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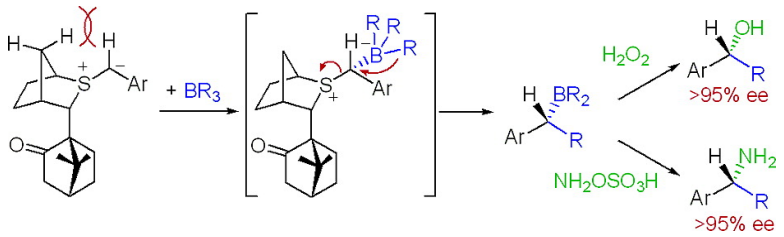

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Synthesis and Applications of Chiral Organoboranes Generated from Sulfonium Ylides

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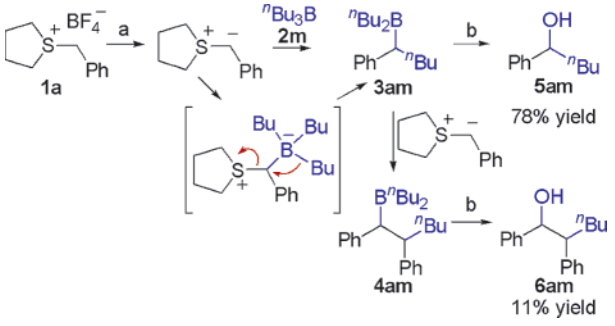
Chiral organoboranes are versatile synthetic intermediates, and two general routes have been developed for their synthesis: asymmetric hydroboration of alkenes[1] and Grignard addition to chiral α-chloroalkyl boronic esters.[2] Our interest in chiral sulfonium ylides led us to consider an alternative approach: reaction of an ylide with an organoborane. However, literature precedent was not encouraging; nonstabilized sulfur ylides react with organoboranes furnishing polymers[3] while ester-stabilized sulfur ylides react only once, but the intermediate α-boronyl ester rearranges to the boron enolate.[4] Clearly, to render the ylide reaction useful for organic synthesis, we needed to inhibit polymerization and avoid carbonyl-stabilized ylides. We believed that the extent of polymerization could be limited by using substituted ylides since the rate of subsequent homologation reactions, which involves reaction of the substituted ylide with an increasingly hindered organoborane, would be reduced.

Thus, we began our investigations with the benzyl sulfonium salt **1a** and tributylborane **2m**. Optimization of base, solvent, order of addition, and concentration resulted in clean homologation to give borane **3am** with only a small amount of the higher homologation product **4am** (Scheme 1). The homologation products were isolated as the alcohols **5am** and **6am**. Homologation products higher than **6am** were not detected. It should be noted that although the reactions were conveniently conducted at 5 °C, the ylide reaction with tributylborane is very fast even at −78 °C (complete after 15 min). The intermediate boranes **3**,**4am** were also converted into the corresponding amines with hydroxylamine-*O*-sulfonic acid[5] (Table 1, entry 2).

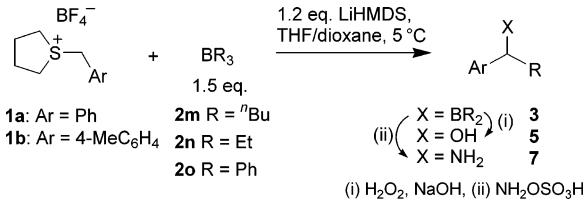
Scheme 1. Reaction of Sulfonium Salt **1a** with Tributylborane **2m**[a]



[a] Conditions: (a) 1.2 equiv LiHMDS, THF/dioxane, −78 °C; (b) H_2O_2/NaOH.

These conditions were applied to reactions of other sulfonium salts (**1a**,**b**) together with other boranes (**2m**−**o**). Reaction of **1a** with triethylborane **2n** gave comparable yields of the alcohol and amine (Table 1, entries 3 and 4). The salt **1b** reacted with triphenylborane **2o** extremely well; after simple basic oxidative workup, carbinol **5bo** was obtained in 87% yield. In this case, no higher homologation products were observed (Table 1, entry 5). However, conversion of the intermediate borane **3bo** into the corresponding amine **7bo** was not efficient, furnishing only 17% yield of the desired product (Table 1, entry 6).

Table 1. Reactions of Sulfonium Salts **1a**,**b** and Boranes



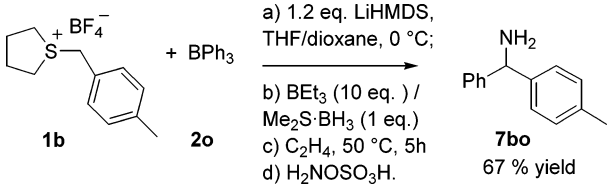
entry	R	Ar	X	compound/yield (%)[a]
1	^{n}Bu	Ph	OH	**5am**/78
2	^{n}Bu	Ph	NH_2	**7am**/74
3	Et	Ph	OH	**5an**/76
4	Et	Ph	NH_2	**7an**/77
5	Ph	4-MeC_6H_4	OH	**5bo**/87
6	Ph	4-MeC_6H_4	NH_2	**7bo**/17

[a] Isolated yield; amines contain up to 10% higher homologated product.

It has been reported that while all three groups of a trialkylborane can be oxidatively cleaved with hydrogen peroxide to give the corresponding alcohol, only two of the three groups (the ones with higher migratory aptitude) can be converted into the corresponding amine.[6] In the case of the mixed organoboranes **3am**/**3an**, the higher migratory aptitude of benzyl groups relative to alkyl groups ensures that good yields are obtained (entries 2 and 4). The low yield in entry 6 can now be rationalized since the mixed organoborane **3bo** possesses two phenyl groups, which presumably have a migratory aptitude higher than that of the benzyl group.

A potential solution to this problem is to exchange the phenyl groups on the borane **3bo** with ethyl groups using a redistribution process with Et_3B catalyzed by $BH_3{\cdot}SMe_2$.[7] This strategy was successful and furnished the amine **7bo** in 67% yield after usual oxidative workup with hydroxylamine-*O*-sulfonic acid (Scheme 2).

Scheme 2. Modified Synthesis of Amine **7bo**



To render the new process asymmetric, chiral sulfide **8**,[8] which had proved to be highly effective in epoxidation, aziridination, and cyclopropanation reactions,[9] was employed. Thus, sulfonium salts **9a**−**c** and **10** were prepared. Applying the optimized protocol to the reaction of sulfonium salts **9a**−**c** with Bu_3B, Et_3B, and Ph_3B, we obtained the corresponding alcohols and primary amines in good yield and >95% ee in all cases (Table 2). Furthermore, even though

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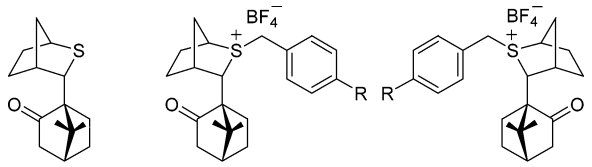
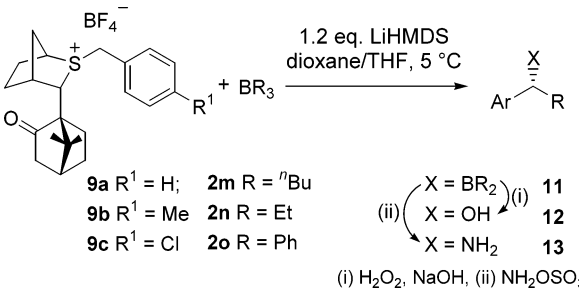


Figure 1. Chiral sulfide **8** and the chiral sulfonium salts **9a**−**c** and **10**.

the process involves an oxidative workup, the sulfide was recovered in over 90% yield.[10] The alcohols were invariably obtained with slightly lower enantioselectivities than the corresponding amines, even though they are derived from a common chiral organoborane. We believe this is caused by a very small amount of oxidation of the borane by traces of adventitious O_2, a process which gives racemic alcohol.[11] Interestingly, the higher homologation products (**12**,**13am**, and **13an**) related to **6am** were isolated as a single enantiomer and diastereomer in every case, whereas **6am** itself (from Scheme 1) was formed as a 1:1 ratio of diastereoisomers.

Table 2. Reactions of Chiral Sulfonium Salts **9a**−**c** with Boranes **2a**−**c**[a]



entry	R	Ar	X	product	yield[b]/ee[c] (%)
1	^{n}Bu	Ph	OH	**12am**	70/95
2	^{n}Bu	Ph	NH_2	**13am**	72/97[d]
3	Et	Ph	OH	**12an**	73/96
4	Et	Ph	NH_2	**13an**	68/97[d]
5	Ph	4-MeC_6H_4	OH	**12bo**	87/95
6	Ph	4-ClC_6H_4	NH_2	**13co**	68/96[d]

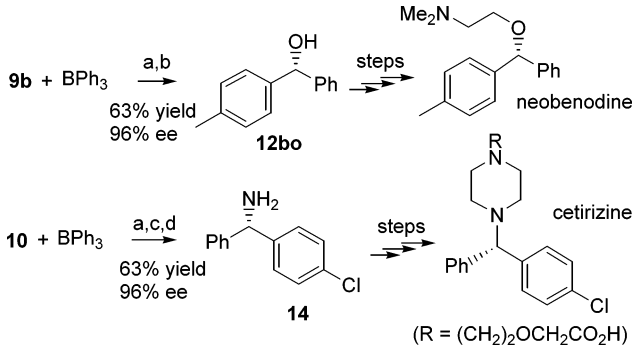
[a] Absolute stereochemistry of **12an** was determined by comparing HPLC data with a commercial authentic sample; others were assumed by analogy. [b] Isolated yield; amines contain up to 10% higher homologated product. These can be separated after derivatization of the amine. [c] The enantiomeric excess was determined by chiral HPLC using a ChiralCel OD column.[d] The enantiomeric excess was determined as its acetamide.

A number of medicinally important compounds contain a chiral diarylmethylamino or diarylmethylalkoxy moiety.[12] Using our methodology, access to either the alcohol or amine in high enantiomeric excess is equally possible. For example, **12bo**, which represents a formal synthesis of the anti-inflammatory agent neobenodine,[13] was easily prepared in 87% yield and 95% ee from sulfonium salt **9b**. Cetirizine, another anti-inflammatory agent, is also easily accessible from amine **14**,[14] which was made from sulfonium salt **10c** and triphenylborane in 63% yield and 96% ee (Scheme 3).

The high enantioselectivity observed is consistent with the model for enantiocontrol in epoxidations in which ylide conformation and face selectivity are controlled through nonbonded interactions (Scheme 4)[15] and where rearrangement occurs with inversion at the migrating terminus.[16]

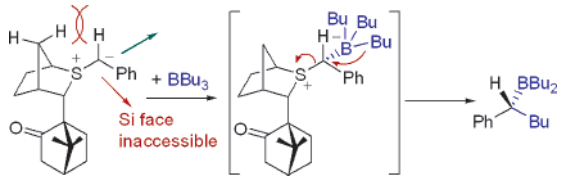
In conclusion, we have found conditions under which semi-stabilized sulfonium ylides react with organoboranes to furnish

Scheme 3. Synthesis of Neobenodine and Cetirizine[a]



[a] Conditions: (a) 1.2 equiv of LiHMDS/THF, −78 °C; (b) H_2O_2/NaOH; (c) BEt_3/$Me_2S{\cdot}BH_3$; (d) H_2NOSO_3H.

Scheme 4. Control of Enantioselectivity



homologated boranes without significant interference from multiple reactions of the ylide. Considering that several bonds are created in the ylide reaction (C−C and C−B bonds), both enantiomers of sulfide **8** are easily accessible, the sulfide can be reisolated, high stereocontrol is achieved, and the configuration of the new stereogenic center is predictable, we believe that this chemistry has much future promise.

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Supporting Information Available: Full experimental procedures, chemical characterization data, and enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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