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Fine Modification of Salen Ligands – Effects on the Salen–Ti-Catalyzed Asymmetric Cyanosilylation of Aldehydes

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New bifunctional *N*-oxide salen–Ti^{IV} complexes and a pyrrolidine salen–Ti^{IV} complex in combination with achiral *N*-oxide were developed and applied to the asymmetric addition of trimethylsilyl cyanide to aldehydes. Notably, both enantiomers of trimethylsilyl ethers of cyanohydrins could be easily prepared by modifying the catalysts employed in this reaction, which are based on the same chiral diamine collar derived from L-tartaric acid. The products were obtained generally with moderate to good enantiomeric excesses and excellent yields by using relatively low catalyst loadings and only 1.05 equivalents of trimethylsilylcyanide (TMSCN).

Introduction

Chiral cyanohydrins are versatile building blocks, because their two functional groups can be readily manipulated to produce 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, which have been widely used as the components of industrially valuable products such as pharmaceuticals, agrochemicals, flavorings, and fragrances.[1,2] For this reason, design and synthesis of chiral catalysts for asymmetric addition of cyanide to carbonyl compounds to form cyanohydrins is of current interest in synthetic chemistry.[2e,3] A variety of enantioselective catalytic systems have been employed for these additions, providing enantiomerically enriched products in many cases.[2,4] The majority of the catalysts are chiral transition metal complexes, which are generated from Ti^{IV}, Al^{III}, V^{IV}, Mn^{III}, some lanthanides, and chiral ligands.[2c,5] Prominent amongst the most effective catalysts for these reactions are metal–salen complexes,[6] especially those of titanium.[2] Meanwhile, adding a base in a metal–salen catalytic system to construct a two-component (dual activation) catalytic system is well known, and this strategy has been used for the asymmetric cyanation of aldehydes[2d] and ketones with trimethylsilyl cyanide,[7] in which process the base additive activates the cyanosilylation agent and facilitates cyanide delivery to the activated substrate.[8] Based on the above dual activation phenomenon, the "two-center catalysis" following the pioneering work of Shibasaki and co-workers[9] is a conceptually new strategy for enantioselective synthesis. This strategy has led many researchers to fabricate single-component bifunctional catalysts to facilitate the reaction in a synergistic manner similar to enzymatic processes.[8] Generally, the catalysts consist of LALB (Lewis acid/Lewis base) or LABB (Lewis acid/Brønsted base) moieties capable of simultaneously activating both electrophiles and nucleophiles. This synergistic function makes the two substrates more reactive and controls their orientation to improve the enantioselectivity.[8,10] So it is no surprise that this type of catalysts have achieved a pinnacle in asymmetric cyanation.

Although impressive enantiomeric excesses have been obtained in some cases, these reactions are still a great challenge in terms of the efficiency, cost, and adaptability of the catalysis,[11] and it is highly desired to develop more efficient and adaptable catalysts that have the ability to efficiently enhance the reactivity and to regulate its orientation in an asymmetric atmosphere. In recent years, metal complexes of chiral *N*-oxide have been disclosed as highly effective bifunctional catalysts in many asymmetric procedures.[12] For example, Feng and co-workers reported that chiral *N*-oxide complexes can efficiently catalyze the asymmetric cyanosilylation of imines,[13] aldehydes,[14] and ketones.[15] Inspired by the above pioneering studies using chiral *N*-oxide complexes as efficient bifunctional catalysts and our early work in asymmetric reactions with salen-type complexes,[16–19] we initiated a study to synthesize some new bifunctional *N*-oxide salen–Ti catalysts and provide a comparison of the catalytic activity and the asymmetric induction ability of *N*-oxide salen–Ti catalysts and a pyrrolidine salen Ti^{IV} complex with achiral *N*-oxide for the cyanosilylation of aldehydes.

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Results and Discussion

The *N*-oxide salen-type ligands **1a**–**1c** (Figure 1) were synthesized from the corresponding salen ligands and *m*-chloroperoxybenzoic acid (*m*-CPBA). With the above bifunctional ligands in hand, we first examined the asymmetric cyanosilylation of benzaldehyde with trimethylsilylcyanide (TMSCN). The catalysts were first prepared in situ by stirring the *N*-oxide salen ligands with $Ti(OiPr)_4$ at ambient temperature for 2 h in dichloromethane, then the experiments were carried out at 0 °C using 2 mol-% catalyst loading for 15 h. The data indicated that the *N*-oxide salen–Ti complexes were able to catalyze the reaction in good yields; however, the enantioselectivity was very poor; the 3,5-di-*tert*-butyl-substituted ligand gave the highest enantioselectivity (Table 1, entries 1–3). For comparison, the conventional 3,5-di-*tert*-butyl-substituted ligand **2a** was also tested in the same reaction, and an 81% *ee* was observed under the same conditions (Table 1, entry 4). The prepared Ti complexes **4** and **5** (Figure 2) derived from ligands **1a** and **2a**, respectively, were directly employed as catalysts, achieving similar results with those of catalysts prepared in situ (Table 1, entries 1, 4–6). On the basis of the above results, *N*-oxide salen–Ti complex **4** and salen complex **5** were employed as catalysts for evaluating the effects of the solvents. Complex **4** promoted the reaction well in all tested solvents. Toluene gave the highest enantioselectivity (Table 1, entry 8). The effect of the solvents was obvious for salen complex **5**, and the best result was obtained in CH_2Cl_2 (Table 1, entry 6). Reaction in $ClCH_2CH_2Cl$ resulted in a comparable outcome both in yield and *ee* (Table 1, entry 15).

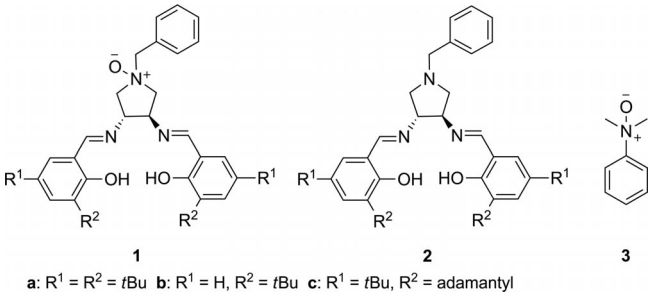
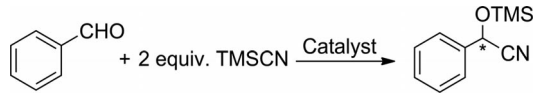


Figure 1. Achiral *N*-oxide and chiral ligands used in this study.

Compared with the structure of complex **5**, **4** possessed an *N*-oxide group in the pyrrolidine ring (Figure 2). The difference led to a great diversity in the enantioselectivity (Table 1, entries 5, 6). A possible explanation for this reduced asymmetric induction ability of **4** is that there may be interaction between the *N*-oxide group and the titanium center of the complex. The other reason is that the *N*-oxide group of the salen unit could activate TMSCN and accelerate the reaction. So, the catalytic effect of the *N*-oxide group is predominant when utilizing a high loading of *N*-oxide salen–Ti catalyst. An interesting observation is that both Ti complexes derived from the same chiral diamine could give rise to different enantiomers of products. The phenomenon is evidently caused by the *N*-oxide group.

Table 1. The screening of reaction conditions for the addition of TMSCN to benzaldehyde.[a]



Entry	Catalyst (mol-%)	Solvent	Conv.[b] [%]	*ee*[c] [%]
1	**1a** + $Ti(OiPr)_4$ (2)	CH_2Cl_2	99	24 (*R*)
2	**1b** + $Ti(OiPr)_4$ (2)	CH_2Cl_2	90	10 (*R*)
3	**1c** + $Ti(OiPr)_4$ (2)	CH_2Cl_2	75	11 (*R*)
4	**2a** + $Ti(OiPr)_4$ (2)	CH_2Cl_2	94	81 (*S*)
5	**4** (2)	CH_2Cl_2	99	25 (*R*)
6	**5** (2)	CH_2Cl_2	98	85 (*S*)
7	**4** (2)	Et_2O	99	29 (*R*)
8	**4** (2)	toluene	98	32 (*R*)
9	**4** (2)	THF	98	11 (*R*)
10	**4** (2)	iPr_2O	98	24 (*R*)
11	**5** (2)	Et_2O	31	57 (*S*)
12	**5** (2)	THF	35	84 (*S*)
13	**5** (2)	toluene	69	77 (*S*)
14	**5** (2)	$CHCl_3$	74	27 (*S*)
15	**5** (2)	$ClCH_2CH_2Cl$	93	84 (*S*)

[a] All reactions are carried out at 0 °C for 15 h. [b] Determined by GC with nonane as internal standard. [c] The enantiomeric excess of silyl ether is determined by chiral GC with a CP-Chirasil-Dex CB column. The absolute configuration is based on the known order of elution of the two enantiomers.

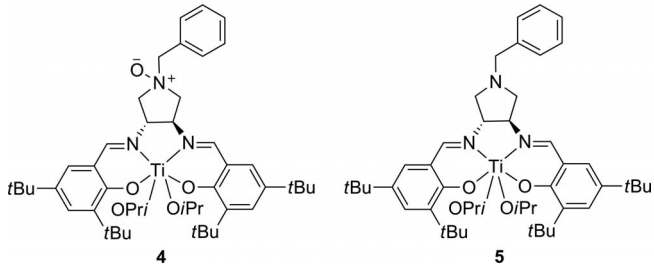
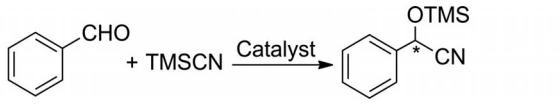


Figure 2. Ti complexes **4** and **5** derived from ligands **1a** and **2a**, respectively.

In order to determine the importance of the role played by the *N*-oxide group of the salen unit in enhancing the reactivity and nucleophilicity of TMSCN, control experiments were carried out with benzaldehyde as substrate and ligand **1a** or **2a** alone as catalyst. As shown in Table 2 (entry 9), ligand **2a** could not promote the addition reaction. Indeed, the addition reaction occurred in the presence of the *N*-oxide salen ligand **1a** (Table 2, entry 1). A new signal that appeared at 0.17 ppm in the ^1H NMR spectrum, between the *N*-oxide salen ligand **1a** and TMSCN, was in agreement with Feng's[7a,7b] reports and could also reveal that coordination existed in the *N*-oxide group and TMSCN (see Supporting Information, Figure S1).

Encouraged by the above findings, we set out to examine other reaction factors. Generally, the enantioselectivity could be improved by lowering the temperature of the reaction. When the temperature was lowered to –20 °C, catalyst **4** gave the product quantitatively in a 41% *ee* (Table 2, entry

Table 2. The screening of reaction conditions for the addition of TMSCN to benzaldehyde.[a]



Entry	TMSCN [equiv.]	*T* [°C]	Catalyst (mol-%)	Conv.[b] [%]	*ee*[c] [%]
1	2	0	**1a** (2)	36	0
2	2	–20	**4** (2)	98	41 (*R*)
3	2	–40	**4** (2)	97	39 (*R*)
4	1.5	–20	**4** (1)	98	70 (*R*)
5	1.2	–20	**4** (1)	97	71 (*R*)
6	1.05	–20	**4** (1)	95	70 (*R*)
7	1.05	–20	**4** (0.5)	98	78 (*R*)
8	1.05	–20	**4** (0.2)	69	65 (*R*)
9	2	0	**2a** (2)	0	0
10	1.5	0	**5** (2)	87	85 (*S*)
11	1.5	0	**5** (2) + **3** (2)	99	82 (*S*)
12	1.5	0	**5** (1) + **3** (1)	99	86 (*S*)
13	1.5	0	**5** (0.5) + **3** (0.5)	73	67 (*S*)
14	1.2	0	**5** (1) + **3** (1)	99	87 (*S*)
15	1.05	0	**5** (1) + **3** (1)	99	86 (*S*)
16	1.05	–10	**5** (1) + **3** (1)	98	90 (*S*)
17	1.05	–20	**5** (1) + **3** (1)	89	86 (*S*)

[a] Conditions: runs in entries 1–8 were carried out in toluene for 20 h, runs in entries 9–15 were carried out in CH_2Cl_2 for 15 h, and runs in entries 16–17 were carried out in CH_2Cl_2 for 24 h. [b] Determined by GC with nonane as internal standard. [c] The enantiomeric excess of silyl ether was determined by chiral GC with a CP-Chirasil-Dex CB column. The absolute configuration is based on the known order of elution of the two enantiomers.

2). Continuously lowering the temperature led to a slight decrease of the enantioselectivity. It is well known that enantioselectivity could be increased by reducing the catalyst loading in the asymmetric addition of TMSCN to aldehydes.[5b,5c] In this regard, the effect of varying the ratio of catalyst and substrate was also investigated. As shown in Table 2, the enantiomeric excess of product could be improved significantly from 41% to 78% when the catalyst loading was reduced to 0.5 mol-% (Table 2, entry 7). The parameters of this reaction promoted by complex **5** were also screened. As a control experiment, an achiral *N*-oxide **3** was introduced to the reaction.[7a] By the aid of the *N*-oxide **3**, the amount of TMSCN could also be reduced to 1.05 equiv. compared to the amount of aldehyde. At –10 °C, silyl ether could be formed in 98% yield and 90% *ee* with 1.0 mol-% **5** and 1.0 mol-% *N*-oxide **3** (Table 2, entry 16). Further lowering of the temperature resulted in a decrease both in yield and enantioselectivity (Table 2, entry 17). Hence, the optimal conditions were 1.0 mol-% **5** and 1.0 mol-% achiral *N*-oxide **3** (TMSCN/aldehyde = 1.05), CH_2Cl_2, –10 °C.

The purpose of this work is to compare the catalytic activity and the asymmetric induction ability of the two catalytic systems. After screening the reaction conditions, the reactions of various aldehydes, including aromatic, olefinic, and aliphatic derivatives, with TMSCN were carried out under the optimal conditions, by employing bifunctional *N*-oxide salen–Ti complex **4** or salen–Ti complex **5** together with *N*-oxide **3** as catalysts. The results are summarized in Table 3.

Table 3. Cyanation of aldehydes with TMSCN.

Entry	Aldehyde	Catalyst **4**[a]		Catalyst **5**[b]	
		Yield[c] [%]	*ee*[d] [%]	Yield[c] [%]	*ee*[d] [%]
1	benzaldehyde	95	78 (R)	96	90 (*S*)
2	4-methyl-benzaldehyde	94	68 (R)	60	86 (*S*)
3	3-methyl-benzaldehyde	92	70 (R)	98	87 (*S*)
4	2-methyl-benzaldehyde	90	58 (R)	93	67 (*S*)
5	4-methoxy-benzaldehyde	94	88 (R)	56	87 (*S*)
6	3-methoxy-benzaldehyde	91	79 (R)	98	84 (*S*)
7	2-methoxy-benzaldehyde	85	71 (R)	85	82 (*S*)
8	4-chloro-benzaldehyde	93	69 (R)	95	89 (*S*)
9	2-chloro-benzaldehyde	92	42 (R)	96	51 (*S*)
10	2,6-dichloro-benzaldehyde	91	9	97	39
11	2-bromo-benzaldehyde	95	38	96	27
12	4-trifluoromethyl-benzaldehyde	98	56 (R)	93	35 (*S*)
13	furfural	91	46 (R)	80	69 (*S*)
14	cinnamaldehyde	97	59 (R)	70	61 (*S*)
15	trimethyl-acetaldehyde	86	21 (R)	88	48 (*S*)
16	heptaldehyde	93	34 (R)	90	78 (*S*)

[a] All reactions were carried out in the present of 0.5 mol-% of **4** in toluene for 20 h at –20 °C. [b] All reactions were catalyzed by 1 mol-% of **5** in combination with 1 mol-% of **3** in CH_2Cl_2 for 24 h at –10 °C. [c] Isolated yield. [d] The enantiomeric excess of silyl ether was determined by chiral GC with a CP-Chirasil-Dex CB column. The absolute configurations were determined by comparison the known order of elution of the two enantiomers or the sign of the optical rotation with literature data.

The data shown in Table 3 indicated that higher enantiomeric excesses were obtained with electron-rich aromatic aldehydes, while electron-deficient aromatic aldehydes gave lower enantiomeric excesses for both catalyst systems. It is evident that the steric properties of the aromatic aldehydes have a great effect on the *ee* values of the products in this reaction. The *ortho*-substituted aromatic aldehydes gave lower *ee* than the *meta*-substituted and *para*-substituted aromatic aldehydes. In terms of chemical yield, *para*-substituted aromatic aldehydes were superior to *meta*- or *ortho*-substituted ones. Curiously, the electron-rich 4-methyl benzaldehyde and 4-methoxybenzaldehyde were converted with moderate yields and better enantioselectivities when employing complex **5** and *N*-oxide **3** as catalyst. For these two

substrates, using complex **4** as catalyst led to excellent yields (Table 3, entries 2, 5). Moderate enantioselectivities were achieved in the cyanation of furfural and cinnamaldehyde with the two catalyst systems; a better yield was observed by using complex **4** (Table 3, entries 13, 14). The reactions of *n*-heptaldehyde and trimethylacetaldehyde gave a high catalytic activity and low asymmetric induction ability (Table 3, entries 15, 16).

Conclusions

Two catalytic systems based on the same chiral diamine derived from L-tartaric acid have been developed for the addition of TMSCN to aldehydes by employing relatively low catalyst loading and 1.05 equiv. of TMSCN. The performance of bifunctional catalyst **4** and catalyst **5** in combination with **3** is compared. A variety of aldehydes were converted into the corresponding trimethylsilyl ether of cyanohydrins in good yields with moderate to excellent enantioselectivities. Bifunctional catalyst **4**, bearing an *N*-oxide group in the ligand, shows better catalytic activity than complex **5** even at low catalyst loading. However, the asymmetric induction ability of catalyst **4** is inferior to **5** together with *N*-oxide compound **3**. These studies also indicated that an entire reversal of enantioselectivity was achieved by adding an *N*-oxide group onto the ligand. Further investigations to clarify the reaction mechanism and efforts to extend the use of the present catalytic system in other asymmetric reactions are currently in progress.

Experimental Section

General Procedure for the Asymmetric Addition of Trimethylsilylcyanide to Aldehydes with Complex 4 as Catalyst: Complex **4** (1.6 mg, 0.002 mmol, 0.5 mol-%) and substrate (0.4 mmol) were added to the solvent toluene (3 mL) under an Ar atmosphere in a test tube, and the solution was stirred for 10 min at –20 °C. Then, TMSCN (1.05 equiv., 0.42 mmol) was added to the solution, and the reaction mixture was kept at –20 °C for 20 h. After that, the *ee* was analyzed by GC (CP-Chirasil-Dex CB column). The desired products were obtained by short silica gel column chromatography (200–300 mesh, 5:1 petroleum ether/ethyl acetate as eluent).

General Procedure for the Asymmetric Addition of Trimethylsilylcyanide to Aldehydes with Complex 5 and *N*-Oxide 3 as Catalyst: Complex **5** (3.1 mg, 0.004 mmol, 1 mol-%) and *N*-oxide **3** (0.004 mmol, 1 mol-%) were added to the solvent CH_2Cl_2 (1 mL) under an Ar atmosphere in a test tube, and the solution was stirred for 40 min at –10 °C. Then, the substrate (0.4 mmol) was added to this solution, and the mixture was stirred for 30 min. Finally, TMSCN (1.05 equiv., 0.42 mmol) was added to the solution, and the reaction mixture was kept at –10 °C for 24 h. After that, the *ee* was analyzed by GC (CP-Chirasil-Dex CB column). The desired products were obtained by short silica gel column chromatography (200–300 mesh, 5:1 petroleum ether/ethyl acetate as eluent).

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data for products, copies of NMR spectra of the products, and copies of GC spectra.

Acknowledgments

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