### Asymmetric Cyanohydrin Synthesis Catalyzed by Al(salen)/Triphenylphosphane Oxide

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Various aldehydes undergo asymmetric trimethylsilylcyanation with (CH<sub>3</sub>)<sub>3</sub>SiCN (TMSCN) in the presence of a chiral Al(salen) complex and Ph<sub>3</sub>PO as the catalyst. This is a double activation where Al(salen) plays the role of Lewis acd and POPh3 acts as a Lewis base. Various kind of aldehydes were subjected to the enantioselective addition of (CH<sub>3</sub>)<sub>3</sub>SiCN at

#### Introduction

Chiral cyanohydrins are useful intermediates because the two functional groups can be easily transformed into various homochiral ones, including  $\alpha$ -hydroxy acids,<sup>[1,2]</sup>  $\alpha$ -hydroxy aldehydes,<sup>[3]</sup>  $\alpha$ -hydroxy ketones,<sup>[3]</sup>  $\beta$ -hydroxy amines,<sup>[2,3]</sup> and  $\alpha$ -amino acid derivatives.<sup>[4]</sup> A number of catalysts for the asymmetric addition of cyanide to aldehydes<sup>[5]</sup> are known, including synthetic peptides and chiral transition metal complexes. Belokon,<sup>[6]</sup> Shibasaki,<sup>[7]</sup> Deng,<sup>[8]</sup> Hoveyda and Snapper,<sup>[9]</sup> Bu,<sup>[10]</sup> and Feng<sup>[11]</sup> have made considerable contributions to the development of catalysts for chiral silvlcyanation, and we have reported achiral silvlcyanation of aldehydes and ketones catalyzed by Nmorpholine N-oxide and various alkali fluorides.<sup>[12]</sup> The salen structure has been employed as a base with which numerous metal ions can be combined to make effective catalysts. Belokon and North et al.<sup>[6]</sup> have reported various Ti<sup>IV</sup>-salen complexes that are effective for silvlcyanation.  $[Ti(salen)(\mu-O)]_{2}^{[6b]}$  proved to be the best catalyst (52–92%) ee). The same authors<sup>[6e]</sup> also used VO(salen) as the catalyst to give 68-95% ee. Bu et al.<sup>[10]</sup> modified the substituents on the benzene ring of the salen ligand (tert-pentyl group) and combined it with  $Ti(OiPr)_4$  to give the products in 84–94% yield and 92-97% ee. We would like to report here the chiral silvlcyanation of aldehydes utilizing Al(salen) and Ph<sub>3</sub>PO as the catalyst.

### **Results and Discussion**

The quantity of Al(salen) and Ph<sub>3</sub>PO was varied at room temp. to determine the optimal yield and ee. Entries 3-6 in Table 1 show similar outcomes with different reaction times.

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temperatures between -40 °C and -50 °C. Hydrolysis of the adducts gave cyanohydrins with over 90 % yield and 80 %~eein most cases.

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The reaction conditions of entry 3 were chosen for the reaction at room temp. because of the shorter reaction time. Neither Al(salen) nor Ph<sub>3</sub>PO alone induce any enantioselectivity (entries 7 and 8). Molecular sieves (MS) or  $tBu_3PO$  were also used as the additive but gave poor *ee* (entries 9 and 10). This may indicate a double activation process occurring through the catalysis of both the chiral Lewis acid and achiral Lewis base. The Al(salen) complex functions as a Lewis acid to activate the aldehyde while Ph<sub>3</sub>PO acts as a Lewis base for the activation of TMSCN. The reaction temperature was then varied and found to be optimal at -50 °C (entry 13). The attack of cyanide should occur at the si face of the aldehyde carbonyl to afford an (R)-cyanohydrin because the *re* face is effectively blocked by bonding between the carbonyl oxygen and the Al atom of chiral Al(salen) (Figure 1).

Accordingly, structurally different aldehydes were used as substrates in the reaction under the conditions of entry 13 of Table 1. Benzaldehydes with various electron-donating substituents were transformed into chiral cyanohydrins in over 90% yield and 80% ee (Table 2, entry 1-6). However, p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CHO shows very poor reactivity towards the silvlcvanation and was isolated in low yield (40%) along with numerous other products. trans-Cinnamaldehyde underwent silvlcyanation at relatively high temperature

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Table 1. Silylcyanation of benzaldehyde catalyzed by Al(salen) under various conditions in CH<sub>2</sub>Cl<sub>2</sub>.

Entry	Substrate	Al(salen) catalyst [mol-%]	Additive Ph <sub>3</sub> PO [mol-%]	Temp.	Time	% Yield <sup>[a]</sup>	% ee	
1		5	10	r.t.	30 min	95	61	
2		1	20	r.t.	20 min	95	70	
3		1	10	r.t.	30 min	94	69	
4		1	5	r.t.	2 h	91	60	
5		0.5	10	r.t.	1 h	94	69	
6		0.1	10	r.t.	3 h	94	69	
7	$\sim$	1		r.t.	1 h			
8	Н		10	r.t.	1 h			
9		1	10 (4-Å mol. sieves)	r.t.	2 h	93	41	
10		1	10 [( <i>t</i> Bu) <sub>3</sub> PO]	r.t.	20 min	92	44	
11		1	5	-40 °C	24 h	32 <sup>[b]</sup>		
12		1	10	-40 °C	18 h	95	78	
13		1	10	-50 °C	18 h	94	86	
14		1	10	−70 °C	3 d	45 <sup>[b]</sup>		

[a] Yield of isolated product. [b] Conversion.



Figure 1. Transition state involved in the enantioselective cyanosilylation of aldehydes by double-activation catalysis.

(-40 °C) with 91% yield and 78% *ee.* Furaldehyde (entry 8) requires a shorter reaction time. 3-Phenylpropanal (entry 9) reacts smoothly with  $(CH_3)_3SiCN$  to give the chiral cyanohydrin. The reaction of trimethylsilyl cyanide with citral requires a longer reaction time and occurs with 72% *ee* (Table 2).

#### Conclusions

A highly efficient double activation catalysis has been developed for the enantioselective silylcyanation of various aldehydes. The Al atom of chiral Al(salen) activates the carbonyl oxygen for the formation of Si–O bond. Ph<sub>3</sub>PO functions as a base for transfer of the N≡C group to the carbon atom of the carbonyl. The chirality of Al(salen) controls the direction of approach of both groups to give the (R)-form of the cyanohydrin.

#### **Experimental Section**

**General Remarks**: All aldehydes and Al(salen) were purchased from Sigma–Aldrich. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Varian Jemini 2000 (200 MHz) or a Varian Unity Inova 400 (400 MHz) NMR spectrometer. Hewlett–Packard 5890A Gas Chromatograph/Jeol JMS-DX303 Mass Spectrometer was used to collect HRMS data.

Silylcyanation of the Aldehydes: The aldehyde (2 mmol) was added to a stirred CH<sub>2</sub>Cl<sub>2</sub> solution of the catalyst [1 mol-% Al(salen), 10 mol-% Ph<sub>3</sub>PO] and the mixture stirred for 30 min at between-40 °C and -50 °C. TMSCN (2.4 mmol) was then added with a syringe pump and the mixture was stirred at the same temperature for 18-20h. The solvent was then evaporated, 2 N HCl (10 mL) was added, and the mixture was stirred vigorously at room temp. for 1 h to hydrolyze the trimethylsilyl ether. After addition of ethyl acetate (30 ml), the mixture was stirred for 30 min. The organic layer was separated and washed with H<sub>2</sub>O. The aqueous layer was extracted with ethyl acetate (2×20 mL), and the combined organic layers were washed with brine and dried with Na2SO4. The crude product was further purified by flash chromatography (hexane/ ethyl acetate, 9:1) to give the cyanohydrin in more than 90% yield. The enantiomeric excess of the products was determined after conversion to acetyl ester, ethyl carbonate, or tert-butyl dimethylsilyl ether by known methods. The sample was identified by <sup>1</sup>H and <sup>13</sup>C

#### Table 2. Trimethylsilylcyanation of aldehydes with Al(salen) and Ph<sub>3</sub>PO.

0 	Al(salen) (1%), Ph <sub>3</sub> PC	D(10%) H	OSiMe <sub>3</sub>	ОН <sub>Н2</sub> О Н <sub>/////</sub>	I
Ar	H -40 to -50 °C CH <sub>2</sub>		CN	Ar	`CN
Entry	Substrate	Time	Temp.	% Yield	% ee
1	Н	[n] 18		94	( <i>R</i> or S) 86 ( <i>R</i> )
2	CI H	18	50	96	86 ( <i>R</i> )
3	MeO	18	50	92	82 ( <i>R</i> )
4	н,с н	22	-45	94	72 ( <i>R</i> )
5	N N N N N N N N N N N N N N N N N N N	21	45	93	73 ( <i>R</i> )
6	CHO CHO	20	50	93	81 ( <i>R</i> )
7	Clio	26	40	91	78 ( <i>R</i> )
8	O H	18	-50	93	78 ( <i>R</i> )
9	CHO	21	50	93	79 ( <i>R</i> )
10	СНО	24	-50	93	72 ( <i>R</i> )

NMR spectroscopy and HRMS, and the *ee* was determined on a chiral HPLC column (DAICEL CHIRALCEL OD and DAICEL CHIRALCEL AS). All data was in accordance with literature values. Absolute configurations were determined by optical rotation.<sup>[6b,13]</sup>

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