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Catalysis Based on Reversible Covalent Interactions of Organoboron Compounds

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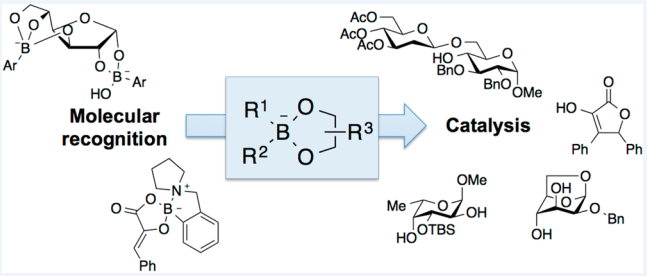
CONSPECTUS: An Account of the development of organoboron-catalyzed methods for chemo- or regioselective activation of pyruvic acids, diols, and carbohydrate derivatives is presented. These methods are based on reversible, covalent interactions that have been exploited extensively in host–guest chemistry, but were comparatively underutilized in catalysis. Important differences between the established properties of organboron compounds in molecular recognition and their behavior as catalysts emerged over the course of this work: for instance, borinic acids, which have largely been ignored in molecular recognition, proved to be a particularly useful class of catalysts. Nonetheless, the high selectivity that has enabled applications of organoboron compounds in molecular recognition (e.g., the selective binding of *cis*-1,2-diol groups in carbohydrates) also appears to play a key role in the outcomes of catalytic reactions.



This research program began as a modest, narrowly defined project aimed at developing direct aldol reactions based on established interactions between pyruvic acids and boronic acids. While this goal was achieved, it was unexpected observations related to the nature of the nucleophile in this transformation (a putative tetracoordinate boron enolate) that attracted our attention and pointed toward broader applications in the catalyst-controlled, regioselective functionalization of polyols. This line of research proved to be fruitful: diarylborinic-acid-based precatalysts were found to promote efficient monoalkylations, sulfonylations, and alkylations of a range of diol substrates, as well as *cis*-1,2-diol motifs in pyranoside-derived triols. Extension of this chemistry to glycosyl donors as electrophiles enabled the regioselective, catalyst-controlled synthesis of disaccharides from readily accessible feedstocks, and was also employed to modify the oligosaccharide component of a complex, glycosylated natural product.

Mechanistic studies have played an important role in our efforts to optimize catalyst activity and expand substrate scope for this class of transformations. For instance, it was kinetic studies of the sulfonylation of diols that motivated us to investigate heteroboraanthracene-derived borinic acids as catalysts, despite their low affinity for these substrates. Likewise, preliminary studies suggesting an S_N2-type pathway for organoboron-catalyzed glycosylations were instrumental in our development of a method for selective formation of β-2-deoxyglycosides. Details of these mechanistic studies, along with prospects for applying catalyst-controlled glycosylation in oligosaccharide synthesis and natural product glycorandomization, are discussed.

I. INTRODUCTION

Insights gained from studies of molecular recognition have served to inspire catalyst design and discovery. Using host–guest interactions to bring a substrate into proximity with a reactive group was among the first strategies explored for the development of enzyme mimics.[1] Recent applications of chiral hydrogen bond donors in asymmetric catalysis provide another illustration of the connections that can be made between the fields of molecular recognition and catalysis: parallels exist between the ability of donors such as ureas, thioureas, guanidines, and squaramides to form complexes with Lewis bases, and their activity as catalysts for enantioselective addition, substitution, and rearrangement reactions.[2] As a graduate student with Prof. Eric Jacobsen, I was involved with a project that uncovered a close connection of this type: chiral thioureas were found to activate *N*-acyliminium ions toward enantioselective Pictet–Spengler and Mannich reactions (Scheme 1).[3] Although the mechanism by which the chiral hydrogen bond donor imparted enantioselectivity was initially unclear, a hypothesis involving activation of the acyliminium chloride ion pair through thiourea–chloride binding emerged, along with extensions of this mode of catalytic reactivity to other transformations involving ion-paired intermediates.[4] This "anion binding catalysis" finds precedent in the documented behavior of ureas and thioureas as anion receptors.[5]

The prospect of drawing on the molecular recognition literature to develop new catalysts was the basis for two initial directions of my research group at the University of Toronto. An interest in applying relatively poorly understood non-covalent interactions in catalysis motivated our studies of halogen bonding between electron-deficient haloorganics and Lewis bases in solution.[6] We also sought to take advantage of interactions that had been applied in solution-phase molecular recognition, but were comparatively underexploited in catalysis. The reversible covalent interactions between boronic acids and

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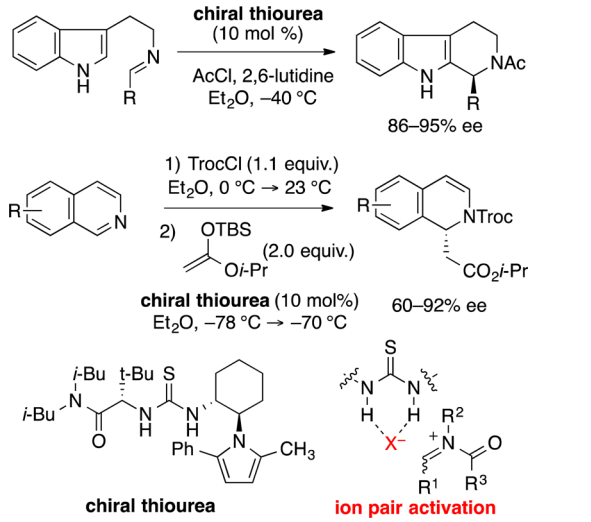
Scheme 1. Enantioselective, Thiourea-Catalyzed Reactions of *N*-Acyliminium Ions, and Proposed Ion Pair Activation Mode

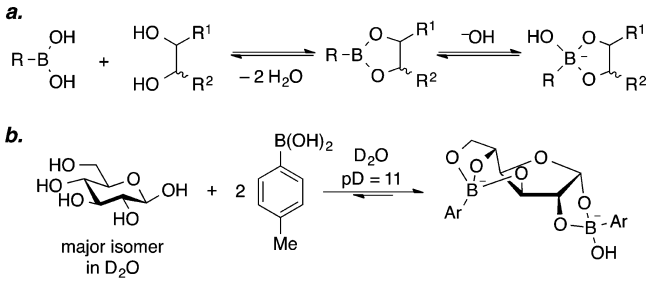


diols belong to this latter class: they have been studied for decades and underlie the most successful strategy for recognition of carbohydrates in aqueous solution, but their applications in catalysis had not been explored systematically. The present Account documents our efforts to harness the strength and selectivity of organoboron–diol and related interactions to solve problems related to chemo-, regio-, and stereoselectivity.

II. ORGANOBORON–DIOL INTERACTIONS IN MOLECULAR RECOGNITION

Organoboron compounds occupy a prominent position in host–guest chemistry due to their reversible interactions with compounds having two acidic X–H groups. The effect of boric acid on the specific rotation of sugar alcohols had been noted in the late 19th century,[7] and by the early 20th century it had been proposed that this phenomenon resulted from interactions involving diol moieties.[8] Boronic acids $RB(OH)_2$ also participate in such equilibria: in neutral or mildly basic aqueous solvent, condensation with a 1,2- or 1,3-diol is often accompanied by hydration, generating the corresponding tetracoordinate boronate (Scheme 2a). Related complexations take place between boronic acids and other bis-functionalized partners, including catechols, hydroxy acids, pyruvic acids, amino acids, and diamines.

Scheme 2. (a) Boronic Acid–Diol Complexation; (b) Stabilization of the α-Furanose Isomer of Glucose by an Arylboronic Acid in Water



Two features of boronic acid–diol interactions have contributed to their applications in molecular recognition, especially in the design of synthetic hosts for carbohydrates.[9] First, they generally display relatively high association constants, even in polar, protic solvents: depending on the ring size, the pK_a values of the boronic acid and diol, and the solution pH, both the formation of the boronic ester and the subsequent acid/base equilibrium can contribute favorably to the thermodynamics of complexation.[10] For example, the 2-fluoro-5-nitrophenylboronic acid–glucose association constant is 47 M^{-1} in pH 7.5 aqueous phosphate buffer:[10] achieving comparable affinities using noncovalent interactions such as hydrogen bonding has proved to be difficult, requiring multiple complementary functional groups in a preorganized arrangement. Second, selectivity between structurally similar diol partners can often be achieved: for example, *p*-tolylboronic acid interacts selectively with the α-furanose form of glucose in water (via complexation of the *O*-1,*O*-2-vicinal diol: Scheme 2b), despite the negligible concentration of this isomer in the absence of the organoboron compound.[11] The diversity of applications is impressive, ranging from the detection of specific oligosaccharide biomarkers, the design of glucose-responsive hydrogels for insulin delivery, and array-based sensing of structurally similar, glycosylated natural products.[12] In comparison, attempts to exploit these reversible condensations as the basis for catalyst–substrate complexation were limited when we initiated our research in 2007. The most well-developed applications of organoboron compounds in catalysis take advantage of their behavior as Lewis acids, with species capable of two-point binding (e.g., diols, hydroxy acids, or amino acid derivatives) often being employed as nontransferable ligands that modulate steric/electronic properties or impart chirality.[13] Viewed in this context, the idea that interaction with boron could trigger reactivity of a bound diolate or related species was somewhat speculative.

III. BORINIC ACID-CATALYZED DIRECT ALDOL REACTIONS OF PYRUVIC ACIDS

Our initial venture into organoboron catalysis stemmed from observations reported by Anslyn and co-workers in their account of the development of protocols for high-throughput enantiomeric excess determinations for α-hydroxy acids and diols.[14] Combinations of chiral, amine-functionalized boronic acid receptors and colorimetric or fluorescent indicators were employed to simultaneously determine concentration and enantiomeric excess, with potential applications in the combinatorial screening of chiral catalysts. Although the focus of this work was assay optimization and the development of an experimental protocol and mathematical modeling method, the authors noted that phenylpyruvic acid (a precursor to enantioenriched phenyllactic acid by asymmetric reduction) displayed a similar affinity for amine–boronate **1a** as did phenyllactic acid. Binding of the enol tautomer of the pyruvic acid (Scheme 3a) was invoked to account for this surprising result. In fact, a spectrometric assay for arylpyruvic acid keto–enol equilibration had been developed earlier, taking advantage of the interaction of the α-hydroxyacrylic acid tautomer with boric acid.[15]

The reversible generation of a boron enolate under mild conditions caught our attention as a potential starting point for a direct, catalytic aldol reaction (Scheme 3b).[16,17] Identifying catalysts for pyruvic acid aldol reactions was of interest to us given the existence of enzymes that promote such trans-

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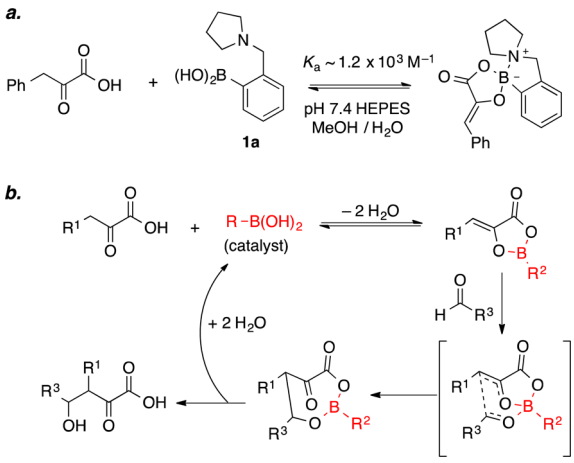
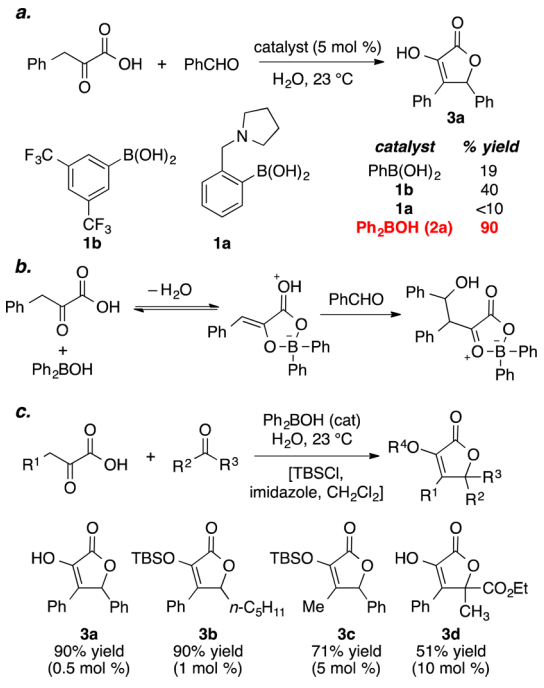
Scheme 3. (a) Anslyn and Co-Workers' Observation of Pyruvate Enol−Boronic Acid Complexation; (b) Envisioned Boronic Acid-Catalyzed Aldol Reaction of Pyruvic Acids



formations, and their utility in the synthesis of carbohydrate derivatives and mimetics. We envisioned that the tricoordinate complex generated by boronic acid/pyruvic acid condensation could react with an aldehyde through a "closed" transition state, as is typical for aldol reactions of boron enolates. In line with this proposal, we found that arylboronic acids accelerated the condensation of phenylboronic acid and benzaldehyde, generating isotetronic acid **3a** (Scheme 4a). Electron-deficient **1b** displayed higher catalytic activity than phenylboronic acid for this transformation, which proceeded most efficiently in aqueous suspension. Although this latter observation was not expected, it was apparently consistent with the "water tolerance" of boronic acid−pyruvate and related interactions.[14,15]

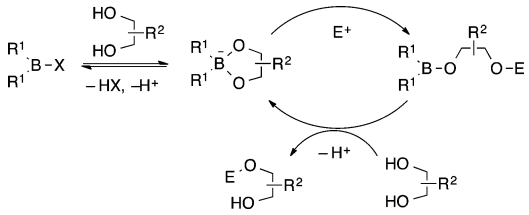
Scheme 4. (a) Activities of Organoboron Catalysts for Direct Aldol Reactions of Phenylpyruvic Acid; (b) Proposed Pathway for C−C Bond Formation Using Ph_2BOH; (c) Representative Isotetronic Acids Generated by Ph_2BOH-Catalyzed Direct Aldol Reactions



IV. ORGANOBORON-CATALYZED REGIOSELECTIVE MONOFUNCTIONALIZATION OF PYRANOSIDE DERIVATIVES

The reactivity that emerged from the study described above, namely, the use of a borinic acid to generate a tetracoordinate enolate from a substrate capable of two-point binding, differed from our intended boronic acid-catalyzed transformation, and suggested interesting opportunities for further exploration. Although applications of boronic acids and esters in catalysis had been studied in some depth, those of borinic acids were relatively uncommon.[17a,18] We sought to extend the reactivity of tetracoordinate borinate derivatives as catalytically generated nucleophiles to complexes derived from other substrate classes, with diol activation being of particular interest (Scheme 5). If

Scheme 5. Proposal for Borinic-Acid-Catalyzed Monofunctionalization of Diols



the selectivity of boronic acids for binding to particular diol motifs were to hold for borinic acids, and if one of the two alkoxy groups of the dioxaborolane intermediate were to react selectively with an electrophile (E^+), regioselective, catalytic transformations of hydroxylated substrates such as carbohydrates could result.[19] Catalysts able to influence regiocontrol in reactions of sugar derivatives have numerous potential applications: emerging methods for rapid oligosaccharide synthesis (e.g., one-pot glycosylation sequences and solid-phase synthesis) may create increased demand for selectively protected monosaccharide building blocks, and selective transformations of complex, glycosylated natural products

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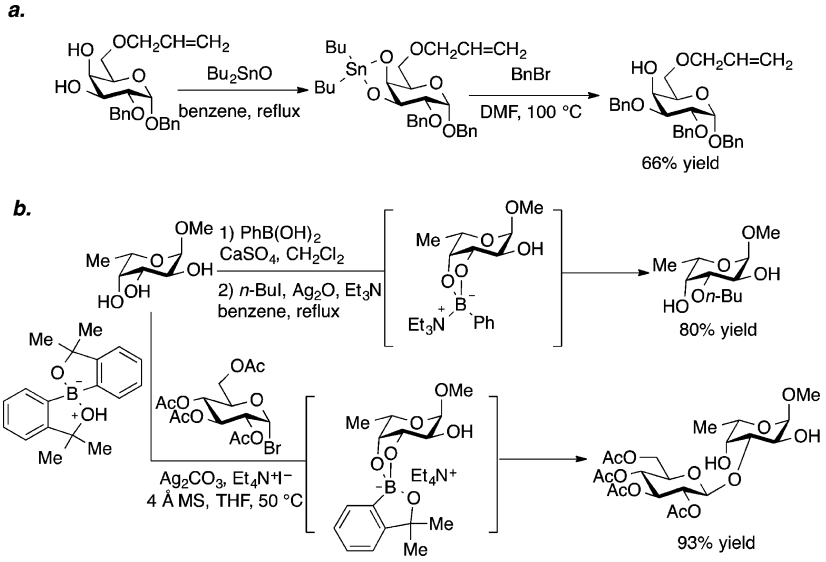
Scheme 6. Regioselective Transformations of Pyranosides Promoted by (a) Organotin and (b) Organoboron Reagents

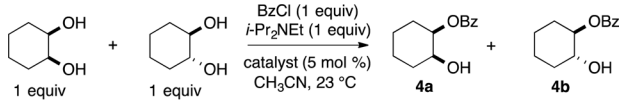


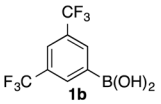
could be used to explore structure−activity relationships in medicinal chemistry or to develop new biological probes.

Two types of documented reactivity suggested that the reaction design shown in Scheme 4 was worth pursuing. First, carbohydrate-derived stannylene acetals had been employed in regioselective acylations, sulfonylations, alkylations, phosphorylations and glycosylations (Scheme 6a).[20] While the initially reported protocols required stoichiometric quantities of the diorganotin(IV) reagents, catalytic variants had been reported,[19d,21] and others emerged over the course of our studies.[22] Although the mechanisms of the stannylene acetal-based transformations may differ from the proposal shown in Scheme 5 − the ability of Sn(IV) complexes to adopt coordination numbers higher than four raises possibilities that are unlikely for the corresponding organoboron adducts, including pathways involving dimers or oligomers−we envisioned that the reactivity of the organoboron species might parallel that of the organotin complexes in some way. Second, the group of Aoyama had reported two transformations that exploited the nucleophilicity of tetracoordinate organoboron complexes to achieve selective pyranoside derivatizations.[23] Addition of triethylamine to the phenylboronates of methyl α-fucopyranoside and β-arabinopyranoside triggered *O*-alkylation at the 3-position, presumably through amine−boronate complexation (Scheme 6b). Selective Koenigs−Knorr-type glycosylation of pyranosides was also achieved, using boronic esters having a pendant coordinating alkoxide group. These results demonstrated that the behavior of organoboron complexes of carbohydrates could be switched from deactivation (i.e., protection of diols as boronic esters) to activation, by changing the coordination number from three to four. Whether a catalytic protocol could be developed based on this type of reactivity remained an important question.

We evaluated catalysts for their ability to selectively monoacylate *cis*-1,2-cyclohexanediol in the presence of its *trans* diastereomer (Scheme 7).[24] While DMAP and Me_2SnCl_2 were unselective, benzoylation of the *cis*-configured diol was observed using organoboron catalysts **1b** and **2a**. The activity of electron-deficient boronic acid **1b** as an acylation catalyst did not appear to be consistent with the behavior of boronic esters as protective groups for 1,2- and 1,3-diol groups. In light of our

Scheme 7. Competition Experiment for Evaluation of Acylation Catalysts



catalyst	% conversion	4a:4b
	30	1:1
Me_2SnCl_2	96	1:1
 **1b**	90	2:1
 **2b**	70	11:1

subsequent study on boronic acid/Lewis base cocatalysis for pyranoside silylation,[25] a pathway involving a tetracoordinate complex of the boronic ester with acetonitrile (the reaction solvent) is possible. In any case, it was borinic ester **2b** that provided highest *cis* selectivity, in apparent agreement with our design hypothesis.

Borinate **2b** proved to be a broadly useful catalyst for monofunctionalization of di- and triol substrates (Scheme 8). When galacto- or manno-configured pyranosides were employed, products of selective protection of the equatorial position of the *cis*-1,2-diol moiety were obtained from reactions with acyl chlorides, *p*-toluenesulfonyl chloride and activated alkylating agents (benzylic halides or chloromethyl ethers).[26] It should be noted that secondary hydroxyl groups not belonging to *cis*-1,2-diol motifs (e.g., those of glucopyranoside or xylopyranoside substrates) cannot be selectively functionalized using **2b**. Likewise, an unprotected diol group at C-4 and C-6 presents an alternative binding mode for the catalyst, and we have not found conditions that allow for monofunctionalization of substrates bearing both a *cis*-1,2-diol and this type of 1,3-diol group.

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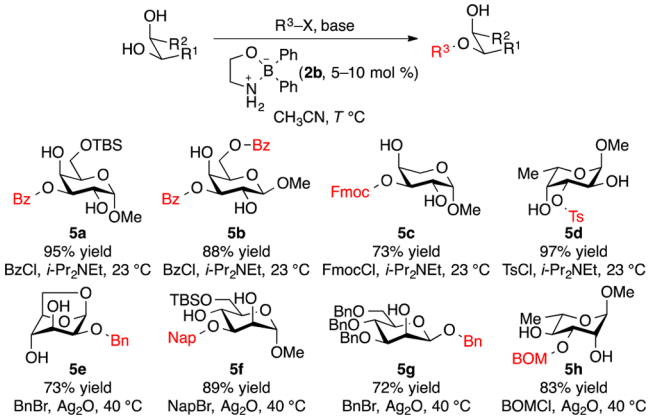
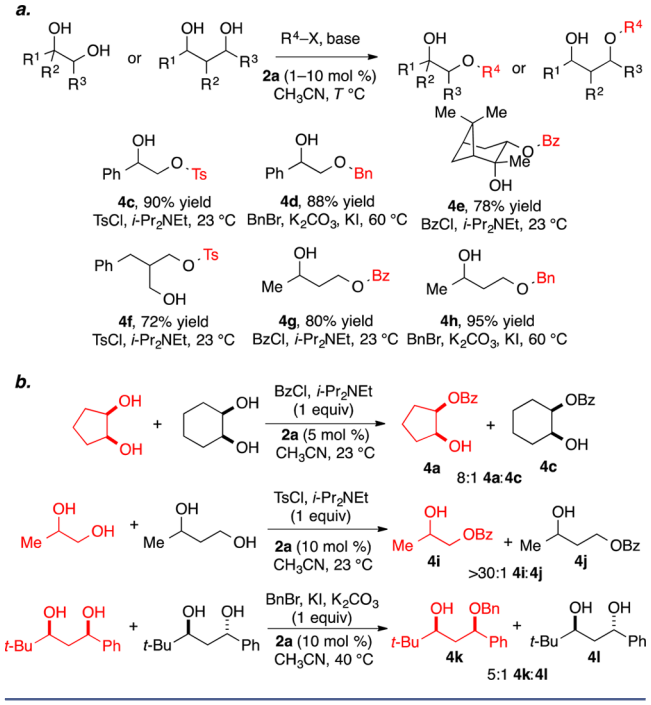
Scheme 8. Regioselective Acylation, Sulfonylation, and Alkylation of Pyranoside Substrates Using Catalyst 5a: Representative Examples



The utility of catalyst **2b** is not restricted to reactions of carbohydrate derivatives. Various 1,2- or 1,3-diol-bearing substrates can be monoprotected or -sulfonylated at the less sterically encumbered OH group (Scheme 9a). Competition

Scheme 9. Regioselective Acylation, Sulfonylation and Alkylation of Diols: (a) Representative Substrates; (b) Competition Experiments Illustrating Relative Reactivities of Diol Pairs



experiments (Scheme 9b) illustrate the ability of catalyst **2b** to exploit relatively subtle differences between diol motifs. In each case, the preferred substrate is the one predicted to form a more favorable tetracoordinate organoboron complex, based on reported association constants for boronic acid–diol interactions under basic conditions.

Our mechanistic hypothesis for diol activation by **2b** arose from studies of the sulfonylation of *cis*-1,2-cyclohexanediol. First-order kinetic dependence on the concentration of **2b** and TsCl, zero-order kinetics in *i*-Pr_2NEt, and saturation kinetics in the diol substrate were determined by ^{1}H NMR spectroscopy. This rate law is consistent with the cycle shown in Scheme 10a, with sulfonylation of the tetracoordinate borinate being turnover-limiting. Using ^{1}H NMR spectroscopy in CD_3CN with added *i*-Pr_2NEt, a Ph_2BOH–*cis*-cylohexanediol association constant of 70 M^{-1} was determined, consistent with the observed saturation kinetics in substrate. (We also studied Ph_2BOH–diol interactions in aqueous pH 7 phosphate buffer, and found notable differences in both the kinetics and thermodynamics of borinic versus boronic acid–diol complexation reactions.[27]) Borinic ester **2b**, a white, crystalline solid that displays improved stability toward air oxidation relative to Ph_2BOH, is a precatalyst according to this proposal. Rapid and irreversible *N*,*O*-bis-sulfonylation of the ethanolamine ligand (rather than displacement by diol substrate) triggers entry of **2b** into the catalytic cycle.

Substituted diarylborinic acid catalysts **2c** and **2d** were found to give rise to lower rates of diol sulfonylation than Ph_2BOH itself (Scheme 10b). The observation of decreased rates for both electron-withdrawing (σ_{meta} = +0.46 for CF_3) and electron-donating (σ_{para} = −0.12 for OCH_3) substituents was initially puzzling. In light of the kinetic data, we considered the influence of substitution on the rate of sulfonylation of the tetracoordinate borinic acid–diol adduct. A tetracoordinate borinate is likely a potent electron-donating group, and so it is possible that the methoxy substituent acts as an inductively electron-withdrawing (and thus deactivating) group in this context. This hypothesis was supported by trends in calculated Mulliken charges and electrostatic potential surfaces for the ethylene glycol esters of Ph_2BOH, **2c**, and **2d**.

The kinetics and substituent effect experiments shaped our thinking on how to tune the organoboron catalyst structure to improve activity (see below). However, they did not lead to a rationale for the selective functionalization of the equatorial OH group observed for pyranoside substrates. This selectivity pattern could reflect a steric effect, since equatorial sites having an axially positioned vicinal substituent are often the least hindered secondary OH groups in carbohydrate derivatives.[19d] However, DFT modeling of pyranoside-derived diphenylborinates showed significant distortion from the chair geometry, causing the two boron-bound oxygen atoms to be in more similar steric environments than in the unbound substrate. Although the calculations suggested a reduced steric differentiation between equatorial and axial positions upon borinate formation, they pointed toward enhanced electronic differences: both the calculated gas-phase proton affinities and Fukui indices (a metric for rationalizing regiochemical outcomes of reactions involving multifunctional substrates) were higher for the position that underwent functionalization, perhaps due to changes in orientations of C–O bond dipoles in the borinate adduct. Steric and electronic factors may both contribute to the observed regioselectivity, with their relative importance varying for different substrates.

In principle, an advantage of organoboron catalysts is the accessibility of structural variants, enabling fine-tuning of their properties. However, identifying borinic acids possessing improved catalytic activity for diol functionalization was a challenge. We reasoned that increasing the rate of the turnover-limiting functionalization of the tetracoordinate borinate demanded an electron-rich borinic acid, but our substituent effect studies suggested that potent electron-donating groups would be required to achieve a significant beneficial effect. The increased sensitivity of electron-rich borinic acids toward

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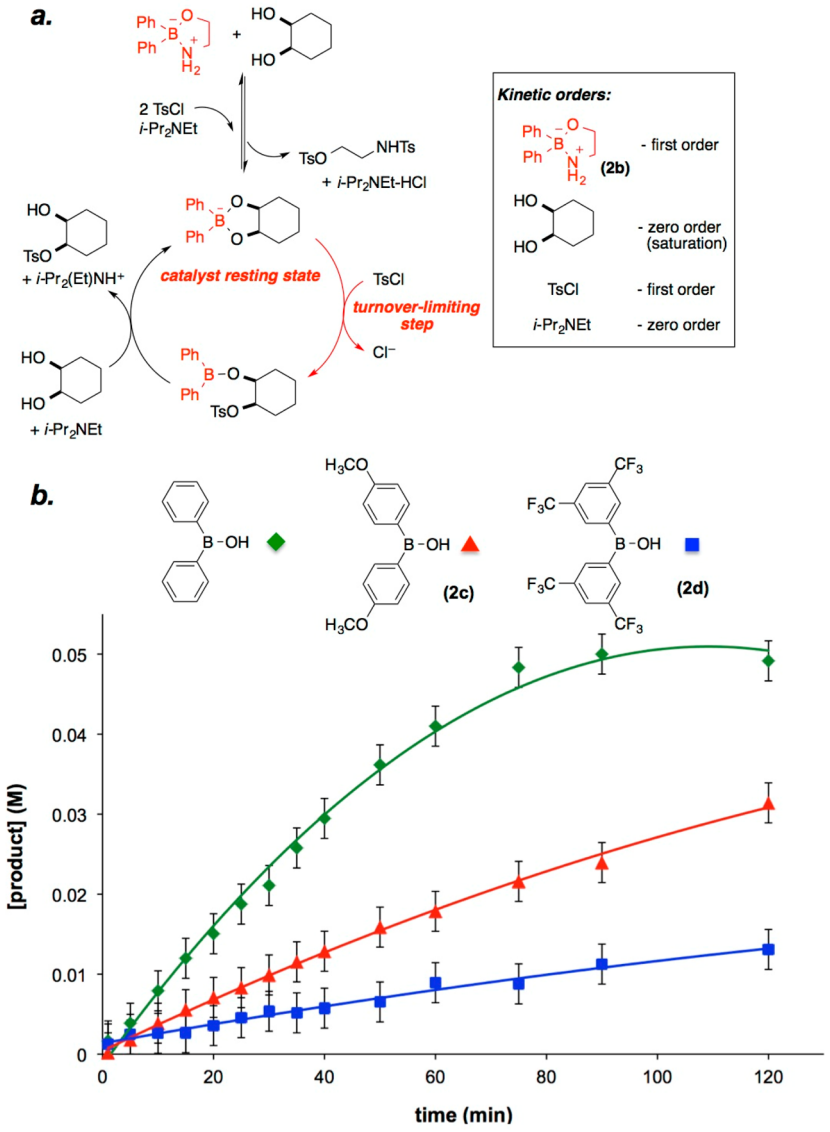
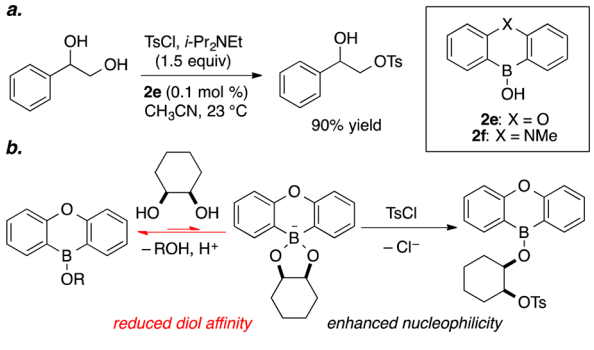
Scheme 10. (a) Proposed Catalytic Cycle for 2b-Catalyzed Sulfonylation of *cis*-1,2-Cyclohexanediol; (b) Relative Diol Sulfonylation Activities of Substituted Diarylborinic Acids



oxidation was a concern. Heteroboraanthracenes **2e** and **2f** provided an interesting solution to this set of problems (Scheme 11a).[28] Donation of electron density from the heteroatom to boron attenuates the Lewis acidity of these compounds: the **2e**–catechol association constant is at least 2 orders of magnitude lower than that of Ph_2BOH–catechol. Nonetheless, **2e** displayed higher activity than **2b** for sulfonylation of a representative 1,2-diol, and could be employed at loadings as low as 0.1 mol %. Apparently, the enhanced nucleophilicity of the heteroboraanthracene-derived borinate in the turnover-limiting step more than compensates for its reduced affinity for the diol substrate (Scheme 11b). In agreement with this hypothesis, sulfonylation of *cis*-cyclohexanediol catalyzed by **2e** displayed first-order kinetics in diol substrate, rather than the saturation kinetics found for **2b**. Another advantage of **2e** and **2f** is their improved stability toward oxidation, which permits storage for months in the solid state. The ethanolamine-derived byproducts that accompany the use of a borinate ester precatalyst may thus be avoided, and in certain instances, **2f** may be recovered from reaction mixtures after use as a catalyst.

Scheme 11. (a) Heteroboraanthracene-Derived Borinic Acids for Diol Activation; (b) Rationale for Enhanced Activity of Heteroboraanthracene Catalysts



As discussed above, the reactivity of Lewis base adducts of pyranoside-derived boronic esters described by Aoyama provided the blueprint for our borinic acid-catalyzed trans-

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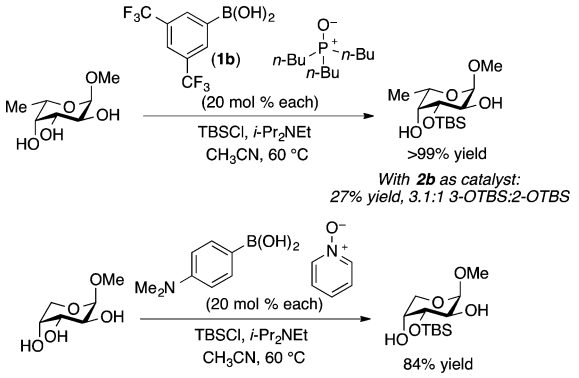
formations. The ability of borinic acids to generate tetracoordinate diol adducts in the absence of exogenous Lewis base, and their increased Lewis acidity relative to boronic acids, were our primary considerations in pursuing this class of catalysts. However, the possibility of activating diols with boronic acid/Lewis base combinations, employing both in catalytic amounts, also attracted our attention due to the availability and ease of handling of boronic acids, and the prospect of screening numerous Lewis base/boronic acid combinations. We have developed a protocol for selective *O*-silylation of pyranoside-derived triols based on this approach (Scheme 12).[25] Low reactivity and modest regiocontrol were

Scheme 12. Silylation of Pyranosides Using Boronic Acid/Lewis Base Cocatalysis



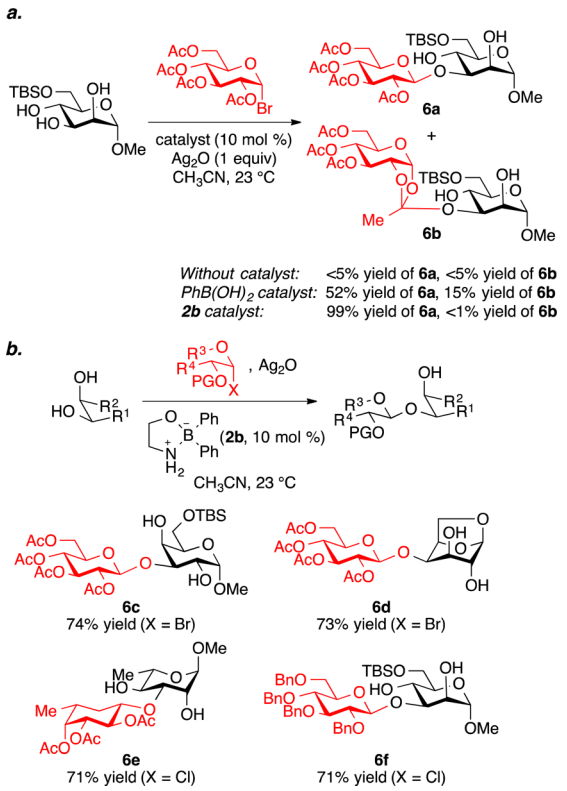
observed when **2b** was used as a catalyst for the reaction of methyl α-L-fucopyranoside with *tert*-butyldimethylsilyl chloride (TBSCl). We have not studied this behavior in detail, but the speculation of unfavorable steric interactions between the diarylborinate and this bulky electrophile motivated us to pursue boronic acid/Lewis base cocatalyst systems. Screening pairwise combinations of four boronic acids with seven Lewis bases revealed that boronic acid **1b**, in combination with *n*-Bu_3PO, provided the 3-*O*-silylated pyranoside in excellent yield. This protocol was applied to other carbohydrate-derived substrates, although in the case of methyl β-arabinopyranoside, highest yield was obtained using another catalyst combination (4-(dimethylamino)phenylboronic acid/pyridine-*N*-oxide).

V. ACTIVATION OF GLYCOSYL ACCEPTORS BY BORINIC ACID CATALYSTS

Of the various classes of electrophiles that could be evaluated for compatibility with borinic acid activation, glycosyl donors were of particular interest. Whereas a range of catalytic strategies had been applied to selective protection of carbohydrate derivatives (including phase-transfer, Lewis base, Brønsted base, Brønsted acid, Lewis acid and transition metal catalysis[19]), methods for regioselective glycosylation employing synthetic catalysts had not been reported. This dearth of synthetic catalysts stood in contrast to the impressive advances that had been achieved in the development of chemoenzymatic methods for regioselective glycosylation, and in their applications to oligosaccharide total synthesis and glycodiversification of natural products.[29] We sought to determine whether a synthetic catalyst could be developed to address challenges in glycosylation (reactivity, regioselectivity and/or stereoselectivity), and whether such catalysts would be complementary to the existing chemoenzymatic systems.

Regioselective glycosylations of pyranosides using stoichiometric quantities of organotin(IV) and organoboron promoters had been conducted under Koenigs–Knorr-type conditions, with a glycosyl halide donor activated by a silver(I) salt. We employed such donors for our initial evaluation of organoboron catalysts (Scheme 13a).[30] Under conditions that provided a low

Scheme 13. (a) Evaluation of Catalysts for the Synthesis of Disaccharide 6a; (b) Representative Products of Borinic-Acid-Catalyzed Glycosylation



yield of disaccharide **6a** without catalyst (hydrolysis of the glycosyl bromide predominating), borinate **2b** promoted a β-selective glycosylation at the 3-OH group of the mannopyranoside acceptor. Phenylboronic acid also promoted the glycosylation, possibly through a Lewis base-assisted pathway of the type shown in Scheme 12. However, orthester **6b**, resulting from anchimeric assistance by the acetoxy group at C-2, was also generated. The fact that both types of catalyst provided rate acceleration, but yielded different product distributions, hinted that acceptor nucleophilicity could be modulated by organoboron coordination.

Representative disaccharides accessed using borinic ester catalyst **2b** are shown in Scheme 13b. The pattern of regiocontrol and glycosyl acceptor scope for this transformation paralleled those of the borinic acid-catalyzed protections discussed previously. Glycosyl halides of *gluco* or *galacto* configuration were tolerated, with peracetylated ("disarmed") donors providing highest yields and regioselectivities. Perbenzylated ("armed") donors were also tolerated, although the less ionization-prone glycosyl chlorides were required to achieve useful yields. For both armed and disarmed donors, glycosides of 1,2-*trans* relative configuration were obtained from the corresponding 1,2-*cis*-configured glycosyl halide. While this outcome was not surprising in the case of donors bearing an

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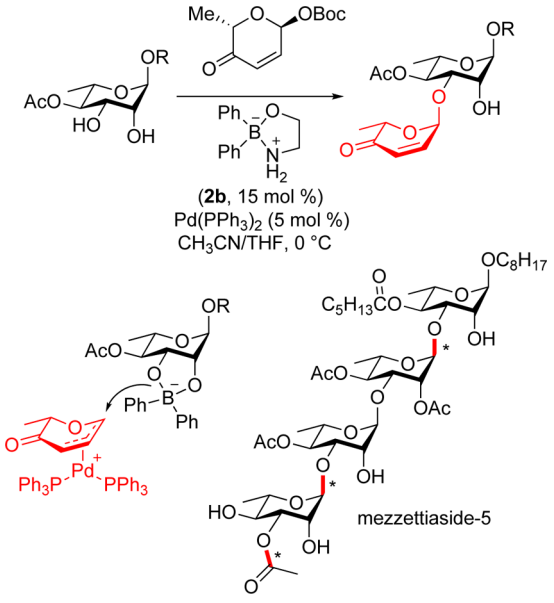
ester group at C-2, it was noteworthy that the same relative configuration was obtained using donors having a C-2 substituent incapable of neighboring group participation. A mechanistic rationale for these observations will be discussed below.

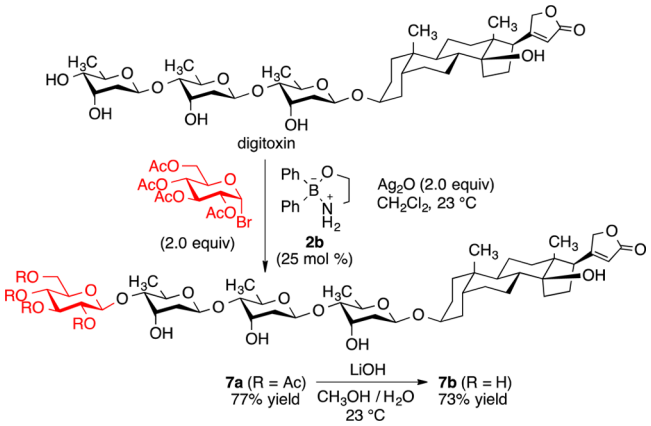
Ongoing research in our laboratories is aimed at employing catalyst-controlled glycosylation to facilitate oligosaccharide synthesis by reducing the number of protective group manipulations. The group of O'Doherty has also been active in this regard, having employed borinic acid catalysis in an efficient synthesis of the mezzettiaside natural products.[31] The key glycosylation steps in the syntheses of these acylated oligorhamnopyranosides combine borinic acid activation of the glycosyl acceptor with Pd(0)-based activation of 6-hydroxypyranone-derived donors, a strategy pioneered by O'Doherty. For example, the synthesis of mezzetiaside-5 was accomplished using two dual organoboron/palladium-catalyzed glycosylations, along with a borinic acid-catalyzed selective acylation of a tetraol (Scheme 14).

Scheme 14. Organoboron/Palladium-Catalyzed Regioselective Glycosylation by O'Doherty and Co-Workers: Proposed Activation Mode, and Structure of Mezzettiaside 5 (with Bonds Constructed by Borinic Acid Catalysis Highlighted)



The ability to regioselectively activate glycosyl acceptors also suggested opportunities to alter the glycosylation patterns of polyol natural products. Glycosylation is a common modification of hydroxylated secondary metabolites, and the identity and position of the appended carbohydrate moieties can significantly influence biological activity.[32] Given the interest in "glycorandomization" of natural products by metabolic engineering or chemoenzymatic synthesis,[29b] and considering the challenges posed by complex natural products as substrates for catalysis, we investigated borinic acid-catalyzed glycosylations of the cardiac glycoside digitoxin (Scheme 15).[33,34] Of the five hydroxyl groups of digitoxin, it was the equatorial 4″-OH group that underwent selective coupling with peracetylated glucopyranosyl bromide in the presence of Ag_2O and **2b**. Deacetylation completed the semisynthesis of purpurea glycoside A (desacetyl lanatoside A, **7b**), another secondary

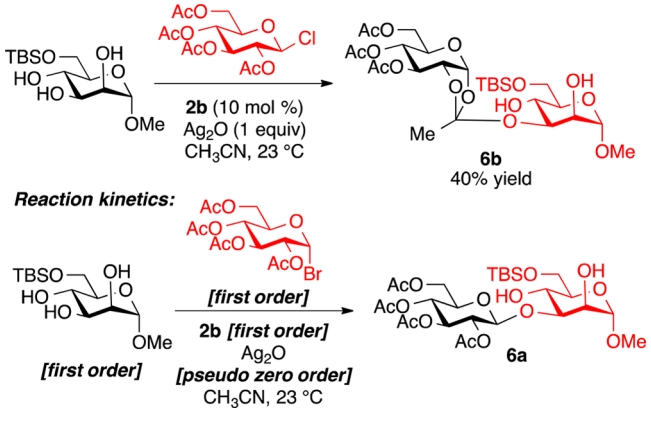
Scheme 15. Catalyst-Controlled Glycosylation of Digitoxin



metabolite of the foxglove *Digitalis purpurea*. 4″-*O*-Glycosylated product **7a** was not obtained in the absence of the catalyst, and an attempted glycosylation with the corresponding trichloroacetimidate (TMSOTf, CH_2Cl_2, −78 to 23 °C) resulted in cleavage of the sensitive *β*-2-deoxyglycosidic linkages of digitoxin and recovery of the aglycon, digitoxigenin. These observations reflect the significant rate acceleration that is obtained using **2b**, and the mild nature of the catalytic glycosylation conditions. Analogues bearing peracetylated *β*-D-galactosyl, *α*-D-arabinosyl, *β*-L-fucosyl, *β*-lactosyl, and *β*-cellobiosyl moieties at the 4″-position were accessed in 51−74% yields using **2b** as catalyst. We hope to extend this type of reactivity to other classes of natural products such as macrolide antibiotics.

We have studied the mechanism of the organoboron-catalyzed glycosylation reaction, focusing on the effect of the catalyst on the nature of the transition state (S_N1-like versus S_N2-like pathway). This type of insight is not easily obtained, and only a handful of nonenzymatic glycosylation reactions have been studied in sufficient depth to enable a detailed description of the displacement step.[35] Although our mechanistic data are somewhat limited, they are consistent with the hypothesis that organoboron activation of the glycosyl acceptor promotes an S_N2-like reaction of the glycosyl halide. When a *β*-configured glycosyl chloride was employed instead of the *α*-isomer under the catalytic conditions, orthoester **6b** was obtained, rather than disaccharide **6a** (Scheme 16). This result

Scheme 16. Evidence Supporting an S_N2-Type Pathway for Organoboron-Catalyzed Glycosylation



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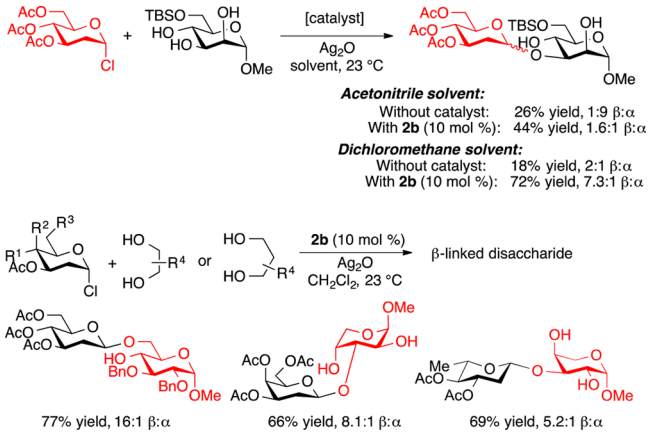
indicated that the disaccharide was not generated by Lewis-acid-promoted rearrangement of an initially formed orthoester, and suggested that a "free" oxacarbenium ion was not a likely intermediate en route to **6a**. The fact that perbenzylated α-glycosyl chlorides reacted with inversion of stereochemistry to give β-configured products (see above) provided additional, indirect evidence for an S_N2-type pathway. Finally, the first-order kinetics in glycosyl donor, glycosyl acceptor, and catalyst inferred from initial rate measurements also appeared to be consistent with this hypothesis.

The idea that borinate-activated acceptors could show enhanced S_N2-type reactivity motivated us to investigate glycosylations in which the organoboron catalyst could influence both regio- and stereoselectivity. β-Selective couplings of 2-deoxyglycosyl halides were chosen as a target: obtaining this stereochemical outcome is difficult due to the lack of a tunable protected hydroxyl group at C-2, and these linkages are prevalent in biologically active natural products. Several of the existing strategies for generating β-2-deoxyglycosides were premised on displacement of an α-configured leaving group by inversion of configuration, with suppression of the ionization of these "armed" 2-deoxy donors being the key challenge.[36] This had generally been achieved by tuning parameters related to the glycosyl donor (leaving group, activation method, and protective groups), and so using a catalyst to accelerate an S_N2-like pathway by acceptor activation interested us as a potential alternative approach. Upon employing a peracetylated 2-deoxyglycosyl chloride (which could be obtained as the α-anomer from either the glycosyl acetate or the free hemiacetal) under the "standard" conditions described above, a promising effect of the catalyst on the stereochemical outcome was evident (Scheme 17).[37] Replacing acetonitrile with dichloromethane, a less polar and less Lewis basic solvent, provided synthetically useful β-selectivity under operationally simple conditions. The optimized protocol facilitated β-selective couplings of a variety of 2-deoxy and 2,6-dideoxy donors with acceptors having free 1,3- or *cis*-1,2-diol groups, as exemplified by the products shown in Scheme 17. Consistent with the proposal described above, changes in glycosyl donor structure that would favor ionization (e.g., replacement of ester protective groups with ethers) resulted in diminished β-selectivity. Other challenging types of glycosidic linkages, including β-mannosides and β-rhamnosides, can potentially be generated by promoting an S_N2-type pathway, and so further extensions of the scope of the organoboron-catalyzed glycosylation are worthy of exploration.

Scheme 17. Organboron-Catalyzed Regio- and Stereoselective Formation of β-2-Deoxyglycosidic Linkages



VI. CONCLUSIONS

The simple idea that compounds useful as receptors for diols and related analytes might also have applications in catalysis has provided opportunities to explore the reactivity of organoboron complexes, particularly those of carbohydrate derivatives. The requirements for efficient binding and catalysis are not identical, and so our initial proposals of boronic acid catalysis quickly expanded to include the less familiar and less well-explored borinic acids. In our view, these remain an underexploited class of boron-based compounds, and room exists to further explore their synthesis and applications as receptors or catalysts. Nonetheless, the parent diphenylborinic acid is a versatile catalyst, promoting aldol reactions of pyruvic acids as well as regioselective acylations, sulfonylations, and etherifications of pyranosides, and influencing both regio- and stereocontrol in glycosylation reactions.

Catalysis is poised to take on several current challenges in carbohydrate chemistry and glycobiology, including automated oligosaccharide synthesis, the development of sustainable and scalable methods for preparation of carbohydrate derivatives, and the exploration of structure–activity relationships for complex, glycosylated natural products. The diversity of approaches toward catalytic activation of carbohydrate derivatives that have emerged over the past decade, and the increased willingness of catalysis research groups to venture into carbohydrate chemistry, augur well in this regard. Considering organoboron catalysis specifically, a number of hurdles remain if this chemistry is to have maximal impact on the problems listed above. Variants of the organoboron-catalyzed glycosylation employing donors other than halides could broaden the scope and applications of this method. The mild, heterogeneous conditions for glycosyl halide activation appear to be somewhat unique, as our efforts to employ other classes of glycosyl donors (e.g., thioglycosides and trichloroacetimidates) have been unsuccessful, perhaps due to the presence of acids or oxidants as promoters. Based on our mechanistic studies, donors that react through S_N2-type pathways may be promising candidates. At present, the borinic acid-catalyzed method often enhances existing differences in the reactivity of pyranoside-derived hydroxyl groups. Catalysts able to overcome these differences to provide complementary regiochemical outcomes would be valuable. From this perspective, as well as for applications in enantioselective desymmetrizations or kinetic resolutions, chiral organoboron catalysts are an interesting target. Finally, the substrates that have been efficiently functionalized with borinic acid catalysis are of low complexity relative to those that can be glycosylated selectively using enzymes: for instance, the monosialylation of a hexasaccharide bearing 17 free hydroxyl groups has been achieved, exploiting the ability of the sialyltransferase to recognize *N*-acetyllactosamine acceptors.[38] More complex, highly functionalized organoboron catalysts will likely be needed to target mono- or disaccharide motifs in an oligosaccharide substrate, rather than diol motifs in a monosaccharide. However, the documented examples of selective mono- and oligosaccharide recognition using tailored organoboron compounds suggest that this goal may be attainable. Achieving it would not only provide opportunities in synthesis, but might also enable analysis or tagging of such

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components in heterogeneous samples. More broadly, the catalyst-controlled modification of complex natural products is a problem that appears to be particularly amenable to approaches involving a molecular recognition component. New insights and concepts from supramolecular chemistry may continue to drive progress toward solving this fascinating challenge in reactivity and catalysis.

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Notes

The author declares no competing financial interest.

Biography

Mark Taylor was born in Oxford, England. He obtained a B.Sc. degree from the University of Toronto in 2000, and received his Ph.D. degree from Harvard University in 2005. His doctoral research was carried out under the supervision of Prof. Eric Jacobsen. After postdoctoral research with Prof. Timothy Swager at MIT, Mark began his independent career at the University of Toronto in 2007. He is currently Associate Professor of Chemistry and Canada Research Chair in Molecular Recognition and Catalysis.

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REFERENCES

(1) Kirby, A. J. Enzyme Mechanisms, Models, and Mimics. *Angew. Chem., Int. Ed.* **1996**, *35*, 707−724.
(2) Taylor, M. S.; Jacobsen, E. N. Enantioselective Catalysis by Chiral Hydrogen Bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543.
(3) (a) Taylor, M. S.; Jacobsen, E. N. Highly Enantioselective Catalytic Acyl-Pictet−Spengler Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. Enantioselective Thiourea-Catalyzed Acyl-Mannich Reactions of Isoquinolines. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700−6704.
(4) Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561.
(5) Beer, P. D.; Gale, P. A. Anion Recognition and Sensing: The State of the Art and Future Perspectives. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516.
(6) (a) Sarwar, M. G.; Dragisic, B.; Salsberg, L. J.; Gouliaras, C.; Taylor, M. S. Thermodynamics of Halogen Bonding in Solution: Substituent, Structural and Solvent Effects. *J. Am. Chem. Soc.* **2010**, *132*, 1646−1653. (b) Sarwar, M. G.; Dragisic, B.; Sagoo, S.; Taylor, M. S. A Tridentate Halogen-Bonding Receptor for Tight Binding of Halide Anions. *Angew. Chem., Int. Ed.* **2010**, *49*, 1674−1677.
(7) Fischer, E. Synthesen in de Zuckergruppe II. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3189−3232.
(8) Böeseken, J. Über die Lagerung der Hydroxyl-Gruppen von Polyoxy-Verbindungen im Raum. Die Konfiguration der gesättigten Glykole und der α- und β-Glykose. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 2612−2628.
(9) Nishiyabu, R.; Kubo, Y.; James, T. D.; Fossey, J. S. Boronic Acid Building Blocks: Tools for Sensing and Separation. *Chem. Commun.* **2011**, *47*, 1106−1123.
(10) Yan, J.; Springsteen, G.; Deeter, S.; Wang, B. The Relationship Among pK_a, pH, and Binding Constants in the Interactions Between Boronic Acids and Diols—It is Not as Simple as it Appears. *Tetrahedron* **2004**, *60*, 11205−11209.
(11) Norrild, J. C.; Eggert, H. Evidence for Mono- and Bisdentate Boronate Complexes of Glucose in the Furanose Form. Application of $^1J_{C-C}$ Coupling Constants as a Structural Probe. *J. Am. Chem. Soc.* **1995**, *117*, 1479−1484.
(12) McClary, C. A.; Taylor, M. S. Applications of Organoboron Compounds in Carbohydrate Chemistry and Glycobiology: Analysis, Separation, Protection, and Activation. *Carbohydr. Res.* **2013**, *1381*, 112−122.
(13) Ishihara, K. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2001; Vol. *1*, pp 89−133, 135−190.
(14) Zhu, L.; Zhong, Z.; Anslyn, E. V. Guidelines in Implementing Enantioselective Indicator-Displacement Assays for α-Hydroxycarboxylates and Diols. *J. Am. Chem. Soc.* **2005**, *127*, 4260−4269.
(15) Knox, W. E.; Pitt, B. M. Enzymic Catalysis of the Keto−Enol Tautomerization of Phenylpyruvic Acids. *J. Biol. Chem.* **1957**, *225*, 675−688.
(16) Lee, D.; Newman, S. G.; Taylor, M. S. Boron-Catalyzed Direct Aldol Reactions of Pyruvic Acids. *Org. Lett.* **2009**, *11*, 5486−5489.
(17) (a) Mori, Y.; Manabe, K.; Kobayashi, S. Catalytic Use of a Boron Source for Boron Enolate Mediated Stereoselective Aldol Reactions in Water. *Angew. Chem., Int. Ed.* **2001**, *40*, 2816−2818. (b) Aelvoet, K.; Batsanov, A. S.; Blatch, A. J.; Grosjean, C.; Patrick, L. G. F.; Smethurst, C. A.; Whiting, A. A Catalytic Aldol Reaction and Condensation through in Situ Boron "Ate" Complex Generation in Water. *Angew. Chem., Int. Ed.* **2008**, *47*, 768−770.
(18) Dimitrijević, E.; Taylor, M. S. Organoboron Acids and Their Derivatives as Catalysts for Organic Synthesis. *ACS Catal.* **2013**, *3*, 945−962.
(19) (a) Sculimbrene, B. R.; Miller, S. J. Discovery of a Catalytic Asymmetric Phosphorylation through Selection of a Minimal Kinase Mimic: A Concise Total Synthesis of D-myo-Inositol-1-Phosphate. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126. (b) Hu, G.; Vasella, A. Regioselective Benzoylation of 6-*O*-Protected and 4,6-*O*-Diprotected Hexopyranosides as Promoted by Chiral and Achiral Ditertiary 1,2-Diamines. *Helv. Chim. Acta* **2003**, *86*, 4369−4391. (c) Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. A Catalytic One-Step Process for the Chemo- and Regioselective Acylation of Monosaccharides. *J. Am. Chem. Soc.* **2007**, *129*, 12890−12895. (d) Lee, D.; Taylor, M. S. Catalyst-Controlled Regioselective Reactions of Carbohydrate Derivatives. *Synthesis* **2012**, *44*, 3421−3431.
(20) David, S.; Hanessian, S. Regioselective Manipulation of Hydroxyl Groups via Organotin Derivatives. *Tetrahedron* **1985**, *41*, 643−663.
(21) Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matusumura, Y.; Moriyama, N.; Onomura, O. Regioselective Protection of Sugars Catalyzed by Dimethyltin Dichloride. *Org. Lett.* **2008**, *10*, 5075−5077.
(22) Muramatsu, W.; Yoshimatsu, H. Regio- and Stereochemical Controlled Koenigs−Knorr Type Monoglycosylation of Secondary Hydroxy Groups in Carbohydrates Utilizing the High Site Recognition Ability of Organotin Catalysts. *Adv. Synth. Catal.* **2013**, *355*, 2518−2524.
(23) (a) Oshima, K.; Kitazono, E.-i.; Aoyama, Y. Complexation-Induced Activation of Sugar OH Groups. Regioselective Alkylation of Methyl Fucopyranoside via Cyclic Phenylboronate in the Presence of Amine. *Tetrahedron Lett.* **1997**, *38*, 5001−5004. (b) Oshima, K.; Aoyama, Y. Regiospecific Glycosidation of Unprotected Sugars via Arylboronic Activation. *J. Am. Chem. Soc.* **1999**, *121*, 2315−2316.
(24) Lee, D.; Taylor, M. S. Borinic Acid-Catalyzed Regioselective Acylation of Carbohydrate Derivatives. *J. Am. Chem. Soc.* **2011**, *133*, 3724−3727.
(25) Lee, D.; Taylor, M. S. Regioselective Silylation of Pyranosides Using a Boronic Acid/Lewis Base Co-catalyst System. *Org. Biomol. Chem.* **2013**, *11*, 5409−5412.

(26) (a) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. Regioselective, Borinic Acid-Catalyzed Monoacylation, Sulfonylation and Alkylation of Diols and Carbohydrates: Expansion of Substrate Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2012**, *134*, 8260−8267. (b) Chan, L.; Taylor, M. S. Regioselective Alkylation of Carbohydrate Derivatives Catalyzed by a Diarylborinic Acid Derivative. *Org. Lett.* **2011**, *13*, 3090−3093.
(27) Chudzinski, M. G.; Chi, Y.; Taylor, M. S. Borinic Acids: A Neglected Class of Organoboron Compounds for Recognition of Diols in Aqueous Solution. *Aust. J. Chem.* **2011**, *64*, 1466−1469.
(28) Dimitrijević, E.; Taylor, M. S. 9-Hetero-10-boraanthracene-derived Borinic Acid Catalysts for Regioselective Activation of Polyols. *Chem. Sci.* **2013**, *4*, 3298−3303.
(29) (a) Hancock, S. M.; Vaughan, M. D.; Withers, S. G. Engineering of Glycosidases and Glycosyltransferases. *Curr. Opin. Chem. Biol.* **2006**, *10*, 509−519. (b) Gantt, R. W.; Peltier-Pain, P.; Thorson, J. S. Enzymatic Methods for Glyco(diversification/randomization) of Drugs and Small Molecules. *Nat. Prod. Rep.* **2011**, *28*, 1811−1853.
(30) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. Regioselective Activation of Glycosyl Acceptors by a Diarylborinic Acid-Derived Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 13926−13929.
(31) Bajaj, S. O.; Sharif, E. U.; Akhmedov, N. G.; O'Doherty, G. A. De Novo Asymmetric Synthesis of the Mezzettiaside Family of Natural Products via the Iterative Use of a Dual B-/Pd-Catalyzed Glycosylation. *Chem. Sci.* **2014**, *5*, 2230−2234.
(32) Thorson, J. S.; Vogt, T. Glycosylated Natural Products. In *Carbohydrate-based Drug Discovery*: Wong, C.-H., Ed.; Wiley-VCH: Weinheim, 2003; pp 685−711.
(33) Beale, T. M.; Taylor, M. S. Synthesis of Cardiac Glycoside Analogs by Catalyst-Controlled, Regioselective Glycosylation of Digitoxin. *Org. Lett.* **2013**, *15*, 1358−1361.
(34) Yoshida, K.; Furuta, T.; Kawabata, T. Perfectly Regioselective Acylation of a Cardiac Glycoside, Digitoxin, via Catalytic Amplification of the Intrinsic Reactivity. *Tetrahedron Lett.* **2010**, *51*, 4783−4918.
(35) (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. Continuum of Mechanisms for Nucleophilic Substitutions of Cyclic Acetals. *Org. Lett.* **2008**, *10*, 4907−4910. (b) Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144−1153. (c) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. E.; Crich, D. Dissecting the Mechanisms of a Class of Chemical Glycosylation Using Primary ^{13}C Kinetic Isotope Effects. *Nat. Chem.* **2012**, *4*, 663−667. (d) Chan, J.; Sannikova, N.; Tang, A.; Bennet, A. J. Transition-State Structure for the Quintessential S_N2 Reaction of a Carbohydrate: Reaction of α-Glucopyranosyl Fluoride with Azide Ion in Water. *J. Am. Chem. Soc.* **2014**, *136*, 12225−12228.
(36) Hou, D.; Lowary, T. L. Recent Advances in the Synthesis of 2-Deoxy-glycosides. *Carbohydr. Res.* **2009**, *344*, 1911−1940.
(37) Beale, T. M.; Moon, P. J.; Taylor, M. S. Organoboron-catalyzed Regio- and Stereoselective Formation of β-2-Deoxyglycosidic Linkages. *Org. Lett.* **2014**, *16*, 3604−3607.
(38) Hanashima, S.; Manabe, S.; Ito, Y. Divergent Synthesis of Sialylated Glycan Chains: Combined Use of Polymer Support, Resin Capture−Release, and Chemoenzymatic Strategies. *Angew. Chem., Int. Ed.* **2005**, *44*, 4218−4224.