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Dehydrative Glycosidations of 2-Deoxysugar Derivatives Catalyzed by an Arylboronic Ester

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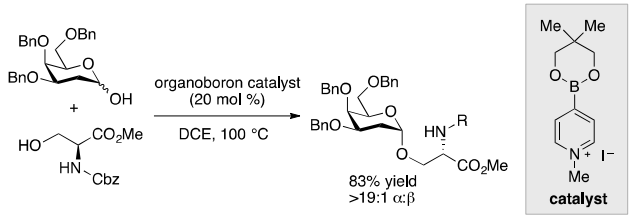
Abstract

An *N*-methylpyridinium-4-boronic ester acts as a catalyst for dehydrative glycosidations of 2-deoxy sugar-derived hemiacetals. The catalytic protocol is tolerant of functionalized acceptors, including alcohols bearing isopropylidene ketal, *tert*-butyl carbamate or benzyl carbamate groups. The results demonstrate that organoboron-catalyzed substitution reactions of alcohols, which have previously been conducted on π-activated (benzylic, allylic or propargylic) substrates, can also be used to achieve C–O bond formation from carbohydrate-derived hemiacetals.

Graphical abstract



Keywords:

Boronic acid

Catalysis

2-Deoxyglycoside

Glycosidation

1. Introduction

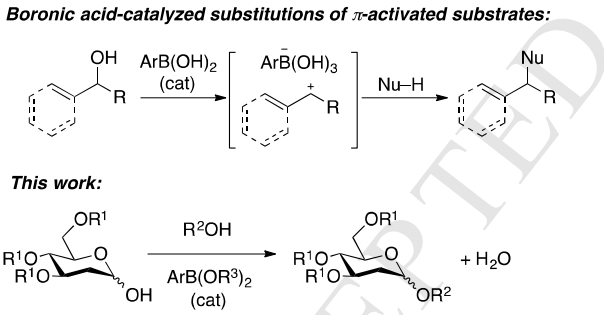
The formation of an *O*-glycosidic bond generally involves the displacement of a leaving group from the anomeric position of a carbohydrate-based electrophile (the glycosyl donor) by a compound bearing a nucleophilic hydroxyl group (the glycosyl acceptor). Much of the development of efficient chemical glycosylation methods has been centered around the identification of leaving groups (often in conjunction with electrophilic activating reagents) that provide advantages from such standpoints as reactivity, stereo- and/or regioselectivity, functional group tolerance and operational simplicity. Broadly employed classes of glycosyl donors include halides, trichloroacetimidates, sulfoxides, thioglycosides, glycal epoxides and pentenyl glycosides; their properties and applications have been summarized in review articles and monographs.[1,2,3,4,5,6]

The prospect of achieving a dehydrative glycosidation by formal nucleophilic displacement of hydroxide at the anomeric position has attracted sustained interest. The Fischer glycosidation stands as the prototype of such a process, wherein a *C*(1)-hemiacetal is activated by strong Brønsted acid catalyst through the presumed intermediacy of its acyclic hydroxy aldehyde tautomer.[7] Although limitations of the method can be identified – including its incompatibility with certain acid-labile functional groups and glycosidic linkages, and its reversible nature under most commonly employed reaction conditions – the Fischer glycosidation continues to be employed extensively, aided by the development of new protocols and catalysts.[8,9,10] Over the years, several other methods for dehydrative glycosidation have been developed, involving in situ formation of such intermediates as glycosyl sulfonates, halides, imidates, oxophosphonium salts, isoureas, oxotitanium complexes and oxosulfonium triflates.[11,12] A common feature of these methods is the requirement for a stoichiometric quantity of dehydrating reagent.

Catalytic protocols (other than the classic Fischer glycosylation) for activation of 1-hydroxyglycosyl donors are relatively uncommon: Lewis acids that have been successfully employed in such catalytic, dehydrative glycosidations are $Yb(OTf)_3$/ methoxyacetic acid,[13] combinations of hexamethyldisiloxane with $Sn(OTf)_2$, $Yb(OTf)_3$, $Ln(OTf)_3$ or $SnCl_2$,[14] silver(I) perchlorate with diphenyltin sulfide or Lawesson's reagent,[15] and triphenylmethyl tetraarylborate salts.[16,17] Dehydrative glycosidations using amphiphilic sulfonic acids as catalysts in aqueous solution have also been developed.[18] Herein we report that electron-deficient boronic acids serve as catalysts for dehydrative glycosylations of *C*(1)-hemiacetals derived from 2-deoxysugars. Generation of activated glycosyl donors from 1-hydroxysugars appears to represent a new application of the reversible carbohydrate–boronic acid interactions that have been shown to be useful for protections, separations and chemical sensing of sugars.[19,20,21]

In previous work we have demonstrated that borinic acids (R_2BOH) activate the equatorial hydroxyl groups of carbohydrate-derived *cis*-1,2-diol motifs towards reactions with acyl, alkyl, sulfonyl and glycosyl halide electrophiles. The proposed mechanism, which has been supported by kinetic studies and computational modeling involves a tetracoordinate borinate ester as an activated nucleophile. We have also employed boronic acids as protecting groups and activating agents for carbohydrate derivatives.[22,23,24,25,26] The proposal that coordination of hydroxyl groups by organoboron compounds could trigger electrophilic, rather than nucleophilic, reactivity of carbohydrates draws on observations reported by the groups of McCubbin and Hall. Electron-deficient fluoroaryl-, pyridinium- or ferrocenium-based boronic acids or boronic esters were shown to activate ionizable (benzylic, allylic and propargylic) alcohols towards Friedel–Crafts reactions,[27,28,29,30,31] 1,3-transpositions,[32] carbo- and heterocyclizations[33] and other nucleophilic

substitution reactions.[34,35] Experimental evidence consistent with the organoboron-promoted generation of carbocation intermediates was presented for certain catalyst/substrate combinations. We sought to determine whether this mode of reactivity could be extended to the generation of glycosyl donors by coordination of boronic acids or esters to the 1-OH group of carbohydrate substrates (Scheme 1).[36] Given that the majority of alcohol substrates that have been employed in organoboron-catalyzed substitutions bear one or more carbocation-stabilizing groups, it was unclear whether 1-hydroxycarbohydrates would be viable candidates for catalysis.[37,38] We selected *C*(1)-hemiacetals of 2-deoxysugars as test substrates because the lack of an electron-withdrawing oxygen substituent at *C*(2) facilitates the generation of oxocarbenium ions. This same feature contributes to the poor stability profiles of conventional 2-deoxyglycosyl donors, and has served as motivation for the development of dehydrative glycosylations for this class of compounds.[39,40,41,42,43,44]



Scheme 1. Boronic acid-catalyzed substitution reactions of π-activated (*e.g.*, allylic, benzylic) alcohols, and envisioned extension to anomeric hemiacetals.

2. Results and Discussion

2.1. Catalyst optimization

The boronic acids and esters depicted in Figure 1 were evaluated as catalysts for the coupling of hemiacetal **2a** and isopropanol in 1,2-dichloroethane (DCE) at 100 °C in sealed vials. The results are summarized in Table 1. Whereas phenylboronic acid (**1a**) displayed low activity,

perfluorinated **1b** catalyzed the formation of **3a** in 55% yield as a mixture of anomers. Using the more Lewis acidic catechol esters in place of the free boronic acids resulted in increased activity (catalysts **1c**–**1f**). Esters of *N*-methylpyridinium-4-boronic acid[33,45] (**1g**–**1i**) provided the highest glycosidation yields of the catalysts examined. When pyridinium-based catecholboronic ester **1i** was used as the catalyst, side product **4** was detected in the ^{1}H NMR spectrum of the unpurified reaction mixture. The particularly high Lewis acidity of **1i** may have been responsible for the formation of **4** by elimination and Ferrier rearrangement.[46] Neopentyl glycol ester **1h** was selected as the optimal catalyst based on the data from Table 1.

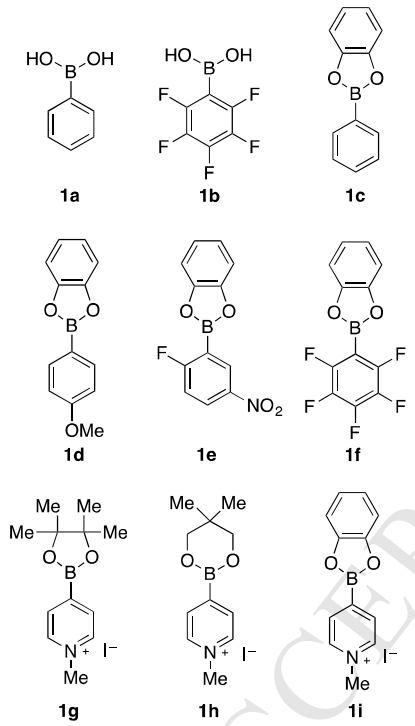
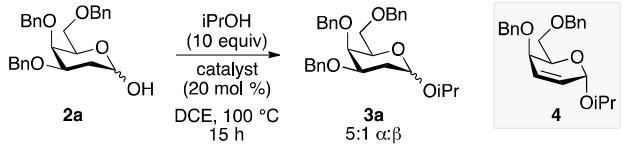


Figure 1. Structures of organoboron catalysts evaluated as catalysts for glycosidation of **2a**.

Table 1

Glycosidation of hemiacetal **2a** with catalysts **1a**–**1i**.



Entry	Catalyst	Conversion of **2a**[a]	Yield of **3a**[a]
1	**1a**	10%	10%
2	**1b**	65%	55%
3	**1c**	50%	50%
4	**1d**	70%	60%
5	**1e**	60%	60%
6	**1f**	70%	50%
7	**1g**	100%	90%
8	**1h**	100%	90%
9	**1i**	100%	85%[b]

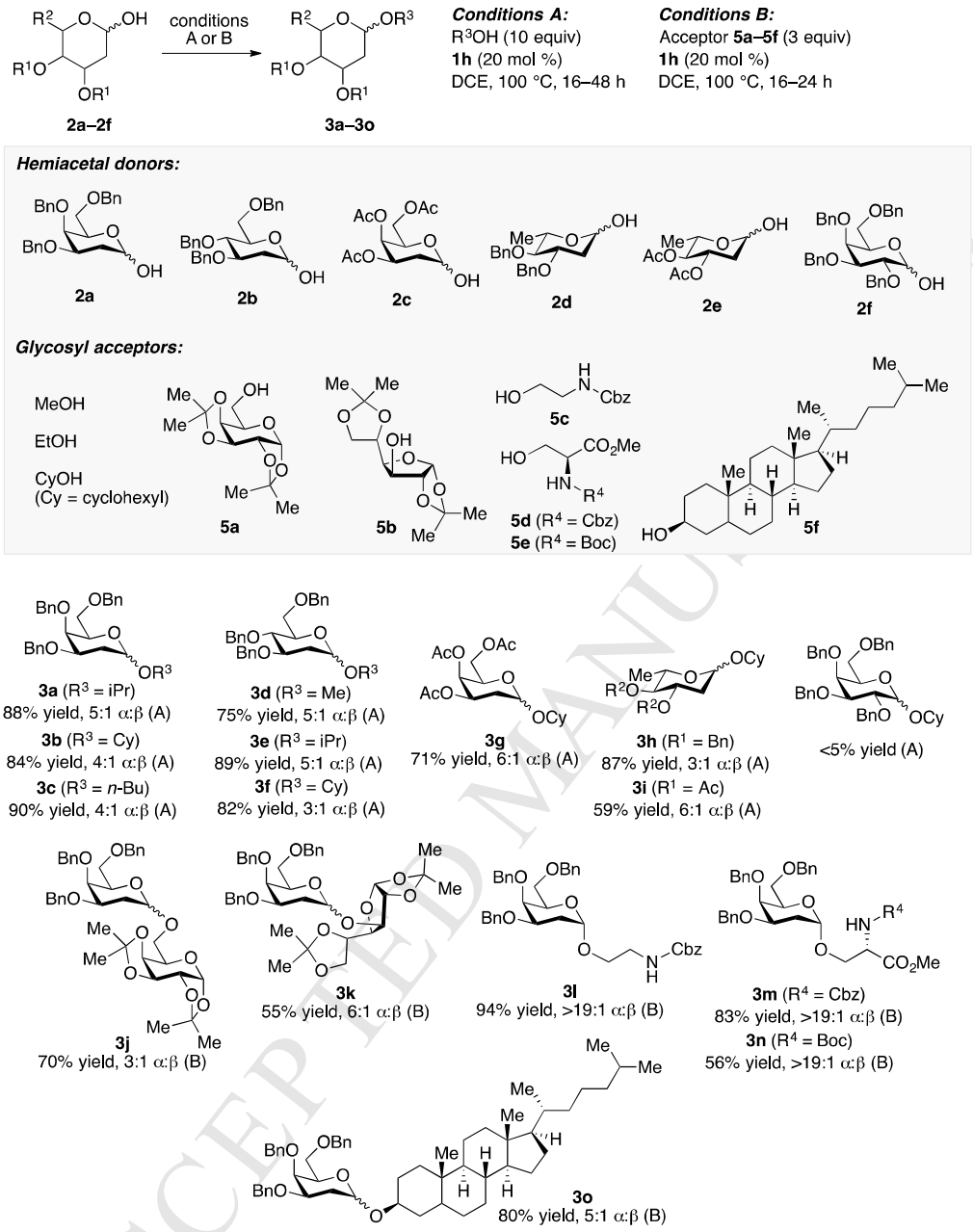
[a] Conversion, yield and α:β ratio were determined by ^{1}H NMR spectroscopy using a quantitative internal standard. [b] Signals corresponding to side product **4** were evident in the ^{1}H NMR spectrum of the unpurified reaction mixture.

The organoboron-catalyzed protocol was applied to a range of glycosyl donors and acceptors (Scheme 2). In a preparative experiment, compound **3a** was isolated in 88% yield as a mixture of anomers after purification by chromatography on silica gel. In general, good yields were obtained for couplings of aliphatic alcohols (methanol, *n*-butanol, isopropanol and cyclohexanol) with benzyl-protected hemiacetals **2a** and **2b**. The ratios of anomers were in agreement with those obtained using other catalytic protocols for dehydrative glycosidation,[14,17] and would be consistent with thermodynamic control under these conditions. In keeping with this hypothesis,

treatment of cyclohexyl glycoside **3b** with isopropanol (10 equiv) in the presence of catalyst **1h** under the optimized conditions resulted in transglycosylation, generating a 5:1 mixture of products **3a** and **3b** (Scheme 3). This observation indicates that glycosylation of **2a** is indeed reversible under the conditions developed in this study. A decrease in reactivity relative to **2a** was observed for the glycosidation of acetyl-protected hemiacetal **2c**, as expected based on the disarming effect of the ester protective groups.[47] 2,6-Dideoxyglycosides (**3h**, **3i**) were also prepared using catalyst **1h**. In contrast, 2,3,4,6-tetra-*O*-benzylgalactopyranose **2f** did not undergo glycosidation under these conditions, presumably due to the destabilizing effect of the 2-alkoxy substituent on species having oxocarbenium character.

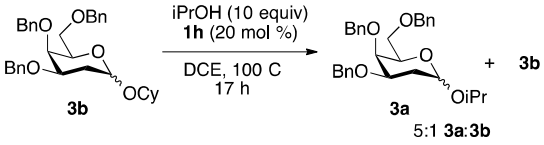
The boronic ester-catalyzed dehydrative glycosidations were extended to more complex acceptor alcohols (**5a**–**5f**). For these reactions, three equivalents of the glycosyl acceptor (rather than ten, as was the case for the aliphatic alcohols) were employed. Isopropylidene ketals, as well as benzyl and *tert*-butyl carbamate (Cbz and Boc) groups, were tolerated under the catalytic conditions. The reactions of protected amino alcohols **5c**–**5e** were significantly more α-selective than those of the other glycosyl acceptors. Several other methods for the synthesis of α-2-deoxyglycosides derived from protected amino alcohols have been reported previously.[48,49,50,51,52,53,54,55] A rationale for the higher stereoselectivity observed using **5c**–**5e** under the conditions of the present study is not readily apparent. To probe the possibility of a specific interaction between the organoboron catalyst and the amino alcohol acceptor, the effect of **5e** on the ^{11}B NMR spectrum of **1h** was evaluated. No appreciable change in the ^{11}B NMR chemical shift of **1h** was observed upon addition of **5e**, suggesting that the two compounds do not interact in a way that significantly alters the coordination environment at boron.

Scheme 2. Dehydrative glycosidations catalyzed by boronic ester **1h**.[a]



[a] Isolated yields after purification by silica gel chromatography without separation of anomers. The conditions used for the synthesis of each product (Conditions A or B) are denoted in parentheses after the yield and α:β ratio.

Scheme 3. Evidence for reversible glycosidation under the optimized conditions using catalyst **1h**.



3. Conclusions

In conclusion, we have identified a boronic ester that serves as a catalyst for dehydrative glycosidations of 2-deoxysugar-derived hemiacetals. A range of 2-deoxy- and 2,6-dideoxyglycosides, derived from functionalized acceptors such as partially protected carbohydrates and amino alcohol derivatives as well as simple aliphatic alcohols, can be synthesized using the organoboron-catalyzed protocol. Unlike the majority of previously reported catalysts for such dehydrative glycosidations, the organoboron catalysts allow for considerable tuning of steric and electronic properties, as well as the potential for incorporation of other catalytically reactive functional groups.[56,57,58,59] In general, the method provides modest levels of selectivity for the formation of α-glycosides. In the case of carbamate-protected amino alcohol acceptors, the reactions display a significantly higher preference for formation of the α-glycoside products.

The results indicate that organoboron catalysis of direct substitution reactions of alcohols can be extended from π-activated substrates (the focus of previous research efforts in this area) to anomeric hemiacetals. While the results presented here constitute a first step in this direction, significant challenges remain. The relatively high reaction temperature (100 °C) and catalyst loading (20 mol %), along with the failure to achieve glycosidation of the fully oxygenated galactopyranosyl donor **2f**, indicate that the activity of the optimal boronic ester identified in this study is somewhat modest: it appears that glycosyl hemiacetals are at the threshold of the level of reactivity needed for activation by boronic acids and their derivatives. Further evaluations of such

substrates may be of interest as part of the ongoing effort to develop more active organoboron catalysts for direct substitution reactions of alcohols.[34,35,60]

4. Experimental

4.1. General Methods

All reactions were carried out under an argon atmosphere, unless specifically indicated. Stainless steel needles and gas-tight syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using neutral silica gel (Silicycle). Analytical thin layer chromatography (TLC) was carried out using aluminium-backed silica gel 60 F254 plates (EMD) and visualized using short-wave UV light or $KMnO_4$ stain with appropriate heating. 1,2-Dichloroethane was obtained from sure-seal 1L bottle (Sigma-Aldrich), under a balloon of argon. Distilled water was obtained from an in-house supply. All other reagents and solvents were purchased from Sigma Aldrich, Caledon, Carbosynth or Alfa Aesar and used without further purification. Nuclear magnetic resonance (NMR) solvents were purchased from Cambridge Isotope Laboratories. High resolution mass spectrometry (HRMS) was by direct analysis in real time in positive ion mode (DART+) on a JEOL AccuTOF JMS-T1000LC.

Note regarding ^{1}H NMR spectral data for compounds isolated as mixtures of anomers. Signals from the ^{1}H NMR spectrum corresponding to the major anomer are reported first (including those overlapping with signals from the minor anomer), followed by well-resolved signals corresponding to the minor anomer. The integrations were normalized to a well-resolved signal corresponding to a single hydrogen from the major anomer, and the integrals for signals corresponding to the minor anomer are reported relative to this normalized value for the major

anomer. For peaks resulting from overlapping signals from the major and minor anomers, the total integration is reported. These overlapping signals thus give integrals that are higher than the expected number of corresponding hydrogens arising from the major anomer.

4.2. Catalyst 1h

4-Pyridineboronic acid (1 mmol, 122.9 mg) and neopentyl glycol (1 mmol, 104.15 mg) were transferred to a long screw-cap vial. Toluene (4 mL) was added and the reaction was heated at 100 °C overnight. The resulting mixture was concentrated *in vacuo* and water was removed by azeotrope with fresh toluene three times. To this crude product iodomethane (5 mmol, 311 μL) and acetonitrile (4 mL) were added and heated at reflux (85 °C) overnight. After rotary evaporation in a fume hood (an operation that removes excess iodomethane), the residue was purified by trituration with hexanes to afford **1h** as a yellow powder in quantitative yield. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.18 (d, *J* = 6.1 Hz, 2H), 8.28 (d, *J* = 6.1 Hz, 2H), 4.72 (s, 3H), 3.83 (s, 4H), 1.04 (s, 6H). **^{13}C NMR: 125 MHz, $CDCl_3$):** δ 144.2, 132.2, 72.8, 49.5, 32.0, 21.8. **^{11}B NMR (128 MHz, $CDCl_3$):** δ 25.5. **HRMS (ESI+)** Calculated for $C_{11}H_{17}BNO_2$ [M+]: 205.1383, found: 205.1381.

4.3. General procedure for glycosidation reactions

Glycosyl donor (0.2 mmol, 1 equiv.), glycosyl acceptor (0.6–2.0 mmol, 3–10 equiv.), and catalyst (0.04 mmol, 0.2 equiv.), were transferred to a 2-dram vial containing a magnetic stir bar. Anhydrous 1,2-dichloroethane (1 mL, 0.2 M) was added to the vial, and purged with a stream of argon, and then quickly capped and sealed with Teflon™ tape. The reaction was heated at 100 °C for 16–48 hours and monitored by TLC. The crude reaction mixture was concentrated and purified by silica gel chromatography.

4.4. Isopropyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranoside (3a, 5:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of isopropanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (pentanes/EtOAc, 95:5 → 90:10) The title compound was obtained as a colorless oil. Combined yield (**3a**) = 83.8 mg, 0.176 mmol, 88%. The α:β ratio was determined to be 5:1 based on the relative integrations of the signals at 5.10 ppm (α) and 3.47 ppm (β). Spectral data were consistent with previous reports.[61] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.39–7.21 (m, 18H), 5.13–5.06 (br d, *J* = 3.2 Hz, 1H, H-1α), 4.97–4.89 (d, *J* = 11.7 Hz, 1H), 4.69–4.57 (m, 4H), 4.54–4.41 (m, 3H), 4.05–3.92 (m, 3H), 3.92–3.84 (septet, *J* = 6.2 Hz, 1H, *CH-isopropyl*), 3.66–3.52 (m, 3H), 2.31–2.19 (m, 1H), 1.98–1.90 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H, *CH_3-isopropyl*), 1.13 (d, *J* = 6.3 Hz, 3H, *CH_3-isopropyl) Representative signals corresponding to β anomer*: 3.84–3.80 (m, 0.2H), 3.80–3.76 (m, 0.4H), 3.46 (m, 0.2H), 2.11 (m, 0.2H), 2.01 (m, 0.2H), 1.23 (d, *J* = 6.2 Hz, 0.6H, CH_3-isopropyl). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 139.1, 139.0, 138.8, 138.7, 138.3, 138.3, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.4, 97.3, 95.7, 75.2, 75.0, 74.4, 74.2, 73.7, 73.6, 73.6, 73.3, 73.2, 70.6, 70.6, 70.3, 70.2, 69.9, 69.7, 69.1, 68.4, 31.8, 30.5, 23.5, 21.5. **HRMS (DART+):** calculated for $C_{30}H_{40}NO_5$ $[M+NH_4]^+$: 494.2907, found: 494.2907.

4.5. Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranoside (3b, 4:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of cyclohexanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (pentanes/EtOAc, 100:0 → 80:20). The title compound was obtained as a colorless oil. Combined yield (**3b**) = 86.3 mg, 0.167 mmol, 84%. The α:β ratio was determined to be 4:1 based on the relative integrations of the signals at 5.12 ppm (α) and 2.11 ppm (β). Spectral data for the α anomer were consistent with previous reports.[53] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.43–7.20 (m, 19H), 5.16–5.11 (d, *J* = 3.6 Hz, 1H), 4.97–4.91 (d, *J* = 11.7 Hz, 1H), 4.70–4.39 (m, 7H), 4.05–3.89 (m, 3H), 3.69–3.48 (m, 5H), 2.31–2.18 (m, 1H), 1.98–1.91 (m, 1H), 1.91–1.78 (m, 2H), 1.78–1.61 (m, 3H), 1.54–1.46 (m, 1H), 1.44–1.03 (m, 8H). *Representative signals corresponding to β anomer*: 3.82–3.80 (m, 0.25H), 3.79–3.75 (m, 0.25H), 3.48–3.43 (m, 0.25H), 2.18–2.05 (m, 0.25H), 2.04–2.00 (m, 0.25 H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.1, 138.8, 138.3, 128.5, 128.5, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.6, 127.4, 127.4, 98.3, 95.7, 75.2, 74.6, 74.4, 73.6, 73.5, 73.3, 70.6, 70.0, 69.8, 33.6, 31.9, 31.8, 25.8, 24.5, 24.3, 24.2. **HRMS (DART+):** calculated for $C_{33}H_{44}NO_5$ $[M+NH_4]^+$: 534.3220, found: 534.3228.

4.6. *n*-Butyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranoside (3c, 4:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of *n*-butanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 16.5 hours. Purification was by flash chromatography on silica gel (hexanes/diethyl ether 95:5 → 70:30). The title compound was obtained as a colorless oil. Combined yield (**3c**) = 87.8 mg, 0.179 mmol, 90%. The α:β ratio was determined to be 4:1 based on the relative integrations of the signals at 4.97 ppm (α) and 3.83 ppm (β). **^{1}H NMR (400 MHz,**

$CDCl_3$) *Signals corresponding to α anomer*: δ 7.39–7.22 (m, 19H), 4.97 (br. d, *J* = 3.8, 1H), 4.93 (d, *J* = 11.6 Hz, 1H), 4.68–4.38 (m, 7H), 4.00–3.85 (m, 3H), 3.69–3.52 (m, 4H), 3.44–3.32 (m, 1H), 2.27–2.17 (m, 1H), 2.02–1.96 (m, 1H), 1.57–1.44 (m, 3H), 1.43–1.30 (m, 3H), 0.94–0.89 (t, *J* = 7.4 Hz, 3H). *Representative signals corresponding to β anomer*: 3.83 (m, 0.25H), 3.49–3.45 (ddd, *J* = 6.9, 5.6, 1.2 Hz, 0.25H), 2.14–2.03 (m, 0.5H). 0.92–0.89 (t, *J* = 7.3 Hz, 0.75H). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 138.9, 138.9, 138.6, 138.3, 138.1, 138.1, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.4, 127.3, 127.3, 100.4, 97.7, 74.9, 74.2, 73.5, 73.4, 73.0, 70.4, 70.1, 69.8, 69.6, 67.2, 31.6, 31.3, 19.4, 13.9. **HRMS (DART+):** calculated for $C_{31}H_{42}NO_5$ $[M+NH_4]^+$: 508.3063, found: 508.3063.

4.7. Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranoside (3d, 5:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of methanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (hexanes/diethyl ether, 95:5 → 70:30). The title compound was obtained as a colorless oil. Combined yield (**3d**) = 67.4 mg, 0.150 mmol, 75%. The α:β ratio was determined to be 5:1 based on the relative integrations of the signals at 2.28 ppm (α) and 2.34 ppm (β). Spectral data were consistent with previous reports.[61] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.39–7.16 (m, 18H), 4.93–4.87 (d, *J* = 10.9 Hz, 1H), 4.87–4.83 (m, 1H), 4.73–4.47 (m, 6H), 4.04–3.89 (ddd, *J* = 11.5, 8.7, 5.1 Hz, 1H), 3.83–3.56 (m, 5H), 3.55–3.40 (m, 1H), 3.34–3.27 (s, 3H), 2.31–2.25 (m, 1H), 1.79–1.68 (m, 1H). *Representative signals corresponding to β anomer*: 4.38–4.33 (dd, *J* = 9.7, 2.0 Hz, 0.2H), 2.37–2.31 (m, 0.2H), 1.68–1.57 (m, 0.2H). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 138.8, 138.7, 138.5, 138.4, 138.3, 128.6, 128.5,

128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 100.9, 98.6, 79.5, 79.3, 78.3, 77.8, 75.3, 75.0, 74.9, 73.6, 71.9, 71.6, 70.8, 70.7, 69.4, 69.1, 56.7, 54.7, 36.7, 35.5. **HRMS (DART+):** calculated for $C_{28}H_{36}NO_5$ $[M+NH_4]^+$: 466.2594, found: 466.2599.

4.8. Isopropyl 3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranoside (3e, 5:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to general procedure (**4.3**) with 10 equivalents of isopropanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (hexanes/diethyl ether, 95:5 → 70:30). The title compound was obtained as a colorless oil. Combined yield (**3e**) = 84.9 mg, 0.178 mmol, 89%. The α:β ratio was determined to be 5:1 based on the relative integrations of the signals at 5.08 ppm (α) and 2.32 ppm (β). Spectral data were consistent with previous reports.[62] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.37–7.16 (m, 18H), 5.08 (m, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.73–4.43 (m, 7H), 4.08–3.95 (m, 1H), 3.94–3.84 (h, *J* = 6.2 Hz, 1H), 3.85–3.58 (m, 5H), 2.27–2.21 (ddd, *J* = 12.8, 5.1, 1.4 Hz, 1H), 1.77–1.70 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.14–1.10 (d, *J* = 6.1 Hz, 3H). *Representative signals corresponding to β anomer*: 3.51–3.45 (m, 0.2H), 3.44–3.38 (dd, *J* = 5.2, 1.9 Hz, 0.2H), 2.33–2.28 (ddd, *J* = 12.5, 5.1, 2.0 Hz, 0.2H), 1.70–1.62 (m, 0.2H), 1.28–1.25 (d, *J* = 6.1 Hz, 0.6H, *CH3-isopropyl*). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 139.0, 138.7, 138.6, 138.6, 138.5, 138.3, 128.6, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.2, 128.2, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 98.0, 95.2, 79.8, 78.6, 78.4, 78.0, 75.3, 75.2, 75.1, 73.6, 73.6, 71.9, 71.5, 70.8, 69.7, 69.1, 68.3, 37.4, 36.1, 23.7, 23.5, 22.0, 21.4. **HRMS (DART+):** calculated for $C_{30}H_{36}NO_5$ $[M+NH_4]^+$: 494.2920, found: 494.2916.

4.9. Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranoside (3f, 3:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of cyclohexanol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (hexane/diethyl ether 95:5 → 70:30). The title compound was obtained as a colorless oil. Combined yield (**3f**) = 84.9 mg, 0.164 mmol, 82%. The α:β ratio was determined to be 3:1 based on the relative integrations of the signals at 2.24 ppm (α) and 2.31 ppm (β). Spectral data were consistent with previous reports.[62] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.41–7.14 (m, 20H), 5.12 (d, *J* = 3.8 Hz, 1H), 4.94–4.85 (d, *J* = 10.8 Hz, 1H), 4.72–4.47 (m, 8H), 4.08–3.97 (m, 1H), 3.90–3.51 (m, 7H), 2.27–2.20 (ddd, *J* = 12.8, 5.1, 1.4 Hz, 1H), 1.93–1.79 (m, 2H), 1.79–1.61 (m, 3H), 1.54–1.47 (m, 2H), 1.46–1.07 (m, 7H). *Representative signals corresponding to β anomer*: 3.50–3.44 (m, 0.3H), 3.44–3.38 (ddd, *J* = 9.6, 5.2, 1.9 Hz, 0.3H), 2.35–2.28 (ddd, *J* = 12.5, 5.1, 1.9 Hz, 0.3H), 2.05–1.95 (m, 0.3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 139.0, 138.7, 138.6, 138.6, 138.4, 138.3, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 97.9, 95.2, 79.8, 78.7, 78.4, 78.0, 75.3, 75.2, 74.5, 73.6, 73.5, 73.5, 71.9, 71.4, 71.1, 70.9, 69.7, 69.2, 37.4, 36.2, 33.9, 33.6, 32.1, 31.6, 25.9, 24.4, 24.2. **HRMS (DART+):** calculated for $C_{33}H_{44}NO_5$ $[M+NH_4]^+$: 534.3220, found: 534.3222.

4.10. Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-D-galactopyranoside (3g, 6:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of cyclohexanol, from 3,4,6-tri-*O*-acetyl-2-deoxy-D-galactopyranose (58.0 mg). The reaction time was 48 hours. Purification was by flash chromatography on silica gel (pentanes/EtOAc, 100:0 → 80:20). The title compound was obtained as a colorless oil. Combined yield (**3g**) = 52.5 mg, 0.141 mmol, 71%. The α:β ratio was determined to be 6:1 based on the

relative integrations of the signals at 5.17 ppm (α) and 5.24 ppm (β). Spectral data for the α anomer were consistent with previous reports.[63] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 5.35–5.26 (m, 2H), 5.18–5.14 (m, 1H), 4.27–4.03 (m, 3H), 3.59–3.50 (m, 1H), 2.14 – 2.11 (s, 3H), 2.11–2.05 (m, 2H), 2.04 (s, 3H), 1.97 (s, 3H), 1.91–1.78 (s, 3H), 1.78–1.68 (m, 3H), 1.68–1.47 (m, 2H), 1.46–1.11 (m, 7H). *Representative signals corresponding to β anomer*: 5.24 (m, 0.17H), 5.03–4.95 (m, 0.17H), 4.80–4.75 (dt, *J* = 7.0, 1.3 Hz, 0.17H), 4.68–4.63 (m 0.17H), 3.80–3.75 (m, 0.2H), 3.69–3.61 (m, 0.2H), 1.99 (s, 0.5H), **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture – representative signals corresponding to the β anomer are listed)* δ 170.6, 170.5, 170.2, 98.3, 95.7, 75.6, 71.0, 68.9, 67.0, 66.8, 66.6, 65.5, 62.8, 61.9, 33.7, 33.5, 32.7, 32.0, 31.7, 30.9, 25.7, 24.4, 24.1, 21.0, 20.9, 20.9. **HRMS (DART+):** calculated for $C_{18}H_{32}NO_8$ $[M+NH_4]^+$: 390.2128, found: 390.2133.

4.11. Cyclohexyl 3,4-di-*O*-benzyl-2-deoxy-L-rhamnopyranoside (3h, 3:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of cyclohexanol, from 3,4-di-*O*-benzyl-2-deoxy-L-rhamnopyranose (65.7 mg). The reaction time was 19 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 90:10) The title compound was obtained as a colorless oil. Combined yield (**3h**) = 71.3 mg, 0.174 mmol, 87 %. The α:β ratio was determined to be 3:1 based on the relative integrations of the signals at 2.25 ppm (α) and 2.30 ppm (β). Spectral data were consistent with previous reports.[64] **^{1}H NMR (400 MHz, $CDCl_3$)** *Signals corresponding to α anomer*: δ 7.39–7.26 (m, 13H), 5.02 (m, 1H), 4.98–4.93 (d, J = 10.8 Hz, 1H), 4.72–4.61 (m, 4H), 4.03–3.94 (m, 1H), 3.86–3.77 (m, 1H), 3.56–3.45 (m, 1H), 3.19–3.08 (m, 1H), 2.27–2.21 (ddd, *J* = 12.6, 5.1, 1.4 Hz, 1H), 1.92–1.77 (m, 2H), 1.77–1.60 (m, 4H), 1.60–1.44 (m, 2H), 1.43–

1.12 (m, 12H). *Representative signals corresponding to β anomer*: 4.95 (d, J = 10.8 Hz, 0.3 H), 4.61–4.57 (m, 0.3H), 4.57–4.52 (dd, J = 9.8, 2.0 Hz, 0.3H), 3.68–3.57 (m, 0.6H), 3.37–3.26 (m, 0.3H), 2.34–2.27 (ddd, *J* = 12.5, 5.1, 2.0 Hz, 0.3H), 2.00–1.92 (m, 0.3H). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 138.8, 138.7, 138.6, 138.5, 128.3, 128.1, 128.0, 127.7, 127.6, 127.6, 127.5, 97.3, 94.7, 84.6, 84.6, 83.7, 79.4, 77.6, 75.3, 75.3, 74.7, 74.2, 71.7, 71.2, 67.2, 67.1, 37.7, 37.5, 36.3, 33.7, 33.7, 33.4, 33.0, 31.9, 31.5, 25.7, 24.3, 24.0, 18.2, 18.1. **HRMS (DART+):** calculated for $C_{26}H_{38}NO_4$ $[M+NH_4]^+$: 428.2801, found: 428.2810.

4.12. Cyclohexyl 3,4-di-*O*-acetyl-2-deoxy-L-rhamnopyranoside (3i, 6:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 10 equivalents of cyclohexanol, from 3,4-di-*O*-acetyl-2-deoxy-L-rhamnopyranose (46.5 mg). The reaction time was 48 hours. Purification was by flash chromatography on silica gel (pentanes/ethyl acetate, 100:0 → 90:10) The title compound was obtained as a colorless oil. Combined yield (**2.62**) = 37.2 mg, 0.118 mmol, 59 %. The α:β ratio was determined to be 6:1 based on the relative integrations of the signals at 5.02 ppm (α) and 4.96 ppm (β). **^{1}H NMR (500 MHz, $CDCl_3$):** *Signals corresponding to α anomer*: δ 5.37–5.25 (ddd, *J* = 11.7, 9.4, 5.4 Hz, 1H), 5.02 (d, *J* = 3.8 Hz, 1H), 4.78–4.68 (m, 1H), , 3.98–3.88 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.58–3.49 (m, 1H), 2.20– 2.12 (ddd, *J* = 12.7, 5.4, 1.3 Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.89–1.66 (m, 6H), 1.61–1.47 (m, 2H), 1.45–1.18 (m, 7H), 1.18–1.13 (d, *J* = 6.3 Hz, 3H). *Representative signals corresponding to β anomer*: 5.00–4.92 (ddd, *J* = 11.9, 9.4, 5.3 Hz, 0.17H), 4.68–4.63 (dd, *J* = 9.7, 2.0 Hz, 0.17H), 3.68–3.60 (m, 0.17H), 3.48–3.41 (dq, *J* = 9.6, 6.2 Hz, 0.17H), 2.27–2.22 (ddd, *J* = 12.5, 5.3, 2.0 Hz, 0.17H), 2.04 (s, 0.5H), 2.02 (s, 0.5H), **^{13}C NMR (125 MHz, $CDCl_3$)**

δ 170.5, 170.4, 170.4, 170.1, 97.1, 94.6, 76.8, 75.3, 74.9, 74.3, 71.0, 70.0, 69.4, 65.6, 37.1, 36.0, 33.6, 33.5, 31.9, 31.5, 25.7, 25.7, 24.3, 24.3, 24.1, 24.0, 21.1, 21.1, 21.0, 20.9, 17.8, 17.6. **HRMS (DART+):** calculated for $C_{16}H_{30}NO_6$ $[M+NH_4]^+$: 332.2073, found: 332.2072.

4.13 6-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (3j, 3:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 3 equivalents of acceptor, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 21 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 50:50). The title compound was obtained as a colorless oil. Combined yield (**3j**) = 96.8 mg, 0.140 mmol, 70%. Spectral data were consistent with previous reports.[53,65] Note: the product was isolated as a mixture of anomers, but individual fractions of pure α and β anomers obtained upon column chromatography were used for characterization purposes. The α:β ratio was determined to be 3:1 based on the relative integrations of the signals at 4.23 ppm (α) and 4.18 ppm (β). **^{1}H NMR (500 MHz; $CDCl_3$):** δ (α anomer): 7.39–7.23 (m, 15H, CH_2*Ph*), 5.54 (d, *J* = 5.0 Hz, 1H, H-1'), 5.04 (br. d, *J* = 3.0 Hz, 1H, H-1), 4.94 (d, *J* = 11.6 Hz, 1H, C*H*$_2$Ph), 4.64 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.62–4.57 (m, 3H, H-3', C*H*$_2$Ph), 4.51 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.44 (1H, d, *J* = 11.8 Hz, C*H*$_2$Ph), 4.32 (dd, *J* = 5.0 Hz, 2.5 Hz, 1H, H-2'), 4.23 (dd, J = 8.0 Hz, 1.9 Hz, 1H, H-4'), 4.01–3.94 (m, 4H, H-3, H-4, H-5, H-5'), 3.77 (dd, *J* = 10.7 Hz, 6.7 Hz, 1H, H-6a), 3.69 (dd, *J* = 10.7 Hz, 6.4 Hz, 1H, H-6b), 3.64 (dd, *J* = 9.2 Hz, 7.5 Hz, 1H, H-6a'), 3.57 (dd, *J* = 9.2 Hz, 5.7 Hz, 1H, H-6b'), 2.24 (app td, *J* = 12.5 Hz, 3.7 Hz, 1H, H-2a), 2.05 (m, 1H, H-2b), 1.53 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.35 (s, 6H, 2 x CH_3). **^{13}C NMR (125 MHz; CDCl3):** δ (α anomer): 139.0, 138.7, 138.2, 128.5, 128.3, 128.3, 127.9, 127.7,

127.6, 127.5, 127.4, 109.4, 108.6, 97.6, 96.5, 74.8, 74.4, 73.5, 73.0, 71.2, 70.8, 70.7, 70.5, 69.9, 69.3, 65.9, 65.6, 31.2, 26.2, 26.1, 25.1, 24.7. **^{1}H NMR (500 MHz; $CDCl_3$):** δ (β anomer): 5.54 (d, *J* = 5.0 Hz, 1H, H-1'), 4.92 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.64 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.62–4.52 (m, 3H, H-3', C*H*$_2$Ph), 4.48 (dd, *J* = 9.7 Hz, 2.2 Hz, 1H, 1H, H-1), 4.46 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.42 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.29 (dd, *J* = 5.0 Hz, 2.4 Hz, 1H H-2'), 4.18 (dd, *J* = 7.9 Hz, 1.9 Hz, 1H, H-4'), 4.06 (dd, *J* = 11.1 Hz, 2.9 Hz, 1H, H-5'), 3.99 (m, 1H, H-6a'), 3.62–3.44 (m, 5H, H-3, H-4, H5, H-6a, H-6b), 2.18 (m, 1H, H-2a), 2.08 (m, 1H, H-2b), 1.52(s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). **^{13}C NMR (125 MHz; CDCl3):** δ (β anomer): 139.1, 138.5, 138.2, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 109.4, 108.8, 101.1, 96.5, 74.3, 74.1, 73.6, 71.9, 71.7, 70.9, 70.6, 70.2, 69.3, 68.8, 68.1, 32.8, 30.5, 29.9, 26.2, 26.1, 25.2, 24.5. **HRMS (DART+):** calculated for $C_{39}H_{48}NO_{10}$ $[M+NH_4]^+$: 694.3585, found: 694.3589.

4.14. 3-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-1,2:5,6-di-*O*-isopropylidene-D-glucofuranoside (3k, 6:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 3 equivalents of diacetone glucose, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 19 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 80:20). The title compound was obtained as a colorless oil. Combined yield (**3k**) = 72.6 mg, 0.107 mmol, 54%. The α:β ratio was determined to be 6:1 based on the relative integrations of the signals at 5.24 ppm (α) and 5.99 ppm (β). Spectral data were consistent with previous reports.[53,61,65] For the following ^{1}H NMR data, a mixture of an alpha/beta anomer peak was used as the reference proton corresponding to 1H. **^{1}H NMR (500**

MHz; $CDCl_3$): *Signals corresponding to α anomer*: δ 7.44–7.21 (m, 18H), 5.85–5.79 (d, *J* = 3.6 Hz, 1H), 5.27–5.21 (m, 1H), 4.96–4.89 (d, *J* = 11.6 Hz, 1H), 4.69–4.65 (d, *J* = 3.6 Hz, 1H), 4.65–4.36 (m, 7H), , 4.23–4.20 (d, *J* = 2.8 Hz, 1H), 4.20–4.13 (m, 1H), 4.12–4.02 (m, 2H), 4.00–3.76 (m, 5H), 3.76–3.65 (m, 1H), 3.65–3.45 (m, 3H), 2.27–2.19 (dd, *J* = 12.7, 3.8 Hz, 1H), 2.04–1.91 (dd, *J* = 12.7, 4.5 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.32 (s, 4H), 1.20 (s, 3H). *Representative signals corresponding to β anomer*: 6.00–5.97 (d, *J* = 3.7 Hz, 0.16H), 5.04–5.00 (m, 0.16H), 4.26 (m, 0.16H). **^{13}C NMR (126 MHz, $CDCl_3$)** *(anomeric mixture)* δ 139.1, 138.8, 138.6, 138.5, 138.3, 138.1, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 125.7, 112.3, 111.9, 109.2, 106.5, 105.4, 100.9, 100.0, 99.6, 97.7, 84.1, 83.7, 81.4, 81.0, 79.6, 79.4, 75.1, 74.6, 74.5, 74.4, 73.7, 73.6, 73.4, 73.1, 73.1, 72.9, 72.7, 71.3, 71.1, 70.6, 70.5, 70.2, 70.0, 69.8, 69.4, 67.7, 67.3, 36.8, 31.2, 30.5, 30.3, 29.8, 27.3, 27.0, 26.9, 26.7, 26.3, 25.5, 24.1, 24.1.**HRMS (DART+):** calculated for $C_{39}H_{52}NO_{10}$ $[M+NH_4]^+$: 694.3585, found: 694.3567.

4.15. *O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-*N*-[(carboxybenzyl)]-ethanolamine (3l, >19:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 3 equivalents of acceptor, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 16 hours. Purification was by flash chromatography on silica gel (pentanes/EtOAc, 100:0 → 70:30). The title compound was obtained as a colorless oil. Combined yield (**3l**) = 115.5 mg, 0.189 mmol, 94%. **^{1}H NMR (500 MHz; $CDCl_3$):** δ (α anomer) 7.38–7.23 (m, 20H, CH_2*Ph*), 5.38 (br t, *J* = 5.60 Hz, 1H, N*H*), 5.09 (br s, 2H, C*H*$_2$Ph - CBz group), 4.98 (br d, *J* = 3.4 Hz, 1H, H-1), 4.92 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph), 4.60 (d, *J* = 11.8 Hz, 1H, C*H*$_2$Ph),

4.59 (br s, 2H, CH_2Ph), 4.49 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.40 (d, J = 12.0 Hz, 1H, CH_2Ph), 3.94–3.83 (m, 3H, H-3, H-6, H-6'), 3.72–3.63 (m, 1H, H-ethanolamine), 3.63–3.53 (m, 2H, H-4, H-ethanolamine), 3.53–3.45 (m, 1H, H-5), 3.45–3.30 (m, 2H, H-ethanolamine), 2.23 (app dt, *J* = 12.9 Hz, 4.0 Hz, H-2_{ax}), 1.98 (m, 1H, H-2_{eq}) **^{13}C NMR (125 MHz; $CDCl_3$)** δ 156.6, 138.9, 138.6, 138.0, 136.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.7, 127.7, 127.4, 98.5 (C-1α), 74.8, 74.3, 73.6, 73.1, 70.6, 70.5, 70.4, 70.0, 67.6, 66.8, 41.2, 31.3). **MS (DART+):** found: 629.3. $[\alpha]_D^{20}$: 21.4 (*c* 1.0, $CHCl_3$)

4.16. *O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-*N*-[(carboxybenzyl)]-L-serine methyl ester (3m, >19:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 3 equivalents of acceptor, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 18 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 50:50). The title compound was obtained as a colorless oil. Combined yield (**3m**) = 110.9 mg, 0.166 mmol, 83%. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.37–7.21 (m, 20H, CH_2*Ph*), 5.80 (d, *J* = 8.7 Hz, 1H, N-*H*), 5.11 (d, *J* = 12.2, 1H, CH_2Ph), 5.09 (d, *J* = 12.2, 1H, CH_2Ph), 4.92 (br. d, *J* = 3.5 Hz, 1H, H-1), 4.90 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.62–4.54 (m, 3H, CH_2Ph), 4.54–4.49 (m, 1H, *H*-serine), 4.48 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.38 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 3.96 (dd, *J* = 10.7 Hz, 3.7 Hz, 1H, H_{S1}), 3.90–3.79 (m, 4H, H3, H4, H_{S2}, H6), 3.73 (s, 3H, serine ester CH_3), 3.60–3.48 (m, 2H, H5, H6'), 2.19 (app td, *J* = 12.4 Hz, 3.9 Hz, 1H, $H2_{ax}$), 1.93 (app dd, *J* = 12.4 Hz, 4.5 Hz, 1H, $H2_{eq}$); **^{13}C NMR (125 MHz; $CDCl_3$)** δ 170.9, 156.2, 138.8, 138.4, 138.1, 136.3, 128.6, 128.5, 128.5, 128.3, 128.3, 128.3, 127.9, 127.7, 127.7,

127.7, 127.5, 127.5, 99.2, 74.4, 74.4, 74.5, 72.8, 70.6, 70.6, 69.5, 68.8, 67.2, 54.6, 52.7, 31.1. **MS (DART+):** found: 670.3. $[\alpha]_D^{20}$: 33.8 (*c* 1.0, $CHCl_3$).

4.17. *O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-*N*-[(*tert*-butyloxycarbonyl)]-L-serine methyl ester (3n, >19:1 α:β)

The reaction was conducted on a 0.2 mmol scale according to the general procedure (**4.3**) with 3 equivalents of diacetone glucose, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 17 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 80:20). The title compound was obtained as a colorless oil. Combined yield (**3n**) = 70.6 mg, 0.111 mmol, 56%. Spectral data were consistent with previous reports.[53] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40–7.21 (m, 15H), 5.44 (d, *J* = 9.0 Hz, 1H, N-*H*), 4.96–4.87 (m, 2H), 4.69–4.37 (m, 6H), 3.96–3.78 (m, 5H), 3.72 (s, 3H), 3.57 (m, 2H), 2.25–2.15 (m, 1H), 1.94 (dd, *J* = 12.7, 4.6 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 155.6, 138.9, 138.5, 138.1, 128.5, 128.5, 128.3, 127.9, 127.8, 127.7, 127.7, 127.5, 99.0, 80.2, 74.5, 74.4, 73.6, 72.8, 70.6, 70.4, 69.3, 68.7, 54.1, 52.6, 31.1, 30.5, 28.5. **HRMS (ESI+):** calculated for $C_{36}H_{46}NO_9$ $[M+H]^+$: 636.3167, found: 636.3165.

4.18. Dihydrocholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranoside (3o, 5:1 α:β)

The reaction was conducted on a 0.2 mmol scale ac cording to the general procedure (**4.3**) with 3 equivalents of dihydrocholesterol, from 3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose (86.9 mg). The reaction time was 21 hours. Purification was by flash chromatography on silica gel (pentanes/diethyl ether, 100:0 → 80:20). The title compound was obtained as a colorless oil. Combined yield (**3o**) = 129.2 mg, 0.161 mmol, 80%. The α:β ratio was determined to be 5:1 based on the relative integrations of the signals at 5.14 ppm (α) and 3.80 ppm (β). **^{1}H NMR (500**

MHz; $CDCl_3$): *Signals corresponding to α anomer*: δ 7.40–7.21 (m, 18H), 5.14 (m, 1H), 4.98–4.91 (d, *J* = 11.6 Hz, 1H), 4.67–4.40 (m, 7H), 4.05–3.89 (m, 3H), 3.69–3.47 (m, 4H), 2.27–2.18 (td, *J* = 12.3, 3.8 Hz, 1H), 2.03–1.92 (m, 2H), 1.92–1.76 (m, 2H), 1.75–1.60 (m, 2H), 1.59–1.42 (m, 4H), 1.42–0.85 (m, 31H), 0.78 (s, 3H), 0.64 (s, 3H), 0.62–0.55 (m, 1H). *Representative signals corresponding to β anomer*: 4.92 (d, *J* = 11.5 Hz, 0.2H), 3.80 (m, 0.2H), 3.47–3.43 (m, 0.2H), 2.14–2.04 (m, 0.2H). **^{13}C NMR (125 MHz; CDCl3):** *(anomeric mixture)* δ 139.1, 139.1, 138.8, 138.5, 138.4, 138.3, 128.6, 128.5, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.4, 127.4, 98.1 (C-1β), 95.7 (C-1α), 75.6, 75.3, 74.4, 74.3, 74.2, 73.7, 73.5, 73.4, 71.8, 71.5, 70.6, 70.3, 70.0, 69.9, 69.7, 56.6, 56.4, 54.6, 54.5, 45.1, 44.9, 42.7, 40.2, 39.7, 37.2, 37.0, 36.3, 36.1, 35.9, 35.8, 35.7, 35.7, 35.6, 34.5, 33.5, 32.3, 32.2, 31.9, 30.5, 29.9, 29.5, 29.0, 28.9, 28.4, 28.2, 27.7, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.4, 12.2. **HRMS (ESI+):** calculated for $C_{54}H_{80}NO_5$ $[M+NH_4]^+$: 822.6031, found: 822.6040.

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Declarations of Interest

None

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for catalyst **1h** and glycosides **3a**–**3o**. Supplementary data related to this article can be found online at [insert link].

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Highlights:

- a boronic ester catalyzes dehydrative glycosidations of carbohydrate-derived hemiacetals
- 2-deoxy and 2,6-dideoxy donors can be activated by the boronic ester catalyst
- the method is tolerant of functional groups such as isopropylidene ketals and carbamates