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Unsymmetrical Salen Ligands: Synthesis and Use in Chromium Mediated Asymmetric Epoxidation

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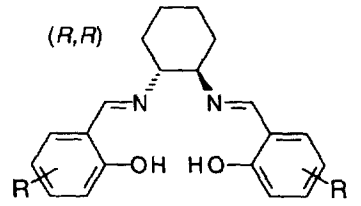
Abstract: Chiral non-racemic salen ligands with two different salicylidene moieties can be synthesised *via* trapping of the intermediate mono-salicylidene using (+)-*O,O'*-dibenzoyl-D-tartaric acid. The chromium complexes of these ligands can be used in asymmetric epoxidation of alkenes. The presence of triphenylphosphine oxide substantially raises the selectivity (ee) of the epoxidation.

In recent years there has been widespread use in asymmetric synthesis of metal complexes of chiral non-racemic salen ligands **1** derived from 1,2-diaminocyclohexane.[1] As far as we are aware there have only been two reports of salen ligands wherein the substituents on the two salicylidene moieties are different.[2,3] The earlier of these involved a chromatographic separation using gel permeation chromatography.[3] The other more recent publication,[2] the results of which we have been unable to replicate,[4] reports a synthesis *via* mono-imine **2**. This has prompted us to report our own synthesis, also *via* **2**, of unsymmetrical salen ligands **3** and **4**, the formation of their corresponding oxochromium(V) complexes **5** and the subsequent use of the latter for asymmetric epoxidation.



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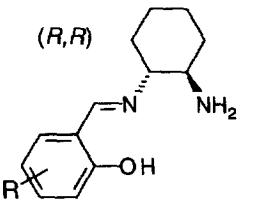

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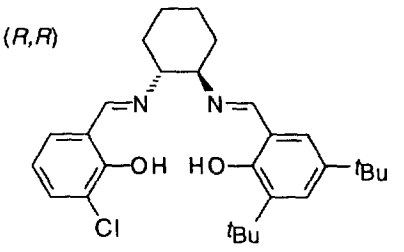

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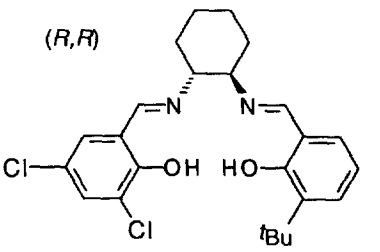

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Our interest in this area stems from our previous reports[5-7] on the use of chromium salen complexes such as **5** (X=X', Z=Z') for the catalytic asymmetric epoxidation of *trans*-alkenes[8] (Scheme 1). With the *β*-

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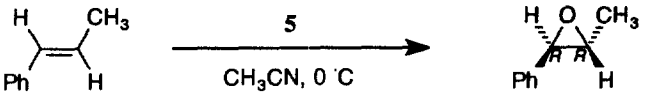
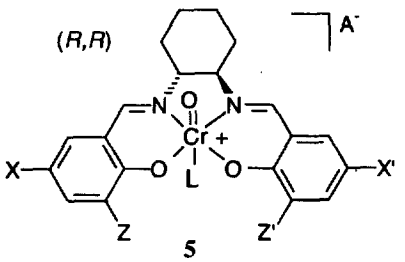
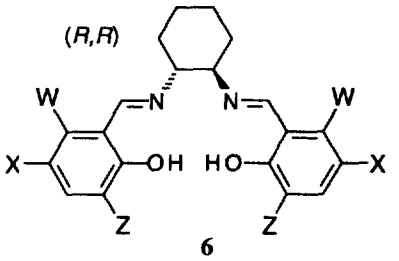
methylstyrenes as substrates, this system provided the first example of consistently higher asymmetric induction for the *trans*-isomer than the *cis*-isomer. This called into question the standard side-on approach mechanism for alkene epoxidation by metal-oxo species[9] and led us to an initial working hypothesis[6,7] that the salen-ligands in complexes **5** are bent. Since this involves loss of the C_2 symmetry we postulated[6] that unsymmetrical salen complexes should be no worse than the symmetrical and might possibly be better.

Scheme 1





5



6

Also from our survey[7] of the effectiveness of various salen ligands in the epoxidation reaction we found that substitution at the Z/Z' positions in **5** is generally favourable for inducing high ee (>80%), while the presence of electron withdrawing groups was necessary for reasonable reaction rates. Combination of the steric effects of e.g. a *tert*-butyl group and the electronic effects of e.g. a chloro group on opposite sides of the chiral diimine bridge would provide further asymmetry in the ligand-metal system, possibly increasing enantioselection. We attempted therefore to develop a synthesis of unsymmetrical salen ligands **3** and **4**.

The formation of bis-imine ligands from aldehyde and amine is under thermodynamic control and dominated by the stability of the bis-imine product. Thus a 1:1 mixture of a salicylaldehyde and 1,2-diaminocyclohexane in ethanol often yields an equilibrium mixture of small amounts of the mono condensation product **2**, the normal bis-Schiff base ligand **1** and starting bis-amine. Attempted purification leads only to a mixture containing the same proportions. However we made the interesting and potentially useful observation that the ratio of the mono- to bis-products is dependent on the substituents on the salicylaldehyde. In particular, increasing electron withdrawal favours the mono-Schiff base product, Table 1.

Table 1 : Equilibrium ratios[a] in the formation of some salen ligands **6** derived from 1,2-diaminocyclohexane.

Ligand	W	X	Z	Ratio[b] of Schiff Base Ligands	
				2 (mono)	6 (bis)
6a	H	H	Cl	3	1
6b	H	Cl	Cl	6	1
6c	Cl	Cl	Cl	10	1
6d	H	NO_2	H	30	1

[a] Determined at room temperature in $CDCl_3$ after reflux of a 1:1 mixture of the salicylaldehyde and cyclohexanediamine in ethanol for 2 hours followed by removal of solvent; [b] Calculated by integration of the imine signals.

We therefore attempted to trap the mono-Schiff base product by addition of a reagent which would react with the free amine functionality and allow easy separation of the resulting adduct. After a great deal of

experimentation the most successful reagent for this process was found to be (+)-*O,O'*-dibenzoyl-D-tartaric acid which, when added to a solution of the mono- and bis-products in diethyl ether, yielded the (+)-*O,O'*-dibenzoyl-D-tartrate salt of **2**. The salt is insoluble in ether and can be collected by filtration. Further reaction of this salt with a different salicylaldehyde leads to the unsymmetrical ligand, accompanied by small amounts of the symmetrical cases due to unavoidable equilibration. Careful chromatography then yielded the unsymmetrical salen ligands, **3** and **4** in low yield.[10]

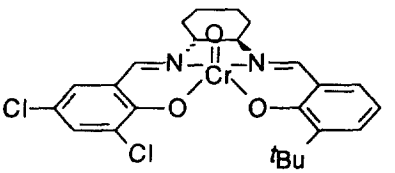
The corresponding chromium complexes **5a,b** of these ligands were synthesised[11] and subsequently used in the stoichiometric epoxidation of *E*-ß-methylstyrene according to Scheme 1. The results (Table 2) were initially disappointing to us since the highest ees obtained are in all cases lower than those obtained for the corresponding symmetrical ligands. However it is noticeable that the ee is substantially increased by the presence of donor ligand such as triphenylphosphine oxide (Ph_3PO) in the reaction system.

Table 2 Stoichiometric asymmetric epoxidation[a] of *E*-ß-methylstyrene according to Scheme 1.

Complex	A	X	Z	X'	Z'	Enantiomeric Excess (%) symmetrical analogues[b] in brackets	
						L = none	L = Ph_3PO
5a	PF_6	H	Cl	tBu	tBu	25 (80/65)	71 (86/71)
5b	NO_3	Cl	Cl	H	tBu	41 (67/84)	68 (83/79)

[a] at 0 °C, according to epoxidation procedure in reference 7, footnote 14, yields were low (10-12%); [b] at -10 °C, from refs. 5 and 7.

The most likely explanation for the lower selectivities in the unsymmetrical cases is that in fact complexes **5** (X=X', Z=Z') are not bent but rather maintain their C_2 symmetry. Then in the cases of **5a,b** two diastereomers can be formed e.g. **I** and **II** in the case of **5b**. As a result there will be two active oxygen transfer species present in the reaction system, one of which may give high ee and the other low. In addition one of these species may be more reactive than the other.



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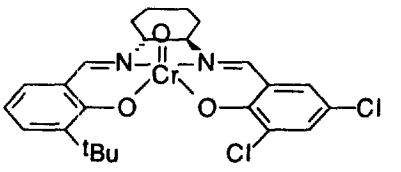

II

A possible explanation for the dramatic effect of Ph_3PO on ee is that it may bind more efficiently to one of the diastereoisomeric oxochromium species thereby increasing the reactivity and/or selectivity of that species. This theory is consistent with incomplete reaction of the alkene (which is the case in these systems[7]) since otherwise the enantioselectivity obtained would be a result of both **I** and **II** contributing equally to the formation of product. On the other hand **I** and **II** could be in equilibrium *via* the Cr(III) product of reaction. In Table 2, Ph_3PO was added after the generation of the oxochromium species so it can not predispose one face of the catalyst to oxygen addition. Addition beforehand produced no significant difference in selectivity which is unsurprising because phosphine oxides are known not to bind strongly to Cr(III) salen species.[12]

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2. Lopez, J.; Liang, S.; Bu, X.R. *Tetrahedron Lett.* **1998**, *39*, 4199-4202.
3. Fujii, Y.; Ebino, F.; Yanagisawa, M.; Matsuoka, H.; Kato, T. *J. Inorg. Organomet. Polym.* **1994**, *4*, 273-289.
4. We would question the claim of Lopez *et al.*[2] that it is possible to synthesise an "almost pure" sample of mono-imine **2 (R=H)** using the procedure as described[2] Indeed the number of ^{1}H-nmr signals quoted for **2 (R=H)** is not consistent with the assigned structure (there being too many), but quite consistent with a mixture of mono- and bis-products. Indeed in our hands and strictly following their procedure, just such a mixture was formed in a 3:1 ratio. Attempted condensation of this mixture with 3,5-di-*tert*-butylsalicylaldehyde, also used by Lopez *et al.*, yields a 4:3:3 mixture of the unsymmetrical ligand and the two symmetrical ligands. The fact that a correct elemental analysis is quoted does not necessarily indicate the presence of pure unsymmetrical ligand since a mixture of the three possible Schiff bases will also give the same analysis.
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6. Reported as a series of oral presentations at 211th National Meeting of the American Chemical Society, New Orleans, March 24-28th, **1996**; ORGN 161-165, Dalton, C.T.; Ryan, K.M.; Coyne, E.J.; Wall, V.M.; Bousquet, C.; Gilheany, D.G.
7. Ryan, K.M.; Bousquet, C.; Gilheany, D.G. *Tetrahedron Lett.* preceding paper.
8. *E*- and *Z*-1,2-disubstituted alkenes are referred to as *trans*- and *cis*-alkenes respectively.
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10. Experimental procedure for synthesis of **3**: (a) Trapping of mono Schiff base (**2, R=3 Cl**) as a salt: a mixture of 3-chlorosalicylaldehyde (1.00 g, 6.4 mmol) and (-)-*trans*-1,2-cyclohexanediamine (0.73 g, 6.4 mmol) was dissolved in diethyl ether (140 ml) and stirred for 30 minutes. A solution of (+)-*O,O'*-dibenzoyl-D-tartaric acid (1.83 g, 5.1 mmol) in diethyl ether (100 ml) was added. After 2 hours the resulting precipitate of (-)-*N,N'-trans*-1-(3'-chlorosalicylidene)-2-(dibenzoyl-D-tartrate)-cyclohexanediamine was filtered, 2.24 g, 58%. ^{1}H NMR 270 MHz ($CDCl_3$, TMS): 1.47-1.98 (m, 8H), 3.33-3.37 (m, 1H), 6.71-7.64 (m, 9H), 8.25 (s, 1H), 14.35 (s, 1H). (b) Synthesis of **3**: to a suspension of the salt from (a) (1.86 g, 3.05 mmol) in ethanol (140 ml) was added 3,5-di-*tert*-butylsalicylaldehyde (0.71g, 3.05 mmol) and the mixture refluxed for 1 hour. The ethanol was removed under reduced pressure to yield an oil which was separated by flash column chromatography (silica gel, dichloromethane) to yield **3**, 0.18 g, 13%. ^{1}H NMR 270 MHz ($CDCl_3$, TMS): 1.19-1.96 (m, 26H), 3.22-3.31 (m, 1H), 3.36-3.46 (m, 1H), 6.66-6.69 (m, 1H), 6.98-7.05 (m, 2H), 7.31-7.35 (m, 2H), 8.25 (s,1H), 8.26 (s,1H), 13.54 (s, 1H), 14.35 (s, 1H). **2 (R=3,5 Cl)** and consequently **4** were synthesised similarly.
11. The chromium(III)salen chloride (A = Cl^-) complexes were synthesised according to Martinez, L.E.; Leighton, J.L.; Carsten, D.H.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1995**, *117*, 5897-98. From this **5a** was synthesised: to a solution of the chromium salen chloride complex (1 equivalent) in sufficient methanol, a solution of potassium hexafluorophosphate (1.5 equivalent) in water (10 mL) was added dropwise. The resulting solution was stirred overnight and concentrated *in vacuo* to 10-15 mL. The final precipitate was collected by filtration, washed with water (2 x 10 mL) and dried in an oven at 100 °C. **5b** was synthesised similarly using silver nitrate.
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