



Pergamon

# Dibutyltin dimethoxide-catalyzed aldol reaction of enol trichloroacetates

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**Abstract**—A catalytic aldol condensation of aldehydes with enol trichloroacetates was achieved using dibutyltin dimethoxide as a novel catalyst in a mixed solvent consisting of THF and MeOH. Various  $\beta$ -hydroxy ketones were diastereoselectively obtained in high yields up to 99%.

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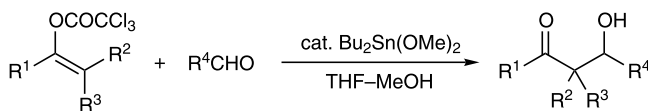
Aldol reaction is a beneficial method to prepare  $\beta$ -hydroxy carbonyl compounds, which can be further transformed into useful organic molecules.<sup>1</sup> In addition, the functionality is often seen in natural products and that is a reason why the reaction has so far been frequently applied to organic synthesis. We report here a novel example of catalytic aldol reaction of enol trichloroacetates catalyzed by dibutyltin dimethoxide,  $\text{Bu}_2\text{Sn}(\text{OMe})_2$  (Scheme 1).

Trialkyltin(IV) enolates are known to have good nucleophilicity towards aldehydes;<sup>2</sup> however, their use in aldol reaction is rather limited due to their toxicity.<sup>3</sup> To solve this problem, we have developed a new aldol reaction of an enol ester catalyzed by tributyltin methoxide, which is recycled by the addition of methanol.<sup>4</sup> Although the reaction is environmentally benign because the amount of organotin compound is reduced to a catalytic amount, this process has the disadvantage that aliphatic aldehydes show almost no reactivity. Thus, we planned to develop an alternative catalytic aldol reaction of enol esters employing more

reactive metal methoxide. First, we examined catalytic ability of several methoxysilanes and methoxystannanes (VI) in the reaction of 1-trichloroacetoxy cyclohexene<sup>5</sup> with benzaldehyde in the presence of 1 equiv. of MeOH, and found that  $\text{Bu}_2\text{Sn}(\text{OMe})_2$  gave the desired aldol adduct in the highest yield, whereas employment of less toxic methoxysilanes led to totally unsatisfactory results. Yields of the product obtained by the reaction employing 10 mol% of the catalyst in THF at room temperature: for  $\text{Me}_2\text{Si}(\text{OMe})_2$  (25 h), <1%; for  $\text{MeSi}(\text{OMe})_3$  (109 h), <1%; for  $\text{Si}(\text{OMe})_4$  (117 h), 7%; for  $\text{Bu}_3\text{SnOMe}$  (2 h), 28%; for  $\text{Bu}_2\text{Sn}(\text{OMe})_2$  (2 h), 56%.

Then, the catalyst was fixed for the tin dimethoxide and some enol esters of cyclohexanone were screened under similar reaction conditions. As a result, the enol trichloroacetate was found to be the enol ester of choice.<sup>6</sup> The reaction of 1-acetoxy cyclohexene was sluggish at room temperature and the corresponding enol triflate and enol diphenylphosphate showed almost no reactivity even at 80°C. In contrast, the targeted product was obtained in moderate yield from enol trifluoroacetate of cyclohexanone but this latent enolate was sensitive to hydrolysis.

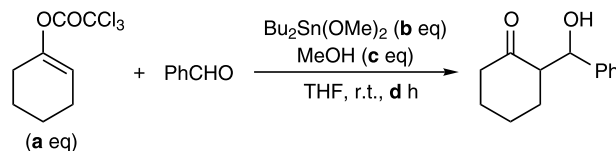
We then optimized the reaction conditions and found that an increase in MeOH improved the chemical yield (entries 1–4, Table 1). Since it was desired to decrease the amount of environmentally less benign organotin compounds from a practical viewpoint, we attempted the reaction using less than 0.1 equiv. of  $\text{Bu}_2\text{Sn}(\text{OMe})_2$  and found that 75% yield of the product was obtained under the influence of 0.05 equiv. of the catalyst (entry 5). However, use of 2 mol% of the catalyst resulted in unsatisfactory results (53–36% yield, entries 6–8). Fur-



**Scheme 1.**

**Keywords:** catalytic aldol reaction; dibutyltin dimethoxide; enol trichloroacetates; aldehydes;  $\beta$ -hydroxy ketones.

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**Table 1.** Optimization of aldol reaction of 1-trichloroacetoxy cyclohexene with benzaldehyde catalyzed by dibutyltin dimethoxide<sup>a</sup>

Entry	a (equiv.)	b (equiv.)	c (equiv.)	d (h)	Yield (%) <sup>b,c</sup>
1	1	0.1	1	2	49
2	1	0.1	2	2	63
3	1	0.1	3	2	75
4	1	0.1	5	2	72
5	1	0.05	3	2	75
6	1	0.02	3	2	36
7	1	0.02	5	2	42
8	1	0.02	5	4	53 <sup>d</sup>
9	2	0.02	5	4	91
10	2	0.02 <sup>e</sup>	5	4	<1
11	2	0.01	5	4	63 <sup>f</sup>
12	2	0.01	10	4	71 <sup>g</sup>

<sup>a</sup> Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.01–0.1 equiv.), 1-trichloroacetoxy cyclohexene (1 or 2 equiv.), and benzaldehyde (1 equiv.) in dry THF containing MeOH (1–10 equiv.) at room temperature for 2 or 4 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> The *syn/anti* ratios of the product were 75/25–67/33.

<sup>d</sup> A dehydrated product was obtained in 4% yield.

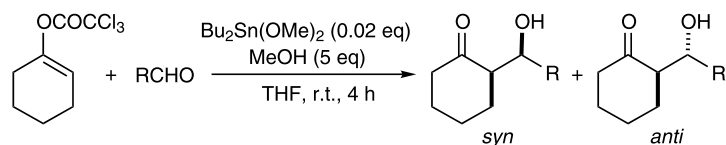
<sup>e</sup> Bu<sub>3</sub>SnOMe was used as catalyst instead of Bu<sub>2</sub>Sn(OMe)<sub>2</sub>.

<sup>f</sup> A dehydrated product was obtained in 12% yield.

<sup>g</sup> A dehydrated product was obtained in 7% yield.

ther improvement in the yield was achieved when 2 equiv. of the enol trichloroacetate was introduced and the highest yield (91%) was attained by the reaction for 4 h without formation of any dehydrated products (entry 9). It is noteworthy that the reaction still proceeds smoothly even in the presence of 1 mol% of Bu<sub>2</sub>Sn(OMe)<sub>2</sub> (entries 11 and 12). Reactivity of the tin dimethoxide is remarkable compared to that shown by Bu<sub>3</sub>SnOMe (entries 9 vs 10).

Optimal reaction conditions were thus established using 2 mol% of the tin catalyst, 2 equiv. of the enol ester, and 5 equiv. of MeOH, and we next carried out the catalytic aldol reaction with various aldehydes under these conditions. The results are summarized in Table 2.<sup>7</sup> From aromatic aldehydes, the corresponding aldol adducts were obtained in almost quantitative yield with *syn*-diastereoselectivity (entries 1–3). In the reaction with (*E*)-cinnamaldehyde, an  $\alpha,\beta$ -unsaturated aldehyde,

**Table 2.** Bu<sub>2</sub>Sn(OMe)<sub>2</sub>-catalyzed aldol reaction of 1-trichloroacetoxy cyclohexene with various aldehydes<sup>a</sup>

Entry	RCHO	Yield (%) <sup>b</sup>	<i>syn/anti</i> <sup>c</sup>
1	PhCHO	91	73/27
2	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	98	64/36
3	4-BrC <sub>6</sub> H <sub>4</sub> CHO	98	75/25
4	( <i>E</i> )-PhCH=CHCHO	93	66/34
5 <sup>d</sup>	Ph(CH <sub>2</sub> ) <sub>2</sub> CHO	78	35/65
6	<i>c</i> -C <sub>6</sub> H <sub>11</sub> CHO	85	11/85
7 <sup>e</sup>		<1	–

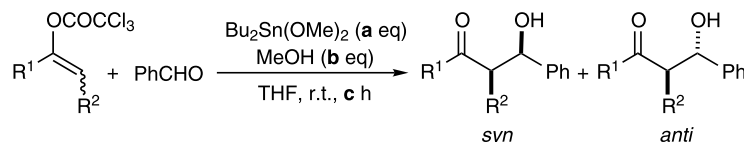
<sup>a</sup> Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.02 equiv.), 1-trichloroacetoxy cyclohexene (2 equiv.), and aldehyde (1 equiv.) in dry THF containing MeOH (5 equiv.) at room temperature for 4 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by <sup>1</sup>H NMR analysis.

<sup>d</sup> 10 equiv. of MeOH was used.

<sup>e</sup> Bu<sub>3</sub>SnOMe was used as catalyst instead of Bu<sub>2</sub>Sn(OMe)<sub>2</sub>.

**Table 3.** Bu<sub>2</sub>Sn(OMe)<sub>2</sub>-catalyzed aldol reaction of various enol trichloroacetates with benzaldehyde<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	a (equiv.)	b (equiv.)	c (h)	Yield (%) <sup>b</sup>	<i>syn/anti</i> <sup>c</sup>
1		-(CH <sub>2</sub> ) <sub>3</sub> -	0.02	5	1	>99	58/42
2		-(CH <sub>2</sub> ) <sub>5</sub> -	0.02	10	4	>99	78/22
3	Et	Me <sup>d</sup>	0.05	20	12	85	86/14
4	Ph	H	0.1	5	8	80	
5	Ph	Me <sup>e</sup>	0.05	20	24	77	91/9

<sup>a</sup> Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.02–0.1 equiv.), enol trichloroacetate (2 equiv.), and benzaldehyde (1 equiv.) in dry THF containing MeOH (5–20 equiv.) at room temperature for 1–24 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by <sup>1</sup>H NMR analysis.

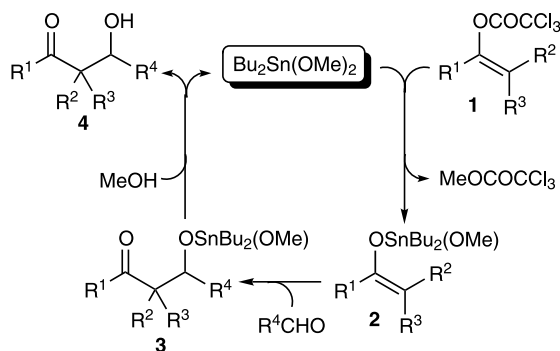
<sup>d</sup> The *E/Z* ratio was 13/87.

<sup>e</sup> The *E/Z* ratio was 91/9.

a 1,2-adduct was formed exclusively (entry 4). Aliphatic aldehydes also showed high reactivity with the opposite *anti*-selectivity (entries 5 and 6), though employment of Bu<sub>3</sub>SnOMe resulted in almost no yield (entry 7).

The utility of the present Bu<sub>2</sub>Sn(OMe)<sub>2</sub>-catalyzed aldol reaction was further demonstrated by employing enol trichloroacetates derived from different types of ketones (Table 3). Not only cyclic substrates, but acyclic ketone derivatives also reacted *syn*-selectively with benzaldehyde in high yields. Acyclic enol trichloroacetates indicated higher *syn*-selectivity than that given by cyclic ones irrespective of the double-bond geometry (entries 3 and 5). In the case of acyclic substrates, increased amounts of the catalyst and/or MeOH and longer reaction time were necessary in order to acquire satisfactory yields (entries 3–5).

Figure 1 provides a plausible catalytic mechanism of the reaction of an enol trichloroacetate **1** with an aldehyde. Initially, the enol ester **1** reacts with Bu<sub>2</sub>Sn(OMe)<sub>2</sub>, forming the tin enolate **2** and methyl trichloroacetate. The enolate **2** is then able to add to



**Figure 1.** A plausible catalytic mechanism for the aldol reaction catalyzed by Bu<sub>2</sub>Sn(OMe)<sub>2</sub>.

the aldehyde to provide the tin alkoxide of aldol adduct **3**. Finally, protonation of **3** with MeOH completes the catalytic cycle yielding **4** and regenerating the tin dimethoxide. From the aforementioned results, MeOH is considered to react with the alkoxide **3** more rapidly than with the in situ generated tin enolate **2**.

In summary, we have demonstrated a novel example of aldol reaction of enol trichloroacetates catalyzed by dibutyltin dimethoxide. The catalytic activity of Bu<sub>2</sub>Sn(OMe)<sub>2</sub> is much higher than that of previously reported Bu<sub>3</sub>SnOMe.<sup>4</sup> The procedure can be performed without any difficulty employing readily available chemicals and can provide a variety of β-hydroxy ketones not only from aromatic and α,β-unsaturated aldehydes but also from aliphatic aldehydes mainly with *syn*-selectivity in high yields up to 99%. The present method is environmentally friendlier since the amount of the toxic organotin catalyst is decreased to up to 2 mol%. Further work is now in progress on the catalytic reaction.

## Acknowledgements

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- Yields of the product obtained by the reaction using various enol esters of cyclohexanone: for enol acetate (rt, 8 h), 3%; for enol trichloroacetate (rt, 2 h), 49%; for enol trifluoroacetate (rt, 1 h), 42%; for enol triflate (80°C, 6 h), <1%; for enol diphenylphosphate (80°C, 6 h), 5%.
- Typical procedure for aldol reaction of aldehydes with enol trichloroacetates catalyzed by dibutyltin dimethoxide*: Synthesis of 2-(hydroxyphenylmethyl)cyclohexanone (entry 9 in Table 1 and entry 1 in Table 2). 1-Trichloroacetoxy cyclohexene (487 mg, 2.00 mmol) and benzaldehyde (0.102 mL, 1.00 mmol) were dissolved in dry THF (5 mL) under argon atmosphere and then a solution of dibutyltin dimethoxide (5.9 mg, 0.020 mmol) in dry THF (1 mL) was added to the resulting solution at room temperature. To the mixture was added dropwise MeOH (0.203 mL, 5.00 mmol). After being stirred for 4 h at this temperature, the mixture was treated with MeOH (2 mL), brine (2 mL), and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off and the filtrate was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give a mixture of the aldol adducts (185 mg, 91% yield) as white solids. The *syn/anti* ratio was determined to be 73/27 by <sup>1</sup>H NMR analysis. Spectral data (TLC, IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) of the *syn* and *anti* isomers indicated good agreement with reported data.<sup>8</sup>
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