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Asymmetric aldol reaction of enol trichloroacetate catalyzed by tin methoxide and BINAP·silver(I) complex

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Abstract—Enol trichloroacetate of cyclohexanone has been found to react with benzaldehyde in the presence of a catalytic amount of tributyltin methoxide and stoichiometric amount of MeOH to give an aldol adduct. Methanolysis of the in situ generating tin alkoxide of aldol adduct regenerates the tin methoxide, and thus the aldol reaction can proceed catalytically. The use of BINAP·silver(I) complex as an additional catalyst results in formation of optically active aldol products. This catalytic method has been further applied to the asymmetric reaction of diketene with benzaldehyde. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Organotin(IV) enolates, existing commonly in O–Sn form and/or C–Sn form, are known as versatile reagents which show high nucleophilicity toward electrophiles[1] and have been utilized in various organic reactions, e.g. alkylation,[2] acylation,[3] aldol reaction,[4] palladium-catalyzed cross-coupling reaction,[5] etc. Among them, aldol reaction is a beneficial method to prepare β-hydroxy carbonyl compounds, and has caught much attention from organic chemists.[6] Transmetallation of lithium enolates with trialkyltin halides is a simple and popular method of generating tin enolates.[7] In contrast, reaction of enol acetates with trialkyltin methoxide is a convenient alternative which can provide tin enolates without a contamination of lithium halides.[8] Trialkyltin enolates prepared from cyclohexanone by this way have been reported to undergo aldol condensation with aldehydes at −78°C, showing *anti* selectivity.[9] The diastereoselectivity is highly temperature dependent and the *syn* adduct predominates at higher temperature (45°C). The aldol reaction has such an interesting characteristic on diastereoselectivity markedly different from that of ordinary Mukaiyama type aldol reaction using silyl enol ethers,[10] however, the former aldol process possesses the disadvantage of requiring the stoichiometric use of toxic trialkyltin compounds. We describe here an example of the aldol condensation using a catalytic amount of tin enolate and the asymmetric process of this reaction with BINAP·silver(I) catalyst.[11]

2. Results and discussion

Fig. 1 shows an our original idea on the catalytic aldol reaction. Reaction of enol ester **1** with trialkyltin methoxide generates the corresponding trialkyltin enolate **2** which is anticipated to smoothly add to an aldehyde to produce aldol product **3**. We envisaged that if the tin alkoxide of aldol adduct **3** could successively react with the starting enol ester **1** to form ester of the aldol product **4** and regenerate the tin enolate **2**, the aldol reaction might advance catalytically.

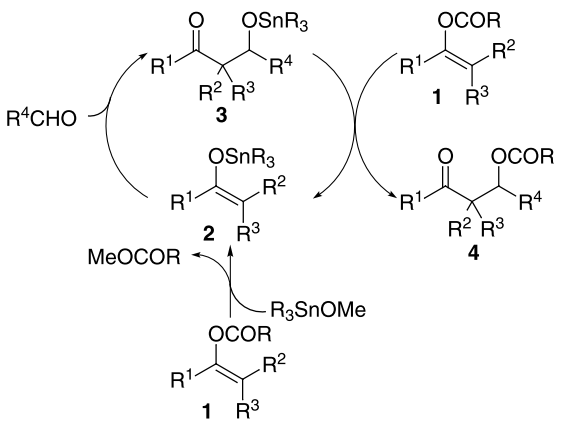

Figure 1. A possible catalytic cycle of tin methoxide-catalyzed aldol reaction.

Keywords: asymmetric aldol reaction; enol trichloroacetate; diketene; aldehyde; BINAP·silver(I) complex; tin methoxide.

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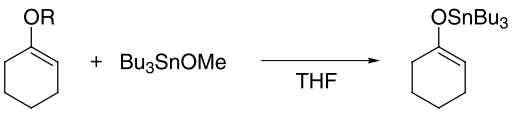
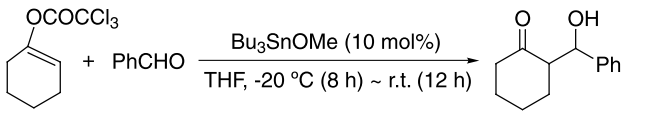
First of all, we studied the exchange reaction between enol acetate of cyclohexanone and tributyltin methoxide[8] to find out the optimum reaction conditions (Eq. (1)). In the reaction at −20 to 0°C, however, the desired tin enolate was not formed at all. In contrast, the corresponding enol trichloroacetate[12] was almost quantitatively converted to the tributyltin enolate within 30 min at −20°C (Eq. (1))[13]



(1)

R = $COCH_3$ (-20 ~ 0 °C, 30 min): <1%
R = $COCCl_3$ (-20 °C, 30 min): >99%

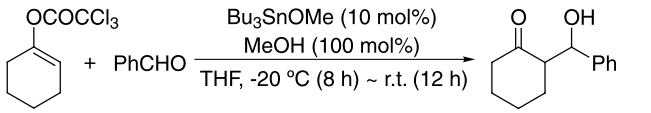
Accordingly, we selected the 1-trichloroacetoxy cyclohexene as a substrate for the tin-catalyzed aldol reaction. Although a mixture of the enol trichloroacetate and benzaldehyde was treated with a 10 mol% of tributyltin methoxide in dry THF at −20°C for 8 h and successively at room temperature for 12 h, the targeted aldol product was formed in an unacceptable yield with *syn* selectivity (Eq. (2)). As a result, the exchange reaction between the tin alkoxide of aldol product **3** and the enol trichloroacetate **1** (R=CCl_3) was found to proceed very slowly. We thereupon attempted an alternative possible tin-catalyzed reaction in the presence of MeOH. The catalytic cycle is shown in Fig. 2. Reaction of R_3SnOMe with an enol trichloroacetate **5** generates methyl trichloroacetate and the trialkyltin enolate **2**, which is then allowed to react with an aldehyde. Finally, protonation of the resulting tin alkoxide **3** by MeOH reproduces the tin methoxide. The rate of methanolysis is considered to be the key to success in the catalytic cycle



16% (*anti*/*syn* = 36/64)

(2)

In fact, when a similar reaction was performed in the presence of MeOH (100 mol%), the aldol adduct was obtained in 71% yield with an *anti*/*syn* ratio of 29/71, which obviously showed the occurrence of the catalytic reaction (Eq. (3)). From this result, the in situ-generated tin enolate was found to react selectively with the aldehyde even though the presence of an equal amount of MeOH and thus, tributyltin methoxide was shown to be effectively regenerated by the following reaction of the resulting tin alkoxide of aldol adduct with MeOH



71% (*anti*/*syn* = 29/71)

(3)

The aforementioned results further provoked us to employ BINAP·silver(I) complex[14] as a chiral catalyst for the tin alkoxide-catalyzed aldol reaction. We have previously shown that BINAP·AgOTf complex is a good chiral catalyst for asymmetric aldol reaction of tributyltin enolates.[15] Various methods for the catalytic asymmetric aldol reaction have been developed; however, most of these are the chiral Lewis acid-catalyzed Mukaiyama aldol reactions using silyl enol ethers or ketene silyl acetals,[16–18] and there has been no example using enol esters as the latent enolates. Yamagishi and co-workers independently examined the

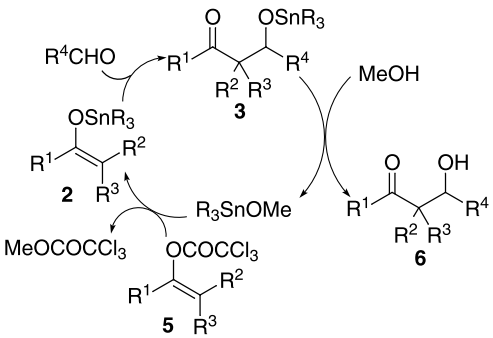
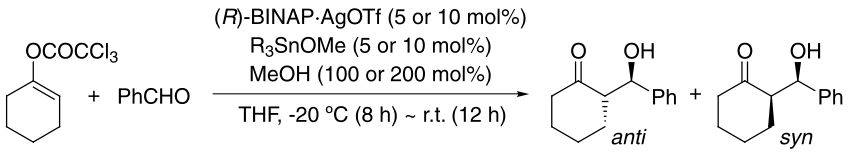


Figure 2. An alternative possible catalytic cycle of tin methoxide-catalyzed aldol reaction.

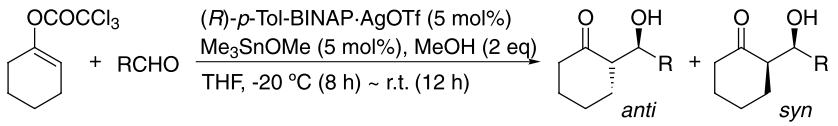
Table 1. BINAP·Ag(I) and tin methoxide catalyzed enantioselective aldol reaction of enol trichloroacetate of cyclohexanone

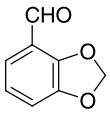


Entry	(*R*)-BINAP·AgOTf (mol%)	R_3SnOMe (mol%)	MeOH (mol%)	Product		
				Yield (%)[a]	*anti*/*syn*[b]	ee%[c]
1	10	10 (R=Bu)	100	62	84/16	93
2	10	10 (R=Bu)	200	94	92/8	95
3	5	5 (R=Bu)	200	82	92/8	95
4	5	5 (R=Me)	200	88	93/7	94
5	5[d]	5 (R=Me)	200	86	94/6	96

Unless otherwise noted, the reaction was carried out using (*R*)-BINAP·AgOTf (5 or 10 mol%), trialkyltin methoxide (5 or 10 mol%), enol trichloroacetate of cyclohexanone (1 equiv.), and benzaldehyde (1 equiv.) in THF containing MeOH (100 or 200 mol%) at −20°C for 8 h and then at room temperature for 12 h.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] The value corresponds to the *anti* isomer. Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries Ltd).
[d] (*R*)-*p*-Tol-BINAP·AgOTf was used.

Table 2. *anti*- and enantioselective aldol reaction of enol trichloroacetate of cyclohexanone with various aldehydes catalyzed by (*R*)-*p*-Tol-BINAP·AgOTf and Me_3SnOMe



Entry	Aldehyde	Yield (%)[a]	*anti*/*syn*[b]	ee%[c]
1	PhCHO	86	94/6	96
2	4-$MeOC_6H_4CHO$	66	94/6	95
3		49	80/20	77
4	1-Naphthyl-CHO	74	96/4	92
5	(*E*)-PhCH=CHCHO	76	78/22	90
6	(*E*)-$CH_3(CH_2)_2CH$=CHCHO	61	76/24	83
7	$Ph(CH_2)_2CHO$	29	84/16	79
8[d]	$CH_3(CH_2)_4CHO$	<1	–	–
9[e]	*i*-PrCHO	<1	–	–

Unless otherwise noted, the reaction was carried out using (*R*)-*p*-Tol-BINAP·AgOTf (5 mol%), trimethyltin methoxide (5 mol%), enol trichloroacetate of cyclohexanone (1 equiv.), and aldehyde (1 equiv.) in THF containing MeOH (2 equiv.) at −20°C for 8 h and then at room temperature for 12 h.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] The value corresponds to the *anti* isomer. Determined by HPLC analysis (Chiralcel OD-H or Chiralpak AD, Daicel Chemical Industries Ltd).
[d] The reaction was performed at −20°C for 4 h and then at room temperature for 21 h.
[e] The reaction was performed using isobutyraldehyde (5 equiv.) at −20°C for 5 h and then at room temperature for 15 h.

BINAP·Ag(I)-catalyzed asymmetric Mukaiyama aldol reaction using trimethylsilyl enol ethers and found that the reaction was accelerated by BINAP·$AgPF_6$ in DMF containing a small amount of water to give the aldol product with high enantioselectivity.[19] In contrast, we studied diverse reaction conditions of the BINAP·Ag(I) and tin methoxide-catalyzed aldol reaction of enol trichloroacetate of cyclohexanone and found that a combination of *p*-Tol-BINAP·AgOTf and trimethyltin methoxide (Me_3SnOMe) gave the highest enantioselectivity and a satisfactory chemical yield (Table 1). When benzaldehyde was treated with the enol trichloroacetate under the influence of (*R*)-BINAP·AgOTf complex (10 mol%), tributyltin methoxide (Bu_3SnOMe, 10 mol%), and MeOH (100 mol%) in dry THF at −20°C for 8 h and then at room temperature for 12 h, a 84/16 mixture of optically active *anti* and *syn* aldol adduct was formed in 62% combined yield (entry 1). The *anti* isomer revealed 93% 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.[15] An increase in the amount of MeOH to 200 mol% caused much improvement in the chemical yield and diastereoselectivity (entry 2). Since it was necessary to reduce the amount of toxic organostannanes from a practical point of view, we further attempted the reaction using less than 10 mol% of the tin methoxide and found that 82% yield of the product was still obtained even in the presence of 5 mol% of both catalysts (entry 3). Alkyl substituents of tin methoxide somewhat affected the catalytic activity, and Me_3SnOMe[20] provided a higher yield without lowering diastereo- and enantioselectivities (entry 4). Finally, a change of (*R*)-BINAP for (*R*)-*p*-Tol-BINAP[21] resulted in slightly better selectivities (*anti*/*syn*= 94/6, *anti*-isomer: 96% ee) with an analogous yield (86% yield, entry 5).

We further performed the Me_3SnOMe and (*R*)-*p*-Tol-BINAP·AgOTf catalyzed aldol reaction with various aromatic and α,β-unsaturated aldehydes under the optimum reaction conditions and the corresponding aldol adducts were obtained with satisfactory diastereo- and enantioselectivities (entries 1–6, Table 2). In the reaction with an α,β-unsaturated aldehyde, a 1,2-adduct was obtained exclusively (entries 5 and 6). Aliphatic aldehydes showed low or no reactivity even at room temperature (entries 7–9).

A probable catalytic cycle of this asymmetric aldol reaction is indicated in Fig. 3. First, R_3SnOMe reacts with enol trichloroacetate **5** to generate trialkyltin enolate **2** as described in Fig. 2. Subsequently, the tin enolate **2** adds to an aldehyde enantioselectively under the influence of (*R*)-BINAP·AgOTf complex to give the tin alkoxide of aldol adduct **7**. Finally, methanolysis of **7** furnishes the

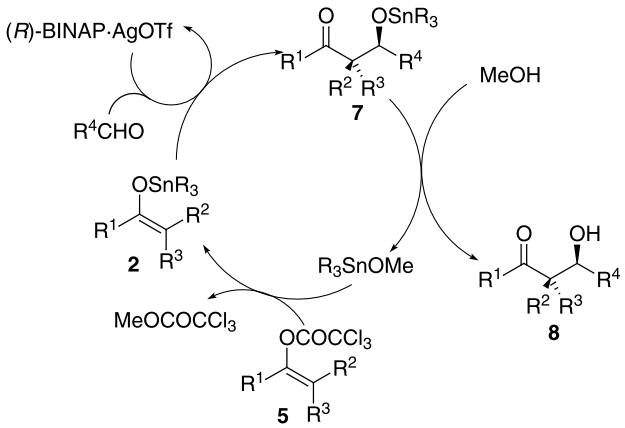
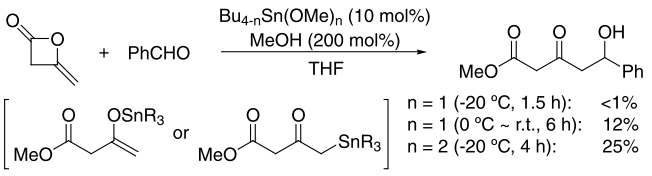


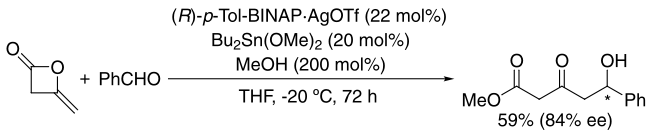
Figure 3. A proposed catalytic mechanism for the asymmetric aldol reaction catalyzed by (*R*)-BINAP·AgOTf and tin methoxide.

optically active aldol product **8** and regenerates the tin methoxide.

With this mechanistic guidance it became of interest to apply the present asymmetric catalytic process to a reaction of diketene with an aldehyde in which a tin enolate, generated from a trialkyltin methoxide and diketene, might be recycled in the presence of MeOH (Eq. (4)).[22] However, the reactivity of Bu_3SnOMe (n=1) toward diketene was low and the reaction required a temperature of more than 0°C. In contrast, under the influence of 10 mol% of dibutyltin dimethoxide [$Bu_2Sn(OMe)_2$, n=2], the reaction took place catalytically even at −20°C and the desired aldol adduct was obtained in 25% yield after 4 h of stirring. Then, we attempted the asymmetric version of the reaction using a BINAP·Ag(I) catalyst. Various reaction conditions and amounts of the catalysts were examined and as a result, the highest enantioselectivity (84% ee) was gained along with a satisfactory chemical yield when a mixture of diketene (5 equiv.) and benzaldehyde (1 equiv.) was exposed to 20 mol% of $Bu_2Sn(OMe)_2$ and 22 mol% of (*R*)-*p*-Tol-BINAP·AgOTf in THF containing MeOH (200 mol%) at −20°C for 72 h (Eq. (5))



(4)



(5)

One possible reason why MeOH reacts with the aldol adduct, faster than with in situ generating tin enolate, is that probably because the tin alkoxide exists as a pentacoordinate structure rather than a tetracoordinate structure (Fig. 4). Corriu et al. have reported that pentacoodinate silicates show higher reactivity than that of tetracoordinate silanes toward nucleophiles and in fact, *t*-BuMgBr is known to react with a pentacoordinate silicate, $[PhMeSiF_3]^-[K,18\text{-Crown-6}]^+$, a hundred times faster than the corresponding tetracoodinate silane, $PhMeSiF_2$.[23] So, we attempted NMR studies on the aldol reaction of benzaldehyde with tributyltin enolate of cyclohexanone followed by protonation by MeOH to examine the reactivity of the in situ generating tributyltin alkoxide of aldol adduct, and the tin alkoxide was found to react with MeOH below −20°C by ^1H NMR analysis (Fig. 5). 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, $CDCl_3$, rt, Me_4Sn; δ 0.0 ppm) of the tin alkoxide showed two peaks at δ 101.9 ppm (*anti*) and 100.7 ppm (*syn*) with an *anti*/*syn* ratio of 23/77.[9c] These signals, however, appeared at field almost similar to that of tributyltin methoxide (δ 108–110 ppm) or tributyltin enolate of cyclohexanone (δ 98.1 ppm) which is regarded as a tetracoodinate tin compound.[1b] A typical example of pentacoordinate tin compound has been reported to show a high field shifted peak at 43.5 ppm.[24] As a consequence, contribution of the pentacoordinate tin species to the catalytic cycle is not significant. However, an intramolecularly weakly coordinated tin alkoxide is a possible alternative.

The mechanism of the BINAP·AgOTf-catalyzed aldol reaction of trialkyltin enolate, generated from enol trichloroacetate and trialkyltin methoxide, has not been fully elucidated; however, the BINAP·AgOTf complex is considered to act as a chiral Lewis acid catalyst rather than a silver enolate, based on the following NMR results. When tributyltin enolate of cyclohexanone was treated with an equimolar mixture of (*R*)-BINAP·AgOTf complex and DMF in THF-d_8 at room temperature, peaks of the tin enolate disappeared and a set of new peaks assignable to 1-cyclohexenyl group appeared, while peaks of tributyltin triflate were not observed at all (Fig. 6). These observations are positive proof that the silver enolate was not generated. From the above NMR results and the facts that the diastereoselectivity of the BINAP·AgOTf-catalyzed aldol reaction of trialkyltin enolate depends on the geometry of enol stannane,[15] the cyclic transition-state structure shown in Fig. 6 can be viewed as a possible model for the aldol reaction.

3. Conclusion

We have demonstrated an example of aldol reaction of enol

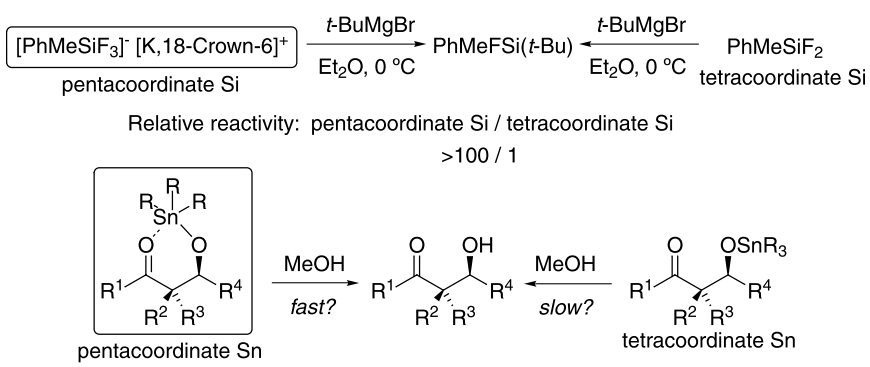


Figure 4. Reactivity of pentacoordinate silicon and tin compounds.

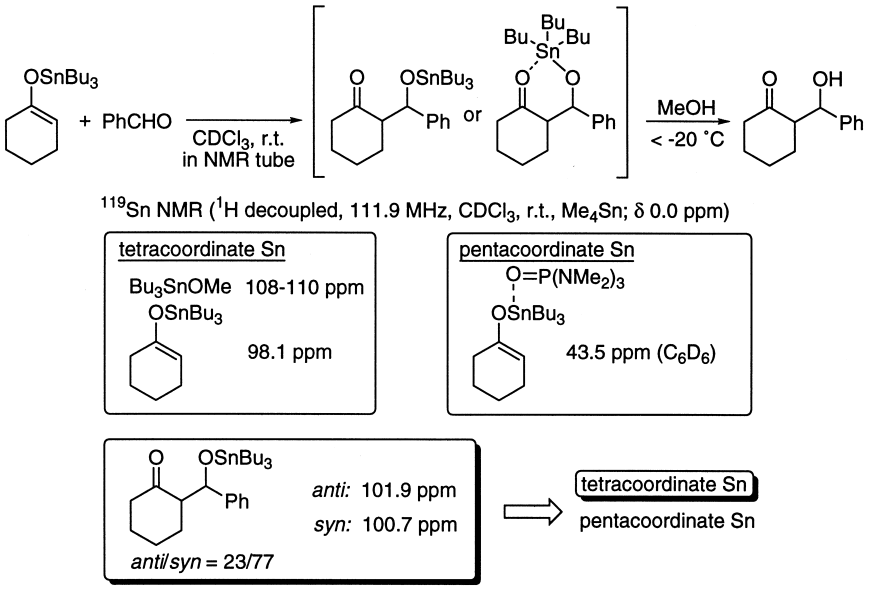


Figure 5. NMR studies on the aldol adducts.

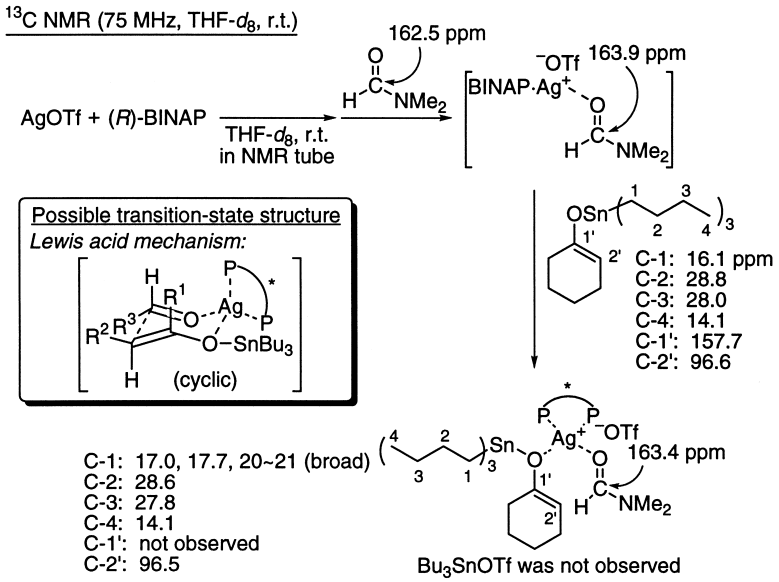


Figure 6. NMR studies on BINAP·AgOTf-catalyzed aldol reaction of tin enolate.

trichloroacetate of cyclohexanone or diketene catalyzed by tin methoxide in the presence of MeOH and the asymmetric version using BINAP·AgOTf or *p*-Tol-BINAP·AgOTf complex as a chiral catalyst. The main features of the present method are: (1) the procedure is operationally simple using readily available chemicals and can provide optically active *anti* β-hydroxy ketones with high enantioselectivity up to 96% ee; (2) diketene can be converted to an optically active methyl 5-hydroxy-3-oxopentanoate derivative by applying this method; (3) the in situ generating tin enolate reacts with an aldehyde much faster than with MeOH and the resulting tin alkoxide of aldol adduct is readily protonated by MeOH to regenerate tin methoxide; (4) this process is environmentally friendlier because the amount of toxic trialkyltin compounds is reduced to a catalytic amount. Hence, this catalytic procedure is useful and should be broadly applicable in organic synthesis.

4. Experimental

4.1. General methods

Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted using silica gel 60 (E. Merck 9385, 230–400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-300 (300 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (δ 0) or chloroform (δ 7.26). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were measured on a Varian Gemini-300 (75 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectra were reported relative to $CDCl_3$ (δ 77.0). Analytical high-performance liquid chromatography (HPLC) was done with a Shimadzu 10A

instrument using a chiral column (4.6 mm×25 cm, Daicel CHIRALCEL OD-H or CHIRALPAK AD). Optical rotation was measured on a JASCO DIP-1000 polarimeter.

All experiments were carried out under an atmosphere of standard grade argon gas (oxygen<10 ppm) and exclusion of direct light. Dry THF was used as purchased from Wako Pure Chemical (dehydrated, >99.5%, water: <0.005%). MeOH was purified by distillation over Mg turnings. Silver triflate (99+%) was used as purchased from Aldrich. (*R*)-BINAP (guaranteed reagent) was used as purchased from Nacalai Tesque. (*R*)-*p*-Tol-BINAP was donated by the Takasago International Corporation. Aldehydes were purified by distillation before use. 1-Trichloroacetoxy cyclohexene was prepared by treatment of cyclohexanone with trichloroacetic anhydride in the presence of a catalytic amount of *p*-toluenesulfonic acid and purified by distillation before use.[12] Tributyltin methoxide (Aldrich), dibutyltin dimethoxide (Aldrich), and diketene (Wako) were purified by distillation before use. Trimethyltin methoxide was prepared by treatment of (dimethylamino)trimethyltin (Aldrich) with MeOH and purified by distillation before use.[20] Other chemicals were used as purchased.

4.2. Typical experimental procedure for asymmetric reaction of benzaldehyde with 1-trichloroacetoxy cyclohexene catalyzed by (*R*)-*p*-Tol-BINAP·AgOTf complex and tributyltin methoxide

4.2.1. Synthesis of (2*S*,1′*R*)-2-(hydroxyphenylmethyl)-cyclohexanone (*anti*-isomer, entry 5 in Table 1 and entry 1 in Table 2).[25] A mixture of AgOTf (12.9 mg, 0.050 mmol) and (*R*)-*p*-Tol-BINAP (37.3 mg, 0.055 mmol) was dissolved in dry THF (6 mL) under argon atmosphere and with direct light excluded, and stirred at 20°C for 10 min. To the resulting solution were added dropwise MeOH (81 μL, 2.00 mmol), benzaldehyde (100 μL, 0.98 mmol), 1-trichloroacetoxy cyclohexene (243.2 mg, 1.00 mmol), and trimethyltin methoxide (0.52 M in THF, 100 μL, 0.052 mmol) successively at −20°C. After being stirred for 4 h at this temperature and then for 12 h at room temperature, the mixture was treated with MeOH (2 mL). The mixture was then treated with brine (2 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite® and silica gel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to afford a mixture of the aldol adducts (172.8 mg, 86% yield) as a colorless oil. The *anti*/*syn* ratio was determined to be 94/6 by ^{1}H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 96% ee and 18% ee, respectively, by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): $t_{syn\text{-minor}}$=14.2 min (2*S*,1′*S*), $t_{syn\text{-major}}$=15.7 min (2*R*,1′*R*), $t_{anti\text{-major}}$=17.4 min (2*S*,1′*R*), $t_{anti\text{-minor}}$=24.2 min (2*R*,1′*S*). The absolute configurations of all stereoisomers were unambiguously established by Denmark and co-workers.[25d] Spectral data of the *anti* isomer (oil, 96% ee): TLC R_f 0.11 (1/5 ethyl acetate/hexane); IR (neat) 3700–3140, 2940, 2863, 1700, 1605, 1497, 1453, 1401, 1312, 1296, 1227, 1204, 1130, 1042, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.37 (m, 1H, one proton of CH_2), 1.47–1.81 (m, 4H, 2 CH_2), 2.05–2.13 (m, 1H, one proton of CH_2), 2.31–2.42 (m, 1H, one proton of CH_2), 2.45–2.52 (m, 1H, one proton of CH_2), 2.57–2.67 (m, 1H, CH), 3.96 (d, 1H, *J*=2.8 Hz, OH), 4.79 (dd, 1H, *J*=2.8, 8.8 Hz, C*H*(OH)), 7.28–7.40 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 27.6, 30.6, 42.4, 57.3, 74.5, 126.9 (2 C), 127.7, 128.3 (2 C), 140.9, 215.3; $[\alpha]_D^{32}$=+19.7° (*c* 1.0, $CHCl_3$); elemental analysis calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90%; found: C 76.35, H 7.96%. Spectral data of the *syn* isomer (white solids, 18% ee): TLC R_f 0.13 (1/5 ethyl acetate/hexane); IR (KBr) 3600–3125, 2940, 2855, 1701, 1603, 1495, 1449, 1406, 1320, 1132, 1063, 986, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.80 (m, 4H, 2 CH_2), 1.81–1.91 (m, 1H, one proton of CH_2), 2.04–2.15 (m, 1H, one proton of CH_2), 2.32–2.51 (m, 2H, CH_2), 2.56–2.65 (m, 1H, CH), 3.01 (d, 1H, *J*=3.2 Hz, OH), 5.40 (d, 1H, *J*=2.4, 3.2 Hz, C*H*(OH)), 7.25–7.37 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.9, 27.8, 42.5, 57.1, 70.5, 125.7 (2 C), 126.8, 128.0 (2 C), 141.5, 214.5; $[\alpha]_D^{33}$=+37.6° (*c* 1.0, $CHCl_3$); elemental analysis calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90%; found: C 76.10, H 8.23%. Spectral data (TLC, IR, ^{1}H NMR, and ^{13}C NMR) of the *anti* and *syn* isomers indicated good agreement with reported data.[11,25,26]

4.2.2. 2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexanone (entry 2 in Table 2).[27] The *anti*/*syn* ratio was determined to be 94/6 by ^{1}H NMR analysis. Spectral data of the *anti* isomer (white solids, 95% ee): TLC R_f 0.17 (1/3 ethyl acetate/hexane); IR (KBr) 3700–3250, 2932, 1705, 1686, 1516, 1250, 1173, 1129, 1028, 830 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.33 (m, 1H, one proton of CH_2), 1.48–1.81 (m, 4H, 2 CH_2), 2.04–2.12 (m, 1H, one proton of CH_2), 2.30–2.41 (m, 1H, one proton of CH_2), 2.44–2.52 (m, 1H, one proton of CH_2), 2.55–2.64 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.94 (d, 1H, *J*=2.5 Hz, OH), 4.74 (dd, 1H, *J*=1.9, 8.8 Hz, C*H*(OH)), 6.88 (d, 2H, *J*=8.5 Hz, aromatic), 7.24 (d, 2H, *J*=8.8 Hz, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 27.8, 30.8, 42.6, 55.2, 57.5, 74.2, 113.7 (2C), 128.1 (2C), 133.1, 159.2, 215.7; $[\alpha]_D^{29}$=+20.5° (*c* 1.2, $CHCl_3$); elemental analysis calcd for $C_{14}H_{18}O_3$: C 71.77, H 7.74%; found: C 71.70, H 7.86%. The enantioselectivity was determined to be 95% ee by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): t_{major}=20.5 min, t_{minor}=27.7 min. Specific rotation of the *syn* isomer (white solids, 12% ee): $[\alpha]_D^{30}$=+22.0° (*c* 0.5, $CHCl_3$); elemental analysis calcd for $C_{14}H_{18}O_3$: C 71.77, H 7.74%; found: C 71.61, H 7.78%. The enantioselectivity was determined to be 12% ee by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): t_{major}=16.9 min, t_{minor}=17.7 min. Spectral data (TLC, IR, ^{1}H NMR, and ^{13}C NMR) of the *syn* isomer indicated good agreement with reported data.[26,27]

4.2.3. 2-[Hydroxy(2,3-methylenedioxyphenyl)methyl]-cyclohexanone (entry 3 in Table 2). The *anti*/*syn* ratio was determined to be 80/20 by ^{1}H NMR analysis. Spectral data of the *anti* isomer (white solids, 77% ee): TLC R_f 0.13 (1/3 ethyl acetate/hexane); IR (KBr) 3550–3200, 2931, 2852, 1717, 1684, 1559, 1541, 1509, 1489, 1456, 1254,

1127, 1048, 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (m, 1H, one proton of CH_2), 1.54–1.74 (m, 3H, CH_2 and one proton of CH_2), 1.82 (m, 1H, one proton of CH_2), 2.11 (m, 1H, one proton of CH_2), 2.31–2.54 (m, 2H, CH_2), 2.78–2.90 (m, 1H, CH), 3.98 (s, 1H, OH), 4.95 (d, 1H, J=8.7 Hz, C*H*(OH)), 5.95 (s, 1H, one proton of CH_2), 5.98 (s, 1H, one proton of CH_2), 6.79 (m, 1H, aromatic), 6.85 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 27.8, 30.5, 42.6, 55.9, 70.4, 100.0, 100.8, 108.0, 120.6 (2 C), 121.8 (2 C), 215.5; $[\alpha]_D^{31}$=+8.9° (*c* 1.0, $CHCl_3$); elemental analysis calcd for $C_{14}H_{16}O_4$: C 67.72, H 6.51%; found: C 67.78, H 6.73%. The enantioselectivity was determined to be 70% ee by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): t_{major}=23.5 min, t_{minor}=28.3 min. Spectral data of the *syn* isomer (white solids, 10% ee): TLC R_f 0.21 (1/3 ethyl acetate/hexane); IR (KBr) 3670–3160, 2954, 1698, 1636, 1559, 1541, 1509, 1489, 1458, 1252, 1115, 1050, 967, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52–1.89 (m, 5H, one proton of CH_2 and 2 CH_2), 2.08 (m, 1H, one proton of CH_2), 2.33–2.50 (m, 2H, CH_2), 2.75 (m, 1H, CH), 3.06 (s, 1H, OH), 5.50 (br s, 1H, C*H*(OH)), 5.90 (s, 1H, one proton of CH_2), 5.98 (s, 1H, one proton of CH_2), 6.76 (d, 1H, J=8.1 Hz, aromatic), 6.84 (t, 1H, J=7.8 Hz, aromatic), 6.76 (d, 1H, J=7.8 Hz, aromatic); $[\alpha]_D^{29}$=+1.2° (*c* 1.2, $CHCl_3$); elemental analysis calcd for $C_{14}H_{16}O_4$: C 67.72, H 6.51%; found: C 67.65, H 6.71%. The enantioselectivity was determined to be 10% ee by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): t_{major}=15.9 min, t_{minor}=17.4 min.

4.2.4. 2-[(1-Naphthyl)hydroxymethyl]cyclohexanone (entry 4 in Table 2).[25c,d] The *anti*/*syn* ratio was determined to be 96/4 by ^1H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 92% ee and 42% ee, respectively, by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): $t_{syn\text{-minor}}$=15.9 min, $t_{syn\text{-major}}$=20.0 min, $t_{anti\text{-minor}}$=33.7 min (2*R*,1′*S*), $t_{anti\text{-major}}$=35.3 min (2*S*,1′*R*). The absolute configurations of the *anti* isomers were assigned by Denmark and co-workers.[25c,d] Specific rotation of the *anti* isomer (92% ee): $[\alpha]_D^{27}$=+8.4° (*c* 1.0, $CHCl_3$); elemental analysis calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13%; found: C 80.29, H 7.31%. Specific rotation of the *anti* isomer (42% ee): $[\alpha]_D^{27}$=+54.3° (*c* 0.58, $CHCl_3$); elemental analysis calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13%; found: C 80.27, H 7.27%. Other spectral data (TLC, IR, ^1H and ^{13}C NMR) of the *anti* and *syn* isomers indicated good agreement with reported data.[25c,d,26b]

4.2.5. 2-[(*E*)-1-Hydroxy-3-phenyl-2-propenyl]cyclohexanone (entry 5 in Table 2).[11,25b–d] The *anti*/*syn* ratio was determined to be 78/22 by ^1H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 90% ee and 43% ee, respectively, by HPLC analysis using a chiral column (Chiralpak AD, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=40/1, flow rate=0.5 mL/min): $t_{syn\text{-minor}}$=36.7 min, $t_{syn\text{-major}}$=46.1 min, $t_{anti\text{-major}}$=49.6 min (2*S*,1′*R*), $t_{anti\text{-minor}}$=57.3 min (2*R*,1′*S*). The absolute configurations of the *anti* isomers were assigned by Denmark and co-workers.[25b–d] Spectral data of the *anti* isomer (oil, 90% ee): TLC R_f 0.14 (1/3 ethyl acetate/hexane); IR (neat) 3630–3130, 2938, 2863, 1700, 1599, 1495, 1449, 1130, 1055, 970, 750, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.73 (m, 3H, CH_2 and one proton of CH_2), 1.83–1.93 (m, 1H, one proton of CH_2), 2.05–2.17 (m, 2H, CH_2), 2.30–2.55 (m, 3H, CH_2 and CH), 3.65 (d, 1H, J=3.4 Hz, OH), 4.44 (ddd, 1H, J=3.4, 7.4, 7.9 Hz, C*H*(OH)), 6.19 (dd, 1H, J=7.4, 15.9 Hz, CH), 6.62 (d, 1H, J=15.9 Hz, CH), 7.22–7.40 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 27.5, 30.4, 42.4, 56.0, 72.8, 126.3 (2C), 127.5, 128.3 (2C), 128.8, 131.8, 136.4, 214.7; $[\alpha]_D^{27}$=−28.7° (*c* 0.51, $CHCl_3$); elemental analysis calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88%; found: C 78.22, H 8.14%. Spectral data of the *syn* isomer (white solids, 43% ee): TLC R_f 0.18 (1/3 ethyl acetate/hexane); IR (KBr) 3580–3250, 2934, 2857, 1698, 1599, 1495, 1451, 1424, 1314, 1130, 1123, 970, 760, 739, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52–1.78 (m, 3H, CH_2 and one proton of CH_2), 1.86–1.96 (m, 1H, one proton of CH_2), 2.05–2.17 (m, 2H, CH_2), 2.30–2.49 (m, 2H, CH_2), 2.53–2.62 (m, 1H, CH), 2.96 (d, 1H, J=5.0 Hz, OH), 4.77 (ddt, J=1.8, 5.0, 6.0 Hz, 1H, C*H*(OH)), 6.22 (dd, 1H, J=6.0, 16.0 Hz, CH), 6.64 (dd, 1H, J=1.3, 16.0 Hz, CH), 7.21–7.40 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 27.3, 27.5, 42.5, 55.5, 70.5, 126.3 (2C), 127.5, 128.5 (2C), 129.0, 130.8, 136.7, 214.2; $[\alpha]_D^{27}$=−34.9° (*c* 1.0, $CHCl_3$); elemental analysis calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88%; found: C 78.12, H 8.12%. Spectral data (TLC, IR, ^1H and ^{13}C NMR) of the *anti* and *syn* isomers indicated good agreement with reported data.[11,25b–d,26b]

4.2.6. 2-[(*E*)-1-Hydroxy-2-hexenyl]cyclohexanone (entry 6 in Table 2).[27b] The *anti*/*syn* ratio was determined to be 76/24 by ^1H NMR analysis. Spectral data of the *anti* isomer (colorless oil, 83% ee): TLC R_f 0.20 (1/3 ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.5 Hz, CH_3), 1.30–1.47 (m, 3H, CH_2 and one proton of CH_2), 1.61–1.74 (m, 2H, CH_2), 1.87 (m, 1H, one proton of CH_2), 1.96–2.11 (m, 4H, 2 CH_2), 2.27–2.44 (m, 3H, CH_2 and CH), 3.59 (s, 1H, OH), 4.19 (t, 1H, J=8.0 Hz, C*H*(OH)), 5.40 (dd, 1H, J=7.8, 15.3 Hz, CH), 5.68 (dt, 1H, J=6.9, 15.6 Hz, CH); $[\alpha]_D^{26}$=−3.1° (*c* 0.82, $CHCl_3$). The enantioselectivity was determined to be 83% ee by HPLC analysis using a chiral column (Chiralpak AD, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=40/1, flow rate=0.5 mL/min): t_{major}=32.6 min, t_{minor}=34.7 min. Spectral data of the *syn* isomer (colorless oil, 48% ee): TLC R_f 0.25 (1/3 ethyl acetate/hexane); IR (neat) 3650–3120, 2960, 2932, 2869, 1706, 1456, 1312, 1129, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.4 Hz, CH_3), 1.34–1.46 (m, 2H, CH_2), 1.53–1.77 (m, 3H, CH_2 and one proton of CH_2), 1.83–2.13 (m, 5H, 2 CH_2 and one proton of CH_2), 2.27–2.50 (m, 3H, CH_2 and CH), 2.82 (d, 1H, J=4.8 Hz, OH), 4.49 (br s, 1H, C*H*(OH)), 5.47 (dd, 1H, J=6.6, 15.6 Hz, CH), 5.68 (dt, 1H, J=6.8, 15.6 Hz, CH); $[\alpha]_D^{26}$=−11.5° (*c* 0.87, $CHCl_3$). The enantioselectivity was determined to be 48% ee by HPLC analysis using a chiral column (Chiralpak AD, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=40/1, flow rate=0.5 mL/min): t_{minor}=27.5 min, t_{major}=31.3 min. Spectral data (IR and ^1H NMR) of the *anti* and *syn* isomers indicated good agreement with reported data.[27b]

4.2.7. 2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (entry 7 in Table 2).[25c,d] The *anti*/*syn* ratio was determined

to be 84/16 by ^{1}H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 79% ee and 60% ee, respectively, by HPLC analysis using two chiral columns (Chiralcel OD-H and Chiralpak AD, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=20/1, flow rate=0.5 mL/min): $t_{anti\text{-major}}$=46.4 min, $t_{syn\text{-minor}}$=48.5 min, $t_{anti\text{-minor}}$=54.1 min, $t_{syn\text{-major}}$=58.7 min. Spectral data of a 84/16 mixture of the *anti* and *syn* isomers (colorless oil): TLC R_f 0.21 (1/3 ethyl acetate/hexane); IR (neat) 3630–3125, 3027, 2938, 2863, 1698, 1603, 1497, 1453, 1312, 1130, 749, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.97 (m, 6H, $3CH_2$), 2.03–2.14 (m, 2H, CH_2), 2.25–2.45 (m, 3H, CH_2 and CH), 2.64–2.75 (m, 1H, one proton of CH_2), 2.85–2.94 (m, 1H, one proton of CH_2), 3.56 (d, 0.84H, J=3.6 Hz, OH), 3.70 (m, 0.16H, OH), 3.76 (m, 0.84H, C*H*(OH)), 4.12 (m, 0.16H, C*H*(OH)), 7.16–7.32 (m, 5H, aromatic); $[\alpha]_D^{25}=-14.5°$ (*c* 1.68, $CHCl_3$); elemental analysis calcd for $C_{15}H_{20}O_2$: C 77.55, H 8.68%; found: C 77.44, H 8.92%. Spectral data (TLC, IR, and ^{1}H NMR) of the mixture of the *anti* and *syn* isomers indicated good agreement with reported data.[25c,d]

4.3. Typical experimental procedure for asymmetric reaction of benzaldehyde with diketene catalyzed by (*R*)-*p*-Tol-BINAP·AgOTf complex and dibutyltin dimethoxide

4.3.1. Synthesis of optically active methyl 5-hydroxy-3-oxo-5-phenylpentanoate (Eq. (5)).[28] A mixture of AgOTf (56.5 mg, 0.22 mmol) and (*R*)-*p*-Tol-BINAP (162.9 mg, 0.24 mmol) was dissolved in dry THF (6 mL) under argon atmosphere and with direct light excluded, and stirred at 20°C for 10 min. To the resulting solution were added dropwise MeOH (80 μL, 2.00 mmol), benzaldehyde (100 μL, 0.98 mmol), diketene (385 μL, 4.99 mmol), and dibutyltin dimethoxide (47 μL, 0.20 mmol) successively at −20°C. After being stirred for 72 h at this temperature, the mixture was treated with MeOH (2 mL). After warming to room temperature, the mixture was treated with brine (2 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite® and silica gel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to afford the aldol adduct (129.4 mg, 59% yield) as a colorless oil. The enantioselectivity was determined to be 84% ee by HPLC analysis using a chiral column (Chiralpak AD, Daicel Chemical Industries Ltd, hexane/*i*-PrOH=9/1, flow rate=0.5 mL/min): t_{major}=29.6 min, t_{minor}=33.2 min. The absolute configuration of the major enantiomer is not known. Spectral data of the product: TLC R_f 0.09 (1/3 ethyl acetate/hexane); IR (neat) 3700–3125, 2955, 1742, 1710, 1495, 1437, 1320, 750, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (dd, 1H, J=3.5, 17.4 Hz, one proton of CH_2), 2.98 (br s, 1H, OH), 3.02 (dd, 1H, J=8.9, 17.4 Hz, one proton of CH_2), 3.52 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 5.20 (dd, 1H, J=3.5, 8.9 Hz, C*H*(OH)), 7.28–7.38 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 51.5, 52.4, 69.7, 125.6 (2C), 127.8, 128.5 (2C), 142.5, 167.2, 202.6; $[\alpha]_D^{30}=+51.8°$ (*c* 1.0, $CHCl_3$).

4.4. Experimental procedure for the NMR studies on aldol reaction of benzaldehyde with tributyltin enolate of cyclohexanone followed by protonation with MeOH (Fig. 5)

A solution of tributyltin enolate of cyclohexanone (175 μL, 0.50 mmol)[15] in dry $CDCl_3$ (0.7 mL, distilled from CaH_2) was placed into a dried 5 mm NMR tube. After addition of benzaldehyde (50 μL, 0.49 mmol) at room temperature under an argon stream, the resulting mixture was shaken for a few minutes followed by measurement of the ^{119}Sn NMR spectrum (111.9 MHz, rt, Me_4Sn; δ 0.0 ppm) to show two peaks of the in situ generating tributyltin alkoxide of aldol adduct at δ 101.9 ppm (*anti*-isomer) and 100.7 ppm (*syn*-isomer) with an *anti*/*syn* ratio of 23/77. To the mixture, dry MeOH (25 μL, 0.62 mmol) was added at −40°C and then, ^{1}H NMR (300 MHz) measurement of the mixture was performed at −40, −20°C, and room temperature to indicate the formation of the protonated product at −40°C and the disappearance of the tin alkoxide at room temperature.

4.5. Experimental procedure for the ^{13}C NMR measurement of a 1:1 mixture of (*R*)-BINAP·AgOTf and DMF in THF-d_8 (Fig. 6)

AgOTf (51.3 mg, 0.20 mmol) and (*R*)-BINAP (125.3 mg, 0.20 mmol) were placed into a dried 5 mm NMR tube and the mixture was dissolved in dry THF-d_8 (0.5 mL) under argon atmosphere and with direct light excluded, and stirred at room temperature for 10 min. To the resulting clear solution, dry DMF (15 μL, 0.19 mmol, distilled from $MgSO_4$) was added at room temperature and ^{13}C NMR (75 MHz) measurement of the mixture was performed at this temperature, showing a shifted peak of DMF at δ 163.9 ppm (uncomplexed DMF: δ 162.5 ppm). Subsequently, tributyltin enolate of cyclohexanone (70 μL, 0.20 mmol)[15] was added to the mixture at room temperature followed by measurement of the ^{13}C NMR spectrum to reveal a peak of DMF at δ 163.4 ppm and set of shifted peaks attributable to (1-cyclohexenyloxy)tributyltin shown in Fig. 6.

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