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Regioselective Activation of Glycosyl Acceptors by a Diarylborinic Acid-Derived Catalyst

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Supporting Information

ABSTRACT: A derivative of diphenylborinic acid promotes catalytic, regioselective Koenigs−Knorr glycosylations of carbohydrate derivatives bearing multiple secondary hydroxyl groups. Robust levels of selectivity for the equatorial OH group of *cis*-1,2-diol motifs are demonstrated in reactions of seven acceptors derived from galactose, mannose, fucose, and arabinose using a variety of glycosyl halide donors. Catalyst control presents a new means of generating defined glycosidic linkages from unprotected or minimally protected carbohydrate feedstocks.

Oligosaccharides play central roles in a wide range of biological processes, including cell−cell signaling, immune response, cancer metastasis, and progression of human disease.[1] Laboratory synthesis often represents the only means of access to homogeneous, well-defined oligosaccharides for use in medical or biochemical research or as new therapeutic agents. The preparation of oligosaccharides from readily available carbohydrate derivatives requires efficient methods for the construction of O-glycosidic bonds, and solutions to this problem have been pursued for more than a century.[2]

Regioselectivity represents a key challenge for oligosaccharide synthesis: an acceptor bearing multiple potentially reactive hydroxyl (OH) groups must undergo glycosylation at a single site. The problem of regioselectivity has generally been addressed through the use of protecting groups to suppress glycosylation at undesired positions; the additional operations required to install and remove these protecting groups and the accompanying generation of chemical waste represent disadvantages of this approach.[3] In certain instances, inherent differences in the steric and/or electronic properties of OH groups may be exploited to achieve selective glycosylation.[4,5] Such reactions are generally optimized on a case-by-case basis, and the regiochemical outcome may depend on the structure of the glycosyl donor.[6] A third strategy employs activating agents to enhance the reactivity of specific OH groups: in particular, organotin derivatives promote regioselective reactions of carbohydrate derivatives with a variety of electrophiles, including glycosyl donors.[7] These methods generally require an additional synthetic step to install the activating group, and the use of stoichiometric quantities of toxic, lipophilic organotin species constitutes a limitation. None of these strategies rivals biological machinery in its ability to achieve regioselective, enzyme-catalyzed glycosylation of unprotected sugars.[8] Here we report the first example of a synthetic "small-molecule" (nonenzymatic) catalyst capable of regioselective activation of glycosyl acceptors.[9,10] This method enables the facile construction of a variety of glycosidic linkages from unprotected or minimally protected carbohydrate building blocks using a commercially available diarylborinic acid derivative.

We sought to test the hypothesis that an organoboron catalyst could activate glycosyl acceptors through the formation of tetracoordinate adducts of *cis*-1,2-diol motifs. Precedent for this proposal includes (1) an extensive literature of carbohydrate recognition by organoboron derivatives through selective interactions with *cis*-1,2-diol groups;[11] (2) studies of the stoichiometric reactivity of sugar-derived boronate esters, which demonstrated that tetracoordinate adducts of this type undergo regioselective glycosylation;[12a] and (3) our recent discovery that arylborinic acid derivatives catalyze the acylation and alkylation of carbohydrate derivatives, with high selectivity for functionalization of the equatorial hydroxyl group of *cis*-1,2-diol moieties.[13,14]

Experiments assessing the ability of organoboron catalysts **1a**−**e** to promote regioselective Koenigs−Knorr glycosylation of mannose derivative **2a** are summarized in Table 1. A glycosyl acceptor in which the primary OH group was protected was chosen to avoid complications arising from two-point binding of the organoboron catalyst to O6 and O4, a known mode of coordination in boron-based sugar receptors.[11b] In the absence of an organoboron catalyst, use of silver(I) oxide as an activating reagent gave only a trace amount (<5%) of disaccharide **3a**; ^{1}H NMR analysis with a quantitative internal standard indicated 37 and 77% recovery of the glycosyl donor and acceptor, respectively. Phenylboronic acid **1a** promoted the formation of β-[1,3]-linked disaccharide **3a** in 52% yield, and the corresponding orthoester **4a** (15% yield) was formed as one of several byproducts. Varying the electronic properties of the boronic acid catalyst did not significantly improve the efficiency of the reaction (entries 3 and 4). However, diphenylborinic acid derivative **1d** delivered **3a** as the only observed disaccharide in 99% isolated yield. Borinic acids provide superior catalytic activity and regioselectivity relative to boronic acids in the context of acylations and alkylations of monosaccharides;[13] the variation in the ratio of disaccharide to orthoester observed here appears to reflect differences in the nature of the nucleophilic species obtained upon activation of diols by these two classes of catalysts.[15] Mechanistic studies (see below) suggested that borinate ester **1d** serves as a precatalyst from which the ethanolamine ligand is displaced under the reaction conditions. Triphenylborane (**1e**) promoted the formation of **3a** in moderate yield (entry 6); orthoester **4a** and recovered glycosyl donor were also evident in the crude reaction mixture. The identity of the Ag(I) salt was crucial to the success of this transformation: lower yields of **3a** were obtained using other insoluble (Ag_2CO_3) or soluble (AgOTf, AgOAc) promoters.

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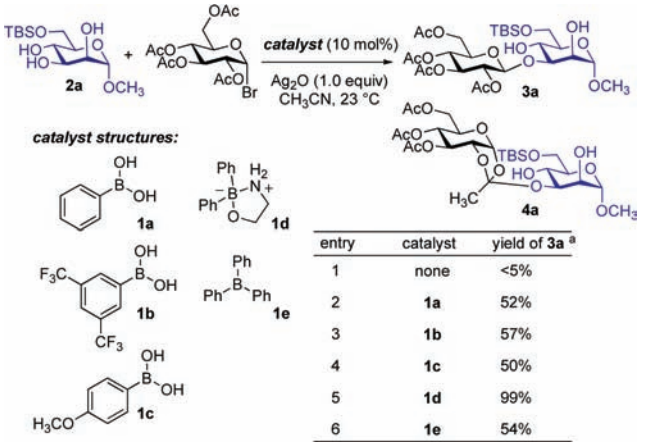
Table 1. Optimization of Organoboron-Catalyzed Regioselective Glycosylation of Mannose Derivative 2a



entry	catalyst	yield of 3a [a]
1	none	<5%
2	**1a**	52%
3	**1b**	57%
4	**1c**	50%
5	**1d**	99%
6	**1e**	54%

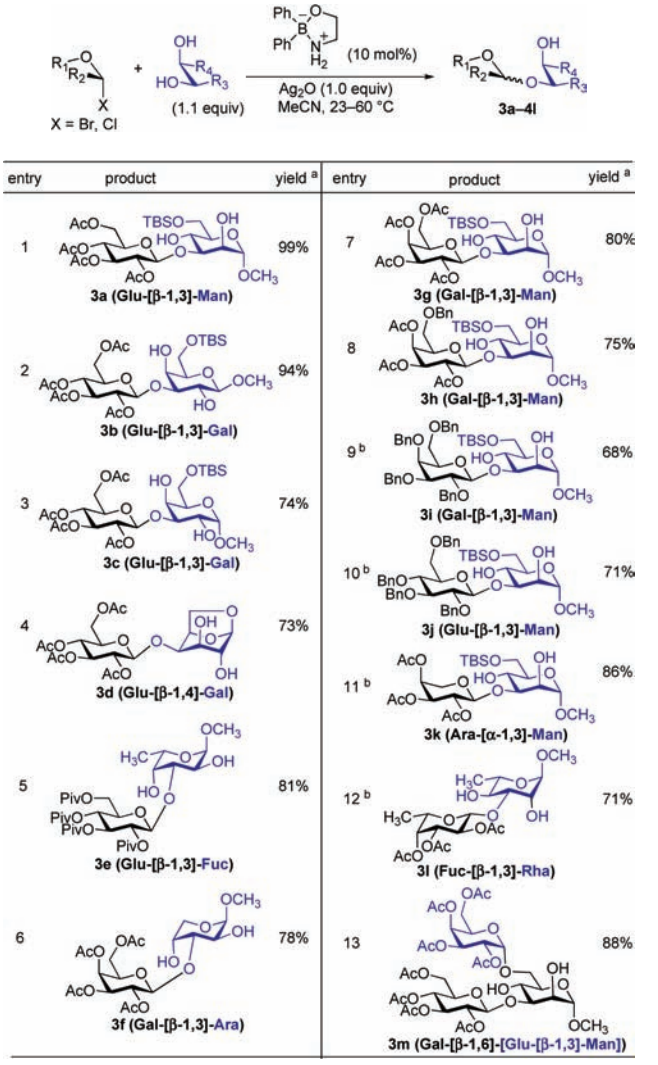
[a] Isolated yields after purification by chromatography on silica gel.

Likewise, other classes of donors (trichloroacetimidates, phosphates, thioglycosides) did not give rise to regioselective organoboron-catalyzed glycosylation.[16] The optimized reaction conditions are noteworthy from the standpoint of their operational simplicity: rigorous exclusion of moisture (or the addition of drying agents) is not needed, and the deliberate addition of 4 equiv of water relative to glycosyl acceptor resulted in only a moderate decrease in the yield of **3a** (72 vs 99%).

Table 2 illustrates the range of glycosidic linkages that can be accessed by this catalyst-controlled method. Selective glycosylation at O3 was observed for derivatives of mannose, galactose, fucose, arabinose, and rhamnose, each bearing three potentially reactive secondary hydroxy groups, with varied relative stereochemistry at the anomeric position. Employing 1,6-anhydrogalactopyranose resulted in glycosylation at O4, a regiochemical outcome distinct from that achieved using the nonbridged galactopyranoside substrates. Our model for the observed regioselectivity invokes the selective formation of tetracoordinate borinate adducts of the *cis*-1,2-diol moiety as described above: the boron-bound oxygen atom predicted to be most nucleophilic by Fukui index calculations[13,17] corresponds to the site of observed reactivity for each substrate. Steric effects may also play a role (e.g., the selective glycosylation of **3d** at O4 rather than O3 corresponds to reaction of the less hindered hydroxyl group). Desilylation of **3a** was followed by catalyst-controlled glycosylation at O6 (presumably through binding to the 4- and 6-positions), generating branched trisaccharide **3m**.

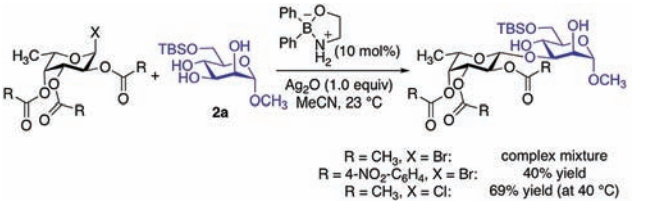
Variation of the structure of the glycosyl donor was also investigated. Galactosyl, fucosyl, and arabinosyl moieties were introduced in good yields (entries 6−9, 11, and 12), and glycosyl donors bearing benzyl (rather than acetyl) protecting groups were tolerated (entries 8−10). The use of glycosyl chlorides rather than bromides was crucial for achieving regioselective glycosylation with relatively reactive donors (e.g., fucosyl, arabinosyl, and perbenzylated glycosyl halides). The nature of this effect is illustrated in Scheme 1. Attempted glycosylation of **2a** using peracetylated fucosyl bromide as the donor resulted in a complex mixture of products, but the yield of disaccharide was improved by employing either the 4-nitrobenzoyl-protected glycosyl bromide or the peracetylated glycosyl chloride, with the latter providing the best result. Both the introduction of

Table 2. Borinic Ester-Catalyzed Regioselective Glycosylation: Variation of Glycosyl Donor and Acceptor Structures



[a] Isolated yields after purification by chromatography on silica gel; reactions were carried out using the glycosyl bromide (X = Br) as the donor, unless otherwise noted. [b] The reaction was carried out using the glycosyl chloride (X = Cl).

Scheme 1. Tuning of the Glycosyl Halide Reactivity in Catalyst-Controlled Regioselective Glycosylation



electron-withdrawing protecting groups and the stronger C−X bond of the glycosyl chloride relative to the bromide are expected to destabilize oxocarbenium-like intermediates (consistent with

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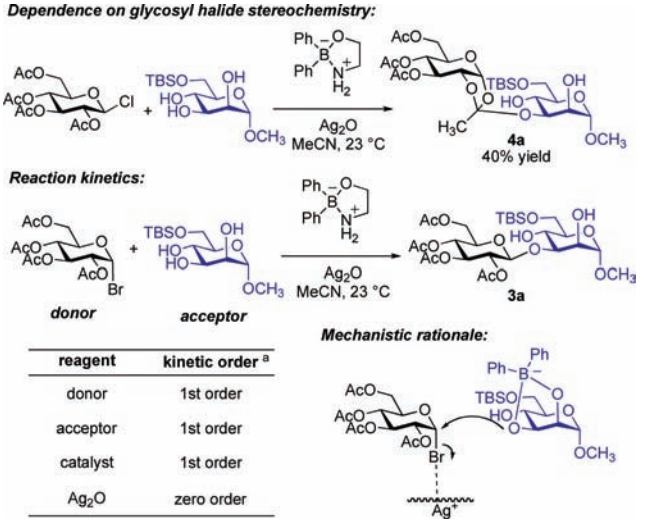
Scheme 2. Investigation of the Mechanism of Borinic Acid-Catalyzed Regioselective Glycosylation[a]



reagent	kinetic order [a]
donor	1st order
acceptor	1st order
catalyst	1st order
Ag_2O	zero order

[a] Kinetic orders were based on initial rates determined by ^{1}H NMR analysis (see the Supporting Information).

the extensive literature of armed−disarmed effects in glycosylation chemistry[18]) in favor of a pathway with significant S_N2 character. The observation of more efficient borinic acid-mediated glycosylation with substrates that disfavor oxocarbenium ion formation is consistent with stereochemical and kinetic studies suggesting an S_N2-type mechanism for the catalytic process (see below).

At present, this catalyst-controlled glycosylation protocol provides efficient access to *trans*-1,2 linkages from donors having a gluco or galacto configuration. Preliminary attempts to prepare *cis*-1,2 linkages (e.g., by organoboron-catalyzed variants of the halide ion catalysis method[19]) did not yield synthetically useful results. However, when the range of donors and acceptors employed is taken into account, the scope of the method is considerably broader than those of previously developed stoichiometric activation protocols based on organotin or organoboron reagents.[7,12]

Experiments relevant to the mechanism of the borinic acid-catalyzed glycosylation reaction are summarized in Scheme 2. The outcome of the transformation is dependent on the configuration of the glycosyl halide: subjecting the β-anomer of acetochloroglucose to the optimized reaction conditions delivered orthoester **4a** (rather than **3a**) in moderate yield.[20] This result suggests that **3a** is generated by an S_N2-type inversion[21] rather than through the intermediacy of an oxocarbenium ion and is consistent with previous observations regarding reactions of glycosyl halides in the presence of insoluble silver-based promoters.[22] Kinetic orders based on initial rates determined by ^{1}H NMR experiments were also consistent with this proposal: the reaction showed first-order kinetics with respect to the glycosyl donor, the acceptor, and the catalyst and zeroth-order kinetics with respect to Ag_2O. The zeroth-order kinetics may reflect saturation-type behavior of reactive sites on the Ag_2O surface. The initial rates of reactions promoted by diphenylborinic acid (Ph_2BOH) were higher than those in which its ethanolamine ester **1d** was employed, consistent with the hypothesis that the latter serves as a precatalyst under the reaction conditions.

The ability to influence the regiochemical outcome of glycosylation reactions using a synthetic catalyst represents a new mode of reactivity that presents interesting opportunities for improving the efficiency of the synthesis of oligosaccharide targets. Efforts to expand the scope of this method and apply it to target-oriented synthesis are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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