Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-02-2020-000373.R2
Article Type:	Communication
Date Submitted by the Author:	10-Mar-2020
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COMMUNICATION

1,2-*cis*-Selective Glucosylation Enabled by Halogenated Benzyl Protecting Groups

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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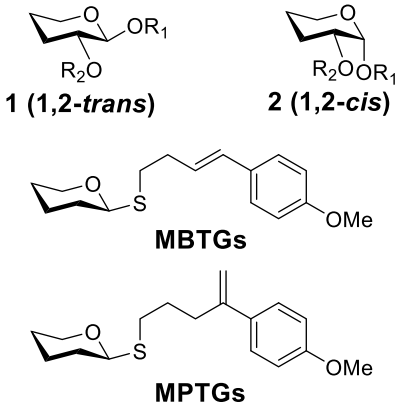
We report on our initial results from a systematic effort to implement electron-withdrawing protecting groups and Lewis basic solvents/additives as an approach to 1,2-*cis*(α)–selective *O*-glucosylation. 1,2-*cis*-selective *O*-glucosylations are reported with thioglucosides and glucosyl trichloroacetimidates and a range of acceptors. A correlation between electron-withdrawing effects and 1,2-*cis* selectivity has been established. This phenomenon may prove to be broadly applicable in the area of chemical *O*-glycosylation.

O-Glycosylation has been a relevant topic of research in organic synthesis for over a century, and investigators have made great strides to develop efficient, high-yielding *O*-glycosylations whether by chemical or enzymatic means.[1] While formation of 1,2-*trans* glycosidic linkages (**1**, Figure 1) is relatively straightforward due to implementation of participating groups at 2-position oxygen or nitrogen, the efficient and highly selective formation of 1,2-*cis* glycosidic linkages (**2**, Figure 1) is a topic of ongoing investigation.[2] A number of creative solutions to this problem have been reported, and 1,2-*cis*-*O*-glycosylation has proven to be an important vehicle for discovery in carbohydrate chemistry.[2a] Nevetheless, a generalized approach to 1,2-*cis* selectivity remains elusive. An approach that requires a minimal number of extra synthetic steps in the synthesis of glycosyl donors as well as in the subsequent manipulation of glycosidic products and their protecting groups is especially desirable.

We have recently reported the development of 4-(4-methoxyphenyl)-3-butenylthioglycosides[3a] and 4-(4-methoxyphenyl)-4-pentenylthioglycosides[3b] (MBTGs and MPTGs, respectively, Figure 1) as stable donors for glycosylation that are nevertheless activated readily with catalytic trifluoromethanesulfonic acid (HOTf) at room temperature. MBTGs/MPTGs represent rare examples of alkylthioglycosides that are activated with catalytic acid. Acknowledging that adaptation of any new *O*-glycosylation donor to 1,2-*cis*-selective *O*-glycosylation protocols is an important test in establishing its appeal to the synthetic community, we set out to develop a 1,2-*cis*-selective *O*-glycosylation using MBTGs and MPTGs. In the course of our studies, we have identified a strategy toward 1,2-*cis* selectivity that may prove broadly applicable. Our initial results are reported herein.

Figure 1: *O*-Glycosidic Linkage Stereochemistry, MBTGs, and MPTGs



We reasoned that protonation of MBTGs/MPTGs (as exemplified with MPTGs **3**, Scheme 1) will result in glycosylsulfonium intermediates **5**. Backside displacement of sulfide **6** from **5** could result in stereospecific formation of 1,2-*cis*-*O*-glycosides **9**.[4] Competing formation of oxocarbenium ion **7** would lead to unselective formation of both 1,2-*cis* and 1,2-*trans* *O*-glycosides by S_N1 mechanism. In instances in which formation of **7** is facile, addition of excess Lewis-basic additives or Lewis-basic solvents (LB:) could ensure the formation of adducts **8** with equatorially disposed anomeric leaving groups. In particular, additives/solvents such as tetraalkylammonium bromides,[5a] *N,N*-dialkylamides,[5b,c] triphenylphosphine oxide,[5c] and dialkyl ethers[1a,5d] promote 1,2-*cis* selectivity through **8**-like adducts generated from hexopyranosyl donors. A critically

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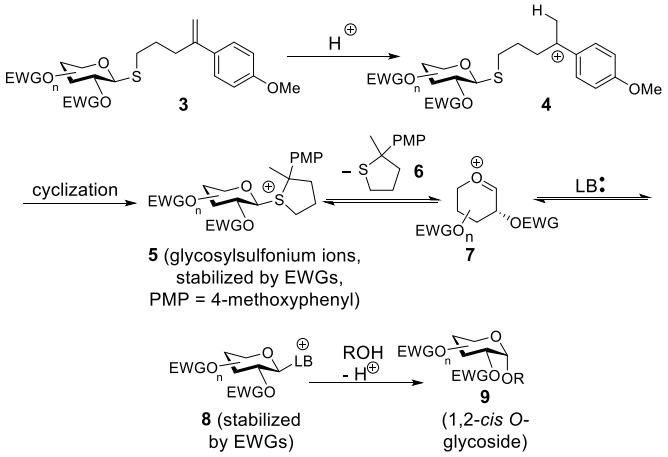
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

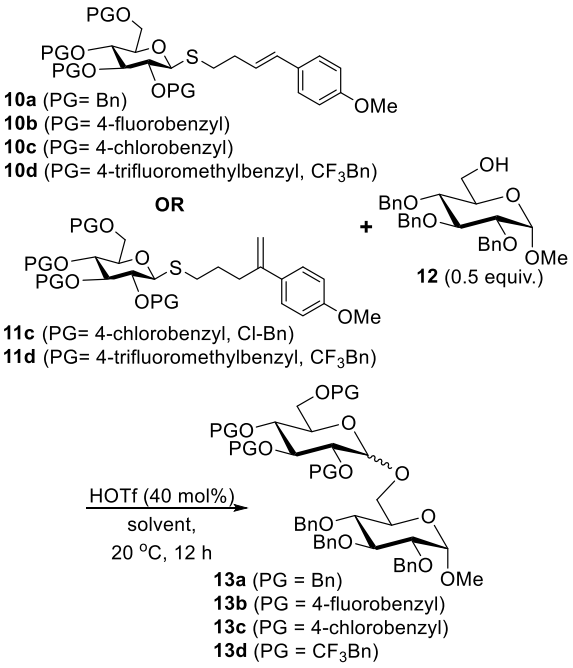
important aspect of this strategy involves destabilizing **7** and stabilizing **5/8**. Therefore, implementation of electron-withdrawing and non-participating protecting groups (symbolized as "EWG" in Scheme 1) should shift equilibria toward **5/8**. Halogenated benzyl groups were particularly appealing to us at the outset of these studies. Indeed, protection with halobenzyl groups has been used to promote 1,2-*cis* *O*-glycosylation by Boltje,[4c] Zhang,[6a] and Hung[6b] when more electron-rich benzyl groups failed to promote high selectivity. Others have exploited this form of substitution for stabilization of fucosidic linkages and orthogonality in multistep synthesis.[6c,d]

Scheme 1: Synergy of Electron-Withdrawing Groups and Lewis Bases in the Generation of 1,2-*cis* *O*-Glycosides



At the outset of this project, we synthesized a series of MBTGs and MPTGs (**10-11**, Table 1) derived from D-glucose and protected at the 2, 3, 4, and 6-positions with benzyl (Bn), 4-fluorobenzyl, 4-chlorobenzyl, and 4-trifluoromethylbenzyl (CF_3Bn) in preparation for studies on 1,2-*cis*-selectivity. These groups were chosen because of synthetic practicability: the benzyl halide precursors are commercially available in all cases and can be installed using Williamson etherification. Meanwhile, difficulties were incurred with 4-nitrobenzyl protection while installation of 4-cyanobenzyl requires an extra synthetic step.[4c] Further, we chose C-6 hydroxyl-bearing α-methyl-2,3,4-tri-*O*-benzylglucoside (**12**) as the acceptor for initial method development due to its history of poor 1,2-*cis* selectivity.[2] The results of our initial studies are depicted in Table 1. Subjection of benzyl-protected MBTG substrate **10a** to previously reported standard conditions (10 mol. % HOTf, CH_2Cl_2, 20 °C)[3] resulted in 84% yield of disaccharide **13a** and a poor selectivity for 1,2-*cis* (α) to 1,2-*trans* (β) glycosides (1.8:1 α/β, entry 1). We next repeated the conditions of entry 1 with a sundry of additives predicted to behave as "LB:" (see **8**, Scheme 1) including thiophene and ethyl phenyl sulfide,[4a] various dialkyl sulfides, DMF,[5b,c] and triphenylphosphine oxide (TPPO).[5c] In the case of thiophene and sulfides, little if any enhancement of 1,2-*cis* selectivity was noted (data not shown). In the case of DMF and TPPO, reactions were sluggish to the point of being impractical. This was likely due to the Bronsted basicity of these additives and their attendant buffering effect on HOTf. This may not prove to be a problem with less stable glycosyl *O*-trichloroacetimidates.[5c]

Table 1: Protecting Group Screen/Optimization[a]



entry	donor	solvent (ml)	yield %	α:β[c]
1[b]	**10a**	DCM (1 ml)	84%	1.8:1
2	**10a**	1,4-dioxane (1 ml)	69%	3.8:1
3	**10b**	1,4-dioxane (1 ml)	83%	4.9:1
4	**10c**	1,4-dioxane (1 ml)	75%	6.0:1
5	**10d**	1,4-dioxane (1 ml)	88%	9.2:1
6	**11c**	1,4-dioxane (1 ml)	81%	6.7:1
7	**11d**	1,4-dioxane (1 ml)	87%	6.5:1
8[b]	**10d**	DCM (1 ml)	90%	2.7:1
9[b]	**11d**	DCM (1 ml)	97%	2.2:1
10	**11d**	1,4-dioxane (2.5 ml)	77%	8.7:1
11	**10d**	1,4-dioxane (5 ml)	53%	14.5:1
12	**11d**	1,4-dioxane (5 ml)	78%	13.0:1
13	**11d**	DCM (5 ml)	43%	5.6:1
14[d]	**11d**	1,4-dioxane (5 ml)	71%	1:1

[a]Unless otherwise stated, 0.15 mmol of donors **10**/**11** and 0.075 mmol of acceptor **12** were implemented along with 40 mol. % HOTf (relative to donor). Reactions were stirred magnetically at 20 °C for 12 h. [b]10 mol. % HOTf was used. [c]Anomeric ratios were estimated

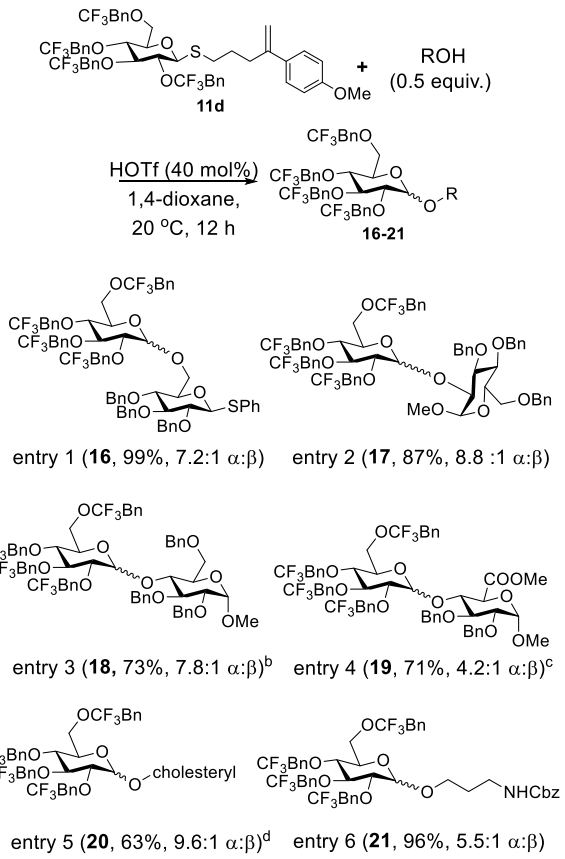
from purified mixtures of anomers by integration of key signals in the ^{1}H NMR spectrum. [d]Tf_2NH was used as acid.

Switching solvent from CH_2Cl_2 to 1,4-dioxane (entry 2) and implementation of 40 mol. % HOTf (reactions were sluggish with lower loadings) resulted in 69% yield of a nearly 4:1 mixture of **13a** favoring 1,2-*cis* isomer. Use of ethereal solvents, especially 1,4-dioxane,[5d] is known to promote 1,2-*cis* selectivity possibly through the formation of adducts like **8** (Scheme 1). In effort to further improve these results, we implemented MBTGs **10b**, **10c**, and **10d** wherein Bn is replaced with 4-fluorobenzyl, 4-chlorobenzyl, and 4-trifluoromethylbenzyl (CF_3Bn) as seen in entries 3,4, and 5, respectively. We saw steadily improving selectivity up to ~9:1 in favor of 1,2-*cis* that roughly follows the increasingly positive Hammett σ values for H, F, Cl, and CF_3. We attribute this to steadily increasing electron-withdrawing effects. We were encouraged by this trend, however, the historically low reactivity of MBTGs toward the most deactivated acceptors[3a,b] prompted us to also explore MPTGs **11c** and **11d** which we predicted to be more reactive toward the most deactivated acceptors. Entries 6 and 7 depict 1,2-*cis*-selectivity with the implementation of **11c** and **11d**. Further, to rule out the possibility that 1,2-*cis* selectivity with the halobenzyl groups of **10**/**11** is not solvent dependent, we performed glycosylation of **12** with CF_3Bn-protected **10d** and **11d** using CH_2Cl_2 as solvent and observed dramatically decreased selectivities that were similar to those of entry 1 (entries 8 and 9).

We were intrigued by the potential roles of additional parameters including temperature, concentration, and acid. We conducted a series of experiments at 0 °C and -20 °C (data not shown). Because of the high melting point of 1,4-dioxane (11.8 °C), we implemented solvent mixtures with Et_2O. Nevertheless, glycosylation proceeded at prohibitively low rates under these conditions. Dilution of reaction mixtures, to contrast, proved fruitful. Lowering donor concentration from ~0.15 M to ~0.06 M by adding 2.5 mL instead of 1 mL solvent (entry 10) using donor **11d** resulted in an increased selectivity of ~9:1 in favor of 1,2-*cis* (see entry 7 for comparison). Further decrease of donor concentration to ~0.03 M (entries 11, 12) by adding 5 mL solvent using donors **10d** and **11d** (respectively) resulted in further increases in selectivity (to ~ 13:1 (*cis*/*trans*) in the case of donor **11d**). Once again (as with entries 8/9), switching to CH_2Cl_2 at this higher dilution (~0.03 M) resulted in dramatic decreases both in yield and selectivity (entry 13) compared to the entry 12 results. Subsequent experiments performed at higher dilution resulted in similar selectivity to that of entries 11 and 12 with dramatically decreased yield of product **13d** (data not shown). Finally, substituting HOTf (pKa = -14.7) with similarly acidic trifluoromethanesulfonimide (Tf_2NH, pKa = -12.3) as shown in entry 14 results in dramatically reduced 1,2-*cis* selectivity suggesting that counteranions play a non-innocent role in these glycosylations. There is a wealth of evidence that glycosyl triflates are generated in the presence of glycosyl oxocarbenium ions[7] whereas at least one report suggests that trifluoromethanesulfonimide anion does not promote the formation of glycosyl trifluoromethanesulfonimides.[8] The role of these phenomena in the reported glycosylations is not clear. The transient formation of glycosyl triflate analogs of **8** (Scheme 1) as an explanation for high 1,2-*cis* selectivity cannot be ruled out at this time.

We conducted a short substrate scope study (Scheme 2) screening a range of acceptor reactivities. We chose donor **11d** due to its predicted reactivity toward less reactive acceptors than **12** in combination with conditions from entry 12 of Table 1. Reaction of the 6-position of β-phenylthioglucoside with **11d** provided a satisfactory 7.2:1 1,2-*cis*/1,2-*trans* ratio (entry 1) while similar ratios of 8.8:1 and 7.8:1 were obtained with the 2- and 4-positions of tribenzylated methyl glucosides (entries 2 and 3). Reaction of **11d** with the 4-position of methyl glucuronate afforded a disappointing ratio of 4.2:1 in favor of 1,2-*cis*. The counterintuitive decreasing selectivity with decreasing acceptor reactivity compared to acceptor **12** as in entries 2-4 may reflect competition between more associative (S_N2-like processes as in **8**→**9**, Scheme 1) and dissociative (S_N1) processes in which the less reactive acceptors undergo a higher proportion of the latter. Reaction with cholesterol (entry 5) resulted in comparable selectivity to that seen in entries 1-3 whereas the highly reactive acceptor *N*-carbobenzyloxy-3-aminopropan-1-ol (entry 6) provided lower selectivity.

Scheme 2: Substrate Scope[a]

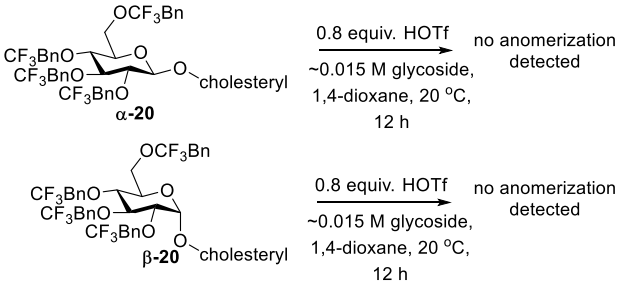


[a]Unless otherwise stated, 0.15 mmol of donor **11d** and 0.075 mmol of acceptors were implemented along with 40 mol. % HOTf (relative to donor) and 5 mL 1,4-dioxane. Reactions were

stirred magnetically at 20 °C for 12 h. [b]Donor:acceptor ratio was 2.36:1. [c]Donor:acceptor ratio was 2.17:1. [d]Due to purification challenges, two chromatographic purifications were performed. Anomeric ratios were determined after the first purification, and yields were determined after the second purification.

At this stage, we were interested in determining what, if any, anomerization might be occurring after initial glycosylation considering the relatively high concentration of HOTf at room temperature (Scheme 3). Therefore, we conducted two experiments with α- and β-**20**. We chose these cholesteryl glucosides due to the relatively electron-rich aglycone (increasing the odds of ionization) and ease of analysis with ^{1}H NMR. In both cases, we were not able to detect anomerization of either stereoisomer after stirring for 12 h in the presence of 0.8 equiv. HOTf. We conclude that the stereoselectivities reported herein are the result of kinetic control.

Scheme 3: Probing for Anomerization



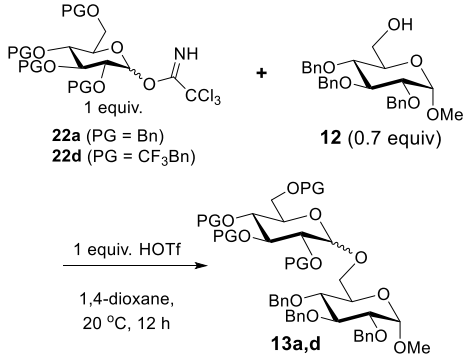
We were interested in probing the generality of the observed protecting group phenomenon. For this purpose, we synthesized glucosyl trichloroacetimidates protected with Bn and CF_3Bn (22a and 22d, respectively) and subjected them to conditions similar to the entry 10 and 12 conditions from Table 1 (see Table 2). A short investigation indicated that donor/acceptor ratios of 1:0.7 and use of 1 equiv. of HOTf (relative to donor) provided the best yields of products **13** (data not shown). Strikingly, we were able to reproduce both the dilution effect (compare entries 2 and 4 of Table 2 with entries 10 and 12 of Table 1) using trichloroacetimidate **22d**. Further, stereoselectivities increased dramatically when replacing Bn with CF_3Bn (compare entries 1/3 with 2/4 in Table 2). These observations suggest that use of electron-withdrawing protecting groups and Lewis-basic additives/solvents may provide a general solution to 1,2-*cis* selectivity in *O*-glycosylation.

Finally, we demonstrate the facile removal of Bn and CF_3Bn groups from substrate **13d** using catalytic hydrogenolysis (Scheme 4).[9]

Conclusions

Herein, we have reported on our initial results from a research program designed to systematically study the synergy of electron-withdrawing protecting groups with Lewis basic additives or solvents in the generation of 1,2-*cis* glycosidic linkages. While observed stereoselectivites with optimized procedures range from modest (*e.g.* 4.2:1) to high (*e.g.* 13:1) in favor of 1,2-*cis* glycosides, there is a correlation between the electron-withdrawing effects of the benzylic protecting groups and 1,2-*cis* selectivity in addition to moderate to high yields at 20 °C. This phenomenon has proven applicable to MBTGs and MPTGs previously developed in our group as well as the more traditional glucosyl trichloroacetimidates. Further investigations on electron-withdrawing benzylic and other non-participating protecting groups and additional Lewis-basic additives are underway in our lab and will be reported in due course. In particular, we will strive to develop methods that require less acid catalyst while exploring and perhaps even developing electron-withdrawing protecting groups that are installed with a level of ease and low cost that is similar to that of benzyl groups.

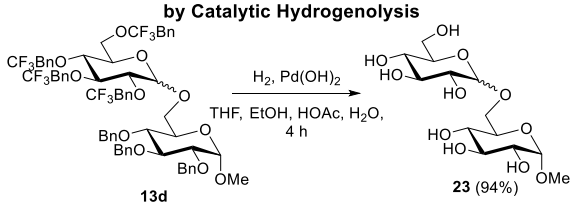
Table 2: Studies with Trichloroacetimidates[a]



entry	donor	solvent volume	yield %	α:β[b]
1	**22a**	2.5 ml	76%	5.2: 1
2	**22d**	2.5 ml	83%	10.0:1
3	**22a**	5 ml	94%	5.0:1
4	**22d**	5 ml	78%	14.0:1

[a]0.15 mmol of donors **22** and 0.105 mmol of acceptor **12** were implemented along with 1 equiv. HOTf (relative to donor) and either 2.5 or 5 mL 1,4-dioxane. Reactions were magnetically stirred at 20 °C for 12 h. [b]Anomeric ratios were estimated from purified mixtures of anomers by integration of key signals in the ^{1}H NMR spectrum.

Scheme 4: Removal of Bn and CF_3Bn by Catalytic Hydrogenolysis



Conflicts of interest

There are no conflicts to declare.

Acknowledgments

This research was supported by the U.S. National Science Foundation (CHE-1665208). We thank Ms. Connie David for assistance with high-resolution mass spec., and we thank Dr. Thomas Weldeghiorghis for assistance with NMR.

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