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Asymmetric addition of KCN and Ac_2O to aldehydes catalyzed by recyclable polymeric salen-Ti(IV) complexes

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Abstract—Polymeric salen-Ti(IV) complexes were employed in the enantioselective *O*-acetyl cyanation of aldehydes with KCN and Ac_2O. The polymeric catalysts with appropriate crosslinking degree exhibited good activities and enantioselectivities, up to 94% yield and 91% ee were obtained at −20 °C with 1 mol% of catalyst (based on bimetallic catalytic unit). Moreover, the crosslinked polymeric catalyst could be easily recovered and reused for six consecutive runs without obvious decrease in activity and enantioselectivity.

Chiral cyanohydrins have attracted great interests due to their potential applications in pharmaceuticals, agrochemicals and other fields. Many efficient and successful methods have been developed to synthesize the chiral cyanohydrins. It is no doubt that the catalytic process with metal complexes is one of the most attractive methods because of the multiplications of chirality.[1,2] Among the metal-complex catalysts, chiral salen-Ti(IV) complexes have shown excellent catalytic efficiency in asymmetric trimethylsilylcyanation of aldehydes.[3–5] Recently, many methods have been developed to improve the catalytic efficiency and to recycle the salen–metal complexes, such as, ionic liquids,[6,7] organic or inorganic supported catalysts.[8–12] However, volatile and expensive trimethylsilyl cyanide was used in the above-mentioned processes. Although some less expensive cyanide sources, such as ethyl cyanoformate and benzoyl cyanide, have been employed in synthesis of O-protected cyanohydrins,[13–18] exploring a nonvolatile and cheap cyanide source is still interesting.

Our research was inspired by the studies of Belokon and co-workers.[19,20] In their process, *O*-acetyl cyanohydrins in high ee were obtained with KCN, Ac_2O and aldehydes catalyzed by salen bimetallic Ti–(μ-O)$_2$–Ti complex **1** (Fig. 1). In the past years, we have developed some efficient chiral polymeric salen catalysts, which were successfully employed in the enantioselective epoxidation and hydrolytic kinetic resolution (HKR) of epoxides, and could be easily recovered and reused.[21–25] We reasoned that the Ti(IV) complexes derived from these types of polymeric salen ligands could be used as the catalysts for preparation of chiral *O*-acetyl cyanohydrins and kept their easily recycling properties. Considering that a bimetallic Ti–(μ-O)$_2$–Ti moiety in complex **1** played a key role in obtaining high ee and high activity,[4,5] we estimated that linear polymeric salen ligands would be very difficult to form the Ti–(μ-O)$_2$–Ti species for the spatial reason. Therefore, our research was focused on the crosslinked polymeric salen ligands **3**

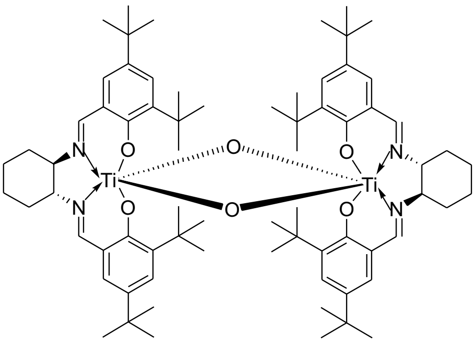

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Figure 1. The bimetallic salen-Ti(IV) complex.

Keywords: *O*-Acetyl cyanohydrins; Recyclable polymeric salen-Ti(IV) complexes; Potassium cyanide; Aldehyde; Asymmetric cyanation.

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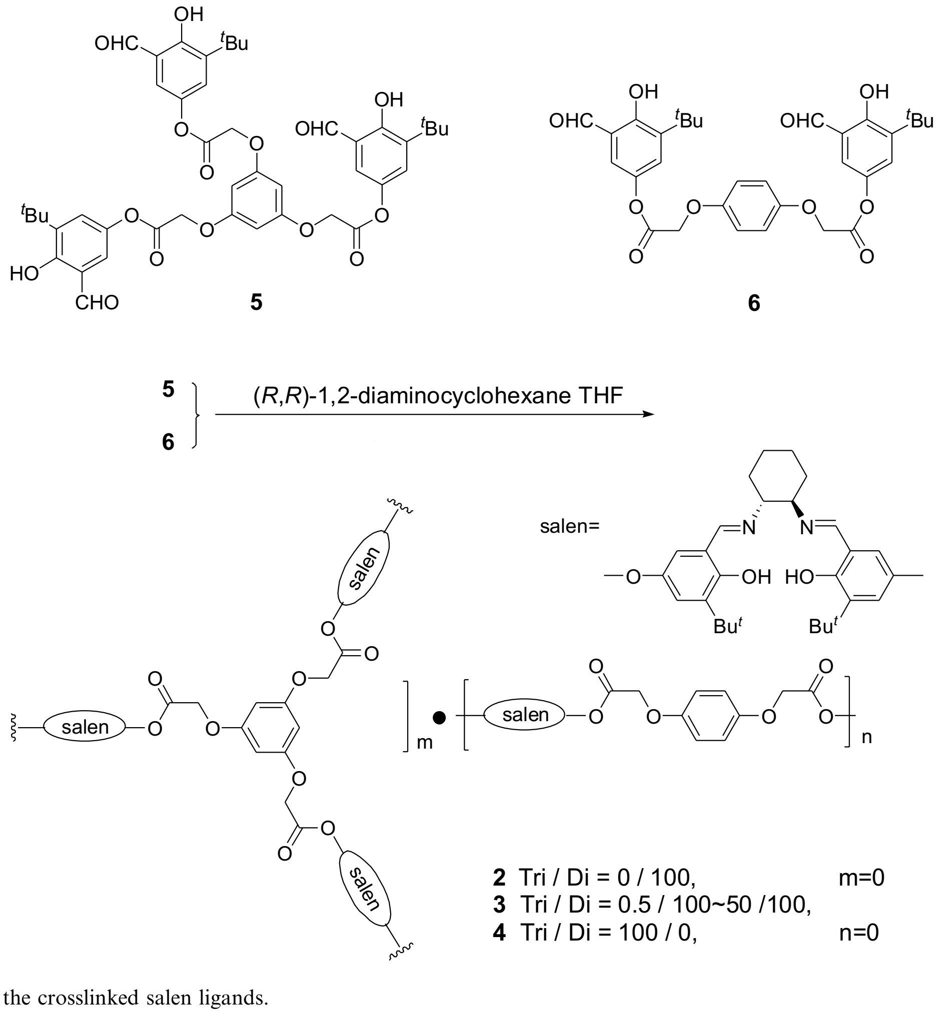
(Scheme 1).[24] We envisioned that the appropriate distance between two metal centres in the Ti(IV) complexes of **3** was beneficial to form the bimetallic Ti–(μ-O)$_2$–Ti species, a similar bimetallic structure as in complex **1**. As a result, we herein reported the efficient asymmetric addition of KCN and Ac$_2$O to aldehydes catalyzed by a series of crosslinked polymeric salen-Ti(IV) complexes, which could be easily recovered and reused without obvious decrease in activity and enantioselectivity even after six consecutive runs.

The crosslinked polymeric salen ligands **3** were prepared according to our previous reported methods (Scheme 1).[24] The preparation of the bimetallic Ti–(μ-O)$_2$–Ti salen complexes and the subsequent *O*-acetyl cyanation of aldehydes were carried out according to the literature procedures (Scheme 2).[4,19,20] The effect of the crosslinking degree of the polymeric ligands in *O*-acetyl cyanation of benzaldehyde was firstly investigated, and the results were summarized in Table 1 (entries 2–9). In order to show the validity of the developed polymeric catalysts, the result by salen-Ti(IV) bimetallic complex **1** was listed in entry 1 as a comparison.[19,20] The crosslinking degree of the polymeric catalysts was easily adjusted by the change of the proportion of trisalicylaldehyde **5** (the crosslinking agent) and disalicylaldehyde **6**. When the proportion of **5** and **6** was between 0.5/100 and 2/100, the comparable results with catalyst **1** were obtained (Table 1, entries 2–4). However, the enantioselectivities decreased gradually with the increase of the ratio of **5** to **6** (Table 1, entries 5–9). When the completely crosslinked ligand **4** was used, the reactivity and enantioselectivity of the catalyst were decreased dramatically (Table 1, entry 10). The same trend was observed at both 20 and −20 °C (Table 1), and better results were obtained at −20 °C. From the above



Scheme 1. Synthesis of the crosslinked salen ligands.

Scheme 2. Synthesis of chiral *O*-acetyl cyanohydrins promoted by chiral polymeric salen-Ti(IV) complexes.

Table 1. Enantioselective synthesis of *O*-acetyl cyanohydrin from benzaldehyde, KCN and Ac_2O catalyzed by different salen-Ti(IV) complexes[a]

Entry	Ligand (**5/6**)[b]	20 °C		−20 °C		Conf.[e]
		Conv.[c]	Ee[d]	Conv.[c]	Ee[d]	
1	(*R*)-**1**[f]	>90	74		88	*S*
2	(*R*)-**3** (0.5:100)	83	78	91 (100)[g]	89 (89)[g]	*S*
3	(*R*)-**3** (1:100)	88	78	89	88	*S*
4	(*R*)-**3** (2:100)	92	78	85 (99)[g]	87 (87)[g]	*S*
5	(*R*)-**3** (6:100)	95	75	84	85	*S*
6	(*R*)-**3** (14:100)	86	63	79	81	*S*
7	(*R*)-**3** (18:100)	87	59	60	77	*S*
8	(*R*)-**3** (25:100)	92	56	60 (99)[g]	79 (79)[g]	*S*
9	(*R*)-**3** (50:100)	ND[h]	ND[h]	39	70	*S*
10	(*R*)-**4** (100:0)	35	44	13	55	*S*
11	(*R*)-**2** (0:100)	72	62	58 (83)[g]	89 (89)[g]	*S*
12	(*R*)-**7**	77	47	52	68	*S*
13	(*R*)-**8**	ND[h]	ND[h]	68 (96)[g]	86 (83)[g]	*S*

[a] Reaction conditions: benzaldehyde (1 mmol), KCN, Ac_2O (ratio = 1:4:4) in 5 mL mixture solvents (mol ratio: $CH_2Cl_2/^tBuOH/H_2O$ = 2500:10:1) in present of catalyst prepared from 2 mol% (*R*)-ligand and 2 mol% Ti(*i*-OPr)$_4$, stirred for 4 h.

[b] The proportion of trisalicylaldehyde **5** and disalicylaldehyde **6** was the ratio of weight.

[c] Based on GC integral area.

[d] Determined by GC analysis using a chiral capillary column (cyclodex-β, 2,3,6-methylated, 30 m × 0.25 mm (id)).

[e] Absolute configurations were assigned by comparison of literature date with the Ref. 20.

[f] Results were obtained by catalyst **1** in the Ref. 20.

[g] The results in parentheses were obtained in reaction for 16 h.

[h] ND, not determined.

results, we could conclude that the ratio of **5** to **6** played an important role in forming the bimetallic Ti–(μ-O)$_2$–Ti species. When the proportion of **5** and **6** was between 0.5/100 and 2/100, the species could be formed, thus a comparable ee could be obtained. When the polymeric ligand was with excess of **5**, which had a more rigid structure, it was difficult to form the key species. To further clarify the importance of the crosslinking degree, we used oligomeric ligand **2** without the crosslinking agent **5** to perform the asymmetric cyanation under the identical conditions, the results showed that ligand **2** had the same enantioselective induction as that of with the ligand **3** (0.5/100), but the lower conversion was observed even in prolonged reaction time (Table 1, entry 11). The dissatisfactory results obtained by linear polymeric salen ligand **7** (Fig. 2) could further confirm our presumption that the crosslinking degree had the important effect, because this more rigid polymeric salen was much more difficult to form Ti–(μ-O)$_2$–Ti species (Table 1, entry 12). Finally, monomeric analogue salen ligand **8** (Fig. 3) was screened, and the similar enantioselectivity and activity as **1** were obtained (Table 1, entry 13), which indicated that the phenolic ester group in the ligand had little influence in the asymmetric *O*-acetyl cyanation of benzaldehyde.

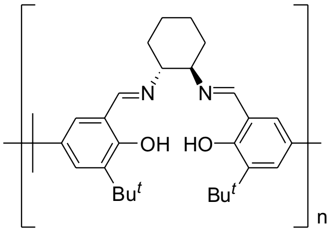


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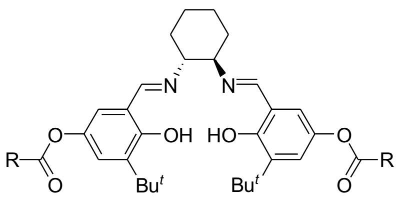
Figure 2. The linear polymeric salen ligand.



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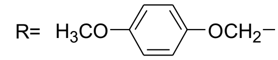

Figure 3. The monomeric analogue salen ligand.

Under the optimized conditions, a variety of substituted benzaldehydes as well as several aliphatic aldehydes and heteroaromatic aldehydes were used as substrates for this *O*-acetyl cyanation with the catalyst prepared from ligand **3** (**5**:**6** = 0.5/100) and Ti(*i*-OPr)$_4$. The results were listed in Table 2. The substituents of benzaldehyde had a great influence on the reactivity and enantioselectivity. When 4-fluorobenzaldhyde was used, the best result was obtained as 91% ee and 94% yield (Table 2, entry 5). As for the aliphatic aldehydes, the chiral products were obtained in 81–86% ees with moderate to good yields (Table 2, entries 11–13), except that the chain secondary aldehyde (isobutyraldhyde) gave 67% ee (Table 2, entry 14). The results of substituted benzaldehydes and aliphatic aldehydes were comparable to those with catalyst **1** at lower reaction temperature (−42 °C).[19,20] *O*-Acetyl cyanation of heteroaromatic aldehydes could also proceed smoothly. When 2-furaldehyde and 2-thiophenecarboxaldehyde were used, good enantioselectivities and activities could be obtained (Table 2, entries 15 and 16),

Table 2. Enantioselective synthesis of *O*-acetyl cyanohydrins from aldehydes, KCN and Ac_2O catalyzed by crosslinked polymeric catalyst[a]

Entry	Substrate	Time (h)	Yield (%)[b]	Ee (%)[c] (configuration)[d]
1	PhCHO	16	93	89 (*S*)
2	2-$CH_3C_6H_4CHO$	16	85	88 (*S*)
3	3-$CH_3C_6H_4CHO$	16	88	86 (*S*)
4	4-$CH_3C_6H_4CHO$	16	93	89 (*S*)
5	4-FC_6H_4CHO	16	94	91 (*S*)
6	4-ClC_6H_4CHO	16	93	85 (*S*)
7	4-BrC_6H_4CHO	16	93	81 (*S*)
8	4-$CF_3C_6H_4CHO$	4	89	70 (*S*)
9	4-$MeOC_6H_4CHO$	40	58	87 (*S*)
10	3-$PhOC_6H_4CHO$	16	95	84 (*S*)
11	$PhCH_2CH_2CHO$	16	94	83 (*S*)
12	Cyclohexanecarboxaldehyde	16	89	81 (*S*)
13	Me_2CHCH_2CHO	20	62	86 (*S*)
14	Me_2CHCHO	20	61	67 (*S*)
15	2-Furaldehyde	16	64	66 (ND)[e]
16	2-Thiophenecarboxaldehyde	16	73	78 (ND)[e]
17	2-Pyridinecarboxaldehyde	16	ND[e]	6.4 (ND)[e]

[a] Reaction conditions: aldehyde (1 mmol), KCN, Ac_2O (ratio = 1:4:4) in 5 mL mixture solvents (mol ratio: $CH_2Cl_2/^tBuOH/H_2O = 2500:10:1$) in present of catalyst prepared from 2 mol% (*R*)-ligand **3** (**5**/**6** = 0.5:100) and 2 mol% Ti(*i*-OPr)$_4$, stirred at −20 °C.

[b] Isolated yield based on the aldehydes, after flash chromatography (silica gel).

[c] Determined by GC analysis using a chiral capillary column (cyclodex-β, 2,3,6-methylated, 30 m × 0.25 mm (id)).

[d] Absolute configurations were assigned by comparison of literature date with the Ref. 20, unless otherwise indicated.

[e] ND, not determined.

while only 6.4% ee was obtained, when 2-pyridinecarboxaldehyde was used (Table 2, entry 17).

In our previous research, we have reported that the catalysts derived from polymeric ligands had the advantage of easy recovery and reusable, as well as the comparable catalytic ability in the enantioselective epoxidation and HKR of epoxides with monomeric salen–metal catalysts.[21–24] We then would like to know whether the catalysts derived from these crosslinked polymeric ligands could also be recycled in *O*-acetyl cyanation of benzaldehyde. Initially, the optimized ligand **3** (**5**/**6** = 0.5/100) was applied in the recycling experiment, however, the result was discouraged that the recovered catalyst showed extremely low activity and enantioselectivity, which was probably due to the instability of the lower crosslinked ligand. We then used the ligand **3** (**5**/**6** = 25/100) with higher crosslinking degree to examine the recycling ability,[26] and the results were listed in Table 3. As expected, the higher crosslinked polymeric catalyst showed excellent reusability in the *O*-acetyl cyanation of benzaldehyde, even after seven consecutive runs, up to 74% ee and 95% conversion was obtained. It was the first example of asymmetric addition of KCN and Ac_2O to aldehydes catalyzed by recyclable catalysts.

Table 3. The recycle of crosslinked polymeric salen-Ti(IV) catalyst in enantioselective synthesis of *O*-acetyl cyanohydrin from benzaldehyde, KCN and Ac_2O[a]

Cycle	Time (h)	Conv. (%)[b]	Ee (%)[c]
Fresh	9	99	80
1	16	99	78
2	16	98	78
3	16	99	78
4	16	99	80
5	20	99	80
6	20	95	74

[a] The reaction conditions are the same as in Table 2, but 4 mol% of the ligand **3** (**5**/**6** = 25/100) and 4 mol% of Ti(*i*-OPr)$_4$ were used. The used catalyst was precipitated by addition of hexane, then filtered, washed with water and hexane thoroughly, dried at 50 °C in vacuum, and then employed in another run.

[b] Based on GC integral area.

[c] Determined by GC analysis using a chiral capillary column (cyclodex-β, 2,3,6-methylated, 30 m × 0.25 mm (id)).

In conclusion, polymeric salen-Ti(IV) complexes were successfully employed in the asymmetric addition of KCN and Ac_2O to aldehydes. A series of *O*-acetyl cyanohydrins in moderate to good ee were obtained when crosslinked polymeric salen **3** (**5**/**6** = 0.5/100–2/100) was used as ligand. Moreover, the crosslinked polymeric salen-Ti(IV) catalysts exhibited excellent recycling performance. The different efficiencies between the crosslinked ligands **3** and the linear ligand **7** might be meaningful for the design of the polymeric catalysts in this field.

Acknowledgements

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