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Chiral Aluminium Complexes as Phospho-Transfer Catalysts

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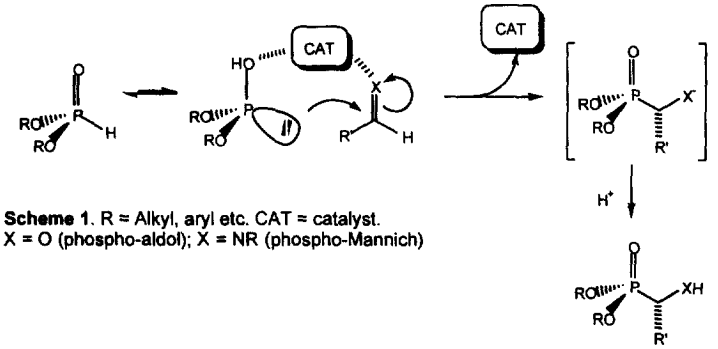
Abstract: Readily accessible, chiral complexes of aluminium are effective and enantioselective catalysts for the phospho-aldol reaction under aerobic conditions.

A key objective of our research programme in phospho-transfer chemistry is the development of catalysts for the enantioselective phospho-aldol[1] reaction (Scheme 1) which are: *(i) simple to prepare, (ii) inexpensive, (iii) tuneable, (iv) compatible with air and water, (v) tolerant to substrates without drying or special purification, and (vi) reusable without reprocessing.* Such a variant would offer an extremely effective, simple and broad-based route to phosphorus chemicals with biological and medicinal applications including bio-phosphate mimics,[2] transition state models,[3] anti-biotic,[4] anti-viral[5] and anti-tumour activity.[6]

Existing phospho-transfer catalysts satisfy the above criteria to varying degrees but we wished to open up a new class of catalyst which satisfies all criteria whilst, at the same time, moves away from binaphthol[7] as the principal existing source of effective chiral recognition in this process.



Scheme 1. R = Alkyl, aryl etc. CAT = catalyst.
X = O (phospho-aldol); X = NR (phospho-Mannich)

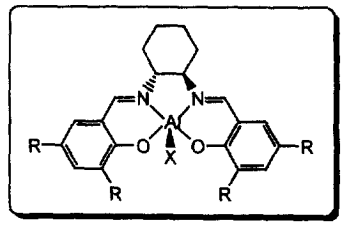


Figure 1
R = H (**1**); ^{t}Bu (**2**)
X = Me (**a**), Cl (**b**), O_3SCF_3 (**c**), $OSiMe_2{}^t$Bu (**d**)

Due to their ease of synthesis, stability and structural variability, the SALEN class of Schiff's base ligand is widely used in coordination chemistry.[8] Our interest was drawn to such systems based on the *trans*-1,2-diaminocyclohexane backbone, championed principally by Jacobsen,[8] as potential phospho-transfer catalysts since of the two main classes of ambiphilic phospho-aldol catalyst, organic (*Class I*) and metallo-organic (*Class II*),[9] the latter have proved the more active and stereoselective.[7,10]

Complexes **1** and **2a-c** are accessible *via* standard procedures.[11] **1-2a** are formally examples of *Class II* phospho-aldol catalysts whilst **1-2b,c** are Lewis acid variants of the same class.[9] Consistently, compounds **1-2b,c** are extensively dissociated in methanol solution possessing similar degrees of dissociation to KCl and [^{n}Bu$_4$N][OSO_2CF_3]; Λ_M (0.01 moles dm^{-3}; MeOH; 298 K) for **1b**, **1c**, KCl and [^{n}Bu$_4$N][OSO_2CF_3] are 40, 43, 57 and 46 Ω^{-1}mol^{-1}cm^2 respectively. Single crystals of the six-co-ordinate bis-methanol solvate of **2b** and methyl complex **1a** result upon cooling saturated methanol **2b** or dichloromethane **1a** solutions to -35°C (Figures 2 and 3).[14] Structural parameters are similar to those reported for related achiral derivatives.[15]

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Methanol co-ordination in solution is supported by the ^{27}Al-NMR shift of **1b**, δ_{Al} +45.9 ppm ($\Delta_{1/2}$ 4.2 kHz; MeOH); within the range expected for six-co-ordinate aluminium.[16] Compound **1a** has δ_{Al} of +52.6 ppm ($\Delta_{1/2}$ 4.1 kHz; $CHCl_3$), consistent with five-co-ordinate aluminium.[16]

Complexes **1a** and **2a** are effective catalyst precursors for the addition of diorgano-H-phosphonates to carbonyls;[17] *importantly, catalysis is tolerant of oxygen and water and does not require that starting materials be dried or degassed prior to use.* In the Table are collected enantioselectivities (e.e.'s) for the addition of H-phosphonates to benzaldehydes catalysed by *R,R*-**1a** under both dry, inert and aerobic, non-dry conditions, determined *in situ* using quinine as a chiral solvating agent.

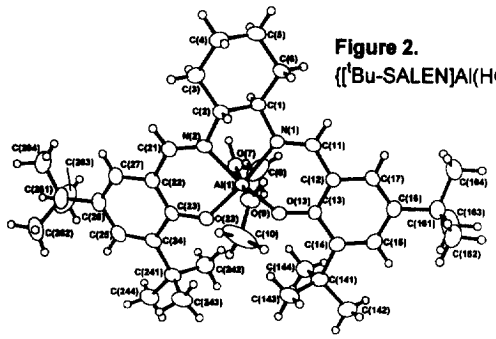


Figure 2. {[^{t}Bu-SALEN]Al(HOMe)$_2$}Cl

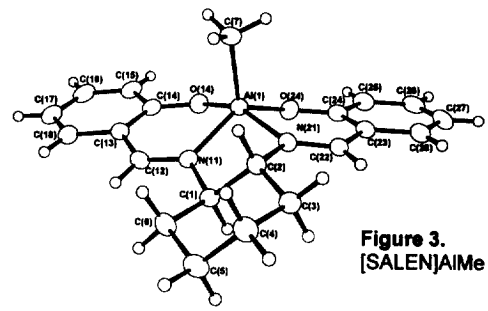


Figure 3. [SALEN]AlMe

Reaction System[a]	Catalyst[b,c]	% e.e.[d]	% e.e.[e]
DMHP / PhCHO	**1a**	37 (*R*)	41 (*R*)
DMHP / PhCHO	**1a:1b**	43 (*R*)	45 (*R*)
DMHP / 4-BrC_6H_4CHO	**1a**	27 (*R*)	24 (*R*)
DMHP / 4-BrC_6H_4CHO	**1a:1b**	29 (*R*)	25 (*R*)
DMHP / 4-MeC_6H_4CHO	**1a**	44 (*R*)	49 (*R*)
DMHP / 4-MeC_6H_4CHO	**1a:1b**	54 (*R*)	40 (*R*)
DMHP / 4-MeOC_6H_4CHO	**1a**	39 (*R*)	46 (*R*)
DMHP / 4-MeOC_6H_4CHO	**1a:1b**	44 (*R*)	31 (*R*)
DMHP / 4-$NO_2C_6H_4$CHO	**1a**	15 (*R*)	10 (*R*)
DMHP / 4-$NO_2C_6H_4$CHO	**1a:1b**	14 (*R*)	17 (*R*)
DMHP / 4-ClC_6H_4CHO	**1a**	30 (*R*)	19 (*R*)
DMHP / 4-ClC_6H_4CHO	**1a:1b**	26 (*R*)	28 (*R*)
DMHP / 2-ClC_6H_4CHO	**1a**	12 (*R*)	12 (*R*)
DMHP / 2-ClC_6H_4CHO	**1a:1b**	13 (*R*)	14 (*R*)
DMHP / 2-MeC_6H_4CHO	**1a**	25 (*R*)	20 (*R*)
DMHP / 2-MeC_6H_4CHO	**1a:1b**	22 (*R*)	42 (*R*)
DMHP / 2-MeOC_6H_4CHO	**1a**	20 (*R*)	27 (*R*)
DMHP / 2-MeOC_6H_4CHO	**1a:1b**	25 (*R*)	27 (*R*)

[a] Reactions performed in THF using 1:1 ratio (1 mmol.) of carbonyl:H-phosphonate. Catalyst dissolved in THF, cooled to -78°C and H-phosphonate added. Mixture then warmed to room temperature before PhCHO added at -78°C and then allowed to warm to ambient slowly. Enantiopurities screened *via* ^{31}P-NMR after 48h, using quinine (4 mol equiv.$CDCl_3$) as a chiral solvating agent[18] (e.e. ±2% error). No racemisation is observed in the presence of either **1a** or **1b** within 7 days. Absolute configurations determined by correlation of ^{31}P-NMR resonances of phosphonate:quinine (1:4 mol:mol) mixtures to $[\alpha]^D$ values of the phosphonate. [b] 5 mol% catalyst for **1a** systems and 2.5 mol% each in **1a:1b** systems. [c] All reactions are quantitative within 24h at ambient temperature, no side-products were observed. [d] Recorded after 48h (20°C). Non-aerobic conditions. Configuration in parentheses. [e] Recorded after 48h (20°C). Aerobic conditions. Configuration in parentheses

Thus, DMHP adds to a range of aldehydes RCHO to afford $(MeO)_2P(=O)CHR(OH)$ cleanly at 25°C in the presence of **1a** (5 mol%). Conversions are *quantitative* within 3-6h. Enantioselectivities are as yet modest but 40-50% has been achieved with these first generation catalyst systems.

Jacobsen and co-workers recently described the potential of **2b** as a chiral Lewis acid catalyst for the hydrocyanation of imines (the Strecker reaction).[19] Although **1-2b,c** are not phospho-aldol catalysts themselves, they are excellent co-catalysts with **1a**. Thus a dual-component catalyst system comprising **1a:1b** (2.5 mol% in each) results in significant rate enhancement over reactions catalysed by **1a** alone at 5 mol% loading (all reactions now quantitative within 1h at 298K) although there is little significant difference in enantioselectivity. Most encouraging is the fact that aerobic catalysis is equally enantioselective to reactions

performed under inert atmosphere and does not lose any turnover activity.[17] Moreover, the catalyst is completely reusable, re-charging a given reaction catalysed by **1a** with further aliquots of reagent and substrate results in *continued, quantitative and equally enantioselective* catalysis. Catalyst loading appears to have little influence on enantioselectivity; **1a** loadings between 1mol% and 15mol% lead to Δe.e. of only 7%.

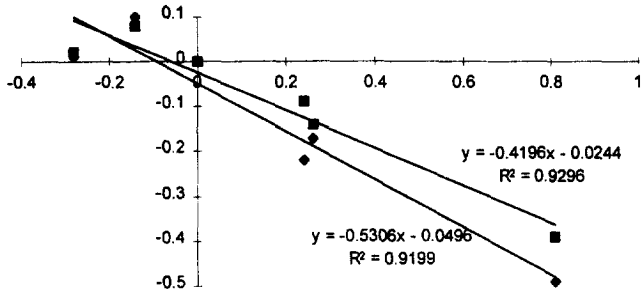
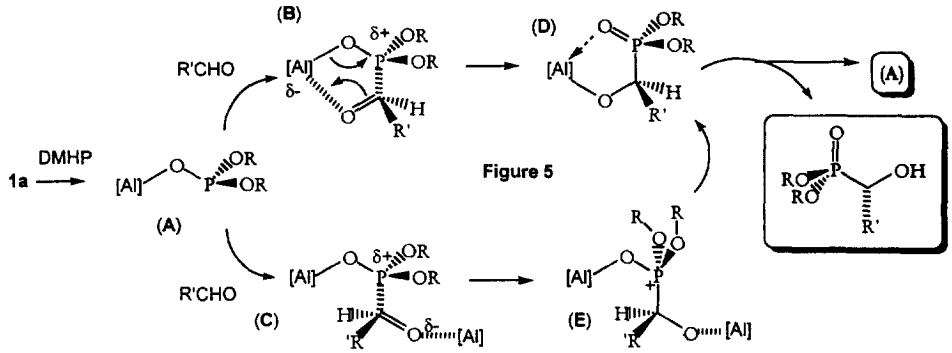


Figure 4. Plot of Log[(e.e.$_A$/e.e.$_{Ph}$)] (*vertical*) vs Hammett σ_p (*horizontal*) for reaction of DMHP, 4-XC$_6$H$_4$CHO catalysed by **1a** (■ ρ = -0.4) and **1a:1b** (◆ρ = -0.5) in THF solvent .[19]

A reasonable linear free energy relationship exists between e.e. and σ_p parameters of *para*-substituents in aldehyde substrates (Table) such that higher e.e.'s are afforded by the more electron-releasing benzaldehydes (Figure 4; ρ = -0.4).[20] Such a correlation is consistent with binding of the carbonyl to a Lewis acidic centre being important in the enantiodetermining step as reported recently by Shibuya *et al.*[21] We recognise that the ρ values observed in the aluminium systems are significantly smaller to those observed in Shibuya's lanthanum binaphthol system (ρ = -1.3) suggesting a weaker overall electronic influence consistent with the poorer Lewis acidity of aluminium over lanthanum. Benzaldehyde substitution in the *ortho* position leads consistently to lower e.e.'s; presumably steric factors are likely to play a larger role here.

Monitoring the reaction between DMHP and PhCHO catalysed with **1a** (5mol%) by solution conductivity (THF solvent; 298K) produces no conclusive evidence for charged intermediates.



At this early stage we are able to provide only a working mechanistic picture based on accepted steps for carbonyl hydrophosphonylation and our preliminary observations.[7,9,21] The initial step with **1a** as pre-catalyst is envisaged to involve generation of a tervalent phosphito species (A)[22] *via* deprotonation which is capable of then phosphonylating a carbonyl *via* either closed (B) or open (C) transition states (Figure 5). Rearrangement *via* a number of pathways [(B)-(D)-(A) or (E)-(D)-(A)] may be envisaged to afford product ester and regenerate catalytic intermediate (A). Of course, (A) can undergo competing, slower, reaction with carbonyl unactivated by metal; presumably this will result in lower e.e.'s. On the basis of the structure-activity results above, we envisage that higher e.e.'s result from the increased interaction between carbonyl and a metal (negative ρ values). Consequently, Figure 5 outlines catalytic possibilities *via* a single metal centre [(B)-(D)-(A) and co-operative asymmetric catalysis involving two metal centres (E)-(D)-(A)], the latter having precedent in Jacobsen's work[23] and both are consistent with the structure-activity results above. The fact that the dual component catalyst system of **1a:1b** results in rate enhancement over **1a** alone also suggest some co-operativity in this system. More detailed kinetic studies to probe this are in progress. Consistently,

we find that **2a** catalyses the addition of DMHP to aldehydes much slower than **1a** and to essentially racemic products (e.e. < 5%). We envisage that the sterically demanding t-butyl groups restrict access of the carbonyl substrate to aluminium thus hindering the more stereo-differentiating closed transition state (**B**) over open form (**C**) and significantly affecting product enantiopurity. Consequently, our strategy is to manipulate the substitution patterns of *unsymmetrical* Schiffs base complexes[24] with sterically anisotropic substituents. Studies are not yet sufficiently advanced to rationalise consistent production of *R*-configuration ester from *R,R*-**1a** although this will be a key step in developing second generation catalysts.

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