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Strained Olefin Enables Triflic Anhydride Mediated Direct Dehydrative Glycosylation

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For the first time, we demonstrated that the Tf₂O 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 (Tf₂O) 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 Tf₂O 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 pathways.

However, for very long time, it is known that anomic O-triflate intermediate could not react with alcohol in the presence 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 Tf₂O 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 (Tf₂O and 2-Cl pyridine were used for their case). This time, they found that a combination of Tf₂O and Ph₅SO 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.

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 Tf₂O mediated dehydrative glycosylation and the method development will be reported herein.

At the beginning, we examined the reaction between 2,3,4,6-O-tetra benzyl glucopyranose I and Tf₂O, without or with beta(-)-
pinene as acid scavenger. Without beta-(-)-pinene, when compound 1 was reacted with TfO 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. beta-(-)-Pinene (2) enabled the TfO mediated direct dehydrative glycosylation. Reaction conditions: a) TfO 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 TfO 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 2ACl 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 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 Ph3SO. It was found that ammonium salts reduced the glycosylation yield, while bases, molecular sieves, and Ph3SO completely inhibited the glycosylation. Collectively, these results suggested that typical nitrogen containing organic bases and typical inorganic bases are inhibitors of TfO mediated direct dehydrative glycosylation, while strained olefin, as a unique neutral “base”, could promote this straightforward conversion.

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid scavenger</th>
<th>Additive</th>
<th>Yield (alpha:beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>73% (1:0.33)</td>
</tr>
<tr>
<td>2</td>
<td>Ph3SO</td>
<td></td>
<td>44% (1:1.4)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>42% (1:1.0)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>31% (1:1.0)</td>
</tr>
<tr>
<td>7</td>
<td>TBAI</td>
<td></td>
<td>35% (1:1.0)</td>
</tr>
<tr>
<td>8</td>
<td>TBAOTf</td>
<td></td>
<td>37% (1:1.1)</td>
</tr>
<tr>
<td>9</td>
<td>DPEA</td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>Na2CO3</td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
<td>Na2PO4</td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>12</td>
<td>Ph3SO</td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>n.d.</td>
</tr>
</tbody>
</table>

[a] Reaction condition for entry 1: a) 1.3 equiv. of TfO, 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.

Table 1. Initial screening with different bases and olefins.

Donors:

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

Scheme 3. TfO Mediated direct dehydrative glycosylation with per-O-Bn 1-OH pyranosyl donors. [a] Reaction conditions: a) 1.3 equiv. Of TfO, 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). It was not surprising, since the disarming effect of peracylation could significantly decrease the reactivity of the glycosyl donor.

Scheme 4. TfO Mediated direct dehydrative glycosylation with per-O-Ac 1-OH mannosyl donor. Reaction conditions: a) 1.3 equiv. Of TfO, 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 glucosides 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:[b]

Donors:

Acceptors:

Products (Yields and alpha:beta):[b]
Scheme 5. TfO 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 TfO, 5 equiv of beta-

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 anomic oxocarbenium ion is inevitable, and the latter species might be mediocre in terms of reactivity.

Conclusions

In conclusion, of conceptual importance, we first demonstrated that TfO 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 TfO 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.

Acknowledgements

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Notes and references


8. 2,3,4,6-O-Benzoyl manno.pyranoside was used as starting material under the same reaction condition as described in Scheme 4, however no benzyl 2,3,4,6-O-benzoyl manno.pyranoside could be separated after several attempts.


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