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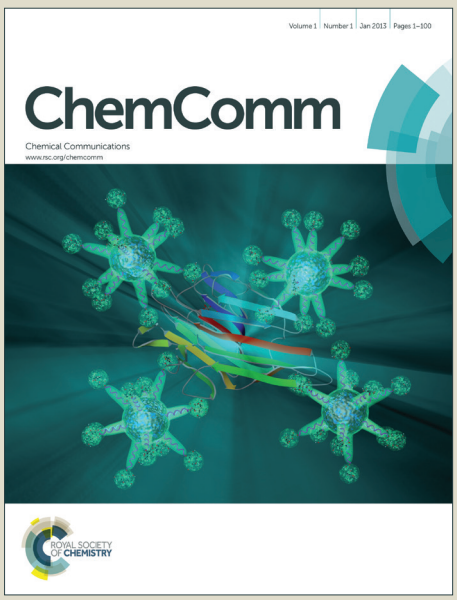

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A general method for *N*-glycosylation of nucleobases promoted by $(p\text{-Tol})_2SO/Tf_2O$ with thioglycoside as donor

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Based on a preactivation strategy with $(p\text{-Tol})_2SO/Tf_2O$ system, a series of nucleosides were synthesized by coupling various thioglycosides with pyrimidines and purines under mild conditions. High yields and excellent β-stereoselectivities were obtained with either armed or disarmed *N*-glycosylation donors by tuning the amount of $(p\text{-Tol})_2SO$ additive.

Nucleoside is arguably one of the most preminent compounds since the structure of DNA was elucidated by Watson and Crick[1]. To date, the modified nucleoside has been used increasingly in expanding genetic code[2], developing new antiviral and antitumor drugs[3], as well as creating biological probes[4]. Therefore, the study on nucleoside synthesis has continuously been a topical subject, and a large number of studies have been reported[5, 6]. Among various methodologies to construct nucleoside, the *N*-glycosylation reaction involving the direct coupling of a sugar moiety with nucleobase is the simplest synthetic strategy, which has been classified into three types: (1) acid-catalyzed fusion of peracylated sugars with nucleobases[7]; (2) the metal salt of heterocyclic systems reacts with protected sugar halides[8]; (3) the silyl-Hilbert-Johnson method developed by Vorbrüggen et al.[9]. Especially, the Vorbrüggen reaction has been used widely and developed into the most prevailing route for nucleoside synthesis[10]. Most recently, further more efficient methods were devised to enhance the product yield and the selectivity of the coupling reaction. For example, Yu et al. coupled the glycosyl ortho-alkynylbenzoates with nucleobases using a gold(I) complex as an activator in high regioselectivity[11] and stereoselectivity[12]. Fraser-Ried[13] and co-workers utilized the reverse synthesis strategy permitting prior extensive structural modifications to the ribose unit. In addition, Jamison's research group[14] telescoped cumbersome nucleoside synthesis processes into a continuous one-flow multistep sequence using pyridinium triflates as catalyst. According to these advances, many novel nucleoside analogues have been successfully synthesized. However, it is still desired to develop new universal strategies for various armed/disarmed sugar donors and pyrimidine/purine acceptors to synthesize nucleosides under mild conditions.

Thioglycoside, one of the most useful donors for *O*-glycosylation, is convenient to prepare and stable under many reaction conditions[15a]. However, fewer literatures[16] using thioglycoside for nucleoside synthesis were reported. Moreover, the substrate scope was mainly limited to the pentose sugars and pyrimidine nucleobases. Especially, low yields and poor selectivities were obtained with ambident and weakly nucleophilic purines as acceptors[16c-f]. Over the years, the preactivation protocol with $(p\text{-Tol})_2SO/Tf_2O$ system, developed from the traditional Ph_2SO/Tf_2O pair,[15b] has been demonstrated to be a practical, straightforward, and high stereoselectivity method for *O*- and *C*-glycosylations using *N*-acetyl-5-*N*,4-*O*-oxazolidione protected thiosialoside as donor[17]. In continuation of our studies on this glycosylation protocol, we are intrigued whether this method is suitable for *N*-glycosylation, and finally establish one general method for synthesis of various *O*-, *C*, and *N*-glycoconjugates.

Herein, we report a facile and general method, based on the preactivation strategy promoted by $(p\text{-Tol})_2SO/Tf_2O$, for the production of nucleoside analogues from armed/disarmed sugar donors and various nucleobases in high yields and stereoselectivities.

With donor **1a** in hand, we initially performed the model *N*-glycosylation of **1a** with trimethylsilylated uracil **2a** by the preactivation protocol. A solution of **1a** and $(p\text{-Tol})_2SO$ (1.2 equiv) was preactivated by Tf_2O (1.2 equiv) in dichloromethane at -70°C for 0.5 h, followed by addition of **2a** (3.0 equiv) in CH_3CN. The resulted mixture was stirred for 2 h, and then warmed up to -50 °C for another 2 h. The coupling product **3** (Table 1, entry 1) was obtained in 60% yield with exclusive β-stereoselectivity. Based on our previous findings[17] that an excessive amount of $(p\text{-Tol})_2SO$ can raise the glycosylation yields by stabilizing the active intermediates derived from donors, we increased the amount of $(p\text{-Tol})_2SO$ from 1.2 equiv to 3.0 equiv, and found that the corresponding yields were not increased dramatically (Table 1, entries 2-3). These inferior results, which we attributed to the deactivating effect of the acetyl protecting group on donor **1a**, prompted us to optimize the reaction conditions by modulating both the temperature of preactivation and the amount of $(p\text{-Tol})_2SO$ at the same time. Surprisingly, when the preactivation temperature was elevated to -60°C, the isolated product yield jumped significantly from 66% to 99% with increasing the amount of $(p\text{-Tol})_2SO$ from 1.2 equiv to 3.0 equiv (Table1, entries 4-6).

During above optimization studies, it was revealed that the efficiency of the *N*-glycosylation was significantly dependent on the preactivation temperature and $(p\text{-Tol})_2SO$ amount,

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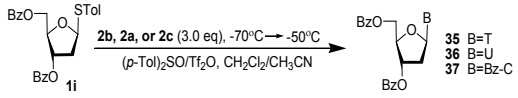
which are closely related to the donor reactivity and the stability of the glycosylation transition state respectively. Higher preactivation temperature could benefit the unreactive donors, and more (p-Tol)$_2$SO amount would be helpful to trap the less stable glycosylation intermediates.

Table 1 Effect of the (p-Tol)$_2$SO amount and preactivation temperature on *N*-glysosylation with **1a** as the donor



Entry	T	(p-Tol)$_2$SO	Yield	α/β
1		1.2 equiv	60%	β
2	-70°C	2.0 equiv	57%	β
3		3.0 equiv	79%	β
4		1.2 equiv	66%	β
5	-60°C	2.0 equiv	91%	β
6		3.0 equiv	99%	β

Next, a series of frequently used thioglycosides **1a-f** and nucleobase derivatives **2a-f** (Fig. 1) were prepared to explore the substrate scope of the *N*-glycosylation promoted by (p-Tol)$_2$SO/Tf$_2$O. We first investigated the reaction of pyrimidine nucleobases **2a-c** with donors **1a-f**, derived from D-galactose, D-glucose and D-ribose (Scheme 1). Under the optimized reaction conditions (-60°C→-40°C, (p-Tol)$_2$SO (3.0 equiv)), the coupling reactions of **1a** with TMS-thymine **(2b)** and TMS-N4-benzoylcytosine **(2c)** provided the nucleosides **4** and **5** in excellent yields (> 96%).

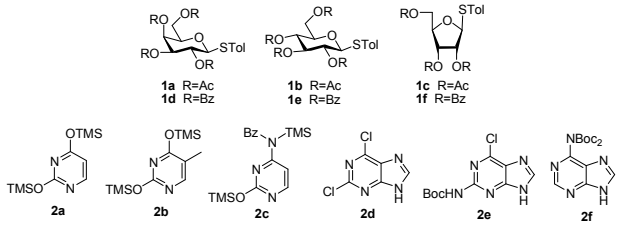
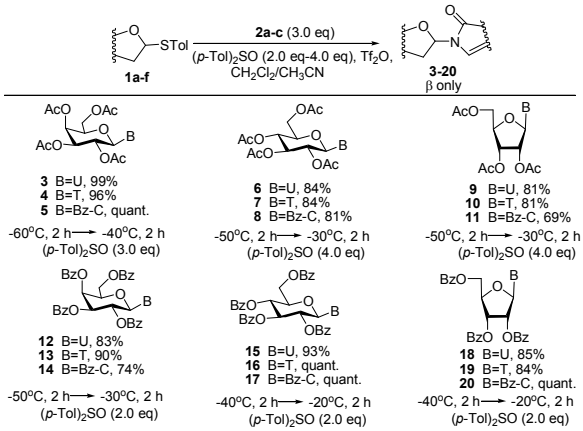


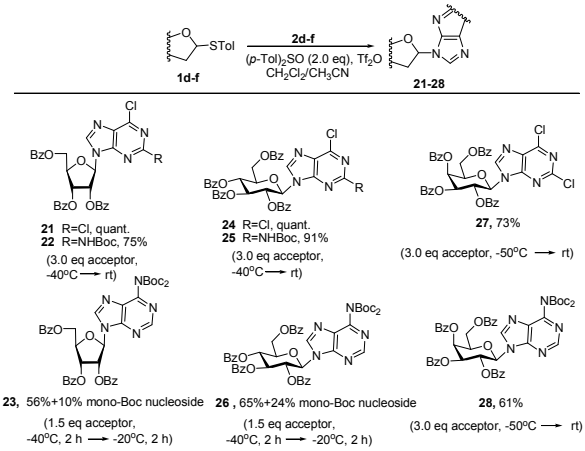
Fig. 1 Structures of glycosyl donors and acceptors for nucleosides syntheses

Under the same reaction conditions for **1a**, the *N*-glycosylation of **1b** with **2a** afforded product **6** in a higher yield (76%) than that observed by Yu[11] (67%) with glycosyl ortho-alkynylbenzoate as donor. Moreover, repetition of the experiment of **1b** and **2a** by warming up the preactivation temperature to -50°C, a much higher yield (84%, Scheme 1) was obtained, so were **2b** and **2c**. In addition, the peracylated ribofuranose **1c** reacted with TMS-pyrimidines **(2a-c)** to provide the desired β nucleosides **9-11** in good yields.

Taking into account that the benzoyl protected donors are less reactive than the corresponding acetyl protected donors[18], we performed the coupling reactions of **1d-f** with nuclebases **(2a-c)** with a higher preactivation temperature. Much to our delight, among all these *N*-glycosylation reactions, satisfactory yields of the coupling products **12-20** were provided with eight out of nine examples ≧ 83% (Scheme 1).



Scheme 1 *N*-Glycosylation of glycosyl donors with pyrimidines



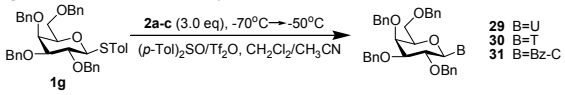
Scheme 2 *N*-Glycosylation of glycosyl donors with purines

Then, we focused on the real challenge of *N*-glycosylation with purines. Since the Boc-protected purine nucleobases have been prepared[19a] and used in *N*-glycosylations and other reactions with good solubility and high N9/N7 regioselectivity[10,11,19b-d], we selected the purine analogues, such as 2,6-dichloropurine **(2d)**, N2-*tert*-butoxycarbonyl-2-amino-6-chloropurine **(2e)** and N6-bis(*tert*-butoxycarbonyl)-adenine **(2f)**, as acceptors to extend the *N*-glycosylations with thioglycosides as donors. As expected, donor **1f** was coupled with acceptor **2d** smoothly and furnished the exclusive product **21** quantitatively. Notably, the structure of the coupling product **21** was determined unequivocally on the basis of the precedent[20] as well as the combined analysis of 1D and 2D NMR (^{1}H, ^{13}C, HSQC, HMBC) experiments. In particular, the strong HMBC correlation between H-1' and C4 rather than H-1' and C5 was telltale (see ESI for details) to confirm compound **21** is N9 product. Similarly, the N2-*tert*-butoxycarbonyl-2-amino-6-chloropurine **(2e)** also underwent *N*-glycosylation with **1f** to preponderantly give the desired N9-nucleoside **22** in good yield (75%). In the case of N6-bis(*tert*-butoxycarbonyl)adenine **(2f)**, the coupling product **23** was isolated along with the corresponding mono-Boc-protected nucleoside as a side product (Scheme 2).

In a similar manner, the coupling reactions of the three purine nucleobases **(2d-f)** with **1d** and **1e** were also examined. The N9-nucleosides **24-28** were obtained in moderate to excellent yields (61-100%, Scheme 2), and the corresponding

N7-nucleosides were not detected. The structures of **22-28** were definitely corroborated from NMR experiments as described for the nucleoside **21**.

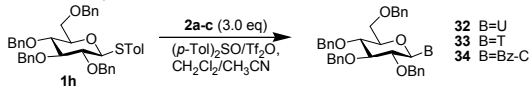
Table 2 *N*-glycosylation of perbenzyl protected donor **1g** with **2a-c** using different amount of $(p\text{-Tol})_2SO$.



Entry	Product	$(p\text{-Tol})_2SO$	Yield[a]	α/β[b]
1		1.2 equiv	76%	1:2.5
2		2.0 equiv	92%	1:2.7
3	**29**	3.0 equiv	99%	1:3.7
4		4.0 equiv	97%	1:7.9
5		6.0 equiv	quant.	>1:30
6	**30**	6.0 equiv	quant.	β
7	**31**	6.0 equiv	quant.	β

[a] Isolated yields, [b] Determined by NMR.

Table 3 *N*-glycosylation of perbenzyl protected donor **1h** with **2a-c** under different preactivation conditions.



Entry	Product	*T*	$(p\text{-Tol})_2SO$	Yield[a]	α/β[b]
1		-70°C	4.0 equiv	64%	1:4.3
2			6.0 equiv	56%	1:4.6
3	**32**	-60°C	2.0 equiv	92%	1:5.6
4			4.0 equiv	quant.	1:8.7
5			6.0 equiv	99%	1:17
6	**33**	-60°C	2.0 equiv	93%	1:3.6
7			6.0 equiv	99%	1:25
8	**34**	-60°C	6.0 equiv	80%	1:20

[a] Isolated yields, [b] Determined by NMR.

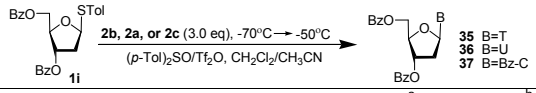
Next, in an effort to ascertain the efficiency of the *N*-glycosylation based on $(p\text{-Tol})_2SO/Tf_2O$ preactivation protocol thoroughly, and especially to probe the influence of different added amount of $(p\text{-Tol})_2SO$ on the reaction, some complementary experiments with perbenzyl protected thioglycosides **(1g** and **1h)** as donors were performed (Tables 2 and 3).

The exploratory reactions of **1g** with **2a** were undertaken with different amount of $(p\text{-Tol})_2SO$. As shown in Table 2, with increasing the amount of $(p\text{-Tol})_2SO$ from 1.2 equiv to 6.0 equiv, both the yield and stereoselectivity of the reaction were increased significantly (Table 2, entries 1-5). Remarkably, the similar excellent yields (~100%) and β-stereoselectivities were also obtained in the syntheses of **30** and **31** with 6.0 equiv. of $(p\text{-Tol})_2SO$ used for the *N*-glycosylations (Table 2, entries 6-7). To the best of our knowledge, this is the first time to obtain the perbenzyl protected nucleosides in so high stereoselectivity and yield simultaneously without the anchimeric assistance at the C2 position of glycosyl donors[21].

Continuously, Table 3 illustrates the results of our efforts to scope the *N*-glycosylations between perbenzyl protected glucopyranoside **(1h)** and nucleobases. Interestingly, when the preactivation temperature was -70°C, the results of the reaction were not satisfactory, even 6.0 equiv of $(p\text{-Tol})_2SO$ was used (Table 3, entry 1, 2). The somewhat surprising fact was comparable with the previous observations (Table 1), which probably arised from the low reactivity of donor **1h** at very low reaction temperature. Whereupon, analogous reactions of **1h** with TMS-pyrimidines **(2a-c)** were done using different amounts of $(p\text{-Tol})_2SO$ with the preactivation temperature elevated to -60°C. More efficeient *N*-glycosylations were achieved (Table 3, entries 5, 7-8), indicating that the yield and stereoselectivity of *N*-glycosylations could be tunable to a certain degree by changing the amount of $(p\text{-Tol})_2SO$ and the preactivation temperature according to the characteristics of the used donors.

In addition, above *N*-glycosylation protocol was also applied into the syntheses of 2-deoxyribonucleosides with 2-deoxy-β-thioriboside **1i** and TMS-thymine **(2b)** as glycosyl donor and acceptor, respectively (Table 4). More interestingly, when the amount of $(p\text{-Tol})_2SO$ additive increased from 0.8 equiv to 4.0 equiv, the product yield of 2-deoxyribonucleoside **35** was elevated from 53% to ~100%, whereas the β-stereoselectivity of the reaction was decreased from β/α = 7.8:1 to 2.8:1 (Table 4, entries 1-5). The results are similar to our previous research findings for another kind of deoxysugar, sialic acid, wherein the α-stereoselectivity was dropped down with increasing the Ph_2SO amount,[17a,17d] indicating that the detailed glycosylation mechanism could be different between deoxysugar and ordinary sugar involved reactions. It is noted that much lower β-stereoselectivity (β/α = 1.6:1) and reaction yield (43%) were obtained in the same *N*-glycosylation of **1i** and **2b** with NIS/TfOH[16e] as promoter. Considering the influences of both reaction yield and β-stereoselectivity on the coupling, 1.2 equiv of $(p\text{-Tol})_2SO$ was employed for the following *N*-glycosylation of TMS-uracil (**2a)** and TMS-N4-benzoylcytosine **(2c).** The expected 2-deoxyribonucleosides **36** and **37** were prepared in good β-stereoselectivities (β/α = 4.5:1 to 5.1:1, Table 4, entries 6-7) and 79-54% yields.

Table 4 *N*-glycosylation of perbenzoyl protected 2-deoxy-β-thioriboside **1i** with nucleobases **2a-c**.



Entry	Product	$(p\text{-Tol})_2SO$	Yield[a]	α/β[b]
1		0.8 equiv	53%	1:7.8
2		1.2 equiv	75%	1:6.6
3	**35**	1.6 equiv	86%	1:5.1
4		2.0 equiv	99%	1:3.2
5		4.0 equiv	quant.	1:2.8
6	**36**	1.2 equiv	79%	1:4.5
7	**37**	1.2 equiv	54%	1:5.1

[a] Isolated yields, [b] Determined by NMR.

In summary, a series of nucleosides were prepared efficiently by coupling the facilely available thioglycosides with pyrimidine and purine nucleobases based on $(p\text{-Tol})_2SO/Tf_2O$ preactivation protocol under mild conditions. The *N*-glycosylation outcome is highly dependent on the preactivation temperature, and especially the added amount of $(p\text{-Tol})_2SO$ in the reaction. Generally, high yields and excellent β-stereoselectivities were obtained even perbenzyl protected sugars and 2-deoxy-β-thioriboside were used as donors by tuning the amount of $(p\text{-Tol})_2SO$ additive. Combined with our previous work[17], the $(p\text{-Tol})_2SO/Tf_2O$ preactivation protocol disscussed in this study has been demonstrated its

usefulness and generality for the efficient syntheses of various glycoconjugates including *N*-, *O*- and *C*-glycosides.

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