Pergamon

Tetrahedron Letters 41 (2000) 6181–6184

TETRAHEDRON LETTERS

New chiral catalysts for phospho-transfer

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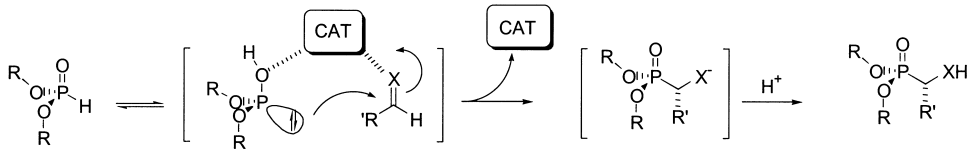
Received 19 May 2000; accepted 14 June 2000

Abstract

Chiral salcyan complexes of aluminium are effective air and water tolerant enantioselective catalysts for the hydrophosphonylation of carbonyls. Complexes of the form [(*R*,*R*)-salcyan]AlX (X = OH, OR) result in product enantioselectivity *changes* (Δee) of ca. 100% compared to those returned in the presence of related complexes [(*R*,*R*)-salcyen]AlX even though they both possess a chiral ligand framework with the same absolute stereochemistry.

Keywords: salcyan; aluminium complexes; hydrophosphonylation; asymmetric; catalysis.

The enantioselective hydrophosphonylation of carbonyls (or phospho–aldol[1] reaction) is a crucial and highly valuable phospho-transfer reaction for the synthesis of α-functionalised (commonly amino or hydroxy) phosphonate esters (Scheme 1). Such phosphorus compounds have considerable medicinal application including bio-phosphate mimics,[2] transition state models,[3] anti-biotic,[4] anti-viral[5] and anti-tumour activity.[6] Various metal complexes have been found to act as effective catalysts for the reaction, including titanium[7] and lanthanide[8] systems. We have been examining salcyen–metal complexes[9] as catalysts for carbonyl hydrophosphonylation and recently reported that complexes of the general form [(*R*,*R*)-salcyen]AlX (X = Me, $OSiMe_2^tBu$) afford ee's < 50% in the addition of dimethyl-*H*-phosphonate (DMHP) to substituted benzaldehydes.



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

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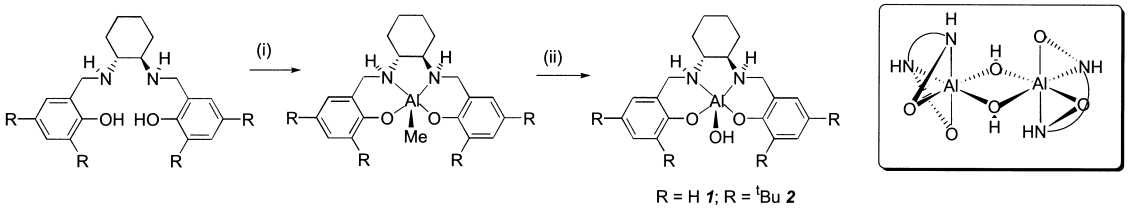
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01002-9

We report here the first examples of chiral salan complexes of aluminium and their application in asymmetric catalysis, specifically in the phospho-aldol reaction. Complexes [(*R*,*R*)-salcyan]-Al(OH) **1** and [(*R*,*R*)-^{t}Bu$_4$-salcyan]Al(OH) **2** were prepared using procedures developed by Atwood and co-workers[10] for achiral variants (Scheme 2). We find that both **1** and **2** act as highly active precursors for the catalytic addition of dimethyl-*H*-phosphonate (DMHP) to benzaldehydes but significant differences in catalytic behaviour to their close relatives, [(*R*,*R*)-salcyen]AlMe **3** and [(*R*,*R*)-^{t}Bu$_4$-salcyen]AlMe **4**, are noteworthy.



Scheme 2. Syntheses of **1** and **2**; (i) $AlMe_3$; (ii) H_2O. Dimeric structure of **2** from X-ray diffraction

Unsubstituted complex **3** affords greater stereoselectivities than the *t*-butyl derivative **4**[9] in the phospho–aldol reaction whereas the *reverse* is true of (*R*,*R*)-salcyan systems. Complex **1** affords ee's $<10\%$, whereas ee's $<60\%$ result in the presence of complex **2** (Table 1). Moreover, it is intriguing to note that with the (*R*,*R*)-salcyen systems the dominant product stereochemistry is *R*, whereas with the (*R*,*R*)-^{t}Bu$_4$-salcyan systems it is *S*![11] Indeed, in some cases a Δee of ca. 100% is observed between these two ligand systems.[9]

Enantioselectivities increase as catalyst loading decreases (runs 1–7) but seem to level off at ca. 1%. We envisage these results to suggest a more stereoselective catalytic species is generated as dilution increases, similar to the findings of North and co-workers in a related system for carbonyl hydrocyanation employing titanium salcyen complexes.[12] Water appears to be a competitive inhibitor of reaction but neither kills the catalyst nor affects enantioselectivity (runs 8 and 9). Consistently, the addition of a 4 Å molecular sieve prior to catalysis increases reaction yield but not ee (runs 10–13). Switching from THF solvent to either CH_2Cl_2 or toluene does not affect ee but significantly compromises yield, especially for CH_2Cl_2 (runs 17–21). With the notable exception of 4-$Me_2NC_6H_4CHO$, the presence of electron withdrawing groups in the 4-position of the aldehyde substrate results in lower ee's than for the electron donating groups. This is consistent with carbonyl activation upon metal binding being conducive to higher ee's as found in the salcyen systems.[9] We presume that competitive achiral catalysis results from the basic NMe_2 function leading to the lower than expected ee of 22% (run 16). There is little difference in the ee between DMHP (runs 5, 10, 12, 14 and 15) and DEHP (runs 22–26) although the latter results in lower turnover numbers, presumably for steric reasons.

From structural analyses of several chiral salcyen complexes[9] it is clear that the salcyen ligand prefers a meridional rather than a twisted facial coordination geometry, a feature well-documented in achiral salen chemistry.[13] However, in **2** the conformationally more flexible salcyan ligand adopts a twisted facial coordination geometry in the solid-phase as part of a bridged dimeric structure (Scheme 2, box). This has been confirmed by a single-crystal X-ray analysis of **2**. Although the solution is not of sufficient quality to warrant more detailed analysis, it clearly identifies both a dimeric hydroxy-bridged structure with the twisted ligand geometry shown in Scheme 2. Such a structure should reveal itself by four distinct ^{t}Bu-resonances in the solution ^{1}H

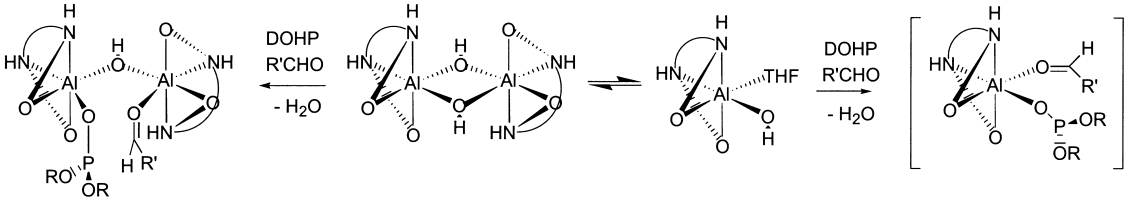
Table 1
Addition of DOHP (DMHP = dimethyl-*H*-phosphonate; DEHP = diethyl-*H*-phosphonate) to aldehydes in various distilled solvents in the presence of complex **2**. All reactions were performed in air at 298K unless specified otherwise. [a]Conversions (Con) obtained after 4 h. No product other than α-hydroxyphosphonate ester was observed. [b]Determined by $^{31}P\{^{1}H\}$ NMR in the presence of quinine as a chiral solvating agent (±2%). Absolute configurations determined to be *S* by correlation of ^{31}P NMR shifts to optical rotations. [c]Yield = 87% and ee = 53% (*S*) when reaction was performed at 273K. [d]After 12 h. [e]After 24 h. [f]With 20 mol% water added. [g]100 mol% water added. [h]In presence of 4 Å molecular sieves

Run	Cat. load[a] (%)	DOHP	Solvent	4-XC_6H_4CHO	Con. (%)[a]	E.E. (%)[b]
1	45	DMHP	THF	X = H	100	18 (*S*)
2	20	DMHP	THF	X = H	100	26 (*S*)
3	10	DMHP	THF	X = H	100	39 (*S*)
4	5	DMHP	THF	X = H	100	48 (*S*)[c]
5	1	DMHP	THF	X = H	95	59 (*S*)
6	0.5	DMHP	THF	X = H	74[d]	58 (*S*)
7	0.2	DMHP	THF	X = H	54[e]	52 (*S*)
8	5	DMHP	THF[f]	X = H	87	50 (*S*)
9	5	DMHP	THF[g]	X = H	81	52 (*S*)
10	1	DMHP	THF	X = Br	75	42 (*S*)
11	1	DMHP	THF[h]	X = Br	85	42 (*S*)
12	1	DMHP	THF	X = Me	76	57 (*S*)
13	1	DMHP	THF[h]	X = Me	88	53 (*S*)
14	1	DMHP	THF	X = OMe	91	47 (*S*)
15	1	DMHP	THF	X = NO_2	64	18 (*S*)
16	1	DMHP	THF	X = NMe_2	45	22 (*S*)
17	1	DMHP	CH_2Cl_2	X = Br	32	40 (*S*)
18	1	DMHP	CH_2Cl_2	X = Me	8	53 (*S*)
19	1	DMHP	C_7H_8	X = H	26	42 (*S*)
20	1	DMHP	C_7H_8	X = Br	60	41 (*S*)
21	1	DMHP	C_7H_8	X = Me	45	52 (*S*)
22	1	DEHP	THF	X = H	50	61 (*S*)
23	1	DEHP	THF	X = Br	47	49 (*S*)
24	1	DEHP	THF	X = Me	52	56 (*S*)
25	1	DEHP	THF	X = OMe	69	48 (*S*)
26	1	DEHP	THF	X = NO_2	14	15 (*S*)

NMR spectrum; however, NMR analyses in both $CDCl_3$ and C_6D_6 suggest a considerably more complex scenario with more than ten such resonances observable.

Although a full solid and solution phase structural analysis of **2** is currently underway, we suggest a dimer↔monomer equilibrium in solution with the monomer retaining a twisted ligand geometry (Scheme 3). Effective stereocontrol may then be achieved through complexation of both H-phosphonate and carbonyl in either a single-metal or twin-metal scenario (Scheme 3). We envisage further that since monomer should be favoured at an increasing catalyst dilution, increasing the ee's in this order may point to the monomeric form being the more stereoselective. Similarly, we propose that excessive water in the system leads to catalytic inhibition due to competitive binding of water to aluminium. Electrospray mass spectrometric analysis of **2** in a THF/MeOH solvent reveals both dimeric species *m*/*z* 1168 due to $\{[Al]\text{-}O\text{-}[Al]\}^+$ and *m*/*z* 608 due to monomeric [Al]-OMe with the latter dominating. Detailed studies to address the important questions: (i) what is the exact nature of the catalytically active metal complex(es); (ii) what are

the important features influencing stereocontrol; and (iii) how can we combine mechanistic and structure–activity studies to optimise stereoselectivities in phosphonylation processes, are in progress.



Scheme 3. Suggested role of **2** in phospho-aldol catalysis

Acknowledgements

We thank the China Scholarship Council for financial support (to M.J.), Thomas Podesta and Colin Kilner for their efforts on the X-ray structure of **2**, and the EPSRC National Mass Spectrometry Service (Swansea) for electrospray analysis of **2**. We are grateful also to Professor David Atwood (University of Kentucky) for helpful communications.

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