Switching Enantiofacial Selectivities Using One Chiral Source: Catalytic Enantioselective Synthesis of the Key Intermediate for (20*S*)-Camptothecin Family by (*S*)-Selective Cyanosilylation of Ketones

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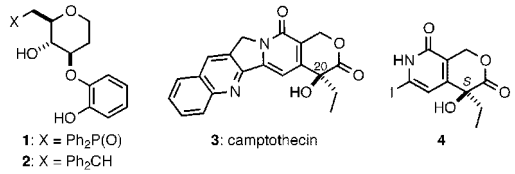
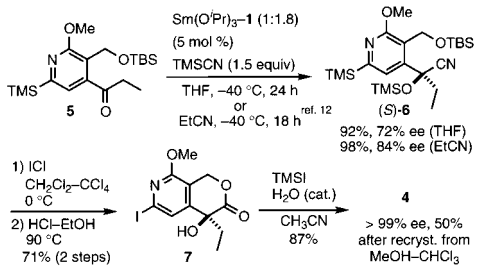
Chiral ketone cyanohydrins are important and versatile synthetic intermediates, which can be easily converted to α-hydroxy carbonyl compounds that contain chiral quaternary stereocenters.[1,2] Recently, we have developed a novel chiral ligand **1** derived from D-glucose and found that the Ti−**1** complex catalyzes a highly enantioselective cyanosilylation of ketones, giving (*R*)-cyanohydrins from a broad range of ketones.[3,4] We planned to apply this reaction to the catalytic enantioselective synthesis of (20*S*)-camptothecin **3** and its analogues, which are among the most promising agents for the treatment of solid tumors.[5,6] For this purpose, however, more expensive L-glucose was needed as the chiral source.[7] The synthetic utility of the reaction is highly improved if both of the product enantiomers can be similarly accessible using a readily available chiral source.[8] We describe here the development of (*S*)-selective cyanosilylation of ketones using the catalyst with the D-glucose derived ligand and a short-step catalytic asymmetric synthesis of the camptothecin intermediate **4**.



On the basis of the established synthetic route from one of the author's laboratories, α-hydroxy lactone **4** offers a general synthetic intermediate for the synthesis of the camptothecin family.[5] Therefore, we selected ethyl ketone **5** as a substrate for the catalytic enantioselective cyanosilylation. When previously optimized reaction conditions catalyzed by Ti−**1** complex (20 mol %) were applied to **5**, the reaction proceeded only very slowly at ambient temperature, and the product cyanohydrin **6** was obtained in 34% yield after 6 days with 18% ee. As expected from the previous results, the absolute configuration of **6** was the undesired *R*.

Scheme 1. Catalytic Enantioselective Synthesis of **4**



To improve the catalyst activity, we screened the Lewis acid metal and found that the lanthanide complexes showed much higher activity. Thus, the reaction proceeded at −40 °C in the presence of 5 mol % of catalyst prepared from **1** and $Sm(O^iPr)_3$[9] in 1:1 ratio, giving **6** with 20% ee. Moreover, the absolute configuration of the obtained **6** was switched to the desired one (*S*). Encouraged by these results, we next optimized the ratio of Sm and ligand **1**. It was found that the ratio of 1:1.8 was the optimum and **6** was obtained in 92% yield with 72% ee at −40 °C for 24 h (THF).[10−12] Therefore, the switch of the enantioselectivity, as well as higher activity of this new lanthanide catalyst, is noteworthy. The higher activity of the catalyst is advantageous, especially when the substrate contains multi-functionalities to deactivate the catalyst by coordination to the Lewis acid metal, which is often the case in natural product synthesis.

From (*S*)-cyanohydrin **6**, key intermediate **4** for the synthesis of the camptothecin family was synthesized in three steps (Scheme 1). Enantiomerically pure **4** was obtained in 50% yield by recrystallization from MeOH−$CHCl_3$ (8:1).

Next, to probe the generality of this catalytic (*S*)-selective cyanosilylation, we tried acetophenone (**8a**) as a substrate. Thus, in the presence of 5 mol % of Sm−**1** complex (1:1.8), the reaction in THF was completed at −40 °C for 2 h, giving (*S*)-cyanohydrin **9a** in 85% yield with 82% ee. The ee was further improved to 89%, when Gd was used instead of Sm. The optimum ratio of Gd to **1** was determined to be 1:2, as shown in Figure 1, although ee seemed to reach a plateau at the ratio of **1**/Gd = 1.5/1. Under the optimized conditions, **9a** was obtained in 92% yield with 92% ee (Table 1, entry 1). Results of other ketones are also summarized in Table 1.[13] The reaction gave good to excellent enantioselectivities when aromatic ketones or enones were used as substrates (entries 3−8). Enones gave cyanohydrins with complete regioselectivity. Although aliphatic ketones gave less satisfactory results (entry 9), these products could be easily synthesized by hydrogenation of the cyanohydrins from enones in quantitative yield without any loss of the enantiomeric purity.[14] Therefore, the present reaction can afford a broad range of (*S*)-ketone cyanohydrins using readily available D-glucose as a chiral source. Combined with the previous Ti−**1** catalyzed reaction (e.g., Table

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(1) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649−3682.

(2) For a review of catalytic enantioselective synthesis of chiral quaternary centers, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(3) (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691−694.

(4) For other examples, see: (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195−6196. (b) Belokon', Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron*, **2001**, *57*, 771−779.

(5) For the enantioselective synthesis of the (20*S*)-camptothecin family, see Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67−83 and references therein.

(6) For a review of target-oriented catalytic enantioselective reactions, see: Hoveyda, A. H. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 145.

(7) For example, Aldrich supplies D-glucose with $7.8/kg and L-glucose with $26,170/kg.

(8) For examples of synthesis of both enantiomers using the same or similar chiral sources, see: Kobayashi, S.; Kusakabe, K.-i.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220−4221, and references cited therein.

(9) Purchased from Kojundo Chemical Laboratory Co., Ltd. (Fax: +81-492-84-1351).

(10) Effect of Sm/**1** ratio: 20% ee (1:1), 62% ee (1:1.5), 72% ee (1:1.8), 56% ee (1:2). Effect of metal (Ln/**1** = 1: 1.8): 52% ee (Gd), 20% ee (Pr).

(11) For lanthanide metal effect on the catalytic enantioselective reaction, see: (a) Sasai, H.; Suzuki, T.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851−854. (b) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165−167.

(12) After submitting this paper, we have found that ee of **6** was further improved to 84% when propionitrile was used as solvent (98% yield).

(13) A representative procedure: To a suspension of **1** (12.7 mg, 0.030 mmol) in THF (0.3 mL), $Ln(O^iPr)_3$ (0.2 M solution in THF, 75 μL, 0.015 mmol) was added at 0 °C, and the mixture was stirred at 45 °C for 30 min. The solvent was evaporated at ambient temperature, and the resulting white powder was dried under reduced pressure (∼5 mmHg) for 1 h. The catalyst was dissolved in THF (0.1 mL), and TMSCN (60 μL, 1.5 equiv) was added at the temperature shown in Table 1. After stirring for 15 min, the reaction was started by adding a solution of a ketone (0.300 mmol) in THF (0.1 mL).

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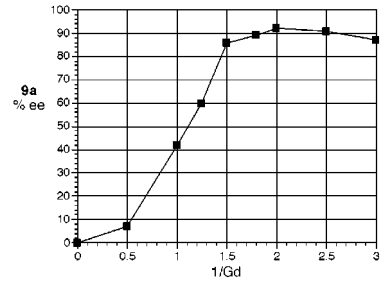
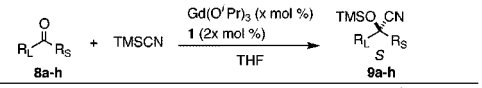
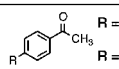
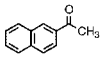
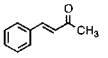
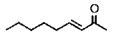


Figure 1. Relationship between ee and 1/Gd ratio.

Table 1. Catalytic Asymmetric Cyanosilylation of Ketones[a]



entry	ketone		catalyst (x mol %)	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1		R = H **8a**	5	-40	2	92	92 (*S*)[d]
2[e]		**8a**	10	-30	36	85	92 (*R*)
3		R = Cl **8b**	5	-60	55	89	89
4		**8c**	5	-60	24	95	87
5		**8d**	5	-60	14	93	97
6		**8e**	10	-60	14	97	86
7		**8f**	15	-60	18	87	80
8		**8g**	15	-60	4	95	89
9		**8h**	5	-60	1	90	62

[a] The method for preparation of the catalyst and the general procedure of the reaction, see ref. 13. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. See Supporting Information. [d] The absolute configuration was determined by the comparison with the reported value of optical rotation. [e] Reaction using Ti-**1** catalyst. See ref. 3(a)

1, entry 2), both of the enantiomers can be synthesized by the catalysts derived from one chiral source.

A preliminary catalyst structure and the reaction mechanism are postulated in Figure 2 on the basis of the following experiments. When Pr(O^{i}Pr)$_3$ and **1** were mixed in 1:2 ratio,[15] complete ligand exchange was observed by ^{1}H NMR analysis, indicating the generation of presumed complex **10** and free **1**. After evaporating ^{i}PrOH, an excess amount of TMSCN (>4 mol equiv) was added at −40 °C. Then, peaks corresponding to monosilylated **1** (0.34 ppm, derived from **11**) and disilylated **1** (0.38, 0.50 ppm) were observed in ca. 90% yields from **10** and free **1**, respectively. These observations indicated that **10** was converted to praseodymium cyanide **11** by monosilylation of **1**[16] and free **1** was disilylated.[17] Furthermore, the molecular formula of complex **11** (Ln = Gd) was confirmed by ESI-MS.[18] The relationship between the ee of the product and **1**/Gd ratio (Figure 1) was also consistent with these results. Therefore, the active catalyst was determined to be 2:3 complex **11**.

The higher activity of the lanthanide−**1** catalyst compared to Ti−**1**, as well as catalyst structure **11** would suggest that the active nucleophile is the lanthanide metal cyanide, not TMSCN itself. This was confirmed by the following results. First, we found a facile CN-scrambling between the gadolinium cyanide of the catalyst and TMSCN. Thus, after complex **11** (1 equiv) containing

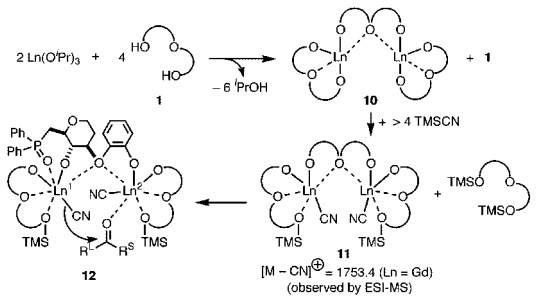


Figure 2. Working model of catalyst structure and reaction mechanism.

^{13}CN was prepared from TMS^{13}CN, acetophenone (**8a**) (1 equiv) and a variable amount of TMS^{12}CN (1, 2, or 3 equiv) were added. ^{13}C NMR analysis of the product cyanohydrin indicated that the incorporation of ^{13}CN was simply dependent on the ratio of added TMS^{13}CN and TMS^{12}CN. Moreover, only one signal corresponding to a cyanide (117 ppm) was observed on ^{13}C NMR analysis of **11** (Ln = Pr) labeled by ^{13}CN in the presence of a variable amount of TMS^{13}CN (0 or 2 equiv) at −60 °C. With the confirmation of preequilibrium in hand, we performed kinetic studies and determined the order with regard to TMSCN to be 0. In contrast, the Ti−**1**-catalyzed reaction, in which TMSCN activated by the phosphine oxide acts as the active nucleophile, showed 0.7 order dependency with regard to TMSCN. Therefore, in the present reaction catalyzed by Ln−**1**, the lanthanide metal cyanide acts as the active nucleophile.

On the basis of these findings, we proposed a bimetallic transition state **12** in Figure 2 as a working model. The Ln^1 cyanide should be more electron-rich, and therefore more active as a nucleophile, because Ln^1 is bound to two alkoxides and coordinated by the phosphine oxide of the linker ligand. On the other hand, the Ln^2 should be more Lewis-acidic. The intramolecular cyanide transfer from the nucleophilic Ln^1 cyanide to a ketone activated by the more Lewis-acidic Ln^2 should control the direction of the cyanide entry, giving products with high enantioselectivity. Consistent with this model, the order dependency of the reaction rate with regard to the catalyst was determined to be 0.8. The essential contribution of the Lewis-basic phosphine oxide in this reaction was highlighted from the results by the catalyst prepared from control ligand **2**. Thus, Gd−**2** (1:2) promoted the reactions of **8a** and **8h** much more slowly,[14] giving **9a** and **9h** with only 7% ee (98% yield at −40 °C for 10 h) and 2% ee (97% yield at −40 °C for 18 h), respectively. Therefore, the phosphine oxide should facilitate the lanthanide metal cyanide formation and stabilize the active 2:3 complex **11**, together with activating the lanthanide metal cyanide.[19]

In conclusion, we developed an (*S*)-selective cyanosilylation of ketones utilizing lanthanide−**1** complex and achieved a catalytic enantioselective synthesis of a versatile intermediate for the camptothecin family. Combined with the reaction catalyzed by Ti−**1** complex, both enantiomers of various ketone cyanohydrins are accessible by using the ligand derived from D-glucose. Further improvement of enantioselectivities and studies on determination of the catalyst structure using X-ray spectroscopy are in progress.

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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.

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(14) See Supporting Information.

(15) Praseodymium complex was used for NMR studies, because gadolinium is strongly paramagnetic. Pr−**1** (1: 2) complex gave **9a** in 96% yield with 77% ee at −40 °C for 2 h.

(16) Structure of monosilylated **1** appeared to be a silyl phenoxide because the phenol proton of recovered silylated **1** was not observed on ^{1}H NMR.

(17) Consistent with these discussions, no disilylated **1** was observed when **11** was prepared from Pr(O^{i}Pr)$_3$ and **1** in 1: 1.5 ratio.

(18) Mass value and isotope distribution were completely matched with calculated ones. Positions of silyl phenoxides were temporarily assigned. See Supporting Information for details.

(19) NMR studies revealed that less TMSCN was consumed during catalyst formation of Pr−**2** (1:2) than during that of Pr−**1**, indicating formation of less lanthanide metal cyanide in the case of Pr−**2** catalyst compared with Pr−**1** catalyst. No peaks corresponding to Gd−**2** complex were observed under any conditions by ESI-MS, which might indicate no defined structure.