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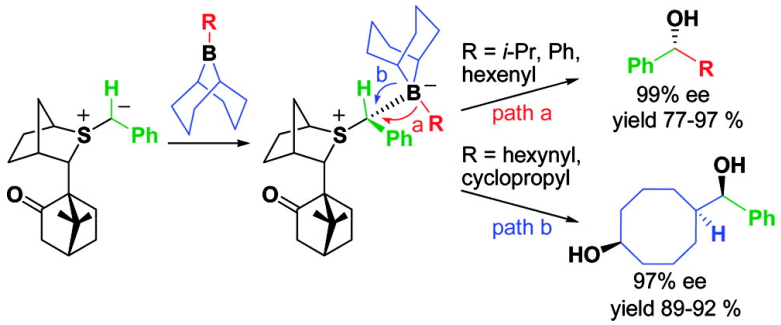

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Asymmetric Sulfur Ylide Reactions with Boranes: Scope and Limitations, Mechanism and Understanding

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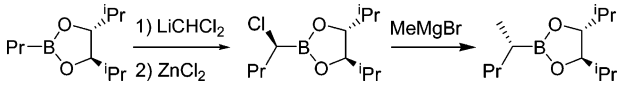
Abstract: The reactions of aryl-stabilized sulfur ylides with organoboranes has been studied under a variety of conditions. At 5 or −78 °C, the reaction with Et_3B gave a mixture of the first and second homologation products, but at −100 °C, only the first homologation product was obtained even with just 1.1 equiv of Et_3B. Under these optimized conditions, the chiral sulfur ylides (derived from camphor sulfonic acid) with different aryl groups were reacted with Et_3B to give the corresponding alcohols (95−98% yield, 96−98% ee) and amines (74−77% yield, >98% ee). The origin of the high enantioselectivity is discussed. The use of nonsymmetrical 9-BBN derivatives was also explored. It was found that whereas primary alkyl substituents gave mixtures of products derived from competing migration of the boron substituent and the boracycle, all other groups resulted in either exclusive migration of the boron substituent (Ph, hexenyl, *i*-Pr) or exclusive migration of the boracycle (hexynyl, cyclopropyl). The factors responsible for the outcome of the reactions involving a hindered (*i*-Pr) and an unhindered (propynyl) substituent were studied by DFT calculations. This revealed that, in the case of an unhindered substituent, the conformation of the ate complex is the dominant factor whereas, in the case of a hindered substituent, the barriers to interconversion between the conformers of the ate complex and subsequent migration control the outcome of the reaction.

Introduction

Organoboranes are versatile synthetic intermediates because they can be transformed into a broad range of functional groups,[1] often with complete retention of configuration of the original C−B bond.[2] Their usefulness in organic synthesis was further enhanced by the simple and straightforward route to chiral boranes introduced by H. C. Brown.[3] Indeed, the hydroboration of alkenes using (−)-diisopinocamphenylborane in 1961 provided the first nonenzymatic asymmetric synthesis of any kind that resulted in truly practical levels of enantioselection.[4] Rh-catalyzed hydroboration was developed much later, and through the use of chiral ligands, it provided a catalytic asymmetric route to organoboranes.[5] In the early 1980s, Matteson reported a conceptually different method for the preparation of organoboronic esters with very high enantioselectivity: the reaction of

Scheme 1. Matteson's Asymmetric Synthesis of Chiral Organoboronates



$LiCHCl_2$ with a chiral boronic ester followed by the addition of a Grignard reagent (Scheme 1).[6] The reaction involves a series of 1,2-metalate rearrangements[7] that all occur with high levels of selectivity. This chemistry has been applied ingeniously in synthesis.[8]

The elegant work by Matteson involves substrate control: the stereochemistry of the diol attached to the boronic acid controls the stereochemistry of the 1,2-metalate rearrangement. Although it is possible to change the stereochemistry of the product by interchanging the groups attached to Mg and the boronic ester, this is sometimes limited by the availability of reagents. Alternatively, the stereochemistry of the diol attached to the boronate ester can be inverted (by exchange) to prepare the opposite stereoisomer, but this involves a three step sequence. We reasoned that an alternative approach involving reagent control might be more versatile as either stereoisomer of the product could be made by using either enantiomer of the reagent.

(1) (a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: New York, 1995. (b) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. (c) Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975. (d) Weill-Raynal, J. *Synthesis* **1976**, 633. (e) Pelter, A.; Smith, K.; Brown. H. C. *Borane Reagents*; Academic Press: New York, 1988. (f) Bubnov, Y. In *Science of Synthesis*; Kaufmann, D. E., Matteson, D. S., Eds.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 6, pp 945−1072.
(2) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879.
(3) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287.
(4) (a) Brown, H. C.; Zewifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486. (b) Zewifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 4393.
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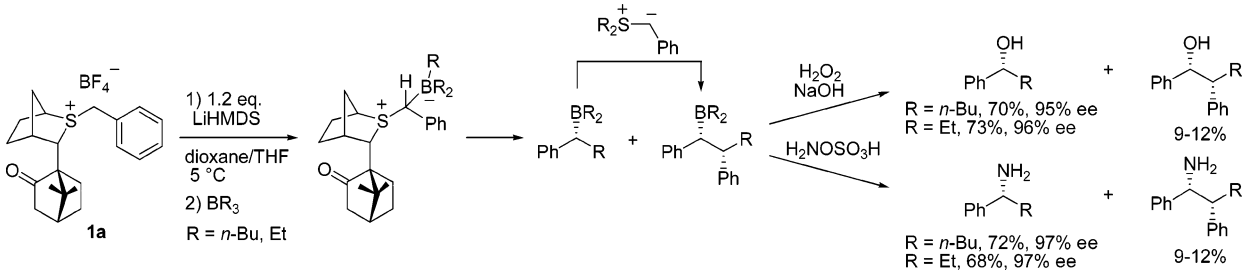
(6) (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590. (b) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. S. *Organometallics* **1983**, *2*, 1536. For a review see: (c) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (d) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (e) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.
(7) Kociensky, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.
(8) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.

10.1021/ja074110i CCC: $37.00

Scheme 2. Reactions of Chiral Ylide **1a** and Symmetric Boranes at 5 °C

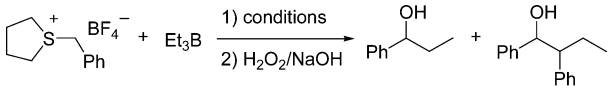


To effect homologation of boranes, the "reagent" required the following properties: (i) it had to be nucleophilic to react with the borane, (ii) it had to possess a good leaving group at the same nucleophilic carbon to effect a 1,2-metalate rearrangement, and (iii) it had to have the potential to be chiral. Ylides possessed all of these requirements, and of the S-,[9] N-,[10] and P-ylides,[11] sulfur ylides possessed the best leaving group for the 1,2-metalate rearrangement.[12,13] Furthermore, we had successfully prepared a class of chiral sulfides that furnished very high enantioselectivity in sulfur ylide mediated epoxidation.[14] In our preliminary communication,[15] we reported that chiral sulfur ylides reacted with organoboranes, furnishing homologated products with high enantioselectivity (>95% ee) and that either enantiomer could be obtained from either enantiomer of the sulfide (Scheme 2). However, there were two practical issues that needed to be addressed. First, the homologation reaction was accompanied by a second homologation product in approximately 10% yield, and second, only symmetrical boranes had been employed (Et_3B, Bu_3B, Ph_3B). If the borane substituent was valuable, this would clearly be a waste. In this paper, we address both of these issues and provide additional information on the origins of selectivity that improves the foundations of this potentially useful reaction.

Results and Discussion

Elimination of the Second Homologation Product. As alluded to in the introduction, reaction of a sulfonium benzylide **1a** with 1.5 equiv of a trialkyl/triaryl borane furnished the monohomologated product in 70−87% yield together with significant amounts of the second homologation product (Table 1, entry 1). Of course, unsubstituted sulfur ylides (Me_2SCH_2 or $Me_2S(O)CH_2$) are well known to undergo polyhomologation with boranes[16] because, after monohomologation, the new borane has similar steric hindrance to the original borane. This polyhomologation reaction has been exploited by Shea in "living polymerization" reactions[17] and ingeniously used to make large macrocyclic ketones.[18] The success of our reaction in which polymerization was mostly eliminated can be attributed to the increased steric hindrance of the homologated borane, which makes it less reactive toward the ylide than the original borane, and so the rates of successive homologations are slowed down. To reduce the extent of the second homologation further we needed to consume all of ylide before any homologated borane had been generated, that is, we needed to "stop" the reaction at the stage of the ate complex. Since both the ylide and borane are highly reactive, ate-complex formation should be rapid and this should be followed by slow migration of one of the groups on boron. Indeed, density functional theory (DFT) calculations on a range of ylides (Me_2SCH_2, Me_2SCHPh) with a range of boranes (Me_3B, Me_2BPh) have all shown that ate complex formation is highly exothermic with low enthalpic barrier to its formation.[12,19] This is followed by rate-limiting migration of one of the substituents on boron. Thus, by working at low temperature, one can expect the ylide to be completely converted into the ate complex, thereby preventing higher homologations since the ylide would never be present with the first homologation product. However, even at −78 °C, the reaction still resulted in 25% of the second homologation product **3**, indicating that, even at this temperature (Table 1), we had not been able to arrest the progress of the ate complex. Gratifyingly, reducing the temperature further still (−100 °C, N_2/ether)

Table 1. Optimization of the Reaction Conditions for the Homologation Reaction



entry	solvent	temp. (°C)	equiv of Et_3B	yield (**2a**)	yield (**3**)
1[a]	dioxane	5	1.5	78%[c]	11%[c]
2[b]	THF	−78	1.5	63%[d]	25%[d,e]
3[b]	THF−CH_2Cl_2[f]	−100	1.1	98%[c]	0

[a] LiHMDS was added slowly to the mixture of the sulfonium salt and the borane. [b] Borane was added to the ylide solution, which was preformed from the corresponding sulfonium salt and LiHMDS at −78 °C. [c] Isolated yield. [d] Yield determined by ^1H NMR with internal standard. [e] Some higher homologation products were also observed. [f] CH_2Cl_2 was added to solubilize the salt and to prevent freezing of the reaction mixture.

(9) (a) Tufariello, J. J.; Wojtkowski, P.; Lee, L. T. C. *Chem. Commun*. **1967**, 505. (b) Tufariello, J. J.; Lee, L. T. C.; Wojtkowski, P. *J. Am. Chem. Soc*. **1967**, *89*, 6804. (c) Tufariello, J. J.; Lee, L. T. C. *J. Am. Chem. Soc*. **1966**, *88*, 4757.
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(13) In a very elegant study, Blakemore has described the use of α-chloro-organolithiums to effect the same type of reaction with boronic esters: Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett*. **2006**, *8*, 773. Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 3068.
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(17) (a) Shea, K. J. *Chem.−Eur. J*. **2000**, *6*, 1113. (b) Busch, B. B.; Paz, M. M.; Shea, K. J.; Staiger, C. L.; Stoddard, J. M.; Walker, Y. R.; Zhou, X.-Z.; Zhu, H. *J. Am. Chem. Soc*. **2002**, *124*, 3636.
(18) (a) Shea, K. J.; Lee, S. Y.; Busch, B. B. *J. Org. Chem*. **1998**, *63*, 5746. (b) Wagner, C. E.; Kim, J.-S.; Shea, K. J. *J. Am. Chem. Soc*. **2003**, *125*, 12179.
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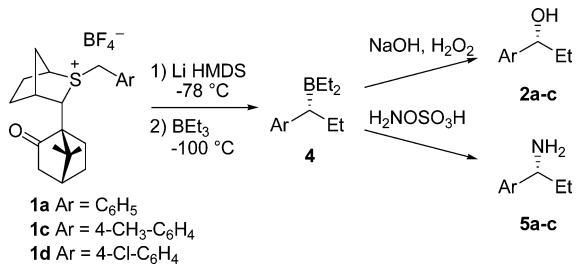
Table 2. Reactions of Et_3B with Chiral Sulfonium Ylides **1** under Optimized Conditions



entry	Ar	X	compound	yield (%)[a]	ee(%)[b]
1	C_6H_5	OH	2a	98	98
		NH_2	5a	78	98
2	4-CH_3-C_6H_4	OH	2b	95	97
		NH_2	5b	74	>99
3	4-Cl−C_6H_4	OH	2c	97	96
		NH_2	5c	77	>99

[a] Isolated yield. [b] Enantiomeric excesses were determined by HPLC, and ee of amines were determined as their acetamides.

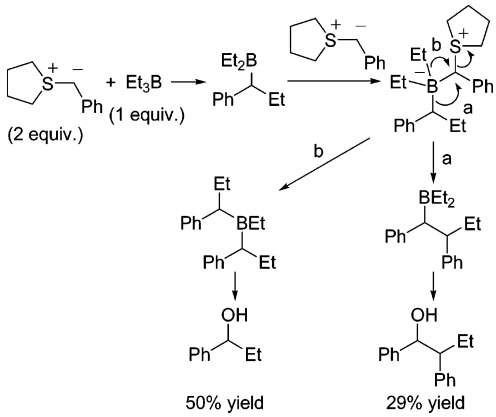
resulted in clean monohomologation without observing any of the second homologation products. The procedure involved preformation of the ylide in CH_2Cl_2−THF (2:1, v/v) at −78 °C, cooling to −100 °C with subsequent slow addition of the borane solution (1 N in THF), followed by warming the reaction to trigger the migration. Dichloromethane was necessary to solubilize the sulfonium salt and to prevent freezing of the reaction mixture at −100 °C. Using this modified procedure, we were also able to reduce the amount of the organoborane to 1.1 equiv without detriment to the yield (Table 1, entry 3).

Applying the modified procedure to our chiral sulfonium salt was also successful, and so we briefly explored its scope. Reactions of a series of sulfonium salts with Et_3B were carried out, and the homologated boranes were converted into the corresponding alcohols and amines (Table 2).

The yields of the alcohols obtained were exceptionally high (almost quantitative), whereas the amines were obtained in slightly reduced yields, which may be a reflection of the fact that only two of the groups in **4** migrate effectively in amination reactions with H_2NOSO_3H.[20] The lack of the second homologation product considerably assisted purification of the amines, which in the previous procedure were invariably obtained as mixtures of the mono- and bis- homologation adducts. A further advantage of the new procedure was the significant increase in enantioselectivity: the amines were obtained in greater than 98% e.e. and the alcohols with slightly lower selectivity. Since the homologated borane **4** is a common intermediate in the formation of both the alcohol and the amine, it must be formed in at least 98% ee, which means there is some erosion during the oxidation process to the alcohol. This could originate from a very small amount of homolysis of the benzylic-boron bond followed by recombination or oxidation of the benzylic radical.[21] Nevertheless, this competing process is extremely minor as the ee's were still >96%. The origin of the high enantioselectivity is discussed later.

The second homologation product was originally obtained in 10% yield as a single diastereoisomer and single enantiomer. The high selectivity made us consider the possibility of exploiting this reaction in synthesis. However, when we used 2 equiv of the ylide, we were still unable to increase the yield of the second homologation product to practical levels (Scheme 3).

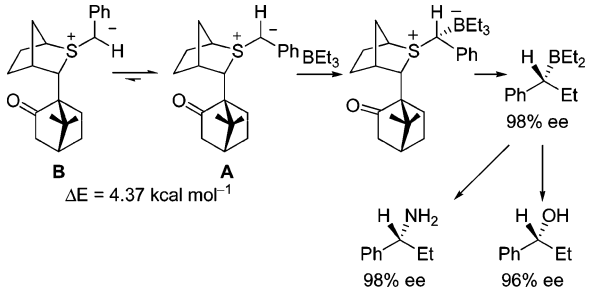
Scheme 3. Use of 2 equiv of Sulfur Ylide: Attempts to Maximize the Second Homologation Product



It *seemed* that without very low-temperature we could not avoid the second homologation, but then when we tried to maximize it, there was some stubborn resistance to increasing its extent. A possible explanation for these observations is that there were actually no problems in forming the second ate complex, just issues over which groups migrated. Migration of the benzyl substituent (pathway a) would lead to the second homologation product, whereas ethyl migration (pathway b) would lead to a borane, which upon oxidation would give the mono homologation product (Scheme 3).[22] Because of these issues, we decided to terminate further work on the multiple homologation of the borane.

Origin of Enantioselectivity. Since addition of the ylide to the borane is expected to be nonreversible, the high selectivity can be accounted for by using the same (established) model to account for enantioselectivity in epoxidation. Thus, ylide **1a** can adopt either conformers **A** or **B**, but **B** suffers significant nonbonded interactions (Scheme 4). Indeed, the energy difference between the two conformers has been calculated to be 4.37 kcal mol^{-1}.[23] Reaction of the borane on the less hindered Re face of the ylide followed by stereospecific migration of the ethyl group (with inversion of configuration at the ylidic carbon) then leads to the enantiomer observed.[24]

Scheme 4. Origin of the Enantioselectivity in the Borane Ylide Reaction

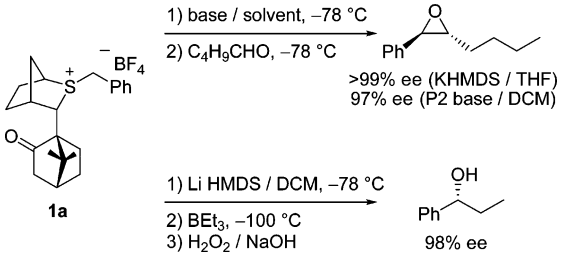


As the selectivity issues for both the epoxidation and borane homologation reactions focus on the ylide (conformation and face selectivity) and not on the electrophile, one would expect

(20) Brown, H. C.; Kim, K. W.; Srebnik, M.; Singram, B. *Tetrahedron* **1987**, *43*, 4071.
(21) Davies, A. G.; Hook, S. C. W.; Roberts, B. P. *J. Organomet. Chem.* **1970**, *22* (3), C37.

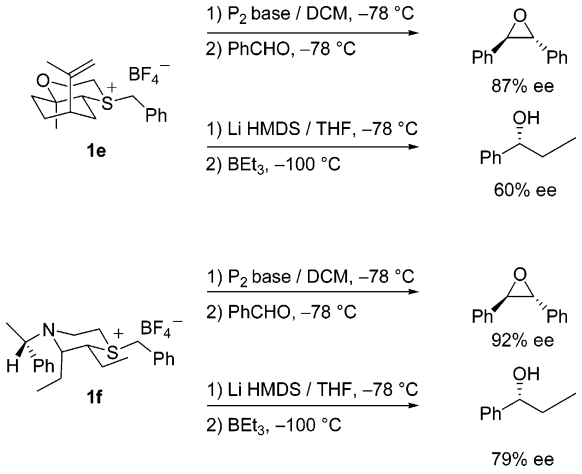
similar levels of selectivity for both classes of reactions. This is indeed observed for sulfonium salt **1a** (Scheme 5).[25]

Scheme 5. Comparison of Borane Homologation with Epoxidation Using Ylide **1a**



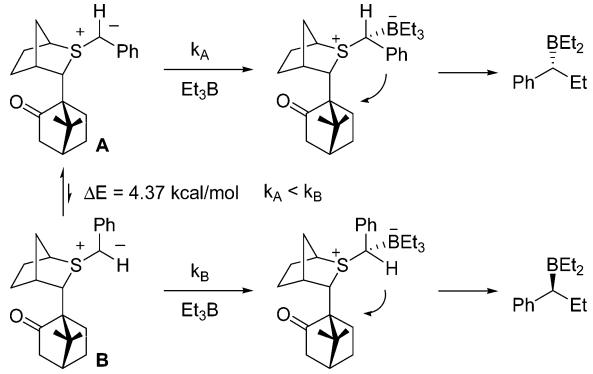
Here the enantioselectivities are already very high, and as such, it is difficult to assess any differences between them. However, when we compared two other salts **1e**[26] and **1f**,[27] the enantioselectivities for the two processes were markedly different (Scheme 6). Even though the borane reactions were carried out at much lower temperature than the epoxidations, we were surprised to find that the enantioselectivities were considerably poorer.

Scheme 6. Comparison of Borane Homologation with Epoxidation Using Ylides **1e** and **1f**



These differences in selectivity between the epoxidations (which gave higher ee's) and borane reactions are best accounted for by assuming that the rates of reaction of the two ylide conformers are substantially different (Curtin Hammett) in the borane reactions.[28] In the borane reactions, the major conformer must react more slowly ($k_A < k_B$), which would account for the lower ee's compared to the epoxidation reactions. This can be rationalized by considering the TS's of the reactions of the two conformers (Scheme 7). In the case of the major conformer, the phenyl group of the ylide substituent is pushed toward the large camphor moiety, whereas in the case of the minor conformer the hydrogen of the ylide substituent is pushed toward the camphor moiety. These factors could reasonably result in $k_A < k_B$. Indeed, DFT calculation of the ylide−borane reaction (see later for details) and the ylide−aldehyde reaction have revealed that there is substantially greater pyramidalization in the TS of the former reaction (Figure 1). The greater degree of pyramidalization in the TS of the ylide−borane reaction compared to the epoxidation reaction results in the ylide substituents being pushed further toward the sulfonium scaffold in the ylide−borane reaction, which in turn means that the reaction will be more sensitive to the steric environment around the ylidic carbon, thus supporting our conjecture that k_A is significantly less that k_B.

Scheme 7. Origin of the Enantioselectivity in the Borane−Ylide Reactions



This model highlights a fundamental problem in the design of chiral sulfides for the ylide−borane reaction: to achieve high enantioselectivity, one face of the ylide should be effectively blocked. However, effective blocking of one face of the ylide by substituents on the sulfonium scaffold will also reduce the reactivity of the same ylide conformer since, during reaction with the borane, the groups attached to the ylide carbon are pushed toward the same substituents attached to the sulfonium scaffold. If these two effects balance out, no enantioselectivity will be observed. The very high enantioselectivities observed with the camphor-derived sulfonium salt **1a** are thus all the more remarkable and must originate from the fortuitous position of bicyclic camphor moiety, which effectively blocks one face of the ylide without having a big impact on the relative rates of reaction of the two conformers.

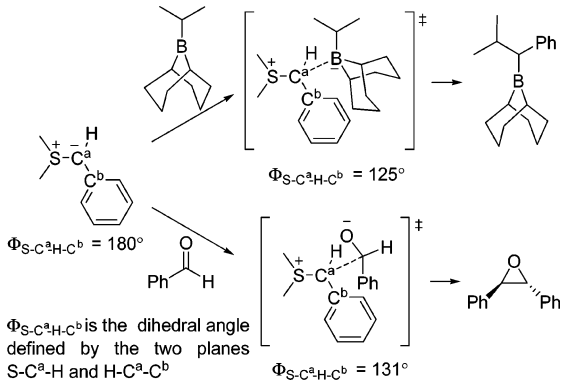
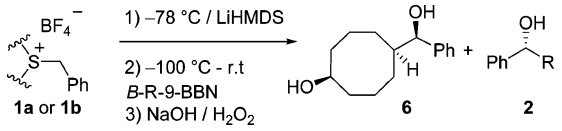


Figure 1. Comparison of degree of pyramidalization of the ylidic carbon in the transition states of the ylide−borane and ylide−aldehyde reactions.

(22) For a discussion on the use of borinic and boronic esters in this type of homologation, see the Supporting Information.
(23) Aggarwal, V. K.; Charmant, J.; Dudin, L.; Porcelloni, M.; Richardson, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 5467.
(24) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644.
(25) Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.
(26) Badine, D. M.; Hebach, C.; Aggarwal, V. K. *Chem. Asian, J.* **2006**, *1*, 438.
(27) Hansch, M.; Aggarwal, V. K. In preparation.
(28) A related model has been extended by Goodman, to account for the selectivity observed in epoxidations using C_2 symmetric chiral thiolanes: Silva, M. A.; Bellenie, B. R.; Goodman, J. M. *Org. Lett.* **2004**, *7*, 2559.

Use of Nonsymmetrical Boranes: 9-BBN Derivatives. Having established conditions for clean monohomologation of boranes with high enantioselectivity, we sought nonsymmetrical boranes in which only one group would migrate. To achieve this, we were drawn to 9-BBN derivatives as Brown had shown that in reactions of α-haloesters, α-haloketones, and α-halonitriles selective transfer of the boron substituent rather than migration of the ring occurred.[29] However, a broader search of the literature revealed that in fact these were the only cases in which selective transfer of the boron substituent occurred; in most cases, ring migration occurred preferentially![30] Because none of the alternative "nonmigrating" groups reported in the literature were universally selective, we elected to test a range of 9-BBN derivatives in their reactions with the sulfonium benzylide **1b** (Table 3).

Table 3. Reactions of Sulfonium Ylide with 9-BBN Derivatives



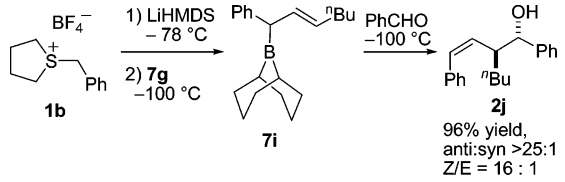
entry	sulfonium salt	*B*-R-9-BBN	yield of **6**	yield of **2**
1	**1b**	Hexyl (**7a**)	56%	41% (**2e**)
2	**1b**	Allyl (**7b**)	51%	39% (**2f**)
3	**1b**	Benzyl (**7c**)	51%	35% (**2g**)
4	**1b**	*i*-Pr (**7d**)	trace	77% (**2h**)
5	**1b**	Cyclopropyl (**7e**)	89%	trace
6	**1b**	Ph (**7f**)	trace	94%[a]
7	**1b**	1-Hexenyl (**7g**)	trace	21%[b] (**2i**)
8	**1b**	1-Hexynyl (**7h**)	92%	trace
9	**1a**	*i*-Pr (**7d**)	-	97%[c] (**2h**)
10	**1a**	1-Hexynyl (**7h**)	90%[d]	–

[a] Yield of diphenylmethane. [b] Yield of 1-phenylhept-1-en-3-ol (**2i**). [c] 99% ee. [d] 97% ee.

Although little selectivity was observed for primary alkyl, allyl, and benzyl substituents (entries 1−3), essentially complete selectivity was observed for migration of the secondary alkyl group (*i*-Pr) (entry 4). In sharp contrast, the cyclopropyl group did not migrate at all; only migration of the ring substituent occurred (entry 5). Phenyl and alkenyl substituents migrated preferentially presumably because of assistance from the π system (entries 6 and 7).[19,31] In sharp contrast, the alkynyl group remained rooted to boron and the ring substituent migrated instead (entry 8).

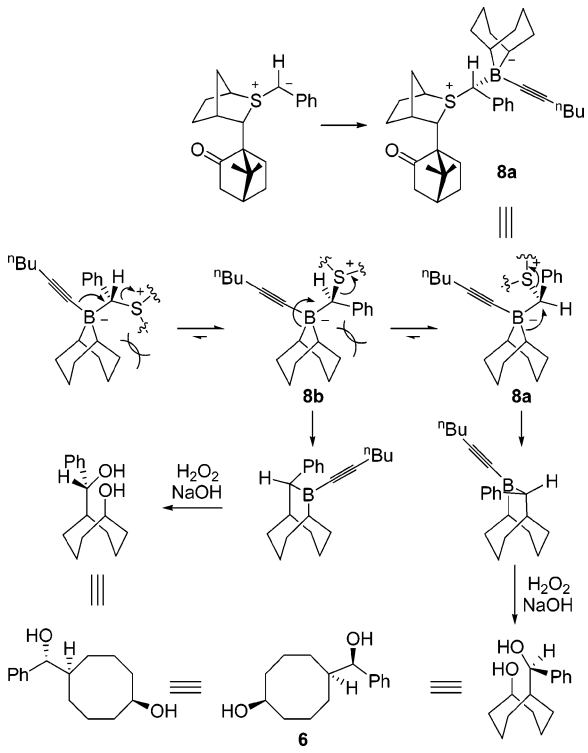
The low yield in the reaction of **1b** with hexenyl-*B*-9-BBN (entry 7) was due to competitive protodeborination during oxidation.[32] It has been reported that benzylic boranes with further anion stabilizing groups attached are especially prone to such a process.[33] In contrast, quenching the borane with benzaldehyde gave the corresponding homoallylic alcohol **2j** in 96% yield with very high anti selectivity and high Z selectivity (Scheme 8). This showed that the borane **7i**, resulting from alkenyl migration, was formed in high yield. This useful reaction has been developed and exploited further.[34]

Scheme 8. Highly Selective Homologation and Allylation Reaction Sequence



The isopropyl and hexynyl 9-BBN derivatives, which afforded **2h** and **6**, respectively in a highly selective manner in the reaction with **1b**, were reacted with the chiral sulfonium salt **1a**, and in each case, alcohols were isolated with very high enantioselectivity (entries 9 and 10). The origin of the enantioselectivity of the products are the same as discussed above, but additional comment is warranted for the formation of diol **6**. Interestingly, the two conformations **8a** and **8b** of the ate complex formed in the reaction of **1a** with **7h** result in migration of different carbons (Scheme 9), however, they ultimately lead to the same enantiomer (and diastereomer). Indeed, diol **6** was always formed as the same single diastereoisomer in all cases, and its stereochemistry has been proven by X-ray analysis.

Scheme 9. Rationalization of the Enantioselectivity of the Reaction of **1a** and hexynyl-*B*-9-BBN

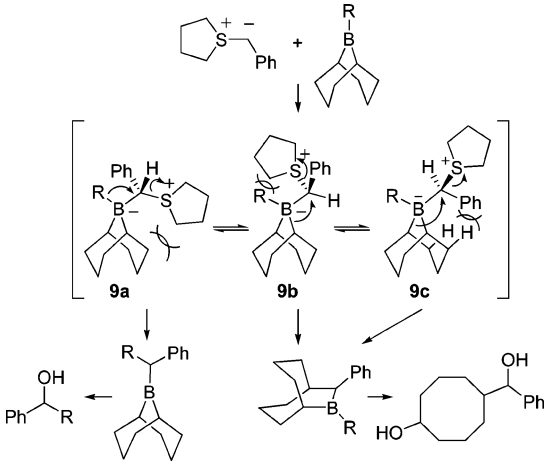


Rationale for the Observed Selectivity in Migrating Groups. The results in Table 3 show that aryl and vinyl groups show a strong preference for B-substituent migration over ring migration, presumably because they have greater migratory

(29) (a) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc*. **1968**, *90*, 5280. (b) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc*. **1968**, *90*, 5281. (c) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc*. **1968**, *90*, 5283.
(30) For a brief discussion of the factors involved in migration of borate complexes see: Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Applied Chem.* **2006**, *78*, 215.
(31) (a) Nakamura, K.; Osamura, Y. *Tetrahedron Lett.* **1990**, *31*, 251. (b) Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112. (c) Winstein, S.; Lindegren, C. R.; Marshall, H.; Ingraham, L. L. *J. Am. Chem. Soc*. **1953**, *75*, 147. (d) Wistuba, E.; Ruchardt, C. *Tetrahedron Lett.* **1981**, *22*, 4069. (e) Brown, H. C.; Kim, C. J. *J. Am. Chem. Soc.* **1968**, *90*, 2082. (f) Winstein, S.; Morse, B. K.; Grunwald, E.; Schreiber, K. C.; Corse, J. *J. Am. Chem. Soc.* **1952**, *74*, 1113.
(32) Bubnov, Y. N.; Mikhailov, B. M.; Tsyban, A. V. *J. Organomet. Chem.* **1978**, *154*, 113.
(33) Kabalka, G. W.; Maddox, J. T.; Bogas, E. *J. Org. Chem.* **1994**, *59*, 5530.
(34) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 359.

power.[19,31] The remaining groups (primary/secondary alkyl, cyclopropyl, and alkynyl) show different degrees of substituent vs ring migration, and it is believed that this is largely controlled by conformation of the ate complex. The three possible staggered conformers **9a**−**c** of the different ate complexes are shown in Scheme 10.

Scheme 10. Staggered Conformations of Ate Complexes



Because of the requirement that the migrating group has to align antiperiplanar to the leaving group, conformer **9a** will lead to migration of the B-substituent whereas **9b** and **9c** will lead to migration of the ring. Since **9b** and **9c** lead to the same product and **9b** is favored over **9c** because of steric repulsion between the phenyl group and the boracycle, we will restrict discussion to conformers **9a** and **9b**. The conformer distribution (**9a**:**9b**) will depend on the competing steric interactions of what was the ylide component with the boracyclic ring and the ylide component with the boron substituent. Thus, for small boron substituents (hexynyl), conformer **9b** will be strongly favored, resulting in ring migration. As the boron substituent increases in size from primary alkyl to secondary alkyl, increasing amounts of migration of the boron substituent was observed. The exclusive migration of the *i*-Pr group in particular can be rationalized by considering the interactions between the methyl groups of the *i*-Pr group and the ylide component in the conformers **10a** and **10b** (Figure 2). In conformer **10b**, the *i*-Pr substituent will align the hydrogen above the boracyclic ring, and this would result in *syn*-pentane interactions with both the sulfonium ion and the phenyl group. Conformer **10a** has only one *syn*-pentane interaction together with steric interactions between the sulfonium ion and the ring, but evidently these combined interactions are less troublesome than the steric interactions in **10b**.

Perhaps the most difficult example to rationalize is the reaction of cyclopropyl-*B*-9-BBN with **1b**, in which the cyclopropyl moiety behaves as though it is smaller than an unbranched alkyl group. The low steric bulk of the cyclopropyl group allows one of the ring carbons to protrude into space above the boracycle ring, which leaves an H and a "small" CH_2 eclipsing the phenyl group and ylide sulfonium ion (**11b**, Figure 2). These interactions are apparently less severe than the interaction between the tetrahydrothiophene moiety and the boracycle in **11a**. The cyclopropyl group is thus behaving as a very small group (similar to alkynyl) in this case.

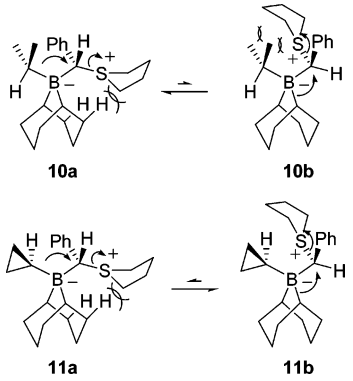


Figure 2. Sterical interactions in the ate complexes **10** and **11**.

It is clear that conformer distribution (**9a**:**9b**) dictates which group will migrate. To favor migration of the boron substituent, conformer **9a** has to be strongly favored over conformer **9b**. We can now easily understand why H. C. Brown's homologations with chloro-esters/nitriles/ketones worked so well: the small chloro substituent was easily accommodated over the ring resulting in migration of the boron substituent. Thus, small leaving groups are key to enhancing the extent of migration of the boron substituent in 9-BBN derivatives.

Computational Study of 9-BBN Derivatives. The above experimental results (Table 3) show that there is an inherent preference for bulky groups or groups with high migratory aptitude to undergo the 1,2-migration in the intermediate 9-BBN ate complexes. Moreover, we have recently shown[19] that the selectivity of the 1,2-migration in the reaction of dimethylphenylborane with $PhCHSMe_2$ is dependent upon several factors: (i) differential conformational stability of rotamers of the ate complexes, (ii) electronic effects of the nonmigrating boron substituents, (iii) migratory power of the different substituents, (iv) steric bulk of the migrating group, and (v) electronic effects of the ylide substituent. We were interested to find out which of these effects was responsible for controlling the selectivity in the reactions of sulfur ylides with 9-BBN derivatives. We therefore decided to investigate the potential energy of two different reactions: (i) sulfur ylide **12** with isopropyl-*B*-9-BBN (**7d**), for which the isopropyl group migrates exclusively and (ii) sulfur ylide **12** with 1-hexyne-*B*-9-BBN (**7h**) where the side-chain migration product **6** was obtained. The calculations were performed at the MP2/6-311+G**//B3LYP/6-31G* level of theory as this has been shown to be a good method for similar systems.[19] DFT calculations were carried out using the Jaguar 6.0 pseudo spectral program package,[35] and for the MP2 single-point calculations, the Gaussian 03 program package[36] was employed. Due to computational limitations, the 1-hexyne group of **7h** was approximated with 1-propyne (**7j**). Harmonic frequencies have been calculated at the level of optimization for all structures to characterize the calculated stationary points.

The following computational study involved exploration of the possible reaction paths for migration of the isopropyl and 1-propyne moiety as well as the boracycle to the ylidic carbon. It was found that the potential energy surface of these processes is rather complicated as it involves formation of several different

(35) *Jaguar 6.0*; Schrödinger, LLC.: Portland, OR, 2005.
(36) Frisch, M. J.; et al. *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.

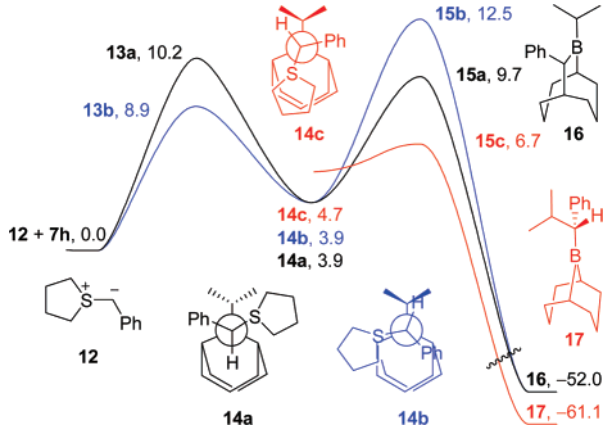


Figure 3. Calculated potential energy surface of the reaction of **12** with **7h** (MP2/6-311+G**//B3LYP/6-31G*). Energies are given in kcal mol^{-1}.

ate complexes, interconversion between the different ate complexes, and subsequent 1,2-migration to afford the corresponding products.

The reaction of **12** with **7h** (Figure 3) is initiated by formation of three different conformers of the ate complex (**14a**−**c**) which form via TS **13a** and **13b** (we were unable to locate a corresponding TS for the formation of **14c**). Due to the considerable steric bulk of the boracycle and isopropyl groups, repulsive nonbonding interactions make formation of ate complexes **14a**−**c** endothermic. The subsequent 1,2-migration in each of these conformers via TS **15a**−**c** affords the products **16**−**17** in an exothermic reaction. Although the computational results indicate a slight preference for formation of **14b** via **13b**, the 1,2-migration via **15b** has the highest activation energy of the three possible pathways due to the sterically congested transition state. The migration via **15a** has an activation energy that is almost the same as the activation energy for dissociation via **13a** to **12** and **7h**, indicating that the formation of this particular ate complex may be reversible.

The energetically most favored 1,2-migration occurs from **14c**, in which the leaving group is antiperiplanar to the isopropyl group, via **15c** ($\Delta E^{\ddagger}$= 2.0 kcal mol^{-1}) and leads to **17**. The low barrier in this case could be explained by the high exothermicity of the rearrangement. Formation of **16** is 8.9 kcal mol^{-1} less favorable due to steric interactions between the phenyl and isopropyl groups and the boracycle. Ate complex **14c** can be formed from **14b** by B−C bond rotation via **18c** (Figure 4) with a very low activation energy ($\Delta E^{\ddagger}$ = 5.1 kcal mol^{-1}). The low barrier for rotation is a consequence of the eclipsed conformation of **14b**, which relatively easily allows this transformation to occur. The transformations **14a** → **14b** (**18a**) and **14a** → **14c** (**18b**) have much higher barriers for rotation ($\Delta E^{\ddagger}$ = 16.8 and 14.1 kcal mol^{-1}, respectively) since, during the rotation, one of the sterically bulky sulfonium or phenyl groups must be eclipsed with the large isopropyl group.[37] These results suggest that product **17**, which is obtained in the reaction of **11** with **7h** (Table 3), is formed via the pathway (**11** + **7h**) → **13b** → **14b** → **18c** → **14c** → **15c** → **17**. Although TS **13a** leading to **14a** is 1.3 kcal mol^{-1} higher than TS **13b**, this energy difference is relatively small; hence, this competing addition pathway may also occur. The observation of only traces of product derived from **16** means either that our calculations underestimate the energy gap between TSs **13a** and **13b** (the present values predict a ratio **16**/**17** of ca. 1/10 at 0 °C) or that formation of **14a** is indeed reversible as suggested above.

(37) Conversion of **14a** to **14b** or **14c** also requires rotation of the isopropyl group around the B−C bond. Given that **18a** and **18b** already lie much higher in energy than other relevant transition states, TSs for these isopropyl rotations were not located.

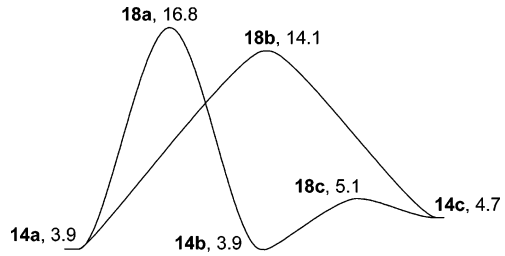


Figure 4. Calculated (MP2/6-311+G**//B3LYP/6-31G*) potential energy surface for interconversion of the ate-complex rotamers **14a**−**c** through B−C bond rotation. Energies are given in kcal mol^{-1}.

The computational results for the reaction of **12** with **7j** showed that in contrast to the isopropyl system, but as for the less congested cases studied previously,[19] ate complex formation to yield **20a**−**c** (Figure 5) via transition states **19a**−**c** is exothermic and also involves low activation energies. This observation can be rationalized by the low steric bulk of the 1-propyne group, which allows the bulky tetrahydrosulfonium and phenyl groups to occupy a sterically unhindered position synclinal to the 1-propyne group. The most stable rotamer of the ate complex (**20a**, −16.8 kcal mol^{-1}) has the leaving sulfonium group antiperiplanar to one of the α-carbons of the boracycle. Furthermore, formation of the product from **20a** proceeds via the most stable transition state for 1,2-migration (**21a**, $\Delta E^{\ddagger}$ = −7.1 kcal mol^{-1}). Migration from the other two rotamers, **20b**−**c** proceeds via higher-lying TSs **21b**−**c**.

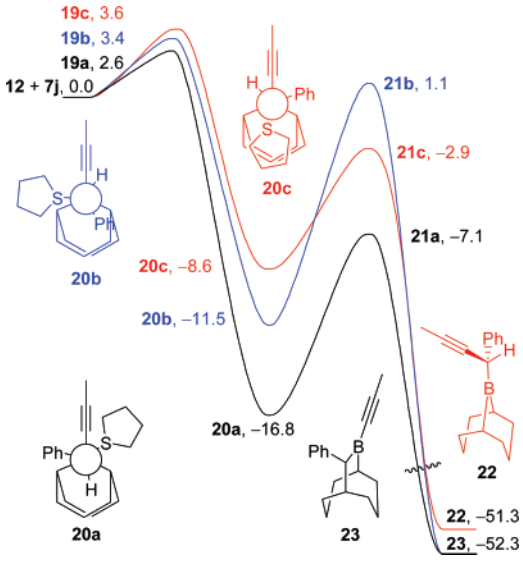


Figure 5. Calculated potential energy surface of the reaction of **12** with **7j** (MP2/6-311+G**//B3LYP/6-31G*). Energies are given in kcal mol^{-1}.

The potential energy surface for B−C bond rotation is depicted in Figure 6 and indicates that the most stable ate complex (**20a**) can be formed from the less stable ones (**20b**−**c**) with fairly low activation energies. The rotation of **20c** to **20a** via **24b** (−1.0 kcal mol^{-1}) is unlikely to occur because of the lower lying migration transition state (**21c**, Figure 5), however, a more energetically favored path leads to **20b** via

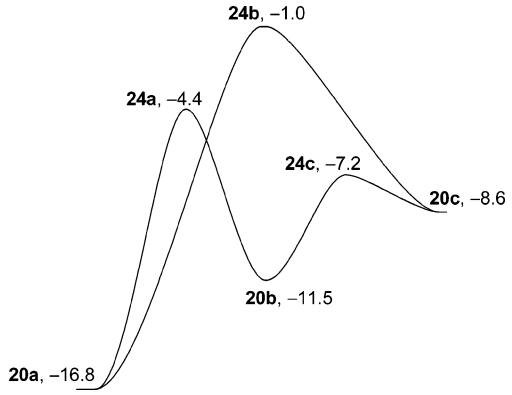


Figure 6. Calculated potential energy surface of the B−C bond rotation of **20a−c** (MP2/6-311+G**//B3LYP/6-31G*). Energies are given in kcal mol^{-1}.

24c (−7.2 kcal mol^{-1}). Before rotation around the C−B bond can occur to form **20a** from **20b**, the tetrahydrothiophene ring needs to rotate into a sterically less demanding position, and the associated TS **24a** is in fact the only barrier involved in converting **20b** to **20a**. From **24a**, the potential energy surface appears to lead directly downhill to **20a**.

These computational results show that some of the factors presented earlier[19] remain important for defining selectivity, but some new features appear. First, it is clear that relative stability of the different conformers of the ate complexes play an important role in defining the final products observed [factor (i)], for example, in the reaction of alkynyl borane **7j** where the high stability of adduct **20a** drives formation of **23**. This is despite the high barrier ($\Delta E^{\ddagger}$ = 9.7 kcal mol^{-1}) for ring migration, which may be due to the electronic withdrawing character of the spectator propynyl ligand [factor (ii)]. One noticeable difference with respect to our previous work is that, in all cases studied here, there is a potential energy barrier to formation of the ate complex, and the latter is significantly less stable compared to reactants. Both of these effects are clearly due to the much greater steric bulk of the present systems. The increased steric bulk also contributes to increased barriers for interconversion of the conformers of the ate complexes, which again has an impact on the selectivity of which group migrates.

Conclusion

Aryl-stabilized sulfur ylides react with boranes (trialkyl/triaryl) to give homologated products. When the reactions are carried out at 5 or −78 °C, the first homologation adducts were obtained in high yield accompanied by a small amount of the second homologation product (up to 10%). However, at −100 °C, clean monohomologation was observed presumably because the ate complex did not evolve into the first homologation product at this low temperature, allowing all of the ylide to be consumed. Use of the camphor derived sulfonium salt **1a** leads to intermediate boranes that have been converted efficiently into alcohols (95−98% yield, 96−98% ee) and amines (74−77% yield, >98% ee). The high enantioselectivity originates from very high control of ylide conformation and face selectivity, although this is somewhat compromised by the faster rate of reaction of the minor ylide conformer.

The use of nonsymmetrical boranes for selective group transfer was partially successful. Using a range of 9-BBN derivatives, it was found that phenyl, hexenyl, and isopropyl resulted in exclusive migration of the boron substituent whereas hexynyl and cyclopropyl resulted in exclusive migration of the boracycle, furnishing a diol. These processes could all be rendered asymmetric, and high ee's were achieved (96−99%). Primary alkyl groups gave almost equal mixtures of migration of the boron substituent and the boracycle. Calculations showed that although conformation of the ate complex is the determining factor responsible for the outcome of the reaction involving alkynyl substituents, the situation with the isopropyl substituent is more complex. In this case, a combination of factors including the barriers to interconversion of the different ate complexes and their respective barriers to migration, which is affected by the exothermicity of the reaction, control the outcome of the reaction leading to exclusive migration of the isopropyl substituent. The greater migratory power of phenyl and hexenyl is an additional factor that is believed to contribute to the exclusive migration of these groups. The ylide-borane reaction offers a new route to chiral organoboranes that is conceptually related to Matteson homologation but is governed by reagent rather than substrate control. In certain cases, this will have significant benefits in synthesis.

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Supporting Information Available: Synthesis and characterization of compounds **2a−j**, **5a−c**, **6**, and **7a−h**, X-ray structure of **6**, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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