Tetrahedron Letters, Vol.32, No.34, pp 4333-4336, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Peptide-Metal Complex as an Asymmetric Catalyst. A Catalytic Enantioselective Cyanohydrin Synthesis.

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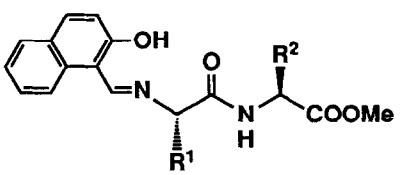
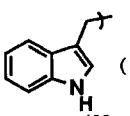
Key Words: peptide-metal complex; titanium alkoxide; enantioselective; cyanohydrin; asymmetric catalyst

Abstract: *An acyclic dipeptide ester, 2-hydroxy-1-naphthylideneimino-(S)-valyl-(S)-tryptophane methyl ester (**1a**: Nap-S-Val-S-Trp-OMe), whose terminal amino group is modified to a Schiff base, is designed as a chiral auxiliary of an asymmetric catalyst. The mixture of **1** with titanium alkoxide catalyzes enantioselective hydrocyanation of benzaldehyde to afford optically active (R)-mandelonitrile with stereoselectivities up to 94 : 6.*

The design of asymmetric catalyst has been widely studied using numerous entries of chiral auxiliaries.[1] In particular, amino acids[2] and their derivatives such as amino alcohols[2a, 3] are recognized as successful ligands in various asymmetric syntheses mediated by main group and transition metals. In contrast, synthetic peptides, oligomer or polymer composed of more than two amino acid residues, have not been utilized as a chiral ligand *despite enzymes, natural polypeptides, deliver perfect levels of stereoselection in vivo.* On the other hand, one of our interests has been centered on the biomimetic function of synthetic peptides,[4] the interest which prompted us to exploit the design of peptide-metal complex catalyzed asymmetric reactions.



1a: R^1 = Me_2CH, R^2 =  (Nap-S-Val-S-Trp-OMe)

1b: R^1 = Me_2CH, R^2 = CH_2Ph (Nap-S-Val-S-Phe-OMe)

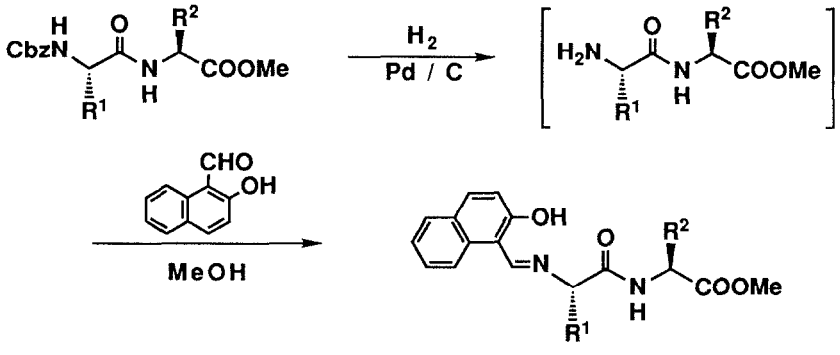
1c: *enantio*-1b (Nap-R-Val-R-Phe-OMe)

1d: Nap-R-Val-S-Phe-OMe

In this communication, we report that the mixture of titanium alkoxide and acyclic dipeptide (**1**) whose amino terminal is modified to a phenolic Schiff base[5] catalyzes the asymmetric addition of hydrogen cyanide to aldehydes to give cyanohydrins with high degree of enantioselectivities.[4a, 6]

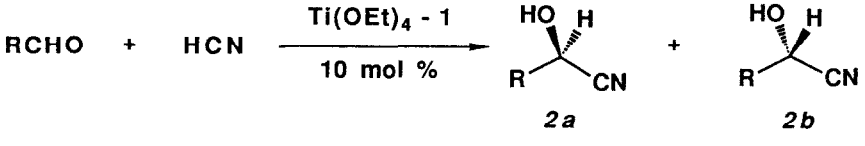
As illustrated in Scheme 1, the peptide (**1**) was prepared by the hydrogenolysis of the corresponding carbobenzoxy dipeptide followed by the condensation of the peptide with 2-hydroxy-1-naphthaldehyde. Among various combinations of amino acid residues examined, the peptide composed of (S)-valine and (S)-tryptophane (**1a:** 2-hydroxy-1-naphthylideneimino-(S)-valyl-(S)-tryptophane methyl ester) was found to be optimum in the stereoselectivity as well as the catalytic activity.

Scheme 1



1

The representative experimental procedure of the enantioselective hydrocyanation is as follows: To a suspension of **1a** (0.05 mmol) in 3 mL of toluene was added titanium (IV) ethoxide (0.05 mmol) at room temperature under argon. The mixture immediately turned to homogeneous yellow solution. After stirring for 30 min, the reaction mixture was cooled to -78°C followed by addition of benzaldehyde (0.5 mmol) and hydrogen cyanide[7] (0.75 mmol). Stirring was continued at -40°C for 3 h and the reaction was terminated by acidic work-up to give the cyanohydrin (**2**) in 88% yield with the enantioselectivity of 94 : 6 with stereochemical preference of *R*. The reactions of several aromatic aldehydes similarly afforded the corresponding cyanohydrins with high enantiopurities. The results on enantioselective hydrocyanation of aldehydes catalyzed by the mixture of **1** with titanium alkoxide are summarized in Table 1.

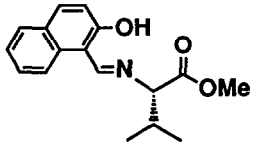


2a *2b*

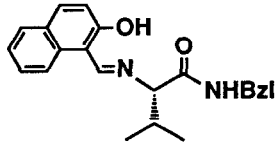
Table 1. Enantioselective cyanohydrin synthesis catalyzed by mixture of 1 and $Ti(OR)_4$[a)]

entry	aldehyde	peptide	titanium	temp (°C)	time (h)	yield of 2 (%)[b)]	ratio (2a/2b)[c)]
1	C_6H_5CHO	**1a**	$Ti(OEt)_4$	-40	3	88	94 / 6
2		**1b**	$Ti(OEt)_4$	-40	4	85	93 / 7
3		**1b**	$Ti(OEt)_4$	-20	4	91	91 / 9
4		**1b**	$Ti(OPr^i)_4$	-20	4	94	89 / 11
5		**1c**	$Ti(OEt)_4$	-40	7	86	8 / 92
6		**1d**	$Ti(OPr^i)_4$	-20	4	84	31 / 69
7		none	$Ti(OPr^i)_4$	-20	4	43	----
8		**3**	$Ti(OPr^i)_4$	-20	4	17	50 / 50
9		**4**	$Ti(OPr^i)_4$	-20	2	99	65 / 35
10	2-naphthaldehyde	**1a**	$Ti(OEt)_4$	-40	7.5	88	95 / 5
11	furfural	**1a**	$Ti(OEt)_4$	-40	7.5	74	93 / 7
12	3-$PhOC_6H_4CHO$	**1c**	$Ti(OEt)_4$	d)	d)	85	7 / 93
13	cyclo-$C_6H_{11}CHO$	**1b**	$Ti(OEt)_4$	-40	1.5	99	77 / 23[e)]
14	n-$C_6H_{13}CHO$	**1b**	$Ti(OEt)_4$	-40	1.5	99	87 / 13[e)]

a). The reactions were carried out in toluene using 10 mol% of titanium alkoxide, 10 mol% of the peptide and 1.5 equiv of HCN (based on the quantity of aldehyde). b). Based on the measurement of ^1H NMR. c). Unless otherwise noted, the ratio was determined by ^1H NMR measurement of the corresponding menthyl carbonic ester: See ref 4a. d). At -40°C for 11 h followed by at -20°C for 12 h. e). Determined by GC analysis of the corresponding (+)-2,2,2-methoxy-trifluoromethyl-phenylacetic acid (MTPA) ester.



3: Nap-S-Val-OMe



4: Nap-S-Val-NHBzl

It should be noted that the employment of the acyclic dipeptide ester as a chiral auxiliary is essential to the stereoselectivity as well as the catalytic reactivity. The peptide composed of two amino acid residues with the same configuration gave very high selectivity. On the other hand, when the configurations of the two amino acid residues were opposite to each other, the selectivity was much lower (entry 6). In sharp contrast to the dipeptides (**1a-c**), the derivatives of a single amino acid resulted in low selectivity (entries 8 and 9). In the case of an amino acid ester (entry 8), the yield was also low, indicating the importance of the amide (peptide) group[8] in the

catalytic activity of the peptide-Ti(OR)$_4$ system. Thus, the acyclic dipeptide ester is essential to the successful enantioselective cyanohydrin synthesis.

Since it is possible to design and synthesize a number of peptide by choosing the combination of amino acid residues, peptides, if efficiently designed, can be potential practical ligands of a variety of metal catalyzed asymmetric reactions.

References and Notes

1. Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1989; Vol. 5, pp 115-198.
2. (a) Coppola, G. M.; Schuster; H. F. *Asymmetric Synthesis. Contribution of Chiral Molecules using Amino Acids*; Wiley: New York, 1987. (b) Takasu, M.; Yamamoto, H. *Synlett*, **1990**, 194. Sartor, D.; Saffrich, J.; Helmchen; G. *ibid*, **1990**, 197. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.*, **1974**, *39*, 1615.
3. For use of amino alcohols as chiral auxiliaries: Evans, D. A.; Woerpel; K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.*, **1991**, *113*, 726. Corey, E. J.; Imai; N.; Zhang, H.-Y. *ibid*, **1991**, *113*, 728. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *ibid*, **1987**, *109*, 7111. Corey, E. J.; Bakshi, R. K.; Shibata, S. *ibid*, **1987**, *109*, 5551.
4. (a) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.*, **1990**, *55*, 181. Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.*, **1989**, 2119. (b) Aoyama, M.; Watanabe, J.; Inoue, S. *J. Am. Chem. Soc.*, **1990**, *112*, 5542 and references therein.
5. The 2-hydroxy-1-naphthylideneimino group has been used as a protective group in peptide synthesis: Seehan, J. C.; Grenda, T. V. *J. Am. Chem. Soc.*, **1962**, *84*, 2417. McIntire, F. C. *ibid*, **1949**, *69*, 1377.
6. For asymmetric cyanohydrin synthesis using cyanotrimethylsilane: Minamikawa, H., Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem., Soc., Jpn.*, **1988**, *61*, 4379. Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.*, **1986**,*39*, 4721. Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.*, **1990**, 1364. Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.*, **1991**, 541. See also: Garner, C. M.; Fernandes, J. M.; Gladysz, J. A. *Tetrahedron Lett.*, **1989**, *30*, 3931.
7. *CAUTION: Severe poison. All procedures should be carried out in the hood with good ventilation.*
8. A related rate enhancement by amide group in a similar catalyst system was also observed in transhydrocyanation: Mori, A.; Inoue, S. *Chem. Lett.*, **1991**, 145.

(Received in Japan 24 April 1991)