Research Article

Journal of Physical Organic Chemistry

Received: 23 January 2008, Revised: 7 April 2008, Accepted: 7 April 2008, Published online in Wiley InterScience: 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1388

Electrochemical glycosylation in the presence of a catalytic chemical mediator

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Electrochemical glycosylation of thioglycoside donors proceeds efficiently in an undivided cell in the presence of a catalytic amount of the chemical mediator (4-bromophenyl) ammoniumyl hexachloroantimonate (BAHA). In comparison with electrochemical glycosylation alone, the use of a catalytic amount of BAHA greatly increases the rate of reaction, reduces the potential required and inhibits ester-protecting group migrations. Copyright © 2008 John Wiley & Sons, Ltd.

Supplementary electronic material for this paper is available in Wiley InterScience at http://www.mrw.interscience.wiley.com/suppmat/0894-3230/suppmat/

Keywords: glycosylation; oligosaccharides; electrochemistry; oxidation; catalysis

INTRODUCTION

The fundamental importance of oligosaccharides in a plethora of vital biological processes is now extremely well recognised.[1,2] Consequentially, oligosaccharides have attracted the attention of synthetic chemists, not only for use as biological tools and probes, but also as challenging targets for total synthesis, the complexities of which have necessitated the development of significant new synthetic methodologies.

Central to the synthesis of any oligosaccharide are the glycosylation reactions by which the constituent monosaccharide building blocks are assembled into the highly complex oligosaccharide architecture. Extremely notable developments in the field of glycosylation over the past century have led to the establishment of useful and relatively robust methodologies[3] particularly with respect to the variety of anomeric leaving groups and activation methods available, ranging from the classic Koenigs–Knorr reaction[4] to the Schmidt trichloroacetimidate approach.[5] Other recent developments have focussed on the improvement of the speed of assembly of complex structures from monosaccharide building blocks, for example by reactivity tuning[6–14] or programmable solid phase synthesis,[15–18] whilst others have attempted to improve the stereo control of glycosylation for the formation of 'difficult' anomeric linkages.[19–29] However, despite these impressive developments no one particular method of glycosylation appears to be universally superior to the others, or even applicable in all situations. The net result is that the development of new methods for the formation of the glycosidic bond still remains an interesting challenge, particularly in terms of development of new 'green chemistry' techniques that avoid the use of toxic and expensive reagents, and which facilitate the rapid and straightforward assembly of glycoside building blocs into oligosaccharide structures in a regio- and stereoselective fashion.

In particular circumstances electrochemically mediated synthesis can represent an attractive and more environmentally benign synthetic technique which may display marked advantages, particularly where the traditional chemical reagents required are toxic and/or expensive. In the context of oligosaccharide synthesis, electrochemically mediated glycosylation has over the recent years been successively investigated by Noyori,[30] Sinaÿ and Amatore,[31–33] Lubineau,[34–36] Yoshida,[37–39] ourselves[40,41] and Torii.[42] These extensive studies have in many cases facilitated the synthesis of di- and oligosaccharides without recourse to the use of toxic, expensive or sensitive activators. However recent investigations into electrochemical glycosylation of a variety of aryl-substituted thio-mannosides[43] revealed the strong tendency for ester-protecting groups to migrate from the glycosyl donor to the glycosyl acceptor under the reaction conditions. Consequently yields of glycosylation were markedly decreased when ester-protected glycosyl donors were used, and it was also observed that reactions were particularly sluggish in most of these cases. These general findings contrast disfavourably with the ready and high yielding glycosylation of thioglycosides by chemical activation methods, which in particular are not plagued by donor-protecting groups limitations.

During the course of their investigations into electrochemical glycosylation, Sinaÿ and Amatore[44,45] and latterly Pinto[46] reported the activation of thioglycosides by the use of stoichiometric quantities of the salt *tris*-(4-bromophenyl) ammoniumyl hexachloroantimonate **1** (BAHA, Fig. 1). Although efficient, the use of at least a stoichiometric amount of this hazardous antimony-based activator was required in order to achieve successful glycosylation, unfortunately representing little significant advance over alternative

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Journal of Physical Organic Chemistry

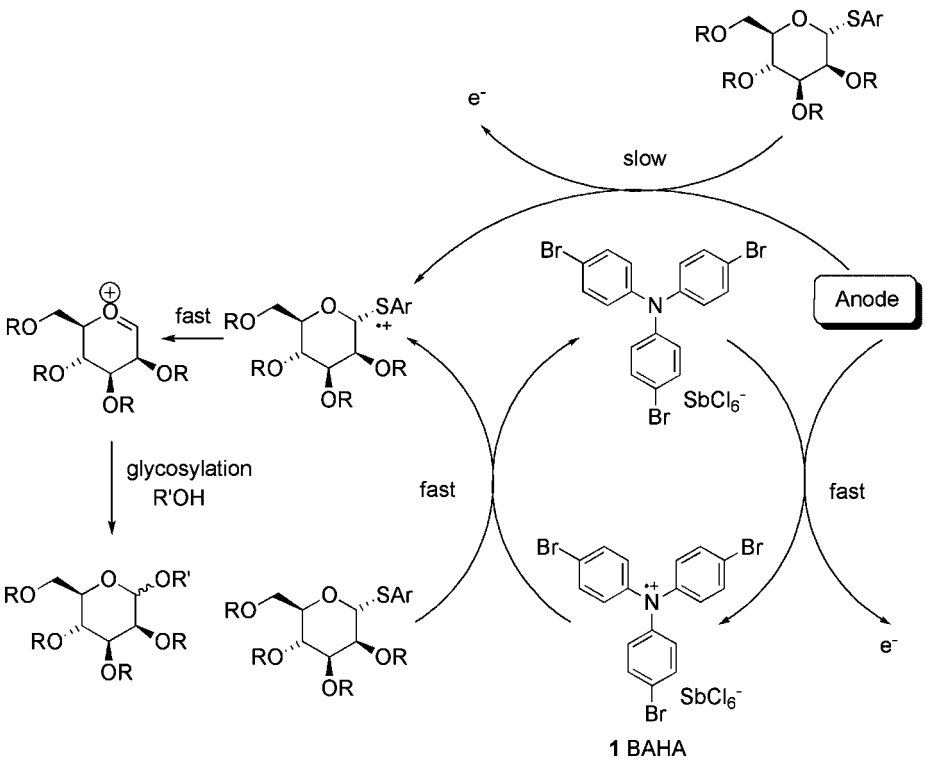


Figure 1. Catalysis of electrochemical glycosylation of a thioaryl glycoside donor in the presence of a sub-stoichiometric quantity of BAHA **1**

toxic stoichiometric activators of thioglycosides. However in one publication Sinaÿ and Amatore referred to the possible use of catalytic quantities of BAHA in conjunction with electrochemical regeneration of the radical cation *in situ*; they suggested that such a process might be used for the synthesis of disaccharides, although further details were not provided.[44] In fact both Steckhan and coworkers[47,48] had already described the similar use of catalytic quantities of electrochemical mediators both for the low potential anodic decarboxylation of carboxylates and for the electrochemical removal of 1,3-dithiane-protecting groups. However, since the initial suggestion from Sinaÿ and Amatore there have been no further reports in this area. An investigation into whether the more general advantages of electrochemistry as a means of activation of thioglycosides could in fact be combined with the use of a catalytic quantity of BAHA was therefore considered worthwhile. Such an approach may allow one to 'have the best of both worlds' in so far as avoiding the need for stoichiometric chemical activator, whilst in addition possibly avoiding some of the more general limitations of electrochemical glycosylation, particularly in terms of donor-protecting group identity, and speed and efficacy of glycosylation.

EXPERIMENTAL

General

Melting points were recorded on a Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz), Bruker DPX 400 (400 MHz), Bruker AV 400 (400 MHz) or Bruker AMX 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker DPX 400 (100.6 MHz) or a Bruker AMX 500 (125.75 MHz) spectrometer. Multiplicities were assigned using APT or DEPT sequence. All chemical shifts are quoted on the δ-scale. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20–250, Micromass Platform 1 APCI or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionisation (NH_3 DCI), electron impact (EI), electron spray ionisation (ESI), chemical ionisation (NH_3 CI), atmospheric pressure chemical ionisation (APCI) and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Laboratory, Oxford. Thin layer chromatography (t.l.c.) was carried out on Merck glass backed sheets, pre-coated with $60F_{254}$ silica. Plates were developed using 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and available reagents were dried and purified before use according to standard procedures.

General procedure for electrochemical glycosylation with/without mediator

Electrochemical glycosylation was achieved using a conventional three-electrode potentiostatic system by means of a working electrode (Pt), an auxiliary electrode (Pt) (dimensions of both, 25 mm × 25 mm × 0.198 mm) and a pseudo-reference electrode (Ag). The cell volume was 25 ml. Under an atmosphere of argon, donor (~70–150 mg, 1.0 equiv.), acceptor (~30–70 mg, 1.2 equiv.), *n*-Bu_4NClO_4 (~650 mg) and 3 Å molecular sieves were suspended in anhydrous acetonitrile (20 ml), and the reaction mixture was stirred at 25 °C for 30 min. For reactions in the presence of mediator, the required quantity of $(4\text{-}BrC_6H_4)_3NSbCl_6$ (~10 mg, 0.1 equiv.) was then added. Electrolysis was carried out at the stated potential (+1.5 to +2.2 V) until the required charge

was reached (typically 2.5 F mol^{-1}). The mixture was then filtered through Celite®, concentrated under reduced pressure, and the residue was dissolved in diethyl ether. Any remaining solid was removed by filtration through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (petroleum ether/ethyl acetate, 9:1) to afford the desired disaccharide.

General procedure for glycosylation mediated by stoichiometric (4-BrC_6H_4)$_3NSbCl_6$ (BAHA) alone

Under an atmosphere of argon, donor (~30–90 mg, 1.0 equiv.), acceptor (~20–50 mg, 1.2 equiv.) and 3 Å molecular sieves were suspended in anhydrous acetonitrile (10 ml) and the reaction mixture was stirred at room temperature for 30 min prior to addition of (4-BrC_6H_4)$_3NSbCl_6$ (~120–340 mg, 1.2–3.0 equiv.). After the reaction was complete as monitored by t.l.c. (90–150 min), the mixture was filtered and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica (petroleum ether/ethyl acetate; 9:1) to afford the desired disaccharide.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α, β-D-mannopyranosyl)-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 4a

4-Methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside **2a** (112 mg, 0.17 mmol), 1,2:3,4-diacetone-α-D-galactopyranoside **3** (44 mg, 0.17 mmol) and *n*-Bu_4NClO_4 (700 mg, 2.05 mmol), anhydrous acetonitrile (24 ml), + 1.5 V, 40 C (5 h) gave disaccharide **4a** (118 mg, 89%, α:β, 73:27); **4aα**: 73%; yellowish oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.6; $[\alpha]_D^{22}$ -48 (*c*, 1.7 in $CHCl_3$) (lit.,[49,50] $[\alpha]_D^{20}$ -2.6 (*c*, 2.3 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.34 (2 × 3H, s, 2 × CH_3), 1.45 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.71 (1H, dd, *J* 10.5 Hz, *J* 6.5 Hz, CH), 3.75 (1H, dd, *J* 4.5 Hz, *J* 12.5 Hz, CH), 3.78–3.88 (5 × 1H, m, 5 H), 3.92 (1H, dd, *J* 9.5 Hz, *J* 3.0 Hz, CH), 3.98 (1H, dat, *J* 5.5 Hz, *J* 7.0 Hz, CH), 4.17 (1H, dd, *J* 1.5 Hz, *J* 8.0 Hz, H-2b), 4.33 (1H, dd, *J* 2.5 Hz, *J* 5.0 Hz, H-2a), 4.51–4.79 (8H, m,), 4.88 (1H, dd, *J* 10.5 Hz, CH_2Bn), 5.04 (1H, d, *J* 1.5 Hz, H-1b), 5.54 (1H, d, *J* 5.0 Hz, H-1a), 7.10–7.42 (20 × 1H, m, 20 × ArH); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_3), 24.9 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 65.3 (CH), 65.4 (CH_2), 69.3 (CH_2), 70.8 (CH), 70.9 (CH), 71.1 (CH), 72.3 (CH), 72.3 (CH_2), 72.5 (CH_2), 73.5 (CH_2), 74.7 (CH), 75.0 (CH), 75.3 (CH_2), 80.2 (CH), 96.5 (C-1a), 97.4 (C-1b), 108.8 (Cq), 109.5 (Cq), 127.6 (CH), 127.7 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 127.8 (4 × ArCH), 128.0 (4 × ArCH), 128.2 (4 × ArCH), 128.5 (4 × ArCH), 138.5 (ArC), 138.6 (ArC), 138.7 (ArC), 138.8 (ArC); *m/z* (ESI$^+$) 800.44 ($[M + NH_4]^+$, 100%), 841.49 ($[M + CH_3CN + NH_4]^+$, 92%), 1583.64 ($[2M + NH_4]^+$, 10%), 1624.04 ($[2M + CH_3CN + NH_4]^+$, 3%); **4aβ**: 27%; yellowish oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.4; $[\alpha]_D^{23}$ -52 (*c*, 0.6 in $CHCl_3$) (lit.,[49,50] $[\alpha]_D^{20}$ -72.6 (*c*, 2.7 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.48 (3H, s, CH_3), 3.44 (1H, ddd, *J* 2.5 Hz, *J* 5.0 Hz, *J* 9.5 Hz, CH), 3.47 (1H, dd, *J* 3.0 Hz, *J* 9.5 Hz, CH), 3.62 (1H, dd, *J* 8.5 Hz, *J* 11.0 Hz, CH), 3.76–3.81 (2 × 1H, m, 2 × CH), 3.90 (1H, at, *J* 9.5 Hz, CH), 4.01 (1H, d, *J* 3.0 Hz, CH), 4.10 (1H, dat, *J* 2.0 Hz, *J* 2.0 Hz, *J* 8.5 Hz, CH), 4.22 (1H, dd, *J* 2.0 Hz, *J* 6.0 Hz, CH), 4.23–4.25 (1H, m, CH), 4.33 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.34 (1H, dd, *J* 2.5 Hz, *J* 5.0 Hz, H-2a), 4.43–4.63 (4H, m, 3H CH_2Bn, CH), 4.46 (1H, d, *J* 2.0 Hz, H-1b), 4.60 (1H, dd, *J* 10.0 Hz, CH_2Bn), 4.90 (1H, d, *J* 10.5 Hz, CH_2Bn), 4.93 (1H, d, *J* 12.5 Hz, CH_2Bn), 5.02 (1H, d, *J* 12.5 Hz, CH_2Bn), 5.60 (1H, d, *J* 5.0 Hz, H-1a), 7.14–7.52 (20 × 1H, m, 20 × ArH); δ_C (100 MHz, $CDCl_3$) 24.4 (CH_3), 25.1 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 68.0 (CH), 69.5 (CH_2), 69.9 (CH_2), 70.5 (CH), 70.8 (CH), 71.0 (CH_2), 71.6 (CH), 72.5 (CH), 73.5 (CH), 74.7 (CH_2), 75.1 (CH_2), 75.8 (CH), 77.2 (CH_2), 81.8 (CH), 96.4 (C-1a), 102.4 (C-1b), 108.7 (Cq), 109.5 (Cq), 127.6 (4 × ArCH), 127.9 (2 × ArCH), 128.0 (4 × ArCH),128.1 (4 × ArCH), 128.3 (4 × ArCH), 128.7 (2 × ArCH) 138.1 (ArC), 138.4 (ArC), 138.6 (ArC); *m/z* (ESI$^+$) 800.57 ($[M + NH_4]^+$, 70%), 841.57 ($[M + CH_3CN + NH_4]^+$, 100%), 1624.47 ($[2M + CH_3CN + NH_4]^+$, 2%).

6-*O*-(3,4,6-Tri-*O*-benzyl-2-*O*-pivaloyl-α,β-D-mannopyranosyl)-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 4b

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-pivaloyl-1-thio-α-D-mannopyranoside **2b** (93 mg, 0.14 mmol), 1,2:3,4-diacetone-α-D-galactopyranoside **3** (44 mg, 0.17 mmol), *n*-Bu_4NClO_4 (575 mg, 0.70 mmol), acetonitrile (15 ml), 1.5 V, 17 C (3 h), gave disaccharide **4b** (66 mg, 60%, α:β, 76:24); **4bα**: 76%; yellowish oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.8; $[\alpha]_D^{20}$ -6 (*c*, 1.2 in $CHCl_3$); ν_{max} (film) 1732 (s, νC═O), 1371 (s, νC—O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.21 (3 × 3H, s, $(CH_3)_3C$), 1.33 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.72 (1H, dd, $J_{5a,6a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6a), 3.72–3.74 (1H, m, H-6b), 3.80 (1H, dd, $J_{5,6'a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6′a), 3.78–3.82 (1H, m, H-6′b), 3.83–3.87 (1H, m, H-5b), 3.91 (1H, at, $J_{3b,4b}$ 9.5 Hz, $J_{4b,5b}$ 9.5 Hz, H-4b), 3.95 (1H, dat, $J_{4a,5a}$ 1.5 Hz, $J_{5a,6a}$ 6.5 Hz, $J_{5a,6'a}$ 6.5 Hz, H-5a), 3.99 (1H, dd, $J_{2b,3b}$ 3.0 Hz, $J_{3b,4b}$ 9.5 Hz, H-3b), 4.22 (1H, dd, $J_{3a,4a}$ 8.0 Hz, $J_{4a,5a}$ 1.5 Hz, H-4a), 4.31 (1H, dd, $J_{1a,2a}$ 5.0 Hz, $J_{2a,3a}$ 2.5 Hz, H-2a), 4.49 (1H, d, *J* 11.0 Hz, CH_2Bn), 4.50 (1H, d, *J* 11.0 Hz, CH_2Bn), 4.51 (1H, d, *J* 13.0 Hz, CH_2Bn), 4.60 (1H, dd, $J_{2a,3a}$ 2.5 Hz, $J_{3a,4a}$ 8.0 Hz, H-3a), 4.68 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.69 (1H, d, *J* 11.0 Hz, CH_2Bn), 4.82 (1H, d, *J* 11.0 Hz, CH_2Bn), 4.88 (1H, d, $J_{1b,2b}$ 2.0 Hz, H-1b), 5.40 (1H, dd, $J_{1b,2b}$ 2.0 Hz, $J_{2b,3b}$ 3.0 Hz, H-2b), 5.51 (1H, d, $J_{1a,2a}$ 5.0 Hz, H-1a), 7.15–7.36 (15 × 1H, m, 15 × ArH); δ_C (126 MHz, $CDCl_3$) 24.5 (CH_3), 24.9, (CH_3), 25.0 (CH_3), 26.1 (CH_3), 27.1 ($(CH_3)_3C$), 38.9 (CqPiv), 65.8 (C-5a), 65.9 (C-6), 68.1 (C-2b), 68.8 (C-6), 70.6 (C-3a), 70.7 (C-2a), 70.8 (C-4a), 71,4 (CH_2Bn), 71.5 (C-5b), 73.1 (CH_2Bn), 74.1 (C-4b), 75.1 (CH_2Bn), 78.3 (C-3b), 96.3 (C-1a), 97.8 (C-1b), 108.6 (Cq), 109.3 (Cq), 107.4 (ArCH), 127.4 (2 × ArCH), 127.6 (ArCH), 127.9 (2 × ArCH), 128.1 (2 × ArCH), 128.2 (2 × ArCH), 128.2 (2 × ArCH), 128.3 (2 × ArCH), 138.3, 138.3, 138.4 (ArC), 138.4 (ArCH), 177.6 (C═O); (HRMS (ESI$^+$) Calcd. For $C_{44}H_{56}NaO_{12}$ ($M + Na^+$) 799.3664. Found 799.3662); **4bβ**: 24%; colourless oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.5; $[\alpha]_D^{20}$ -39 (*c*, 0.2 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.24 (3 × 3H, s, $(CH_3)_3C$), 1.29 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.46 (1H, dat, $J_{4b,5b}$ 3.5 Hz, $J_{5b,6b}$ 3.5 Hz, $J_{5b,6b'}$ 9.5 Hz, H-5b), 3.65 (1H, dd, $J_{2b,3b}$ 3.0 Hz, $J_{3b,4b}$ 9.5 Hz, H-3b), 3.69 (1H, dd, $J_{5a,6a}$ 10.5 Hz, $J_{6a,6a'}$ 4.0 Hz, H-6a), 3.74–3.79 (3 × 1H, m, H-6b, H-6′b, H-6′a), 3.97 (1H, ddd, $J_{4a,5a}$ 1.5 Hz, $J_{5a,6a}$ 10.5 Hz, $J_{5a,6a'}$ 4.0 Hz, H-5a), 4.02 (1H, dd, $J_{3b,4b}$ 9.5 Hz, $J_{4b,5b}$ 3.5 Hz, H-4b), 4.20 (1H, dd, $J_{3a,4a}$ 8.0 Hz, $J_{4a,5a}$ 1.5 Hz, H-4a), 4.28 (1H, dd, $J_{1a,2a}$ 5.0 Hz, $J_{2a,3a}$ 2.5 Hz, H-2a), 4.46 (1H, d, *J* 11.5 Hz, CH_2Bn), 4.50 (1H, d, *J* 10.5 Hz, CH_2Bn), 4.55 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.56 (1H, dd, $J_{2a,3a}$ 2.5 Hz, $J_{3a,4a}$ 8.0 Hz, H-3a), 4.63 (1H, brs, H-1b), 4.68 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.74 (1H, d, *J* 11.5 Hz, CH_2Bn), 4.83 (1H, d, *J* 11.0 Hz, CH_2Bn), 5.50 (1H, d, $J_{1a,2a}$ 5.0 Hz, H-1a), 5.61 (1H, d, $J_{2b,3b}$ 3.0 Hz, H-2b), 7.10–7.40 (15 × 1H, m, 15 × ArH); δ_C (100 MHz, $CDCl_3$) 24.3 (CH_3), 25.0 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 27.2 ($(CH_3)_3C$), 39.0 (CqPiv), 67.5 (C-2b), 67.8 (CH), 68.8 (C-6), 69.0 (C-6), 70.5 (C-3a), 70.6 (C-2a), 70.9 (CH_2Bn), 71.2 (C-4a), 73.2 (CH_2Bn), 74.2 (CH), 75.1 (CH_2Bn), 75.4 (CH), 80.3 (C-3b), 96.2 (C-1a), 99.3 (C-1b), 108.7 (Cq), 109.2 (Cq), 127.4 (ArCH), 127.6 (2 × ArCH), 127.6 (ArCH), 127.6 (ArCH), 128.0 (2 × ArCH), 128.1 (2 × ArCH), 128.2 (2 × ArCH), 128.2 (2 × ArCH), 128.3 (2 × ArCH), 176.6 (C═O), 137.9 (ArC), 138.5 (2 × ArC).

6-*O*-(3,4,6-Tri-*O*-benzoyl-2-*O*-benzyl-α,β-D-mannopyranosyl)-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 4c

4-Methoxyphenyl 3,4,6-tri-*O*-benzoyl-2-*O*-benzyl-1-thio-α-D-mannopyranoside **2c** (123 mg, 0.17 mmol), 1,2:3,4-diacetone-α-D-galactopyranoside **3** (65 mg, 0.25 mmol), *n*-Bu_4NClO_4 (685 mg, 2.00 mmol), acetonitrile (20 ml), 2.2 V, 156 C, gave disaccharide **4c** (59 mg, 41%, α:β, 86:14); **4c** α: 86%; yellow oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.5; $[\alpha]_D^{24}$ -14 (*c*, 0.9 in $CHCl_3$); ν_{max} (film) 3020 (w, νCHAr), 2934 (w, νCH), 1725 (s, νC═O), 1601, 1598, 1500, 1452 (m, νC═CAr), 1270, 1069 (s, νCO), 711 (m, δCH) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.34 (6H, s, 2 × CH_3), 1.44 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.81 (1H, dd, $J_{5a,6a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6a), 3.94 (1H, dd, $J_{5a,6'a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6′a), 4.07 (1H, dat, $J_{4a,5a}$ 1.5 Hz, $J_{5a,6a}$ 6.5 Hz, $J_{5a,6'a}$ 6.5 Hz, H-5a), 4.13 (1H, dd, $J_{1b,2b}$ 1.5 Hz, $J_{2b,3b}$ 3.0 Hz, H-2b), 4.26 (1H, dd, $J_{3a,4a}$ 8.0 Hz, $J_{4a,5a}$ 1.5 Hz, H-4a), 4.34 (1H, dd, $J_{1a,2a}$ 5.0 Hz, $J_{2a,3a}$ 2.5 Hz, H-2a), 4.45 (1H, dd, $J_{4b,5b}$ 10.0 Hz, $J_{5b,6b}$ 5.0 Hz, $J_{5b,6'b}$ 2.5 Hz, H-5b), 4.48 (1H, dd, $J_{5b,6b}$ 5.0 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6b), 4.57 (1H, dd, $J_{5b,6'b}$ 2.5 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6′b), 4.64 (1H, dd, $J_{2a,3a}$ 2.5 Hz, $J_{3a,4a}$ 8.0 Hz, H-3a), 4.65 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.69 (1H, d, *J* 12.0 Hz, CH_2Bn), 5.11 (1H, d, $J_{1b,2b}$ 1.5 Hz, H-1b), 5.55 (1H, d, $J_{1a,2a}$ 5.0 Hz, H-1a), 5.69 (1H, dd, $J_{2b,3b}$ 3.0 Hz, $J_{3b,4b}$ 10.0 Hz, H-3b), 6.06 (1H, at, $J_{3b,4b}$ 10.0 Hz, $J_{4b,5b}$ 10.0 Hz, H-4b), 7.15–7.38 (11 × 1H, m, 11 × ArH), 7.45–7.53 (3 × 1H, m, 3 × ArH), 7.92–8.10 (6 × 1H, m, 6 × ArH); δ_C (126 MHz, $CDCl_3$) 24.7 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 63.6 (C-6b), 66.2 (C-5a), 66.7 (C-6a), 67.4 (C-4b), 69.1 (C-5b), 70.7 (C-2a), 70.8 (C-3a), 71.1 (C-4a), 72.4 (C-3b), 73.1 (CH_2Bn), 75.7 (C-2b), 96.5 (C-1a), 97.9 (C-1b), 108.8 (Cq), 109.5 (Cq), 127.6, 128.4, 128.5, 129.9 (16 × ArCH), 127.7 (ArCH), 29.4 (ArC), 129.5 (ArC), 130.0 (ArC), 132.9 (ArCH), 133.3 (2 × 1ArCH), 137.8 (ArC), 165.5 (C═O), 165.9 (C═O), 166.4 (C═O); (HRMS (ESI^+) Calcd. For $C_{46}H_{52}NO_{14}$ ($M + NH_4^+$) 842.3382. Found 842.3422); **4cβ**: 14 %; colourless oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.4; $[\alpha]_D^{24}$ -7 (*c*, 0.2 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.33 (6H, s, 2 × CH_3), 1.42 (3H, s, CH_3), 1.55 (3H, s, CH_3), 3.75 (1H, dd, $J_{5a,6a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6a), 3.89 (1H, dd, $J_{5a,6'a}$ 6.5 Hz, $J_{6a,6'a}$ 10.5 Hz, H-6′a), 4.00 (1H, dd, $J_{1b,2b}$ 1.5 Hz, $J_{2b,3b}$ 3.5 Hz, H-2b), 4.02 (1H, dat, $J_{4a,5a}$ 2.0 Hz, $J_{5a,6a}$ 6.5 Hz, $J_{5a,6'a}$ 6.5 Hz, H-5a), 4.09 (1H, ddd, $J_{4b,5b}$ 10.0 Hz, $J_{5b,6b}$ 2.0 Hz, $J_{5b,6'b}$ 4.0 Hz, H-5b), 4.23 (1H, dd, $J_{3a,4a}$ 8.0 Hz, $J_{4a,5a}$ 2.0 Hz, H-4a), 4.25 (1H, at, $J_{3b,4b}$ 10.0 Hz, $J_{4b,5b}$ 10.0 Hz, H-4b), 4.32 (1H, dd, $J_{1a,2a}$ 5.0 Hz, $J_{2a,3a}$ 2.5 Hz, H-2a), 4.58 (1H, dd, $J_{5b,6b}$ 2.0 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6b), 4.62 (1H, dd, $J_{2a,3a}$ 2.5 Hz, $J_{3a,4a}$ 8.0 Hz, H-3a), 4.63 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.68 (1H, d, *J* 12.0 Hz, CH_2Bn), 4.79 (1H, dd, $J_{5b,6b}$ 4.0 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6b), 5.05 (1H, d, $J_{1b,2b}$ 1.5 Hz, H-1b), 5.43 (1H, dd, $J_{2b,3b}$ 3.5 Hz, $J_{3b,4b}$ 10.0 Hz, H-3b), 5.53 (1H, d, $J_{1a,2a}$ 5.0 Hz, H-1a), 7.16–7.31 (5 × 1H, m, 5 × ArH), 7.36–7.47 (6 × 1H, m, 6 × ArH), 7.53–7.61 (3 × 1H, m, 3 × ArH), 8.01–8.11 (6 × H, m, 6 × ArH); δ_C (126 MHz, $CDCl_3$) 24.7 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 64.1 (C-6b), 66.2 (C-5a), 66.2 (C-4b), 66.4 (C-6a), 70.7 (C-2a), 70.8 (C-3a), 71.1 (C-4a), 71.6 (C-5b), 73.1 (CH_2Bn), 74.7 (C-3b), 76.2 (C-2b), 96.5 (C-1a), 97.8 (C-1b), 108.9 (Cq), 109.5 (Cq), 127.6, 128.4, 128.5, 128.6, 130.0 (16 × ArCH), 127.8 (ArCH), 129.7 (2 × ArC), 130.0 (ArC), 133.2 (ArCH), 133.4 (2 × ArCH), 138.0 (ArC), 166.9 (C═O), 167.2 (2 × C═O).

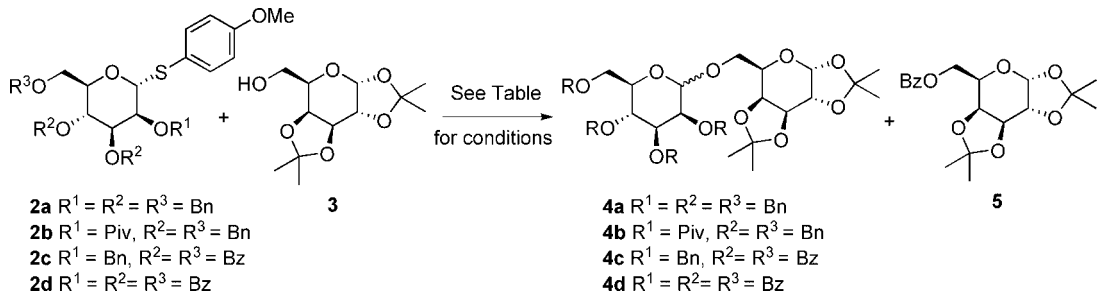
6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-α,β-D-mannopyranosyl)-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 4d

4-Methoxyphenyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside **2d** (104 mg, 0.14 mmol), 1,2:3,4-diacetone-α-D-galactopyranoside **3** (48 mg, 0.18 mmol), *n*-Bu_4NClO_4 (658 mg, 1.92 mmol), acetonitrile (20 ml), 2.2 V, 39 C, gave disaccharide **4d** (59 mg, 49%, α:β, 80:20); **4d** α: 80%; colourless oil; t.l.c. (petroleum ether/ethyl acetate, 7:3) R_f 0.4; $[\alpha]_D^{19}$ -61 (*c*, 0.3 in $CHCl_3$); ν_{max}(film) 3010 (w, νCHAr), 2988 (w, νCH), 1728 (s, νC═O), 1601, 1595, 1500, 1452 (m, νC═CAr), 1263, 1060 (s, νCO) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.36 (6H, s, 2 × CH_3), 1.43 (3H, s, CH_3), 1.63 (3H, s, CH_3), 3.89 (1H, dd, $J_{5a,6a}$ 6.5 Hz, $J_{6a,6'a}$ 11.0 Hz, H-6a), 3.97 (1H, dd, $J_{5a,6'a}$ 6.5 Hz, $J_{6a,6'a}$ 11.0 Hz, H-6′a), 4.12 (1H, dat, $J_{4a,5a}$ 2.0 Hz, $J_{5a,6a}$ 6.5 Hz, $J_{5a,6'a}$ 6.5 Hz, H-5a), 4.34 (1H, dd, $J_{3a,4a}$ 8.0 Hz, $J_{4a,5a}$ 2.0 Hz, H-4a), 4.35 (1H, dd, $J_{1a,2a}$ 5.0 Hz, $J_{2a,3a}$ 2.5 Hz, H-3a), 4.50 (1H, dd, $J_{5b,6b}$ 3.0 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6b), 4.59 (1H, brdat, $J_{4b,5b}$ 10.0 Hz, $J_{5b,6b}$ 3.0 Hz, $J_{5b,6'b}$ 3.0 Hz, H-5b), 4.67 (1H, dd, $J_{2a,3a}$ 2.0 Hz, $J_{3a,4a}$ 8.0 Hz, H-3a), 4.69 (1H, dd, $J_{5b,6'b}$ 3.0 Hz, $J_{6b,6'b}$ 12.0 Hz, H-6′b), 5.16 (1H, d, $J_{1b,2b}$ 2.0 Hz, H-1b), 5.57 (1H, d, $J_{1a,2a}$ 5.0 Hz, H-1a), 5.74 (1H, dd, $J_{1b,2b}$ 2.0 Hz, $J_{2b,3b}$ 3.0 Hz, H-2b), 5.91 (1H, dd, $J_{2b,3b}$ 3.0 Hz, $J_{3b,4b}$ 10.0 Hz, H-3b), 6.14 (1H, at, $J_{3b,4b}$ 10.0 Hz, H-4b), 7.25–7.28 (2 × 1H, m, 2 × ArH), 7.33–7.45 (7 × 1H, m, 7 × ArH), 7.48–7.53 (1H, m, ArH), 7.55–7.62 (2 × 1H, m, 2 × ArH), 7.84 (2 × 1H, dd, *J* 8.5 Hz, *J* 1.5 Hz, 2 × ArH), 7.96 (2 × 1H, dd, *J* 8.5 Hz, *J* 1.5 Hz, 2 × ArH), 8.06 (2 × 1H, dd, *J* 8.5 Hz, *J* 1.5 Hz, 2 × ArH), 8.12 (2 × 1H, dd, *J* 8.5 Hz, *J* 1.5 Hz, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 24.6 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 63.0 (C-6b), 66.8 (C-5a), 67.0 (C-4b), 67.7 (C-6a), 69.0 (C-5b), 70.4 (C-3b), 70.5 (C-2b), 70.8 (C-3a), 71.0, 71.1 (C-2a, C-4a), 96.5 (C-1a), 98.0 (C-1b), 108.9 (Cq), 109.6 (Cq), 128.4 (2 × ArCH), 128.5 (2 × ArCH), 128.6 (2 × ArCH), 128.7 (2 × ArCH), 129.2 (ArC), 129.3 (ArC), 129.5 (ArC), 129.8 (2 × ArCH), 129.9 (2 × ArCH), 129.9 (2 × ArCH), 130.0 (2 × ArCH), 130.1 (ArC), 133.1 (ArCH), 133.3 (ArCH), 133.5 (ArCH), 133.6 (ArCH), 165.5 (C═O), 165.5 (C═O), 165.6 (C═O), 166.4 (C═O); (HRMS (ESI^+) Calcd. For $C_{46}H_{50}NO_{15}$ ($M + NH_4^+$) 856.3175. Found 856.3167).

RESULTS AND DISCUSSION

The general concept underlying the potential use of a catalytic quantity as a chemical mediator for electrochemical glycosylation of a thioglycoside is outlined in Fig. 1. Cyclic voltammetry of BAHA in acetonitrile at 50 $mV \cdot s^{-1}$ previously revealed[51] an electrochemically reversible couple with a formal oxidation potential of +0.78 V. Therefore at applied potentials above +0.8 V fast oxidation of the reduced form of the mediator would occur at the anode to provide the BAHA radical cation *in situ*. Oxidation of the thioglycoside by the BAHA radical cation could then occur, probably more rapidly than direct oxidation of the thioglycoside at the anode, allowing catalysis of thioglycoside oxidation. Subsequent fragmentation would provide an intermediate glycosyl cation, which would then undergo glycosylation with the glycosyl acceptor R'OH. The consequential formation of the reduced form of the mediator during oxidation of the thioglycoside would complete the cycle; the catalytic mediator could then be rapidly electrochemically re-oxidised in order to promote further glycosylation sequences (Fig. 1).

Electrochemical glycosylation of the thiophenyl mannoside donors **2a**–**2d** was undertaken in the presence of diacetone galactose **3** as a glycosyl acceptor (Scheme 1). A second series of electrochemical glycosylation reactions was also performed in which a catalytic amount (0.1 equivalents) of BAHA was added to the mixtures of donors and acceptor as a chemical mediator before the external potential was applied. Finally, for the purpose of comparison, glycosylation of the donors **2a**–**2d** and acceptor **3** was also performed simply by using an excess of BAHA in the



Scheme 1. Glycosylation reactions of donors **2a**–**d** with diacetone galactose **3**

absence of any applied external potential. The results of these three series of glycosylation reactions are reported in Table 1.

Direct electrolysis of benzylated donor **2a** at +1.5 V for 5 h in the presence of DAG **3** afforded the disaccharide **4a** in 89% yield as a diastereomeric mixture of anomers (α:β, 73:27) (Table 1, entry 1(i)). Alternatively when the electrolysis was undertaken at the higher potential of +2.2 V for 15 h, the disaccharide **4a** was formed in 80% yield, again as a diastereomeric mixture (α:β, 73:27) (Table 1, entry 1(ii)). Interestingly when the electroglycosylation was performed at +1.5 V in the presence of a catalytic amount of BAHA (0.1 equiv.), the disaccharide **4a** was formed in 87% yield, but with a much shorter reaction time (30 min), indicating that the presence of the mediator had significantly increased the reaction rate. On this issue a referee suggested that the rate of reaction is in fact determined by the current, and not the other way around. Since these reactions are performed at constant potential, the flow of current and the rate of reaction are indeed linked; it is our view that it is the rate of reaction which is accelerated by the addition of the BAHA, which then has the corresponding effect that the required charge is passed over a shorter period of time; that is the increased rate of reaction increases the current, and not the other way around. When the glycosylation was performed simply using a significant excess of BAHA (3.0 equiv.) the reaction was complete after 90 min, but **4a** was only produced in 64% yield, again as a diastereomeric mixture (α:β, 53:47). However, when this reaction was repeated in the presence of supporting electrolyte (n-Bu_4NClO_4, 1M), glycosylation occurred more efficiently giving the disaccharide **4a** in 95% yield and with an improved diastereomeric ratio (α:β, 73:27), suggesting a significant influence of the electrolyte salt on the diastereoselectivity of the glycosylation reaction.

Since it has been widely demonstrated that ester-protecting groups on the glycosyl donor can be problematic for electrochemical glycosylation purposes, attention then turned to the use of a variety of ester-protected donors. In this respect optimum results had previously been obtained by the use of 2-*O*-Piv protected donors, such as **2b**, and thioglycoside **2b** was therefore selected as the next donor for comparative purposes. Direct electrolysis of **2b** at +1.5 V for 4 h led to the formation of the expected disaccharide **4b** in 60% yield, as a diastereomeric mixture (α:β, 76:24) (Table 1, entry 2(i)). When the electrolysis was repeated at +2.2 V for 15 h the disaccharide **4b** was obtained in 55% yield (α:β, 82:18) (Table 1, entry 2(ii)). Contrastingly electrolysis of the donor **2b** in the presence of a catalytic amount of BAHA (0.1 equiv.) at +1.5 V gave the desired disaccharide **4b** in 53% yield only after 45 min, again as a diastereomeric mixture (α:β, 9:1) (Table 1, entry 2). Finally the use of an excess of BAHA alone (1.7 equiv.) afforded the

Table 1. Glycosylation reactions of thioaryl glycosyl donors **2a**–**d** with diacetone galactose **3** mediated by electrochemical means alone, by electrochemical activation in the presence of catalytic BAHA, and by chemical activation with an excess of BAHA

Entry	Donor	Electrochemical activation alone [potential, (time)% yield, anomeric ratio]	Electrochemical activation mediated by catalytic BAHA [potential, (time)% yield, anomeric ratio]	Chemical activation with stoichiometric BAHA [(time),% yield, anomeric ratio]
1	**2a**	(i) +1.5 V (5 h) **4a** 89% (α:β, 73:27) (ii) +2.2 V (15 h) **4a** 80% (α:β, 73:27)	+1.5 V (0.5 h) **4a** 87% (α:β, 73:27)	(1.5 h) **4a** 64% (α:β, 53:47)[a] **4a** 95% (α:β, 73:27)[b]
2	**2b**	(i) +1.5 V (4 h) **4b** 60% (α:β, 76:24) (ii) +2.2 V (15 h) **4b** 55% (α:β, 82:18)	+1.5 V (0.75 h) **4b** 53% (α:β, 9:1)	(2.5 h) **4b** 96% (α:β, 88:12)[a]
3	**2c**	+2.2 V (15 h) **4c** 41% (α:β, 86:14) **5** 30%	+1.5 V (0.75 h) **4c** 60% (α:β, >20:1)	(2 h) **4c** 68% (α:β, >20:1)[a]
4	**2d**	+2.2 V (15 h) **4d** 49% (α:β, 4:1) **5** 30%	+1.5 V (0.9 h) **4d** 49% (α:β, >20:1)	(1.5 h) **4d** 59% (α:β, 87:13)[a]

[a] Chemical activation with BAHA performed in the absence of any electrolyte.
[b] Chemical activation with BAHA performed in the presence of 1 M n-Bu_4NClO_4.

desired disaccharide **4b** in 96% yield (α:β, 88:12) after 2.5 h (Table 1, entry 2).

Ester-protecting group lability and tendency to migrate to the acceptor hydroxyl during electrochemical glycosylation is not limited to ester protection of the 2-position of the glycosyl donor. Investigation of glycosylation of 2-*O* benzyl donor protected donor **2c** bearing benzoate protection of the hydroxyls at positions 3-, 4- and 6- was undertaken next. Direct electrolysis of **2c** at +2.2 V produced the desired disaccharide **4c** in 41% yield, as a diastereomeric mixture (α:β, 86:14). However in addition to glycosylation, transesterification also occurred and the 6-benzoyl protected acceptor **5** was produced in 30% yield (Table 1, entry 3).[43] Notable also was the fact that glycosylation was particularly sluggish at +1.5 V, and the significant over-potential of +2.2 V was required to make the reaction go to completion. However, pleasingly, the use of the catalytic amount of the mediator BAHA improved the electrochemical glycosylation process. In this case the desired disaccharide **4c** was obtained in 60% yield as predominantly a single anomer (α:β, >20:1) after only 45 min at the lower oxidation potential of +1.5 V (Table 1, entry 3). Moreover, importantly no migration of benzoyl-protecting groups occurred, and thus compound **5** was not observed. In this instance chemical activation using BAHA (1.5 equiv.) as a stoichiometric oxidant afforded **4c** in 68% yield, again effectively as a single anomer (α:β, >20:1) after 2 h (Table 1, entry 3).

Finally investigations turned to the use of the per-benzoylated thioglycoside donor **2d**. Electrolysis of donor **2d** in the presence of **3** could only be achieved at the higher potential of +2.2 V, and afforded the corresponding disaccharide **4d** in 49% yield (α:β, 4:1), along with the *trans*-esterification product **5** (30% yield) (Table 1, entry 4). Electrochemical activation in the presence of a catalytic amount of BAHA (0.1 equiv.), at the lower potential of +1.5 V, furnished the desired disaccharide **4d** in a similar yield of 49% (α:β, >20:1) after 0.9 h (Table 1, entry 4); notably although the yield of disaccharide product was similar to electrochemical glycosylation alone, once again the benzoylated acceptor **5** was not observed. Finally it was noted that chemical glycosylation using stoichiometric BAHA (1.2 equiv.) gave a slightly better yield of disaccharide **4d** (59%, α:β, 87:13) after 1.5 h (Table 1, entry 4).

Overall these results taken together indicate that not only is the use of a catalytic quantity of BAHA beneficial to the electrochemical glycosylation reaction in terms of rate and efficiency, but also in particular that the use of catalytic BAHA stops *trans*-esterification of the glycosyl acceptor when glycosyl donors bearing labile ester-protecting groups are used. Although electrochemical activation in the presence of catalytic BAHA is not always superior in terms of product yield to the use of excess BAHA alone, the advantages of the use of this material in catalytic form, not least of which are cost and impact by the reduction in the use of toxic antimony salts, are significant.

CONCLUSIONS

Although 'direct' electrochemically mediated glycosylation has been demonstrated as a feasible synthetic technique, its widespread applicability, particularly for the assembly of complex oligosaccharides, remains undemonstrated. Limitations of the methodology in comparison with more conventional chemical glycosylation are the lengthier reaction times required, the low yields of disaccharide often produced, and, in particular, the problems associated with use of ester-protecting groups. Herein we have demonstrated the potential advantages of the use of a catalytic quantity of BAHA as a mediator for the electrochemical activation of a series of aryl thiomannosides. On comparison, the desired disaccharides were obtained in generally improved yields, and in all cases more rapidly and at lower potentials than that obtained by the use of electrochemical activation alone. Additionally electrochemical glycosylation mediated by BAHA was not accompanied by the migration of benzoyl-protecting groups from donor to acceptor as was invariably the case for electrochemical glycosylation alone. It may be expected that the use of a catalytic chemical mediator is amenable to, and may present advantages for, the electrochemical oxidation of a variety of sulfur-containing substrates or other, more generally any oxidisable species. However, despite the incremental advantages demonstrated herein, BAHA itself remains a toxic and hazardous material. The search therefore will now broaden to investigate the potential of other less toxic chemical mediators to facilitate electrochemical glycosylation and other electrochemical transformations.

Acknowledgements

We gratefully acknowledge financial support from the EPSRC (Project studentship GR/T24692/01 to L. D.).

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