# AN α-SELECTIVE GLYCOSYLATION *VIA* DECARBOXYLATION OF MIXED CARBONATE CATALYZED BY THE COMBINATION OF LEWIS ACID AND SILVER PERCHLORATE†

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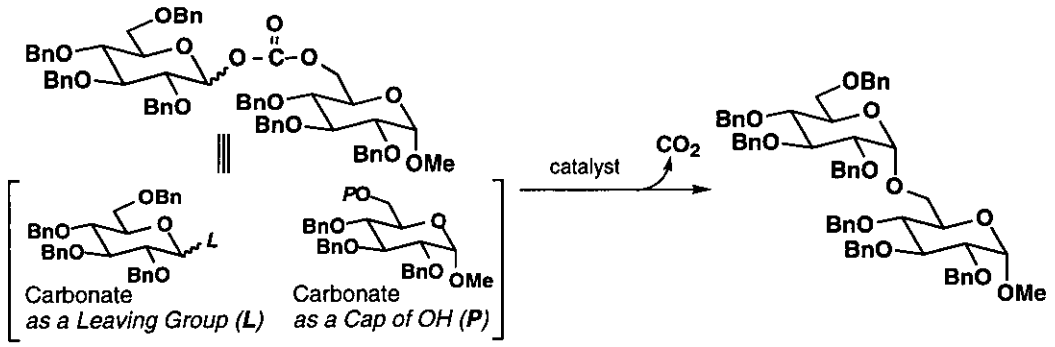
*Abstract*—A catalytic amount of $SnCl_4$-$AgClO_4$ or $Cp_2HfCl_2$-$2AgClO_4$ promoted decarboxylation of the 1-*O*-carbonates of the sugars to afford the α-glycosides stereoselectively. In this glycosylation reaction, the carbonate acts a leaving group of the glycosyl donor and also a cap of hydroxyl group in the acceptor alcohol.

Considerable efforts have been made for attaining efficient synthesis of oligosaccharides in this decade. Especially, while study of the interglycosidic bond formation has been rapidly expanded, high-yielding and stereoselective glycosylation methods have been developed thus far.[1] These glycosidic bond formations are generally based on the activation of glycosyl donors with leaving groups by appropriate promoters,[1] but a different type of glycosylation is an engaging alternative, which can furnish flexible strategies for oligosaccharide synthesis.[2] Along this line, we developed a decarboxylative glycosylation method which involves 1) linking two sugar moieties using carbonate as a connector and 2) removing internal carbon

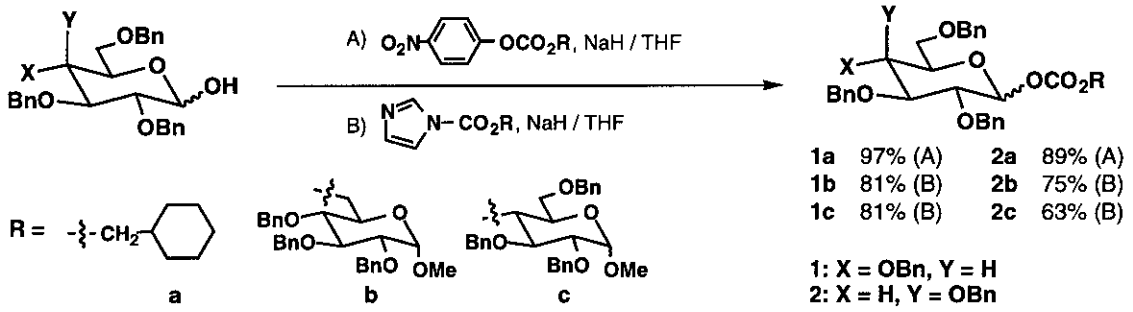



dioxide by the aid of Lewis acid to form glycosidic bond.[3]

A stoichiometric amount of promoter was required for the second decarboxylative transformation in our original procedure.[3] However, the glycosylation should proceed catalytically because the carbonate can play two roles as shown in the above figure; one is a leaving group of the glycosyl donor [4] and another is a cap of the hydroxylic proton of the acceptor which often disturbs a catalytic cycle in glycosylations.

† Dedicated to the memory of Dr. Shun-ichi Yamada, Professor Emeritus Tokyo Unversity.

**Scheme 1**



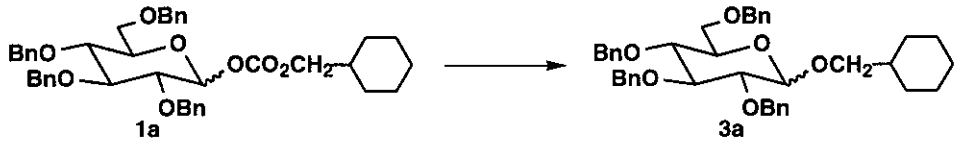

From this point of view, we explored a catalytic version of decarboxylative glycosylation and present herein.

Mixed carbonates, substrates of our decarboxylative glycosylation, were easily prepared by using 4-nitrophenyl carbonates (Method A in Scheme 1) or the imidazolides (Method B in Scheme 1). The imidazolides were chosen when the glycosyl acceptors were sugar alcohols such as **b** or **c** because a tedious chromatographic separation was necessary to remove a by-product (bis(4-nitrophenyl) carbonate) in the method A.[3]

We previously reported that a stoichiometric amount of trialkylsilyl triflate (TMSOTf or TBDMSOTf) was required in the decarboxylative conversion of **1a** into **3a** (Entry 1 in Table 1). At that time, we observed that a catalytic amount of TMSOTf could effectively promote the reaction but a longer reaction time to complete the reaction resulted in the increase of a by-product (the hydrolyzed product). Considering this observation, we examined several modifications of the experimental procedure to keep the strictly anhydrous conditions during the reaction, and then could attain the catalytic decarboxylative glycosylation (Entry 2 in Table 1).

With this successful result in hand, we re-surveyed the catalysts which have been reported to promote glycosylation of 1-*O*-acyl sugars. A combination of tin(IV) chloride and silver perchlorate has been used

**Table 1.** A Catalytic Decarboxylative Glycosylation.[a]



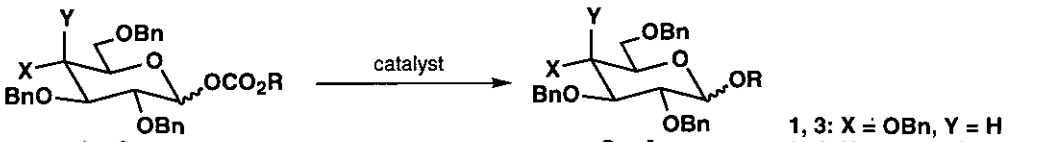

| | | Reaction Conditions | | | | |
|---|---|---|---|---|---|---|
| Entry | Promoter (equiv.) | Solvent | Temp. (°C) | Time | Yield (%) | α : β[b] |
| 1[c] | TMSOTf (1.1) | toluene | 0 | 30 min | 76 | 16 : 84 |
| 2 | TMSOTf (0.2) | toluene | 0 | 2 h | 79 | 21 : 79 |
| 3 | $SnCl_4$-$AgClO_4$ (0.2) | $Et_2O$ | 20 | 3 h | 78 | 92 : 8 |
| 4 | $SnCl_4$-$AgClO_4$ (0.2) | $CH_2Cl_2$ | 0 | 15 min | 77 | 82 : 18 |
| 5 | $Cp_2HfCl_2$-$2AgClO_4$ (0.2) | $Et_2O$ | 20 | 5 h | 80 | 95 : 5 |
| 6 | $Cp_2HfCl_2$-$2AgClO_4$ (0.2) | $CH_2Cl_2$ | 0 | 30 min | 73 | 34 : 66 |

[a] The reaction was carried out in 0.1 mmol scale. [b] Determined by HPLC analysis. [c] Reported values in the reference 3.

as a catalyst of α-selective glycosylations between 1-*O*-acyl sugars and silylated alcohols.[5] Employing this catalyst system for the decarboxylative glycosylation of the glucopyranosyl 1-*O*-carbonate (**1a**), the glycoside (**3a**) was obtained in 78% yield with α-selectivity (α : β = 92 : 8; Entry 3 in Table 1). Similar to Mukaiyama's system,[5] switching the solvent to $CH_2Cl_2$ caused a lower selectivity, and the reaction was much faster in this case (15 min, 77%, α : β = 82 : 18; Entry 4). The employment of $Cp_2HfCl_2$-$AgClO_4$ in 1 : 2 ratio for the glycosylation of glycosyl fluorides has been reported by Suzuki and his co-workers.[6] This catalyst system also activates 1-*O*-acyl sugars in the glycosylation with phenol derivatives.[7] A mechanistic insight of the glycosylation promoted by $Cp_2HfCl_2$-$2AgClO_4$ suggested that this promoter system might work catalytically in our decarboxylative transformation. In fact, 0.2 equiv of this promoter system converted **1a** into **3a** in 73% yield in $CH_2Cl_2$, but unfortunately the stereoselctivitiy was not so high (Entry 6). However, when $Et_2O$ was used in place of $CH_2Cl_2$ as the solvent, a high α-stereoselective transformation was achieved (α : β = 95 : 5; Entry 5). Here we could found two promoter systems which catalyze an α-selective glycosylation *via* the anomeric carbonate.

Applications of these catalyst systems to disaccharide synthesis are summarized in Table 2. By using $SnCl_4$-$AgClO_4$ in $CH_2Cl_2$, considerable decreases of the stereoselectivity were observed in the cases of glucopyranose 1-*O*-carbonates (**1b** and **1c**) and galactopyranose 1-*O*-carbonates (**1a** - **1c**). On the contrary, when $Et_2O$ was used as the solvent, α-glycosides (**2a** - **2c** and **3a** - **3c**) were predominantly produced in *ca.* 50 - 80% yields (Entries 1 - 5 in Table 2). In the $Cp_2HfCl_2$-$AgClO_4$-catalyzed glycosylation which was

**Table 2.** Decarboxylative Glycosylation Catalyzed by $SnCl_4$-$AgClO_4$ or $Cp_2HfCl_2$-$2AgClO_4$.[a]




| Entry | X | Y | R[b] | Solvent: $Et_2O$ Yield (%) | $Et_2O$ α : β[c] | $CH_2Cl_2$ Yield (%) | $CH_2Cl_2$ α : β[c] |
|---|---|---|---|---|---|---|---|
| Catalyst = $SnCl_4$-$AgClO_4$ | | | | | | | |
| 1 | OBn | H | **b** | 82 | 83 : 17 | 86 | 68 : 32 |
| 2 | OBn | H | **c** | 62 | 86 : 14 | 82 | 58 : 42 |
| 3 | H | OBn | **a** | 48 | 93 : 7 | 52 | 75 : 25 |
| 4 | H | OBn | **b** | 72 | 92 : 8 | 73 | 73 : 27 |
| 5 | H | OBn | **c** | 84 | 90 : 10 | 66 | 54 : 46 |
| Catalyst = $Cp_2HfCl_2$-$2AgClO_4$ | | | | | | | |
| 6 | OBn | H | **b** | 66 | 92 : 8 | | |
| 7 | OBn | H | **c** | 63 | 87 : 13 | | |
| 8 | H | OBn | **a** | 68 | 65 : 35 | | |
| 9 | H | OBn | **b** | 64 | 95 : 5 | | |
| 10 | H | OBn | **c** | 67 | 93 : 7 | | |

[a] Reaction conditions. $SnCl_4$-$AgClO_4$ in $Et_2O$: 20 °C, 3 h. $SnCl_4$-$AgClO_4$ in $CH_2Cl_2$: 0 °C,15 min. $Cp_2HfCl_2$-$2AgClO_4$ in $Et_2O$: 20 °C, 7 h. [b] See Scheme 1. [c] Determined by HPLC analysis.

shown to have the highest selectivity in the model experiment (entry 5 in Table 1), the carbonates attached to sugar alcohols as the glycosyl acceptors were converted into the glycosides with high stereoselectivities ($\alpha$ : $\beta$ = 87 : 13 – 95 : 5; Entries 6, 7, 9, and 10). While the reason was not clear at this time, the cyclohexylmethyl galactoside (**4a**) showed a very low selectivity ($\alpha$ : $\beta$ = 65 : 35; Entry 8). However, by choosing the appropriate catalyst system, we could attain the high $\alpha$-selectivity for all the substrates examined herein.

Since catalytic glycosylations promoted by Lewis acids generally require silylated acceptor alcohols, the silylation step has to be added to the whole glycosylation scheme. On the contrary, carbonates can act as the silylated acceptors; a catalytic reaction of them into glycosides can be achieved without an additional step. As another advantage of this glycosylation procedure over the others is that glycosyl donor part is attached to glycosyl acceptor in the opposite mode,[3] extending these abilities to oligosaccharide synthesis is under exploration in this laboratory.

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