Enantioselective Aldol Reactions Catalyzed by Tin Methoxide and BINAP·Silver(I) Complex

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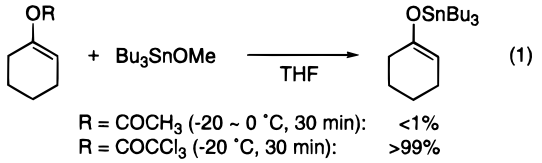
Aldol reaction is a useful method of preparing β-hydroxy carbonyl compounds and has attracted a great deal of attention from synthetic organic chemists.[1] Organotin(IV) enolates, existing usually in O−Sn form and/or C−Sn form, are versatile nucleophiles which exhibit high reactivity toward various electrophiles and can react with aldehydes in the absence or presence of a Lewis acid;[2] however, the aldol process has the disadvantage of requiring the stoichiometric use of toxic trialkyltin compounds. We report here the first example of the aldol reaction using a catalytic amount of tin enolate and the asymmetric version with BINAP·silver(I) catalyst.

Reaction of enol acetate **1** (R = CH_3) with trialkyltin methoxide is a convenient route to trialkyltin enolate **2** without the contamination by lithium halides (Figure 1).[3] Trialkyltin enolate **2** has been reported to undergo aldol condensation with aldehydes even at low temperature.[4] We envisaged that if the aldol product **3** could further react with a coexisting enol ester **1** to give the tin enolate **2** and ester **4**, the aldol reaction might proceed catalytically.

Thus, we initially examined the exchange reaction between cyclohexanone-derived enol acetate and tributyltin methoxide[3] to determine the optimal reaction conditions (eq 1). In the reaction at −20 °C and even at 0 °C, the formation of tin enolate was not observed at all. In marked contrast, the corresponding enol trichloroacetate[5] was nearly quantitatively transformed into the tributyltin enolate of cyclohexanone within 30 min at −20 °C (eq 1).[6]



We thus chose the 1-trichloroacetoxy cyclohexene as a substrate for the catalytic aldol reaction. The enol trichloroacetate was treated with benzaldehyde in the presence of 10 mol % of tributyltin methoxide in dry THF at −20 °C for 8 h and then at room temperature for 12 h; however, the aldol product was obtained in only 16% yield. As a consequence, the reaction between the tin alkoxide of aldol adduct and the enol trichloroacetate was found to progress sluggishly. We then verified another possibility of tin-catalyzed reaction (Figure 2). First, R_3SnOMe reacts with an enol trichloroacetate **5** to generate the trialkyltin enolate **2** and methyl trichloroacetate. Subsequently, the tin enolate **2** can be added to an aldehyde to give the aldol adduct **3**. Finally, protonolysis of the alkoxide by MeOH regenerates the tin methoxide. The rate of methanolysis is regarded as the key to success in the catalytic cycle.

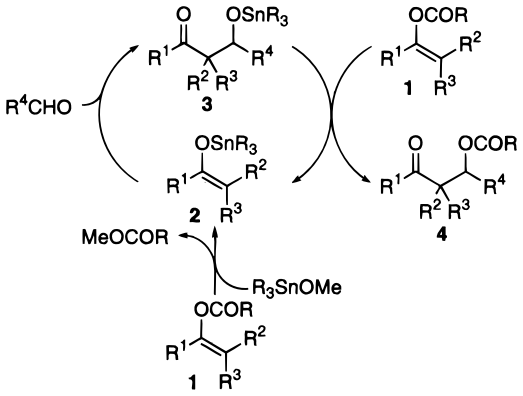


Figure 1. A possible catalytic cycle.

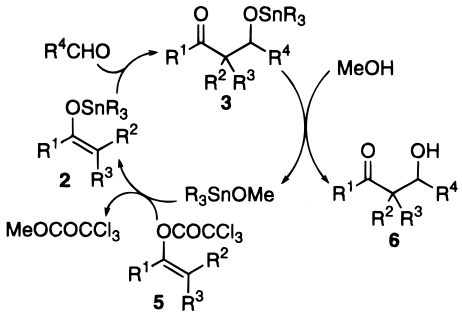


Figure 2. An alternative possible catalytic cycle.

Thus, when 10 mol % of tributyltin methoxide was slowly added to an equimolar mixture of the cyclohexanone-derived enol

(1) Reviews: (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 133 and related chapters. (b) Braun, M. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21, p 1603.

(2) Reviews: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987; p 286. (b) Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997; p 185.

(3) (a) Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97. (b) Lutsenko, I. F.; Baukov, Y. I.; Belavin, I. Y. *J. Organomet. Chem.* **1970**, *24*, 359. (c) Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima, S. *Chem. Lett.* **1984**, 497. Tributyltin enolates should be purified by distillation immediately before use.

(4) (a) Shenvi, S.; Stille, J. K. *Tetrahedron Lett.* **1982**, *23*, 627. (b) Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329. (c) Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima, S. *Chem. Lett.* **1983**, 851.

(5) Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* **1969**, *25*, 1679.

(6) Methyl trichloroacetate has been reported to be hydrolyzed in aqueous alkaline solution faster than methyl acetate, see: Barthel, J.; Bäder, G.; Schmeer, G. *Z. Phys. Chem.* **1968**, *62*, 63.

(7) The tributyltin alkoxide of aldol adduct was found to react with MeOH below −20 °C by ^{1}H NMR analysis. We further performed ^{119}Sn NMR experiments to investigate whether a pentacoordinate structure of the tin aldol product exists and contributes to its higher reactivity toward MeOH or not. The ^{119}Sn NMR spectrum (111.9 MHz, $CDCl_3$, room temperature, Me_4Sn; δ 0.0 ppm) of the tin alkoxide showed two peaks at δ 101.9 (*anti*) and 100.7 ppm (*syn*) with an *anti/syn* ratio of 23/77.[4c] These signals, however, appeared at a field almost similar to that of tributyltin methoxide (δ 108−110 ppm), which is regarded as a tetracoodinate tin compound.[2b]

(8) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

(9) Examples of catalytic asymmetric aldol reactions with silyl enol ethers or ketene silyl acetals, reviews: (a) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (c) Braun, M. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21, p 1730. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (e) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. Notable recent communications: (f) Chen, C.-T.; Chao, S.-D.; Yen, K.-C.; Chen, C.-H.; Chou, I.-C.; Hon, S.-W. *J. Am. Chem. Soc.* **1997**, *119*, 11341. (g) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (h) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918. Related catalytic asymmetric Mannich-type reactions: (i) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (j) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. Examples of direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones: (k) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (l) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561.

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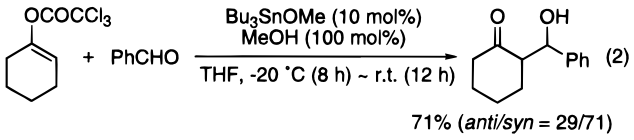
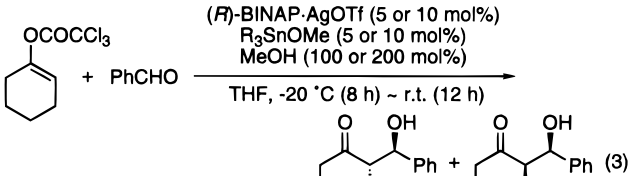
trichloroacetate and benzaldehyde in the presence of MeOH (100 mol %) in dry THF at −20 °C and then the mixture was stirred at −20 °C to room temperature for 20 h, the aldol adduct was produced in 71% yield with an *anti/syn* ratio of 29/71, which clearly proved the occurrence of the catalytic reaction (eq 2). This result showed that the in situ-generated tin enolate reacted selectively with the aldehyde despite the presence of an equal amount of MeOH, and tributyltin methoxide was regenerated by the subsequent reaction of the resulting tin alkoxide of aldol adduct with MeOH.[7]

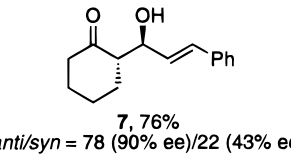


The above result further prompted us to use BINAP·silver(I) complex[8] as a chiral catalyst for the tin alkoxide-catalyzed aldol reaction (eq 3).[9] Treatment of benzaldehyde with the aforementioned enol trichloroacetate in the presence of (*R*)-BINAP·AgOTf complex (5 mol %), tributyltin methoxide (R = Bu, 5 mol %), and MeOH (200 mol %) in dry THF at −20 °C for 8 h and then at room temperature for 12 h gave a 92:8 mixture of optically active *anti* and *syn* aldol adduct in 82% combined yield (entry 3). The *anti* isomer showed 95% ee with (2*S*,1′*R*)-configuration, a level of enantioselectivity similar to that observed for a BINAP·silver(I) catalyzed aldol reaction of tributyltin enolates.[10] Alkyl substituents of tin methoxide to some extent influenced the catalytic activity, and trimethyltin methoxide (R = Me)[11] furnished a higher yield without decreasing diastereo- and enantioselectivities (entry 4). Use of (*R*)-*p*-Tol-BINAP[12] instead of (*R*)-BINAP resulted in a similar yield (86% yield) with slightly better selectivities (*anti/syn* = 94/6, *anti*-isomer: 96% ee, *syn*-isomer: 18% ee, entry 5). We additionally performed the Me_3SnOMe and (*R*)-*p*-Tol-BINAP·AgOTf catalyzed aldol reaction with (*E*)-cinnamaldehyde under the optimal reaction conditions and the aldol adduct **7** was obtained with satisfactory diastereo- and enantioselectivities.

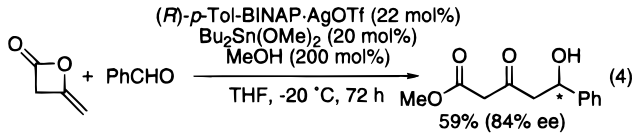


entry	mol% (*R*)-BINAP·AgOTf	mol% R_3SnOMe	mol% MeOH	product yield (%) *anti* (% ee)/*syn* (% ee)
1	10	10 (R = Bu)	100	62 84 (93)/16 (18)
2	10	10 (R = Bu)	200	94 92 (95)/ 8 (16)
3	5	5 (R = Bu)	200	82 92 (95)/ 8 (17)
4	5	5 (R = Me)	200	88 93 (94)/ 7 (6)
5	5[a]	5 (R = Me)	200	86 94 (96)/ 6 (18)

[a] (*R*)-*p*-Tol-BINAP was used.



We applied the present asymmetric catalytic process to the reaction of diketene with aldehydes in which a tin enolate, generated from a trialkyltin methoxide and diketene, is to be recycled in the presence of MeOH.[13] Although tributyltin methoxide could not give us the desired product in satisfactory yields,[14] the highest enantioselectivity (84% ee) was obtained along with a good chemical yield when the combination of diketene (5 equiv) and benzaldehyde (1 equiv) was treated with 22 mol % of (*R*)-*p*-Tol-BINAP and 20 mol % of $Bu_2Sn(OMe)_2$ in the presence of MeOH (200 mol %) in THF at −20 °C for 72 h (eq 4).



Acknowledgment. We thank Takasago International Corporation for its generous gift of (*R*)-*p*-Tol-BINAP. This paper is dedicated to Professor Ryoji Noyori on the occasion of his 60th birthday.

Supporting Information Available: Experimental procedures and spectral data for all products in eqs 3 and 4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA982857Q

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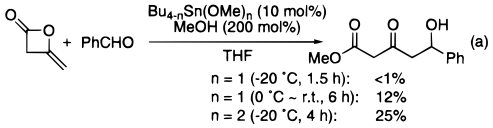
(11) Amberger, E.; Kula, M.-R.; Lorberth, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 138. See also: Jones, K.; Lappert, M. F. *J. Organomet. Chem.* **1965**, *3*, 295.

(12) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(13) For an example of enantioselective reaction of diketene with aldehydes with a stoichiometric amount of Ti(O-*i*-Pr)$_4$ and a catalytic amount (20 mol %) of chiral Schiff base, see: Oguni, N.; Tanaka, K.; Ishida, H. *Synlett* **1998**, 601.

(14) The reactivity of tributyltin methoxide (n = 1) toward diketene was low and the reaction required a temperature of more than 0 °C as shown in equation a.



In contrast, under the influence of 10 mol % of dibutyltin dimethoxide (n = 2), the reaction was found to proceed catalytically even at −20 °C and an aldol adduct was formed in 25% yield after 4 h of stirring.