Tertiary Pentyl Groups Enhance Salen Titanium Catalyst for Highly Enantioselective Trimethylsilylcyanation of Aldehydes

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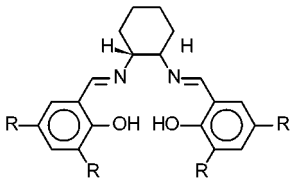
Abstract: *tert*-Pentyl groups are recognized to be highly effective steric groups that can enhance enantioselectivity of salen titanium complexes when they are used in asymmetrical cyanation of aromatic aldehydes. High ee (92−97%) has been obtained with several aldehyde substrates. Compared to its *tert*-butyl analogue, the *tert*-pentyl group has been found to improve enantioselectivity and in some cases quite dramatically.

The enantioselective carbon−carbon formation for chiral cyanohydrins has been the subject of considerable current interest since chiral cyanohydrins are versatile building blocks important to both pharmaceutical and material sciences. They are not only precursors to optically active multifunctional molecules such as amino hydroxyls, hydroxy acids, and amino acids,[1−3] but also excellent chiral dopants for ferroelectric liquid crystals.[4] One attractive approach which uses chiral catalysts,[5−9] particularly Schiff base titanium-based complexes,[10−19] has received great attention upon the emergence of the Jacobsen's catalyst.[20] Despite prosperity, one of the major limitations is generally low enantioselectivity. The use of existing bulky groups such as *tert*-butyl for steric effect has met with only limited success. This is in marked contrast to the significant role played by salen metal complexes in asymmetrical epoxidation[20] and cyanation of imines.[21]



1; R = *t*-Pen

Figure 1. Structure of salen ligands.

The utilization of steric control to achieve high selectivity demands a more effective steric group. The preferred steric groups are those possessing ideal characters of not only steric effectiveness and excellent solubility but also easy availability for facile preparation and cost-effectiveness. In recognition of the design difficulty based on the fact that not all of large steric groups are effective for enantioselectivity,[22] we have screened over a series of salen ligands with a variety of steric groups of different size. Here we wish to report a most effective chiral salen titanium catalyst that achieves generally high enantioselectivity for asymmetrical cyanation where *tert*-pentyl (Pen) groups offer superb steric effect for high enantioselectivity.

We found that a new salen catalyst from **1** (Figure 1, R = *t*-Pen) dramatically enhanced enantioselectivity in asymmetrical cyanation of aromatic aldehydes. The important structural feature of the ligand is to possess bulky *tert*-pentyl groups at 3- and 5-positions on the salen aromatic rings. The new catalyst is formed in situ by the reaction of **1** with titanium isopropoxide in methylene dichloride. To our surprise, the use of only 5 mol % of the catalyst in the cyanation of benzaldehyde with trimethylsilyl cyanide gave mandelonitrile with 97% ee. This significant result revealed that the high enantioselectivity offered by the catalyst appears to be general for its analogues as well. The 92−95% ee has been obtained when the reaction utilizes benzaldehyde derivatives that contain alkyl groups ranging from methyl to *tert*-butyl, suggesting that the size of the substituents does not affect enantioselectivity. When halogen-substituted benzaldehydes are used, the ee has been found to be even higher (96−97%). In addition to benzaldehyde and its analogues, the catalyst was also found to give high ee (>97%) for the reaction with 2-naphthaldehyde. Overall, the generally high enantioselectivity of 92−97% has been obtained with the use of 5% mol of the catalyst (Scheme 1 and Table 1).

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Scheme 1

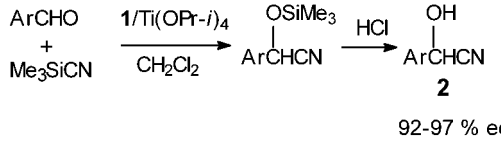

Table 1. Yields and Enantioselectivity Results from the Reaction of Trimethylsilyl Cyanide with Different Aldehydes

entry	aldehyde substrates	product yields, %	ee (%)[a]	config[b]
1	PhCHO	**2a**: 92	97	(*S*)
2	3-MeC_6H_4CHO	**2b**: 85	92	(*S*)
3	4-MeC_6H_4CHO	**2c**: 96	94	(*S*)
4	4-EtC_6H_4CHO	**2d**: 84	94	(*S*)
5	4-i-PrC_6H_4CHO	**2e**: 93	93	(*S*)
6	4-t-BuC_6H_4CHO	**2f**: 94	95	(*S*)
7	4-ClC_6H_4CHO	**2g**: 89	97	(*S*)
8	3-ClC_6H_4CHO	**2h**: 87	97	(*S*)
9	4-FC_6H_4CHO	**2i**: 92	96	(*S*)
10	2-naphthaldehyde	**2j**: 93	>97	(*S*)

[a] Determined by G-TA capillary column (0.25 mm × 20 m) on the TFA ester unless indicated otherwise. [b] Comparison of optical rotation with those reported in the literature.[6,10,14,29]

The current titanium complex proved to be the most effective salen catalyst, which leads to much higher enantioselectivity than any other known Schiff base counterparts. The previous best result from a tetradentate Schiff base−titanium complex (10 mol %) gave 87% ee for the cyanation of benzaldehyde.[14] The previous best results for the cyanation of 3- and 4-chlorobenzaldehyde were 62% ee and 84% ee,[14] respectively. In marked contrast, the present catalyst (5 mol %) gave 97% ee in all three cases.

Equally significant is the fact that the current system exceeds or matches the best known catalytic metal complex systems. Cyanation of benzaldehyde has been examined with a variety of catalytic metal complex systems[5,6,23] and noncatalytic metal complex systems.[10,24,25] The previous best result from a binaphthol-based aluminum complex catalyst is 96% ee.[26] Moreover, the cyanation of 2-naphthaldehyde using existing catalysts usually gives the ee in the range of 73−90%,[10,13,27] and barely above 90%.[5] A previous best Schiff base titanium complex only gave 73% ee.[11] An amide−titanium complex gave 96% ee.[5]

It is surprising that the present catalyst has led to strikingly different results from those by the *tert*-butyl analogue. A survey of the catalytic reactivity of the in-situ-prepared catalyst from **3** (Figure 1, R = *t*-Bu)/titanium isopropoxide found that the reaction of benzaldehyde with trimethylsilyl cyanide gave only 72% ee,[11] compared with 97% ee from the present catalyst. The similar dramatic difference has also been found from benzaldehyde derivatives. For example, enantioselectivity for the cyanation of 4-methylbenzaldehyde is 88% by **3**/titanium isopropoxide,[11] but 94% ee by the current system. Furthermore, Belokon and North et al. also disclosed that the in-situ-prepared salen titanium complex catalysts such as **3**/titanium isopropoxide had low activity and gave low ee. A large amount of catalyst (20 mol %) and extended reaction time (100−200 h) as well as −80 °C were needed. The isolated catalyst from **3**/titanium isopropoxide improved the enantioselectivity to 86% ee upon application to benzaldehyde.[15]

Table 2. Temperature Effect on the Enantioselectivity of Cyanohydrin from the Reaction of Trimethylsilyl Cyanide with Benzaldehyde in the Presence of the Catalyst

run	*T* (°C)	ee (%)
1	20	56
2	−10	90
3	−40	95
4	−78	97

High enantioselectivity can be obtained at various temperatures, not necessary at −78 °C. The reaction of benzaldehyde with trimethylsilyl cyanide has been investigated in four different temperatures (Table 2). Although low temperature generally improves the ee, the reaction at −10 °C already affords 90% ee. The reaction at −40 °C leads to 95% ee.

In summary, a highly efficient Schiff base titanium complex catalyst has been developed. The catalyst was formed in situ from a salen ligand with *tert*-pentyl groups with titanium isopropoxide with no need of tedious isolation. The steric effect from *tert*-pentyl groups is the key to high enantioselectivity. The facile and inexpensive synthesis of ligand and complex has offered a great advantage over other catalyst systems. The high enantioselectivity achieved by this catalyst exceeds or matches the best known catalysts.

Experimental Section

General. All the reactions were manipulated in nitrogen atmosphere. Dry solvents used in the reactions were obtained in the following treatments: methylene chloride was distilled from CaH_2 and so was toluene. Ethanol was dried over 4 Å molecular sieves and directly used without distillation. The enantiomeric excess was determined on a GC with a G-TA capillary column (0.25 mm × 20 m) of the TFA ester of the cyanohydrins. Optical rotation was determined in a digital polarimeter with a sodium lamp. The combustion analysis was performed by Atlantic Microlab, Norcross, GA.

Preparation of 3,5-Di-*tert*-pentylsalicylaldehyde. In dry toluene (40 mL) and under nitrogen atmosphere, 0.555 g (2.13 mmol) of tin(IV) chloride,[28] 0.913 g (8.52 mmol) of 2,6-lutidine, 5.000 g (21.33 mmol) of 2,4-di-*tert*-pentylphenol were stirred at room temperature for 30 min. Paraformaldehyde (1.620 g, 54 mmol) was added, and the reaction mixture was refluxed at 80 °C for 8 h. Water (150 mL) was added, and the solution was acidified to pH 2 with 1 M HCl. The solution was extracted with diethyl ether and washed several times with brine water. The organic layer was dried with anhydrous $MgSO_4$ and evaporated. The residue was purified with silica gel using hexane:EtOAc (4:1 v/v) to give 3,5-di-*tert*-pentylsalicylaldehyde (3.27 g, 58%). IR (neat) ν_{max} 3421.50 (br, OH), 1651.00 (m, C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.64 (1H, s), 9.87 (1H, s), 7.47 (1H, d, J = 2.10 Hz), 7.30 (1H, d, J = 2.10), 1.90 (2H, q, J = 7.5 Hz), 1.63 (2H, q, J = 7.44 Hz), 1.38 (6H, s), 1.30 (6H, s), 0.63−0.72 (6H, 2t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.87, 159.50, 140.10, 136.19, 134.34, 129.32, 120.39, 39.03, 37.99, 37.38, 28.76, 28.04, 9.95, 9.56.

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Salen Schiff Base Ligand 1. In dry ethanol (10 mL), 1.50 g (5.72 mmol) of 3,5-di-*tert*-pentylsalicylaldehyde and 0.360 g (3.14 mmol) of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane were stirred under nitrogen atmosphere at room temperature for 8 h. The ethanol was reduced and cooled in an ice bath. The solid Schiff base was filtered and washed with cold ethanol. The yellow product was purified by recrystallization in hexane to afford salen Schiff base ligand **1** (1.53 g, 89%). IR (KBr) ν_{max} 1629.8 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.53 (br s, 2H), 8.17 (s, 2H), 7.08 (d, J = 2.4 Hz, 2H), 6.80 (d, J = 2.4 Hz, 2H), 3.20−3.23 (m, 2H), 1.88−1.92 (m, 2H), 1.75−1.86 (m, 6H), 1.44 (m, 8H), 1.27 (s, 12H), 1.10 (s, 12H), 0.55 (t, J = 7.40 Hz, 6H), 0.52 (t, J = 7.42 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.40, 158.34, 138.36, 134.99, 129.05, 127.16, 118.08, 72.92, 39.05, 37.52, 37.20, 33.57, 33.11, 28.86, 28.70, 27.84, 27.79, 24.74, 9.86, 9.47. Anal. Calcd for $C_{40}H_{62}N_2O_2$ C: 79.68, H: 10.37, N: 4.64. Found: C: 79.50, H: 10.31, N: 4.59.

A Typical Procedure for Cyanation of Benzaldehyde. Schiff base ligand **1** (15 mg, 0.0248 mmol), $Ti(iOPr)_4$ (7 mg, 0.0246 mmol), and 2 mL of dry CH_2Cl_2 were added to a 50 mL round-bottom flask and were stirred at room temperature for 1 h. The solvent was then evaporated under vacuum, and 1 mL of freshly dried CH_2Cl_2 was added and evaporated under vacuum again. A 1 mL amount of freshly dried CH_2Cl_2 and 53 mg (0.5 mmol) of benzaldehyde were added. The reaction mixture was cooled to −78 °C, and 100 mg (1.0 mmol) of Me_3SiCN in 1 mL of dry CH_2Cl_2 was added dropwise to the reaction flask. The reaction was stirred for 12 h at −78 °C and then allowed to rise to room temperature for 6 h. The reaction mixture was purified through silica gel with 4:1 hexane:EtOAc solvent. The solvent was evaporated, and 10 mL of CH_2Cl_2 was added to the residue along with 10 mL of 1 N HCl. The resulting mixture was stirred at room-temperature overnight to yield the cyanohydrin. The organic layer was washed several times with water and then dried with Na_2SO_4. The cyanohydrin was then further purified with silica gel using 10:1 (v/v) hexane:EtOAc as the solvent.

Derivatization of Cyanohydrins. In methylene chloride, 10 mg of cyanohydrin was allowed to react with an excess of trifluoroacetic anhydride for 1 h. The solution was cooled in an ice bath, and an aqueous solution of 5% sodium bicarbonate was added dropwise until the solution was neutralized. The organic layer was separated and washed several times with water and dried with anhydrous sodium sulfate. The organic layer was then analyzed by GC.

(*S*)-(−)-Mandelonitrile 2a. The TFA ester of mandelonitrile was compared to converted TFA ester of commercial (*R*)-(+)-mandelonitrile. IR (neat) ν_{max} 3417.7 (OH), 2248.9 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (br, 1H), 5.44 (s, 1H), 7.34−7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.01, 119.26, 127.07, 129.61, 130.25, 135.69.

(−)-3-Methyl-α-hydroxyphenylacetonitrile 2b.[29] Colorless oil, $[\alpha]^{22}_D$ −41.3 (c = 0.5, $CHCl_3$); IR (neat) ν_{max} 3423.4 (OH), 2248.9 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.28 (s, 1H), 5.27 (s, 1H), 7.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.23, 62.22, 118.16, 122.68, 126.24, 127.95, 129.39, 134.14, 137.99. MS of TFA ester: 243 (M^+).

(−)-4-Methyl-α-hydroxyphenylacetonitrile 2c.[29] Colorless oil, $[\alpha]^{22}_D$ −48.5 (c = 0.5, $CHCl_3$); IR (neat) ν_{max} 3415.7 (OH), 2246.9 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.58 (s, 1H), 5.42 (s, 1H), 7.18 (d, J = 7.79 Hz, 2H), 7.34 (d, J = 8.09 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.67, 63.95, 119.32, 127.10, 130.27, 132.81, 140.45. MS of TFA ester: 243 (M^+).

(−)-4-Ethyl-α-hydroxyphenylacetonitrile 2d. Colorless oil, $[\alpha]^{22}_D$ −15.6 (c = 0.9, $CHCl_3$); IR (neat) ν_{max} 3423.45 (OH), 2248.87 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J = 7.61 Hz, 3H), 2.60 (q, J = 7.60 Hz, 2H), 2.81(s, 1H), δ5.40 (d, J = 6.74 Hz, 1H), 7.19 (d, 2H), 7.35 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.80, 29.01, 64.07, 119.17, 127.18, 129.15, 133.06, 146.82. MS of TFA ester: 257 (M^+).

(−)-4-Isopropyl-α-hydroxyphenylacetonitrile 2e.[29] Colorless oil, $[\alpha]^{22}_D$ −51.5 (c = 1.0, $CHCl_3$); IR (neat) ν_{max} 3425.38 (OH), 2250.80 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.84 Hz, 6H), 2.85 (m, J = 6.92 Hz, 1H), 2.89 (s, 1H), 5.40 (d, J = 6.6 Hz, 1H), 7.22 (d, J = 8.19 Hz, 2H), 7.36 (d, J = 8.16 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.24, 34.35, 119.3, 127.21, 127.72, 133.15, 151.38. MS of TFA ester: 271 (M^+).

(−)-4-*tert*-Butyl-α-hydroxyphenylacetonitrile 2f. Colorless oil, $[\alpha]^{22}_D$ −25.0 (c = 0.8, $CHCl_3$); IR (neat) ν_{max} 3421.5 (OH) 2248.9 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.88 (s, 1H), 5.42 (s, 1H), 7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.63, 35.18, 63.75, 119.46, 126.55, 126.94, 132.79, 153.54. MS of TFA ester: 285 (M^+).

(−)-4-Chloro-α-hydroxyphenylacetonitrile 2g.[29] Colorless oil, $[\alpha]^{22}_D$ −39.4 (c = 0.5, $CHCl_3$); IR (neat) ν_{max} 3417.66 (OH), 2250.80 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (s, 1H), 5.45 (s, 1H), 7.37 (d, 2H), 7.34 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.33, 118.87, 128.44, 129.84, 134.04, 136.37. MS of TFA ester: 263 (M^+).

(−)-3-Chloro-α-hydroxyphenylacetonitrile 2h.[29] Colorless oil, $[\alpha]^{22}_D$ −54.4 (c = 0.8, $CHCl_3$); IR (neat) ν_{max} 3504.5 (OH), 2239.2 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 1H), 5.46 (s, 1H), 7.33 (m, 3H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 63.20, 118.73, 125.04, 127.17, 130.39, 130.85, 135.55, 137.34. MS of TFA ester: 263 (M^+).

(−)-4-Fluoro-α-hydroxyphenylacetonitrile 2i. Colorless oil, $[\alpha]^{22}_D$ −36.4 (c = 0.8, $CHCl_3$); IR (neat) ν_{max} 3417.7 (OH), 2250.8 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (d, J = 6.74 Hz, 1H), 5.46 (d, J = 6.63 Hz, 1H), 7.06 (m, 2H), 7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.26, 116.54, 116.76, 119.14, 129.10, 131.51, 162.59, 165.07. MS of TFA ester: 247 (M^+).

(−)-2-(α-Hydroxyacetonitrile)naphthalene 2j.[29] Light yellow solid, $[\alpha]^{22}_D$ −14.5 (c = 1.0, $CHCl_3$); IR (neat) ν_{max} 3469.74 (OH), 2243.08 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (d, J = 6.83 Hz, 1H), 5.63 (d, J = 6.50 Hz, 1H), 7.49 (m, 3H), 7.83 (m, 3H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.37, 119.02, 124.04, 126.65, 127.43, 127.71, 128.23, 128.75, 129.86, 132.85, 133.38, 134.15. MS of TFA ester: 279 (M^+).

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