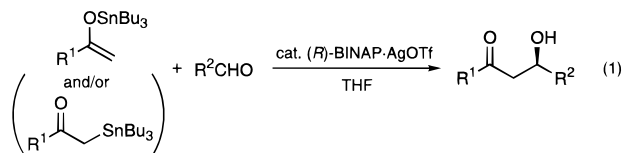# Enantioselective Aldol Reaction of Tin Enolates with Aldehydes Catalyzed by BINAP·Silver(I) Complex

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The catalytic asymmetric aldol reaction has been extensively studied during the past decade since it provides a favorable route to optically active β-hydroxy carbonyl compounds.[1] Although numerous successful methods have been developed, most of these are the chiral Lewis acid-catalyzed Mukaiyama aldol reactions using silyl enol ethers or ketene silyl acetals,[2-7] and there has been no report which includes enol stannanes. We report herein the first example of catalytic enantioselective aldol addition of tributyltin enolates to aldehydes employing BINAP· silver(I) complex as a catalyst (eq 1).

Table 1. Enantioselective Aldol Reaction of Tin Enolates with Aldehydes Catalyzed by BINAP·AgOTf Complex[a]

entry	tin enolate	aldehyde	yield, %[b]	% ee[c]
1		PhCHO	73	77
2		Ph⌕CHO	83	53
3		Ph⌕CHO	61	59
4		PhCHO	78	95
5		Ph⌕CHO	69	86
6		Ph⌕CHO	75	94
7	+ O–Sn form (4:1)	PhCHO	57	71
8		Ph⌕CHO	33	41
9		Ph⌕CHO	40	50

[a] Unless otherwise specified, the reaction was carried out using (R)-BINAP·AgOTf (10 mol%), tin enolate (1 equiv) and aldehyde (1 equiv) in THF at -20 °C for 8 h. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel OD-H, AD, or OB-H, Daicel Chemical Industries, Ltd.).

The tributyltin enolate is easily prepared from the corresponding enol acetate and tributyltin methoxide in the absence of solvent.[8] The tin enolate thus obtained exists in O−Sn form and/or C−Sn form; however, both species can be used for the aldol reaction of the present system. The tin enolate itself possesses adequate reactivity toward an aldehyde,[8b] for example, treatment of the tin enolate of acetone ($R^1 = CH_3$, C−Sn form, eq 1) with benzaldehyde ($R^2 = $ Ph) in dry THF at room temperature for 14 h gave the aldol adduct in 84% yield. In the presence of 10 mol % of (R)-BINAP·AgOTf complex,[9] however, the reaction proceeded much faster even at −20 °C and afforded the aldol product in 73% yield and 77% ee with R-configuration.[10] Several different solvents were tested for the reaction and THF was found to provide the best result.[11]
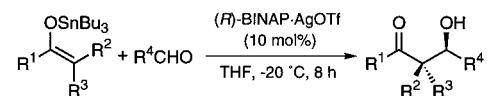
Optimal conditions were established using THF as solvent, and we then employed these conditions in catalytic enantioselective aldol reaction of a variety of tributyltin enolates with typical aromatic, α,β-unsaturated, and aliphatic aldehydes. The results are summarized in Table 1, and the characteristic features are as follows: (1) All reactions proceeded to furnish satisfactory yield in the presence of 10 mol % of (R)-BINAP·AgOTf complex at −20 °C for 8 h except reactions of acetophenone-derived tin enolate which gave relatively low yield (entries 7−9) and no dehydrated aldol adduct was observed; (2) with an α,β-unsaturated aldehyde, the 1,2-addition reaction took place exclusively (entries 2, 5, and 8); (3) a bulky alkyl substituent of tin enolate increased the enantioselectivity of the aldol reaction. For instance, the highest ee (95% ee) was obtained

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(11) Results using other solvents (solvent, yield, enantioselectivity): DME, 53% yield, 64% ee; $(MeO)_2CO$−THF (1:1), 46% yield, 55% ee; $(EtO)_2CO$, 75% yield, 55% ee; DMF, 37% yield, 34% ee; CH_3CN, 39% yield, 12% ee; $C_2H_5NO_2$, 16% yield, 46% ee.

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Table 2. Diastereo- and Enantioselective Aldol Reaction of Tin Enolates with Aldehydes Catalyzed by BINAP·AgOTf Complex[a]

entry	tin enolate	aldehyde	yield, %[b]	anti/syn[c]	% ee[d]
1[e]	OSnBu₃ (cyclopentenyl)	PhCHO	92	89/11	92[f]
2[g]	OSnBu₃ (cyclohexenyl)	PhCHO	94	92/8	93[h]
3[g,i]		PhCHO	95	93/7	94[j]
4[k]	OSnBu₃ (cycloheptenyl)	PhCHO	90	85/15	96[l]
5[m]	OSnBu₃, t-Bu	PhCHO	81	<1/99	95
6[m]		Ph-CHO	77	<1/99	95
7[n]	OSnBu₃, t-Bu	PhCHO	98	<1/99	91[o]

[a] Unless otherwise specified, the reaction was carried out using (*R*)-BINAP·AgOTf (10 mol%), tin enolate (1 equiv) and aldehyde (1 equiv) in THF at -20 °C for 8 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [e] O-Sn/C-Sn = 53/47. [f] The *syn*-isomer: 54% ee. [g] O-Sn/C-Sn > 99/1. [h] The *syn*-isomer: 25% ee. [i] 1 mol % of the catalyst was used. [j] The *syn*-isomer: 33% ee. [k] O-Sn/C-Sn > 99/1. [l] The *syn*-isomer: 41% ee. [m] O-Sn/C-Sn > 99/1. The *E/Z* ratio of O-Sn isomer was <1/99. [n] O-Sn/C-Sn > 99/1. The *E/Z* ratio of O-Sn isomer was <1/99. [o] Determined by HPLC analysis (Chiralcel OD-H) of the benzoate ester of the product.

when the tin enolate prepared from pinacolone was added to benzaldehyde (entry 4).

Employment of substituted enol stannanes for the present catalytic aldol reaction is quite attractive from the viewpoint of diastereoselectivity (*anti/syn* selectivity). In general, silyl enol ethers have been found to react with aldehydes with *syn* (*erythro*) selectivity irrespective of the stereochemistry (*E* or *Z*) in the presence of a catalytic amount of chiral Lewis acid.[2a,g,3b] Denmark et al. recently reported that the opposite *anti* aldol products were selectively obtained with excellent enantioselectivity in the chiral phosphoramide-catalyzed aldol reaction of a trichlorosilyl enolate of cyclohexanone with aldehydes.[12] We examined the BINAP·silver(I) catalyzed reaction of (*E*)- and (*Z*)-tin enolates (Table 2). Addition of the cyclohexanone-derived enol tributylstannane (*E*-enolate) to benzaldehyde under the influence of 10 mol % of (*R*)-BINAP·AgOTf in THF at −20 °C produced the optically active *anti* aldol adduct preferentially with an *anti/syn* ratio of 92/8,[13] contrary to the *syn* selectivity shown by typical chiral Lewis
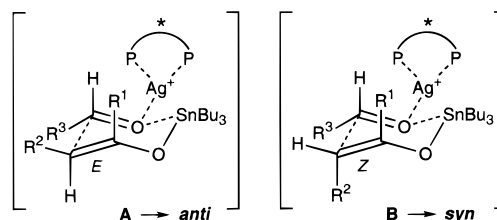
Figure 1. Probable cyclic transition-state structures.

acid catalysts.[2a,g,3b] The *anti* isomer indicated 93% ee (entry 2). Noteworthy was the fact that even if the amount of catalyst was reduced to 1 mol %, the *anti* selective aldol reaction still proceeded to provide high yield without any loss of the enantioselectivity (entry 3). The cyclopentanone and cycloheptanone derivatives also showed high *anti* selectivity (entries 1 and 4). In contrast, the *Z*-enolate derived from *tert*-butyl ethyl ketone provided the *syn* aldol adduct nearly exclusively with 95% ee in combination with benzaldehyde and hydrocinnamaldehyde (entries 5 and 6). Similarly, a remarkable *syn* selectivity was observed for the tin enolate of *tert*-butyl propyl ketone (entry 7).

These results clearly show that the diastereoselectivity depends on the geometry of enol stannane and that cyclic transition-state structures (**A** and **B**, Figure 1) are probable models. Thus, from the *E*-enolate, the *anti*-aldol product can be obtained via a cyclic transition state model **A**, and another model **B** connects the *Z*-enolate to the *syn* product. Similar six-membered cyclic models containing a BINAP-coordinated silver atom instead of tributylstannyl group are also possible alternatives when the transmetalation to silver enolate is sufficiently rapid.

The reaction reported herein represents a new class of highly enantioselective aldol reaction of aldehydes with tributyltin enolates using a catalytic amount of BINAP·Ag(I) complex. The reaction can be performed on a substantial scale using ordinary laboratory equipment, since no complex preparation of catalysts is required. Further work is now in progress on application of the catalytic asymmetric aldol addition and the detailed reaction mechanism.

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(13) (1-Cyclohexenyloxy)tributyltin reacted with benzaldehyde at −45 °C in the absence of catalyst to give the *anti* isomer selectively, while at 45 °C the *syn* isomer predominated.[8b] See also: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 162.