VIP Synthetic Methods

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An Efficient Titanium Catalyst for Enantioselective Cyanation of Aldehydes: Cooperative Catalysis**

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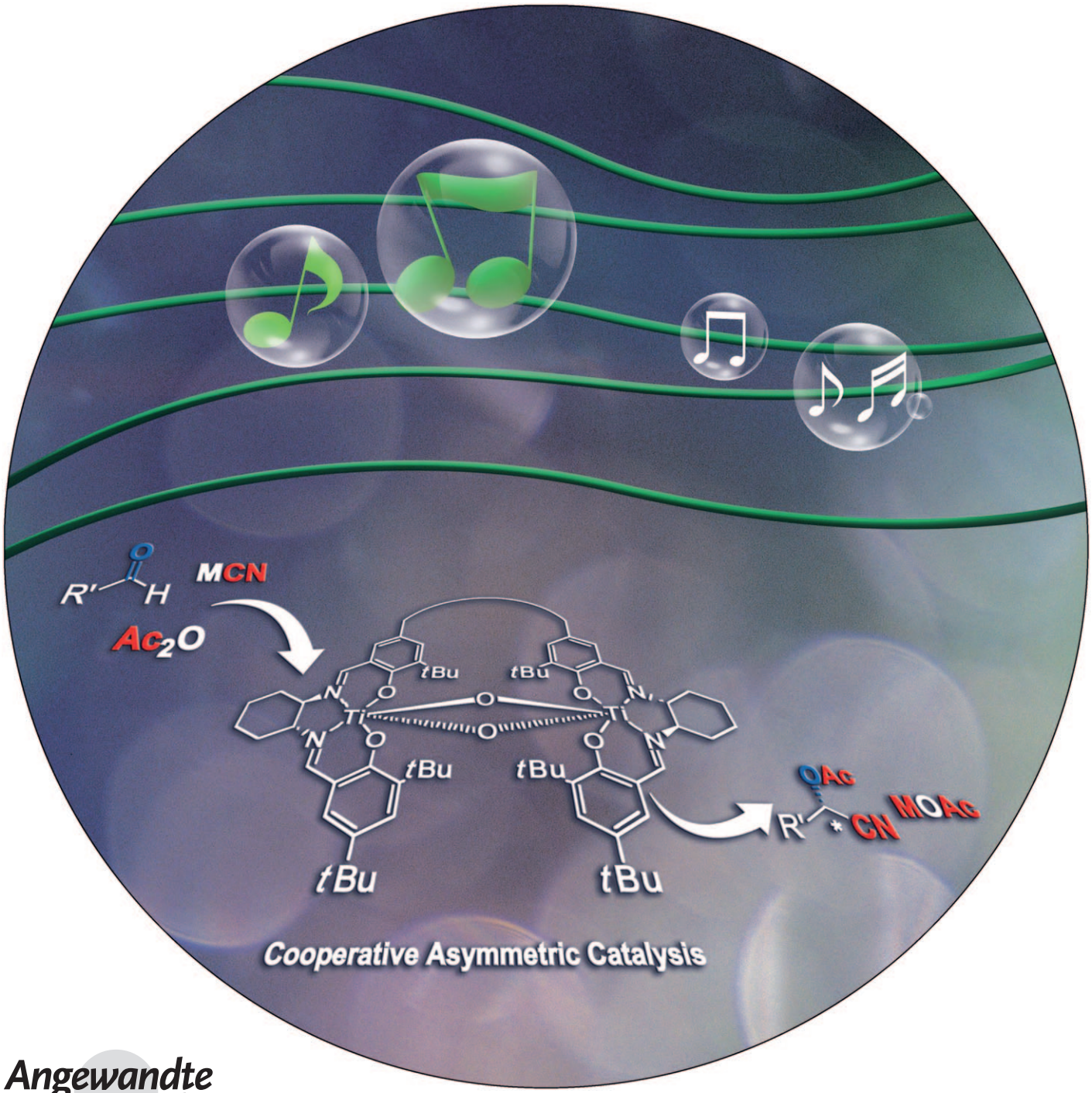
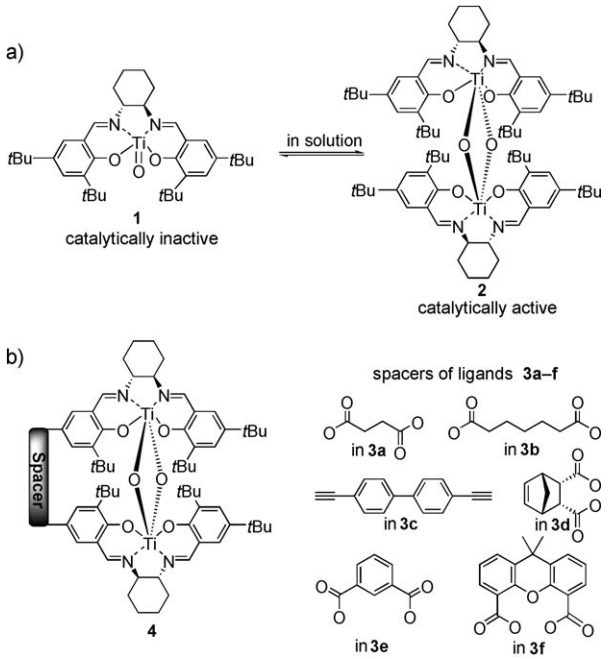


Cyanohydrins contain a nitrile and an alcohol, and can be readily manipulated to produce a large range of biologically important compounds including α-hydroxy acids and esters, α-hydroxy aldehydes and ketones, α-amino acids, and β-amino alcohols, which have been widely used as the components of industrially valuable products such as pharmaceuticals, agrochemicals, flavorings, and fragrances.[1–3] The addition of cyanide to a carbonyl compound to form a cyanohydrin is one of the most fundamental carbon–carbon bond-forming reactions in organic chemistry.[4] Since the first report of the enantioselective addition of hydrogen cyanide to benzaldehyde catalyzed by an extract of almonds,[5] numerous enzymatic methods for the synthesis of enantioenriched cyanohydrins have been developed.[6,7] However, it is still a great challenge in terms of the efficiency, cost, and adaptability of the catalysis. Alternatively, catalytic enantioselective synthesis of optically active cyanohydrin derivatives using either an artificial chiral Lewis acid, base, or a hybrid bifunctional Lewis acid/base catalyst has been reported to give very high enantioselectivity.[4,8–13] Most of the reported methods have seen limited applications on preparative scales since the practical catalysts must enable reactions to be rapid, capable of being scaled up, and selective in the product formation.[14] The remaining challenges include low activity and high cost of the catalysts, or the requisite use of expensive cyanide sources. Herein we report an efficient method for asymmetric syntheses of highly enantioenriched natural or nonnatural cyanohydrin derivatives using an elegantly designed catalyst to control the key cyanation step.

Among various artificial chiral catalysts discovered for enantioselective synthesis of optically active cyanohydrin derivatives,[2–4,8–13] titanium complexes[15,16] are very promising because of their low cost and ready availability. A very important achievement in this area was the discovery of a catalytically active dimeric titanium complex [{(salen)Ti(μ-O)}$_2$] (**2**; Scheme 1 a) in the addition of trimethylsilyl cyanide (TMSCN) to aldehydes with high efficiency (at 0.1 mol% of catalyst loading with 50–92% enantioselectivity).[17,18] A kinetic study disclosed a catalyst order of 1.3–1.8, indicating that more than one metal center is involved in the catalysis; the two salen–Ti=O units are thought to simultaneously activate the aldehyde and cyano nucleophile.[19] However, the monomeric (**1**) and dimeric species (**2**) of the titanium complexes were found to exist as a concentration-dependent equilibrium in solution.[20] We envisaged that such an equilibrium may reduce the concentration of active dimeric species (**2**) and accordingly is detrimental to the catalysis. Therefore, appropriate linking of two metallosalen units may overcome the problem of dissociation of the catalytically active dimer, which would result in the predominance of an intramolecular bimetallic catalyst that promotes the cooperative activation of both the nucleophile and electrophile.



Scheme 1. Working hypothesis for catalyst design: From an inactive monomeric salen/Ti=O complex **1** (a) to the tethered intramolecular bimetallic catalyst **4** (b).

A key issue in the design of intramolecular analogues of **2** is how one can bridge two metallosalen units properly so as to maximize cooperative actions favored in the catalysis (**4**; Scheme 1 b).[21] On the basis of the working hypothesis mentioned above, we therefore designed and synthesized a variety of bis(salen) ligands (**3a–f**, Scheme 1 b) bridged by spacers with diverse length and spatial orientations to investigate the impact of bridging spacers on the cooperative catalytic performance. The titanium complexes **4a–f** were prepared by the reaction of the respective ligands **3a–f** with 2 equivalents of Ti(O*i*Pr)$_4$ in CH_2Cl_2 and subsequent addition of 20 equivalents of H_2O. After removal of the solvent, the catalyst can be used directly. As shown in Table 1, the spacers in the catalysts indeed have significant impact upon the activity and enantioselectivity of the catalysis. The catalyst **4d** (0.05 mol%) having a *cis*-5-norbornene-*endo*-2,3-dicarboxylate bridge demonstrates the best performance in the addition of TMSCN to benzaldehyde (**5a**), in terms of both activity and enantioselectivity, affording the corresponding adduct **6a** in 98% yield and 96% *ee* after 5 minutes at room temperature (entry 4, Table 1). However, the catalysts with linear spacers (**4a–c**), particularly the rigid 4,4′-diethynylbiphenyl linkage (**4c**), show dramatically low activity and enantioselectivity as shown in entries 1–3 of Table 1; the low reactivity is probably a result of the difficulty to establish the intramolecular cooperative activation of the substrates by the

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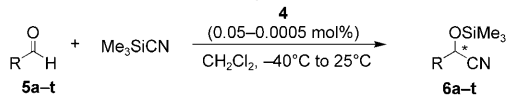
Table 1: Asymmetric aldehyde cyanation: The impact of the spacer in **4** and evaluation of the substrate scope.



Entry	R (**5**)	**4** (mol%)	*T* [°C]	*t* [h]	Yield [%][f]	*ee* [%][g]
1[a]	C_6H_5 (**5a**)	**4a** (0.05)	25	24	97	90 (*S*)
2[a]	C_6H_5 (**5a**)	**4b** (0.05)	25	24	93	76 (*S*)
3[a]	C_6H_5 (**5a**)	**4c** (0.05)	25	72	29	51 (*S*)
4[a]	C_6H_5 (**5a**)	**4d** (0.05)	25	< 0.1	98	96 (*S*)
5[a]	C_6H_5 (**5a**)	**4e** (0.05)	25	2	95	78 (*S*)
6[a]	C_6H_5 (**5a**)	**4f** (0.05)	25	24	85	58 (*S*)
7[b]	C_6H_5 (**5a**)	**4d** (0.01)	25	5	99	97 (*S*)
8[b]	*p*-$MeOC_6H_4$ (**5b**)	**4d** (0.02)	0	24	98	97 (*S*)
9[b]	*p*-MeC_6H_4 (**5c**)	**4d** (0.01)	0	48	99	90 (*S*)
10[b]	*p*-ClC_6H_4 (**5d**)	**4d** (0.01)	0	10	99	93 (*S*)
11[b]	*p*-BrC_6H_4 (**5e**)	**4d** (0.01)	0	10	99	93 (−)
12[b]	*p*-$O_2NC_6H_4$ (**5f**)	**4d** (0.01)	0	10	99	90 (*S*)
13[b]	*p*-FC_6H_4 (**5g**)	**4d** (0.01)	0	5	99	96 (*S*)
14[b]	*m*-$MeOC_6H_4$ (**5h**)	**4d** (0.01)	0	18	99	97 (*S*)
15[b]	*o*-$MeOC_6H_4$ (**5i**)	**4d** (0.01)	25	24	99	92 (*S*)
16[b]	*m*-ClC_6H_4(**5j**)	**4d** (0.02)	−40	48	99	96 (*S*)
17[b]	*o*-ClC_6H_4 (**5k**)	**4d** (0.02)	−40	48	99	95 (*S*)
18[b]	(*E*)-PhCH=CH (**5l**)	**4d** (0.02)	−40	48	95	96 (*S*)
19[b]	$PhCH_2CH_2$ (**5m**)	**4d** (0.01)	−40	48	89	72 (−)
20[b]	2-naphthalenyl (**5n**)	**4d** (0.01)	0	5	99	96 (−)
21[b]	1-naphthalenyl (**5o**)	**4d** (0.01)	−40	48	99	92 (*S*)
22[b]	(*E*)-MeCH=CH (**5p**)	**4d** (0.01)	25	48	93	82 (−)
23[b]	2-furyl (**5q**)	**4d** (0.02)	0	48	97	95 (−)
24[b]	*m*-$PhOC_6H_4$ (**5r**)	**4d** (0.01)	0	48	87	92 (*S*)
25[b]	Me_2CH (**5s**)	**4d** (0.01)	0	48	96	64 (−)
26[b]	cyclohexyl (**5t**)	**4d** (0.01)	0	48	99	67 (*S*)
27[c]	C_6H_5 (**5a**)	**4d** (0.01)	25	0.5	99	96 (*S*)
28[d]	C_6H_5 (**5a**)	**4d** (0.005)	25	1	99	97 (*S*)
29[e]	C_6H_5 (**5a**)	**4d**(0.0005)	25	72	86	95 (*S*)

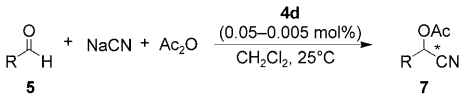
[a] Reactopm conditions: **5a** (2.5 mmol), Me_3SiCN (1.1 equiv), CH_2Cl_2 (3 mL). [b] **5** (6.25 mmol), Me_3SiCN (1.1 equiv), CH_2Cl_2 (7.5 mL). [c] **5a** (6.25 mmol), Me_3SiCN (1.1 equiv), CH_2Cl_2 (1.5 mL). [d] **5a** (12.5 mmol), Me_3SiCN (1.1 equiv), CH_2Cl_2 (1.5 mL). [e] **5a** (125 mmol), Me_3SiCN (1.1 equiv), CH_2Cl_2 (15 mL). [f] The yield of isolated **6** after silica gel chromatography. [g] The *ee* value was determined by GC or HPLC analysis on a chiral stationary phase after conversion of the product into the corresponding acetate. The *ee* values of the products in entries 12 and 18 were determined directly by HPLC and GC analysis, respectively, using a chiral stationary phase. The absolute configuration, given in parentheses, was determined by comparison of the optical rotation with that reported in literature.

catalyst. Moreover, the catalysts with isophthalate (**4e**) and 9,9-dimethyl-9*H*-xanthene-4,5-dicarboxylate (**4f**) linkers only demonstrate moderate catalytic activity and enantioselectivity (entries 5 and 6, Table 1) in the reaction. All these facts clearly indicate that both the length of the spacers and mutual orientation of active sites in the catalysts have a significant influence on the activity and enantioselectivity of the reaction.

With the optimal catalyst **4d** in hand, the reactions of various aldehydes (**5b–t**), including aromatic, olefinic, and aliphatic derivatives with TMSCN were carried out with catalyst loadings of 0.01–0.02 mol% under the reaction conditions shown in Table 1, affording the corresponding products **6b–t** in 87–99% yields with enantiomeric excesses of 64–97% (entries 7–26). The catalyst is particularly effective for the reaction of aromatic aldehydes regardless of the presence of an electron-withdrawing or electron-donating group at either the *para*, *meta*, or *ortho* position of the aromatic ring. The comparison of the performance of the present designer catalyst **4d** with the parent catalyst **2**[17,18] clearly indicated that the catalytic activity of **2** was dramatically enhanced by 1–2 orders of magnitude. Practically, the products **6k–n** and **6r** obtained by the reactions of *ortho*-chlorobenzaldehyde (**5k**), cinnamaldehyde (**5l**), 3-phenylpropanal (**5m**), 2-naphthaldehyde (**5n**), and *meta*-phenoxybenzaldehyde (**5r**), respectively, are the key components of chiral pharmaceuticals, such as Clopidogrel (an antiplatelet agent) and angiotensin-converting enzyme inhibitors including pril-type drugs,[22] and chiral agrochemicals such as various pyrethroids.[4,23] Notably, the catalyst **4d** is extremely efficient in the catalysis of TMSCN addition to **5a**, and the catalyst loading can be additionally reduced to as low as 0.005–0.0005 mol% at a higher substrate concentration (ca. 3 M) to afford adduct **6a** in 99–86% yield with 97–95% *ee* (entries 28 and 29, Table 1). As an example to demonstrate the feasibility for practical and scaleable synthesis of cyanohydrin derivatives with **4d**, a total of 13.265 g (125 mmol) of freshly distilled **5a** and 17.3 mL (137.5 mmol) of TMSCN in 15 mL of CH_2Cl_2 in the presence of 0.8 mg (6.25×10^{-4} mmol, 0.0036 wt% of **6a**) of the chiral catalyst **4d** was converted into 22.100 g of **6a**. To the best of our knowledge, such a high efficiency at room temperature is comparable or even higher than that of (*R*)-oxynitrilase, in which a total of 185.5 g of benzaldehyde was converted into 226 g of (*R*)-mandelonitrile using 78 mg of (*R*)-oxynitrilase (0.035 wt%) in a series of four consecutive experiments.[1]

Although low catalyst loadings, high yields, and excellent enantioselectivity have been realized in these aldehyde cyanations catalyzed by **4d**, TMSCN is expensive, volatile, and extremely toxic.[24] These drawbacks of the reagent cause serious practical and safety liabilities that limit application on preparative scale. In contrast, sodium cyanide (NaCN) and potassium cyanide (KCN) are inexpensive and nonvolatile. However, the use of these cyanide salts as the alternative sources for cyanation has found limited application in catalytic asymmetric cyanations developed to date.[25] This may be attributed to the poor solubility of cyanide salts in organic solvents, or the lower compatibility of the known catalysts to the reaction. Fortunately, the present catalyst **4d** is also highly efficient for the cyanation of benzaldehyde in the presence of NaCN and acetic anhydride to give the corresponding *O*-acetyl cyanohydrin **7a**. The reaction of benzaldehyde with NaCN (3 equiv) and acetic anhydride (3 equiv) in the presence of 0.01 mol% of **4d** and 10 mol% of acetic acid in CH_2Cl_2 at room temperature affords cyanohydrin acetate **7a** in 99% yield with essentially same enantioselectivity (entry 1, Table 2) as that using TMSCN (entry 27, Table 1). The reaction is heterogeneous and the addition of a small amount (10 mol%) of acetic acid can facilitate the reaction by improving the solubility of NaCN or favoring the release of HCN by reacting with NaCN. Even though the catalyst loading is additionally reduced to 0.005 mol%, the

Table 2: Practical enantioselective aldehyde cyanation using NaCN as a cyanide source.[a]



5 7

Entry	R (**5**)	**4d** [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**5a**)[d]	0.01	10	99	96 (*S*)
2	Ph (**5a**)[d]	0.005	24	99	94 (*S*)
3	*o*-ClC_6H_4 (**5k**)	0.04	5	99	90 (*S*)
4	(*E*)-PhCH=CH (**5l**)	0.01	18	90	90 (*S*)
5	2-naphthalenyl (**5n**)	0.005	48	97	92 (*S*)
6	*m*-$PhOC_6H_4$ (**5r**)[d]	0.005	20	99	93 (*S*)
7	*p*-HOC_6H_4 (**5u**)[e]	0.01	8	98	91 (+)
8	*m*-$AcOC_6H_4$ (**5v**)	0.01	12	97	93 (−)
9	*o*-$AcOC_6H_4$ (**5w**)[f]	0.05	8	98	92 (+)
10	*o*-$MeO_2CC_6H_4$ (**5x**)[d]	0.05	6	98	92 (−)

[a] Runs on 10 mmol scale of **5** with 3 equiv of NaCN and Ac_2O in 12.5 mL of CH_2Cl_2. [b] The yields of isolated **7** after silica gel chromatography. [c] The *ee* value was determined by GC or HPLC analysis using a chiral stationary phase. The absolute configuration, given in parentheses, was determined by comparison of the optical rotation with that reported in literature. [d] Added 10 mol% of HOAc. [e] The R group in product **7u** of entry 7 is *p*-$AcOC_6H_4$. [f] Used 2 mmol scale of aldehyde with 3 equiv of NaCN and Ac_2O in 2.5 mL of CH_2Cl_2.

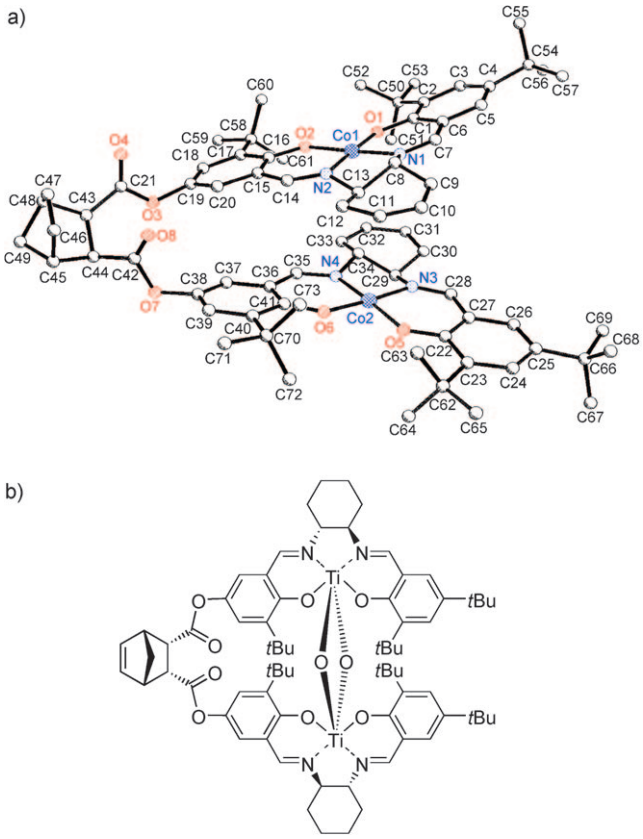


Figure 1. a) The X-ray crystal structure of the analogous Co^{II} complex of **3d**. b) Proposed structure for catalyst **4d**.

enantioselectivity of the catalysis still remains at high level (entry 2, Table 2) albeit with a slight drop of catalytic activity.

The high practicality of the present reaction system with catalyst **4d** using the cheap and nonvolatile NaCN as the cyanide source prompted us to extend this methodology to the reactions of useful substrates such as **5k**, **5l**, **5n**, and **5r** (entries 3–6, Table 2), and some challenging functionalized substrates including aromatic aldehydes having different substitution patterns (**5u**, **5v**, **5w**, and **5x**; entries 7–10). As shown in Table 2, the reactions proceed smoothly in the presence of 0.05–0.005 mol% of **4d** at room temperature on gram scale, affording the corresponding *O*-acetyl cyanohydrin derivatives in excellent yields (90–99%) with 90–93% *ee* values. Again, the catalytic activity of **4d** is enhanced by 1–2 orders of magnitude in comparison with that of the parent $[\{(salen)Ti(\mu\text{-}O)\}_2]$ (**2**), a commercially available catalyst.[4]

A preliminary mechanistic study has been carried out to shed some light on the underlying basis for the exceptional catalytic efficiency in the aldehyde cyanation reaction promoted by catalyst **4d**. The composition and molecular structure of **4d** were first studied using various methods. Elemental analysis and mass spectroscopy data indicated that **4d** contains the ligand **3d** and two Ti=O units. Although many trials for getting a single crystal of **4d** failed, the molecular structure of an analogous **3d**/Co^{II} complex was successfully determined by single-crystal X-ray diffraction methods.[26] As shown in Figure 1a, two metallosalen units in the complex are aligned face to face in a head-to-tail orientation with a Co^{II}–Co^{II} distance of 5.387 Å. On the basis of the analytical data of complex **4d** and the molecular structure of the Co^{II} complex of the same ligand (**3d**) mentioned above, as well as the X-ray crystal structure of the related dimeric $[\{(salen)Ti(\mu\text{-}O)\}_2]$ (**2**) reported by North, Belokon, and co-workers[17,18,25c] a possible structure for catalyst **4d** was proposed as shown in Figure 1b. Such a precise spatial arrangement of two active centers is obviously favorable for cooperative activation of both substrates and thereby allows a subsequent intramolecular reaction of the activated species to realize high catalytic activity and fine control of the selectivity. An additional indication of intramolecular bimetallic pathway in **4d**-catalyzed aldehyde cyanation was provided by investigating the nonlinear effect[27,28] of the reaction system. Under the experimental conditions (see Figure S2 in the Supporting Information), a strict linear relationship between the enantiomeric excesses of product **6a** and those of catalyst **4d** is observed, as would be expected for exclusively intramolecularly cooperative catalysis.

In summary, an exceptionally efficient chiral catalyst for enantioselective cyanation of aldehydes using either TMSCN or NaCN as the cyanide source has been developed on the basis of cooperative dual activation concept, affording the corresponding enantioenriched natural or non-natural cyanohydrin derivatives with turnover numbers of 1960–172000 and up to 97% *ee*. This catalyst is highly robust and compatible with cyanide salts which are safer, cheaper, and easier to handle than other cyanide sources. Some of the cyanohydrin products can be used as the key intermediates for the synthesis of chiral pharmaceuticals and agrochemicals. The practical feature and mechanistic implication of this discovery may extend beyond cyanation itself and provide a

useful model for other reaction variants.[29] Future efforts will focus on the detailed mechanistic issues of the catalytic system.

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