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Achiral 2-Hydroxy Protecting Group for the Stereocontrolled Synthesis of 1,2-*cis*-α-Glycosides by Six-Ring Neighboring Group Participation

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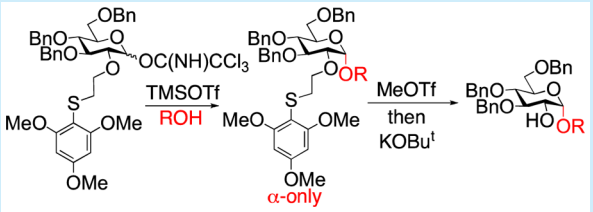
Supporting Information

ABSTRACT: Glycosylation of a fully armed donor bearing a 2-*O*-(trimethoxybenzenethiol) ethyl ether protecting group is completely α-selective with a range of carbohydrate alcohol acceptors. Low-temperature NMR studies confirm the intermediacy of cyclic sulfonium ion intermediates arising from six-membered β-sulfonium ring neighboring group participation. Selective protecting group removal is achieved in high yield in a single operation by S-methylation and base-induced β-elimination.



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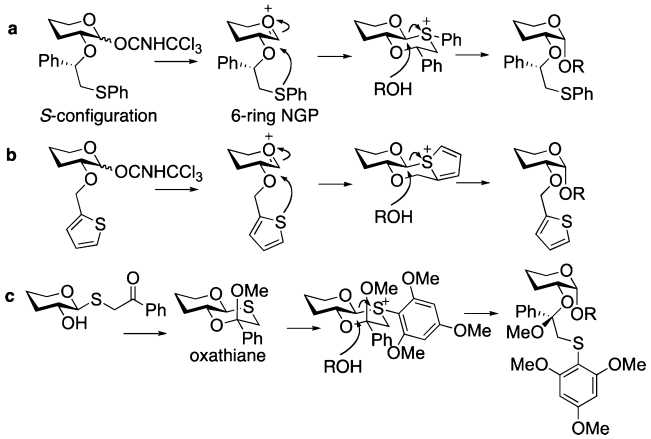
Despite significant effort by different generations of synthetic chemists, a universal solution has yet to be found for control of anomeric stereochemistry during glycosylation. The use of five-membered ring neighboring group participation (NGP) of 2-*O*-acyl-protected glycosyl donors is long established and, despite occasional difficulties, generally allows the stereocontrolled formation of 1,2-*trans* glycosidic linkages. However, the synthesis of 1,2-*cis* glycosidic linkages is considerably more difficult[1]

The ingenuity of different researchers has provided multiple solutions to the different facets of this general problem; for example, the numerous tailor-made solutions for the synthesis of α-glucosides[2] or the "notorious" β-mannoside linkage.[3] Intramolecular glycosylation processes[4] offer an attractive and potentially "general" solution to 1,2-*cis* glycoside formation. However, their extra inherent steps, via the temporary linking of donor and acceptor, have made these approaches less attractive than more straightforward but less stereoselective intermolecular glycosylation reactions. However, the use of new types of NGP,[5] and in particular those involving six-membered ring intermediates, could provide a general solution applicable to the synthesis of all α-1,2-*cis* glycosidic linkages (e.g., α-*gluco*, α-*galacto*, etc.). Boons and co-workers have been pioneers in the field[6] and since its inception have described significant advances, building upon the use of chiral auxiliaries at the 2-position of donors that operate via six-ring NGP to control the diastereoselectivity of glycosylation (Scheme 1a). Key to the high α-selectivity of these glycosylations is the configuration of the stereogenic center of the auxiliary; the Ph group occupies an equatorial position in the *trans*-decalin intermediate.

Seeking to build upon these important disclosures, we undertook studies that sought to combine six-ring NGP with the participating effect of thiophene[7] with the aim of discovering a simpler achiral 2-OH protecting group that could give similar high levels of stereocontrol (Scheme 1b).

Scheme 1. α-1,2-*cis*-Glycosylation via Cyclic Sulfonium Ions[a]



[a](a) Glycosylation via 6-ring NGP of an OH-2 (*S*)-auxiliary; (b) via 6-ring NGP of a 2-O-(thiophene-2-yl) methyl ether; (c) via a preformed cyclic β-sulfonium ion derived from an oxathiane.

Although reasonably good stereoselectivity was observed, the approach was still less selective than the Boons methodology. In the meantime, Turnbull[8] adopted a different approach (Scheme 1c), preferring to preform β-configured cyclic oxathiane glycosyl donors, which, following a two-step activation process involving oxidation and electrophilic substitution, gave high levels of α-selectivity. Subsequently, Boons also adopted this approach and demonstrated its compatibility with a wide range of protecting groups and its application with a variety of glycosyl acceptors.[9]

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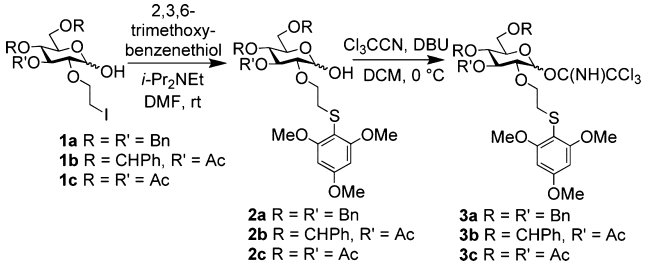
Although the Boons and Turnbull approaches give high levels of α-selectivity, the synthesis of the required donors (bicyclic or containing a chiral auxiliary), together with the double-activation procedure required for the oxathiane-derived donors, make them rather protracted. It was therefore thought worthwhile to study the potential use of achiral-substituted ethyl ethers at the 2-position of glycosyl donors. Preliminary investigations revealed that ethers containing iodine or selenium did not result in either increased levels of α-selectivity or effective 6-ring neighboring group participation as evidenced by low-temperature NMR studies.[10] In spite of these disappointments, we sought to augment the participating effect of 2-*O*-ethyl ethers and turned our attention to the use of more electron-rich participating groups. Given the intermediacy of the trimethoxy-substituted thiophenonium ion in the Turnbull approach, it was decided to investigate whether highly electron-rich aromatic thiols would prove more effective at six-membered ring NGP. A series of glycosyl donors **3a**−**c** was synthesized (Scheme 2) starting from the previously reported

Scheme 2. Synthesis of Glycosyl Donors[a]



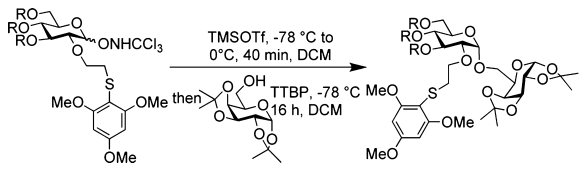
[a]Reagents and conditions: (a) 2,3,6-trimethoxybenzenethiol (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), DMF, rt, 16 h; **1b**, 71%; **2b**, 87%; **3b**, 73%; (b) Cl_3CCN (10 equiv), DBU (0.4 equiv), DCM, 0 °C; **1c**, 7 h, 93%; **2c**, 6 h, 92%; **3c**, 6 h, 89%.

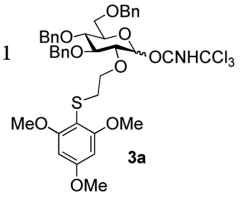
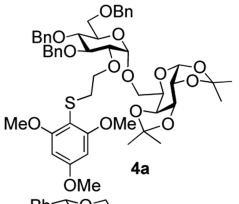
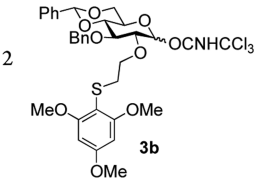
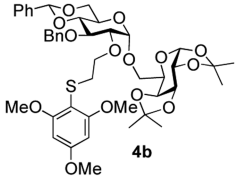
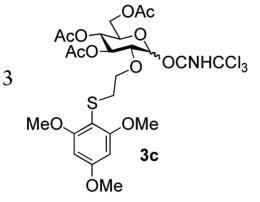
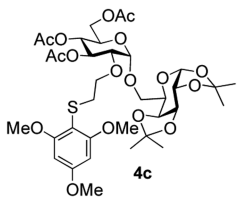
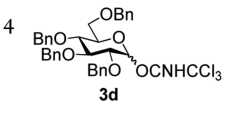
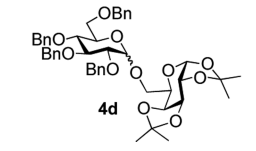
iodides **1a**−**c**[10] by treatment with trimethoxybenzenethiol in the presence of Hunig's base and conversion to the corresponding trichloroacetimidates. Three different protecting group regimes were selected in order to investigate any effect of protecting group pattern on the stereochemical outcome of glycosylation.

Donors **3a**−**c** were then glycosylated using diacetone galactose as acceptor (Table 1). The glycosylation conditions used were based on "Protocol B" as reported by Boons. Herein, the donor is treated with a stoichiometric equivalent of TMSOTf at −78 °C. The mixture is allowed to warm to 0 °C over a period of 40 min before it is recooled to −78 °C. The glycosyl acceptor and the hindered base tri-*tert*-butylpyrimidine (TTBP) are then added, and the mixture is stirred and warmed to rt overnight. Under these conditions, the reaction of donor **3a** was completely stereoselective and disaccharide **4a** was isolated as only the α-anomer. However, the partially disarmed donors **3b** and **3c** were less selective. In both cases, the disaccharide was produced as an anomeric mixture in favor of the desired α-anomer (α:β, 5:1). As control, a glycosylation reaction of the perbenzylated imidate **3d** was undertaken; this produced disaccharide **4d** as predominantly the β-anomer (α:β, 1:2.5).

That the partially disarmed **3b** and fully disarmed **3c** donors were less stereoselective than the fully armed donor **3a** is in contrast to a previous report by Boons.[6d] In that case, rationalization of the higher stereoselectivity achieved with

Table 1. Glycosylation Reactions of Donors 3a−d with Diacetone Galactose



entry	donor	product	yield /%	α:β
1			69	α only
2			66	5:1
3			63	5:1
4			64	1:2.5

disarmed donors was proposed to be due to the lower stability of the corresponding glycosyl cation, which thereby limited nonstereoselective reactions via acyclic species. However, glycosyl cations are expected to have no appreciable lifetime in DCM at −78 °C, and under the activation conditions applied here, acyclic species are more likely to be glycosyl triflates.

Low-temperature NMR studies were undertaken to investigate the identity of species involved in glycosylation and whether NGP occurred upon activation of donors **3a** and **3b** (Figure 1 and Supporting Information). Study of the activation of fully armed donor **3a** by ^{1}H NMR (400 MHz) at −78 °C in CD_2Cl_2 provided significant evidence for the formation of a β-configured six-membered cyclic intermediate **3a**′ by NGP. In the ^{1}H NMR spectrum (Figure 1) of **3a**, a significant upfield shift of H-1 (δ 6.50 ppm, $J_{1,2}$ 3.2 Hz to δ 5.56, $J_{1,2}$ 10 Hz) was observed upon activation; the large vicinal coupling constant implied an equatorial orientation of the anomeric substituent in the intermediate. Additionally, the two H-8 protons, which had very similar chemical shifts in **3a** (δ 2.75 ppm, m), were split into two distinct peaks upon activation (δ 3.64 and δ 4.69 ppm), implying that one adopted an axial (H-8_{ax}) and one an equatorial orientation (H-8_{eq}) in the cyclic intermediate. Furthermore, after activation the HMBC spectrum revealed correlation between C-1 and one of the H8 protons (δ 3.64 ppm, circled in Figure 1). No oxacarbenium ion, anomeric triflate, or α-sulfonium ions were detected. In contrast, low-

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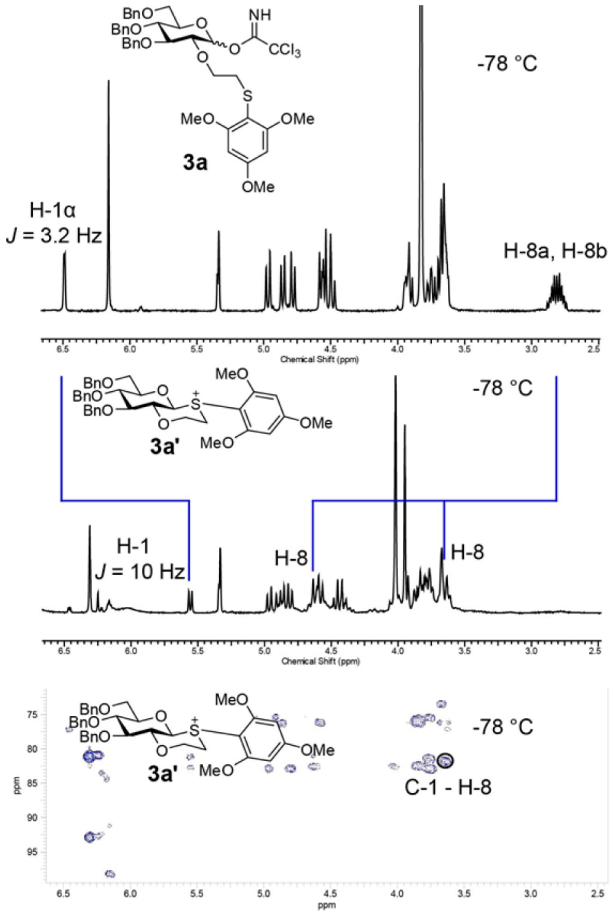


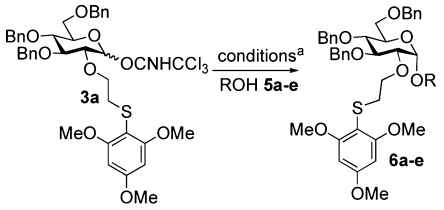
Figure 1. Low-temperature 400 MHz NMR study of donor **3a** at −78 °C in CD_2Cl_2.

temperature NMR studies of **3b** (Supporting Information, Figure S5) did not provide evidence for the formation of a cyclic intermediate; in this case, the chemical shift of H-1 (δ 6.50 ppm, $J_{1,2}$ 5.2 Hz) and the absence of any correlations between H-1/C-8 and C-1/H-8 in the HMBC spectrum pointed toward the intermediacy of an α-configured anomeric triflate. The difference in behavior between **3a** and **3b** is therefore probably due to the greater stability of the anomeric triflate derived in the latter case: it is known that α-anomeric triflates are more stable in the presence of a 4,6-benzylidene protecting group.[11]

Low-temperature NMR studies must be analyzed with caution, as there are numerous examples of reactions proceeding via higher energy intermediates that are not seen by NMR. Indeed, the formation of an α-anomeric triflate in the case of **3b** may at first appear incompatible with the α-selectivity of these reactions. However, as Crich[12] has pointed out in similar *gluco* systems, the reaction almost certainly proceeds via an S_N2 displacement of a β-triflate intermediate not seen by NMR. Likewise, the fact that a β-configured cyclic intermediate is observed upon activation does not automatically mean that this is the reactive species through which glycosylation process proceeds.[10] However, the complete α-selectivity observed for donor **3a** does suggest that this is case here.

The reaction scope donor was investigated by glycosylation of donor **3a** with a variety of glycosyl acceptors encompassing primary and secondary carbohydrate alcohols (Table 2). In all

Table 2. Glycosylation Reactions of Donor 3a



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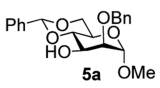
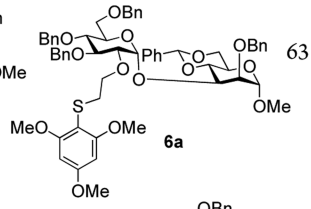
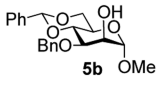
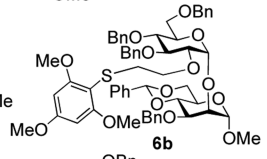
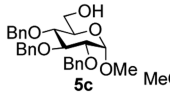
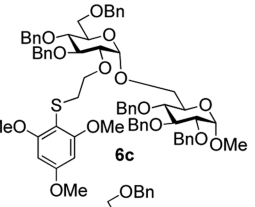
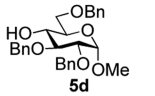
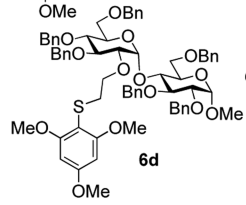
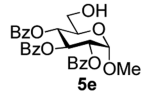
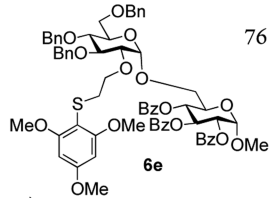
1			63	α only
2			65	α only
3			68	α only
4			61	α only
5			76	α only

[a]Conditions: TMSOTf (1.0 equiv), CH_2Cl_2, −78 to 0 °C, 40 min then add ROH (1.2 equiv), TTBP (2.0 equiv), −78 °C to rt, 16 h.

cases, only the α-disaccharide product was observed. A necessary requirement for a useful stereodirecting OH-2 protecting group is that it also may be removed selectively and in high yield. A variety of conditions were investigated for selective cleavage of the 2-[(trimethoxyphenyl)thio]ethyl ether, including oxidation/sulfoxide elimination and different acid-catalyzed hydrolysis reactions. None proved satisfactory, so an alternative approach, involving methylation of sulfur by treatment with MeOTf and then treatment of the sulfonium salt with potassium *tert*-butoxide, was developed. An optimal one-pot procedure was arrived at in which the base was simply added to the reaction mixture following the methylation. This simple procedure resulted in selective single-step high-yielding protecting group cleavage (Scheme 3). That the protecting group cleavage occurred via a β-elimination pathway of the sulfur ylide produced upon deprotonation of the methylsulfo-

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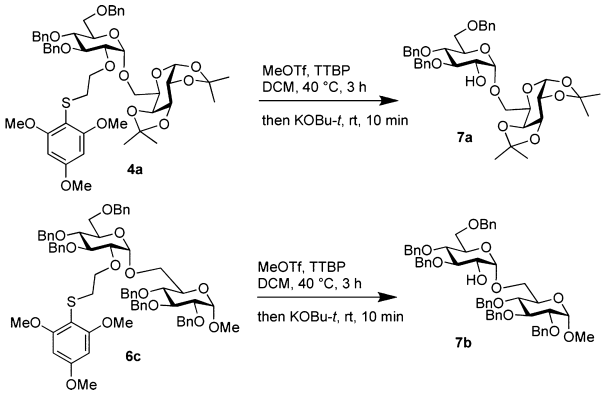
Scheme 3. Deprotection Reactions[a]



[a]Reagents and conditions: MeOTf (1.5 equiv), TTBP (2.0 equiv), DCM, 40 °C, 3 h, then addition of KOBu-*t* (2.0 equiv), rt, 10 min; **7a**, 88%; **7b**, 86%.

nium ion, analogously to a similar amino acid protecting group,[13] was demonstrated by mass spectrometric analysis of the crude reaction mixture (Supporting Information, Figure S10). The simple one-pot procedure yielded alcohols **7a** and **7b** in high yield (Scheme 3).

In summary, a novel achiral participating protecting group has been developed that, when present at postion 2, can promote completely selective α-glycosylation of fully armed glucosyl donors with a range of carbohydrate acceptors. High-yielding selective protecting group removal may be effected in a single operation. This novel participating protecting group is expected to be useful more generally for the synthesis of oligosaccharides containing α-1,2 *cis* glycosidic linkages.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02226.

Full experimental details, including full compound characterization and spectra and low-temperature NMR studies (PDF)

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Notes

The authors declare no competing financial interest.

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