Oligosaccharide Synthesis

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Reagent-Controlled α-Selective Dehydrative Glycosylation of 2,6-Dideoxy- and 2,3,6-Trideoxy Sugars

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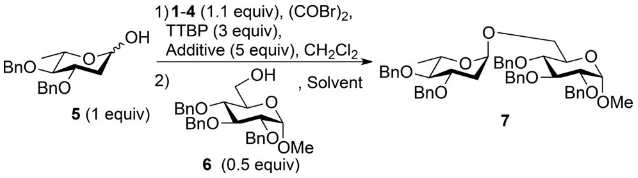
Abstract: *We have found that activating either 2,3-bis(2,3,4-trimethoxyphenyl)cyclopropenone or 2,3-bis(2,3,4-trimethoxyphenyl)cyclopropene-1-thione with oxalyl bromide results in the formation of a species that promotes the glycosylation between 2,6-dideoxy-sugar hemiacetals and glycosyl acceptors in good yield and high α-selectivity. Both reactions are mild and tolerate a number of sensitive functional groups including highly acid-labile 2,3,6-trideoxy-sugar linkages.*

Deoxyhexoses are a common structural motif in a variety of natural products that exhibit antibiotic or anticancer properties.[1] Often these sugars are essential for a molecule's biological activities. Furthermore, altering the sugar-chain composition by glycorandomization can have a profound effect on the biological activity of a natural product. The use of glycorandomization in drug discovery remains underexplored,[2] however, due in large part to the difficulties associated with the stereoselective construction of deoxy-sugar oligosaccharides.[3] The most commonly used approaches to the stereoselective synthesis of deoxy-sugar oligosaccharides rely on either indirect methods that introduce a temporary prosthetic group at the C2 position,[4] or de novo synthesis.[5] However, these approaches require additional steps to remove temporary substituents or manipulate oxidation states after glycosylation. This has led to the development of a number of direct approaches to the stereoselective construction of deoxy-sugar linkages, including the displacement of glycosyl halides, Umpolung strategies, and Brønsted acid activation of glycals.[6] Our own group is working to address this issue through a reagent-controlled approach, where selectivity in the reaction is entirely under the control of the glycosylation promoter.[7]

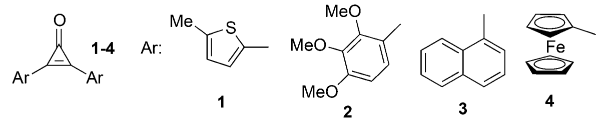
Through the course of these studies, we previously reported an approach to α-linked deoxy sugars that relied on the use of 1,1-dibromo-2,3-diphenylcyclopropene and tetrabutylammonium iodide (TBAI) to activate hemiacetals.[7b] While powerful for the construction of glycosidic linkages to primary glycosyl acceptors, the procedure had several drawbacks. These included long reaction times, tedious purification due to large amounts of TBAI, and low yields with secondary glycosyl acceptors. To address these issues, we sought to develop a new promoter system that does not rely on the use of excess TBAI to drive the reaction.

Our initial investigations focused on determining whether a more electron-rich cyclopropenium cation promoter would lead to faster, more selective reactions. To this end, we examined the ability of a combination of oxalyl bromide and several cyclopropenones with substituents known to stabilize cyclopropenium cations (**1**–**4**, Table 1)[8,9] to activate 2,6-dideoxy-sugar hemiacetals for glycosylation. To establish whether the combination of oxalyl bromide and cyclopropenone derivative was sufficient to promote selective glycosylation, we first examined the reaction in the absence of TBAI (Table 1). Cyclopropenones **1**–**4** were activated with oxalyl bromide and treated with hemiacetal donor **5** and 2,4,6-tri-*tert*-butylpyrimidine (TTBP). Due to its instability,[10] the resulting intermediate was not isolated, but rather directly treated with primary glycosyl acceptor **6**. Under these conditions, **1**, **2**, and **4** reacted with **5** to form a species that underwent glycosylation with **6** in good yield and selectivity (Table 1, entries 1, 2, and 4).[11] We next examined these promoters in the presence of 5 equivalents of TBAI, however, this did not offer any improvement to the selectivity (Table 1 entries 5–7). No reaction was observed with cyclopropenone **1** under these conditions. Finally, the optimal cyclopropenone,

Table 1: Cyclopropenone screening with and without TBAI additive.



Entry	Cyclopropenone	Additive	Solvent	Yield [%][a]	α:β[b]
1	**1**	–	CH$_2$Cl$_2$	53	8:1
2	**2**	**–**	**CH$_2$Cl$_2$**	**87**	**7:1**
3	**3**	–	CH$_2$Cl$_2$	ND	–
4	**4**	–	CH$_2$Cl$_2$	68	6:1
5	**1**	TBAI	CH$_2$Cl$_2$	NR	–
6	**2**	TBAI	CH$_2$Cl$_2$	70	7:1
7	**3**	TBAI	CH$_2$Cl$_2$	64	7:1
8	**2**	TBAI	1,4-dioxane	50	5:1



[a] Yield of isolated product; ND = not determined; NR = no reaction observed. [b] Selectivity determined by ^{1}H NMR spectroscopy.

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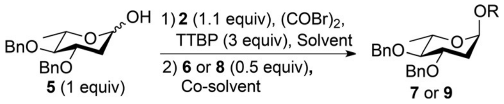
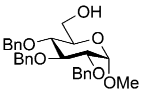
2, was further examined in the presence of TBAI using 1,4-dioxane as a co-solvent in an attempt to take advantage of the well-known α-directing effect of ether solvents. These conditions did not lead to any improvement (Table 1, entry 8).

We next examined the effect of different co-solvents on the selectivity of the reaction (Table 2). We first examined ether solvents, which had previously led to increases in selectivity in our hands,[7b] however, no improvement was observed with the current promoter system (Table 2, entries 2–4). Surprisingly, nitriles such as acetonitrile and pivalonitrile did not erode the selectivity despite their well-known β-directing ability, indicating that the reaction may not be proceeding through an oxocarbenium cation intermediate (Table 2, entries 5 and 6). We next examined 1,1,2-trichloroethylene (TCE) as Woerpel et al. had shown it to favor S_N2-like reactions on activated glycosyl donors.[12] This solvent led to an increase in selectivity to α:β = 11:1 (Table 2, entry 7). Cyclopropenone **2** was not soluble in TCE alone so a small amount CH_2Cl_2 was needed to solubilize the reagent. Handling and storage of the TCE was also seen to be crucial, as the yield of the reaction dropped significantly when the solvent was distilled over $CaCl_2$ (Table 2, entries 8 and 9).[13] Due to solubility issues of the cyclopropenone, TCE was then examined as co-solvent added with the acceptor. This approach increased the operational ease of the procedure without having an impact on yield and selectivity (Table 2, entries 10–12). Importantly, we saw no adverse effects upon scaling up the reaction (Table 2, entry 11). Perhaps even more encouraging was the decrease in reaction time, from more than 16 to less than 3 hours. Finally, we examined the reaction with secondary acceptor **8** under our optimal conditions (Table 2, entry 13). Again, the reaction proceeded in good yield, albeit with diminished selectivity.

Table 2: Solvent optimization with cyclopropenone **2**.



Entry	R′OH	Solvent	Co-solvent[a]	Time [h]	Yield [%][b]	α:β[c]
1	**6**	CH_2Cl_2	CH_2Cl_2	16	87	7:1
2	**6**	CH_2Cl_2	1,4-dioxane	16	65	8:1
3	**6**	CH_2Cl_2	Et_2O	16	68	7:1
4	**6**	CH_2Cl_2	THF	17	77	7:1
5	**6**	CH_2Cl_2	MeCN	16	79	8:1
6	**6**	CH_2Cl_2	*t*BuCN	2.5	71	9:1
7[d]	**6**	TCE	TCE	17	67	11:1
8[e]	**6**	TCE	TCE	16	47	11:1
9[e]	**6**	TCE	1,4-dioxane	16	43	10:1
10	**6**	**CH_2Cl_2**	**TCE**	**2.5**	**74**	**10:1**
11[f]	**6**	**CH_2Cl_2**	**TCE**	**1.5**	**80**	**9:1**
12	**6**	CH_2Cl_2	TCE	1.5	69	10:1
13	**8**	CH_2Cl_2	TCE	1.5	72	7:1



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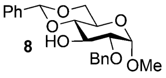

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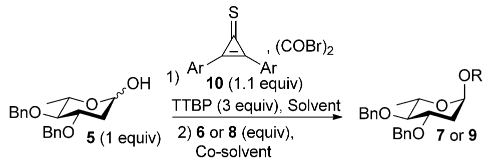
[a] TCE stored over 4 Å molecular sieves that have been microwaved in a conventional microwave five times for 20 seconds. [b] Yield of isolated product. [c] Selectivity determined by ^1H NMR spectroscopy. [d] 0.2 mL of CH_2Cl_2 added to help solubilize **2**. [e] TCE distilled over $CaCl_2$, and 0.2 mL of CH_2Cl_2 added to help solubilize **2**. [f] Reaction run on 500 mg scale.

To further increase the utility of the method, we chose to look into the conversion of the cyclopropenone into the corresponding thione. The sulfur atom of diarylcyclopropene-1-thiones has been shown to have a higher nucleophilicity than the oxygen atom of cyclopropenones.[14] We reasoned that this may increase the rate of activation with oxalyl bromide, thereby leading to a more efficient reaction with hindered acceptors. Based on the results of the initial cyclopropenone screen (Table 1), we chose to examine thione **10** in the reaction.[15] Thione **10** was found to promote glycosylations between **5** and **6**, albeit with moderate yield and selectivity (Table 3, entries 1 and 2). Changing the solvent system to only TCE resulted in an increase in yield (Table 3, entry 3). Unable to obtain improved results with primary acceptor **6**, we turned our attention to secondary acceptor **8**. When the reaction was run in TCE alone we saw similar selectivity to what we observed with the cyclopropenone in CH_2Cl_2/TCE (Table 3, entry 4 vs. Table 2, entry 13). After a short solvent screen, it was found that the addition of either Et_2O or THF increased the selectivity of the reaction without

Table 3: Reaction optimization with thione **10**/oxalyl bromide promoter.[a]



Entry	R′OH	Solvent	Co-solvent	Time [h]	Yield [%][b]	α:β[c]
1	**6**	CH_2Cl_2	CH_2Cl_2	1.5	50	8:1
2	**6**	CH_2Cl_2	*t*BuCN	2.5	57	10:1
3	**6**	TCE	TCE	1.0	75	8:1
4	**8**	TCE	TCE	2.0	80	7:1
5	**8**	TCE	Et_2O	1.5	68	9:1
6	**8**	TCE	THF	1.25	75	9:1
7	**8**	TCE	Glyme	1.5	27	5:1
8	**8**	TCE	Diglyme	1.75	90	7:1
9	**8**	TCE	1,4-dioxane	2.0	70	7:1
10[d]	**8**	TCE	THF	1.75	75	9:1
11[e]	**8**	**TCE**	**THF**	**1.25**	**74**	**9:1**
12[f]	**8**	TCE	THF	2.25	62	8:1
13[g]	**8**	TCE	THF	1.5	27	5:1
14[h]	**8**	TCE	THF	1.5	54	>20:1
15[h]	**6**	TCE	THF	4.5	39	8:1
16	**6**	TCE	THF	2.75	59	10:1
17	**6**	CH_2Cl_2	TCE	2.0	48	7:1
18	**8**	CH_2Cl_2	TCE	2.0	54	20:1

[a] Donor:acceptor ratio 2:1 unless otherwise noted; Ar = 2,3,4-trimethoxyphenyl. [b] Yield of isolated product. [c] Selectivity determined by ^1H NMR spectroscopy. [d] **10** activated in the presence of donor and TTBP. [e] Activation time decreased to 5 min. [f] Donor: acceptor ratio 1:2. [g] **10** not present; $(COBr)_2$ added directly to **5**. [h] Ketone **2** used in place of **10.**

compromising the yield significantly (Table 3, entries 5 and 6). Interestingly, other ether solvents (glyme, diglyme, and dioxane) had a deleterious effect on the selectivity (Table 3, entries 7–9). Furthermore, activating the thione in the presence of the donor, or decreased activation times did not affect the reaction (Table 3, entries 10 and 11). Switching the donor:acceptor ratios from 2:1 to 1:2 also did not hinder the reaction, increasing the utility of these conditions (Table 3, entry 12). Without the use of **10**, the reaction proceeded in low yield and with decreased selectivity (Table 3, entry 13). Examining the use of ketone **2** in place of **10** led to a decrease in yield with both primary and secondary acceptors (Table 3, entries 14 and 15). Using **10** to promote the reaction between **5** and primary acceptor **6** under the optimal conditions led to a drop in yield compared to the reaction promoted by **2** (Table 3, entry 16). Finally, using the optimal solvent combination for activation with **2** (CH_2Cl_2/TCE) with **10** led to diminished yields with both primary and secondary acceptors (Table 3, entries 17 and 18).

With two sets of promoter systems in hand, we examined the scope of the reaction; the donors and acceptors used are shown in Figure 1. Along with donor **5** we also examined orthogonally protected L-olivose donors **11** and **12** and the L-rhodinose hemiacetal donor **13**. With orthogonally protected donors, this would ultimately permit the synthesis of larger molecules, while L-rhodinose is an important monosaccharide in various natural products.[1] The donors were glycosylated with primary alcohol acceptors **6** and **14** (Table 4), as well as with secondary alcohol acceptors **8, 15**, and **16** (Table 5). Based on our optimization studies, we chose to use promoter **2** for the primary acceptors, and **10** for the secondary acceptors.

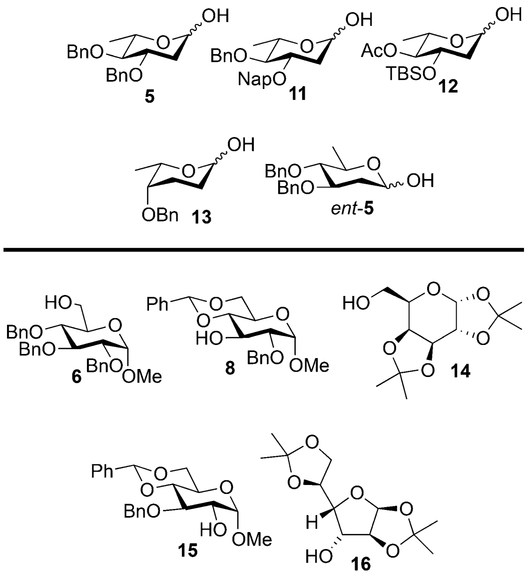
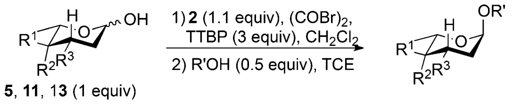


Figure 1. Donors and acceptors used for substrate screening.

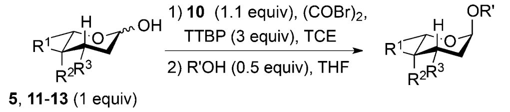
Table 4: Glycosylation of primary alcohols using **2** and oxalyl bromide.



Entry	Donor	R′OH	Time [h]	Product	Yield [%][a]	α:β[b]
1	**5**	**6**	2.5	**7**	74	10:1
2	**5**	**14**	1.5	**17**	69	10:1
3	**11**	**6**	1.2	**18**	67	11:1
4	**13**	**6**	2.75	**19**	71	6:1

[a] Yield of isolated product. [b] Selectivity determined by ^{1}H NMR spectroscopy.

Table 5: Glycosylation of secondary alcohols using **10** and oxalyl bromide.

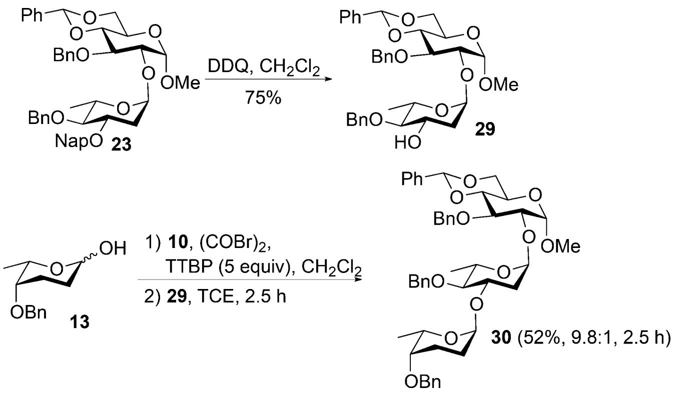


Entry	Donor	R′OH	Time [h]	Product	Yield [%][a]	α:β[b]
1	**5**	**8**	1.25	**9**	74	9:1
2	**5**	**15**	3.5	**20**	52	α-only
3	**5**	**16**	1.25	**21**	74	14:1
4	**11**	**8**	1.2	**22**	74	11:1
5	**11**	**15**	2.5	**23**	53	α-only
6	**12**	**8**	1.25	**24**	25	α-only
7[c]	**13**	**8**	2.5	**25**	65	17:1
8	**13**	**15**	4.0	**26**	67	α-only
9	**13**	**16**	2.0	**27**	67	9:1
10	*ent*-**5**	**8**	1.5	**28**	69	9:1

[a] Yield of isolated product. [b] Selectivity determined by ^{1}H NMR spectroscopy. [c] 5 equiv of TTBP used.

Both **6** and acid-sensitive **14** were glycosylated with the di-*O*-benzylated L-olivose donor **5** in good yield and with high selectivity (Table 4, entries 1 and 2). Orthogonally protected L-olivose donor **11** also afforded the glycosylated product with primary acceptor **6** in good yield and with high selectivity (Table 4, entry 3). Finally, L-rhodinose donor **13** also reacted in high yield, though with moderate α-selectivity (Table 4, entry 4).

Turning our attention to secondary acceptors, we found that the combination of oxalyl bromide and **10** was an extremely effective promoter for most substrates examined. With the di-*O*-benzylated L-olivose donor **5**, reaction with secondary alcohol acceptors **8**, **15**, and **16** afforded moderate to good yields and high selectivities (Table 5, entries 1–3). Of note, the glycosylation with hindered alcohol acceptor **15** was α-specific, presumably due to the lower nucleophilicity of this acceptor.[16] The use of orthogonally protected L-olivose donor **11** allowed for glycosylations with high selectivity and moderate to good yields (Table 5, entries 4 and 5), indicating that these conditions could be used for the synthesis of larger oligosaccharides. The low yield observed with donor **12** (Table 5, entry 6) could be accounted for by the disarming nature of the acetate protecting group, nonetheless the reaction was α-specific. More encouragingly, the rhodinose donor **13** reacted with high levels of α-selectivity with all of the secondary alcohol acceptors examined (Table 5, entries 7–9). Finally, the D-olivose donor *ent*-**5** reacted with **8** to afford the product with similar yield and selectivity as when **5** was used in the reaction, indicating that selectivity here is



Scheme 1. Synthesis of trisaccharide **30**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Nap = 2-naphthylmethyl.

independent of the configuration of the donor (Table 5, entry 10).

Lastly, we sought to examine a disaccharide acceptor in the reaction (Scheme 1). To this end, DDQ-mediated removal of the Nap ether group in **23** afforded disaccharide acceptor **29** in 75 % yield. Its reaction with L-rhodinose donor **13** using oxalyl bromide and **10** as the promoter system afforded trisaccharide **30** in 52 % yield with 9.8:1 α:β selectivity.

We next turned to NMR spectroscopy to identify any reaction intermediates. Initial attempts at following the reaction directly by conducting them in deuterated solvents only resulted (according to NMR spectra) in complex mixtures, however, we did find that we could isolate and observe the intermediates using vacuum-line techniques.[6p] The NMR spectra from both reactions appeared to show formation of the same intermediate.[17] The intensity of the resonances from the cyclopropenone did not correlate well with the intensity of the resonances from the donor, leading us to suspect that the intermediate may be a glycosyl bromide. This was further supported by the presence of an anomeric proton resonance at $\delta = 6.25$ ppm in both reactions. To confirm the identity of the species, we prepared the bromide independently according to the method of Thiem and Meyer.[18] Although we observed some decomposition, the major component of this reaction correlated well with our samples.[17,19]

In summary, we have developed two new promoter systems for room-temperature α-selective glycosylation reactions with 2-deoxy-sugar donors. By using either cyclopropenone **2** or cyclopropene-1-thione **10**, we were able to provide a means to glycosylate both primary and secondary alcohols in good yield and selectivity. These conditions tolerate a number of functional groups, including fairly labile 2,3,6-trideoxy-sugar linkages. Furthermore, orthogonally protected donors can be used in the reaction, highlighting its potential utility in oligosaccharide synthesis.

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