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## COMMUNICATION

## Synthesis of allylic and homoallylic alcohols from unsaturated cyclic ethers using a mild and selective C–O reduction approach<sup>†</sup>

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Unsaturated cyclic ethers can be mildly and selectively reduced with catalytic amounts of  $B(C_6F_5)_3$  in the presence of an alkylsilane. The allylic position is preferentially reduced with minimal or no scrambling of olefin geometry. For electronically equivalent substrates, steric factors guide the reducing agent to the least substituted site.

Fluorinated boron Lewis acids have gained popularity in recent years as catalysts for a variety of interesting synthetic transformations. Within this class of Lewis acids,  $B(C_6F_5)_3$  is most commonly employed.<sup>1</sup> While the majority of applications are in its utilization as a co-catalyst for metallocene-driven olefin polymerizations,<sup>2</sup> new reductions<sup>3</sup> and the formation of frustrated Lewis acid-base pairs<sup>4</sup> have surfaced as new application avenues for  $B(C_6F_5)_3$ . We first learned of this reagent during two of our synthetic campaigns,<sup>5</sup> wherein catalytic amounts of  $B(C_6F_5)_3$  in the presence of a silane proved to be the only conditions that successfully deprotected the complex aryl methyl ether substrates we were employing. Inspired by the mildness of this etheral reduction approach first reported by Gevorgyan and Yamamoto,<sup>6</sup> absence of further investigations and lack of synthetic applications beyond the deprotection of aryl methyl ethers,<sup>7</sup> we decided to study how unsaturated cyclic ethers (2,5-dihydrofurans<sup>8</sup> and 3,6-2*H*-dihydropyrans)<sup>9</sup> behaved when subjected to this reduction approach (Scheme 1).

There are several reasons why we chose 2,5-dihydrofurans and 3,6-2*H*-dihydropyrans as substrates for this study: (1) 2,5-dihydrofurans contain two allylic etheral C–O bonds, which allow evaluation of the impact of sterics *vs.* electronics in the reduction step as well as any E-Z olefin scrambling arising from potential intermediate cationic species; (2) 3,6-2*H*-dihydropyrans would provide an opportunity to compare the B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> reduction behaviour of allylic *vs.* non-allylic C–O bonds as a function of steric and electronic parameters; (3) reduction results from these two heterocyclic classes could provide valuable new mechanistic insights; and (4) if the olefin geometry of the heterocycle is not



Scheme 1 Challenges with Unsaturated Cyclic Ether Reductions.

scrambled during the reaction, this would represent an attractive approach for accessing allylic and *homo*-allylic alcohols.<sup>10,11</sup>

The results from the 2,5-dihydrofuran catalytic reduction studies are shown in Table 1. All of the etheral reductions proceeded cleanly in high yield. With the exception of entries 3 and 6, the product olefins have not migrated or scrambled.

Table 1 Catalytic Reduction of 2,5-Dihydrofuran C-O bonds

Entry	Substrate	Product	Time (h)	Yield <sup><math>a</math></sup> (%)
1	$\langle \rangle$	HO	1	79
2	C7H15	HO HO	2	88
3	C Ph	HOPh	0.5	91
4	C <sub>6</sub> H <sub>13</sub>	∕OH	2	87
5	∠Ph	∕=< ──OH	2	91
6	$C_4H_9$ $C_4H_9$	$HO \longrightarrow C_4H_9$	4	94
7		ОН	8	83
8			4	72 <sup><i>b</i></sup>

Conditions: 5 mol% B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, <sup>*a*</sup> 1.1 equiv. Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, rt then TBAF, <sup>*b*</sup> 4.5 equiv. Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, rt.<sup>12</sup>

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The data suggests that the reducing agent is impacted by steric and electronic factors. For example, entries 2 and 8 suggest that sterics play a key role while entries 3 and 6 suggest that for a strongly cation stabilizing group this selectivity can be reversed to favour electronics. For entry 8, the less hindered and electronically richer ether bond is selectively reduced.

Following the success in reducing 2,5-dihydrofurans, we were eager to learn how selective reductions of 3.6-2H-dihydropyran substrates would be. All of the fifteen substrates presented in Table 2 were reduced in high yield to produce homoallylic alcohol products using these catalytic reduction conditions. Olefin migration or scrambling was observed for three substrates (entries 4-6), wherein in one case the double bond migrated into conjugation with the phenyl group (entry 6) while for the other two it isomerized (entries 4-5). It is important to note, as we observed for entry 3 in Table 1, that when the phenyl group in the 2-position is replaced with an alkyl group olefin isomerization is suppressed for all but one substrate (entry 5). These results demonstrate that electronics dictate which C-O bond is reduced. In all cases, the allylic C-O bond is reduced regardless of whether it is sterically more incumbered than the non allylic C-O bond (entries 3-8 and 11-15). This new method provides a mild controlled access to homoallylic alcohols with di- (entries 6-8), tri- (entries 1, 3-4, 9-10 and 12-15) or tetra- (entries 2, 5 and 11) substituted olefins that might otherwise be challenging to access selectively using standard carbonyl olefination protocols. Although isomerization is observed for entry 4 it is an impressive reminder of the electronic control of this reaction, which completely favors reduction of the quaternary substituted allylic site over unsubstituted non-allylic site. Entry 15 is noteworthy as it illustrates how this mild method could be used to selectively incorporate deuterium at allylic positions simply by replacing Et<sub>3</sub>SiH with Et<sub>3</sub>SiD.

The twenty three examples presented in Tables 1 and 2 clearly demonstrate that this mild catalytic reduction reaction is controlled by electronic factors. This is most apparent in the reduction of 3,6-2H-dihydropyrans (Table 2), where in all cases the more stabilized allylic position is preferentially reduced regardless of how sterically congested it is. The 2,5-dihydrofuran examples showcase how this reduction proceeds when presented with two similar allylic bonds. For this scenario, sterics trump electronics in all cases except when a strongly stabilizing group (Table 1, entry 3) is present. Based on our results and mechanistic studies done by Gevorgyan and Yamamoto,<sup>6</sup> we propose the following catalytic cycle (Scheme 2). A silylium ion, generated by the reaction of triethylsilane (Et<sub>3</sub>SiH) with the catalyst  $(B(C_6F_5)_3)$ , reacts with the ether oxygen atom of the unsaturated cyclic ether. Our data strongly suggests, as shown by vast majority of substrates studied, that reduction of this silvlium activated ether proceeds fast to the product as suggested by the lack of any olefin isomerization for these substrates. The substrates that undergo olefin isomerization (entries 3 and 6 in Table 1 and entries 4-6 in Table 2) all contain a strongly cation stabilizing groups (phenyl or dialkyl). These special substitutents facilitate carbocation formation, olefin migration followed by reduction.

In conclusion, we have shown that  $B(C_6F_5)_3$  in combination with  $Et_3SiH$  can be used to mildly and selectively reduce the

 Table 2
 Catalytic Reduction of 3,6-2H-dihydropyran C–O bonds

Entry	Substrate	Product	Time (h)	Yield (%)
1	Ph	HO	0.7	87
2	Ph	HO	0.7	96
3		НО	1.5	90
4	Ph	HO	10	75 (1:5:1)
5	Ph	HO	1	82 (1:5:1)
6	O Ph	OH Ph OH Ph	0.25	94 (1:1:2)
7	0 C <sub>6</sub> H <sub>13</sub>	HO C <sub>6</sub> H <sub>13</sub>	2	98
8	0 C <sub>7</sub> H <sub>15</sub>	HO C <sub>7</sub> H <sub>15</sub>	3	88
9	Ph	HO	1.5	88
10	C7H15	HO C <sub>7</sub> H <sub>15</sub>	1.5	86
11		HO C7H15	3	90
12		HO HO	2	90
13	C <sub>4</sub> H <sub>9</sub> O C <sub>4</sub> H <sub>9</sub> C <sub>7</sub> H <sub>15</sub>	HO C <sub>4</sub> H <sub>9</sub> C <sub>7</sub> H <sub>15</sub>	2.5	82
14	0 C <sub>7</sub> H <sub>15</sub>	HO C <sub>7</sub> H <sub>15</sub>	3	78
15 <sup>a</sup>	C7H15	HO D	2.5	94

Conditions: 5 mol%  $B(C_6F_5)_3$ , 1.1 equiv.  $Et_3SiH$ ,  $CH_2Cl_2$ , rt then TBAF, <sup>a</sup>  $Et_3SiD$  was used instead.



Scheme 2 Proposed Mechanism for Reduction of 3,6-2H-dihydropyrans.

C–O bond of cyclic unsaturated ethers without scrambling the initial olefin geometry of the starting material. For this catalytic reduction approach electronics play a key role with allylic/benzylic C–O bonds being preferentially reduced over less hindered non-stabilized C–O bonds. These mechanistic insights strongly suggest the reduction of the activated ether occurs fast so as to suppress formation of a free allyl cation and therefore scrambling of olefin geometry. This etheral reduction strategy should prove especially attractive in accessing allylic and *homo*-allylic alcohols containing *tri*- and tetra-substituted olefins, which can be challenging to access using other methods. Furthermore, this approach lends itself well to selective deuterium labelling applications.

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12 As shown in entry 8 the triethylsilyl ethers, which are the initial reduction products, can be isolated and used. For this study, we chose to treat the crude reduction mixture with TBAF to make isolation of products (alcohols) a trivial column filtration.