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Short Communication

A practical Ti-salen catalyst based on dimeric salen ligand for asymmetric addition of trimethylsilyl cyanide to aldehydes

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ABSTRACT

A dimeric salen ligand derived from L-tartaric acid was synthesized through linking two salen units with 1,6dibromohexane. The corresponding Ti complex was proved to be an efficient catalyst for asymmetric addition of trimethylsilyl cyanide to aldehydes, providing the corresponding optically active trimethylsilyl ether of cyanohydrins with moderate to good enantiomeric excesses and excellent yields under relatively low catalyst loading condition.

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1. Introduction

Chiral cyanohydrins are important intermediates because their two functional groups can be readily transformed into a large range of biologically important compounds, including α -hydroxy acids and esters, α -hydroxy aldehydes and ketones, α -amino acids, and β amino alcohols [1,2]. The asymmetric addition of cyanide to carbonyl compounds is one of the most useful carbon-carbon bond forming reactions in organic synthesis for producing optically active cyanohydrin derivatives. Many efforts have been devoted to this reaction and a great number of effective chiral catalysts have been developed [3-8]. After the pioneering work by Oguni and Hayashi on the enantioselective silylcyanation of aldehydes using an optically active Schiff base ligand [9-11], the Ti-salen complexes are recognized as highly promising catalysts for asymmetric addition of trimethylsilyl cvanide to aldehvdes because of their easy availability [6.7.12–14]. Recently, the major breakthrough for enantioselective cyanation of aldehydes has been done by Ding and coworkers using binuclear Tisalen catalysts connected by organic linkages to dramatically enhance the catalytic activity and enantioselectivity based on cooperative catalysis [15]. A feature of these most effective catalysts is the need for forming the intramolecular bimetallic Ti-salen centers which activate the cyanide and aldehyde, respectively [16-20].

Inspired by these pioneering works for the development of practical and highly effective catalytic systems for the synthesis of chiral cyanohydrins and our early works in asymmetric reactions by metal salen catalysts [21–24], herein we describe the preparation and application of the dimeric salen ligand in the Ti-catalyzed asymmetric silylcyanation of aldehydes.

2. Experimental

2.1. General

All reactions were carried out under argon in dried glassware. CH_2Cl_2 , $CHCl_3$ and $ClCH_2CH_2Cl$ were distilled from CaH_2 and stored under argon prior to use. Toluene was distilled from Na and stored under argon prior to use. Et_2O was freshly distilled from Na/benzophenone under argon. $Ti(O^iPr)_4$ (from Alfa) was distilled and diluted to 0.1 M in CH_2Cl_2 . The synthesis of *N'*, *N''*-bis(3,5-di-*tert*-butylsalicylidene)-pyrrolidine-(3*R*, 4*R*)-diamine (1) was carried out according to the reported procedures [25].

2.2. Preparation of chiral pyrrolidine dimeric salen ligand 2

A solution of pyrrolidine salen ligand 1 (1 mmol), 1,6-dibromohexane (0.45 mmol) and DIPEA (3 mmol) in toluene 3 mL under an argon atmosphere was stirred at 90 °C for 48 h. Then the reaction mixture purified by column chromatography on silica gel (petroleum ether/ EtOAc = 15:1) to afford the corresponding ligand.

Yield, 35%; $[\alpha]_D^{20} = -241$ (c = 1.0, CH_2Cl_2); FT-IR (KBr): 2958, 2867, 1649, 1626, 1595, 1469, 1439, 1391, 1025; ¹H NMR (400 MHz, CDCl₃): $\delta = 13.44$ (s, 4H, OH), 8.22 (s, 4H, CH N), 7.37 (d, J = 2.4 Hz,

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Scheme 1. The synthesis of dimeric salen ligand 2.

4H, ArH), 7.04 (d, J=2.4 Hz, 4H, ArH), 3.96 (t, J=5.2 Hz, 4H, CH), 3.12–3.09 (m, 4H, CH₂), 2.95–2.93 (m, 4H, CH₂), 2.61–2.57 (m, 2H, CH₂), 2.51–2.47 (m, 2H, CH₂), 1.60–1.56 (m, 4H, CH₂), 1.43 (s, 36H, CH₃), 1.33 (s, 4H, CH₂), 1.27 (s, 36H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ =166.4, 157.9, 140.2, 136.6, 127.8, 127.1, 117.6, 75.3, 60.8, 56.3, 35.0, 34.1, 31.4, 29.4, 28.6, 27.5. HRMS (ESI-MS) calcd. for C₇₄H₁₁₃N₆O₄ [M + H]⁺: 1149.8823, found: 1149.8800.

2.3. Preparation of Ti catalyst 3 based on chiral pyrrolidine dimeric salen ligand 2

A solution of Ti($O^{i}Pr$)₄ (2 equiv., 0.1 M in CH₂Cl₂) was added to a solution of ligand 2 (1 equiv.) in CH₂Cl₂ under argon. The mixture was allowed to stir at room temperature for 12 h before H₂O (10 equiv.) was added. Then the mixture was stirred for additional 5 h followed by evaporation of the solvent and the volatile compounds under reduced pressure at room temperature. The resulting yellow solid dried *in vacuo*.

FT-IR (KBr): 2958, 2867, 2795, 1626, 1555, 1468, 1440, 1098, 1024, 803, 701, 475; Anal. Calcd for $C_{74}H_{108}N_6O_6Ti_2 \cdot 2H_2O \cdot CH_2Cl_2$: C 64.60; H 8.24; N 6.03; Found: C 64.22; H 8.43; N 5.80; MALDI-MS, *m*/*z* = 1391.7.

2.4. General procedure for the asymmetric addition of trimethylsilylcyanide to aldehydes employing 2 as catalyst



The Ti catalyst 3 (0.005 mmol) 0.1% and substrate (0.5 mmol) were added to the solvent of CH_2Cl_2 (0.5 mL) under Ar atmosphere in the test

tube and the solution was stirred for 30 min at 0 °C. Then 1.05 equiv of TMSCN (0.51 mmol) was added to the solution and the reaction was kept at 0 °C for 24 h. After that the *ee* was analyzed by GC (CP-Chirasil-Dex CB column). The products were obtained by short silica gel column chromatograph (200–300 mesh, 5:1 petroleum ether/ethyl acetate as eluent). Absolute configurations were determined by comparison of the known order of elution of the two enantiomers or the sign of optical rotation with literature data.

3. Results and discussion

We presumed to synthesize dimeric salen ligand with different length linkers and evaluated the impact on the cooperative catalytic performance. Unfortunately, the reaction between salen ligand 1 and 1,3-dibromopropane was complicated and the products were difficult to isolate. As literature reported the linker that has six atoms was favorable to enhance the enantioselectivity and reactivity of the bimetallic salen catalyst. However, the catalysts with seven or nine atom linkers have shown low activity and enantioselectivity [15]. So 1,6-dibromohexane was chosen as linker and reacted with salen ligand 1 to synthesize dimeric salen ligand 2 using a procedure described by Jacobsen (Scheme 1) [26]. The di- μ -oxotitanium catalyst 3 was prepared by the reaction of the ligand 2 and 2 equiv. of Ti(OⁱPr)₄ in CH₂Cl₂ and subsequent addition of 10 equiv. of H₂O. The emergence of new peak at 803 and 701 cm⁻¹ of the FT-IR spectrum (Fig. 1) clearly



Fig. 2. The structure of Ti catalyst 3.



Table 1

The screening of reaction conditions for the addition of TMSCN to benzaldehyde using catalyst 3^a.

					OTMS	
	CHO + TMSC	N —	Ti-Catalyst 3			
Entry	Catalyst (mol%)	TMSCN	Temp. (°C)	Solvent	Conv. (%) ^b	Ee (%) ^c
1	0.2	1.5	0	CH_2Cl_2	99	82
2	0.2	1.5	0	Et ₂ O	60	35
3	0.2	1.5	0	toluene	99	69
4	0.2	1.5	0	CHCl ₃	97	61
5	0.2	1.5	0	ClCH ₂ CH ₂ Cl	99	22
6	0.1	1.2	0	CH_2Cl_2	99	81
7	0.1	1.05	0	CH_2Cl_2	99	83
8	0.05	1.05	0	CH_2Cl_2	98	74
9	0.1	1.05	-10	CH_2Cl_2	86	49
10	0.1	1.05	20	CH_2Cl_2	99	55

^a All reactions were carried out at listed temperature in table for 24 h.

^b Determined by GC with n-nonane as internal standard.

^c Enantiomeric excess of silyl ether is determined by GC with a CP-Chirasil-Dex CB column.

indicated that oxo-bridges were formed in the Ti catalyst 3 [16,27]. Based on the earlier reports [15], the data of the elemental analyses and mass spectrum also supported the existence of the intramolecular Ti-O-Ti bonds in catalyst 3 (Fig. 2).

The asymmetric addition of trimethylsilyl cyanide (TMSCN) to benzaldehyde was investigated with Ti catalyst 3. Indeed, the addition reaction proceeded smoothly even in a relatively low catalyst loading (as low as 0.1 mol%) [28,29]. Further reducing the catalyst loading resulted in a lower enantioselectivity (Table 1, entry 8). Among the tested solvents, CH_2Cl_2 was the best choice for the asymmetric silylcyanation of aldehydes. The effect of the temperature was also surveyed, and the reaction at 0 °C for 24 h was a viable option.

Based on the results achieved with benzaldehyde, the asymmetric addition of trimethylsilylcyanide to various aldehydes including aro-

Table 2

Asymmetric trimethylsilylcyanation of aldehydes catalyzedby Ti catalyst 3^a.

RCHO + 1.	05 eq. TMSCN <u>3, 0.1 mol %</u> , CH ₂ CL ₂ 0 °C	OTMS R * CN	
Entry	Aldehyde	Yield (%) ^b	ee (%) ^c
1	Benzaldehyde	98	82 (S)
2	4-methylbenzaldehyde	97	75 (S)
3	3-methylbenzaldehyde	90	86 (S)
4	2-methylbenzaldehyde	90	66 (S)
5	4-methoxybenzaldehyde	73	75 (S)
6	3-methoxybenzaldehyde	92	76 (S)
7	2-methoxybenzaldehyde	94	85 (S)
8	4-chlorobenzaldehyde	98	81 (S)
9	2-chlorobenzaldehyde	95	57 (S)
10	2,6-dichlorobenzaldehyde	96	37
11	2-bromobenzaldehyde	96	41
12	4-trifluoromethylbenzaldehyde	95	62 (S)
13	Furfural	93	70 (S)
14	Cinnamaldehyde	66	12(S)
15	Trimethylacetaldehyde	70	13 (S)
16	Heptaldehyde	90	64 (S)

 $^{\rm a}$ All reactions were carried out using 0.1 mol% of Ti catalyst 3 in $\rm CH_2Cl_2$ at 0 °C for 24 h.

^b Isolated yield.

^c Enantiomeric excess of silyl ether is determined by chiral GC with a CP-Chirasil-Dex CB column. Absolute configurations were determined by comparison of the known order of elution of the two enantiomers or the sign of optical rotation with literature data.

matic and aliphatic derivatives catalyzed by 3 was investigated under the optimized conditions, and the data were listed in Table 2. The results indicated that introduction of an electron-withdrawing group on the benzene ring disfavored to the stereocontrol of the reaction (Table 2, entries 9–12). On the other hand, the electron-rich aromatic aldehydes were transformed into the corresponding chiral products of cyanohydrins in similar or a slightly lower enantioselectivities than that of benzaldehyde. The steric properties of the aromatic aldehydes have great effect on the ee values of the products in this reaction. The orthosubstituted aromatic aldehydes gave lower ee value and yield than the meta-substituted and para-substituted aromatic aldehydes. Furfural also gave rise to a lower *ee* value than that of benzaldehyde (Table 2, entry 13). Aliphatic aldehydes, such as heptaldehyde, also reacted smoothly in a 64% ee. Unfortunately, trimethylacetaldehyde did not furnish a satisfactory result due to the hindrance of corresponding tert-Butyl group (Table 2, entry 15). These results also provide evidence that steric congestion is determinant for the reactivity and enantioselectivity. In terms of reactivity, reaction of all aromatic and aliphatic aldehydes could give good chemical yield with relatively low catalyst loading except trimethylacetaldehyde and cinnamaldehyde.

4. Conclusion

In summary, we synthesized a dimeric salen ligand and the corresponding Ti complex from chiral pyrrolidine diamine. The Tisalen complex was successfully utilized as catalyst in the asymmetric silylcyanation of aldehydes, showing moderate to good catalytic activity and stereoselectivity under mild conditions. Further studies will focus on expanding the scope of these ligands derived from chiral pyrrolidine diamine in asymmetric reactions.

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