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Minimal protection based glycosidation (MPG) reaction employing synergistic action of [Au]/[Ag]-catalytic system

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Minimal protection based glycosidations (MPG) where a minimally protected glycosyl donor is used for the synthesis of glycosides is highly rewarding over the conventional glycosidation reactions. The unique feature of this semi-classical protocol is that it not only eliminates multiple steps for the glycosyl donor synthesis but also provides higher glycosidation yields. In this article, a convenient and efficient MPG reaction under synergistic action of [Au]/[Ag]-catalytic system has been identified. Glycosyl donors are effortlessly prepared in two steps from the easily accessible unprotected sugars. Glycosidations are mild, fast and high yielding (>85%) with broad substrate scope. A systematic study of solvent and temperature effect on the anomeric selectivity has been also demonstrated.

Keywords: Glycosidation, carbonate donors, gold catalysis, glycoside, minimal protection.

Introduction

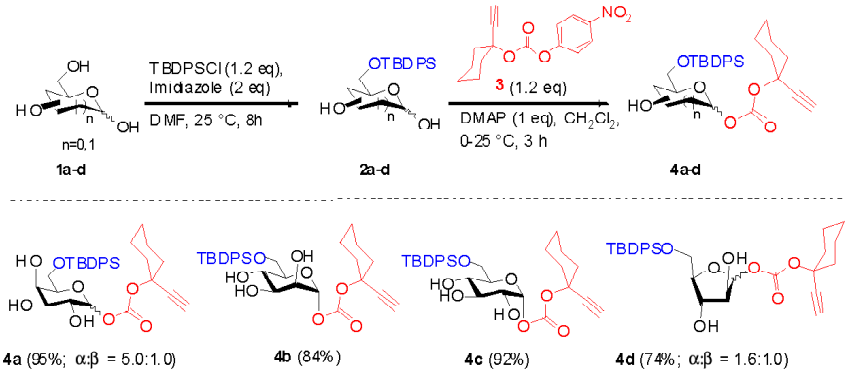
Carbohydrates, also known as "the sweet molecules of life"[1] are mostly present as glycoproteins, glycolipids and peptidoglycans and plays crucial roles in many biological processes such as intercellular communication and carbohydrate-mediated recognition, cell development and cell-cell differentiation[1]. Connections of carbohydrates with disease progress (e.g. inflammation, tumour growth) and pathogenic infections are also well established[2]. In addition, application of carbohydrate-based functional biomaterials in biomedical field is remarkable[3]. Thus, design and synthesis of carbohydrates and their analogues can have great implications in modern medicine and material science.

Despite the tremendous advancements in synthetic approaches (donor development[4], protection-deprotection strategy[5], automation[6] etc.), owing to the structural complexity, synthesis of oligosaccharides is still challenging. Unavailability of a universal glycosidation protocol and involvement of several protection-deprotection steps make the overall synthetic strategy more complicated and less efficient.

In this context, glycosidation of unprotected sugars[7] is a viable option as it minimises the unnecessary protection-deprotection steps. Nonetheless, associated problems such as (i) regioselective glycosyl donor preparation from unprotected sugar, (ii) non-stereo and regioselective glycoside formation, (iii) undesired side product formation and (iv) limited substrate scope with lower yields restricted its wide applications. A better alternative is the glycosidation with minimal protections[8]. This strategy not only maximizes the overall glycosidation yield significantly but also helps to precede the glycosidation reaction in a more stereo-, chemo- and regioselective fashion. In this premise, we investigated our recently developed [Au]/[Ag]-catalyzed alkynyl carbonate donor protocol[9] for minimal protection based glycosidation (MPG) reactions.

Results and discussion

Our explorations on the feasibility of MPG protocol began by the treatment of D-galactose with the ethynylcyclohexyl *p*-nitrophenyl carbonate and DMAP with a wishful thinking to afford the glycosyl carbonate; however, to our dismay, we noticed formation of a C1,6-dicarbonate albeit in poor yield due to the poor solubility of the sugar. This experiment encouraged us to consider introduction of a silyl ether at the C6-position. Commercially available D-galactose (**1a**)



Scheme 1. Synthesis of minimally protected glycosyl donors.

was first converted to 6-*O*-TBDPS protected D-galactose **2a** by treating with TBDPSCl/imidazole in DMF, followed by regioselective carbonate formation at anomeric position using 1.2 equivalent of carbonate reagent **3**[9a]/DMAP in CH_2Cl_2. As ensued, the regioselective formation of anomeric (*C*-1) carbonate **4a** over other positions (*C*-2, *C*-3 and *C*-4) was quite satisfying. Regioselective carbonate formation using the carbonate reagent not only reduced two extra steps for protection/deprotection but also made the donor easily accessible for MPG reactions. This two-step donor protocol was further exploited for the synthesis of other sugar carbonates (**4b-d**) in 74–90% yields (Scheme 1).

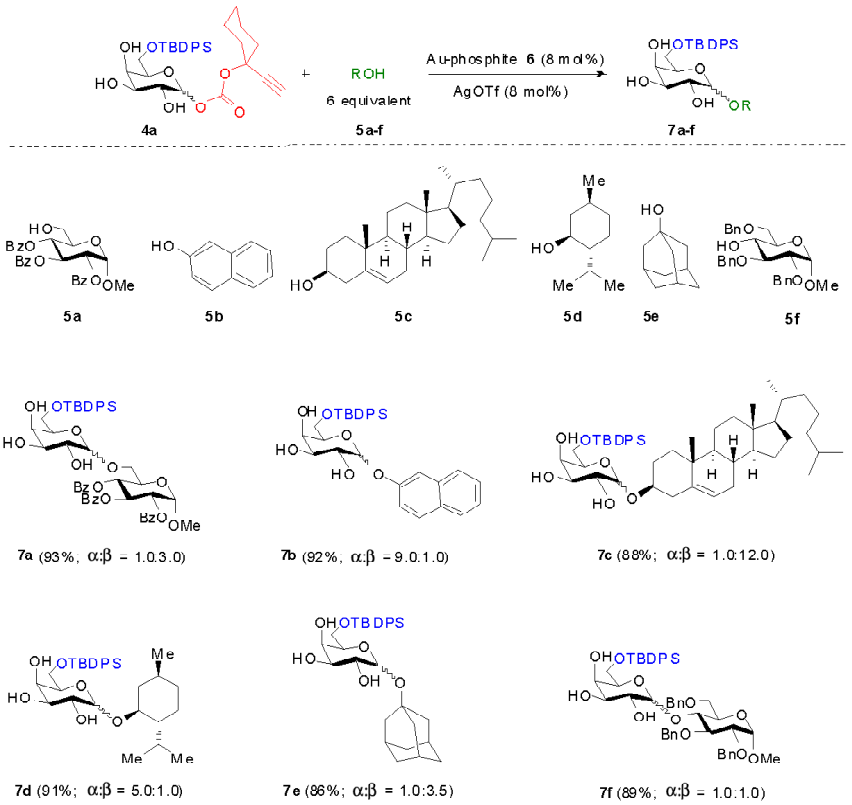
Having pyranosyl and furanosyl donors (**4a**-**4d**) in our hand, we embarked on identifying suitable reaction conditions for glycosidations. For this, at first carbonate donor **4a** was chosen as a model glycosyl donor which was treated with acceptor **5a** in presence of 8 mol% each of Au-phosphite **6**[9a] and AgOTf in various routinely employed solvents (Scheme 2). Chlorinated solvents such as CH_2Cl_2 and $ClCH_2CH_2Cl$ produced equimolar mixture of α/β-anomers **7a** whereas use of $CHCl_3$ increased the β-anomer comparatively (Scheme 2). It was quite interesting to notice that the β-anomer ratio increased in toluene; chlorobenzene just reversed the selectivity (Scheme 2). CH_3CN also increased the β-selectivity over α-, but the glycosidation yield dropped significantly (~20%) in CH_3CN solvent. Affinity of active $[Au]^+$ cation to CH_3CN triple bond could be the reason for diminished yield. A 50% reduction in the glycosidation yield with no significant change in the selectivity was observed in Et_2O (Scheme 2). Surprisingly, no glycoside product was observed in 1,4-dioxane and CH_3NO_2 solvents. In both the cases, the starting materials (i.e. donor and acceptor) remained as they are (Scheme 2) that could probably be poised to the sparingly soluble nature Au(I) salts in those solvents.

Variation in reaction temperature from 25°C to as low as –60°C in CH_2Cl_2 showed a steady increase in the β-selectivity over α- one with concurrent reduction in the yield of glycosidation from 98% to 57% (Scheme 2). Similar trends were observed in other solvents too. It is worthy to note that yields for glycoside **7a** reduced drastically at lower temperatures in Et_2O and CH_3CN solvents (Scheme 2).

Acceptor **5b** gave a significant increase in α-selectivity in CH_2Cl_2 as well as in chlorobenzene solvent as noticed earlier[8a] (Scheme 2). Glycosidation reaction of acceptor **5c** with glycosyl donor **4a** under similar reaction condition (e.g. –20°C, chlorobenzene) also provided β-glycoside **7c** as a major glycoside with an overall yield of 88% (Scheme 2). However, treatment of other acceptors (**5d-5f**) with galactosyl carbonate donor **4a** at –20°C in chlorobenzene resulted glycosides **7d-7f** with different anomeric selectivity. For instance, sugar acceptors **5d** provided glycosides **7d** having α-anomer as the major product whereas acceptor **5e** resulted in glycoside **7e** as the major product and acceptor **5f** ended up in **7b** as 1:1 (α:β) mixture of anomers respectively (Scheme 2). It was observed that the stereochemical outcome (i.e. α/β) of MPG reactions under [Au]/[Ag]-catalyzed conditions highly depended on the structure, reactivity of acceptors, the solvent and the temperature[10].

Materials and methods:

Unless otherwise noted all the materials were purchased from commercial sources and were used with no further purification. Analytical thin layer chromatography was performed on a pre coated Merck silica plates, compounds visualised



Scheme 2. Minimal protection based glycosidations.

Acceptor	Solvent	Temp. (°C)	Time (h)	α:β[a]	Yield (%)[b]
5a	CH_2Cl_2	25	0.25	1.0:1.1	98
5a	$[CH_2]_2Cl_2$	25	0.25	1.0:1.2	92
5a	$CHCl_3$	25	0.25	1.0:2.3	96
5a	Toluene	25	0.5	1.0:2.0	90
5a	Chlorobenzene	25	0.5	1.4:1.0	97
5a	CH_3CN	25	24	1.0:1.7	20
5a	Et_2O[a]	25	24	1.0:1.0	45
5a	CH_3NO_2	25	24	–	NR
5a	1,4-Dioxane	25	24	–	NR
5a	CH_2Cl_2	0	0.5	1.0:2.0	95
5a	CH_2Cl_2	–20	2	1.0:3.6	93
5a	CH_2Cl_2	–40	6	1.0:4.0	74
5a	CH_2Cl_2	–60	12	1.0:4.0	57
5a	Chlorobenzene	0	0.5	1.0:1.4	97
5a	Chlorobenzene	–20	0.5	1.0:2.8	95
5a	Chlorobenzene	–40	0.5	–	NR
5a	Toluene	–20	3	1.0:3.3	72
5a	Toluene	–40	24	1.0:3.7	50
5a	Et_2O	–20	24	1.0:1.5	25
5a	Et_2O	–60	24	1.0:1.8	12
5a	CH_3CN	–20	24	1.0:2.0	5
5a	CH_3CN	–60	24	–	NR
5b	CH_2Cl_2	25	0.25	4.5:1.0	98
5b	CH_2Cl_2	0	0.5	4.5:1.0	98
5b	CH_2Cl_2	–20	2	5.5:1.0	98
5b	Chlorobenzene	–20	2	10.0:1.0	92
5c	Chlorobenzene	–20	2	1.0:12.0	88
5d	Chlorobenzene	–20	2	5.0:1.0	91
5e	Chlorobenzene	–20	2	1.0:3.5	85

[a]α/β ratios were determined from ^{1}H NMR spectra of partially purified products; [b]Isolated yield after purification; NR means No Reaction.

by UV light or stained by anisaldehyde. NMR spectra were recorded either in Jeol 400 MHz or Bruker 600 MHz with $CDCl_3$ as the solvent and TMS as the internal standard.

Experimental

*General procedure for synthesis of ethynylcyclohexyl glycosyl carbonate donors (**4a-d**):* To a rapidly stirring solution

of commercially available D-sugar (50 mmol) in DMF was added imidazole (100 mmol) and stirred at 25°C for 20 min. TBDPSCl (60 mmol) was added drop-wise and stirred at 25°C. After 8 h, the reaction mixture was diluted with water and extracted with EtOAc (3×50 mL) and combined EtOAc layers were washed with brine solution. EtOAc layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a pale-yellow coloured liquid that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford mono-TBDPS protected compound **2a-d** in 85–94% yields as colourless syrup. In continuation, mono-TBDPS protected compound (20 mmol) prepared *vide supra* was redissolved in anhydrous CH_2Cl_2 and cooled to 0°C using ice bath. DMAP (50 mmol) was added and stirred for 30 min. A solution of carbonate reagent **3** (50 mmol) in anhydrous CH_2Cl_2 was further added drop-wise over a period of 1 h at 0°C and allowed to warm to 25°C. After 12 h, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution followed by brine solution. CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a pale yellow coloured solid that was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford glycosyl carbonate donors **4a-d** in 74–95% yields as thick syrup.

We found that, slow addition of carbonate reagent **3** was crucial to obtain higher yields of glycosyl donors.

*General glycosylation procedure for synthesis of O-glycosides (**7a-f**):* To a solution of glycosyl donor (1.0 mmol) and acceptor (6.0 mmol) in anhydrous solvent was added freshly activated 4 Å MS powder (50 mg/mL) and stirred for 30 min at 25°C. The reaction mixture was stirred for 10 min. at mentioned temperature (e.g. 0°C, –20°C, –40°C etc.). Premixed Au-phosphite **6** and AgOTf (8 mol% each) in anhydrous CH_2Cl_2 was added drop-wise to the reaction mixture and stirred further. The reaction was stopped by addition of Et_3N and the glycosylated products were purified using silica gel column chromatography (*n*-hexane/EtOAc) to obtain compounds **7a-f** in 86–93% yield.

NMR characterisation:

*1-O-(((1-Ethynylcyclohexyl)oxy)carbonyl)-6-O-tert-butyldiphenylsilyl α/β-D-galactopyranoside [α:β (5.0:1.0)] (**4a**):* ^{1}H NMR (400.37 MHz, $CDCl_3$): δ 0.82–1.07 (m, 20H), 1.09–2.64 (m, 18H), 3.27–3.58 (m, 2H), 3.58–3.73 (m, 4H), 3.77–3.94 (m, 6H), 3.95–4.65 (m, 8H), 5.33 (d, *J* 8.0 Hz, 1H), 7.19–7.47 (m, 6H), 7.50–7.79 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2 (4C), 22.6, 23.2, 24.9, 25.2, 26.9 (6C), 36.5 (2C), 37.0 (2C), 62.2, 62.9, 69.0 (2C), 70.3 (2C), 72.4, 73.1,73.7, 74.9, 75.2, 75.7, 78.7 (2C), 82.6 (2C), 97.3, 97.7, 127.9 (8C), 129.9 (4C), 133.0 (4C), 135.7 (8C), 151.3 (2C).

*1-O-(((1-Ethynylcyclohexyl)oxy)carbonyl)-6-O-tert-butyldiphenylsilyl α-D-mannopyranoside (**4b**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.15–2.25 (m, 10H), 2.60 (s, 1H), 3.43–3.73 (m, 2H), 3.74–3.81 (m, 1H), 3.81–4.17 (m, 6H), 5.96 (d, *J* 1.7 Hz, 1H), 7.23–7.48 (m, 6H), 7.57–7.80 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3 (2C), 22.7, 25.0, 26.9 (3C), 36.6, 37.1, 64.8, 69.3, 69.4, 71.1, 73.5, 75.6, 78.5, 82.6, 96.5, 127.9 (4C), 130.0 (2C), 133.0 (2C), 135.7 (4C), 150.9.

*1-O-(((1-Ethynylcyclohexyl)oxy)carbonyl)-6-O-tert-butyldiphenylsilyl α-D-glucopyranoside (**4c**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.00–1.14 (m, 10H), 1.17–2.38 (m, 9H), 2.65 (s, 1H), 3.44–3.79 (m, 4H), 3.80–4.26 (m, 4H), 4.29–4.66 (m, 1H), 5.46 (d, *J* 8.0 Hz, 1H), 7.33–7.49 (m, 6H), 7.63–7.83 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.3 (2C), 22.6, 24.9, 26.9 (3C), 36.5, 37.0, 63.9, 70.9, 72.4, 75.8, 76.0, 76.4, 78.6, 82.5, 97.1, 127.8 (4C), 129.8 (2C), 133.1 (2C), 135.7 (4C), 151.4.

*1-O-(((1-Ethynylcyclohexyl)oxy)carbonyl)-5-O-tert-butyldiphenylsilyl α/β-D-arabinofuranoside [α:β (1.5:1.0)] (**4d**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.10–1.19 (m, 18H), 1.18–1.45 (m, 4H), 1.50–1.79 (m, 8H), 1.83–2.28 (m, 6H), 2.60 (m, 2H), 3.58–3.66 (m, 2H), 3.75–3.81 (m, 4H), 3.88–3.99 (m, 4H), 4.26–4.34 (m, 4H), 4.53–4.61 (m, 2H), 4.83–5.11 (m, 2H), 7.38–7.51 (m, 12H), 7.66–7.81 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.1(2C), 19.3 (2C), 22.6, 23.2, 24.9, 25.6, 26.8 (3C), 26.9 (3C), 36.8 (2C), 36.9 (2C), 63.4, 64.2, 74.6, 75.1, 75.6, 76.4, 78.0, 79.2, 82.9, 83.7, 86.2, 86.8, 87.3, 88.8, 103.4, 104.3, 128.0 (4C), 128.1 (4C), 130.0 (2C), 130.1 (2C), 132.0 (2C), 132.8 (2C), 135.5 (4C), 135.7 (4C), 152.5, 153.1.

*Methyl 2,3,4-tri-O-benzoyl-6-O-(6-O-tert-butyldiphenylsilyl α/β-D-galactopyranosyl) α-D-glucopyranoside [α:β (1.0:2.8)] (**7a**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.74–1.40 (m, 18H), 3.35–3.46 (m, 6H), 3.48–3.67 (m, 6H), 3.68–4.02 (m, 12H), 4.03–4.30 (m, 8H), 4.85–5.43 (m, 4H), 5.49–5.90 (m, 2H), 5.99–6.25 (m, 2H), 7.20–7.31 (m, 6H), 7.33–7.52 (m, 24H), 7.61–7.71 (m, 8H), 7.81–8.09 (m, 12H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2, 19.3, 26.9 (6C), 55.8 (2C), 62.9, 63.8, 65.4, 67.5, 68.3 (2C), 68.7, 68.7, 68.8, 69.1, 70.5, 70.7, 71.1,

71.4, 72.1, 72.2, 73.7 (2C), 75.0 (2C), 97.2, 97.3, 98.8, 103.5, 127.9 (12C), 128.5 (4C), 128.6 (4C), 129.9 (15C), 130.0 (15C), 133.2 (3C), 133.5 (3C), 135.7 (2C), 135.8 (2C), 165.9 (2C), 165.9 (2C), 166.1 (2C).

*1-O-(2-Napthyl)-6-O-tert-butyldiphenylsilyl α/β-D-galactopyranoside [α:β (10.0:1.0)] (**7b**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.92–1.05 (m, 18H), 2.87–3.45 (s, 2H), 3.47–3.64 (m, 2H), 3.65–3.81 (m, 2H), 3.82–3.97 (m, 6H), 4.01–4.38 (m, 6H), 5.70 (d, *J* 3.6 Hz, 2H), 7.07–7.48 (m, 20H), 7.52–7.79 (m, 14H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2, 19.3, 26.8 (3C), 26.9 (3C), 63.6, 64.0, 69.5 (2C), 70.1 (2C), 70.9 (2C), 71.3 (2C), 97.8, 101.6, 111.4, 111.7, 118.9, 119.1, 124.4 (2C), 126.4 (2C), 127.4 (2C), 127.7 (2C), 127.8 (2C), 129.6 (2C), 129.9 (2C), 132.9 (2C), 134.4 (2C), 135.6 (8C), 135.7 (12C), 154.5, 155.1.

*Cholesteryl 6-O-tert-butyldiphenylsilyl α/β-D-galactopyranoside [α:β (1.0:12.0)] (**7c**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.81–0.95 (m, 22H), 0.94–1.08 (m, 32H), 1.18–1.31 (m, 18H), 1.37–1.65 (m, 18H), 1.75–2.40 (m, 18H), 3.09–3.95 (m, 14H), 4.03 (d, *J* 2.9 Hz, 2H), 4.27–5.07 (m, 2H), 5.12–5.37 (m, 2H), 7.32–7.46 (m, 12H), 7.62–7.75 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 11.9, 14.1 18.7 (2C), 19.2 (2C), 19.4 (2C), 21.1 (2C), 22.6 (2C), 22.7, 22.8, 23.8 (2C), 24.3 (2C), 26.6 (2C), 26.8 (3C), 28.0, 28.2, 29.4 (2C), 31.6 (2C), 31.9 (2C), 32.0 (2C), 35.8 (2C), 36.2 (2C), 36.6, 36.7, 37.3 (2C), 38.8 (2C), 39.5 (2C), 39.8, 40.2, 42.3 (2C), 50.2 (2C), 56.2 (2C), 56.8 (2C), 63.1 (2C), 69.0, 70.2 72.1 (2C), 73.7 (2C), 74.5 (2C), 78.9 (2C), 96.7, 101.3, 122.1 (2C), 127.7 (4C), 127.8 (4C), 129.7 (2C), 129.8 (2C),133.0 (2C),133.1 (2C), 135.6 (8C), 140.2, 140.3.

*Menthyl 6-O-tert-butyldiphenylsilyl α/β-D-galactopyranoside [α:β (5.0:1.0)] (**7d**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.64–0.99 (m, 22H), 0.99–1.10 (m, 18H), 1.14–1.42 (m, 12H), 1.53–1.71 (m, 4H), 1.99–2.27 (m, 4H), 2.74–2.99 (m, 2H), 3.43–3.51 (m, 2H), 3.54–3.59 (m, 2H), 3.65–3.99 (m, 6H), 4.03–4.23 (m, 2H), 4.24–5.00 (m, 2H), 7.33–7.49 (m, 12H), 7.61–7.75 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 15.7, 15.8, 19.2, 19.2, 21.0, 21.2, 22.3, 22.7, 22.8, 23.1, 25.1, 25.5, 26.8 (3C), 26.8 (3C), 31.6, 31.9, 34.2, 34.4, 40.6, 42.7, 47.8, 48.7, 62.9, 63.3, 68.9, 69.5, 69.9, 70.4, 71.6, 72.2, 73.8, 74.4, 80.8 (2C), 100.0, 104.1, 127.8 (4C), 127.8 (4C), 129.9 (2C), 129.9 (2C), 133.0 (2C), 133.1 (2C), 135.6 (4C), 135.6 (4C).

*Adamantyl 6-O-tert-butyldiphenylsilyl α/β-D-galactopyranoside [α:β (1.0:3.5)] (**7e**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.93–1.08 (m, 18H), 1.16–1.31 (m, 10H), 1.49–1.63 (m, 8H), 1.67–1.90 (m, 10H), 1.99–2.12 (m, 4H), 2.15 (s, 2H), 3.22–3.67 (m, 6H), 3.67–4.06 (m, 8H), 4.36–5.32 (m, 2H), 7.21–7.45 (m, 12H), 7.56–7.78 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2 (2C), 26.8 (3C), 26.9 (3C), 30.6 (3C), 30.7 (3C), 36.2 (6C), 42.6 (3C), 42.7 (3C), 63.4, 63.9, 69.2, 69.3, 69.9 (2C), 71.6, 71.8, 73.8 (2C), 74.8, 74.9, 75.6 (2C), 91.6, 96.1, 127.8 (8C), 129.9 (4C), 133.3 (4C), 135.7 (8C).

*Methyl 2,3,6-tri-O-benzyl-4-O-(6-O-tert-butyldiphenylsilyl α/β-D-galactopyranosyl) α-D-glucopyranoside [α:β (1.0:1.0)] (**7f**):* ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.94–1.09 (m, 18H), 2.61–2.83 (s, 2H), 2.88–3.26 (m, 4H), 3.27–3.39 (m, 8H), 3.43–3.78 (m, 14H), 3.79–4.10 (m, 8H), 4.37–4.74 (m, 12H), 4.74–4.86 (s, 2H), 4.92–5.86 (m, 2H), 6.91–7.21 (m, 8H), 7.21–7.43 (m, 36H), 7.54–7.70 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.2 (2C), 26.9 (6C), 55.3 (2C), 62.1, 62.5, 68.1, 68.6, 69.6, 69.7, 70.8, 71.2, 73.0 (3C), 73.5 (2C), 73.7 (3C), 74.2 (2C), 75.1 (2C), 76.4 (2C), 79.2, 79.6, 79.9, 80.7, 97.8 (2C), 98.3, 103.1, 127.3 (6C), 127.8 (6C), 127.9 (6C), 128.1 (6C), 128.3 (6C), 128.5 (6C), 128.7 (6C), 130.0 (8C), 135.6 (2C), 135.7 (2C), 138.0 (6C).

Conclusions

In summary, we wish to report a convenient and efficient [Au]/[Ag] catalyzed MPG reaction where glycosyl donors are prepared from easily accessible unprotected sugars in two steps. Glycosidation reactions are fast, high yielding (>85%) and stereoselective in some cases. A solvent and temperature dependent selectivity tuning of MPG reactions have also been explored which further can facilitate solid phase glycoconjugate synthesis[8a].

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