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Chromium Catalysed Asymmetric Alkene Epoxidation. Greater selectivity for an *E*-alkene versus its *Z*-isomer.

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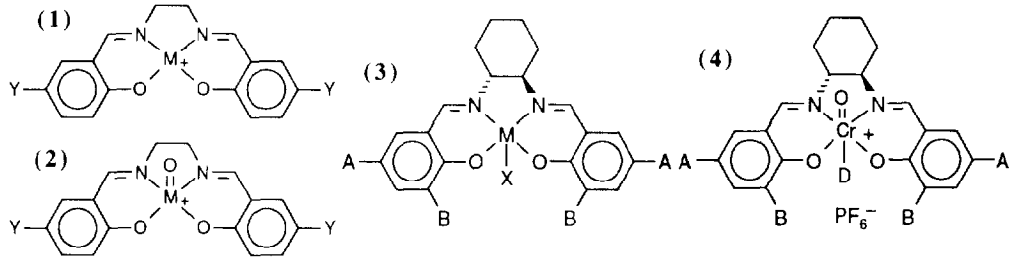
Abstract: *E*-β-methylstyrene can be asymmetrically epoxidised stoichiometrically with up to 83% ee and catalytically with up to 77% ee by chiral chromium complexes in the presence of phosphine oxides, DMSO or DMF. In all cases the analogous reaction with *Z*-β-methylstyrene gives lower ee.

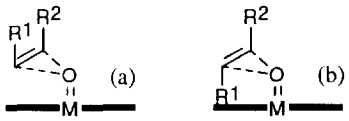
The catalytic asymmetric epoxidation of isolated alkenes has been an important goal of synthetic chemistry since the landmark work of Sharpless[1]. The many catalysts reported since then are mainly based on either metal-porphyrin or metal-salen complexes[2]. In the latter case Kochi and co-workers[3,4] have provided most of the background detail in their studies of the kinetics and mechanism of epoxidation by the achiral chromium and manganese compounds (**1**: M=Cr,Mn; Y=H,Cl,OMe,NO_2) with iodosylbenzene as oxygen source. They showed that the active species in both cases was probably the metal oxo salen complex (**2**) but only in the chromium case was this species isolable. The use of bleach as stoichiometric oxidant (attractive industrially) was developed for metal-porphyrin catalysts by Meunier[5a] and applied to metal-salen catalysis by Burrows[5b].



Chiral metal-salen complexes were known[6] and had been assayed for catalytic hydrogenation but their first use for catalytic asymmetric oxidation seems to have been the vanadium catalysed oxidation of sulphides using catalyst (**3**: M=V(IV), X=(=O), A=H, B=H,^{t}Bu,OR) reported by Fujita[7]. Later Nishinaga[8] reported the use of similar cobalt-based catalysts for styrene oxidation but it was not until Jacobsen[2,9] and subsequently Katsuki[10] reported the chiral manganese-salen catalysts (**3**: M=Mn(III), X=Cl, A=B=^{t}Bu[2,9]; A=H, B=CHEtAr[10]) that significant success was achieved in catalytic asymmetric alkene epoxidation. Subsequent reports by other workers disclosed related systems[11]. Much development work has since been reported by Jacobsen[2b] who has shown that the epoxidation of certain *cis*-disubstituted alkenes can be achieved with high ee in a preparatively useful system with bleach as the oxygen source. Recently he has ingeniously shown how *trans*-epoxides can be generated with high ee starting with the *cis*-alkenes[12].

That *cis*-alkenes showed the best enantioselectivity in epoxidation was not considered surprising because this had been invariably found for the porphyrins and is traditionally explained by the operation of the side-on approach mechanism[2,10c,12] wherein there is a less hindered approach for the *cis*-alkene (Figure). This idea, originally proposed by Groves[13], has become a useful working model in the design of transition metal-based epoxidation catalysts[2a]. Moderate ees have been achieved in the epoxidation of *trans*-alkenes, notably by Katsuki[14], but in relevant cases the *cis*-isomer still gives a higher selectivity. Thus the epoxidation of *trans*-alkenes with high ee remains a challenging problem and indeed it has been speculated[12] that this may never be possible for catalysts bearing salen, porphyrin and related tetradentate ligands, if the side-on approach mechanism is indeed in operation.

Figure. The side-on approach model for oxygen transfer showing the less-hindered approach for *cis*-alkenes (a) than for *trans*-alkenes (b)



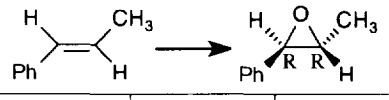
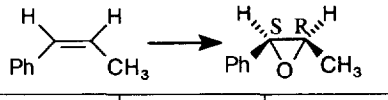
We were particularly interested in chromium-salen catalysed epoxidation because: (i) the stoichiometric variant of the reaction gives a rare opportunity to study stereoselection in a catalytic process in the absence of factors related to the catalytic cycle; (ii) the chromium mechanism is completely different to manganese (electrophilic vs. radical - *vide infra*) with rates for *trans*-alkenes greater than *cis* and with better diastereoselectivity[15]; (iii) additives powerfully affect the rates and product mix which calls to mind the concept of *ligand accelerated catalysis* [16] so that if the additive were chiral, better selection might be possible; (iv) Kochi[3] had shown that, as well as amine oxides, sulphoxides and amides, phosphine oxides are beneficial additives in the chromium series which fitted into our ongoing general survey of the generation and uses of P-chiral phosphorus compounds for catalytic asymmetric synthesis[17]. Very recently Jacobsen has reported the use of chromium-salen complexes as catalysts for ring-opening of epoxides[18]. However herein we now report that such complexes can epoxidise a *trans*-alkene with a promising selectivity which is greater than that obtained for the related *cis*-isomer.

The first difficulty which must be addressed when examining the chromium series is that rates are slow with the unsubstituted salen ligand complexes and essentially only alkenes which are electron rich can be epoxidised, the reaction mechanism being an electrophilic attack of chromium on the alkene[3]. Therefore our starting point was to make and test chromium-salen complexes (**4**) with electron withdrawing substituents in the hope of speeding up the reaction. It was therefore very gratifying when we found that not only did the reaction speed up but also significant levels of enantiomeric excess (ee) could be achieved in the epoxidation of *trans*-alkenes. Some of our initial results for stoichiometric epoxidation of β-methylstyrene are shown in the Table and it can be seen that in all cases the ee for the *E*-isomer exceeds that of the *Z*-isomer with the best result being 83% ee from the combination of tetrachlorosalen and triphenylphosphine oxide ligands[19]. In the corresponding catalytic reaction[20] with iodosylbenzene as stoichiometric oxidant the same ligand/additive combination approaches this limit at 77% ee, the highest reported so far for this substrate. For comparison to the manganese series we found that (**4**: A=B=^{t}Bu, D=Ph_3PO) gave 71% ee in the stoichiometric epoxidation of *E*-β-methylstyrene. It is also noteworthy that the profile of product configurations is different from the manganese series; thus *R,R*-Cr complex gives 1*R*,2*R*-1-phenylpropylene oxide from *E*-β-methylstyrene (same as Mn-analogue) but 1*S*,2*R*-1-phenylpropylene oxide from *Z*-β-methylstyrene (opposite to Mn-analogue).

It can also be seen from the Table that the nature of the donor ligand D is very significant, changing the ee attainable by up to 30%. This has been previously observed in the manganese series[2,10b,12c] with *N*-oxide as

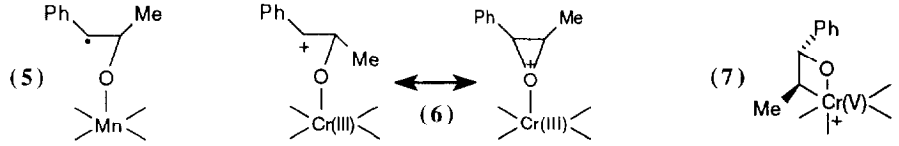
additive. However it can be seen that, at least for β-methylstyrene, *N*-oxide was found by us to be detrimental while other double-bonded oxygen species are beneficial[21]. In preliminary studies we also tried bleach as stoichiometric oxidant but found that the ees obtained were poorer (20-50% for *E*-β-methylstyrene). We believe that this may be related to the presence of chloride ion, the addition of which was found to cause decomposition of Cr(V)-oxo species (**4**)[22]. This shows the value of being able to separately study the stoichiometric reaction.

Table. Enantiomeric Excesses[a] in the Stoichiometric Epoxidation[b] of *E*- and *Z*-β-Methylstyrene with *R,R*-(**4**)

						
Ligand D	**A,B=H**	**A=Cl,B=H**	**A,B=Cl**	**A,B=H**	**A=Cl,B=H**	**A,B=Cl**
none	58	58	67	26	33	43
Ph_3PO	72	71	83	27	35	56
DMSO	66	69	81	28	35	50
DMF	69	70	79	28	36	55
pyridine-*N*-oxide	68	74	50	31	37	40

[a] All ees measured directly by chiral gc and in most cases determined for both enantiomers of salen ligand. Products configurations determined by comparison of elution orders with enantiomerically enriched samples of known absolute configuration[9b].

[b] Reactions performed in CH_3CN at 0°C with 2 eqv of D, 10 eqv of alkene; yields: 65-80%; <0.5% of *cis*-epoxide was detected in the oxidation of *trans*-alkene and up to 12% of *trans*-epoxide was obtained from *cis*-alkene.



Turning to the mechanism of stereoselection, we feel it premature to speculate freely with the present relatively restricted degree of variation in the chromium coordination sphere but it is undoubtedly different to that operating in the manganese analogues. This is not very surprising to us since Kochi[3,4] has shown convincingly that chromium oxidation is a polar process, electrophilic at Cr, while manganese is a radical process. In particular our observations that the *trans*-alkene gives the better selectivity and the selectivity profile is different must call into question the usefulness of the side-on approach model in the case of chromium. Likely initial intermediates (**5**) for manganese have been identified by both Kochi[4] and Jacobsen[2b] for conjugated alkenes while Jacobsen[2b] suggests a concerted mechanism for isolated alkenes. On the other hand Kochi[3] has identified (**6**) as a likely initial intermediate for the chromium case while acknowledging the possibility of a [2+2] cycloaddition process of the kind first suggested by Sharpless[23] which would give oxametallocycle (**7**), or a similar hexacoordinated species, formed on temporary loss of ligand D. We are very much in sympathy with this latter suggestion which brings the reacting centres close to the source of chirality and we note that Masnovi[24] has adduced some evidence for the intervention of such species in the reaction of chromium(V)-oxo-salen complexes with alkynes. However we stress again that our investigations are at a very early a stage.

In summary we have found that chromium-salen complexes may be useful in the catalytic asymmetric epoxidation of *trans*-alkenes and we will report soon on efforts in our group to raise the attainable ees.

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15. Unlike Mn, Cr epoxidation of a *trans*-alkene results in a *trans* epoxide with <0.5% of the *cis* isomer.
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19. Reaction is complete in <1 min, and, as expected[3], reaction rates with *trans*-alkene are faster than with *cis*.
20. Using 10% of deoxy-(**4**) with portionwise addition of iodosylbenzene.
21. This is not a general effect however as we have found the reverse to be true for other substrates.
22. In addition the phosphate buffer used may be acting as donor ligand D.
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