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Salen-Ti(OR)$_4$ Complex Catalysed Trimethylsilylcyanation of Aldehydes

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Abstracts: Chiral salen-titanium complexes were found to be efficient catalysts for the enantioselective trimethylsilylcyanation of aldehydes. An enantioselectivity up to 87.1% e.e. was obtained by using 10mol% Ti(Ⅳ)-salen 2d as catalyst. The reaction mechanism was proposed and proved experimentally. © 1997 Published by Elsevier Science Ltd.

Introduction

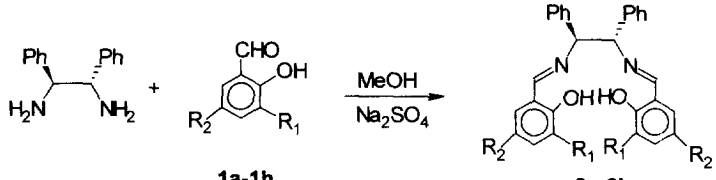
Optically active cyanohydrins are versatile synthetic intermediates. The two functional groups can be easily manipulated into a wide range of other homochiral products, such as α-hydroxyl acids, [1,2] α-hydroxyl aldehydes,[3] α-hydroxyl ketones, [3] β-hydroxyl amines, [2,3] and α-amino acid derivatives.[4] Cyanohydrins are used as starting materials in the synthesis of some pharmaceutical compounds.[5] In addition, cyanohydrins are found as components of some natural products such as the glucoside amygdalin.[6] Therefore, many efficient methods have been developed for the synthesis of optically pure cyanohydrins by biochemical[7] and chemical methods. Of the latter, Elliot and Johnson reported the highly diastereoselective addition of trimethylsilylcyanide to the chiral acetals.[8] Reetz reported that boron[9a] and titanium complexes[9b] with chiral binaphthol and other chiral ligands catalysed the trimethylsilylcyanation of aldehydes. Narasaka also tried the asymmetric trimethylsilylcyanation of aldehydes by means of a stoichiometric amount of catalyst prepared in situ from titanium dichloride diisopropoxide and chiral 1,4-diol in the presence of molecular sieves(MS) 4A.[10] Inoue and his co-workers carried out the enantioselective hydrocyanation of aldehydes catalysed by chiral basic cyclodipeptides with a L-histidine residue.[11] Corey used C_2-symmetry bis(dihydrooxazole)-Mg(Ⅱ) as a chiral catalyst to promote the trimethylsilylcyanation of aldehydes and obtained excellent chemical yield and enantiomeric excess with 20 mol% catalytic amount.[12] Oguni et al reported a highly enantioselective silylcyanation of a variety of aldehydes catalysed by a chiral schiff base-Titanium alkoxide catalyst system.[13] Very recently, Bolm found a novel chiral sulfoximine/titanium reagent for enantioselective cyanohydrin formation with good enantioselectivity using stoichiometric amount.[14] Chiral salen transition metal complexes

have been proved to work as efficient catalysts for epoxidation of olefins,[15] hydrogen-transfer reduction of ketones,[16] and oxygenation of alkenes.[17] In this paper, we describe a new and efficient procedure for the enantioselective addition of trimethylsilylcyanide to aldehydes using salen-titanium alkoxide complexes as catalysts.[18]

Results and Discussion

Preparation of Chiral Salen-Titanium Alkoxide Catalysts.

The chiral salens were prepared by condensation of 2-hydroxyl benzaldehyde (salicylaldehyde) (**1d**) or its derivatives with (1S, 2S)-1,2-diphenylethylenediamine in methanol (**Scheme 1**) (**Table 1**).

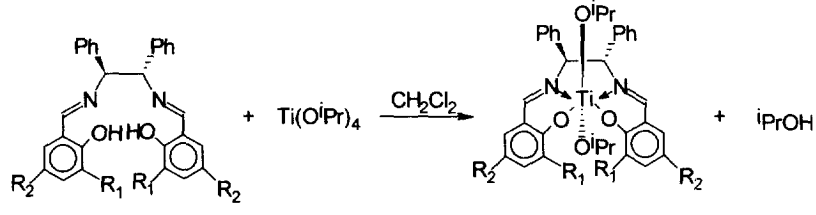


Scheme 1

Table 1 . Chiral Salens Used in Asymmetric Trimethylsilylcyanation of Benzaldehyde

Salen	R_1	R_2	$[\alpha]^{20}_D$ (c, solvent)
(1S, 2S)-**2a**	$-C(CH_3)_3$	$-C(CH_3)_3$	+32.4 (c = 0.25, $CHCl_3$)
(1S, 2S)-**2b**	$-CHPh_2$	$-CH_3$	+164.4 (c = 1.0, $CHCl_3$)
(1S, 2S)-**2c**	$-OCH_3$	-H	-11.9 (c = 1.0, $CHCl_3$)
(1S, 2S)-**2d**	-H	-H	-17.1 (c = 1.0, $CHCl_3$)
(1S, 2S)-**2e**	-H	$-NO_2$	-32.1 (c = 1.0, DMF)
(1S, 2S)-**2f**	-H	-Br	+2.2 (c = 1.0, CH_2Cl_2)
(1S, 2S)-**2g**	-H	Cl	-12.2 (c = 1.0, CH_2Cl_2)
(1S, 2S)-**2h**	-H	$-OCH_3$	+4.9 (c = 4.0, CH_2Cl_2)

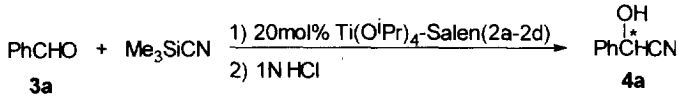
The chiral salen-titanium isopropoxide catalysts were prepared by mixing 1.1 equimolar amount of chiral salen to titanium tetraalkoxide(**Scheme 2**).



Scheme 2

Asymmetric Trimethylsilylcyanation of Benzaldehyde Catalysed by Chiral Salen-Titanium Alkoxide Complexes.

First of all, the steric effect of substituents on salen on the enantioselectivity of the reaction was studied. The reaction of benzaldehyde with trimethylsilylcyanide was carried out in dichloromethane at -78℃ for 24 h catalysed by 20 mol% titanium catalysts prepared in situ from a variety of chiral salen ligands (**2a-2d**) and titanium alkoxide (**Scheme 3**). The results for the asymmetric silylcyanation of benzaldehyde catalysed by salen-titanium alkoxide complexes are listed in **Table Ⅱ**.



3a **4a**

Scheme 3

Table Ⅱ. The Steric Effect of Substituents on Salens on the Enantioselectivity of Trimethylsilylcyanation of Benzaldehyde [a]

Salen	Yield %[b]	e.e.% [c](conf.)[d]
(1S, 2S)-2a	70	38.8 (R)
(1S, 2S)-2b	30	5.0 (R)
(1S, 2S)-2c	50	24.3 (R)
(1S, 2S)-2d	82	83.9 (R)

a. Reaction was catalysed by 20 mol% Salen-Titanium complexes at -78℃. b. Isolated yield. c. Determined by GC on CYDEX-β 25 m× 0.22 mm(i.d.) after derivatisation with trifluoroacetic anhydride. d. Determined by comparison of the sign of optical rotation values with those in the literature.[19]

The results indicated that the enantioselectivity was influenced by the structures of the ligands. To our surprise, the reaction catalysed by the titanium(Ⅳ) complex of salen 2d with the smallest steric hindrance among the chiral ligands gave the highest optical yield (83.9 % e.e.). This phenomenon was dramatically different from that observed in trimethylsilylcyanation of aldehydes catalysed by schiff base-titanium(Ⅳ) complexes,[13] but the same as Katsuki's olefin cyclopropanation.[20] Then, we investigated the electronic effects of substituents on ligands (**2e-2h**) on the e.e. of products (**Table Ⅲ**). The results showed that the ligands with stronger electron-withdrawing groups gave less enantioselectivity. For the electron-withdrawing groups NO_2, Cl, Br, the enantiomeric excess was obtained in 5.8% e.e., 30% e.e. and 38.9% e.e. respectively. However for the electron-donating group OCH_3, the enantiomeric excess increased to 78.2% e.e.. These results were similar to those of the epoxidation catalysed by Mn-salen.[21] In order to optimise the reaction conditions for higher enantiomeric excess, the effects of a molar ratio of Ti(O^{i}Pr)$_4$ to salen (**2d**), and amounts of catalyst on enantioselectivity were examined in detail. When the molar ratio of ligand 2d to Ti(O^{i}Pr)$_4$ was 1.1: 1, the best enantioselectivity was obtained, but the enantioselectivity did not appreciably vary with the change of molar

ratio, which was different from the results catalysed by mono-Schiff base-Ti(O^iPr)$_4$ complexes.[22] The catalytic activity of Ti(O^iPr)$_4$ was much less than that of its complexes,[23, 13b] so the e.e. decreased slightly when the ratio of ligand (2d) to Ti(O^iPr)$_4$ was 0.5:1. As excess ligand had no catalytic activity, the enantiomeric excess did not change when the reaction was catalysed by the system with the ratio of ligand (**2d**) to Ti(O^iPr)$_4$>1.1:1.

Table Ⅲ. The Electronic Effects of Substituents on Salen on Enantioselectivity of Trimethylsilylcyanation of Benzaldehyde[a]

Salen	Yield %[b]	e.e.%[c](conf.)[d]
(1S, 2S)-2d	72	87.1
(1S, 2S)-2e	21	5.8
(1S, 2S)-2f	26	30.0
(1S, 2S)-2g	31	38.9
(1S, 2S)-2h	73	78.2

a. Reaction was catalysed by 10 mol% salen-Titanium complexes. b. Isolated yield. c. Determined by GC on CYDEX-β 25 m× 0.22 mm(i.d.) after derivatisation with trifluoroacetic anhydride. d. Determined by comparison of the sign of optical rotation values with those in the literature.[19]

Table Ⅳ. Effect of the Amounts of Catalyst on the Enantioselectivity of Trimethylsilylcyanation of Benzaldehyde[a]

Amount of catalyst (mol %)	Yield %	e.e.% (conf.)
100[b]	92	36.7 (R)
100[c]	91	52.5 (R)
100[d]	90	80.0 (R)
100[e]	97	85.0 (R)
50	93	59.1 (R)
20	82	83.9 (R)
10	72	87.1 (R)
5	70	81.1 (R)

a. The reaction used Ti(O^iPr)$_4$ -**2d** as catalyst. b. The concentration of catalyst was 0.33 mol.l^{-1}. c. iPrOH was removed, and the concentration of catalyst was 0.33 mol.l^{-1}. d. The concentration of catalyst was diluted to 0.1 mol.l^{-1}. e. The concentration of catalyst was 0.33 mol.l^{-1} and THF was used as solvent.

The amounts of catalyst also dramatically influenced the enantioselectivity (**Table Ⅳ**). Interestingly, the enantiomeric excess decreased as amounts of catalyst increased. The enantioselectivity was 87.1% e.e. using 10 mol% catalyst. 5mol % amount of catalyst was sufficient to achieve high enantioselectivity. But

using 100 mol% catalyst (0.33 mol/l) the enantiomeric excess was only 36.7% e.e.. Use of freeze-dried catalyst, prepared by complete removal of isopropyl alcohol, resulted in 52.5% e.e. When the concentration was diluted by three fold (0.1mol/l), the enantiomeric excess increased to 80% e.e.. However, the e.e. resumed to 85.0% with 100 mol% catalyst (0.33 mol/l) and with THF as solvent. The reason for these phenomena is probably due to the formation of multinuclear aggregates.[24]

Enatioselective Trimethylsilylcyanation of a variety of aldehydes

We investigated the asymmetric silylcyanation of various aldehydes such as aromatic, α, β-unsaturated and aliphatic aldehydes in the presence of 10 mol% salen 2d and Ti(O^{i}Pr)$_4$. For most of these aldehydes, moderate to high enantioselectivity was observed. The results are listed in Table Ⅴ. Among benzaldehyde derivatives, those of 4-substituents resulted in 74.1-84.0% e.e.. But 2- and 3-substituent benzaldehydes gave 62.1-75.5% e.e.. α, β-Unsaturated aldehydes were silylcyanated to the corresponding α-cyano allylic alcohol in good optical yield (72.1-74.6% e.e.). Aliphatic aldehydes were silylcyanated in 40.6%-77.9% e.e. (but 1-nonanal only in 22.4% e.e.)

Table Ⅴ. Eantioselective Addition of Trimethylsilylcyanide to Aldehydes Catalysed by Salen 2d-Titanium Alkoxide Complex

Entry	Aldehydes	Time/h	Yield %[a]	e.e.%(conf.)[b]
1	Benzaldehyde(**3a**)	24	72	87.1[c](R)
2	4-Chlorobenzaldehyde(**3b**)	36	76	84.0[d](R)
3	3-Chlorobenzaldehyde(**3c**)	36	69	62.1[d](R)
4	2-Chlorobenzaldehyde(**3d**)	22	80	66.0[c](R)
5	4-Methylbenzaldehyde(**3e**)	36	60	82.0[d](R)
6	3-Methylbenzaldehyde(**3f**)	36	69	75.5[d](R)
7	4-Methoxybenzaldehyde(**3g**)	36	68	74.1[d](R)
8	(E)-Cinnamaldehyde(**3h**)	36	73	74.6[d](R)
9	(E)-Crotonaldehyde(**3i**)	36	70	72.0[e](R)
10	1-Nonanal (**3j**)	36	58	22.4[e](R)
11	2-Methylpropionaldehyde(**3k**)	36	61	77.9[e](R)
12	Trimethylacetaldehyde(**3l**)	36	85	73.0[e](R)
13	Cyclohexylcarboxaldehyde(**3m**)	36	86	40.6[e](R)

a. Isolated yield. b. All absolute configuration were determined by comparison of the sign of optical rotation values with those in the literature.[19] c. Determined by GC on CYDEX-β 25 m× 0.22 mm(i.d.) after derivatisation with trifluoroacetic anhydride. d. Determined by HPLC on OD column after derivatisation with acetyl chloride. e. Determined by GC on CYDEX-β 25 m× 0.22 mm(i.d.) after derivatisation with acetyl chloride.

Reaction Mechanism

If aldehydes reacted with trimethylsilylcyanide successfully at low temperature, the carbonyl group had to be activated. [25] In such a six coordinated titanium complex catalyst system, aldehyde and titanium complex maybe form six coordinated cationic transition state to activate the carbonyl group (**Fig.1**).[26]

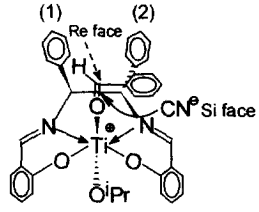
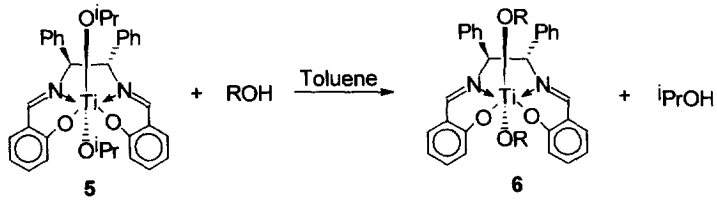


Fig 1

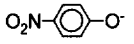
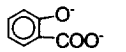
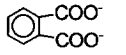
In this transition state (**Fig. 1**), the enantioselectivity would not change, when the $^{-}O^{i}Pr$ was replaced by a counter ion of different steric hindrance and Lewis basicity. So we selected a series of counter ions with different Lewis basicity and steric hindrance to replace the isopropyl group (**scheme 4**), [24a,c] and examined the influence of counter ions on enantioselectivity. The results are summarised in **Table VI**. It is interesting that the enantioselectivity did not depend on the ratio of the counter ions to catalyst and steric hindrance of counter ions. In the mono-Schiff base system, [23, 13b] titanium reagents affected the enantioselectivity drastically. $Ti(O^{i}Pr)_4$ exhibited the highest reactivity and enantioselectivity(85% e.e.), however $Ti(OEt)_4$ and $Ti(O^{t}Bu)_4$ could only induce 43% e.e. and 12% e.e. respectively. But in this salen system, $Ti(O^{n}Bu)_4$ and $Ti(OEt)_4$ both exhibited high reactivity and enantioselectivity (82.6% e.e., 84.5% e.e. respectively) which were almost the same as $Ti(O^{i}Pr)_4$ (87.1% e.e.).

The configuration of cyanohydrins can be predicted according to this reaction intermediate (**Fig.1**). The phenyl group of benzaldehyde was away from phenyl group (1) of salen because of the steric hindrance. [20,26] The cyanide ion arised from the reaction of isopropyloxy ions with trimethylsilylcyanide would attack the Si face with smaller steric hindrance of the activated benzaldehyde leading to cyanohydrin with R configuration.



Scheme 4

Table VI. Effects of Counter Ions on Enantioselectivity of trimethylsilylcyanation of Benzaldehyde[a]

Counter ions (RO^-)	Counter ions/ catalyst	Time/h	Yield %[b]	e.e.%[c](conf.)
α-$C_{10}H_7O^-$	1:1	18	91	82.6 (R)
	2:1	18	90	82.6 (R)
	1:1	18	---	82.6 (R)[d]
	2:1	18	---	82.6 (R)
	1:1	12	78	80.0 (R)
	1:1	12	80	82.4 (R)
$(CH_2CO_2^-)_2$	1:1	12	95	81.8 (R)
EtO^- [e]	2:1	36	75	84.5 (R)
n-BuO^- [e]	2:1	36	70	82.6 (R)

a. The reaction was catalysed by 10 mol% complex **6**. b. Isolated yield. c. Determined by GC on CYDEX-β 25 m× 0.22 mm(i.d.) after derivatisation with trifluoroacetic anhydride. d. Determined by comparison with the retention time in GC analysis. e. The method for preparation of complex **6** was same as described in **Scheme 2**.

In conclusion, asymmetric trimethylsilylcyanation of a variety of aldehydes with the catalyst prepared from Ti(O^iPr)$_4$ and salen (**2d**) without substituents provided a novel and efficient method for synthesis of optically active cyanohydrins. High enantiomeric excess was obtained using 10 mol% titanium-salen (**2d**) as the catalyst. A six coordinated cationic intermediate is proposed for this reaction.

Experimental Section

General: All melting point were uncorrected. ^{1}HNMR were measured at FT-80A and Bruker 300 MHz NMR spectrometer. Elementary analysis data were recorded on Carlo Erba-1106 instrument. GC analysis were performed on SC-7 gas chromography. HPLC analysis were performed on Beckman-110A chromatography with Beckman 165 variable wavelength detector. CYDEX-β 25 m× 0.22 mm(i.d.) capillary column was purchased from SGE company. OD column was purchased from Daicel Chemical Industries, LTD. Catalytic reactions were carried out under pure N_2.

Material: CH_2Cl_2 was distilled from P_2O_5. Toluene and THF were distilled from sodium benzophenone. Ti(O^iPr)$_4$, Ti(OEt)$_4$, Ti(O^nBu)$_4$ were purchased from Aldrich. All aldehydes were purchased from Aldrich, and purified before use.

(1S, 2S)-1, 2-diphenylethylenediamine was prepared according to literature[27] with slight modification. M.p. 82-84℃, $[\alpha]_D^{20}$ = -106.7 (c =1.0, MeOH) [lit., m. p. 82-84℃,; $[\alpha]_D^{20}$= -105.2 (c = 1.0, MeOH).

(1S,2S)-N,N'-bis(3',5'-bis[(tert-Butyl)-2'-hydroxylphenylmethene]-1,2-diphenylethylenediimine (salen 2a): 3,5-Bis(tert-butyl)-2-hydroxylbenzaldehyde was prepared according to the procedure reported by Karhu.[28] A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (500 mg, 2.35 mmol), anhydrous Na_2SO_4 and 3,5-bis(tert-butyl)-2-hydroxylbenzaldehyde(1100 mg, 4.7 mmol) was refluxed for 14 h. The mixture was

filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give 2a (1436 mg, 95%), m.p. 199-200℃; $[\alpha]_D^{20}$ = +32.4 (c = 0.25, $CHCl_3$); IR: 3152, 1625, 1465, 1454, 1442 cm^{-1}. ^{1}HNMR($CDCl_3$) δ 13.61(s, 2H, disappeared with D_2O exchanging), 8.38(s, 2H), 6.95-7.16(m, 14H), 4.70(d, J = 7Hz, 2H), 1.41(s, 18H), 1.21(s, 18H). Anal. Calcd. for $C_{44}H_{56}N_2O_2$: C, 81.94; H, 8.57; N, 4.34. Found: C, 81.73; H, 8.65; N, 4.17.

(1S,2S)-N,N'-bis(3'-diphenylmethyl-5'-methyl-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2b): 3-Diphenylmethyl-5-methyl-2-hydroxylbenzaldehyde was prepared according to the procedure reported by Yamada.[29] A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (110 mg, 0.5 mmol), anhydrous Na_2SO_4 and 3-diphenylmethyl-5-methyl-2-hydroxylbenzaldehyde(300 mg. 1.0 mmol) was refluxed for 14 h. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2b** (335 mg, 91%), m.p. 134-136℃; $[\alpha]_D^{20}$ = +164.4 (c = 1.0, $CHCl_3$); IR: 3189, 1694, 1556, 1456 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 13.27(s, 2H, disappeared with D_2O exchanging), 8.22(s, 2H), 6.73-7.21(m, 34H), 5.97(s, 2H), 4.58(d, J = 8Hz, 2H), 2.12(s, 6H). Anal. Calcd. for $C_{56}H_{48}N_2O_2$: C, 86.12; H, 6.20; N, 3.59. Found: C, 86.31; H, 6.37; N, 3.64.

(1S,2S)-N,N'-bis(3'-methoxy-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2c): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (200 mg, 1.0 mmol), anhydrous Na_2SO_4 and 3-methoxy-2-hydroxylbenzaldehyde (300 mg, 2.0 mmol) was refluxed for 14 h. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2c** (424 mg, 89%), m.p. 89-91℃; $[\alpha]_D^{20}$ = -11.9 (c = 1.0, $CHCl_3$); IR: 3167, 1625, 1463, 1081 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 13.79(s, 2H, disappeared with D_2O exchanging), 8.34(s, 2H), 6.76-7.24(m, 16H), 4.68(d, J = 7Hz, 2H), 3.86(s, 6H). Anal. Calcd. for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83. Found: C, 74.75; H, 5.68; N, 5.74.

(1S,2S)-N,N'-bis(2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2d): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (1060 mg, 5 mmol), anhydrous Na_2SO_4 and 2-hydroxylbenzaldehyde (1220 mg, 10 mmol) was stirred for 12 h at room temperature. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2d** (2037 mg, 97%), m.p. 157-159℃; $[\alpha]_D^{20}$ = -17.1 (c = 1.0, $CHCl_3$); IR: 3250, 1629, 1622, 1540, 1500, 1435 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 13.32(s, 2H, disappeared with D_2O exchanging), 8.30(s. 2H), 6.77-7.29(m, 18H), 4.73(d, J = 9Hz, 2H). Anal. Calcd. for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.85; H, 5.87; N, 6.53.

(1S,2S)-N,N'-bis(5'-nitro-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2e): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (1060 mg, 5 mmol), anhydrous Na_2SO_4 and 5-nitro-2-hydroxylbenzaldehyde (1670 mg, 10 mmol) was refluxed for 24 h. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2e** (2370 mg, 93%), m.p. 150-152℃; $[\alpha]_D^{20}$ = -32.1 (c = 1.0, DMF); IR: 3167, 1633, 1540, 1482, 1462, 1453, 1380, 830 cm^{-1}

^{1}. ^{1}HNMR (DMSO-d_6) δ 14.0(br, s, 2H, disappeared with D_2O exchanging), 8.71(s, 2H), 6.91-8.36(m, 16H), 5.25(d, J = 8Hz, 2H). Anal. Calcd. for $C_{28}H_{22}N_4O_6$: C, 65.88; H, 4.34; N, 10.97. Found: C, 65.93; H, 4.27; N, 10.84.

(1S,2S)-N,N'-bis(5-bromo-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2f): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (1060 mg, 5 mmol), anhydrous Na_2SO_4 and 5-bromo-2-hydroxylbenzaldehyde (2010 mg, 10 mmol) was refluxed for 24 h. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2f** (2715 mg, 94%), m.p. 156-158℃; $[\alpha]_D^{20}$ = +2.2 (c = 1.0, CH_2Cl_2); IR: 3353, 1629, 1474 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 13.34(br, s, 2H, disappeared with D_2O exchanging), 8.17(s, 1H), 8.11(s, 1H), 6.15-7.63(m, 16H), 5.10(d, J = 9Hz, 2H). Anal. Calcd. for $C_{28}H_{22}N_2O_2Br_2$: C, 58.15; H, 3.83; N, 4.84. Found: C, 58.34; H, 3.67; N, 4.91.

(1S,2S)-N,N'-bis(5'-chloro-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2g): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (1060 mg, 5 mmol), anhydrous Na_2SO_4 and 5-chloro-2-hydroxylbenzaldehyde(1565 mg, 10 mmol) was refluxed for 24 h. The mixture was filtered off, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from ethanol to give **2g** (2256 mg, 89%), m.p. 86-88℃; $[\alpha]_D^{20}$ = -12.2 (c = 1.0, CH_2Cl_2); IR: 3248, 1631, 1479, 1468, 1453 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 13.18(br, s, 2H, disappeared with D_2O exchanging), 8.14(s, 2H), 6.81-7.23(m, 16H), 4.74(d, J = 9Hz, 2H). Anal. Calcd. for $C_{28}H_{22}N_2O_2Cl_2$: C, 68.72; H, 4.53; N, 5.72. Found: C, 68.84; H, 4.40; N, 5.83.

(1S,2S)-N,N'-bis(5'-methoxy-2'-hydroxylphenylmethene)-1,2-diphenylethylenediimine (salen 2h): A mixture of methanol, (1S, 2S)-1, 2-diphenylethylenediamine (1060 mg, 5 mmol), anhydrous Na_2SO_4 and 5-methoxy-2-hydroxylbenzaldehyde (1520 mg, 10 mmol) was refluxed for 24 h. The mixture was filtered off, and then the filtrates were evaporated. The residue was chromatographed on silica gel (eluent, petroleum: ether = 3:1) to give red oil **2h** (2256mg, 94%); $[\alpha]_D^{20}$ = +4.9 (c = 4.0, CH_2Cl_2); IR: 3261, 1690, 1633, 1490, 1453, 1160 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 12.83(br, s, 2H, disappeared with D_2O exchanging), 8.25(s, 2H), 6.63-7.26(m, 16H), 4.71(d, J = 9Hz, 2H), 3.71(s, 6H). Anal. Calcd. for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83. Found: C, 75.03; H, 5.64; N, 5.92.

Determination of the enantiomeric excess of cyanohydrin

Method A (for benzaldehyde and 2-chlorobenzaldehyde): To a small portion of pure cyanohydrin (10 mg) was added ethyl acetate (0.35 ml) and trifluoroacetic anhydride (0.40 ml). The mixture was refluxed for 30 min. Then, the solvent and excess trifluoroacetic anhydride were evaporated under reduced pressure at room temperature. Water (0.5 ml) and chloroform (0.3 ml) were added to the residue. The organic layer was isolated and dried over anhydrous Na_2SO_4 which was analysed by GC on CYDEX-β 25 m× 0.22 mm(i.d.).

Method B (for unsaturated aliphatic aldehydes and aromatic aldehydes): To a small portion of pure cyanohydrin (10 mg) was added acetyl chloride(0.5 ml), pyridine (0.1 ml) and chloroform(2 ml). The mixture was stirred at room temperature for 1 h after which it was poured into water (5 ml) and extracted with

chloroform (2× 5 ml). The combined extracts were washed with brine (2× 10 ml), dried over anhydrous Na_2SO_4 and concentrated. Then the residue was chromatographed on silica gel column (eluent, acetyl acetate: petroleum = 1:3) to afford the corresponding cyanchydrin acetyl esters, which were analysed by HPLC on OD column or GC on CYDEX-β 25 m× 0.22 mm(i.d.).

General procedure for trimethylsilylcyanation of benzaldehyde: $Ti(O^iPr)_4$ (0.09 ml, 0.3 mmol) was added to the solution of salen (0.335 mmol) in dichloromethane (3 ml), the mixture was stirred for 2 h at room temperature and then cooled to -78℃, freshly distilled aldehyde (3 mmol) and trimethylsilylcyanide (0.8 ml, 6 mmol) were added. When the reaction was complete (22-36h, monitored by GC), the mixture was poured into 1N HCl (30 ml) and ethyl acetate (60 ml), and stirred for 4 h. The aqueous layer was extracted with ethyl acetate (3× 60 ml). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (eluent, petroleum: ethyl acetate = 4:1) to give the cyanohydrin.

General procedure for trimethylsilylcyanation of benzaldehyde catalysed by complex 6: $Ti(O^iPr)_4$ (0.09 ml, 0.3 mmol) was added to the solution of salen (**2d**) (140.86 mg, 0.335 mmol) in toluene (3 ml), the mixture was stirred for 0.5h at room temperature and then added to 4-nitrophenol (or other analogue, 0.67 mmol). The mixture was stirred for 2h and distilled under vacuum. The freshly distilled CH_2Cl_2 (3 ml), benzaldehyde (0.3 ml, 3 mmol) and trimethylsilylcyanide (0.8 ml, 6 mmol) were added to the mixture. When the reaction was complete (12-36h, monitored by GC), the mixture was poured into 1N HCl (30 ml) and ethyl acetate (60 ml), and stirred for 4 h. The aqueous layer was extracted with ethyl acetate (3× 60 ml). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (eluent, petroleum: ethyl acetate = 4:1) to give 2-hydroxy-2-phenylacetonitrile (4a).

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