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# Mechanism of the Enantioselective Oxidation of Racemic Secondary Alcohols Catalyzed by Chiral Mn(III)−Salen Complexes

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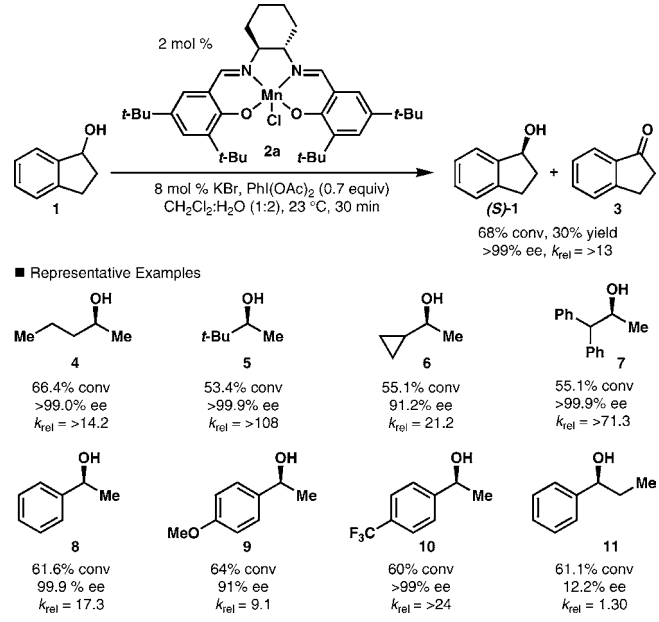
***Abstract:*** The experiments described here clarify the mechanism and origin of the enantioselectivity of the oxidation of racemic secondary alcohols catalyzed by chiral Mn(III)−salen complexes using HOBr, $Br_2/H_2O/KOAc$ or $PhI(OAc)_2/H_2O/KBr$ as a stoichiometric oxidant. Key points of the proposed pathway include (1) the formation of a Mn(V)−salen dibromide, (2) its subsequent reaction with the alcohol to give an alkoxy-Mn(V) species, and (3) carbonyl-forming elimination to produce the ketone via a highly organized transition state with intramolecular transfer of hydrogen from carbon to an oxygen of the salen ligand.

## Introduction

Chungu Xia and his group showed that chiral Mn(III)−salen complexes can catalyze the oxidation of racemic secondary alcohols of the type $R_1R_2CHOH$ at partial conversion to a mixture of the corresponding ketone and chiral $R_1R_2CHOH$ with excellent enantioselection under the optimized conditions.[1−4] It was reported that the addition of substoichiometric amounts of a bromide salt to a mixture of catalyst **2a**, $PhI(OAc)_2$, and a biphasic $CH_2Cl_2/H_2O$ medium is important for high enantioselectivity and that $k_{rel}$ in favorable cases can be as high as 450 (Scheme 1).[1b] Kita and co-workers[5] had earlier noted that KBr accelerated the oxidation of secondary alcohols by PhIO. The Xia group proposed that the active oxidant for the oxidation of secondary alcohols may be a species having composition salen−Mn(V)−OIPh but provided no explanation for the effect of bromide on the enantioselectivity or for the absolute stereochemical course of the reaction.[1b] Representative examples of the enantioselective oxidation of racemic secondary alcohols

***Scheme 1.*** Enantioselective Oxidation of Racemic Secondary Alcohols as Reported by Xia and Coworkers[a]




[a] For further details, see ref 1 and the Supporting Information.

are displayed in Scheme 1.[6] There are limitations of the Xia method with $R_1R_2CHOH$ substrates in which $R_1$ and $R_2$ have similar steric bulk. Alcohols such as 1-phenylpropanol (**11**), for example, are oxidized with only poor selectivity.[1d]

Our group recently proposed a logical mechanistic explanation for the absolute stereochemical course of the Mn(III)−salen-catalyzed epoxidation of olefins (Jacobsen epoxidation)[7] that is in cases highly enantioselective.[8] The key features of this pathway are as follows: (1) the epoxidation involves electrophilic

(1) (a) Sun, W.; Wang, H.; Xia, C.; Li, J.; Zhao, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042–1044. (b) Li, Z.; Tang, Z. H.; Hu, X. X.; Xia, C. G. *Chem.—Eur. J.* **2005**, *11*, 1210–1216. (c) Sun, W.; Wu, X.; Xia, C. *Helv. Chim. Acta* **2007**, *90*, 623–626. (d) Cheng, Q.; Deng, F.; Xia, C.; Sun, W. *Tetrahedron: Asymmetry* **2008**, *19*, 2359–2362.

(2) (a) Kantam, M. L.; Ramani, T.; Chakrapani, L.; Choudary, B. M. *J. Mol. Catal. A: Chem.* **2007**, *274*, 11–15. (b) Pathak, K.; Ahmad, I.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2007**, *274*, 120–126. (c) Kureshy, R. I.; Ahmad, I.; Pathak, K.; Khan, N. H.; Abdi, S. H. R.; Prathap, J. K.; Jasra, R. V. *Chirality* **2007**, *19*, 352–357. (d) Han, F.; Zhao, J.; Zhang, Y.; Wang, W.; Zho, Y.; An, J. *Carbohydr. Res.* **2008**, *343*, 1407–1413.

(3) In one example, Katsuki and co-workers reported an enantioselective oxidation of 3,3-dimethyl-1-indanol with Mn−salen-based complexes, but low selectivities were observed. See: Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017–10028.

(4) For non-enantioselective oxidation of alcohols promoted by Mn−salen complexes, see: (a) Kumbhat, V.; Sharma, P. K.; Banerji, K. K. *J. Chem. Res., Synop.* **2001**, *5*, 179–181. (b) Kim, S. S.; Borisova, G. *Synth. Commun.* **2003**, *33*, 3961–3967. (c) Mardani, H. R.; Golchoubian, H. *Tetrahedron Lett.* **2006**, *47*, 2349–2352.

(5) (a) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328–337. (b) Tohma, H.; Maegawa, T.; Kita, Y. *Synlett* **2003**, 723–725.

(6) For reviews regarding kinetic resolution, see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

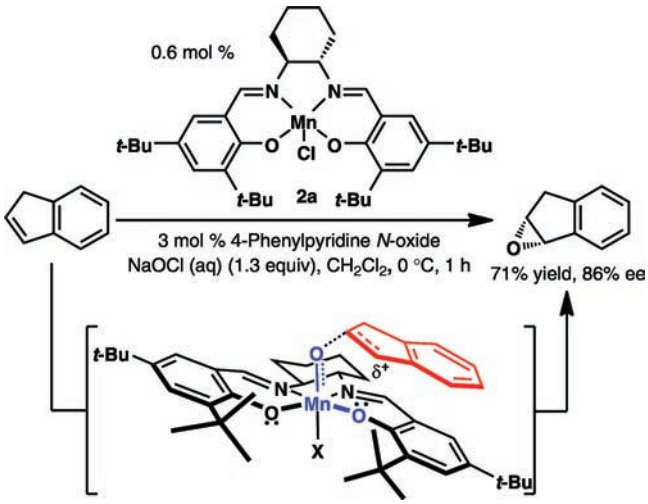



***Figure 1.*** An explanation for the origin of enantioselectivity in the Jacobsen epoxidation.

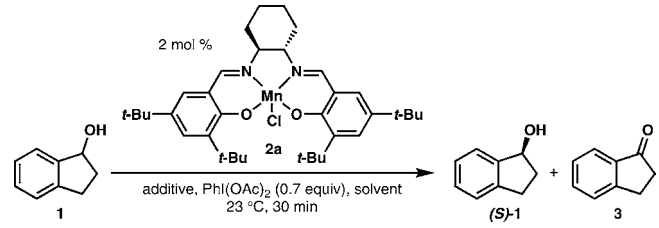
attack by the oxygen of a salen−Mn(V)−oxo complex on one of the olefinic carbons to form the more stable carbocationic intermediate; (2) the relative orientation of the olefinic substrate and the Mn(V)−oxo complex is determined by the electrostatic attraction between the cationic carbon and one of the oxygens of the salen ligand; and (3) the olefinic $\pi$-face selectivity arises from differences in steric repulsion for the two diastereomeric complexes. This model leads, for example, to the pre-transition-state assembly shown in Figure 1 for the epoxidation of indene by Mn−salen complex **2a**.

We believe that some features of this model for the Jacobsen epoxidation of olefins carry over to the enantioselective oxidation of secondary alcohols developed by Xia.[1] This line of analysis based on our earlier work[8] together with the experiments described herein have led to a new and rational explanation for the Mn−salen-catalyzed enantioselective oxidation of secondary alcohols. We have followed a heuristic that has been extremely useful in many of our previous research efforts on the design and understanding of enantioselective chemical reactions.[9] In its simplest form, that heuristic is as follows: (1) for cases in which a chemical reaction is highly enantioselective and also wide in scope, the pre-transition-state assembly is likely to be highly organized in the sense that there is one preferred three-dimensional assembly of the atoms involved; (2) that condition very sharply limits the number of mechanistic pathways by which the reaction can occur; and (3) the favored pathway can often be derived from three-dimensional modeling and an analysis of the steric, electrostatic, and stereoelectronic effects that determine the reaction energetics and rates.

## Results and Discussion

**Role of the Additive Bromide Ion.** We start by examining the role of the additive bromide ion on enantioselectivity in the oxidation of racemic secondary alcohols since Xia et al.[1] reported that potassium bromide is absolutely crucial for fast and highly enantioselective oxidation. Several points regarding

***Table 1.*** Survey of Reaction Conditions for the Biphasic Oxidation of **1**




| entry | solvent | additive | conv (%)[a] | ee (%)[b] | $k_{rel}$[c] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2/H_2O$ (1:2) | 8 mol % KBr | 68 | >99 | >13 |
| 2 | $CH_2Cl_2/H_2O$ (1:2) | 8 mol % KCl | 12 | <2 | 1.0 |
| 3 | $CH_2Cl_2/H_2O$ (1:2) | 8 mol % KI | 29 | 22 | 4.1 |
| 4 | $CH_2Cl_2/H_2O$ (1:2) | − | 13 | <2 | 1.0 |
| 5 | $CH_2Cl_2$ | 8 mol % $Et_4NBr$ | 63 | 55 | 3.2 |
| 6[d] | $CH_2Cl_2/H_2O$ (1:2) | 8 mol % KBr | 49 | − | − |

[a] Determined by $^1$H NMR (500 MHz) analysis of the unpurified reaction mixtures. [b] Determined by HPLC analysis with a chiral column. [c] $k_{rel} = \ln[(1 - \text{conv})(1 - \text{ee})]/\ln[(1 - \text{conv})(1 + \text{ee})]$. [d] The reaction was carried out in the absence of catalyst **2a**.

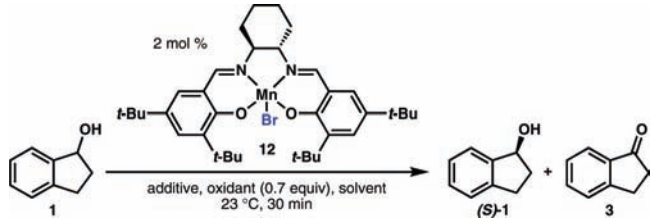
the data are noteworthy (see Table 1). Reactions in which potassium bromide was replaced by potassium chloride afforded only low conversion of (±)-1-indanol (**1**) (Table 1, entry 2). Reactions with potassium iodide gave poorer conversion than reactions with potassium bromide (Table 1, entry 3).[10] Reactions carried out in the absence of any halide ion or with added chloride ion were inefficient (Table 1, entry 4). Water is a necessary component for high enantioselectivity (Table 1, entry 5). There is a significant Mn-independent background reaction, since the oxidation of **1** with $PhI(OAc)_2$ and potassium bromide without any Mn complex **2a** was nearly complete within 30 min (Table 1, entry 6). The enantioselective oxidation of **1** in the presence of Mn complex **2a** and KBr is much faster and was complete in less than 10 min. This acceleration of the Mn−salen oxidation by bromide ion is clearly large enough to dominate over the competing, nonenantioselective background process (without any Mn−salen) and thus leads to enantioselectivity.

Because one possible role of bromide might be the conversion of the salen−Mn−chloro complex **2a** into the corresponding salen−Mn−Br complex **12**, we prepared complex **12**. As expected and as indicated in Table 2, oxidation of **1** catalyzed by **12** under the optimized conditions gave results identical to those for **2a** (compare Table 1, entry 1 with Table 2, entry 1). However, the use of additional potassium bromide with salen−Mn−Br complex **12** is essential for achieving optimum stereoselection in the oxidation of **1** (Table 2, entry 2), as it is for the corresponding salen−Mn−chloro complex.[1] The bromide attached to Mn in **12** provides only a modest improvement in oxidative enantioselection relative to catalyst **2a** in the absence of additional potassium bromide (compare Table 1, entry 4 with Table 2, entry 2).[11]

We determined experimentally that bromide ion is oxidized by $PhI(OAc)_2$ to $Br_2$ (and therefore to HOBr, which in the presence of $H_2O$ is known to be in equilibrium with $Br_2$) according to reactions R1 and R2:[12]

(7) For a review regarding the Cr- and Mn-promoted epoxidation of olefins, see: McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563–1602.
(8) Kürti, L.; Blewett, M. M.; Corey, E. J. *Org. Lett.* **2009**, *11*, 4592–4595.
(9) For example, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.
(10) In accordance with results published by Xia and coworkers (ref 1), enantioselective oxidation of 1-phenylethanol under the conditions presented in entry 3 of Table 1 resulted in <10% conversion.
(11) Enantioselective oxidation of 1-phenylethanol under the conditions presented in entry 2 of Table 2 resulted in 33% conversion and <10% ee.

***Table 2.*** Biphasic Oxidation of **1** with salen−Mn(III)−Br Catalyst **12**




| entry | solvent | additive | oxidant | conv (%)[a] | ee (%)[b] | $k_{rel}$[c] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2/H_2O$ (1:2) | 8 mol % KBr | $PhI(OAc)_2$ | 65 | >99 | >16 |
| 2 | $CH_2Cl_2/H_2O$ (1:2) | − | $PhI(OAc)_2$ | 64 | 72 | 4.8 |
| 3[d] | $CH_2Cl_2/H_2O$ (1:2) | 2.0 equiv of KOAc | $Br_2$[e] | 65 | 98 | 14 |
| 4[d] | $CH_2Cl_2$ | 2.0 equiv of *n*-$Bu_4NOAc$ | $Br_2$[e] | 27 | <5 | 1.3 |
| 5[d] | $CH_2Cl_2/H_2O$ (1:2) | 1.3 equiv of KOAc | HOBr[f] | 69 | 97 | 9.5 |
| 6[d] | $CH_2Cl_2/H_2O$ (1:2) | 1.0 equiv of KOAc | *t*-BuOBr[g] | 66 | 98 | 13 |
| 7[d] | $CH_2Cl_2/H_2O$ (1:2) | 1.0 equiv of $NaHCO_3$ | *t*-BuOBr[g] | 66 | 89 | 7.4 |

[a] Determined by $^1H$ NMR (500 MHz) analysis of the unpurified reaction mixtures. [b] Determined by HPLC analysis with a chiral column. [c] $k_{rel} = \ln[(1 - conv)(1 - ee)]/\ln[(1 - conv)(1 + ee)]$. [d] The reaction was carried out with 10 mol % **12** and oxidant added over 30 min. See the Supporting Information for details. [e] Using 0.75 equiv of $Br_2$. [f] Using 0.90 equiv of HOBr. [g] Using 0.80 equiv of *t*-BuOBr.

$$PhI(OAc)_2 + 2KBr \rightarrow PhI + Br_2 + 2KOAc \quad (R1)$$

$$PhI(OAc)_2 + KBr + H_2O \rightarrow PhI + HOBr + HOAc + KOAc \quad (R2)$$

The fact that a positive Br species is formed under the Xia conditions suggests that $PhI(OAc)_2$ can be replaced by $Br_2$ or HOBr as the stoichiometric oxidant in the enantioselective oxidation. Indeed, highly enantioselective oxidations can be carried out with $Br_2$ or HOBr as the stoichiometric oxidant [no $PhI(OAc)_2$ added] provided that sufficient potassium acetate is used to neutralize the HBr generated during the oxidation and buffer the reaction mixture (Table 2, entries 3 and 5). Sodium bicarbonate can also be used to neutralize HBr in the enantioselective oxidation of **1** (Table 2, entry 7). It is important that the oxidant be added slowly enough to prevent the detrimental build up of HBr. Reactions carried out with $Br_2$ or HOBr as the stoichiometric oxidant in the absence of potassium acetate were nonselective because of the adverse effect of HBr, and lower selectivities were observed ($k_{rel} \approx 4-9$) when the oxidant was added rapidly.[12] As evidenced by the experiment summarized in Table 2, entry 4, the presence of water in the biphasic reaction mixture is necessary for the highly enantioselective reaction to occur. Our best procedure involved the slow addition of $Br_2$ or HOBr (0.75−0.90 equiv; see Table 2) to a mixture of secondary alcohol (1.0 equiv), potassium acetate (2.0 equiv for $Br_2$ or 1.0 equiv for HOBr), and salen−Mn−Br complex **12** (10 mol %) in 1:2 $CH_2Cl_2/H_2O$ with stirring. Under the optimized reaction conditions, *t*-BuOBr afforded results that were almost identical to those for $Br_2$ or HOBr (Table 2, entry 6).[13]

Our experimental results indicate that either $Br_2$ or HOBr alone can convert the chiral (*S*,*S*)-Mn(III)−salen complex **12** into an oxidizing species that catalyzes the transformation of (±)-1-indanol into a mixture of 1-indanone and (*S*)-1-indanol with essentially the same enantioselectivity as that achieved under the most effective Xia procedure, with comparable reaction conditions (1:2 $CH_2Cl_2/H_2O$, 23 °C). The role of $PhI(OAc)_2$ in the presence of bromide ion in the Xia procedure is to generate HOBr and $Br_2$. There is no obvious reason why it needs to be invoked as an integral component of the transition-state assembly for enantioselective oxidation.[1]

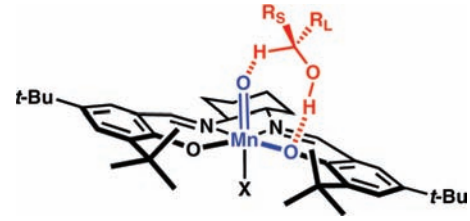



***Figure 2.*** Pre-transition-state assembly with the Mn(V)−oxo complex predicts an incorrect absolute stereochemistry for the recovered alcohol.

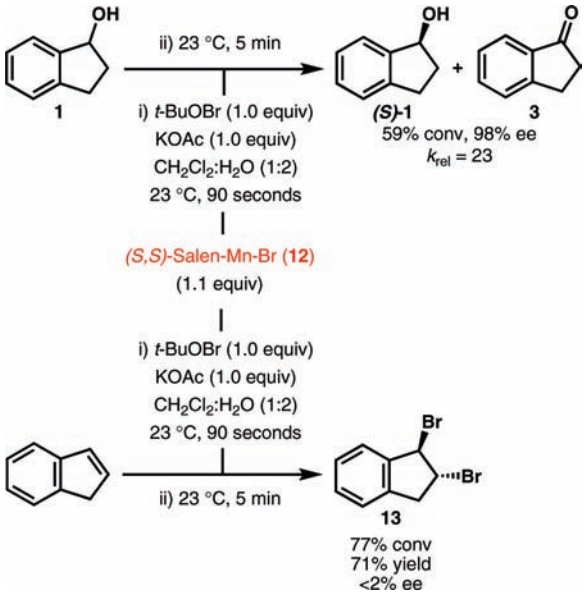
It should be emphasized that the Xia process for the enantioselective oxidation of secondary alcohols is biphasic with a $CH_2Cl_2$ layer and a water layer. The Mn(V)−salen catalyst and the PhI(III) oxidant are concentrated in the $CH_2Cl_2$ phase, as are 1-indanol and the product 1-indanone. Any bromide ion is concentrated in the aqueous phase, whereas $Br_2$ and HOBr are probably available in both the $CH_2Cl_2$ and water layers. Essentially all of the acetate ion buffer is in the water layer,[12] and for this reason among others, this species is unlikely to be involved in the oxidation itself. Furthermore, under the Xia conditions, acetate ion is not present and therefore cannot be involved in the transition state for secondary alcohol oxidation.

At the outset of this study, perhaps the most obvious pathway for enantioselective oxidation of secondary alcohols by the reagents Mn(III)−salen, KBr, and $PhI(OAc)_2$ under the conditions of Xia et al.[1] that would follow from our earlier mechanistic proposal for the Jacobsen epoxidation (Figure 1)[8] seemed to be the one summarized in Figure 2. Such a pathway involving abstraction of the carbinol C−H by the oxygen of a salen−Mn(V)−oxo complex with H bonding of the hydroxyl proton and one of the oxygens of the salen ligand can definitely be ruled out, as this process would lead to the wrong enantiopreference. As illustrated in Figure 2, such a model incorrectly predicts that (*S*)-1-indanol would oxidize in preference to (*R*)-1-indanol with (*S*,*S*)-Mn(III)−salen complexes, which is contrary to fact.

(12) See the Supporting Information for details.

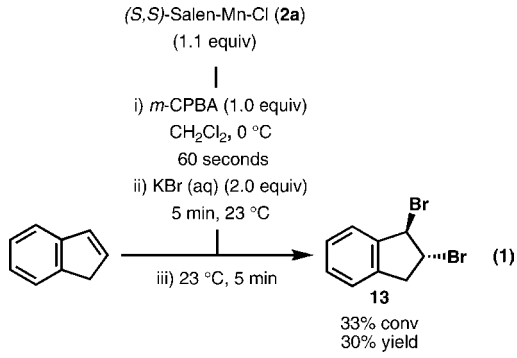
(13) It is recommended that HOBr be generated in situ from *t*-BuOBr in 1:2 $CH_2Cl_2/H_2O$ rather than from the previously described reaction of $Br_2$ and HgO in $H_2O$ because the yield of HOBr can vary with the latter procedure. For the preparation of HOBr from HgO and $Br_2$, see: Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; Wiley-Interscience: New York, 1999.

***Scheme 2.*** Stoichiometric Reactions with salen−Mn(III)−Br Complex **12**



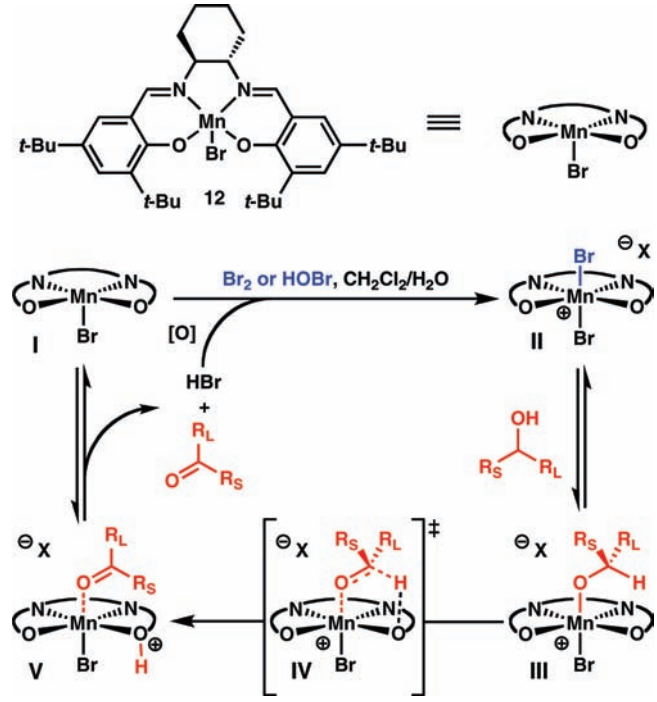

We have obtained strong evidence that any mechanism involving direct C−H abstraction by a Mn(V)−oxo complex is unlikely on the basis of the following observations: (1) under conditions that are conducive to formation of Mn(V)−oxo complexes (and epoxidation of olefins), enantioselective oxidation of secondary alcohols is inefficient and nonselective, since treatment of Mn complex **2a** (1.1 equiv) with *m*-CPBA[14] or PhIO[15] (1.0 equiv) in 1:2 $CH_2Cl_2/H_2O$ at 23 °C followed by addition of **1** (1.0 equiv) led to poor conversion and enantioselectivity (<25% conv, <10% ee);[12] (2) treatment of salen−Mn−Br complex **12** (1.1 equiv) with *t*-BuOBr (1.0 equiv) and KOAc (1.0 equiv) in 1:2 $CH_2Cl_2/H_2O$ (optimal conditions for enantioselective oxidation of **1**) converted indene to dibromide **13** rather than to the epoxide (<2% observed), as would be expected if a Mn−oxo complex were generated (Scheme 2).[16]

Further evidence against direct catalytic involvement of a salen−Mn(V)−oxo complex in the enantioselective oxidation of alcohols was obtained from an experiment showing that bromide ion is rapidly oxidized to $Br_2$ by the salen−Mn(V)−oxo species. Experimentally, the salen−Mn(V)−oxo complex was generated by reaction of the corresponding Mn(III) complex with 1.0 equiv of *m*-CPBA and then treated with 2.0 equiv of aqueous KBr. Addition of indene and isolation of indene dibromide as outlined in eq 1 established that bromide ion is indeed oxidized to $Br_2$ by the Mn(V)-oxo salen complex.




(1)

***Scheme 3.*** Plausible Catalytic Cycle




**Pathway for Enantioselective Mn−salen-Catalyzed Oxidation of Secondary Alcohols.** All of our data are in accord with a pathway in which HOBr or $Br_2/H_2O$ converts the Mn(III)−salen complex (**I**) into a brominated Mn(V)−salen species, such as $[salen-Mn(V)-Br_2]^+$ (**II**), which then reacts reversibly with the secondary alcohol to form the alkoxy complex $[salen-Mn(V)-Br-OR]^+$ (**III**) as the key reaction intermediate and precursor of the ketonic product, as shown in Scheme 3. We surmise further that the Mn(V)−alkoxide complex **III** is converted to the Mn(III) species **V** by intramolecular hydrogen transfer from the carbinol C−H to the neighboring phenolic oxygen along a five-membered cyclic pathway via **IV**. This cyclic pathway is reasonable because the electron lone pair density on one of the metal-bound phenoxy oxygens is properly oriented to facilitate the carbonyl-forming elimination process in a fashion analogous to the electrostatic effect of that oxygen in organizing the transition state and stabilizing the positive charge during the Jacobsen epoxidation of olefins, as pictured in Figure 1.[8] There is also an obvious analogy with the Westheimer chromate ester pathway for oxidation of secondary alcohols by Cr(VI) reagents.[17] The mechanism outlined in Scheme 3 is attractive because it provides a uniquely simple explanation for the absolute stereocourse of the Mn−salen-promoted enantioselective oxidation. Intermolecular processes for proton abstraction from the Mn(V)−alkoxide complex **III** (e.g., deprotonation by any $H_2O$ present in the $CH_2Cl_2$ layer) seems a highly unlikely alternative, as that would lead to a large number of geometrical paths for oxidation and provide no rational basis for the enantioselectivity. We do not rule out the

(14) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457–5460.
(15) Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 1718–1719.
(16) The identical reaction carried out in the absence of Mn complex **12** leads to a mixture of *trans*-dibromide, *cis*-dibromide, and *trans*-bromohydrin in a 33:17:10 ratio.
(17) Westheimer, F. H. *Chem. Rev.* **1949**, *45*, 419–451.

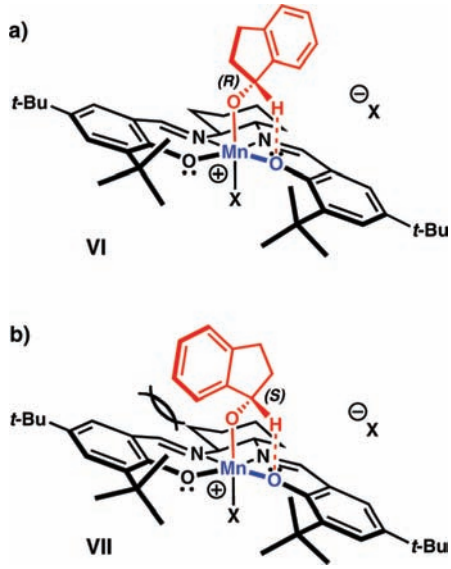



***Figure 3.*** Plausible pre-transition-state assemblies for the (a) favored and (b) disfavored modes of oxidation.

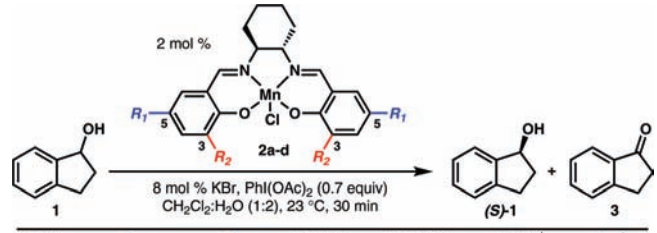
possibility that a water molecule may be involved in the formation of ketone from **IV**.

We have obtained evidence that the rate-limiting step of the oxidation involves C−H cleavage (**III** → **V**), as might be anticipated, and not alcohol−Mn(V) complexation (**II** → **III**). Measurement of the relative rates of oxidation of 1-deuterio-labeled 1-indanol and 1-indanol indicated a small but definite primary kinetic isotope effect, with $k_H/k_D = 2.7 \pm 0.6$.[12] Although this is below the values of $k_H/k_D$ generally observed for the Cr(VI)-mediated oxidation of secondary alcohols,[17] we believe that it is entirely consistent with expectations for a more exothermic process for the Mn(V) oxidation and an earlier, and bent, transition state.[18,19]

The above pathway involves the same canted (i.e., nonplanar) geometry for the Mn(V)−salen complex **III** as proposed recently for the Jacobsen epoxidation.[7,8] That canted conformation places one of the ortho *tert*-butyl groups above and one below the $N_2O_2$ ligand plane, with the further assumption that the hydrogen is transferred to that phenoxy oxygen with the proper orientation of the one electron pair acceptor.[20] Two possible stereoelectronically favorable pre-transition-state structures emerge, one for the *R* enantiomer and one for the *S* enantiomer (**VI** and **VII**, respectively; Figure 3). This model leads to the expectation that the oxidation of the *S* enantiomer (via **VII**) should be slower than the oxidation of the *R* enantiomer (via **VI**) because of the serious repulsive steric clash of the indanol aryl subunit in **VII** with the *tert*-butyl group next to the chelate ring.

In accord with this proposal was the finding that catalysts **2b** and **2c**, in which the proximate *tert*-butyl group (at C3) is

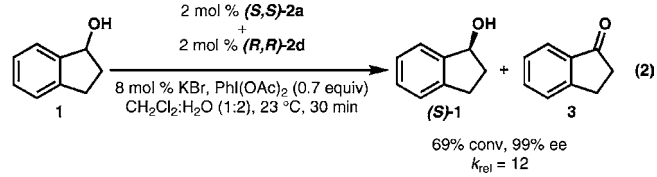
***Table 3.*** Effect of Catalyst Structure on the Efficiency of Enantioselective Oxidation




| entry | $R_1$ | $R_2$ | catalyst | conv (%)[a] | ee (%)[b] | $k_{rel}$[c] |
|---|---|---|---|---|---|---|
| 1 | *t*-Bu | *t*-Bu | **2a** | 68 | >99 | >13 |
| 2 | *t*-Bu | $CH_3$ | **2b** | 65 | 34 | 1.9 |
| 3 | *t*-Bu | H | **2c** | 67 | 50 | 2.6 |
| 4 | $NO_2$ | *t*-Bu | **2d** | 68 | 26 | 1.6 |

[a] Determined by $^1$H NMR (500 MHz) analysis of the unpurified reaction mixtures. [b] Determined by HPLC analysis with a chiral column. [c] $k_{rel} = \ln[(1 - \text{conv})(1 - \text{ee})]/\ln[(1 - \text{conv})(1 + \text{ee})]$.

replaced by $CH_3$ and H, respectively (see Table 3, entries 2 and 3), led to much-diminished enantioselectivity ($k_{rel}$ = 1.9−2.6). Further support for the mechanistic model came from the study of catalyst **2d** (Table 3) having nitro in place of *t*-Bu as a substituent at C5 of the benzenoid ring. As indicated in Table 3, entry 4, the effect of the change was greatly diminished enantioselectivity ($k_{rel}$ = 1.6) for catalyst **2d** relative to the standard catalyst **2a** (Table 3, entry 1).[8,21] This result is readily understandable on the basis of the internal proton transfer from carbon to oxygen that is shown in structure **VI**. Since the nitro substituent at C5 of the benzenoid ring of catalyst **2d** is para to the phenolic oxygen serving as the proton acceptor in **VI**, it markedly decreases the electron density at that oxygen and hence reduces the rate of the enantioselective pathway. Dramatic confirmation of this rate retardation was obtained in a competition experiment involving a 1:1 mixture of the *S*,*S* enantiomer of **2a** and the *R*,*R* enantiomer of catalyst **2d** (eq 2). As indicated in eq 2, the presence of an equimolar amount of the nitro-substituted catalyst **2d** had virtually no effect on the enantioselective oxidation of **1** by catalyst **2a**. Thus, it can be concluded that the effect of the nitro substituent in **2d** is to decrease the rate of oxidation of **1** as well as to negate the enantioselective pathway.[22]




Although our mechanistic model is not based on the X-ray crystal structure of the Mn(III)−alkoxide complex **14** (measured in this work[23]) or that of the Mn(IV)−alkoxide complex **15** (previously reported[24]), which appear in Figures 4 and 5,

(18) Small kinetic isotope effects ($k_H/k_D \approx 1.3$) for the carbinol C−H were observed in Pd-catalyzed oxidation of primary and secondary alcohols. These studies concluded that ketone formation was rate-determining. For example, see: Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005–7013.

(19) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265–273.

(20) The canted structure has been proposed for salen−Mn(V)−oxo complexes in the Jacobsen epoxidation (see refs 7 and 8). This conformation has been observed in X-ray crystal structures of both Mn(III)−and Mn(IV)−salen complexes (see ref 24); two examples are presented in Figures 4 and 5. The canted conformation of the Mn−salen complex forces the phenolic oxygen lone pairs to adopt pseudoaxial and pseudoequatorial arrangements.

(21) (a) Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem.—Eur. J.* **1996**, *2*, 974–980. (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948–954.

(22) We also examined briefly the effect of replacing the C5 *tert*-butyl substituent in catalyst **2a** by methoxy and found that there is very little change in the rate of oxidation and a modest decrease in enantioselectivity, which is not inconsistent with the similarity of the Hammett $\sigma$ constants (−0.20 for *t*-Bu and −0.27 for OMe). See: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

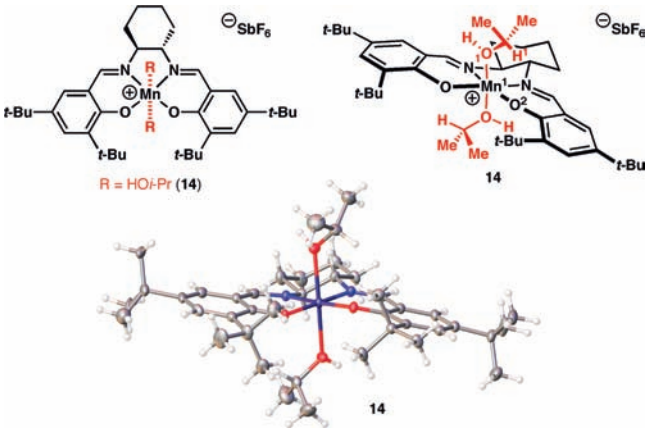



***Figure 4.*** X-ray crystal structure of Mn(III) complex **14**.[23] Selected distances (Å): $Mn_1-O_1$, 2.25; $H_1-O_2$, 2.59.

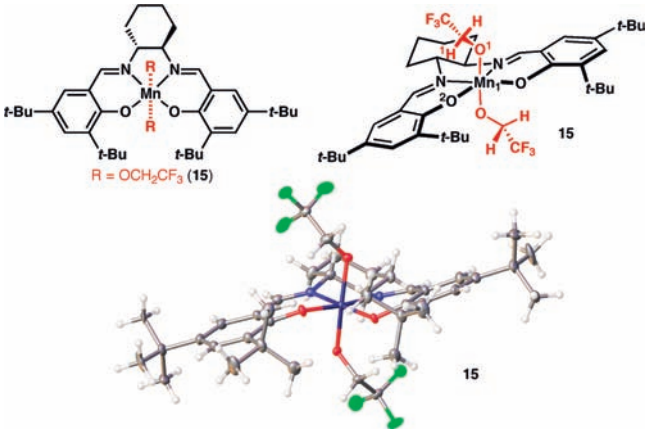



***Figure 5.*** X-ray crystal structure of Mn(IV) complex **15** (structure originally reported by Fujii and co-workers[24]). Selected distances (Å): $Mn_1-O_1$, 1.88; $H_1-O_2$, 2.22.

respectively, it is interesting to note that in each structure the alkoxy ligand is oriented with the carbinol C−H aligned over a phenolic oxygen, similar to the arrangement that we have proposed for the pre-transition-state assembly **VI** in Figure 3. This fact may be entirely coincidental but is nonetheless worth mentioning.

Although a priori it is not unreasonable that the enantioselective Mn−salen-mediated oxidation of secondary alcohols might involve a Mn(IV)−salen complex[25] and a Mn(IV) ⇄ Mn(II) redox cycle (as in the $MnO_2$ oxidation of secondary alcohols to ketones), experimental evidence argues against this possibility. In a typical experiment, it was found that the stoichiometric reaction of the Mn(II)−salen complex (0.50 equiv) and HOBr (0.50 equiv) in 1:2 $CH_2Cl_2/H_2O$ at 23 °C with **1** (1.0 equiv) was ineffective, as there was very little reaction and the recovered 1-indanol was racemic.[12]

## Conclusions

In conclusion, we have presented evidence to explain the mechanistic and stereochemical pathway for the enantioselective Mn−salen-catalyzed oxidation of racemic secondary alcohols reported by Xia et al.[1] The salient features of the proposed mechanism are as follows: (1) A positive bromine species is generated under the reaction conditions by oxidation of bromide ion with $PhI(OAc)_2$. (2) It is the positive bromine species that oxidizes the Mn(III)−salen complex to a Mn(V)−salen complex. (3) The most likely composition of the Mn(V)−salen complex is that of a dibromo-Mn(V) species (**II**, Scheme 3). (4) An additional effect of added bromide ion arises from its ability to reduce the salen−Mn(V)−oxo complex with formation of $Br_2$. (5) The dibromo-Mn(V) species **II** undergoes reversible ligand exchange with (±)-1-indanol as the substrate to generate a Mn(V)−alkoxy complex (**III**, Scheme 3). (6) Oxidation of the secondary alcohol occurs by intramolecular hydrogen transfer from carbon to a phenoxy oxygen of the salen ligand. (7) The stereochemical course of the enantioselective oxidation is easily rationalized by comparing the degree of steric repulsion in the structures **VI** and **VII** that are shown in Figure 3.

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**Supporting Information Available:** Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Solvent molecules and the counterion have been omitted for clarity. A second molecule of Mn complex **14** that exists in a helical conformation is present in the unit cell. See the Supporting Information for structural data.

(24) Kurahashi, T.; Hada, M.; Fujii, H. *J. Am. Chem. Soc.* **2009**, *131*, 12394–12405. The solvent molecule has been omitted for clarity.

(25) For references regarding Mn(IV)−salen complexes, see: (a) Fujiwara, M.; Matsushita, T.; Shono, T. *Polyhedron* **1985**, *4*, 1895–1900. (b) Law, N. A.; Machonkin, T. E.; McGorman, J. P.; Larson, E. J.; Kampf, J. W.; Pecoraro, V. L. *J. Chem. Soc., Chem. Commun.* **1995**, 2015–2016. (c) Asada, H.; Fujiwara, M.; Matsushita, T. *Polyhedron* **2000**, *19*, 2039–2048. (d) Campbell, K. A.; Lashley, M. R.; Wyatt, J. K.; Nantz, M. H.; Britt, R. D. *J. Am. Chem. Soc.* **2001**, *123*, 5710–5719. (e) Feth, M. P.; Bolm, C.; Hildebrand, J. P.; Köhler, M.; Beckmann, O.; Bauer, M.; Ramamonjisoa, R.; Bertagnolli, H. *Chem.—Eur. J.* **2003**, *9*, 1348–1359. (f) Kurahashi, T.; Fujii, H. *Inorg. Chem.* **2008**, *47*, 7556–7567. (g) Reference 24.