CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201203418

Highly Stereoselective Glycosyl-Chloride-Mediated Synthesis of 2-Deoxyglucosides

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Dedicated to Professor Chin-Hsing Chou on the occasion of his 65th birthday

The presence of 2-deoxy- or 2,6-dideoxyglycosides, either as a single structural element or as the components of oligosaccharides in either α or β linkages, is essential to the activity of many natural products, especially for antibiotics and anticancer agents.[1] However, the stereoselective 2-deoxyglycosylation reaction remains a long-standing challenge in carbohydrate chemistry. Owing to the lack of C2 functionality, which governs the stereoselectivity of the reaction and stabilizes the intermediary oxonium ion, glycosylation reactions that involve these glycosides are usually held back by poor stereoselectivity and the high susceptibility of 2-deoxyglycosides to acid hydrolysis.[2,3] Although numerous strategies and conditions, including the use of glycal precursors,[4] have been developed[3] and the anomeric effect leads to the preferential formation of α-anomers, moderate yields and poor stereoselectivities are usually encountered in the synthesis of 2-deoxyglucosides.

To control the stereoselectivity of this reaction, indirect methods that introduce iodine,[5] bromine,[6] or fluorine atoms,[7] as well as thio[8] or seleno[9] groups at the C2 position, are typically adopted. The 1,2-migration–glycosylation of thioglycosides[10] and the reduction of the C2 oxygen[11] or nitrogen[12] moieties also provide alternatives. These indirect approaches are reliable but need additional synthetic steps to remove these stereo-governing groups. Direct methods, without the need for modifying the C2 functionality, are more concise but usually lead to anomeric mixtures.[3]

The *O*-glycosylation of serine and threonine is an omnipresent post-translational modification of proteins and peptides. Studies have shown that even the decoration of a peptide with a single *N*-acetylglucosamine or *N*-acetylgalactosamine group can alter its secondary structure, in which the 2-acetamido moiety is believed to play a decisive role.[13] To further confirm this structure–activity relationship, we wanted to synthesize *O*-glycopeptides **1** and **2**, which were decorated with 2-deoxy-glucoside. Therefore, easy access to α- or β-2-deoxyglucosyl-L-serine (**3**) and -threonine (**4**) is critical (Figure 1).

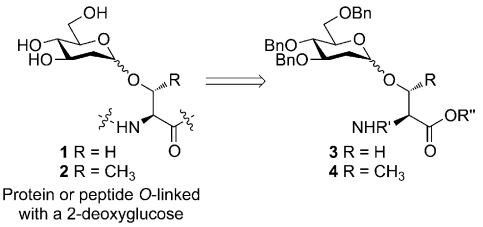

Figure 1. Retrosynthesis of glycoproteins or peptides **1** and **2**.

Thioglycoside is one of the most commonly used glycosyl donors,[14] owing to its high stability as well as its high reactivity in the presence of numerous promoters. The relative reactivity values (RRVs) of thioglycosides with different protecting patterns are quantifiable for one-pot multiple glycosylation reactions.[15] Recently, 2-deoxyglycosyl donors that were equipped with a conformation-constraining group or a directing functionality at the C6 position were reported to provide good stereoselectivity.[16] For ease of preparation, we chose a direct synthesis of 2-deoxyglycosides by using easily prepared per-*O*-benzylated 2-deoxythioglucoside **5**.[17] However, the stereoselective glycosylation of highly reactive compound **5** without the assistance of any conformation-constraining and directing group is considered to be more challenging.[3]

The iterative one-pot synthesis of oligosaccharides, established by Huang, Ye, and co-workers in 2004[18] by using *para*-toluenesulfenyl triflate (*p*-TolSOTf) as the promoter,[19] which is generated in situ by mixing *para*-toluenesulfenyl chloride (*p*-TolSCl) and silver triflate (AgOTf), has allowed the activation of the thioglycosides in the absence of acceptors. Multiple glycosyl bonds can be constructed in the same reaction vessel by using the thioglycosides as both the donors and the acceptors. Numerous oligosaccharides have been prepared by using this preactivation procedure[20] and the α-glycosyl triflate is believed to be a plausible intermedi-

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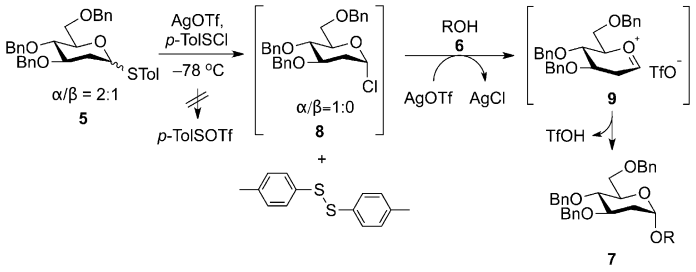
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203418.

ate that stabilizes the transient oxocarbenium cation before the formation of the glycosyl bond.

First, we tried to control the stereoselectivity of the 2-deoxyglycosyl bond formation by utilizing the configuration of the α-glycosyl-triflate intermediate under these conditions. Thus, we treated compound **5** ($\alpha/\beta = 2:1$) with AgOTf (1.1 equiv) and *p*-TolSCl (1.0 equiv) in CH_2Cl_2 at −78 °C. The acceptor was introduced 15 min after the addition of *p*-TolSCl, when compound **5** had been fully consumed (by TLC). After serine and threonine derivatives **6a** and **6b** were added as the acceptor and the mixture was stirred for a further 2 to 3 h, we isolated our desired α-2-deoxyglucosyl-L-serine (**7a**) and -L-threonine derivatives (**7b**) in excellent yields and α selectivity (**7a**: 84 %, α only; **7b**: 92 %, $\alpha/\beta = 15:1$; Table 1, entries 1 and 2). Encouraged by these results, we further extended the scope of this 2-deoxyglycosylation reaction to monosaccharide acceptors. As shown in Table 1, entries 3–7, acceptors that contained secondary hydroxy group, that is, compounds **6c**, **6d**, and **6g**, gave their corresponding products (**7c**, **7d**, and **7g**) in good yields and excellent α selectivity, although those with primary hydroxy groups (**6e** and **6f**) showed slightly lower selectivity. Furthermore, a good yield and high α selectivity could also be obtained when 2-naphthol (**6h**) was used as the acceptor; the use of other non-sugar alcohols, such as MeOH (**6i**), 2-adamantanol (**6j**), 1-adamantanol (**6k**), and benzyl alcohol (**6l**), as the acceptors also resulted in excellent yields and α selectivity (Table 1, entries 9–12).

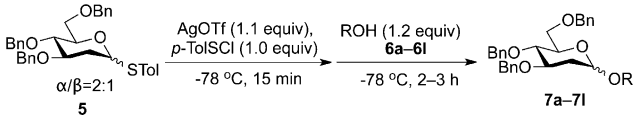
Being curious of these good results, we started to investigate the mechanism of this reaction (Scheme 1) and we tried to characterize the intermediate in this reaction before

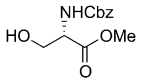
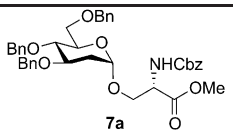
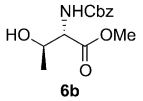
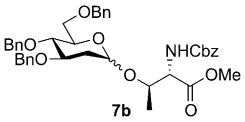
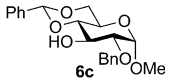
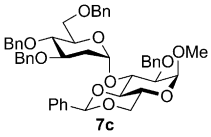
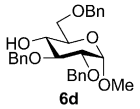
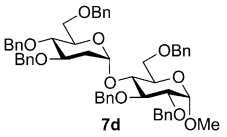
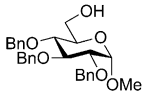
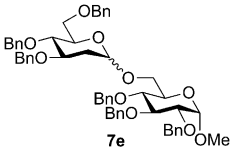
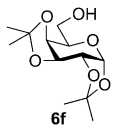
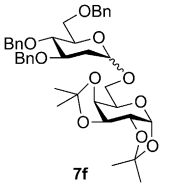
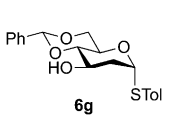
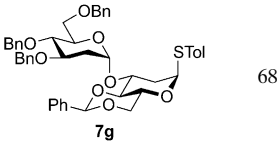
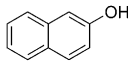
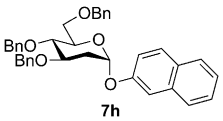
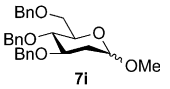
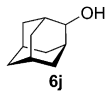
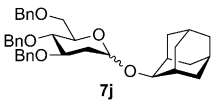
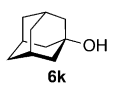
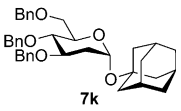
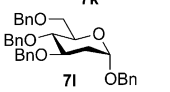


Scheme 1. Proposed reaction mechanism.

the addition of the acceptor by using NMR spectroscopy at −78 °C. We expected to observe the signals for a glycosyl-triflate intermediate because the in situ generated *p*-TolSOTf was commonly believed to be the promoter of this reaction.[18–20] However, instead of glycosyl triflate **9**, subzero NMR spectroscopy revealed a mixture of *para*-tolyl disulfide and α-glycosyl chloride **8**,[21] which could even be carefully isolated by using column chromatography on silica gel at room temperature; its physical data were in agreement with literature values (see the Supporting Information).[21] As well as 2-deoxyglucoside **5**, we also found that *para*-tolyl per-*O*-benzylated thioglucoside, -galactoside, and -mannoside all afforded their corresponding glycosyl chlorides (data

Table 1. Preactivated direct glycosylations of 2-deoxythioglucopyranoside **5**.



Entry	Acceptor	Product	Yield [%][a]	α/β[b]
1	 **6a**	 **7a**	84	α only
2	 **6b**	 **7b**	92	15:1
3	 **6c**	 **7c**	66	α only
4	 **6d**	 **7d**	85	α only
5	 **6e**	 **7e**	79	5:1
6	 **6f**	 **7f**	70	15:1
7	 **6g**	 **7g**	68	α only
8[22]	 **6h**	 **7h**	82	α only
9	MeOH **6i**	 **7i**	82	10:1
10	 **6j**	 **7j**	92	15:1
11	 **6k**	 **7k**	66	α only
12	BnOH **6l**	 **7l**	88	α only

[a] Yield of isolated product. [b] Determined from the yields of both isomers.

not shown). Without adding the acceptor, glycosyl chloride **8** and AgOTf (1.1 equiv) could not be consumed and the precipitation of AgCl could not be observed (and, hence, isolated), even after stirring for an additional 3–4 h and warming to 0 °C. This result suggested that *p*-TolSOTf was not generated at the preactivation stage. After the addition of the acceptor, the precipitation of AgCl was observed and isolated and the glycosylation reaction finished within 2–3 h. We found that glycosyl chloride **8** could be formed in the presence of a catalytic amount of AgOTf (0.05 equiv), but that one equivalent of *p*-TolSCl was necessary. However, after the addition of the acceptor, the glycosylation reaction was sluggish unless one equivalent of AgOTf was resupplied. We also observed that the precipitation of AgCl occurred immediately after the addition of AgOTf and that the formation of the product and the precipitation of AgCl were proportional to the amount of AgOTf that was added. To confirm that glucosyl chloride **8** was the reaction intermediate, we treated isolated compound **8** with compound **6d** and one equivalent of AgOTf at −78 °C to perform a standard Koenigs–Knorr reaction; this reaction proceeded smoothly and afforded disaccharide **7d** (67 %) with an unchanged α/β ratio.

As shown in Scheme 1, although we confirmed that α-glycosyl chloride **8** was the intermediate before the addition of the acceptor, owing to the high α selectivity, we hypothesized that the glycosylation reaction after the introduction of the acceptor could still be mediated by the corresponding glycosyl triflate.[23]

Although we did not observe the β-chloride by subzero NMR spectroscopy, we still could not rule out the possibility that the β-chloride was the species that reacted with the acceptors to form the α products, as studied by Lemieux et al. in halide-ion glycosylation[24] and, lately, further investigated by Demchenko and co-workers.[25] Notably, the addition of an equivalent amount of tetrabutylammonium iodide or chloride as the additive neither accelerated the reaction nor altered its stereoselectivity.

Indeed, the triflate ion seems unlikely to directly replace the chloride from a nucleophilic-strength perspective. As mentioned above, we found that compound **8** remained unreactive, even with an equimolar amount of AgOTf, until the acceptor was introduced. After the introduction of the acceptor, the AgCl precipitated, which provided the driving force for the activation of glucosyl chloride.[26] Then, the counterions were exchanged and, hence, the transient oxocarbenium cation (**9**) could be generated. In a test reaction, we introduced one equivalent of AgOTf but only 0.4 equivalents of the acceptor (**6d**). The disaccharide (**7d**) was formed but, surprisingly, glucosyl chloride **8** was still observed as one of the major compounds in the ^{1}H NMR spectrum, even after 5 h. Therefore, we inferred that the Koenigs–Knorr reaction between AgOTf and the glycosyl chloride needs the participation of an equimolar amount of the acceptor, otherwise this AgOTf-mediated Koenigs–Knorr glycosylation cannot proceed. Such a reaction seems unlikely to be promoted by the proton from the acceptor because the remaining TfOH in the reaction mixture neither reacted with the glucosyl chloride (**8**) nor activated the remaining AgOTf to perform further ion exchange to produce AgCl; thus, the remaining glucosyl chloride (**8**) remained unreacted.

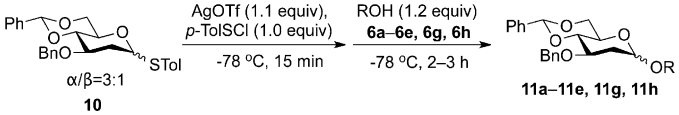
To analyze the role of the silver ion and the triflate ion, we individually replaced AgOTf with trimethylsilyl trifluoromethanesulfonate (TMSOTf) or silver tetrafluoroborate ($AgBF_4$). We found that the transformation of compound **5** into compound **8** by using *p*-TolSCl was smoothly catalyzed by 0.1 equivalents of both TMSOTf and $AgBF_4$ at −78 °C in 15 min. However, after the introduction of an acceptor (**6d**), the reaction that was further promoted by an equimolar amount of TMSOTf was sluggish. After stirring overnight, no precipitation was observed, chloride **8** was not consumed, and only 21 % of compound **7d** and the hydrolyzed donor could be isolated, although the stereoselectivity remained fully α-selective. In contrast, for the reaction that was further promoted by one equivalent of $AgBF_4$, again, compound **8** remained intact before the introduction of acceptor **6d**, AgCl precipitation was found after the addition of compound **6d**, and the reaction finished in 2–3 h. Disaccharide **7d** (82 %) was isolated but the α/β ratio was changed into 1.2:1.

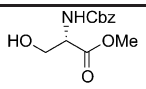
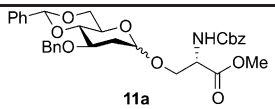
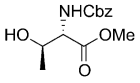
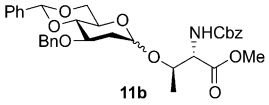
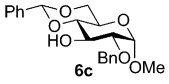
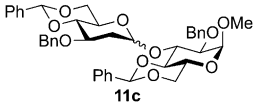
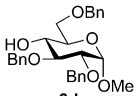
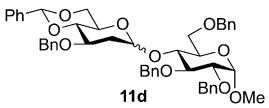
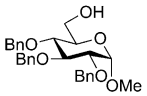
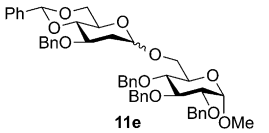
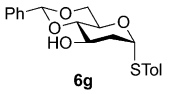
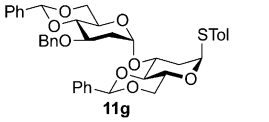
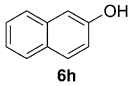
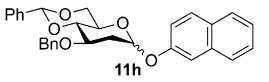
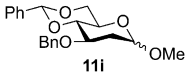
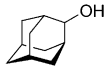
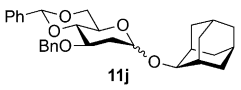
Based on these studies, we can preliminarily conclude that the precipitation of AgCl provides an indispensable driving force for this reaction to proceed through a chloride/triflate counterion-exchange pathway. In this case, the dependence of α/β selectivity on the counterions, that is, triflate and tetrafluroborate, supports the formation of transient ion pairs. Moreover, this ion exchange does not occur simply between glycosyl chloride and AgOTf. An equimolar amount of acceptor is also required to promote this reaction.

Even with these studies in hand, we could still only conservatively propose that the glycosyl bond was formed between the acceptor and oxocarbenium cation **9** in an S_N1 manner and that the very high α selectivity could simply be attributed to the anomeric effect, although we found that the counterion did affect the stereoselectivity of the reaction. Alternatively, as very recently reported by Crich et al.,[23] the α-glycosyl bond could be formed in equilibria between the β-glycosyl triflate, the β-contact ion pair (β-CIP), and the solvent-separated ion pair (SSIP). However, these hypotheses need to be further confirmed. Recently, a highly α-selective sialylation reaction, by using a conformation-constrained sialic-acid donor under this preactivation system, was reported, but the plausible intermediate was not identified or discussed.[27] Although the selectivity could be attributed to the conformation-constraining group, we infer that this reaction might also proceed through the corresponding sialyl-chloride pathway.

It has been reported that the 4,6-*O*-benzylidene-directed glycosylation reaction favors β selectivity for 2-deoxyglucosylation.[16a–c] Therefore, we tested the selectivity by using 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxythioglucoside (**10**; $\alpha/\beta =$ 3:1) as the donor in this system (Table 2). Again, the corre-

Table 2. Preactivated direct glycosylations of 4,6-*O*-benzylidene-2-deoxythioglucopyranoside **10**.



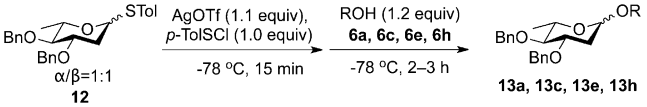
Entry	Acceptor	Product	Yield [%][a]	α/β[b]
1	 **6a**	 **11a**	83	2:1
2	 **6b**	 **11b**	86	5:1
3	 **6c**	 **11c**	81	1:3
4	 **6d**	 **11d**	82	2:1
5	 **6e**	 **11e**	66	1:6
6	 **6g**	 **11g**	74	α only
7	 **6h**	 **11h**	80	20:1
8	MeOH **6i**	 **11i**	76	1:8.5
9	 **6j**	 **11j**	65	1:3

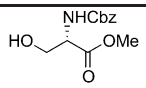
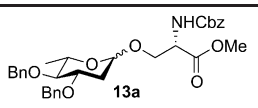
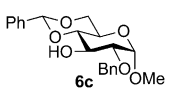
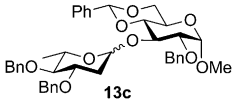
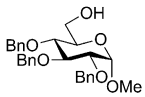
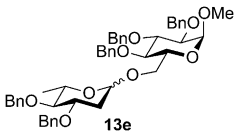
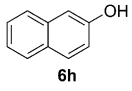
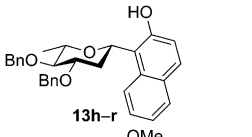
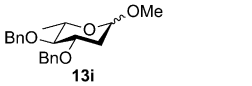
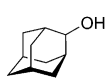
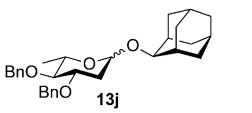
[a] Yield of isolated product. [b] Determined from the yields of both isomers.

sponding α-glycosyl chloride can be observed and isolated (see the Supporting Information). Indeed, a different trend in stereoselectivity was observed. For secondary compound **6c** and primary monosaccharide acceptor **6e** (Table 2, entries 3 and 5), β-major disaccharides **11c** (81%, $\alpha/\beta=1:3$) and **11e** (66%, $\alpha/\beta=1:6$) were isolated in good yields. Regarding the glycosylation of L-serine and threonine derivative **6a** and **6b** and secondary compound **6d** (Table 2, entry 1, 2, and 4), although compounds **11a** (83%, $\alpha/\beta=2:1$), **11b** (86%, $\alpha/\beta=5:1$), and **11d** (82%, $\alpha/\beta=2:1$) were still the major products, an increased ratio the of β products was observed compared to the previous "α-only" results (Table 1). However, for 4,6-*O*-benzylidene-2-deoxyglucose acceptor **6g** and 2-naphthol (**6h**), still almost-completely α-selective products **11g** (74%, α only) and **11h** (80%, $\alpha/\beta=20:1$) could be furnished. However, in Table 2, entries 8 and 9, the glycosylation reactions with MeOH (**6i**) and 2-adamantanol (**6j**) gave β-major products **11i** and **11j** ($\alpha/\beta=1:8.5$ and 1:3, respectively). Therefore, we deduce that acceptors with weaker nucleophilicity cannot efficiently form glycosyl bonds in the equilibria between α-covalent glycosyl triflate and the SSIP; therefore, it still reacts with the SSIP or within the equilibria between the SSIP, the β-contact ion pair (β-CIP), and the covalent β-triflate to give the α-anomers as the major products.[23] Again, this hypothesis needs to be confirmed.

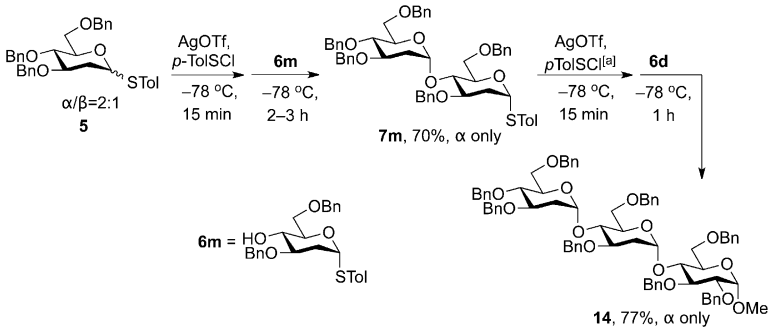
The glycosylation reactions of 2,6-dideoxysugars are known to be more difficult, owing to their lack of an additional stabilizing oxygen moiety at the C6 position, which not only makes their reactivity higher but also renders the control of stereoselectivity more difficult.[28] A direct synthesis of β-linked 2,6-deoxyoligosaccharides has been achieved several years ago by Takahashi and co-workers.[29] We applied our preactivation conditions to 2,6-dideoxythioglycoside **12** ($\alpha/\beta=1:1$; Table 3). Despite its higher reactivity, good-to-excellent yields and good stereoselectivities were achieved. Notably, the glycosylation of serine derivative **6a** (Table 3, entry 1) gave glycosyl serine **13a** in 81% yield with an α/β ratio of 12:1; the reactions of secondary monosaccharide acceptor **6c** (Table 3, entry 2) and primary hydroxy compound **6e** (Table 3, entry 3) afforded disaccharides **13c**

Table 3. Preactivated direct glycosylations of 2,6-dideoxythioglucopyranoside **12**.



Entry	Acceptor	Product	Yield [%][a]	α/β[b]
1	 **6a**	 **13a**	81	12:1
2	 **6c**	 **13c**	88	5:1
3	 **6e**	 **13e**	82	5:1
4	 **6h**	 **13h–r**	88	β only
5	MeOH **6i**	 **13i**	86	4:1
6	 **6j**	 **13j**	68	10:1

[a] Yield of isolated product. [b] Determined from the yields of both isomers.



Scheme 2. Iterative synthesis of trisaccharide **14**: a) *p*-TolSCl (0.9 equiv) was used and the yield of compound **14** was calculated based on *p*-TolSCl.

and **13e** in 88 and 82% yield, respectively, both with good α/β ratios (5:1). The reaction with phenol-type acceptor **6h** furnished the rearranged "β-only" product (**13h-r**) in excellent yield (88%), thus suggesting complete α-selectivity during the glycosylation process. Glycosylation with MeOH (**6i**) resulted in excellent yield (94%) with moderate stereoselectivity ($\alpha/\beta = 4{:}1$; Table 3, entry 5). Finally, the sterically hindered compound **6j** gave the product (Table 3, entry 6) in a lower yield (68%) but higher selectivity ($\alpha/\beta = 10{:}1$).

To test the applicability of this method to the synthesis of oligosaccharides and the stereoselectivity for a donor with longer sugar units, trisaccharide **14** was synthesized in two steps (Scheme 2). Preactivation glycosylation of compound **5** with compound **6m** afforded disaccharide **7m** with complete α selectivity in 70%. Notably, this α selectivity remained when disaccharide donor **7m** and acceptor **6d** were coupled under this promoter system and gave trisaccharide **14** in 77% yield.

In summary, we have developed an efficient, simple, and highly stereoselective glycosylation of 2-deoxy- and 2,6-dideoxy-thioglycosides without the need for a 2,3-*O*-conformation-constraining group by using a *p*-TolSCl/AgOTf promoter system in a preactivation manner. The reaction remained highly α-selective when this system was applied to a disaccharide donor. In fact, the glycosyl chloride was the intermediate before the addition of the acceptor, which suggested that *p*-TolSOTf was not formed, as is commonly believed, in this very useful preactivation system for iterative thioglycoside couplings. In fact, although *p*-TolSCl and AgOTf were mixed together, the thioglycosides were first turned into their corresponding glycosyl chlorides by *p*-TolSCl. Such a transformation could be catalyzed by a Lewis acid, such as AgOTf, TMSOTf, or $AgBF_4$. After the addition of the acceptor, the glycosylation reaction between the glycosyl chloride and the acceptor was further promoted by an equimolar amount of a Koenigs–Knorr donor, such as AgOTf or $AgBF_4$ (but not TMSOTf), through an ion-exchange pathway that was driven by the formation of AgCl. The stereoselectivity could be influenced by the counterions, which indirectly suggested the formation of transient oxocarbenium cation **9**. Furthermore, we also found, to the best of our knowledge, for first time, that the AgOTf-mediated Koenigs–Knorr glycosylation reaction requires the participation of an equimolar amount of the acceptor. However, whether other Koenigs–Knorr promoters, such as Ag_2O, Ag_2CO_3, $Hg(CN)_2$, and $HgBr_2$, act in the same way in this reaction requires further clarification. These results also imply that thioglycosides are often the precursors to glycosyl halides as the "real" donors when halide-containing promoter systems are used. We have preliminarily studied the preactivation of thioglycosides by using NBS-TfOH and NCS-TfOH combinations as the promoters and we observed that the corresponding glycosyl bromide and -chloride were formed as the intermediates, respectively, before the addition of the acceptor. In our laboratory, further research of this mechanism is underway, as well as the syntheses of natural products and peptides that contain 2-deoxysugars.

Experimental Section

General procedure: A suspension of the donor (100 mg), molecular sieves (4 Å, 300 mg), and AgOTf (1.1 equiv) in CH_2Cl_2 (4 mL) was stirred at −78 °C under a N_2 atmosphere for 1 h. *para*-Toluenesulfenyl chloride (1.0 equiv) was added into the reaction mixture at −78 °C and the mixture was stirred for 15 min at the same temperature. Next, the acceptor (1.2 equiv, dissolved in 0.5 mL CH_2Cl_2) was added into the reaction mixture and the mixture was stirred for a further 2–3 h at the same temperature. Upon the completion of the reaction, it was quenched with Et_3N and filtered through a pad of Celite. The filtrate was evaporated in vacuo to furnish the crude product, which was purified by flash column chromatography on silica gel to give the final product.

Acknowledgements

This work was supported by the National Science Council of Taiwan (NSC 99–2113M-001–010-MY2 and NSC 101–2113M-001–011-MY2) and Academia Sinica.

Keywords: glycosides · glycosyl chloride · glycosylation · Koenigs–Knorr reaction

[1] a) J. M. Langenhan, N. R. Peters, I. A. Guzei, M. Hoffman, J. S. Thorson, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 12305–12310; b) P. T. Daniel, U. Koert, J. Schuppan, *Angew. Chem.* **2006**, *118*, 886–908; *Angew. Chem. Int. Ed.* **2006**, *45*, 872–893; c) A. K. V. Iyer, M. Zhou, N. Azad, H. Elbaz, L. Wang, D. K. Rogalsky, Y. Rojanasakul, G. A. O'Doherty, J. M. Langenhan, *ACS Med. Chem. Lett.* **2010**, *1*, 326–330.

[2] W. Overend, C. Rees, J. Sequeira, *J. Chem. Soc.* **1962**, 3429–3440.

[3] a) C. H. Marzabadi, R. W. Franck, *Tetrahedron* **2000**, *56*, 8385–8417; b) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911–1940, and references therein.

[4] a) V. Bolitt, C. Mioskowski, S.-G. Lee, J. R. Falck, *J. Org. Chem.* **1990**, *55*, 5812–5813; b) B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am.*

Chem. Soc. **2004**, *126*, 4510–4511; c) H.-C. Lin, J.-F. Pan, Y.-B. Chen, Z.-P. Lin, C.-H. Lin, *Tetrahedron* **2011**, *67*, 6362–6368; d) E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem.* **2012**, *124*, 9286–9289; *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155.

[5] a) J. Thiem, H. Karl, J. Schwentner, *Synthesis* **1978**, 696–697; b) J. Thiem, in *Trends in Synthetic Carbohydrate Chemistry*, (Eds: D. Horton, L. D. Hawkins, G. J. McGarvey), ACS Symposium Series 386, American Chemical Society, Washington, DC, **1989**, Chapter 8, pp. 131–149; c) W. R. Roush, K. Briner, D. P. Sebesta, *Synlett* **1993**, 264–266; d) W. R. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **1999**, *121*, 3541–3542; e) W. R. Roush, B. W. Gung, C. E. Bennett, *Org. Lett.* **1999**, *1*, 891–893.

[6] a) K. Tatsuta, K. Fujimoto, M. Kinoshita, S. Umezawa, *Carbohydr. Res.* **1977**, *54*, 85–104; b) J. Thiem, M. Gerken, *J. Org. Chem.* **1985**, *50*, 954–958; c) J. Thiem, B. Schottmer, *Angew. Chem.* **1987**, *199*, 591–592; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 555–557.

[7] a) C. Bucher, R. Gilmour, *Angew. Chem.* **2010**, *122*, 8906–8910; *Angew. Chem. Int. Ed.* **2010**, *49*, 8724–8728; b) E. Durantie, C. Bucher, R. Gilmour, *Chem. Eur. J.* **2012**, *18*, 8208–8215.

[8] a) Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1987**, *28*, 2723–2726; b) G. Grewal, N. Kaila, R. W. Franck, *J. Org. Chem.* **1992**, *57*, 2084–2092; c) R. W. Franck, N. Kaila, *Carbohydr. Res.* **1993**, *239*, 71–83; d) S. Ramesh, R. W. Franck, *Chem. Commun.* **1989**, 960–961.

[9] a) A. G. M. Barrett, T. Miller, *Tetrahedron Lett.* **1988**, *29*, 1873–1874; b) M. Perez, J.-M. Beau, *Tetrahedron Lett.* **1989**, *30*, 75–78; c) D. P. Sebesta, W. R. Roush, *J. Org. Chem.* **1992**, *57*, 4799–4802; d) K. C. Nicolaou, J. Pastor, S. Barluenga, N. Winssinger, *Chem. Commun.* **1998**, 1947–1948.

[10] a) F.-I. Auzanneau, D. R. Bundle, *Carbohydr. Res.* **1991**, *212*, 13–24; b) H. M. Zuurmond, P. A. M. van der Klein, G. A. van der Marel, J. H. van Boom, *Tetrahedron* **1993**, *49*, 6501–6514; c) Z. Yang, B. Yu, *Carbohydr. Res.* **2001**, *333*, 105–114; d) B. Yu, Z. Yang, *Org. Lett.* **2001**, *3*, 377–379; e) F. Sajtos, L. Lazar, A. Borbas, I. Bajza, A. Liptak, *Tetrahedron Lett.* **2005**, *46*, 5191–5194; f) L. Lázár, I. Bajza, Z. Jakab, A. Lipták, *Synlett* **2005**, 2242–2244; g) D. Hou, T. L. Lowary, *Org. Lett.* **2007**, *9*, 4487–4490; h) D. Hou, T. L. Lowary, *J. Org. Chem.* **2009**, *74*, 2278–2289.

[11] a) M. K. Gurjar, P. K. Ghosh, *Indian J. Chem.* **1988**, *27B*, 1063–1064; b) M. Trumtel, A. Veyrieres, P. Sinay, *Tetrahedron Lett.* **1989**, *30*, 2529–2532; c) J. C. Castro-Palomino, R. R. Schmidt, *Synlett* **1998**, 501–503.

[12] G. Capozzi, A. Dios, R. W. Franck, A. Geer, C. Marzabadi, S. Menichetti, C. Nativi, M. Tamarez, *Angew. Chem.* **1996**, *108*, 805–807; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 777–779.

[13] a) S. E. O'Connor, B. Imperiali, *Chem. Biol.* **1998**, *5*, 427–437; b) D. H. Live, R. A. Kumar, X. Beebe, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 12759–12761; c) E. E. Simanek, D. H. Huang, L. Pasternack, T. D. Machajewski, O. Seitz, D. S. Millar, H. J. Dyson, C.-H. Wong, *J. Am. Chem. Soc.* **1998**, *120*, 11567–11575.

[14] a) P. J. Garegg, *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205; b) J. D. C. Codée, R. Litjens, L. J. van den Bos, H. S. Overkleeft, G. A. van der Marel, *Chem. Soc. Rev.* **2005**, *34*, 769–782.

[15] a) Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753; b) X.-S. Ye, C.-H. Wong, *J. Org. Chem.* **2000**, *65*, 2410–2431.

[16] a) R. Pongdee, B. Wu, G. A. Sulikowski, *Org. Lett.* **2001**, *3*, 3523–3525; b) D. Crich, O. Vinogradova, *J. Org. Chem.* **2006**, *71*, 8473–8480; c) K. S. Kim, J. Park, Y. J. Lee, Y. S. Seo, *Angew. Chem.* **2003**, *115*, 475–478; *Angew. Chem. Int. Ed.* **2003**, *42*, 459–462; d) Y.-S. Lu, Q. Li, L.-H. Zhang, X.-S. Ye, *Org. Lett.* **2008**, *10*, 3445–3448; e) J. Park, T. J. Boltje, G.-J. Boons, *Org. Lett.* **2008**, *10*, 4367–4370; f) Y.-S. Lu, Q. Li, Y.-H. Wang, X.-S. Ye, *Synlett* **2010**, 1519–1524.

[17] J. S. Yadav, B. V. Subba Reddy, E. Vijaya Bhasker, S. Raghavendra, A. V. Narsaiah, *Tetrahedron Lett.* **2007**, *48*, 677–680.

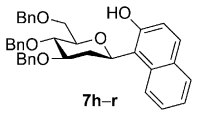
[18] X. Huang, L. Huang, H. Wang, X.-S. Ye, *Angew. Chem.* **2004**, *116*, 5333–5336; *Angew. Chem. Int. Ed.* **2004**, *43*, 5221–5224.

[19] a) F. Dasgupta, P. J. Garegg, *Carbohydr. Res.* **1988**, *177*, c13-c17; b) V. Martichonok, G. M. Whitesides, *J. Org. Chem.* **1996**, *61*, 1702–1706; c) D. Crich, S. Sun, *Tetrahedron* **1998**, *54*, 8321–8348; d) D. Crich, W. Cai, *J. Org. Chem.* **1999**, *64*, 4926–4930.

[20] a) L. Huang, X. Huang, *Chem. Eur. J.* **2007**, *13*, 529–540; b) A. Miermont, Y. Zeng, Y. Jing, X.-S. Ye, X. Huang, *J. Org. Chem.* **2007**, *72*, 8958–8961; c) Z. Wang, L. Zhou, K. El-Boubbou, X.-S. Ye, X. Huang, *J. Org. Chem.* **2007**, *72*, 6409–6420; d) B. Sun, B. Srinivasan, X. Huang, *Chem. Eur. J.* **2008**, *14*, 7072–7081; e) Z. Wang, Y. Xu, B. Yang, G. Tiruchinapally, B. Sun, R. Liu, S. Dulaney, J. Liu, X. Huang, *Chem. Eur. J.* **2010**, *16*, 8365–8375.

[21] J. M. Nogueira, S. H. Nguyen, C. S. Bennett, *Org. Lett.* **2011**, *13*, 2814–2817.

[22] A rearranged isomer, **7h-r**, was isolated (94% yield) if the reaction was stirred for another 15 h.



7h–r

[23] M. Huang, G. E. Garrett, N. Birlirakis, L. Bohe, D. A. Pratt, D. Crich, *Nat. Chem.* **2012**, *4*, 663–667.

[24] R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

[25] S. Kaeothip, J. P. Yasomanee, A. V. Demchenko, *J. Org. Chem.* **2012**, *77*, 291–299.

[26] a) R. U. Lemieux, T. Takeda, B. Y. Chung, *ACS. Symp. Ser.* **1976**, *39*, 90–155; b) S. Hanessian, J. Banoub, *Carbohydr. Res.* **1977**, *53*, C13-C16.

[27] B. Sun, H. Jiang, *Tetrahedron Lett.* **2011**, *52*, 6035–6038.

[28] M. Shan, E. U. Sharif, G. A. O'Doherty, *Angew. Chem.* **2010**, *122*, 9682–9685; *Angew. Chem. Int. Ed.* **2010**, *49*, 9492–9495.

[29] H. Tanaka, A. Yoshizawa, T. Takahashi, *Angew. Chem.* **2007**, *119*, 2557–2559; *Angew. Chem. Int. Ed.* **2007**, *46*, 2505–2507.

Received: September 24, 2012
Revised: October 20, 2012
Published online: December 11, 2012

