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Tandem and Two-Directional Asymmetric Catalysis of the Mukaiyama Aldol Reaction

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Abstract: *Upon addition of an excess amount of an aldehyde 3, the Mukaiyama aldol reaction of a silyl enol ether 2 proceeds in tandem and two-directional fashion by the asymmetric catalysis of a binaphthol-derived chiral titanium complex (BINOL-Ti: 1) to give the silyl enol ether 4 in 77% isolated yield in more than 99% ee and 99% de. The present asymmetric catalytic Mukaiyama aldol reaction is characterized by amplification phenomena of the product chirality on going from the one-directional aldol intermediate 6 (98.5% ee, R) to the two-directional product 4 (99.6% ee, R,R). Further transformation of the pseudo C_2 symmetric product 4 (> 99% ee, > 99% de) in its' protected form as the silyl enol ether is established leading to a potentially potent analogue of HIVP inhibitor 9a.*
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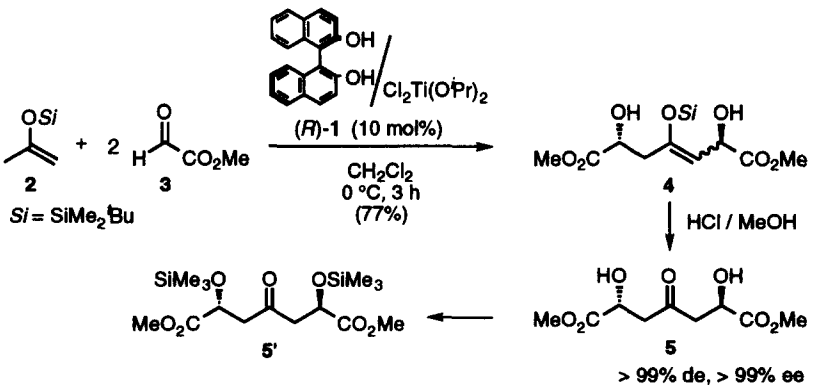
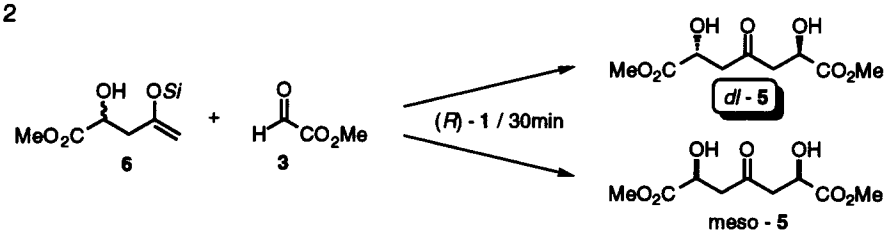
The aldol reaction constitutes one of the most fundamental bond construction processes in organic synthesis.[1] Therefore, a detailed understanding of the reaction mechanisms of aldol processes[2] and their asymmetric catalysis[3] have attracted recent attention. In the course of our studies on the asymmetric catalysis of the Mukaiyama aldol reaction (the Lewis acid-promoted carbonyl-addition of silyl enol ethers of ketones),[4] we made an unexpected observation: Upon addition of an excess amount of an aldehyde, the Mukaiyama aldol reaction proceeded in a two-directional fashion by the asymmetric catalysis of a binaphthol-derived chiral titanium complex (BINOL-Ti: **1**)[5] (Scheme 1). Tandem[6] and two-directional prototropic ene-type[7,8,9] aldol reactions are quite useful, because the regiochemical problem in enolate generation during the secondary step is inherently solved and, in addition, because the number of operations for carbon-carbon bond extention is reduced relative to the step-wise aldol reaction.[10] The kinetic future and synthetic application of this tandem and two-directional asymmetric catalysis of the Mukaiyama aldol reaction is the subject of this communication.

Scheme 1



The reaction was carried out by adding the *tert*-butyldimethylsilyl enol ether **2** and an excess amount of glyoxylate **3** (2 equiv.) at 0 °C to a dichloromethane solution containing 10 mol% of the chiral titanium complex (**1**), that was prepared from (*R*)-binaphthol and diisopropoxytitanium dichloride as reported previously.[11] The reaction was completed within 3 h as determined by TLC monitoring. Hydrolytic work-up with saturated sodium bicarbonate at 0 °C followed by flash column chromatography gave the silyl enol ether **4** in 77% isolated yield as a 1 : 4 geometrical (*E* / *Z*) mixture.[12] The enantiomeric and diastereomeric purity of the product **4** was determined to be more than 99% ee and 99% de by chiral capillary GLC (CP-Cyclodextrin-B-2,3,6-M-19, 25 m) (t_R (155 °C): (*R*, *R*) - **5**, 113.2 min; (*S*, *S*) - **5**, 114.4 min; meso-**5**, 114.4 min. t_R (150 °C): (*R*, *R*) - **5'**, 89.4 min; (*S*, *S*) - **5'**, 89.4 min; meso-**5'**, 92.6 min.) and ^{1}H NMR (300 MHz) analyses after hydrolysis to dihydroxyketone **5** or bis-silylation thereof to **5'** with bis(trimethylsilyl)trifluoroacetamide (BSTFA).

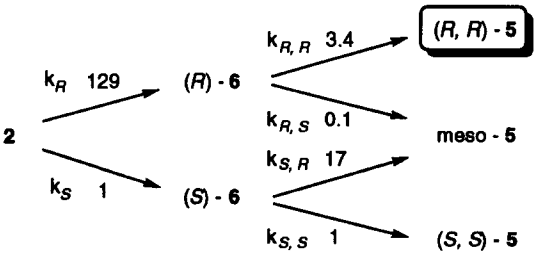
Scheme 2



6	yield	*dl*	:	meso
98.5% ee (*R*)	47%	98.4 (99.6% ee)	:	1.6
95.9% ee (*S*)	44%	5.9	:	94.1

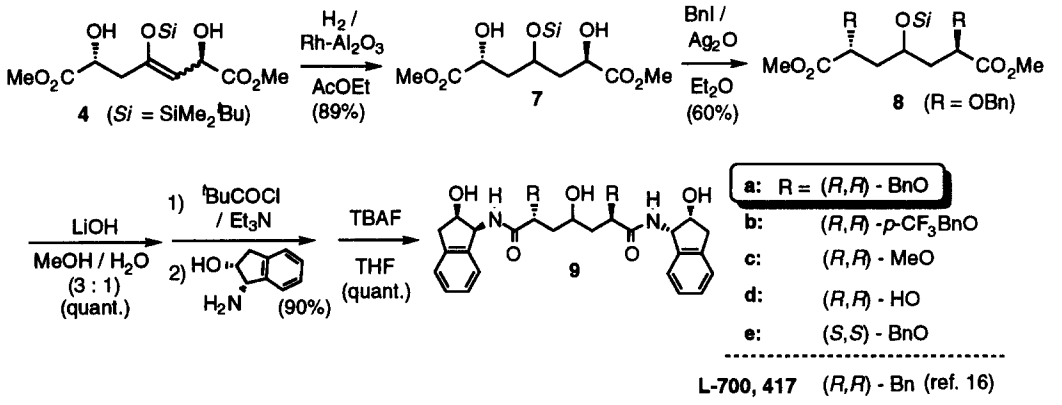
The two-directional asymmetric catalytic Mukaiyama aldol reaction is characterized by an unique kinetic feature of the one-directional aldol intermediates (*R*)- *vs.* (*S*)-**6**. Therefore, the amplification phenomena of the product chirality is observed on going from the one- (98.5% ee, *R*) to the two-directional product (99.6% ee, *R,R*) as shown in a control experiment (Scheme 2).[13] The secondary aldol reaction of the primary ene-type aldol adduct (*R*)-**6** in 98.5% ee was found, by catalysis of the (*R*)-catalyst (**1**), to provide 98.4% of the secondary product (*R,R*)-**5** in 99.6% ee along with 1.6% of the *meso*-diastereomer (**5**). On the contrary, the secondary reaction of the (*S*)-enantiomer (**6**) (95.9% ee, *S*) by the same catalyst (*R*)-**1** resulted mainly in the formation of *meso*-diastereomer **5** (94.1%) with 5.9% of the (*S,S*)-**5**. Thus, the secondary reaction of (*R*)-**6** catalyzed by the (*R*)-catalyst (**1**) leading to (*R,R*)-**5** is calculated to be 3.4 times as fast as the (*S*)-counterpart (**6**) to give the (*S,S*)-enantiomer and, therefore, the product chirality is amplified upon going from the one- to the two-directional product (Scheme 3).

Scheme 3



The pseudo C_2 symmetric nature of the two-directional product (> 99% ee and > 99% de) in its' protected form as the silyl enol ether should provide valuable synthetic applications in the context of the synthesis of C_2 symmetric HIV protease (HIVP) inhibitors **9**.[14] The complex of **9a** with HIVP is calculated to be more stable by 6.76 kcal/mol than the HIVP/L-700,417 complex. Thus, the synthesis of the potentially potent[15] homologue (**9a**) of the HIVP inhibitor, L-700,417[16,17] was established by hydrogenation (H_2/Rh-Al_2O_3, ethyl acetate), alkylation (BnBr/Ag_2O, ether), hydrolysis (LiOH/methanol-H_2O (3 : 1)), amide formation by the mixed anhydride method following the literature procedure[17] and de-silylation (TBAF, THF). A similar transformation produced other HIVP inhibitor analogues with different side chains (**9b** ~ **9e**).

Scheme 4



In summary, we have uncovered the first example of the tandem and two-directional asymmetric catalysis of the Mukaiyama aldol reaction with complete control of the absolute and relative stereochemistries of the pseudo C_2-symmetric product. We have further disclosed the amplification phenomena of the product chirality on going from the one-directional aldol intermediate to the two-directional aldol product.

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