A bimetallic aluminium(salen) complex for asymmetric cyanohydrin synthesis

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ABSTRACT

In the presence of a phosphine oxide cocatalyst, a bimetallic aluminium(salen) complex was found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes. Under optimised conditions, enantioselectivities of 53–96% were obtained using 2 mol % of the catalyst. An analysis of the reaction kinetics showed that the reactions exhibited first-order kinetics, with the rate of reaction being independent of the aldehyde concentration.

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Bimetallic aluminium(salen) complex **1** was first introduced by Jacobsen in 2003 as a catalyst for the asymmetric Michael addition of doubly stabilised anions to α,β-unsaturated imides.[1,2] Michael additions of other nucleophiles including azide,[2] nitroalkanes,[2] cyanide,[3] oximes[4] and heterocycles[5] were also found to be catalysed by complex **1**. Subsequently, complex **1** was also found to catalyse a disparate range of other reactions. Thus, we showed that it was an exceptionally active catalyst for the synthesis of cyclic carbonates from epoxides and carbon dioxide,[6] and Zhu reported that it catalysed Passerini-type reactions between aldehydes, isocyanides and hydrogen azide.[7] In this Letter, we report for the first time that complex **1** is a highly effective catalyst for a fourth class of reaction, namely the asymmetric 1,2-addition of trimethylsilyl cyanide to aldehydes[8] forming enantiomerically enriched cyanohydrin trimethylsilyl ethers (Scheme 1).

The asymmetric addition of trimethylsilyl cyanide to aldehydes is a 100% atom economical reaction[9], which produces a product that contains a stereocentre and two functional groups, one of which is conveniently protected (Scheme 1). Prominent amongst the most effective catalysts for this reaction[8] are metal(salen) complexes, especially those of titanium[10] **2** or vanadium[11] **3** which have been commercialised.[12] Manganese,[13] lithium[14] and mononuclear aluminium(salen) complexes[15,16] have also previously been used to catalyse asymmetric cyanohydrin synthesis. However, the use of bimetallic aluminium complex **1** as a catalyst for the asymmetric cyanation of aldehydes has not previously been reported.[17] Since the titanium[10] and vanadium(salen) complexes[11] are known to be catalytically active as bimetallic complexes, we reasoned that catalyst **1** might form a highly active catalyst for this reaction.

Initial studies into the activity of complex **1** as a catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes were carried out using benzaldehyde as substrate in dichloromethane as solvent. The enantiomeric excess of the mandelonitrile trimethylsilyl ether formed was determined by chiral GC after conversion into mandelonitrile acetate by the method of Kagan,[18] which is known not to cause any racemisation. Results are summarised in Table 1. As shown by entries 1 and 2, complex **1** displayed only a low level of catalytic activity, though both the conversion and enantioselectivity could be improved by increasing the catalyst loading 10-fold.
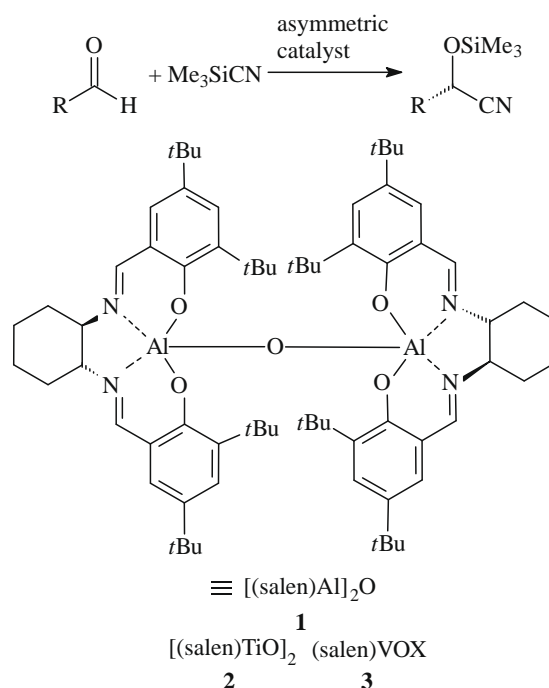
Scheme 1. Asymmetric cyanohydrin synthesis.

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Table 1
Synthesis of mandelonitrile trimethylsilyl ether using catalyst **1**[a]

Entry	**1** (mol %)	Ph$_3$PO (mol %)	Time (h)	T (°C)	Conversion[b] (%)	ee[c] (%)
1	1	—	16	rt	30	30 (S)
2	10	—	16	rt	55	50 (S)
3	1	10	2	rt	100	67 (S)
4	1	10	6	0	100	68 (S)
5	1	10	16	−20	100	80 (S)
6	1	10	16	−40	60	90 (S)
7	1	15	16	−20	100	73 (S)
8	1	7	16	−20	100	77 (S)
9	1	5	16	−20	100	73 (S)
10	1	2	16	−20	0	—
11	1	1	16	−20	0	—
12	—	10	16	rt	100	0
13	2	10	16	−40	80	89 (S)
14	3	10	16	−40	80	70 (S)

[a] All reactions were carried out in dichloromethane using 1.6 equiv of trimethylsilyl cyanide.
[b] Conversions were determined by ^{1}H NMR spectroscopy.
[c] Enantioselectivities were determined by chiral GC analysis after conversion of the cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin acetates.

Table 2
Synthesis of cyanohydrin trimethylsilyl ethers using catalyst **1**[a]

Aldehyde	**1** (mol %)	Time (h)	T (°C)	Conversion[b]	ee[c]
2-MeC$_6$H$_4$CHO	2	16	−40	88	93 (S)
3-MeC$_6$H$_4$CHO	2	16	−40	61	96 (S)
4-MeC$_6$H$_4$CHO	2	16	−40	54	83 (S)
4-MeC$_6$H$_4$CHO	2	24	−40	63	81 (S)
4-MeC$_6$H$_4$CHO	3	16	−40	63	81 (S)
4-MeC$_6$H$_4$CHO	2	16	−20	100	71 (S)
4-F$_3$CC$_6$H$_4$CHO	2	16	−40	100	87 (S)
4-F$_3$CC$_6$H$_4$CHO	2	16	−60	35	79 (S)
4-FC$_6$H$_4$CHO	2	16	−40	83	90 (S)
4-ClC$_6$H$_4$CHO	2	16	−40	83	87 (S)
3-ClC$_6$H$_4$CHO	2	16	−40	90	84 (S)
Me(CH$_2$)$_7$CHO	2	16	−40	100	68 (S)
Me$_3$CCHO	2	16	−40	91	63 (S)
Me$_3$CCHO	2	16	−60	100	37 (S)
CyCHO	2	16	−40	100	53 (S)

[a] All reactions were carried out in dichloromethane using 1.6 equiv of trimethylsilyl cyanide and 10 mol % of triphenylphosphine oxide.
[b] Conversions were determined by ^{1}H NMR spectroscopy.
[c] Enantioselectivities were determined by chiral GC analysis after conversion of the cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin acetates.

Literature precedent[15] suggested that whilst aluminium(salen) complexes can function as effective chiral Lewis acids for asymmetric cyanohydrin synthesis, they require the additional presence of a Lewis base to activate the trimethylsilyl cyanide.[19] Therefore, the effect of adding triphenylphosphine oxide as an inexpensive Lewis basic additive was investigated. As shown by entries 3–6, addition of 10 mol % of triphenylphosphine oxide had a very beneficial effect on both the conversion and enantioselectivity of the reaction. At room temperature (entry 3), the reaction was complete in just 2 h, though the enantioselectivity remained modest. Reducing the reaction temperature (entries 4–6) significantly improved the enantioselectivity of the reaction (up to 90% at −40 °C), though at the expense of an increase in reaction time, and at −40 °C the reaction was not complete after 16 h. The effect of changing the amount of triphenylphosphine oxide additive employed was investigated at −20 °C, though as entries 5 and 7–11 show, use of less than 10 mol % reduced the enantioselectivity and if 1 or 2 mol % of additive was used, no reaction occurred at this temperature. Use of more than 10 mol % of triphenylphosphine oxide was detrimental to the enantioselectivity (entry 7), an effect which could be traced to triphenylphosphine oxide acting as an achiral catalyst in the absence of complex **1** (entry 12).

Since the highest enantioselectivity was obtained using 10 mol % of triphenylphosphine oxide at −40 °C, these were adopted as preferred conditions, and the amount of complex **1** used was increased to 2 mol % (entry 13), which increased the conversion to 80% whilst not significantly affecting the enantioselectivity of the reaction (89%). Further increase in the amount of complex **1** to 3 mol % was, however, counterproductive as the enantioselectivity of the reaction decreased to 70% (entry 14). Finally, the use of other additives was investigated under the conditions of entry 6 in an attempt to allow the amount of complex **1** used to be reduced. However, ^{n}Oct$_3$PO (10 mol %) gave just 10% conversion after a reaction time of 16 h and a conversion of 73% (89% ee) after 48 h. Similarly, pyridine N-oxide (10 mol %) gave conversions of 25% (85% ee) and 83% (80% ee) after reaction times of 16 and 48 h, respectively. Thus, although both these additives formed highly enantioselective catalysts, the rate of reaction was much slower than that observed using triphenylphosphine oxide.

The conditions of Table 1 and entry 13 were taken as the starting point for a study on the trimethylsilylation of various aldehydes,[20] the results of which are shown in Table 2. 2-Methylbenzaldehyde was found to be an excellent substrate, and the 3-methyl isomer also gave a product with very high enantiomeric excess, though

the conversion was reduced in this case. 4-Methylbenzaldehyde was a more difficult substrate, giving a moderate conversion and enantioselectivity. The conversion could be increased to 63% either by increasing the reaction time or by increasing the amount of complex **1** used to 3 mol %, though neither of these increased the enantioselectivity of the reaction. Increasing the reaction temperature to −20 °C did result in complete reaction after 16 h, but at the expense of a further 10% decrease in the enantioselectivity.

Electron-deficient aromatic aldehydes were found to be good to excellent substrates. Thus, 4-trifluoromethylbenzaldehyde gave complete conversion and 87% enantioselectivity under the standard conditions. In view of the high reaction rate exhibited by this substrate at −40 °C, an attempt was made to enhance further the enantioselectivity by performing the reaction at −60 °C. However, this resulted in a dramatic decrease in conversion and a decrease in the enantioselectivity. It appears that at the lower temperature, the triphenylphosphine oxide-catalysed racemic reaction becomes more favourable than the non-racemic Lewis acid/Lewis base-catalysed process involving complex **1**. The three halo-substituted benzaldehydes studied all gave conversions and enantioselectivities between 80% and 90% under the standard conditions. The three aliphatic aldehydes studied all gave high conversions under the standard conditions, but with moderate enantioselectivities (53–68%). The lower enantioselectivities observed with aliphatic substrates are in line with results obtained with other catalytic systems.[8] With pivaldehyde as substrate, an attempt was again made to increase the enantioselectivity by reducing the reaction temperature to −60 °C, but again this resulted in a large decrease in the enantioselectivity, consistent with catalysis by triphenylphosphine oxide alone at the lower temperature.

To investigate the mechanism of catalysis, the reaction kinetics at 0 °C were studied using UV spectrophotometry at 246 nm to monitor the consumption of benzaldehyde as previously reported for the related titanium[10] **2** and vanadium[11] **3** complexes. Reactions catalysed by complex **1** were found to follow overall first-order kinetics (rate = k_{obs}[Me$_3$SiCN]) to at least 80% conversion (Fig. 1).[21] This is the same rate equation previously found for reactions catalysed by bimetallic titanium complex **2**. In contrast, reactions catalysed by monometallic vanadium complexes **3** were usually found to follow second-order kinetics, though depending on the structure of the counterion X and the reaction temperature, zero or first-order kinetics were sometimes observed.[11]

The concentrations of complex **1** and triphenylphosphine oxide do not vary during the reaction, so the observed rate constant (k_{obs})
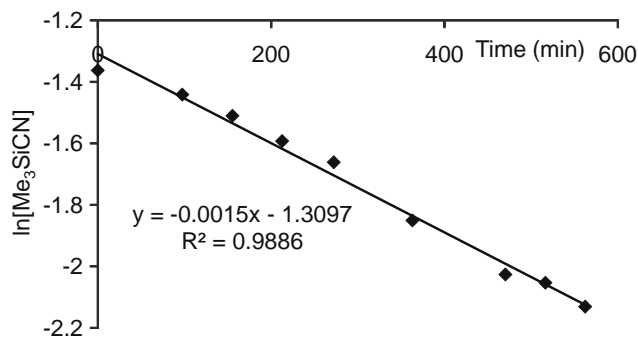
Figure 1. First-order kinetics plot for the addition of trimethylsilyl cyanide to benzaldehyde at 0 °C catalysed by complex **1** (2 mol %) in dichloromethane. $[PhCHO]_0 = 0.26$ M, $[Me_3SiCN]_0 = 0.26$ M, $[\mathbf{1}] = 0.0051$ M, $[Ph_3PO] = 0.025$ M.

is given by: $k_{obs} = k[\mathbf{1}]^x[Ph_3PO]^y$. Hence, carrying out reactions at various concentrations of complex **1** and triphenylphosphine oxide allows the order with respect to each of these components to be determined. Figure 2 shows the results of experiments carried out at different concentrations of catalyst **1** and triphenylphosphine oxide, and clearly indicates that the reaction is first order with respect to both these components.

Thus, the full rate equation can be deduced as rate = $k[\mathbf{1}][Ph_3PO][Me_3SiCN]$. A possible catalytic cycle consistent with these rate data is shown in Scheme 2. In this catalytic cycle, the trimethylsilyl cyanide is first activated by the triphenylphosphine oxide as previously reported,[19] and then complexes to catalyst **1** to form adduct **4** in the rate-determining step of the catalytic cycle. Coordination of benzaldehyde to the second metal ion of adduct **4** gives **5,** which is set up to undergo intramolecular transfer of cyanide to the Lewis acid-activated aldehyde, forming complex **6** and establishing the new stereocentre within the chiral environment of the bimetallic salen complex. Transfer of a trimethylsilyl group to the aluminium-bound cyanohydrin releases the cyanohydrin trimethylsilyl ether and regenerates complex **1** and triphenylphosphine oxide.

In conclusion, we have shown that in the presence of triphenylphosphine oxide, aluminium complex **1** is an effective catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes. The enantioselectivities obtained using catalyst **1** are comparable to those obtained using mononuclear (salen)AlCl complexes,[15b,c,f] but the synthesis of complex **1** from the chiral salen ligand can
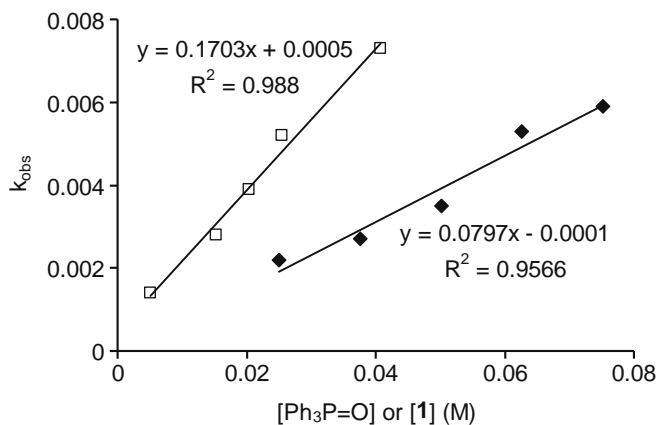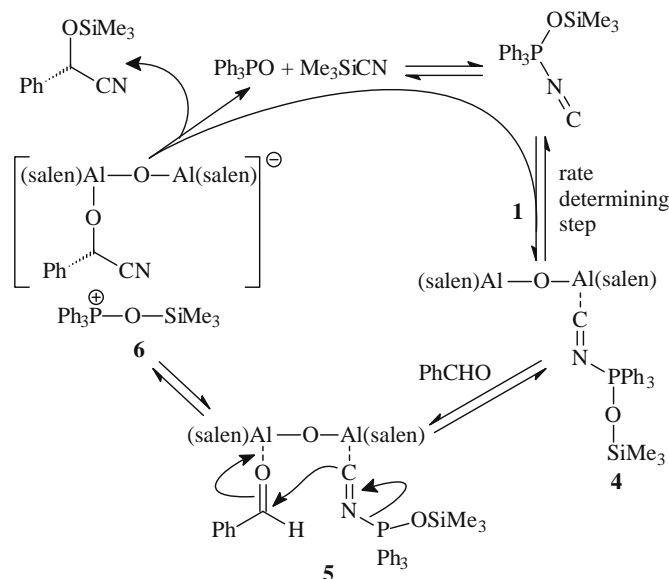

Figure 2. Plot of k_{obs} against [**1**] (open squares) and [Ph_3PO] (filled diamonds) for the addition of trimethylsilyl cyanide to benzaldehyde at 0 °C catalysed by complex **1** in dichloromethane. $[PhCHO]_0 = 0.26$ M, $[Me_3SiCN]_0 = 0.26$ M (filled diamonds) or 0.42 M (open squares), $[Ph_3PO] = 0.025$ M (open squares), $[\mathbf{1}] = 0.0051$ M (filled diamonds).

Scheme 2. Possible catalytic cycle consistent with the kinetics results.

be accomplished[6] using triethoxyaluminium rather than highly pyrophoric diethylaluminium chloride.

Acknowledgement

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17. Whilst our work was in progress, a single example of the use of a bimetallic aluminium(salen) complex similar to complex **1**, but derived from a different diamine as a catalyst for the asymmetric cyanosilylation of acetophenone in the presence of *N,N*-dimethylaniline N-oxide as a Lewis basic additive, was reported: see Ref. 15e.
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20. Typical experimental procedure: Complex **1** (0.0095–0.014 mmol, 2–3 mol %) and Ph$_3$PO (0.047 mmol, 10 mol %) were dissolved in CH$_2$Cl$_2$ (1 mL). The aldehyde (0.48 mmol) was added, and the solution was adjusted to the required reaction temperature. Me$_3$SiCN (0.76 mmol, 1.6 equiv) was then added, and the solution was stirred at the reaction temperature for 16–24 h. The solution was then passed through a short silica plug eluting with CH$_2$Cl$_2$. The eluent was evaporated in vacuo, and the residue was analysed by ^{1}H NMR spectroscopy to determine the conversion. To determine the enantiomeric excess, the cyanohydrin trimethylsilyl ether was dissolved in MeCN (1.0 mL), and Ac$_2$O (2.1 mmol, 0.2 mL) and Sc(OTf)$_3$ (5 mg, 0.010 mmol) were added. After 20 min, the reaction mixture was passed through a short silica plug eluting with MeCN. The resulting solution was analysed by chiral GC using a Supelco Gamma DEX 120 fused silica capillary column (30 m × 0.25 mm) with hydrogen as a carrier gas (flow rate 2.0 mL/min, column pressure 10 psi). Initial temperature 95 °C, final temperature 180 °C, ramp rate 5.0 °C/min except for the cyanohydrin derivative derived from 2-MeC$_6$H$_4$CHO, where a ramp rate of 2.0 °C/min was used.
21. Experiments carried out at different initial concentrations of benzaldehyde and trimethylsilyl cyanide confirmed that the reactions were first order in trimethylsilyl cyanide rather than benzaldehyde.