Glycosylation via Cp_2ZrCl_2/$AgClO_4$-Mediated Activation of Anomeric Sulfoxides

Peter Wipf* and Jonathan T. Reeves

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

pwipf+@pitt.edu

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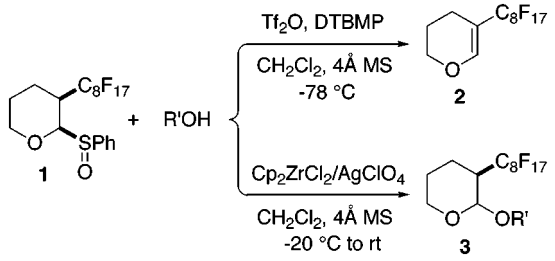
Introduction

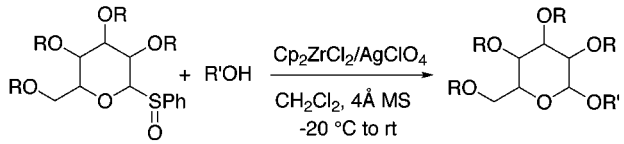
The presence of saccharide moieties in biologically active molecules has provided major impetus for recent advances in the state of the art of carbohydrate synthesis.[1] Of central importance is the construction of the glycosidic bond. A multitude of glycosyl donors and activating systems have been developed for this purpose, producing varying levels of stereoselectivity.[1,2] Nevertheless, the field as a whole still lags behind the state of the analogous areas of peptide and nucleotide coupling chemistry.[3,4] Additional efficient and stereoselective methods for formation of O-glycosidic bonds are therefore desirable.

Kahne and co-workers introduced the use of anomeric sulfoxides as glycosyl donors in 1989.[5] Activation of the glycosyl sulfoxide is generally accomplished with triflic anhydride in the presence of stoichiometric 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) as a triflic acid scavenger.[6] In our recent work on the development of a fluorous THP protecting group,[7] we initially employed the Tf_2O/DTBMP conditions to activate sulfoxide **1** but obtained primarily elimination product **2** instead of the desired acetal **3** (Scheme 1). In contrast, in the presence of a 1:2 ratio of Cp_2ZrCl_2/$AgClO_4$ to activate the sulfoxide, good yields of acetals **3** were obtained with no elimination product. In an extension of pioneering studies by Mukaiyama on the activation of glycosyl fluorides with $SnCl_2$/$AgClO_4$,[8] Suzuki and co-workers were first in exploring the combination of zirconocene dichloride and silver perchlorate for glycosyl fluoride transfer.[9]

Scheme 1



Scheme 2



Herein,we report the application of this reagent combination to coupling of carbohydrate-derived sulfoxide donors (Scheme 2).

Results and Discussion

The glycosylation under cationic zirconocene conditions was first investigated using the peracetylated donor **4**, prepared in four steps from D-glucose (Figure 1).[10] Addition of **4** to a −20 °C solution of a 1:2:2 molar ratio of Cp_2ZrCl_2/$AgClO_4$/benzyl alcohol in CH_2Cl_2, however, yielded no O-glycoside product after 8 h. Variation of temperature, reagent stoichiometry, and solvent also failed to lead to any product. The corresponding axial sulfoxide **5** was prepared[11] but also found to be unreactive. The lack of reactivity of tetraacetates **4** and **5** can be attributed to deactivation of the sulfoxide oxygen by the electron withdrawing inductive effect of the acetyl groups. This is a well-known property of ester-bearing (disarmed) versus ether-bearing (armed) glycosyl donors and has been exploited in polysaccharide synthesis, first by Fraser-Reid and co-workers with *n*-pentenyl glycosides[12] and later for other donor systems.[13]

Given the unreactive nature of the peracylated donors under our reaction conditions and the known increase of reactivity with peralkylated donors, we prepared the glycosyl sulfoxide **6**[14] in six steps from D-glucose (Table 1). Under otherwise identical reaction conditions, this donor afforded benzyl glycoside **8** as a 4.4:1 α/β mixture of anomers in 80% combined yield. Secondary and tertiary alcohols also afforded good yields of products, with a shift toward β-selectivity as the steric bulk of the acceptor alcohol increased. Changing the solvent from CH_2Cl_2 to benzene gave decreased selectivity (α/β =

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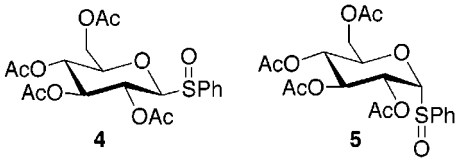
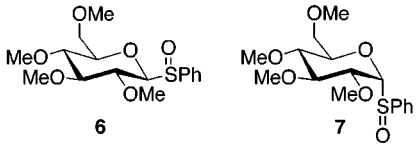
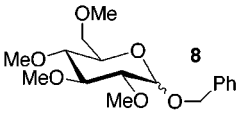
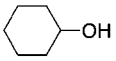
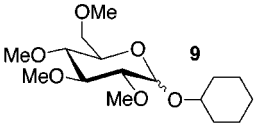
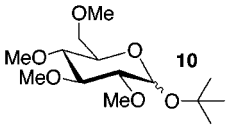


Figure 1. Unreactive anomeric sulfoxide donors.

Table 1. Glycosylation with Glucose-Derived Permethylated Donor Sulfoxides



Alcohol	Sulfoxide	Product	Yield[a]	α:β selectivity
Ph-CH2-OH	6		80	4.4:1[b]
	7		79	1:1.15[c]
	6		81	1:1.2[b]
	7		76	1:1.3[c]
	6		59	1:2.8[b]

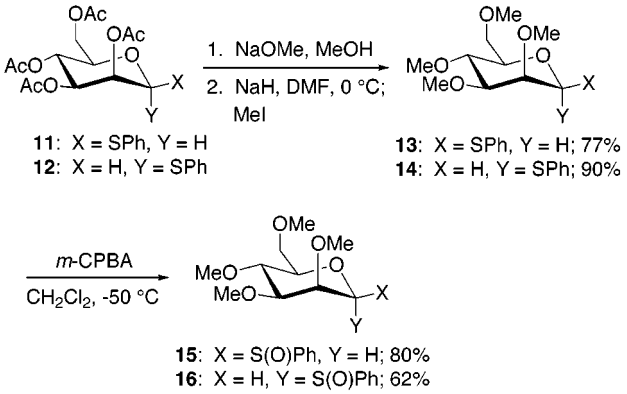
[a] Combined yield of α- and β-anomers. [b] Determined after isolation of individual anomers by chromatography on SiO_2. [c] Determined by ^1H NMR analysis of anomeric mixture.

1.3:1, 70% combined yield) in the glycosylation of benzyl alcohol, and no reaction occurred in Et_2O. Lower initial temperature (−78 °C) inhibited the reaction; however, upon warming to room temperature, a similar yield and selectivity were obtained (α/β = 3.8:1, 77% combined yield). The process was found to require stoichiometric quantities of $Cp_2ZrCl_2/AgClO_4$ reagent, giving only a trace of product when 10 mol % of Cp_2ZrCl_2 and 20 mol % of $AgClO_4$ were used. The corresponding axial sulfoxide **7**[14] was also prepared in five steps from D-glucose and tested in the glycosylation procedure. This donor was slightly β-selective in the coupling with benzyl alcohol and cyclohexanol.

To examine the effect of an axial C-2 substituent on the stereoselectivity of the reaction the mannose-derived donors **15** and **16** were prepared from the known tetraacetates **11**[15] and **12**[16] (Scheme 3). Zemplèn deacetylation[17] followed by exhaustive methylation gave the tetra-methylated sulfides **13** and **14**, which were oxidized with *m*-chloroperoxybenzoic acid at low temperature to give sulfoxides **15** and **16**.

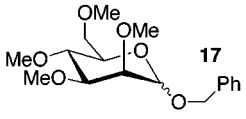
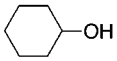
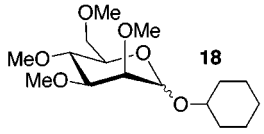
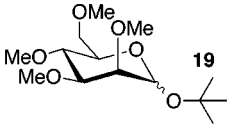
Under the optimized conditions developed with glucose-derived donors, **15** gave excellent yields and high α-selectivity for primary, secondary and tertiary alcohols. α-Sulfoxide **16** gave decreased α-selectivity in the glycosylation of primary and secondary alcohols (Table 2).

Scheme 3



11: X = SPh, Y = H
12: X = H, Y = SPh
13: X = SPh, Y = H; 77%
14: X = H, Y = SPh; 90%
15: X = S(O)Ph, Y = H; 80%
16: X = H, Y = S(O)Ph; 62%

Table 2. Glycosylation with Mannose-Derived Donors

Alcohol	Sulfoxide	Product	Yield[a]	α:β selectivity
Ph-CH2-OH	15		82	20.5:1[b]
	16		67	5.8:1[c]
	15		77	18.8:1[b]
	16		68	4.1:1[c]
	15		58	17.1:1[b]

[a] Combined yield of α- and β-anomers. [b] Determined after isolation of individual anomers by chromatography on SiO_2. [c] Determined by ^1H NMR analysis of anomeric mixture.

The possibility of epimerization of the kinetically formed product ratio of anomers to a thermodynamic distribution by either the zirconium complex or traces of $HClO_4$ formed under the reaction conditions was examined next. A pure sample of β-**17** was subjected to a 1:2:1 ratio of $Cp_2ZrCl_2/AgClO_4$/BnOH in CH_2Cl_2 for 6 h at room temperature. ^1H NMR of the crude product after workup revealed only the starting β-anomer, with no trace of α-anomer. Similarly, pure α-**17** was subjected to the reaction conditions, and no epimerization to the β-anomer was detected by ^1H NMR. Thus, it appears that the isolated product distributions are obtained in a kinetically controlled fashion, and that the $Cp_2ZrCl_2/AgClO_4$ reagent system is unable to activate the product *O*-glycosides toward transacetalization. This result also suggests that $HClO_4$ is not produced under the reaction conditions. However, to verify that initial activation of the sulfoxide occurs by a zirconium species rather than by $HClO_4$, the reaction of sulfoxide **16** with BnOH was conducted in the presence of 1.0 equiv of 2,6-di-*tert*-butyl-4-methyl pyridine. Under these conditions, glycoside **17** was obtained in similar yield and anomeric selectivity (70%, α/β = 6:1) as in the absence of the proton scavenger. It can be concluded, therefore, that sulfoxide activation is indeed accomplished by a cationic zirconium complex rather than by in situ produced protic acid.

Importantly, this new methodology for anomeric sulfoxide activation is not limited to the coupling of methyl

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(15) Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010.
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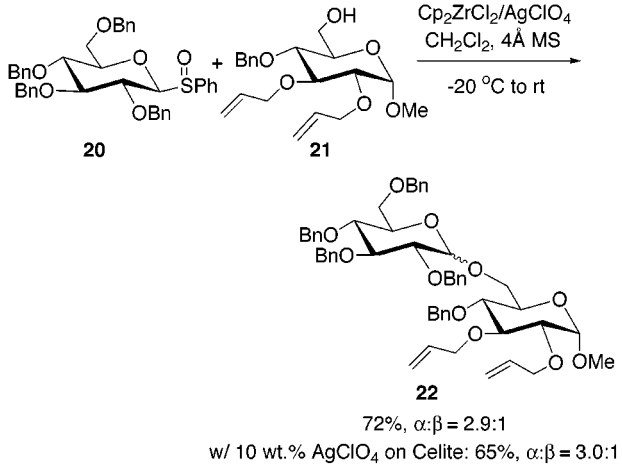
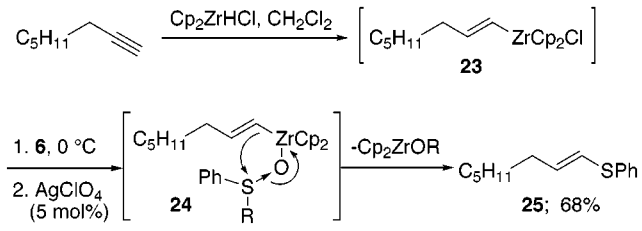
Scheme 4



Scheme 5



ether-protected substrates, which are difficult to deprotect. More commonly, benzyl and allyl ethers are employed as carbohydrate protective groups. Scheme 4 demonstrates the convenient preparation of a fully protected glucosylglucose derivative by the Cp_2ZrCl_2/$AgClO_4$ reagent. Disaccharide **22** is obtained in 72% yield as a 2.9:1 mixture of α- to *β*-anomers. Alternatively, the use of $AgClO_4$ adsorbed on Celite[18e] provides **22** in comparable yield and stereoselectivity.

We have previously studied the Ag(I)-catalyzed opening of oxiranes with alkenylzirconocenes, which also follows a cationic reaction pathway.[18] Accordingly, we were interested to test the potential of glycosyl sulfoxides to serve as acceptors in C-glycosylation reactions with organozirconocenes. However, addition of 5 mol % $AgClO_4$ to a mixture of sulfoxide **6** and in situ prepared[19] zirconocene **23** only led to vinyl sulfide **25**, possibly via an intramolecular displacement of the S−O bond in complex **24** (Scheme 5). Nonetheless, the conversion of 1-octyne to vinyl sulfide **25** represents a new method for aryl vinyl thioether synthesis that complements the method of Huang et al.[20]

Conclusions

We have developed a new method for activating glycosyl sulfoxides for the construction of O-glycosidic linkages using the easy to handle Cp_2ZrCl_2/$AgClO_4$ reagent combination. Both Cp_2ZrCl_2 and $AgClO_4$ are readily available solids that are more convenient to weigh and much less air- and moisture-sensitive than the triflate derivatives that have traditionally been used for anomeric sulfoxide activation.[21] In particular, $AgClO_4$ adsorbed onto Celite is prepared from an aqueous slurry and can be stored for years without loss in activity.[18e] With electron-rich (i.e., methyl-, benzyl-, or allyl ether-protected) donors, the reaction gives good yields of glycosides with primary, secondary and tertiary alcohols, and the process readily lends itself to the preparation of differentially protected disaccharide building blocks. The mechanism of the glycosylation reaction likely involves sulfoxide activation by a cationic zirconium-acceptor alcohol complex. After ionization of the donor, the coordinated acceptor alcohol can trap the resultant oxonium ion from either the α- or *β*-face. The facial selectivity seems to rely heavily on the geometry of the sulfoxide; e.g., *β*-sulfoxide donors favor α-attack, whereas α-sulfoxides favor *β*-attack. These considerations, in combination with the inherent steric effects of the donor−carbohydrate interaction, determine the ultimate anomeric ratio of products. The high α-selectivity found for the mannose-derived *β*-sulfoxides can be explained not only by a delivery of the acceptor alcohol to the oxonium ion from the opposite (α) face of the starting sulfoxide, but also by the gauche interaction of a *β*-mannosidic substituent and the stronger anomeric effect present in C-2 axial sugars.[22] Work is currently underway to apply the Cp_2ZrCl_2/$AgClO_4$ reagent system to other glycosidic bond formation chemistry.

Experimental Section

General Methods. All reactions were performed under an atmosphere of N_2 and all glassware was dried in an oven at 140 °C prior to use. Et_2O was dried by distillation over Na/benzophenone. Dry CH_2Cl_2 was obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used without further purification. NMR spectra were recorded at 300 MHz/75 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA. Commercially available anhydrous $AgClO_4$ was used without special precautions. **CAUTION**: Anhydrous $AgClO_4$, especially solvated crystals containing organic compounds, can explode when struck. $AgClO_4$ is also hygroscopic and light sensitive, decomposes at or above 450 °C, and explodes readily at 800 °C. Several companies, including Aldrich and Strem, offer anhydrous $AgClO_4$; most suppliers of fine chemicals offer silver perchlorate monohydrate which can be dried by azeotropic distillation. $AgAsF_6$ has been suggested as a safe, but ca. 10× more expensive, alternative to $AgClO_4$.[23] Alternatively, $AgClO_4$ monohydrate can also be used but reactions proceed more slowly. $AgClO_4$ adsorbed onto Celite is a viable alternative for the use of anhydrous $AgClO_4$.[18e]

General Procedure A for Glycosylation. Benzyl 2,3,4,6-Tetra-*O*-methyl-D-glucopyranoside (8). A suspension of Cp_2ZrCl_2 (1.20 g, 4.11 mmol, 1.0 equiv), $AgClO_4$ (1.70 g, 8.21 mmol, 2.0 equiv), and 4 Å molecular sieves (500 mg) in CH_2Cl_2 (50 mL) was stirred at room temperature for 15 min. Benzyl alcohol (0.85 mL, 8.2 mmol, 2.0 equiv) was added, and the temperature was lowered to −20 °C. A solution of sulfoxide **6** (1.43 g, 4.16 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added dropwise, and the reaction mixture was allowed to warm gradually to room temperature. After 6 h, saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with

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(23) Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483.

CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 85:15 → 70:30) gave α-**8** (884 mg, 2.71 mmol, 65%) and β-**8** (201 mg, 0.617 mmol, 15%) as viscous oils. **α-8:** $[\alpha]_D$ +47.3 (*c* 0.13, $CHCl_3$); IR (neat) 2927, 1450, 1156, 1101, 1046 cm^{-1}; ^1H NMR δ 7.35−7.27 (m, 5 H), 4.97 (d, 1 H, *J* = 3.7 Hz), 4.70 (d, 1 H, *J* = 12.2 Hz), 4.57 (d, 1 H, *J* = 12.2 Hz), 3.61 (s, 3 H), 3.60−3.43 (m, 4 H), 3.52 (s, 3 H), 3.38 (s, 6 H), 3.24−3.14 (m, 2 H); ^{13}C NMR δ 137.0, 128.2, 128.1, 127.6, 95.0, 83.1, 81.4, 79.2, 70.7, 70.0, 69.0, 60.7, 60.3, 59.0, 58.3. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.67; H, 8.05. **β-8:** $[\alpha]_D$ −68.0 (*c* 0.10, $CHCl_3$); IR (neat) 2932, 1452, 1369, 1096 cm^{-1}; ^1H NMR δ 7.36−7.26 (m, 5 H), 4.94 (d, 1 H, *J* = 12.1 Hz), 4.62 (d, 1 H, *J* = 12.1 Hz), 4.34 (d, 1 H, *J* = 7.5 Hz), 3.69−3.54 (m, 2 H), 3.62 (s, 3 H), 3.59 (s, 3 H), 3.53 (s, 3 H), 3.42 (s, 3 H), 3.30−3.04 (m, 4 H); ^{13}C NMR δ 137.6, 128.4, 127.7, 102.4, 86.4, 83.8, 79.4, 74.6, 71.4, 70.9, 60.9, 60.6, 60.5, 59.4. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.76; H, 7.98. **From Sulfoxide 7.** According to the general procedure A, Cp_2ZrCl_2 (112 mg, 0.384 mmol), $AgClO_4$ (158 mg, 0.763 mmol), benzyl alcohol (80 μL, 0.76 mmol), and sulfoxide **7** (130 mg, 0.378 mmol) gave **8** (98 mg, 0.30 mmol, 79%, α/β = 1:1.15).

Cyclohexyl 2,3,4,6-Tetra-*O*-methyl-D-glucopyranoside (9). According to the general procedure A, Cp_2ZrCl_2 (108 mg, 0.369 mmol), $AgClO_4$ (152 mg, 0.734 mmol), cyclohexanol (74 mg, 0.74 mmol), and sulfoxide **6** (127 mg, 0.369 mmol) gave α-**9** (43 mg, 0.14 mmol, 38%) and β-**9** (52 mg, 0.16 mmol, 43%) as viscous oils. **α-9:** $[\alpha]_D$ +138.4 (*c* 0.25, $CHCl_3$); IR (neat) 2931, 1442, 1362, 1097 cm^{-1}; ^1H NMR δ 5.08 (d, 1 H, *J* = 3.6 Hz), 3.72−3.48 (m, 5 H), 3.62 (s, 3 H), 3.53 (s, 3 H), 3.45 (s, 3 H), 3.40 (s, 3 H), 3.23−3.17 (m, 2 H), 2.00−1.67 (m, 4 H), 1.55−1.15 (m, 6 H); ^{13}C NMR δ 93.8, 83.2, 81.5, 79.6, 75.1, 71.0, 69.8, 60.9, 60.5, 59.2, 58.2, 33.3, 31.4, 25.6, 24.6, 24.2. Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.43; H, 9.48. **β-9:** $[\alpha]_D$ −26.2 (*c* 0.20, $CHCl_3$); IR (neat) 2931, 1453, 1358, 1156, 1030 cm^{-1}; ^1H NMR δ 4.31 (d, 1 H, *J* = 7.7 Hz), 3.65−3.53 (m, 3 H), 3.61 (s, 3 H), 3.58 (s, 3 H), 3.51 (s, 3 H), 3.39 (s, 3 H), 3.28−3.21 (m, 1 H), 3.17−3.05 (m, 2 H), 3.00−2.93 (m, 1 H), 2.00−1.75 (m, 2 H), 1.75−1.60 (m, 2 H), 1.55−1.20 (m, 6 H); ^{13}C NMR δ 101.5, 86.5, 83.8, 79.5, 77.2, 74.6, 71.6, 60.8, 60.6, 60.4, 59.4, 33.6, 31.7, 25.7, 24.0, 23.8. Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.49; H, 9.49. **From Sulfoxide 7.** According to the general procedure A, Cp_2ZrCl_2 (101 mg, 0.346 mmol), $AgClO_4$ (144 mg, 0.696 mmol), cyclohexanol (74 μL, 0.70 mmol), and sulfoxide **7** (120 mg, 0.348 mmol) gave **9** (84 mg, 0.26 mmol, 76%, α/β = 1:1.3).

***tert*-Butyl 2,3,4,6-Tetra-*O*-methyl-D-glucopyranoside (10).** According to general procedure A, Cp_2ZrCl_2 (91 mg, 0.31 mmol), $AgClO_4$ (129 mg, 0.62 mmol), *tert*-butyl alcohol (46 mg, 0.62 mmol), and sulfoxide **6** (106 mg, 0.311 mmol) gave α-**10** (14 mg, 0.048 mmol, 15%) and β-**10** (39 mg, 0.13 mmol, 42%) as viscous oils. **α-10:** $[\alpha]_D$ +8.2 (*c* 0.17, $CHCl_3$); IR (neat) 2978, 2827, 1461, 1366, 1156, 1105 cm^{-1}; ^1H NMR δ 5.19 (d, 1 H, *J* = 3.7 Hz), 3.78 (dt, 1 H, *J* = 10.0, 2.6 Hz), 3.63 (s, 3 H), 3.62−3.45 (m, 3 H), 3.55 (s, 3 H), 3.46 (s, 3 H), 3.40 (s, 3 H), 3.24 (dd, 1 H, *J* = 9.8, 9.0 Hz), 3.15 (dd, 1 H, *J* = 9.7, 3.7 Hz), 1.26 (s, 9 H); ^{13}C NMR δ 90.7, 83.1, 81.9, 79.6, 75.2, 71.0, 69.3, 60.8, 60.5, 59.2, 58.4, 28.6. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.45; H, 9.60. **β-10:** $[\alpha]_D$ −8.3 (*c* 0.23, $CHCl_3$); IR (neat) 2978, 1469, 1358, 1093 cm^{-1}; ^1H NMR δ 4.37 (d, 1 H, *J* = 7.8 Hz), 3.62 (s, 3 H), 3.61−3.52 (m, 2 H), 3.56 (s, 3 H), 3.51 (s, 3 H), 3.37 (s, 3 H), 3.24 (ddd, 1 H, *J* = 9.4, 4.9, 2.0 Hz), 3.17−2.91 (m, 3 H), 1.26 (s, 9 H); ^{13}C NMR δ 97.6, 86.7, 84.0, 79.7, 74.4, 71.8, 60.8, 60.6, 60.4, 59.4, 28.7. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.59; H, 9.58.

Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-β-D-mannopyranoside (13). A solution of tetraacetate **11** (6.77 g, 15.4 mmol) in MeOH (75 mL) was treated with NaOMe (810 mg, 15.0 mmol). After 1 h, the reaction mixture was neutralized with Amberlite H^+ resin, filtered, and concentrated. The residue was dried under high vacuum at 65 °C for 1 h, dissolved in DMF (100 mL), cooled to 0 °C, and treated portionwise with 60% NaH (4.70 g, 0.118 mol, 7.7 equiv). After 45 min, MeI (5.75 mL, 0.0923 mol, 6.0 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature. After 3 h, the solution was quenched with H_2O, diluted with Et_2O, washed with H_2O, dried ($MgSO_4$), and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 75:25) gave **13** (3.89 g, 11.9 mmol, 77%) as a viscous oil: $[\alpha]_D$ −95.6 (*c* 0.59, $CHCl_3$); IR (neat) 2907, 1584, 1485, 1069 cm^{-1}; ^1H NMR δ 7.52−7.48 (m, 2 H), 7.32−7.20 (m, 3 H), 4.71 (s, 1 H), 3.89 (d, 1 H, *J* = 2.8 Hz), 3.72−3.68 (m, 1 H), 3.70 (s, 3 H), 3.60 (dd, 2 H, *J* = 10.8, 5.8 Hz), 3.53 (s, 3 H), 3.48−3.41 (m, 1 H), 3.39 (s, 3 H), 3.31 (ddd, 1 H, *J* = 9.5, 5.8, 1.8 Hz), 3.23 (dd, 1 H, *J* = 9.2, 3.1 Hz); ^{13}C NMR δ 135.5, 130.7, 128.9, 127.1, 87.5, 86.1, 79.7, 79.1, 76.4, 71.9, 62.1, 60.9, 59.4, 58.1. Anal. Calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.62; H, 7.41.

Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside (14). According to the protocol used for the conversion of **11** to **13**, thioether **14** (6.19 g, 90%) was obtained as a viscous oil from tetraacetate **12** (9.2 g): $[\alpha]_D$ +128.6 (*c* 4.6, $CHCl_3$); IR (neat) 3061, 2931, 1580, 1481, 1109 cm^{-1}; ^1H NMR δ 7.54−7.51 (m, 2 H), 7.35−7.20 (m, 3 H), 5.68 (d, 1 H, *J* = 1.5 Hz), 4.15−4.09 (m, 1 H), 3.86 (dd, 1 H, *J* = 3.1, 1.7 Hz), 3.71−3.49 (m, 4 H), 3.57 (s, 3 H), 3.55 (s, 3 H), 3.48 (s, 3 H), 3.41 (s, 3 H); ^{13}C NMR δ 134.6, 131.0, 129.0, 127.2, 84.6, 81.5, 78.7, 76.2, 72.1, 71.2, 60.7, 59.1, 58.1, 57.7. Anal. Calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.52; H, 7.39.

Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-β-D-mannopyranoside *S*-Oxide (15). A solution of **13** (1.60 g, 4.89 mmol) in CH_2Cl_2 (50 mL) was treated at −50 °C with 50−60% *m*-CPBA (1.40 g, 4.88 mmol based on 60% peroxide content). After 30 min, a few drops of dimethyl sulfide were added, and the reaction mixture was allowed to warm to room temperature. Saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 30:70) gave **15** (1.34 g, 3.90 mmol, 80%) as a viscous oil: $[\alpha]_D$ +98.7 (*c* 0.31, $CHCl_3$); IR (neat) 2935, 1442, 1097, 1038 cm^{-1}; ^1H NMR δ 7.76−7.72 (m, 2 H), 7.54−7.48 (m, 3 H), 4.29 (d, 1 H, *J* = 2.3 Hz), 3.91 (d, 1 H, *J* = 0.6 Hz), 3.79 (s, 3 H), 3.60−3.35 (m, 3 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 3.30 (s, 3 H), 3.20 (dd, 1 H, *J* = 9.3, 2.8 Hz), 3.08 (ddd, 1 H, *J* = 12.6, 4.2, 2.8 Hz); ^{13}C NMR δ 142.3, 131.3, 128.8, 124.8, 96.0, 85.7, 80.3, 76.0, 72.8, 71.3, 61.8, 61.0, 59.1, 57.9. Anal. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02. Found: C, 55.87; H, 6.87.

Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside *S*-Oxide (16). According to the protocol used for the conversion of **13** to **15**, sulfide **14** (6.02 g) was converted to viscous, oily sulfoxide **16** (3.92 g, 62%): $[\alpha]_D$ −53.9 (*c* 0.43, $CHCl_3$); IR (neat) 2931, 2820, 1446, 1117, 1038 cm^{-1}; ^1H NMR δ 7.62−7.59 (m, 2 H), 7.49−7.45 (m, 3 H), 4.48 (d, 1 H, *J* = 1.7 Hz), 4.12 (dd, 1 H, *J* = 3.4, 1.9 Hz), 3.86 (ddd, 1 H, *J* = 10.0, 5.1, 2.0 Hz), 3.76 (dd, 1 H, *J* = 9.3, 3.4 Hz), 3.56−3.44 (m, 3 H), 3.50 (s, 3 H), 3.48 (s, 3 H), 3.28 (s, 6 H); ^{13}C NMR δ 141.6, 131.2, 129.0, 124.2, 94.8, 80.8, 77.2, 75.2, 73.4, 71.3, 60.5, 59.1, 58.1, 57.7. Anal. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02. Found: C, 55.93; H, 6.88.

Benzyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyranoside (17). According to the general procedure A, Cp_2ZrCl_2 (333 mg, 1.14 mmol), $AgClO_4$ (472 mg, 2.28 mmol), benzyl alcohol (0.24 mL, 2.28 mmol), and sulfoxide **15** (391 mg, 1.14 mmol) gave α-**17** (291 mg, 0.893 mmol, 78%) and β-**17** (14 mg, 0.043 mmol, 4%) as viscous oils. **α-17:** $[\alpha]_D$ +75.3 (*c* 0.58, $CHCl_3$); IR (neat) 2907, 1453, 1113 cm^{-1}; ^1H NMR δ 7.25−7.18 (m, 5 H), 4.90 (d, 1 H, *J* = 1.5 Hz), 4.64 (d, 1 H, *J* = 11.8 Hz), 4.38 (d, 1 H, *J* = 11.8 Hz), 3.58−3.44 (m, 5 H), 3.42 (s, 3 H), 3.40−3.36 (m, 1 H), 3.38 (s, 3 H), 3.34 (s, 3 H), 3.30 (s, 3 H); ^{13}C NMR δ 137.2, 128.3, 127.8, 127.7, 96.2, 81.2, 77.1, 76.4, 71.6, 71.4, 69.0, 60.4, 59.0, 58.8, 57.6. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.58; H, 8.08. **β-17:** $[\alpha]_D$ −79.1 (*c* 1.5, $CHCl_3$); IR (neat) 2895, 1453, 1362, 1105, 1042 cm^{-1}; ^1H NMR δ 7.35−7.26 (m, 5 H), 4.97 (d, 1 H, *J* = 12.1 Hz), 4.58 (d, 1 H, *J* = 12.1 Hz), 4.41 (s, 1 H), 3.72−3.58 (m, 3 H), 3.66 (s, 3 H), 3.51 (s, 3 H), 3.47 (s, 3 H), 3.42 (s, 3 H), 3.39−3.24 (m, 2 H), 3.15 (dd, 1 H, *J* = 9.0, 3.2 Hz); ^{13}C NMR δ 137.4, 128.3, 127.8, 127.7, 100.0, 84.0, 77.0, 76.5, 75.6, 71.9, 70.6, 61.7, 60.7, 59.3, 57.3. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.50; H, 8.05. **From Sulfoxide 16.** According to the general procedure A, Cp_2ZrCl_2 (192 mg, 0.658 mmol), $AgClO_4$ (271 mg, 1.31 mmol), benzyl alcohol (0.13 mL, 1.31 mmol), and sulfoxide **16** (225 mg, 0.654 mmol) gave **17** (143 mg, 0.439 mmol, 67%, α/β = 5.8:1).

Cyclohexyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyranoside (18). According to the general procedure A, Cp_2ZrCl_2 (383 mg,

1.31 mmol), $AgClO_4$ (542 mg, 2.62 mmol), cyclohexanol (0.280 mL, 2.62 mmol), and sulfoxide **15** (451 mg, 1.31 mmol) gave α-**18** (305 mg, 0.959 mmol, 73%) and *β*-**18** (16 mg, 0.050 mmol, 4%) as viscous oils. **α-18:** $[\alpha]_D$ +63.1 (*c* 0.49, $CHCl_3$); IR (neat) 2931, 1453, 1109, 1053 cm^{-1}; ^1H NMR *δ* 4.94 (d, 1 H, *J* = 1.4 Hz), 3.60−3.30 (m, 7 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.29 (s, 3 H), 1.80−1.70 (m, 2 H), 1.65−1.55 (m, 2 H), 1.50−1.35 (m, 1 H), 1.35−1.00 (m, 5 H); ^{13}C NMR *δ* 94.5, 81.1, 77.6, 76.4, 74.5, 71.5, 71.0, 60.3, 58.9, 58.6, 57.4, 33.0, 31.2, 25.4, 23.9, 23.6. Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.45; H, 9.49. ***β*-18:** $[\alpha]_D$ −73.2 (*c* 0.25, $CHCl_3$); IR (neat) 2931, 1446, 1370, 1109, 1069 cm^{-1}; ^1H NMR *δ* 4.48 (d, 1 H, *J* = 0.5 Hz), 3.70−3.53 (m, 4 H), 3.64 (s, 3 H), 3.50 (s, 3 H), 3.47 (s, 3 H), 3.38 (s, 3 H), 3.32−3.20 (m, 2 H), 3.16 (dd, 1 H, *J* = 9.1, 3.2 Hz), 2.00−1.60 (m, 4 H), 1.50−1.10 (m, 6 H); ^{13}C NMR *δ* 99.0, 84.1, 77.6, 76.6, 76.1, 75.6, 72.1, 61.7, 60.7, 59.2, 57.3, 33.2, 31.3, 25.7, 23.7, 23.6. Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.43; H, 9.54. **From Sulfoxide 16.** According to the general procedure A, Cp_2ZrCl_2 (217 mg, 0.743 mmol), $AgClO_4$ (306 mg, 1.48 mmol), cyclohexanol (0.16 mL, 1.5 mmol), and sulfoxide **16** (256 mg, 0.745 mmol) gave **18** (161 mg, 0.506 mmol, 68%, *α*/*β* = 4.1:1).

***tert*-Butyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyranoside (19).** According to the general procedure A, Cp_2ZrCl_2 (1.18 g, 4.04 mmol), $AgClO_4$ (1.67 g, 8.07 mmol), *tert*-butyl alcohol (0.78 mL, 8.16 mmol), and sulfoxide **15** (1.41 g, 4.10 mmol) gave α-**19** (655 mg, 2.24 mmol, 55%) and *β*-**19** (39 mg, 0.13 mmol, 3%) as viscous oils. **α-19:** $[\alpha]_D$ +48.1 (*c* 2.5, $CHCl_3$); IR (neat) 2978, 2820, 1457, 1366, 1109 cm^{-1}; ^1H NMR *δ* 5.17 (d, 1 H, *J* = 1.8 Hz), 3.71 (ddd, 1 H, *J* = 9.3, 4.1, 2.1 Hz), 3.58−3.33 (m, 5 H), 3.50 (s, 3 H), 3.47 (s, 3 H), 3.44 (s, 3 H), 3.35 (s, 3 H), 1.22 (s, 9 H); ^{13}C NMR *δ* 91.2, 81.0, 78.6, 76.5, 75.2, 71.6, 70.7, 60.5, 59.1, 58.6, 57.6, 28.4. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.35; H, 9.50. ***β*-19:** $[\alpha]_D$ −64.4 (*c* 1.3, $CHCl_3$); IR (neat) 2977, 2831, 1464, 1363, 1112, 1072 cm^{-1}; ^1H NMR *δ* 4.51 (d, 1 H, *J* = 0.6 Hz), 3.65−3.49 (m, 3 H), 3.64 (s, 3 H), 3.49 (s, 3 H), 3.47 (s, 3 H), 3.36 (s, 3 H), 3.30−3.14 (m, 3 H), 1.25 (s, 9 H); ^{13}C NMR *δ* 95.5, 83.7, 78.1, 76.2, 75.2, 74.7, 71.7, 61.5, 60.3, 58.7, 56.9, 28.1. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.45; H, 9.65.

Glycosylation in the Presence of 2,6-Di-*tert*-butyl-4-methylpyridine. A mixture of Cp_2ZrCl_2 (245 mg, 0.839 mmol), $AgClO_4$ (351 mg, 1.70 mmol), 4 Å molecular sieves (100 mg), and CH_2Cl_2 (8 mL) was stirred at room temperature for 10 min. Benzyl alcohol (0.17 mL, 1.65 mmol) was added, followed by 2,6-di-*tert*-butyl-4-methylpyridine (172 mg, 0.839 mmol). The reaction mixture was cooled to −20 °C, and a solution of sulfoxide **16** (289 mg, 0.840 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 8.5 h, saturated aqueous $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 70:30) gave **17** (192 mg, 0.589 mmol, 70%, *α*/*β* = 6:1).

Methyl 2,3-Di-*O*-allyl-4-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (22). A suspension of Cp_2ZrCl_2 (90.0 mg, 0.309 mmol), $AgClO_4$ (128 mg, 0.618 mmol), and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) was stirred at room temperature for 15 min. Alcohol **21**[24] (225 mg, 0.618 mmol) in CH_2Cl_2 (0.5 mL) was added, and the temperature was lowered to −20 °C. A solution of sulfoxide **20**[25] (200 mg, 0.309 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise, and the reaction mixture was allowed to warm gradually to room-temperature overnight. Saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 85:15) gave **22** (197 mg, 0.222 mmol, 72%, *α*/*β* = 2.9:1) as a viscous oil: $[\alpha]_D$ +62.2 (*c* 4.95, $CHCl_3$); IR (neat) 3064, 1491, 1453, 1358 cm^{-1}; ^1H NMR (600 MHz) *δ* 7.50−7.20 (m, 25 H), 6.15−5.95 (m, 2 H), 5.42−5.26 (m, 4 H), 5.16−5.04 (m, 3 H), 4.97−4.87 (m, 3 H), 4.85−4.80 (m, 2 H), 4.77−4.64 (m, 3 H), 4.60−4.48 (m, 3 H), 4.42−4.08 (m, 4 H), 3.97−3.75 (m, 6 H), 3.73−3.68 (m, 2 H), 3.67−3.52 (m, 1 H), 3.49, 3.47 (2 s, 3 H), 3.46−3.44 (m, 1 H); ^{13}C NMR (151 MHz) *δ* 138.81, 138.51, 138.47, 138.46, 138.42, 138.35, 138.23, 138.09, 137.97, 135.34, 135.32, 134.90, 134.87, 128.42, 128.39, 128.35, 128.30, 128.04, 127.93, 127.92, 127.90, 127.83, 127.80, 127.74, 127.68, 127.67, 127.65, 127.63, 127.61, 127.57, 117.71, 117.53, 116.58, 116.46, 103.84, 98.09, 98.03, 97.30, 84.80, 82.10, 81.75, 81.74, 81.56, 80.06, 79.73, 79.50, 77.95, 77.89, 77.70, 77.60, 75.75, 75.54, 75.04, 75.03, 74.99, 74.92, 74.90, 74.31, 74.30, 73.44, 73.42, 72.61, 72.57, 72.44, 70.23, 69.82, 69.00, 68.63, 68.43, 66.16, 55.12, 55.06.

Glycosylation Using 10 wt % $AgClO_4$ on Celite. A suspension of Cp_2ZrCl_2 (57.0 mg, 0.195 mmol), $AgClO_4$ on Celite (∼10 wt %, 810 mg, 0.390 mmol),[18e] and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature for 15 min. Alcohol **21** (142 mg, 0.390 mmol) in CH_2Cl_2 (0.5 mL) was added, and the temperature was lowered to −20 °C. A solution of sulfoxide **20** (126 mg, 0.195 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise, and the reaction mixture was allowed to warm gradually to room-temperature overnight. Saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 85:15) gave **22** (112 mg, 0.127 mmol, 65%, *α*/*β* = 3.0:1).

***(E)*-1-(Phenylthio)-1-octene (25).** A solution of 1-octyne (86.0 *μ*L, 0.582 mmol) in CH_2Cl_2 (2.5 mL) was treated with $Cp_2Zr(H)Cl$ (150 mg, 0.582 mmol). The reaction mixture was stirred at room temperature for 15 min, cooled to 0 °C, and treated with a solution of *β*-sulfoxide **6** (100 mg, 0.291 mmol) in CH_2Cl_2 (0.5 mL), followed by $AgClO_4$ (6.0 mg, 0.029 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **25** (43.6 mg, 0.198 mmol, 68%) as an oil that provided ^1H NMR and HRMS data in agreement with literature values.[26]

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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