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Pre-activation based stereoselective glycosylations: Stereochemical control by additives and solvent

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Stereochemical control is an important issue in carbohydrate synthesis. Glycosyl donors with participating acyl protective groups on 2-*O* have been shown to give 1,2-*trans* glycosides reliably under the pre-activation based reaction condition. In this work, the effects of additives and reaction solvents on stereoselectivity were examined using donors without participating protective groups on 2-*O*. While several triflate salt additives did not have major effects, the amount of AgOTf was found to significantly impact the reaction outcome. Excess AgOTf led to lower stereochemical control presumably due to its coordination with the glycosyl triflate intermediate and a more S_N1 like reaction pathway. In contrast, the stereoselectivity could be directed by reaction solvents, with diethyl ether favoring the formation of α glycosides and dichloromethane leading to β isomers. The trend of stereochemical dependence on reaction solvent was applicable to a variety of building blocks including the selective formation of β-mannosides.

stereoselectivity, pre-activation based glycosylation, additives, solvent effects

1 Introduction

During the past two decades, there has been tremendous growth in the development of novel glycosylation methodologies and reagents, resulting in our much improved abilities to form the glycosidic linkages [1, 2]. However, reliable stereochemical control remains as a major issue in carbohydrate synthesis. The glycosidic bond can be linked either in 1,2-*cis* or 1,2-*trans* manner. Synthesis of oligosaccharides containing 1,2-*trans* glycosidic linkages is typically accomplished by the installation of an acyl protective group on 2-*O* position of the glycosyl donor [1]. Upon donor activation, neighboring group participation of the 2-*O* acyl group will direct the formation of 1,2-*trans* linkages with a high degree of stereo-control. By contrast, efficient formation of 1,2-*cis* glycosidic linkages is a more difficult task [3]. Several innovative methods have been developed, which include benzylidene protected mannosyl donor [4, 5] and intramolecular aglycon delivery [6, 7] for β-mannoside formation, thioether chiral auxiliary assisted formation of disarmed α-glucosides and galactosides [8]. Despite the successes in these special cases, in general, anomeric controls still mostly rely on the anomeric effect and/or steric hindrance, which can vary depending on structures of the coupling partners and often demand individual analysis [4, 9–14].

Recently, we have developed a pre-activation based one-pot glycosylation method using thioglycosides, where multiple sequential glycosylation reactions can be performed without intermediate purification [15]. This is a powerful strategy for glyco-assembly, which has been applied to the constructions of complex oligosaccharides containing both 1,2-*cis* and 1,2-*trans* linkages [16, 17]. Using donors bearing participating acyl groups on 2-*O* position, 1,2-*trans* glycoside products can be formed reliably [16, 17]. On the other hand, the formation of 1,2-*cis* linkages has not been systematically evaluated. Herein, we report our results on

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the exploration of various factors impacting stereo-selectivity using donors without participating neighboring groups on 2-*O* position.

2 Experimental

All reactions were carried out under nitrogen with anhydrous solvents in flame-dried glassware. All glycosylation reactions were performed in the presence of molecular sieves, which were flame dried right before the reaction under high vacuum. Glycosylation solvents were dried using a solvent purification system and used directly without further drying. Chemicals used were of reagent grade as supplied except where noted. Analytical thin-layer chromatography was performed using silica gel 60 F_{254} glass plate. Compound spots were visualized by UV light (254 nm) and by staining with a yellow solution containing $Ce(NH_4)_2(NO_3)_6$ (0.5 g) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (24.0 g) in 6% H_2SO_4 (500 mL). Flash Column chromatography was performed on silica gel 60 (230–400 Mesh). NMR spectra were referenced using Me_4Si (0 ppm), residual $CHCl_3$ (δ ^{1}H NMR 7.24 ppm, ^{13}C NMR 77.0 ppm). Peak and coupling constant assignments are based on ^{1}H NMR, ^{1}H-^{1}H gCOSY and (or) ^{1}H-^{13}C gHMQC and ^{1}H-^{13}C gHMBC experiments. All optical rotations were measured at 25 °C using the sodium D line. ESI mass spectra were recorded in the positive ion mode. High-resolution mass spectra were recorded on a Micromass electrospray. Figure 1 shows the structures of compounds **1–18**.

2.1 Procedures for pre-activation based glycosylation

Method A

Donor (120 mg) was dissolved in Et_2O (5 mL) and stirred at −78 °C with freshly activated molecular sieves MS 4 Å (100 mg) under nitrogen atmosphere for 30 min. AgOTf (1 equiv) dissolved in Et_2O (1 mL) was added to the reaction mixture. After 5 min, *p*-TolSCl (1 equiv) was added via a microsyringe. As the reaction temperature was below the freezing point of *p*-TolSCl, *p*-TolSCl should be directly added to the reaction mixture without touching the flask wall. The characteristic yellow color of *p*-TolSCl dissipated within a few seconds. The donor was completely consumed after 1 min as confirmed by TLC analysis. Glycosyl acceptor (0.9 equiv) dissolved in Et_2O (2 mL) was then added dropwise to the reaction mixture. The reaction was warmed up to −20 °C over 1 h under N_2 at which point, the acceptor was completely consumed as confirmed by TLC. The reaction was quenched with Et_3N then concentrated to dryness. The residue was diluted with CH_2Cl_2 (20 mL) and filtrated over Celite. The Celite was further washed with CH_2Cl_2 until no organic compound was present in the filtrate as determined by TLC. The fractions were combined, concentrated to dryness and the residue purified by silica gel flash chromatography.

Method B

Donor (120 mg) was dissolved in CH_2Cl_2 (5 mL) and stirred at −78 °C with freshly activated molecular sieves MS 4 Å (100 mg) under nitrogen atmosphere for 30 min. AgOTf

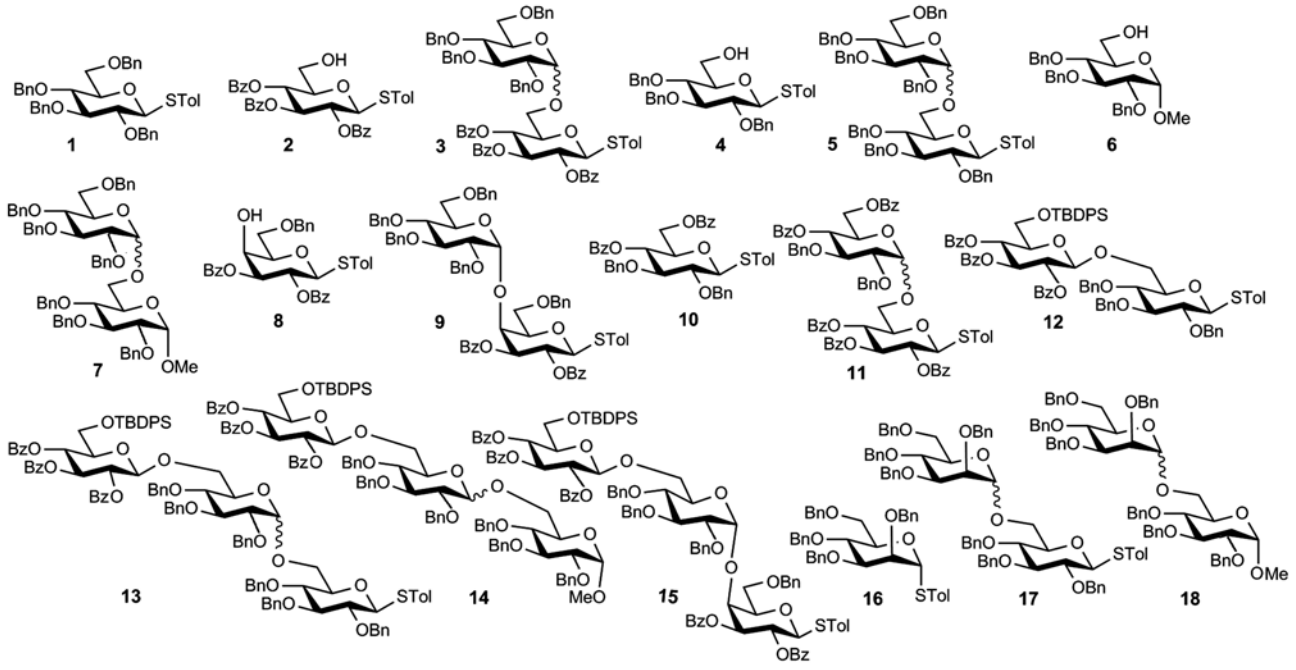


Figure 1 Structures of **1–18**.

(1 equiv) dissolved in acetonitrile/CH_2Cl_2 (*v*:*v* = 1:4, 0.5 mL) was added to the reaction mixture. After 5 min, *p*-TolSCl (1 equiv) was added via a microsyringe. As the reaction temperature was below the freezing point of *p*-TolSCl, *p*-TolSCl should be directed added to the reaction mixture without touching the flask wall. The characteristic yellow color of *p*-TolSCl dissipated within a few seconds. The donor was completely consumed after 5 min as confirmed by TLC analysis. Glycosyl acceptor (0.9 equiv) dissolved in CH_2Cl_2 (1 mL) was then added dropwise to the reaction mixture. The reaction was warmed up to −20 °C over 1 h under N_2 at which point, the acceptor was completely consumed as confirmed by TLC. The reaction was quenched with Et_3N then concentrated to dryness. This was followed by dilution with CH_2Cl_2 (20 mL) and filtration over Celite. The Celite was further washed with CH_2Cl_2 until no organic compounds was present in the filtrate. The fractions were combined then concentrated to dryness. The residue was purified by silica gel flash chromatography.

2.2 Characterization of anomeric stereochemistry

The stereochemistry of the newly formed glycosidic linkages are determined by $^3J_{H1,H2}$ through ^{1}H NMR and/or $^1J_{C1,H1}$ through gHMQC 2-D NMR (without ^{1}H decoupling). Smaller coupling constants of $^3J_{H1,H2}$ (around 3 Hz) indicate α linkages and larger coupling constants $^3J_{H1,H2}$ (7.2 Hz or larger) indicate β linkages for glucosides and galactosides. This can be further confirmed by $^1J_{C1,H1}$ (~170 Hz) for α linkages and $^1J_{C1,H1}$ (~160 Hz) for β linkages for all glycosidic linkages [32].

*p-Tolyl 2,3,4-tri-O-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside (**3**)*

Using method A of general procedure for glycosylation, donor **1** reacted with acceptor **2** to give desired product **3** in 69% yield (α/β 6:1) after column purification (hexanes/ethyl acetate 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) α anomer δ 2.15 (s, 3H), 3.48 (dd, 1H, J^3 = 1.8, 10.8 Hz), 3.54 (dd, 1H, J^3 = 3.0, 9.6 Hz), 3.62 (dd, 1H, J^3 = 1.8, 10.2 Hz), 3.66 (t, 1H, J^3 = 9.6 Hz), 3.71 (dd, 1H, J^3 = 3.0, 10.8 Hz), 3.89 (dd, 1H, J^3 = 7.8, 10.8 Hz), 3.93–3.98 (m, 2H), 4.05–4.12 (m, 1H), 4.43 (d, 1H, J^3 = 12.0 Hz), 4.50 (d, 1H, J^3 = 10.8 Hz), 4.58 (d, 1H, J^3 = 12.0 Hz), 4.60 (d, 1H, J^3 = 12.0 Hz), 4.65 (d, 1H, J^3 = 3.6 Hz), 4.75 (d, 1H, J^3 = 12.0 Hz), 4.79 (d, 1H, J^3 = 10.8 Hz), 4.81 (d, 1H, J^3 = 10.8 Hz), 4.92 (d, 1H, J^3 = 10.8 Hz), 5.40 (t, 1H, J^3 = 10.2 Hz), 5.42 (t, 1H, J^3 = 10.2 Hz), 5.83 (t, 1H, J^3 = 9.0 Hz), 6.98–7.02 (m, 2H), 7.10–7.98 (m, 37 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.31, 67.52, 68.63, 69.88, 70.42, 70.89, 73.62, 73.70, 74.64, 75.23, 75.98, 77.54, 77.96, 80.40, 82.23, 87.34, 97.54, 127.69, 127.78, 127.85, 128.02, 128.06, 128.12, 128.35, 128.44, 128.49, 128.62, 128.63, 128.67, 129.12, 129.58, 129.97, 130.13, 133.39, 133.49, 133.70, 133.93, 138.22, 138.48, 138.68, 138.74, 139.24, 165.32, 165.39, 166.00; HRMS $C_{68}H_{64}NaO_{13}S$ [M + Na^+] calcd 1143.3965 found 1143.3999.

*p-Tolyl 2,3,4-tri-O-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside (**5**)*

Using method A of general procedure for glycosylation, donor **1** reacted with acceptor **4** to give desired product **5** in 80% yield (α/β 5.7:1) after column purification (hexanes/ethyl acetate/CH_2Cl_2, 5.5:1:0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ α anomer 2.23 (s, 3H), 3.27 (t, 1H, J^3 = 9.2 Hz), 3.42–3.92 (m, 10 H), 4.01 (t, 1H, J^3 = 9.2 Hz), 4.47 (d, 1H, J^3 = 12.0 Hz), 4.52 (d, 1H, J^3 = 11.2 Hz), 4.58 (d, 1H, J^3 = 9.6 Hz), 4.63 (d, 1H, J^3 = 10.0 Hz), 4.64 (d, 1H, J^3 = 12.0 Hz), 4.68 (d, 1H, J^3 = 11.2 Hz), 4.76–4.95 (m, 8 H), 5.00 (d, 1H, J^3 = 10.8 Hz), 5.04 (d, 1H, J^3 = 3.2 Hz), 7.06–7.12 (m, 2H), 7.13–7.52 (m, 37H); β anomer 2.30 (s, 3H, $SPhCH_3$), 3.46–3.56 (m, 4H), 3.63–3.70 (m,3H), 3.73–3.81 (m, 3H), 4.24 (dd, 1H, J^3 = 1.8 Hz, 11.2 Hz,), 4.47 (d, 1H, J^3 = 7.6 Hz), 4.57–4.67 (m, 4H, CH_2Ph), 4.70 (d, 1H, J^3 = 9.8 Hz), 4.75–5.02 (m, 10H, CH_2Ph), 7.06–7.52 (m, 39H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ α anomer 21.32, 68.79, 70.47, 72.70, 73.67, 75.18, 75.21, 75.71, 75.89, 75.92, 77.85, 77.93, 79.01, 80.42, 81.37, 82.03, 86.93, 88.73, 97.62, 127.78, 127.90, 127.93, 128.00, 128.08, 128.15, 128.23, 128.50, 128.59, 128.61, 128.65, 128.66, 128.71, 130.03, 133.15, 138.03, 138.26, 138.35, 128.45, 138.70, 138.75, 138.81, 139.14; β anomer 29.98, 60.65, 68.87, 69.18, 73.79, 75.08, 75.16, 75.63, 75.98, 76.00, 77.49, 78.13, 78.25, 79.12, 81.06, 82.48, 84.97, 86.99, 87.90, 100.05, 127.74, 127.84, 128.03, 128.20, 128.36, 128.44, 128.54, 129.94, 130.24, 130.27, 132.39, 137.66, 138.29, 138.60, 138.86. HRMS $C_{68}H_{70}NaO_{10}S$ [M + Na^+] calcd. 1101.4587 found 1101.4531.

*Methyl 2,3,4-tri-O-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**7**)*

Using method B of general procedure for glycosylation, donor **1** reacted with acceptor **6** to give the desired product **7** in 79% yield (α/β 1:9) after column purification (hexanes/ethyl acetate 3:1). Comparison of ^{1}H NMR spectra with literature values [33] confirmed the identity of compound **7**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.44–3.47 (m, 2H), 3.51–3.71(m, 14H), 3.74 (d, 1H, J^3 = 1.5 Hz), 3.76 (d, 1H, J^3 = 2 Hz), 3.84–3.87 (m, 1H), 4.0–4.04 (m, 2H), 4.22 (dd, 1H, J^3 = 2, 11 Hz), 4.39 (d, 1H, J^3 = 8 Hz), 4.50–4.85 (m, 18H), 4.92–4.95 (m, 1H), 4.98–5.02 (m, 3H), 7.14–7.38 (m, 64H, aromatic), 7.81–7.86 (m, 6H, aromatic).

*p-Tolyl 2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranosyl-(1→4)-2,3-di-O-benzoyl-6-O-benzyl-1-thio-β-D-galatcopyranoside (**9**)*

Using method A of general procedure for glycosylation, donor **1** reacted with acceptor **8** to give desired product (**9**) in 60 % yield as α isomer after column purification (hexanes/

ethyl acetate 3:1). Comparison of ^{1}H NMR with literature values [15] confirmed the identity of compound **9**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.14 (s, 3H $SPhCH_3$), 2.88 (dd, 1H, J^3 = 1.8, 11.4 Hz), 3.13 (dd, 1H, J^3 = 1.8, 10.8 Hz), 3.49 (dd, 1H, J^3 = 3.0, 9.6 Hz), 3.65(t, 1H, J^3 = 9.6 Hz), 3.76 (m, 1H), 3.74–3.77. (m, 1H), 3.89–3.96 (m, 4H), 4.04 (d, 1H, J^3 = 12 Hz, CH_2Ph), 4.34–4.41 (m, 5H), 4.61 (d, 1H, J^3 = 11.4 Hz, CH_2Ph), 4.74–4.92 (m, 6H), 5.29 (dd, 1H, J^3 = 3.0, 10.2 Hz), 5.65 (t, 1H, J^3 = 10.2 Hz), 6.99–7.00 (m, 2H, aromatic), 7.10–7.14 (m, 4H, aromatic), 7.20–7.19 (m, 29H, aromatic), 7.89–7.94 (m, 4H, aromatic).

*p-Tolyl 2,3-di-O-benzyl-4,6-di-O-benzoyl-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside (**11**)*

Using method A of general procedure for glycosylation, donor **10** reacted with acceptor **2** to give the desired product 11 in 69% yield (α/β 6:1 as determined from $SPhCH_3$ singlet and H-3 ratios) after column purification (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ + 33 (c = 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.18 (s, 3H, $SPhCH_3$, α), 2.27(s, $SPhCH_3$ β), 3.56 (m, 1H), 3.72 (dd, 1H, J^3 = 3.6, 9.6 Hz), 3.95–4.00 (m, 1H), 4.14–4.24 (m, 3H), 4.32–4.36 (m, 1H), 4.42 (dd, 1H, J^3 = 2.4, 12 Hz), 4.64–4.68 (m, 2H), 4.74 (d, 1H, J^3 = 3 Hz, H-1), 4.81 (d, 1H, J^3 = 12 Hz, CH_2Ph), 4.89 (d, 1H, J^3 = 12 Hz, CH_2Ph), 4.99 (d, 1H, J^3 = 9.6 Hz, H-1), 5.38–5.45 (m, 3H), 5.84 (t, 1H, J^3 = 12 Hz), 7.07–7.56 (m, 32H, aromatic), 7.77–8.04 (m, 11H, aromatic). ^{13}C NMR (150 MHz, $CDCl_3$), δ 21.07, 62.99,66.76, 68.01, 69.42, 70.54, 70.76, 73.62, 74.41, 75.69, 76.79, 77.0, 77.21, 79.42, 79.98, 87.07 ($J_{C\text{-}1,H\text{-}1}$ = 159.07 Hz, C-1^a), 97.01 ($J_{C\text{-}1,H\text{-}1}$ = 169.76 Hz, C-1^b) 114.77, 127.49, 127.79, 127.98, 128.13, 128.2, 128.26, 128.32, 128.37, 128.47, 128.52, 128.81, 128.89, 129.31, 129.54, 129.74, 129.78, 129.82, 129.83, 129.87, 132.44, 132.94,133.1,133.2, 133.3, 133.5, 138.06, 138.17, 138.2, 165.02, 165.08, 165.31, 165.77, 166.04. HRMS $C_{68}H_{60}NaO_{15}S$ $[M + Na]^+$ calcd 1171.3551 found 1171.3600.

*p-Tolyl 2,3,4-tri-O-benzoyl-6-O-tert-butyldiphenylsilyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-1-thio-β-D-glucopyronoside (**13**)*

Using method A of general procedure for glycosylation, donor **13** reacted with acceptor **4** to give the desired product 13 in 70 % yield exclusively as α-isomer after column purification (hexanes/ethyl acetate/CH_2Cl_2, 6:1:0.5). $[\alpha]_D^{20}$ + 22 (c = 0.35, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (s, 9H, $(CH_3)_3CSi$), 2.19 (s, 3H, $SPhCH_3$), 3.18 (t, 1H, J^3 = 9.6 Hz), 3.27–3.37 (m, 1H), 3.40–3.44 (m, 2H), 3.56–3.63 (m, 2H), 3.69–3.72 (m, 2H), 3.76–3.88 (m, 5H), 4.17 (d, 1H, J^3 = 9 Hz), 4.26 (d, 1H, J^3 = 11.4 Hz), 4.45 (d, 1H, J^3 = 11.4 Hz), 4.50 (d, 1H, J^3 = 9 Hz, H1^c), 4.56 (d, 1H, J^3 = 10.8 Hz), 4.59–4.64 (m, 4H), 4.70 (d, 1H, J = 8.4 Hz, H-1^a), 4.71–4.90 (m, 5H), 5.01 (d, 1H, J^3 = 3.6 Hz, H-1^b), 5.54–5.58 (m, 2H), 5.81 (t, 1H, J^3 = 10.2 Hz), 6.96–7.65 (m, 49H, aromatic), 7.67–7.71 (m, 2H, aromatic), 7.81–7.89 (m, 7H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$), δ 19.4, 21.3, 24.9, 26.86, 26.9, 29.9, 36.9, 63.1, 69.6, 69.9, 72.4, 72.6, 73.6, 74.8, 75.1, 75.6, 75.7, 75.8, 77.0, 77.3, 77.46, 77.5, 77.9, 78.0, 79.0, 80.3, 81.4, 81.7, 86.9, 89.0 ($J_{C\text{-}1,H\text{-}1}$ = 170.04 Hz, C-1^c), 97.5 ($J_{C\text{-}1,H\text{-}1}$ = 170.72 Hz, C-1^b), 101.5 ($J_{C\text{-}1,H\text{-}1}$ = 161.68 Hz, C-1^a), 127.5, 127.56, 127.6, 127.7, 127.8,127.83, 127.89, 127.92, 128.03, 128.06, 128.1, 128.43, 128.49, 128.53, 128.54, 128.58, 128.6, 128.65, 128.7, 129.2, 129.5, 129.58, 129.86, 129.89, 129.9, , 130.0,130.1, 130.5, 133.1, 133.2, 133.22, 133.28, 133.3, 133.4, 135.8, 135.9, 138.0, 138.4, 138.5, 138.7, 138.8, 138.9, 139.2, 165.16, 165.26, 166.19; HRMS $C_{104}H_{108}NO_{18}SSi$ $[M+NH_4]^+$ calcd 1718.7135, found 1718.7137.

*Methyl 2,3,4-tri-O-benzoyl-6-O-tert-butyldiphenylsilyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyronoside (**14**)*

Compound **14** was synthesized from donor **12** and acceptor **6** in 76% yield as β isomer using method B of general procedure and purified by flash column chromatography (hexanes/ethyl acetate/CH_2Cl_2, 4:1:0.5). $[\alpha]_D^{20}$ + 12 (c = 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H, $(CH_3)_3CSi$), 3.33 (d, 1H, J^3 = 8.5 Hz), 3.35 (s, 3H, OCH_3), 3.39–3.41 (m, 2H), 3.43–3.49 (m, 2H), 3.52–3.56 (m, 2H), 3.61–3.65 (m, 1H), 3.70–3.72 (m, 1H), 3.76–3.79 (m, 1H), 3.83–3.85 (m, 2H), 3.96 (t, 1H, J^3 = 9.5 Hz), 4.00 (dd, 1H, J^3 = 1.8, 10.8 Hz), 4.17 (d, 1H, J^3 = 7.5 Hz, H-1^b), 4.20 (dd, 1H J^3 = 1.8, 11.4 Hz), 4.39 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.44 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4 59 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.61 (d, 1H, J^3 = 6 Hz, H-1^a), 4.64 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.67 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.71 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.75–4.77 (m, 2H, CH_2Ph), 4.82 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.85 (d, 1H, J^3 = 8Hz, H-1^c), 4.91 (d, 1H, J^3 = 11 Hz, CH_2Ph), 4.95 (d, 1H, J^3 = 11 Hz, CH_2Ph), 5.50–5.53 (m, 1H, H-2^c), 5.61 (t, 1H, J^3 = 9.5 Hz, H-4^c), 5.78 (t, 1H, J^3 = 9.5 Hz, H-3^c), 7.08–7.40 (m, 49H aromatic), 7.49–7.52 (m, 1H, aromatic), 7.66–7.68 (m, 2H, aromatic), 7.79–7.81 (m, 2H, aromatic), 7.81–7.86 (m, 6H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$), δ 19.4, 26.9, 55.65, 55.7, 63.1, 68.1, 69.5, 69.9, 72.4, 73.5, 73.6, 74.9, 75.08, 75.1, 75.4, 75.77, 75.8, 77.0, 77.3, 77.46, 77.5, 77.9, 78.0, 79.95, 82.1, 82.2, 85.0, 98.4 ($J_{C\text{-}1,H\text{-}1}$ = 168.69 Hz, C-1^a), 101.7 ($J_{C\text{-}1,H\text{-}1}$ = 159.14 Hz, C-1^c), 103.7 ($J_{C\text{-}1,H\text{-}1}$ = 159.32 Hz, C-1^b), 127.68, 127.71, 127.74, 127.8, 127.9, 128.0, 128.13, 128.16, 128.38, 128.49, 128.53, 128.54, 128.56, 128.58, 128.61, 128.7, 129.2, 129.5, 129.7, 129.84, 129.88, 129.96, 130.0, 133.2, 133.31, 133.34, 133.4, 135.7, 135.9, 138.3, 138.4, 138.7, 138.8, 139.2, 165.20, 165.24, 166.1; HRMS $C_{98}H_{104}NO_{19}SSi$ $[M + NH_4]^+$ calcd 1626.6972, found 1626.6976.

*p-Tolyl 2,3,4-tri-O-benzoyl-6-O-tert-butyldiphenylsilyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-O-benzoyl-6-O-benzyl-1-thio-β-D-galactopyranoside (**15**)*

Using method A of general procedure for glycosylation,

donor **12** reacted with acceptor **8** to give the desired product **15** in 74% yield exclusively as α isomer after column purification (hexanes/ethyl acetate/CH_2Cl_2, 6:1:0.5). $[\alpha]_D^{20}$ +41 (c = 0.55, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H, $(CH_3)_3CSi$), 2.10 (s, 3H, $SPhCH_3$), 3.29 (dd, 1H, J^3 = 3, 10.2 Hz), 3.35–3.42 (m, 2H), 3.46–3.50 (m, 1H), 3.66–3.70 (m, 1H), 3.73–3.74 (m, 2H), 3.82–3.91 (m, 4H), 4.17 (d, 1H, J^3 = 11.5 Hz), 4.22 (d, 1H, J^3 = 8 Hz, H-1^c), 4.28–4.38 (m, 4H), 4.48 (d, 1H, J^3 = 12 Hz, CH_2Ph), 4.66 (d, 1H, J^3 = 10.2 Hz), 4.67 (d, 1H, J^3 = 9 Hz), 4.80 (d, 1H, J^3 = 11 Hz), 4.82 (d, 1H, J^3 = 10 Hz, H-1^a), 4.90 (d, 1H, J^3 = 3.5 Hz, H-1^b), 5.34–5.43 (m, 2H), 5.50–5.69 (m, 3H), 6.95–7.03 (m, 4H, aromatic), 7.06–7.40 (m, 41H, aromatic), 7.44–7.51 (m, 4H aromatic), 7.64–7.65 (m, 2H, aromatic), 7.77–7.79 (m, 3H, aromatic), 7.82–7.85 (m, 4H, aromatic), 7.87–7.89 (m, 2H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$), δ 29.9, 26.9, 21.3 19.3, 21.3, 26.9, 29.9, 63.1, 67.8, 68.17, 68.2, 69.5, 70.5, 72.2, 73.5, 73.6, 74.1, 74.34, 74.39, 75.0, 75.34, 77.0, 77.3, 77.5, 78.5, 80.3, 81.6, 86.3 ($J_{C\text{-}1,H\text{-}1}$ = 170.04 Hz, C-1^b), 98.97 ($J_{C\text{-}1,H\text{-}1}$ = 163.06 Hz, C-1^c), 101.7 ($J_{C\text{-}1,H\text{-}1}$ = 159.71Hz, C-1^a), 127.55, 127.57, 127.64, 127.83, 127.84, 127.95, 127.97, 128.0, 128.02, 128.04, 128.40, 128.45, 128.48, 128.53, 128.57, 128.60, 128.64, 128.7, 129.24, 129.38, 129.6, 129.63, 129.8, 129.84, 129.88, 129.95, 129.99, 130.3, 133.0, 133.2, 133.24, 133.3, 133.34, 133.37, 133.4, 135.8,138.06, 138.1,138.7, 139.0, 139.2, 165.1, 165.2, 165.9, 166.2; HRMS $C_{104}H_{104}NO_{20}SSi$ $[M + NH_4]^+$ calcd 1746.6636 found 1746.6638.

*p-Tolyl 2,3,4-tri-O-benzyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside (**17**)*

Using method A of general procedure for glycosylation, donor **16** reacted with acceptor **4** to give the desired product **17** in 61% yield after column purification (hexanes/ethyl acetate/CH_2Cl_2, 5.5:1:0.5). $[\alpha]_D^{20}$ +27 (c = 0.15, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.20 (s, 3H, $SPhCH_3$), 3.36–3.46 (m, 3H), 3.65–3.69 (m, 2H), 3.71–3.74 (m, 2H), 3.77–3.80 (m, 1H), 3.84–3.89 (m, 3H), 4.04 (t, 1H, J^3 = 9.6 Hz), 4.47–4.53 (m, 3H), 4.58 (dd, 1H, J^3 = 1.8, 10.2 Hz), 4.61–4.62 (m, 2H), 4.66 (d, 1H, J^3 = 12 Hz), 4.73–4.84 (m, 5H), 4.89–4.95 (m, 3H), 5.05(s, 1H), 7.01–7.03 (m, 2H, aromatic), 7.14–7.20 (m, 2H, aromatic), 7.23–7.35 (m, 29H, aromatic), 7.41–7.43 (m, 6H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$), δ 21.3, 29.9, 66.6, 69.4, 72.2, 72.6, 73.5, 74.8, 75.1, 75.23, 75.3, 75.7, 76.1, 77.0, 77.3, 77.5, 77.8, 78.6, 79.9, 81.3, 86.9, 88.3 ($J_{C\text{-}1,H\text{-}1}$ = 169.9 Hz, C-1$^{b)}$, 98.8 ($J_{C\text{-}1,H\text{-}1}$ = 157.7 Hz, C-1^a), 127.96, 127.63, 127.78, 127.81, 127.88, 127.9, 127.93, 127.95, 127.99, 128.01, 128.04, 128.05, 128.43, 128.45, 128.48, 128.49, 128.57, 128.60, 128.63, 128.64, 128.67, 128.69, 128.7, 129.89, 129.96, 130.1, 131.96, 133.1, 138.1, 138.27, 138.59, 138.62, 138.67, 138.95; HRMS $C_{68}H_{74}NO_{10}S$ $[M + NH_4]^+$ calcd 1096.5033 found 1096.5031.

*Methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-1-methyl-α-D-glucopyranoside (**18**)*

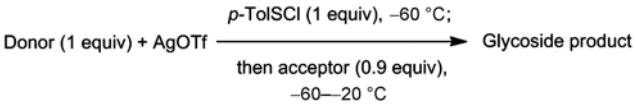
Using method A of general procedure for glycosylation, donor **16** reacted with acceptor **6** to give the desired product **18** in 79% yield after column purification (hexanes/ethyl acetate 3:1). α/β = 1:3 as determined by integration of OCH_3 peaks and $J_{C1\text{-}H1}$ coupling constants. Comparison with literature data confirmed its identity [34]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.30 (s,OCH_3-α), 3.31 (s, 3H, OCH_3-β), 3.36–3.46 (m, 6H), 3.48 (dd, 1H, J^3 = 3.6, 9.6 Hz), 3.59–3.87 (m, 10H), 3.96–4.02 (m, 2H), 4.11 (s, 1H), 4.13 (d, 1H, J^3 = 10 Hz, H-1), 4.19–4.71 (m, 15H), 4.76–4.88 (m, 8H), 4.91(d, 1H, J^3 = 12 Hz), 4.46 (d, 1H, J^3 = 3 Hz, H-1), 4.51 (d, 1H, J^3 = 12 Hz), 7.06–7.40 (m, 49H, aromatic).

3 Results

Our investigation started from the per-benzylated glucoside **1**. As ethereal solvents can enhance α selectivity [19–23], we first performed the glycosylation in diethyl ether. Donor **1** dissolved in diethyl ether was pre-activated by 1 equiv of *p*-TolSOTf, formed *in situ* through the stoichiometric reaction of *p*-TolSCl [15] with AgOTf. 3 equiv of AgOTf was typically added as a standard protocol [16, 17, 24]. Upon the rapid complete activation of **1** within 1 min as judged by TLC, acceptor **2** was added, which led to the formation of disaccharide **3** with close to equal amounts of α and β anomers (α:β = 1.1:1) in 67% total yield (Table 1, entry 1). While 10 equiv of AgOTf produced more β anomer (α:β = 1:1.5) (Table 1, entry 2), interestingly, decreasing the amount of AgOTf to 1.1 equiv significantly improved α selectivity (α:β = 6:1) (Table 1, entry 3). The α selectivity could be further enhanced by performing the reaction under a more dilute condition. Increasing the volume of diethyl ether by 10 folds under otherwise identical conditions produced disaccharide **3** in a 10:1 α:β ratio (Table 1, entry 4).

As α selectivity was obtained, it would be desirable that from the same glycosyl donor and acceptor, simple changes of the reaction condition can lead to a switch to β products. Following formation of *p*-TolSOTf, the thioglycosyl donor is first converted to a disulfonium ion (Figure 2), which can evolve into other intermediates such as glycosyl triflate. Crich and coworkers have reported that with benzylidene protected thio-glycosides including glucosides without 2-*O* acyl groups, the α glycosyl triflates were the predominant intermediates following pre-activation as observed by low temperature NMR studies [25, 26]. Similarly, in our low temperature NMR studies, we did not observe the presence of the glycosyl disulfonium ion [27], suggesting transient nature of this species. As the most likely intermediate is the glycosyl triflate and the stereochemical outcome in glycoside formation is dependent upon the balance between glycosyl

Table 1 Evaluation of stereoselectivity using donors with no 2-*O* acyl groups



Entry	Donor	Acceptor	AgOTf	Reaction condition	Pdt	Yield % (α:β)
1	**1**	**2**	3	a	**3**	67 (1.1:1)
2	**1**	**2**	10	a	**3**	66 (1:1.5)
3	**1**	**2**	1.1	a	**3**	69 (6:1)
4	**1**	**2**	1.1	a*	**3**	55 (10:1)
5	**1**	**2**	3	b	**3**	92 (1:1.8)
6	**1**	**2**	1.1	b	**3**	90 (1:8)
7	**1**	**4**	1.1	a	**5**	80 (5.7:1)
8	**1**	**4**	1.1	b	**5**	71 (1:1.7)
9	**1**	**6**	1.1	a	**7**	86 (2:1)
10	**1**	**6**	1.1	b	**7**	79 (1:9.4)
11	**1**	**8**	1.1	a	**9**	69 (α only)
12	**10**	**2**	1.1	a	**11**	69 (6:1)
13	**10**	**2**	1.1	b	**11**	56 (1:1.2)
14	**12**	**4**	1.1	a	**13**	70 (α only)
15	**12**	**4**	1.1	b	**13**	90 (1:1.2)
16	**12**	**6**	1.1	a	**14**	65 (2:1)
17	**12**	**6**	1.1	b	**14**	92 (β only)
18	**12**	**6**	1.1	b**	**14**	90 (β only)
19	**12**	**8**	1.1	a	**15**	74 (α only)
20	**16**	**4**	1.1	a	**17**	61 (α only)
21	**16**	**6**	1.1	a	**18**	58 (2:1)
22	**16**	**6**	1.1	b	**18**	71 (1:3)

a) Reaction was performed in diethyl ether (donor concentration was 50 mM). b) Reaction was performed in dichloromethane (donor concentration was 50 mM). * Donor concentration is 5 mM. ** Toluene (5% of final volume) was added to the reaction to dissolve AgOTf.

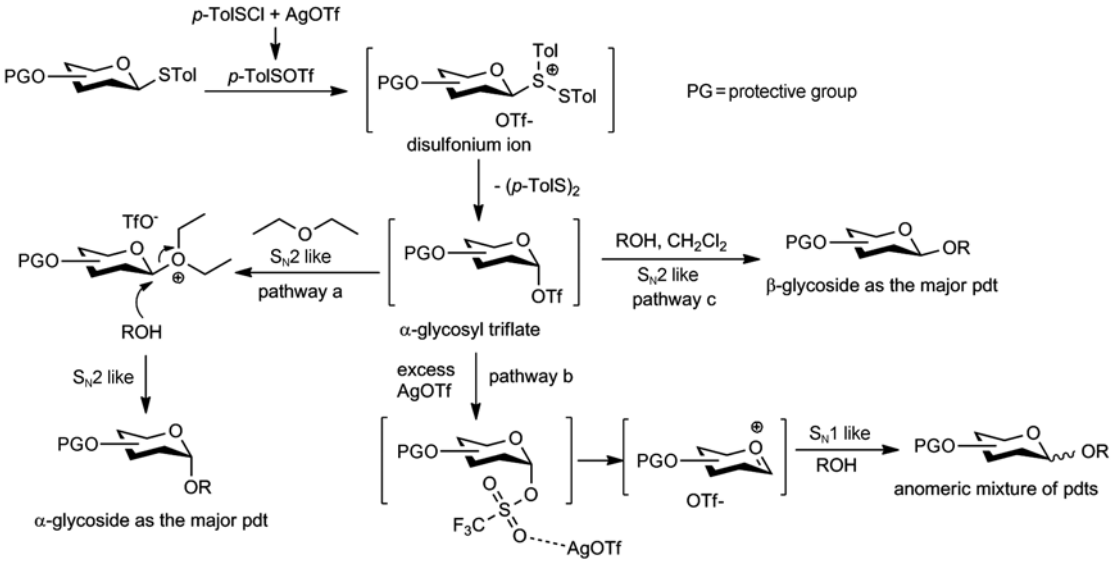


Figure 2 Proposed mechanism of the effects of solvents and excess AgOTf on stereoselectivity.

triflates and the oxacarbenium ion [28], we envision that addition of exogenous triflate ion could potentially shift the equilibrium towards glycosyl triflate. This would favor the formation of the β glycoside product through a S_N2 like reaction pathway, which could be supported by our observation that excess AgOTf led to more β products (Table 1, entry 2). To test this hypothesis, we explored the effects of triflate salts on stereoselectivity. The reaction between **1** and **2** was performed with 1.1 equiv of AgOTf in the presence of up to 10 equiv of triflate salts including NaOTf, $Hf(OTf)_4$ and the more organic solvent soluble tetrabutylammonium triflate. However, none of these salts affected the stereoselectivity, which ruled out that the additional triflate anion could significantly influence the reaction pathway.

Next, we tested the reactions in a variety of solvents including dichloromethane, cyclopentyl methyl ether, THF, toluene, toluene/1,4-dioxane [23] and acetonitrile. THF, toluene, toluene/1,4-dioxane and acetonitrile did not lead to productive coupling. Cyclopentyl methyl ether has been reported to improve *cis* selectivity [19]. However, in our reaction, it gave similar results as diethyl ether. Interestingly, a selectivity shift was observed when the reaction between **1** and **2** was performed in dichloromethane with 3 equiv of AgOTf, which gave disaccharide **3** with 92% total yield with the β anomer becoming the major product (α:β = 1:1.8) (Table 1, entry 5). Decreasing the amount of AgOTf to 1.1 eq greatly enhanced the β selectivity (α:β = 1:8) (Table 1, entry 6). Therefore, the stereochemical outcome of the reaction can be controlled by simply switching the reaction solvent, with diethyl ether favoring α glycoside and dichloromethane generating more β product.

With the stereoselective reaction conditions in hand, we examined their generality. Pre-activation of donor **1** in diethyl ether by 1 equiv of *p*-TolSCl and 1.1 equiv of AgOTf followed by addition of the electron rich glucoside acceptor **4** gave disaccharide **5** in 90% yield with the α anomer as the major isomer (α:β = 5.7:1) (Table 1, entry 7). Exchanging the reaction solvent to dichloromethane produced the β isomer as the major product (α:β = 1:1.7) (Table 1, entry 8). The same trend held for a variety of building blocks, including glucoside acceptor **6** without the STol aglycon, galactoside acceptor **8** with a secondary hydroxyl group, electron poor glucosyl donor 10 and disaccharide donor **12** (Table 1, entries 7–19). β-Mannoside formation is a challenging problem for carbohydrate synthesis. The excellent methodology developed by Crich and coworkers for stereoselective β-mannoside formation required the installation of a benzylidene moiety on the mannosyl donor [4]. It is noteworthy that under the β selective reaction condition, the per-benzylated electron rich mannosyl donor **16** without the benzylidene glycosylated glucoside **6** in dichloromethane forming β-mannoside **18** as the major product (Table 1, entry 22).

4 Discussion

As the glycosyl triflate is a likely intermediate formed after pre-activation, when the reaction is performed in diethyl ether, it is possible that it goes through a double inversion mechanism (Figure 2, pathway a). The diethyl ether can act as a nucleophile, displacing the triflate in an S_N2 like fashion from the β-face. Subsequent S_N2 like displacement of the ether molecule by the nucleophilic acceptor can lead to α glycoside as the major product. Under a dilute condition, the larger amount of diethyl ether can participate more effectively thus resulting in higher α selectivity. In the presence of excess AgOTf, it is most likely that AgOTf coordinates with the oxygen atom of the triflate, leading to its activation and glycosylation through a more S_N1 like pathway (Figure 1, pathway b). This would result in the formation of anomeric mixtures.

When the glycosylation is performed in dichloromethane, due to the low solubility of AgOTf in dichloromethane, a solution of AgOTf in acetonitrile was added to the reaction. Although the amount of acetonitrile is small (2% of the final solvent volume for the reaction), it is possible that the β selectivity observed is a result of acetonitrile participating from the α face due to the known nitrile effect [29–31]. To test this possibility, we replaced acetonitrile with toluene in reaction of **13** with **6**. The β linked disaccharide was the only product isolated (Table 1, entry 18), which suggests that acetonitrile does not play a significant role in determining the stereochemical outcome of the reaction. The β selectivity observed with dichloromethane as the reaction medium is thus likely due to the non-nucleophilic and non-polar nature of the solvent. The reaction goes through a more S_N2 like pathway with the acceptor directly displacing the α-glycosyl triflate leading to β glycosides (Figure 1, pathway c).

In conclusion, glycosyl donors with participating acyl protective groups on 2-*O* have been shown previously to give 1,2-*trans* glycosides reliably under the pre-activation based reaction condition. In this work, we discovered that the stereoselectivity of the pre-activation based glycosylation using donors without participating protective group on 2-*O* can be controlled by the reaction solvent, with diethyl ether favoring the formation of α glycosides and dichloromethane leading to β isomers. Besides its role in generating the promoter *p*-TolSOTf, AgOTf can also exert significant impact on stereoselectivity presumably due to coordination with the glycosyl triflate intermediate. The stereochemical dependence can be applied to a variety of building blocks including the formation of β-mannosides. Other factors including donor and acceptor structures and protective groups also affect the outcome. A general strategy that can be applied to a wide range of building blocks for on demand stereospecific glycosylation requires further development

and thorough understanding of the multiple factors guiding the stereoselectivity.

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