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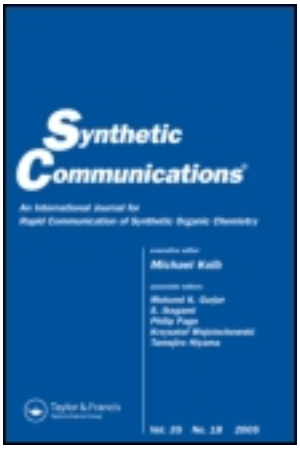

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Enantioselective Aldol-Type Reaction Using Diketene

Takahiro Kawase [a], Shinobu Takizawa [a], Doss Jayaprakash [a] & Hiroaki Sasai [a]
[a] The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka, 567-0047, Japan
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Enantioselective Aldol-Type Reaction Using Diketene

Takahiro Kawase, Shinobu Takizawa, Doss Jayaprakash, and Hiroaki Sasai*

The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka, Japan

ABSTRACT

An aldol-type reaction catalyzed by a Ti-(*S*)-BINOL complex using with a diketene as substrate is described herein. The complex derived from 1.0 molar equivalent of Ti(*O-i*-Pr)$_4$ and 2.0 molar equivalents of (*S*)-BINOL gave (*S*)-isopropyl 5-hydroxy-7-phenyl-3-oxo-6-heptenoate with high enantioselectivity.

Key Words: Aldol-type reaction; Diketene; Enantioselective; Titanium-BINOL complexes.

*Correspondence: Hiroaki Sasai, The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan; E-mail: sasai@sanken.osaka-u.ac.jp.

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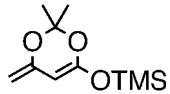
Optically active 5-hydroxy-3-oxoester derivatives **1** and **2** (which is easily obtained from **1**) are useful synthetic intermediates for various biologically active compounds.[1] An enantioselective aldol-type reaction of silylenolate **3** with an aldehyde catalyzed by a chiral metal complex serves an effective method for the preparation of **1**.[2,3]

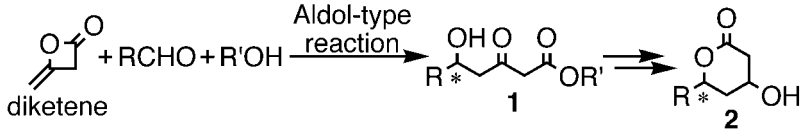


3

However, **3** must be synthesized from diketene and is unstable against aqueous conditions. Thus, the direct use of diketene in this reaction is desirable (Sch. 1).[4] Recently, the catalytic enantioselective reaction of diketene with aldehyde promoted by a chiral Schiff base and Ti(O-*i*-Pr)$_4$ was reported to be achieved by Oguni et al. and Yanagisawa et al. (Sch. 2).[5,6]

In the present study, a simple and efficient alternative to the aldol-type reaction was explored. Among the chiral ligands and Lewis acids screened for the reaction, the Ti-(*S*)-BINOL complex[7] generated from Ti(O-*i*-Pr)$_4$ and (*S*)-BINOL provided the most encouraging results; it afforded adduct **4** with 53% ee (Table 1, entry 1).[8,9] The ester moiety of the adduct originated from titanium alkoxide; therefore, the effect of alkoxide on the enantiomeric excess was examined. However, the use of various titanium alkoxides with smaller alkoxide than isopropoxide groups was not effective, and enantiomeric excesses of the products were always low ($<$29% ee).[10] In addition, the reaction did not proceed when Ti(O-*t*-Bu)$_4$ was used. In an effort to improve the enantioselectivity of this reaction, catalysts generated using various ratios of Ti(O-*i*-Pr)$_4$ and (*S*)-BINOL were examined. In contrast to the catalyst derived with 1.0 molar equivalent of (*S*)-BINOL (entry 1), the catalyst derived with 2.0 molar equivalents of (*S*)-BINOL afforded higher selectivity[11] (entry 2). In the absence of (*S*)-BINOL, the reaction afforded a racemic adduct in high yield (entry 4).

The low yield may be attributed to the strong coordination of the oxo-functionalized product to the highly oxophilic titanium center, thereby inhibiting further reaction. The formation of byproduct **5** as a result of proton



Scheme 1. Direct aldol-type reaction using diketene.

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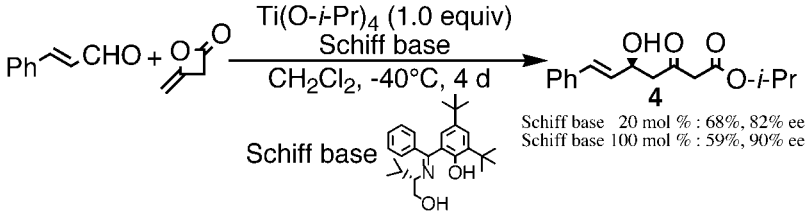
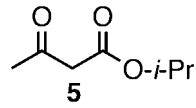


Scheme 2. Catalytic enantioselective reaction of diketene using Schiff bases as a ligand.

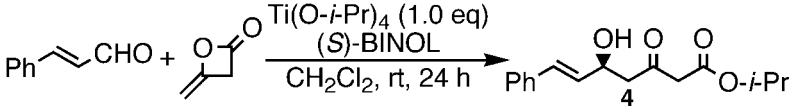
abstraction by the reaction intermediate was confirmed by NMR analysis of the crude products.



The use of a Proton-Sponge as an additive to this reaction was then examined in an effort to further improve the yields of the product. As expected, in the presence of the Proton-Sponge, the reaction proceeded smoothly, yielding the adduct in an 85% yield. Interestingly, the absolute configuration of the major enantiomer was reversed and the (*S*)-product was obtained with 25% ee (Sch. 3).

The use of a Proton-Sponge was determined to enhance the yield of **4**; therefore, the ability of a chiral amine [(*R*)-**6**][12] to promote this reaction in the absence of (*S*)-BINOL was examined. The reaction was completed in

Table 1. Aldol-type reaction of cinnamaldehyde and diketene catalyzed by Ti(O-*i*-Pr)$_4$-BINOL complexes.



Entry	BINOL (equiv)	Yield (%)	ee (%)
1	1.0	28	53
2	2.0	40	90
3	3.0	35	84
4	none	88	—

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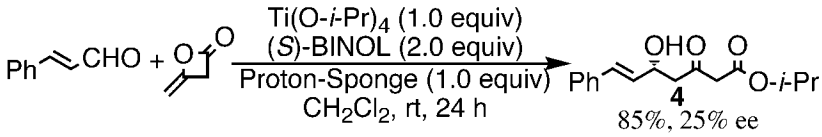

Scheme 3. Effect of Proton-Sponge as additive.

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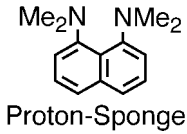
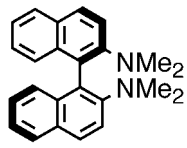
only 6 h and the product was obtained in 92% yield. To our disappointment, however, the obtained product was almost racemic.



Proton-Sponge



(*R*)-**6**

In conclusion, the direct use of diketene in an aldol-type reaction with cinnamaldehyde was attempted. The catalyst was prepared using 1.0 equivalent of Ti(O-*i*-Pr)$_4$ and 2.0 equivalents of BINOL, and yielded the (*S*)-**4** with high enantioselectivity. Further investigation of the aldol-type reactions using diketene will be the focus of our continued research efforts.

EXPERIMENTAL

General Procedure

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 (^{1}H NMR-270 MHz, ^{13}C NMR-67.7 MHz, Japan). All signals were expressed as ppm down field from tetra methylsilane, which was used as the internal standard. IR spectra were obtained using a SHIMADZU FTIR-8300 (Japan). Optical rotations were measured on a JASCO DIP-370 Polarimeter (Japan). Column chromatography was performed on Kanto Silica Gel 60 (40–100 μm, Japan). Anhydrous CH_2Cl_2 was distilled from calcium hydride.

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General Procedure for Ti-(*S*)-BINOL Catalyzed Aldol-Type Reaction Using Diketene

A mixture of (*S*)-BINOL (286 mg, 1.0 mmol) and Ti(O-*i*-Pr)$_4$ (148 μL, 0.50 mmol) in 2.5 mL of CH_2Cl_2 was stirred at rt for 2 h. Cinnamaldehyde (63 μL, 0.50 mmol) and diketene (77 μL, 1.0 mmol) were added to this solution, and the reaction mixture was stirred for 24 h. The reaction was quenched with 1 N HCl. After stirring for 2 h the mixture was extracted using CH_2Cl_2. The extract was washed with saturated $NaHCO_3$, dried over $MgSO_4$, and then concentrated. The residue was purified by silica column chromatography (hexane/ethyl acetate = 3/1) to give the product as a yellow oil (55.3 mg, 40%). The optical purity of the product was determined as 90% by HPLC analysis using a chiral stationary phase column [DAICEL CHIRALPAK AD (Japan), hexane/*i*-PrOH = 16/1, flow rate = 0.5 mL/min]: t_R = 50.2 min (*R*), t_R = 57.4 min (*S*). $[\alpha]_D^{25}$ −15.2° (C = 1.2, $CHCl_3$) [Lit.[5b] (90% ee); $[\alpha]_D^{24}$ −16.7° (C = 1.0, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$): δ 1.26 (d, *J* = 6.2 Hz, 6H), 2.86 (d, *J* = 5.9 Hz, 2H), 2.94 (br s, 1H), 3.47 (s, 2H), 4.79 (q, *J* = 5.9 Hz, 1H), 5.06 (m, *J* = 6.2 Hz, 1H), 6.20 (dd, *J* = 15.9, and 6.2 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.7, 49.6, 50.3, 68.4, 69.2, 126.4, 127.7, 128.4, 129.8, 130.5, 136.2, 166.2, 202.6. IR (neat): 3518, 2982, 1734, 1707, 1312, 1103 cm^{-1}. FAB-MS. 277 $[M + H]^+$.

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9. Results of other titanium alkoxides; Ti(O-*n*-Bu)$_4$ (29% ee), Ti(OEt)$_4$ (22% ee), Ti(OMe)$_4$ (5% ee).
10. Effect of reaction temperature: −20°C (37%, 23% ee, 96 h), −40°C (23%, 9% ee, 96 h), reflux (trace, 24 h). Result of other solvents: THF (30%, 23% ee, 24 h), ether (trace, 24 h), MeCN (trace, 24 h).
11. Results of reactions using other aldehydes under identical condition; 4-methoxycinnnamaldehyde (31%, 83% ee), 2-methoxycinnamaldehyde (34%, 73% ee), cyclohexanecarboxaldehyde (18%, 31% ee).
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