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Chromium Salen Catalysed Asymmetric Alkene Epoxidation. Influence of Substituents at the 3,3'-positions on the Salen rings.

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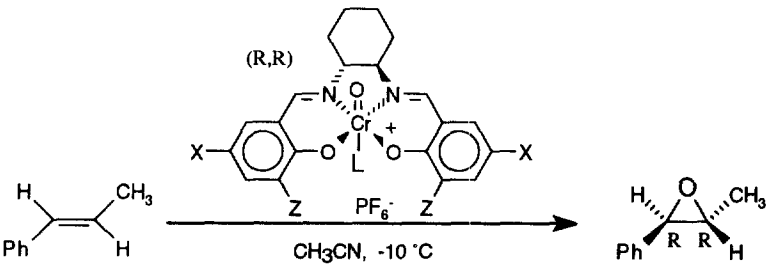
Abstract: Any substituent at the 3,3'-positions is sufficient to give greater than 80% ee in the epoxidation of *E*-β-methylstyrene with chromium-salen complexes.

We have previously reported[1,2] on the use of chiral non-racemic chromium salen complexes for both stoichiometric and catalytic asymmetric epoxidation of alkenes. With the β-methylstyrenes as substrates, this system provided the first example of consistently higher asymmetric induction for the *E*-isomer than the *Z*-isomer, our highest ee (83%) being achieved with the 3,3',5,5'-tetrachloro-substituted complex in stoichiometric mode, Scheme 1 (X=Z=Cl, L=Ph_3PO). In catalytic mode (5-10% complex, PhIO as terminal oxidant) ees were slightly lower, showing the value of being able to study the stoichiometric reaction. In most cases the presence of a second oxo-containing ligand (donor ligand, L) such as triphenylphosphine oxide or pyridine-*N*-oxides was found to be significant, changing the ee attainable by up to 30%.



Scheme 1

The greater induction in the case of the *E*-isomer was in stark contrast to results both from the manganese series,[3] and with metal-porphyrin complexes,[4] and called into question the standard side-on approach model[4,5] for alkene epoxidation with metal oxo compounds, Figure 1(a,b). To rescue that model our initial working hypothesis[2] was that the oxo-chromium salen complex should be bent,[6] Figure 1(c). In such a complex one oxygen of the salen ligand has moved out of the salen plane to occupy an apical position. We have since modified that view in the light of our own results from unsymmetrical salen complexes[7] and of proposals from the groups of Katsuki[8] and Houk[9] who showed that the catalyst could simply be twisted rather than fully bent.[10]

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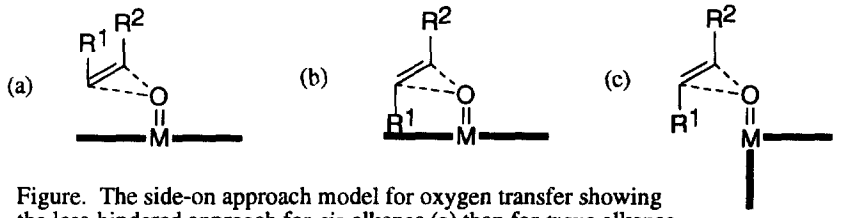

Figure. The side-on approach model for oxygen transfer showing the less-hindered approach for *cis*-alkenes (a) than for *trans*-alkenes (b) and the simplest modification (c) to allow *trans*-alkene approach.

Since our initial report we have embarked on a comprehensive study of factors which might influence the asymmetric induction in this system and we record here the first of our findings. Our starting point was indicated by the results recorded in studies with the analogous manganese complexes wherein great importance was discovered for the 3,3'-positions on the salen rings. Thus Jacobsen and co-workers[3,11] noted that bulky substituents (e.g. ^{t}Bu) at these positions were essential for high ee. Katsuki and co-workers also noted that the same positions were especially important in the epoxidation of *trans*-substrates,[12] even to the extent that the introduction of 3,3'-chirality could outweigh the chirality on the ethylene diamine bridge.[13] The results of our study into the importance of these 3,3'-positions in the stoichiometric asymmetric epoxidation of *E*-β-methylstyrene are given in Table 1.

Table 1 Stoichiometric asymmetric epoxidation[a] of *E*-β-methylstyrene according to Scheme 1 with various 3,3'-substituted oxo-chromium(V) salen complexes in the presence of various donor ligands.

Ligand	**Enantiomeric excess[c] and yields[c] (in italics) for various Z[d]**									
L[b]	**H[e]**	**OMe[f]**	**Me**	**^{t}Bu**	**Ph**	**Bz**	**Cl**	**F**	**Cl,Cl[e,g]**	**F,F[h]**
none	58	49 *6*	78 *8*	84 *16*	66 *12*	74 *11*	80[i] *27*	70 *39*	67	71 *41*
Ph_3PO	72	58 *17*	82 *12*	79 *17*	85 *14*	82 *15*	86 *43*	86 *45*	83	83 *46*
4-PhpyNO[j]	67	52 *9*	70 *10*	70 *19*	69 *12*	80 *10*	74 *23*	85 *16*	50	89 *14*
DMF	69	57 *9*	77 *14*	78 *13*	77 *15*	74 *9*	78 *48*		79	80 *48*
DMSO	66			79 *11*	76 *11*	72 *12*	78 *8*		81	78 *46*
Time[k]	12 h	10 m	2 d	7-10 d	2 d	2 d	30 m	1 h	1 h	20 m

[a] Procedure (CARE) as described in note 14, all at -10 °C, unless noted otherwise; [b] 1 eq. used; [c] ee/yield determined by chiral GC, see note 14; [d] X=H, unless otherwise noted; [e] from ref. 1; [f] at room temperature, donor ligand and alkene added before iodosylbenzene; [g] X=Cl; [h] X=F; [i] result obtained by Dr. I. Langan; [j] 4-phenylpyridine-*N*-oxide; [k] time to discharge of green colour to orange.

The most general observation from Table 1 is that, in the presence of suitable donor ligands L, almost any substituent at the 3,3'-positions is sufficient for enantiomeric excesses ≥80% with the exception being a methoxy substituent. This is in notable contrast to the manganese series where only bulky substituents are effective.

The next observation is that there are significant rate differences between the different complexes. Reactions with the halogen-substituted cases are all over in less than 1 hour whereas alkyl-substitution increases the reaction time greatly to days and even a week in one case (^{t}Bu). That electron deficient complexes react fastest is not surprising since the reaction mechanism involves an electrophilic attack of chromium on the alkene.[10] On this basis the methoxy-substituted complex seems anomalous. However the reaction time of 30 minutes is

misleading in this case, because in fact this complex has been found to be very unstable and readily decomposes in a matter of minutes. It did react sufficiently however to determine the enantiomeric excess. The best yields are also obtained with the halogen substituted catalysts and we ascribe this to the reaction rate with alkene - the slower this is, the more that decomposition of complex intervenes. Consistent with this is recovery of significant amounts of alkene in the alkyl-substituted cases. Indeed the lower yields in Table 1 mainly reflect the presence of unreacted alkene. Other products present in small amounts include the diol and benzyl methyl ketone. The former derives from acid catalysed hydrolysis while the latter is a known side-product in this type of reaction[10,15] derived either from rearrangement of the cationic reaction intermediate or by Lewis acid catalysed epoxide rearrangement.

Turning to the effect of the added ligand L, we find that triphenylphosphine oxide is the best behaved ligand in that it is most consistent in raising the ee, in many cases by 10-20% with one exception (^{t}Bu). DMF shows a similar pattern although the elevation is less in this case (0-10%), again with ^{t}Bu an exception. DMSO is similar. However 4-phenylpyridine-*N*-oxide is more capricious in that it lowers ee by as much as 14% in some cases, has little effect in others and with fluorine substituents raises ee by as much as 18% leading to our highest ee to date (89% with 3,3',5,5'-tetrafluoro-substitution). Unfortunately in these latter cases the yields are also reduced. Reaction times for various L do not differ greatly but all are slightly (10-20%) faster than the case of no ligand.

Table 2 Catalytic asymmetric epoxidation[a] of *E*-β-methylstyrene using Cr(III) salen complexes with iodosylbenzene as stoichiometric oxidant at room temperature.

Entry	Complex	L (1 eq)	time[b]	% ee[c]	Stoichiometric limit[d] at -10 °C	yield[c]
1	Z = Cl	Ph_3PO	3 h	79	86	71
2	Z = Cl	DMF	3 h	74	78	62
3	X, Z = F	none	2 h	63	68	46
4	X, Z = F	Ph_3PO	2 h	74	83	65

[a] Procedure as described in note 14, all at room temperature; [b] Time for reaction mixture to turn completely orange; [c] EE and yield determined by chiral GC as described in note 14; [d] from Table 1.

The stoichiometric results in Table 1 are also reflected in the catalytic version of the reaction (Table 2) in which the rates are reduced but the selectivities are maintained. The amount of rate reduction is consistent with the lower concentration of chromium species. In some cases the oxoCr(V) salen complexes was also be used as the catalyst with the same results. Thus, for example, with the dichloro-substituted catalyst (Table 2, entry 1), the best ee achieved was 86% in the stoichiometric reaction (at -10 °C) which is approached at 80% ee in the catalytic reaction (at room temperature). A similar difference is observed with DMF acting as donor ligand (entry 2). These are only slight differences but greater differences are observed with other catalysts, e.g. 9% ee with the tetrafluoro-substituted case, and with Ph_3PO as donor ligand (entry 4). Even allowing for temperature differences between the two reactions, there appears a slight discrepancy between stoichiometric and catalytic reactions, which we are currently investigating. One immediately obvious possibility would be some kinetic resolution from Cr(III) salen promoted ring-opening[16] but this was discounted by control reactions on racemic epoxide. The terminal oxidant, iodosylbenzene, does not cause epoxidation in the absence of catalyst and its addition in either 10 small portions or in a single addition does not result in any difference in ee. It is also gratifying that yields are much improved with the catalytic reactions. This difference can be attributed to the lower concentration of the Lewis acidic chromium complex with a concomitant reduction in the rate of ring

opening to diol. It also appears that the addition of donor ligand results in a decrease in the Lewis acidic nature of the complexes, facilitating higher epoxide yield (Table 2, entries 3/4).

Finally we comment on the recyclability of the chromium salen complexes which is again in stark contrast to the manganese series. Thus in either stoichiometric or catalytic mode, addition of ether at the end of the reaction returns a high yield of complex which has a similar infrared spectrum and gives the same ee in subsequent reaction. Interestingly somewhat better yields and faster reaction are obtained with the recycled catalyst which we believe may be due to the purification[17] of the complex during the recycling process.

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14. Experimental procedure: CARE - Cr(V)=O species are known carcinogens and, except where noted otherwise, all complexes were generated *in situ*. Stoichiometric oxidation: oxochromium(V)salen hexafluorophosphate complex (40-60 mg, 1 eq.) in acetonitrile (3 ml) was treated with donor ligand L (1 eq.), the resulting dark green solution cooled to -10 °C, treated with *E*-β-methylstyrene (9-12 µl, 1 eq.) and left until an orange colour persisted. After evaporation and short path chromatography (alumina, Et_2O), analysis was by glc on a Supelco α-cyclodextrin capillary column with n-decane as internal standard. Catalytic oxidation: a mixture of alkene (0.43 mmol), donor ligand L (0.043 mmol) and Cr(III)salen hexafluorophosphate complex (0.043 mmol) in acetonitrile (3 ml) was treated at room temperature with iodosylbenzene (0.43 mmol) and worked up as above.
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17. It is an understatement to say that these complexes do not crystallise well. So in common with all previous workers in this area (very few of whom have recorded analytical data) we have found it extremely difficult to prepare analytically pure material. We estimate that our initially prepared complexes are contaminated with 2-5% of presently unidentified material.