

Novel Enantioselective Reaction of Diketene with Aldehydes Promoted by Chiral Schiff Base–Titanium Alkoxide Complex

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Reaction of a variety of aldehydes with diketene in the presence of chiral Schiff base–titanium alkoxide complexes proceeds with high enantioselectivity to afford the corresponding 5-hydroxy-3-oxoesters.

There are many optically active secondary alcohols bearing biological and physiological activities. Methods for the synthesis of optically active alcohols have been developed recently to give a variety of precursors leading to optically active natural products.¹ Among those, optically active 5-hydroxy-3-oxoesters can be easily converted to 6-substituted-4-hydroxy-lactones which are an important component of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase such as compactin and mevinolin.² There have been several reports concerning the asymmetric synthesis of lactone moieties of the above compounds.³ For example, Johnson *et al.*, reported the diastereoselective addition of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene to chiral acetal to give the 5-alkoxy-3-oxoesters in high optical purity.^{3d} Saburi and coworkers reported the asymmetric hydrogenation of 3,5-dioxoesters catalysed by Ru-binap complex, giving the 6-substituted-5,6-dihydro-2-pyrones of 71–81% optical purity.^{3f,g}

Here, we disclose the first report on the highly enantioselective reaction of diketene with aldehydes promoted by chiral Schiff base–titanium alkoxide complexes to give 5-hydroxy-3-oxoesters (Scheme 1).⁴

At first, the enantioselective reactions of benzaldehyde with diketene were examined by using an equimolar amount of chiral titanium complexes prepared *in situ* from a variety of chiral Schiff bases and titanium tetraalkoxide in dichloromethane at -20°C for 48 h. It was found that the enantioselectivity was influenced by the type of chiral Schiff bases (Table 2). The existence of a *tert*-butyl group at the 3-position of 2-hydroxybenzaldehyde was necessary to achieve a highly enantioselective reaction. That is, when the Schiff base **1a** without *tert*-butyl group was used, only low level of reactivity and enantioselectivity [23% yield, 16% enantiomeric excess

(e.e.)] were observed, whereas, high chemical and optical yield (85% yield, 84% e.e.) were attained by the use of Schiff base **1b** possessing a *tert*-butyl substituent at the 3 position on the benzene ring; the *tert*-butyl group at the 5-position on the benzene ring in the Schiff base was not so effective. Among the promoter systems examined, the combination of $\text{Ti}(\text{OPr}^i)_4$ and Schiff base **1b**, which was the combination giving the highest e.e. in the asymmetric silylcyanation⁵ also afforded the best results in the reaction of diketene with aldehydes. The e.e. of the product was determined by HPLC analysis (CHIRALPAK AD, Daicel). However, the reaction using a catalytic amount of the promoter caused a decrease of chemical yield even after a prolonged reaction time (20 mol%, -20°C , 88 h, 29% yield), though the enantioselectivity (82% e.e.) was high regardless of the amount of catalyst. Therefore, an equimolar or more than 50 mol% of the titanium complexes were found to be necessary in order to attain satisfactory yield.

The results obtained from the reaction of a variety of aldehydes with diketene are summarized in Table 3. In all reactions, moderate to high enantioselectivity (67–81% e.e.) was attained. As for the stereochemical outcome of the reaction, when the Schiff base **1b** possessing *S*-configuration was used, it was found that aldehydes were attacked from the *si* face by nucleophile. This result was consistent with the one obtained from the enantioselective addition of trimethylsilyl cyanide to aldehydes.⁵

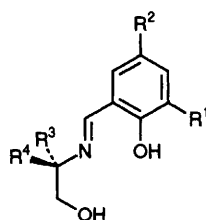


Table 1 Chiral Schiff bases used in asymmetric reaction

Schiff base 1	R ¹	R ²	R ³	R ⁴
(<i>S</i>)- a	H	H	Pr ⁱ	H
(<i>S</i>)- b	Bu ^t	H	Pr ⁱ	H
(<i>S</i>)- c	Bu ^t	H	Bu ^t	H
(<i>S</i>)- d	Bu ^t	Bu ^t	Pr ⁱ	H



Scheme 1 Reagents and conditions: i, 1 equiv. $\text{Ti}(\text{OPr}^i)_4$ –Schiff base, CH_2Cl_2 , -20°C , 48 h; ii, Pr^iOH ; iii, 1 mol dm^{-3} HCl

Table 2 Enantioselective addition of diketene to benzaldehyde promoted by chiral Schiff base–titanium alkoxide complexes^a

Schiff base 1	Product	
	% Yield ^b	% E.e. ^c
(<i>S</i>)- a	23	16
(<i>S</i>)- b	85	84 ^d
(<i>R</i>)- c	85	80
(<i>S</i>)- d	75	82

^a All reactions were carried out in CH_2Cl_2 using equimolar amount of chiral titanium complexes; $T = -20^{\circ}\text{C}$, $t = 48$ h. ^b Isolated yield. ^c HPLC analysis (CHIRALPAK AD). ^d $[\alpha]_D^{25} -39.8$ (c 1.1, CHCl_3).

Table 3 Enantioselective addition of diketene to a variety of aldehydes promoted by chiral Schiff base **1b**–titanium isopropoxide complexes^a

Aldehyde	Product		
	% Yield ^b	% E.e. ^c	$[\alpha]_D^{25}$ (c) ^d
4-Methylbenzaldehyde	90	81	-37.5 (1.2)
2-Thiophenecarboxaldehyde	88	70	-21.8 (1.0)
Methacrylaldehyde	82	68	-27.1 (1.1)
(<i>E</i>)-Cinnamaldehyde	86	78	-11.0 (1.1)
3-Phenylpropionaldehyde	69	73	-5.1 (1.1)
<i>n</i> -Butanal	84	67	-18.4 (1.1)

^a All reactions were carried out in CH_2Cl_2 at -20°C for 48 h using equimolar amount of chiral titanium complexes. ^b Isolated yield. ^c HPLC analysis (CHIRALPAK AD). ^d Measured in chloroform.

The typical experimental procedure is as follows: in a flame-dried Schlenk tube were placed Schiff base **1b** {(S)-2-[N-(3'-*tert*-butylsalicylidene)amino]-3-methylbutan-1-ol} (1.45 g, 5.4 mmol) and CH₂Cl₂ (5 ml). To this solution was added Ti(OPrⁱ)₄ (1.48 ml, 4.9 mmol) at room temperature and the resulting solution was stirred for 1 h, and the mixture was then cooled to -20 °C. *n*-Butanal (0.44 ml, 4.9 mmol) and diketene (2 ml, 25 mmol) were added to the solution, and the whole was stirred for 48 h at this temperature. After this, isopropyl alcohol (0.76 ml, 9.8 mmol) was added to the mixture and then stirred for 3 h. This solution was poured into a mixture of 1 mol dm⁻³ HCl (50 ml) and diethyl ether (50 ml) and stirred vigorously for 24 h at this temperature. The mixture was then extracted with diethyl ether (50 ml × 3), and the combined extracts were washed with saturated NaHCO₃ solution (50 ml × 2) brine (50 ml × 2) and dried over Na₂SO₄. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, benzene-diethyl ether (3 : 1)] to give isopropyl 5-hydroxy-3-oxooctanoate (0.90 g, 84%). [α]_D²⁵ -18.4 (*c* 1.1, CHCl₃). The e.e. was determined as 67% by HPLC analysis [column, CHIRALPAK AD; eluent, hexane-ethanol (95 : 5) + trifluoroacetic acid (0.1%), 1.0 ml min⁻¹]; *t*_R of *S*-isomer: 8 min; *t*_R of *R*-isomer: 11 min. Absolute configuration was determined as *R* by the comparison of the optical rotation value after conversion into (*R*)-6-propyl-5,6-dihydro-2*H*-pyran-2-one.^{3g}

The reaction mechanism will be assumed to proceed through aldol type reaction between aldehydes and the titanium enolate formed by the reaction of catalyst with diketene.

In conclusion, the enantioselective reaction of diketene with aldehydes using the catalyst system consisting of Ti(OPrⁱ)₄ and chiral Schiff bases possessing a *tert*-butyl substituent provides a novel and efficient method for the synthesis of optically active 5-hydroxy-3-oxoesters.[†]

Received, 14th September 1993; Com. 3/05534E

Footnote

[†] The reaction of benzaldehyde with diketene promoted by titanium alkoxide-chiral diols other than chiral Schiff base such as L-(+)-diisopropyl tartrate (DIPT) and (*R*)-(+)-1,1'-binaphthol complexes resulted in low chemical and optical yield: L-(+)-DIPT [in absence of molecular sieves (MS) 4A, 50% yield, 1% e.e., 0 °C, 42 h; in the presence of MS 4A, 22% yield, 29% e.e., -20 °C, 72 h]; (*R*)-(+)-1,1'-binaphthol (in the absence of MS 4A, 14% yield, 0% e.e., -20 °C, 55 h; in the presence of MS 4A, 0% yield, -20 °C, 83 h).

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