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# Methanol-Assisted Catalysis by Chiral Tin Methoxides: An Alternative Asymmetric Aldol Process

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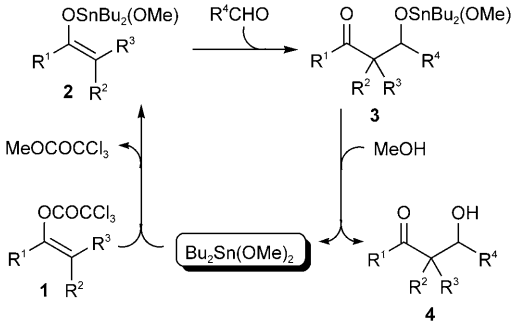
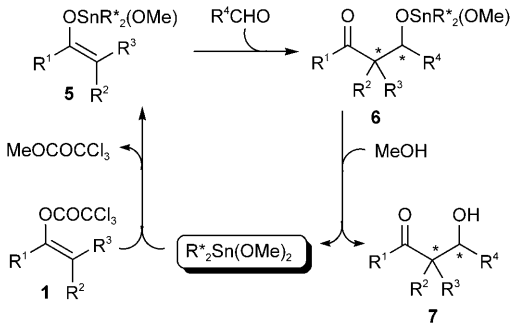
The catalytic asymmetric aldol reaction is one of the most popular routes to nonracemic β-hydroxy carbonyl compounds.[1] Numerous chiral catalysts have been designed and prepared in an effort to develop an aldol process that has superior stereoselectivity and chemical yield. Catalyst/nucleophile combinations in catalytic systems are roughly classified into three types: 1) chiral Lewis acid/trialkylsilyl enolate system (Mukaiyama aldol type),[2] 2) chiral Lewis base/trichlorosilyl enolate system,[3] and 3) chiral organocatalyst/carbonyl compound system (direct aldol type).[4] However, to the best of our knowledge, there are few examples of the catalytic enantioselective aldol reaction via a chiral metal enolate.[5] We report here the synthesis of binaphthol-based chiral organotin(IV) compounds and the asymmetric aldol reaction of alkenyl trichloroacetates using the chiral tin compound as a catalyst, which is regenerated in the presence of methanol. This asymmetric aldol reaction proceeds via a chiral tin enolate according to a catalytic mechanism that is different from those of the above-mentioned conventional aldol processes.

We have previously found that dibutyltin dimethoxide ($Bu_2Sn(OMe)_2$) catalyzes the aldol reaction between alkenyl trichloroacetates and aldehydes including aliphatic aldehydes in the presence of MeOH.[6] The proposed catalytic mechanism is shown in Scheme 1. First, alkenyl trichloroacetate **1** reacts with $Bu_2Sn(OMe)_2$ to give tin enolate **2** and methyl trichloroacetate. Then, an aldehyde is added to tin enolate **2** to form tin alkoxide of aldol adduct **3**. Finally, protonation of tin alkoxide **3** with methanol completes the catalytic cycle and $Bu_2Sn(OMe)_2$ is regenerated together with target aldol product **4**. The low rate of protonation of tin enolate **2** with methanol compared to the rate of addition of tin enolate **2** to aldehyde is the key to the successful catalytic reaction.




Scheme 1. Proposed catalytic cycle for the aldol reaction of alkenyl trichloroacetates with aldehydes catalyzed by $Bu_2Sn(OMe)_2$.

We envisioned that if a chiral tin dimethoxide, $R^*_2Sn(OMe)_2$, is used as a chiral catalyst in the present catalytic system, an asymmetric version of the catalytic aldol reaction might be possible in which nonracemic aldol product **7** or its tin alkoxide **6** is formed via chiral tin enolate **5** (Scheme 2).




Scheme 2. Plausible catalytic cycle for the asymmetric version of the aldol reaction.

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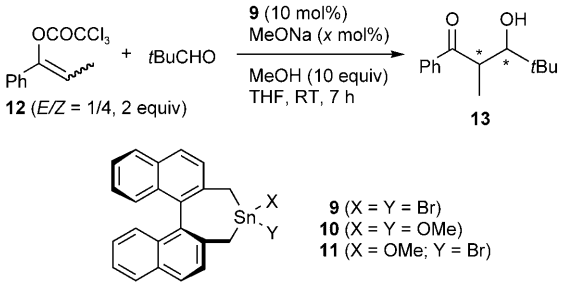
As the chiral tin catalyst, we chose a binaphthol-derived organotin compound as numerous chiral catalysts with a binaphthyl structure have been developed and shown to be effective in various asymmetric reactions.[7] We first planned to synthesize chiral tin dimethoxide **10** from (*S*)-BINOL (**8**). According to the reported methods,[8] chiral tin dibromide **9** was prepared from **8** in 20% overall yield; however, we failed to obtain the desired tin dimethoxide **10** by treatment of tin dibromide **9** with two equivalents of sodium methoxide in methanol because of the low stability of **10** (Scheme 3).



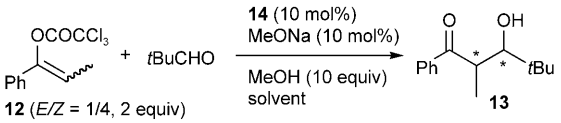

Scheme 3. Synthesis of aldol **13**. Catalyst **10** (formed from **9** and MeONa; $x=20$), yield: $<1$%. Catalyst **11** (formed from **9** and MeONa; $x=10$), yield: 10%, *syn*/*anti* 78:22, *ee* = 24% (*syn*).

Thus, we tried to generate **10** in situ and to use it directly as a chiral catalyst in the aldol reaction of propiophenone-derived alkenyl trichloroacetate **12** with pivalaldehyde at room temperature for 7 h. Unfortunately, desired aldol product **13** was not formed at all (Scheme 3). In contrast, corresponding tin bromide methoxide **11**, which was generated from an equimolar mixture of **9** and sodium methoxide in MeOH, showed high reactivity and in fact, the reaction gave **13** in 10% yield although the enantioselectivity of the major *syn* isomer was low (Scheme 3).

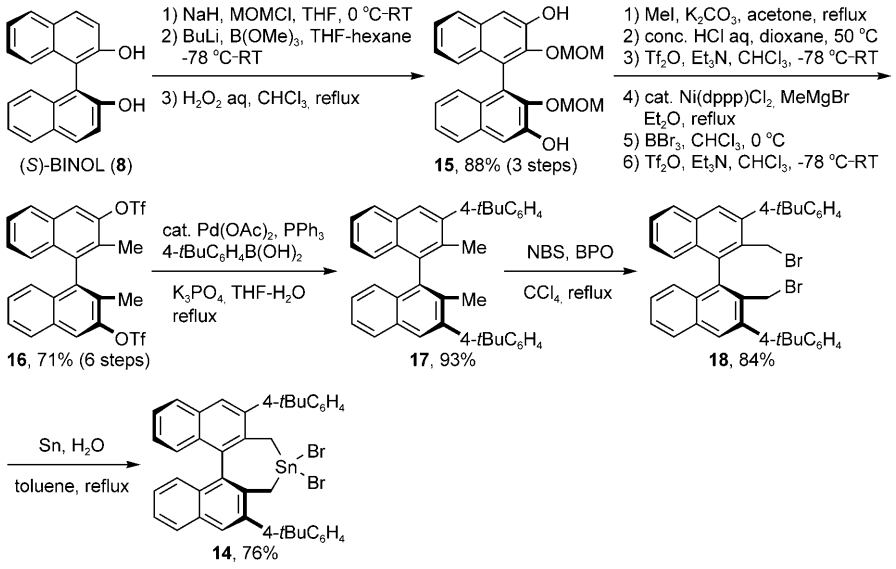
As the latter reaction conditions were found to be favorable, we attempted to synthesize chiral tin dibromide **14** having a 4-*tert*-butylphenyl group at 3- and 3′-positions, which is anticipated to be highly effective in the asymmetric induction for the present asymmetric aldol reaction.[9] The total synthesis of **14** from (*S*)-BINOL (**8**) is shown in Scheme 4. Methoxymethyl ether (MOM) protection of **8** followed by a lithiation–oxidation sequence gave 3,3′-dihydroxy BINOL derivative **15** in 88% overall yield through three steps from **8**. The subsequent six-step transformation of **15** by 1) methylation, 2) deprotection of MOM groups, 3) trifluoromethanesulfonylation of 2,2′-OH groups, 4) Ni-catalyzed cross-coupling reaction with methylmagnesium bromide, 5) demethylation, and 6) trifluoromethanesulfonylation of 3,3′-OH groups produced **16** in 71% overall yield. Ditriflate **16** underwent the Suzuki–Miyaura coupling with 4-*tert*-butylphenylboronic acid to provide coupling product **17** in 93% yield. Benzylic bromination (**18**,[10] 84% yield) and subsequent oxidative addition by metallic tin (76% yield) completed the synthesis of targeted tin dibromide **14**.

With chiral tin dibromide **14** in hand, we examined the catalytic ability of the corresponding tin bromide methoxide generated from a 1:1 mixture of **14** and MeONa in the aldol reaction of alkenyl trichloroacetate **12** with pivalaldehyde under the optimized reaction conditions shown in Scheme 3. Consequently, expected aldol adduct **13** was formed in 47% yield with a *syn*/*anti* ratio of 90/10 through the reaction for 7 h. The level of asymmetric induction was approximately 90% *ee* (Table 1). In order to improve the chemical yield, the reaction conditions were slightly modified and the choice of a higher reaction temperature (40 °C) and/or toluene as solvent gave improved yields without significant loss of enantioselectivity (Table 1).

Table 1. Optimized conditions for the formation of aldol **13**.




| | Solvent | $T$ [°C] | $t$ [h] | Yield [%] | *syn*/*anti* | *ee* [%] (*syn*) |
|---|---|---|---|---|---|---|
| 1 | THF | RT | 7 | 47 | 90:10 | 87 |
| 2 | THF | 40 | 2 | 65 | 97:3 | 86 |
| 3 | toluene | 40 | 1.5 | 70 | 94:6 | 85 |

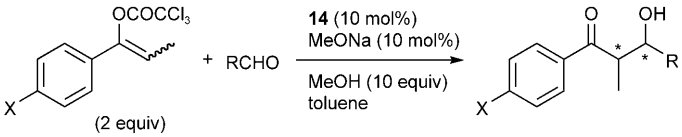



Scheme 4. Synthesis of chiral tin dibromide **14**.

The above result further prompted us to perform the chiral-tin-catalyzed asymmetric aldol reaction of different combinations of acyclic alkenyl trichloroacetates and aldehydes in toluene (Table 2). Treatment of 2-methyl-2-phenyl-

Table 2. Diastereo- and enantioselective aldol reaction of alkenyl trichloroacetates with aldehydes using chiral tin dibromide **14** and sodium methoxide.[a]



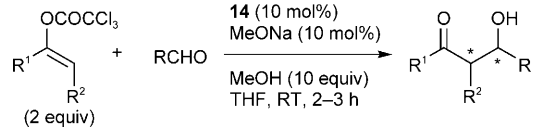

| | X | R | Conditions | Yield[b] [%] | *syn*/*anti*[c] | *ee* [%][d] (*syn*) |
|---|---|---|---|---|---|---|
| 1 | H (**12**, *E*/*Z* = 1:4) | $Me_2PhC$ | 40 °C, 4 h | 80 | 95:5 | 93 |
| 2 | Ph (*E*/*Z* = 1:99) | *i*Pr | RT, 18 h | 80 | >99:1 | 94 |
| 3 | Ph (*E*/*Z* = 1:99) | *t*Bu | RT, 16 h | 65 | >99:1 | 97 |
| 4 | Ph (*E*/*Z* = 1:99) | $Me_2PhC$ | RT, 14 h | 75 | 85:15 | 98 |
| 5 | Ph (*E*/*Z* = 1:99) | $Me_2PhC$ | 0 °C, 30 h | 41 | 89:11 | 99 |
| 6 | MeO (*E*/*Z* = 9:91) | $Me_2PhC$ | 40 °C, 4 h | 63 | 96:4 | 88 |
| 7 | Br (*E*/*Z* = 1:4) | *t*Bu | RT, 14 h | 54 | 99:1 | 95 |

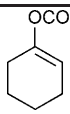
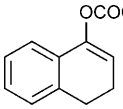
[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **14** (10 mol%), sodium methoxide (10 mol%), alkenyl trichloroacetate (2 equiv), and aldehyde (1 equiv) in toluene under the specified reaction conditions. [b] Isolated yield. [c] Determined by $^1$H NMR analysis. [d] The value corresponds to the *syn* isomer—determined by HPLC analysis.

propanal with propiophenone-derived alkenyl trichloroacetate **12** in the presence of chiral tin dibromide **14** (10 mol%), MeONa (10 mol%), and MeOH (10 equiv) in dry toluene at 40 °C for 4 h gave a 95:5 mixture of optically active *syn* and *anti* aldol adduct in 80% combined yield (entry 1). The *syn* isomer showed 93% *ee*. The introduction of a phenyl substituent to the para position of the alkenyl trichloroacetate enabled the reaction to occur smoothly at a lower temperature and in fact, approximately 70% yield of the optically active aldol product was obtained *syn*-selectively with 94–98% *ee* in the reaction with several aliphatic aldehydes (entries 2–4). The reaction with 2-methyl-2-phenylpropanal at 0 °C furnished an almost enantiomerically pure product (entry 5). Satisfactory enantioselectivity was also observed for a substrate with an electron-donating group and one with an electron-withdrawing group (entries 6 and 7). However, use of aromatic aldehydes as acceptors resulted in low enantioselectivity.[11]

We then examined the chiral-tin-catalyzed aldol reaction of cyclic alkenyl trichloroacetates with aldehydes (Table 3). Addition of the cyclohexanone-derived alkenyl trichloroacetate to benzaldehyde produced the *syn* aldol adduct preferentially with a *syn*/*anti* ratio of 67:33, contrary to the *anti* selectivity shown by achiral tin methoxide-chiral silver catalyst system.[6b–d] The *syn* isomer indicated a low enantiomeric excess (entry 1). In the present asymmetric aldol reaction of cyclic alkenyl trichloroacetates, aliphatic aldehydes are suitable electrophiles again to achieve a high level of asymmetric induction. Indeed, butyraldehyde and 3-methylbutanal

Table 3. Catalytic asymmetric aldol reaction of cyclic alkenyl trichloroacetates with aldehydes using chiral tin dibromide **14** and sodium methoxide.[a]




| | Alkenyl trichloroacetate | R | Yield[b] [%] | *syn*/*anti*[c] | *ee* [%][d] (*syn*, *anti*) |
|---|---|---|---|---|---|
| 1 |  | Ph | 75 | 67:33 | 7, 11 |
| 2 |  | $nC_3H_7$ | 99 | 47:53 | 90, 51 |
| 3 | | $Me_2CHCH_2$ | 95 | 51:49 | 91, 58 |

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **14** (10 mol%), sodium methoxide (10 mol%), alkenyl trichloroacetate (2 equiv), and aldehyde (1 equiv) in THF at room temperature for 2–3 h. [b] Isolated yield. [c] Determined by $^1$H NMR analysis. [d] Determined by HPLC analysis.

afforded the *syn* product with more than 90% *ee* in the reaction with the alkenyl trichloroacetate of 1-tetralone though the *syn*/*anti* ratio of the products was almost 1:1 (entries 2 and 3).[12]

In conclusion, we have developed a highly enantioselective method for the catalytic aldol reaction between alkenyl trichloroacetates and aldehydes. The catalytic cycle via a chiral tin enolate provides an alternative asymmetric aldol process. This method is environmentally friendlier because the amount of toxic organotin compounds is reduced to a catalytic amount. Extensions of this catalytic system to other asymmetric reactions are in progress.

## Experimental Section

**General experimental procedure for aldol reaction of aldehydes with alkenyl trichloroacetates catalyzed by chiral tin dibromide 14 (Tables 1 and 2)**: 1 M MeONa in MeOH (50 μL, 0.05 mmol) and MeOH (0.15 mL) were added to a solution of chiral tin dibromide **14** (41.2 mg, 0.05 mmol) in toluene (3 mL) under argon atmosphere, and then the resulting mixture was stirred at room temperature for 30 min. Subsequently, alkenyl trichloroacetate (1 mmol) and aldehyde (0.5 mmol) was added to the mixture at this temperature. After being stirred for the specified time at room temperature or 40 °C, the reaction mixture was treated with MeOH (1 mL), brine (3 mL), and solid KF (ca. 0.5 g) at ambient temperature for 30 min. The resulting precipitate was filtered off and the filtrate was dried over $Na_2SO_4$ followed by concentration in vacuo. The residual crude product was purified by column chromatography on silica gel to give a *syn*/*anti* mixture of the corresponding aldol adduct. The *syn*/*anti* ratio was determined by $^1$H NMR and $^{13}$C NMR spectroscopy.

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**Keywords:** aldehydes · aldol reaction · asymmetric catalysis · enolates · tin

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[11] For example, treatment of 4-methoxybenzaldehyde with **12** in the presence of **14** (10 mol%), MeONa (10 mol%), and MeOH (10 equiv) in dry THF at 40 °C for 2 h gave a 66:34 mixture of *syn* and *anti* aldol adduct in 95% combined yield. The *syn* isomer showed 14% *ee*.

[12] The cyclohexanone-derived alkenyl trichloroacetate shown in entry 1 of Table 3 did not react with an aliphatic aldehyde (2-methyl-2-phenylpropanal) under the similar reaction conditions at all.

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