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A Catalytic Asymmetric Michael Reaction of Silyl Enol Ethers with α,β-Unsaturated Ketones Using a Chiral Titanium Oxide

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In the presence of a catalytic amount of [(R)-1,1'-bi-2-naphthalenediolato(2-)-O,O']oxotitanium, silyl enol ethers of thioesters reacted with α,β-unsaturated ketones to afford the corresponding Michael adducts (1,5-dicarbonyl compounds) in high yields with moderate to high enantiomeric excesses.

Development of enantioselective carbon-carbon bond-forming reactions using chiral catalysts is now one of the most challenging tasks in organic synthesis.[1)] Recently in this field, the catalytic asymmetric aldol reactions of silyl enol ethers with aldehydes have been advanced greatly, and several enantioselective aldol reactions using chiral tin(II), boron, titanium Lewis acids[2)] have been developed. On the other hand, the Michael reactions of silyl enol ethers with α,β-unsaturated ketones are also among the most useful carbon-carbon bond-forming reactions performed under acidic conditions,[3)] and have been applied in the syntheses of natural products.[4)] However, the asymmetric version of this reaction is unprecedented as far as we know.[5)] In this paper, we disclose for the first time the asymmetric Michael reaction of silyl enol ethers with α,β-unsaturated ketones using a chiral titanium oxide as the catalyst.

The catalytic asymmetric Michael reaction was carried out by using [(R)-1,1'-bi-2-naphthalenediolato(2-)-O,O']oxotitanium (**1**), which was reported in our previous paper to be an excellent catalyst in the aldol reaction of silyl enol ethers with aldehydes.[6,7)] First, the reaction of the t-butyldimethylsilyl enol ether of S-t-butyl ethanethioate with 2-cyclopentenone was carried out in toluene at -78 °C in the presence of 20 mol% of **1**. The reaction proceeded smoothly to afford the corresponding Michael adduct in a 59% yield. The enantiomeric excess of the adduct was proved to be 59% ee. The reaction also proceeded smoothly in dichloromethane, however the enantiomeric excess was low (73% yield, 17% ee). The effect of the ester groups of the silyl enol ethers is shown in Table 1 (entries 1-3). While a moderate enantiomeric excess was obtained by using the silyl enol ether of the S-benzyl thioester (**2b**), the corresponding O-ester gave lower selectivity (66% yield, 9% ee). The best result was obtained when the silyl enol ether derived from S-diphenylmethyl ethanethioate (**2c**) was employed, and synthetically valuable cyclopentanone derivative **3c** was prepared in 90% ee.

The present asymmetric Michael reaction using **1** as a catalyst could be applied to other systems and selected examples are summarized in Table 1 (entries 4-7). 2-Cyclohexenone also reacted with **2c** to give Michael adduct **3d** in a 76% yield with 70% ee. The yield and selectivity in the reaction of 2-cycloheptenone with **2c** were moderate. Chalcone also reacted with **2c** under the present reaction conditions to give the corresponding

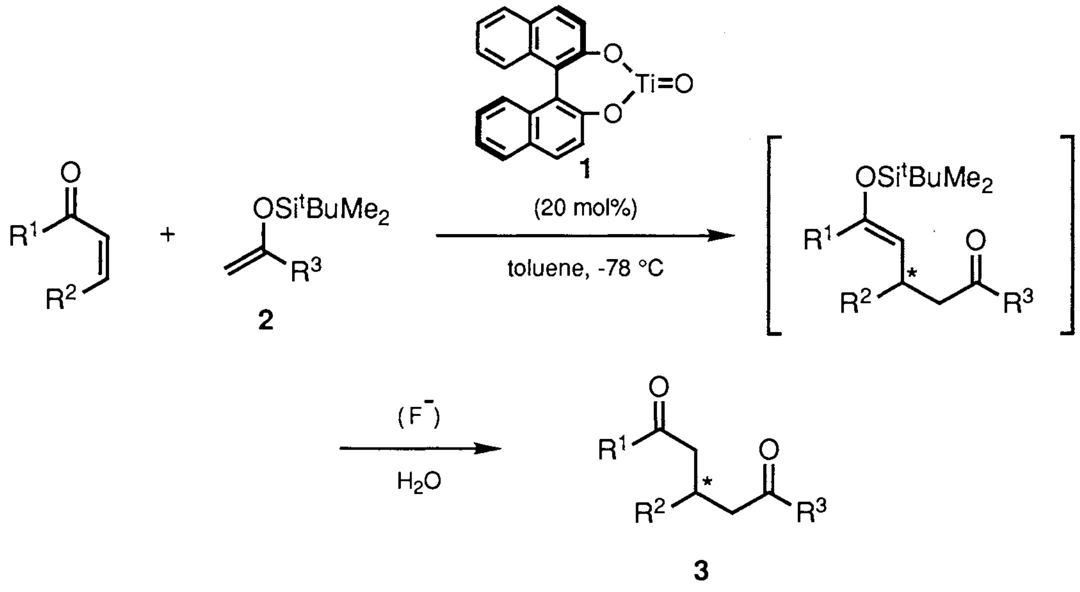

Table 1. Catalytic Asymmetric Michael Reaction using **1** as a Catalyst

Entry	R^1	R^2	R^3	Product	Yield/%[a]	ee/%[b]
1	$-(CH_2)_2-$		S^tBu (**2a**)	**3a**	59	59
2	$-(CH_2)_2-$		SCH_2Ph (**2b**)	**3b**	68	50
3	$-(CH_2)_2-$		$SCHPh_2$ (**2c**)	**3c**	75	90
4	$-(CH_2)_3-$		$SCHPh_2$ (**2c**)	**3d**	76	70
5	$-(CH_2)_4-$		$SCHPh_2$ (**2c**)	**3e**	33	40
6	Ph	Ph	$SCHPh_2$ (**2c**)	**3f**	82	36
7	p-MeO Ph	Ph	$SCHPh_2$ (**2c**)	**3g**	87	42

a) Isolated yields. b) Determined by HPLC analysis using a chiral column (see, experimental procedure).

Michael adduct (**3f**) with a moderate enantiomeric excess. The selectivity was rather improved when 4'-methoxychalcone was used.

A typical experimental procedure is described for the reaction of **2c** with 2-cyclopentenone; **1** (0.06 mmol), prepared by mixing a stoichiometric amount of (R)-binaphthol and $(iPrO)_2Ti=O$ in benzene, followed by azeotropic removal of the resulting 2-propanol, was dissolved in toluene (3 ml) and cooled to -78 °C. **2c** (0.36 mmol) and 2-cyclopentenone (0.3 mmol) in toluene (2 ml) were added, the mixture was stirred for 15 h, and then quenched with phosphate buffer (pH=7). After removal of insoluble materials by filtration, the aqueous layer was extracted with dichloromethane. The combined organic layer was dried and the solvent was removed under reduced pressure. The residue was treated with HF aq. in acetonitrile at -23 °C and then was purified by thin layer chromatography (silica gel) to yield Michael adduct **3c** in a 75% yield. The enantiomeric excess was determined to be 90% by using the HPLC analysis (Daicel CHIRALCEL OD).

Thus, the catalytic asymmetric Michael reaction of silyl enol ethers with α,β-unsaturated ketones was attained, for the first time, by using **1** as a catalyst. Although the selectivities are not yet satisfactory for some examples, especially in the reaction of acyclic α,β-unsaturated ketones, the adducts prepared from 2-cyclopentenone or 2-cyclohexenone would be useful intermediates for the synthesis of optically active terpenoides, prostagrandins, etc., and the present reaction provides a useful method for the preparation of these compounds. Further studies along this line to clarify the reaction mechanism and to improve the selectivities are now in progress.

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