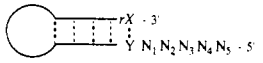
Table I. Approximate Half-Times for Various Template Reactions Studied in This and Previous Papers[1,2]



rX	N_1'	$N_1N_2N_3N_4N_5$	$t_{1/2}$ (h)
G	G	C C C C C	3
A	G	C C C C C	5
C	G	C C C C C	6
U	G	C C C C C	8
G	C	G C C C C	18
G	A	T C C C C	24
G	U	A C C C C	96
G	C	G G C C C	24[a]
			48[b]
C	C	G G C C C	24

[a] In the presence of 2-MeImpC only. [b] In the presence of 2-MeImpC and 2-MeImpG.

the family of C-rich oligonucleotides that can be copied efficiently. We have now shown that runs of G residues may be present, but that A and T residues must be isolated from each other and from G residues. The sequences TT, GT, and TG are partial barriers to copying, and the sequences AT, TA, AA, GA, and AG are almost total barriers.

The half-times of some of the reactions that we have studied are collected in Table I. They illustrate the relative rates of the most successful copying reactions. The incorporation of G after any of the four (isolated) bases is rapid. The incorporation of the three other bases after G is substantially slower. The slow rate of incorporation of U after G is already a substantial obstacle to observing efficient template reactions involving incorporation of U in our system. After 4 days the hydrolysis of the activated nucleotides is significant, so the incorporation of several isolated U residues in a product could only be accomplished by replenishing the supply of 2-MeImpU from time to time.

There are other obstacles to copying, in addition to those revealed by the present studies. Intramolecular self-structure is one such obstacle. It is likely to be particularly important for copolymers that include large proportions of both C and G. Another obstacle is the aggregation of G-rich copolymers via the formation of tetrahelical segments.

A minimal self-replicating system consists of two complementary sequences each of which is capable of facilitating the synthesis of the other. Is such a system possible within the framework of our model system? Clearly a copolymer of C and G cannot qualify. If the two complements contain roughly equal amounts of C and G they are disqualified because they give rise to extensive intramolecular self-structure. If one polymer is rich in C, the other must be rich in G and so is disqualified because it forms a stable intermolecular tetrahelical self-structure.

Can the introduction of isolated A and T residues save the situation? This seems unlikely, but one cannot be sure without more experimental information on the efficiency of template-directed synthesis on oligoG sequences that contain an isolated A or T residue, for example, –GGAGG– and related sequences. We are accumulating the information needed to answer this question.

Experimental Section

Materials. The sources of all reagents, and all experimental procedures, were the same as those reported in earlier papers of the series.[1,2]

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Registry No. S_1, 143214-82-8; S_2, 143214-80-6; S_3, 143214-86-2; S_4, 143214-87-3; S_5, 143214-83-9; S_6, 143214-84-0; S_7, 143214-85-1; S_8, 143214-90-8; S_9, 143214-91-9; S_{10}, 143214-88-4; S_{11}, 143214-89-5; S_{12}, 143214-76-0; S_{13}, 143214-77-1; S_{14}, 143214-78-2; S_{15}, 143214-75-9; S_{16}, 143214-81-7; 2-MeImpC, 85179-51-7; 2-MeImpG, 80242-42-8; 2-MeImpA, 31008-65-8; 2-MeImpU, 85179-50-6.

Peptide–Titanium Complex as Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehyde

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Abstract: The complex of titanium ethoxide and an acyclic dipeptide ester whose terminal amino group is modified to a salicylal-type Schiff base catalyzes the asymmetric addition of hydrogen cyanide to aldehydes with high enantioselectivity. In the reaction of benzaldehyde and hydrogen cyanide, (*R*)-mandelonitrile is obtained with an enantiomeric excess of 90% when *N*-((2-hydroxy-1-naphthyl)methylene)-(*S*)-valyl-(*S*)-tryptophan methyl ester is employed. In place of the dipeptide, the amide derivatives of an amino acid modified by substituted salicylaldehyde, such as *N*-(3,5-dibromosalicylidene)-(*S*)-valine piperidide, exhibit an entirely opposite stereoselectivity to yield *S*-cyanohydrins with optical purities up to 97% ee. This novel peptide–titanium complex, therefore, enables us to afford optically active cyanohydrins of both absolute configurations by using natural *S*-amino acids as chiral auxiliaries.

Introduction

The development of a method to synthesize optically active compounds has always received much attention in various areas of organic and biological chemistry.[1] In recent years the design of chiral metal complexes as catalysts for asymmetric organic reactions has been widely studied.[2] In particular, highly stereoselective procedures have been explored in various organic reactions using the ligands of C_2-symmetry, as represented by the

(1) For a review, see: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5.

(2) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1989; Vol. 5, pp 115–198.

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Table I. Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde, Catalyzed by the Mixture of Metal Alkoxide and Dipeptide Nap-X-Y-OMe[a]

	dipeptide						
	X[b]	Y[b]					
compd	(N-terminal amino acid)	(C-terminal amino acid)	$M(OR)_4$	temp, °C	time, h	convn,[c] %	% ee[d]
1a	Val	Phe	$Ti(O^iPr)_4$	−20	4	94	78(*R*)
			$Ti(O^nBu)_4$	−20	4	84	78
			$Ti(OEt)_4$	−20	4	91	82
			$Ti(OEt)_4$	−40	4	85	86
			$Ti(OEt)_4$	−40	0.1	38	68
			$Ti(OEt)_4$	−40	4	93	66[e]
			$Zr(O^nPr)_4$	−20	44	60	17
1b	Ile	Phe	$Ti(OEt)_4$	−40	4	85	85
1c	Leu	Phe	$Ti(O^iPr)_4$	−20	4	93	75
1d	Phe	Phe	$Ti(O^iPr)_4$	−20	7.5	94	67
1e	Ala	Phe	$Ti(O^iPr)_4$	−20	4	80	59
1f	Phgly[f]	Phe	$Ti(O^iPr)_4$	−20	20	62	25
1g	Val	Trp	$Ti(O^iPr)_4$	−20	2.5	99	79
			$Ti(OEt)_4$	−20	2.5	99	82
			$Ti(OEt)_4$	−40	3	88	89
			$Ti(OEt)_4$	−60	16	83	90
1h	Val	Val	$Ti(OEt)_4$	−40	4	64	87
1i	Val	Leu	$Ti(OEt)_4$	−40	4	72	59
1j	Val	Phgly[f]	$Ti(O^iPr)_4$	−20	4	86	24
1k	(*R*)-Val	Phe	$Ti(O^iPr)_4$	−20	4	84	38(*S*)

[a] Unless specified, all reactions were carried out using 10 mol % of metal alkoxide, 10 mol % of dipeptide, and 1.5 equiv of hydrogen cyanide based on benzaldehyde in toluene. [b] Natural *S*-amino acids were employed except for the N-terminal amino acid of **1k**. [c] Based on the ^1H NMR analyses of the mixture of cyanohydrin and unreacted aldehyde. [d] The enantiomeric excess was determined by ^1H NMR measurement after the transformation of cyanohydrin to the corresponding menthyl carbonic ester. [e] 100 mol % of catalyst was used. [f] 2-Phenylglycine.

derivatives of binaphthol, tartaric acid, and semicorrin.[3] Amino acids and their derivatives, such as amino alcohols, have also been applied to successful ligands as readily available chiral auxiliaries.[4] In contrast, peptides have rarely been reported as effective ligands of metallic species in asymmetric reactions. It should be a challenging subject, we considered, to reveal that peptides, if effectively designed, can be potentially useful chiral auxiliaries because enzymes, natural polypeptides, exhibit remarkably high stereospecificities and stereoselectivities in biochemical reactions.

We report the design of the peptide–titanium complex as an asymmetric catalyst for enantioselective cyanohydrin synthesis by the addition of hydrogen cyanide to aldehydes.[5] Optically active cyanohydrins have been recognized to be versatile compounds since they can be easily converted to a variety of chiral molecules, such as α-hydroxy carboxylic acids, α-hydroxy esters, and β-amino alcohols. Therefore, much effort has been focused on an asymmetric cyanohydrin synthesis using enzymes,[6] synthetically designed organic bases,[7] and metallic compounds as chiral Lewis acids.[8]

The peptides we used were acyclic dipeptide esters whose amino terminals were modified to Schiff bases of salicyaldehyde derivatives to facilitate complexation with metallic compounds,[9] and titanium(IV) alkoxides were used as metallic species. The phenolic Schiff base was reported to be utilized as a protective group of α-amino acid in peptide synthesis.[10] However, peptides or amino acids bearing the Schiff bases have not been used as chiral auxiliaries for asymmetric synthetic reactions. When titanium(IV) ethoxide and a dipeptide, *N*-((2-hydroxy-1-naphthyl)-methylene)-(*S*)-valyl-(*S*)-tryptophan methyl ester (**1g**), for example, were used as catalysts, excellent enantioselectivity of up to 90% was realized in the reaction of benzaldehyde as substrate

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(4) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Costruction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (d) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (e) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (f) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, *197*. (g) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (h) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (i) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (j) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (k) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

(5) Mori, A.; Nitta, H.; Kudo, M.; Inoue, S. *Tetrahedron Lett.* **1991**, *32*, 4333. Preliminary communication.

(6) Oxinitrilase, an enzyme, is known to catalyze the asymmetric addition of hydrogen cyanide to benzaldehyde to afford optically pure (*R*)-mandelonitrile. For asymmetric hydrocyanation of aldehydes catalyzed by oxinitrilase: (a) Becker, W.; Freund, H.; Pfeil, E. *Angew. Chem.* **1965**, *77*, 1139; *Angew. Chem., Int. Ed. Engl.* **1966**, *4*, 1079. (b) Ziegler, T.; Hörsch, B.; Effenberger, F. *Synthesis* **1990**, 575. (c) Ognyanov, V. I.; Datcheva, V. K.; Kyler, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 6992.

(7) We previously reported the asymmetric addition of hydrogen cyanide to aldehydes catalyzed by synthetic cyclic dipeptide: (a) Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229. (b) Kobayashi, Y.; Asada, S.; Watanabe, I.; Hayashi, H.; Motoo, Y.; Inoue, S. *Bull Chem. Soc. Jpn.* **1986**, *59*, 893. (c) Hayashi, H.; Kobayashi, Y.; Miyaji, K.; Inoue, S. *J. Chem. Soc. Jpn.* **1987**, 345. (d) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (e) Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.* **1989**, 2119. See also: Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740. Danda, H. *Synlett* **1991**, 263 and references cited therein.

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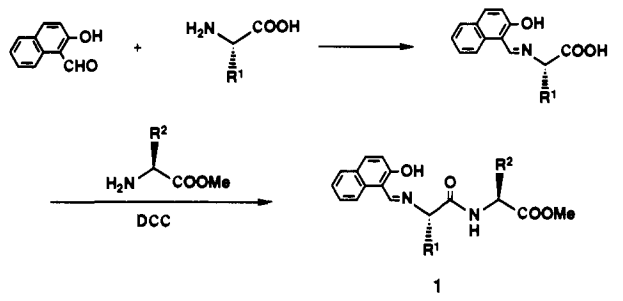
(9) Asymmetric syntheses using salicylal-type Schiff base compounds: (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1968**, *24*, 3655. (b) Takeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391. (c) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839. (d) Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483. Nakajima, K.; Sasaki, C.; Kojima, M.; Aoyama, T.; Ohba, S.; Satio, Y.; Fujita, J. *Ibid.* **1987**, 2189. (e) Colonna, S.; Manfredi, A.; Spadoni, M.; Casella, L.; Gullotti, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 71. (f) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *Ibid.* **1991**, *113*, 7063. (g) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Ibid.* **1991**, *32*, 1055.

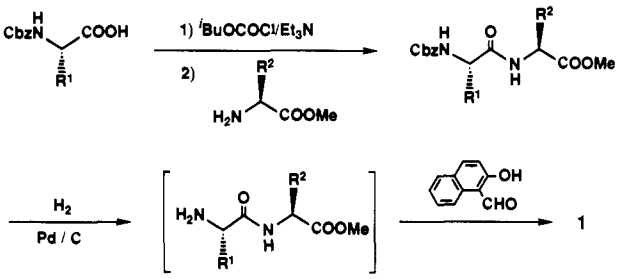
(10) (a) McIntrie, F. C. *J. Am. Chem. Soc.* **1947**, *69*, 1377. (b) Sheehan, J. C.; Grenda, V. J. *J. Am. Chem. Soc.* **1962**, *84*, 2417.

Scheme I

Method A



Method B

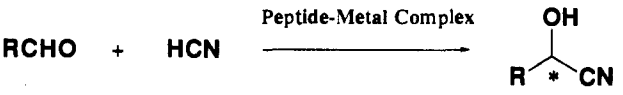


to give (*R*)-mandelonitrile. On the other hand, when the titanium complex of *N*-(3,5-dibromosalicylidene)-(*S*)-valine piperidide (**3c**) was used, (*S*)-cyanohydrin was obtained in an enantiomeric excess of up to 97%. Therefore, the catalyst systems enabled us to deliver both enantiomers of cyanohydrins with high optical purities from natural (*S*)-amino acids as chiral auxiliaries. The above characteristics have not been observed in previous methods in asymmetric cyanohydrin syntheses.[6-8]

Results and Discussion

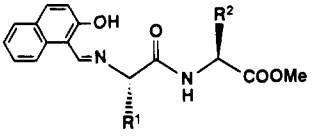
Syntheses of the dipeptides bearing salicylal-type Schiff base **1** were carried out by following two methods as illustrated in Scheme I. Method A is a procedure described in the literature[10b] which involves coupling of an amino acid, whose amino group is modified in advance to a Schiff base by condensation with 2-hydroxy-1-naphthaldehyde, with another amino acid methyl ester by using dicyclohexylcarbodiimide (DCC). Another route to **1** is shown in method B. Coupling of a carbobenzoxy amino acid with another amino acid methyl ester afforded the corresponding carbobenzoxy dipeptide methyl ester, which was hydrogenolyzed by palladium–carbon for deprotection of an amino group followed by condensation with 2-hydroxy-1-naphthaldehyde to yield the desired compound **1**. Both methods gave the product in good yield, and method B was quite useful when an amino acid containing Schiff base was too unstable to isolate[10a] in method A.

The asymmetric addition of hydrogen cyanide to aldehyde was carried out by using 10 mol % (based on aldehyde) of dipeptide and titanium alkoxide. The dipeptide was suspended in toluene,



and an equimolar amount of titanium alkoxide was added under nitrogen atmosphere. In most cases the mixture immediately turned to a yellow homogeneous solution.[11] After being stirred for 30 min at room temperature, the resulting solution was cooled to −78 °C. Aldehyde and hydrogen cyanide were added successively, and stirring was continued at −60 to −20 °C. The product was isolated by chromatography on silica gel after usual acidic workup. The optical purity of the resulting cyanohydrin was determined by ^{1}H NMR measurement or GC analysis after the transformation of the cyanohydrin to the corresponding menthyl carbonate[7c] or the ester of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA).[7c,12]

Table I summarizes the results of the reaction of benzaldehyde with various combinations of two amino acid residues in the dipeptide **1**. Titanium alkoxides, $Ti(OR)_4$, were used as successful metallic species, while the use of other metallic alkoxides was disappointing. For example, $Zr(O\text{-}^nPr)_4$ showed a very low selectivity and catalytic reactivity, and the reaction did not proceed in cases of other metallic alkoxides, such as $Al(O\text{-}^iPr)_3$, $VO(OEt)_3$, $Nb(OEt)_5$, and $TiCl_2(O\text{-}^iPr)_2$. The influence of the structure of *N*-terminal amino acid residue of the dipeptide on asymmetric induction was investigated by employing *S*-phenylalanine as a C-terminal amino acid (**1a–f**). High selectivities to afford (*R*)-mandelonitrile were observed when (*S*)-valine or (*S*)-isoleucine was used, which shows that alkyl chain branching at the β-position leads to high selectivity. Next we examined the influence of a C-terminal amino acid residue employing (*S*)-valine as an N-terminal amino acid (**1a,g-j**). (*S*)-Tryptophan, (*S*)-valine, and



1a: $R^1 = CH(CH_3)_2$, $R^2 = CH_2Ph$ (Nap-*S*-Val-*S*-Phe-OMe)

1g: $R^1 = CH(CH_3)_2$, R^2 =  (Nap-*S*-Val-*S*-Trp-OMe)

(*S*)-phenylalanine exhibited high selectivities as C-terminal amino acid residues, while (*S*)-leucine and (*S*)-2-phenylglycine considerably decreased the selectivity. In addition, **1k** (Nap–*R*-Val-*S*-Phe-OMe), with the opposite absolute configurations of the two amino acids to each other, resulted in rather low selectivity to afford (*S*)-mandelonitrile. It was thus revealed that the stereochemical preference of the resulting cyanohydrin is mainly controlled by the absolute configuration of the N-terminal amino acid, but the enantioselectivity is also affected to some extent by the chirality of C-terminal amino acid residue.

The optical yields were lower in the stoichiometric reaction as well as the catalytic reaction at low conversion. Among these results, as shown in Table I, the highest selectivity was realized by the use of 10 mol % (based upon aldehyde) of the mixture of titanium ethoxide and the dipeptide **1g** (Nap-*S*-Val-*S*-Trp-OMe) at −60 °C, affording (*R*)-mandelonitrile with an enantiomeric excess of 90%.

The acyclic dipeptide ester plays a significant role in the catalytic reactivity as well as in the selectivity. As shown in Table II, the hydrocyanation catalyzed by $Ti(O\text{-}^iPr)_4$ in the absence of the peptide resulted in a rather low yield. Moreover, when a derivative of valine methyl ester, *N*-((2-hydroxy-1-naphthyl)-methylene)-(*S*)-valine methyl ester (**2a**; Nap-*S*-Val-OMe) was used in place of the dipeptide **1**, the reactivity also decreased with no asymmetric induction. Amide derivatives of valine, *N*-((2-hydroxy-1-naphthyl)methylene)-(*S*)-valine benzylamide (**2b**,

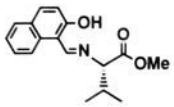
Table II. Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde, Catalyzed by the Mixture of $Ti(O^iPr)_4$ and Valine Derivatives[a]

compd	valine derivative	time, h	convn, %	ee, %
	none	4	43	
2a	Nap-*S*-Val-OMe	4	17	0
2b	Nap-*S*-Val-NHBzl	2	99	30(*R*)
2c	Nap-*S*-Val-NHCy	4	97	40(*R*)
1g	Nap-*S*-Val-(*S*)-Trp-OMe	2.5	99	79(*R*)

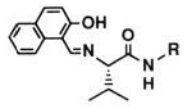
[a] The reaction was carried out at −20 °C. See also footnote *a* of Table I.

(11) The mixture of $Ti(OR)_4$ and **1g** did not completely turn to be homogeneous after stirring for 30 min. In the cases of **1c**, **d**, **e**, and **f**, the mixture immediately turned to dark brown solutions.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.



2a: Nap- *S*-Val-OMe



2b: R = CH_2Ph (Nap- *S*-Val-NHBzl)
2c: R = *c*-C_6H_{11} (Nap- *S*-Val-NHCy)
2d: R = $C(CH_3)_3$ (Nap- *S*-Val-NH ^{t}Bu)

Nap-*S*-Val-NHBzl) and *N*-((2-hydroxy-1-naphthyl)-methylene)-(*S*)-valine cyclohexylamide (**2c**, Nap-*S*-Val-NHCy), in contrast, exhibited similar reactivities compared with dipeptide **1** although the selectivity was considerably low (30–40% ee). These results indicate that the presence of amide group is essential to realize the high catalytic reactivity of this peptide–$Ti(OR)_4$ system.[13] Consequently, the structure of the acyclic dipeptide has proved to be necessary both to the stereoselectivity and to the catalytic reactivity.

The reactions of several aldehydes were also examined using $Ti(OEt)_4$ and **1a** or **1g** (Table III). Most of aromatic aldehydes afforded the corresponding *R*-cyanohydrins with high degrees of enantioselectivities. Aliphatic aldehydes, which reacted more rapidly compared with aromatic aldehydes even with a smaller amount of the catalyst (5 mol % based on aldehyde), also resulted in moderate to high enantioselectivities.

Since the hydrocyanation catalyzed by $Ti(OR)_4$ was much slower than that catalyzed by the peptide-$Ti(OR)_4$ system and **1a** (Nap-*S*-Val-*S*-Phe-OMe) itself did not promote the reaction, a catalytically active species is considered to be generated in the mixture of $Ti(OR)_4$ and **1a**. ^1H NMR measurement of the mixture of an equimolar amount of $Ti(OEt)_4$ and **1a** in C_6D_6 was carried out in order to investigate the structure of the peptide–titanium complex. The ^1H NMR spectrum showed complicated broad signals, but an imino proton (—CH=N—), a phenolic proton, and an amide proton of **1a** were observed as sharp signals, which revealed that one of the ethoxy groups of $Ti(OEt)_4$ did not completely exchange with the phenolic hydroxy group of **1a**. Further assignment of these complicated broad signals was not easy from ^1H NMR analysis of this mixture. The mixture of $Ti(OEt)_4$ and an amide derivative, *N*-((2-hydroxy-1-naphthyl)-methylene-(*S*)-valine *tert*-butylamide (**2d**, Nap-*S*-Val-NH-^{t}Bu), however, gave clear signals corresponding to the complex. Among the signals observed in the mixture of an equimolar amount of $Ti(OEt)_4$ and **2d** in C_6D_6, the most remarkable were broad singlet signals at 10.02 and 8.39 ppm, which could be assigned to the protons of imino and amide groups of the complex, respectively, coordinating to the titanium atom, and shifted from those of **2d** (8.71 and 5.81 ppm, respectively). The spectrum also indicated the presence of unreacted **2d** in the mixture by the signals at 14.96 (phenolic hydrogen), 8.71 and 5.81 ppm, with the intensity ratio of the signals of the complex to those of **2d** being about 4:1 under these conditions. When 1.5 equiv of $Ti(OEt)_4$ was mixed with **2d**, the ^1H NMR spectrum showed the increase of the intensity ratio of the signals of the complex to those of **2d** to be about 8.6:1. On the other hand, when 2 equiv (based on **2d**) of ethanol was added to the mixture of an equimolar amount of $Ti(OEt)_4$ and **2d**, the ratio decreased to about 2.0:1. These results indicate that a 1:1 titanium–**2d** complex was generated from a mixture of $Ti(OEt)_4$ and **2d** and was in equilibrium with $Ti(OEt)_4$, **2d**, and ethanol. Therefore, in the mixture of dipeptide **1** and $Ti(OEt)_4$ as well, a 1:1 titanium complex, which would be the active species of the reaction, is considered to be formed.

The catalytic hydrocyanation presumably proceeds as illustrated in Scheme II, where hydrogen cyanide reacts with the aldehyde activated by the peptide–titanium complex to form the titanium alkoxide cyanohydrin followed by exchange of the alkoxide with EtOH leading to the cyanohydrin product and regeneration of the catalyst.[14]

(13) A related rate acceleration by amide group in a similar amide–Ti-$(OR)_4$ system was also observed in transhydrocyanation by acetone cyanohydrin: Mori, A.; Inoue, S. *Chem. Lett.* **1991**, 145.

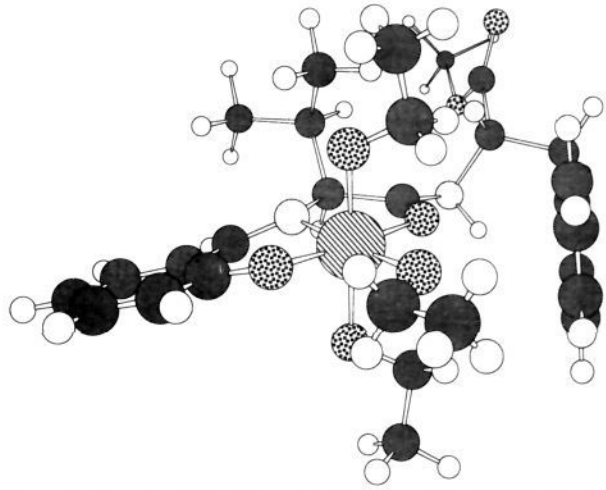
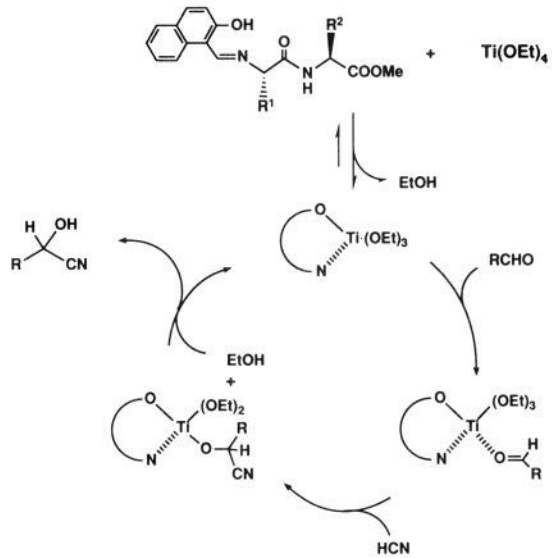


Figure 1. Complex derived from *N*-salicylidene-(*S*)-valyl-(*S*)-phenylalanine methyl ester and $Ti(OEt)_4$ calculated by MM2 using the CAChe system.

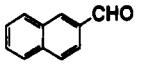
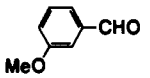
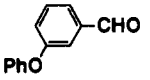
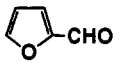
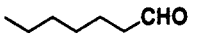
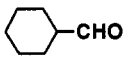
Scheme II



Since the chirality of C-terminal amino acid residue is important in realizing high asymmetric induction in hydrocyanation, an interaction of the amide group with a titanium atom in the complex needs to be considered. Molecular mechanics (MM2) calculation of the titanium complex of *N*-salicylidene-(*S*)-valyl-(*S*)-phenylalanine methyl ester by the CAChe system revealed that the chelate structure formed by the coordination of amide oxygen to titanium atom (Figure 1) is approximately 7.6 kcal more stable than the chelate structure coordinated by amide nitrogen. The addition of aldehyde and hydrogen cyanide to the complex is considered to cause the coordination of the aldehyde to one of the apical positions of the octahedral titanium along with the formation of cyanide ion by reaction of alkoxide with HCN as illustrated in Figure 2. On the other hand, the coordination of aldehyde to the other apical position is not considered favorable because of the steric requirement of the isopropyl group of the valine residue. In addition, the coordination to equatorial position also seems difficult since the presence of C-terminal phenylalanine residue makes anti complexation of titanium with respect to the R group of the aldehyde unfavorable.[15] Thus, attack of cyanide

(14) It was confirmed by ^1H NMR experiment that the mixture of HCN and $Ti(OEt)_4$ in C_6H_6 did not form the corresponding titanium cyanide. Therefore, the first stage of the proposed catalytic cycle could be the coordination of aldehyde to the titanium complex.

Table III. Asymmetric Addition of Hydrogen Cyanide to Aldehydes, Catalyzed by the Mixture of $Ti(OEt)_4$ and **1a** (Nap-*S*-Val-*S*-Phe-OMe) or **1g** (Nap-*S*-Val-*S*-Trp-OMe)[a]

aldehyde	dipeptide	temp, °C	time, h	yield,[b] %	% ee[c]	$[\alpha]^{26}_D$ (*c*, solv), deg
	**1g**	−40	7.5	55 (88)	90(*R*)	29.4 (0.98, $CHCl_3$)[d]
	**1g**	−40	4	71 (80)	85(*R*)	27.5 (1.12, $CHCl_3$)[e]
	*ent*-**1a**[f]	−40	48	56	91(*S*)	−24.4 (2.00, $CHCl_3$)[g]
	**1g**	−40	7.5	20[h] (74)	87(*S*)	14.8 (0.65, $CHCl_3$)[i]
	**1a**	−60	8.5	71	66(*R*)[j]	9.1 (2.82, $CHCl_3$)[k]
	1a[l]	−60	13	(96)	76(*R*)[j]	
	**1a**[l]	−40	1.5	85 (99)	54(*R*)[j]	4.7 (3.82, $CHCl_3$)[m]

[a] Unless otherwise specified, the reaction was carried out by using 10 mol % of titanium ethoxide, 10 mol % of dipeptide, and 1.5 equiv of HCN based on aldehyde in toluene. [b] Isolated yield. In parentheses, yields were based on ^1H NMR analyses of the mixture of cyanohydrin and unreacted aldehyde. [c] Unless otherwise specified, the enantiomeric excess was determined by ^1H NMR measurement after the transformation of cyanohydrin to the corresponding menthyl carbonic ester. [d] Lit.[8e] $[\alpha]^{24}_D$ 10.9° (*c* 1.1, EtOH) for 73% ee of *R*-isomer. [e] Lit.[7c] $[\alpha]^{rt}_D$ −2.95° (*c* 5, $CHCl_3$) for 5% ee of *S*-isomer. [f] Nap-*R*-Val-*R*-Phe-OMe. [g] Lit.[7c] $[\alpha]^{25}_D$ −24.8° (*c* 1.2, $CHCl_3$). [h] The product was not stable for chromatographic isolation. [i] Datum for 70% ee of *S*-isomer. [j] Determined by GC analysis after conversion of the cyanohydrin to the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester. [k] Lit.[6c] $[\alpha]^{23}_D$ 16.1° (*c* 1, $CHCl_3$) for 92% ee of *R*-isomer. [l] Using 5 mol % of $Ti(OEt)_4$ and 5 mol % of the dipeptide based on aldehyde. [m] Lit.[6c] $[\alpha]^{23}_D$ 4.8° (*c* 1, $CHCl_3$) for 96% ee of *R*-isomer.

Table IV. Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde, Catalyzed by the Mixture of $Ti(OEt)_4$ and the Amide or Dipeptide Bearing 3-Substituted Salicylaldimine[a]

	amide or dipeptide	temp, °C	time, h	convn, %	% ee
3a	Ps-*S*-Val-NHCy	−40	5	81	60(*S*)
		−60	19	81	70(*S*)
3b	Ps-*S*-Val-Pip	−60	37	73	83(*S*)
3c	Dbs-*S*-Val-Pip	−60	34	93	87(*S*)
3d	Dbs-*S*-Val-*S*-Phe-OMe	−60	34	56	34(*R*)

[a] For the reaction conditions, see footnote *a* of Table III.

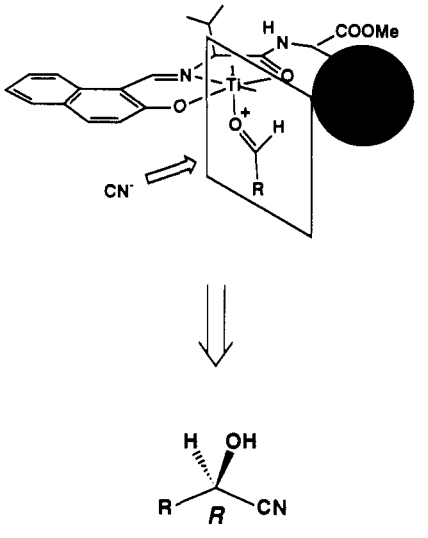


Figure 2.

would prefer the *si* face of the aldehyde carbonyl to afford an *R*-cyanohydrin, where the *re* face is effectively covered with the aromatic ring of the phenylalanine residue.

If the enantioface selection takes place as proposed in Figure 2, it would be possible to invert the course of stereochemistry in the asymmetric hydrocyanation by eliminating the sterically congested N-terminal amino acid residue and by introducing a bulky substituent at the 3-position of the salicylidene moiety as illustrated in Figure 3. On the basis of the above working hypothesis, *N*-(3-substituted-salicylidene)-(*S*)-valine amides such as **3a–c** were designed and used for the catalyst as the titanium complex. Table IV summarizes the results of asymmetric hydrocyanation of benzaldehyde. A moderate asymmetric induction to give (*S*)-mandelonitrile was observed in the use of **3a** (Ps-*S*-Val-NHCy), and the optical yield was increased up to 70% ee by lowering the reaction temperature to −60 °C. A higher optical

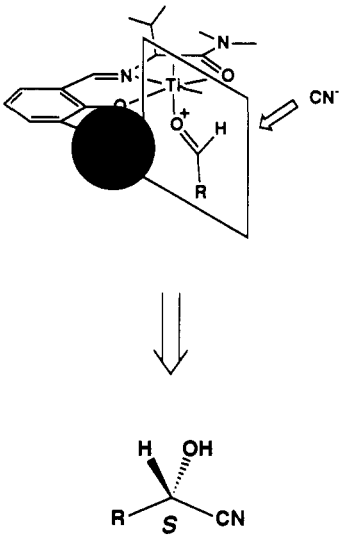
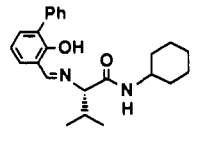
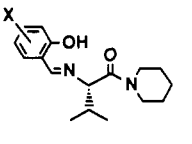


Figure 3.



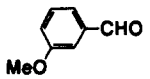
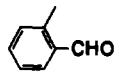
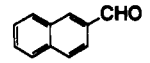
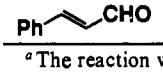
3a: Ps- *S*-Val-NHCy



3b: X = 3-Ph (Ps-*S*-Val-Pip)
3c: X = 3,5-diBr (Dbs- *S*-Val-Pip)

(15) Gung, B. W. *Tetrahedron Lett.* **1991**, *32*, 2867. Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

Table V. Asymmetric Addition of Hydrogen Cyanide to Aldehydes, Catalyzed by the Mixture of $Ti(OEt)_4$ and **3c** (Dbs-(*S*)-Val-Pip)[a]

aldehyde	time, h	yield, %	% ee	$[\alpha]^{26}_D$ (*c*, solv), deg
	41	79	97(*S*)	−37.5 (2.08, $CHCl_3$)[b]
	38	96	92(*S*)	−26.4 (2.04, C_6H_6)[c]
	84	63	72(*S*)	−12.2 (1.14, EtOH)[d]
	84	40	62(*S*)[e]	−19.0 (1.00, $CHCl_3$)

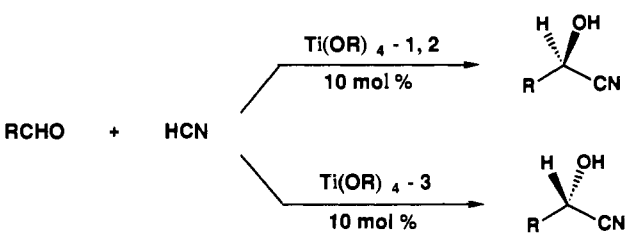
[a] The reaction was carried out at −60 °C. For other reaction conditions, see footnote *a* of Table III. [b] See footnote *e* of Table III. [c] Lit.[7c] $[\alpha]^{rt}_D$ −2.88° (*c* 5, C_6H_6) for 7% ee of *S*-isomer. [d] See footnote *d* of Table III. [e] Determined by chiral HPLC (SUMICHIRAL OA-4100) analysis.

yield was realized when **3b** (Ps-*S*-Val-Pip), was employed at −60 °C (73% convn, 83% ee). Excellent enantioselectivity was observed when **3c** (*N*-3,5-dibromosalicylidene-(*S*)-valine piperidide, Dbs-*S*-Val-Pip) was employed (87% ee). On the other hand, it is quite reasonable to obtain a considerably low optical yield of (*R*)-mandelonitrile when the dipeptide ester of the 3,5-dibromosalicylidene derivative (**3d**, Dbs-*S*-Val-*S*-Phe-OMe) was employed (56% convn, 34% ee).

The reactions of a variety of aldehydes were carried out employing the titanium complex of **3c** as a catalyst, as shown in Table V. In every case, the *S*-cyanohydrin was preferentially formed in good optical yield, especially in the case of *m*-anisaldehyde and *o*-tolualdehyde. Thus, the piperidide derivatives of valine (**3b,c**) have turned out to exhibit high stereoselectivities to afford *S*-cyanohydrins.

Conclusions

The mixture of $Ti(OR)_4$ and a dipeptide ester bearing a salicylal-type Schiff base catalyzes the asymmetric addition of hydrogen cyanide to aldehydes with high enantioselectivities. It



should be pointed out that modification of the salicylal moiety and C-terminal amino acid leads to completely opposite stereochemistries of the resulting cyanohydrins. The catalyst systems enable the production of optically active cyanohydrins of both absolute configurations with high enantiopurities by employing easily available natural (*S*)-amino acids as chiral auxiliaries, which have not been possible by previous asymmetric catalysts for cyanohydrin syntheses. Since peptides have proved to be effective ligands of metallic species as chiral auxiliaries of catalysts in this asymmetric reaction, synthetic peptides, if appropriately designed, will be potentially powerful ligands of various metal-catalyzed asymmetric reactions.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were recorded on a JEOL JNM-270 spectrometer. Infrared (IR) spectra were recorded on a Hitachi 260-30 spectrophotometer. Optical rotations were taken on a JASCO DIP-360 digital polarimeter. Gas chromatographic analyses were performed on a Shimadzu GC 14 A instrument with a flame ionization detector and capillary column CBP20-M25-025. HPLC analyses were performed on a JASCO LC-800 system using an optically active column (SUMICHIRAL OA-4100, 4.0 mm × 25 cm). Thin-layer chromatography (TLC) was performed on Merck precoated TLC plates (kieselgel 60 F_{254}, 0.25 mm). For column chromatography, Wako silica gel (Wakogel C-200, 100-200 mesh) was used. Molecular mechanics calculations (MM2) were performed using the CAChe system (SONY/Tektronix).

Materials. Toluene, THF, benzene, and benzene-d_6 (C_6D_6) were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. All aldehydes except for 2-naphthaldehyde were purified by distillation prior to use. Metal alkoxides were purchased and used without further purification. Dichlorodiisopropoxytitanium was prepared from titanium chloride and titanium isopropoxide according to the literature method.[16] All metallic species were employed as 0.1 M solutions in toluene. Hydrogen cyanide[17] was prepared by adding an aqueous solution of sodium cyanide dropwise into dilute sulfuric acid according to the reported procedure[18] and stored in a freezer as a 1 M solution in toluene. The preparation and reaction of hydrogen cyanide should be carried out in a hood with good ventilation. Other solvents and chemicals were used without further purification.

***N*-((2-Hydroxy-1-naphthyl)methylene)-(*S*)-valyl-(*S*)-phenylalanine Methyl Ester (1a, Nap-*S*-Val-*S*-Phe-OMe).** The reported procedure was used with slight modification. To a suspension of (*S*)-valine (2.34 g, 20 mmol) in a mixture of ethanol (500 mL) and methanol (40 mL) was added 2-hydroxy-1-naphthaldehyde (5.17 g, 30 mmol). After being stirred for 16 h, valine had dissolved, and the resulting yellow solution was concentrated in vacuo to leave the mixture of *N*-((2-hydroxy-1-naphthyl)methylene)-(*S*)-valine and excess 2-hydroxy-1-naphthaldehyde. The residue was washed well with ether to remove the excess 2-hydroxy-1-naphthaldehyde by filtration to yield a yellow solid of *N*-((2-hydroxy-1-naphthyl)methylene)-(*S*)-valine (5.31 g, 98%). To a solution of (*S*)-phenylalanine methyl ester hydrochloride (1.29 g, 6 mmol) in water (10 mL) was added potassium carbonate (1.24 g, 9 mmol). After the mixture was stirred at room temperature for 10 min, the aqueous layer was extracted with ether (20 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford free (*S*)-phenylalanine methyl ester as a viscous oil (0.97 g, 90%). To a suspension of *N*-((2-hydroxy-1-naphthyl)methylene)-(*S*)-valine (1.36 g, 5 mmol) in dichloromethane (30 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (DCC) (1.03 g, 5 mmol) at 0 °C followed by freshly prepared (*S*)-phenylalanine methyl ester (0.90 g, 5 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 24 h. The resulting white precipitate was removed by filtration through Celite, and the filtrate was concentrated to give the crude product as a yellow solid which was purified by column chromatography on silica gel (dichloromethane–ethyl acetate, 4:1) to yield, 1.43 g (66%) of **1a** which was recrystallized from methanol: mp 216.1–217.9 °C; $[\alpha]^{26}_D$ −28.2° (*c* 1.0, dioxane) [lit.[10b] mp 217–219 °C, $[\alpha]^{26}_D$ −25.6° (*c* 1, dioxane)]; IR (KBr) 3460 (br), 3200, 3025, 2970, 1740, 1660, 1625, 1540, 1510, 1490, 1430, 1405, 1360, 1310, 1275, 1210, 1170, 1140, 1095, 1010, 880, 860, 835, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.38 (br s, 1 H), 9.05 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.84 (d, *J* = 9.4 Hz, 1 H), 7.75 (d, *J* = 7.3 Hz, 1 H), 7.49–7.55 (m, 1 H), 7.32–7.38 (m, 1 H), 7.13–7.28 (m, 6 H), 6.42 (br d, *J* = 7.7 Hz, 1 H), 4.86–4.93 (m, 1 H), 3.73 (d, *J* = 4.3 Hz, 1 H), 3.68 (s, 3 H), 3.20 ($^1/_2$ AB qd, *J* = 13.7, 5.6 Hz, 1 H), 3.05 ($^1/_2$ AB qd, *J* = 13.7, 7.7 Hz, 1 H), 2.39–2.51 (m, 1 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H). Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.08; H, 6.48; N, 6.40.

Preparation of *N*-((2-Hydroxy-1-naphthyl)methylene)-(*S*)-valyl-(*S*)-tryptophan Methyl Ester (1g, Nap-*S*-Val-*S*-Trp-OMe). To a suspension of (*S*)-tryptophan methyl ester hydrochloride (2.54 g, 10 mmol) in anhydrous THF (20 mL) was added triethylamine (1.39 mL, 10 mmol), and the mixture was stirred at room temperature for 1 h to afford the free amino acid methyl ester as a suspension. Carbobenzoxy-(*S*)-valine (2.51 g, 10 mmol) was dissolved in THF (15 mL), and to the vigorously stirred solution were added triethylamine (1.39 mL, 10 mmol) and isobutyl chloroformate (1.31 mL, 10 mmol) at 0 °C. To this mixture was added the suspension of (*S*)-tryptophan methyl ester, and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for 16 h. The solvent was evaporated under reduced pressure to leave a white solid which was dissolved in a mixture of CH_2Cl_2 (100 mL) and water (30 mL). The organic layer was successively washed with 0.5 M boric acid, saturated brine, saturated sodium bicarbonate solution, saturated brine, and water (50 mL each), and then dried over Na_2SO_4 and concentrated in vacuo to give crude carbobenzoxy-(*S*)-valyl-(*S*)-tryptophan methyl ester (3.79 g, 84%) as a white solid which was directly used for the following reaction without further purification. Carbobenzoxy-(*S*)-valyl-(*S*)-tryptophan methyl ester (1.35 g, 3 mmol) was dissolved in methanol (50 mL) and stirred at room temperature under a hydrogen

(16) Dijkaraaf, C.; Rousseau, J. P. G. *Spectrochim. Acta, Part A* **1968**, *24*, 1213.
(17) CAUTION! Severe poison.
(18) In *Handbook of Preparative Inorganic Chemistry*, 2nd ed.; Brauer, G., Ed.; Academic Press: New York, 1963; Vol. 1, pp 658–660.

atmosphere in the presence of 5% palladium–carbon (100 mg) for 5 h. After completion of the reaction was confirmed by TLC, the palladium–carbon catalyst was removed by filtration to give a colorless solution, to which was added 2-hydroxy-1-naphthaldehyde (0.78 g, 4.5 mmol). After the solution was stirred at room temperature for 24 h, the solvent was evaporated under reduced pressure to give a yellow solid which was purified by column chromatography on silica gel (dichloromethane–ethyl acetate, 5:1) to yield 0.89 g (63%) of **1g** which was recrystallized from methanol: mp 194.8–195.3 °C; $[\alpha]^{26}_D$ + 25.7° (*c* 1.06, $CHCl_3$); IR (KBr) 3390 (br), 3055, 2960, 1740, 1650, 1630, 1540, 1485, 1435, 1400, 1350, 1210, 1135, 1095, 850, 830, 735, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.46 (br s, 1 H), 8.99 (s, 1 H), 8.05 (s, 1 H), 7.98 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 7.55 (d, J = 7.7 Hz, 1 H), 7.48–7.54 (m, 1 H), 7.32–7.38 (m, 1 H), 7.03–7.27 (m, 6 H), 6.48 (br d, J = 7.7 Hz, 1 H), 4.88–4.95 (m, 1 H), 3.78 (d, J = 3.0 Hz, 1 H), 3.65 (s, 3 H), 3.31–3.33 (AB m, 2 H), 2.39–2.51 (m, 1 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.80 (d, J = 6.8 Hz, 3 H). Anal. Calcd for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.04; H, 6.09; N, 8.92.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valine Piperidide (3c, Dbs-*S*-Val-Pip).** **3c** was prepared according to the procedure for **1g**. Carbobenzoxy-(*S*)-valine piperidide prepared above (0.32 g, 1 mmol) was hydrogenolyzed followed by condensation with 3,5-dibromosalicylaldehyde (0.42 g, 1.5 mmol) to yield 0.30 g (68%) of **3c** which was recrystallized from methanol: mp 143.2–145.4 °C; $[\alpha]^{26}_D$ +50.1° (*c* 0.97, $CHCl_3$); IR (KBr) 3460 (br), 2940, 2860, 1630, 1500, 1465, 1420, 1380, 1265, 1220, 1105, 1000, 860, 710, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.43 (br s, 1 H), 8.28 (s, 1 H), 7.71 (d, J = 2.6 Hz, 1 H) 7.35 (d, J = 2.1 Hz, 1 H), 4.12 (d, J = 8.5 Hz, 1 H), 3.50–3.62 (m, 4 H), 2.26–2.39 (m, 1 H), 1.44–1.71 (m, 6 H), 1.01 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H). Anal. Calcd for $C_{17}H_{22}Br_2N_2O_2$: C, 45.76; H, 4.97; N, 6.28. Found: C, 45.61; H, 5.21; N, 6.37.

Other peptides (**1b–f, h–k**), amino acid ester (**2a**), and amino acid amides (**2b–d, 3a,b, and d**) were synthesized in a manner similar to that described above.

General Procedure for Asymmetric Addition of Hydrogen Cyanide to Aldehyde. To a yellow suspension of **1a** (0.05 mmol) in toluene (2 mL) was added titanium ethoxide (0.05 mmol, 0.5 mL, 0.1 M in toluene) at room temperature under nitrogen. After being stirred at room temperature for 30 min, the mixture was cooled to −78 °C, and benzaldehyde (0.5 mmol) and hydrogen cyanide (0.75 mmol, 0.75 mL, 1 M in toluene) were successively added in the hood using gloves. The reaction mixture was then warmed to −40 °C, and stirring was continued for 4 h. After the reaction, the mixture was poured into 2 N hydrochloric acid and the aqueous layer was extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to leave a crude oil which was subjected to column chromatography on silica gel (Hexane–EtOAc, 10:1) to afford mandelonitrile in 83% yield as a colorless oil: $[\alpha]^{26}_D$ 22.7 (*c* 1.07, $CHCl_3$) as 64% ee of *R*-isomer, lit.[6c] $[\alpha]^{23}_D$ 40.6 (*c* 1, $CHCl_3$) as 92% ee of *R*-isomer. Spectroscopic characters of thus obtained mandelonitrile were identical with those of authentic samples.[7d]

The optical yield was determined by three methods. For aromatic aldehydes, to the residual crude cyanohydrin were added (−)-menthyl chloroformate and pyridine to afford the corresponding menthyl carbonic ester. The optical yield was determined by ^1H NMR analysis of this diastereomeric carbonic ester, showing a couple of singlets around δ 6 corresponding to the methyne proton at the α-position to the cyano group. The major stereoisomer of the cyanohydrin carbonate was identified as the *R*-isomer.[7d] For aliphatic aldehydes, to a small portion of the crude cyanohydrin were added (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA-Cl][12] and pyridine to afford the corresponding MTPA ester whose diastereomeric excess was determined by GC analysis. For cinnamaldehyde, the enantiomeric excess of the cyanohydrin was determined by chiral HPLC analysis (eluent; hexane/1,2-dichloroethane/ethanol/acetic acid, 2000:500:25:10; flow rate; 0.5 mL/min; detection; UV 254 nm). t_R = 27.4 (*R*), 28.7 (*S*) min.

^1H NMR Measurement of a Mixture of $Ti(OEt)_4$ and 1a (Nap-*S*-Val-*S*-Phe-OMe) or 2d (Nap-*S*-Val-NH-Bu). (i) $Ti(OEt)_4$:2d or 1a = 1:1. To a suspension of **2d** (16.3 mg, 0.05 mmol) for **1a** (21.6 mg, 0.05 mmol) in C_6D_6 (2 mL) was added $Ti(OEt)_4$ (0.05 mmol, 0.5 mL, 0.1 M in C_6D_6) under a nitrogen atmosphere. After the mixture was stirred at room temperature for 30 min, a part of the homogeneous solution (0.75 mL) was transferred to an NMR tube. **(ii) $Ti(OEt)_4$:2d = 1.5:1.** The experiment was carried out according to the procedure described above except for using 0.075 mmol (0.75 mL, 0.1 M in C_6D_6) of $Ti(OEt)_4$. **(iii) $Ti(OEt)_4$:2d:EtOH = 1:1:2.** To a suspension of **2d** (16.3 mg, 0.05 mmol) in C_6D_6 (2 mL) was added $Ti(OEt)_4$ (0.05 mmol, 0.5 mL, 0.1 M in C_6D_6) under a nitrogen atmosphere. After the mixture was stirred at room temperature for 30 min, ethanol (6 μL, 0.1 mmol) was added to the solution, and the mixture was stirred at room temperature for 10 min. A part of the homogeneous solution (0.75 mL) was transferred to an NMR tube.

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Supplementary Material Available: Spectroscopic properties and analytical data of **1b–f,h–k, 2a–d,** and **3a–b,d,** and a different view (top view) and geometry of the peptide–titanium complex in Figure 1, as calculated using CAChe MM2 (11 pages). Ordering information is given on any current masthead page.