

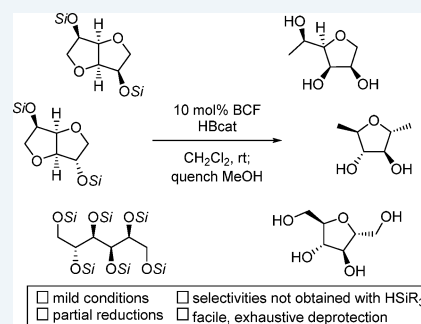
Boron-Catalyzed Site-Selective Reduction of Carbohydrate Derivatives with Catecholborane

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Supporting Information

ABSTRACT: Catalytic sp^3 C–O bond cleavage using $\text{B}(\text{C}_6\text{F}_5)_3/\text{HBcat}$ is reported. This method is first demonstrated on simple ethers and silyl protected alcohols, which exhibit reactivity parallel to the known $\text{B}(\text{C}_6\text{F}_5)_3/\text{HSiR}_3$ system. In more complex carbohydrate derivatives, however, unique selectivities that are not possible with hydrosilane reductants have been achieved, including regioselective cyclizations. Preliminary computational studies suggest that diboryl oxonium ions are disfavored and that four-coordinate boronium ions may contribute to selectivity.



KEYWORDS: boron, deoxygenation, boranes, sugars, chemoselectivity

Hydroboranes have long been known to add across unsaturated carbon–carbon bonds in a process generically referred to as hydroboration.¹ While the simplest borane, BH_3 , can readily hydroborate alkenes, the milder reagents pinacolborane (HBpin) and catecholborane (HBcat) are less Lewis acidic and consequently less reactive.^{2,3} This attenuation has provided the opportunity to develop metal catalysts for this transformation, and numerous accounts of catalyzed alkene and alkyne hydroborations have been reported.^{4–6} More recent work has shown hydroboration of carbonyl derivatives, imines, and *N*-heteroarenes.^{7–10}

Despite their propensity to react with π -bonds, HBpin and HBcat are not yet known as reagents to reductively deoxygenate sp^3 C–O bonds.¹¹ In contrast, silanes can be activated by numerous catalysts to achieve this outcome,¹² as we^{13–18} and others^{19–26} have achieved selective C–O bond reduction in multifunctional compounds with the metal-free catalyst tris(pentafluorophenyl)borane ($\text{B}(\text{C}_6\text{F}_5)_3$). As elucidated by Piers²⁷ and Yamamoto,²⁸ $\text{B}(\text{C}_6\text{F}_5)_3$ heterolytically activates the hydrosilane through a transient borane–silane adduct ($(\text{C}_6\text{F}_5)_3\text{B} \cdots \text{H} \cdots \text{SiR}_3$). Invertive nucleophilic attack (at Si)²⁹ by oxygen on the adduct produces a silyl oxonium/borohydride ion pair, the recombination of which cleaves the C–O bond and regenerates the catalyst. This method has also been effective for a variety of other functional groups, including alkenes, imines, and carbonyls.³⁰

We considered the possibility that silane activation pathways might similarly apply to hydroboranes, and for the problem of C–O activation catalysis, the formation of strong B–O bonds (193 kcal/mol) might provide a suitable driving force for deoxygenation chemistry. Evidence supporting the feasibility of a heterolytic B–H bond activation process was found by Stephan in the reaction of HBcat with a stoichiometric amount

of $\text{B}(\text{C}_6\text{F}_5)_3$ and PtBu_3 ,³¹ which yields a $[\text{H} \cdots \text{B}(\text{C}_6\text{F}_5)_3] \cdots [\text{tBu}_3\text{P} \cdots \text{Bcat}]$ ion pair (Scheme 1a) and parallels silane reactivity.^{32,33} Low-temperature NMR studies led Stephan to suggest the intermediacy of a phosphine–HBcat adduct, which would not exist along a silane heterolysis reaction coordinate. This reactivity has not been applied to achieve catalytic chemistry to date. Crudden has also demonstrated that $\text{B}(\text{C}_6\text{F}_5)_3$ can activate HBpin with the help of DABCO for imine reduction (Scheme 1b).^{34–37} In this case, spectroscopic monitoring implied the intermediacy of the stabilized boronium ion pair, $[\text{H} \cdots \text{B}(\text{C}_6\text{F}_5)_3][\text{DABCO} \cdots \text{Bpin}]$, and the DABCO–HBpin adduct. Lewis adducts of HBcat and HBpin are calculated to be more hydridic than $[\text{H} \cdots \text{B}(\text{C}_6\text{F}_5)_3]$ ³⁸ and therefore should be better able to achieve B–H activation by $\text{B}(\text{C}_6\text{F}_5)_3$. Despite the similarities between silane activation and the boronium results of Stephan and Crudden, the actual catalyst in the Crudden imine reduction is the boronium ion, with $\text{B}(\text{C}_6\text{F}_5)_3$ acting only as initiator. Oestreich demonstrated alkene hydroboration with tris[3,5-bis(trifluoromethyl)phenyl]borane but via a strikingly different reaction pathway compared to similar hydrosilylation methods.^{39–41} The 1,4-hydroboration of pyridine using HBpin was shown by Wang to occur through a Piers'-like mechanism, by which the B–H bond of the reductant was heterolyzed by the boron catalyst (though $\text{B}(\text{C}_6\text{F}_5)_3$ was again ineffective), and here a dipyrityl boronium intermediate was suggested (Scheme 1d).⁴² These mechanistic similarities and differences suggested that if boranes could be heterolytically activated and utilized for catalytic sp^3 C–O bond activation, this would not only

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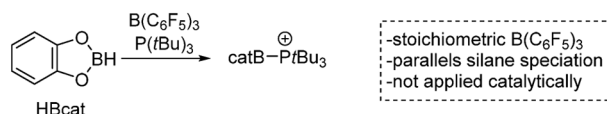
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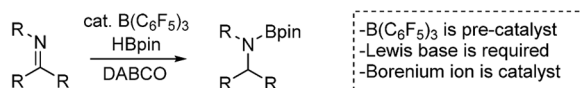
Scheme 1. Chemistry of Fluorinated Aryl Boranes with Hydroboranes

B–H activation using B(C₆F₅)₃ and Lewis base

a) Stephan (2008)

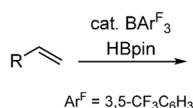


b) Cruden (2012)

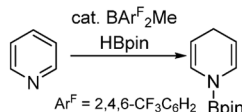


Hydroboration using non-commercial fluorinated aryl boranes (B(C₆F₅)₃ ineffective)

c) Oestreich (2017)

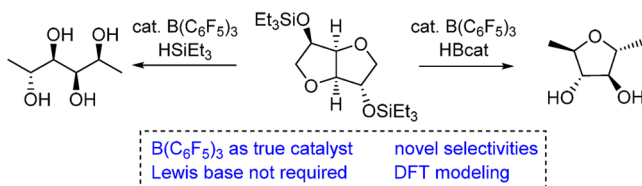


d) Wang (2015)



C–O reduction using silane and borane reductants with B(C₆F₅)₃

e) Gagné (2015)



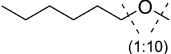
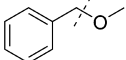
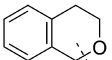
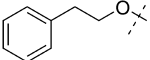
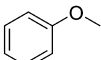
represent an advancement in its own right but also might enable unique reaction selectivities compared to hydrosilanes.

Herein, we report that the combination of commercially available B(C₆F₅)₃ and HBcat enables the reduction of the sp³ C–O bonds of a number of simple ethers and alcohols, and to site selectively deoxygenate more complex multifunctional carbohydrate derivatives. Most interestingly, the products can be substantially different from those obtained when a hydrosilane is used as the reductant (Scheme 1e). This divergence in selectivity will be emphasized throughout the study.

As a proof of concept, we began by investigating the reductive ability of hydroboranes on the sp³ C–O bond of ethers, a class of substrates shown by the Yamamoto group to be easily reduced by hydrosilanes.²⁸ Using the B(C₆F₅)₃ catalyst (5 mol %), methyl and benzyl ethers were reduced within minutes with both HBcat and HBpin (Table 1). When a true borenium catalyst was generated from the combination of [Ph₃C][B(C₆F₅)₄], HBcat, and DABCO or 2,6-lutidine, a productive deoxygenation catalyst was *not* generated.³⁴ Tetrahydropyran (THP), which contains only primary ether bonds, was slower, taking several days for full conversion. In contrast to silane reactivity, anisole was completely unreactive under these conditions.

Monitoring the reduction of THP by ¹⁹F{¹H} NMR spectroscopy showed that the B(C₆F₅)₃ catalyst rests as the borohydride [H–B(C₆F₅)₃][–], but once the reaction was complete, B(C₆F₅)₃ is reformed, and the slight excess of HBcat remained unreacted. In the ¹H NMR, a triplet (–OCH₂–) downfield from both starting material and product maintained the same integration during the course of the

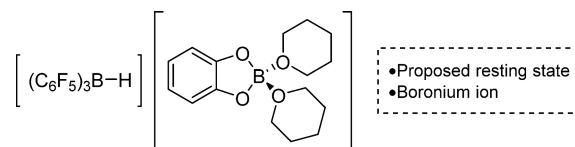
Table 1. HBcat and HBpin Reduction of Simple Ether Substrates

$\text{R}-\text{O}-\text{R}' \xrightarrow[\text{CD}_2\text{Cl}_2, \text{rt}]{5 \text{ mol\% B(C}_6\text{F}_5)_3, 1.5 \text{ eq. HBL}_2} \text{R}-\text{O}-\text{BL}_2 + \text{R}'$ $\text{L}_2 = \text{cat, pin}$				
Entry	Substrate	Time (h)	Yield (%) ^a	
			HBcat	HBpin
1		<1	99	91
2		<1	99	99
3		2	85	99
4		1	96	90
5		5 d	99	99
6		--	NR	NR

^aYields were determined by NMR spectroscopy using hexamethylbenzene as internal standard.

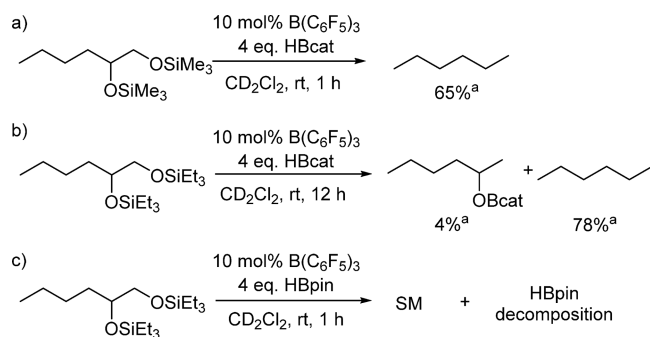
reaction, but disappeared once the reaction was complete. Considering the catalyst loading in this experiment, this resonance integrates for two equivalents of THP per B(C₆F₅)₃. Present in the ¹¹B NMR spectrum were the expected doublets at –25 (¹J_{B,H} = 92.0 Hz) and 29 ppm (¹J_{B,H} = 192.9 Hz) for [H–B(C₆F₅)₃][–] and HBcat, respectively, as well as a broad peak at 12 ppm, consistent with a four-coordinate boronium species.^{34,42} Based on this NMR analysis, the ion pair [THP₂Bcat][H–B(C₆F₅)₃] is proposed to be the resting state in this catalytic reaction (Scheme 2).

Scheme 2. Spectroscopically Determined Ion Pair in C–O Reduction of THP



We next used the B(C₆F₅)₃/HBcat and HBpin combination to test for reduction of simple silyl ethers as carbohydrates, one of our targets in the biomass deoxygenation area,^{13,14} are often preprotected to increase solubility and to bypass dehydrocoupling (which leads to H₂ formation and the need for excess reductant). The reduction of trimethylsilyl-hexanediol quickly generated *n*-hexane upon addition of HBcat (Scheme 3a).^{13,43} When the bulkier triethylsilyl group was used to protect the hexanediol, *n*-hexane was again the major product and a small amount of boryl-protected 2-hexanol was observed (Scheme 3b). This silyl for boryl exchange⁴⁴ in protecting group was verified by generating authentic samples using 2-hexanol (Figure S6 and S7). The use of only two equivalents of HBcat in both cases above led to incomplete conversion of

Scheme 3. $B(C_6F_5)_3$ Catalyzed Reduction of Silyl Ethers with HBcat



^aYields were determined by NMR spectroscopy using hexamethylbenzene as internal standard.

starting material. In contrast to HBcat, HBpin was ineffective for silyl ethers (Scheme 3c). In situ $^{13}C\{^1H\}$ NMR spectroscopy suggested that the HBpin decomposes by the $B(C_6F_5)_3$ /silane system in a catalyzed reductive pinacol rearrangement (Figure S9).²² HBcat is therefore the preferred reductant, but these data also indicate that silyl/boryl exchange can compete with C–O cleavage. The cleavage of sp^3 C–O bonds under catalyst control demonstrates novel reactivity for HBcat and HBpin.

With these results in hand, we began to investigate isosorbide (1), a platform biorenewable chemical,⁴⁵ as a substrate for C–O reduction using HBcat. An excess of HBcat with the free alcohol first effects dehydrocoupling to yield doubly Bcat-protected isosorbide (1-Bcat, $B(C_6F_5)_3$ is not needed for this step). In the presence of 10 mol % $B(C_6F_5)_3$, the remaining hydroborane is then available to reduce C–O bonds, and the observed preference is for cleaving the two primary positions to yield the 1,6-dideoxytetraol 2 (71% yield, Table 2, entry 1).⁴⁶ This product is accessible from several starting materials (sorbitol, isosorbide) using silane reductants, but this result demonstrates site-selectivity is indeed possible in $B(C_6F_5)_3$ -catalyzed borane deoxygenations.¹⁴ No additional reduction occurs with excess borane.

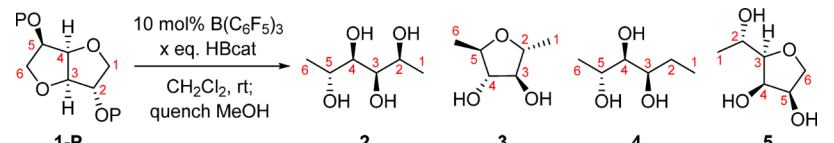
Since the size of the protecting group can significantly impact reactivity and selectivity in densely functionalized starting materials, we preprotected isosorbide with a variety of silyl groups to see how this influenced the selectivity of C–O reduction. Unexpectedly, 1-SiEt₃, which is asymmetric, reacted

with two equivalents of HBcat to produce the symmetrical, partially deoxygenated 1,6-dideoxysorbitan 3 in 62% isolated yield (Table 2, entry 2). We have previously reported the condensative conversion of 2-SiMe₂Et to 3 using stoichiometric¹⁴ or catalytic⁴⁷ amounts of “SiR₃”. The $B(C_6F_5)_3$ /HBcat protocol thus achieves a *catalytic* synthesis of 3 by the direct *reduction* of a platform biorenewable for the first time. While two equivalents of HBcat converts 1-SiEt₃ to 3, three equivalents takes it all the way to triol 4 (Table 2, entry 3). In this latter case, the reaction is less selective as 2 and 5 were also obtained in variable yields. When the O-protecting groups were the bulky -SiPh₃ (1-SiPh₃), 1.0 equiv of HBcat cleanly provided 1-deoxysorbitan 5 (Table 2, entry 4).⁴⁸ An excess of HBcat converts 1-SiPh₃ to tetraol 2 (Table 2, entry 5); no additional reduction occurs. 1-Si^tBuMe₂ also provided 4 in 57% yield along with recovered starting material; increasing HBcat equivalents did not improve the yield.⁴⁹

It is unclear at this time whether these reductions occur through borenium ($catB-L^+$) or boronium ($catB-L_2^+$) intermediates, though our experiments exploring catalyst speciation with THP suggest the latter (vide supra). For the sake of simplicity, however, we will discuss the mechanism as though the key intermediates are three-coordinate borenium ions, as boronium ions should behave similarly despite their more complex coordination chemistry.

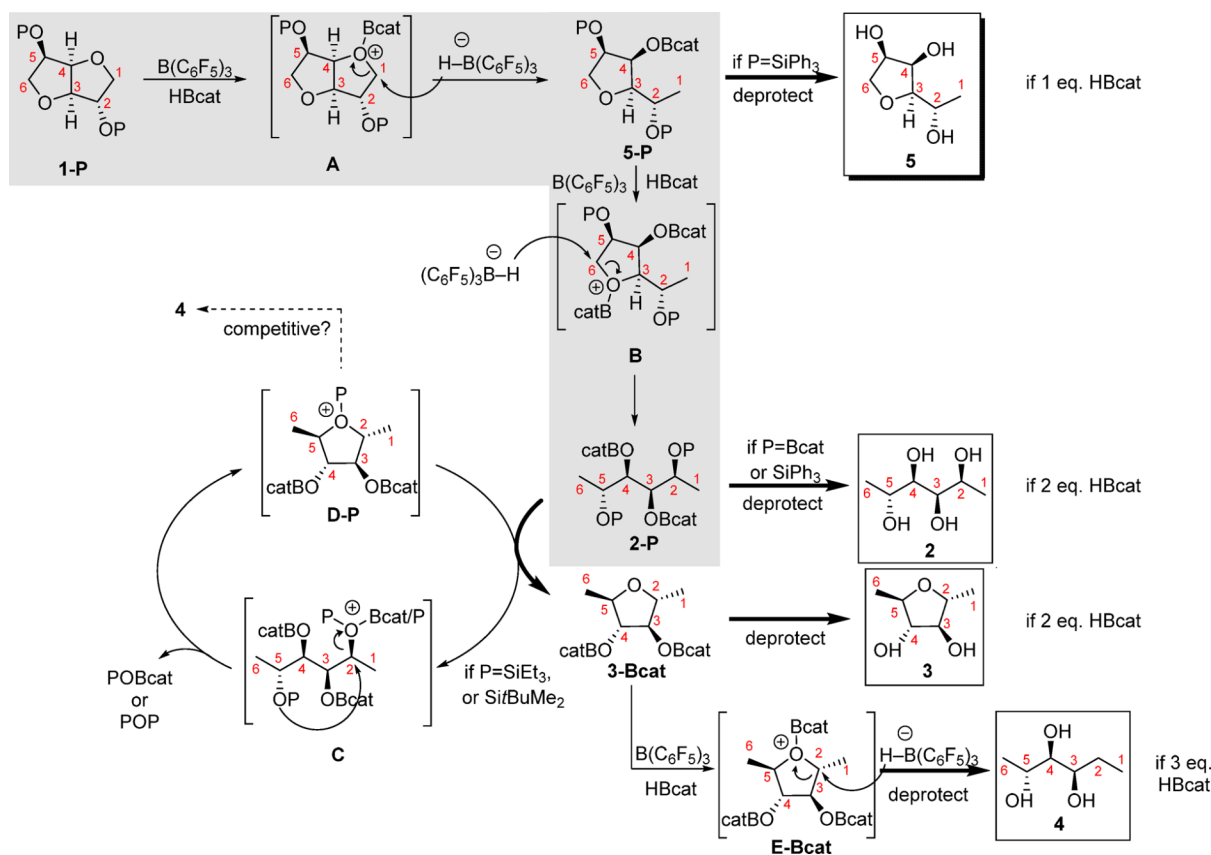
The selective conversion of 1 to each of the compounds in Table 2 can be explained by a series of C–O activation processes that sequentially open the two THF-rings at the 1° positions (shaded area in Scheme 4). How far the reductions proceed down this pathway is sensitive to the O-protecting group (and the equivalents of reductant). When the protecting group is Bcat (1-Bcat, entry 1), one generates, via intermediates A and B (Scheme 4), tetra-Bcat protected 2 (2-Bcat), and for reasons proposed in the following paragraph, this intermediate is *not* susceptible to further reaction. A similar sequence with 1-SiEt₃ would generate the putative 2-SiEt₃ (not observed), which differs from 2-Bcat in that the C2 and C5 alcohols are -SiEt₃ protected. This difference is significant enough to make 2-SiEt₃ more reactive than 2-Bcat. The combination of $B(C_6F_5)_3$ /HBcat then initiates a cyclization through intermediates C and D to form 3-Bcat. Once the cyclization is initiated (to form D, P = SiEt₃), the intermediate can transfer SiEt₃⁺ back to 2-SiEt₃ to reinitiate the conversion to 3-Bcat. If another equivalent of HBcat is present then 3-Bcat is further reduced to triol 4.

Table 2. Reduction of Isosorbide

							
entry	protecting group (P)	x (equiv)	time (h)	2 (%) ^a	3 (%)	4 (%)	5 (%)
1	-Bcat	6	24	71	— ^b	—	—
2	-SiEt ₃	2.1	<1	—	62	—	—
3	-SiEt ₃	3	16	>10	—	48	>10
4	-SiPh ₃	1	12	—	—	—	93
5	-SiPh ₃	4	12	69	—	—	—
6	-Si ^t BuMe ₂	2	24	—	—	57 ^c	—

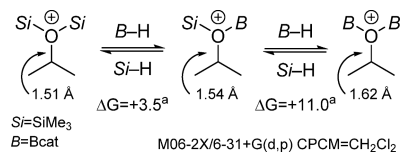
^aIsolated yields. ^bA dash (—) indicates that the compound was not detected in the crude $^{13}C\{^1H\}$ NMR spectrum (600 MHz cryoprobe) and was not isolated. ^cWith 42% deprotected starting material recovered.

Scheme 4. Proposed Pathway to Partially Reduced Products of 1-P with HBcat



DFT calculations examining the relative stability of silyl/boryl oxonium ions shed light on why **2-Bcat** is not cyclized while **2-SiEt₃** is able to convert to **3-Bcat** efficiently. The exchange of one trimethylsilyl group for a catecholboryl group on the disilyl oxonium ion of 2-propanol led to an optimized structure whose free energy was 3.5 kcal mol⁻¹ higher than the analogous disilyl oxonium (Scheme 5). The diboryl oxonium

Scheme 5. DFT Study of Silyl/Boryl Oxonium Ions of 2-Propanol



^aΔG values in kcal mol⁻¹.

that resulted from a second boryl exchange was even more destabilized (11.0 kcal mol⁻¹), making it 14.5 kcal mol⁻¹ more destabilized than the original disilyl oxonium. These relative stabilities imply that it is much more difficult to activate a borate ester by a Bcat⁺ ion than to activate a silyl ether. Because **2-Bcat** has boryl groups at all positions, no additional activation occurs because this would necessitate the intermediacy of diboryl oxonium ions, and their high energy ensures that the tetraol reacts no further even with excess HBcat. Because O2 and O5 of **2-SiEt₃** are silylated, they can be further activated by HBcat by generating mixed silyl boryl oxonium ions, which are much closer in energy to disilyl

oxonium ions. These relative stabilities thus rationalize why **2-SiEt₃** can cyclize while **2-Bcat** is unreactive.

We next turned our attention to isomannide (**6**), the mannitol-derived stereoisomer of isosorbide. Dehydrocoupling with an excess of HBcat generated **6-Bcat** in situ, which, upon addition of $B(C_6F_5)_3$, is singly reduced to the previously unreported 1-deoxysorbitan **7** and doubly reduced to 1,6-dideoxytetraol **8** (Table 3, entry 1). We have previously obtained **8** from silane reductions of per-silyl protected mannitol.¹⁴ Unlike our previous work with isomannide,¹⁴ which only reduced the *secondary* C3 and C4 positions, HBcat selectively reduced the *primary* positions. With **6-SiEt₃**, we

Table 3. Reduction of Isomannide

6-P

10 mol% $B(C_6F_5)_3$
x eq. HBcat

CH₂Cl₂, rt;
quench MeOH

7

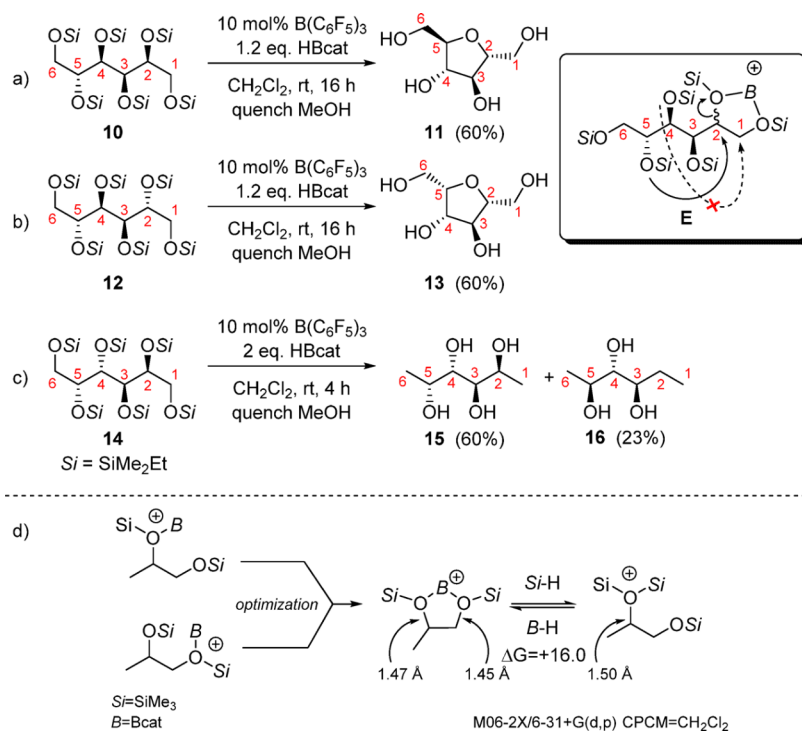
8

9

entry	protecting group (P)	x (equiv)	time (h)	7 (%) ^a	8 (%)	9 (%)
1	-Bcat	6	24	10	44	— ^b
2	-SiEt ₃	2	4	54	40	—
3	-SiEt ₃	10	16	—	67	—
4	-SiPh ₃	2	16	51	49	—
5	-SiPh ₃	4	16	—	90	—
6	-Si ^t BuMe ₂	1	2	—	—	47

^aIsolated yields. ^bA dash (—) indicates that the compound was not detected in the crude ¹³C{¹H} NMR spectrum (600 MHz cryoprobe) and was not isolated.

Scheme 6. Reduction of Dimethylethylsilyl-Protected Hexitols. (a) Sorbitol, (b) Mannitol, (c) Galactitol; (d) DFT Study of TMS-Propanediol^a



^aΔG values in kcal mol⁻¹.

obtained **7** in higher yields along with **8**. With an excess of HBcat, **6-SiEt₃** was exclusively converted to **8** (67% yield, Table 3, entry 3). Yields for **8** were optimum using **6-SiPh₃** (Table 3, entry 5). For **6-SiⁱBuMe₂**, a single secondary position is reduced, and the known 4-deoxysorbitan **9** was obtained in 47% yield (Table 3, entry 6).

Another class of compounds we have previously studied are silyl-protected hexitols, hydrogenated forms of hexoses.¹⁴ Sorbitol, the precursor to isosorbide and directly derived from glucose, is also an attractive target for reduction.⁵⁰ We initially attempted to dehydrocouple sorbitol with HBcat in dichloromethane, but even after a day, significant insoluble material remained. Presilylated sorbitol **10** (Si = Me₂EtSi), however, was soluble and was reacted with a range of HBcat amounts. When an excess of HBcat was used (6 equiv), significant amounts of *n*-hexane was observed by *in situ* ¹³C{¹H} NMR analysis. By contrast, full reduction of sorbitol with silane gave mixtures of hexane isomers.¹³ While poor selectivity was still observed for 2 and 4 equiv (mixture of partially reduced species), a good yield of the symmetric 2,5-anhydro-D-mannitol **11** was obtained using 1.2 equiv of HBcat (Scheme 6a). Hydrosilane reductants only provide the tetraol **2** and triol **4**.¹⁴ In the case of Me₂EtSi-mannitol **12**, a similar, but now unsymmetrical sorbitan (2,5-anhydro-D-glucitol, **13**) was formed in good yield with 1.2 equiv of HBcat (Scheme 6b). When Me₂EtSi-galactitol **14** was used, no sorbitan was formed with 1.2 equiv of HBcat and triol **15** and tetraol **16** were isolated in good yields only with 2 equiv (Scheme 6c).

Insights into this high regio-preference to form **11** and **13** emerged on computing geometry optimized structures of disilyl propanediol·Bcat⁺, which invariably converged to a boronium ion that chelates the two silyl ethers (Scheme 6d). These intermediates are reminiscent of the 1,2-diol activation

schemes reported by Morandi, which preferentially activate the primary position.¹⁹ The boronium ion chelation is calculated to be 16 kcal mol⁻¹ lower in energy than a secondary disilyl oxonium (Scheme 6d). In the context of **10**, this chelation enables the activation of a more hindered secondary C–O bond (C2 and C5), which enables the ring closing mode shown in **E** (solid arrow). While C1 is also activated in this chelate (and is the site of reduction in the Morandi examples),¹⁹ a cyclized product formed by this pathway is not observed. We suspect that 1,2-chelation affects the available conformations of **10**, **12**, and **14**, and this phenomenon influences the selectivity for cyclization (**10**, **12**) versus reduction (**14**). In the absence of a chelated activation mode, for example, in “SiR₃⁺” catalyzed condensative cyclizations of linear hexitols,⁴⁷ site-selective activation of the terminal O-position occurs to yield the O4 onto C1 product (Scheme 6, **E**, dashed arrow), in clear contrast to the reactivity demonstrated herein.

To conclude, we have demonstrated that catecholborane can reduce sp³ carbon–oxygen bonds in both simple ethers and more complex carbohydrate derivatives. The formation of strong boron–oxygen bonds helps to drive a heterolytic B–H activation mechanism by the B(C₆F₅)₃ catalyst, which first activates the oxygen with a Bcat⁺ equivalent and then cleaves the C–O bond with the H–B(C₆F₅)₃[−] hydride. Computational studies imply that more potent O-activation occurs with Bcat⁺ equivalents than with SiR₃⁺ equivalents and moreover that a chelation assisted mechanism for C–O activation may assist in influencing site-selectivity in multifunctional structures. This study marks the first example of achieving mild sp³ C–O reduction catalysis with the commercially available B(C₆F₅)₃ with both HBpin and HBcat, with HBcat being the more robust reductant. While the reactivity largely parallels

hydrosilanes for simple substrates, judicious choice of protecting group and reductant amount in multifunctional carbohydrate derivatives has led to a marked divergence in reactivity with the HBcat reductant, with products not obtained previously or in higher yields than when a hydrosilane is used. This furthers the goal of obtaining diverse high-value chemicals from biorenewable sources.⁵¹

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02337.

Experimental procedure for all deoxygenation reactions and NMR spectra of starting material and novel compounds, as well as DFT work (PDF)

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Notes

The authors declare no competing financial interest.

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