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TETRAHEDRON: *ASYMMETRY*

# Synthesis of new chiral Schiff bases and their application in the asymmetric trimethylsilylcyanation of aromatic aldehydes

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**Abstract**—The new chiral Schiff base ligands **1a**–**1c** were synthesized from (1*R*)-(+)-camphor and found to be efficient catalysts for the enantioselective silylcyanation of aromatic aldehydes. The corresponding aromatic cyanohydrins were obtained in good yields and with enantiomeric excesses (e.e.s) of up to 73%. © 2001 Elsevier Science Ltd. All rights reserved.

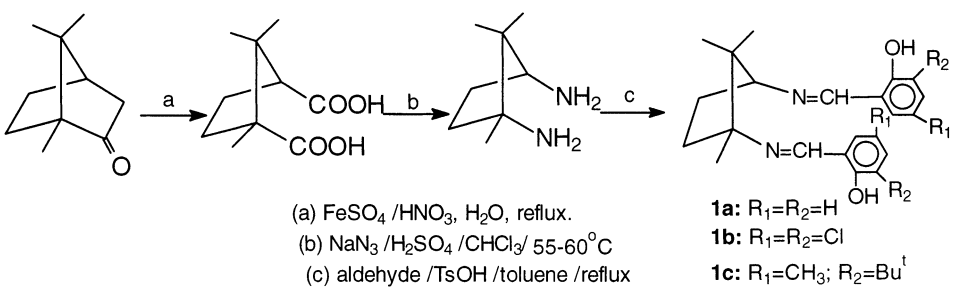
## 1. Introduction

Cyanohydrins are highly versatile synthetic intermediates, which can be easily converted into a wide variety of important products including α-hydroxy acids, α-amino acids and β-amino alcohols. They are also important components of many biologically active compounds. In view of their importance, the synthesis of optically active cyanohydrins has been a topic of major interest in recent years.[1–3] A number of catalysts for the asymmetric addition of cyanide to aldehydes have been reported, the most useful of which are enzymes,[1] synthetic peptides[2,3] and chiral transition metal complexes.[4–6] Although the structural modification of enzymes to increase their substrate compatibility is a long and difficult undertaking, the structural modification of chiral transition metal complexes is more viable. Previous work on the transition metal-induced asymmetric cyanohydrin synthesis has largely concentrated on titanium complexes. The chiral ligands which have been utilized in conjunction with titanium include Schiff bases, phosphorus ligands, binol and diammine. Herein, we report the synthesis of a new series chiral Schiff bases **1a**–**1c** from (1*R*)-(+)-camphor and their use in the asymmetric silylcyanation of aldehyde.

## 2. Results and discussion

### 2.1. Preparation of chiral Schiff base ligands

The chiral Schiff bases **1a**–**1c** were prepared from (1*R*)-(+)-camphor as shown in Scheme 1. Firstly (1*R*)-(+)-camphor was oxidized to (+)-*cis*-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid, which was treated with sodium azide to give (+)-*cis*-1,2,2-trimethyl-1,3-diamino-cyclopentane. Because this diamine is difficult to purify, it was used directly in the reaction with salicylaldehyde or its derivatives to produce ligands **1a**–**1c**.




**Scheme 1.**

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### 2.2. Asymmetric trimethylsilylcyanation of arylaldehydes catalyzed by chiral Schiff base 1a–1c

The Schiff bases **1a**–**1c** were found to be efficient in the enantioselective silylcyanation of aldehydes. The reactions were carried out in methylene chloride using $Ti(O\text{-}Pr^i)_4$ as pre-catalyst. To optimize the reaction, the effects of amounts of catalyst, molar ratio of ligand and $Ti(O\text{-}Pr^i)_4$, the use of *iso*-propyl alcohol as an additive, the reaction temperature and substrates on the enantioselectivity of the process were examined. All the results were summarized in Table 1.

As shown in Table 1, the enantioselectivity was markedly influenced by the nature of the Schiff base employed. The best ligand was found to be compound **1a**, which was derived from salicylaldehyde (entries 1–3).

The amount of catalyst had a dramatic influence on the enantioselectivity of the reaction. Thus, the use of 20 mol% of catalyst led to the expected cyanohydrin in high yield with e.e. of 70% (entry 9), while the use of 50 mol% catalyst only gave moderate enantioselectivity (entry 10, 48% e.e.). Moreover, it was found that the optimal molar ratio of ligand **1** to $Ti(O\text{-}Pr^i)_4$ is 1.1:1. We found that the use of *iso*-propyl alcohol as an additive led to a dramatic decrease the enantioselectivity (entry 5), which was different from Oguni's results.[6c]

The reaction temperature was also found to be an essential factor to the enantioselectivity of the reaction. For example, when the reaction was carried out at 0°C, the enantiomeric excess of the product was only 46% (entry 4), whereas reaction at −30°C increased the e.e. of the product to 66% (entry 8); furthermore, 70% e.e. was obtained in the reaction at −40°C (entry 9).

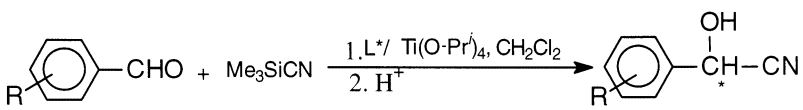
Having optimized reaction conditions, the asymmetric additions of trimethylsilylcyanide to a range of aromatic aldehydes catalyzed by 20 mol% of $Ti(O\text{-}Pr^i)_4$ and 22 mol% of **1a** were investigated. The results showed that better selectivities were obtained with electron-rich aromatic aldehydes, while electron-deficient aromatic aldehydes gave lower product e.e.s.

In conclusion, this work has resulted in the discovery of a new class of ligands for the titanium-catalyzed asymmetric addition of trimethylsilyl cyanide to aromatic aldehyde. Moderate to fair e.e.s were obtained using ligand **1a**.

## 3. Experimental

$^1H$ NMR spectra were recorded in $CDCl_3$ as solvent on AC-P200 instruments using TMS as internal standard. Elemental analyses were conducted on MF-3 automatic analyzer. Optical rotations were measured

**Table 1.** Asymmetric silylcyanation of aromatic aldehyde catalyzed by **1a**–**1c**




| Entry | R | Schiff base (mol%) | $Ti(O\text{-}Pr^i)_4$ (mol%) | Temp. (°C) | Yield (%)[a] | $[\alpha]_D^{25}$ ($c$ 1, $CHCl_3$) | E.e.[b] (%) | E.e.[c] (%) | Config. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | **1a** (10) | 10 | −20 | 94.0 | +19.5 | 43 | 47.8 | *R* |
| 2 | H | **1b** (22) | 20 | −20 | 94.0 | +6.2 | 9 | | *R* |
| 3 | H | **1c** (22) | 20 | −20 | 75.2 | +12.4 | 28 | | *R* |
| 4 | H | **1a** (20) | 20 | 0 | 97.7 | +20.5 | 46 | | *R* |
| 5[d] | H | **1a** (22) | 20 | 0 | 97.7 | +8.6 | 19 | | *R* |
| 6 | H | **1a** (5.5) | 5 | −30 | 94.0 | +13.7 | 30 | | *R* |
| 7 | H | **1a** (11) | 10 | −30 | 100 | +24.9 | 61 | | *R* |
| 8 | H | **1a** (22) | 20 | −30 | 97.7 | +29.7 | 66 | | *R* |
| 9 | H | **1a** (22) | 20 | −40 | 97.7 | +31.4 | 70 | 66.1 | *R* |
| 10 | H | **1a** (55) | 50 | −30 | 94.0 | +19.5 | 48 | | *R* |
| 11 | H | **1a** (20) | 10 | −30 | 94.0 | +25.9 | 58 | | *R* |
| 12 | *p*-Cl | **1a** (22) | 20 | −40 to 50 | 92.5 | +13.5 | 33 | 30.0 | *R* |
| 13 | *p*-$CH_3$ | **1a** (22) | 20 | −40 to 50 | 92.0 | +33.3 | 65 | | *R* |
| 14 | *o*-$CH_3O$ | **1a** (22) | 20 | −40 to 50 | 92.0 | +19.4 | 72 | | *R* |
| 15 | *p*-$CH_3O$ | **1a** (22) | 20 | −40 to 50 | 89.0 | +36.0 | 73 | | *R* |

[a] Isolated yield.

[b] Determined by the comparison of specific rotation values: R = H, $[\alpha]_D^{20}$ = +45 ($c$ 1, $CHCl_3$) in Ref. 1; R = Cl, $[\alpha]_D^{25}$ = +27.2 ($c$ 1.487, $CHCl_3$) with 66% e.e. in Ref. 11; R = $CH_3$, $[\alpha]_D^{25}$ = +47.4 ($c$ 1.822, $CHCl_3$) with 92% e.e. in Ref. 11; R = *o*-$OCH_3$, $[\alpha]_D^{20}$ = −21.0 ($c$ 1.25, $CHCl_3$) with 77% e.e. in Ref. 1; R = *p*-$OCH_3$, $[\alpha]_D^{25}$ = +49 ($c$ 1, $CHCl_3$) with >99% e.e. in Ref. 10.

[c] Determined by chiral GC on Supelco β-DEX120 after acetylation with acetic acid anhydride.

[d] 20 mol% *iso*-propanol was used.

on a Perkin–Elmer 241MC polarimeter. Ti(O-Pr$^i$)$_4$ was purchased from Fluka. $CH_2Cl_2$ was distilled from calcium hydroxide. $Me_3SiCN$ was prepared according to the literature.[7]

### 3.1. Preparation of (+)-*cis*-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid[8]

A mixture of (1*R*)-(+)-camphor (19.0 g, 0.125 mol), $FeSO_4 \cdot 7H_2O$ (1.0 g, 0.0036 mol), $H_2O$ (85 mL) and $HNO_3$ (65–68% 180 mL) was refluxed at 100–105°C for 30 h, then the resulting solution was cooled to room temperature. The white solid precipitate was collected by filtration and washing with $H_2O$ (2×10 mL) afforded the desired product (+)-*cis*-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid (12.2 g, 49%). Mp 202–205°C, $[\alpha]_D^{25} = +44.5$ (*c* 10, EtOH). (lit.: yield: 53.5%, mp: 204–205°C).

### 3.2. Preparation of (+)-*cis*-1,2,2-trimethyl-1,3-diaminocyclopentane[9]

A mixture of (+)-*cis*-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid (20.3 g, 0.1 mol), $CHCl_3$ (200 mL) and $H_2SO_4$ (60 mL) was stirred at 55–60°C with $NaN_3$ (18.6 g, 0.286 mol) added at intervals, and reacted until gas evolution ceased. The resulting solution was cooled to room temperature and adjusted to pH >14 with saturated NaOH. The solution was deposited overnight and filtered, and washed with $CHCl_3$ (2×30 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2×30 mL). The combined organic layer was dried over anhydrous sodium sulfate, then the solvent was removed in vacuo to give crude (+)-*cis*-1,2,2-trimethyl-1,3-diaminocyclopentane (12.2 g, 86%).

### 3.3. Preparation of ligand 1a (typical procedure)

A mixture of toluene (40 mL), salicylaldehyde (2.44 g, 20 mmol), (+)-*cis*-1,2,2-trimethyl-1,3-diaminocyclopentane (1.42 g, 10 mmol), and *p*-toluenesulfonic acid (0.01 g) was stirred under reflux for 2 h. After evaporation of the solvent, the crude product was recrystallized from ethyl acetate to give a yellow solid (2.80 g, 80%). Mp 159–161°C; $[\alpha]_D^{25} = +34.0$ (*c* 2, $CHCl_3$); $^1$H NMR ($\delta$, ppm): 0.95 (s, 3H, $CH_3$), 0.97 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 2.15 (m, 4H, $2CH_2$), 3.71 (t, 1H, CH), 7.11 (m, 8H, Ar-H), 8.45 (s, 2H, OH). Anal. calcd for $C_{22}H_{26}N_2O_2$: C, 75.36; H, 7.49; N, 7.99. Found: C, 75.15; H, 7.50; N, 7.88%.

### 3.4. Preparation of ligand 1b

Yellow solid, 77% yield, mp 237–240°C. $[\alpha]_D^{25} = +37.7$ (*c* 1, $CHCl_3$); $^1$H NMR ($\delta$, ppm): 0.95 (s, 3H, $CH_3$), 0.97 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 2.04 (m, 4H, $2CH_2$), 3.68 (t, 1H, CH), 7.29 (m, 4H, Ar-H), 8.24 (s, 2H, OH). Calcd for $C_{22}H_{22}Cl_4N_2O_2$: C, 54.12; H, 4.54; N, 5.74. Found: C, 54.08; H, 3.96; N, 5.63%.

### 3.5. Preparation of ligand 1c

Yellow solid, 80% yield, mp 137–139°C. $[\alpha]_D^{25} = +41.9$ (*c* 1.5, $CHCl_3$); $^1$H NMR ($\delta$, ppm): 0.96 (s, 6H, $2CH_3$), 1.32 (s, 3H, $CH_3$), 1.40 (d, 18H, Bu-H), 2.28 (m, 7H, $CH_3$+$2CH_2$), 3.54 (t, 1H, CH), 7.20 (m, 4H, Ar-H), 8.34 (s, 1H, OH), 13.24 (s, 1H, OH). Anal. calcd for $C_{32}H_{46}N_2O_2$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.14; H, 9.36; N, 5.45%.

### 3.6. Typical procedure for the trimethylsilylcyanation of aldehydes

To a solution of Schiff base **1a** (154 mg, 0.44 mmol) in $CH_2Cl_2$ (5 mL) was added Ti(O-Pr$^i$)$_4$ (114 mg, 0.4 mmol) and the mixture was stirred for 1 h at room temperature. The reaction mixture was cooled to between −40 and −50°C, then freshly distilled benzaldehyde (212 mg, 2 mmol) and trimethylsilylcyanide (400 mg, 4 mmol) were added. After stirring for 24 h at this temperature, the mixture was poured into a mixture of HCl (1N, 30 mL) and ethyl acetate (60 mL) and stirred for 4 h at room temperature, washing the organic layer with distilled water and saturated $NaHCO_3$ (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, 98%). After measuring the optical rotation, the pure cyanohydrin 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% $H_2SO_4$, distilled water and saturated $NaHCO_3$ (each 20 mL), drying with anhydrous sodium sulfate and concentrating 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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