenza enantioselettività. Questo modello fornisce una razionalizzazione per i ridotti ee che si ottengono sperimentalmente in assenza di una di queste tre specifiche.*

Abstract in German: *Die Ursache für die Enantioselektivität in der Jacobsen – Katsuki Reaktion wurde mit Hilfe von Dichtefunktionalrechnungnen in Kombination mit Kraftfeldmethoden untersucht. Die Ergebnisse der Berechnungen lassen den Schluss zu, dass ein hoher enantiomerer Überschuss drei Kriterien bedingt: 1) Eine chirale Diimin Brücke, welche eine Faltung des Salen Liganden, und damit die Ausbildung einer chiralen Reaktionstasche bewirkt; 2) sperrige Gruppen in den 3,3′ Positionen des Salen Liganden, die zu einem bevorzugten Angriff über die Seiten der aromatischen Ringe führen; und 3) π-Konjugation der olefinischen Doppelbindung, wodurch Regioselektivität und folglich auch Enantioselektivität induziert wird. In Verbindung mit experimentellen Studien vermag dieses Modell auch die Verringerung der erhaltenen ee Werte zu erklären, wenn eines der drei erwähnten Charakteristika nicht gegeben ist.*

Models and computational details

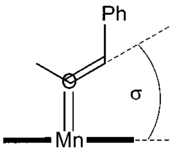
Models: All the models that we considered correspond to the TS for CBMS attack at the Mn=O moiety of the neutral complexes **1**–**1d** of Scheme 1. The elements of chirality which are relevant to the present discussion are briefly recalled here.



Scheme 1. The investigated Mn^V catalysts, and the four different approaches for CBMS attack at the Mn=O linkage.

First, to denote the absolute configuration of the chiral C atoms of the bridge, we use the standard *R*,*S* CIP nomenclature. Only models with an *R*,*R* chiral bridge have been considered in the present work. This particular chirality induces a preferential *gauche* (−) conformation on the diimine bridge in order to have the N atoms in equatorial positions. For models comprising the ligand **1a**, which does not have a chiral bridge, we considered only situations with a *gauche* (−) conformation at the bridge, for the sake of comparison with the other models. Other elements of chirality are the two enantiofaces of the prochiral CBMS olefin. To denote the two enantiofaces, we adopted the *Re*,*Si* nomenclature,[16] in order to avoid confusion with the chirality of the ligand. Furthermore, since the chirality of the two CBMS enantiofaces is unequivocally determined by the chirality of one olefinic C atom only, we decided to denote the two enantiofaces by using the chirality of the $C(CH_3)$atom only, that is, the atom that will attack the Mn=O linkage.

Various parameters and nomenclature systems have been proposed to describe the geometry of the approach of the



Scheme 2. The skew angle σ for side-on attack of the olefin at the Mn=O linkage.

olefin to the Mn=O linkage. Deviations from the idealized parallel side-on approach of the olefin[17–19] are measured by the skew angle σ $\measuredangle$(Mn-O-C(CH$_3$)-C(Ph)) (Scheme 2), already defined by Jacobsen and co-workers.[19, 20] We note that for attack of the *Si* and *Re* CBMS enantiofaces, the parallel approach corresponds to values of σ equal to -90° and 90°, respectively.

Various nomenclature systems have also been proposed for directions of olefin approach to the Mn=O moiety.[3, 4, 13] To put the discussion on more quantitative grounds, we adopted the definition of Houk and co-workers.[13] The olefin approach to the Mn=O linkage is described by the dihedral angle ϕ, defined as $\measuredangle$(X$_{OO}$-Mn-O-C(CH$_3$)), X$_{OO}$ being the midpoint of the two O atoms of the salen ligand. Thus, values of ϕ equal to 0°, -90°, 180° and 90° correspond to directions e, c, a and c′ shown in Figure 1 of reference [3].

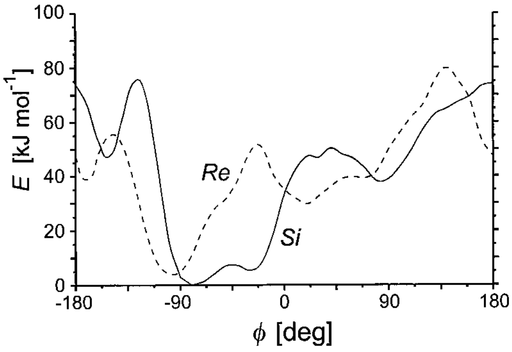


Figure 1. Rotational pure MM energy profiles, as a function of the angle ϕ, for approximated models of CBMS approach at the Mn=O moiety of complex **1.** The full and dashed lines correspond to attack of the *Si* and *Re* enantiofaces of CBMS, respectively.

Since several directions have been proposed for olefin attack at the Mn=O linkage, we performed MM calculations based on this issue. With this aim, we calculated the rotational profiles around the angle ϕ, incremented by steps of 10°. The profiles are shown are in Figure 1. The MM geometry of all the points of the profiles has been optimized with the exclusion of the C(CH$_3$)–O distance, and of the Mn-O-C(CH$_3$) angle (fixed at 2.0 Å and 122° on the basis of our previous calculations[11]) and of the skew angle σ (fixed at $|90|^\circ$). Furthermore, we kept the coordination of the salen ligand in **1** around the Mn strictly planar. The MM force field AMBER95[21] was adopted for these calculations. Parameters which are not part of AMBER95 were taken from the UFF force field.[22]

Both curves of Figure 1 clearly indicate that a few minimum energy approaches are available to both CBMS enantiofaces, and that they roughly correspond to values of ϕ equal to 0°, $\pm 90^\circ$ and 180°. The relative stability of the minima is not reliable, owing to the approximations that we made. Nevertheless, on the basis of our experience with MM calculations on organometallic compounds,[23–27] it is our opinion that only the few approaches suggested by these MM calculations are possible, and that they can easily be reached from approaches starting from the "idealized" and unbiased attacks at ϕ^0 equal to 0°, $\pm 90^\circ$ and 180°. Here, ϕ^0 is the dihedral angle for the initial attack, which should be differentiated from the final TS dihedral angle ϕ. A much more reliable estimate of the energy and geometry corresponding to the various approaches is found in the next section by using the more refined QM/MM method.

Computational details: Stationary points on the potential-energy surface were calculated with the Amsterdam density functional (ADF) program system,[28] developed by Baerends et al.[29, 30] The electronic configuration of the molecular systems were described by a triple-ζ STO basis set on manganese for 3s, 3p, 3d, 4s, and 4p. (ADF basis set IV augmented with two 4p functions). Double-ζ STO basis sets were used for chlorine (3s,3p), oxygen, nitrogen, and carbon (2s,2p), and hydrogen (1s), augmented with a single 3d, 3d, and 2p function, respectively (ADF basis set III).[28] The inner shells of manganese and chlorine (including 2p), and oxygen, nitrogen, and carbon (1s), were treated within the frozen core approximation. Energies and geometries were evaluated by using the local exchange-correlation potential by Vosko et al.,[31] augmented in a self-consistent manner with Becke's[32] exchange-gradient correction and Perdew's[33, 34] correlation-gradient correction.

The ADF program was modified by one of us[35] to include standard molecular mechanics force fields in such a way that the QM and MM parts are self-consistently coupled.[36] The model QM system and the real QM/MM systems are structure **2**, and structures **1**, and **1a–d**, respectively, as shown in Scheme 1. The partitioning of the systems into QM and MM parts only involves the skeleton of the salen ligand. Hence, the olefins under consideration are always composed entirely of pure QM atoms. Our previous study,[11] and a DFT study of Schiff's base complexes of cobalt performed by Henson and co-workers,[37] indicate that within the chosen computational approach, the simplified system **2** is an appropriate model for the description of the main electronic features of the full salen complexes **1–1d**.

The connection between the QM and MM parts occurs by means of the so-called "capping" dummy hydrogen atoms, which are replaced in the real system by the corresponding "linking" carbon atom.[35, 36] In the QM/MM optimizations, the ratio between the C–C bonds crossing the QM/MM border, and the corresponding optimized C–H distances, was fixed at 1.36. A more detailed description of the coupling scheme, as well as further comments on the methodology, can be found in previous papers.[25, 26, 35] The AMBER95 force field[21] was used for the MM potentials, except for Mn, which was treated with the UFF force field.[22] To eliminate spurious stabilizations by the long-range attractive part of the Lennard-Jones potential,[26, 38] we used an exponential expression fitted to the repulsive part of the Lennard-Jones potential.[24, 26, 39, 40]

The following structures are all stationary points on the combined QM/MM potential surface. TS geometries were

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approached by a linear-transit procedure, using the distance between the C(olefin) and O(Mn=O) atoms, which form the new C–O bond, as the reaction coordinate, while optimizing all the other degrees of freedom. Full transition-state searches were started from geometries corresponding to maxima along the linear-transit curves. At the end of each transition-state search, the approximated Hessian presented one negative eigenvalue. To further check for the true nature of the transition states, we also performed geometry optimizations by relaxing several transition-state geometries on both sides, and we checked that they converged into the reactants and the products.

Optimized geometries and final energies of all structures reported in this work can be found in the Supporting Information.

Results and Discussion

Before we address the problem of enantioselectivity, the regioselectivity of olefin attack at the Mn=O bond has to be established. Based on the geometries obtained in our previous studies,[11] we localized the TS for attack at both the C(CH_3) and C(Ph) position of the C=C bond. The simplified Mn complex **2** was used as a model for the catalyst in order to avoid the possible influence of steric effects, and to focus on electronic contributions only. In agreement with experiments[15] and similar theoretical studies,[18] attack at C(CH_3) is favored (by 12 $kJ\,mol^{-1}$) since the radical being formed has an unpaired electron mostly localized on the C(Ph) atom, and is stabilized by the adjacent phenyl group.

We then localized the TS of attack of both the enantiofaces of CBMS at the oxo center of **1**; the salen ligand was given the *R*,*R* configuration. As a starting point for the preliminary linear transit calculations, we set the distance $d_{C\cdots O}$ between the C(CH_3) and O (Mn=O) atoms at 5.0 Å. As discussed in the previous section, the angle ϕ^0 for initial attack was set at 0°, ±90°, and 180°. During the linear transit approach, only $d_{C\cdots O}$ was kept fixed, while ϕ was always optimized.

Attack at the *Si* enantioface of the olefin is clearly favored from $\phi^0 = -90°$, and the geometries resulting from ϕ^0 equal to 180°, 90° and 0° are higher in energy by 10 to 20 $kJ\,mol^{-1}$ (Table 1). On the other hand, attacks at the *Re* enantioface, with $\phi^0 = -90°$ and 90° are almost isoenergetic, with a slight preference for $\phi^0 = 90°$. The approach along $\phi^0 = 0°$ and 180° is clearly disfavored by about 5 to 10 $kJ\,mol^{-1}$ (Table 1). Of paramount importance, however, is the fact that the most favorable TS corresponding to the attack of the *Si* enantioface (along $\phi^0 = -90°$) is 10 $kJ\,mol^{-1}$ more stable in energy than the TS corresponding to the easiest attack of the *Re* enantioface (along $\phi^0 = 90°$). This is in agreement with the experimental finding that catalysts with the *R*,*R* configuration favor the formation of the *R*,*S* epoxide (generated by attack of the *Si* enantioface), when oxidation of CBMS is performed.[3, 4]

Table 1. Relative energies ΔE [$kJ\,mol^{-1}$] of the transition states of CBMS attack at the oxo center of catalyst systems **1**, and **1a–d**.

Olefin Enantioface	ϕ [°]	Catalyst **1**	**1a**	**1b**	**1c**	**1d**
Si	–90	0	0	0	0	0
Si	180	19	–	–	–	–
Si	90	21	–	–	–	–
Si	0	9	–	–	–	–
Re	–90	11	12	9	9	10
Re	180	21	22	19	–	–
Re	90	10	10	8	5	10
Re	0	16	18	6	–	–

The structures of the most favored TS for attack of the *Si* and *Re* enantiofaces are shown in Figure 2. They strongly resemble the putative TS predicted by Jacobsen (compare Figures 2a–c of this paper with Figures 2A–C in refer-

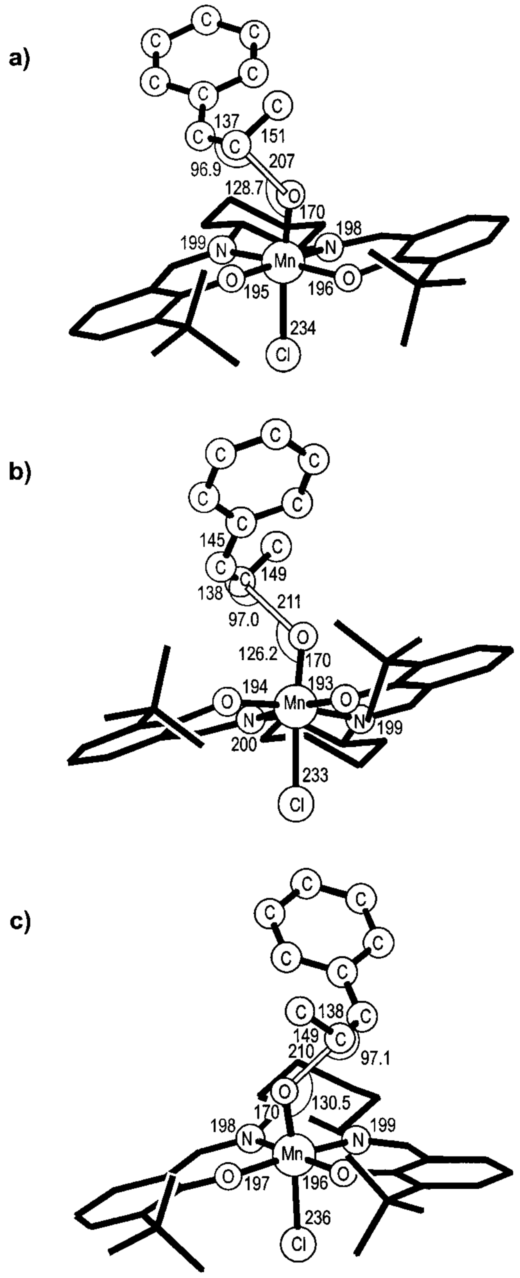

Figure 2. QM/MM geometry (distances in pm) of the transition states corresponding to attack of the *Si*, part a, and of the *Re*, parts b and c, enantiofaces of CBMS at the Mn=O linkage of complex **1**. Attack of the *Si* enantioface (part a) is along the $\phi^0 = -90°$ direction, while attack of the *Re* enantioface (parts b and c) is along the $\phi^0 = -90°$ and 90° directions, respectively.

ence[2]). For both enantiofaces, the approach along directions $\phi^0 = 180°$ and 0° is hampered by the repulsive interactions with either the diimine bridge or the bulky *tert*-butyl groups.

A close inspection of the most favored structure (Figure 2a) explains why the *Si* approach along $\phi^0 = -90°$ is the preferred mode of attack of the olefin at the Mn=O bond when the catalyst has the *R*,*R* configuration. The two flat aromatic subunits of the salen ligand do not lie in the equatorial coordination plane defined by the N and O atoms, but are folded away in opposite directions. This slight distortion is a consequence of different hybridizations of the N and C atoms of the N-C-C-N linkage.[4, 9, 41] It ensures a minimum-energy *gauche* conformation around the sp^3-sp^3 C–C bond of the diimine bridge, and it preserves planarity around the sp^2 N atoms. The degree of folding amounts to approximately 20°, if measured by the angle between the plane of the aromatic rings of the salen ligand and the equatorial mean plane of coordination around the Mn atom.

The chelating group evidently binds to the metal center in a flexible way, and a distortion of its coordination around the metal to meet geometric constrains does not require much energy. This can also be observed in the solid-state structure of such systems. The examination of several X-ray structures of [Mn^{III}(salen)] complexes indicate that both planar and slightly folded geometries are common.[42–44]

The actual directions of attack ϕ that result from the initial "ideal" approaches are shown in Figure 3, and are reported in Table 2. In addition, the skew angles σ are also given in Table 2. In terms of the approach angle ϕ, substantial deviations from the "ideal" values (vide supra) are found. In particular, the initial approach from $\phi^0 = 0°$ results in a TS vector close to $\pm 30°$, which is commonly known as "approach d" in the literature.[3] This indicates how the bulky *tert*-butyl groups are able to shield the metal center from a $\phi^0 = 0°$ approach. Positive and negative deviations from the idealized vectors for attacks from $\phi^0 = \pm 90°$are found for both the *Si* and *Re* CBMS enantiofaces. These deviations amount to approximately 15°, and the resulting direction for the favored *Si* olefin attack is somewhere between "approaches c and d".[3] The two competitive attacks of the unfavorable *Re* CBMS enantioface occur from directions quite close to "approaches c and c′".[3]

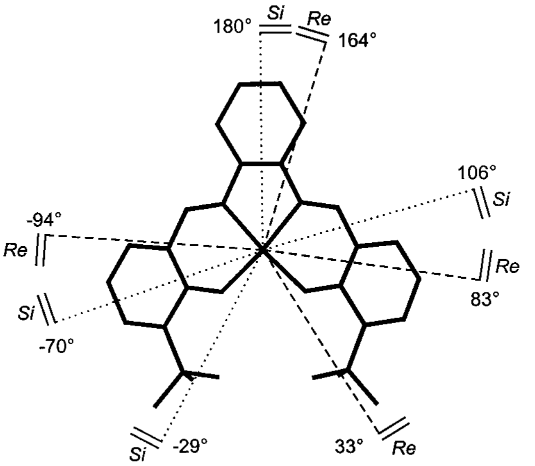

Figure 3. Sketch of the resulting directions ϕ of CBMS attack at the Mn=O linkage of complex **1**. The dotted and dashed lines refer to the *Si* and *Re* enantiofaces of CBMS, respectively.

Table 2. Side-on geometries[a] of the transition state of CBMS attack at the oxo center of **1**.

Olefin Enantioface	Attack angle ϕ^0	ϕ	$\phi - \phi^0$	Skew Angle σ^0	σ	$\sigma - \sigma^0$
Si	– 90	– 70	20	– 90	– 77	13
Si	180	180	0	– 90	– 61	29
Si	90	106	16	– 90	– 87	3
Si	0	– 29	– 29	– 90	– 89	1
Re	– 90	– 94	– 4	90	90	0
Re	180	164	– 16	90	116	26
Re	90	83	– 7	90	85	– 5
Re	0	33	33	90	93	3

[a] Angles in °.

In most cases, the skew angle σ comes close to the ideal absolute value of $|90|°$ for the parallel side-on approach. Larger deviations are found in situations in which the olefin is in close proximity to the chiral diimine bridge. However, the main conclusion here is that the calculated structures are consistent with, and support, the side-on mechanism.[17–19, 45–47]

Previous MM calculations of Houk and co-workers suggested that the preferred direction of approach of the olefin to the Mn=O linkage should occur from situations quite close to $\phi = 0°$.[13] In contrast, our results indicate that attack from $\phi^0 = 0°$ is shielded by the bulky *tert*-butyl groups (vide infra). Considering the limited amount of computational details given by Houk and co-workers in their preliminary communication, it is difficult to rationalize these differences.

Finally, the linear-transit calculations along the $C(CH_3)\cdots O$ coordinate indicate that the potential energy surface in the 1.9–2.2 Å region is substantially flat. In fact, within this range of the C–O distance, the energy variations from the TS are usually smaller than 3 kJ mol^{-1}. This implies that the exact position of the transition state, which determines enantioselectivity, is prone to subtle electronic effects owing to different substitution patterns at the salen ligand. This aspect conforms with the experimental work carried out by Jacobsen and co-workers, who established a strong correlation between $\Delta\Delta H^{\ddagger}$ and the electronic character of the catalyst.[14]

In order to elucidate the role played by the different functional groups of the salen ligand, we performed additional TS searches on systematically simplified ligand systems **1a**, **b**, as well as on the catalyst with additional methyl groups at the 2,2′-positions of the diimine bridge (**1c**), or with additional *tert*-butyl groups at the 5,5′-position of the aromatic rings (**1d**; Scheme 1). In the first set of calculations, the cyclohexyl bridge was replaced with an ethyl bridge, complex **1a**, and the second set of calculations was performed on the model system **1b**, in which the *tert*-butyl groups at the 3,3′-positions were substituted by simple H atoms. Again, a *gauche* (–) conformation was adopted for the diimine bridge.

For the *Si* enantioface, only attack from $\phi^0 = -90°$ was considered, and was the reference state at 0 kJ mol^{-1}, since it represents the most favored approach. For the *Re* enantioface, all four approaches with ϕ^0 equal to 0°, ±90°, and 180° were investigated, and their energies were calculated relative to the energy of the TS corresponding to attack of the *Si* enantioface, $\phi^0 = 0°$. All the energy values related to these calculations are reported in Table 1.

These calculations reveal that the model systems **1** and **1a** behave in essentially the same manner. The relative energies of the attack of the *Re* enantioface along the four directions, as calculated for complex **1a**, are virtually identical to the results obtained for the full system **1**. This suggests that the cyclohexyl ring does not directly contribute to the discrimination of the olefin enantioface. Its only role is to confer stereorigidity to the catalyst. On the contrary, when going from **1** to **1b**, attack of the *Re* enantioface becomes less disfavored, the relative energies being higher by about 5 to 20 kJ mol^{-1}. In particular, the approach of the *Re* enantioface along $\phi^0 = 0°$ competes with the attack of the *Si* enantioface. This finding is in qualitative agreement with the well-known fact that bulky groups at the 3,3′-positions are needed to achieve good enantioselectivity.

In order to further validate the conclusions obtained so far, we performed additional calculations on complex **1c**, which possesses two methyl groups at the 2,2′-positions of the diimine bridge. Experimentally, this substitution resulted in an unexpected decrease in enantioselectivity.[48] According to our calculations, the energy difference between the TS of the most favored attacks of the *Si* and *Re* enantiofaces of CBMS (along $\phi^0 = -90°$ and 90°, respectively) amounts to only 5 kJ mol^{-1} in favor of the *Si* enantioface. This value has to be compared with the ΔE value obtained for complex **1** (11 kJ mol^{-1}). The decreased preference for the *Si* enantioface is due to repulsive interactions between the incoming olefin and one of the additional methyl groups. As shown in Figure 4, this methyl group occupies an axial position at the diimine bridge, and points directly towards the olefin. To relieve the steric pressure, the angle O-C(CH_3)-C(Ph) opens from 96° to 100° (Compare Figure 2a and Figure 4). This result is also consistent with the hypothesis that the initial attack occurs at $\phi^0 = -90°$ with an *R,R* catalyst. It would be rather difficult to rationalize the decreased enantioselectivity of complex **1c** if the preferred approach were to occur from the side of the bulky *tert*-butyl groups ($\phi^0 = 0°$).

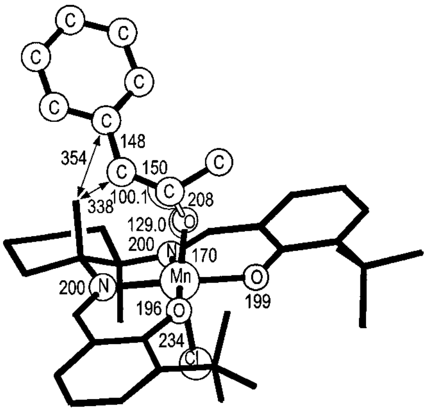

Figure 4. QM/MM geometry (distances in pm) of the transition state corresponding to attack of the *Si* enantioface of CBMS at the Mn=O linkage of complex **1c**. Attack of the *Si* enantioface is along the $\phi^0 = -90°$ direction.

Our calculations for attack of CMBS at the Mn^{V}–oxo complex derived from Jacobsen's catalyst **1d** lead to essentially the same energetic discrimination that was found for the model system **1**. The distance between the *tert*-butyl groups at the 5,5′-positions of the aromatic ring and CBMS is too large (ca. 6–7 Å for both attacks at $\phi^0 = \pm 90°$, see Figure 5) so that these groups cannot exert any steric influence on the C–O bond-formation reaction. The ligands at the 5,5′-positions probably only allow for an electronic tuning of the catalyst, without any steric effect.[49] This is, in principle, the same conclusion that emerged from the mechanistic study of Jacobsen et al.[14]

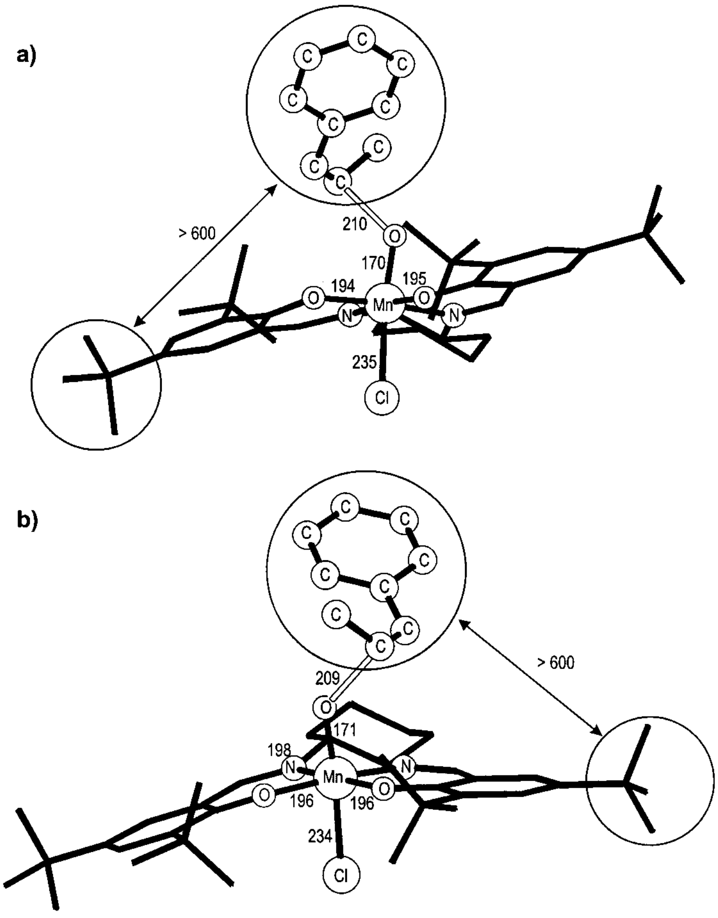

Figure 5. QM/MM geometry (distances in pm) of the transition state TS corresponding to attack of the *Re* enantioface of CBMS at the Mn=O linkage of complex **1d**. Attack of the *Re* enantioface is along the $\phi^0 = -90°$ and $\phi^0 = 90°$ directions, parts a and b, respectively.

The last point we want to address is the oxidation of *cis*-1-cyclohexylpropene (CCP) by complex **1**. Epoxidation of this olefin results in lower *ee* values than that of CBMS, although both substrates can be considered to offer similar steric hindrance.[4] Here, we had to review the question of the regioselectivity of the olefin attack, since the forming radical is not stabilized by an adjacent aromatic group. For the attack along the favorable $\phi^0 = -90°$ direction, the energetic preference for the *Si* enantioface of CCP amounts to only 5 kJ mol^{-1}.

The lower energy difference than in CBMS is caused by the similar reactivity of the two C atoms of the double bond, and the attack of CCP at the Mn=O linkage is hardly regioselective. The *Si* enantioface reacts at C(CH_3) of the double bond, whereas for the *Re* enantioface, C–O bond formation takes place at C(Cy). The lowest energy structure of the TS corresponding to the *Re* enantioface is shown in Figure 6.[50]

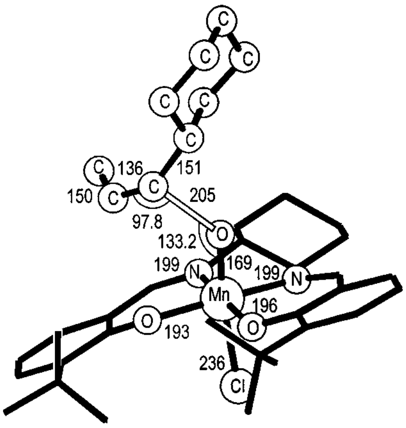

Figure 6. QM/MM geometry (distances in pm) of the transition state corresponding to attack of the *Re* enantioface of CCP at the Mn=O linkage of complex **1**. Attack of the *Re* enantioface is along the $\phi^0 = -90°$ direction.

This result explains the well-known fact that substantial enantioselectivity requires an aryl, alkenyl or alkynyl group in conjugation with the double bond to be oxidized, and that very low enantioselectivity is generally observed in the epoxidation of isolated *cis*-disubstituted alkenes.[3, 4]

Conclusion

The model for chirality transfer in the catalytic epoxidation of prochiral olefins with [Mn(salen)] complexes, which we developed in the present work, relates the enantioselectivity to three specific features: 1) The two sp^3 centers of the chiral diimine bridge induce a preference for *gauche* conformations of the bridge, which in turn causes the salen ligand to fold slightly. This folding shapes a chiral pocket, and the role of the chiral bridge is to favor only one of the two possible *gauche* conformations, thus conferring stereorigidity to the [Mn(salen)] complex; 2) the bulky groups at the 3,3′-positions restrict access to the reactive chiral pocket from one side only; 3) the aryl, alkenyl, or alkynyl substituents on the olefin confer regioselectivity, and therefore enantioselectivity.[51] When one of these features is missing, our model is able to rationalize the experimentally observed decrease in enantioselectivity.

Calculations on a model system derived from Jacobsen's catalyst suggest that substituents at the 5,5′-positions do not exhibit any steric influence, and thus allow for the tuning of the electronic properties of the catalytic system. Finally, a qualitative agreement is found between the shallow potential surface around the TS for olefin attack at the Mn=O bond, and the strong correlation between the enantioselectivity and the electronic character of the catalyst owing to different substitution patterns of the salen ligand.

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[49] Since H and *tert*-butyl ligands at the aromatic rings exhibit different electron-donating strengths, one might expect our calculations to show different energies for the TS of C–O bond formation. However, with the present QM/MM methods, only steric influences are considered at the interface between the QM and MM subunits.
[50] As a further check, a geometry optimization starting from the structure shown in Figure 6, and replacing CCP by CBMS, resulted in a geometry that is 11 kJ mol^{-1} higher in energy than the structure shown in Figure 2a.
[51] A well-documented example of how regiochemistry influences enantioselectivity can be found in G. Guerra, L. Cavallo, G. Moscardi, M. Vacatello, P. Corradini, *J. Am. Chem. Soc.* **1994**, *116*, 2988.

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