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Short Communication

Enantioselective cyanation of aldehydes catalyzed by bifunctional salen–aluminum complex

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ABSTRACT

Chiral *N*-oxide salen ligands and their corresponding Al complexes were synthesized. Notably, the catalytic activity and asymmetric induction ability of the bifunctional *N*-oxide salen-Al for asymmetric cyanosilylation were compared with that of bi-component catalyst system including chiral pyrrolidine salen–Al complex and Ph_3PO. Interestingly, introducing *N*-oxide group in salen unit could enhance the activity and enantioselectivity of bifunctional catalyst without further adding Ph_3PO as co-catalyst and inverse configurations were generated from the two systems. In addition, excellent yields and high *ee* values could be obtained under milder conditions in bifunctional catalyst system compared with that of bi-component catalyst system.

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1. Introduction

Catalytic enantioselective cyanation of carbonyl compound is a pivotal process for synthesis of enantiomerically pure cyanohydrins, which are important subunits frequently found in biologically active compounds and versatile building blocks for pharmaceuticals, agrochemicals and specialty materials [1–6]. In view of their importance, much effort has been devoted to designing and synthesizing of more efficient chiral catalyst for the asymmetric cyanation of carbonyl compound [3,4,7–9]. Among the various catalysts, chiral Ti or Al–salen complexes are the most widely used and effective ones for the asymmetric cyanation reaction [10–16]. In the systems catalyzed by chiral Ti-salen complexes, Ding [14], Belokoń and North [15] gained unprecedented progress. Although significant progress has been also made in chiral Al-salen catalyzed systems [12,17], additives such as Ph_3PO or derivatives are essential to achieve high efficiency and enantioselectivity. That's to say, it was necessary to additionally add some additives to activate the cyanosilylation agent and facilitate cyanide delivery to the activated substrate. Recently, it is popular to design bifunctional asymmetric catalysts consisting of Lewis acid and Lewis base/Brønsted base moieties, which activate both electrophiles and nucleophiles at defined positions simultaneously, to avoid the use of additives. Interestingly, a number of 1,1′-bi-2-naphthol (BINOL)-based bifunctional chiral catalysts have been successfully applied in asymmetric cyanation of carbonyl compound [18–20].

On the other hand, chiral *N*-oxides have been extensively used in asymmetric reactions, such as the allylation of aldehydes [21,22], the addition of Et_2Zn to aldehyde [23], Strecker and Aldol reaction [24] and the reduction of ketones [25] and so on [26,27]. Especially, chiral *N*-oxide compounds have been relative systemically investigated for the asymmetric cyanosilylation and Feng et al. have made a significant progress in this respect [4].

In conjunction with the project on developing new tetradentate complexes as catalysts for asymmetric reactions [28–33], we wanted to apply the *N*-oxide salen ligands which have been used in the asymmetric cyanosilylation by our group (Fig. 1), and their corresponding Aluminum complexes (Fig. 2, **4**) as bifunctional catalysts to asymmetric addition of trimethylsilyl cyanide (TMSCN) to benzaldehyde. Herein, the catalytic activity and the asymmetric induction ability of the bifunctional catalysts were compared with that of the bi-component system including simple pyrrolidine salen-Al (Fig. 2, **3**) in combination with Ph_3PO. To be delighted, introducing *N*-oxide group in salen unit really enhanced the activity and enantioselectivity of bifunctional catalyst without further adding Ph_3PO as co-catalyst and inverse configurations were generated from the two systems [29].

2. Experimental

2.1. Preparation of the corresponding Al complexes 3 or 4

Chiral *N*-oxide salen and chiral pyrrolidine salen ligands were prepared as we described before [29]. The corresponding Al complex were synthesized by the reaction of equimolar amounts of ligand **1b** or **2a** and $AlEt_2Cl$ (25% w/w in heptane) in dry CH_2Cl_2 under an argon atmosphere stirring for 10 h at room temperature. Then the solvent was evaporated under vacuum and the crude product was washed with hexane to give the salen-Al **3** or **4** as a brown solid. Compound **3**:

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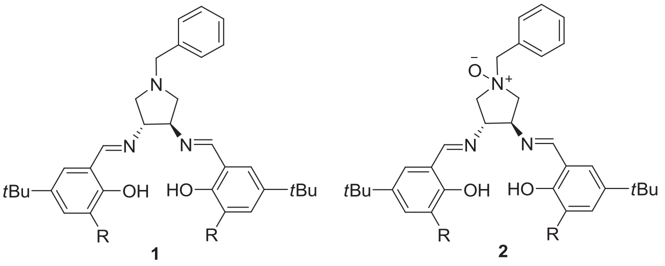


a: R = *t*Bu **b**: R = adamantyl

Fig. 1. Chiral ligands used in the study.

IR (KBr): 2958, 2906, 1623, 1555, 1540, 1466, 1438, 1391. HRMS (ESI-MS) calcd. for $C_{41}H_{55}N_3O_2Al$: $[M\text{-}Cl\text{-}O]^+$: 648.4110, found: 648.4099. Compound **4**: IR (KBr): 2957, 2906, 2868, 2796, 1626, 1469, 1440. HRMS (ESI-MS) calcd. for $C_{53}H_{67}N_3O_2Al$: $[M\text{-}Cl]^+$: 804.5049, found: 804.5029.

2.2. General procedure for the asymmetric addition of trimethylsilylcyanide to aldehydes employing complex 4 as catalyst

To a solution of complex **4** (2.8 mg, 0.004 mmol, 1 mol%) and substrate (0.4 mmol) in toluene (1 mL) under Ar atmosphere stirred for 10 min at 0 °C, 1.2 equiv. of TMSCN (0.48 mmol) was added and the reaction mixture was kept at 0 °C for 10 h. After that the *ee* was analyzed by GC (CP-Chirasil-Dex CB column). The yields 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 the known order of elution of the two enantiomers or the sign of optical rotation with literature data [34,35].

3. Results and discussion

In the preliminary experiments, the asymmetric addition of TMSCN to benzaldehyde was chosen as the model reaction to evaluate the activity and enantioselectivity of the catalyst systems. Firstly, the activities of the catalysts prepared in situ by stirring ligands with $AlEt_2Cl$ at room temperature for 2 h in dichloromethane were investigated (Table 1, entries 1, 2, 6 and 7). Interestingly, substituents at 3, 3′-position of salen ligands **1** had some effect on the *ee* values and had no influence on the yields. It was shown that adamantly larger group was beneficial to the enantioselectivity and *t*Bu group even abolished the asymmetric inductivity completely. On the other hand, the yields and the *ees* had almost no relationship with the substituents of ligand **2**. Additionally, there is only slightly increase in enantioselectivity directly employing Al-complex **3** or **4** as catalyst (entries 2 *vs* 3, and 6 *vs* 8). Obviously, Ph_3PO was important for **3** and the enantioselectivity or yield of mandelonitrile was dramatically decreased without it (entries 3 *vs* 4). However, there is no change in yield and *ee* employing **4** as the catalyst neither in the presence or absence of Ph_3PO (entries 8 *vs* 9).

Subsequently, the parameters of the reaction conditions were systematically optimized employing **3** or **4** as the catalyst respectively (see Supporting Information, Table S1 and Table S2). After rough optimization, the reaction conditions for **3** were 1 mol% catalyst, 10 mol% Ph_3PO and 2 equiv. of TMSCN in $CHCl_3$ at −10 °C for 24 h (Table 1, entry 5); on the other hand, 1 mol% catalyst and 1.2 equiv. of TMSCN in toluene at 0 °C for 10 h were the optimized conditions by employing **4** as the catalyst (Table 1, entry 10). As a whole, excellent yields and high *ee* values could be obtained under milder conditions in bifunctional catalyst system compared with that of bi-component catalyst system. Interestingly, inverse configurations were generated from the two systems.

Encouraged by the results, we further examined the utility and generality of the approach for the asymmetric addition of trimethylsilylcyanide to different aldehydes including aromatic, allylic and aliphatic derivatives catalyzed by the bifunctional *N*-oxide catalyst **4** and the data were summarized in Table 2. Most aromatic aldehydes could be transformed into the desired product with moderate to excellent *ees* and good yields (Table 2, entries 1–12). Obviously, the results indicated that the steric hindrance had great impact on the *ees* and had no significant influence on yields. The *ees* were lower for most ortho-substituted benzaldehyde than others with meta- or para-substitute (entries 2, 9, 10 and 11), especially for 2,6-dichloro benzaldehyde. However, unexpected phenomena that 4-methoxybenzaldehyde was converted with high yield in combination with low enantioselectivities and 2-methoxybenzaldehyde gave good yield and selectivity were observed (entries 5 and 7). On the other hand, the *ees* and yields have slightly relationship with the electronic effect. Particularly, 92% *ee* could be acquired employing 4-tri-fluoromethyl benzaldehyde as the substrate (entry 12). Additionally, furfural gave approximate *ee* and yield with benzaldehyde (entry 13). Furthermore, allylic aldehyde also afforded 68% *ee* with good yields (entry 14). Aliphatic aldehydes, such as heptaldehyde, reacted smoothly with TMSCN and gave a high catalytic activity with moderate asymmetric induction ability (entry 16). Unfortunately, trimethylacetaldehyde did not furnish a satisfactory result due to the influence of the corresponding *t*Bu group (entry 15). Besides,

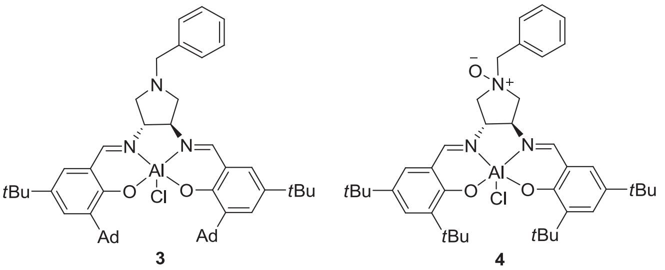
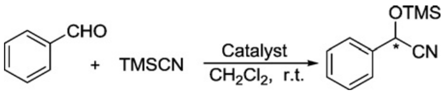


Fig. 2. The corresponding Al-complexes derived from ligands **1b** and **2a**.

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



Entry	Cat. (mol%)	TMSCN (equiv)	Ph_3PO (mol%)	Conv.[b] (%)	Ee[c] (%)
1	**1a** + $AlEt_2Cl$ (2)	1.5	10	93	rac
2	**1b** + $AlEt_2Cl$ (2)	1.5	10	92	9 (S)
3	**3** (2)	1.5	10	96	13 (S)
4	**3** (2)	1.5	0	16	8 (R)
5[d]	**3** (1)	2.0	10	99	82 (S)
6	**2a** + $AlEt_2Cl$ (2)	1.5	0	99	23 (R)
7	**2b** + $AlEt_2Cl$ (2)	1.5	0	99	25 (R)
8	**4** (2)	1.5	0	99	30 (R)
9	**4** (2)	1.5	10	99	30 (R)
10[e]	**4** (1)	1.2	0	99	80 (R)

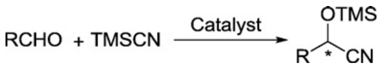
[a] Conditions: entries 1–4 are carried out at rt for 20 h, entries 6–9 are carried out for 10 h.
[b] GC yield, *n*-nonane as internal standard.
[c] Enantiomeric excess of silyl ether is determined by chiral GC with a CP-Chirasil-Dex CB column. Absolute configuration is based on the known order of elution of the two enantiomers.
[d] T = −10 °C, t = 24 h.
[e] T = 0 °C, t = 10 h.

the comparison experiments were also done employing **3** and Ph_3PO as the catalyst. Similar results were obtained and summarized in Table S3.

4. Conclusion

In conclusion, bifunctional *N*-oxide salen-Al complex with new diamine backbone for asymmetric cyanosilylation has been developed. The catalytic activity and asymmetric induction ability of bifunctional catalyst were compared with that of simple chiral pyrrolidine salen-Al(III) complex in combination with Ph_3PO. Interestingly, employing bifunctional *N*-oxide salen-Al complex as catalyst could promote the reaction smoothly without adding Ph_3PO as co-catalyst and give excellent yields and high *ee* values under milder conditions (0 °C, 1.2 equiv. TMSCN and 10 h) than bi-component catalyst system. Furthermore, inverse configurations were generated from the two systems. Developing new, efficient and highly enantioselective ligands and further studies on asymmetric catalysis are currently underway in our laboratory.

Table 2
Cyanation of aldehydes with TMSCN catalyzed by catalyst **4**.[a]



Entry	Aldehyde	Cat. **4**	
		Yield[b] (%)	Ee[c] (%)
1	Benzaldehyde	97	80 (R)
2	4-Methyl benzaldehyde	93	76 (R)
3	3-Methyl benzaldehyde	93	80 (R)
4	2-Methyl benzaldehyde	89	67 (R)
5	4-Methoxy benzaldehyde	95	45 (R)
6	3-Methoxy benzaldehyde	96	86 (R)
7	2-Methoxy benzaldehyde	93	84 (R)
8	4-Chloro benzaldehyde	96	82 (R)
9	2-chloro benzaldehyde	88	54 (R)
10	2,6-Dichloro benzaldehyde	90	12
11	2-Bromo benzaldehyde	85	72
12	4-Tri-fluoromethyl benzaldehyde	98	92 (R)
13	Furfural	94	76 (R)
14	Cinnamaldehyde	91	68 (R)
15	Trimethyl acetaldehyde	9	54 (R)
16	Heptaldehyde	90	76 (R)

[a] All reactions are carried out in the present of 1 mol% of **4** in toluene at 0 °C for 10 h with 1.2 equiv TMSCN.
[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 the known order of elution of the two enantiomers.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.06.025.

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