# Development of Novel Glycosylation Reaction under Pd-catalyzed Reductive Conditions

| | |
|---|---|
| | りー　げふぇい |
| 氏　　名 | 李　格非 |
| 研究科，専攻の名称 | 東北大学大学院工学研究科（博士課程）バイオ工学専攻 |
| 学 位 論 文 題 目 | Development of Novel Glycosylation Reaction under Pd-catalyzed Reductive Conditions<br>（パラジウム触媒を用いる還元的新規グリコシル化反応の開発） |
| 論 文 審 査 委 員 | 主査　東北大学教授　正田　晋一郎　東北大学教授　服部　徹太郎<br>東北大学教授　冨重　圭一 |

# 論文内容要約

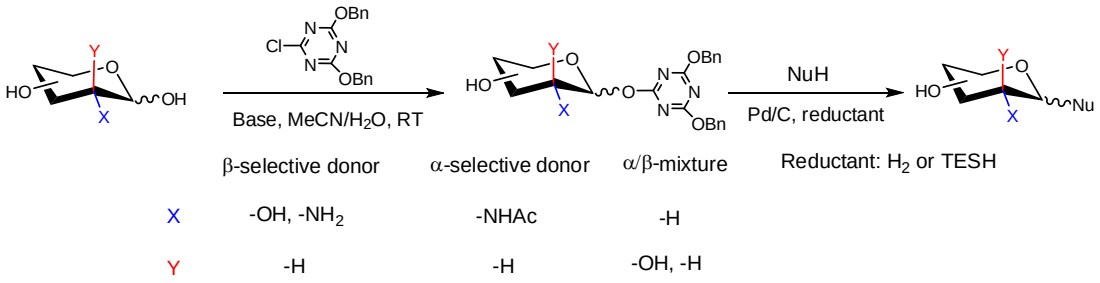
**Chapter 1　Introduction**

Chemical glycosylation plays crucial role for the synthesis of sugar-containing molecules which have widespread applications in biological and pharmaceutical fields, such as amphiphilic smart gelators, biosurfactants, and drugs. [1] Owing to this reason, series of glycosyl donors (e.g., thioglycoside, glycosyl halides, glycosyl trichloroacetimidates, propargyl glycoside) and advanced promoters (e.g., bismuth(V) compound, chiral phosphoric acid, Au(I)-complex) have been developed offering the efficient and chemoselective glycosylation strategies. [2] However, the multiple hydroxy groups of sugar cause serious synthetic barriers with regard to their selective activation, which usually requires laborious protection-deprotection manipulations or the strict compliance with special reaction conditions. In addition, the general side-reaction induced by acidic promoters including the hydrolysis of the inner glycosidic bond of glycosyl donors is another trouble in carbohydrate chemistry. Herein, we developed a novel chemical glycosylation with triazinyl glycosyl donors which proceeds under Pd-catalyzed reductive conditions. The triazinyl glycoside donors were directly synthesized from unprotected sugars in aqueous solutions. The subsequent glycosylation reactions were carried out with these triazinyl glycoside donors and series of alcohols under Pd-catalyzed reductive conditions, giving rise to the corresponding glycoside products stereo-selectively in good yields. Noteworthy, the oligosaccharides can be coupled with alcohols successfully without affecting their inner glycosidic bonds under this mild promoter conditions.

**Chapter 2　Pd-induced glycosylation with unprotected DBT-glycosyl donors**

The syntheses of 4,6-dibenzyloxy-1,3,5-triazin-2-yl glycoside (DBT-glycoside) donors were carried out through a nucleophilic substitution with unprotected sugars in the presence of base under aqueous media, giving rise to the corresponding DBT-glycosides in good yields (60%~80%) (Scheme 1). Excellent stereoselectivity was also achieved for these novel donors after the simple separation. The neighboring (C-2) groups on sugars play critical roles for the resulting stereoselectivity. Herein, the β-selective glycosyl donors were obtained using sugars with an equatorial hydroxy group or amino group. Meanwhile, the corresponding DBT-α-glycosides were converted to the 1,2-$(DBT)_2$-α-glycoside derivatives through the further substitution. An acceptable explanation is that the hydrogen bond interactions between the triazine and neighboring -OH facilitates the

further substitution for these 1,2-*cis* DBT-glycosides. In addition, with *N*-acetyl glucosamine, completely α-selective donors were synthesized with the removal of sugar oxazoline generated from the β-type product. The anomeric mixture was generated using the sugars with an axial neighboring OH (such as mannose). The DBT-glycosides of higher oligosaccharides such as melibiose, lactose, cellobiose and maltopentaose were also prepared without affecting their inner glycosidic bonds. The corresponding stereoselectivity of the achieved DBT-oligosaccharides were determined by their terminal sugars.

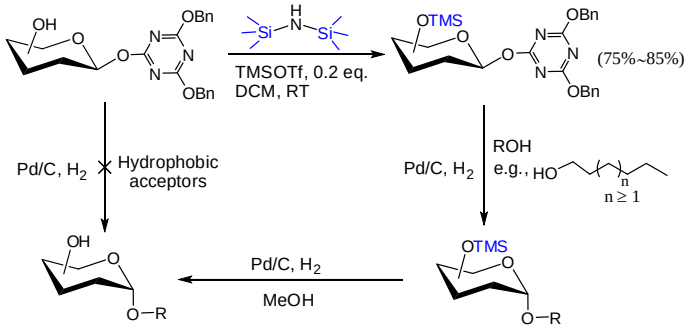



**Scheme 1** Synthesis of DBT-glycoside donors for the Pd-induced reductive glycosylation

Glycosylation of the resulting DBT-glycosides was carried out in various alcohols under Pd-catalyzed hydrogenolysis conditions, giving rise to the corresponding glycoside products in good yields. When primary alcohols were used as acceptors, the high stereoselectivity was observed, suggesting an $S_N2$-like reaction course. The α-selective glycoside products were synthesized with the DBT-β-glycoside donors. Inversely, the coupling reaction using DBT-α-glycosides caused the β-type products. With triethylsilane (TESH) as the reductant instead of $H_2$, the unsaturated alcohols can be glycosylated in the absence of the hydrogen addition on the unsaturated bond. On the other hand, the longer reaction time was spent in case of using secondary or tertiary alcohols as the acceptors due to their lower nucleophilicity. The present method of hydrogenolysis allows even an acid-labile oligosaccharide to be glycosylated without cleavage of the inner glycosidic bonds.

**Chapter 3 Glycosylation with silylated DBT-glycosyl donors**

A convenient and mild glycosylation method has been established based on the Pd-induced reductive debenzylation. However, the DBT-glycosyl donors usually suffer from low solubility in hydrophobic solvent, causing the failed reaction in the coupling with long-chain alcohols. To improve the solubility of DBT-glycosides, the protecting groups, or to be more accurate, the solubilizing groups were introduced to the DBT-glycoside donors. In our experiments, the trimethyl silyl groups (TMS) were introduced to the DBT-glycosides to improve their solubility in hydrophobic alcohols or organic solvents (Scheme 2). These silylated glycosyl donors have proven to be especially useful starting materials in the coupling with hydrophobic alcohols. More importantly, the silyl groups could be removed under the same reductive conditions by the addition of methanol to the



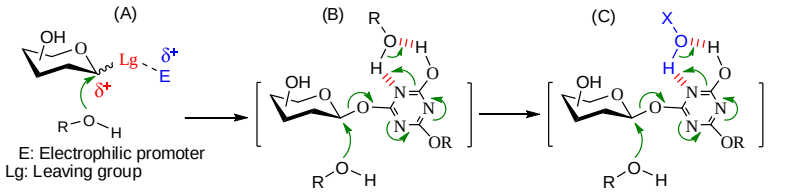

**Scheme 2** Coupling of sugars and hydrophobic alcohols with the silylated DBT-glycoside donors

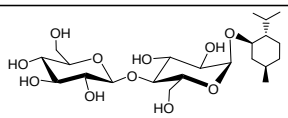
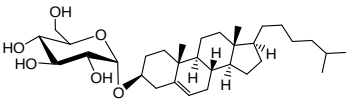
reaction mixture upon glycosylation finished, affording a one-pot process including glycosylation and deprotection. In addition, the improved stereo-selectivity was also observed in the glycosylation with silylated donors, highlighting another advantage of introducing TMS solubilizing group.

**Chapter 4 Additive-assisted glycosylation reaction**

In most chemical glycosylations, activation of the leaving group (Lg) with an electrophilic promoter ($E^+$) is following by nucleophilic attack of the acceptor (ROH), resulting electro-deficient anomeric carbon of glycosyl donor (Table 1, A). The interaction between leaving group and promoter is the trigger for the efficient cleavage of Lg, leading to the coupling reaction. In our reductive glycosylation, the Pd-catalyzed hydrogenolysis just promoted the debenzylation, giving rise to the 4,6-dihydroxy-1,3,5-triazn-2-yl (DHT) glycosyl intermediate. The subsequent substitution reaction was speculated to be activated by the H-bond interactions between the alcohol acceptors and DHT-glycosides (Table 1, B), causing the tremendous differences in the coupling results with good nucleophiles (primary alcohols) and poor nucleophiles (secondary and tertiary alcohols). Usually, the long reaction time and poor yield were observed using secondary and tertiary alcohols. Therefore, the H-bond donating additives (XOH), such as chloral or hexafluoroisopropanol (HFIP), were employed in the reductive glycosylation to support stronger H-bond interactions (Table 1, C). Compared with the blank case, the improvement including the reaction rate and yield was noticed under the additive-assisted coupling reaction (Table 1, entries 2 and 4). The upfield shift of the anomeric proton was found in the mixture of amine-stabilized DHT-glycosides and additives by the $^1$HNMR analysis, suggesting the reactivity of DHT-glycosyl intermediate was improved with the utilization of H-bond donating additives. [3] In addition, the desilylation side-reaction was noticed with the hydrogenolytic glycosylation when employing the chloral or hexachloroacetone as the additive. Sometimes, a deceased stereoselectivity occurred owing to the additive-induced desilylation effect.

**Table 1** Comparison of the reductive glycosylation with or without additives



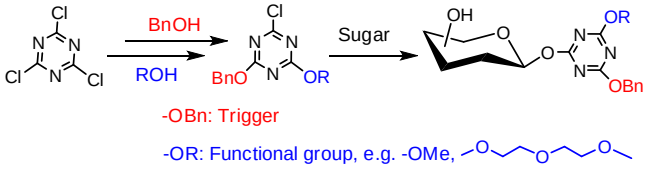

| Entry | Product | Additive (1.0 *equiv*) | Time (h) | Yield (%) | α/β |
|---|---|---|---|---|---|
| 1 |  Menthyl-cellobioside | - | 168 | 38 | 10/1 |
| 2 | | $CCl_3CHO$ | 24 | 60 | α only |
| 3 |  Cholesteryl-glucoside | - | 48 | - | - |
| 4 | | $CCl_3CHO$ | 48 | 40 | α only |

**Chapter 5 Glycosylation with modified triazinyl glycosides**

Dibenzyloxy triazine (DBT) behaved as an excellent leaving group in the hydrogenolytic glycosylation. We speculated that the non-symmetric triazine with only one benzyloxy group also can be used as the efficient leaving group for the reductive glycosylation. Another site on triazine could be modified with some functional groups. Hence, on the basis of this

mon-symmetric concept, we reported some modified triazinyl leaving groups synthesized through the nucleophilic substitution of cyanuric chloride with different alcohols (Scheme 3). Herein, the syntheses of hydrophilic 4-(2-(2-methoxy ethoxy) ethoxy)-6-benzyloxy-1,3,5-triazin-2-yl (MEEBT) glycoside donors were carried out in aqueous solution without using any organic solvent, affording a green activation pathway. Moreover, the glycosylation of MEEBT-maltopentaoside proceeded smoothly because of the improved solubility. By contrast, the DBT-maltopentaoside was failed to be glycosylated due to its limited solubility. Despite the fact that these non-symmetric triazinyl glycoside donors behaved lower reactivity than DBT-glycoside donors, the employment of H-bond donating additives was proved to optimize this limitation. The non-symmetric triazinyl leaving groups offered new avenues for the design of direct glycosylation methods and allowed the activation of sugars proceeding under greener conditions.

**Scheme 3** Synthesis of modified glycoside donors with asymmetric leaving groups




**Chapter 6 Summary**

A novel glycosylation reaction has been established under the Pd-catalyzed hydrogenolysis conditions. [4] The new glycosyl donors, DBT-glycosides, were prepared directly from unprotected sugars in aqueous solution. Excellent stereoselectivity was also achieved in the syntheses of donors with the removal of 1,2-$(DBT)_2$-α-glycosides or sugar oxazoline. The neighboring group of sugar was convinced to play key roles for the resulting stereoselectivity. The acid-labile inner glycosidic bonds in oligosaccharides were not affected under the reductive conditions. Some complex glycosides were synthesized through the improved strategy by using silyl solubilizing groups and H-bond donating additives. The solubility of glycosyl donors can also be regulated based on the non-symmetric leaving groups. It is hoped that these new results will assist glycochemists in designing new glycosylation methodologies and develop the library of glycosyl donors without acid promoters.

**References**

[1] D. P. Galonic, D. Y. Gin, *Nature*, **2007**, 446, 1000-1007.

[2] X. M. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, 48, 1900-1934.

[3] X. Liang, H. Bin, J. Yang, *Org. Lett.* **2013**, 15, 2834-2837.

[4] M. Ishihara, Y. Takagi, G. Li, M. Noguchi, S. Shoda, *Chem. Lett.* **2013**, 42, 1235-1237.