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Enantioselective Silylcyanation of Aldehydes and Ketones by a Titanium Catalyst Prepared from a Partially Hydrolyzed Titanium Alkoxide and a Schiff Base Ligand

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Dedicated to the late Ms. Haruna Teraoka.

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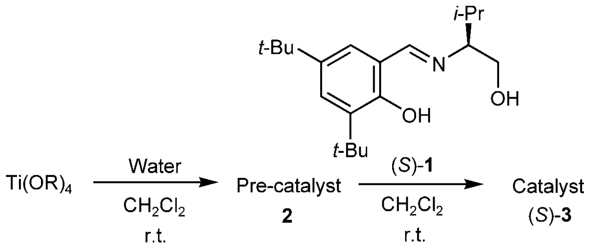
Abstract: In the presence of small amount (0.2–1.0 mol%) of a titanium complex catalyst prepared from a partially hydrolyzed titanium alkoxide and an optically active tridentate Schiff base ligand, the enantioselective silylcyanation of aldehydes and ketones proceeded in a short reaction time at room temperature to afford the corresponding optically active cyanohydrin derivatives in excellent chemical yield with high enantiomeric excess (86–97% *ee*). The results indicate that partially hydrolyzed titanium alkoxides are a promising titanium source for the preparation of efficient catalysts for asymmetric synthesis.

Keywords: asymmetric catalysis; cyanohydrins; Schiff bases; titanium; water

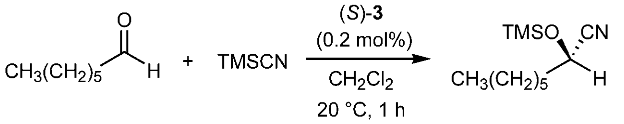
The enantioselective silylcyanation of carbonyl compounds is one of the most useful carbon-carbon bond-forming reactions in organic synthesis for producing optically active cyanohydrin derivatives. This is because these compounds can be converted to a variety of chiral building blocks such as optically active α-hydroxy carboxylic acids and α-amino alcohols.[1] After the pioneering work by Hayashi and Oguni on the catalytic enantioselective silylcyanation of aldehydes using an optically active Schiff base ligand with Ti(O-*i*-Pr)$_4$ as a Lewis acidic metal compound,[2] a wide variety of chiral molecular catalysts have been developed.[3] Additionally, because of the importance of the enantioselective construction of quaternary stereocenters, the catalytic asymmetric silylcyanation of prochiral ketones has attracted considerable attention.[4] However, the enantioselective silylcyanation of a broad range of substrates including aliphatic aldehydes and ketones with low catalyst loading under mild reaction conditions is still a challenge. Herein, we would like to describe a simple and practical method for the enantioselective silylcyanation of aldehydes and ketones using a novel titanium catalyst prepared from a partially hydrolyzed titanium alkoxide as a Lewis acidic metal compound and an optically active tridentate Schiff base ligand. The titanium catalyst afforded the corresponding cyanohydrin derivatives in excellent chemical yield with high enantiomeric excess at room temperature.

The novel titanium catalyst (*S*)-**3** was prepared from pre-catalyst **2**, Ti(O-*n*-Bu)$_4$ hydrolyzed with 1.0 equivalent of water, and chiral Schiff base (*S*)-**1** (Scheme 1). In the presence of 0.2 mol% of the catalyst (*S*)-**3**, the reaction of heptanal with trimethylsilyl cyanide (TMSCN) rapidly proceeded to afford the desired optically active cyanohydrin trimethylsilyl ether quantitatively with 87% *ee* in 1 hour at room temperature (Table 1, entry 5). In contrast, a combined use of Ti(O-*n*-Bu)$_4$ and the ligand (*S*)-**1** under strictly an-



Scheme 1. Preparation of catalyst **3** from pre-catalyst **2**, a partially hydrolyzed titanium alkoxide, and optically active tridentate Schiff base ligand (*S*)-**1**.

Table 1. Asymmetric silylcyanation of heptanal catalyzed by titanium catalyst (*S*)-**3**.[a]



Entry	Titanium alkoxide	H_2O/Ti [mol/mol]	Conv.[b] [%]	*ee*[c] [%]
1	Ti(O-*n*-Bu)$_4$	–	43	<5
2	Ti(O-*n*-Bu)$_4$	0.5	70	28
3	Ti(O-*n*-Bu)$_4$	0.75	>99	85
4	Ti(O-*n*-Bu)$_4$	0.85	>99	85
5	Ti(O-*n*-Bu)$_4$	1.0	>99	87
6	Ti(O-*n*-Bu)$_4$	1.1	>99	87
7	Ti(O-*n*-Bu)$_4$	1.2	99	86
8	Ti(O-*n*-Bu)$_4$	1.3	70	83
9	Ti(O-*n*-Bu)$_4$	1.5	10	<5
10	Ti(OEt)$_4$	1.0	>99	87
11	Ti(O-*n*-Pr)$_4$	1.0	>99	88
12	Ti(O-*i*-Pr)$_4$	1.0	<5	<5

[a] The reactions were performed with TMSCN (1.5 equiv.) in the presence of (*S*)-**3** prepared from (*S*)-**1** (0.2 mol%) and Ti(OR)$_4$ (0.2 mol%) under a nitrogen atmosphere.

[b] Determined by GC analysis.

[c] Determined by GC analysis. The absolute configuration was determined as (*S*) by comparison of the sign of optical rotation with literature data. See the Supporting Information.

hydrous conditions gave a racemic product for the reaction with low efficiency (Table 1, entry 1). We investigated the effect of water for the preparation of the pre-catalyst **2** on the asymmetric silylcyanation of heptanal as a model substrate with TMSCN (Table 1, entries 2–9). It should be noted that the ratio of water to titanium is crucial to achieve high enantioselectivity and efficiency. The results clearly show the suitable ratio of water to titanium is approximately one.[5]

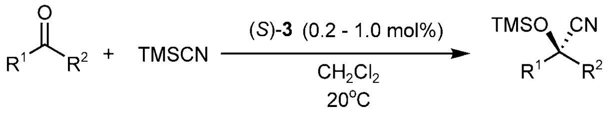
Other titanium alkoxides as a titanium source were examined in place of Ti(O-*n*-Bu)$_4$ (Table 1, entries 10–12). Ti(OEt)$_4$ and Ti(O-*n*-Pr)$_4$ were found to be also efficient titanium sources. The performance of the catalysts prepared from these titanium alkoxides were comparable to those prepared from Ti(O-*n*-Bu)$_4$. However, a combined use of (*S*)-**1** and a hydrolyzed product from Ti(O-*i*-Pr)$_4$ showed poor catalytic performance under the same reaction conditions because hydrolysis of Ti(O-*i*-Pr)$_4$ afforded an insoluble white precipitate.

Pre-catalyst **2**, partially hydrolyzed titanium alkoxide, is a key component for the preparation of an efficient catalytic system for the enantioselective silylcyanation. Water should be added to the titanium alkoxide before addition of the ligand (*S*)-**1** in order to achieve high selectivity and efficiency. The addition of water to the combined mixture of Ti(O-*n*-Bu)$_4$ and the ligand was less effective.[6] The structure of pre-catalyst **2** is unclear at the present, however, we assume it to be composed of a titanium oxo-alkoxide, an oligomer including a Ti–O–Ti structure,[7,8] generated from the hydrolysis of titanium alkoxides.[9] The oligomeric structure may be maintained in catalyst (*S*)-**3** since a positive non-linear effect (NLE) between enantiomeric excesses (*ee*s) of the ligand and *ee*s of the product was observed for the reaction of heptanal with TMSCN in the presence of catalyst (*S*)-**3**.[10,11]

Recently, several effective catalysts containing a metal-O-metal structure have been reported for enantioselective silylcyanation.[3e,s,4a,c,d] In previous reports, multi-metallic activation systems, in which both CN and C=O are activated by two metal centers simultaneously, have been proposed to explain the high performance of the catalysts. We assume that cyanation using our catalyst system would proceed *via* a similar multi-metallic activation pathway.[12]

The novel catalyst for the enantioselective silylcyanation was successfully applied to various aldehydes (Table 2). The silylcyanation of benzaldehyde proceeded quantitatively with 89% *ee* (entry 1). Substituted benzaldehydes were also transformed into the corresponding cyanohydrin silyl ethers in good yield

Table 2. Enantioselective silylcyanation of aldehydes and ketones catalyzed by catalyst (*S*)-**3**.[a]



Entry	R^1	R^2	Catalyst [mol%]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1[d]	Ph	H	0.5	2	>99	89 (*S*)
2	4-MeO-C_6H_4	H	0.5	2	91	89 (*S*)
3	2-F-C_6H_4	H	0.5	2	91	92[f]
4	4-CF_3-C_6H_4	H	1.0	2	86	89[f]
5[d]	*n*-C_6H_{13}	H	0.2	0.33	97	86 (*S*)
6[d]	Et_2CH	H	0.2	2	99	97 (*S*)
7	*c*-C_6H_{11}	H	0.2	1	89	97 (*S*)
8[d,e]	Ph	Me	0.4	24	96	88 (*S*)
9[e]	*c*-C_6H_{11}	Me	0.2	24	97	90[f]

[a] Unless noted otherwise, the reactions were performed with TMSCN (1.5 equiv.) in the presence of (*S*)-**3** [(*S*)-**1**/Ti(O-*n*-Bu)$_4$ = 1, H_2O/Ti = 0.75] under a nitrogen atmosphere.

[b] Isolated yield.

[c] Determined by GC analysis. The absolute configurations were determined by comparison of the sign of optical rotation with literature data. See the Supporting Information.

[d] H_2O/Ti = 1.1.

[e] (*S*)-**1** (0.2 mol%), Ti(O-*n*-Bu)$_4$ (0.4 mol%) [(*S*)-**1**/Ti(O-*n*-Bu)$_4$ = 0.5].

[f] The absolute configurations were not determined.

with good enantiomeric excess (entries 2–4). The substituent on the benzene ring did not exert a significant influence on the enantioselectivity of the reaction. In the case of aliphatic aldehydes, the corresponding cyanohydrin silyl ethers were obtained in high yield with high enantioselectivities. The reaction of heptanal was completed in 20 min in the presence of 0.2 mol% of catalyst (*S*)-**3** to give the desired product with 86% *ee* (entry 5). Excellent results were obtained for secondary aldehydes such as 2-ethylbutyraldehyde and cyclohexanecarbaldehyde (entries 6 and 7).

The catalyst system was also effective for the silylcyanation of aromatic and aliphatic ketones; acetophenone and cyclohexylmethylketone afforded the corresponding cyanated products in 24 h with 88% *ee* and 90% *ee*, respectively (entries 8 and 9). The catalyst system was applicable for the highly enantioselective silylcyanation of a wide range of carbonyl compounds.

In summary, we have demonstrated that partially hydrolyzed titanium alkoxides are a promising titanium source for the preparation of an efficient catalyst for asymmetric synthesis. The reaction in the presence of catalyst (*S*)-**3** proceeded smoothly to afford products with high enantioselectivity with high efficiency at room temperature. A detailed study of the titanium catalyst structure and the scope and limitations of the substrates is now underway.

Experimental Section

Typical Experimental Procedure

An optically active Schiff-base ligand (*S*)-**1** was synthesized according to the reported method.[2b] Ti(O-*n*-Bu)$_4$ was hydrolyzed with wet dichloromethane containing 1.0 equiv. of water per titanium at room temperature. A solution of catalyst (*S*)-**3** was prepared from a solution of ligand (*S*)-**1** and the partially hydrolyzed titanium *n*-butoxide [the molar ratio of ligand (*S*)-**1**/Ti = 1/1]. Asymmetric silylcyanation was carried out using 0.2–1.0 mol% of the catalyst (*S*)-**3** and TMSCN (1.5 equiv. to substrates) in anhydrous dichloromethane at 20 °C.

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