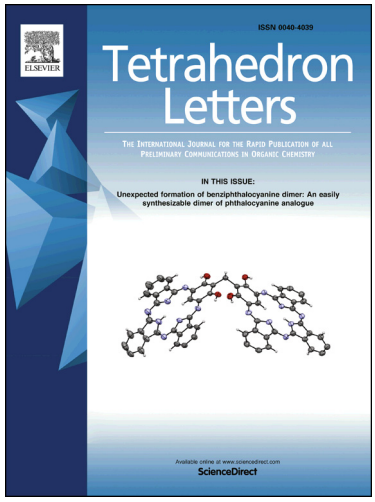

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Graphical Abstract

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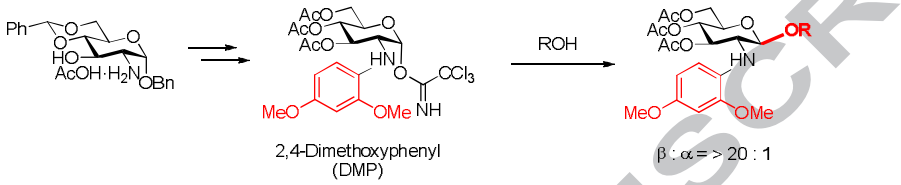

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Syntheses of *N*-aryl-protected glucosamines and their stereoselectivity in chemical glycosylations

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ABSTRACT

N-Aryl-protecting groups were introduced in glucosamines to achieve β-selective glycosylation. Various *N*-aryl aminosugars were synthesized via Buchwald–Hartwig reaction. Glycosylation using glycosyl trichloroacetimidates of *N*-aryl aminosugars smoothly proceeded in the presence of trimethylsilyl trifluoromethanesulfonate. Use of a glycosyl donor comprising an electron-donating 2,4-dimethoxyphenyl (DMP) group led to the glycosylation proceeding with high β selectivity. This stereoselectivity seemed to be derived from the formation of an aziridine intermediate. The DMP-protecting group can be removed immediately by using ammonium hexanitratocerate (IV).

1. Introduction

In the field of synthetic carbohydrate chemistry, stereocontrol at the anomeric center is one of the most important subjects of chemical glycosylation.[1] Stereoselectivity to produce 1,2-*trans* glycosides has been achieved through the participation of neighboring acyl- or carbamate-protecting groups located at the 2-position of the glycosyl donor. On the other hand, 1,2-*cis* glycosides have been obtained by solvent effect of ether or DMF[2], the intramolecular aglycone delivery (IAD) method[3], and other approaches. Recently, various participating groups introduced at the 2-OH of the glycosyl donor have been applied to chemical glycosylation. For example, the dialkylphosphate group,[4] picolinyl group,[5] 2-nitrobenzyl group,[6] and 2-cyanobenzyl group[7] have been developed to assist the synthesis of 1,2-*trans* glycosides. Conversely, the phenylthiophenylbenzyl[8] and thiophen-2-ylmethyl groups[9] have been developed to assist the synthesis of 1,2-*cis* glycosides. In the case of 2-aminosugars, the phthaloyl group and carbamate groups, such as Troc, are frequently used for β-glycosylation with high selectivity. In some cases, however, the use of these groups is not compatible, particularly when approaching a complex carbohydrate because of the difficulty of the removal step. Therefore, the development of new *N*-protecting groups is still an important task in oligosaccharide synthesis.

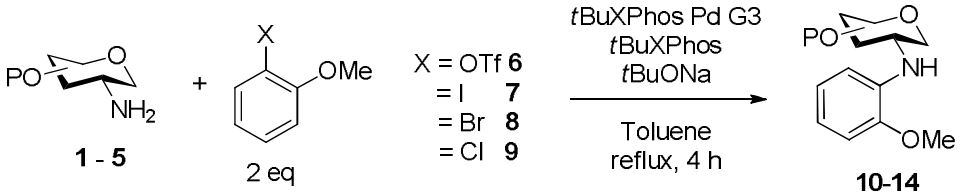
With the exception of the 2,4-dinitrophenyl group, which can be removed under strong basic conditions, *N*-aryl groups have been rarely used as protecting groups. The 2,4-dinitrophenyl group was used for the 2-*N* protection of a glucosaminyl donor.[10] No neighboring group participation was observed, hence, glycosylation in this case leads to the formation of an anomeric mixture (2:1–3.5:1 α/β ratio). We thought that the electron density of the lone pair on nitrogen would be readily controlled by the introduction of appropriate functional groups on the aromatic ring; electron-donating substituents should increase the nucleophilicity of the nitrogen to enable the neighboring group to participate in the glycosylation, whereas electron-withdrawing substituents on the aromatic ring should afford non-participating protecting groups. In the present study, we synthesized various *N*-aryl derivatives[11] utilizing the Buchwald–Hartwig reaction[12] and investigated the effects of substituted *N*-aryl groups on the stereoselectivity of glycosylation.

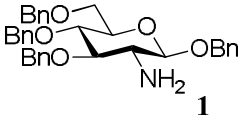
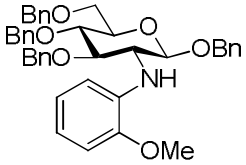
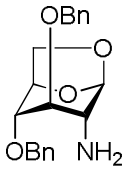
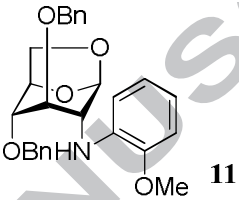
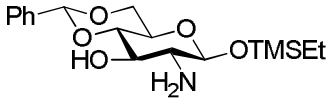
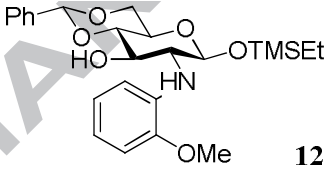
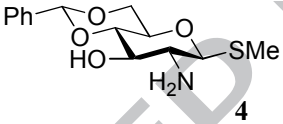
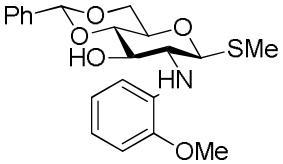
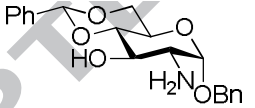
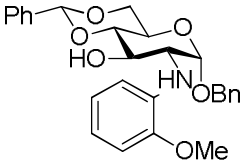
2. Results and discussion

Initially, we investigated the Buchwald–Hartwig reaction of the aminosugars **1**–**5** and 2-methoxyphenyl triflate **6** in the presence of *t*BuXPhos Pd G3 and *t*BuXPhos as a catalyst[12] and *t*BuONa as a base under reflux condition in toluene (Table 1). The reaction of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine **1**, which was reported as a model compound for a copper-catalyzed *N*-arylation,[13] gave only a trace amount of the desired product **10** (Entry 1). Next, we used 1,6-anhydro 3,4-di-*O*-benzyl-D-glucosamine **2**, which has a $^{1}C_{4}$ conformation, and obtained the desired product **11** in 44% yield (Entry 2). We then examined 4,6-benzylidene-D-glucosamine derivatives **3**–**5** that contain a free hydroxy group at the C-3 position, which has no influence on the cross-coupling reaction. Although the reaction with β-trimethylsilylethyl (TMSEt) glycoside **3** provided the desired product **12** in low yield probably due to the steric hindrance of the TMSEt group (Entry 3), the use of β-methylthio glycoside **4** or α-benzyl glycoside **5** improved the yield to 73% and

79%, respectively (Entries 4 and 5). The reaction conditions with benzyl glycoside **5** were then optimized to afford **14** in 90% yield (Entry 6). On the other hand, use of aryl iodide, bromide, and chloride (**7**–**9**) decreased the yields of the desired products (Entries 7–9).

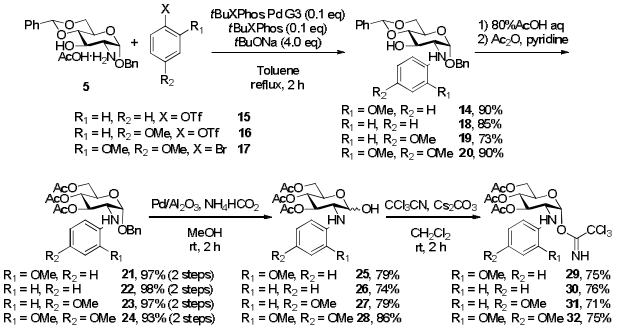
Table 1. Screening of conditions for *N*-aryl aminosugar synthesis



Entry	Aryl-X	Aminosugar	Products	Isolated Yield
1[a]	6	 **1**	 **10**	trace
2[a]	6	 **2**	 **11**	44%
3[a]	6	 **3**	 **12**	22%
4[a]	6	 **4**	 **13**	73%
5[a]	6	 **5**	 **14**	79%
6[b]	6	**5**	**14**	90%
7[b]	7	**5**	**14**	48%
8[b]	8	**5**	**14**	43%
9[b]	9	**5**	**14**	50%

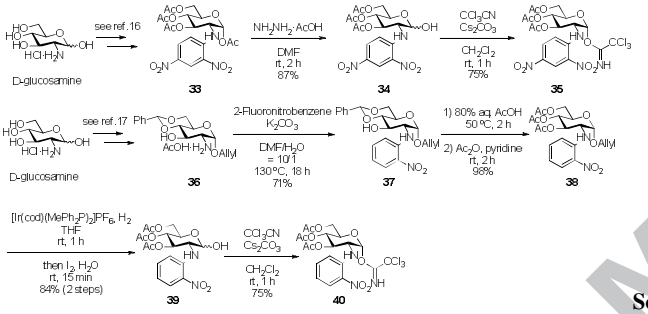
[a] *t*BuXPhos Pd G3 0.3 eq, *t*BuXPhos 0.3 eq, *t*BuONa 3.0 eq was used
[b] *t*BuXPhos Pd G3 0.1 eq, *t*BuXPhos 0.1 eq, *t*BuONa 4.0 eq was used

With optimized conditions (Table 1, Entry 6), we prepared phenyl, 4-methoxyphenyl, and 2,4-dimethoxyphenyl (DMP) derivatives of **5** via the coupling reaction (Scheme 1). The phenyl derivative **18** and the 4-methoxyphenyl derivative **19** were synthesized from the corresponding phenyl triflate **15** and 4-methoxyphenyl triflate **16**, respectively. On the other hand, the DMP derivative **20** was obtained from the commercially available DMP bromide **17**. Removal of benzylidene groups from **14**, **18**, **19**, and **20** with 80% acetic acid (AcOH) in water, followed by acetylation with acetic anhydride and pyridine, gave **21**, **22**, **23**, and **24** in good yields (2 steps), respectively. Subsequently, the removal of benzyl group of **21** with Pd black as a catalyst afforded the desired product only in low yield. Use of Pd/Al_2O_3 as a catalyst and HCO_2NH_4 as a hydrogen source,[14] a combination of reactants known as a catalytic transfer hydrogenation (CTH) condition, led the yield of the reaction to the increase to 79%. Similarly, analogous reaction conditions with **22**, **23**, and **24** produced **26** (74% yield), **27** (79% yield), and **28** (86% yield), respectively. Next, introduction of a trichloroacetimidate group in the anomeric position provided the desired products **29**–**32** in 71%–76% yield.



Scheme 1. Coupling reactions and syntheses of glycosyl trichloroacetimidates.

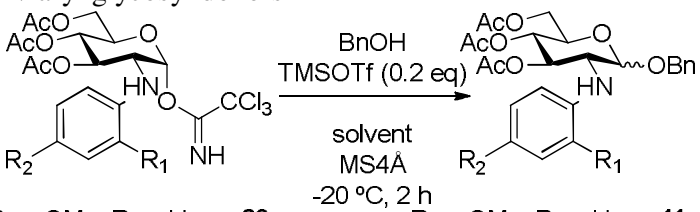
In order to investigate the substituent effects of *N*-aryl groups in the glycosylation, 2,4-dinitrophenyl derivative **35** and 2-nitrophenyl derivative **40**[15] were also synthesized by S_NAr reaction using the corresponding aryl fluorides (Scheme 2). Compound **33**[16] was readily converted to compound **34** by treatment with hydrazine acetate, followed by trichloroacetimidation. On the other hand, *N*-2-nitrophenyl glucosamine **37** was synthesized from the partially protected glucosamine **36**[17] because 2-nitrophenylation required strongly basic conditions. The product was then treated with 80% AcOH in water, and the hydroxyl group was acetylated. The allyl group of **38** was forced to isomerize with an Ir complex[18], and the resulting compound was oxidatively cleaved by I_2 and water to give **39**, which was converted to trichloroacetimidate **40**.



Scheme 2. Syntheses of glycosyl trichloroacetimidates containing nitrophenyl group.

The stereoselectivity of the glycosylation was then investigated using benzyl alcohol as a glycosyl acceptor at −20 °C in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) acting as a Lewis acid (Table 2) in either CH_2Cl_2 or diethyl ether. The glycosidation of *N*-2-methoxyphenyl glucosamine **29** performed in the mentioned conditions in CH_2Cl_2 for 2 h led to the formation of glycoside **41** in 81% yield with a 1:19 α/β selectivity ratio (Entry 1). In diethyl ether, glycoside **41** was obtained in 93% yield with low selectivity (1:1.4 α/β ratio) owing to the α-orienting solvent effect of ether (Entry 2). The glycosidation of *N*-phenyl derivative **30**, *N*-4-methoxyphenyl derivative **31**, and *N*-DMP derivative **32** also proceeded to give the corresponding glycosides **42**, **43**, and **44** with β-selectivity in CH_2Cl_2 (Entries 3, 5, and 7). In addition, the extent of β-selectivity increased with the number of methoxy groups on the aryl ring; notably, glycosidation of the *N*-DMP derivative **32** proceeded with the highest selectivity (1:49 α/β ratio) (Entry 7). By contrast, glycosidation of 2,4-dinitrophenyl derivative **35** and 2-nitrophenyl derivative **40** proceeded with α-selectively (5.7:1 and 14:1 α/β ratio, respectively) in diethyl ether (Entries 10 and 12). These results suggested that the glycosylations proceed via the aziridine intermediate derived from the intermolecular nucleophilic attack of the aromatic amine from the α-face. β-Selectivity of the glycosylation is brought about by the neighboring participation, as suggested by the evidence that β-selectivity increases with the number of electron-donating groups on the aryl ring, which in turn enhance the nucleophilicity of the amine. We also confirmed that *N*-nitrophenyl groups are non-participating protective groups and therefore can be used for α-selective glycosylations.

Table 2. Glycosidation of *N*-aryl glycosyl donors



R_1 = OMe, R_2 = H	**29**		R_1 = OMe, R_2 = H	**41**	
R_1 = H, R_2 = H	**30**		R_1 = H, R_2 = H	**42**	
R_1 = H, R_2 = OMe	**31**		R_1 = H, R_2 = OMe	**43**	
R_1 = OMe, R_2 = OMe	**32**		R_1 = OMe, R_2 = OMe	**44**	
R_1 = NO_2, R_2 = NO_2	**35**		R_1 = NO_2, R_2 = NO_2	**45**	
R_1 = NO_2, R_2 = H	**40**		R_1 = NO_2, R_2 = H	**46**	

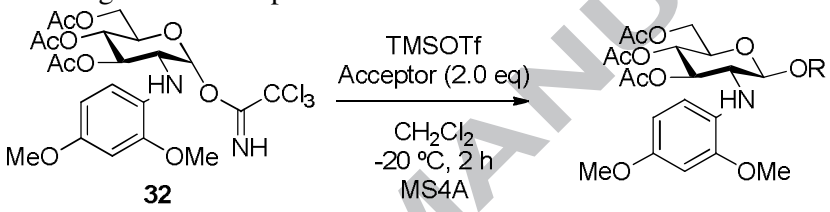
Entry	Donor	Solvent	Product	Selectivity*(α : β)	Isolated Yield
1	**29**	CH_2Cl_2	**41**	1 : 19	80% (β)
2	**29**	Et_2O	**41**	1 : 1.2	93% (α + β)

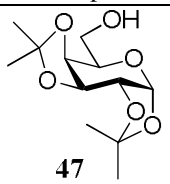
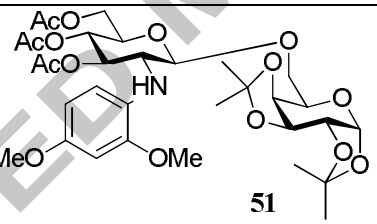
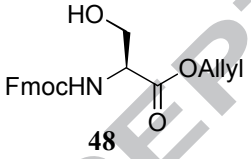
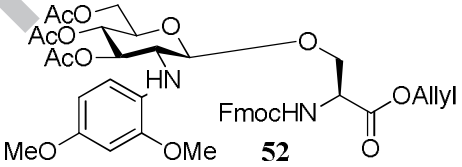
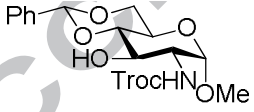
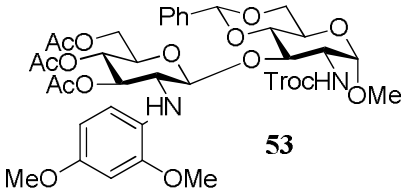
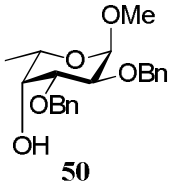
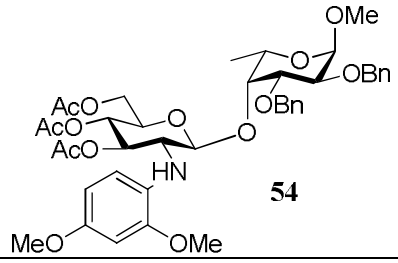
3	**30**	CH_2Cl_2	**42**	1 : 3.6	85% (α + β)
4	**30**	Et_2O	**42**	1 : 4.0	78% (α + β)
5	**31**	CH_2Cl_2	**43**	1 : 15	62% (β)
6	**31**	Et_2O	**43**	1 : 12	86% (β)
7	**32**	CH_2Cl_2	**44**	1 : 49	95% (β)
8	**32**	Et_2O	**44**	1 : 5.6	72% (β)
9	**35**	CH_2Cl_2	**45**	1 : 1.4	95% (α + β)
10	**35**	Et_2O	**45**	5.6 : 1	95% (α + β)
11	**40**	CH_2Cl_2	**46**	1 : 1.0	quant. (α + β)
12	**40**	Et_2O	**46**	14 : 1	quant. (α + β)

* The anomer ratio was determined by HPLC (UV260nm)

The scope and limitations of glycosidation using the *N*-DMP glycosyl donor **32** were then investigated by using derivatives of galactose **47**, serine **48**, glucosamine **49**, and fucose **50** as glycosyl acceptors (Table 3). Glycosylation of **47** and **48**, which have a primary hydroxyl group, afforded the desired products in high yields and high β-selectivities (Entries 1 and 2). Glycosylation of acceptors **49** and **50** that have secondary hydroxyl groups also smoothly proceeded to give the corresponding disaccharides with high β-selectivity in good or moderate yields (Entries 3 and 4).

Table 3. Glycosylation using various acceptors

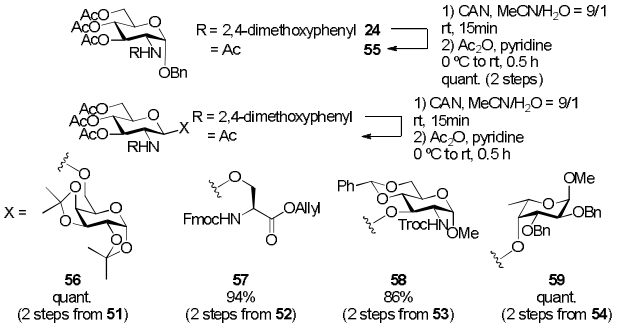


Entry	Acceptor	Products	Selectivity*(α : β)	Isolated Yield
1	 **47**	 **51**	1 : 27	92%
2	 **48**	 **52**	1 : 50 <	93%
3	 **49**	 **53**	1 : 50 <	90%
4	 **50**	 **54**	1 : 27	67%

* The anomer ratio was determined by HPLC (UV260nm)

Finally, the DMP-protecting group was removed from the product of the glycosylation reaction using ammonium hexanitratocerate (IV) (CAN)[19]; the following step consisted in an acetylation of the resulting compound with acetic anhydride and pyridine (Scheme 3). In the cases of **24** and **51**–**54**, removal proceeded smoothly to give the desired products in good yields. Conditions for this removal step

are orthogonal to those necessary for the removal of important hydroxyl and amino protecting groups, such as Ac, benzyl, allyl, isopropylidene, benzylidene, Fmoc, and Troc. This feature makes the described approach highly suitable to the synthesis of complex carbohydrates. The DMP group is stable in acidic, basic, and reducing conditions, as well as in the presence of various nucleophiles, and it can be removed with an oxidizing agent, such as CAN.



Scheme 3. Removal of the DMP-protecting group using CAN and *N*-acetylation.

4. Conclusion

In summary, we succeeded in synthesizing glucosamine derivatives that comprise various *N*-aryl structures through the Buchwald–Hartwig reaction. We used these compounds as glycosyl donors in chemical glycosylations and found that the *N*-DMP glucosaminyl donor showed high β-selectivity. It has been reported that glycosylation with an *N*,*N*-dibenzyl glucosaminyl donor affords β-glycosides via the aziridinium intermediate.[20] Because increasing the electron-donating property of the aromatic ring of the *N*-aryl groups enhances β-selectivity, glycosylation probably proceeds via the aziridine intermediate. The DMP-protecting group can be readily removed by using CAN, but it is otherwise stable under various conditions. Therefore, use of this protecting group is expected to be applicable to various carbohydrate syntheses.

Acknowledgments

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References and notes

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A. Supplementary data

B. Supplementary data associated with this article can be found, in the online version, at xxxxxxxxxxxxxxx.

- *N*-Aryl groups can be introduced to glucosamine through Pd-catalyzed C-N coupling.
- *N*-2,4-Dimethoxyphenyl (DMP) glucosaminyl donor was synthesized in good yield.
- β-Selective glycosylation was achieved by using *N*-DMP protected donor.
- Glycosylation with donors having nitroaryl group preferentially afforded α-glycoside.
- DMP group can be readily deprotected by using CAN.