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Regioselective, Borinic Acid-Catalyzed Monoacylation, Sulfonylation and Alkylation of Diols and Carbohydrates: Expansion of Substrate Scope and Mechanistic Studies

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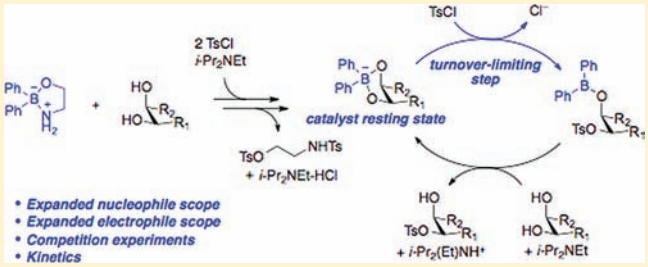
Supporting Information

ABSTRACT: Synthetic and mechanistic aspects of the diarylborinic acid-catalyzed regioselective monofunctionalization of 1,2- and 1,3-diols are presented. Diarylborinic acid catalysis is shown to be an efficient and general method for monotosylation of pyranoside derivatives bearing three secondary hydroxyl groups (7 examples, 88% average yield). In addition, the scope of the selective acylation, sulfonylation, and alkylation is extended to 1,2- and 1,3-diols not derived from carbohydrates (28 examples); the efficiency, generality, and operational simplicity of this method are competitive with those of state-of-the-art protocols including the broadly applied organotin-catalyzed or -mediated reactions. Mechanistic details of the organoboron-catalyzed processes are explored using competition experiments, kinetics, and catalyst structure−activity relationships. These experiments are consistent with a mechanism in which a tetracoordinate borinate complex reacts with the electrophilic species in the turnover-limiting step of the catalytic cycle.



INTRODUCTION

The selective manipulation of hydroxyl (OH) groups in di- and polyols is a frequently encountered problem in organic synthesis, in contexts ranging from reactions of simple hydroxylated feedstocks to the preparation of complex, highly functionalized natural products. This problem is of central importance in carbohydrate chemistry, where regioselectivity is the major obstacle to the preparation of novel medicinal agents or probes of biological function from readily available monosaccharide derivatives. Many protocols for selective protection of hydroxyl groups have been developed,[1] but procedures that display high levels of substrate generality (especially in the context of more complex substrates such as carbohydrates), as well as step and atom economy, remain an unmet need. Catalysis offers considerable promise in this regard, and several examples of catalyst-controlled regio- or stereoselective transformations of polyols, including carbohydrates, have been disclosed.[2−7]

We recently described a new mode of organoboron catalysis in which a diarylborinic acid derivative mediates the acylation,[8] alkylation,[9] and glycosylation[10] of a wide range of carbohydrate derivatives, with high levels of regioselectivity for the equatorial OH group of *cis*-1,2-diol pairs.[11] The regiochemical outcome was interpreted in terms of a mechanism involving selective complexation of the *cis*-vicinal diol pairs generating tetracoordinate borinate complexes that display enhanced nucleophilicity at oxygen.[12] This proposed catalyst−substrate interaction is related to the reversible, covalent bonding between boronic acids and diols that has been studied extensively in molecular recognition and chemical sensing of carbohydrates.[13,14] It also draws on previous work by Aoyama and co-workers in which stoichiometric quantities of organoboron reagent were used to activate carbohydrate derivatives toward regioselective alkylation and glycosylation through the formation of putative tetracoordinate boronate complexes.[15] The broad scope of these processes, the low toxicity and ease of handling of the borinic acid-derived precatalyst, and the mild reaction conditions employed are features that compare favorably with those of existing methods for regioselective carbohydrate protection. The regioselective glycosyl acceptor activation represents the first example of such a process using a synthetic (nonenzyme) catalyst and may offer new prospects for the efficient preparation of oligosaccharide derivatives.

Herein, we report expansions of the scope of the borinic acid-catalyzed diol activation developed in our laboratory including applications of this method to noncarbohydrate-derived 1,2- and 1,3-diols, and the development of a regioselective sulfonylation variant that is applicable to both carbohydrate derivatives and simpler substrates. We also describe competition experiments, kinetics studies, and catalyst structure−activity relationships that shed light on the mechanism of these transformations.

RESULTS AND DISCUSSION

Regioselective Sulfonylation of Carbohydrate Derivatives. Sulfonylation of carbohydrates is of interest in light of

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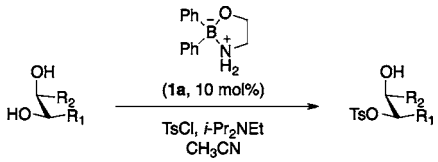
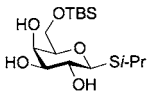
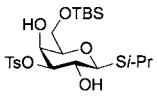
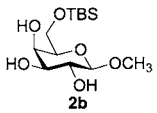
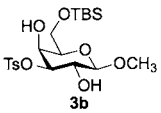
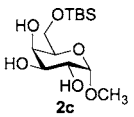
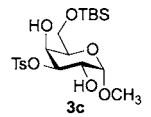
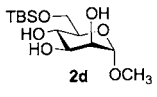
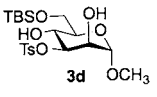
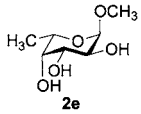
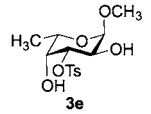
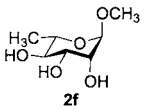
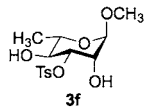
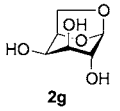
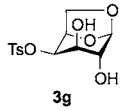
the utility of arenesulfonate esters as protective groups,[1b] as well as the potential for carrying out nucleophilic displacement reactions of such compounds.[16] Regioselective sulfonylation of sugar derivatives can be accomplished by two-step procedures involving stoichiometric generation of stannylene acetals, followed by electrophilic attack by a sulfonylating agent, typically *p*-toluenesulfonyl chloride (TsCl).[17] The groups of Martinelli,[18] Burke,[19] and Onomura[4b] developed regioselective methods for sulfonylation of di- and polyols using *catalytic* Bu_2SnO or Me_2SnCl_2, thus reducing the amount of toxic, lipophilic Sn(IV) waste generated. The fluorous dialkyltin catalyst of Curran and co-workers represents another important development from the latter perspective.[20]

Given the utility of borinic ester **1a** as a precatalyst for regioselective reactions of carbohydrate derivatives with acyl, alkyl, and glycosyl halides, and, considering the ease of handling and favorable safety profile of this organoboron derivative, we have studied its application in regioselective sulfonylation reactions. The results (Table 1) indicate that **1a** promotes selective monotosylation of *cis*-vicinal diol moieties, with the equatorial O3 group undergoing selective tosylation in

Table 1. Borinic Acid-Catalyzed Monotosylation of Carbohydrate Derivatives[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **2a**	 **3a**	90
2	 **2b**	 **3b**	99
3	 **2c**	 **3c**	83
4	 **2d**	 **3d**	85
5	 **2e**	 **3e**	97
6	 **2f**	 **3f**	77
7	 **2g**	 **3g**	83

[a]Reaction conditions: substrate (1.0 mmol), catalyst **1a** (10 mol %), TsCl (1.5 mmol), *i*-Pr_2NEt (1.5 mmol), CH_3CN (5 mL), 23 °C. See the Supporting Information. [b]Isolated yield.

pyranoside derivatives of galactose (**2a**, **2b**, **2c**), mannose (**2d**), fucose (**2e**), and rhamnose (**2f**). A thioglycoside functional group is tolerated by this catalyst system (**2a**), as is variation of the stereochemistry of the anomeric substituent (**2b** vs **2c**). Using 1,6-anhydrogalactopyranose (**2g**) resulted in sulfonylation at O4 providing a switch in selectivity from the unbridged galactopyranoside. These regiochemical outcomes are consistent with our previous results using catalyst **1a**; computational studies suggest that electronic effects contribute to differences in nucleophilicity between the two boron-bound oxygen atoms in a tetracoordinate borinate complex.[8,9] However, given that the electrophile is delivered to the more accessible equatorial position, the possibility of steric effects on the regioselectivity of these transformations cannot be discounted.[21] Extensions of this method to diols not derived from carbohydrates reveal several instances in which regioselectivity appears to be under steric control (below). In comparison to previously reported organotin-catalyzed monotosylations of carbohydrate derivatives, the borinic acid-catalyzed protocol displays a broad substrate scope and is notable for its high selectivity for functionalization of *cis*-diol motifs.

Monofunctionalization of Non-Carbohydrate-Derived Diols. Whereas regioselective reactions of carbohydrate derivatives are of particular interest (given both the fundamental challenges involved and the utility of the products in oligosaccharide synthesis), the monoprotection of simpler diol substrates is also an important problem. We have investigated the extension of the borinic acid-catalyzed protocols to a range of acyclic and cyclic 1,2- and 1,3-diols, and have found that they are useful for monoprotection of such substrates. The results are described in detail below.

Acylation and Sulfonylation. Diverse methods for monoacylation of 1,2-diols have been developed: systems that deliver high selectivity for mono- over bis-functionalized products (especially when a sterically unhindered acylating agent is employed), or that enable useful levels of regiocontrol for substrates lacking a strong steric bias for one of the two OH groups, are of particular interest. Successful approaches include the use of solid-supported substrates or reagents,[22] ring-opening of cyclic acetals and related species,[23] and enzymatic,[24] nucleophilic, or Lewis acid catalysis[4a,25,26] including enantioselective variants.[27] In contrast, fewer methods for monosulfonylation of 1,2-diols have been developed, despite the utility of this transformation for the preparation of enantioenriched epoxides. The organotin-mediated and -catalyzed protocols described above represent the state-of-the-art methods; Ag_2O-promoted[28] and montmorillonite-catalyzed[29] monosulfonylations, as well as enantioselective variants with Lewis acid[30] and Lewis base catalysts,[31] have also been developed.

Using diarylborinic acid derivative **1a**, various 1,2-diols were monoacylated and -tosylated efficiently (Table 2). The selectivity for mono- over bis-functionalization was high: for example, the reaction of ethylene glycol with 1.5 equiv of benzoyl chloride generated 2-hydroxyethyl benzoate in 84% yield (entry 1). For diols containing both primary and secondary hydroxyl groups, the primary OH was selectively functionalized over the secondary position (**4b**, **4c**, **4k**). Cycloalkanediols of various ring sizes were selectively monofunctionalized with high yields (**4d**, **4e**, **4f**).[8] Sterically hindered (−)-pinanediol was monotosylated at the secondary over the tertiary OH group (**4i**). In addition to vicinal diols, 1,3-diols **4j** and **4k** were also activated by precatalyst **1a**.

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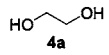
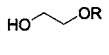
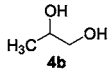
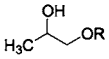
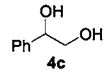
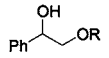
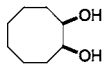
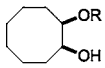
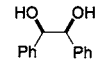
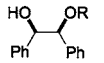
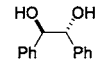
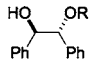
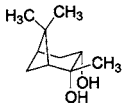
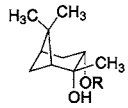
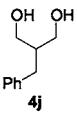
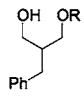
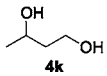
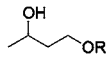
Table 2. Borinic Acid-Catalyzed Monofunctionalization of 1,2- and 1,3-Diols[a]

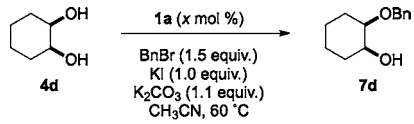
Entry	Substrate	Product		Yield (%)[b]
1	 4a		5a: R = PhCO	84
2	 4b		5b: R = PhCO	97
3			6b: R = Ts	81
4			7b: R = Bn	72[c]
5	 4c		8c: R = CH_3CO	88
6			5c: R = PhCO	82
7			6c: R = Ts	90
8			7c: R = Bn	88
9	 4d		5d: R = PhCO	>99
10			6d: R = Ts	>99
11			7d: R = Bn	>99
12			9d: R = PMB	80
13			10d: R = Nap	91
14	 4e		5e: R = PhCO	94
15			6e: R = Ts	83[d]
16			7e: R = Bn	93
17	 4f		5f: R = PhCO	>99
18			6f: R = Ts	97
19			7f: R = Bn	99
20	 4g		7g: R = Bn	85
21	 4h		7h: R = Bn	93
22	 4i		6i: R = Ts	99
23			7i: R = Bn	78[e]
24	 4j		6j: R = Ts	72
25			7j: R = Bn	>99
26	 4k		5k: R = PhCO	80
27			6k: R = Ts	63
28			7k: R = Bn	95

[a]Reaction conditions. For acylation and sulfonylation: substrate (1.0 mmol), catalyst **1a** (1−10 mol %), electrophile (1.1−1.5 mmol), *i*-Pr_2NEt (1.1−1.5 mmol), CH_3CN (5 mL), 23 °C. For alkylation: substrate (0.2 mmol), catalyst **1a** (10 mol %), BnBr (0.3 mmol), KI (0.2 mmol), K_2CO_3 (0.22 mmol), CH_3CN (1 mL), 60 °C. See the Supporting Information. [b]Isolated yield. Entries 9, 14, and 17 were previously reported in ref 8. [c]Product isolated along with 19% of the regioisomeric product. [d]Product isolated along with 6% of the bis-tosylated product. [e]Product isolated along with 11% of the regioisomeric product.

Alkylation. Selective installation of the benzyl ether protective group and its substituted congeners is a useful transformation: benzyl ethers are robust, do not readily migrate, and are easily removed under mild conditions. Several methods have been developed for the selective installation of benzyl and related ether groups. One of the earlier reports of selective monoalkylation of diols involves the use of polymer supports.[32] Reductive ring-opening of cyclic acetals[33] and alkylation of stannylene acetals[34] are other established and broadly applied methods. In addition to methods that employ stoichiometric quantities of metal additives (such as Ag(I) salts),[35] several transition metal-[36] and Lewis acid-catalyzed processes have been developed.[37] Other catalytic strategies include the use of crown ethers[38] and phase transfer agents.[39] Of particular relevance to this work is a recent report by the group of Onomura in which arylboronic acids were employed as catalysts for monoalkylation of (*R*,*R*)-hydrobenzoin and 1,2-cyclohexanediol (both the cis and trans diastereomers).[37]

With the aim of developing a protocol that would avoid the use of Ag(I)-based activators (such as Ag_2O, which was employed in the borinic acid-catalyzed alkylation of carbohydrate derivatives[9]), we investigated the use of halide additives. A screen of iodide salts revealed that one equivalent of KI, in the presence of potassium carbonate as base, enabled efficient monoalkylation of 1,2-diols with BnBr in acetonitrile at 60 °C (Table 2). Under these conditions, 4-fluorophenylboronic acid (the optimal organoboron catalyst from Onomura's study) was less efficient than diphenylborinic acid derivative **1a**, yielding products **7c** and **7k** in 56% and 11% yields, respectively. The optimized conditions were tolerant of a wide range of substrates, including 1,3-diols, and were suitable for installation of substituted benzyl ethers such as the 4-methoxybenzyl (PMB) and 2-naphthylmethyl (Nap) protective groups. In certain cases, the monobenzylation may be conducted at low catalyst loadings: Table 3 indicates that as little as 0.5 mol % of **1a** may be employed for efficient monoalkylation of *cis*-cyclohexanediol.

Table 3. Effects of Catalyst Loading on the Monobenzylation of 4d



entry	mol % **1a**	yield (%)[a]
1	0	15
2	0.5	90
3	2	>99
4	5	95
5	10	95

[a]Yield determined by ^1H NMR with mesitylene as a quantitative internal standard.

Competition Experiments. Competition experiments were undertaken to evaluate the ability of catalyst **1a** to distinguish between structurally similar alcohol substrates. In each case, the electrophile was employed as the limiting reagent so that the product ratios would reflect relative rates of activation by the organoboron catalyst. In our previous studies of acylations catalyzed by **1a**, similar competition experiments revealed a high level of selectivity for *cis*- versus *trans*-1,2-cycloalkanediols, an observation that formed the basis for applications in carbohydrate activation.[8] The competition experiments conducted in the present study indicate that diols are activated in preference to simple alcohols (Scheme 1, eqs 1, 2), with 1,2-diols undergoing sulfonylation at considerably higher rates than 1,3-diols (eq 3). In a competition experiment between (*R*,*R*)- and *meso*-hydrobenzoin, a 6:1 ratio favoring benzylation of the (*R*,*R*)-diastereomer was observed (eq 4). Selective alkylation of *syn*- over *anti*-1,3-diols was promoted by **1a** (eqs 5, 6); in the last of these two examples, the less sterically hindered OH group of a nonsymmetrical *syn*-1,3-diol was selectively benzylated.

The selectivities described above can be rationalized according to known trends in the thermodynamics of binding of diols to organoboron compounds.[13] Boronic acids show a strong preference for binding of 1,2-diols to generate 1,2-

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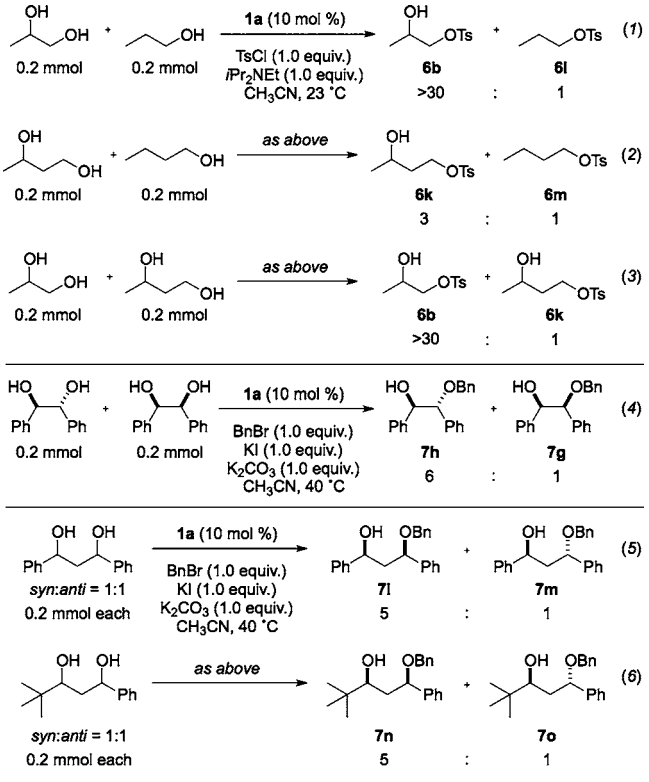
Scheme 1. Competition Experiments

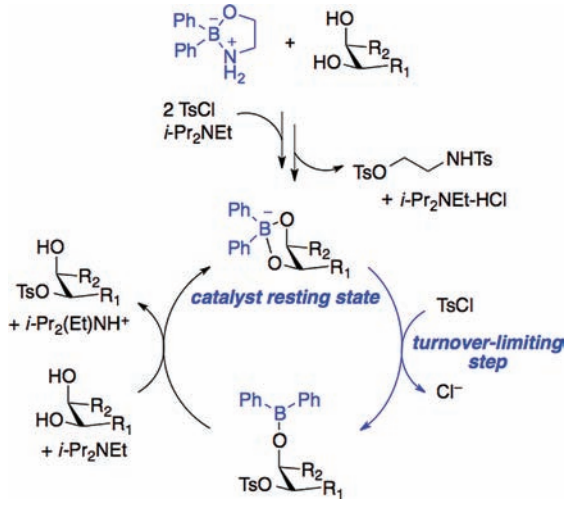


dioxaborolanes, over binding of 1,3-diols to form 1,3-dioxaborinanes. Selective complexation of (*R*,*R*)-hydrobenzoin over its meso diastereomer results from destabilization of the latter complex by eclipsing of the phenyl groups. Similarly, selective complexation of *syn*- over *anti*-1,3-diols is expected because both substituents can occupy equatorial positions in the resulting dioxaborinane. The observed relationship between the thermodynamics of diol binding and rates of activation is consistent with our studies of reaction rates, which indicate saturation kinetics in the diol substrate (below). Given the extensive literature describing the thermodynamics of organoboron−diol interactions, relationships of this type may be useful in planning applications of this method to more complex polyol substrates. In particular, the ability to activate *syn*-1,3-diol units preferentially may be of utility in selective manipulation of building blocks for polyketide synthesis.

Kinetics of Borinic Acid-Catalyzed Sulfonylation. *i). Proposed Catalytic Cycle.* Kinetics experiments are consistent with the proposed catalytic cycle for monosulfonylation of *cis*-1,2-cyclohexanediol (**4d**) depicted in Scheme 2. Entry of aminoethyl diphenylborinate **1a** into the catalytic cycle is triggered by irreversible bis-sulfonylation of the ethanolamine ligand and binding of the diol to form an activated 'ate' complex. The reaction of this tetracoordinate adduct with TsCl is the turnover-limiting step. Rapid, thermodynamically favorable displacement of the product by diol returns the catalyst to its resting state. Details of the experimental observations that support this mechanistic proposal are described below.

ii). Experimental Details. Rates of the borinic acid-catalyzed sulfonylation of *cis*-cyclohexanediol (**4d**) were determined by ^{1}H NMR. Aliquots from reaction mixtures carried out in acetonitrile at 23 °C were quenched by addition of excess methanol and the product concentration was assessed by NMR

Scheme 2. Proposed Catalytic Cycle for Sulfonylation Promoted by 1a



spectroscopy with mesitylene as a quantitative internal standard. In cases where excess TsCl and *i*-Pr$_2$NEt were employed, the product of bis-sulfonylation could not be detected by ^{1}H NMR.

*iii). Entry of **1a** and Ph$_2$BOH into the Catalytic Cycle, and Determination of the Ph$_2$BOH−**4d** Association Constant.* The ability of substrate **4d** to displace the ethanolamine ligand from precatalyst **1a** was probed by NMR experiments and rate studies. Experiments in which 0.5−20 equiv of diol **4d** were added to a solution of **1a** in CD$_3$CN (either in the presence or absence of *i*-Pr$_2$NEt) provided no evidence for diplacement of ethanolamine. Thus, whereas ethanolamine interacts weakly with Ph$_2$BOH in pH 7.0 phosphate buffer (K_a < 5 M^{-1}),[40] its displacement by substrate under the conditions of catalysis appears to be difficult. In contrast, similar experiments probing the interaction of Ph$_2$BOH and **4d** (CD$_3$CN solvent, in the presence of 5 equiv of *i*-Pr$_2$NEt relative to **4d**) resulted in the appearance of new signals in the ^{1}H NMR spectrum within a few minutes of mixing the two components, consistent with slow binding on the NMR time scale (part a of Figure 1). Analysis by the method of continuous variation (Job plot, part b of Figure 1) was consistent with a 1:1 stoichiometry of binding. From these data, an association constant of 70 ± 20 M^{-1} was estimated for the Ph$_2$BOH−**4d** interaction under these conditions. In the absence of *i*-Pr$_2$NEt, the spectral changes corresponding to complexation of **4d** by Ph$_2$BOH were not observed, consistent with previous studies of the pH-dependence of organoboron−diol interactions.[41]

The experiments described in the preceding paragraph indicate that kinetic and/or thermodynamic barriers prevent the rapid entry of **1a** into the catalytic cycle through displacement of ethanolamine by **4d**. However, sulfonylation reactions catalyzed by **1a** displayed no detectable induction period, and reaction rates using **1a** and Ph$_2$BOH as sulfonylation catalysts were essentially identical (Figure 2).[42] Moreover, inhibition by added ethanolamine was not observed. These results indicate that both **1a** and Ph$_2$BOH enter rapidly into the catalytic cycle. The contrast between the NMR experiments and rate studies can be understood according to a mechanism in which the ethanolamine ligand reacts with TsCl prior to displacement by **4d**. Indeed, subjecting **1a** to TsCl and *i*-Pr$_2$NEt in acetonitrile resulted in the formation of the

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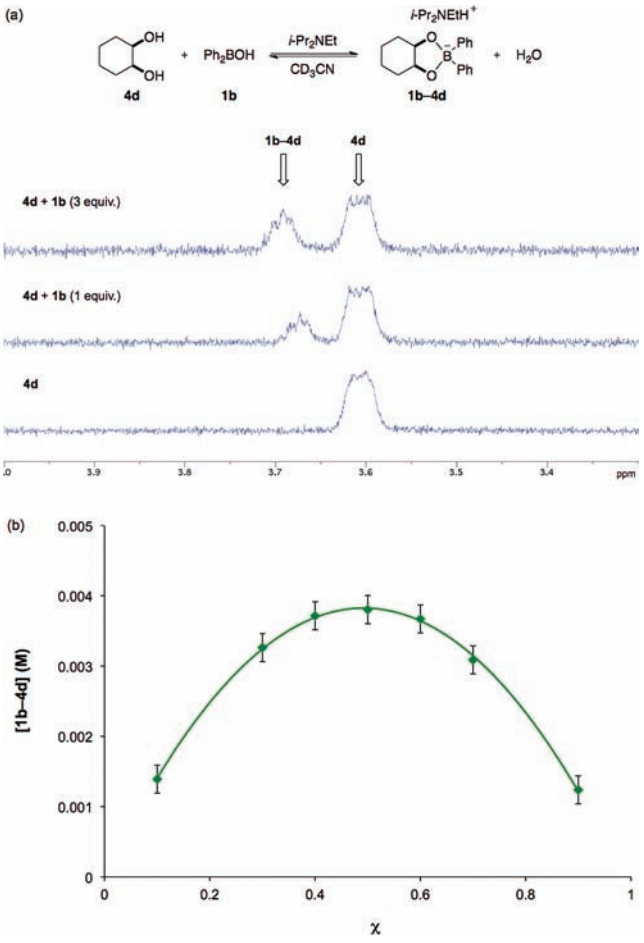

Figure 1. (a) Changes in the ^{1}H NMR spectrum (400 MHz, CD_3CN, 295 K) of *cis*-1,2-cyclohexanediol (**4d**) upon addition of Ph_2BOH (**1b**), in the presence of *i*-Pr_2NEt (5 equiv). From bottom to top, the spectra of **4d** in the presence of 0 equiv, 1 equiv, and 3 equiv of Ph_2BOH are depicted. The signals shown correspond to the methine groups of free and bound **4d**. (b) Job plot for the **4d**–**1b** interaction: concentration of the **4d**–**1b** complex, as determined by integration of the ^{1}H NMR spectrum, is plotted against the mole fraction χ of **4d**. The total concentration [**4d**] + [**1b**] was held constant at 16.7 mM.

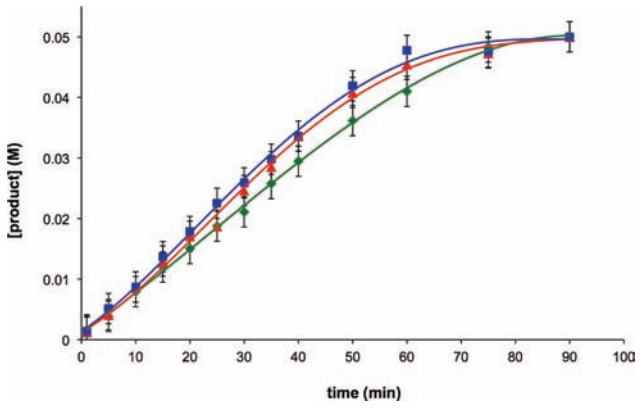

Figure 2. Effect of catalyst identity on the rate of sulfonylation of **4d**: diphenylborinic acid **1b** (◆, green), 2-aminoethyl diphenylborinate **1a** (▲, red), and [**1a** + ethanolamine] (■, blue). Reaction conditions: **4d** (0.5 mmol), catalyst (1 mol %), TsCl (5 equiv), *i*-Pr_2NEt (5 equiv), CH_3CN (10 mL), 23 °C.

sulfonamido tosylate derived from *N*,*O*-bis-tosylation of ethanolamine, which could be detected by ^{1}H NMR. Similarly, *N*,*O*-bis-benzoylation of precatalyst was observed previously in acylation reactions catalyzed by **1a**.[8]

iv). Kinetic Orders in Diol 4d, Ph_2BOH, TsCl, and i-Pr_2NEt. As is evident in Figure 2, the rates of reactions carried out with 5 equiv of base and TsCl, using 1 mol % catalyst (either Ph_2BOH or **1a**), were found to be effectively invariant until roughly 60% of the substrate had been consumed (i.e., the reactions displayed apparent zero-order kinetics in substrate). Monitoring reactions carried out with TsCl as the limiting reagent and Ph_2BOH as catalyst, using varying (excess) quantities of **4d**, provided additional support for this contention (Figure 3). These observations are consistent with

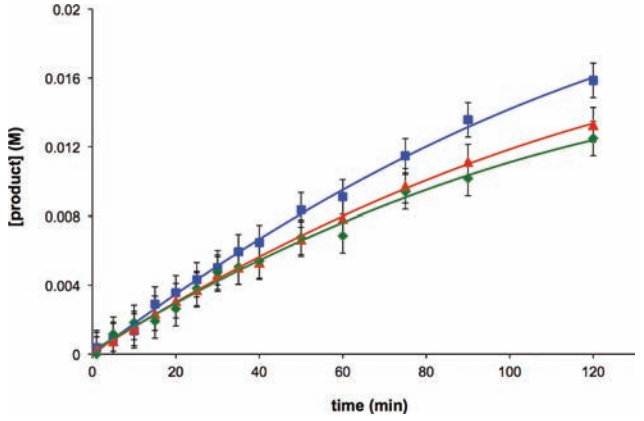

Figure 3. Product concentration versus time for Ph_2BOH-catalyzed reactions of TsCl (1 equiv) with varying concentrations of diol **4d**: 1 equiv **4d** (■, blue), 2 equiv **4d** (▲, red), and 5 equiv **4d** (◆, green). Reaction conditions: TsCl (0.5 mmol), **4d** (1–5 equiv), **1b** (1 mol %), *i*-Pr_2NEt (5 equiv), CH_3CN (10 mL), 23 °C.

saturation kinetics, a scenario that is encountered quite frequently in catalysis.[43] The Ph_2BOH–**4d** association constant determined by ^{1}H NMR (K_a = 70 M^{-1}, above) is compatible with the observation of saturation kinetics: based on this value of K_a, catalyst–substrate complex would be expected to account for roughly 80% of the total Ph_2BOH concentration at the outset of a sulfonylation of **4d** under the standard conditions.

Kinetic orders in catalyst, TsCl, and base were determined by measurements of initial rates of reactions carried out using one equivalent of substrate and excess base/TsCl (2–13 equiv). Given the lack of an observable induction period, and the fact that the reaction rates were essentially constant until relatively high conversions due to zero-order kinetics in **4d** (above), the use of initial rates appears to be justified. Plots of initial rates versus concentration revealed a first-order kinetic dependence on Ph_2BOH concentration (Figure 4), first-order kinetics in TsCl (Figure 5), and zero-order kinetics in *i*-Pr_2NEt (Figure 6). The rate law implied by these kinetic orders is consistent with a mechanism involving turnover-limiting sulfonylation of the borinic acid–diol adduct.

v). Comparison with Kinetics of Selective Glycosyl Acceptor Activation. We previously carried out kinetics experiments, using initial rates determined by ^{1}H NMR, for the regioselective glycosylation of a mannopyranoside substrate catalyzed by borinic ester **1a**. The rate law for sulfonylation described above differs from that determined previously for glycosylation: for the latter process, first-order kinetics in

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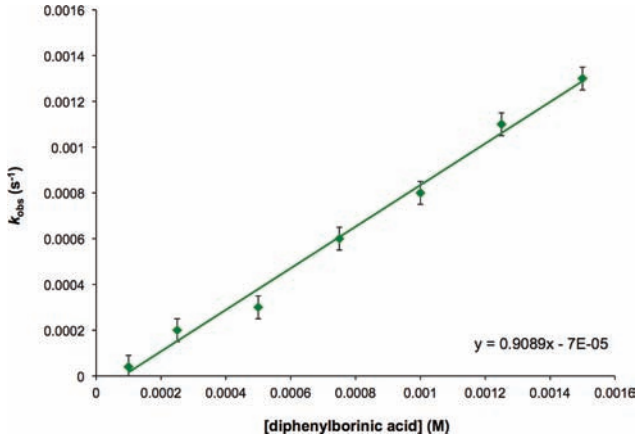

Figure 4. Dependence of the initial rate of sulfonylation of **4d** (k_{obs}) on the concentration of Ph_2BOH. Reaction conditions: **4d** (0.2 mmol), **1b** (0.1−1.5 mol %), TsCl (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_3CN (2 mL), 23 °C.

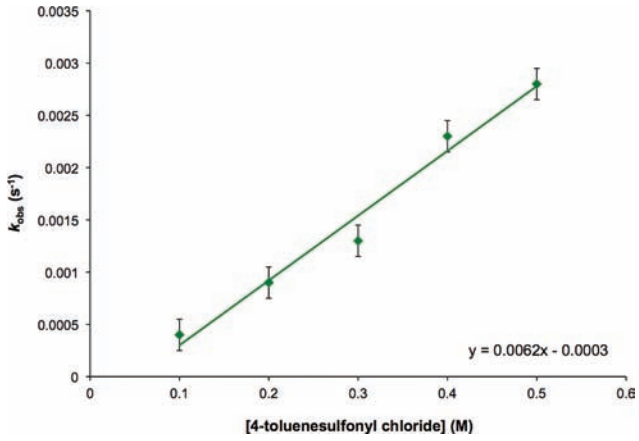

Figure 5. Dependence of the initial rate of sulfonylation of **4d** (k_{obs}) on the concentration of TsCl. Reaction conditions: **4d** (0.2 mmol), **1b** (1 mol %), TsCl (1−5 equiv), *i*-Pr_2NEt (5 equiv), CH_3CN (2 mL), 23 °C.

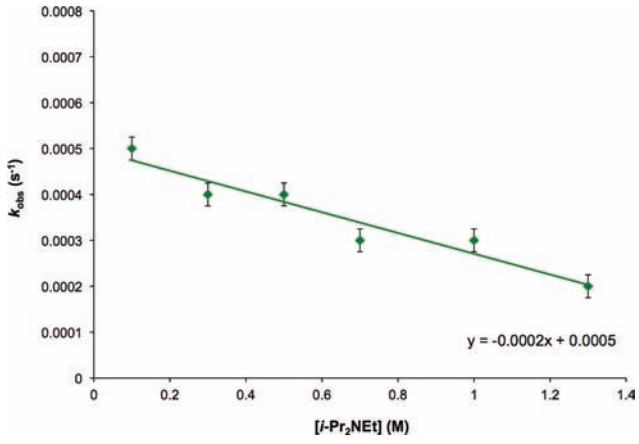

Figure 6. Dependence of the initial rate of sulfonylation of **4d** (k_{obs}) on the concentration of *i*-Pr_2NEt. Reaction conditions: **4d** (0.2 mmol), **1b** (1 mol %), TsCl (1 equiv), *i*-Pr_2NEt (1−13 equiv), CH_3CN (2 mL), 23 °C.

glycosyl acceptor, glycosyl donor, and catalyst were observed, along with zero-order kinetics in Ag_2O, which plays the role of halide-abstracting agent and Brønsted base.[44] The saturation kinetics in substrate observed for the sulfonylation reaction as opposed to first-order kinetics for the glycosylation reaction is the distinguishing factor.

The dependence of the Ph_2BOH−diol association constant on base concentration, along with the distinct natures of the Brønsted bases employed for sulfonylation and glycosylation (*i*-Pr_2NEt and Ag_2O, respectively), hints at an explanation for the observed difference in kinetic behavior. In the absence of a soluble Brønsted base, catalyst−substrate binding is relatively weak under the conditions of glycosylation leading to first-order kinetics in substrate. The presence of *i*-Pr_2NEt in the sulfonylation reaction enhances the catalyst−substrate association constant to the point that saturation kinetics in substrate are observed.

vi). Electronic Effects on Catalyst Activity. The rates of sulfonylation reactions catalyzed by substituted arylborinic acids **1c** and **1d** were investigated. Both the 4-methoxy- and 3,5-bis(trifluoromethyl)-substituted derivatives provided qualitatively similar rate profiles to that observed using diphenylborinic acid showing no evident induction period and apparent zero-order kinetics in substrate; however, **1c** and **1d** provided lower rate constants than did the unsubstituted catalyst **1b** (Figure 7). The fact that both electron-donating and electron-withdrawing substituents on the diarylborinic acid resulted in lower sulfonylation activties was somewhat surprising.

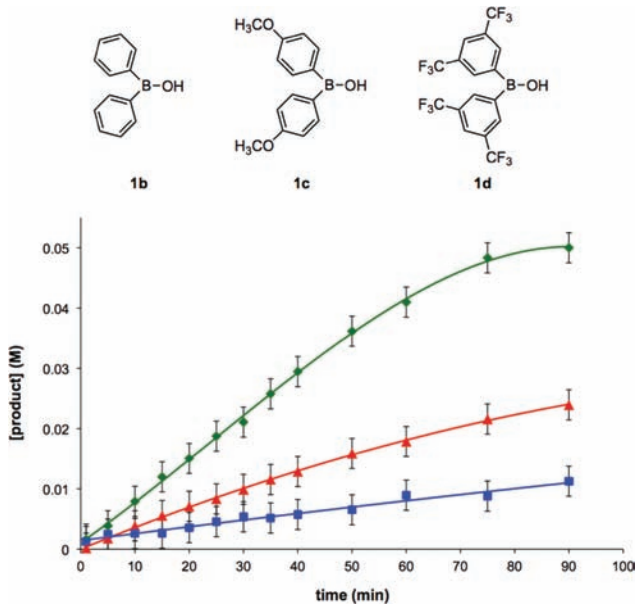

Figure 7. Electronic effects on the activity of diarylborinic acid catalysts **1b**−**1d** for sulfonylation of diol 4**d**: catalyst **1b** (◆, green), **1c** (▲, red), and **1d** (■, blue). Reaction conditions: **4d** (0.5 mmol), catalyst (1 mol %), TsCl (5 equiv), *i*-Pr_2NEt (5 equiv), CH_3CN (10 mL), 23 °C.

Given the rate law obtained for diol sulfonylation catalyzed by **1b**, we have attempted to interpret this effect in terms of the influence of substituents on the reactivity of the tetracoordinate 'ate' complexes toward sulfonylation. To this end, gas-phase DFT calculations (B3LYP/6-31+G(d,p)) of the anionic adducts of ethylene glycol with **1b**−**1d** were undertaken. We have previously found that B3LYP/6-31+G(d,p) gas-phase calculations of Fukui indices for monosaccharide-derived borinates are consistent with the observed regiochemical

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outcomes of organoboron-catalyzed transformations suggesting that this level of theory is appropriate for modeling electronic effects in such systems.[8] Here, the calculated Mulliken charges of the ethylene glycol-derived oxygen atoms were found to decrease in absolute value in the order **1b** > **1c** > **1d**, mirroring the trend in catalytic activity. Calculated absolute values of the molecular electrostatic potential at oxygen followed the same order. Thus, calculations appear to indicate that both the 3,5-bis(trifluoromethyl) and 4-methoxy groups exert inductive electron-withdrawing effects in the context of borinate esters, despite the negative value of σ^- for the latter (σ^- for 4-OCH_3 is −0.2).[45] It should be noted that we cannot discount the possibility that the methoxy group impairs substrate binding rather than attenuating the nucleophilicity of the catalyst−substrate complex.

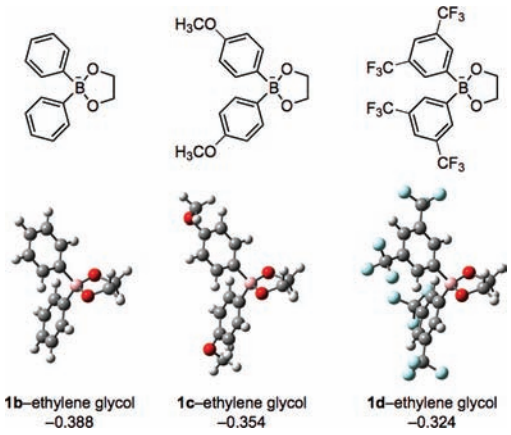

Figure 8. Calculated geometries of the anionic adducts of ethylene glycol with catalysts **1b**−**1d**, and average Mulliken charges of ethylene glycol-derived oxygen atoms.

CONCLUSIONS

The results described herein emphasize that diphenylborinic acid catalysis is a useful method for selective monofunctionalization of diols. The selective activation of equatorial OH groups of *cis*-1,2-diol moieties has been successfully applied to sulfonylation, enabling the high-yielding synthesis of monotosylates derived from diverse pyranoside substrates. This mode of catalysis has been extended to the selective acylation, sulfonylation, and alkylation of simpler 1,2- and 1,3-diol substrates, and provides significant advantages in terms of efficiency and operational simplicity for this important class of transformations. In particular, the high-yielding, diphenylborinic acid-catalyzed monosulfonylation of 1,2-diols may be of significant interest as an alternative to well-established protocols requiring the use of diorganotin catalysts. Similarly, the borinic acid-catalyzed monobenzylation of 1,2-diols compares favorably to existing methods and employs relatively benign and inexpensive reagents. These results should encourage applications of this method outside the area of carbohydrate chemistry.

Mechanistic experiments have provided strong support for the proposal that anionic, tetracoordinate borinate esters are key intermediates in this class of processes. Competition experiments establish a link between the thermodynamics of two-point covalent binding of diols to organoboron compounds and the relative rates of diol activation in the presence of diphenylborinic acid. NMR experiments have enabled the determination of a diphenylborinic acid−diol association constant under the conditions of catalysis. The rate law (first-order kinetics in catalyst and electrophile, zero-order kinetics in Brønsted base, saturation kinetics in diol substrate) is consistent with the reaction of such an adduct in the turnover-limiting step of the catalytic cycle. Computational modeling of the tetracoordinate borinates provides data that are consistent with experimentally observed regiochemical outcomes and catalyst substituent effects. These results may provide a useful starting point for efforts toward identifying novel diorganoboron catalysts that exhibit increased activity or altered regioselectivity for reactions of this type, and for extending these methods to more complex polyol substrates.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, details of kinetics experiments, binding studies and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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