

# Tin-catalyzed conversion of trioses to alkyl lactates in alcohol solution

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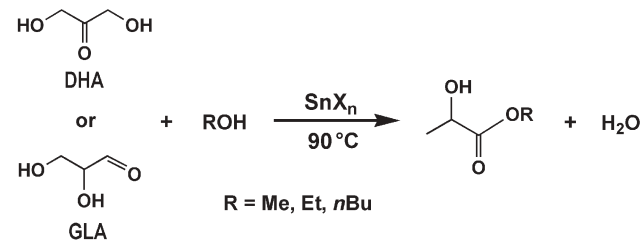
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Tin chlorides,  $\text{SnCl}_2$  and  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  are excellent catalysts for the reactions of trioses, dihydroxyacetone and glyceraldehyde with alcohols (MeOH, EtOH and *n*BuOH) to give alkyl lactates, whose reaction mechanism involves the intermediary formation of pyruvic aldehyde followed by its esterification, which is distinctively promoted by tin halides.

Lactic acid-based polymers are promising biomass-derived biodegradable materials used in many fields ranging from commodity plastics to biomedical materials because of their unique physical and biological properties.<sup>1</sup> The development of effective methods for the production of lactic acid from biomass, therefore, has been of great industrial interest.<sup>2,3</sup> Although the fermentation of dextrose using lactic acid bacilli is currently practiced in industry to produce lactic acid,<sup>4,6</sup> biological processes, in general, have various drawbacks: low reaction rates causing long reaction times and huge reactors, low concentrations of products usually in water solutions ending up with high energy consumptions for their separations, and so on. The chemical methods for producing lactic acid<sup>7,8</sup> or its esters<sup>9,10</sup> reported so far, on the other hand, have not yet been put into practice for some specific reasons. For example, although  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  has been reported to be an effective catalyst for the direct formation of *n*-butyl lactate from dihydroxyacetone (DHA) and *n*BuOH, it is not only toxic but also requires a prolonged reaction time (15 h at 115 °C) and shows lower reactivities with other alcohols than *n*BuOH.<sup>9</sup> In this paper, it is reported that tin halides can be used as effective catalysts in the reactions of trioses, DHA and glyceraldehyde (GLA) with several alcohols (MeOH, EtOH and *n*BuOH) to give the corresponding alkyl lactates (Scheme 1), which are useful precursors for the production of polylactide. Since trioses can be obtained by the stoichiometric<sup>11</sup> or catalytic<sup>12</sup> oxidation of glycerol, a major by-product in the ester exchange reaction of oil and fat producing so-called biodiesel fuel (BDF), the present reaction may provide a



**Scheme 1** Reactions of trioses with alcohols that produce the corresponding alkyl lactates.

practical alternative route to the industrial production of lactic acid from biomass.

Catalytic activity of various metal compounds was examined for the reaction of DHA in MeOH, and their effects on the formation of alkyl lactates are summarized in Table 1. The reaction was performed in air at 90 °C in a tightly closed 15 mL pressure-resistant glass tube,<sup>†</sup> and all chemicals were used as received. The formed alkyl lactates were analyzed by GLC. Tin compounds without halogens tested so far exhibited little catalytic activity. Among the several compounds of  $\text{SnX}_n$  (X = Cl, Br and I; *n* = 2 or 4), in particular,  $\text{SnCl}_2$  and  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  could promote smooth conversions of DHA and GLA to methyl lactate in yields up to 80–90% (Table 1, entries 1, 6, 13, 14). These tin chlorides were not inactivated after the reaction, and allowed repeatedly added trioses (at least 5 times) to be converted to methyl lactate in over 80% yield. Tin chlorides less than 10 mol% (vs. trioses) made the reaction remarkably slow: in the case with 5 mol% of  $\text{SnCl}_2$ , it took 12 h to complete the reaction, which gave a lower yield (< 80%) of methyl lactate. They could also act as effective catalysts in the reactions with EtOH and *n*BuOH to produce the corresponding

**Table 1** Catalytic conversions of trioses to alkyl lactates<sup>a</sup>

Entry	Triose	Catalyst	Yield (%) <sup>b</sup> of HOCH(CH <sub>3</sub> )CO <sub>2</sub> R		
			R = Me	R = Et	R = <i>n</i> Bu
1	DHA	$\text{SnCl}_2$	89 (2)	78 <sup>c</sup>	84 <sup>c</sup>
2		$\text{SnBr}_2$	83 (8)		
3		$\text{SnI}_2$	71 (8)		
4		$\text{SnSO}_4$	1 (1)		
5		$\text{Sn}(\text{OAc})_2$	trace (0)		
6		$\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$	82 <sup>c</sup> (9)	84 <sup>d</sup>	91 <sup>d</sup>
7		$(\text{acac})_2\text{SnCl}_2$	76 <sup>c</sup> (3)		
8		$\text{Bu}_2\text{SnCl}_2$	1 <sup>c</sup> (0)		
9		$\text{Bu}_2\text{Sn}=\text{O}$	2 <sup>c</sup> (0)		
10		$\text{Ph}_2\text{Sn}=\text{O}$	2 <sup>c</sup> (0)		
11		$\text{SnBu}_3(\text{OTf})$	8 (3)		
12		Sn powder	0 (0)		
13	GLA	$\text{SnCl}_2$	85 <sup>c</sup> (4)	85	82 <sup>c</sup>
14		$\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$	81 (7)	88 <sup>d</sup>	82 <sup>d</sup>
15	DHA	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$	50 (16)		
16		$\text{ZrCl}_4$	13 (58)		
17		$\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$	62 (14)		
18		$\text{RhCl}_3 \cdot x\text{H}_2\text{O}$	2 (61)		
19		$\text{CuCl}_2$	trace (71)		
20		$\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$	trace (24)		
21		$\text{MoCl}_3$	trace (11)		
22		$\text{MnCl}_2$	trace (0)		
23		$\text{ZnCl}_2$	trace (0)		
24	Pyruvic aldehyde	no catalyst	2 (0)	0	0
25		$\text{SnCl}_2$	88 (5)	74	78

<sup>a</sup> Triose (2.5 mmol), catalyst (10 mol%), ROH (4 mL), 90 °C, 3 h.

<sup>b</sup> GLC yield based on triose. <sup>c</sup> Reaction time is 2 h. <sup>d</sup> Reaction time is 1 h. <sup>e</sup> Reaction time is 6 h. Yield in parentheses is that of pyruvic aldehyde dimethylacetal.

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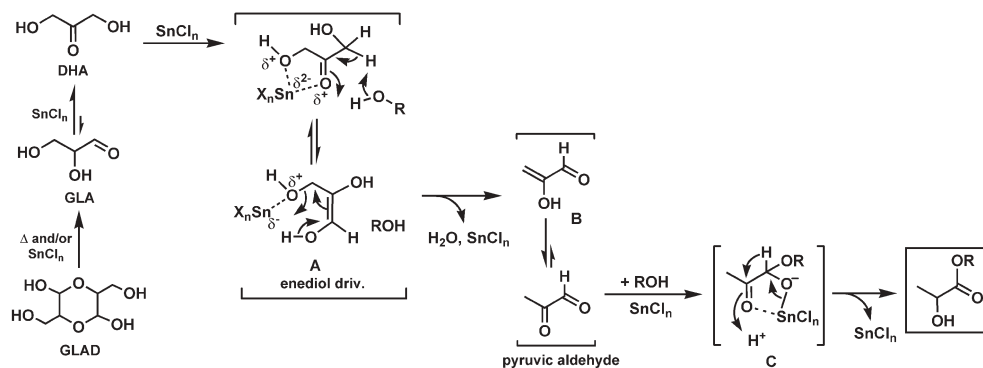
alkyl lactates. The six-coordinated tin environment of  $(\text{acac})_2\text{SnCl}_2$  did not inhibit the reaction, but neither  $\text{Bu}_2\text{SnCl}_2$  nor dialkyl tin oxides which can arise from hydrolytic decomposition of  $\text{R}_2\text{SnX}_2$ , showed any catalytic activity (Table 1, entries 7–10). Besides alkyl lactate, a small amount of the corresponding pyruvic aldehyde dialkylacetal was detected as the main by-product in each alcohol solution by GC-MS analysis. The other metal chlorides used as catalysts under the same reaction conditions exhibited a low selectivity for the formation of methyl lactate. Among the cases in which the reaction proceeded to some extent,  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  gave methyl lactate in moderate yields, while pyruvic aldehyde dimethylacetal was predominantly formed with  $\text{ZrCl}_4$ ,  $\text{CuCl}_2$  or  $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$  (Table 1, entries 15–19). Notably, upon using simple metal chlorides except  $\text{SnCl}_n$  as catalysts, a considerable amount of another by-product was commonly observed, which could not be isolated from the reaction mixture, but could be identified as the further acetalized product of pyruvic aldehyde dimethylacetal,  $\text{CH}_3\text{C}(\text{OMe})_2\text{CH}(\text{OMe})_2$ , by its NMR data and GC-MS analysis.† Such further acetalized products, however, were not confirmed in the reaction mixtures with  $\text{EtOH}$  and  $n\text{BuOH}$ .

It is now particularly important that GLA exhibits almost the same reactivity as DHA. DHA and GLA exist in their dimerized forms (DHAD and GLAD) in the solid state. Once DHAD was dissolved into  $\text{CD}_3\text{OD}$ , even at  $5^\circ\text{C}$ , it was gradually converted to DHA. Upon the addition of  $\text{SnCl}_2$  or  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  to the solution of DHAD in  $\text{CD}_3\text{OD}$ , DHA was instantly revived, and gradually converted to methyl lactate even at room temperature, while a similar reaction with GLAD could not produce GLA or methyl lactate below *ca.*  $80^\circ\text{C}$ . Based on this observation, the almost equivalent reactivity of DHA and GLA in the present reaction can be explained by the following reaction mechanism (Scheme 2). First, GLAD would be converted to GLA by heat and/or such an interaction with  $\text{SnCl}_n$  as seen for DHAD, which could be then converted to DHA through the aldose–ketose isomerization reaction catalyzed by  $\text{SnCl}_n$ . Recently, it has been reported that the isomerization of GLA to DHA is promoted by some  $\text{Zn}^{2+}$  salts such as  $\text{ZnCl}_2$  in neutral solution,<sup>13</sup> as well as occurring in alkaline aqueous solution.<sup>14,15</sup> Since  $\text{SnCl}_n$  tends to be coordinated by a hydroxyl group rather than form a  $\text{Sn}-\text{O}-\text{C}$  bond,<sup>16–18</sup> DHA derived from DHAD or GLAD as described above, may strongly interact with  $\text{SnCl}_n$  to give a cyclic intermediate containing  $\text{Sn}-\text{OH}$  and  $\text{Sn}-\text{O}=\text{C}$  bonds, whose isomerization to its enediol derivative may also be promoted by the presence of ROH (Scheme 2, A). The

enediol form **A** would give rise to enol-pyruvic aldehyde (Scheme 2, **B**), which has been observed as a transient intermediate by NMR measurements in the decomposition process of DHA-phosphate to pyruvic aldehyde *via* its enediol-phosphate (methylglyoxal synthetase reaction).<sup>19</sup> The enol form **B** is immediately isomerized to pyruvic aldehyde. The presence of pyruvic aldehyde dialkylacetals in the reaction solutions proves the intermediary formation of pyruvic aldehyde.<sup>20,21</sup> Therefore, the difference between  $\text{SnCl}_n$  and other metal chlorides which promoted the formation of pyruvic aldehyde dimethylacetal, might be attributed to their ways of interacting with pyruvic aldehyde. Namely, usual metal species simply act as a Lewis acid for the acetalization of carbonyl compounds<sup>22</sup> to give a hemi-acetal derivative as an intermediate, which immediately allows another molecule of alcohol to attack, whereas  $\text{SnCl}_n$  might strongly coordinate to the substrate to form a specific intermediate such as **C** (Scheme 2), which can cause a 1,2-hydride shift from the terminal carbon to the central one to predominantly yield alkyl lactate.<sup>7,8</sup> For the use of  $(\text{acac})_2\text{SnCl}_2$  as a catalyst, one of the  $\text{acac}^-$  ligands is considered to be dissociated, rather than a  $\text{Cl}^-$  ligand.<sup>23</sup>

The direct reaction of pyruvic aldehyde (40% in water solution) with ROH catalyzed by  $\text{SnCl}_2$  produced alkyl lactates in the yields of 88% ( $\text{R} = \text{Me}$ ), 74% ( $\text{R} = \text{Et}$ ) and 78% ( $\text{R} = n\text{Bu}$ ) under similar reaction conditions, while the non-catalytic reaction with ROH gave little alkyl lactate (Table 1, entries 24, 25). Furthermore, upon monitoring the reaction of DHAD or GLAD with  $\text{SnCl}_2$  or  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  in  $\text{CD}_3\text{OD}$  by NMR measurements, the incorporation of one deuterium atom from the solvent into each methyl group of methyl lactate and pyruvic aldehyde dimethylacetal was clearly observed,<sup>7,8</sup> but when starting with pyruvic aldehyde (40% in water solution), no incorporation of deuterium atom was confirmed. These observations reasonably support our suggested reaction mechanism.

In conclusion, we have achieved the effective conversion of trioses with alcohols to alkyl lactates catalyzed by tin halides, in which  $\text{SnCl}_2$  and  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  are the most active catalysts. Trioses, DHA and GLA, exhibit almost the same reactivities under our reaction conditions, which can be rationalized by several reactions consecutively promoted by tin halides: (monomerization of GLAD and) isomerization of GLA to DHA, the formation of the enediol form of DHA, and the esterification of pyruvic aldehyde. This reaction should be extended for the direct conversion of larger sugars such as monosaccharide and oligosaccharide to alkyl lactates, which can allow us to further



**Scheme 2** Possible reaction mechanism for the tin-catalyzed conversions of DHA and GLA to alkyl lactates.

develop the science fields of materials related to lactic acid-based polymers, organic synthesis of carbohydrates, and so on.

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## Notes and references

† A solution of DHAD or GLAD (1.25 mmol (= 2.5 mmol based on [DHA] or [GLA])), metal catalyst (0.25 mmol based on [metal]) in alcohol (4 mL) was heated at 90 °C for 1 h – several h as shown in Table 1. The reaction mixture was cooled to room temperature, followed by GLC analysis using a Shimadzu GC-14A gas chromatograph with a 30 m × 0.25 mm glass capillary column (DB-FFAP) and GC-MS analysis using a Shimadzu QP-5050A mass spectrometer with a Shimadzu GC-17A gas chromatograph (using Stabilwax-DA as a glass capillary column).

‡  $CH_3C(OMe)_2CH(OMe)_2$ :  $^1H$  NMR (400 MHz,  $CD_3OD$ , 25 °C, TMS)  $\delta$  4.23 (s, 1H, –CH–), 3.48 (s, 6H, –OMe), 3.35 (s, 6H, –OMe), 1.20 (s, 3H, –Me),  $^{13}C$  NMR (100 MHz,  $CD_3OD$ , 25 °C)  $\delta$  107.2 (–CH–), 67.8 (–C–), 57.7 (–OMe), 49.8 (–OMe), 16.6 (–Me); GC-MS analysis  $m/z$  = 149 [ $M - Me$ ]<sup>+</sup>, 133 [ $M - OMe$ ]<sup>+</sup>, 89 [ $M - CH(OMe)_2$ ]<sup>+</sup>. The  $^1H$  and  $^{13}C$  NMR spectra were measured using JEOL JNM-AL400 and Varian INOVA-400 spectrometers. This compound can be converted to pyruvic aldehyde dimethylacetal only by purification of the reaction mixture through a  $SiO_2$  short-pad.<sup>24,25</sup> Note that this species appears at a retention time close to that of methyl lactate under the GLC and GC-MS equipment described above.

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