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Oxovanadium(V)-catalyzed enantioselective Meerwein–Ponndorf–Verley cyanation of aldehydes using acetone cyanohydrin

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Abstract—Oxovanadium(V)(salen) complex **4** was found to catalyze Meerwein–Ponndorf–Verley cyanation of aliphatic aldehydes with good to high enantioselectivity. This cyanation showed a positive nonlinear effect.

Asymmetric cyanation of carbonyl compounds is a current topic in organic synthesis, because cyanohydrins are versatile building blocks. Thus, many catalysts including peptide derivatives and metal complexes have been developed and good to excellent levels of enantioselectivity have been achieved.[1,2] Of these catalysts, some serve as a Lewis acid[3] but most of the catalysts giving satisfactory results possess a function for dual activation of carbonyl and cyanide compounds.[1b] For example, Shibasaki's catalysts carry Lewis acid/Lewis base parts.[2] On the other hand, chiral salen ligands have been proven to be excellent chiral auxiliaries for various asymmetric reactions.[4] In 1996, two groups independently reported asymmetric cyanation using a Ti(salen) complex as catalyst.[5] Later, Bu et al. also reported asymmetric cyanation using a slightly modified Ti(salen) complex as the catalyst.[6,7] Although high enantioselectivity has been achieved in these reactions, temperature as low as −78 °C is required. However, introduction of a di-μ-oxo-Ti(salen) complex **1** brought about a breakthrough in metallosalen-catalyzed asymmetric cyanation: high enantioselectivity was achieved in the reaction at room temperature.[8] This reaction has been proposed to proceed through a *cis*-β-μ-oxo Ti complex **2**, in which both the aldehyde and the cyanide are, respectively, coordinated to the titanium ion and react in an intramolecular fashion with enantioselectivity higher than 80% ee (Fig. 1). Furthermore, an oxovanadium(IV)(salen) complex was found to be a better catalyst especially for asymmetric cyanation of aromatic aldehyde.[9] This reaction has also been proposed to proceed through the same reaction pathway as the reaction using **1** as the catalyst. These reactions, however, need toxic hydrogen cyanide or relatively expensive trimethylsilyl cyanide as a cyanide source. On the other hand, Maruoka et al. recently reported Zr-catalyzed asymmetric Meerwein–Ponndorf–Verley (MPV) cyanation using more manageable acetone cyanohydrin as a cyanide source, in which the cyanohydrin and aldehyde were coordinated to the metal ion and reacted intramolecularly, showing high enantioselectivity.[10] This reaction needs low temperature to obtain high enantioselectivity. Since 1993, we have demonstrated that salen ligands including a binaphthyl unit are excellent chiral auxiliaries and their metal complexes catalyze various types of reactions with excellent enantioselectivities.[4] In the course of our study, we have also found that Ti(salen) complex **3** bearing this type of salen ligand can be converted to the corresponding *cis*-β-di-μ-oxo-Ti(salen) complex under the reported conditions[8] and the complex is an excellent catalyst for asymmetric sulfoxidation using hydrogen peroxide, in which the complex is converted into a monomeric peroxoTi species bearing a *cis*-β salen ligand and oxidizes sulfides.[11] This result suggests that a metallosalen complex

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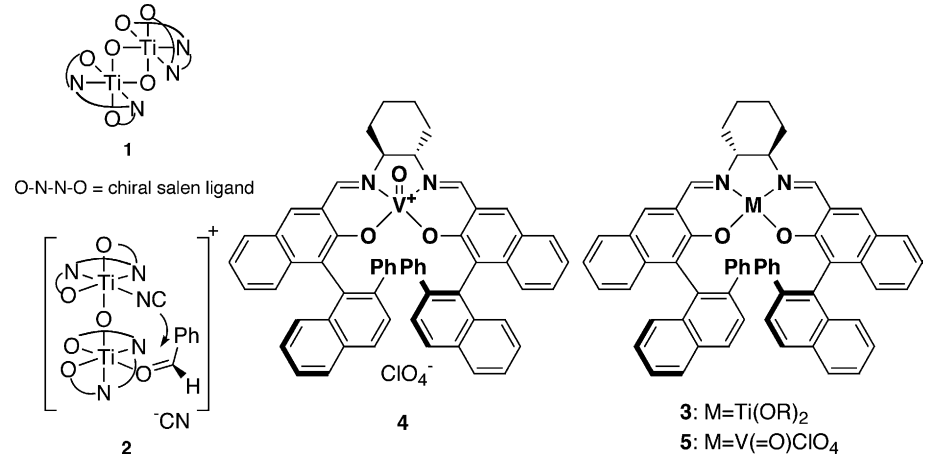


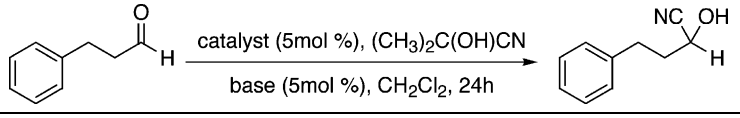
Figure 1.

bearing our ligand can take a *cis*-β structure under appropriate conditions and allow coordination of two substrates *cis* to each other.[12] Thus, we expected that a monomeric *cis*-β Ti(salen) species would catalyze MPV cyanation with high enantioselectivity. Indeed, complex **3** catalyzed the cyanation but, contrary to our expectation, enantioselectivity of the reaction was poor (<5% ee).

Different from oxovanadium(IV) complexes with salen ligands that usually adopt five-coordinate square-pyramidal geometry even in the donor solvent, oxovanadium(V) complexes exhibit a tendency to retain octahedral six-coordination, in which the donor solvent or counter ion coordinates in an apical position.[13] Therefore, we expected that oxovanadium(V) complexes would adopt a monomeric *cis*-β structure more easily than oxovanadium(IV) complexes[14] and be a suitable catalyst for asymmetric cyanation using acetone cyanohydrin. Here, we report asymmetric MPV cyanation using oxovanadium(V)(salen) complexes **4** and **5** as the catalyst.

MPV cyanation of 3-phenylpropanal with acetone cyanohydrin (4 equiv) was carried out at room temperature in CH_2Cl_2 in the presence of complex **4** (5 mol%) (Table 1, entry 1). As expected, good enantioselectivity of 84% ee was observed but the reaction was slow. Addition of triethylamine accelerated the reaction but reduced enantioselectivity to a considerable extent (entry 2). Addition of the amine might also promote reversed hydrocyanation of acetone cyanohydrin generating a cyanide anion that undergoes direct cyanation and diminish the enantioselectivity. Thus, we next examined the additive effect of less basic pyridine derivatives. Addition of pyridine did not affect enantioselectivity, but the rate of enhancement was small (ca. 2.6 times), probably because the presence of pyridine hindered the coordination of the aldehyde (entry 3). Therefore, we examined the additive effect of 2,4,6-collidine and 2,6-dichloropyridine. Addition of 2,4,6-collidine accelerated the reaction remarkably, albeit with slightly diminished enantioselectivity (entry 4). In contrast, addition of 2,6-dichloropyridine decelerated the reaction (entry 5). Lowering the reaction temperature to 10 °C in the presence of 2,4,6-collidine

Table 1. MPV cyanation of 3-phenylpropanal using oxovanadium(V) complex **4** or **5** as catalyst



Entry	Catalyst	Base	Temp (°C)	Yield (%)[a]	ee (%)[b] (config)[c]
1	**4**	None	rt	13	84 (*R*)
2	**4**	Et_3N	rt	>99	65 (*R*)
3	**4**	Pyridine	rt	34	85 (*R*)
4	**4**	2,4,6-Collidine	rt	99	70 (*R*)
5	**4**	2,6-Dichloropyridine	rt	4	72 (*R*)
6	**4**	2,4,6-Collidine	10	57	86 (*R*)
7[d]	**4**	2,4,6-Collidine	10	87	82 (*R*)
8[d]	**4**	2,4,6-Collidine	0	25	90 (*R*)
9	**5**	2,4,6-Collidine	rt	99	48 (*S*)

[a] Yield was determined by ^1H NMR (400 MHz) analysis.
[b] ee was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane–2-propanol = 98:2).
[c] Absolute configuration was determined by comparison of the optical rotation of the cyanohydrin with the literature value (Ref. 10).
[d] Reaction time was 48 h.

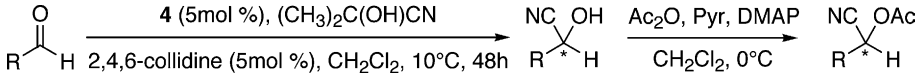
improved enantioselectivity to 86% ee, though the chemical yield was reduced (entry 6). The reaction at 0 °C further improved enantioselectivity to 90% ee, but the reaction was very slow (entry 8). Prolonged reaction time increased the yield of the product but its enantiopurity somewhat decreased, suggesting the product was racemized slowly through equilibrium between the reactant and the product under the conditions (entry 7). The reaction using **5**, the diastereomer of **4**, showed only moderate selectivity (entry 9).

Under the optimized conditions, reactions of several other aldehydes were examined (Table 2). Nonbranched aliphatic aldehydes gave the corresponding cyanohydrin in moderate to good yields with high enantioselectivity (entries 1 and 2).[15,16] Cyanation of cyclohaxanecaboxaldehyde also showed good enantioselectivity (entry 3). However, the reaction of 2,2-dimethylpropanal was slow, albeit with good enantioselectivity. On the other hand, the yield of benzaldehyde cyanohydrin was very low and enantioselectivity was modest (entry 5). However, as described above, the present cyanation seemed reversible and the retro-cyanation of the cyanohydrin of this reaction was considered to be rapid. Thus, we exposed racemic benzaldehyde cyanohydrin that was prepared by Maruoka's method[10] to the present reaction conditions in the presence of acetone and found that the reversed reaction occurred and the enantiomer corresponding to the major enantiomer of the above cyanation product was decomposed in preference to the enantiomer corresponding to the minor one: the chirality of the recovered cyanohydrin (50% ee, ca. 50% conversion, 12 h) was opposite to that of the product of the above cyanation. This explains why the ee of benzaldehyde cyanohydrin that underwent the reversed reaction at a considerable rate was only modest and also the observation that the ee of the cyanation product decreased as the reaction time was prolonged (vide supra).

Although the mechanism of asymmetric induction in this reaction is unclear at present, we have assumed that the present reaction proceeds in an intramolecular manner with the participation of the *cis*-*β* vanadium(V)(salen) species (vide supra), as Maruoka proposed.[10,17] It has been reported that a simple vanadium(V)(salen) complex can take a non-oxo *cis*-β structure.[18] Asymmetric sulfoxidation with di-μ-oxo-Ti(salen) complex shows strong positive nonlinear effect, indicating that a pair of enantiomeric Ti(salen) complexes make the corresponding di-μ-oxo-Ti complex much easier than a pair of the same complexes.[10b] Thus, we expected that a pair of enantiomeric vanadium(V) species could also produce a dimmer **7** if they can adopt a *cis*-β structure, and the reaction with **4** as catalyst would show a nonlinear effect (Scheme 1). Indeed, a positive nonlinear effect was observed as shown in Figure 2. We also observed that, when a solution of enantiomeric (a*S,R*)-**4** in dichloromethane was added to a solution of (a*R,S*)-**4**, a fern-green solid was precipitated.

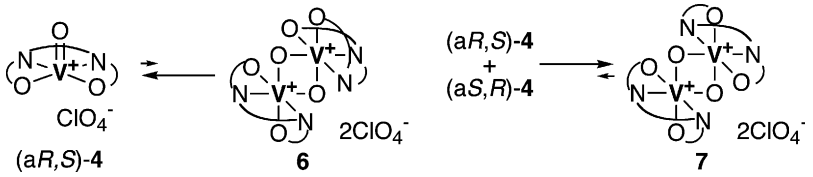
CD measurement of a solution of the solid in dichloromethane demonstrated that it was a 1:1 mixture of (a*S,R*)-**4** and (a*R,S*)-**4**. These results support that

Table 2. MPV cyanation of various aldehydes with oxovanadium(V) complex **4** as catalyst



Entry	R=	Yield (%)[a]	ee (%) (config)[b]
1	*n*-C_7H_{15}	75 (65)	84[c]
2	$PhO(CH_2)_5$	61 (59)	79[d]
3	*c*-Hex	79 (55)	76[c] (*R*)
4	$(CH_3)_3C$	—[f] (29[g])	67[e] (*R*)
5	Ph	13[h]	45[e] (*R*)

[a] Yield of cyanohydrin was determined by ^1H NMR analysis. The number in parentheses is the isolated yield as the corresponding acetate.
[b] Absolute configuration was determined by comparison of the optical rotation of the cyanohydrin with the literature value (Ref. 10).
[c] ee was determined by GLC analysis using Shimadzu GC-1700 [HP Chiral (20% permethylated β-cyclodextrin)].
[d] ee was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane–2-propanol = 90:10).
[e] ee was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane–2-propanol = 90:10).
[f] Not determined.
[g] Isolated yield of the corresponding benzoate.
[h] The reaction time was 12 h.



Scheme 1.

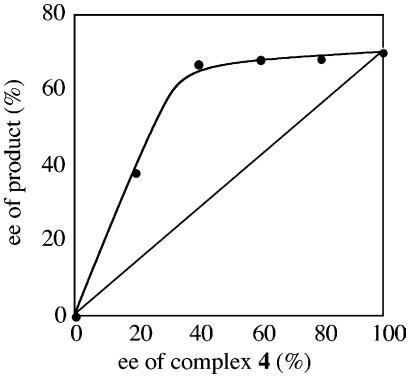


Figure 2. Positive nonlinear effect observed in MPV cyanation of 3-phenylpropanal with oxovanadium(V) complex **4** at room temperature.

complex **4** can be converted into the desired *cis*-β vanadium(V)(salen) complex.[19] On the other hand, cyanation of 3-phenylpropanal with acetone cyanohydrin in the presence of the Belokon's vanadium(IV) complex was sluggish (65% ee, 7%, 7 h at rt), while the corresponding vanadium(V) complex catalyzed the cyanantion smoothly with modest enantioselectivity (45% ee, 99%, 12 h at rt). These results agree with the above assumption that a vanadium(V) complex is a suitable catalyst and demonstrate that use of oxovanadium(V) complex bearing the salen ligand including a binaphthyl unit is essential for achieving high enantioselectivity in the present MPV cyanation, though we could not completely rule out the possibility that the reaction proceeds through a μ-oxo vanadium species as proposed for asymmetric cyanation using trimethylsilyl cyanide.

In conclusion, we were able to demonstrate that oxovanadium(V)(salen) complex **4** serves as a catalyst for asymmetric MPV cyanation. Further study on the mechanism of the present reaction is under way.

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12. (a) Zr(salen) complex catalyzes Baeyer–Villiger reaction, in which a ketone and hydrogen peroxide are coordinated to the zirconium ion and reacted to give a chiral lactone: Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 4481–4485; (b) Watanabe, A.; Uchida, T.; Irie, R.; Katsuki, T. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5737–5742.
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14. Participation of a *cis*-β vanadium(salen) species has been proposed by North and co-workers.[9]
15. Typical experimental procedure was as follows: catalyst **4** (5.0 mg, 5 μmol) was dissolved in a 0.01 M CH_2Cl_2 solution of 2,4,6-collidine (0.5 mL) at room temperature. Acetone cyanohydrin (36.5 μL, 0.40 mmol) was added to the solution. The solution was cooled to 10 °C. Octylaldehyde (15.6 μL, 0.10 mmol) was added and the solution was stirred at the temperature. After 48 h, the reaction was quenched by 1 M HCl and extracted by CH_2Cl_2. The extract was evaporated in vacuo. The resultant cyanohydrin was acetylated by Ac_2O (24 μL, 0.25 mmol), pyridine (20 μL, 0.25 mmol) and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine in CH_2Cl_2 (1.0 mL) at 0 °C. After 2 h, the reaction was quenched by water and extracted by CH_2Cl_2. The extract was concentrated in vacuo and the residue was chromatographed on silica gel (*n*-hexane:AcOEt = 19:1) to give the acetate (11.5 mg, 65%). Enantiomeric excess of the acetylated cyanohydrin was determined by GLC analysis as described in the footnote of Table 2.
16. All the cyanohydrins and the corresponding acetates gave satisfactory ^1H NMR spectra that were in agreement with the reported ones (Ref. 10), except for the cyanohydrin and the acetate derived from 6-phenoxyhexanal. The cyanohydrin and acetate are unknown compounds. The benzoate derived from 2,2-dimethylpropanal also gave a satisfactory ^1H NMR spectrum.
17. This assumption requires participation of a *cis*-β vanadium(V)(salen) species (see also Ref. 19), because coordination of two neutral ligands (acetone cyanohydrin

and aldehyde) at the apical site of *trans*-oxovanadium(salen) complex **4** is considered to be unlikely due to the presence of the bulky 2-phenylnaphthyl group at C3 and 3′.

18. Non-oxo *cis*-β structure of vanadium(V)(salen)benzilate complex has been identified by ^{51}V NMR study: Vergopoulos, V.; Jantzen, S.; Rodewald, D.; Rehder, D. *J. Chem. Soc., Chem. Commun.* **1995**, 377–378.

19. There are two possible mechanisms described in the following scheme, for MPV cyanation catalyzed by a *cis*-β vanadium(V)(salen) species. At present, we cannot determine which mechanism is more likely