

A study of silver (I) perchlorate as an effective promoter for chemical glycosylation with thioimidates and thioglycosides

Scott J Hasty
Sneha C Ranade
Alexei V Demchenko

Department of Chemistry and
Biochemistry, University of
Missouri–St Louis, St Louis,
Missouri, USA

Abstract: It has been previously acknowledged that perchlorate salts may be beneficial for the formation of 1,2-cis glycosides. Here, we demonstrate the effectiveness of silver (I) perchlorate as a powerful promoter of glycosyl thioimide activation. Improved 1,2-cis selectivity was obtained, compared against that obtained with other silver (I) salts, including commonly-used triflate. The use of a combination of silver (I) perchlorate and methyl sulfonyl bromide to activate thioglycosides was also investigated. The cooperative use of these activation protocols was applied to a one-pot, two-step sequential activation, using thioimide and thioglycoside building blocks.

Keywords: carbohydrates, glycosylation, perchlorate, methodology, promoter

Introduction

Aspiration to understand the involvement of carbohydrates in practically all life-sustaining, and many life-threatening biological processes has been the major driving force in the glycosciences.¹ A key to understanding the biological roles that carbohydrates play is to have straightforward access to synthetic oligosaccharides and their conjugates. Chemical synthesis of complex oligosaccharides, particularly those containing challenging 1,2-cis glycosidic linkages,^{2–4} has long been considered a major challenge. Various factors, such as protecting and leaving groups, promoter/activator, solvent, temperature, etc, may have a significant impact on the course and the outcome of the glycosylation reaction.⁵ Nevertheless, there are still significant gaps in our knowledge of the glycosylation reaction and its mechanism.^{6–9} For instance, the effect of the counter-anion remains unclear. Since a vast majority of promoters rely on the use of triflates (trifluoromethanesulfonates) (Tf),¹⁰ the function of triflate as the counter-anion (or as the covalently-bound reaction intermediate) during the glycosylation reaction is established, and has been extensively studied.^{11,12} Another well-studied phenomenon is halide anion-mediated glycosylation, wherein the involvement of bromide¹³ and iodide^{14,15} anions has been related to high 1,2-cis selectivity. The effect of other counter-ions is largely unknown, although it has been noticed that high 1,2-cis stereoselectivity can be achieved using tritylium perchlorate^{16–18} or iodonium(di- γ -collidine)perchlorate^{19,20} as promoters, or lithium perchlorate^{21–25} as an additive. To the best of our knowledge, no systematic studies of perchlorate salts as promoters of glycosylation have yet been reported.²⁶ Expanding upon previous use of AgClO_4 as the promoter²⁷ or as an additive in glycosylations,^{24,28} we here report our preliminary study of this promoter for the activation of various thioimidoyl and thioglycosyl donors.

Correspondence: Alexei V Demchenko
University of Missouri–St Louis,
One University Boulevard, 315 Benton
Hall (MC27), St Louis, MO 63121, USA
Tel +1 314 516 7995
Fax +1 314 516 5342
Email demchenkoa@umsl.edu

Experimental

General

Column chromatography was performed on EM Science Silica Gel 60 (70–230 mesh) (Cambridge Scientific, Watertown, MA, USA); reactions were monitored by thin layer chromatography (TLC) on EM Science Kieselgel 60 F254. Compounds were detected by examination under ultraviolet light, and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at 40°C. CH_2Cl_2 and $\text{ClCH}_2\text{CH}_2\text{Cl}$ were distilled from CaH_2 immediately prior to usage. Acetonitrile was dried by refluxing with CaH_2 , then distilled and stored over molecular sieves (3 Å). Tetrahydrofuran (THF) was refluxed for 2 hours, then distilled over sodium, using benzophenone as an indicator under argon, directly before use. Acetone was dried by refluxing with K_2CO_3 , then distilled and stored over molecular sieves (3 Å). The molecular sieves used for reactions (3 Å) were crushed and activated in vacuo at 390°C for 8 hours, in the first instance, and then for 2–3 hours at 390°C , directly prior to application. AgClO_4 (Sigma-Aldrich, St Louis, MO, USA) was used as is. Warning: avoid or control reaction with peroxides. All transition metal perchlorates should be considered as potentially explosive; avoid storing with fluorobenzenes, nitromethane, acetylene, peroxides, strong mineral acids, metals, and metal hydrides; refer to the manufacturer's specifications for full recommendations regarding hazards, handling, and storage. AgPF_6 (Acros Organics, Thermo Fisher Scientific, Bridgewater, NJ, USA) and AgBF_4 (Acros Organics) were used as is. Silver (I) triflate (AgOTf) (Acros Organics) was co-evaporated with toluene (3 × 10 mL) and dried in vacuo for 2–3 hours directly prior to application. Optical rotations were measured using a Jasco P-1020 polarimeter (Jasco Inc, Easton, MD, USA). Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded in CDCl_3 at 300 MHz and Carbon-13 nuclear magnetic resonance ($^{13}\text{C-NMR}$) spectra were recorded in CDCl_3 at 75 MHz (Avance, Bruker Corp, Billerica, MA, USA), unless otherwise noted. High resolution mass spectroscopy (HRMS) determinations were made using a JMS-700 MStation™ mass spectrometer (JEOL, Tokyo, Japan).

Synthesis of glycosyl donors

Phenyl 3,4,6-tri-O-benzoyl-2-O-benzyl-1-thio- β -D-glucopyranoside (4)

A 5.0 mL solution of NaSPh in THF, freshly prepared from 60% NaH (2.36 mmol) and HSPh (2.36 mmol), and 15-crown-5 (0.16 mL, 0.8 mmol) were added to a stirring solution of 3,4,6-tri-O-benzoyl-2-O-benzyl- α -D-glucopyranosyl

bromide³⁵ (0.85 g, 1.6 mmol) in dry THF (5.0 mL), then the reaction mixture was stirred under argon for 2.5 hours at room temperature. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (~100 mL), washed first with water (10 mL), then with saturated aqueous solution (sat aq) of NaHCO_3 (10 mL), then with water (3 × 10 mL). The organic phase was then separated, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound in 73% yield (0.65 g) as a white foam. Analytical data for 4: $R_f=0.48$ (ethyl acetate/hexanes: 3/7, v/v); $[\alpha]_D^{22}$ 10.4 (c=1.0, CHCl_3); $^1\text{H-NMR}$: δ , 3.78 (dd, 1H, $J_{2,3}=9.4$ Hz, H-2), 4.07 (m, 1H, $J_{5,6a}=6.1$, $J_{5,6b}=2.8$ Hz, H-5), 4.45 (dd, 1H, $J_{6a,6b}=12.2$ Hz, H-6a), 4.61 (dd, 1H, H-6b), 4.72 (dd, 2H, $^2J=10.7$ Hz, CH_2Ph), 4.91 (d, 1H, $J_{1,2}=9.7$ Hz, H-1), 5.50 (dd, 1H, $J_{4,5}=9.8$ Hz, H-4), 5.78 (dd, 1H, $J_{3,4}=9.3$ Hz, H-3), 7.02–8.12 (m, 25H, aromatic) ppm; $^{13}\text{C-NMR}$: δ , 63.5, 69.6, 75.3, 75.9, 76.1, 78.5, 87.8, 127.9, 128.0, 128.1, 128.4 (×3), 128.5 (×7), 128.9, 129.1 (×2), 129.4, 129.8 (×2), 129.9 (×3), 130.0 (×2), 130.3, 132.5, 133.0, 133.3, 133.6, 137.2, 165.6, 165.7, 166.2 ppm; HR-FAB MS $[\text{M}+\text{Na}]^+$ calculated (calcd) for $\text{C}_{40}\text{H}_{34}\text{O}_8\text{SNa}^+$ 697.1872, found 697.1868.

2-benzimidazolyl 3,4,6-tri-O-benzoyl-2-O-benzyl-1-thio- β -D-glucopyranoside (7)

Potassium 2-benzimidazolethione³⁶ (KSBiz) (0.66 g; 3.5 mmol) and 18-crown-6 (0.12 mg; 0.46 mmol) were added to a stirring solution of 3,4,6-tri-O-benzoyl-2-O-benzyl- α -D-glucopyranosyl bromide (1.25 g; 2.3 mmol) in dry acetone (10 mL), then the reaction mixture was stirred under argon for 4 hours at room temperature. Upon completion, the solid was filtered off and rinsed successively with CH_2Cl_2 . The combined filtrate (~250 mL) was washed first with water (20 mL), then with sat aq NaHCO_3 (20 mL), and then with water (3 × 20 mL). The organic phase was separated, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-toluene gradient elution) to afford the title compound in 62% yield (0.82 g) as a white foam. Analytical data for 7: $R_f=0.051$ (ethyl acetate/hexanes: 1/1, v/v); $[\alpha]_D^{22}$ -130.9 (c=1.0, CHCl_3); $^1\text{H-NMR}$: δ , 3.75 (d, 1H, $J_{2,3}=9.3$ Hz, H-2), 4.18 (m, 1H, $J_{5,6a}=6.6$, $J_{5,6b}=2.2$ Hz, H-5), 4.62 (dd, 1H, $J_{6a,6b}=12.5$ Hz, H-6a), 4.77 (dd, 1H, H-6b), 4.85 (dd, 2H, $^2J=10.8$ Hz, CH_2Ph), 5.05 (d, 1H, $J_{1,2}=9.5$ Hz, H-1), 5.53 (dd, 1H, $J_{4,5}=9.8$ Hz, H-4), 5.83 (dd, 1H, $J_{3,4}=9.3$ Hz, H-3), 7.06–8.18 (m, 24H, aromatic), 10.64 (br. s, 1H, NH) ppm; $^{13}\text{C-NMR}$: δ , 62.9, 68.9, 75.3, 75.5, 78.5, 84.5, 123.1, 128.1, 128.4 (×4), 128.5 (×3), 128.7 (×2), 128.8 (×4), 128.9 (×2), 129.2, 129.6, 129.9 (×3), 130.0

($\times 3$), 130.2 ($\times 3$), 133.4, 133.8, 140.0, 143.8, 165.4, 165.7, 167.4 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{41}H_{34}N_2O_8SNa^+$ 737.1934, found 737.1930.

2-O-benzyl-3,4,6-tri-O-benzoyl-1-thio- β -D-glucopyranosyl O-methyl phenylcarbamothioate (8)

O-Methyl phenylcarbamothioate (HSNea) (0.22 g, 1.29 mmol) and KOH (0.048 g, 0.85 mmol) were added to a stirring solution of 3,4,6-tri-O-benzoyl-2-O-benzyl- α -D-glucopyranosyl bromide (0.46 g, 0.85 mmol) in dry acetone (6.0 mL), and the reaction mixture was stirred under argon for 2.5 hours at room temperature. Upon completion, the solid was filtered off and rinsed successively with CH_2Cl_2 . The combined filtrate (~ 100 mL) was washed with water (10 mL), then with sat aq $NaHCO_3$ (10 mL), and then with water (3×10 mL). The organic phase was separated, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound in 42% yield (0.22 g) as a white foam. Analytical data for 8: $R_f=0.42$ (ethyl acetate/hexanes: 3/7, v/v); $[\alpha]_D^{22} -14.3$ (c=1.0, $CHCl_3$); 1H -NMR: δ , 3.69 (dd, 1H, $J_{2,3}=9.1$ Hz, H-2), 3.90 (s, 3H, OCH_3), 4.13 (m, 1H, $J_{5,6a}=5.9$, $J_{5,6b}=2.9$ Hz, H-5), 4.44 (dd, 1H, $J_{6a,6b}=12.2$ Hz, H-6a), 4.54 (dd, 2H, $^2J=10.6$ Hz, CH_2Ph), 4.58 (dd, 1H, H-6b), 5.41 (d, 1H, $J_{1,2}=10.0$ Hz, H-1), 5.47 (dd, 1H, $J_{4,5}=9.8$ Hz, H-4), 5.77 (dd, 1H, $J_{3,4}=9.4$ Hz, H-3), 6.79–8.07 (m, 25H, aromatic) ppm; ^{13}C -NMR: δ , 56.6, 63.5, 69.7, 75.4, 76.0, 76.3, 83.1, 121.7 ($\times 2$), 124.12, 128.1, 128.4 ($\times 8$), 128.5 ($\times 3$), 128.9, 129.2 ($\times 2$), 129.3, 129.8 ($\times 4$), 129.9 ($\times 2$), 133.3, 133.4, 133.5, 136.8, 146.8, 155.2, 165.5, 165.7, 166.2 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{42}H_{37}NO_9SNa^+$ 754.2081, found 754.2089.

2-benzoxazolyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio- β -D-glucopyranoside (25)

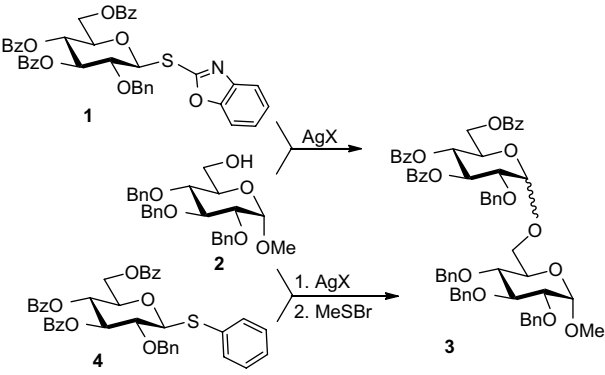
Potassium 2-mercaptobenzoxazole²⁹ (KSBox) (0.600 g, 3.17 mmol) and 18-crown-6 (0.67 g, 0.25 mmol) were added to a stirring solution of 3,4,6-tri-O-acetyl-2-azido-2-deoxy- α -D-glucopyranosyl bromide³⁰ (0.50 g, 1.27 mmol) in dry acetone (10 mL), then the reaction mixture was stirred under argon for 2.5 hours at room temperature. Upon completion, the solid was filtered off and rinsed successively with CH_2Cl_2 . The combined filtrate (~ 250 mL) was washed with water (20 mL), then with sat aq $NaHCO_3$ (20 mL), and then with water (3×20 mL). The organic phase was separated, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the title compound in 37% yield (0.218 g) as an off-white

foam. Analytical data for 25: $R_f=0.49$ (ethyl acetate/hexanes: 1/1, v/v); $[\alpha]_D^{22} 9.1$ (c=1.0, $CHCl_3$); 1H -NMR: δ , 1.99, 2.05, 2.13 (3 s, 9H, $3 \times CH_3$), 3.91 (m, 1H, $J_{5,6a}=2.2$, $J_{5,6b}=4.7$ Hz, H-5) 3.94 (dd, 1H, $J_{2,3}=9.5$ Hz, H-2), 4.12 (dd, 1H, $J_{6a,6b}=12.5$ Hz, H-6a), 4.27 (dd, 1H, H-6b), 5.12 (dd, 1H, $J_{4,5}=9.5$ Hz, H-4), 5.25 (dd, 1H, $J_{3,4}=9.5$ Hz, H-3), 5.42 (d, 1H, $J_{1,2}=10.5$ Hz, H-1), 7.27–7.68 (m, 4H, aromatic) ppm; ^{13}C -NMR: 20.7, 20.8 ($\times 2$), 61.8, 63.1, 70.0, 74.7, 76.6, 84.1, 110.4, 119.3, 124.8, 124.9, 141.7, 152.1, 160.1, 169.8, 170.0, 170.7 ppm; HR-FAB MS $[M+H]^+$ calcd for $C_{19}H_{21}N_4O_8S^+$ 465.1080, found 465.1072.

Typical procedure for glycosidation of thioimidates

A mixture of glycosyl donor (0.033 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3 Å, 125 mg) in 1,2-dichloroethane (1 mL) was stirred under argon for 1 hour. Silver (I) salt (0.068 mmol) was added, and the reaction mixture was monitored by TLC. Upon completion (Tables 1 and 2), the solid was filtered off and the filtrate was diluted with CH_2Cl_2 (15 mL), washed with 1% NaOH (5 mL), then water (3×5 mL). The organic layer was separated, dried with Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the corresponding oligosaccharide.

Table 1 Comparative study of $AgClO_4$ versus other Ag (I) salts



Entry	Donor	AgX	Time (hours)	Yield of 3	α/β ratio ^a
1	I	$AgClO_4$	1	95%	11.9/1
2	I	$AgOTf$	1	94%	7.8/1
3	I	$AgPF_6$	1	87%	2.1/1
4	I	$AgBF_4$	1	91%	1.6/1
5 ^b	4	$AgClO_4$	1.25	89%	10.1/1
6 ^b	4	$AgOTf$	1.25	91%	7.3/1
7 ^b	4	$AgPF_6$	1.75	82%	2.6/1
8 ^b	4	$AgBF_4$	2	87%	2.4/1

Notes: The anomeric ratios have been determined by comparing the integral intensities of the corresponding signals in proton nuclear magnetic resonance spectra; ^bperformed in the presence of MeSBr.

Abbreviations: $AgOTf$, silver (I) triflate; MeSBr, methyl sulfonyl bromide.

Table 2 Investigation of AgClO_4 as promoter of glycosylation with thioimide and thioglycoside donors

Entry	Donor	Acceptor	Time	Product	Yield	α/β ratio
1			1 h		92%	>20/1
2			2 h		93%	11.2/1
3			7 h		92%	6.6/1
4			30 min		91%	β only
5			30 min		88%	β only
6			45 min		94%	β only
7			45 min		92%	β only
8 ^a			20 min		86%	β only
9			15 min		96%	1.3/1
10			15 min		89%	1.6/1
11			15 min		89%	1.4/1

(Continued)

Table 2 (Continued)

Entry	Donor	Acceptor	Time	Product	Yield	α/β ratio
12		2	15 min	16	91%	1.3/1
13 ^a	19	2	20 min	16	86%	1.5/1
14	20	2	15 min		83%	1/1.2
15	21	2	15 min	22	87%	1/1.1
16	23	2	2 h	24	89%	3.4/1
17	25	2	5 min	26	97%	β only
18	27	5	5 min	28	95%	β only
19	27	2	5 min	29	88%	β only
20	30	2	5 min	28	82%	β only
21 ^a	31	2	5 min	28	82%	β only
	32					

Note: ^aPerformed in the presence of MeSBr.

Abbreviations: min, minute; h, hour; MeSBr, methyl sulfonyl bromide.

Typical procedure for glycosidation of thioglycosides

A mixture of glycosyl donor (0.033 mmol), glycosyl acceptor (0.030 mmol), and freshly activated molecular sieves (3 Å, 125 mg) in 1,2-dichloroethane (1 mL) was stirred under

argon for 1 hour. Silver (I) salt (0.068 mmol) was added first, followed by freshly-prepared methyl sulfonyl bromide (MeSBr),³¹ and the reaction mixture was monitored using TLC. Upon completion (Tables 1 and 2), the solid was filtered off and the filtrate was diluted with CH₂Cl₂ (15 mL),

then washed with 1% NaOH (5 mL), then water (3×5 mL). The organic layer was separated, dried with Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution), to afford the corresponding oligosaccharide.

Results and discussion

Over the last decade, we have been interested in syntheses and applications of various glycosyl thioimidates as new, versatile building blocks for chemical glycosylation and expeditious oligosaccharide synthesis.³² S-Benzoxazolyl (SBox),³³ S-thiazolyl (STaz),³⁴ O-methyl phenylcarbamothioate (SNea),³⁵ and S-benzimidazolyl (SBiz)³⁶ are all commonly activated with AgOTf. This activation pathway often gives superior yields and stereoselectivity, compared against those achieved with other activators. However, AgOTf is very sensitive to moisture, and typically requires thorough conditioning prior to use. To address this, we introduced silver (I) tetrafluoroborate (AgBF_4) as a powerful activator for thioimidates.³⁷ Nevertheless, the synthesis of 1,2-cis glycosides, in a majority of applications, using either promoter, provided only marginal stereoselectivity. In our preliminary evaluation of various silver (I) salts, we noticed that AgClO_4 provides consistently superior 1,2-cis selectivity. This observation triggered our interest in a more detailed study of this promoter in its application to glycosylations with thioimide and thioglycoside donors.

To pursue this aim, we obtained SBox donor 1,³⁸ which was subjected to a series of parallel glycosylations using various silver (I) salts (Table 1). Thus, the reaction of glycosyl donor 1 with primary glycosyl acceptor 2,³⁵ in the presence of AgClO_4 , afforded disaccharide 3³⁹ in 95% yield, and very commendable stereoselectivity ($\alpha/\beta=11.9/1$; Entry 1). Very comparable outcomes, in terms of yields and reactivity rates, were detected in cases when AgOTf, silver hexafluorophosphate (AgPF_6), and AgBF_4 were used as promoters of the glycosylation of acceptor 2 with SBox donor 1 (Entries 2–4). In all cases, disaccharide 3 was isolated in good yields (87%–94%), but with significantly reduced selectivity, in comparison to that recorded for AgClO_4 . The stereoselectivity recorded in these parallel experiments ranged from good ($\alpha/\beta=7.8/1$; Entry 2), for AgOTf, to rather poor for AgPF_6 ($\alpha/\beta=2.1/1$; Entry 3) and AgBF_4 ($\alpha/\beta=1.6/1$; Entry 4). Since all other reaction conditions remained the same, and no significant changes in the reaction rate were observed (all reactions were completed within 1 hour), this differential stereoselectivity is arguably

indicative of the effect of the counter-anion. The results surveyed clearly indicate that the perchlorate anion creates the most favorable environment for the formation of α -linked disaccharide 3.

In principle, one could envisage a variety of modes by which the counter-anion may be involved in (and possibly influence) the glycosylation reaction. Nevertheless, this key effect is often overlooked (apart from the effect of triflate, which has been thoroughly studied by Crich et al).^{11,40} As it was previously demonstrated for AgOTf, the activation of the SBox leaving group takes place via the anomeric sulfur.⁴¹ The resultant glycosyl cation may then be stabilized via the oxocarbenium cation (Figure 1A) with counter-anion (triflate – or X, in a more general sense). In the case of nucleophilic counter-anions, such as triflate or perchlorate, but not tetrafluoroborate or pentafluorophosphate, formal covalent attachment of X is another possible intermediate (Figure 1B). If the neighboring substituent at C-2 is an acyl group, glycosylations may also proceed via an acyloxonium intermediate (Figure 1C). The subsequent glycosyl acceptor attack can be influenced by the steric and electronic properties of X, particularly if the reaction proceeds via the intermediacy of either A or B. It should be noted that all reaction intermediates are quite unstable. Therefore, the exact mechanism of chemical glycosylation remains elusive.^{8,9}

We were interested in investigating the effect of perchlorate anion on the glycosidation of thioglycosides, common donors for chemical glycosylation.⁴² Since a silver (I) salt alone fails to activate thioglycosides, its inclusion into the promoter system was explored. Herein, we chose to investigate the combination of MeSBr (introduced by Dasgupta and Garegg as a co-promoter of glycosylation)³¹ and AgX. Another possibility would be to use N-iodosuccinimide (NIS)/AgX combination, because NIS/AgOTf is a rather common promoter system for thioglycoside activation.⁴² To carry out this reaction, MeSBr was added to a mixture

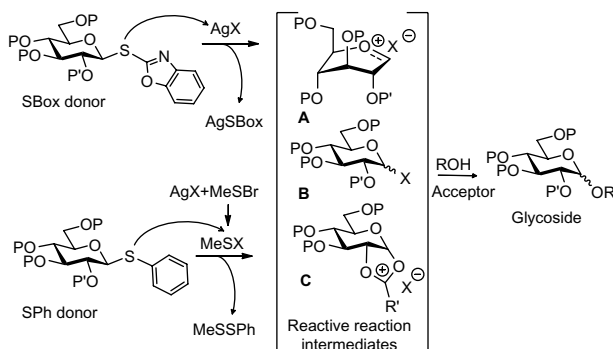


Figure 1 Schematic representation of the reaction mechanism. **Abbreviation:** Box, S-benzoxazolyl.

containing thioglycoside (SPh) donor 4, glycosyl acceptor 2, and AgX (refer to the experimental section for further details). The formation of insoluble yellow precipitate (AgBr) could be detected momentarily. Apparently, MeSX is also formed at this time (Figure 1), which then undergoes nucleophilic attack by the anomeric sulfur, forming the glycosyl sulfonium intermediate. According to the generally accepted activation mechanism,⁶ the leaving group then departs as a disulfide (PhSSMe) leading to the activated intermediates (Figure 1A–C) or a combination thereof, depending on the original structure and other factors (vide supra).

Following this pathway, the activation of SPh donor 4 with MeSBr/AgClO₄ for reaction with primary acceptor 2 afforded disaccharide 3 in 89% yield with very respectable stereoselectivity ($\alpha/\beta = 10.1/1$; Entry 5) (Table 1). Similar outcomes, in terms of yields and reactivity, were detected in cases wherein AgOTf, AgPF₆, and AgBF₄ were used as promoters for glycosylation of acceptor 2 with SPh donor 4 (Entries 6–8). Thus, disaccharide 3 was isolated in good yields (82%–91%), but with significantly reduced selectivity ($\alpha/\beta = 2.4$ – $7.3/1$). Since the difference in the reaction rates between different promoters was insignificant, we believe that it is the effect of the counter-anion that influences the stereoselectivity of glycosylations. Once again, the results indicate that perchlorate is the most favorable counter-ion for the formation of α -glucoside 3. These results were deemed both practical and intriguing. Hence, we decided to undergo subsequent comprehensive investigation of this promising promoter.

To determine the efficacy of AgClO₄ in the context of other classes of glycosidic linkages and substrates, we examined a wider range of glycosyl donors. The key findings of this study are summarized in Table 2. As a direct continuation of our preliminary work, we set up a series of experiments with 2-O-benzyl-3,4,6-tri-O-benzoyl-protected (superdisarmed)⁴³ thioimidoyl donors. First, we performed glycosylation of the secondary glycosyl acceptor 5³⁵ with SBox donor 1. This coupling produced disaccharide 6⁴⁴ in 92% yield, and an impressive stereoselectivity ($\alpha/\beta = >20/1$; Entry 1). Likewise, the glycosyl donor bearing SBiz moiety 7 readily underwent coupling with acceptor 2, producing disaccharide 3 in 93% yield in 2 hours ($\alpha/\beta = 11.2/1$; Entry 2). It was observed that glycosidation involving the acyclic SNea donor 8 took substantially longer (7 hours) but, nevertheless, disaccharide 3 was isolated in 92% yield ($\alpha/\beta = 6.6/1$; Entry 3). Pleased with the activation of the unreactive superdisarmed series, we turned our attention

to glycosidations involving the per-benzoylated (disarmed) glycosyl donors. Thioimidate donors 9,³⁸ 12,³⁶ and 13³⁵ underwent coupling smoothly and produced the expected 1,2-trans-linked disaccharides 10³⁵ and 11³⁵ in excellent yields (88%–94%; Entries 4–7). All reactions were relatively swift, and completed in 30–45 minutes. Disarmed thioglycoside 14⁴⁵ reacted even more quickly (20 minutes) in the presence of MeSBr and AgClO₄ (86% yield; Entry 8).

We then began studying a series of per-benzylated (armed) glycosyl donors. Although all yields recorded were very commendable, the stereoselectivity observed was rather poor, most likely due to our inability to slow this reaction. Lowering the reaction temperature did not help, because it was favoring the formation of the kinetic (β -linked) product. Thus, coupling of SBox donor 15³⁸ with acceptor 2 produced disaccharide 16⁴⁶ in 96% yield within 15 minutes ($\alpha/\beta = 1.3/1$; Entry 9). Similarly, donor 15 glycosidated with secondary glycosyl acceptor 5 to afford disaccharide 17⁴⁶ in 89% yield in 15 minutes ($\alpha/\beta = 1.6/1$; Entry 10). Evaluation of per-benzylated thioimidoyl donors bearing the SBiz 18³⁶ and SNea 19³⁵ moieties was conducted, and their reactivity was found to be similar to that of the previously-mentioned glycosyl donors (89% and 91% yields; $\alpha/\beta = 1.4/1$ and $1.3/1$; Entries 11 and 12, respectively). Thiophenyl donor 20⁴⁷ also rapidly underwent coupling with AgClO₄/MeSBr, producing disaccharide 16 in 86% yield in 20 minutes ($\alpha/\beta = 1.5/1$; Entry 13).

Glycosylations with SBox galactosyl (21),⁴⁸ mannosyl (23),⁴⁹ and 2-azido-2-deoxyglucosyl (25) donors were also conducted. It was observed that galactosyl and mannosyl glycosyl donors 21 and 23 underwent coupling with glycosyl acceptor 2 in the presence of AgClO₄ in 15 minutes, with corresponding disaccharides 22⁵⁰ and 24⁵¹ isolated in 83% and 87% yields, respectively. Unfortunately, no stereoselectivity was observed in these couplings ($\alpha/\beta = 1/1.2$ and $1/1.1$; Entries 14 and 15). When we glycosidated 2-azido-2-deoxy donor 25 with acceptor 2, disaccharide 26⁵² was produced in 89% yield ($\alpha/\beta = 3.4/1$). Finally, we investigated highly reactive (superarmed) glycosyl donors equipped with the 2-O-benzoyl-3,4,6-tri-O-benzyl protecting group pattern.^{48,53} All glycosidations of SBox (27),⁴⁸ SBiz (30),³⁶ and SNea (31)³⁵ donors with glycosyl acceptors 2 and 5, in the presence of AgClO₄, were exceptionally swift (less than 5 minutes). The respective disaccharides 28⁴⁸ and 29⁴⁸ were isolated in 82%–97% yields (Entries 17–20). A similar reaction rate was observed when SPh glycosyl donor 32⁵⁴ was subjected to AgClO₄/MeSBr activation conditions, affording disaccharide 28 in 82% yield (Entry 21). As anticipated, all glycosylations

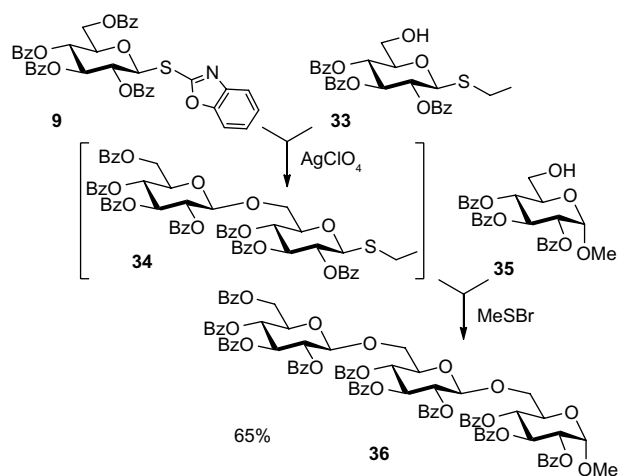


Figure 2 Synthesis of trisaccharide 36 via selective two-step activation in one pot.

with glycosyl donors of the superarmed series proceeded with complete β -selectivity.

Based on these results, it was also determined that a two-step, one-pot sequential activation, using building blocks with thioimidoyl and thioglycosyl leaving groups, was attainable by proper choice of promoter. The sequence envisioned was to first selectively activate thioimidoyl donor with thioglycoside acceptor in the presence of AgClO_4 . The expectation was that the resulting disaccharide could be activated directly, followed by addition of MeSBr and a new acceptor. To explore this possibility, SBox thioimidate donor 9 was coupled with thioglycosyl acceptor 33,⁵⁵ employing AgClO_4 as the promoter (Figure 2). Upon disappearance of acceptor 33, as judged by TLC, the newly formed disaccharide 34 (not isolated) was then activated by the addition of MeSBr and glycosyl acceptor 35. As a result, trisaccharide 36⁵⁶ was obtained in 65% yield.

Conclusion

In conclusion, we demonstrated the effectiveness of silver (I) perchlorate as a powerful promoter towards glycosyl thioimidate activation. It has been utilized with a variety of donors of the gluco, galacto, manno, and glucosamino series. Also investigated was the use of AgClO_4 as an additive, when paired with methyl sulfenyl bromide, to activate glycosyl thioglycosides. With superdisarmed glycosyl donors equipped with the 3,4,6-tri-O-benzoyl-2-O-benzyl protecting group pattern, AgClO_4 was found to display improved 1,2-cis selectivity, in comparison to that obtained with other silver (I) salts, including commonly-used AgOTf . The sequential use of these activation protocols was applied to a one-pot, two-step synthesis of a trisaccharide, using thioimidate and thioglycoside building blocks.

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Disclosure

The authors report no conflicts of interest in this work.

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