Project One. Reductive N-heterocycle and carbocycle formation under $\text{R}_3\text{SiH-B(C}_6\text{F}_5)_3$ catalysis

**Introduction**

Based on our group’s previous study on chemoselective partial reduction of silyl-protected sugars and sugar-derivatives\(^1\), a diverse set of oxygen-functionalized chiral synthons can be synthesized in short steps. The catalytic combination of the strong Lewis acid B(C\(_6\)F\(_5\))\(_3\) and a tertiary silane efficiently generates a reactive equivalent of an highly electrophilic silylium ion (R\(_3\)Si\(^+\)) and a HB(C\(_6\)F\(_5\))\(_3\)-reducing agent\(^2\). The silylium ion “activates” the C-O bond through a favored formation of the strong Si-O bond, pulling electron density from the oxygen atom and weakening the C-O bond. The hydride is delivered by HB(C\(_6\)F\(_5\))\(_3\) to attack the carbon atom and break the C-O bond in an S\(_\text{N}2\) fashion. The catalytic reduction of C-O bonds allows control for stereo-selectivity and site-selectivity in an array of stereo-defined C-O bonds that are ubiquitous in carbohydrates, achieved by mechanism of neighboring group participation and formation of cyclic intermediates.

It has been shown that with low concentration or absence of the reducing species HB(C\(_6\)F\(_5\))\(_3\), intramolecular nucleophilic attack by oxygen lone pair outcompetes intermolecular hydride attack. The resulting O-heterocycle products can be isolated. As heterocycles are common components of various natural products and drugs\(^3\text{a}-\text{c}\), we continued to explore the formation of heterocycles and even carbocycles using sugar derivatives, which are naturally abundant chiral pool compounds and building-blocks for total synthesis\(^4\). In our study, when amine moiety and alkene moiety are incorporated into carbohydrate molecules, the N lone pair and C=C bond act as nucleophiles to achieve intramolecular cyclization. Starting from the bio-renewable enantiopure chiral pool compounds as an alternative for fossil fuels\(^5\), the catalytic combination of $\text{R}_3\text{SiH-B(C}_6\text{F}_5)_3$ enables generation of pharmaceutical precursors containing heterocycle and carbocycle cores in high diastereoselectivity.

**Experimental Procedure**

The substrates for N-heterocycle formation was synthesized via reductive amination of monosaccharides and primary amines, followed by global silyl protection of hydroxyl groups. The silyl protection using $\text{R}_3\text{SiCl}$ prevents the in-situ acid-base reaction of silanes and OH groups and is more economically efficient. An example of substrate prepared from glucose and benzyl amine is provided below:

![Experimental Procedure Diagram]

The substrates for carbocycle formation was synthesized via Wittig olefination of 2-deoxy hexoses, where the absence C-O bond at C\(_2\) prevents S\(_\text{N}2\)/S\(_\text{N}2\)' direct hydride reduction which disables the carbocycle formation. An example of the two-step preparation of
an E/Z mixture of a typical substrate TMS-styryl-2-deoxy glucose is provided below:

**Results and Discussion**

In the first attempt to form N-heterocycles with substrate 1, only 10 mol% B(C₆F₅)₃ was used to activate the C-O bond and induce C-N bond formation, which proved inefficient. Based on previous example of O-heterocycle formation using Silyl-BArF, a more oxophilic species, the silylium ion, was generated *in situ* by stoichiometric combination of Me₂EtSiH and [Ph₃C][B(C₆F₅)₄] to activate C-O bond cleavage. Notably the presence of the non-cordinating counterion [B(C₆F₅)₄]⁻, instead of the reducing HB(C₆F₅)₃⁻ anion is key to the intramolecular C-N bond formation.

Unfortunately the purification of the potential N-heterocycle from an O-heterocycle by-product turned out challenging and a full characterization was not available. The two competitive cyclization pathway are outlined below:

The attempt to form carbocycles turned out to be successful. In this case a product
containing a cyclopropane core with a stereo-defined polyol side chain and a benzyl group side chain is formed, which gives 82% yield and >98% diastereoselectivity. The structure of a “homoallylic alcohol” is required for the cyclopropane formation. The stereo-character of the cyclopropane moiety is characterized using selective 1D gNOESY.

A proposed catalytic cycle for the B(C₆F₅)₃ catalyzed reductive cyclopropanation is outlined below:

An Et₃SiH-B(C₆F₅)₃ adduct is formed in the first step, which selectively activates the most sterically-accessible primary C-O bond at C₇. An intramolecular nucleophilic attack of the O₄ lone pair at C₇ in the second step renders the formation of the five-membered O-heterocycle silyloxonium intermediate, generating the disilylether by-product and a reducing HB(C₆F₅)₃ species. The formation of this intermediate is kinetically favorable based on previous examples. A stereo-structure of the proposed transition state in the cyclopropane formation (step 3) is shown above, which allows for an overlap of the C=π orbital and C-O
σ* orbital. The cleavage of the C-O bond and formation of C-C bond is proposed to occur in a concerted S_N2 manner. The high diastereoselectivity is proposed to be induced by a favorable T.S. with minimal steric congestion between the OTMS group at C_5 and the styryl group. The formation of cyclopropane leads to an intermediate with a positive charge at C_1 stabilized by the neighboring phenyl group, and this intermediate is the proposed resting state of the catalytic cycle. The intramolecular hydride reduction at C_1 gives the final product and regenerates the catalyst.

Notably, in this cyclopropane formation, products generated via two other competitive pathways, reduction at the most sterically-accessible primary C_7 position and cyclopentane formation, are not observed. Although the ring strain for cyclopentane is significantly lower than cyclopropane, the energy barrier for secondary C-O activation at C_6 is too high due to steric hindrance. Therefore, cyclopropanation is kinetically more favorable at this condition (0 °C). In fact, cyclopentane formation was only observed for pentose-derived substrates which happens to provide a 1,5 di-α relation between the C=C bond and the primary C-O bond at the chain end:

![Diagram of reaction mechanism]

Surprisingly, an unusual rearrangement product was observed at low concentration of silane and was proved reproducible:

![Diagram of rearrangement product]

A rationale for this intramolecular skeleton rearrangement is that at low concentration of the reducing agent HBCF, there’s lower chance for the hydride to be delivered at the electrophilic site. It allows for ample “time” for the intramolecular rearrangement to occur prior to intermolecular process. Inspired by previous examples of vinyl shift observed for styryl-hexose substrates, an alkyl shift mechanism is proposed for specific this styryl-2-deoxy hexose substrate:
To probe the proposed mechanism, an experiment with deuterated silane verified the position of hydride reduction at C₁. The proposed oxocarbenium intermediate, though highly electrophilic, turns out not reduced by the external hydride, but rather reacted via intramolecular hydride shift. The 1,2 hydride shift ultimately drives the C=C migration and stabilization of positive charge at benzylic position.

**Conclusion**

Starting from the bio-renewable carbohydrate derivatives, a facile, metal-free, two-step synthesis of compounds containing a cyclopropane core and multiple steric centers with high yield and diastereoselectivity is enabled by the Et₃SiH-B(C₆F₅)₃ catalytic system. This reductive cyclopropane formation provides new access to pharmaceutical precursors and building blocks for natural products from the naturally abundant chiral pool compounds.

**Project Two. Exploring selectivity of C-O bond reduction under borohydrides-B(C₆F₅)₃ catalysis**

**Introduction**

The catalytic combination R₃SiH-B(C₆F₅)₃ has been proved efficient in polarizing and subsequently reducing C-O bonds in a selective manner. The silane Si-H bond is heterolyzed by B(C₆F₅)₃, generating both the oxophilic silylium ion and the reducing hydride.

This project aims at studying an alternative hydride source, the borohydrides, as an attempt to explore potential new reactivity and selectivity. In our study, the analogue Lewis adduct, RO₂BH-B(C₆F₅)₃ / R₂BH-B(C₆F₅)₃, exhibit different reactivity in catalytic reduction of C-O bonds. The difference in hydride donor ability between borohydrides and silanes, as well as the electrophilicity of silylium ion (R₃Si⁺) and borinium ion (R₂B⁺), could explain for the reactivity difference.

Because O-B bond (ΔH° = 125 kcal/mol) is stronger than O-Si (ΔH° = 110 kcal/mol) bond, the polarization of C-O bond by borinium ion (R₂B⁺) or boronium ion (R₂BL⁺) is
thermodynamically more favorable. In addition, the empty p orbital of boron could form dative bond with oxygen lone pair, which might explain the its different behavior in reducing 1,2-disubstitued substrates compared to silanes.

**Experimental Results and Discussion**

The initial study focused on three commercially available borohydride sources, catecholborane (HBCat), pinacolborane (HBPin) and 9-BBN. The hydride donor ability of the three borohydrides derived by computational methods\(^7\) is outlined below:

![Table 1.](image)

<table>
<thead>
<tr>
<th>Hydride Donors</th>
<th>[Lewis Acid-H]</th>
<th>Lewis Acid(^+) + H(^-)</th>
<th>(\Delta G_{\text{H}}) (298K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBCat</td>
<td>(\text{B-H})</td>
<td>(\text{B-H}) (\text{Et}_3\text{SiH})</td>
<td>159.18 (\text{B-H}) (\text{H}(\text{C}_6\text{F}_5)_3)</td>
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<tr>
<td>HBCat</td>
<td>(\text{B-H})</td>
<td>(\text{B-H}) (\text{Et}_3\text{SiH})</td>
<td>99.02 (\text{B-H}) (\text{H}(\text{C}_6\text{F}_5)_3)</td>
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<tr>
<td>HBCat</td>
<td>(\text{B-H})</td>
<td>(\text{B-H}) (\text{Et}_3\text{SiH})</td>
<td>64.95 (\text{B-H}) (\text{H}(\text{C}_6\text{F}_5)_3)</td>
</tr>
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</table>

The borohydrides are generally poorer hydride donor than silane, and 9-BBN is the strongest hydride donor of the three borohydrides. Using \(\text{H}(\text{C}_6\text{F}_5)_3\) as reference, the relative hydride donor ability of HBCat, HBPin and 9-BBN is outlined below:

![Table 2.](image)

<table>
<thead>
<tr>
<th>Borohydride + (\text{H}(\text{C}_6\text{F}_5)_3)</th>
<th>Bornium/silylium cation (\text{OXophilic C-O bond Activator}) + (\text{H}(\text{C}_6\text{F}_5)_3) (\text{Good hydride donor})</th>
<th>(\Delta G) (298K)</th>
<th>Alternative &quot;adduct&quot; form</th>
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<td>(\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H})</td>
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<td>20.92 (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H}) (\text{B-H})</td>
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Based on the relatively higher \(\Delta G\) of complete heterolytic cleavage of B-H, it is more appropriate to draw the catalytic combination as an "adduct" form, where the bonding of hydride is shared between two boron centers.

Initial study of C-O bond reduction on model substrates using the three borohydrides as reducing agent established the general trend of reactivity: HBCat > HBPin > 9-BBN. No C-O bond reduction was observed with 9-BBN-\(\text{B}(\text{C}_6\text{F}_5)_3\) combination. The HBCat has the best performance in selective demethylation of aryl methyl ether substrates, in which the C-O bond of silyl-protected alcohol is not reduced. The experimental results are summarized as follows:
According to the hydride donor ability trend, the catecholborane is the poorest hydride donor among the three borohydrides. However, it turns out to have generated the most efficient catalytic combination with B(C₆F₅)₃ to reduce C-O bonds. To rationalize the result, it can be argued that both electronic and steric effect are crucial in C-O bond activation. It is possible that HBCat, which is nearly a "flat" molecule, introduce least steric congestion in the transition state. Moreover, the ability to activate C-O bond by forming a strong interaction between O and B and weakening the C-O bond is not necessarily in the same trend as hydride donor ability, which describe the relative ease to lose the hydride.

Notably, 9-BBN generally exist in a dimer form and the bridged B-H bonds are probably difficult to be heterolyzed with B(C₆F₅)₃, which might account for the lack of reactivity with 9-BBN.

The model substrates containing C-O bonds in distinct chemical environment have either different Lewis basicity of oxygen lone pair or resonantly-stabilized transition state/intermediate. For model substrates that contain phenyl/diphenyl moiety, the positive charge build-up on the carbon atom of C-O bond being reduced is stabilized via resonance, where increased conversion to reduced products (entry 1,2) was observed. For the α and β anomer of the TMS-glucoside (entry 3,4) where four alkyl ether C-O bonds present in the molecule, the

<table>
<thead>
<tr>
<th>Substrate</th>
<th>9-BBN</th>
<th>HBPin</th>
<th>HBCat</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td>10 mol% BCF 1.5 eq. HBPin CH₂Cl₂, r.t. 18h Deprotection 39% conversion</td>
<td>10 mol% BCF 1.5 eq. HBPin CH₂Cl₂, r.t. 18h Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td>10 mol% BCF 1.5 eq. 9-BBN CH₂Cl₂, r.t. 18h No rxn</td>
<td>10 mol% BCF 1.5 eq. HBPin CH₂Cl₂, r.t. 18h Deprotection Complex Mixture</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /> TMS-α-glucoside</td>
<td>10 mol% BCF 2.0 eq. 9-BBN CH₂Cl₂, r.t. 18h No rxn</td>
<td>10 mol% BCF 2.0 eq. HBPin CH₂Cl₂, r.t. 18h Deprotection 19% conversion</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Image" /> TMS-β-glucoside</td>
<td>10 mol% BCF 2.0 eq. 9-BBN CH₂Cl₂, r.t. 18h Intra molecular competition between ester and TMS-benzylic alcohol</td>
<td>10 mol% BCF 2.0 eq. HBPin CH₂Cl₂, r.t. 18h Deprotection Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Image" /></td>
<td>10 mol% BCF 4.0 eq. 9-BBN CH₂Cl₂, 35°C, 18h No rxn</td>
<td>10 mol% BCF 4.0 eq. HBPin CH₂Cl₂, r.t. 18h Deprotection 24% conversion</td>
</tr>
</tbody>
</table>

* Calculation of conversion based on crude ¹H-NMR

Table 3.
Reductive demethylation leads to the only product, possibly because it is an entropically driven process which emit methane gas. For the model substrates with 1,4-disubstitution of methoxy group and benzyl TMS-alcohol (entry 5), an intramolecular competition between two C-O bond reduction is tested. The C-O reduction of the alcohol is favored over the demethylation due to the strong electron-donating effect of the para-methoxy group at the benzyl position, which lowers the activation energy for reduction of the benzyl C-O bond. For the model substrates with 1,4-disubstitution of methoxy group and alkyl TMS-alcohol (entry 6), the results shows that the aryl methyl ether is more reactive than silyl protected alcohol, despite the fact that its lone pair is delocalized into the benzene ring which reduces its Lewis basicity.

A general trend for substrate reactivity rationalized with relative Lewis basicity of oxygen atom in C-O bonds (more Lewis basic O has lower energy barrier for C-O activation):

Based on the experimental results, this chart provides a rough guide for chemoselectivity of different C-O bond reduction under HBCat/ HBPin-B(C₆F₅)₃ catalysis.

The demethylation product (highlighted in red) indicates potential application of HBCat-B(C₆F₅)₃ in chemoselective demethylation reactions. The optimization of this selective demethylation reaction demonstrated the subtle reactivity difference of C-O bond reduction between an aryl methyl ether and a non-activated TMS-alcohol. When excess HBCat (2.4 equiv.) was used, both C-O bonds are reduced:

The selective demethylation (entry 6, table 3) was also achieved under Et₃SiH-B(C₆F₅)₃ condition in high yield:

An unusual result leads to reevaluation of previous interpretation of the role of borohydrides in the C-O reduction chemistry. In this experiment, the two substrates’s methoxy groups are subject to similar para-activating effect of the alkyl group, but exhibit completely different reactivity.
Given the only difference is the presence of silyl group, two control reactions are performed:

From the control reaction when silyl group is at presence in the reaction mixture, reduction of C-O bonds is observed. Moreover, the secondary C-O bond reduction is favored over demethylation under BCF-HBCat condition, which indicates a possible $S_N$1-like pathway. To make clear the position of silyl group in the product, the product is characterized by $^1$H-NMR in DMSO without deprotection. Surprisingly the silyl protecting group “transferred” from the alcohol to the phenol position:

Two mechanisms are proposed for the observed “silyl transfer” reaction:

(1). HSIE$_3$ was generated in-situ and formed BCF-HSIE$_3$ adduct

(2). Intermolecular activation between two substrate molecules:

Inspired by the reaction where secondary C-O reduction is favored over the demethylation in a 1:1 ratio intermolecular competition, attempt was made to test if BCF-HBCat condition favors secondary C-O bond reduction over primary C-O bond
For the model substrates with 1,2-diol substitution pattern, a desired selective secondary C-O reduction in high conversion was not observed. As silyl-protected 1,2 diol has higher steric hindrance than previous substrate (1,4-disubstituted benzene) and could cause decreased reactivity. Future experiments include mixing TMS-1-hexanol and TMS-2-hexanol in 1:1 ratio under BCF-HBCat condition to create a scenario of intermolecular competition between primary and secondary C-O bond reduction. Furthermore, the C-O bond reduction with BCF-HBCat should be tested on substrates with free alcohol in the absence of silyl protecting group to eliminate potential pathway of generating silanes in situ.

Apart from C-O reduction for ether and silyl-protected alcohol with BCF-HBCat, the system as well as the BCF-Silane system are also tested on substrate containing both arylmethyl ether and aldehyde functional groups. The hydroboration/hydrosilation of “C=O” bond outcompetes the demethylation:

**Conclusion**

An initial study is conducted on the catalytic ability for C-O bond reduction with the combination of $\text{B}(\text{C}_6\text{F}_5)_3$ and borohydrides, including catecholborane, pinacolborane and 9-BBN. Catecholborane shows the best result for catalytic reduction tested on C-O bonds in aryl ether, alkyl ether and silyl-protected alcohol. Selective demethylation of aryl methyl ether over TMS/TESS protected alcohol is achieved using BCF-HBCat or BCF-HSiEt$_3$ combination. Elucidation of the mechanism for C-O bond reduction with borohydrides requires further mechanistic study on roles of silyl protecting groups and the HBCat-BCF adduct.
Reference

4. Martinez, R. “Creativity from the Chiral Pool: Sugar Edition”

Acknowledgement

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