Enantioselective Trimethylsilylcyanation of Some Aldehydes by Chiral Titanium Schiff's Base Complexes

Masahiko Hayashi, Yasunori Miyamoto, Tetsuya Inoue and Nobuki Oguni*

Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi City, Yamaguchi 753, Japan

The complexes formed between titanium tetraalkoxide and chiral Schiff's bases make excellent catalysts for enantioselective trimethylsilylcyanation of aldehydes to optically active cyanohydrins in high optical yield.

Asymmetric hydrocyanation of aldehydes is very important in the field of organic synthesis, and there have been many reports of biological[1] and chemical methods.[2]

Recently, we reported the highly enantioselective silylcyanation of aromatic aldehydes catalysed by a modified Sharpless catalyst.[3]

In this communication we describe the use of the titanium tetraalkoxide [$Ti(OR^i)_4$]–chiral Schiff's base as a catalyst for the asymmetric silylcyanation of aldehydes to give optically active cyanohydrins.

It is noteworthy that chiral Schiff's base complexes of transition metals have been found to become very effective catalysts for asymmetric cyclopropanation,[4] epoxidation of alkenes[5] and oxidation of sulfide.[6]

In this investigation, chiral Schiff's bases were prepared by the usual method (condensation of salicylaldehyde or salicylaldehyde derivatives with chiral β-amino alcohols, such as L-valinol, L-*tert*-leucinol, in methanol).

The results on enantioselective silylcyanation of benzaldehyde with trimethylsilyl cyanide catalysed by the mixture of titanium tetraisopropoxide [$Ti(OPr^i)_4$] and a variety of chiral Schiff's bases (**1–4**) (20 mol% per aldehyde) are summarized in Table 1.

These catalysts exhibit remarkable rate enhancement in the addition of trimethylsilyl cyanide to aldehydes. For example, silylcyanation of benzaldehyde catalysed by *in situ* mixture of $Ti(OPr^i)_4$ and chiral Schiff's base **2** proceeded *ca.* six times faster than that catalysed by $Ti(OPr^i)_4$ (20 mol% per aldehyde, at −25 °C in dichloromethane).

The enantioselectivity was influenced by the particular chiral Schiff's base, reaction temperature and reactant concentration. Substitution of a *tert*-butyl group at the 3-position of salicylaldehyde increased the enantioselectivity of the reaction without decreasing the reactivity (entry 1 and 2 in Table 1). The use of chiral β-amino alcohols bearing bulky substituents also enhanced the enantioselectivity. The reaction catalysed by 20 mol% of $Ti(OPr^i)_4$ and Schiff's base **2** in dichloromethane at −80 °C afforded the highest optical yield [85% enantiomeric excess (e.e.)]. Also high enantioselectivity was attained at high concentration of reagents.

We examined the enantioselective addition of trimethylsilyl cyanide to other aldehydes catalysed by this system. As shown in Table 2, both aromatic and aliphatic aldehydes were trimethylsilylcyanated to give the corresponding cyanohydrins in moderate to high optical yield. For example, the reaction of *p*-anisaldehyde with trimethylsilyl cyanide catalysed by 20 mol% of $Ti(OPr^i)_4$ and Schiff's base **2** gave the cyanohydrin in 91% e.e. (62% yield).

The typical experimental procedure for the enantioselective trimethylsilylcyanation of benzaldehyde is as follows. To a solution of Schiff's base **2** (145 mg, 0.55 mmol) in dichloromethane (2.5 ml) was added $Ti(OPr^i)_4$ (143 mg, 0.50 mmol)

$$RCHO + Me_3SiCN \xrightarrow{i} R\overset{*}{C}H(OSiMe_3)CN$$

Scheme 1 *Reagents and conditions*: i, 20 mol% $Ti(OPr^i)_4$–Schiff's base, CH_2Cl_2, 0 ~ −80 °C, 20–44 h

Table 1 Enantioselective trimethylsilylcyanation of benzaldehyde[a]

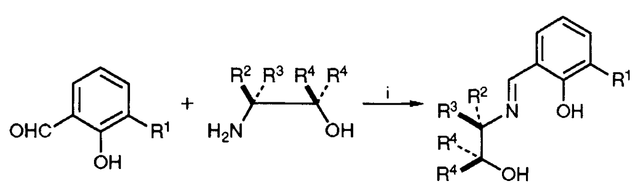
Entry	Schiff's base[b]	Conditions: Temp./°C	Conditions: Time/h	Product: Yield[c] (%)	Product: E.e.[d] (%) (config.)[e]
1	**1**	0	20	69	22 (*S*)
2	**2**	0	20	70	41 (*R*)
3	**2**	−30	44	90	67 (*R*)
4	**2**	−80	24	67	85 (*R*)
5	**3**	−78	24	64	64 (*R*)
6	**4**	−78	36	61	67 (*R*)

[a] All reactions were carried out in dichloromethane. [b] All Schiff's bases have 2*S* configuration. [c] Isolated yield. [d] Determined by HPLC analysis. [e] Absolute configuration of the products were determined by comparison of the optical rotation values with those in the literature.[2b]

Table 2 Enantioselective addition of trimethylsilyl cyanide to various aldehydes[a]

Aldehyde	Cyanohydrin: Yield[b] (%)	Cyanohydrin: E.e.[c,d] (%)
p-Tolualdehyde	68	71[e]
p-Anisaldehyde	62	91[f]
2-Naphthaldehyde	76	73[g]
2-Thiophenecarbaldehyde	60	79[h]
Dodecanol	48	66[i]
Cyclohexanecarbaldehyde	72	65[j]

[a] All reactions were carried out in dichloromethane at −78 °C for 36 h by using 20 mol% of $Ti(OPr^i)_4$ and chiral Schiff's base (*S*)-(+)-**2**. [b] Isolated yield. [c] Determined by HPLC analysis of its MTPA ester. [d] All absolute configurations were determined as *R* by comparison of the optical rotation values with those in the literature.[7] [e] $[\alpha]_D^{24}$ +36.4° (*c* 1.1, $CHCl_3$). [f] $[\alpha]_D^{24}$ +41.7° (*c* 1.4, $CHCl_3$). [g] $[\alpha]_D^{24}$ +10.9° (*c* 1.1, EtOH). [h] $[\alpha]_D^{24}$ +64.1° (*c* 0.6, $CHCl_3$); $[\alpha]_D^{24}$ +42.6° (*c* 0.6, EtOH). [i] $[\alpha]_D^{24}$ +6.7° (*c* 1.3, $CHCl_3$). [j] $[\alpha]_D^{24}$ +6.1° (*c* 3.8, $CHCl_3$).



Schiff's base	R[1]	R[2]	R[3]	R[4]
1	H	Pr[i]	H	H
2	Bu[t]	Pr[i]	H	H
3	Bu[t]	Pr[i]	H	Ph
4	Bu[t]	Bu[i]	H	H

Scheme 2 *Reagents and conditions*: i, Na_2SO_4 (5 equiv.), MeOH, reflux, 18–72 h

and stirred for 2 h at room temperature. The reaction mixture was cooled to −80 °C, freshly distilled benzaldehyde (2.61 g, 2.46 mmol) and then trimethylsilyl cyanide (558 mg, 5.62 mmol) were added. After stirring for 36 h at this temperature, the mixture was poured into a mixture of 1 mol dm^{-3} HCl (30 ml) and ethyl acetate (150 ml) and stirred vigorously for 6 h at room temperature. The usual extractive work-up and silica gel column chromatography of the residue gave (*R*)-cyanobenzyl alcohol (219 mg, 67%). $[\alpha]_D^{25}$ +36.8° (*c* 2.0). The e.e. of the product was determined as 85% e.e. by HPLC analysis of its MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) ester. The t_R of (*R*)-(+)-isomer: 13 min; t_R of (*S*)-(−)-isomer: 15 min (hexane–ethyl acetate 100 : 5, 1.0 ml min^{-1}).

Thus, asymmetric silylcyanation of aldehydes with trimethylsilyl cyanide using the catalyst system consisting of $Ti(OPr^i)_4$ and chiral Schiff's bases provides a new, efficient synthetic tool for the synthesis of optically active cyanohydrins.

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