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ASYMMETRIC TRIMETHYLSILYL-CYANATION OF ALDEHYDES CATALYZED BY CHIRAL SCHIFF BASE-Ti(OⁱPr)₄ COMPLEX

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ABSTRACT

A new chiral Schiff base **4** was synthesized, which was found to be efficient catalyst for the enantioselective silylcyanation of aldehydes. The enantioselectivities of 25.1-72.7% were obtained by using the chiral Schiff base-Ti(OⁱPr)₄ complex.

Enantiomerically pure cyanohydrins are important synthetic intermediates in the synthesis of other chiral compounds and can be prepared by many biological and chemical methods.^{1–3} Recently, Oguni,⁴ Jiang Yaozhong⁵ and North⁶ reported asymmetric trimethylsilylcyanation of aldehydes catalyzed by chiral Schiff base-titanium alkoxide complexes. The chiral source compounds they used derived from chiral compounds **1**, **2** and **3**, respectively. In their papers, the corresponding cyanohydrins have been

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obtained in good chemical yields with moderate to excellent enantiomeric excesses, when $20 \mod \%$ chiral Schiff base and $20 \mod \%$ Ti(OⁱPr)₄ were used.

Because D-camphor is easily obtained and has good stereogenic center, chiral Schiff base **4** was synthesized from it and used in the trimethylcyanation of aldehydes. The results are summarized in Table 1.

From the table, the enantioselectivity of the reaction was affected by the reaction temperature and the amounts of catalyst. The highest enantioselectivity of 66.1% was obtained, when the amounts of catalyst was 22 mol% and the Ti(OⁱPr)₄ was 20 mol%. But when the amounts of catalyst was increased up to 55 mol%, the enantioselectivity of cyanohydrin was decreased, this was in accordance with Jiang's results.⁷



Scheme 1.

At last, the trimethylsilylcyanation of several other aromatic aldehydes proceeded smoothly in the amounts of 22 mol% of Schiff base **4** and 20 mol% of Ti(OⁱPr)₄, in which the product 2-hydroxy-*p*-methoxylphenylacetonitrile was obtained in 72.7% e.e. (Table 2, entry 1). Moreover, the results showed that good enantiomeric excesses were obtained with electronrich aromatic aldehydes, while electron-deficient aromatic aldehyde gave lower enantiomeric excesses. Further investigation to improve the enantioselectivity is still in progress.

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TRIMETHYLSILYLCYANATION OF ALDEHYDES

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Table 1. Enantioselective Addition of Trimethylsilylcyano to Benzaldehyde in Presence of **4**

Entry	Cat. (mol%)	Ti(O ⁱ Pr) ₄ (mol%)	Temp. (°C)	C.Y. (%) ^a	Ee (%) ^b	$\begin{matrix} [\alpha]_{\rm D} \\ (c \ 1, \ CHCl_3) \end{matrix}$	Ee (%) ^c
1	11	10	20	100		+11.3	25.1
2	11	10	0	97		+20.5	45.6
3	5.5	5	$-35 \sim -45$	94		+13.7	30.4
4	11	10	$-35 \sim -45$	97		+24.9	55.4
5	22	20	$-35 \sim -45$	97	66.1	+31.4	70
6	55	50	$-35 \sim -45$	94	47.8	+19.5	43.4
7	20	10	$-35 \sim -45$	94		+25.9	57.4
8	22	20	-78	No reaction	_	_	_

^aIsolated yield; ^bDetermined by chiral GC after derivation with acetic acid anhydride; ^cDetermined by the comparison of specific rotation values $[\alpha]_D^{20} = +45$ (c 1, CHCl₃)⁸.

Table 2. Enantioselective Addition of Trimethylsilylcyano to Aromatic Aldehydes in Presence of **4**

Entry	Compd.	Temp. (°C)	C.Y. (%) ^a	Ee (%)	$\begin{matrix} [\alpha]_{\rm D} \\ (c \ 1, \ CHCl_3) \end{matrix}$	Ee (%) ^c
1 2 3 4	<i>p</i> -CH ₃ OPhCHO <i>p</i> -ClPhCHO <i>p</i> -CH ₃ PhCHO <i>o</i> -CH ₃ OPhCHO	$ \begin{array}{r} -35 \sim -45 \\ -35 \sim -45 \\ -35 \sim -45 \\ -35 \sim -45 \\ -35 \sim -45 \end{array} $	89 92.5 92 92	30.0 ^b	+36 +13.5 +33.3 +19.4	72.7° 32.8° 65 ^f 71.7 ^g

^aIsolated yield; ^bDetermined by chiral GC after derivation with acetic acid anhydride. ^cDetermined by the comparison of specific rotation values; ${}^{d}[\alpha]_{D}^{25} = +49$ (c 1, CHCl₃) with e.e. > 99%; ⁸ ${}^{e}[\alpha]_{D}^{25} = +27.2$ (c 1.487, CHCl₃) with e.e. = 66%; ⁹ ${}^{f}[\alpha]_{D}^{25} = +47.4$ (c 1.822, CHCl₃) with e.e. = 92%; ⁹ ${}^{g}[\alpha]_{D}^{20} = -21.0$ (c 1.25, CHCl₃) with e.e. = 77%.¹

EXPERIMENTAL

¹H NMR were recorded in CDCl₃ as solvent on AC-P200 instruments using TMS as internal standard. Elemental analyses were conducted on MF-3 automatic analyzer. Melting points were determined on MP-500 melting point apparatus. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter. All temperatures were uncorrected.



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Preparation of (+)-Cis-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic Acid 6¹⁰

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A mixture of D-camphor 19.00 g (0.125 mol), FeSO₄·7H₂O 1.00 g (0.0036 mol), 85 mL H₂O and 180 mL HNO₃ (65–68%) was refluxed at 100–105°C for 30 h, then the resulting solution was cooled to room temperature. The white solid deposited was filtered, washing with H₂O(2 × 10 mL), afforded the desired product **6** 12.24 g, yield: 48.9%, m.p. 202–205°C, $[\alpha]_D^{25} = +44.5(c = 10, EtOH)$. (Lit.: Yield: 53.5%, m.p.: 204–205°C).

Preparation of (+)-Cis-1,2,2-trimethyl-1,3-diaminocyclopentane 5¹¹

A mixture of **6** 20.30 g (0.1 mol), CHCl₃ (200 mL) and H₂SO₄ (60 mL) was stirred at 55–60°C with NaN₃ 18.60 g (0.286 mol) added at intervals, reacting until no gas formed. The resulting solution was cooled to room temperature and adjusted to pH > 14 with saturated NaOH. The solution was deposited overnight and filtered, washing with CHCl₃ (2 × 30 mL). The organic layer was separated and the aqueous layer was extracted with CHCl₃ (2 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, then the solvent was removed *in vacuo* to give the crude product **5** 12.23 g. Yield: 86.13%. Because the crude product **5** is difficult to purify, it was used straightly in the next step.

Preparation of Catalyst 4

A mixture of toluene (40 mL), 2-hydroxylbenzaldehyde (2.44 g, 20 mmol), **5** (1.42 g, 10 mmol), *p*-toluenesulfonic acid (0.01 g) was refluxed for 2 h. After evaporation yellow solid was recrystallized from ethyl acetate to give **4** 2.80 g. Yield: 80%. m.p. 159–161°C; $[\alpha]_D^{25} = +34.0$ (c = 2, CHCl₃); ¹H NMR (δ , ppm): 0.95 (s, 3H), 0.97 (s, 3H), 1.36 (s, 3H), 2.15 (m, 4H), 3.71 (t, 1H), 7.11 (m, 8H), 8.45 (s, 2H). Anal. calcd. for C₂₂H₂₆N₂O₂: C, 75.36; H, 7.49; N, 7.99. Found: C, 75.15; H, 7.50; N, 7.88.

Typical Procedure for the Trimethylsilylcyanation of Aldehydes

To a solution of Schiff base 4 (154 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added $Ti(O^iPr)_4$ (114 mg, 0.4 mmol) and stirred for 1 h at room temperature. The reaction mixture was cooled to $-35 \sim -45^{\circ}C$, then freshly

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TRIMETHYLSILYLCYANATION OF ALDEHYDES

distilled benzaldehyde (212 mg, 2 mmol) and trimethylsilyl cyanide (400 mg, 4 mmol) were added. After stirring for 12 h at this temperature, the mixture was poured into a mixture of 1 N HCl (30 mL) and ethyl acetate (60 mL) and stirred for 4 h at room temperature, washing the organic layer with distilled water and saturated NaHCO₃ (each 20 mL), drying with anhydrous sodium sulfate and concentrating the reaction mixture followed by column chromatography (eluent: petroleum ether/ethyl acetate: 5/1) yielded the expected (S)-cyanohydrin (260 mg, 97.7%). After measuring the optical rotation of the pure cyanohydrin, the compound was converted directly into the corresponding acetates by reaction with two equivalents of acetic acid anhydride and pyridine in CH_2Cl_2 (20 mL) at room temperature for 12 h, washing the organic layer with 5% H₂SO₄, distilled water and saturated NaHCO₃ (each 20 mL), drying with anhydrous sodium sulfate and concentrating the reaction mixture followed by column chromatography (eluent: petroleum ether/ ethyl acetate: 5/1) yielded the acetylated cyanohydrin, which was used for further analysis.

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