Mechanistic Insight into a Sugar-Accelerated Tin-Catalyzed Cascade Synthesis of α -Hydroxy- γ -butyrolactone from Formaldehyde

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Applications of the formose reaction, which involves the formation of sugars from formaldehyde, have previously been confined to the selective synthesis of unprotected sugars. Herein, it is demonstrated that α -hydroxy- γ -butyrolactone (HBL), which is one of the most important intermediates in pharmaceutical syntheses, can be produced from paraformaldehyde. In the developed reaction system, homogeneous tin chloride exhibits high catalytic activity and the addition of mono- and disaccharides accelerates the formation of HBL. These observations suggest that the formose reaction may serve as a feasible pathway for the synthesis of important chemicals.

Introduction

C1 chemistry is based on an interconversion with C1 compounds and a methodology for the production of important chemicals containing more than two carbon members by using syngas, methane, or methanol.^[1] Formaldehyde, which is industrially produced by the oxidation of methanol, in particular, has high potential as an electrophile in intermolecular coupling reactions^[2] or as a basic ingredient of polymer products.^[3] Therefore, if the use of formaldehyde leads to the production of important chemicals, a new process for sustainable development in the field of organic industrial chemistry will be achieved.

The formose reaction involves the formation of sugars from formaldehyde.^[4] Butlerov proposed a mechanism for the reaction,^[4a] which consisted of the following steps: two formaldehyde molecules condensed to form glycolaldehyde (GA), which reacted through an aldol reaction with another equivalent of formaldehyde to afford glyceraldehyde (GLA).^[5] The aldoseketose isomerization of GLA forms 1,3-dihydroxyacetone (DHA), which can react with formaldehyde, GA, and GLA; subsequent isomerization results in the formation of tetrose, pentose, and hexose, respectively. To date, successful examples of the formose reaction, developed exclusively for the selective syntheses of unprotected sugars, have been carried out under either a base^[6] or mineral.^[7] However, applications of the formose reaction to important chemicals, with the exception of

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Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201500885. saccharide synthesis, have not been reported, to the best of our knowledge. Strict control of the formose reaction, that is, the coupling frequency of formaldehyde and the handling of product mixtures, appears to be a considerable issue.

We previously reported the catalytic transformation of a triose sugar (DHA) and formaldehyde into α -hydroxy- γ -butyrolactone (HBL; 1);^[8] which is one of the most important intermediates in pharmaceutical syntheses.^[9] Among the examined Lewis acid catalysts, tin chlorides exhibited the best performance in the aforementioned coupling reaction. Herein, we report an unprecedented cascade synthesis of 1 from formaldehyde catalyzed by tin chlorides, and the accelerated formation of 1 upon the addition of mono- and disaccharides. A detailed screening of catalysts was investigated and, to clarify an additional effect of glucose and the reaction mechanism, several experiments were investigated. To consider the condition of the active species, the influence of the abundance ratio of Sn/HCl on the production of 1 was investigated by ¹¹⁹Sn NMR spectroscopy measurements.

Results and Discussion

Screening of catalysts

Initially, the cascade synthesis of **1** from formaldehyde was carried out in the presence of tin chloride (0.043 mmol) in 1,4-dioxane (4.0 mL) at 160 °C (Table 1).^[10] Solid paraformaldehyde does not dissolve in any solvent, and therefore, we cannot calculate the conversion of formaldehyde. Under these conditions, one mole of **1** is produced from four moles of formaldehyde.

The reaction with HCl, which is a model Brønsted acid catalyst, did not lead to the formation of 1, 2, or 3 (Table 1, entry 1). This result indicates the importance of metal catalysts to the reaction. When $SnCl_4$ - $5H_2O$ was applied, a small amount

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Table 1. Transformation of formaldehyde and glucose into 1 by using Lewis acid catalysts. ^[a]						
0 H ¹ H (6.25 mmol)						
Lewis acid catalyst (0.043 mmol)						
	(0.625 mmol)					
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	0_0	ОН	ŎН			
		СН	≪↓_Он			
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Entry	Catalyst	1 [mmol] ^[b]	2 [mmol] ^[c]	3 [mmol] ^[c]		
1 ^[d]	HCI	< 0.01	< 0.01	< 0.01		
2 ^[e]	SnCl ₄ •5 H ₂ O	0.02	< 0.01	< 0.01		
3 ^[e]	$SnCl_2 \cdot 2H_2O$	0.17	< 0.01	< 0.01		
4	SnCl ₄ •5 H ₂ O	0.33	0.026	0.047		
5	$SnCl_2 \cdot 2H_2O$	0.53	0.15	0.084		
6	SnBr ₂	0.51	0.21	0.11		
7	SnBr ₄	0.18	0.032	0.053		
8	Snl ₂	0.27	0.19	0.029		
9	Snl ₄	0.17	0.11	< 0.01		
10	<i>n</i> Bu₃SnCl	0.05	0.093	0.031		
11	Me₄Sn	< 0.01	< 0.01	< 0.01		
12	AICI ₃ •6 H ₂ O	< 0.01	< 0.01	< 0.01		
13	CrCl ₃ •6H ₂ O	< 0.01	< 0.01	< 0.01		
14	FeCl ₂ •4H ₂ O	< 0.01	< 0.01	< 0.01		
15	MgCl ₂ •6H ₂ O	< 0.01	< 0.01	< 0.01		
16 ^[f]	TiCl ₄	< 0.01	< 0.01	< 0.01		
17	$SnCl_2 \cdot 2H_2O$	< 0.01	0.11	0.048		
[a] Reaction conditions: paraformaldehyde (6.25 mmol), glucose (0.625 mmol), 1,4-dioxane (4.0 mL), catalyst (0.043 mmol), naphthalene (20 mg), air, 3 h, 160 °C. All conversions of glucose were > 99%. [b] The amount of 1 was determined by GC flame ionization detector (FID) analysis [c] The amounts of 2 and 3 were determined by ¹ H NMR spectroscopy.						

of 1 was obtained (Table 1, entry 2). The use of SnCl₂•2H₂O afforded 0.17 mmol of 1, which corresponded to a yield of 11%, based on the amount of formaldehyde (Table 1, entry 3). On the other hand, the accelerating effect of the formose reaction in the presence of sugar has been reported. $^{\scriptscriptstyle [11]}$ This reaction proceeded in an aqueous solution of Ca(OH)₂ and was catalyzed by complexes of calcium hydroxide and sugar. On the basis of this report, we attempted to increase the amount of 1 produced by adding glucose. When SnCl₄·5H₂O was applied, 0.33 mmol (Table 1, entry 4) of 1 was obtained; surprisingly, the use of SnCl₂·2H₂O afforded 0.53 mmol of 1 (Table 1, entry 5). These results showed that the addition of glucose drastically increased the amount of 1. We subsequently investigated the influence of the counteranion in the tin halides on the formation of each product by conducting experiments with anhydrous $SnBr_{2},\ SnBr_{4},\ SnI_{2},\ and\ SnI_{4}$ (Table 1, entries 6– 9). The use of SnBr₂ gave almost the same amounts of product as those observed with SnCl₂·2H₂O (Table 1, entry 6), whereas when SnBr₄ was employed the amount of 2 decreased dramatically (Table 1, entry 7). Snl₂ and Snl₄ were both observed to have even lower activities and selectivities (Table 1, entries 8 and 9). When comparing similar catalysts that differ only in the

analysis. [d] 0.086 mmol. [e] Without glucose. [f] Without paraformalde-

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chloride and iodide counterions, the amounts of 1 and 3 remain low, although that of 2 is similar, which confirms that a chloride is the most suitable counteranion for this system. However, the use of either nBu₃SnCl or Me₄Sn showed no improvement on the amount of product, although they had a tetravalent tin center (Table 1, entries 10 and 11). This result shows that an absolute quantity of chloride counterion to a tin center is important for the successful formation of 1. Having established that chloride was the most suitable counterion in this system, we next screened different metal chloride catalysts, namely, AlCl₃, CrCl₃, FeCl₂, MgCl₂, and TiCl₄, and, consequently, all were observed to have no activity in this reaction (Table 1, entries 12-16). These results indicate that both tin metal and a halogen counterion are critical elements for this reaction system. Finally, when glucose was used and paraformaldehyde was not, product 1 was not obtained (Table 1, entry 17).

Based on this experimental result, we added fresh glucose and paraformaldehyde to the reaction mixture after an initial run, and 1, 2, and 3 were afforded in almost the same amount as that obtained in the first run. These results also support the assertion that the tin catalyst continues to behave as a catalyst without deactivation through multiple uses.

Considerations on an additional effect of glucose

As shown in Table 1, the greatest amount of 1 was produced when divalent tin chloride was used. In the presence of glucose, the transformation of glucose into 1 occurs simultaneously owing to 1) the isomerization of glucose to fructose, 2) retro-aldol reaction to DHA or GLA, and 3) an intermolecular aldol reaction with formaldehyde. Therefore, product 1 could be obtained from glucose and formaldehyde in this reaction system. To determine whether the production of 1 was derived from glucose or formaldehyde, an experiment was carried out with $[D_2]$ paraformaldehyde was carried out. As shown in Scheme 1, 0.13 mmol of $[D_2]$ HBL (4) and 0.41 mmol of D_5 -HBL



Scheme 1. Transformation of glucose and [D₂]paraformaldehyde into [D₂]HBL (4) and [D₅]HBL (5). Reaction conditions: [D₂]paraformaldehyde (6.25 mmol), glucose (0.625 mmol), 1,4-dioxane (4.0 mL), SnCl₂·2 H₂O (0.043 mmol), naphthalene (20 mg), air, 3 h, 160 °C.

(5), the carbon selectivities of which were 9 and 27% yield, respectively, were obtained and the total amount was almost identical to the results shown in Table 1, entry 5. The amount of 4 and 5 was determined by GC-FID and ¹H NMR spectroscopy analysis. In addition, GC-MS analysis confirmed the formation of 4 and 5. The m/z [M^+] values of 4 and 5 are 104(1) and

hyde.



107(1), respectively (Figure S2 in the Supporting Information). These results show that the product is a mixture of **4** and **5**. On the other hand, we could not observe unlabeled HBL (1), which would arise from the coupling of two C2 fragments from the retro-aldol of glucose (C2+C4 fragments), based on results from ¹H NMR spectroscopy analysis (Figure S3 in the Supporting Information). This result is attributed to a previous report^[12] that the tin-catalyzed retro-aldol reaction of glucose occurs mainly through resolution into C3+C3 fragments instead of C2+C4 fragments.

On the other hand, an experiment with DHA and $[D_2]$ paraformaldehyde was also examined. As shown in Table S1 in the Supporting Information, product **5** was not obtained at all when either SnCl₂·2H₂O or SnCl₄·5H₂O was applied. This result and that shown in Figure S1 in the Supporting Information show that the combination of DHA and formaldehyde does not lead to the production of **1** based on a formose reaction.

To determine the role of glucose, the influence of a specified amount of glucose on the production of **1**, **2**, and **3** was investigated. As shown in Figure 1, we clarified that the total



Figure 1. Influence of the amount of glucose on the production of 1, 2, and 3. Reaction conditions: glucose, paraformaldehyde (6.25 mmol), $SnCl_2 \cdot 2H_2O$ (0.043 mmol), 1,4-dioxane (4.0 mL), naphthalene (20 mg), air, 3 h, 160 °C. All conversions of glucose were > 99%. The amount of 1 was determined by GC-FID analysis. The amounts of 2 and 3 were determined by ¹H NMR spectroscopy analysis. 1: \Box (×: derived from four formaldehydes, *: derived from glucose and formaldehyde), 2: \triangle , 3: \bigcirc .

amount of **1** increased in proportion to the amount of added glucose and the product derived from four formaldehydes also increased (Figure 1, dotted line). These results, and that shown in Table 1, entry 3, indicate that the transformation of formaldehyde into **1** was accelerated in the presence of glucose.

We subsequently attempted to measure a time profile (Figure 2). When glucose and paraformaldehyde were applied as substrates, the amount of each product increased with time and the production of **1** stopped increasing after 6 h (Figure 2a). On the other hand, when only paraformaldehyde was applied as a substrate, the amount of **1** increased proportional-





Figure 2. a) Time profile measurement with glucose and paraformaldehyde. Reaction conditions: glucose (0.625 mmol), paraformaldehyde (6.25 mmol), SnCl₂·2 H₂O (0.043 mmol), 1,4-dioxane (4.0 mL), naphthalene (20 mg), air. All conversions of glucose were >99%. The amount of 1 was determined by GC-FID analysis. The amounts of 2 and 3 was determined by ¹H NMR spectroscopy analysis. 1: \Box , 2: \triangle , 3: \bigcirc . b) Time profile measurement with only paraformaldehyde. Reaction conditions: glucose (0.625 mmol), paraformaldehyde. Reaction conditions: glucose (0.625 mmol), paraformaldehyde. Reaction conditions: glucose (0.625 mmol), paraformaldehyde. Reaction sof glucose were >99%. The amount of 1 was determined by GC-FID analysis. The amounts of 2 and 3 were determined by GC-FID analysis. The amounts of 2 and 3 were determined by ¹H NMR spectroscopy analysis. 1: \Box , 2: \triangle , 3: \bigcirc .

ly, but **2** and **3** were not formed at all (Figure 2b). These results clearly show an accelerating effect in the initial stage of the reaction.

Finally, we attempted to apply other sugars, such as monoand disaccharides, sugar alcohols, and amino sugars, instead of glucose (Table 2). Initially, we applied fructose, galactose, and mannose as isomers of glucose and 0.50, 0.52, and 0.40 mmol of 1 were obtained, respectively (Table 2, entries 3–5). The use of xylose as a representative of pentose afforded 0.45 mmol of 1 (Table 2, entry 6). We subsequently applied disaccharides cellobiose and sucrose, and 0.32 and 0.54 mmol of 1 were obtained, respectively (Table 2, entries 7 and 8). These results indicate that sugar stereochemistry affects the amount of 1 pro-



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Table 2.	Effect of	the us	e of	sugars	or	sugar	alcohols	instead	of	glucos
on the p	production	n of 1 . ^[a]								

Entry	Accelerator	Amount fo 1 ^[b]	3 ^[c]	
1	-	0.17	< 0.010	< 0.010
2	glucose	0.53	0.15	0.084
3	fructose	0.50	0.18	0.090
4	mannose	0.52	0.17	0.11
5	galactose	0.40	0.12	0.084
6	xylose	0.45	0.15	0.070
7	cellobiose	0.32	0.039	0.051
8	sucrose	0.54	0.17	0.10
9	glucosamine	< 0.01	< 0.01	< 0.01
10	sorbitol	0.16	0.019	0.020

[a] Reaction conditions: accelerators (mono- (0.625 mmol) or disaccharide (0.313 mmol)), paraformaldehyde (6.25 mmol), 1,4-dioxane (4.0 mL), SnCl₂·2H₂O (0.043 mmol), naphthalene (20 mg), air, 3 h, 160 °C. All conversions of accelerator were >99%. [b] The amount of 1 was determined by GC-FID analysis. [c] The amounts of 2 and 3 were determined by ¹H NMR spectroscopy analysis.

duced. Finally, the use of an amino sugar gave no product 1, whereas when we utilized a sugar alcohol the amount of 1 remained unchanged (Table 2, entries 9 and 10). This result shows that amino sugars and sugar alcohols do not accelerate the formation of 1, whereas mono- and disaccharides, in particular, have a distinct effect on the reaction.

Considerations of the reaction mechanism

To consider the reaction mechanism, we investigated the influence of a specific amount of paraformaldehyde on the produc-

tion of 1, 2, and 3 (Figure 3). The amount of 1 and 3 increased commensurately and that of 2 remained unchanged with the amount of formaldehyde used. This result shows that 2 is mainly composed of elements derived from glucose.

The reaction pathway in Scheme 2 is discussed in detail in the next sections and is supported by the presentation of experimental findings based on the results shown in Figures 2 and 3. There are two possible routes: I: the production of C3 sugar, DHA, or GLA through the condensation of three formaldehydes, or II: an intermolecular aldol reaction of two GAs.

Route I

Two formaldehydes were condensed to generate GA and then



Figure 3. Influence of the amount of formaldehyde on the production of 1, 2, and 3. Reaction conditions: glucose (0.625 mmol), paraformaldehyde, SnCl₂·2 H₂O (0.043 mmol), 1,4-dioxane (4.0 mL), naphthalene (20 mg), air, 3 h, 160 °C. All conversions of glucose were >99%. The amount of 1 was determined by GC-FID analysis. The amounts of 2 and 3 were determined by ¹H NMR spectroscopy analysis. 1: \Box , 2: \triangle , 3: \bigcirc .

aldol condensation with another formaldehyde provided the C3 sugar (Scheme 2, steps 1 and 2). Tin can coordinate with enolate **6** due to its strong Lewis acid character, so activated complex **6** is formed and readily undergoes the aldol reaction with formaldehyde to afford **7** (Scheme 2, step 3). If this reaction proceeds based on this route, compounds **1**, **2**, and **3** are generated at a constant rate, as reported previously for DHA and formaldehyde.^[9c]



Scheme 2. Formation of 1 from four formaldehydes through the aldol reaction.



Route II

Another possible mechanistic route to 1 is based on an aldol reaction of two GAs. After aldol coupling and tautomerization, the aldehyde appears prone to elimination of the hydroxyl group in the β position of the unsaturated carbon (Scheme 2, steps 4 and 5). Therefore, dehydration of tetrose 8 at the C3 position occurs to provide 7. If this reaction proceeds based on this route, compounds 1 and 3 are generated at a constant rate, whereas little of 2 is obtained.

Time profile measurements showed that **2** and **3** were not afforded when using only formaldehyde as a substrate. In addition, when the amount of formaldehyde increased, the amount of **2** remained unchanged. Based on these experimental results, this transformation of formaldehyde in the presence of glucose mainly proceeds through route II (Scheme 2).

Catalytic behavior of tin chlorides

Based on the results shown in Table 1, entries 2–5, 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. On the other hand, the transformation of glucose and formaldehyde in the presence of HCl yields no 1, 2, or 3. Although the importance of Lewis acidic tin is clear, we need to confirm the difference in activities between tin(II) and tin(IV). In addition, the balance between Lewis and Brønsted acidity is key to understanding this cascade reaction, and directing it to higher production and selectivities.

The results depicted in Table 1 showed that the reaction was different in the presence of SnCl₂·2H₂O and SnCl₄·5H₂O. Therefore, we initially attempted to investigate the influence of a specific amount of tin catalyst on the production of 1. The amount of each product obtained when either SnCl₂·2H₂O or SnCl₄·5H₂O was utilized is shown in Figure S4a and S4b in the Supporting Information, respectively. When 0.043 mmol of SnCl₂·2H₂O was used, the greatest production of 1 was obtained; on the other hand, only 0.020 mmol of SnCl₄·5H₂O, less than half the catalytic amount, was required to obtain the highest amount of 1. This result indicates that divalent tin may be oxidized in air to generate tetravalent tin. On the other hand, the use of $SnCl_2 \cdot 2H_2O$ provided a greater amount of each product than the use of SnCl₄·5H₂O. Based on this result, we speculated that HCl was obtained in greater amounts with SnCl₄·5H₂O than with SnCl₂·2H₂O and, consequently, unpredictable side reactions could be induced.

We subsequently attempted to investigate the influence of the HCl/Sn ratio on the production of 1, 2, and 3. The amount of each product with different HCl/Sn ratios, when using either SnCl₂·2H₂O or SnCl₄·5H₂O, are shown in Figure 4a and b, respectively. To vary the Lewis and Brønsted acid contents, external HCl was added. As shown in Figure 4a, when SnCl₂ was used, the highest amount of 1 was observed with no extra equivalents of HCl and that of 1 decreased with increasing amounts of HCl. Furthermore, when SnCl₄ was used, the amount of 1 also decreased with increasing amounts of HCl (Figure 4b). On the other hand, the trend for the production of **2** and **3** was similar to that seen for the formation of **1**. These results indicate that the production of **1** and **3** from formaldehyde may be inhibited by an increase in HCl and the production of **2** generated from glucose through a retro-aldol reaction is also inhibited. However, according to the results shown in Table 1, entries 10 and 11, the reaction did not proceed in the absence of halide anions. These results and that shown in Figure 4 and Figure S4 in the Supporting Information indicate that a tetravalent tin cation in the reaction mixture interacts with glucose and coordinates with a chloride anion.

In addition, as shown in Table 1, entries 2–5, the amount of 1 obtained was different in the presence or absence of glucose, leading us to hypothesize that the addition of glucose could change the conditions of the active species. Therefore, we performed ¹¹⁹Sn NMR spectroscopy studies to compare the



Figure 4. Influence of the ratio of HCl/Sn on the production of **1**, **2**, and **3** with SnCl₂·2 H₂O (a) and SnCl₄·5 H₂O (b). Reaction conditions: glucose (0.625 mmol), paraformaldehyde (6.25 mmol), SnCl₂·2 H₂O/SnCl₄·5 H₂O (0.043 mmol), 4 \bowtie HCl in 1,4-dioxane, 1,4-dioxane (4.0 mL), air, 3 h, 160 °C. All conversions of glucose were > 99%. The amount of **1** was determined by GC-FID analysis. The amounts of **2** and **3** was determined by ¹H NMR spectroscopy analysis. **1**: \Box , **2**: \triangle , **3**: \bigcirc .

conditions of tin metal in different reaction environments (Figure 5).

Figure 5 a and b shows the ¹¹⁹Sn NMR spectra of SnCl₂·2H₂O and SnCl₄·5H₂O, respectively, in CD₃CN. The singlets at $\delta = -244$ (\diamond) and -639 ppm (\Box) are observed and may be derived



Figure 5. ¹¹⁹Sn NMR spectra in CD₃CN (1.0 mL) of a) SnCl₂·2 H₂O at RT, b) SnCl₄·5 H₂O at RT, c) SnCl₂·2 H₂O (0.171 mmol) and glucose (0.625 mmol) after heating to 80 °C for 3 h, and d) SnCl₄·5 H₂O (0.171 mmol) and glucose (0.625 mmol) after heating to 80 °C for 3 h.

from di- and tetravalent tin metals, respectively. After the solution of SnCl₂·2 H₂O was heated to 80 °C and stirred for 3 h, the signal at $\delta = -244$ ppm (\diamond) derived from SnCl₂·2 H₂O was completely absent and the signal at $\delta = -639$ ppm (\Box), which was also seen in the spectrum of SnCl₄·5 H₂O, was exclusively observed (Figure 5). We subsequently examined the ¹¹⁹Sn NMR spectrum of SnCl₂·2 H₂O in the presence of glucose (Figure 5 c). As shown in Figure 5 c, the main signal at $\delta = -614$ ppm (\times) is observed. In addition, in case of the combination of SnCl₄·5 H₂O and glucose, the main signal at $\delta = -598$ ppm (\triangle) is different from that observed with SnCl₂·2 H₂O (Figure 5 d). These results indicate that tin metal interacts with glucose, although we could not identify what species these signals were derived from.

Conclusions

In this study, we considered the specific catalytic activity of homogeneous tin chloride for converting formaldehyde into 1 in the presence of glucose. Initially, we screened a number of Lewis acid catalysts and tin halides. Tin chlorides, in particular, had the highest activity in this reaction system. Based on an experiment with [D₂]paraformaldehyde and a study on the amount of glucose used, we discovered that the addition of glucose led to an acceleration of the conversion of formaldehyde into 1. Although the addition of mono- and disaccharides had an effect similar to that of glucose, the use of amino sugars and sugar alcohols did not show an accelerated effect. In addition, a time profile measurement and a study on the amount of paraformaldehyde used suggested that this reaction might not proceed via C3 sugar as an intermediate. On the other hand, we clarified that HCl generated from the chloride anion inhibited this reaction system and a tetravalent tin

cation coordinated with chloride anions could be an active species. Finally, ¹¹⁹Sn NMR spectroscopy measurements provided indications of changing conditions around the tin metal center, particularly with how the tin metal interacted with glucose. The details of this reaction, especially with regard to in-

teractions between tin metal and glucose, are being investigated in our laboratory and will be reported in due course.

On the other hand, almost all carbon atoms coming from glucose as an accelerator were transformed into some byproducts, such as **2**, **3**, or an unexpected one, through side reactions. From the sustainability point of view, we need to consider the effective utilization of glucose, which is representative of mono- and disaccharides, and therefore, the development of catalysts for the conversion of glucose into HBL is a considerable issue to overcome.

Experimental Section

General

Materials were purchased from Wako Pure Chemicals, Tokyo Kasei Co., Kanto Kagaku Co., and Aldrich and were used without further purification. A Shimadzu

GC14B instrument equipped with a 30 m Ultra ALLOY⁺-1 column was used for GC-FID analysis. The temperature program was as follows: 1) 323 K for 2 min, 2) a linear ramp of 3 Kmin⁻¹ to 373 K, 3) 373 K for 5 min, 4) a linear ramp of 10 Kmin⁻¹ to 553 K, and 5) 553 K for 20 min. A Shimadzu QP2010 plus instrument equipped with a DB-1 column was used for GC-MS analysis. Products were confirmed by the comparison of their GC retention time, mass spectrum, and ¹H NMR spectrum with those of authentic samples. ¹H NMR spectra were recorded in CDCl₃ or [D₆]DMSO with an AVANCE 400 spectrometer operated at 400 MHz. The ¹¹⁹Sn NMR spectra were recorded with an AVANCE 400 spectrometer operated at 186.46 MHz. Chemical shift values were determined in relation to an external reference of SnMe₄ (δ =0 ppm).

Typical procedure for the catalytic reaction (Table 1, entry 5)

A 50 mL autoclave with a Teflon liner was charged with glucose (113 mg), paraformaldehyde (188 mg), SnCl₂·2 H₂O (9.7 mg), naphthalene (20 mg, internal standard), and 1,4-dioxane (4.0 mL) and was pressurized with air. The autoclave was heated to the preset temperature of 160 °C. After being stirred at the same temperature for 3 h, the autoclave was cooled and the reaction mixture was analyzed by GC-FID and ¹H NMR spectroscopy. All yields were calculated on a carbon basis, that is, two moles of 1 could be formed from one mole of glucose. Carbohydrate conversion was determined by ¹H NMR spectroscopy in [D₆]DMSO or D₂O.

Typical ¹¹⁹Sn NMR spectroscopy measurement (Figure 5 c)

The reaction was performed in a 20 mL Schlenk flask. SnCl₂·2H₂O (38.6 mg) was combined with glucose (113 mg) and deuterated acetonitrile (1.00 mL, Kanto Kagaku Co.) at room temperature. A magnetic stirrer bar was then added and the flask was placed in an oil bath. After being stirred at 80 °C for 3 h in air, the mixture was cooled to room temperature, and was then inserted directly



into an NMR tube. According to this procedure, the experiments shown in Figure 5 were conducted.

Keywords: carbohydrates • domino reactions • homogeneous catalysis • sustainable chemistry • lactones

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