

Mechanistic Studies on the Cascade Conversion of 1,3-Dihydroxyacetone and Formaldehyde into α -Hydroxy- γ butyrolactone

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The chemical synthesis of commercially and industrially important products from biomass-derived sugars is absolutely vital to establish biomass utilization as a sustainable alternative source of chemical starting materials. α -Hydroxy- γ -butyrolactone is a useful synthetic intermediate in pharmaceutical chemistry, and so novel biomass-related routes for its production may help to validate this eco-friendly methodology. Herein, we report the specific catalytic activity of homogeneous tin halides to convert the biomass-derived triose sugar 1,3dihydroxyacetone and formaldehyde into α -hydroxy- γ -butyro-

Introduction

Woody biomass is expected to serve as one of the alternatives to fossil fuel as there is no competition with food. The main component of wood-based biomass is carbohydrates; hence, the development of an efficient methodology for the production of commercially and industrially important materials from carbohydrates is required to validate new biomass-sourced routes.^[1]

Previously, we have reported the catalytic transformation of a triose sugar, 1,3-dihydroxyacetone (1), and formaldehyde into α -hydroxy- γ -butyrolactone (2).^[2] Compound 1 was formed by a [3+3] retro-aldol reaction of glucose or fructose derived from cellulose, the products of which would convert to the thermodynamically stable lactic derivatives by sequential dehydration and alcohol addition followed by proton transfer (Scheme 1).^[3]

Among the Lewis acid catalysts examined, tin(IV) chloride exhibited the highest performance in the above mentioned coupling reaction between **1** and formaldehyde. However, detailed information on the reaction pathway and catalytic mechanism was not obtained.

Dusselier et al. demonstrated the one-pot catalytic conversion of glycolaldehyde (GA) to four-carbon-atom α -hydroxy

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lactone. A detailed screening of catalysts showed the suitability of tin catalysts for this reaction system, and isotope experiments using [D₂]paraformaldehyde, substrate screening, and time profile measurements allowed us to propose a detailed reaction pathway. In addition, to elucidate the activated species in this cascade reaction, the effect of additional water and the influence of additional Brønsted acids on the reaction preferences for the formation of α -hydroxy- γ -butyrolactone, lactic acid, and vinyl glycolate were investigated. The active form of the Sn catalyst was investigated by ¹¹⁹Sn NMR spectroscopy.

acid (AHA) esters according to a complex cascade network.^[4] Interestingly, a small amount of **2** was also identified as a product (Scheme 1, previous work). This reaction was based on the coupling of two-carbon-atom GA, which was formed by the [4+2] retro-aldol reaction of hexose. This was inspired by the formose reaction, which involves the formation of sugars from formaldehyde.^[5] The reaction is catalyzed by base and a divalent metal and proceeds by aldol and retro-aldol reactions and aldose-ketose tautomerization. The intermediates in this reaction are GA, glyceraldehyde (7), 1, and tetrose sugars. Therefore, we predicted that this reaction pathway would be helpful to understand the reaction pathway of the synthesis of 2 from 1 and formaldehyde.

In this work, we present a complete map of the synthetic pathway to **2** and related byproducts from **1** and formaldehyde. Furthermore, we propose a catalytic mechanism and a valence state of the catalyst in the reaction mixture based on the results of ¹¹⁹Sn NMR spectroscopy.

Results and Discussion

Catalyst screening

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Lewis acid catalysts are known to be effective for the conversion of 1 into lactic acid (3).^[3] In this work, the coupling reaction between 1 and formaldehyde was accomplished through the use of Sn catalysts. In an effort to increase the yield of desired products, a range of experiments that employed different catalysts was conducted. The catalysts used, and the yields of the identified products, **2**, **3**, and vinyl glycolate (**4**), are given



Scheme 1. Retro-aldol reaction of glucose to tetrose and glycolaldehyde or 1 based on [4+2] or [3+3], respectively, and routes toward the formation of 2.^[3]

in Table 1. Unless otherwise noted, the total amount of water in all entries was fixed at 0.86 mmol.

The reaction with HCl, a model Brønsted acid catalyst, did not lead to either 2 or 4, and the only product was 3 (entry 1). This result indicates the importance of metal catalysts in the reaction. A reaction with catalytic amounts of NaOH yielded no products detectable by GC or NMR spectroscopy (entry 2). If SnCl₄·5H₂O was used in the reaction, 2 was obtained in 42% yield, whereas 3 and 4 were generated as byproducts in 12 and 6% yield, respectively (entry 3). We also confirmed that the reaction using only 1 did not afford 2 and 4 by an intermolecular aldol reaction (entry 4). The use of SnCl₂·2H₂O provided 2 in 24% yield (entry 5), whereas SnCl₂·2H₂O with two equivalents of HCl afforded 2 in 37% yield (entry 6). As shown in entries 3, 5, and 6, the yields of 2 and 4 change by similar degrees, although the yield of 3 is relatively constant. This result indicates that the ratio of chloride anions to Sn metal centers is important to the selectivity of the reaction for the desired product. In the presence of anhydrous SnCl₄, 2 was obtained in 40% yield, whereas 3 and 4 were generated in 17 and 4% yields, respectively (entry 7). In addition, the combination of anhydrous SnCl₄ and a small amount of water resulted in improved reaction efficiency compared to the results obtained with SnCl₄·5H₂O and provided 2 in 63% yield, although the yields of 3 and 4 also increased to 20 and 8%, respectively (entry 8). The highest yield observed in this series of experiments was in the reaction that employed SnCl₄ and excess

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formaldehyde, which afforded **2** in 70% yield (entry 9) and showed a dramatic decrease in the yield of **3** compared to that seen with $SnCl_4$ and a stoichiometric amount of aldehyde (entry 8).

We investigated the influence of the counter anion in the tin halides on the formation of each product by conducting experiments with anhydrous SnBr₂, SnBr₄, SnI₂, SnI₄, and nBu₃SnCl (entries 10-14). The use of SnBr₂ gave disappointing product yields similar to those observed with SnCl₂·2H₂O (entry 10 cf. entry 5). However, if SnBr₄ was employed, the yield of 2 decreased even further (entries 10 and 11). Snl₂ and Snl₄ were both observed to have lower activities and selectivities still (entries 12 and 13). If we compare similar catalysts that differ only in their chloride and iodide counterions, the yield of 2 and 4 remains low, although the yield of 3 is similar (entry 13 cf. entry 8), which confirms that chloride is the most

suitable counterion for this system. However, the use of nBu_3SnCl showed no improvement to the yields of any product, although nBu_3SnCl has a tetravalent Sn center and a chloride anion (entry 14). This result shows that an absolute quantity of chloride counterion to a tetravalent Sn center is important for the successful formation of **2**. If other Sn^{II} or Sn^{IV} catalysts were employed, namely, Sn(OAc)₂, Sn(OTf)₂, and SnO₂, the desired product **2** was not obtained (entries 15–17).

Having established that chloride is the most suitable counterion in this system, we next screened different metal chloride catalysts, namely, $AlCl_3$, $ZrCl_4$, and $TiCl_4$, all of which have been reported to activate **1**, as well as $InCl_3$, $GeCl_4$, and $SiCl_4$, all of which appear near Sn in the periodic table. All were observed to have no activity in this reaction (Table S1). These results indicate that both Sn metal and a halogen counterion are critical for this reaction system.

Isotope experiment using [D₂]formaldehyde

To confirm that this transformation of **1** and formaldehyde into **2** proceeds by an intermolecular reaction, an incorporation experiment using [D₂]formaldehyde was conducted. The reaction between **1** and [D₂]formaldehyde using SnCl₄ and a small amount of water to generate [D₂]1,3-dihydroxyacetone (**5**) and [D₂]vinyl glycolate (**6**) in 48 and 5% yield, respectively, is shown in Scheme 2. The ¹H NMR spectra of **2**, **5**, **4**, and **6** are presented in Figure S6. In the spectrum of **2**, peaks at $\delta = 4.42$

 Table 1. Conversion of 1,3-dihydroxyacetone and formaldehyde into 2, 3, and 4 through the use of several acid catalysts and a small amount of water.^(a)

water. ^(a)		OH + H formalde	H shyde		
	ОН	OH	\sim		
HBL (2)		LA (3) VG (4)			
Entry	Catalyst	Conversion		Yield [%]	
		of 1 [%]	2	3	4
1	HCI ^[b]	>99	0	21	0
2	NaOH	92	0	0	0
3	SnCl ₄ •5 H ₂ O	>99	42	12	6
4 ^[c]	SnCl ₄ •5 H ₂ O	>99	0	24	0
5	$SnCl_2 \cdot 2H_2O$	>99	24	14	3
6 ^[d]	SnCl ₂ •2H ₂ O	>99	37	16	4
7 ^[e]	SnCl₄	>99	40	17	4
8	SnCl₄	>99	63	20	8
9 ^[f]	SnCl₄	>99	70	5	8
10	SnBr ₂	>99	27	15	2
11	SnBr₄	>99	21	19	4
12	Snl ₂	>99	17	20	2
13	Snl₄	>99	16	19	2
14	<i>n</i> Bu₃SnCl	>99	25	12	3
15	SnO ₂	95	0	<1	0
16	Sn(OAc) ₂	>99	0	5	0
17	Sn(OTf) ₂	>99	0	36	0
18	no catalyst	79	0	4	0
[a] React catalyst	ion conditions: 1 (0.171 mmol), ^[6] 1,4-c	(1.25 mmol), paraf dioxane (4.0 mL), ^[7]	ormaldehy Ar atmosp	de (1.31 m، المرابع) here, 3 h, 1	mol), 40 °C.

catalyst (0.171 mmol),^[6] 1,4-dioxane (4.0 mL),^[7] Ar atmosphere, 3 h, 140 °C. Conversions and yields are based on 1. [b] 4 μ HCl in 1,4-dioxane (0.68 mmol) was added. [c] Using only 1 as a substrate. [d] 4 μ HCl in 1,4-dioxane (0.34 mmol) was added. [e] No additional water. [f] Excess paraformaldehyde (3.75 mmol) was employed.

(marked \bigstar) and 4.21 ppm (marked \bullet), which represent the two protons next to the ether O atom, are not detected in that of **5** (Figure S6 b). In addition, GC–MS analysis confirmed the formation of **5** (Figure S7). The m/z [M^+] values of **2** and **5** are 103 (1) and 105 (1), respectively, and the m/z [M^+ –HCO₂] values of **2** and **5** are 57 (100) and 59 (100), respectively.

In the ¹H NMR spectrum of **4**, the peaks at $\delta = 5.52$ (marked \blacklozenge) and 5.27 ppm (marked \blacktriangle), which represent the two protons of the terminal vinyl group, are not present in that of **6**, and the shape of the peaks at $\delta = 6.00$ (H_d) and 4.66 ppm (H_e)



Scheme 2. Reaction of 1 and [D₂]formaldehyde catalyzed by SnCl₄ and a small amount of water. Reaction conditions: 1 (1.25 mmol), [D₂]paraformaldehyde (1.31 mmol), SnCl₄ (0.171 mmol), H₂O (0.86 mmol), 1,4-dioxane (4.0 mL), Ar, 3 h, 140 °C. The yield was based on 1.

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change dramatically (Figure S6 d). These results confirm that **2** and **4** are formed by intermolecular coupling between **1** and formaldehyde.

Proposal of the reaction pathway

The reaction pathway shown in Scheme 3 will be discussed in detail and supported by a presentation of the experimental findings. Initially, there are two possible routes: route I) a dehydration of 1 into pyruvic aldehyde (9) or route II) an aldol reaction between 1 and formaldehyde.

Route I: We suggest an initial tautomerization between 1 and 7 because the elimination of the hydroxyl group in the β -position from 7 appears more likely than that from 1 (step 1). Sn can coordinate with multiple –OH or =O bonds because of its strong Lewis acid character,^[8] so the activated complex 10 is formed and undergoes the aldol reaction with formaldehyde readily to afford 11 (step 2). Furthermore, we suggest that this pathway in the route also leads to 3 via the formation of the hemiacetal 14 followed by a proton transfer (step 3). Under acidic conditions, an excess of water promotes the undesired formation of 3.

After the production of key intermediate **11**, there are two parallel routes toward **2** or **4**. After the addition of H_2O to the aldehyde moiety of **11**, compound **15** should be prone to an intramolecular esterification, especially in the presence of HCI generated from Sn halides, which leads to **2** (step 8). A competitive pathway (step 7) is suggested that involves the formation of the reactive intermediate **16** by keto–enol tautomerization between **11** and **13** followed by dehydration. Unsaturated **16** is attacked by H_2O at the terminal aldehyde group followed by proton transfer to provide **4** as a byproduct.

Route II: An another possible mechanistic route to **2** is based on an aldol reaction between **1** and formaldehyde.^[9] After an aldol coupling and tautomerization, the aldehyde **12** appears to be prone to the elimination of the hydroxyl group in the β -position of the unsaturated carbon atom. Therefore, the dehydration of the tetrose at the C3 position occurs to provide **13**.

To validate these proposed reaction pathways, experiments with the substrates shown in Table 2 were performed. Compound **7** and erythrulose (**8**), both of which are proposed as reaction intermediates in routes I and II, respectively, were employed. If **7** was used instead of **1**, the product yields were similar to the original experiments in which **1** was employed

(entry 1 cf. Table 1, entry 3), whereas the use of **8** afforded **2** in only 9% yield and **4** was generated in a 31% yield (entry 2). Finally, we established whether the production of **2** could be reversible. As shown in entry 3, **2** is not decomposed under our reaction conditions.

The use of **7** showed almost the same activity in the formation of **2** as the use of **1**. However, if **8** was used, the yield of **4** increased and that of **2** decreased. In other words, the yields of **2** and **4** were reversed (Table 2, entry 1 cf. entry 2). This suggests that this reaction pathway is not based on an aldol

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Scheme 3. Proposed pathway for the Sn-catalyzed conversion of 1 and formaldehyde to 2. The suggested major reaction pathway is indicated by bold arrows.

Table 2. Yields of products from different potential intermediates in the proposed reaction pathway. $\ensuremath{^{[a]}}$										
Entry	Substrate	Conversion of substrate [%]	2	Yield [%] 3	4					
1 2 ^[b,c] 3 ^[b]	7 8 2	> 99 > 99 < 1	41 9 -	14 0 0	5 31 0					
[a] Reaction conditions: substrate (1.25 mmol), paraformaldehyde (1.31 mmol), SnCl ₄ ·5 H ₂ O (0.171 mmol), 1,4-dioxane (4.0 mL), Ar, 3 h, 140 °C. Conversions and yields are based on 1 . [b] Without paraformaldehyde. [c] Reaction temperature was 90 °C.										

reaction between 1 and formaldehyde but proceeds via 9 and is in competition with the production of 3. The conversion of 11 into 15 may be favored energetically in comparison with the tautomerization of 11 to 13, and it is likely that the dehydration of 13 to 16 also occurs preferentially to the tautomerism.

Time profile

The product formation in a typical batch experiment was monitored as a function of reaction time. Concentration profiles, based on the yield of each product, are shown in Figure 1. The experiment was performed at 100 °C instead of 140 °C to slow the reaction, which makes the changes in the components easier to track.

Compound 1 and formaldehyde were used as the starting materials. After 60 min, 1 was almost completely exhausted, and the presence of intermediate 9 could be detected. Thus 1 first appears to tautomerize to 7 quickly, and 9 is formed as an intermediate product. The concentration of 9 was observed to be highest after very short reaction times. Compound 8 could not be detected, which supports the hypothesis that 9 is the initial intermediate. The addition of water formed hydrated pyruvic aldehyde (14), which underwent proton transfer to give 3. Compound 9 can tautomerize to the enolate 10, and 9 exists in three forms; aldehyde 9, enolate 10, and, with the addition of water, diol 14. With the analytical methods used in this study, it was not possible to distinguish these three spe-

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Figure 1. Study of the conversion of 1 to 2, 3, and 4 under the following conditions: 1 (1.25 mmol), paraformaldehyde (1.31 mmol), $SnCl_4$ -5 H₂O (0.171 mmol), 1,4-dioxane (4.0 mL), Ar, 100 °C. •: 1, •: 2, A: 3, •: 4, \times : 9.

cies, but all are expected to be present. The aldol reaction between enolate **10**, activated by the Sn catalyst, and formaldehyde would provide the tetrose **11**. There are two routes for the conversion of the key intermediate **11**, one through the formation of **2** and the other through the formation of **4** as mentioned above. Initially, an induction period of **2 and 4** is observed and the formation rate of **3** is higher than that of **2** and **4**. In addition, we did not observe the reaction intermediates, which include tetroses, except for **9**. Therefore, we suggest that the rate-determining step of this reaction is an aldol reaction between enolate **10** and formaldehyde.

Effect of additional water

If a small amount of water was added, the yields of **2** and **4** increased and that of **3** was relatively constant (Table 1, entries 7 and 8). However, **1** is converted efficiently to **3** in water as a solvent^[3], therefore, we attempted to investigate the influence of additional water on the formation of each product (Figure 2).

In reactions to which no water was added, **2** was obtained in 40% yield, whereas **3** and **4** were generated in 17 and 4% yield, respectively (Table 1, entry 7). As water was added by degrees, the yields of **2** and **4** increased and reached up to 63 and 8%, respectively, if the total amount of water was 0.86 mmol, which corresponds to the water content of SnCl₄·5 H₂O. However, if more water was used, the yields of **2** and **4** decreased and that of **3** increased. Therefore, a small amount of water was crucial to the success of the reaction.

Based on the above results and the proposed pathway (Scheme 3), compound **9** is likely converted to the Sn enolate **10** by $SnCl_4$, and formaldehyde is activated by hydrogen chloride evolved simultaneously with the formation of **10**,^[10] such that the aldol reaction proceeds more effectively compared to the alternate reaction that generates **3**. The effect of the addi-

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Figure 2. Influence of additional water on the yield of a) **2**, b) **3**, and c) **4**. Reaction conditions: **1** (1.25 mmol), paraformaldehyde (1.31 mmol), anhydrous SnCl₄ (0.171 mmol), 1,4-dioxane (4.0 mL), Ar, 3 h, 140 °C. **•: 2**, **\blacktriangle: 3**, **•: 4**.

tion of a small amount of water seems to promote the generation of hydrogen chloride.

Influence of additional Brønsted acids on the preference for each product

On the basis of the results shown in Table 1, it seems that the interaction between the Lewis and Brønsted acidity derived from the tin chloride salts in the reaction medium is crucial to the overall rate of this cascade reaction. The reaction of 1 and formaldehyde in the presence of HCl yields no 2 or 4 and shows only the formation of 3. The Brønsted acid catalyzed enolate mechanism suggested initially for the aldol addition is thus not a major pathway (Table 1, entry 1). As shown in Table 1, entries 3, 5, and 6, this observation suggests that the condensation of 1 and formaldehyde requires the presence of Lewis acidic Sn. This Lewis acid catalyzed addition is crucial for the feasibility of the cascade, which leads to the formation of 2 and 4. Although the importance of tin chloride is clear, we need to confirm the difference in activities between Sn^{II} and Sn^Ⅳ. In addition, the balance between Lewis and Brønsted acidity is key to understand this cascade reaction and direct it to higher yields and selectivities.

Initially, we attempted to investigate the influence of the HCl/Sn ratio on the yield of each product. The yields of **2**, **3**, and **4** with different HCl/Sn ratios are shown in Figure 3 a, b, and c, respectively. To vary the Lewis and Brønsted acid contents, external HCl is added. If $SnCl_2$ is used, the highest yield of **2** is clearly observed with two extra equivalents of HCl (Figure 3 a). Furthermore, if $SnCl_4$ is used, the yield of **2** decreases with the increasing amount of HCl. Thus, the best H⁺/Sn ratio for this system is 4. Conversely, the highest yield of **3** was observed for a H⁺/Sn ratio of 5 (Figure 3 b). Interestingly, the yields of **3** do not depend on the oxidation state of the Sn salt. The highest yield of **3** was accomplished either if $SnCl_4$ is combined with three extra equivalents of HCl or if $SnCl_4$ is com-





Figure 3. Influence of the ratio of HCI/Sn on the yield of a) **2**, b) **3**, and c) **4**. Reaction conditions: **1** (1.25 mmol), paraformaldehyde (1.31 mmol), catalyst (0.171 mmol), 1,4-dioxane (4.0 mL), Ar, 3 h, 140 °C. If $SnCl_2 \cdot 2 H_2O$ was used, water (0.51 mmol) was added. •: $SnCl_2 \cdot 2 H_2O$, **A**: $SnCl_4 \cdot 5 H_2O$.

bined with one extra equivalent of HCl. Clearly, the formation of **3** shows a different trend to that of **2**. Finally, the yields of **4** are shown in Figure 3 c. If $SnCl_2$ is used, the highest yield of **4** is observed with the addition of two extra equivalents of HCl and decreases with increasing amounts of HCl. If $SnCl_4$ is used, the yield of **4** decreases with increasing amounts of HCl. This trend is similar to that seen for the formation of **2**.

To investigate the influence of different Brønsted acids on the yield of each product we conducted reactions with the addition of several inorganic and organic acids (Table S2). If H_2SO_4 , H_3PO_4 , or *p*-toluenesulfonic acid (TsOH) was added, the yield of **2** decreased and that of **3** increased (entries 3, 5, and 9). However, the addition of other acids gave virtually identical results to that seen if no acid was added. This result indicates that HCl is the most suitable additive as a partner for Sn in this reaction system.

Evaluation of the valence of tin in the reaction mixture by ¹¹⁹Sn NMR spectroscopy

The use of SnCl₂ with two extra equivalents of HCl afforded **2** and **4** in similar yields to the SnCl₄-catalyzed reaction (Table 1, entries 3 and 6, and Figure 3), which leads us to hypothesize that the same species behaves as an activator in each experiment. In addition, a combination of anhydrous SnCl₄ and five equivalents of water showed a high activity in comparison with the use of SnCl₄·5 H₂O (Table 1, entries 3 and 8). Therefore, we performed ¹¹⁹Sn NMR spectroscopy to compare the conditions of Sn in the different reaction environments.^[11]

The ¹¹⁹Sn NMR spectra of anhydrous SnCl₄ and SnCl₄·5 H₂O in [D₃]CD₃CN are shown in Figure 4a and b.^[7] The peaks at $\delta = -684$ (\Rightarrow) and -637 ppm (\Box) may be derived from tetravalent SnCl₄ and six-coordinate SnCl₄(H₂O)₂, respectively.^[11c] We examined the ¹¹⁹Sn NMR spectra of anhydrous SnCl₄ with five equivalents of water (Figure 4b and c). The ¹¹⁹Sn NMR spectrum of SnCl₄ with five equivalents of water corresponded exactly to that of SnCl₄·5 H₂O. Although the yields of each product were



Figure 4. ¹¹⁹Sn NMR spectra in [D₃]CD₃CN of a) anhydrous SnCl₄, b) SnCl₄·5 H₂O, c) anhydrous SnCl₄+5 H₂O, d) SnCl₂·2 H₂O at RT, e–g) SnCl₂·2 H₂O combined with 2–4 equivalents of HCl after heating to 80 °C for 3 h.

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different in entries 3 and 8 of Table 1, we cannot give a definite reason for this difference. However, we demonstrated that SnCl₄·5H₂O dissolved in 1,4-dioxane and anhydrous SnCl₄ did not. On the basis of this experimental result, we predicted that anhydrous SnCl₄ dissolved slowly in 1,4-dioxane with heat and then HCl could be evolved effectively as an activator in comparison with the use of SnCl₄·5H₂O. The spectrum of SnCl₂·2H₂O is shown in Figure 4d, and a peak at $\delta =$ -244 ppm (\diamond) is observed. The ¹¹⁹Sn NMR spectrum of SnCl₂·2H₂O combined with two equivalents of HCl is shown in Figure 4e. After heating to 80 $^{\circ}$ C for 3 h, the peak at $\delta =$ -244 ppm (\diamond) is completely absent and the peak at $\delta =$ -637 ppm (□), which is also seen in the spectrum of SnCl₄(H₂O)₂, is observed exclusively. These results indicate that the combination of SnCl₂ and two equivalents of HCl generates the six-coordinate complex $SnCl_4(H_2O)_2$, which is the optimum catalytic species in this reaction system. Furthermore, as HCI was added to SnCl₂·2H₂O in [D₃]CD₃CN, a new peak at $\delta =$ -660 ppm (\odot) was observed (Figure 4 f), and the addition of four equivalents of HCl led to a single peak (Figure 4 g). On the basis of the above results and a previous report,^[11c] we conclude that the peak at $\delta = -660$ ppm ($_{\odot}$) might be derived from the six-coordinate complex SnCl₆²⁻.

We attempted to follow the catalytic behavior during a reaction. The ^{119}Sn NMR spectrum of SnCl_4·5H_2O in [D_8]dioxane is presented in Figure S9a, which has characteristic peaks at $\delta =$ -635 (\odot) and -661 ppm (\Leftrightarrow). Then **1** was added to the reaction mixture and heated to effect the dehydration of 1. However, the spectrum of this reaction mixture still shows two peaks at $\delta = -635$ (O) and -661 ppm (C), and other reaction species, such as the chelated Sn intermediate, are not detected (Figure S9b). The spectrum of SnCl₄·5H₂O combined with 1 and paraformaldehyde and heated to 100°C for 6 h also shows peaks at $\delta = -635$ (\odot) and -661 ppm (\ddagger ; Figure S9c). This result shows that tin chlorides remain active in the reaction mixture. On the basis of this experimental result, we added fresh 1 and paraformaldehyde to the reaction mixture after an initial run, and 2, 3, and 4 were afforded in almost the same yields as in the first run. These results also support the assertion that the Sn catalyst continues to behave as a catalyst without deactivation through multiple uses.

Conclusions

We investigated the specific catalytic activity of homogeneous tin chloride to convert dihydroxyacetone (1) and formaldehyde into α -hydroxy- γ -butyrolactone (2). Isotope experiments, substrate screening, and time profile measurements allowed us to propose a detailed reaction pathway supported by GC, MS, and NMR spectroscopy. This transformation involves a tautomerization and a dehydration of 1 to pyruvic aldehyde (9), an aldol reaction between tin-activated enolate and formaldehyde, and finally cyclization to form 2.

To investigate the activated species of this reaction, the manner in which the balance between Brønsted and Lewis acid affected the reaction preference for 2, 3, and 4 was examined. The highest yields of 2 and 4 were seen if the H⁺/Sn

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ratio was 4, whereas the highest yield of 3 was observed for a H⁺/Sn ratio of 5. In addition, we performed ¹¹⁹Sn NMR spectroscopy and confirmed that the most active species was a sixcoordinate SnCl₄(H₂O)₂ complex. From these results, we suggested the chelate compound 10 with tin metal as the intermediate in the reaction pathway (Scheme 3).

Compound 2 is not easy to produce but it could become commercially available through this coupling between 1 and formaldehyde. This would be a huge step forward for the establishment of wood biomass as a source for important chemical entries. Furthermore, the results presented here could be important for the further development of more sustainable heterogeneous Sn catalysts.^[12] In particular, the immobilization of Sn in zeolites^[13] or on silica^[3e] could be a solution to regenerate the Sn catalyst.

Glucose or fructose, which are abundant resources, could be utilized as environmentally friendly alternative starting points for the production of 1. Therefore, the establishment of the process for the retro-aldol degradation of glucose is a worthwhile future challenge.

Experimental Section

Catalytic tests

Experiments were performed in 50 mL autoclave reactors. Typically, 1 (1.25 mmol, 113 mg, dimeric form, Aldrich) and paraformaldehyde (1.31 mmol, 39.4 mg, TCI) were combined with Sn catalyst (0.171 mmol), for example, SnCl₄·5 H₂O (60.0 mg, Wako chemicals), in 1,4-dioxane (4.0 mL). If anhydrous catalysts were used, water (0.86 mmol) was added. A magnetic stirring bar was then added, the reaction atmosphere was purged with Ar, and the autoclave was closed with a stainless-steel cap. The vessel was then placed in an oil bath and allowed to react for a certain amount of time. In reactions to which HCl was added, a 4 M HCl in 1,4-dioxane solution (Aldrich) was used. Mesitylene (20.0 mg) was used as the internal standard.

Time profile

Time profile measurements were performed in a 20 mL Schlenk flask. All substrates were used according to the procedure reported in the Catalytic Tests section. A magnetic stirrer bar was added, the reaction atmosphere was purged with Ar, and the vessel was placed in an oil bath. The mixture was allowed to react for a certain amount of time (5 min to 24 h). To better observe the change of product distributions, the reaction was slowed by lowering the usual reaction temperature from 140 to 100°C. In this experiment, naphthalene (20.0 mg) was used as the internal standard.

¹¹⁹Sn NMR spectroscopy

Procedure to obtain the spectrum shown in Figure 4e: the experiment was performed in a 20 mL Schlenk flask. Sn catalyst (0.171 mmol) was combined with 4 M HCl in 1,4-dioxane solution (0.34 mmol) and deuterated acetonitrile (1.00 mL, Kanto Kagaku Co.) at RT. A magnetic stirring bar was added, and the flask was placed in an oil bath. After stirring at 80 °C for 3 h under ambient air, the mixture was cooled to RT and inserted directly into an NMR



tube. The spectra shown in Figure 4 f and g, and Figure S9 were obtained according to this procedure.

Analysis

¹H NMR spectra were recorded in CDCl₃ or $[D_4]$ MeOH by using an AVANCE 400 spectrometer operated at 400 MHz. The ¹¹⁹Sn NMR spectra were recorded by using an AVANCE 400 spectrometer operated at 186.46 MHz. Chemical shift values were determined in relation to an external reference of SnMe₄ (0 ppm). A Shimadzu QP2010 plus instrument equipped with a DB-1 column was used for GC–MS analysis. A Shimadzu GC14B system equipped with a 30 m Ultra ALLOY⁺-1 column was used for GC with flame ionization detection (FID) analysis. The temperature program was as follows: 323 K for 2 min, followed by a linear ramp of 20 Kmin⁻¹ to 553 K, after which this temperature was maintained for 20 min. Materials were purchased from Wako Pure Chemicals, Tokyo Kasei Co., Kanto Kagaku Co., and Aldrich Inc. and were used without further purification.

The reaction intermediates and products 2, 3, and 4 were identified by ¹H NMR spectroscopy, GC–MS analysis, and GC with the retention times of commercial chemicals for reference. The conversion rates and yields were calculated by comparison with the internal standards mentioned above.

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Keywords: biomass • homogeneous catalysis • reaction mechanisms • reactive intermediates • tin

- Reviews on biomass: a) B. Kamm, P. R. Grube, M. Kamm, Biorefineries Industrial Processes and Products, Status Quo and Future Directions, Vol. 1, Wiley-VCH, Weinheim, 2006; b) G. W. Huber, S. Iborra, A. Corma, Chem. Rev. 2006, 106, 4044–4098; c) A. Corma, S. Iborra, A. Velty, Chem. Rev. 2007, 107, 2411–2502; d) J. J. Bozell, G. R. Peterson, Green Chem. 2010, 12, 539–554; e) A. L. Marshall, P. J. Alaimo, Chem. Eur. J. 2010, 16, 4970–4980; Utilization of biomass-derived carbohydrates: f) A. Fukuoka, P. L. Dhepe, Angew. Chem. Int. Ed. 2006, 45, 5161–5163; Angew. Chem. 2006, 118, 5285–5287; g) N. Yan, C. Zhao, C. Luo, P. J. Dyson, H. C. Liu, Y. Kou, J. Am. Chem. Soc. 2006, 128, 8714–8715; h) J. B. Binder, R. T. Raines, J. Am. Chem. Soc. 2009, 131, 1979–1985.
- [2] S. Yamaguchi, K. Motokura, Y. Sakamoto, A. Miyaji, T. Baba, Chem. Commun. 2014, 50, 4600-4602.
- [3] a) Y. Hayashi, Y. Sasaki, Chem. Commun. 2005, 2716–2718; b) E. Taarning, S. Saravanamurugan, M. S. Holm, J. Xiong, R. M. West, C. H. Christensen, ChemSusChem 2009, 2, 625–627; c) M. S. Holm, S. Saravanamurugan, E. Taarning, Science 2010, 328, 602–605; d) J. Wang, Y. Masui, M. Onaka, Appl. Catal. B 2011, 107, 135–139; e) L. Li, C. Stroobants, K. Lin,

P. A. Jacobs, B. F. Sels, P. P. Pescarmona, *Green Chem.* 2011, *13*, 1175–1181; f) C. B. Rasrendra, B. A. Fachri, I. G. B. N. Makertihartha, S. Adisasmito, H. J. Heeres, *ChemSusChem* 2011, *4*, 768–777; g) P. Y. Dapsens, C. Mondelli, J. Pérez-Ramirez, *ChemSusChem* 2013, *6*, 831–839; h) Q. Guo, F. Fan, E. A. Pidko, W. N. P. van der Graaff, Z. Feng, C. Li, E. J. M. Hensen, *ChemSusChem* 2013, *6*, 1352–1356; j) M. Dusselier, P. V. Wouwe, A. Dewaele, E. Makshina, B. F. Sels, *Energy Environ. Sci.* 2013, *6*, 1415–1442.

- [4] a) M. Dusselier, P. V. Wouwe, F. Clippel, J. Dijkmans, D. W. Gammon, B. F. Sels, *ChemCatChem* 2013, *5*, 569–575; b) M. Dusselier, P. V. Wouwe, S. Smet, R. Clercq, L. Verbelen, P. V. Puyvelde, F. E. Prez, B. F. Sels, *ACS Catal.* 2013, *3*, 1786–1800.
- [5] a) J. Kofoed, J.-L. Reymond, T. Darbre, Org. Biomol. Chem. 2005, 3, 1850–1855; b) A. L. Weber, S. Pizzarello, Proc. Natl. Acad. Sci. USA 2006, 103, 12713–12717; c) T. Wang, J. H. Bowie, Org. Biomol. Chem. 2010, 8, 4757–4766; d) S. A. Benner, H.-J. Kim, M.-J. Kim, A. Ricardo, Cold Spring Harbor Perspectives in Biology, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 2010; e) H.-J. Kim, A. Ricardo, H. I. Illangkoon, M. J. Kim, M. A. Carrigan, F. Frye, S. A. Benner, J. Am. Chem. Soc. 2011, 133, 9457–9468.
- [6] Optimization of the amount of catalyst is shown in Figure S5.
- [7] If acetonitrile was applied as a solvent, 2 was also obtained at the same level as if 1,4-dioxane was used, although the use of other solvents, such as DMSO and DMF, did not afford 2 and 4.
- [8] a) S. J. Blunden, P. A. Cusack, P. J. J. Smith, Organomet. Chem. 1987, 325, 141–152; b) Y. Román-Leshkov, M. E. Davis, ACS Catal. 2011, 1, 1566– 1580.
- [9] a) Y. Shigemasa, K. Yokoyama, H. Sashiwa, H. Saimoto, *Tetrahedron Lett.* 1994, 35, 1263–1266; b) H. Saimoto, S. Yanai, H. Sashiwa, Y. Shigemasa, *Tetrahedron Lett.* 1995, 36, 937–938; c) T. Rowicki, L. Synoradzki, M. Wlostowski, *Ind. Eng. Chem. Res.* 2006, 45, 1259–1265; d) A. N. Simonov, O. P. Pestunova, L. G. Matvienko, V. N. Snytnikov, O. A. Snytnikova, Y. P. Tsentalovich, V. N. Parmon, *Adv. Space Res.* 2007, 40, 1634–1640; e) J. A. Castillo, C. Guerard-Helaine, M. Gutierrez, X. Garrabou, M. Sancelme, M. Schurmann, T. Inoue, V. Helaine, F. Charmantray, T. Gefflaut, L. Hecquet, J. Joglar, P. Clapes, G. A. Sprenger, M. Lemaire, *Adv. Synth. Catal.* 2010, 352, 1039–1046.
- [10] a) C. Blackburn, R. F. Childs, R. A. Kennedy, *Can. J. Chem.* **1983**, *61*, 1981;
 b) G. Quinkert, H. Becker, M. Del Grosso, G. Dambacher, J. W. Bats, G. Durner, *Tetrahedron Lett.* **1993**, *34*, 6885.
- [11] a) J. J. Burke, P. C. Lauterbur, J. Am. Chem. Soc. 1961, 83, 326–331;
 b) T. N. Mitchell, Org. Magn. Reson. 1976, 8, 34–39; c) X. A. Mao, X. Z. You, A. B. Dai, Inorg. Chim. Acta 1989, 156, 177–178; d) R. S. Bitzer, W. M. Teles, A. Abras, J. D. Ardisson, C. A. L. Filgueiras, J. Braz. Chem. Soc. 2005, 16, 963–968.
- [12] a) A. Corma, M. E. Domine, L. Nemeth, S. Valencia, J. Am. Chem. Soc. 2002, 124, 3194–3195; b) C. Hammond, S. Conrad, I. Hermans, Angew. Chem. Int. Ed. 2012, 51, 11736–11739; Angew. Chem. 2012, 124, 11906–11909; c) R. Bermejo-Deval, R. Gounder, M. E. Davis, ACS Catal. 2012, 2, 2705–2713; d) H. Y. Luo, L. Bui, W. R. Gunther, E. Min, Y. Roman-Leshkov, ACS Catal. 2012, 2, 2695–2699.
- [13] J. Dijkmans, D. Gabriëls, M. Dusselier, F. Clippel, P. Vanelderen, K. Houthoofd, A. Malfliet, Y. Pontikes, B. F. Sels, *Green Chem.* 2013, 15, 2777– 2785.

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FULL PAPERS



Specific catalytic activity of homogeneous tin halides: We present a complete map of the synthetic pathway to α -hydroxy- γ -butyrolactone and related byproducts from 1,3-dihydroxyacetone

and formaldehyde. Furthermore, we propose a catalytic mechanism and a valence state of the catalyst in the reaction mixture based on the results of ¹¹⁹Sn NMR spectroscopy. S. Yamaguchi, T. Matsuo, K. Motokura, Y. Sakamoto, A. Miyaji, T. Baba*



Mechanistic Studies on the Cascade Conversion of 1,3-Dihydroxyacetone and Formaldehyde into α -Hydroxy- γ -butyrolactone