Anti- and *Syn*-Selective Cyanosilylation Reactions Promoted by a Sugar-Based Bifunctional Catalyst: Stereoselective Syntheses of Essential Building Blocks for HIV Protease Inhibitors and Bestatin

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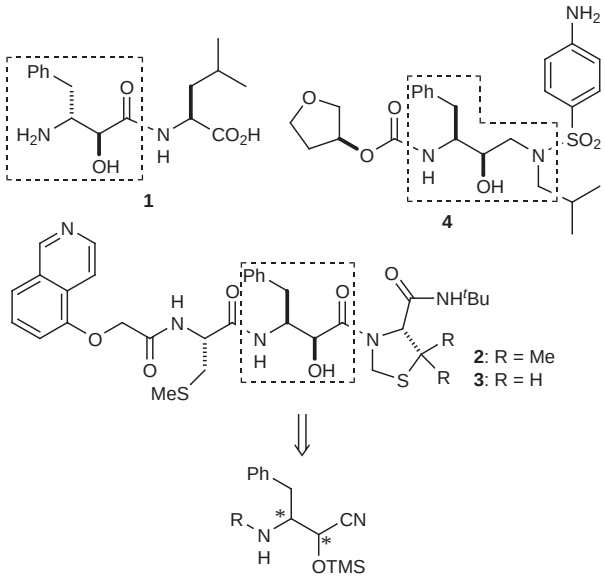
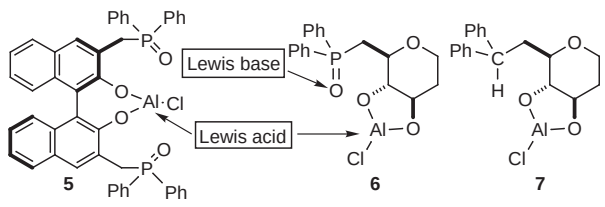
Abstract: Chiral bifunctional catalyst **6** promoted *anti*- and *syn*-selective cyanosilylation reactions from chiral amino aldehydes derived from phenylalanine in excellent yields. Thus, from dibenzyl protected amino aldehyde **9**, *syn* isomer was obtained as the major product (diastereomeric ratio = 93: 7) using 3 mol% of **6**. On the other hand, from Boc protected aldehyde **10**, *anti* isomer was obtained as the major product (diastereomeric ratio = 97: 3) by 1 mol% of **6**. The experimental results can be rationally explained from the dual activation mechanism of **6**. Using *syn*- and *anti*-selective cyanosilylation reactions, efficient syntheses of essential chiral building blocks of HIV protease inhibitors and bestatin were achieved.

Key words: bifunctional catalyst, cyanosilylation, amino aldehyde, HIV protease inhibitors, bestatin

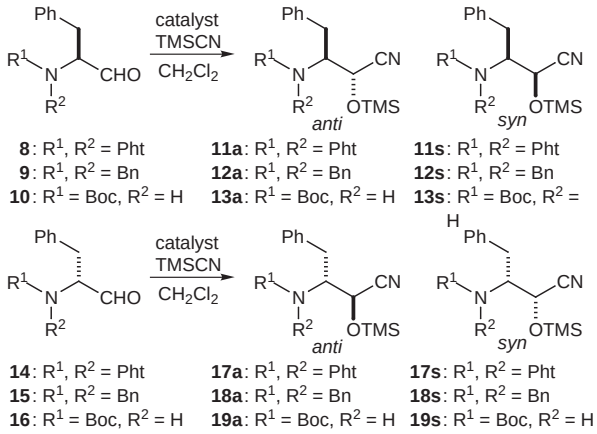


Some of the medicinally important compounds contain optically active 3-amino-2-hydroxycarboxylic acids or 3-amino-2-hydroxyamines as their essential components. For example, bestatin **1** is an aminopeptidase inhibitor that exhibits immunostimulatory, as well as cytotoxic activity.[1] Bestatin is used clinically as an anticancer agent.[2] On the other hand, KNI-227 **2**, KNI-272 **3**,[3] and amprenavir **4**[4] are therapeutically useful HIV protease inhibitors.[5] For the synthesis of essential chiral building blocks of these compounds, the corresponding cyanohydrins can function as versatile precursors. Therefore, considerable research effort has been directed towards the diastereoselective cyanation of chiral amino aldehydes.[6] However, a stoichiometric or excess amount of promoters or reagents is usually required, and the diastereoselectivity is not always very high.[7] In our approach we planned to utilize bifunctional chiral external catalysts instead of achiral promoters. By doing so, a highly selective access to *syn* as well as *anti* diastereomers would be achieved through the proper combination of chiral catalysts and chiral aldehydes. Described herein is a new strategy for stereocontrol in the synthesis of both diastereomers (*syn* and *anti*) of 3-amino-2-hydroxynitrile and its application to practical syntheses of industrially important building blocks of amprenavir and bestatin.

We have recently developed two chiral bifunctional catalysts **5**[8] and **6**[9] that promote efficiently an enantioselective cyanosilylation of aldehydes. From the experimental results, such as the kinetic profiles and the absolute configuration of the products, it is supported that in the transition state, Al-metal and the oxygen atom of the phosphine oxide work cooperatively as a Lewis acid and as a Lewis base to activate an aldehyde and TMSCN, respectively. This dual activation mechanism makes it possible to afford high enantioselectivity from a wide variety of aldehydes. These results suggest that **5** and **6** would be very useful for the present purpose.



At first, we tried cyanosilylation of phthaloyl protected L−aldehyde **8**[10] in the presence of a catalytic amount (9 mol%) of Et_2AlCl at −40 °C. The reaction proceeded very sluggishly, and the product **11** was obtained in only 20%



Scheme 1

yield after 40 h with the diastereomeric ratio of 68:32 (Table, entry 1). After hydrolysis, the major isomer was found to be *syn*-**11s**.[11] On the other hand, when **5** or **6** was used as a catalyst (9 mol%), **11** was obtained in quantitative yields with the diastereomeric ratio of 73:27 (Table, entry 2) and 81:19 (entry 3), respectively. These results clearly show that there is a distinct advantage to utilize the bifunctional catalysts **5** and **6**, instead of achiral catalysts. Since the selectivity of catalyst **6** was better than catalyst **5**, we concentrated our efforts on **6** for further studies.

Table Catalytic Cyanosilylation of Phenylalanine-Derived Aldehydes

entry	cat. (mol %)	aldehyde	°C	h	product	%	*anti* : *syn*	
1	Et_2AlCl (9)	**8**	-40	40	**11**	20	32	68
2	**5** (9)	**8**	-40	40	**11**	100	27	73
3	**6** (9)	**8**	-40	40	**11**	100	19	81
4	**6** (9)	**14**	-60	48	**17**	100	68	32
5	**6** (3)	**9**	-40	48	**12**	93	7	93
6	**6** (3)	**15**	-40	96	**18**	86	25	75
7	**6** (1)	**10**	-60	36	**13**	100	97	3
8	**6** (1)	**16**	-60	36	**19**	100	96	4
9	**7** (9)	**10**	-40	40	**13**	56	93	7
10	**7** (9)	**16**	-40	48	**19**	60	94	6

To investigate the effect of the chirality of the aldehyde, we performed the reaction from D-aldehyde **14** and found that *anti* isomer **17a** to be the major product (68: 32, Table, entry 4).[11] Therefore, in the case of phthaloyl protected aldehyde, chiral catalyst control seemed predominant compared to the intramolecular stereocontrol. Similarly, in the case of dibenzyl protected L−aldehyde **9**[5a], the product was obtained in 93% yield when using 3 mol% of **6** at −40 °C for 48 h, being *syn* isomer **12s** as the major product with higher selectivity (93:7, Table, entry 5).[12] From D−aldehyde **15**, however, the reaction catalyzed by 3 mol% of **6** was slower and the product was obtained in 86% yield after 96 h at −40 °C with the diastereomeric ratio of 75:25, again being *syn* isomer as the major product (Table, entry 6). Therefore, in the case of dibenzyl protected aldehyde **9** and **15**, the intramolecular diastereoface differentiation predominated, although distinct differences in the diastereoselectivity and the reaction rate between matched (**9**) and mismatched (**15**) pair existed.

These results may be explained from the model in Figure 1. In the case of the phthaloyl protected L−aldehyde **8**, the phthaloyl imide group could be considered as the largest substituent on the α-carbon. Therefore, the Felkin-Anh type intramolecular diastereocontrol[13] is matching with the external chiral catalyst control. Via the dual activation transition state **20**, the *syn* isomer **11s** was obtained as the major product. On the other hand, in the case of phthaloyl protected D−aldehyde **14**, if the phthaloyl imide group positions itself perpendicular to the carbonyl plain, TMSCN should attack the aldehyde from the opposite side of the phosphine oxide, thus without any assistance of the Lewis base (**22**). However, if the conformation of the aldehyde is changed to the one in which the phenylmethyl group on the α-carbon is positioned perpendicular to the carbonyl, the activated TMSCN by the phosphine oxide can attack the aldehyde (**21**). Since the bulkiness of the phenylmethyl group is not so different from that of the phthaloyl imide group, the dual activation could compensate the energy loss of the less favorable conformation of the substrate. Consequently, the reaction of **14** should proceed via the dual activation transition state **21**, instead of the mono activation transition state **22**. On the other hand, in the case of dibenzyl protected aldehyde **9** and **15**, since the difference between the size of the phenylmethyl group and the

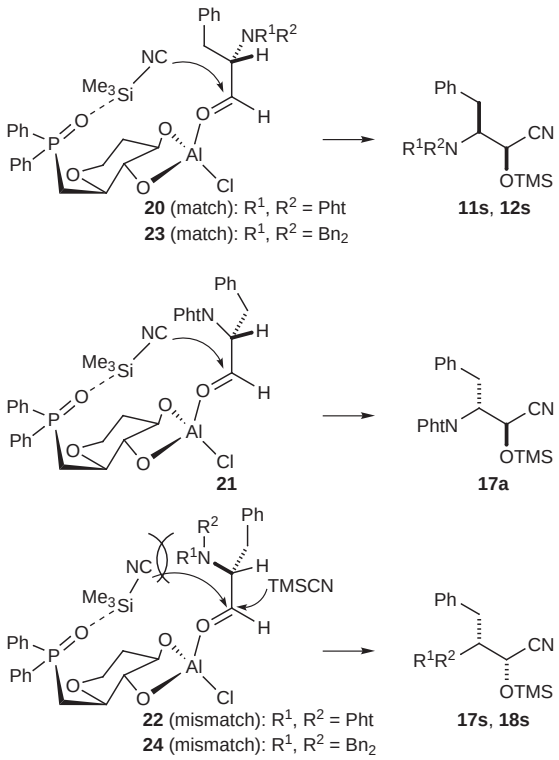
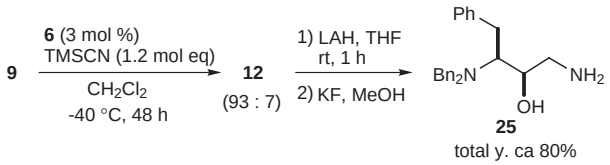


Figure 1

dibenzylamino group should be significantly different, even the dual activation should not be able to compensate the energy difference. Therefore, the reaction should proceed mainly via the 1,2-intramolecular differentiation (**23** and **24**). This model would also explain the qualitative reactivity difference between the enantiomers of the aldehydes. In the case of phthaloyl protected aldehyde, both enantiomers **8** and **14** could react via the dual activation pathway (**20** and **21**), although partial contribution of the reaction pathway via mono activation transition state **22** exists in the case of **14**. As a result, the difference in the reactivity between two enantiomers of the starting aldehyde was not significant. On the other hand, in the case of dibenzyl protected aldehydes **9** and **15**, the matched L−aldehyde **9** should react via the dual activation pathway **23**. However, the mismatched D−aldehyde **15** should react via mono-activation only by the Lewis acid (**24**). Therefore, the reaction rate of D−aldehyde **15** should become significantly slower.

Using the *syn* selective cyanosilylation of **9**, a short-step synthesis of the important chiral building block of a HIV protease inhibitor could be achieved. Reducing cyanohydrin **12** by LAH followed by deprotection of the TMS group by KF in MeOH, Corey's intermediate **25** for the synthesis of amprenavir[5a] was obtained in ca. 80% yield (Scheme 2).



Scheme 2

Interestingly, we discovered that the *anti* isomer **13a** could be obtained as the major diastereomer, using Boc protected aldehyde **10**.[14] Thus, in the presence of 1 mol% of **6**, **13** was obtained in quantitative yield after 36 h, with a very high diastereomeric ratio (**13a** : **13s**) of 97: 3 (Table, entry 7).[11] When D−aminoaldehyde **16** was used with 1 mol% of **6** as catalyst, *anti* isomer **19a** was again obtained as the major isomer with the ratio of 96: 4 (Table, entry 8). Therefore, in the case of the reaction of Boc protected aldehyde, chiral catalyst **6** did not seem to contribute very much to the stereochemical course.[15]

To get further insight into the reaction mechanism in this specific case, we prepared and applied the control catalyst **7**, containing a diphenylmethyl group, instead of diphenylphosphine oxide, and compared the results. Using 9 mol% of **7**, the reaction of L−aminoaldehyde **10** gave the cyanohydrin **13** in only 56% yield with the diastereomeric ratio of 93:7. Again **13a** has been found to be the major isomer (Table, entry 9). When D−aminoaldehyde **16** was used, **19** was obtained in only 60% yield with the ratio (**19a**:**19s**) of 94:6 (Table, entry 10). Consequently, although the diastereoselectivity is always high when Boc protected aldehyde was used, the distinct advantage of the bifunctional catalyst **6** vs **7** is its higher activity.[16] Kinetic studies revealed that the initial reaction rate of **10** by 9 mol% of **6** (matched pair) was 2.3 times faster than that of **16** by 9 mol% of **7** (matched pair). The faster reaction rate by **6** would be derived from the activation of TMSCN by the phosphine oxide, and also from the stability of **6** against ligand silylation under the reaction conditions.[17]

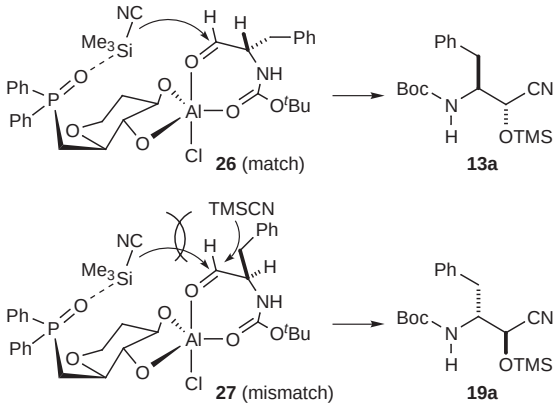
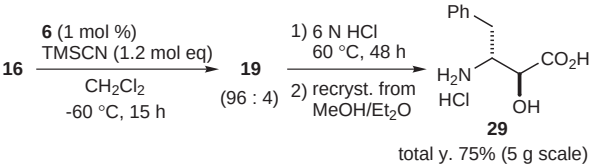


Figure 2

Taking those experimental results into account, the cyclic chelation model shown in Figure 2 seems to be a plausible transition state in the case of Boc protected aldehydes **10** and **16**. These substrates should coordinate to the Lewis acid in a bidentate manner with the oxygens of the aldehyde and the urethane. The cyanide should attack the aldehyde from the side opposite to the larger substituent on the α-carbon (phenylmethyl group), thus giving the *anti* isomer as the major product. The internal phosphine oxide should mainly assist the attack of TMSCN by activating it as the Lewis base, thus being **26** as the matched pair. However, due to the bidentate coordination to the Lewis acid, the conformation of the Boc protected substrate should be restricted. Therefore, the diastereoface of the aldehyde should be better differentiated by the chirality at the α-carbon, instead of by the external chiral catalyst.[18]

Using the *anti*-selective cyanosilylation of Boc protected aldehyde, a practical synthesis of the important building block of bestatin was achieved in 5 g scale (Scheme 3). After acid hydrolysis of **19** and recrystallization from MeOH−Et_2O, enantiomerically and diastereomerically pure **29** was obtained in 75% yield from **16**.[19]



Scheme 3

In summary, this work has demonstrated that the bifunctional catalyst **6** promotes cyanosilylation of chiral α-amino aldehydes in excellent yields and with high diastereoselectivities. Both *anti* and *syn* isomers for the synthesis of HIV protease inhibitor and bestatin are obtained selectively, dependent on the type of protecting group at the nitrogen. The high yields, high selectivity and the easy operation[20] are the main advantages of this new methodology. Furthermore, tendencies of the reactivity and diastereoselectivity of the three protected amino aldehydes are well explained from the dual activation mechanism of the bifunctional catalyst.

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(7) For example, in ref 6a, a stoichiometric amount of BF_3•OEt_2 or $ZnBr_2$ was used as a promotor and only *anti* isomer was obtained with high selectivity (95:5). In ref 6c, 5 mol% of $Eu(fod)_3$ was used, however, the diastereomeric ratio was not high (82:18).

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(11) Relative configurations of **11**, **17**, **13** and **19** were determined, comparing the spectroscopic data with the reported ones after hydrolysis: Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853-1868.

(12) Relative configurations of **12** and **18** were determined, comparing the spectroscopic data with the reported ones. See ref 6d.

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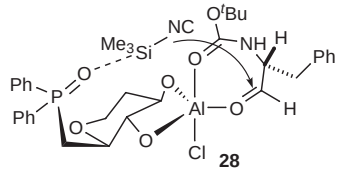
(15) The initial reaction rate of **10** was 1.2 times faster than **16**, when 9 mol% of **6** was used. Considering that **10** gave a slightly higher diastereoselectivity than **16**, the combination of **6** and **10** appeared to be the matched pair.

(16) Using 9 mol% of Et_2AlCl, only 35% yield of **13** was obtained after 48 h with lower diastereomeric ratio (**13a**:**13s**) of 78:22.

(17) The silylated ligand of catalyst **7** gradually appeared on TLC, indicating partial decomposition of the catalyst under the reaction conditions. However, even a trace amount of the silylated ligand of **6** was not observed. The reason why catalyst **6** is more stable than **7** is currently under investigation.

(18) The matched transition state as **28** in the combination of **6** and **16** might have some contribution, although the relative position of the aldehyde and the activated TMSCN seems not optimum.



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(19) Representative procedures: To a solution of the ligand (66 mg, 0.2 mmol) in CH_2Cl_2 (3.5 mL), Et_2AlCl in hexane solution (0.93 M, 0.2 mmol) was added at ambient temperature. After 30 min, a solution of aldehyde **14** (5 g, 20 mmol) in CH_2Cl_2 (50 mL) and TMSCN (3.2 mL, 24 mmol in 3.2 mL of CH_2Cl_2) were added dropwise at −78 °C. The reaction was completed in 15 h in this scale. Adding H_2O and usual workup gave a crude mixture of **17** and the ligand. The mixture was treated with 6 N HCl at 60 °C for 48 h, and then the solution was washed by in CH_2Cl_2. The aqueous layer was evaporated, and recrystallization of the residue from MeOH/Et_2O gave 3.2 g of pure **29** (75% yield).

(20) The chiral ligand of **6** could be obtained in 5 steps from the commercially available D-glucal: 1) hydrogenation (Pd/C, H_2, MeOH), 2) methanolysis (NaOMe, MeOH, then amberlyst−H^+), 3) selective tosylation (TsCl, py), 4) introduction of diphenylphosphino group (Ph_2PK, THF), 5) oxidation (H_2O_2, MeOH.

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