Catalytic Enantioselective Cyanosilylation of Ketones

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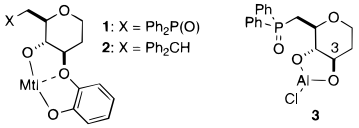
The catalytic asymmetric addition of cyanide to carbonyl compounds[1] such as aldehydes,[2] imines[3] and ketoimines[4] is currently intensively studied. However, no practical asymmetric cyanosilylation of ketones has been reported so far. For example,[5] the best result using chemical catalyst is 72% ee in the case of aryl methyl ketones. However, this catalyst could not be applied to ethyl ketones (∼30% ee) and aliphatic ketones.[6] In view of the importance of the cyanohydrins as precursors of chiral quaternary α-hydroxy carbonyl derivatives, development of an efficient catalytic asymmetric cyanosilylation of ketones with broad generality is long awaited. Herein, we describe the first entry in this category that we believe is useful for synthesizing a variety of quaternary cyanohydrins, catalyzed by a novel titanium catalyst **1**.



During the course of our studies to develop a new asymmetric catalyst from the concept of bifunctional catalysis,[7] we have found that the Lewis acid (Al)−Lewis base (phosphine oxide) catalyst **3** can promote the cyanosilylation of acetophenone, however, with low enantiomeric excess (20%).[8] To improve the enantioselectivity, we planned to introduce a catechol moiety at the C3 hydroxyl group on the basis of the following consideration. The coordination of the ether oxygen at C3 should make it possible to form a complex such as **1**. As a result, the phenyl group of the catechol should be fixed at the position shielding the α-side (*anti* to the phosphine oxide, concave side) of the catalyst, thus defining the position of the coordinating ketone at the *β*-side, *syn* to the Lewis basic phosphine oxide. Therefore, we designed the new catalyst **1**. Ligand **1-L** was readily synthesized in multigram scale from the known alcohol **4**[9] as shown in Scheme 1.[10]

Scheme 1. Synthesis of **1-L**

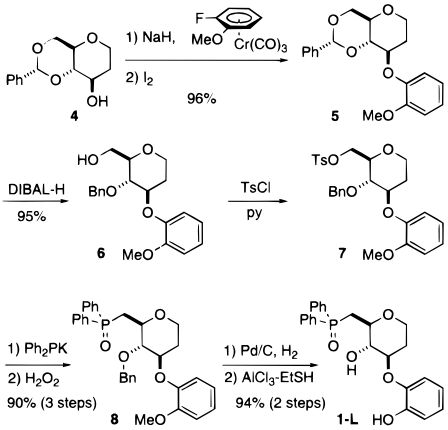
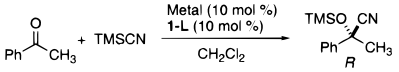
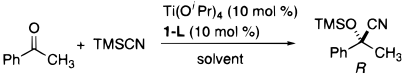


Table 1. Effect of Metals



entry	metal	temp/°C	time/h	yield/%	ee/%	*R*/*S*
1	Et_2AlCl	rt	48	0	-	-
2	$Yb(O^iPr)_3$	rt	2	90	18	*S*
3	$Zr(O^tBu)_4$	rt	36	52	14	*R*
4	$Ti(O^iPr)_4$	rt	48	78	35	*R*
5	$Ti(O^iPr)_4$	−20	36	44	73	*R*

Table 2. Effect of Solvents



entry	solvent	conc/M	temp/°C	time/h	yield/%	ee/%
1	CH_2Cl_2	0.65	−20	36	44	73
2	toluene	0.65	−20	36	40	70
3	THF	0.65	−20	36	58	83
4	THF	3	−30	36	85	92

First, we screened different metals combined with ligand **1-L** for the catalysis of the addition of TMSCN to acetophenone **9a** (Table 1). Although the Yb catalyst showed a remarkable reactivity (Table 1, entry 2), it was found that the Ti catalyst gave the best enantiomeric excess (Table 1, entry 4). Furthermore, when the reaction was conducted at −20 °C, the ee was increased up to 73% (Table 1, entry 5). Next, we examined the effect of solvent (Table 2). Interestingly, both the reaction rate and enantioselectivity increased in a coordinating solvent such as THF compared to less polar solvents such as CH_2Cl_2 or toluene. Gratifyingly, employing more concentrated conditions (3 M in terms of **9a**), the reaction proceeded more efficiently at −30 °C for 36 h to give the product in 85% yield and with 92% ee (Table 2, entry 4). Consequently, the best reaction conditions were determined to involve 10 mol % of $Ti(O^i\ Pr)_4$ and ligand **1-L** in THF solvent.

(1) (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649−3682. (b) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555−1564. (c) North, M. *Synlett* **1993**, 807−820.

(2) For example: (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (b) Belokoń, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968−3973. (c) Hwang, C.-D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762−6763.

(3) For example: (a) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281. (c) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762−766. (e) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160.

(4) (a) Vachal, R.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870. (b) Byrne, J. J.; Chavarot, M.; Chavant, P.-Y.; Vallée, Y. *Tetrahedron Lett.* **2000**, *41*, 873−876.

(5) Belokoń, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147−8150.

(6) Enzymatic reactions have been reported to give cyanohydrins from aliphatic ketones with high enantioselectivity. However, synthesis of cyanohydrins from aromatic ketones and ethyl ketones is not efficient using enzymes. For example: Kiljunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 1551−1557.

(7) (a) Shibasaki, M. *Enantiomer* **2000**, *4*, 513−527. (b) Shibasaki, M. *CHEMTRACTS: Org. Chem.* **1999**, 979−998. (c) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(8) Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405−2409.

(9) Nakamura, H.; Tejima, S.; Akagi, M. *Chem. Pharm. Bull.* **1966**, *14*, 648−657.

(10) See Supporting Information.

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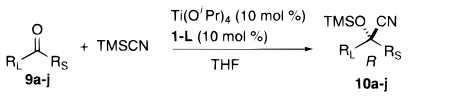
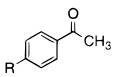
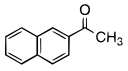
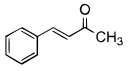
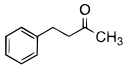
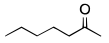
Table 3. Catalytic Asymmetric Cyanosilylation of Ketones[a]



entry	ketone		temp/°C	time/h	yield/%[b]	ee/%[c]
1		R = H **9a**	-30	36	85	92[e]
2		R = CH$_3$ **9b**	-30	84	80	90
3		R = Cl **9c**	-40	80	82	92
4		**9d**	-40	80	82	95
5		**9e**	-40	96	72	69
6		**9f**	-20	64	89	91
7		**9g**	-50	88	72	91
8		**9h**	-50	36	86	90[d]
9		**9i**	-50	36	92	85
10		**9j**	-50	36	88	76[e]

[a] The method for preparation of the catalyst and the general procedure of the reaction, see ref 12. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. See Supporting Information. [d] Ee was determined after conversion to the corresponding benzyl carboxylate. [e] The absolute configurations were determined by the comparison with the reported values of optical rotation.

To get a preliminary insight into the catalyst structure, we performed NMR studies. When a mixture of Ti(O^{i}Pr)$_4$ and **1-L** was heated at 75 °C for 1 h in toluene, generation of 2 equiv of ^{i}PrOH was observed in ^{1}H NMR. Therefore, at this stage, the pre-catalyst contains titanium diisopropoxide (**1**: Mtl = Ti(O^{i}Pr)$_2$). After evaporation of toluene, THF and TMSCN (2 equiv to Ti) were added. Then, peaks corresponding to TMSO-^{i}Pr (0.19, 1.21, and 4.1 ppm) emerged, indicating the generation of titanium cyanide species. After 1 h at ambient temperature, about 70% of titanium seemed to contain monocyanide, deduced from the integration ratio of the remained TMSCN (0.44 ppm) and generated TMSO^{i}Pr. Starting the reaction by further adding acetophenone **9a** (10 equiv to Ti) and TMSCN (15 equiv to Ti), almost complete mono-ligand exchange from isopropoxide to cyanide seemed to take place.[11] Therefore, the actual catalyst should be a complex composed of titanium monocyano monoisopropoxide (**1**: Mtl = Ti(CN)(O^{i}Pr)). As will be described later, complete formation of titanium monocyanide was realized by longer reaction time (10 h) using 1 equiv of TMSCN.

This newly developed catalyst **1** shows a broad applicability for reactions of various ketones with high enantioselectivity, including both aromatic and aliphatic ketones (Table 3).[12]

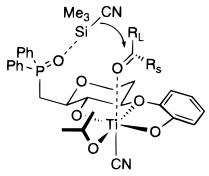


Figure 1. Working model

Specifically, less reactive ketones such as propiophenone **9f** and indanone **9e** gave the product in 89% and 72% yield with 91% and 69% ee's. The enone **9g** gave the 1,2-adduct with complete regioselectivity. Even the simple *n*-alkanone **9j** gave the product in 76% ee.[13] Thus, this is the first example of a general cyanosilylation reported to date. The product **10d** was successfully converted to the quaternary hydroxy ester (HCl-EtOH, 90 °C for 3 h) or aldehyde (DIBAL-H) in a single step without any loss of enantiomeric excess.[10]

To get a further insight into the nature of this reaction, kinetic studies were carried out and the reaction rate was found to show a first-order dependency on the catalyst.[10] Furthermore, from the labeling experiment using TMS^{13}CN,[14] the cyanide appeared to be transferred from TMSCN but not from titanium cyanide.[10] Thus, we prepared the active titanium catalyst containing ^{12}CN from Ti(O^{i}Pr)$_4$, **1-L** (1 equiv) and TMS^{12}CN (1 equiv) (rt for 10 h). After complete consumption of TMS^{12}CN was confirmed by ^{1}H NMR, and then **9a** (1 equiv) and TMS^{13}CN (1 equiv) were added. Incorporation (77%) of ^{13}CN into the product **10a** was confirmed by ^{13}C NMR.[15] These results suggest that the titanium cyanide would act only as a Lewis acid but not as a CN source. Meanwhile, preliminary studies to elucidate the role of the phosphine oxide revealed the importance of this moiety on the enantioselectivity as well as the catalytic activity. Thus, using the control ligand **2** containing a diphenylmethyl group, instead of the phosphine oxide, neither reaction of **9a** nor more reactive **9i** proceeded at low temperature. These reactions proceeded very slowly at ambient temperature to give **10a** and **10i** in only 31% and 33% yields (80 h), respectively, and both with 2% ee. From these observations, as well as the former results from our laboratories,[2a,3a,7] we propose a dual activation mechanism by the catalyst **1**, in which the titanium and the oxygen atom of the phosphine oxide activate the ketone and TMSCN as a Lewis acid and a Lewis base, respectively (Figure 1).

In conclusion, we have developed the first general and highly enantioselective cyanosilylation of ketones by designing the novel bifunctional catalyst **1** containing titanium and phosphine oxide. Products were efficiently converted to chiral quaternary α-hydroxy carbonyl derivatives. This contribution should provide a new synthetic strategy for the construction of chiral quaternary carbon centers as well as facilitate biological studies using quaternary α-hydroxy carboxylic acids as a tool.[16] Studies for clarifying the reaction mechanism and the origin of the enantioselection are currently under investigation.

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Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001643H

(11) For a ligand exchange on titanium from isopropoxide to cyanide by TMSCN, see: Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6229−6232.

(12) A representative procedure: To a suspension of **1-L** (24 mg, 0.0565 mmol) in toluene (1 mL) was added Ti(O^{i}Pr)$_4$ (16 μL, 0.054 mmol) at ambient temperature, and the whole was stirred at 75 °C for 1 h. After the yellow solution was cooled to room temperature, toluene was evaporated under reduced pressure. The resulting pale yellow residue was further dried in vacuo for 1 h. The residue was dissolved in THF (0.18 mL, 0.27 mL for aliphatic ketones), TMSCN (14 μL, 0.108 mmol) was added under ice bath, and the whole was stirred at room temperature for 30 min. To this catalyst solution, the starting ketone (0.54 mmol) was added, followed by the addition of TMSCN (144 μL, 1.08 mmol) at the temperature shown in Table 3. The reaction was monitored by TLC, and after the reaction period described in Table 3, pyridine (0.1 mL) and H_2O (1 mL) were added. Usual workup and purification by silica gel column chromatography gave the product.

(13) The ee was improved to 82% when the reaction was conducted at −60 °C (67% yield for 161 h).

(14) TMS^{13}CN was prepared from K^{13}CN following the reported procedure: Reetz, M. T.; Chatziiosifidis, I. *Synthesis* **1982**, 330.

(15) Incomplete incorporation of ^{13}CN would stem from a partial scrambling between titanium cyanide and TMS^{13}CN.

(16) Quaternary amino acids are often a component of enzyme inhibitors. See refs 4a.