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ARTICLE TYPE

Strained Olefin Enables Triflic Anhydride Mediated Direct Dehydrative Glycosylation

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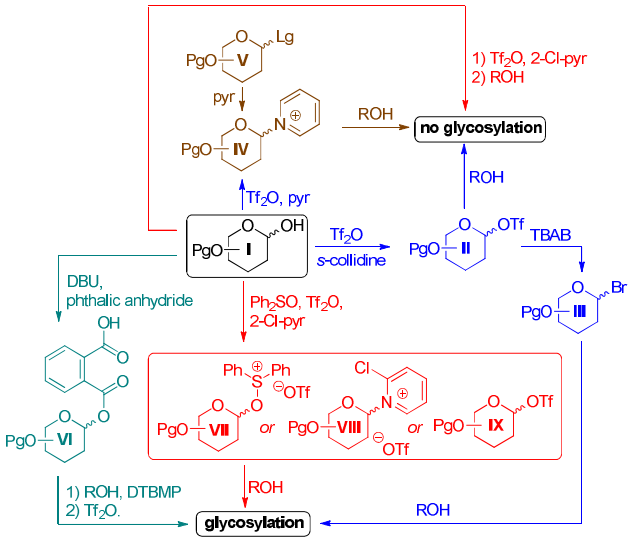
For the first time, we demonstrated that the Tf_2O mediated direct dehydrative glycosylation was possible simply with strained olefins, and other typical bases were inhibitors of this reaction. We optimized the glycosylation condition and found that typical benzyl protected 1-OH pyranosyl donors and certain alcohol acceptors were suitable for our glycosylation system. Furthermore, we found that complete 1,2-*trans* selectivity and wider acceptor scope could be achieved with 2-*O*-Bz 3,4,6-tri-*O*-Bn pyranosyl donors.

The explosive development of glycoscience in the new century calls for more simple and enabling chemical glycosylation methods. Inspecting the arsenal of various glycosylation tools, triflic anhydride (Tf_2O) mediated dehydrative glycosylation is particularly attractive because of the ready availability of the glycosyl donor and its wide applicability.[1] The mechanism sounds deceptively simple: 1-OH sugar reacts with Tf_2O and the resulting 1-OTf intermediate will be attacked by the acceptor to yield the glycoside. Both steps should require the presence of an acid scavenger. By definition, this is probably one of the most straightforward glycosylation pathway.

However, for very long time, it is known that anomeric *O*-triflate intermediate could not react with alcohol in the presense of typical nitrogen bases such as pyridine or triethylamine. Thus, more complex alternative pathways were invented to make this reaction happen (scheme 1): In the early days, A. Perlin *et al.* mixed structure **I** and Tf_2O in the presence of *s*-collidine, and found that the postulated intermediate **II** refused to react with alcohol. Instead, further derivatization with TBAB enabled the glycosylation via structure **III**.[2] After several decades, D. Y. Gin *et al*. encountered the same problem (Tf_2O and 2-Cl pyridine were used for their case). This time, they found that a combination of Tf_2O and Ph_2SO solved the above problem via a complex mechanism, in which **VII**, **VIII** and **IX** can all participate in the glycosylation.[3] Recently, this problem was again tackled by K. S. Kim *et al.* using phthalate intermediate **VI**.[4] In our eyes, the low stability of intermediate **II** may not be the major hurdle preventing a direct coupling between **II** itself and the ROH. Instead, the nitrogen base has more responsibility for this issue. Perlin *et al.* isolated the pyridinium intermediate **IV** and found it reacted with benzoate in refluxing DMF.[2] Other literature indicate that **IV** (produced from different donors **V**) are stable in various hydrolytic or alcoholytic conditions.[5] Thus, we would like to make the following proposal: 1-OTf intermediate **II** could not react with alcohol simply because it is too reactive. With current methods, typical nitrogen-containing acid scavenger such as pyridine or triethylamine form stable complex with **II** and no further reaction could happen.

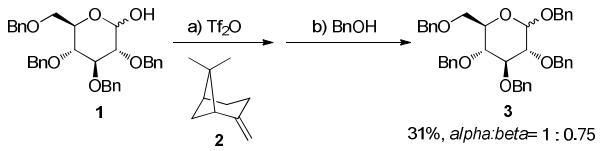


Scheme 1. Some typical Tf_2O mediated dehydrative glycosylation. Pathway colored in blue: works by A. Perlin *et al.*; in red: works by D. Y. Gin *et al.*; in green: works by K. S. Kim *et al.*; in brown: other works demonstrating the low reactivity of anomeric pyridinium salts.

Lately, Y.-L. Chen *et al.* communicated a very mild glycosylation method on complex molecules with glycosyl iodide and strained olefin as acid scavenger, with which the taxanes could be directly glycosylated with good yields.[6] On the basis of above discovery, we further found that strained olefins could promote the direct reaction between structure **I** and ROH. This finding revived the appealing simplicity of Tf_2O mediated dehydrative glycosylation and the method development will be reported herein.

At the beginning, we examined the reaction between 2,3,4,6-*O*-tetrabenzyl glucopyranose **1** and Tf_2O, without or with *beta*-(-)-

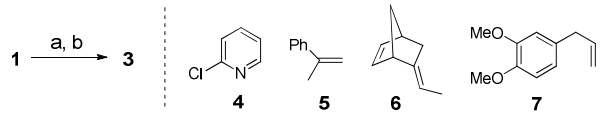
pinene as acid scavenger. Without *beta*-(-)-pinene, when compound **1** was reacted with Tf_2O at -78 °C and then with BnOH, large amount of remaining **1** was observed even after the mixture was warmed to RT. Next, excessive *beta*-(-)-pinene was added during the anomeric *O*-triflate formation step. This did not induce any significant change by TLC inspection. After BnOH being added, still no reaction could be observed at low temperature. However, per-*O*-Bn glucopyranose **2** emerged during warming up. Upon reaction at RT overnight, starting material **1** completely disappeared and the product **2** was isolated with 31% yield (*alpha:beta* = ca. 1:0.75) (Scheme 1).



Scheme 2. *β*-(-)-Pinene (**2**) enabled the Tf_2O mediated direct dehydrative glycosylation. Reaction conditions: a) Tf_2O was added into cold solution of compounds **1** and **2** at -78 °C, the mixture was warmed to 0 °C, treated with BnOH, and stirred at RT overnight. See supporting information for details.

Further optimization of this model reaction increased the yield to 73% (Table 1, entry 1). Several factors were noteworthy: 1) it was important to add the glycosyl donor into pre-cooled Tf_2O and *beta*-(-)-pinene (**2**) solution in DCM. 2) Temperature and duration for 1-OTf intermediate formation had to be proper to ensure the maximum conversion and minimum decomposition. We found that 45 minutes at -50 °C was optimal through large amount of comparison experiments. 3) Solvent effect was also probed and it was found that DCM was a better choice over toluene, ether, or acetonitrile. To compare with our optimized condition: 1) Gin's condition gave 44% yield with donor **1** and BnOH (Table 1, entry 2). 2) Simply using 2-Cl pyridine did not give any glycosylation (Table 1, entry 3), and this is consistent with Gin's finding. 3) Certain olefins, including compounds 5, **6**, and **7** [7] gave the desired glycosylation, but the yields were relatively low (Table 1, entry 4-6). 4) Further experiments with additives were demonstrated in Table 1, entry 7-13: We kept the condition for 1-OTf intermediate formation described in Table 1, entry 1, but added 1 equiv. of additives before injecting BnOH. These additives included ammonium salts, organic and inorganic bases, molecular sieves, and Ph_2SO. It was found that ammonium salts reduced the glycosylation yield, while bases, molecular sieves, and Ph_2SO completely inhibited the glycosylation. Collectively, these results suggested that typical nitrogen containing organic bases and typical inorganic bases are inhibitors of Tf_2O mediated direct dehydrative glycosylation, while strained olefin, as a unique neutral "base", could promote this straightforward conversion.

Table 1. Initial screening with different bases and olefins.[a]

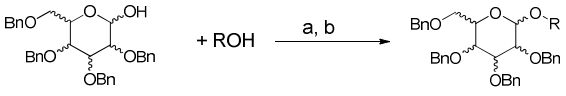


No.	Acid scavenger	Additive	Yield (*alpha:beta*) [b]
1	**2**	-	73% (1:0.33)
2	**4**	Ph_2SO	44% (1:1.4)
3	**4**	-	*n.d.*
4	**5**	-	*n.d.*
5	**6**	-	42% (1:1.0)
6	**7**	-	31% (1:1.0)
7	**2**	TBAI [c]	35% (1:1.0)
8	**2**	TBAOTf [c]	37% (1:1.1)
9	**2**	DIPEA [c]	*n.d.*
10	**2**	Na_2CO_3 [c]	*n.d.*
11	**2**	Na_3PO_4 [c]	*n.d.*
12	**2**	3 Å MS [c]	*n.d.*
13	**2**	Ph_2SO [c]	*n.d.*

[a] Reaction condition for entry 1: a) 1.3 equiv. Of Tf_2O, 5 equiv of *beta*-(-)-pinene (**2**), DCM, -50 °C, then the donor solution in DCM was added, -50 °C, 45 min; b) then 5 equiv. of acceptor was added, warmed to RT in ca. 2 h, and stirred for 4 h. See supporting information for details of entries 2-13. [b] Yield was determined after flash chromatography. Anomeric ratio was determined by NMR. [c] These reagents were added after the formation of 1-OTf intermediate, but before the acceptor.

We further applied the condition in Table 1, entry 1 to different glycosyl donors (including compounds **1**, **8**, and **9**) and acceptors (including isopropanol, cyclohexanol, BnOH, adamantol, and sugar alcohol **10**). As described in Scheme 3, glucose donor **1** gave moderate to good yields with different acceptors, with almost no anomeric selectivity on products **11**, **12**, **13**, and **14**. From mannose donor **8**, the glycosylation yields were similar, but the stereoselectivities were much improved on products **15**, **16**, and **17**. Our dehydrative glycosylation condition worked as well with galactose donor **9** to give product **18** without stereoselectivity. The activity of donors **8** and **9** seemed to be lower to its glucose analogue, since their reaction with acceptor **10** were sluggish (results not displayed). One important factor for the reactions in Scheme 3 was the reaction time for glycosylation step, which varied from 6 h to 18 h, largely depending on the acceptor structure. Primary alcohol including BnOH and compound **10** took shorter reaction time to complete the reaction, and long reaction time reduced the yield significantly. However, for hindered alcohols such as cyclohexanol and adamantol, long reaction time was essential. Taken together, it is clear that our dehydrative condition was generally applicable for different *O*-benzylated sugar donors, although there is still room to improve the yield and stereoselectivity of the new system.

General scheme of the reaction: [a]



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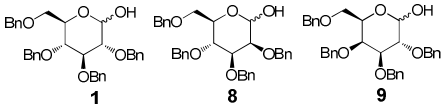

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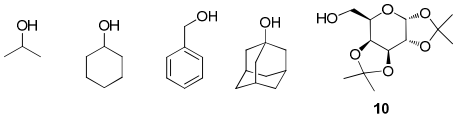

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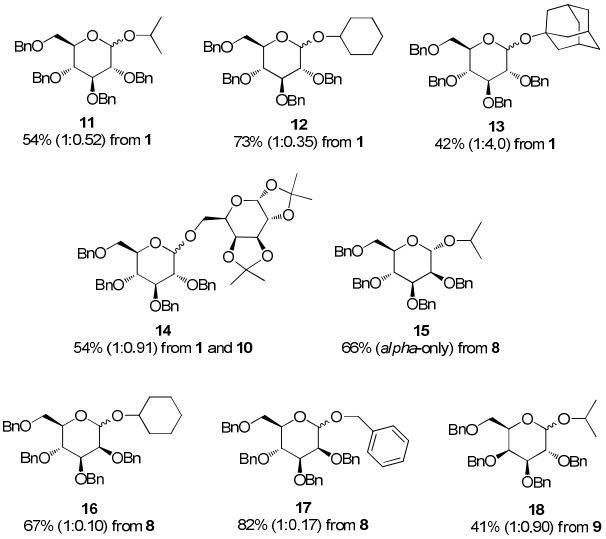
Products (Yields and *alpha:beta*): [b]



11
54% (1:0.52) from **1**

12
73% (1:0.35) from **1**

13
42% (1:4.0) from **1**

14
54% (1:0.91) from **1** and **10**

15
66% (*alpha*-only) from **8**

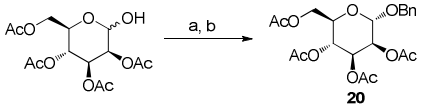
16
67% (1:0.10) from **8**

17
82% (1:0.17) from **8**

18
41% (1:0.90) from **9**

Scheme 3. Tf_2O Mediated direct dehydrative glycosylation with *per-O*-Bn 1-OH pyranosyl donors. [a] Reaction conditions: a) 1.3 equiv. Of Tf_2O, 5 equiv of *beta*-(-)-pinene (**2**), DCM, -50 °C, then the donor solution in DCM was added, -50 °C, 45 min, then 5 equiv of acceptor, warmed to RT in ca. 2 h, and stirred for 4-16 h. [b] Yield was determined after flash chromatography. Anomeric ratio was determined by NMR.

At this stage, it was natural to employ the peracylated sugar donor to increase the anomeric selectivity. However, when mannose derivative **19** was reacted with BnOH using our dehydrative glycosylation condition, only 13% yield of product **20** could be obtained, albeit with good 1,2-*trans* selectivity (Scheme 4). [8] It was not surprising, since the disarming effect of peracylation could significantly decrease the reactivity of the glycosyl donor.

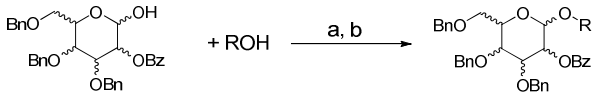


19 → 20
13%, *alpha*-only

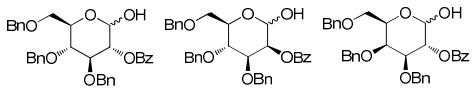
Scheme 4. Tf_2O Mediated direct dehydrative glycosylation with *per-O*-Ac 1-OH mannosyl donor. Reaction conditions: a) 1.3 equiv. Of Tf_2O, 5 equiv of *beta*-(-)-pinene (**2**), DCM, -50 °C, then the donor solution in DCM was added, -50 °C, 45 min, then 5 equiv of acceptor, warmed to RT in ca. 2 h, and stirred for 16 h.

Inspired by the recent superarming effect reported by A. V. Demchenko *et al.*, [9] we next pursued our dehydrative glycosylation method on 2-*O*-Bz 3,4,6-tri-*O*-Bn pyranoses **21**, **22**, and **23**. It is hoped that the 2-*O*-Bz group could control the anomeric selectivity, and boost the donor reactivity along with the rest *O*-Bn protections. As described in Scheme 5, glucose derivative **21** reacted with different acceptors to give glucosides **25**, **26**, **27**, and **28** with complete 1,2-*trans* selectivity and moderate yields. Interestingly, glycosylation with donor **21** could be performed on Florfenicol to give glucoside **29**, without being interrupted by the sulfone and chloroacetamide groups presented on the drug molecule. In a similar manner, mannose donor **22** and galactose donor **23** also gave respectively their glycosides **30** and **31** as well as **32** and **33**, with complete 1,2-*trans* selectivity, and displayed activity similar to the glucosyl donor **21**. Under our reaction conditions, it was found that donors **21**, **22**, and **23** have different reactivity compared to their per-*O*-Bn analogues **1**, **8**, and **9**. For simple alcohol acceptors, the glycosylation yields from donors **21**, **22**, and **23** were lower than the donors **1**, **8**, and **9**. Nevertheless, donors **21**, **22**, and **23** gave far better results with more complex acceptors **10** or **24**, compared to donors **1**, **8**, and **9** (with the exception of the conversion from compound **1** and **10** to **14**, described in Scheme 3). The reaction time for the glycosylation step again has to be monitored carefully for a good yield. Similar to the reactions in scheme 3, primary alcohols required shorter reaction time and the reaction should be quenched in time, while hindered alcohol took longer time to complete the conversion. Thus, 2-*O*-Bz 3,4,6-tri-*O*-Bn pyranose donors could be used along with our dehydrative glycosylation condition to ensure a complete 1,2-*trans* selectivity, and an even broader acceptor scope, compared to their per-*O*-Bn or per-*O*-Ac donor analogues.

General scheme of the reaction: [a]

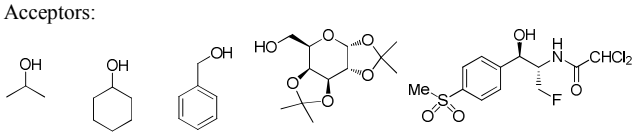


Donors:



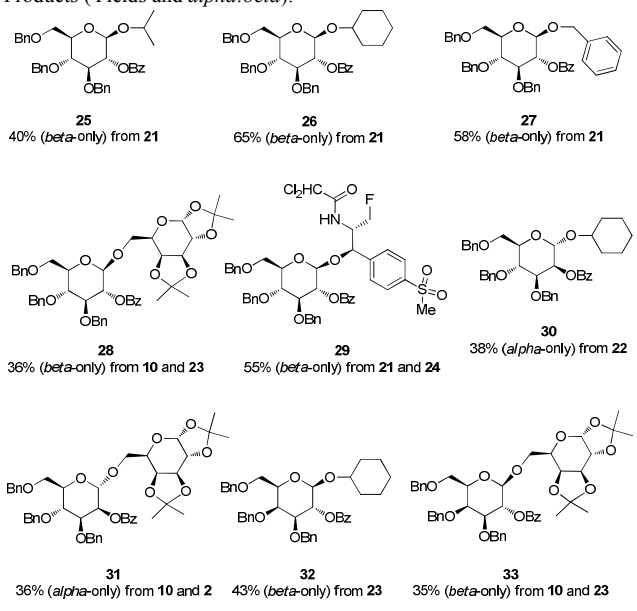
21 22 23

Acceptors:



10 24

Products (Yields and *alpha:beta*): [b]



25
40% (*beta*-only) from **21**

26
65% (*beta*-only) from **21**

27
58% (*beta*-only) from **21**

28
36% (*beta*-only) from **10** and **23**

29
55% (*beta*-only) from **21** and **24**

30
38% (*alpha*-only) from **22**

31
36% (*alpha*-only) from **10** and **2**

32
43% (*beta*-only) from **23**

33
35% (*beta*-only) from **10** and **23**

Scheme 5. Tf_2O Mediated direct dehydrative glycosylation with 2-*O*-Bz, 3,4,6-tri-*O*-Bn 1-OH pyranosyl donors. [a] Reaction conditions: a) 1.3 equiv. Of Tf_2O, 5 equiv of *beta*-(-)-pinene (**2**), DCM, -50 °C, then the donor solution in DCM was added, -50 °C, 45 min, then 5 equiv of acceptor, warmed to RT in ca. 2 h, and stirred for 4-16 h. [b] Yield was determined after flash chromatography. Anomeric ratio was determined by NMR.

In the end, it is important to notice again that the above-described new glycosylation system still has relatively low reactivity and limited acceptor scope. This fact might be associated with the high activity of 1-OTf intermediate **II** (Scheme 1), too: Under our reaction condition, rapid collapse of intermediate **II** to anomeric oxocarbenium ion is inevitable, [10] and the latter species might be mediocre in terms of reactivity.

Conclusions

In conclusion, of conceptual importance, we first demonstrated that Tf_2O mediated direct dehydrative glycosylation was possible with strained olefins, and other typical bases were inhibitors of this reaction. Next, we optimized the glycosylation condition and found that typical per-*O*-Bn 1-OH pyranoses and simple alcohol acceptors were suitable for our glycosylation system. Since the new system still suffered from low stereoselectivity and narrow acceptor scope, we further discovered that 2-*O*-Bz 3,4,6-tri-*O*-Bn pyranoses could be incorporated into our strained olefin promoted dehydrative glycosylation system as effective donors to ensure excellent 1,2-*trans* selectivity and improved acceptor scope. To our best knowledge, so far, strained olefin was the only reagent promoting Tf_2O mediated direct dehydrative glycosylation. Therefore, we believe that this new method has potential to serve as mechanistic study tool for glycosylation reactions. In addition, we are aware that this new glycosylation method should be further optimized for better yield and wider substrate scope. Thus, further studies along this line are being actively pursued in our group and will be disclosed in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, crystallographic data, and copies of NMR spectra. See DOI: 10.1039/b000000x/

‡ These authors contributed equally to this work.

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