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Highly Efficient Preparation of Optically Active 5-Hydroxy-3-oxoesters by Enantioselective Reaction of Diketene with Aldehydes Promoted by Novel Chiral Schiff Base–Titanium Alkoxide Complexes

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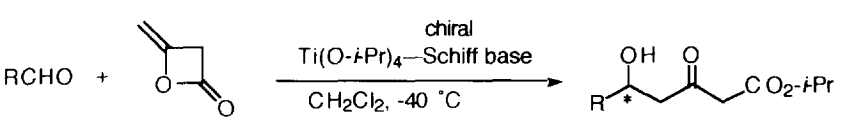
Abstracts: Optically active 5-hydroxy-3-oxoesters **1** can be obtained in up to 91% enantiomeric excess (e.e.) by the enantioselective reaction of diketene with aldehydes promoted by novel chiral Schiff base—titanium alkoxide complexes.

Optically active derivatives **1** can be converted into 6-substituted 4-hydroxy lactones which are common structual components of compactin and mevinolin known as inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase.[1] So far, several methods have been reported to synthesize optically active 6-substituted 4-hydroxy lactones *via* **1** or *syn*-3,5-dihydroxy esters.[2] Most of them, however, required several steps to prepare these compounds. For example, Hiyama et al. recently reported the diastereoselective reduction of chiral 3,5-diketo esters to give *syn*-3,5-dihydroxy esters.[3]

On the other hand, Mukaiyama reported the synthesis of racemic **1** by the reaction of aldehydes with diketene promoted by $TiCl_4$ in 1975.[4] However, a chiral version of this reaction leading to optically active **1** had not been reported before our first report in 1994, which included the enantioselective reaction of diketene with aldehydes promoted by chiral Schiff base—titanium alkoxide complexes (Scheme 1).[5] The 5-phenyl derivatives of **1** was obtained in 84% e.e. when the titanium complex of Schiff base prepared by 3-*tert*-butyl-2-hydroxybenzaldehyde and (*S*)-valinol was used in the reaction of benzaldehyde with diketene. Subsequently, we have searched for more efficient promoters to increase the enantioselectivity of this reaction.

Scheme 1



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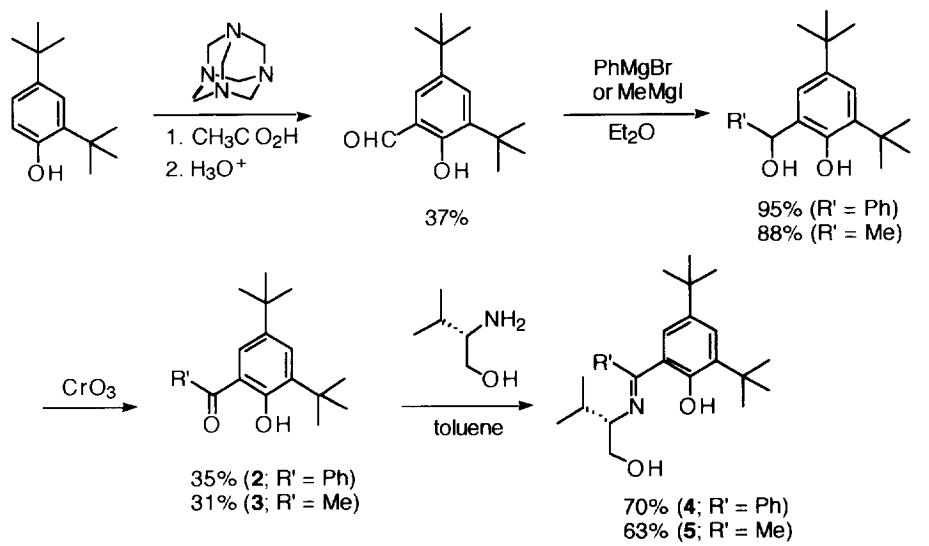
In this paper, we disclose the novel titanium complexes of chiral Schiff bases which catalyze the highly enantioselective reaction of diketene with aldehydes.

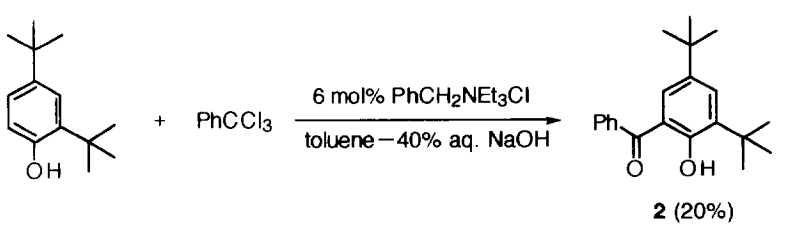
The new chiral Schiff bases **4** and **5** were synthesized by the condensation of 3,5-di-*tert*-butyl-2-hydroxybenzophenone **2** or 3',5'-di-*tert*-butyl-2'-hydroxyacetophenone **3** with (*S*)-valinol. These ketones could be prepared starting from ortho-formylation of 2,4-di-*tert*-butylphenol,[6] followed by the Grignard reaction and oxidation of resulting alcohol (Scheme 2).[7]

Scheme 2



The ketone **2** could also be available in one step by a modified Reimer-Tiemann reaction using phase transfer catalyst system (Scheme 3).[8]

Scheme 3



The reactions of diketene with a variety of aldehydes proceed smoothly at -40 °C in the presence of chiral Schiff base **4** or **5**—titanium alkoxide complexes to give the corresponding 5-hydroxy-3-oxoesters in high enantiomeric purity (Table 1). For example, the reaction of benzaldehyde and (*E*)-cinnamaldehyde afforded the product in 91% e.e. and 90% e.e., respectively, by the promotion of chiral Schiff base **4**—titanium isopropoxide complex.[9]

It should be noted that chiral Schiff bases can be recovered in over 70% yield after usual aqueous work-up without any loss of enantiomeric purity in case of chiral Schiff base **4**.

Table 1. Enantioselective Addition of Diketene to Some Aldehydes Promoted by Chiral Schiff Base—Titanium Isopropoxide Complexes[a]

		product		
aldehyde	Schiff base	% yield[b]	% e.e.[c]	$[\alpha]_D^{24}$ (*c* 1.0)[d]
benzaldehyde	**4**	76	91	-50.1
	5	69	89	
4-methylbenzaldehyde	**4**	74	88	-45.3
	5	72	82	
(*E*)-cinnamaldehyde	**4**	59	90	-16.7
	5	62	89	
3-phenylpropionaldehyde	**4**	60	75	
	5	63	83	-5.9

[a] All reactions were carried out in CH_2Cl_2 using equimolar amount of chiral titanium complex at -40 °C for 96 h. [b] Isolated yield after silica gel column chromatography. [c] HPLC analysis (CHIRALPAK AD). [d] Measured in $CHCl_3$.

A typical experimental procedure is as follows; In a Schlenk tube were placed Schiff base **4** (869 mg, 2.2 mmol) and CH_2Cl_2 (4 mL). To this solution was added Ti(O-*i*-Pr)4 (0.63 mL, 2.2 mmol) at room temperature and the resulting solution was stirred for 1 h, and the mixture was then cooled to -40 °C. 3-Phenylpropionaldehyde (280 mg, 2.1 mmol) and diketene (0.35 mL, 4.2 mmol) were added to the mixture and stirred for 96 h at this temperature. After this, the mixture was poured into a 1 N HCl (60 mL) and stirred vigorously for 1 h. The mixture was then extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with saturated $NaHCO_3$ solution (50 mL x 2), brine (50 mL x 2) and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, hexane—ethyl acetate (5:1)] to give isopropyl 5-hydroxy-7-phenyl-3-oxo-6-heptanoate (350 mg, 60%). $[\alpha]_D^{24}$ -5.9 (*c* 1, $CHCl_3$). The e.c. was determined as 75% by HPLC analysis [column, CHIRALPAK AD; eluent, hexane—ethanol (95:5) + trifluoroacetic acid (0.1%), 1.0 mL/min]: t_R of *S*-isomer: 12 min; t_R of *R*-isomer: 21 min. The absolute configuration of the major product was determined as *R* by the comparison of the optical rotation value after conversion into 4-hydroxy-6-benzylmethyl-*2H*-pyran-2-one. The procedure of this step is as follows: To a solution of isopropyl 5-hydroxy-7-phenyl-3-oxo-6-heptanoate (350 mg, 1.26 mmol) in THF—methanol (4:1, 10 mL) was added triethylborane (1 M in hexane, 1.7 mL, 1.8 mmol) at room temperature and stirred for 2 h. Then, the mixture was cooled to -78 °C, and solid $NaBH_4$ (67 mg, 1.85 mmol) was added. The solution was stirred for 6 h, and a mixture of 31% H_2O_2 (5 mL), phosphate buffer (pH 6.88, 10 mL) and methanol (15 mL) was added. Organic layer was removed and the obtained residue was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated. To the residue was added conc. HCl (1 μL) in methanol (5 mL) and evaporated. This process was repeated four times. Then, the oily residue was chromatographed on silica gel to afford 4-hydroxy-6-(2-phenylethyl)-*2H*-pyran-2-one (272 mg, 98%). $[\alpha]_D^{25}$ +35.9 (*c* 1.1, $CHCl_3$) (lit.[10] $[\alpha]_D^{25}$ +51.3 (*c* 1.1, $CHCl_3$) for 98% e.e. (4*R*, 6*R*)).

In conclusion, the enantioselectivity could be attained by using novel Schiff base—titanium alkoxide catalyst in the reaction of diketene with aldehydes. This new procedure provides an efficient method for the synthesis of

optically active 5-hydroxy-3-oxoesters.

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7. For **4**: mp. 67—69 °C; $[\alpha]_D^{24}$ -29.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3428, 2960, 1612, 1482, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 9H), 1.49 (s, 9H), 1.5 (br s, 1H), 1.8—2.0 (m, 1H), 3.2—3.3 (m, 1H), 3.7—3.8 (m, 2H), 6.63 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.1—7.2 (m, 2H), 7.4—7.5 (m, 3H), 15.9 (br s, 1H). Anal. Calcd for $C_{26}H_{37}NO_2$; C, 78.94; H, 9.43; N, 3.54: Found; C, 78.83; H, 9.38; N, 3.53. **5**: mp. 32—34 °C; $[\alpha]_D^{24}$ -31.6 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3428, 2960, 1614, 1482, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.33 (s, 9H), 1.45 (s, 9H), 1.5 (br s, 1H), 1.9—2.1 (m, 1H), 2.42 (s, 3H), 3.7—3.9 (m, 3H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H). HRMS (EI) *m/z* Calcd for $C_{21}H_{35}NO_2$ (M^+): 333.2668. Found: 333.2657.
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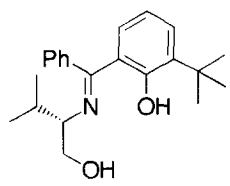
9. The reaction of benzaldehyde and (*E*)-cinnamaldehyde with diketene using Schiff base **6** derived from benzophenone derivatives without *tert*-butyl group at the 5-position gave the product in 88% e.e. (68% yield) and 86% e.e.(61% yield), respectively.



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