



Combined Lewis acid and Brønsted acid-mediated reactivity of glycosyl trichloroacetimidate donors



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ABSTRACT

Biomimetic conditions for a synthetic glycosylation reaction, inspired by the highly conserved functionality of carbohydrate active enzymes, were explored. At the outset, we sought to generate proof of principle for this approach to developing catalytic systems for glycosylation. However, control reactions and subsequent kinetic studies showed that a stoichiometric, irreversible reaction of the catalyst and glycosyl donor was occurring, with a remarkable rate variance depending upon the structure of the carboxylic acid. It was subsequently found that a combination of Brønsted acid (carboxylic acid) and Lewis acid (MgBr_2) was unique in catalyzing the desired glycosylation reaction. Thus, it was concluded that the two acids act synergistically to catalyze the desired transformation. The role of the catalytic components was tested with a number of control reactions and based on these studies a mechanism is proposed herein.

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1. Introduction

The structural and functional characterization of carbohydrate active enzymes holds a unique place in our evolving understanding of sugar biochemistry as well as the structure and functionality of biological catalysts in general.¹ A prominent example of a carbohydrate active enzyme is lysozyme,² a glycoside hydrolase which was the first enzyme whose structure was solved by X-ray diffraction.³ Consequently, lysozyme was among the first enzymes for which a detailed mechanistic proposal was put forth, which led to a more generalized proposal for how enzymes accelerate chemical reactions.⁴ The details of the mechanistic proposal⁵ and its potential generality⁶ continue to be a fertile area of research.

Glycosyl transferases and hydrolases catalyze glycosidic bond formation and hydrolysis with either retention or inversion of the stereochemistry at the anomeric carbon. Both mechanisms typically employ two carboxylic acids contributed by either Glu or Asp side chains. In enzymes that process these reactions with stereochemical inversion at the anomeric center, the sugar substrate and a nucleophile (water or the glycosyl acceptor) are positioned such that one carboxylic acid donates a proton to the oxygen of the glycosidic bond while the nucleophile, assisted by the other carboxylate acting as a general base, attacks the anomeric carbon. The reaction proceeds in a single step via an oxocarbenium ion-like transition state. In retaining enzymes, one carboxylate, acting as a

nucleophile, attacks the anomeric carbon while the other carboxylic acid donates a proton to the oxygen of the glycosidic bond, generating a covalent intermediate. In a second step, a nucleophile attacks the anomeric carbon, releasing the sugar with retention of stereochemistry through a double inversion process.⁷ Enzymes have been thoroughly exploited in the field of glycochemistry for promoting glycosylation reactions, as their inherent reactivity and tunable specificity allow glycosidic bonds to be formed with complete regio- and diastereoselectivity.⁸ Despite these highly attractive characteristics and the simultaneous circumventing of many of the problems traditionally associated with chemical glycosylation (such as extensive protecting group manipulations),⁹ enzymatic glycosylation reactions present their own challenges, particularly when considering reaction scope and scale-up to industrial applications.¹⁰ Synthetic mimics of glycosyl transferases could provide alternatives worth consideration.¹¹

Many important advances in the field of chemical glycosylation have been made in the last decade,¹² including optimization of leaving groups at the anomeric position,¹³ catalytic glycosyl donor activation under mild reaction conditions¹⁴ and even protecting group free strategies.¹⁵ However, chemical glycosylation methods still struggle to replicate the exceptional selectivity routinely displayed by enzymes. We therefore endeavored to develop synthetic enzyme mimics (inspired by the proposed enzyme mechanisms) that could encompass the advantages of chemical glycosylation protocols while also displaying high efficiency and stereochemical fidelity.

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2. Results and discussion

2.1. Initial studies

The high structural variability of carbohydrate-activating enzymes with relatively conserved carboxylic acid active site residues¹ prompted us to investigate how a small peptide presenting convergent carboxylic acid functionalities (to mimic the conserved functionality of carbohydrate active enzymes) might interact with a carbohydrate and whether this knowledge could then be applied to establish a general, catalytic glycosyl transfer reaction (Fig. 1a).

Based in part on our previous studies of glycosylation¹⁶ we decided to initiate this research with a simple glycosyl donor that is amenable to Brønsted acid catalysis, namely a glycosyl trichloroacetimidate¹⁷ (Fig. 1b). As shown in Table 1, in our initial catalyst screening efforts we sought to compare the catalytic activity of simple carboxylic acids with those derived from amino acids.

Our initial survey was characterized largely by low yields, perhaps in part due to mismatched pK_a s—most of the carboxylic acids we evaluated possess pK_a s which are well outside the domain proven competent for trichloroacetimidate activation. This mismatch is well demonstrated by a comparison of the yields obtained when using *p*-toluene sulfonic acid ($pK_a = -3$) and benzoic acid ($pK_a = 4$), which are 92% and 0%, respectively (Table 1, entries 1 and 2). 3,3-Dimethylpentanedioic acid also did not catalyze the glycosylation of cyclohexanol with glycosyl donor **1** (Table 1, entry 3). A small amount of the desired product **2** was formed with (*N*-Boc)Asp(OMe) as catalyst (Table 1, entry 4), and a modest yield of 32% was obtained with tetrapeptide **3** (Table 1, entry 5).

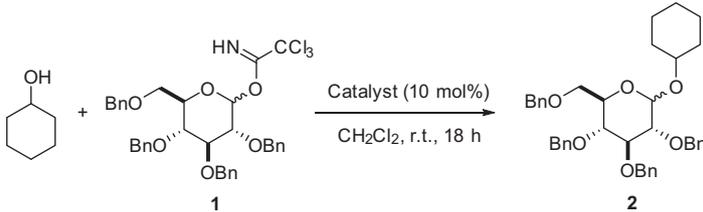
Whilst little to no glycosylation of the acceptor cyclohexanol was observed, upon inspection of the product distribution after the reactions were stopped we found a combination of unreacted starting material and glycosylated catalyst, or ‘catalyst-rebound’ product. The low yields of glycosylated cyclohexanol can potentially be attributed to catalyst consumption via ‘rebounding’ to the glycosyl imidate substrate. Indeed, no reaction was observed when subjecting the glycosylated catalyst to the same reaction conditions.¹⁸

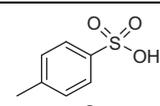
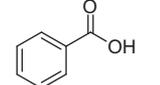
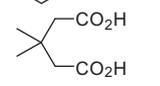
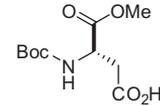
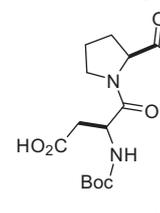
2.2. Kinetics studies

As enzyme-bound glycosyl esters have been proposed to be relevant intermediates in retentive glycosyl transferases,¹⁹ we sought to investigate the details of this transformation more thoroughly. To this end, the kinetics of the rebound reaction of a number of carboxylic acids (including di-acids) was investigated and the results displayed below in Table 2.

In each example, a stoichiometric amount of trichloroacetimidate **1** and carboxylic acid (or di-acid) was mixed at room temper-

Table 1
Initial catalyst screen^a



Entry	Catalyst	Yield 2 (%)
1 ¹⁵		92 (1.5 h reaction time)
2		0 ^b
3		0 ^b
4		12
5		32

^a Ratio of α : β trichloroacetimidate donor varied in each reaction. Reactions were all run multiple times and yield was unaffected by this initial donor ratio.

^b Not observed to a significant extent.

ature and the reaction progress followed by ¹H NMR. The reaction rate was estimated by performing regression analysis of multiple runs. The ¹H NMRs were compared with those of authentic samples of the glycosyl esters (see Supplementary data). We observed a significant broadening of the imidate NH proton peak upon mixing any of the acids with **1**. This broadening was attributed to an interaction between the carboxylic acid and the imidate, likely indicating a fast interaction that reverts in a pre-equilibrium fashion prior to the rate-determining bond forming reaction.

It was found that the rebound reactivity of the carboxylic acids studied varied by a remarkable range of $\sim 10^4$ (at room tempera-

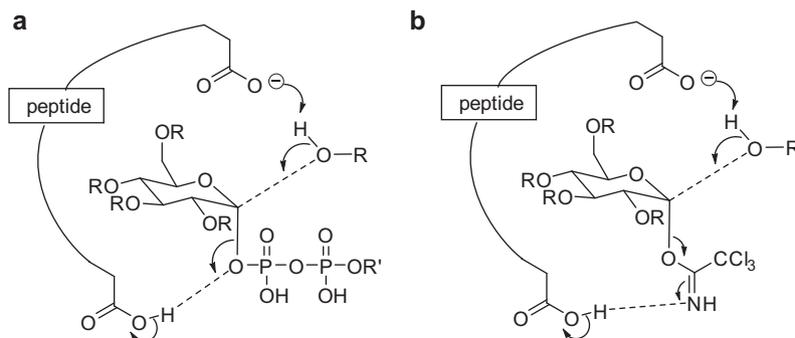
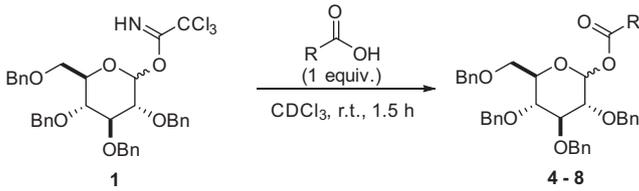
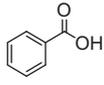
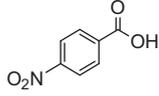
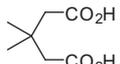
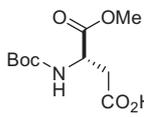
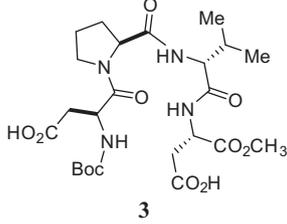


Figure 1. Proposed catalytic action of a peptide containing two carboxylic acid groups on (a) glucose bearing a diphosphate leaving group and (b) glucose bearing a trichloroacetimidate leaving group (‘Schmidt glycosidation’).

Table 2
Rate of rebound reaction with various carboxylic acids^a



Entry	Acid	Acid pK _a	Product	Relative reactivity	Stereochemical outcome ^b
1		4.1	4	10 ⁻⁴	Invertive
2		3.4	5	10 ⁻⁴	Invertive
3		3.8	6	10 ⁻²	>90% Invertive
4		2.1	7	1	Invertive
5		2.1	8	4	1.5:1 Invertive:Retentive

^a Ratio of α : β trichloroacetimidate donor varied in each reaction. Reactions were each run multiple times and yield was unaffected by this initial donor ratio.

^b Stereochemical outcome determined from synthesis of 'NMR standards' of the ester products, using pure α or pure β trichloroacetimidate donor (see [Supplementary data](#)).

ture). For example, both benzoic acid and *p*-nitro benzoic acid (Table 2, entries 1 and 2) rebounded significantly more slowly than (*N*-Boc)aspartate methyl ester (Table 2, entry 4). In contrast, the di-acid **3** (Table 2, entry 5) rebounded four times faster than (*N*-Boc)aspartate methyl ester. These large differences in rebound reactivity might be rationalized by a difference in the stability of the ionized carboxylates. This trend also generally inversely correlates with the pK_a of the carboxylic acid catalyst (higher pK_a leads to lower rate of reaction, as the stability of the corresponding carboxylate anion itself inversely correlates with the pK_a value). The more reactive acids also have the potential for intramolecular hydrogen bond stabilization of the intermediate carboxylate ion (**9**, Scheme 1).

The completely invertive nature of the rebound reaction indicates that the intermediate ion pair(s) generated by reaction of the carboxylic acid and imidate are likely intimate and not solvent separated.²⁰ The data also show that once a carboxylic acid has rebounded, the catalytic cycle stops (Scheme 1).

Divalent magnesium ions are prevalent in biological systems as cofactors to enzymes and have been shown to enhance the catalytic activity of such systems.²¹ Additionally, Lewis acids have previously been shown to promote glycosylation reactions of trichloroacetimidates.²² With these observations in mind, magnesium bromide was investigated as an additive in this reaction, with the hope that an increasingly biomimetic approach would lead to a glycosylation protocol that was catalytic in carboxylic acid.

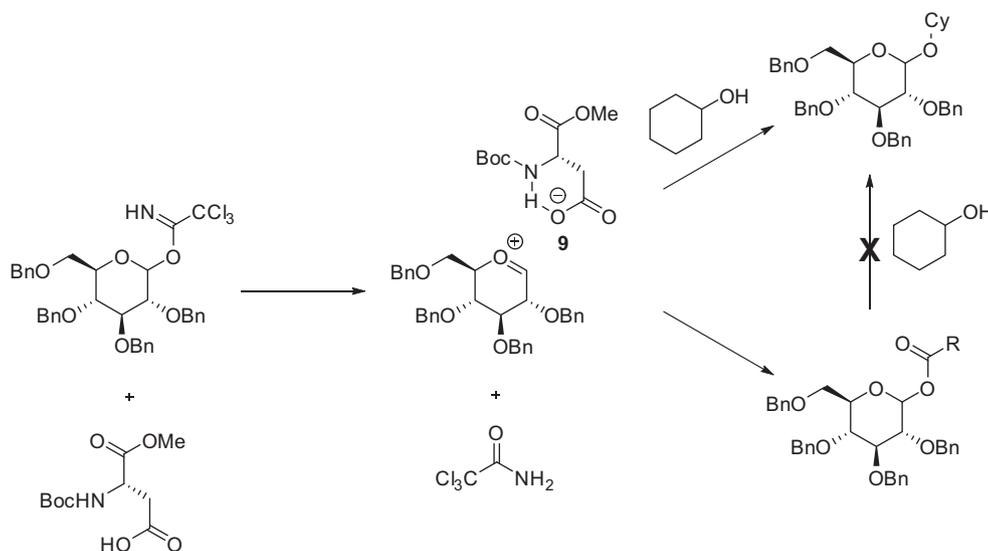
Indeed, when MgBr₂·OEt₂ is used as an additive, the 'rebound' product (glycosylated catalyst) is not observed. Moderate yields

of the desired glycosylated alcohol were achieved, along with two major side products—(tetrabenzyl)-glucose, formed by hydrolysis of the imidate and (tetrabenzyl)-glucosyl bromide (**14**, Scheme 2). As is to be expected, formation of these two side products appears to increase with decreasing nucleophilicity of the alcohol. Unfortunately in this small substrate screen no significant difference in diastereoselectivity was observed when comparing (*N*-Boc)aspartate methyl ester with our peptide catalyst (**3**, see Table 1, entry 4).

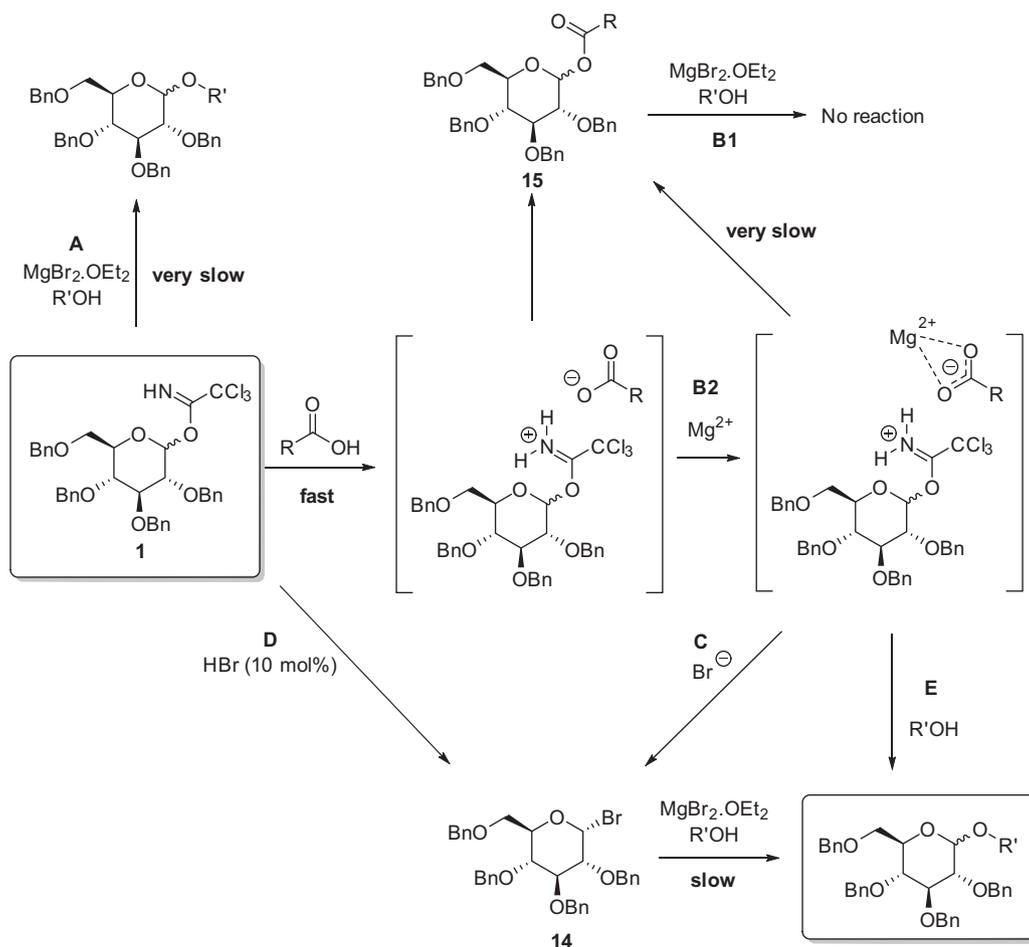
2.3. Mechanistic studies

In light of the biological relevance of combined catalytic carboxylic acids and magnesium ions we found the effect of MgBr₂·OEt₂ to be an intriguing observation. A focused set of experiments was then conducted to attempt to elucidate the role of MgBr₂·OEt₂ in this reaction. Though Lewis acid activation of glycosyl trichloroacetimidates is known,⁹ in this case the magnesium salt itself was not a competent catalyst, giving very low yields of glycosylated product in the absence of a carboxylic acid (Scheme 2, pathway A). Similarly, subjecting the 'rebound product' **15** to MgBr₂·OEt₂ in the presence of cyclohexanol led to no reaction (Scheme 2, pathway B1), suggesting that the reaction does not proceed via the glycosyl ester.

A glucosyl bromide side product, **14** is observed in crude NMR spectra of the reactions shown in Table 3, and appears to be formed by activation of the imidate by the carboxylic acid in the presence of MgBr₂·OEt₂ (Scheme 2, pathway C). The bromide **14** was not



Scheme 1. Proposed reaction pathways.



Scheme 2. Summary of mechanistic investigations.

formed from the reaction of the imidate and MgBr₂·OEt₂ alone, nor was it observed when the imidate was mixed with an alcohol in the presence of MgBr₂·OEt₂ (Scheme 2, pathway A). In the presence of both magnesium salt and carboxylic acid, the glycosyl imidate

forms a mixture of **14** and the 'rebound product' **15**, however the rate of formation of the glycosyl ester is much slower, indicating that the magnesium is acting to inhibit this 'rebound' reaction, possibly via coordination to the carboxylate anion (Scheme 2, pathway

Table 3
Glycosylation of alcohols^a

Entry	Product	Equiv ROH	Catalyst	Conv. ^b (%)	Ratio α:β
1	 2	1.2	(<i>N</i> -Boc)Asp(OMe)	67	1:0.43
		1.2	3	52	1:0.43
2	 10	1.2	(<i>N</i> -Boc)Asp(OMe)	32	1:0.09
		1.2	3	21	1:0.01
3	 11	1.5	(<i>N</i> -Boc)Asp(OMe)	56	1:0.25
		1.5	3	58	1:0.24
4	 12	1.5	(<i>N</i> -Boc)Asp(OMe)	32	12α:12β:13α:13β 0.28:0.27:1:0.50
		1.5	3	36	0.15:0.15:1:0.57

^a Ratio of α:β trichloroacetimidate donor varied in each reaction. Reactions were each run multiple times and both yield and stereochemical outcome were unaffected by this initial donor ratio.

^b Conversion determined by ¹H NMR peak comparison to a mesitylene internal standard.

B2). It is possible that the magnesium carboxylate also serves as a base to assist with the alcohol coupling to the activated donor via pathway **B2** followed by pathway **E**.

The possibility that HBr is being generated in the reaction and acting as a glycosylation catalyst cannot be excluded therefore we set out to test this hypothesis directly. When the imidate was treated with 10 mol% HBr, it was found that 10 mol% of glucosyl bromide **14** was formed (Scheme 2, pathway **D**), along with a significant amount of tetrabenzyl glucose. In a separate reaction, it was also found that when glucosyl bromide **14** is exposed to MgBr₂·OEt₂ in the presence of an alcohol, slow formation of the glycosylated alcohol product was observed. Therefore, the generation of a glucosyl bromide which then acts as the glycosyl donor cannot be excluded as a minor reaction pathway.

Based on these observations, we tentatively propose a mechanistic rationale wherein the mild Lewis acid serves to promote

glycosylation of the alcohol through a catalytically competent ion pair. This species then undergoes displacement at the anomeric center, either directly by the alcohol or by a bromide ion, the latter generating a glucosyl bromide which can itself then act as glycosyl donor to produce the desired glycosylated alcohol product.

3. Conclusions

In conclusion, in this work we first examined the kinetic profiles of the additions of various carboxylic acids to glucosyl trichloroacetimidates to yield glucosyl esters. We observed a significant difference in relative rate of reaction between the five carboxylic acids studied. The stereochemical outcome of these reactions was also studied. It was found that the mono-acids displayed completely invertive reactivity, while the two di-acids yielded a mixture of inverted and retentive products.

These findings were then exploited to develop a glycosylation reaction in which divalent magnesium ions are proposed to inhibit the undesired 'rebound' reaction pathway and allow the formation of glycosylated alcohol and disaccharide products. While the addition of $\text{MgBr}_2 \cdot \text{OEt}_2$ to the reactions did indeed inhibit glycosyl ester formation, the enantiopure amino acid co-catalysts did not influence the selectivity at the anomeric position. Further exploration of metal ion assisted chemical glycosylation is ongoing in our laboratory.

4. Experimental

4.1. General methods

Proton NMR spectra were recorded on a 400 or 500 MHz spectrometer. Proton chemical shifts were reported in ppm (δ) with the residual protium in the NMR solvent as a reference (CHCl_3 , δ 7.26 relative to tetramethylsilane). CDCl_3 for kinetic experiments was filtered through basic alumina immediately before use. The listed spectral data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constants [J = Hz], integration; assignment if determined). Carbon NMR spectra were recorded on a 100 or 126 MHz spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to the solvent signal (CDCl_3 , δ 77.0). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F_{254} pre-coated plates (0.25 mm thickness). TLC visualization was accomplished by irradiation with a UV lamp, an iodine chamber, and/or ceric ammonium molybdate stain (CAM). Liquid chromatography–mass spectrometry (LC/MS) was performed on a Waters Acquity instrument equipped with dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI), a SQ mass spectrometer, and a photodiode array detector. High-resolution liquid chromatography–mass spectrometry (HR-LC/MS) was performed on a Waters XEVO instrument equipped with ESI, a QToF mass spectrometer, and a photodiode array detector. Analytical high-performance liquid chromatography (HPLC) was performed on an Agilent 1100 Series instrument equipped with a diode array detector. Medium-performance liquid chromatography (MPLC) was performed on a Biotage SP4 instrument equipped with a diode array detector and liquid handler. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were purified by a Seca Solvent Purification System from GlassContour (Nashua, NH). All other chemicals were commercially available and used as received.

4.2. Cyclohexyl-(2,3,4,6-tetra-O-benzyl)-glucopyranose (2)

To an oven dried, 4-mL vial were added a stir bar, (2,3,4,6-tetra-O-benzyl)-glucopyranosyl trichloroacetimidate (**1**, viscous oil, 0.045 g, 0.067 mmol, 1.5:1.0 α : β ratio, 1 equiv), and chloroform (0.5 mL). Cyclohexanol was then added (0.015 mL, 0.13 mmol, 2 equiv) and the vial flushed with nitrogen. The appropriate carboxylic acid catalyst (see Table 1) was then added (0.2 equiv) and the reaction then allowed to stir at room temperature for 5 h. After 5 h the sample was loaded directly onto a silica column and purified by column chromatography (0–20% ethyl acetate in hexanes, slow gradient) before analysis. Compound **2**, major (α) anomer: ^1H NMR (500 MHz, CDCl_3): 7.46–7.15 (m, 20H), 7.10–7.00 (m, 2H), 5.00–4.82 (m, 12H), 4.82–4.59 (m, 2H), 4.53 (dd, J = 23.9, 11.6, 3H), 4.41 (t, J = 13.6, 2H), 3.93 (t, J = 9.3, 1H), 3.81 (d, J = 9.5, 1H), 3.67 (dd, J = 10.5, 3.3, 1H), 3.62–3.40 (m, 4H), 1.91–1.60 (m, 4H), 1.58–0.68 (m, 10H); ^{13}C NMR (126 MHz, CDCl_3): 138.96, 138.29, 138.22, 137.97, 128.37, 128.36, 128.35, 128.31, 128.08, 127.98, 127.90, 127.86, 127.77, 127.68, 127.62, 127.49,

94.64 (C1), 82.09, 79.95, 77.86, 75.63, 75.24, 75.12, 73.41, 72.93, 70.02, 68.56, 33.32, 31.42, 25.60, 24.46, 24.17; IR of anomeric mixture (ATR, thin film, cm^{-1}): 3063 (w), 3030 (w), 2931 (s), 2857 (s), 2157 (m), 2033 (m), 1975 (m) 1496 (w), 1452 (m), 1362 (m); MS of anomeric mixture (ESI, $\text{C}_{40}\text{H}_{46}\text{O}_6$): Calcd: 645.32 (100.0%), 646.32 (43.3%), 647.33 (9.1%), Found: 645.22 (100.0%), 646.02 (49.2%), 647.77 (9.9%).

4.3. Kinetic data acquisition

To an oven dried, 4-mL vial were added trichloroacetimidate-(2,3,4,6-O-benzyl)-glucose (**1**, viscous oil, 0.010 g, 0.015 mmol, 1.5:1.0 α : β ratio, 1 equiv), and CDCl_3 (0.5 mL). A stock solution of NMR standard mesitylene in CDCl_3 (0.05 mL, 0.005 mmol mesitylene) was then added to the vial. This solution was then transferred to an NMR tube and a ^1H NMR spectra taken to represent time = 0. The appropriate carboxylic acid catalyst (see Table 2) was then added (0.015 mmol in 0.05 mL CDCl_3) to the NMR tube in a single portion and ^1H NMR spectra acquired periodically (typically every two minutes) over the course of up to 1 h and 40 min. The resulting ^1H NMRs were compared with those of authentic samples of the glycosyl esters (see Supplementary data).

4.4. Mg^{2+} ion assisted glycosylation

Acid catalyst (0.0073 mmol, 0.1 equiv), alcohol (0.1095 mmol, 1.5 equiv), and $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (4.7 mg, 0.0183 mmol, 0.25 equiv) were added to an oven-dried vial (A), fitted with a stir bar. 2,3,4,6-Tetra-O-benzyl-glucopyranose trichloroacetimidate **1** (50 mg, 0.073 mmol, 1.0 equiv) was directly weighed into a separate vial (B). CH_2Cl_2 (600 μL) and mesitylene (1 μL) were added to (B) and the solution was mixed. The solution in (B) was transferred into (A) and that vial was capped, left to stir for 5 h before an ^1H NMR was taken. Basic alumina was added to quench the reaction and the mixture was filtered over celite and washed thoroughly with CH_2Cl_2 . The solvent was removed under vacuum and the product was chromatographed on silica gel (20–40% EtOAc/hexanes).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.carres.2013.09.011>.

References

- (a) For a wealth of information on carbohydrate active enzymes see <http://www.cazy.org/>; (b) Cantarel, B. L.; Coutinho, P. M.; Rancurel, C.; Bernard, T.; Lombard, V.; Henrissat, B. *Nucleic Acids Res.* **2009**, *37*, D233–D238; (c) Singh, S.; Phillips, G. N., Jr.; Thorson, J. S. *Nat. Prod. Rep.* **2012**, *29*, 1201–1237.
- Johnson, L. N. *Nat. Struct. Mol. Biol.* **1998**, *5*, 942–944.
- Canfield, R. E. *J. Biol. Chem.* **1963**, *238*, 2698–2707.
- Vernon, C. A. *Proc. R. Soc. B: Biol.* **1967**, *167*, 389–401.
- Vocadlo, D. J.; Davies, G. J.; Laine, R.; Withers, S. G. *Nature* **2001**, *412*, 835–838.
- Zhang, X.; Houk, K. N. *Acc. Chem. Res.* **2005**, *38*, 379–385.
- Lairson, L. L.; Henrissat, B.; Davies, G. J.; Withers, S. G. *Annu. Rev. Biochem.* **2008**, *77*, 521–555.
- Desmet, T.; Soetaert, W.; Bojarová, P.; Křen, V.; Dijkhuizen, L.; Eastwick-Field, V.; Schiller, A. *Chem. Eur. J.* **2012**, *18*, 10786–10801.
- Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.
- Seeberger, P. H.; Finney, N.; Rabuka, D.; Bertozzi, C. R. Chemical and Enzymatic Synthesis of Glycans and Glycoconjugates. In *Essentials of Glycobiology*; Varki, A., Cummings, R. D., Eds., 2nd ed.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor (NY), 2009. Chapter 49 <http://www.ncbi.nlm.nih.gov/books/NBK1956/>.

11. (a) Ortega-Caballero, F.; Bols, M. *Can. J. Chem.* **2006**, 650–685; (b) Bjerre, J.; Bols, M. *Eur. J. Org. Chem.* **2010**, 3487–3500.
12. McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012**, 2, 1563–1595.
13. (a) Shirahata, T.; Matsuo, J.-I.; Teruya, S.; Hirata, N.; Kurimoto, T.; Akimoto, N.; Sunazuka, T.; Kaji, E.; Omura, S. *Carbohydr. Res.* **2010**, 345, 740–749; (b) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, 16, 1871–1882; (c) Pornsuriyasak, P.; Vetter, C.; Kaeothip, S.; Kovermann, M.; Balbach, J.; Steinborn, D.; Demchenko, A. V. *Chem. Commun.* **2009**, 6379–6381; (d) Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, 47, 4729–4731.
14. (a) Mensah, E. A.; Yu, F.; Nguyen, H. M. *J. Am. Chem. Soc.* **2010**, 132, 14288–14302; (b) Yang, J. M.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, 73, 794–800; (c) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, 5, 987–989; (d) Douglas, S. P.; Whitfield, D.; Krepinsky, J. J. *J. Carbohydr. Chem.* **1993**, 12, 131–136.
15. (a) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, 133, 13926–13929; (b) Kaji, E.; Nishino, T.; Ishige, K.; Ohya, Y.; Shirai, Y. *Tetrahedron Lett.* **2010**, 51, 1570–1573; (c) Kaji, E.; Shibayama, K.; In, K. *Tetrahedron Lett.* **2003**, 44, 4881–4885.
16. Griswold, K. S.; Horstmann, T. E.; Miller, S. J. *Synlett* **2003**, 1923–1926.
17. Schmidt, R. R.; Michel, J. *Chemistry* **1980**, 92, 763–764. *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 731–732.
18. (a) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, 4, 141–169; (b) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2013**. <http://dx.doi.org/10.1002/anie.201302158>.
19. Sinnott, M. L. *Chem. Rev.* **1990**, 90, 1171–1202.
20. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 212–235.
21. Black, C. B.; Huang, H.-W.; Cowan, J. A. *Coord. Chem. Rev.* **1994**, 135/136, 165–202.
22. Mattson, A. L.; Michel, A. K.; Cloninger, M. J. *Carbohydr. Res.* **2012**, 347, 142–146.