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Borinic Acid-Catalyzed Regioselective Acylation of Carbohydrate Derivatives

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Supporting Information

ABSTRACT: Reversible covalent interactions of organoboron compounds are exploited as the basis for regioselective borinic acid-catalyzed acylations of polyols. This catalytic protocol enables differentiation of the secondary OH groups of a wide range of carbohydrate derivatives with diverse acid chloride and chloroformate reagents, using a structurally simple diarylborinic acid-derived catalyst.

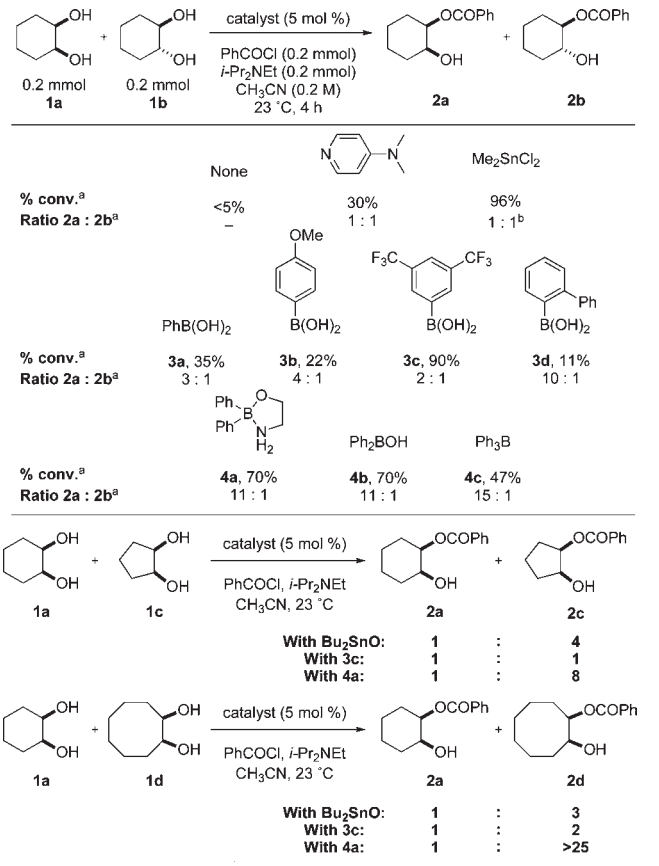
The reversible covalent interactions of organoboron compounds with diols have been employed extensively in the design of receptors for carbohydrates.[1] Key features of these interactions are their tolerance of aqueous medium, favorable kinetics, and selectivity for *cis*-vicinal diol moieties, governed by minimization of angle and torsional strain. Here, we demonstrate that such interactions may be harnessed to achieve organoboron-catalyzed monoacylations of carbohydrate derivatives with robust and general regioselectivity for *cis*-diol motifs. This method enables the differentiation of the secondary hydroxy groups of a wide range of monosaccharide substrates by acylating agents varying significantly in steric and electronic properties, using a commercially available and inexpensive borinic ester precatalyst.

The selective protection of carbohydrates has been pursued intensively for the preparation of value-added intermediates and building blocks for oligosaccharide synthesis from readily available sugar feedstocks.[2] Strategies based on catalysis are of particular interest: recent developments include enzyme-catalyzed[3] and organocatalytic methods,[4] Lewis acid-promoted processes,[5,6] and tandem catalytic reactions of persilylated sugar derivatives.[7] Despite this progress, there remains an unmet need for catalysts displaying the combination of reliable selectivity for a given regiochemical outcome and generality for a wide range of sugar/protective group combinations.

We sought to identify organoboron catalysts capable of promoting selective acylation of *cis*-diol moieties in carbohydrates. Although formation of a boronate ester generally constitutes protection, not activation, of a diol motif,[8] Aoyama and co-workers reported that triethylamine activates fucose- and arabinose-derived boronate esters toward alkylation through a putative ate complex.[9a] In a related strategy, sugar-derived boronate esters bearing a pendant hydroxy group underwent regioselective glycosylation.[10] Each of these processes required the use of a stoichiometric quantity of organoboron reagent that was initially installed in a thermally promoted condensation step, suggesting that developing *catalytic* reactivity of this type might be difficult.

Organoboron species were evaluated as catalysts for the selective benzoylation of 1,2-*cis*-cyclohexanediol **1a** in the presence of its *trans* diastereomer **1b** (Scheme 1). *N,N*-Dimethylaminopyridine (DMAP) promoted indiscriminate acylation of **1a** and **1b**, as did Me_2SnCl_2, a known catalyst of diol acylation.[5] While boronic acids **3a**−**3d** provided varying degrees of rate enhancement, only modest levels of selectivity for the formation of **2a** were observed.[11] In contrast, the ethanolamine ester of diphenylborinic acid (**4a**) promoted acylation of **1a** with good activity and superior selectivity. Similar results were obtained with diphenylborinic acid itself (**4b**), suggesting that **4a** serves as a precatalyst by benzoylation and displacement of the

Scheme 1. Evaluation of Catalysts for Selective Acylation of *cis*-Cycloalkanediols



[a] Determined by ^{1}H NMR. [b] From ref 5a.

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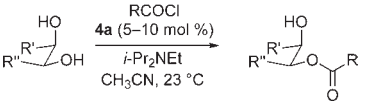
ethanolamine ligand.[12] Triphenylborane (**4c**) was also active, likely by conversion to a borinic acid derivative by either oxidation or protonolysis of a C−B bond.[13] Borinate ester **4a** was chosen as the optimal catalyst due its commercial availability, stability and ease of handling.[14] Although applications of borinic acids in molecular recognition are rare, they are more acidic than boronic acids, and readily generate ate adducts with diols at neutral pH.[15] We have previously employed diphenylborinic acid as a catalyst for direct aldol reactions of pyruvic acids, in which a similar reversible covalent catalyst−substrate adduct was proposed.[16] Borinic acids have also been employed as catalysts of mechanistically distinct reactions, including Mukaiyama aldol reactions,[17] Oppenauer oxidations,[18] and dehydrations.[19]

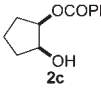
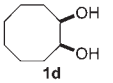
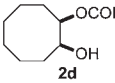
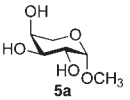
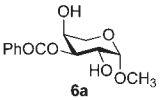
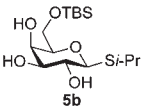
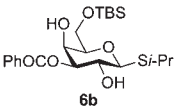
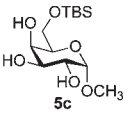
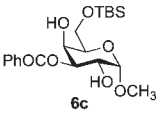
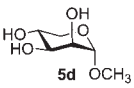
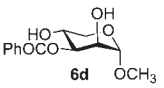
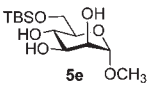
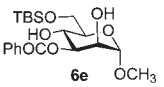
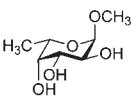
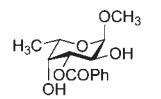
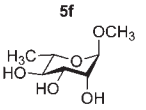
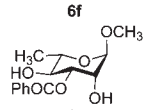
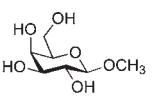
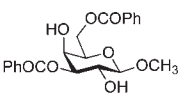
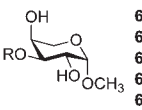
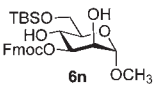
Competition experiments involving *cis*-diols of varying ring sizes provide support for the involvement of a covalent borinic acid−diol adduct in the catalytic pathway (Scheme 1). The preferential acylations of *cis*-cyclopentanediol **1c** and *cis*-cyclooctanediol **1d** over **1a** are consistent with the generation of the less strained boron−diol complex in each case, as assessed by semiempirical (PM3) calculations (see the Supporting Information). The selectivities obtained with **4a** are higher than those observed using boronic acid **3c** or the diorganotin catalyst Bu_2SnO (the latter was employed under conditions optimized by Matsumura and co-workers:[5a] K_2CO_3, THF, 23 °C; Scheme 1). On preparative scale, the borinic acid-catalyzed monobenzoylations of cycloalkanediols proceeded in high yield (Table 1, entries 1−3); diacylated products were not detected.[20]

This catalyst system enables the differentiation of secondary hydroxy groups in a wide range of carbohydrate derivatives (Table 1, entries 4−17). Monoacylation was observed only at *cis*-vicinal diol moieties, with the equatorial OH group undergoing selective benzoylation in derivatives of arabinose (**5a**), galactose (**5b**, **5c**, **5h**), lyxose (**5d**), mannose (**5e**), fucose (**5f**), and rhamnose (**5g**). The secondary OH groups of carbohydrates differ in their nucleophilicity as a function of intramolecular hydrogen bonding, steric, and electronic effects:[21] among the trends observed is a relatively high reactivity of hydroxy groups *cis* to adjacent axial hydroxy or alkoxy groups. When a sterically hindered electrophile such as pivaloyl chloride is employed, selective monoacylation at a secondary OH group is possible in certain cases.[22] To quantify the magnitude of such preferences, each substrate from Table 1 was subjected to conditions favoring controlled monoacylation (1.2 equiv of RCOCl, pyridine, −30 to 23 °C). The yields obtained under these catalyst-free conditions (indicated in parentheses in Table 1) were less than 50% for 12 of the 14 carbohydrate monoacylations studied, and less than 25% for nine of them, due to formation of regioisomeric and/or overacylated products. The results indicate that catalyst **4a** promotes monoacylations of challenging substrate combinations, for which state-of-the-art methods require the use of stoichiometric[23] or catalytic[5] quantities of diorganotin reagent.

Consistent with the results of Scheme 1, and unlike diorganotin catalysts, catalyst **4a** does not promote acylation of secondary OH groups in carbohydrates lacking a *cis*-1,2-diol motif such as glucose and xylose derivatives. Benzoylation of methyl β-galactopyranoside (**5h**) occurred competitively at the 3- and 6-positions, presumably through interactions of the catalyst with the 4,6- and 3,4-diol groups.[24] Diacylated product was obtained efficiently in the presence of excess benzoyl chloride (entry 11). The method is compatible with a thioglycoside, a functional group absent in reported examples of tin-catalyzed acylation (entry 5), and is tolerant of variation of the stereochemistry of the anomeric

Table 1. Borinic Acid-Catalyzed Monoacylation of Cycloalkanediols and Carbohydrate Derivatives[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **2a**	>99 (60)
2	 **1c**	 **2c**	94 (50)
3	 **1d**	 **2d**	>99 (56)
4	 **5a**	 **6a**	91 (<3)
5	 **5b**	 **6b**	80 (64)
6	 **5c**	 **6c**	95 (11)
7	 **5d**	 **6d**	69 (36)
8	 **5e**	 **6e**	86 (47)
9	 **5f**	 **6f**	92 (17)
10	 **5g**	 **6g**	94 (34)
11[c]	 **5h**	 **6h**	88 (20)
12	 **5a**	**6i**: R = $CH_3(CH_2)_2CO$	69 (4)
13		**6j**: R = $(CH_3)_2CHCH_2CO$	88 (3)
14		**6k**: R = $(CH_3)_2CHCO$	75 (<3)
15[d]		**6l**: R = Cbz	69 (7)
16		**6m**: R = Fmoc	73 (5)
17	**5e**	 **6n**	69 (53)

[a] Reaction conditions: substrate (1.0 mmol), catalyst **4a** (5−10 mol %), RCOCl (1.2−2.0 mmol), *i*-Pr_2NEt (1.2−2.0 mmol), CH_3CN (0.2 M). See the Supporting Information. [b] Isolated yield. Numbers in parentheses are the isolated yields obtained in the absence of catalyst, under conditions favoring controlled monoacylation (1.2 equiv of RCOCl, pyridine, −30 → 23 °C). [c] PhCOCl (4.0 mmol), *i*-Pr_2NEt (4.0 mmol). [d] **4b** was employed as catalyst.

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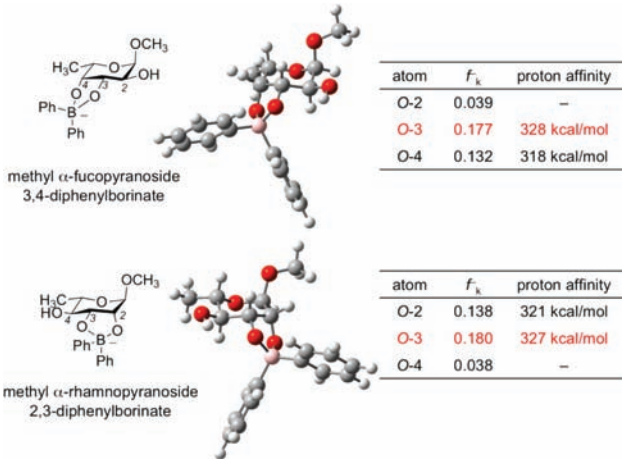

Figure 1. DFT-calculated structures, condensed Fukui functions, and proton affinities of diphenylborinate adducts of representative hexopyranoses (see the text and Supporting Information for details).

position (entries 5 and 11 vs 6). Acid chlorides and chloroformates with varied steric and electronic properties reacted regioselectively with carbohydrate derivatives in the presence of catalyst **4a** (entries 12−17). The compatibility of this method with sterically unhindered electrophiles such as α-unbranched aliphatic acid chlorides (entries 12, 13) and chloroformates (entries 15−17) is noteworthy, as reagents of this type have not been employed in Me_2SnCl_2-catalyzed acylation protocols. Reactions of chloroformates posed a particular challenge, as the products were prone to base-catalyzed acyl migration. Although the formation of regioisomeric byproducts by acyl migrations of this type resulted in modest yields,[25] this represents the first catalytic method for the selective introduction of these useful carbonate protective groups.[26]

Computational studies of the putative diphenylborinic acid adducts of representative pyranosides (derived from fucose and rhamnose) suggest an electronic basis for the observed regioselectivity (Figure 1). For each adduct, the DFT-calculated (B3LYP/6-311+G**) condensed Fukui index f^-_k (a measure of relative nucleophilic reactivity[27]) and proton affinity are highest at O-3, the observed site of acylation. Interaction with tetracoordinate boron increases the electron density of the two bound oxygen atoms, and the relative reactivity of these appears to reflect dipole−dipole interactions (opposition of the C4−O and C5−O bonds and of the C2−O and C1−O bonds in the fucose and rhamnose adducts, respectively).[28] Steric factors may also contribute to the observed selectivity: for example, competing acylation at *O*4 in the galacto series is likely suppressed as the size of the C5 substituent increases.

In conclusion, organoboron catalysis represents a novel method to activate *cis*-1,2-diol groups toward electrophilic attack. The broad scope of this reaction with respect to both carbohydrate substrate and acylating agent, as well as the low toxicity of the borinate ester catalyst and its straightforward removal from reaction mixtures, represent attractive features in comparison to previous protocols employing organotin reagents. Competition experiments demonstrate that borinic acids are able to achieve selectivity based on subtle structural differences that are not easily distinguished by other methods. In light of increasing appreciation of the potential for connections between the fields of supramolecular chemistry and catalysis,[29] the ability to exploit the carbohydrate recognition chemistry of organoboron species for applications in catalysis offers opportunities for the development of new stereo- and regioselective processes. Efforts to expand the scope of boron-catalyzed manipulations of sugars, and to explore chiral organoboron derivatives for enantioselective transformations, are underway.

■ ASSOCIATED CONTENT

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

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(11) The boronate ester generated from **1a** and **3c** was unreactive with PhCOCl under the conditions shown in Scheme 1. Addition of

water (2 equiv) promoted benzoylation (see the Supporting Information). This reactivity appears to be distinct from boronic acid-catalyzed condensations of amines and alcohols with carboxylic acids, in which acyloxyboranes are proposed intermediates.

(12) Consistent with this hypothesis, 2-benzamidoethyl benzoate was observed in unpurified reaction mixtures. It is easily separated from the hydroxy ester products of the reaction by column chromatography.

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(14) Preliminary studies show a modest electronic effect on the activities of substituted arylborinate esters: for the reaction shown in Table 1, entry 4, activity of $ArB(OCH_2NH_2)$ increased in the order $3,5\text{-}(CF_3)_2C_6H_3 < C_6H_5 < 4\text{-}(OCH_3)C_6H_4$. Catalyst selectivity is dependent on the identity of the solvent and base employed: see the Supporting Information for details.

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(20) Catalyst **4a** selectively activates (>20:1) *cis*-1,2-cyclohexanediol over cyclohexanol. This rate difference is likely responsible for the absence of multiply acylated side products in the reactions shown in Table 1.

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