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Borinic Acid Catalyzed Stereo- and Regioselective Couplings of Glycosyl Methanesulfonates

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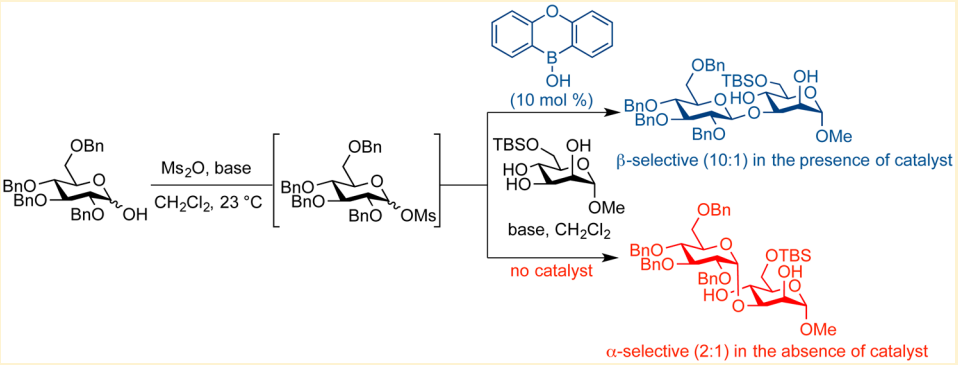
Supporting Information



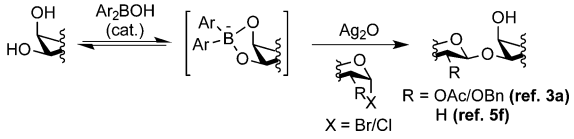
ABSTRACT: In the presence of a diarylborinic acid catalyst, glycosyl methanesulfonates engage in regio- and stereoselective couplings with partially protected pyranoside and furanoside acceptors. The methanesulfonate donors are prepared in situ from glycosyl hemiacetals, and are coupled under mild, operationally simple conditions (amine base, organoboron catalyst, room temperature). The borinic acid catalyst not only influences site-selectivity via activation of 1,2- or 1,3-diol motifs, but also has a pronounced effect on the stereochemical outcome: 1,2-*trans*-linked disaccharides are obtained selectively in the absence of neighboring group participation. Reaction progress kinetic analysis was used to obtain insight into the mechanism of glycosylation, both in the presence of catalyst and in its absence, while rates of interconversion of methanesulfonate anomers were determined by NMR exchange spectroscopy (EXSY). Together, the results suggest that although the uncatalyzed and catalyzed reactions give rise to opposite stereochemical outcomes, both proceed by associative mechanisms.

INTRODUCTION

Control of regio- and stereoselectivity in glycosylation reactions has been a long-standing challenge in carbohydrate chemistry. Modern glycosylation methods rely heavily on protective groups to achieve these two types of selectivity. Hydroxyl group protection provides a means to enforce regiocontrol by blocking undesired sites of reactivity. The ways that protective groups influence stereoselectivity can be more subtle, and include neighboring group participation as well as steric, inductive, conformational, stereoelectronic and directing effects.[1] In recent years, considerable effort has been devoted to an alternative approach involving the use of external reagents or catalysts to achieve regio-[2,3] and/or stereoselective glycosylations.[4,5] Such methods may offer greater efficiency or flexibility in the synthesis of complex glycosides. Enzymes (naturally occurring glycosyltransferases and glycosyl hydrolases, as well as engineered mutants) illustrate the high levels of glycosylation selectivity that can be achieved under catalyst control, and are powerful tools for laboratory synthesis.[6] It remains to be established whether comparable results can be achieved using synthetic glycosylation catalysts, and whether such synthetic catalysts might offer complementary properties relative to enzymes.

In 2011, our group showed that arylborinic acid (Ar_2BOH) derivatives accelerate regioselective glycosylations of acceptors having 1,2- or 1,3-diol groups (Scheme 1).[3a] The proposed mechanism of activation involves the formation of a tetracoordinate borinic ester that displays enhanced oxygen-centered nucleophilicity relative to a free alcohol. Preliminary kinetics experiments, as well as stereochemical outcomes (formation of β-glucopyranosides or β-galactopyranosides from α-configured halides, bearing either ester or ether protective groups) were consistent with the acceleration of an associative (S_N2-type) pathway by the catalyst. In keeping with this idea, the

Scheme 1. Borinic Acid-Catalyzed Regioselective Glycosylation of Partially Unprotected Acceptors



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borinic acid was able to enhance the level of β-selectivity in couplings of α-2-deoxyglycosyl halides.[5f] The borinic acid activation concept has been extended to other classes of glycosyl donors or equivalents, including pyranone-derived allylic carbonates (in the presence of a Pd(0) cocatalyst)[3c] and glycal epoxides.[5h]

Although borinic acid-catalyzed glycosylations have already been applied to facilitate the synthesis of complex, carbohydrate-derived targets,[3c,5h,7] there remains a need for regio- and stereoselective methods that employ readily available glycosyl donors and show high levels of functional group tolerance. In both of these regards, the glycosyl bromide and chloride donors employed in our first-generation catalytic method are less than ideal. Their preparation requires relatively harsh reagents (e.g., HCl, HBr, BCl_3), which may not be compatible with acid-labile functional groups such as silyl ethers, acetals and glycosidic linkages. Certain variants, including "armed"[8] (ether-protected), deoxygenated and furanosyl halides, are prone to hydrolysis upon isolation and/or storage. The use of silver(I) oxide as halide abstracting agent under our catalytic conditions created mechanistic complexity and mass transfer problems due to its low solubility in the reaction medium. We aimed to address these limitations by identifying other glycosyl donors and activation conditions that would be compatible with borinic acid activation of glycosyl acceptors.

Here, we describe a method for regio- and stereoselective couplings of diols and triols with glycosyl methanesulfonates (mesylates), using a diarylborinic acid catalyst. The glycosyl mesylates are generated in situ from the corresponding free hemiacetals under mild conditions (methanesulfonic anhydride (Ms_2O), amine base), and their borinic acid-catalyzed reactions with glycosyl acceptors take place readily at room temperature. The borinic acid has a significant influence on the stereochemical outcome, with reversals of α/β-selectivity relative to the uncatalyzed reaction being observed in several instances. The organoboron-catalyzed reaction enables the preparation of 1,2-*trans*-configured linkages (e.g., β-glucopyranosides, β-galactopyranosides, α-arabinofuranosides) in the absence of neighboring group participation, thus permitting the use of armed donors. Detailed kinetic studies of both the catalyzed and uncatalyzed reactions have been conducted. These suggest that although the catalyzed and uncatalyzed pathways have different stereochemical outcomes, both operate by associative (S_N2-type) mechanisms.

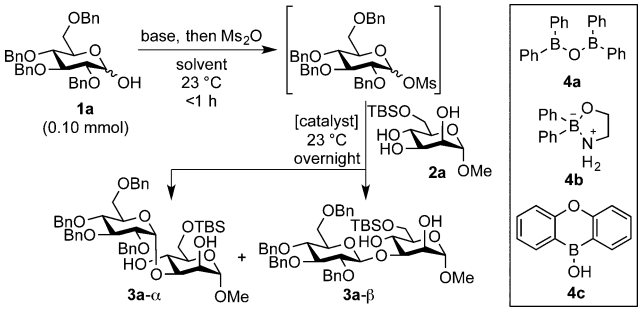
RESULTS AND DISCUSSION

Glycosyl sulfonates[9] attracted our interest as potential electrophiles for reactions with borinic acid-activated acceptors. Previous work from our group indicated that donors requiring activation by a Brønsted or Lewis acid (e.g., trichloroacetimidates, thioglycosides, glycosyl phosphates) did not undergo borinic acid-catalyzed glycosylation.[3a] These activators may have interfered with the formation of the tetracoordinate borinate intermediate, which is favored under basic conditions.[10] The ability of glycosyl sulfonates to react with alcohols in the absence of additives,[9a,b,g] or under basic conditions,[9c−f,h] is thus an important advantage. The trifluoromethanesulfonates (triflates) have been studied thoroughly, and have been implicated as intermediates in several important preparative methods.[1a,11] The chemistry of other classes of glycosyl sulfonates is less well advanced, although important progress regarding arenesulfonates has been achieved by the groups of Gin[12] and Bennett.[13] Gin found that glycosyl benzenesulfonates could be generated from the corresponding free hemiacetals using benzenesulfonic anhydride, dibutyl sulfoxide as a Lewis base catalyst and the hindered Brønsted base 2,4,6-tri-*tert*-butylpyridine (TTBP) at room temperature. Armed donors generally showed modest levels of α-selectivity in couplings with primary and secondary alcohols under these conditions. Bennett and co-workers prepared α-2-deoxyglycosyl toluenesulfonates (tosylates) using a strong base (potassium bis(trimethylsilyl)amide) and toluenesulfonic anhydride or toluenesulfonylimidazole at low temperature (−78 °C). These reacted with strong nucleophiles (thiolates or alkoxides) via inversion of configuration to give β-2-deoxyglycosides.

We were drawn in particular to glycosyl mesylates by two reports detailing their rapid and efficient generation from free hemiacetals, simply by treatment with methanesulfonic anhydride (Ms_2O) and an amine base.[9d,e] These conditions appeared to be suitable for in situ formation of the mesylate, which could then be added directly to a glycosyl acceptor in the presence of the borinic acid catalyst. Reactions with simple acceptors (methanol, isopropanol, cyclohexanol) reported in the 1970s appear to be the only documented examples of *O*-glycosylation using mesylate donors.[9c−e]

Development of Conditions for Borinic Acid-Catalyzed Couplings of Glycosyl Mesylates. We selected the coupling of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1a**) and 6-*O*-silylated α-mannopyranoside triol **2a** to evaluate conditions for borinic acid-catalyzed coupling of a mesylate generated in situ (Table 1). Acceptor **2a** is activated by diarylborinic acids at the 3-OH group, but also shows a relatively high level of "intrinsic" selectivity for reactions at this position. We anticipated that using an acceptor showing this type of regiochemical bias would simplify the analysis of product mixtures, allowing us to focus on the effect of catalyst on the stereochemical outcome of the reaction. Addition

Table 1. Optimization of Catalytic Glycosylation of Acceptor 2a with Glycosyl Hemiacetal 1a



entry	base	equiv Ms_2O	equiv **2a**	catalyst (equiv)	conv (%)[a]	α:β[b]
1	iPr$_2$NEt	1.2	1.5	none	50	2.0:1
2	iPr$_2$NEt	1.2	1.5	**4a** (0.1)	57	1:6.1
3	iPr$_2$NEt	1.2	1.5	**4b** (0.2)	54	1:1.8
4	iPr$_2$NEt	1.2	1.5	**4c** (0.2)	66	1:7.4
5	iPr$_2$NEt	1.5	1.5	**4c** (0.2)	83	1:6.0
6	Et$_3$N	1.5	1.5	**4c** (0.2)	76	1:2.4
7	PMP[c]	1.5	1.5	**4c** (0.2)	88	1:8.7
8	PMP	1.5	1.2	**4c** (0.1)	85	1:8.4
9	PMP	1.5	1.2	none	71	2.0:1
10	PMP	1.5	0.8	**4c** (0.08)	80	1:10

[a]Conversion of **1a** determined by HPLC analysis of the unpurified reaction mixture. [b]Determined by HPLC analysis of the unpurified reaction mixture. [c]PMP denotes 1,2,2,6,6-pentamethylpiperidine.

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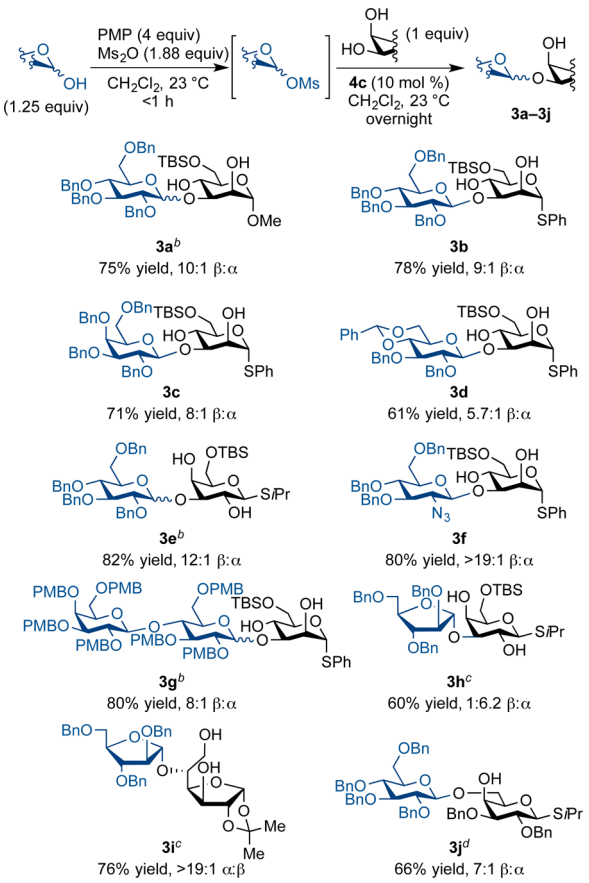
of a solution of Ms_2O to hemiacetal **1a** and iPr_2NEt in dichloromethane resulted in a faint yellow color within minutes of mixing at room temperature. Formation of the glycosyl mesylate under these conditions was supported by nuclear magnetic resonance spectroscopy (see below). Presumably, the ability to generate a reactive sulfene electrophile from Ms_2O and an amine base contributes to the high rate of this transformation.[14] Acceptor **2a** (either with or without a catalytic amount of **4a**, the anhydride of diphenylborinic acid) was then added, and the resulting mixture stirred at room temperature overnight. Analysis by high-pressure liquid chromatography (HPLC) revealed similar levels of conversion of **1a** for the catalyzed and uncatalyzed reactions, with the formation of 1,3-linked disaccharide **3a** being observed in both cases, as anticipated (entries 1 and 2). However, the stereochemical outcomes of the uncatalyzed and catalyzed reactions clearly differed, with the former showing a modest preference for the α-glucopyranoside and the latter yielding the β-glucopyranoside as the major product.

The solvent, base, organoboron catalyst and acceptor concentration were varied with the goal of developing a high-yielding, β-selective process. Dichloromethane provided superior results to acetonitrile, toluene, tetrahydrofuran (THF) and diethyl ether (Table S1, Supporting Information). Borinic ester **4b** resulted in lower β-selectivity than **4a** (entry 3). Since the same catalyst−substrate complex would be generated from **4a** and **4b**, this difference likely reflects a higher contribution from the α-selective background pathway due to slow entry of precatalyst **4b**[10] into the catalytic cycle (see below). An improvement in β:α ratio was obtained using oxaboraanthracene-derived catalyst **4c** (entry 3).[15] We have found that **4c** displays higher catalytic activity than **4b** for several types of diol functionalization reactions: the enhanced nucleophilicity of its tetracoordinate borinates is apparently a result of incorporating the borinic acid group into a 6-π electron system. Variation of the tertiary amine base revealed that the more sterically encumbered piperidine derivative 1,2,2,6,6-pentamethylpiperidine (PMP) improved both conversion and selectivity relative to Hünig's base, while the less encumbered triethylamine had a negative effect (entries 6 and 7). We note that the improvement obtained using PMP rather than iPr_2NEt was rather modest, and that the latter is a viable alternative in situations where the higher cost of PMP is an issue. A further increase in β-selectivity was obtained by changing the concentration of the glycosyl acceptor: a trend of higher β:α ratio at lower concentrations of **2a** is evident (entries 8 and 10). This series of experiments also revealed that the catalyst loading could be reduced to 10 mol % (relative to **2**, the limiting reagent under the conditions of entry 10) without deleterious effect. A comparison of uncatalyzed and catalyzed reactions using the optimized base (PMP) demonstrates the extent to which the catalyst is able to "switch" the stereoselectivity of this glycosidation (entries 8 and 9).

Scope and Limitations. The optimized protocol was used to construct several types of glycosidic linkages (Scheme 2). The β:α ratios reported in Scheme 2 are based on analysis of unpurified reaction mixtures by ^{1}H NMR spectroscopy or HPLC. The yields are for isolation of the major regio- and stereoisomer in pure form by flash chromatography on silica gel, unless otherwise indicated. High levels of 1,2-*trans* selectivity were obtained for armed glucopyranose, galactopyranose and arabinofuranose-derived donors. The ability to reliably generate such linkages in the absence of neighboring group participation is noteworthy. As observed in our previous studies, high levels of

Scheme 2. Borinic Acid-Catalyzed Stereoselective Glycosylation with Glycosyl Methanesulfonates[a]



[a] β:α ratios were determined by ^{1}H NMR or HPLC analysis of unpurified reaction mixtures. Yields are for isolation of the depicted compound in isomerically pure form, unless otherwise indicated. Glycosylation reaction times were not optimized. [b] Isolated as a mixture of anomers. [c] Mesylate formation was carried out at −25 °C. Glycosylation was stirred overnight at −25 °C, then allowed to warm slowly to room temperature over 5 h. [d] **4a** (5 mol %) was used in place of **4c**.

regiocontrol were achieved for glycosyl acceptors having 1,2- or 1,3-diol motifs. Aryl and alkyl thioglycoside-derived glycosyl acceptors were tolerated under these conditions. In the reaction of the glucofuranoside acceptor to generate product **3i**, a preference for activation of the secondary 5-OH group over the primary 6-OH group was observed (8:1 regioselectivity), possibly via the 3,5-*O*-borinate. The isolation of the minor, 6-*O*-glycosylated regioisomer as a mixture of stereoisomers (2:1 α:β) suggests that it arose from an uncatalyzed, background reaction. For the synthesis of β-1−6-linked product **3j**, the more Lewis acidic diphenylborinic acid provided superior results to **4c**.

Scheme 3 depicts substrate combinations that led to relatively low levels of β-selectivity under the catalytic conditions. These illustrate limitations of the methodology, but also provide additional evidence for the catalyst's ability to alter the stereochemical course of reactions of glycosyl mesylate donors. For example, the uncatalyzed reaction of 4,6-*O*-benzylidene-protected galactopyranosyl donor showed a particularly high level of α-selectivity (product **3k**).[16] The catalyst was not able to fully overcome this intrinsic bias, leading to a 1.4:1 α:β mixture. Similarly, the use of a 2-deoxyglucopyranosyl donor led to an α-selective reaction in the absence of catalyst (5.1:1 α:β) and only a

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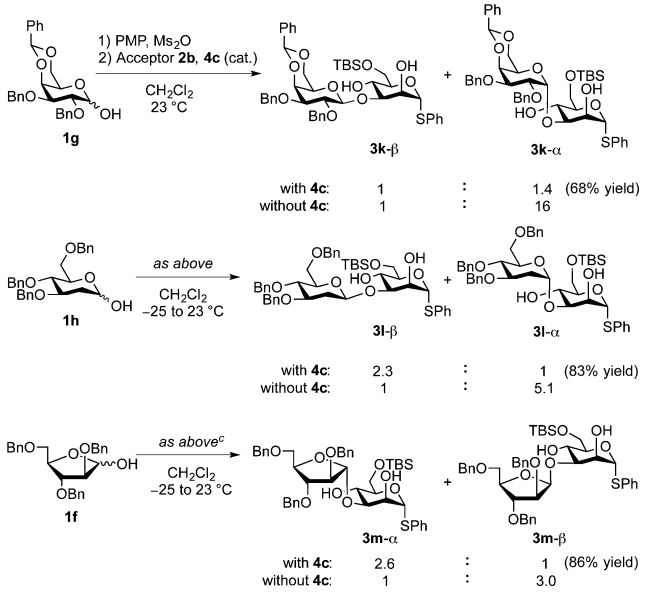
Scheme 3. Catalyzed and Uncatalyzed Stereoselectivites for Glycosylations of 2b with Selected Donors[a,b]

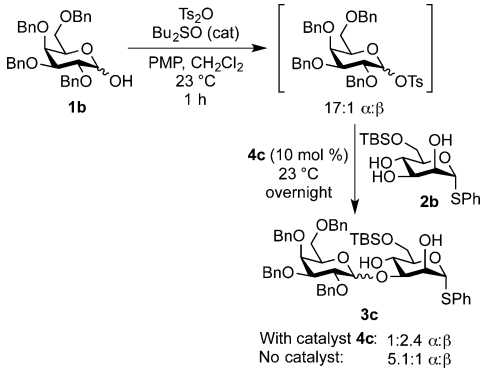


[a]Conditions: Hemiacetal (1.25 equiv), PMP (4 equiv), Ms_2O (1.88 equiv), <1 h; acceptor **2b** (1 equiv), **4c** (10 mol %), overnight. For **1h** and **1f**, the glycosylations were stirred overnight at −25 °C, then allowed to warm slowly to room temperature over 5 h. Reaction times were the same for catalyzed and uncatalyzed reactions, and were not optimized. [b]α:β ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The diastereomeric disaccharides were separated by flash chromatography on silica gel, and the total yield (α + β) is reported. [c]Product **3m** was isolated as a mixture of anomers.

modestly β-selective reaction in the presence of **4c** (1:2.7 α:β, product **3l**). Couplings of the pseudoenantiomeric galacto- and manno-configured acceptors with the D-arabinofuranose-derived mesylate donor appear to show a matching/mismatching effect on stereoselectivity (products **3h** (Scheme 2) and **3m**): an unusually high level of 1,2-*cis*-selectivity was observed for the Araf/Man coupling in the absence of catalyst.[17] Borinic acid catalysis did not give synthetically useful results for couplings of manno-configured glycosyl mesylates. The couplings of **2a** with 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose led to a complex mixture of isomeric glycosides. The use of the mesylate derived from 4,6-*O*-benzylidene-2,3-di-*O*-benzylmannopyranose resulted in an α-selective 3-*O*-glycosylation of acceptor **2a** in the presence of the catalyst, but in low (approximately 25%) yield.

We compared the results obtained using a glycosyl mesylate donor to those using the corresponding tosylate, generated by the reaction of the glycosyl hemiacetal with Ts_2O in the presence of catalytic dibutyl sulfoxide, according to Gin's protocol (but using PMP in place of the hindered pyridine derivative TTBP: Scheme 4).[12a] Formation of the tosylate (albeit not in quantitative yield, 17:1 α:β) was confirmed by ^{1}H NMR spectroscopy in CD_2Cl_2. In the presence of catalyst **4c**, disaccharide **3c** was obtained as a 2.4:1 anomeric mixture favoring the β-glycoside, whereas an α-selective reaction (5.1:1 α:β) took place in the absence of catalyst. The stereoselectivities were determined by ^{1}H NMR spectroscopy of unpurified reaction mixtures. No effort was made to optimize the yields of these reactions, which were lower than those obtained using the glycosyl mesylate. In any case, the effect of the borinic acid on the stereochemical outcome holds for both the mesylate and the tosylate leaving groups, but the mesylate donor provides superior levels of 1,2-*trans* selectivity in the presence of the catalyst (compare Scheme 4 to Scheme 2, product **3c**).

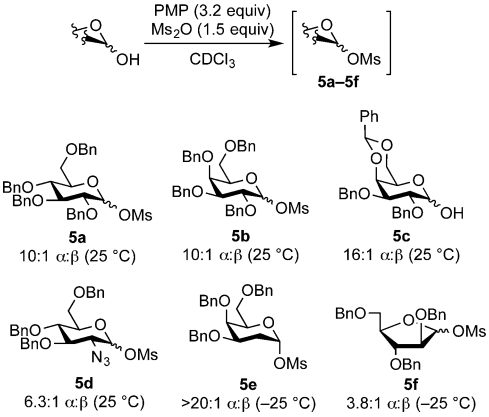
Scheme 4. Generation and Borinic Acid-Catalyzed Reaction of a Glycosyl Tosylate



Studies of Glycosyl Mesylates by NMR Spectroscopy. NMR spectroscopy was used to verify that glycosyl mesylates were formed in the initial step of this protocol, and to evaluate their stabilities and anomeric configurations. Treatment of **1a** with Ms_2O and PMP in $CDCl_3$ (in place of CH_2Cl_2, the solvent for the glycosylation process) resulted in the quantitative formation of mesylate **5a** within 10 min at room temperature. The hydrolysis of the mesylate generated under these conditions has a half-life in excess of 24 h at room temperature in a capped NMR tube. Both anomers of the glycosyl mesylate could be observed, and a 10:1 α:β ratio was determined.

In a similar way, mesylates **5b**−**5e** were generated and characterized by ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ (Scheme 5). With the exception of the 2-deoxy derivative, each mesylate was formed along with a detectable amount of the minor anomer, allowing determination of the α:β ratios shown in the Scheme. Whereas mesylates **5a**−**5d** were sufficiently stable to be characterized at room temperature, the 2-deoxypyranosyl and furanosyl derivatives **5e** and **5f** were studied at lower temperature (−25 °C) to prevent decomposition. (For the same reason, these mesylates were generated and subjected to glycosyl acceptors at −25 °C for the preparative reactions shown in Schemes 2 and 3.)

Scheme 5. Equilibrium Anomeric Ratios of Glycosyl Methanesulfonates Determined by ^{1}H NMR[a,b]



[a]Anomeric ratios were determined by ^{1}H NMR spectroscopy. [b]Temperatures at which NMR spectra were acquired.

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Variable temperature NMR revealed that decomposition of the 2-deoxy mesylate (via elimination to the glycal) took place between −5 and 5 °C. Both the high (>20:1) α:β ratio and the decomposition temperature of this compound are consistent with Bennett and co-workers' observations regarding the corresponding 2-deoxy tosylate (onset of elimination of −5 °C in THF-d_8).[13b]

The interconversion of mesylate anomers **5b**-α and **5b**-β was studied using NMR exchange spectroscopy (EXSY) in $CDCl_3$ at 25 °C.[18] 1D selective EXSY buildup curves were constructed by irradiating the signal corresponding to H-1 of **5b**-α and integrating that corresponding to H-1 of **5b**-β, or vice versa, for a variety of mixing times τ_m. The slopes of the initial, linear regions of the plots of EXSY integral versus τ_m were used to determine observed rate constants for the anomerization reactions (Figure 1a). These were found to be $(1.02 \pm 0.06) \times 10^{-2}$ s^{-1} (**5b**-$\beta \rightarrow$ **5b**-α) and $(9.3 \pm 1.3) \times 10^{-4}$ s^{-1} (**5b**-$\alpha \rightarrow$ **5b**-β). The sensitivity provided by a cryogenically cooled probe was important for determining the rather low rates of exchange. The ratio of rate constants is in good agreement with the equilibrium ratio of anomers that was determined independently by ^{1}H NMR spectroscopy (Scheme 5).

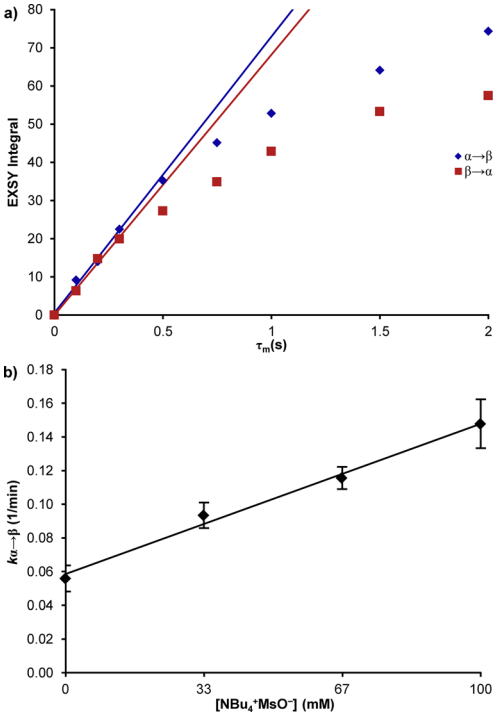


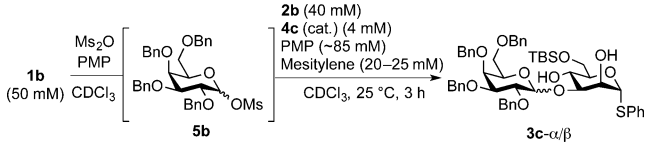
Figure 1. (a) EXSY buildup curves (EXSY signal integration versus mixing time τ_m) for the formation of **5b**-α (red ■) and **5b**-β (blue ◆) by anomerization. The lines used to determine the apparent rate constants are depicted on the graph. (b) Plot of observed rate constant for $\alpha \rightarrow \beta$ isomerization versus concentration of added $Bu_4N^+MsO^-$.

At least one equivalent of an ammonium mesylate salt is present in solutions of glycosyl mesylates generated from hemiacetals using Ms_2O and PMP. We estimate that the concentration of MsO^- in solutions of glycosyl mesylate generated under the conditions shown in Scheme 5 is 65 mM. Nucleophilic substitution by MsO^- is thus a plausible anomerization pathway. The dependence of the $\alpha \rightarrow \beta$ anomerization rate on the concentration of added tetrabutylammonium mesylate ($Bu_4N^+MsO^-$) is consistent with this hypothesis (Figure 1b): the linear relationship suggests first-order kinetics in MsO^-. Given that anomerization of activated donors is an important process in stereoselective glycosidations, further applications of the EXSY technique to related systems may be of interest.

Reaction Progress Kinetic Analysis of Catalyzed and Uncatalyzed Pathways. The ^{1}H NMR spectroscopy studies indicated that glycosyl mesylates **5a**−**5d** could be generated cleanly from **1a**−**1d**, and that their decomposition reactions were slow relative to nucleophilic substitution by a glycosyl acceptor (either in the presence or in the absence of diarylborinic acid catalyst). These features, as well as the ability to conduct the coupling under homogeneous reaction conditions and without additional activation of the donor (e.g., by a Brønsted acid, electrophile or Lewis acid promoter), suggested the possibility of using in situ analysis to study the kinetics of the glycosylation reaction. Mechanistic understanding of nonenzymatic glycosylation reactions has developed slowly relative to the discovery of new protocols,[19] and detailed kinetic studies remain uncommon, especially for preparative glycosylation methods (as opposed to hydrolysis or solvolysis reactions).[20] Previously, we determined initial rates of borinic acid-catalyzed couplings of **1a** with acetobromoglucose by ^{1}H NMR spectroscopy, taking aliquots of reaction mixtures.[3a] The reactions showed first-order kinetics in catalyst, glycosyl donor and glycosyl acceptor, and apparent zero-order kinetics in Ag_2O (presumably reflecting a reaction at the surface of the insoluble promoter). We aimed to conduct a more comprehensive study of the present methodology, using reaction progress kinetic analysis[21] of glycosylations conducted under synthetically relevant conditions.

The coupling of galactopyranosyl mesylate **5b** and 6-*O*-TBS-mannopyranosyl thioglycoside **2b** was chosen for monitoring by in situ ^{1}H NMR spectroscopy (Scheme 6). On a 700 MHz

Scheme 6. Standard Conditions for In Situ Kinetic Studies



instrument equipped with a cryogenically cooled probe, the spectrum was sufficiently well resolved to enable accurate integration of signals corresponding to the two anomers of the glycosyl mesylate, and those of the product glycoside. The reaction was conducted under the standard conditions shown in Scheme 2, but using $CDCl_3$ as the NMR solvent with mesitylene as a quantitative internal standard, collecting a spectrum every 3 min over the course of the experiment. Figure 2 shows the concentrations of glycosyl donor (the sum of the concentrations of the two mesylate anomers), glycosyl acceptor and products **3c**-β and **3c**-α as a function of time. The α:β ratio of the glycosyl mesylate **5b** remained constant over the course of the experiment. Donor concentration data for an experiment conducted in the absence of borinic acid **4c** are also shown. The catalyzed reaction was complete in less than 2.5 h, whereas the uncatalyzed reaction required more than 10 h. It should also be noted that the acceptor and donor were consumed at different rates under this protocol. Although the glycosyl mesylate was present in excess at the outset of the reaction, unreacted acceptor remained at its completion. Hydrolysis and other side reactions

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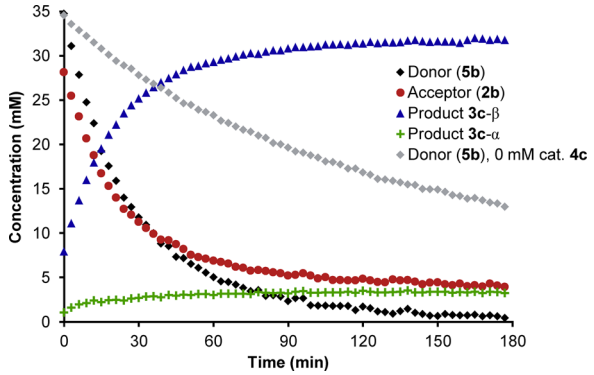

Figure 2. Graph of the concentrations of **5b** (black ◆), **2b** (red ●), **3c**-β (blue ▲) and **3c**-α (green +) versus time for the standard conditions shown in Scheme 3. Concentration of **5b** versus time is also plotted for the uncatalyzed reaction (grey ◆). The starting concentration of **5b** was different for the uncatalyzed reaction, and so the graph has been timeshifted for comparison purposes.

of the donor are responsible for its accelerated consumption relative to the acceptor.

The concentration versus time data for borinic acid-catalyzed formation of β anomer **3c**-β were transformed into rate versus time data by fitting to a differential equation (see the Supporting Information). These were used to construct "graphical rate equations" of rate versus glycosyl donor concentration. The concentration of the β-glycoside (rather than the sum of concentrations of the two product anomers) was used in this analysis based on the hypothesis that the α-anomer arises primarily from the uncatalyzed background pathway (see below). Figure 3a shows graphs of rate versus glycosyl mesylate concentration for reactions conducted at the same starting concentration of donor and catalyst loading, but with three different acceptor concentrations (30 mM, 40 mM and 60 mM). Overlay of the plots corresponding to 40 mM and 60 mM acceptor concentration is evident, indicating zero-order (or apparent zero-order) kinetics in acceptor. The rate profile at 30 mM acceptor concentration overlays with the two others at the early stages of the reaction, but a decrease in rate and departure from linearity are evident at lower donor concentrations. This behavior is discussed in more detail below. Given the zero-order kinetics in glycosyl acceptor, the linear dependence of rate on donor concentration implies first-order kinetics in the glycosyl mesylate.

The data that were used to determine the kinetic orders in catalyst and base are shown in Figures 3b and 3c, respectively. The overlay of rate/[catalyst] versus [donor] graphs for reactions conducted at different catalyst loadings (10 vs 15 mol %) reflect first-order kinetics in borinic acid **4c**. Figure 3c shows concentration of product versus time data for two experiments: one conducted with the standard concentration of PMP (3.2 equiv relative to the starting glycosyl hemiacetal) and one with a higher concentration (4.8 equiv). Since roughly 1.5 equiv of PMP are consumed in the reaction of the hemiacetal with Ms_2O, this corresponds to roughly a doubling of the concentration of "free" PMP in the glycosylation step. The data are presented as concentration of product versus time because glycosyl donor decomposition and side reactions were more evident when the higher concentration of base was used. These issues complicated interpretation of the data, but the similar initial regions of the graphs suggest roughly zero-order kinetics in PMP.

Reaction progress kinetic analysis provides a powerful way to assess catalyst decomposition or product inhibition using "same excess" experiments. These experiments rely on the assumption that the difference in concentration of two reactants (the "excess") remains constant over time if they react in a 1:1 stoichiometry. Unfortunately, side reactions of the glycosyl mesylate (e.g., hydrolysis, formation of isomeric glycosides or bis-glycosylated products: see above) caused a sufficient change in excess over time to compromise the results of this type of experiment. (The "different excess" experiments of the type shown in Figure 3 were possible because concentrations of reactants and products were determined independently using an internal standard.) However, informative results were obtained from an experiment in which tetrabutylammonium mesylate (100 mM) was added to the borinic acid-catalyzed glycosylation. A decrease in rate was observed (Supporting Information, Figure S4), along with a decrease in β-selectivity from 10:1 to approximately 3:1 β:α. Either a common-ion effect[22] or inhibition of the borinic acid by anion binding could be responsible for this behavior. The second explanation seems more reasonable, given (i) the observation of changes in the ^{1}H NMR spectrum of **4c** upon addition of $Bu_4N^+MsO^-$; (ii) the known ability of boronic and borinic acids to act as anion receptors;[23] and (iii) the low likelihood of a dissociative

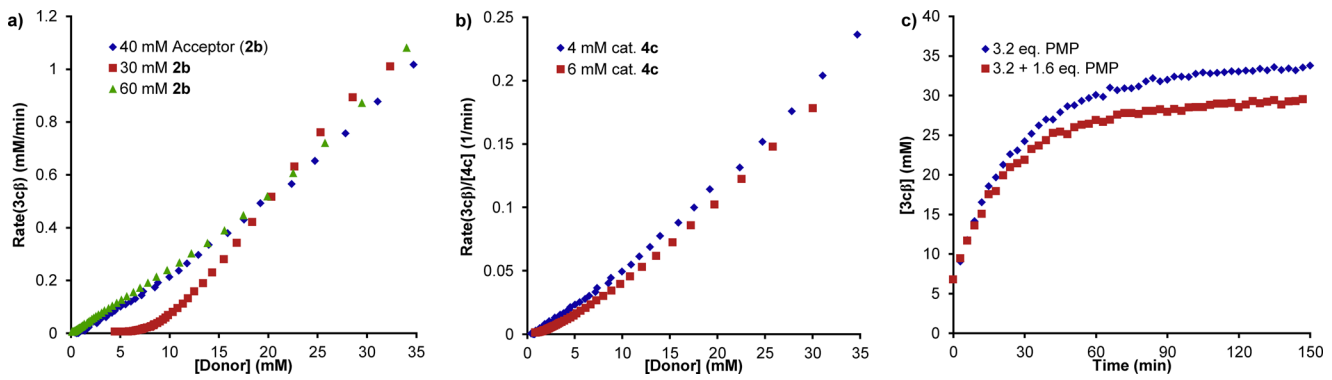

Figure 3. Kinetics of the glycosylation reaction of acceptor **2b** with donor **5b**, catalyzed by borinic acid **4c**. (a) Rate of **3c**-β product formation versus concentration of donor **5b** ([**5b**-α] + [**5b**-β]) for experiments carried out at different acceptor concentrations. (b) Rate of **3c**-β product formation, normalized by catalyst concentration, versus concentration of **5b** ([**5b**-α] + [**5b**-β]) for experiments carried out at different catalyst concentrations. (c) Concentration of **3c**-β versus time for experiments carried out at two concentrations of PMP. The graph for the reaction at the lower PMP concentration has been timeshifted for comparison purposes.

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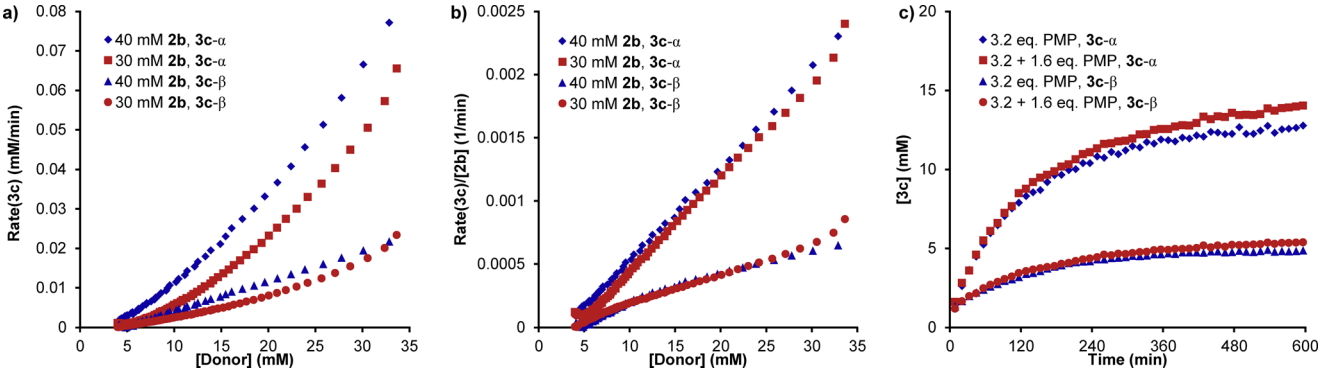


Figure 4. Kinetics of the uncatalyzed glycosylation reaction of acceptor **2b** with donor **5b**. (a) Rates of product formation (**3c**-α and **3c**-β) versus concentration of donor **5b** ([**5b**-α] + [**5b**-β]) for experiments carried out at different acceptor concentrations. (b) Rates of product formation (**3c**-α and **3c**-β), normalized by acceptor concentration, versus concentration of donor **5b** ([**5b**-α] + [**5b**-β]). (c) Concentration of product (**3c**-α and **3c**-β) versus time for experiments carried out at two concentrations of PMP.

mechanism for the borinic acid-catalyzed glycosylation (see below). The decreased β-selectivity is due to the increased contribution of the uncatalyzed pathway, which is not inhibited by $Bu_4N^+MsO^-$, as discussed later in this section.

The kinetic orders for the coupling of **2b** and **5b** catalyzed by borinic acid **4c** are summarized in Figure 5. First-order kinetics in catalyst and glycosyl donor, along with apparent zero-order kinetics in glycosyl acceptor, could arise from acceleration of an associative process by catalyst binding to the glycosyl acceptor, with the apparent zero-order dependence resulting from saturation kinetics. The other possibility is a dissociative (S_N1-like) mechanism involving Lewis acid activation of the glycosyl mesylate by the catalyst. The former proposal is consistent with our mechanistic data for other borinic acid-catalyzed transformations,[3a,10] and with the ability of borinic acids to activate diols toward reactions with electrophiles other than glycosyl donors. Further support for the glycosyl acceptor activation hypothesis was obtained by replacing PMP with the weaker base *sym*-collidine. Borinic acid−diol complexation was not observed in the presence of the latter, and neither rate acceleration by **4c** nor a catalyst-induced change in stereoselectivity was observed for glycosylations using this base. Additional evidence for saturation kinetics can be drawn from the rate profile of the reaction conducted at 30 mM acceptor concentration (Figure 3a). At the point where the data deviate from those at the higher acceptor loadings, the acceptor concentration has reached roughly 6 mM, which is on par with the catalyst concentration (4 mM). A decrease in rate and deviation from an overall first-order rate law is expected at these relative concentrations (and beyond), as saturation kinetics would no longer apply.

We conducted a similar analysis of the kinetics of the uncatalyzed reaction of **2b** with **5c** (Figures 4a−4c). This reaction gives an α:β ratio of 2.6:1, and the rates of formation of the α- and β-anomers of product were analyzed separately. The rate law was found to be the same for the pathways leading to the two anomers of product: first-order kinetics in acceptor **2b**, first-order in donor **5c**, and roughly zero-order in PMP (Figure 5). Inhibition by $Bu_4N^+MsO^-$ was not observed (Supporting Information, Figure S5). Both the observation of a kinetic dependence on acceptor concentration and the lack of a common ion effect suggest that the uncatalyzed glycosylation, like the catalyzed process, proceeds by an associative mechanism.

Having obtained this information regarding the kinetics of the uncatalyzed reaction, we returned to the data for the borinic acid-catalyzed process, examining the rate of formation of the minor

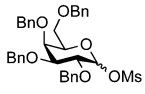
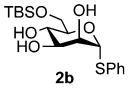
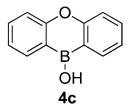
component	catalyzed reaction (formation of **3c**-β)	uncatalyzed reaction (formation of **3c**-α and **3c**-β)
 **5b**	first order	first order
 **2b**	apparent zero order (saturation)	first order
 **4c**	first order	–
PMP	~ zero order	~ zero order
MsO^-	inhibition	zero order

Figure 5. Summary of kinetic orders determined by reaction progress kinetic analysis for the catalyzed and uncatalyzed reactions.

anomer **3c**-α. It proved difficult to accurately determine the concentration of the small amount of α-configured product formed under the conditions of Scheme 6. However, conducting the experiment with higher concentrations of acceptor resulted in a lower level of β-selectivity, thus permitting analysis of the concentration data for the minor α-anomer. Whereas the process leading to the β-configured product showed apparent zero-order (saturation) kinetics in acceptor, the formation of **3c**-α followed first-order kinetics in **2b** (Figure S6). This observation suggests that much of the α-product formed in the presence of **4c** arises from a competing, uncatalyzed pathway, and that the intrinsic β-selectivity of the borinic acid-catalyzed process is very high for this donor−acceptor combination. It provides a rationale for the optimization data from Table 1 showing increased β-selectivity upon decreasing the quantity of acceptor **2b**. It also suggested that reducing the concentration of "free" **2b** in the reaction mixture by slow addition of the acceptor would improve the β-selectivity of the borinic acid-catalyzed process. Indeed, when a solution of **2b** was added to mesylate **5b**, catalyst and PMP over 3 h by syringe pump, an improvement in stereoselectivity was obtained (β:α 14:1, versus 8:1 β:α without using the slow addition protocol). No attempt was made to further optimize the addition rate for this process. This result suggests that slow addition may be a useful approach for improving stereoselectivity in challenging couplings of mesylate donors.

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CONCLUSIONS

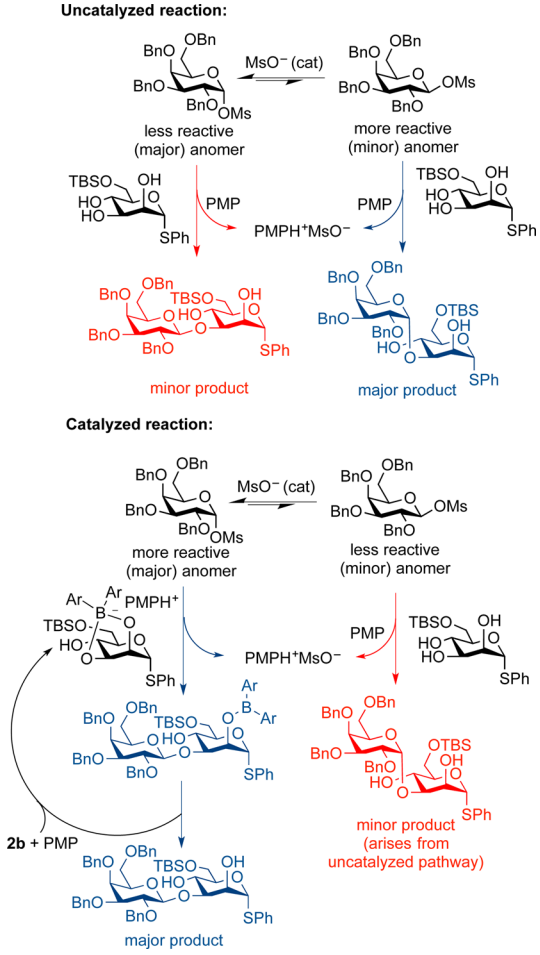
In summary, glycosyl mesylate donors have been employed in borinic acid-catalyzed couplings with diol-containing acceptors, enabling the formation of a variety of regio- and stereodefined linkages. From a preparative standpoint, the catalyst-controlled method represents an operationally simple protocol for generating 1,2-*trans*-configured linkages from armed donors. The glycosyl mesylates are generated efficiently from the corresponding hemiacetals, and can be characterized in solution. They react with glycosyl acceptors under mild conditions (hindered amine base, CH_2Cl_2, room temperature), but the diarylborinic acid catalyst gives significant levels of rate acceleration for couplings of acceptors having 1,2- or 1,3-diol moieties. Our "second-generation" oxaboraanthracene-derived borinic acid, which gives rise to highly nucleophilic borinic ester adducts, has proved to be especially useful in this context. We anticipate that these conditions will prove useful for regioselective glycosylations of more complex substrates.

A noteworthy aspect of this study is the influence of borinic acid catalyst **4c** on the stereoselectivity of reactions of glycosyl mesylates. In several instances (Table 1, Scheme 3), there is a clear reversal in stereochemical outcome for the reaction carried out in the presence of the catalyst versus in its absence. Influencing the stereoselectivity of glycosylations by catalytic activation of the acceptor is an emerging concept, and one that may offer new ways to approach the formation of challenging classes of linkages.[5f−h] The kinetics experiments described here provide insight into how such a switch in stereoselectivity can arise.

Both the uncatalyzed and catalyzed glycosylations show kinetics consistent with associative mechanisms. The rates of MsO^--catalyzed anomerization of glycosyl mesylate **5b** determined by EXSY indicate that the predominant product, both in the presence and the absence of catalyst, can plausibly be generated by inversion of configuration of the corresponding mesylate. The general approach of using EXSY to determine anomerization rates in combination with analysis of reaction kinetics may have broader utility for studying the mechanisms of glycosylations (e.g., for other classes of glycosyl sulfonates). In the present case, the modest preference for the α-configured glycoside product in the absence of catalyst appears to reflect the higher reactivity of the minor β-mesylate, consistent with the Curtin−Hammett principle. This corresponds to the mechanism proposed by Lemieux and co-workers for halide-catalyzed 1,2-*cis*-selective couplings of glycosyl halides.[5a] In the presence of the catalyst, the displacement of the α-mesylate is accelerated, leading to the selective formation of the β-glycoside. The selectivity for acceleration of the pathway leading to the β-anomer appears to be high, since most of the minor α-anomer (in the case of product **3c**) arises from the uncatalyzed "background" pathway. Kinetic isotope effect experiments and computation would be needed to elucidate the transition state structural effects that lead to these differences in behavior between unactivated alcohols and borinate-activated acceptors. However, a reasonable preliminary hypothesis is that the sterically hindered nature of the tetracoordinate borinic ester nucleophile results in selective acceleration of the 1,2-*trans*-selective pathway. This idea is consistent with the scope and limitations depicted in Scheme 2 and 3. The overall mechanistic proposal is summarized in Scheme 7.

The kinetics experiments have not only provided mechanistic insight, but have also pointed toward practical improvements to the borinic acid-catalyzed process. The observation of a lower kinetic order in glycosyl acceptor for the catalyzed versus the uncatalyzed reaction (apparent zero-order (saturation) versus first-order kinetics), led to the use of a slow addition protocol to maximize β-selectivity in the catalytic process. This study has yielded insight into the reactivity of glycosyl sulfonates, and may be a useful starting point for the development of other stereoselective glycosylation methods that take advantage of catalytic glycosyl acceptor activation.

Scheme 7. Mechanistic Proposal for Stereochemical Outcomes of Uncatalyzed and Catalyzed Glycosylation of Mesylate Donor 5b



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06943.

Experimental procedures, characterization data, additional optimization data and kinetic profiles, EXSY buildup curves and exchange rate constants, sample code for fitting kinetic data, and NMR spectra for all new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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