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Asymmetric Alkene Epoxidation with Chromium Oxo Salen Complexes. A Systematic Study of Salen Ligand Substituents

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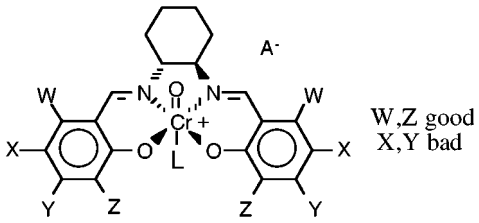
ABSTRACT



In the stoichiometric asymmetric epoxidation of *E*-*β*-methylstyrene with cationic chromium–salen oxo complexes, enantioselectivity is increased by halo-substitution at the 3,3′- and 6,6′-positions and decreased at the 4,4′- and 5,5′-positions on the salen rings. Addition of triphenylphosphine oxide significantly increases selection with 3,3′- or 5,5′-substituents but not with 4,4′- or 6,6′-substituents. Use of nitrate counterion is beneficial in most cases. The results are discussed with respect to the mode of stereoselection in metal–salen epoxidations.

The use of metal complexes of chiral salen ligands in asymmetric synthesis has been widespread in recent years.[1] Especially useful is the manganese−salen-catalyzed asymmetric epoxidation of conjugated *Z*-alkenes studied extensively by Jacobsen and Katsuki.[2] We have reported[3] on the use of the related chiral chromium salen complexes for both stoichiometric and catalytic asymmetric epoxidation of alkenes. We hoped to gain greater understanding of these epoxidation systems through study of the stoichiometric variant, which is available for the Cr series but not for the Mn series. In the event, with *β*-methylstyrenes as substrates, our system produced the first example[3a] of higher asymmetric induction in the case of a *trans*-alkene[4] (Scheme 1) over its *cis*-counterpart.

This was in stark contrast to results from both the Mn series,[2] and with metal−porphyrin complexes,[5] and called into question the accepted side-on approach model for the reaction.[5,6] To rescue the model we proposed[2a,7] an explanation based on the postulate that these Cr-complexes are nonplanar.[8−12]

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(1) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85−93.

(2) (a) Dalton, C. T.; Ryan, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Topics Catal.* **1998**, *5*, 75−91. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 18.2, pp 649−677. (c) Katsuki, T. in *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6B, pp 287−325.

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(4) For convenience, we refer to *E*- and *Z*-1,2-disubstituted alkenes as *trans*- and *cis*-alkenes, respectively.

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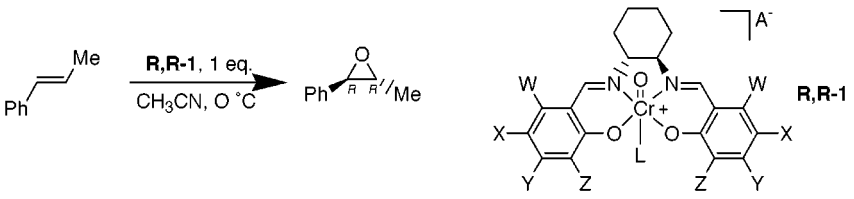
Scheme 1



Subsequently we found[3b] that enantioselectivity depended on the ligand L as well as the 3,3′-salen substituents (Z, Scheme 1). In the Mn series[2] bulky Z-substituents are essential for high ee but, again in contrast, we found[3b] that any Z-substituent was sufficient to induce high ee. Thus, for example, both F and ^{t}Bu give >80% with the best selection to date[3d] provided by trifluoromethyl (Scheme 1, Z = CF_3, L = Ph_3PO, A = NO_3) achieving an ee of 92%, the highest recorded for a *trans*-alkene using a metal-based reagent. We now report on the substituent effects on the salen ring focusing mainly on combinations which include the all-important Z-position and including a comprehensive study of the effect of one substituent at all of the positions. We believe that this is the first such study in metal−salen chemistry.[13] The effect of variations in the donor ligands will be the subject of subsequent papers.

Table 1 shows the results for the epoxidation[14] in Scheme 1 using our standard set of donor ligands L with both hexafluorophosphate and nitrate counterions A. Also included in Table 1 are some of our previously reported results for comparison. We concentrated on halogen substitution because electron-withdrawing groups (EWGs) are required for reasonable rates in the chromium series,[3a,15] and we were able to generate a substantial set of chloro substituents through the availability, in short synthetic sequences, of the required salicylaldehydes. The slower rates for complexes lacking EWGs can be clearly seen (entries 1, 19−21). The anomalous rate of the methoxy-substituted complex (entry 22) is due to its rapid decomposition under these conditions. Successful epoxidation requires a nonnucleophilic counterion[15] and we had previously[3] used hexafluorophosphate but we now find that nitrate gives better selectivity (entries

Table 1. Stoichiometric Asymmetric Epoxidation[a] of *E*-*β*-Methylstyrene According to Scheme 1 with Various Substituted Oxo-chromium(V)−Salen Complexes[b] in the Presence of Various Donor Ligands L[c]

	salen substituent[d]					enantiomeric excesses[e] for various L						
	W	X	Y	Z	time[f]	none	DMSO	DMF	PPNO[g]	Ph_3PO	Δee[h]	$\Delta\Delta G^{\ddagger i}$
1[j,k]	H	H	H	H	12 h	58	66	69	67	72	+14	1073
2				Cl	60 min	80	82[j,l]	78[j,k]	74[j,k]	85/88[m]	+5	715
3			Cl		60 min	61[m]	−	−	65[m]	66/68[m]	+5	546
4[j,k]		Cl			50 min	58	69	70	75	71	+13	983
5	Cl				2 h	72/69[m]	75/78[m]	74	77	74/80[m]	+2	195
6[n,o]			Cl	Cl	60 min	69	−	−	−	70	+1	88
7[j,k]		Cl		Cl	60 min	67	81	79	50	83	+16	1651
8	Cl			Cl	15 min	75	75	75	56	82	+7	835
9[o]		Cl	Cl		60 min	59	−	−	−	61	+2	142
10[o]	Cl	Cl			60 min	68	−	−	−	69	+1	85
11[k]	Cl	Cl		Cl	10 min	68	70	71	41	72	+4	356
12[j]	Cl	Cl	Cl	Cl	5 min	48	−	−	−	62	+14	884
13[j,k]				F	60 min	70	−	−	85	86	+16	1864
14[j,k]		F		F	30 min	71	78	80	89	83	+12	1317
15[j]		Br			10 min	58	69	70	75	71	+13	983
16				Br	5 h	79/81[m]	−	−	−	84/86[m]	+5	680
17		Br		Br	10 min	71/63[m]	69	70	49	79/77[m]	+8	836
18[j]		I		I	12 h	55	56	62	−	75	+20	1551
19[j]			NEt_2		1 d	33	31	30	24	40	+7	354
20[j,k]				Me	2 d	78	−	77	70	82	+4	488
21	Me			Me	2 d	nr	−	−	−	80/80[m]		
22[p,q]				OMe	10 m	49[k]/67[m]	−	−	−	58[k]/66[m]	+9	616

[a] Procedure (CAUTION) as described in note 14, all at 0 °C in acetonitrile, unless noted otherwise, yields 5−40%, remainder unreacted alkene and minor amounts of benzyl methyl ketone, benzaldehyde, and diol. [b] Prepared as described in ref 3d, hexafluorophosphate counterion (A = PF_6), unless noted otherwise. [c] 1 equiv used. [d] Unspecified substituents are H. [e] ee determined by chiral GC, note 14. [f] Time to discharge of green Cr(V) color to orange Cr(III). [g] 4-Phenylpyridine *N*-oxide. [h] Δee = (ee with Ph_3PO − ee without Ph_3PO). [i] $\Delta\Delta G^{\ddagger}$ (J mol^{-1}) = $RT \ln K_{TPPO} - RT \ln K_{none}$ where K = (% major enantiomer/% minor enantiomer). [j] At −10 °C. [k] Previously reported by us, see refs 2a,3a,b. [l] Incorrectly reported as 78 in ref 3b. [m] Nitrate counterion (A = NO_3). [n] Complex has very low solubility and gave results less reproducible than with others, ±3% ee, yield <5%. [o] In dichloromethane. [p] At 20 °C. [q] Complex decomposes rapidly under the reaction conditions.

2, 3, 5, 16, 22) although this is not always so (entries 17, 21).

Introduction of a chloro substituent in the Y-position causes either no change or a reduction in selectivity (entries 1/3, 2/6, 4/9, 11/12). Similarly, a halogen at the X-position is either irrelevant or detrimental (compare entries 1/4, 2/7, 3/9, 5/10, 8/11, 13/14, 1/15, 16/17). This was also observed in our previous comparison of *tert*-butyl substitution at X and Z.[3a,b] Substitution at the W-position has mostly a positive influence in the absence of a Z-substituent (compare 1/5, 4/10). However, W- and Z-substitution are not cooperative, the ee being a composite of the two contributing mono-substituents (compare entries 2/5/8, 7/10/11, 20/21). In the presence of L = Ph_3PO, the larger halogen substituents have an increasingly negative effect on ee (compare entries 2/13/16, 7/14/17/18), although this is less clear with no L. Introduction of groups electron donating by resonance appears to be very detrimental (entries 19 and 22), but there is not enough data for conclusive analysis.

The effect of the donor ligands L is in line with our previous findings.[3b] Triphenylphosphine oxide is the best-behaved ligand, being most consistent in raising the ee (up to 20%). DMF and DMSO usually have similar effects although the elevation is less. However 4-phenylpyridine *N*-oxide is more capricious, lowering ee dramatically (entries 7, 8, 11, 17) or giving the highest for some complexes (entries 4, 5, 14, 15).

There is also interplay between the salen substituents and L. The last column in Table 1 shows the increase in the free energy difference between the transition states leading to the enantiomers ($\Delta\Delta\Delta G^{\ddagger}$) on addition of triphenylphosphine oxide. We have previously[2a,3d] noted, for ligands with a Z-only substituent, that the more enantioselective the system is without L, the less the benefit derived on addition of L. We termed this a "ceiling effect", and it is also apparent here (entries 2/13/16/20, counter example 22). We speculated[3d] that increased stereoselection in the system is due to the attainment of a conformation which is promoted both by Z-substitution and by the donor ligand L, with the latter less effective. In complexes with suitable Z, the conformation without L reaches an optimum, and the effect of L is thus minimal. Finally a loose generalization about W−Z versus L can also be made from Table 1: addition of triphenylphosphine oxide appears to be most beneficial to stereoselection when X and Z or both are substituted (entries 2/4/7/13/14/15/16/1718, counter examples 20/22) while the least benefit accrues when W and Y are substituted (entries 3/5/19) with mixed X−Z/W−Y cases intermediate or worse (entries 6/8/9/10/11/12).

These results have implications for the mode of stereoselection in epoxidation using metal-salen complexes. In the manganese series, and within the side-on approach model, essentially all possible alkene trajectories to the oxo-complex have previously been used as a basis for explaining enantioselectivity.[2a] Thus Jacobsen,[2b] assuming a flat salen geometry, considers alkene approach to the metal-oxo bond along either of pathways a or b (Figure 1). Which one occurs

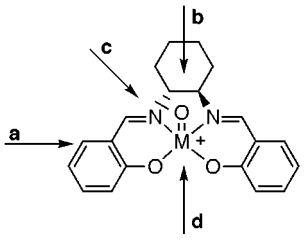


Figure 1. Approach trajectories.

depends on the nature of the imine bridge and on the presence or absence of large groups at the X-position, pathway b applying to the tetra-*tert*-butyl catalyst (Jacobsen's Catalyst). Early on in the development of this area, Katsuki[16] proposed approach c to explain a number of results that were not adequately accommodated by pathway b. He was also able to retain this pathway c when he proposed[10] the nonplanar geometry of the complex. It is more difficult to retain pathway b in a nonplanar geometry because the most commonly proposed deviation from planarity is the stepped conformation, Figure 2 and in it pathway b suffers from some

(8) Previously, Norrby, Linde, and Åkermark[9] had proposed a nonplanar salen ligand in their putative oxametallocylic intermediate for epoxidation in the manganese series. Subsequently, both Katsuki and co-workers[10] and Houk and co-workers[11] adduced evidence for nonplanar manganese salens; the latter on the basis of a reexamination of crystal structures of manganese(III)−salen complexes in the Cambridge Structural Database. The former also called attention to nonplanar crystal structure data to explain the striking effects of certain chiral ligands on epoxidations using achiral manganese−salen complexes. Recently, high level calculations by Plattner, Wiest, and co-workers[12] on these systems have revealed a great amount of detail about the exact nature of the distortions from planarity.

(9) Norrby, P. O.; Linde, C.; Åkermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 7, 11035−11036;

(10) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515−530; Hashihayata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079; Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541−9552; Miura, K.; Katsuki, T. *Synlett* **1999**, 783−785.

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(12) (a) Plattner, D. A.; Feichtinger, D.; El-Bahraoui, J.; Wiest, O. *Int. J. Mass Spectrom.* **2000**, *195/196*, 351−362; (b) El-Bahraoui, J.; Wiest, O.; Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2073−2076.

(13) In addition to the known importance of the Z-position (ref 2), Jacobsen and co-workers have studied comprehensively substitution at the X position: Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948−954 and references therein.

(14) Experimental procedure: CAUTION! Cr(V)═O species are known carcinogens, all complexes were generated in situ. Chromium(III)−salen complex (40−60 mg, 1 equiv) in acetonitrile (3 mL) was treated with iodosylbenzene (1.2 equiv), the resulting green solution filtered after 10 m, treated with donor ligand L (1 equiv), cooled to 0 °C, treated with *E*-β-methylstyrene (9−12 μL, 1 equiv), and left until an orange color persisted. After evaporation and short path chromatography (alumina, Et_2O), analysis was by csp GLC on a Supelco α-cyclodextrin capillary column with *n*-decane as internal standard. Product configuration was determined and precursor chromium(III)−salen complexes prepared as described previously (ref 3d).

(15) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, 107, 7606−7617.

(16) Hosoya, N.; Hatakeyama, A.; Yanai, K.; Fujii, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 641−645. Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479−481.

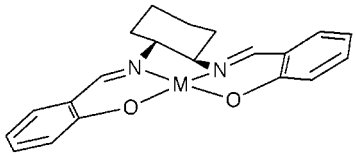

Figure 2. Stepped conformation of metal−salen complexes.

uncomfortable steric interactions. Using his analysis Katsuki made a number of predictions as to the selectivities to be expected with certain complexes, which were borne out when the complexes were synthesized.[17] A completely different view was taken by Houk[11] who proposed a nonplanar complex approached by pathway d. An attractive aspect of his analysis was that it unified the explanations of the selectivities given by complexes with different imine bridges.

For the chromium system, we have favored[2a] approach d to the stepped conformation of the complex (Figures 1/2). First, we had to postulate a nonplanar geometry, and we assumed that the deviation from planarity was greater in the chromium series than for manganese, explaining the better results for *trans*-alkenes than their *cis*-counterparts. Then the highly influential nature of the substituents at Z suggested that they had more than a simple blocking role. Finally, when molecular models are examined there is a natural pathway of approach for a *trans*-alkene along d, which favors high enantioselection for the observed enantiomer. However, in the light of the results reported here, we feel that it is likely that an approach along c similar to that suggested by Katsuki,[16] and which also gives the correct sense of stereoselection, may also be in operation. This is because of the slightly beneficial effect of W-substituents, which is not additive to the beneficial effect of Z-substituents. This would suggest that changes at the two different positions might independently affect two different approaches. For example, approach along c might be favored by Z-substitution while that along d is favored (to a lesser extent) by W-substitution, substitution at X and Y would then have little effect as observed. However we must also remember that substitution, especially by large groups at Z, will have an effect on the degree of nonplanarity of the complex, which in turn influences selection.

The effects of ligand L also bear on the degree of nonplanarity as well as on the rate of the reaction. We have previously speculated[2a] that the effects of both L and the salen substituents are to cause an increase in nonplanarity with the latter being more effective, hence the existence of a ceiling effect. In a recent theoretical study, Wiest, Plattner, and co-workers[12b] have examined the effect of amine oxide as basal ligand in detail and have quantified its influence in the manganese series. They find that indeed the basal ligand increases the degree of nonplanarity, but this effect is electronic in nature rather than steric and the degree of nonplanarity is different for different spin states of the complex. In the chromium series, this is hard to reconcile with our observations of an interplay of the influence of L and the substituents W−Z, especially the absence of much effect when W and Y are substituted. We are presently exploring further the influence of the ligand L and will report on our findings in due course.

In summary we have shown that enantioselectivity in epoxidation using oxo-chromium salen complexes depends on the identity of substituents at all of the positions on the salen rings. We have also delineated how the importance of each position is affected by added ligand L. This complex set of relationships must be accommodated by any theory of stereoselection for these types of system.

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