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Asymmetric Synthesis XXII:Asymmetric Catalytic Trimethylsilylcyanation of Benzaldehyde by Novel Ti(IV)-Chiral Schiff Base Complexes*

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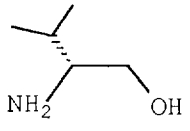
Abstract: Benzaldehyde has been trimethylsilylcyanated with a catalyst prepared in situ from titanium tetraisopropoxide and a novel chiral Schiff base. Both (R) and (S) cyanohydrins are obtained in moderate e.e. values.

Enantiomerically pure cyanohydrins are very versatile synthons for the preparation of a variety of valuable synthetic intermediates and can be prepared by many biological and chemical methods[1-4]. Recently, Oguni and co-workers reported a novel and efficient procedure for the highly enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by chiral Schiff base-titanium alkoxide complexes[5]. The chiral source **1** they used was derived from natural L-amino acids, and (R)-cyanohydrins were easily obtained.



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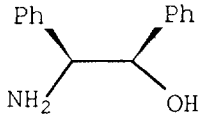
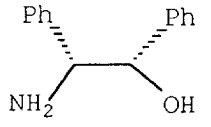
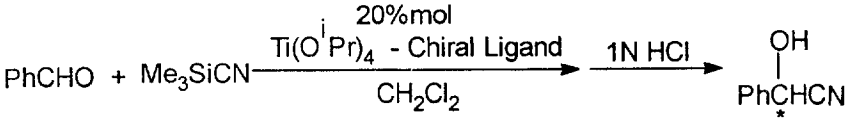


2 (1R,2S)



3 (1S,2R)

Herein we describe novel Schiff bases derived from 2-amino-1,2-diphenylethanols **2** and **3** as chiral ligands in the catalytic trimethylsilylcyanation of benzaldehyde . We have successfully used such amino alcohols in the catalytic addition of diethylzinc to benzaldehyde[6] and in catalytic hydroboronation with high e.e. values[7].



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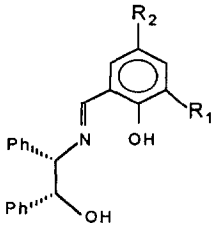
Choosing such amino alcohols as chiral sources is based on two reasons: (1) Both (1R,2S) and (1S,2R) 2-amino-1,2-diphenylethanols are easily obtained. (2) These amino alcohols have two stereogenic centers, and both may be helpful to increase the e.e. values.

The results are summarized in Table 1. From the table, The enantioselectivity of the reaction was increased by low reaction temperatures and bulky R_1 groups of Schiff base **4** . On the other hand, the chiral Schiff bases were destroyed by addition of 1N HCl. In order to recycle the ligand, we prepared ligand **5**, but although ligand **5** was easily recovered, the e.e. value was not satisfactory.(See Entry 9)



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Schiff base	R_1	R_2
4a	H	H
4b	Bu^t	Bu^t
4c	$CHPh_2$	CH_3
4d	OCH_3	H

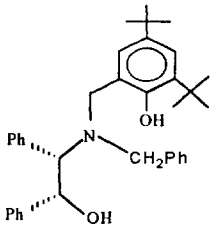

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Table 1 Enantioselective trimethylsilylcyanation of benzaldehyde

Entry	Ligands	Temp.(° C)	Time (hr)	C.Y(%)[a]	G.C. E.e(%)[b]	O.P (%)[c]	Config.
1	**4a**	0	20	94.8	0	0	-
2	**4a**	-80	60	87.8	25.7	28.5	S
3	**4b**(1R,2S)	15	48	92.3	13.5	-	S
4	**4b**(1R,2S)	0	48	95.5	39.4	-	S
5	**4b**(1R,2S)	-80	60	85.3	53.2	56.0	S
6	**4b**(1S,2R)	-80	60	84.0	49.8	52.3	R
7	**4c**	-80	60	82.0	9.4	-	S
8	**4d**	-80	60	88.4	8.5	-	S
9	**5**	-80	60	88.2	30.6	28.6	S

a) Isolated yield b)determined by chiral GC after derivatisation with TPC(N-Trifluoroacetyl-S-(-)-Prolyl Chloride) c)determined by the comparison of the specific rotation values $[\alpha]_D^{20}$= +43.5 (c=0.2, $CHCl_3$) for the (R)-cyanodrin[5].

By using ligand **4b**, we found that increased amounts of catalyst were essential to obtain good enantioselectivity.(Table 2) This result was quite different from that of Oguni, who found that the use of an equimolar amount of chiral titanium complex caused a decrease in enantioselectivity[9].

Table 2 Effect of different amount of catalyst (Schiff base **4b**-Ti)

Amount of Catalyst(%)	C.Y(%)	E.e(%) (Config.)
20	85.3	53.2(S)
40	92.8	68.3(S)
100	97.0	80.0(S)

Furthermore, the enantioselectivity of the reaction was influenced considerably by the central metal. Although Schiff base **4b**-Zn(II) and Schiff base **4b**-Mg(II) catalyze the reaction effectively, the e.e. values were only 5.6%(S) and 4.0%(S) e.e. respectively.

In conclusion,the enantioselectivity of the reaction was sensitive to the ligand structure, reaction temperature, central metal and amount of catalyst. Further investigation to improve the enantioselectivity is in progress.

Experimental Section

All melting points were uncorrected. ^{1}HNMR were measured at 80 MHz. IR spectra were recorded on a Micro Lab 620 MX instrument. Element analysis data were recorded on Carlo Erba-1106 instrument. Kieselgel GF_{254} glass plate were used for TLC. All solvents were distilled before use. GC analyses were performed on a SC-7 gas chromatograph with a 20mX0.25mm column of chirasil-L-Val.

(1R,2S)-2-(N-salicylideneamino)-1,2-diphenyl-1-ethanol **(4a)**: A mixture of methanol, (1R,2S)-1,2-diphenyl-2-amino-ethanol, 2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 48hrs. After evaporation yellow solid was recrystallized from ethanol to give **4a**. Yield: 97%. m.p. 125.6-126.0°C; $[\alpha]_D^{20}$= -17 (c=0.6, $CHCl_3$); IR(cm^{-1}): 3420, 1630, 1500, 1450. ^{1}HNMR($CDCl_3$): δ 4.4(d, 1H, J=7.0Hz), 5.0(d, 1H, J=7.0Hz), 7.25(d, 10H, J=8.2Hz), 8.0(s, 1H). Anal. calcd. for $C_{21}H_{19}NO_2$: C,79.49; H, 5.99; N, 4.42. Found: C,79.08; H,6.13; N, 4.37.

(1R,2S)-2-[N-(3',5'-ditert-Butylsalicylidene)amino]-1,2-diphenyl-1-ethanol **(4b)**: 3,5-ditert-butyl-2-hydroxybenzaldehyde was prepared according to the procedure reported by Karhu[10]. A mixture of methanol, (1R,2S)-1,2-diphenyl-2-amino-ethanol, 3,5-ditert-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 60hrs. After evaporation the yellow solide **4b** was obtained by column chromatography. Yield: 77%. m.p. 67-68°C; IR(cm^{-1}): 3400, 2950, 1630, 1600, 1450, 1390. ^{1}HNMR($CDCl_3$): δ 1.2(s,9H), 1.4(s,9H), 3.4(q,1H, J=7.8Hz), 4.4(d,1H, J=6.0Hz), 4.9(d, 1H, 6.0Hz), 7.15(m, 12H), 8.05(s, 1H). Anal. calcd. for $C_{28}H_{35}NO_2$: C,81.11; H, 8.16; N, 3.26. Found: C,80.96; H,8.22; N,3.00.

(1R,2S)-2-[N-(3'-diphenylmethyl-5'-methylsalicylidene)amino]-1,2-diphenyl-1-ethanol **(4c)** 3-diphenylmethyl-5-methyl-2-hydroxybenzaldehyde was prepared according to the procedure reported by Yamada[11]. A mixture of methanol, (1R,2S)-1,2-diphenyl-2-amino-ethanol, 3-diphenylmethyl-5-methyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 48hrs. After evaporation the yellow solide **4c** was obtained by column chromatography. Yield: 80%. $[\alpha]_D^{20}$= -12 (c=0.4, $CHCl_3$); IR(cm^{-1}): 3420, 1630, 1600, 1490, 1450, 760. ^{1}HNMR($CDCl_3$): δ 2.05(s,3H), 4.35(d,1H, J=7.2Hz), 4.9(q,1H, J=7.2Hz), 5.9(d,1H, J=7.2Hz), 5.9(s, 1H), 7.15(m, 12H), 7.95(s, 1H).

(1R,2S)-2-(N-3'-methoxylsalicylideneamino)-1,2-diphenyl-1-ethanol **(4d)**: A mixture of methanol, (1R,2S)-1,2-diphenyl-2-amino-ethanol, 3-methoxyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 48hrs. After evaporation yellow solid was recrystallized from ethanol to give **4d**. Yield: 86%.

$[\alpha]_D^{20}$= -1.43 (c=1.42, $CHCl_3$); IR(cm^{-1}): 3430, 3230, 1630, 1500, 1450. ^{1}HNMR($CDCl_3$): δ 2.0(s, 1H), 3.85(s, 3H), 4.35(d, 1H, J=7.4Hz), 4.95(d, 1H, J=7.4Hz), 7.25(m, 13H), 7.95(s,1H) Anal. calcd. for $C_{22}H_{21}NO_3$: C,79.28; H, 6.30; N, 4.15 Found: C,79.82; H,5.94; N, 4.15.

(1R,2S)-2-[N-phenylmethyl-N-(3',5'-ditertbutylsalicylideneamin)-1,2-diphenylethanol **5** : 3,5-ditertbutyl-2-hydroxyphenyl-methanol (1g, 4.23mmol) was added to the stirred solution of 4-nitrobenzoyl-chloride (0.73g, 3.94mmol) in dichloromethane, then add 0.5ml pyridine. Stirring of the mixture was continued for 45 minutes at room temperature. After filtration, the percipitate was added to (1R,2S)-N-benzylamino-1,2-diphenyl-1-ethanol (0.43g, 1.42mmol) in the solvent of 20ml THF, reflux for 30hrs, colorless solide was obtained after column chromatography. Yield: 47%. $[\alpha]_D^{20}$= +34.7 (c=1.15, $CHCl_3$); IR(cm^{-1}): 3600, 2980, 1600, 1500, 1450, 1390. Anal. calcd. for $C_{36}H_{45}NO_2$: C, 82.60; H, 8.60; N, 2.67 Found: C,83.05; H,8.80; N, 2.97.

General procedure for the trimethylsilylcyanation of benzaldehyde: To a solution of Schiff base **4b** (172mg, 0.4mmol) in dichloromethane (2ml) was added $Ti(OPr^i)_4$ (104mg, 0.36mmol) and stirred for 2h at room temperature. The reaction mixture was cooled to -80°C, freshly distilled benzaldehyde (0.2ml, 2mmol) and then trimethylsilyl cyanide (450mg, 4.56mmol) were added. After stirring for 60h at this temperature, the mixture was poured into a mixture of 1N HCl (30ml) and ethyl acetate (60ml) and stirred for 6h at room temperature. The usual extractive work-up and silica gel colum chromatography of the residue gave (S)-cyanohydrin (227mg, 85.3%). IR(cm^{-1}): 3400, 2200, 1500, 1450, 1400. ^{1}HNMR($CDCl_3$): δ 3.35(S, 1H), 5.35(S,1H), 7.3(S,5H). Anal. calcd. for C_8H_7NO: C,72.18; H, 5.26; N, 10.52. Found: C, 71.52; H, 5.13; N, 10.40.

Procedure for the derivation of cyanohydrin: Add 2ml of 0.2M TPC to 10ul 0f cyanohydrin, and then 0.1ml pyridine was added, sealed after 10 hrs. Washed by water, organic layer was dried by anhydrous Na_2SO_4. Enantiomers of cyanohydrins were separated on SC-7 gas chromatograph with a 20mX0.25mm Chirasil-L-Val capillary column[12]. Carrier gas was nitrogen. Enantiomers of cyanohydrins were separated to and near to base line. The t_R of (S)-(-)-isomer: 7.66min; t_R of (R)-(+)-isomer: 8.00min.

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