Asymmetric Hydrocyanation of Aldehydes Using Chiral Titanium Reagents

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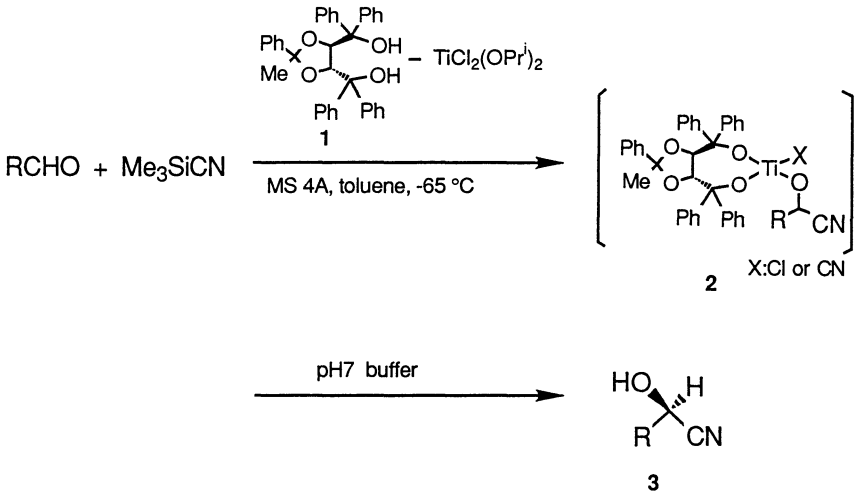
Two highly enantioselective methods for hydrocyanation of aldehydes were developed by using chiral alkoxytitanium reagents. Treatment of benzaldehyde with cyanotrimethylsilane in the presence of a chiral alkoxytitanium affords mandelonitrile in good chemical and optical yields. By the use of the chiral cyanotitanium reagent generated in situ from the chiral alkoxytitanium and cyanotrimethylsilane, aliphatic aldehydes are converted into the corresponding cyanohydrins in a highly enantioselective manner.

Asymmetric synthesis of cyanohydrins is an important process in organic synthesis, because cyanohydrins can be easily converted into a variety of valuable synthetic intermediates such as α-hydroxy carboxylic acids, α-hydroxy ketones, and β-amino alcohols. Since the first report by Bredig and Fiske who discovered that chiral mandelonitrile can be obtained by the quinine-catalyzed reaction of hydrogen cyanide and benzaldehyde,[1] a great progress has been made in the asymmetric synthesis of cyanohydrins, and recently several efficient methods have been reported to prepare cyanohydrins in high optical purity. For example, optically active cyanohydrins are obtained with good selectivity by diastereoselective reactions of cyanating reagents with chiral acetals.[2] However, the chiral auxiliaries are destroyed in the process of removing them from the products and not recovered. In the enantioselective reactions using chiral catalysts, such as boryl compounds,[3] D-oxynitrilase,[4] and synthetic peptides,[5] the optical purities of the resulting cyanohydrins are not sufficient except in the case of the preparation of mandelonitrile derivatives.

We reported an enantioselective Diels-Alder reaction by the use of the chiral alkoxytitanium-Molecular Sieves (MS) 4A system.[6] As another utility of this chiral titanium reagent, we examined the asymmetric hydrocyanation of aldehydes.[7]

Firstly, we examined the reaction of 3-phenylpropanal and cyanotrimethylsilane using the chiral alkoxytitanium generated in situ by mixing dichlorodiisopropoxytitanium(IV) and the chiral 1,4-diol, (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**1**). When 3-phenylpropanal was treated with cyanotrimethylsilane in the presence of the chiral titanium reagent in toluene at −65 °C, the reaction proceeded slowly. On the other hand, by the addition of MS 4A to this solution, the reaction was found to proceed smoothly at the same temperature. Thus, powdered MS 4A were added at room temperature to a toluene solution of dichlorodiisopropoxytitanium(IV), and the chiral diol **1**, then 3-phenylpropanal and excess amounts of cyanotrimethylsilane were added at −65 °C to afford 2-hydroxy-4-phenylbutanenitrile (**3a**, 89% yield, 74% ee). The asymmetric hydrocyanation of 3-phenylpropanal was also investigated in various solvents such as cumene (55% yield, 60% ee, at −65 °C), mesitylene (70% yield, 60% ee, at −45 °C), dichloromethane (23% yield, 72% ee, at −65 °C), acetonitrile (77% yield, 36% ee, at −45 °C), diethyl ether (42% yield, 0% ee, at −65 °C) and tetrahydrofuran (72% yield, 0% ee, at −65 °C): Among them, high enantioselectivity was achieved when the aromatic solvents or dichloromethane was used, but the enantioselectivity decreased when the solvents having



Scheme 1.

Table 1. Asymmetric Hydrocyanation of Aldehydes Using the Chiral Alkoxytitanium and Cyanotrimethylsilane

Entry	Aldehyde R	Reaction time/d	Product	Yield/%	Optical yield/%ee
1	$PhCH_2CH_2$	0.5	**3a**	89	74
2	$PhCH_2$	0.5	**3b**	66	77
3	n-C_8H_{17}	1	**3c**	66	76
4	c-C_6H_{11}	2	**3d**	77	68
5	Ph	0.5	**3e**	79	96

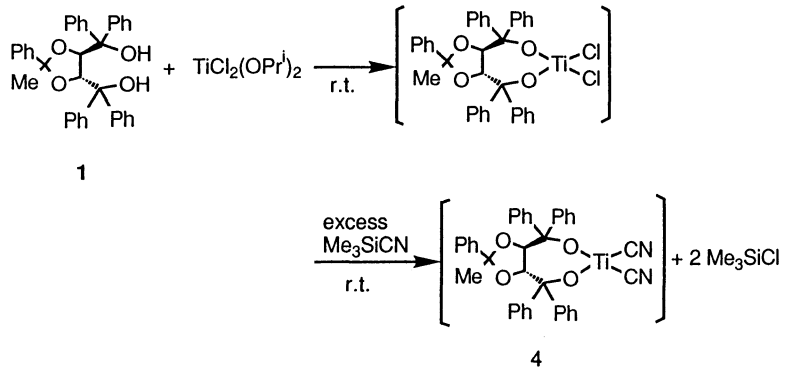
good donor property such as acetonitrile, diethyl ether, and tetrahydrofuran were employed.

It was also found that cyanotrimethylsilane gave the best chemical and optical yields among various cyanating reagents examined: The reaction did not proceed even at room temperature when potassium cyanide with 18-crown-6 or t-butyl isocyanide was employed, and low chiral induction was observed when cyanotributyltin(IV) (52% yield, 0% ee, at −78 °C) or cyanodiethylaluminium (81% yield, 7% ee, at −78 °C) was used as a cyanating reagent. Therefore, the asymmetric hydrocyanation of various aldehydes with cyanotrimethylsilane was examined in toluene at −65 °C (Scheme 1), and the results are summarized in Table 1.

As shown in Table 1, these aldehydes smoothly react with cyanotrimethylsilane to give the optically active cyanohydrins in good optical yield (68—96% ee). Especially, benzaldehyde is converted into (*R*)-mandelonitrile in high optical purity (Entry 5, 96% ee).

When we tried the reaction of 3-phenylpropanal with cyanotrimethylsilane in the presence of a 25% molar amount of the chiral titanium reagent, the chemical yield of the cyanohydrin **3a** was 26%. Furthermore, in every case, no trimethylsilyl ether of a cyanohydrin was detected after the treatment of the reaction mixture with pH 7 phosphate buffer. These results show that cyanohydrins are generated not as silyl ethers but as titanium ethers **2**. The following experiments were carried out in order to examine whether the optically active cyanohydrins were obtained thermodynamically or kinetically. When 3-phenylpropanal was treated with cyanotrimethylsilane in the presence of the chiral titanium reagent and MS 4A at room temperature for 12 h and then the reaction mixture was stirred at −65 °C for 1 d, the optical purity of the resulting cyanohydrin was low (ca. 10% ee). Almost the same level of chiral induction (10% ee) was observed when the above reaction was performed at room temperature for 12 h. These results indicate that the cyanohydrin obtained by the present procedure is not a thermodynamic product but a kinetic product.

In order to get informations on the reaction mechanism, NMR spectrum of cyanotrimethylsilane and the titanium reagent was measured. The ^{1}H NMR spectrum of the mixture of cyanotrimethylsilane and the chiral alkoxytitanium prepared in situ by mixing the chiral diol **1** and dichlorodiisopropoxytitanium(IV) in toluene-d_8 at −65 °C shows a singlet peak at δ=−0.09 which corresponds to cyanotrimethylsilane, and no absorption is observed at δ=0.20 which corresponds to chlorotrimethylsilane irrespective of the presence or absence of MS 4A. This observation seems to suggest that in the reaction at low temperature the chiral alkoxytitanium reagent activates an aldehyde as a Lewis acid and the activated aldehyde reacts with cyanotrimethylsilane to afford a cyanohydrin. On the other hand, when the mixture of the chiral alkoxytitanium and cyanotrimethylsilane is slowly warmed up to room temperature, the ^{1}H NMR spectrum indicates the decreasing of the absorption at δ=−0.09 and the appearance of a singlet peak at δ=0.20. This phenomenon is explained by assuming that the ligand-exchange reaction occurs between the chiral alkoxytitanium and cyanotrimethylsilane at room temperature,



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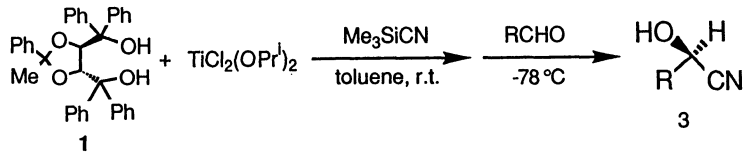
Scheme 2.



Scheme 3.

Table 2. Asymmetric Hydrocyanation of Aldehydes Using the Chiral Cyanotitanium Reagents

Entry	Aldehyde R	Reaction time/h	Product	Yield/%	Optical yield/%ee
1	$PhCH_2CH_2$	20	**3a**	88	(−)-91
2	$PhCH_2$	12	**3b**	67	(+)-61[a]
3	n-C_8H_{17}	23	**3c**	85	(+)-93
4	n-C_9H_{19}	18	**3f**	83	(+)-85[a]
5	$CH_2=CH(CH_2)_8$	16	**3g**	92	(+)-93
6	Ph	122	**3e**	68	(+)-73

a) Reaction temperature is −65 °C.

resulting in the formation of cyanotitanium species and chlorotrimethylsilane. Integration of the peak at δ=0.20 was attributed to 2 molar amounts of chlorotrimethylsilane, that is, titanium dicyanide species **4** might be generated by the addition of excess (5 molar) amounts of cyanotrimethylsilane (Scheme 2). We were interested in utilizing this chiral cyanotitanium species **4** as a chiral cyanating reagent of aldehydes (Scheme 3). Thus, to a toluene solution of dichlorodiisopropoxytitanium(IV) was added the chiral diol **1** and then cyanotrimethylsilane at 1 hour intervals at room temperature to generate the chiral cyanotitanium reagent. Then 3-phenylpropanal was added at −78 °C and the mixture was further stirred for 20 h. Work-up of the reaction mixture afforded 2-hydroxy-4-phenylbutanenitrile (**3a**) in 88% yield and the optical purity rose up to 91% ee as compared with the result of the previous procedure (74% ee).

The same reactions using various aldehydes were examined in toluene at −78 °C and the results are summarized in Table 2. According to this procedure, the optical purity of aromatic cyanohydrins (Entries 2 and 6) are not sufficiently high, but aliphatic cyanohydrins are prepared in good yield with high optical purity (>85% ee, Entries 3, 4, and 5). The absolute configurations of (+)-2-hydroxy-3-phenylpropanenitrile (**3b**), (+)-mandelonitrile (**3e**), and (+)-2-hydroxyundecanenitrile (**3f**) obtained by employing the (2*R*, 3*R*)-diol **1** were determined to be *R* by the comparison of their rotations with those of the literature.[8] As for (+)-2-hydroxydecanenitrile (**3c**) and (+)-2-hydroxy-11-dodecenenitrile (**3g**), there is no literature concerning the absolute configuration. However, from the analogy that straight-chain aliphatic cyanohydrins such as (*S*)-2-hydroxyhexanenitrile, (*S*)-2-hydroxyheptanenitrile, (*S*)-2-hydroxyoctanenitrile and (*S*)-2-hydroxyundecanenitrile have (−)-rotation,[8] they are assumed to have *R* absolute configuration. Exceptionally 2-hydroxy-4-phenylbutanenitrile (**3a**) was obtained with the opposite (−)-rotation, but the absolute configuration was determined to be *R* after the hydrolysis to the known 2-hydroxy-4-phenylbutanoic acid.[9] These results indicate that cyanide attacks the *si*-face of aldehydes when the (2*R*,3*R*)-diol **1** is employed as a chiral auxiliary.

In conclusion, the optically active cyanohydrins can be obtained not only from aromatic aldehydes but also from aliphatic aldehydes in high optical yields by applying either method. The both enantiomers of cyanohydrins can be prepared in high optical purity since each enantiomer of the chiral 1,4-diol **1** is readily prepared from the commercially available (*R*)- and (*S*)-tartaric acids.

Experimental

General. (a) Spectrometers: IR spectra were measured with a Hitachi Model 260-30 spectrophotometer. ^{1}H NMR spectra were recorded with Hitachi R-24B, JEOL FX90Q and Varian EM390 spectrometers. ^{19}F NMR spectra were taken by using a Varian EM390 spectrometer. High-mass spectra were recorded with a JEOL JMS-D300 mass spectrometer operating at 70 eV. The optical rotations were measured with a JASCO DIP-181 digital polarimeter. (b) Chromatography: Column chromatography was conducted under silica gel (E. Merck, 7734, 70—230 mesh). Preparative TLC was carried out on silica gel (Wakogel B-5F). HPLC was performed using a Waters RESOLVE C_{18} (86016) column. (c) Solvents and Reagents: Toluene was distilled and dried over MS 4A. Dichloromethane was distilled from P_2O_5 then from CaH_2, and was dried over MS 4A. Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. Acetonitrile was distilled from P_2O_5, and further distilled from CaH_2, and dried over MS 4A. Mesitylene was distilled and dried over MS 4A. Cumene was distilled from $LiAlH_4$. Dichlorodiisopropoxytitanium(IV) was prepared from titanium(IV) chloride and tetraisopropoxytitanium(IV) according to the literature.[10] Aldehydes

were distilled prior to use. Cyanotrimethylsilane was purified by distillation.

Preparation of (2*R*,3*R*)-2,3-*O*-(1-Phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (1). Dimethyl (2*R*,3*R*)-2,3-*O*-(1-Phenylethylidene)tartrate. To a benzene solution of dimethyl (2*R*,3*R*)-tartrate (10.7 g, 60 mmol) and acetophenone dimethyl acetal (10.6 g, 60 mmol) was added a catalytic amount of *p*-toluenesulfonic acid, and the mixture was heated to reflux to remove liberated methanol azeotropically with occasional addition of benzene until the boiling point reached 80.5 °C. The mixture was washed with sat. aq. $NaHCO_3$ and then with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual oil was purified by column chromatography (8:1 hexane/diethyl ether) to afford the product, which was further purified by distillation to give the pure product (10.7 g, 63% yield). Bp 132 °C/0.30 mmHg (1 mmHg≈133.322 Pa); ^1H NMR ($CDCl_3$) δ=1.58 (s, 3H), 3.30 (s, 3H), 3.64 (s, 3H), 4.65 (s, 2H), and 7.0—7.7 (m, 5H); IR (neat) 1740 cm^{-1}; $[\alpha]_D$ +11° (*c* 2.6, CH_2Cl_2).

(2*R*,3*R*)-2,3-*O*-(1-Phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (1). To a tetrahydrofuran (50 ml) solution of phenylmagnesium bromide (25.0 mmol) was added a tetrahydrofuran (10 ml) solution of dimethyl (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)tartrate (1.4 g, 5.0 mmol) at 0 °C. After stirring for 4 h at room temperature, the reaction was quenched with sat. aq. NH_4Cl solution. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (9:1 hexane/diethyl ether) to afford white amorphous solid. This solid was dissolved in a small amount of hexane, and 2-propanol was added with stirring to afford white crystals. These crystals were recrystallized from 1:1 mixture of hexane and 2-propanol. The crystals thus obtained were a complex of **1** and 2-propanol, and 2-propanol was removed azeotropically with benzene 3 times to afford **1** as white amorphous solid (1.6 g, 60% yield). ^1H NMR ($CDCl_3$) δ=1.30 (s, 3H), 2.32 (s, 1H), 2.45 (s, 1H), 5.04 (d, 1H, *J*=6.0 Hz), 5.08 (d, 1H, *J*=6.0 Hz), and 6.8—7.6 (m, 25H); IR(KBr) 3300, 1490, 1445, and 695 cm^{-1}; $[\alpha]_D^{23}$ +82.9° (*c* 1.3, $CHCl_3$). The elemental analysis was performed after the conversion to the corresponding bis(trimethylsilyl) ether: Found: C, 74.68; H, 7.12%. Calcd for $C_{42}H_{48}O_4Si_2$: C, 74.96; H, 7.19%.

Cyanohydrins: General Procedure for Hydrocyanation of Aldehydes (Method A, Table 1). All reactions were carried out under argon atmosphere. To a toluene (1 ml) solution of dichlorodiisopropoxytitanium(IV) (119 mg, 0.5 mmol) was added a toluene (2 ml) solution of the chiral diol **1** (291 mg, 0.55 mmol) at room temperature. After 1 h, powdered MS 4A (65 mg, heated at 200—300 °C in vacuo prior to use) were added to this solution. Then a toluene (1 ml) solution of aldehyde (0.5 mmol), and a toluene (1 ml) solution of cyanotrimethylsilane (250 mg, 2.5 mmol) were added at −65 °C. After stirring for 0.5—2 d at this temperature, the reaction was quenched with pH 7 phosphate buffer, and the resulting mixture was filtered through Celite. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (hexane/diethyl ether) to afford the corresponding cyanohydrin. The optical purity was assayed by HPLC (40:1 hexane/ethyl acetate) or by ^{19}F NMR analysis of the corresponding (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionate (MTPA).[11]

General Procedure for Hydrocyanation of Aldehydes Using the Chiral Cyanotitanium(IV) Species (Method B, Table 2). To a toluene (1 ml) solution of dichlorodiisopropoxytitanium(IV) (119 mg, 0.5 mmol) was added a toluene (1 ml) solution of the chiral diol **1** (291 mg, 0.55 mmol) at room temperature. After 1 h, a toluene (1 ml) solution of cyanotrimethylsilane (250 mg, 2.5 mmol) was added at room temperature, and after 1 h, a toluene (1 ml) solution of aldehyde (0.5 mmol) was added at −78 °C. After stirring for 12—122 h at this temperature, the reaction was quenched with pH 7 phosphate buffer, and the resulting cyanohydrin was isolated by the same procedure described above.

2-Hydroxy-4-phenylbutanenitrile (3a). ^1H NMR ($CDCl_3$) δ=1.8—2.2 (m, 2H), 2.6—2.9 (m, 2H), 3.7—4.0 (br, 1H), 4.3 (t, 1H), and 7.1 (s, 5H); IR(CCl_4) 3440, 2930, 1600, 1500, 1450, and 1070 cm^{-1}; $[\alpha]_D^{22}$ −6.79° (*c* 2.04, $CHCl_3$, 89% ee). HRMS Found: *m/z* 161.0873. Calcd for $C_{10}H_{11}NO$: M, 161.0841.

2-Hydroxy-3-phenylpropanenitrile (3b). ^1H NMR ($CDCl_3$) δ=2.9—3.1 (m, 3H), 4.4—4.7 (m, 1H), and 7.3 (s, 5H); IR (CH_2Cl_2) 3430, 3020, 2920, 1600, 1480, and 1050 cm^{-1}; $[\alpha]_D^{26}$ +8.3° (*c* 1.10, $CHCl_3$, 65% ee), lit, $[\alpha]_D^{25}$ −0.5° ($CHCl_3$, 1% ee, (*S*)-form major).[8] HRMS Found: *m/z* 147.0654. Calcd for C_9H_9NO: M, 147.0685.

2-Hydroxydecanenitrile (3c). ^1H NMR (CCl_4) δ=0.8—1.8 (m, 17H), 3.2—3.4 (m, 1H), and 4.3—4.5 (m, 1H); IR (CH_2Cl_2) 3590, 3420, 2940, 2870, 2300, and 1430 cm^{-1}; $[\alpha]_D^{25}$ +12.8° (*c* 2.52, $CHCl_3$, 93% ee).

2-Cyclohexyl-2-hydroxyacetonitrile (3d). ^1H NMR ($CDCl_3$) δ=1.2—1.8 (m, 11H), 3.2—3.5 (br, 1H), and 4.1—4.4 (br, 1H); IR($CHCl_3$) 3600, 3430, 2930, 2860, 1450, and 1040 cm^{-1}; $[\alpha]_D^{25}$ +5.45° (*c* 2.96, $CHCl_3$, 58% ee).

Mandelonitrile (3e). ^1H NMR spectra and IR spectra agreed with those of literatures. $[\alpha]_D^{21}$ +45.5° (*c* 3.53, $CHCl_3$, 96% ee), lit, $[\alpha]_D^{25}$ +43.5° (*c* 5, $CHCl_3$, 92.5% ee, (*R*)-form major).[2a]

2-Hydroxyundecanenitrile (3f). ^1H NMR ($CDCl_3$) δ= 0.8—1.2 (m, 19H), 3.2—3.6 (br, 1H), and 4.4 (t, 1H); IR (CH_2Cl_2) 3580, 3410, 2910, 2850, and 1450 cm^{-1}; $[\alpha]_D^{25}$ +7.9° (*c* 4.03, $CHCl_3$, 85% ee), lit, $[\alpha]_D^{25}$ −2.4° ($CHCl_3$, 16% ee, (*S*)-form major).[8]

2-Hydroxy-11-dodecenenitrile (3g). ^1H NMR ($CDCl_3$) δ= 1.2—2.1 (m, 16H), 3.4—3.6 (br, 1H), 4.4 (t, 1H), 4.8—5.1 (m, 2H), and 5.5—6.1 (m, 1H); IR(CCl_4) 3420, 2900, 2250, and 1640 cm^{-1}; $[\alpha]_D^{21}$ +10.5° (*c* 2.68, $CHCl_3$, 93% ee). HRMS Found: *m/z* 195.1592. Calcd for $C_{12}H_{21}NO$: M, 195.1624.

Hydrolysis of 3a. To **3a** (0.36 mmol, 77% ee, $[\alpha]_D^{23}$ −4.46° (*c* 8.40, $CHCl_3$)) was added 4 ml of concentrated hydrochloric acid. After refluxed for 4 h, 4 ml of water was added and organic materials were extracted with ethyl acetate. The combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was recrystallized from benzene to afford white crystals of 2-hydroxy-4-phenylbutanoic acid (59 mg, 91% yield). ^1H NMR ($CDCl_3$) δ=1.7—2.4 (m, 2H), 2.8 (t, 2H), 4.2 (t, 1H), 5.2—6.2 (br, 2H), and 7.2 (s, 5H); IR(KBr) 3470, 2920, 1730, 1600, 1500, 1290, and 1240 cm^{-1}; $[\alpha]_D^{24}$ −6.03° (*c* 1.18, C_2H_5OH), lit, $[\alpha]_D$ −8.6° (*c* 1, C_2H_5OH, (*R*)-form).[9]

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