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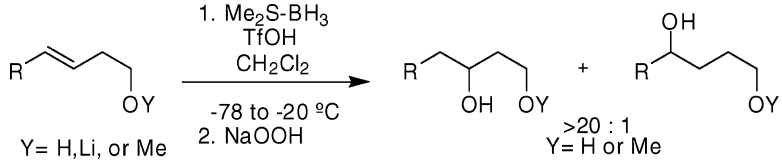

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Oxygen-Directed Intramolecular Hydroboration

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Despite repeated efforts over many years and several tantalizing empirical results that suggest oxygen-directed hydroboration (ODHB), definitive examples of this process have been rare.[1–4] Evans' metal-catalyzed reaction of catecholborane with several unsaturated alcohols, phosphinites, and carboxamides is the only method known to date with established synthetic potential for a range of substrates.[2] Another case of ODHB involving an α-methoxy-β,γ-unsaturated ester was encountered by Panek et al.[3] using $Me_2S\cdot BH_3$. This example approaches the regioselectivity of the Evans result with a homoallylic alcohol (8:1 vs 11:1), but appears to be a special case reflecting unusual reactivity due to the presence of ester as well as methoxy groups in the starting material. The other historical examples reveal interesting perturbations of hydroboration stereoselectivity or regioselectivity by oxygen substituents,[4] but these reactions generally do not give useful product ratios. Our work reported below demonstrates a mechanistically distinct version of ODHB using metal-free conditions that afford unprecedented levels of regiocontrol.

The analogy of amine-directed hydroboration[5] suggested that alcohol borane complexes **6** (Scheme 1) might be accessible from activated boranes **3** or **4** and homoallylic alcohols **5**. This would provide a basis for regiocontrol and intramolecular hydroboration if the potential complications from evolution of H_2 and weak O−B complexation at the stage of **6** could be overcome. An S_N2-like displacement of the leaving group X might then lead from **6** to the π-complex **7**, which would afford hydroboration products via the labile *O*-protonated 1,2-oxaborolane **8** or related intermediates.

A number of conditions were tested in attempts to activate dimethylsulfide borane **1** or thioanisole borane **2**[6] with I_2 or TfOH at −78 °C in the presence of (*E*)-3-pentenol **5a**. The resulting solution was warmed to −20 °C (5−19 h) and then quenched using standard oxidative workup (Table 1) for assay of the isomeric diols **9a** and **10a**. Both reactivity and regioselectivity were marginal in attempts to activate **1** with I_2. A control experiment using **1** without I_2 gave a 2.2:1 ratio of **9a** and **10a** at −20 °C, consistent with at least some HB involving unactivated $Me_2S\cdot BH_3$ in entries 1 and 2. Switching to thioanisole borane **2** improved both reactivity and regioselectivity for the iodine activation (entries 3 and 4), but this required an inconvenient procedure using B_2H_6 gas to generate **2**. Good selectivity was also observed by activating a solution of **5a** and **1** with TfOH at −78 °C, probably because this procedure minimizes any chance of background reaction. However, product recovery was low (∼20%, entry 5).

Preactivating the borane complex **1** with TfOH was found to be crucial for improved product recovery. With this modification, a series of homoallylic alcohols **5** gave useful yields and excellent regioselectivities (Table 2; preactivation at −78 °C and warming to −20 °C). In the highest yielding example, activation of **1** with TfOH followed by addition of **5e** resulted in conversion on a time scale of hours at −20 °C. Diol **9e** was obtained in 80% yield after oxidative workup (1.5 mmol scale), and NMR assay after derivatization[7] established 56:1 regioselectivity in favor of the 1,3-diol **9e** over **10e** (entry 5). Both the (*E*)- and (*Z*)-3-hexenols **5b** and **5c** (entries 2 and 3) reacted with >20:1 selectivity under these conditions, although the *E*-isomer gave the better result (37:1 **9b**:**10b**).[8] The highest regioselectivity was achieved in the conversion of **5f** to **9f** (entry 6), demonstrating that increased branching adjacent to C4 in **5f** compared to **5d** or **5e** (entries 4 and 5) correlates with higher regioselectivity. In contrast to the

Scheme 1

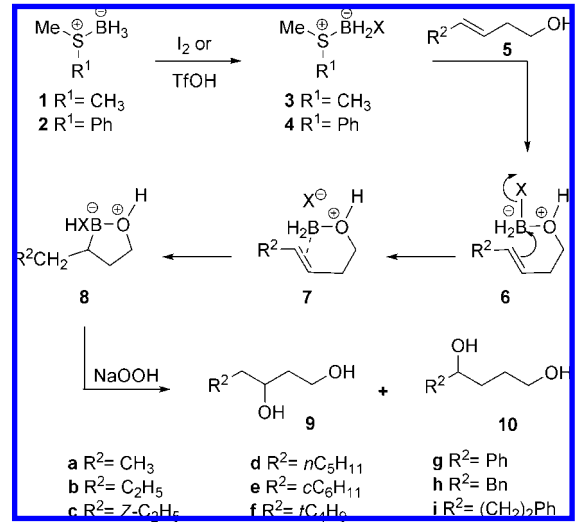

Table 1. Reaction of **5a** with **1** or **2** Activated *in situ*[a]

entry	borane source	activator	time (h)	conversion[b] (%)	**9a**:**10a**[b]
1	**1**	I_2	10	40	4.3:1
2	**1**	I_2	19	>90	4.7:1
3	**2**	I_2	5	>90	7:1[c]
4	**2**	I_2	5	>90	18:1[d]
5	**1**	TfOH	5	>90	>20:1

[a] A 0.1 M solution of **5** and 2 equiv of **1** or **2** at −78 °C in CH_2Cl_2 was treated with 2 equiv of activator, warmed to −20 °C, stirred (time), and quenched with $NaOOH/MeOH\cdot H_2O$. [b] NMR assay. [c] Activated at −20 °C and warmed to −10 °C. [d] Warmed to −10 °C.

Table 2. ODHB of Homoallylic Alcohols **5** with $Me_2S\cdot BH_3$ + TfOH[a]

entry	Stg	R^2	time (h)	yield (%)	**9**:**10**[b]
1	**5a**	CH_3	10	51[c]	>20:1
2	**5b**	C_2H_5	10	66[c]	37:1
3	**5c**	Z-C_2H_5	5	51[d]	28:1
4	**5d**	nC_5H_{11}	10	69	>20:1
5	**5e**	cC_6H_{11}	5	80	56:1
6	**5f**	tC_4H_9	5	56	82:1
7	**5g**	Ph	20	>3	N/D
8	**5h**	Bn	10	22	N/D
9	**5i**	CH_2Bn	5	59	>20:1

[a] Conditions: A 0.2 M solution of **1** (CH_2Cl_2) at −78 °C was treated with 1 equiv of TfOH, stirred 30 min, 0.2 M of **5** in CH_2Cl_2 added dropwise, and oxidative workup performed after (time) at −20 °C. [b] NMR assay. [c] Five equivalents of cyclohexene present. [d] Yield after derivatization.[7]

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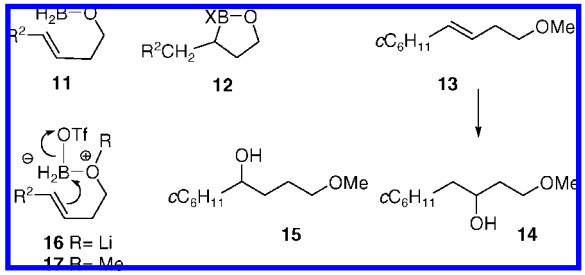
Scheme 2



successful TfOH experiments, attempted preactivation of **1** with iodine over the same temperature range (−78 to −20 °C) resulted in poor reactivity and low conversion.

Surprisingly, phenyl substituents near the C=C subunit decreased reactivity using the TfOH preactivation conditions. Thus, the styrene **5g** gave only trace conversion after 20 h at −20 °C, and the benzyl analogue **5h** reacted very slowly compared to other aliphatic substrates (entry 8). On the other hand, **5i** with a CH_2CH_2 spacer between the olefin and the phenyl group reacted normally, and good conversion was observed after 5 h (entry 9).

Entries 1 and 2 (Table 2) describe experiments where the ODHB reactions of **5a** and **5b** were conducted in the presence of 5 equiv of cyclohexene to confirm an intramolecular pathway. Selective consumption of the homoallylic alcohols was observed in both cases, while cyclohexanol was not detected after oxidative workup, as expected if the oxygen-directed internal pathway has a significant rate advantage. When these experiments were repeated in the absence of the cyclohexene, the yields of diols were somewhat lower (41% from **5a**, 51% from **5b**), suggesting that the cyclohexene additive serves in a protective role by scavenging residual triflic acid.[9]

Although the above experiments establish an intramolecular hydroboration process for the alcohol substrates, attempts to probe the sequence of events suggested in Scheme 1 using NMR spectroscopy provided only limited insight. When **1** was treated with TfOH at −78 °C, the ^{11}B chemical shift of **1** (δ −20.6 ppm) was replaced by a major new signal (δ −2.0 ppm, t, J = 129 Hz) consistent with the activated borane **3** (X = OTf). Addition of substrate **5b** at −78 °C and warming to −20 °C produced broad ^{11}B signals (δ 7.5 to −8.0 ppm; tetravalent boron), but no signals were found from δ 50 to 70 ppm, the range estimated for the hypothetical trivalent $ROBH_2$ (**11**)[10,11] or oxaborolanes **12** (X = H or OTf).[12]

In an attempt to detect **11** or other intermediates, alcohol **5b** was treated with BuLi (1.1 equiv) at −78 °C in DCM, followed by addition of the resulting alkoxide solution to preformed **3** (X= OTf, 2 equiv). The ^{1}H and ^{11}B NMR spectra were not definitive. However, quenching the solution after 5 h at −20 °C by oxidative workup with NaOH/MeOH/H_2O_2 gave the diol **9b** (56%, >20:1 regioselectivity).[8] Using the best substrate **5e** from Table 2, the lithium alkoxide procedure gave a 63:1 ratio of **9e**:**10e** in 64% yield after derivatization.[7] Similar results were obtained in several other examples, indicating that the lithium alkoxides are competent substrates for directed hydroboration. The small difference in regioselectivity compared with Table 2, entry 5, implies that the lithium alkoxide from **5e** need not react via the same regioselectivity-determining transition state as for the alcohol substrate, but a more convincing differentiation was desired. To this end, the methoxy ether **13** was subjected to the usual ODHB conditions using preformed **3** (X = OTf) at −78 °C (15 min) to −20 °C (10 h). After oxidative workup, the product was obtained as a 20:1 mixture of **14**:**15**. In contrast to results with the alcohol substrates, the *in situ* procedure (TfOH added to **13** + **1** at −78 °C, 15 min; −20 °C, 10 h) gave a better result (61% yield, 50:1 **14**:**15**). By comparison, standard hydroboration using THF/borane (0 °C, 4 h, THF) afforded a 1.4:1 mixture of **14**:**15**. These findings prove that ODHB can take place by mechanisms involving neither **6** nor the alkoxyborane **11**, but do not rule out these intermediates for the alcohol substrates. If covalently bound B−O intermediates are involved in all three reactions (alcohol, Li alkoxide, and ether substrates), then each of the distinct species represented by structures **6**, **16**, and **17** may be reactive in ODHB.[13] The ether example via **17** would be mechanistically analogous to the amine borane reactions,[5] but the relative merits of **6** and **16** remain unknown.

Pending the detection of hypothetical intermediates such as **11**, **6**, **16**, or **17**, we cannot comment further on the mechanism of ODHB. However, the preparative results show that the oxygen-directed intramolecular hydroboration is feasible for homoallylic alcohols, alkoxides, and ethers using **3** as an activated reagent equivalent to $TfOBH_2$.[14]

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

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(7) ^{1}H NMR assay of **9**+**10** was best done after diaroylation with 2-$CF_3C_6H_4COCl$ (resolved methine H's for all diol pairs except **9h/10h**).
(8) Diols **9b**, **9c**, and **9f** were difficult to purify due to water solubility and co-elution with Me_2SO_2 formed from Me_2S during oxidative workup.
(9) 1-Phenethyltetrahydrofuran was isolated in 6% yield using ODHB from **5i**. Analogous (volatile) byproducts from TfOH-induced cyclization were detected in ODHB experiments with some of the other alcohols **5**. The corresponding Li alkoxides give no cyclic ethers, but conversion was lower using 2 equiv of **3** (X = OTf) and the procedure more tedious.
(10) Alkoxyboranes similar to **11** are unknown. For detection of ROBHThx, see: Cha, J. S.; Seo, W. W.; Kim, J. M.; Kwon, O. O. *Bull. Korean Chem. Soc.* **1996**, *17*, 892. Activation of **1** afforded 92% of the expected H_2 within 30 min at −78 °C and an additional 0.15 equiv of H_2 vs the starting TfOH upon addition of **5b** and warming to −20 °C, but further hydrogen evolution was too slow to measure. In a control experiment, reaction of **1** with EtOH in DCM at−20 °C gave 5−7% H_2 within 20 min, and very slow H_2 evolution thereafter (9% total after 1.5 h).
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(13) The ^{1}H NMR spectrum after mixing **3** (X = OTf) and **5b** at −78 °C and warming to −20 °C (5 min) revealed a new signal at δ = 12.5 ppm, consistent with the O−H subunit of **6**. This signal disappeared over 15 min at −20 °C, but the olefinic signals were still present. Activation of *n*-Bu_4NBH_4 in CH_2Cl_2 at −78 °C with TfOH (2 equiv), addition of **5d**, and warming to −20 °C gave >20:1 **9d**:**10d** (60%) after oxidative workup, suggesting that Me_2S plays no major role.
(14) Allylic alcohols such as (*E*)-2-octenol are not reactive under the standard conditions of Table 2. Bis-homoallylic alcohols are reactive, but give lower regioselectivity (5:1 ratio favoring the 1,4-diol from (*E*)-hex-4-enol). Homoallylic alcohols containing alkyl groups at C_2 react with ≤1.5:1 dr.

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