
Asymmetric general base catalysis of the phospho-aldol reaction *via* dimeric aluminium hydroxides

Alexandra C. Gledhill, Nichola E. Cosgrove, Tracy D. Nixon, Colin A. Kilner, Julie Fisher and Terence P. Kee*

School of Chemistry, University of Leeds, Woodhouse Lane, Leeds UK. Fax: 44 (0)113 3436565; Tel: 44 (0)113 3436421; E-mail: t.p.kee@leeds.ac.uk

Electronic Supplementary Material

1. Synthetic Details

Synthesis of $\{(R,R)\text{-[salcyan}^t\text{Bu)}_2\text{Al(OH)}_2\}_2$ (2)

A stirred toluene (5 mL) solution containing (*R,R*)-*N,N'*-bis(2'-hydroxy-3'-*tert*-butylbenzyl)-*trans*-1,2-diaminocyclohexane⁷ (0.54 g, 1.22 mmol) and aluminium tris-isopropoxide (0.37 g, 1.83 mmol) was heated to 80°C for 72 h. Following cooling to room temperature and exposed to air the resulting white precipitate was collected by reduced pressure filtration. Recrystallisation from THF afforded the title compound as white crystals. (0.4 g, 74 %).

Anal. found for C₂₈H₄₁N₂O₃Al: C, 69.8; H, 8.6; N, 5.4. Calc. C, 69.9; H, 8.6; N, 5.8.

M.p. 285-286°C.

m/z (EI): 944 [M₂-O]; 943 [M₂-OH].

$\delta^1\text{H}$ (CDCl₃): 7.30 (dd, 2H, Ar-H, ³J_{HH} 7.8Hz, ⁴J_{HH} 1.8Hz), 7.09 (dd 2H, Ar-H, ³J_{HH} 7.7Hz, ⁴J_{HH} 1.7Hz), 6.57 (dd, 4H, Ar-H, ³J_{HH} 7.2Hz, ⁴J_{HH} 1.6Hz), 6.55 (m, 2H, Ar-H, ³J_{HH} 7.4Hz), 6.47 (m, 2H, Ar-H, ³J_{HH} 7.5Hz), 4.80 (m, 2H, NHCH₂), 4.63 (m, 2H, NHCH₂), 3.81 (m, 2H, NHCH₂), 3.65 (m, 2H, NHCH₂), 2.37 (m, 2H, NHCH), 2.18 (m, 2H, NHCH), 1.85 (m, 2H, Cy-CH₂), 1.78 (m, 2H, Cy-CH₂), 1.67 (m, 2H, Cy-CH₂), 1.58 (s, 18H, ^tBu), 1.16 (m, 2H, Cy-CH₂), 0.91 (s, 9H, ^tBu).

$\delta^{13}\text{C}$ {¹H} (CDCl₃): 161.7 (ArC), 159.3 (ArC), 138.4 (ArC), 138.0 (ArC), 127.3 (ArC), 126.7 (ArC), 125.9 (ArC), 125.3 (ArC), 123.6 (ArC), 121.8 (ArC), 114.8 (ArC), 113.6 (ArC), 58.2 (CHNH), 55.6

(CHNH), 49.6 (NHCH₂), 48.0 (NHCH₂), 34.2 (CMe₃), 33.4 (CMe₃), 30.3 (CH₃), 29.2 (CH₂), 29.0 (CH₃), 28.2 (CH₂), 23.5 (CH₂), 23.4 (CH₂).

Synthesis of {(R,R)-[salcyan(⁴Pn)₂]Al(OH)₂} (3)

(R,R)-N,N'-Bis(2'-hydroxy-3'-tert-pentylbenzyl)-trans-1,2-diaminocyclohexane⁷ (1.37 g, 2.94 mmol) was dissolved in dry pentane (10 mL) and trimethylaluminium (2M solution in hexanes, 1.47 mL, 2.94 mmol) added at which point gas was evolved and the solution became cloudy. After 5 h stirring at room temperature the solution was exposed to air and filtered to remove insoluble materials. Volatiles were removed under reduced pressure followed by recrystallisation from toluene to afford the title product as colourless prisms (0.91 g, 61 %).

Anal. found for C₆₀H₉₀Al₂N₄O₆: C, 70.9; H, 9.0; N, 5.3. Calc. C, 70.8; H, 8.9; N, 5.5.

M.p. 257-258°C.

m/z (ES+; CH₃CN): 999 [M₂-OH].

$\delta^1\text{H}$ (CDCl₃): 7.24 (d, 1H, ³J_{HH} 8.5Hz, ⁴J_{HH} 1.5Hz, Ar-H), 7.00 (d, 1H, ⁴J_{HH} 2.5Hz, Ar-H), 6.83 (d, 1H, ⁴J_{HH} 2.5Hz, Ar-H), 6.78 (d, 1H, ⁴J_{HH} 1.5Hz, Ar-H), 6.56 (t, 1H, ³J_{HH} 6.8Hz, Ar-H), 6.48 (t, 1H, ³J_{HH} 7.7Hz, Ar-H), 4.79 (d, 1H, ²J_{HH} 12.5Hz, NHCH₂), 4.54 (d, 1H, ²J_{HH} 11Hz, NH), 3.80 (t, 1H, ²J_{HH} 12Hz, NHCH₂), 3.71 (d, 1H, ²J_{HH} 11Hz, NHCH₂), 2.91 (s, 1H, OH), 2.54 (m, 1H, NHCH), 2.38 (m, 1H, CH₂), 2.16 (m, 1H, CH₂), 2.12 (m, 2H, NHCH), 2.00 (q, 2H, ³J_{HH} 7.7Hz, CH₂CH₃), 1.75 (s, 3H, CH₃), 1.69 (m, 2H, CH₂), 1.44 (s, 3H, CH₃), 1.40 (m, 2H, CH₂CH₃), 1.13 (m, 3H, CH₃), 0.87 (s, 3H, CH₃), 0.78 (t, 3H, ³J_{HH} 8Hz, CH₂CH₃), 0.23 (t, 3H, ³J_{HH} 8 Hz, CH₂CH₃).

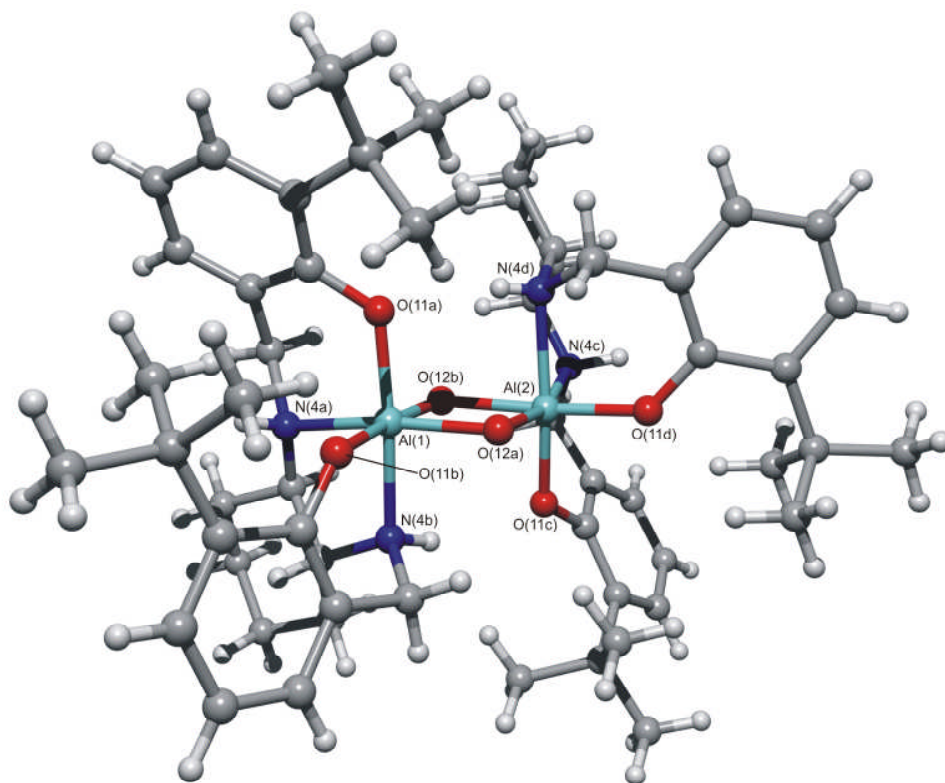
$\delta^{13}\text{C}\{^1\text{H}\}$ (CDCl₃): 162.7 (ArC), 160.2 (ArC), 137.7 (ArC), 137.3 (ArC), 129.0 (ArC), 128.2 (ArC), 128.0 (ArC), 127.0 (ArC), 124.6 (ArC), 122.5 (ArC), 115.4 (ArC), 114.6 (ArC), 59.1 (CHNH), 56.5 (CHNH), 50.5 (NHCH₂), 49.2 (NHCH₂), 38.4 (CMe₂Et), 35.3 (CH₂CH₃), 30.9 (CH₂CH₃), 30.0 (CH₂), 29.5 (CH₂), 29.0 (CH₃), 28.2 (CH₃), 27.5 (CH₃), 26.7 (CH₃), 24.6 (CH₂), 24.4 (CH₂), 10.3 (CH₂CH₃), 9.4 (CH₂CH₃).

2. Single Crystal X-Ray Analyses on compounds 2 and 3.

Compound 2 (CCDC 749041)

Identification code	tdn310
Formula	C ₈₀ H ₁₀₂ Al ₂ Cl ₄ N ₄ O ₆
Formula weight	1411.42

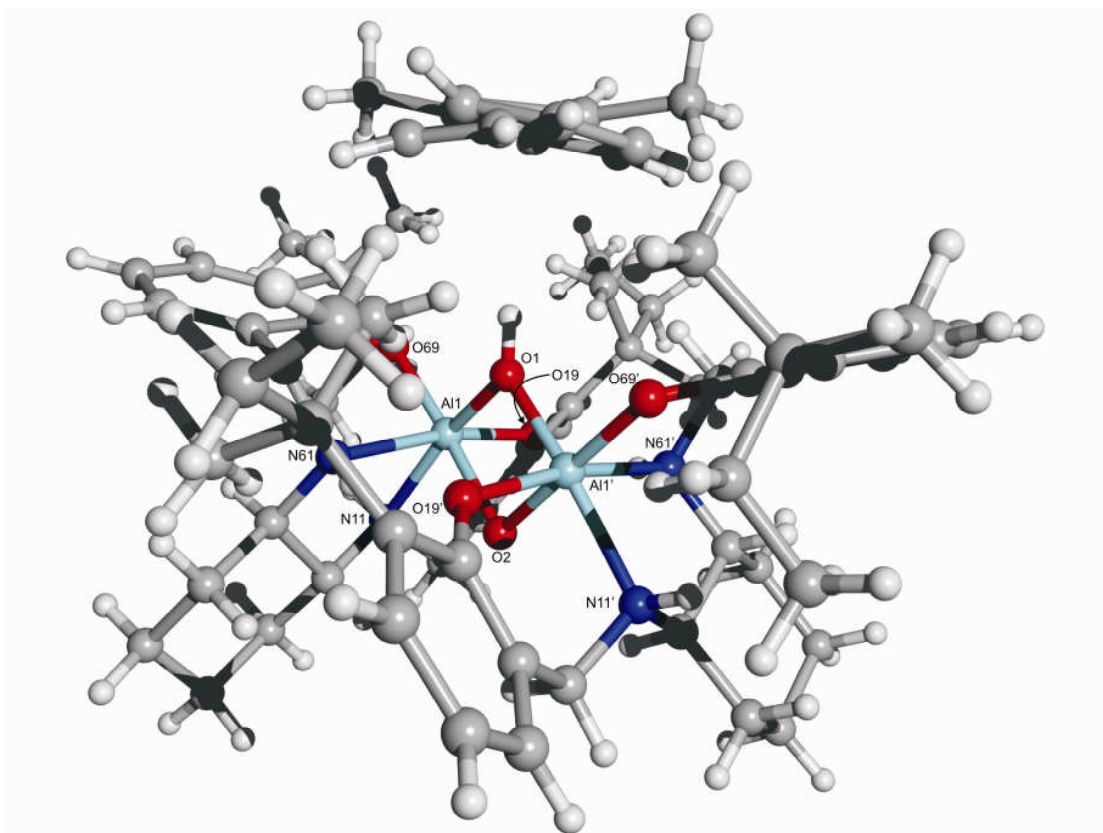
Size	0.27 x 0.18 x 0.09 mm
Crystal morphology	Colourless fragment
Temperature	150(2) K
Wavelength	0.71073 Å [Mo- K_{α}]
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	$a = 11.79800(10)$ Å $\alpha = 90^\circ$ $b = 31.2880(2)$ Å $\beta = 100.3000(3)^\circ$ $c = 20.6198(2)$ Å $\gamma = 90^\circ$
Volume	7488.85(11) Å ³
Z	4
Density (calculated)	1.252 Mg/m ³
Absorption coefficient	0.236 mm ⁻¹
$F(000)$	3008
Data collection range	$2.5 \leq \theta \leq 26^\circ$
Index ranges	$-14 \leq h \leq 14$, $-37 \leq k \leq 38$, $-25 \leq l \leq 25$
Reflections collected	90149
Independent reflections	29189 [$R(\text{int}) = 0.0641$]
Observed reflections	25135 [$I > 2\sigma(I)$]
Absorption correction	none
Max. and min. transmission	
Refinement method	Fullcycle
Data / restraints / parameters	29189 / 0 / 1502
Goodness of fit	1.038
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0855$, $wR_2 = 0.2321$
R indices (all data)	$R_1 = 0.0986$, $wR_2 = 0.2457$
Largest diff. peak and hole	1.819 and $-1.285 \text{ e.}\text{\AA}^{-3}$
Absolute structure parameter	0.08(8)



Compound **3** (CCDC 749040)

Identification code	acg29	
Formula	C ₆₇ H ₉₇ Al ₂ N ₄ O ₆	
Formula weight	1109.45	
Size	0.26 x 0.24 x 0.17 mm	
Crystal morphology	Colourless prism	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K _α]	
Crystal system	Trigonal	
Space group	P3 ₂ 21	
Unit cell dimensions	$a = 18.579(3) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 18.579(3) \text{ \AA}$	$\beta = 90^\circ$
	$c = 15.951(3) \text{ \AA}$	$\gamma = 120^\circ$

Volume	4768.2(13) Å ³
Z	3
Density (calculated)	1.159 Mg/m ³
Absorption coefficient	0.098 mm ⁻¹
F(000)	1806
Data collection range	2.53 ≤ θ ≤ 27.38°
Index ranges	-23 ≤ h ≤ 24, -24 ≤ k ≤ 24, -20 ≤ l ≤ 20
Reflections collected	69370
Independent reflections	3943 [R(int) = 0.0457]
Observed reflections	3671 [I > 2σ(I)]
Absorption correction	multi-scan
Max. and min. transmission	0.9835 and 0.8314
Refinement method	Full
Data / restraints / parameters	3943 / 0 / 397
Goodness of fit	1.059
Final R indices [I > 2σ(I)]	R ₁ = 0.0377, wR ₂ = 0.1066
R indices (all data)	R ₁ = 0.042, wR ₂ = 0.1111
Largest diff. peak and hole	0.536 and -0.201 e.Å ⁻³



Symmetry-related atoms have been indicated using ', for example Al1'. Here ' indicates the symmetry code (x-y, -y, -z+1/3).

3. Diffusion Ordered Spectroscopy Analysis

Three NMR samples were prepared by dissolving $\{(R,R)\text{-[salcyan}^{(13}\text{C)}_2\text{]Al(OH)}_2\}$ (1 mg, 0.98 mmol; 5 mg, 4.9 mmol; 25 mg, 24.6 mmol) in CDCl_3 (0.6 mL). DOSY spectra were obtained under identical conditions and subsequently analysed. When in the same environment, the ratio of experimentally obtained diffusion coefficients for two different approximately spherical molecules is inversely proportional to the ratio of their radii. This relationship enables us to estimate the relative size of a molecule from a comparison of diffusion rates.

The Stokes-Einstein relation (Cameron, K. S.; Fielding, L. *Magn. Reson. Chem.* 2002, **40**, S106-S109) was used to derive a calibration curve for a range of molecular weights in CDCl_3 at ambient temperature. The formula for this straight line is given below:

$$y = 73.275x + 1.1263$$

$$x = 1/3_MW$$

$$y = \text{Diffusion coefficient (cm}^2\text{s}^{-1}) \pm -0.08$$

$$R = 0.927$$

The monomeric compound (*R,R*)-[salcyen(¹Bu)₂]Al(OSiMe₃) was selected as a reference compound as it is similar in terms of composition, shape and molecular weight to the putative (*R,R*)-[salcyan(¹Pn)₂]Al(OH) monomer of interest ($\Delta MW = 40.1$). Diffusion coefficients for the reference compound and of $\{(R,R)\text{-[salcyan}^1\text{Pn}_2\text{]Al(OH)}\}_2$ were both calculated, using the calibration curve, (D_{cal}) and obtained experimentally (D_{obs}) the results of which are shown below.

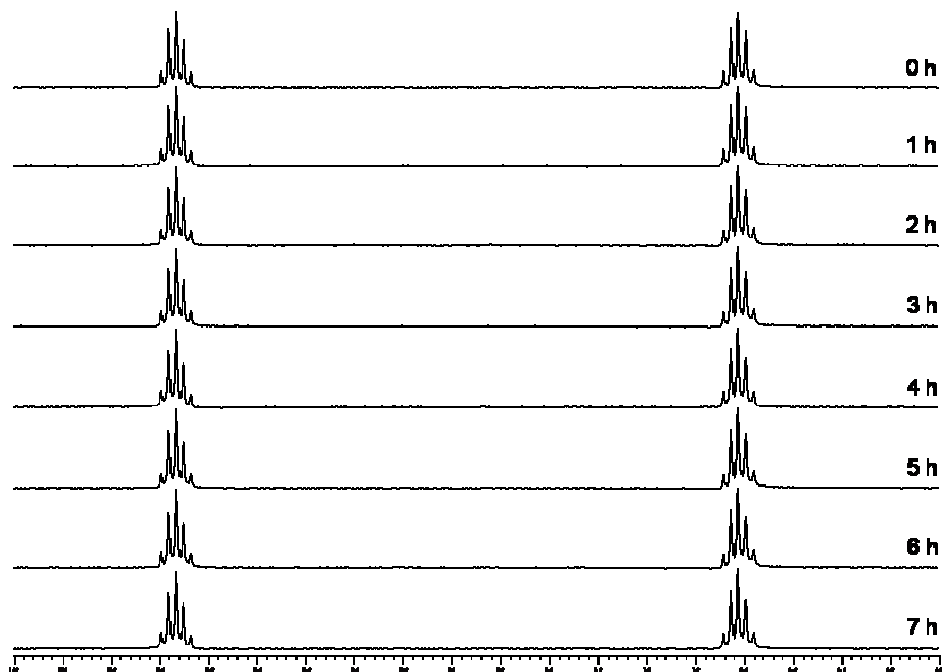
System	Mol. Weight	D_{cal}	D_{obs}
Reference	548.8	10.076	10.180
Monomer	508.7	10.305	-
Dimer	1017.3	8.412	8.341

Both calculated and observed diffusion coefficients for the reference compound were found to be in close agreement confirming reliability of the method. The observed diffusion coefficient for $\{(R,R)\text{-[salcyan}^1\text{Pn}_2\text{]Al(OH)}\}_2$ was shown to be within $0.1 \text{ cm}^2\text{s}^{-1}$ to that calculated for the dimer supporting a dimeric species in solution. Each of the samples at different concentrations returned the same result seemingly ruling out the hypothesis that the catalyst precursor dissociates to form the monomer in lower concentrations.

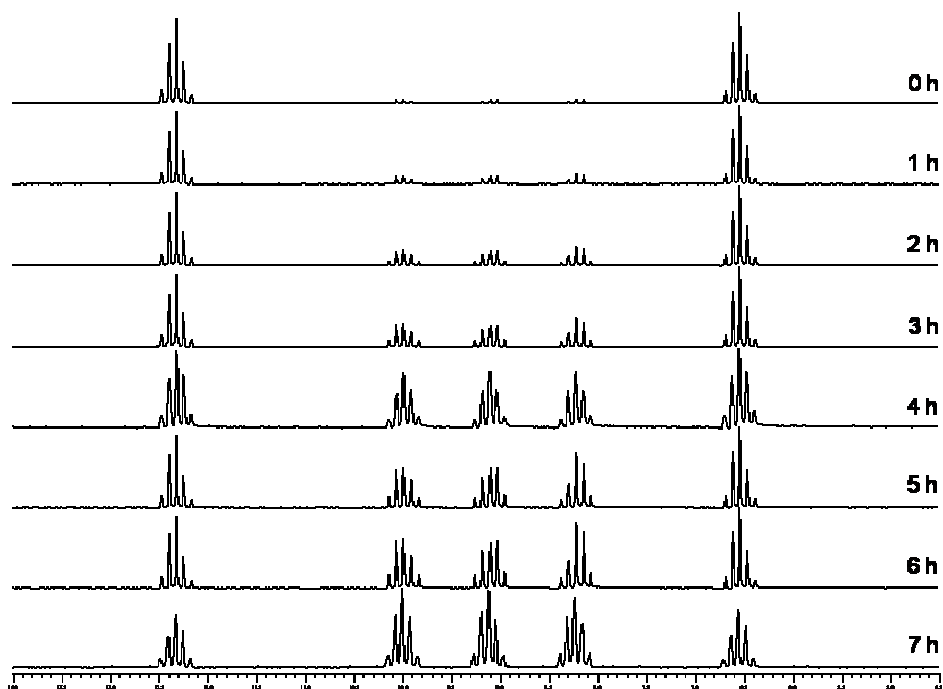
4. Isotope Exchange Studies

A solution of diethyl-H-phosphonate DEHP (0.13 mL) in EtOD (1 mL) was made up and an aliquot (0.1 mL) added to an NMR tube loaded with a D₂O capillary, EtOD (0.4 mL) was added to make up an NMR sample. A second aliquot (0.1 mL) was added to an NMR tube loaded with a D₂O capillary and $\{(R,R)\text{-[salcyan}^1\text{Pn}_2\text{]Al(OH)}\}_2$ (5 mg, 5.0×10^{-6} mol) and EtOD (0.4 mL) added to make up an NMR sample. ³¹P NMR spectrum was obtained of both samples. ³¹P NMR spectra were then acquired of each sample every hour for 7 h. The amount of deuterium exchange that had occurred was calculated from the integrals of each spectrum and a kinetic analysis was carried out under pseudo first order conditions.

The $^{31}\text{P}\{^1\text{H}\}$ spectrum of DEHP appears as a doublet of quintets, if deuterium exchange were to take place we would expect to see new peaks in the form of a triplet of quintets due to coupling to deuterium possessing a nuclear spin of +1.



Spectrum ESI1: Stacked $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of isotope exchange control reaction; at 298 K, in EtOD with D_2O capillary, at 121 MHz.



Spectrum ESI2: Stacked $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of isotope exchange reaction containing $\{(R,R)\text{-[salcyan}({}^1\text{Pn})_2\text{]Al(OH)}\}_2$; at 298 K, in EtOD with D_2O capillary, at 121 MHz.

The results (Spectra ESI1 and ESI2) clearly show that without the presence of a catalyst no deuterium exchange takes place. However, in the presence of $\{(R,R)\text{-[salcyan}({}^1\text{Pn})_2\text{]Al}(\mu\text{-OH})\}_2$ exchange occurs rapidly with a triplet of quintets growing in the spectra as predicted. These results provide strong evidence that $\{(R,R)\text{-[salcyan}({}^1\text{Pn})_2\text{]Al}(\mu\text{-OH})\}_2$ acts as a base to catalyse H/D exchange and presumably also has the same role within the phosphor-aldol reaction. From each spectrum the amount of deuterium exchange was determined and a kinetic analysis was carried out using pseudo first order reaction kinetics as EtOD is in large excess wrt DEHP

$$kt = -\ln([A]_0 - x) + \ln[A]_0$$

Where k represents pseudo first order rate constant

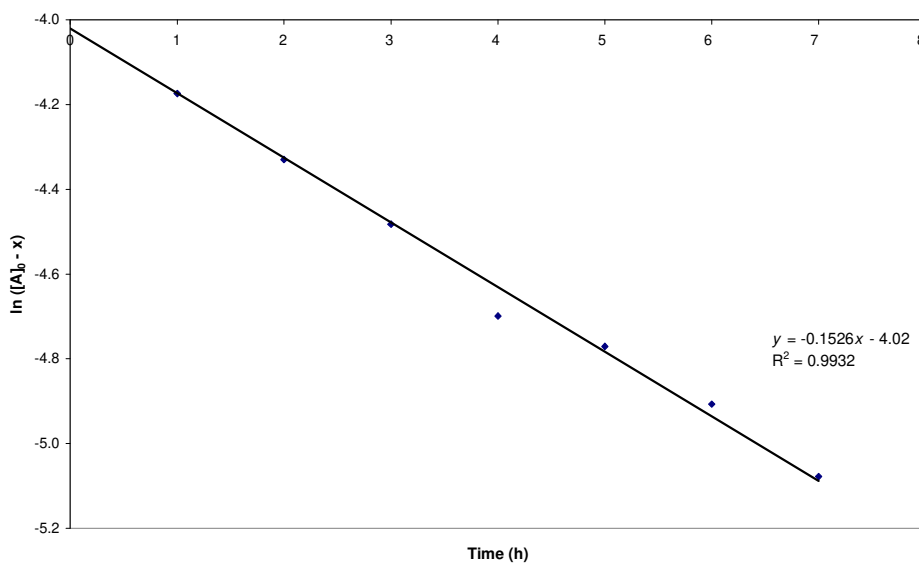
$[A]$ Represents concentration of DEHP

$[A]_0$ Represents maximum concentration of DEHP

Using the first order equation above we can plot $\ln([A]_0 - x)$ against time, if the reaction is pseudo first order as predicted the graph should afford a straight line, from which we can determine the pseudo first order rate coefficient.

Time (h)	D-exchange (%)	x ($\times 10^{-3}$)	$[A]_0^a - x$ ($\times 10^{-2}$)	$\ln ([A]_0 - x)$
0	6.0	1.18	1.85	-3.99
1	21.7	4.27	1.54	-4.17
2	33.0	6.49	1.32	-4.33
3	42.5	8.36	1.13	-4.48
4	53.7	10.56	0.91	-4.70
5	56.9	11.19	0.85	-4.77
6	62.4	12.27	0.74	-4.91
7	68.3	13.43	0.62	-5.08

Table ES11: Kinetic analysis of isotope exchange study. $^a[A]_0 = 1.966 \times 10^{-2}$ M.



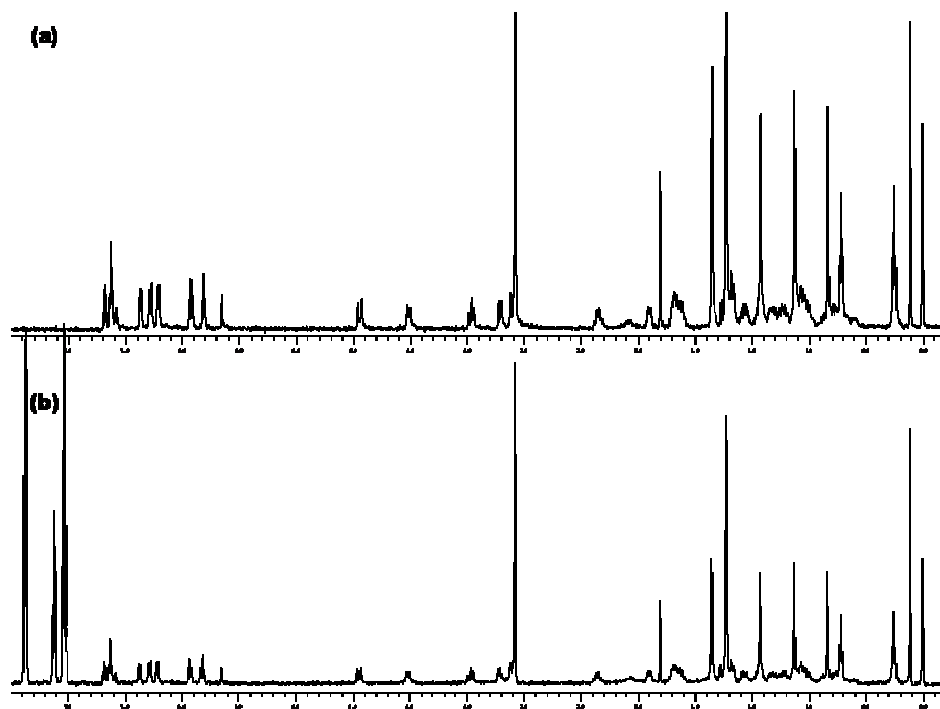
Graph ES11: Kinetic results from isotope exchange study. $k_{\text{pseudo}} = 1.15 \text{ dm}^{-3} \text{ mol}^{-1} \text{ s}^{-1}$

As isotope exchange has only proceeded to 68% conversion, the kinetic analysis must be met with some caution. The results do however indicate that the reaction does obey first order kinetics under the conditions used with rate constant $k_{\text{pseudo}} = 1.15 \text{ dm}^{-3} \text{ mol}^{-1} \text{ s}^{-1}$. The value for $[A]_0$ extrapolated from the graph is 1.80×10^{-2} M which is in good agreement with the experimental value of 1.96×10^{-2} M.

5. Interaction of salcyan complex with benzaldehyde?

NMR studies were carried out to investigate whether, and if so how, the structure of the catalyst precursor changes in the presence of each individual component of the PA process, both starting

materials and product. A $^1\text{H-NMR}$ spectrum of $\{(R,R)\text{-[salcyan}^i\text{Pn)}_2\text{Al(OH)}_2\}$ **3** was obtained followed by spectra of the complex with one equivalent of benzaldehyde after 30 minutes mixing.



Spectrum ESI3: $^1\text{H NMR}$ spectrum of **3** (a); benzaldehyde and **3** (b) at 298 K, in $\text{D}_8\text{-THF}$, 500 MHz, 298 K.

Upon examining and comparing the spectrum of **3** and benzaldehyde with the spectrum of **3** on its own (Spectrum ESI3), no change in chemical shift was observed and no new peaks were formed indicating that the structure of the catalyst precursor remains unchanged in the presence of benzaldehyde. This remained the case over a period of at least 3 weeks.

6. Effects of carbonyl substrate concentration on enantioselectivity

We were interested also to explore whether carbonyl concentration had any effect on e.e. when catalysed by $\{(R,R)\text{-[salcyan}^i\text{Pn)}_2\text{Al(OH)}_2\}$ **3**. The results obtained (Table ESI2) show that when using a 0.5 mol% catalyst loading (wrt DMHP), the e.e.'s remains largely unaffected by increasing amounts of benzaldehyde. Coupled with the observations in section 5 above, this would appear to be more consistent with a mechanism in which carbonyl binding to the metal centres does not play a significant role in influencing stereocontrol.

eq. C ₆ H ₄ CHO	Con. (%)	e.e. (%)
1	100	64 (<i>S</i>)
2	100	66 (<i>S</i>)
5	100	63 (<i>S</i>)
10	100	66 (<i>S</i>)

Table ESI2: Catalytic data for {(*R,R*)-[salcyan(¹Pn)₂]Al(OH)₂} **3** employing a 0.5 mol% catalyst loading with varying quantities of benzaldehyde (THF, 24 h, 298 K).

7. Computational Chemistry

Geometry optimisation calculations using gradient-corrected hybrid density functional theory (DFT), B3LYP, along with the 6-31G* basis set were carried out with the Gaussian 03 program, Revision C.02. Selected MO energies are collated in Table ESI3.

Optimisation using DFT Opt B3LYP/6-31G(d)

Molecular Orbital	Eigenvalue (a.u)	Electron Volts (eV)	Energy (kcal mol ⁻¹)	Difference	
261	-0.0242	-0.658	-15.167	-108.220	LUMO
260	-0.1966	-5.351	-123.387	0.000	HOMO
259	-0.1977	-5.380	-124.071	-0.684	
258	-0.2029	-5.521	-127.316	-3.928	
257	-0.2073	-5.641	-130.070	-6.683	
256	-0.2318	-6.309	-145.482	-22.095	
255	-0.2329	-6.337	-146.135	-22.747	
254	-0.2378	-6.471	-149.216	-25.828	
253	-0.2406	-6.546	-150.960	-27.573	
252	-0.2538	-6.906	-159.256	-35.868	
251	-0.2558	-6.962	-160.542	-37.155	
250	-0.2603	-7.082	-163.322	-39.935	
249	-0.2636	-7.173	-165.418	-42.031	

Total energy -3339.156952 a.u.
 -90865.13897 eV
 -2095354.379 kcalmol⁻¹

