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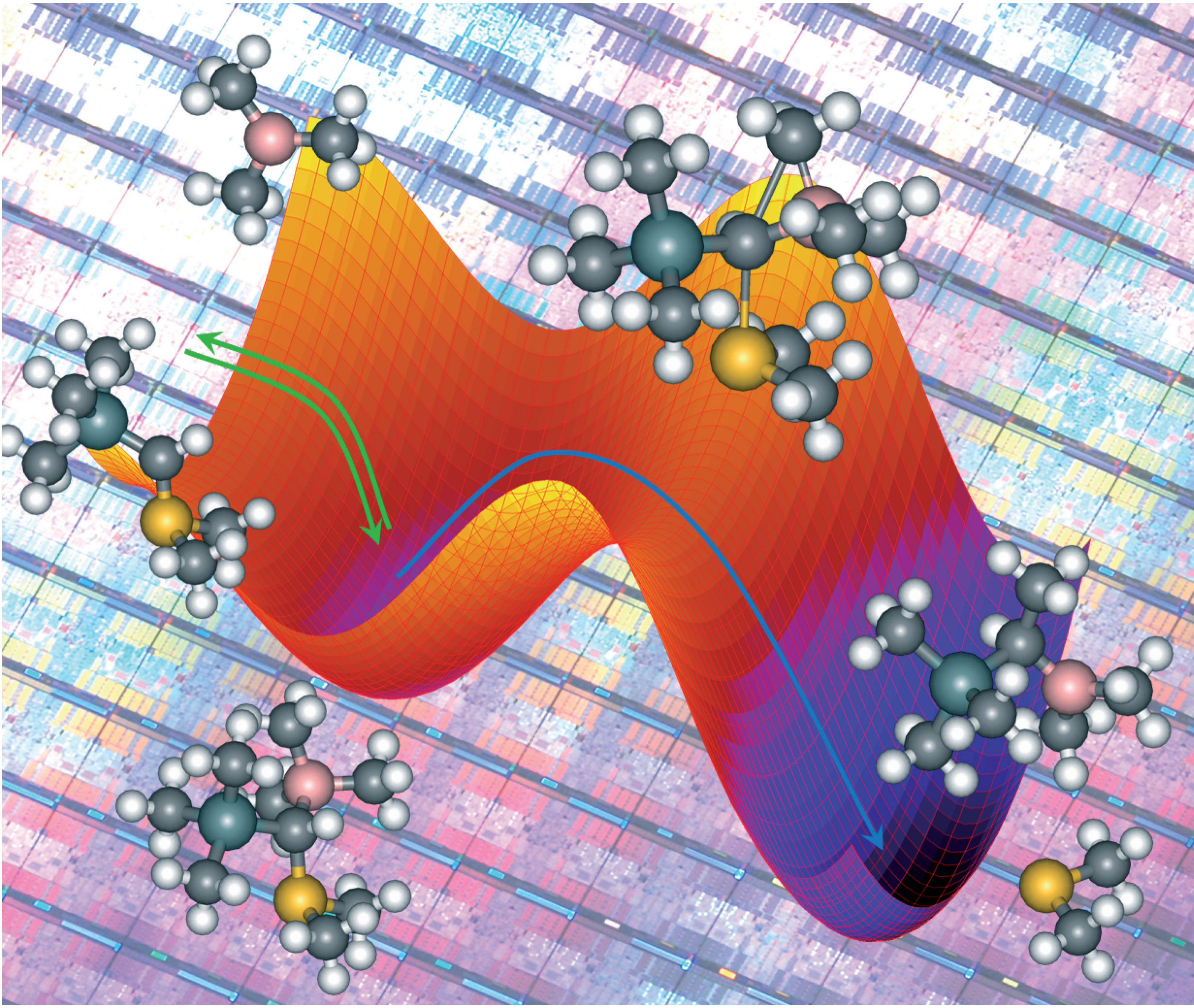

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FULL PAPER
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Reactions of silyl-stabilised sulfur ylides with organoboranes: enantioselectivity, mechanism, and understanding†

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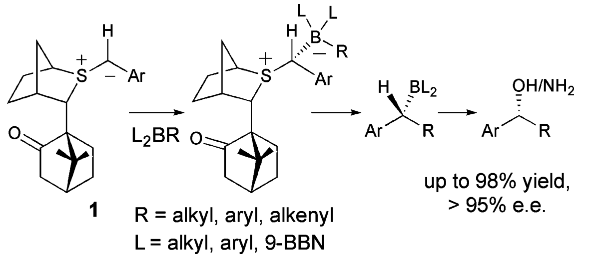
The reaction of trimethylsilyl-substituted sulfonium ylides with organoboranes (Ph_3B, Et_3B) has been studied and although homologated products were obtained in good yield (after oxidation to the corresponding alcohols), the enantiomeric excesses were low with our camphor-based chiral sulfide (up to 40% ee, *cf.* corresponding phenyl-substituted sulfonium ylides gave >95% ee). Cross-over experiments were conducted to ascertain the nature of this difference in selectivity. Thus, aryl- and silyl-substituted sulfonium ylides (1 equiv.) were (separately) reacted with Et_3B (1.5 equiv.) followed by Ph_3B (1.5 equiv.) The experiments were repeated changing the order of addition of the two boranes. It was found that the aryl-substituted sulfonium ylide only trapped the first borane that was added indicating that ate complex formation was non-reversible and so was the selectivity determining step. In contrast the silyl-substituted sulfonium ylide only trapped Ph_3B (it is more reactive than Et_3B) indicating that ate complex formation was reversible and so 1,2-migration was now the selectivity determining step. The reactions have been studied computationally and the experimental observations have been reproduced. They have further revealed that the cause of reversibility in the case of the silyl-substituted sulfonium ylides results from ate complex formation being less exothermic and a higher barrier to 1,2-migration.

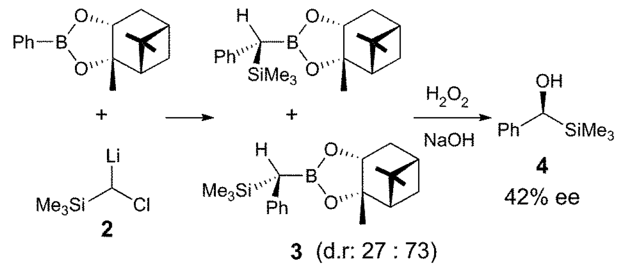
Introduction

The reaction of sulfur ylides with organoboranes to give homologated boranes is emerging as a useful synthetic method in asymmetric synthesis.[1] So far aryl-stabilised ylides **1** have been reacted with alkyl, aryl and vinyl boranes to give the corresponding homologated boranes with very high enantioselectivity (>95% ee). These reactions occur *via* intermediate ate complexes followed by 1,2-metallate rearrangement (Scheme 1).[2]



Scheme 1 Reaction of aryl-stabilised ylides with organoboranes.

In a desire to extend the scope of the reaction we considered the possibility of using silyl-substituted ylides. Such ylides are known and their reactions with carbonyl compounds result in alkene formation (Peterson reaction) rather than epoxidation (Corey–Chaykovsky reaction).[3] Further reactions of silyl-substituted ylides with boranes have not been described although Matteson has reported the reactions of silyl-substituted carbenoid **2** with chiral borate esters (Scheme 2).[4] This gave the corresponding homologated product **3** but with low diastereoselectivity (73 : 27) and thus after oxidation the silylcarbinol **4** was obtained with low enantiomeric excess (42% ee).



Scheme 2 Matteson's homologation of boronic esters with silyl-stabilised carbenoid.

We expected the silyl-stabilised sulfur ylide to react with boranes with similarly high enantioselectivity as the phenyl-stabilised ylide because: (i) both ylides can be expected to have similar pK_a's[5] and so one can expect both reactions to be non-reversible. (ii) Ph and Me_3Si have similar *A* values[6] (2.7[7] and 2.4–2.6[8] respectively) and so ylide conformation, a key factor in achieving high enantioselectivity, should be similarly well controlled. Indeed,

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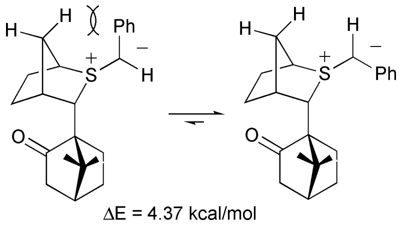
we have found that in the case of the phenyl-stabilised ylide **1** there is a very large preference for one ylide conformation over the other (Scheme 3).[9]



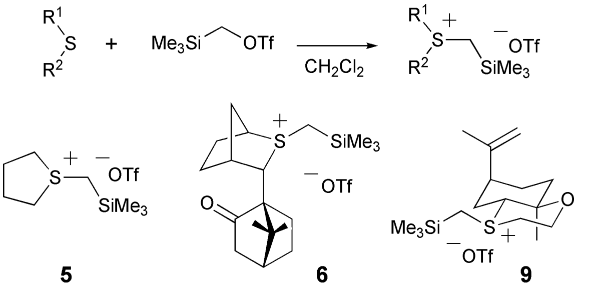
Scheme 3 Energy difference between ylide conformers.

In this paper we describe our studies on the use of silyl-substituted ylides and the surprising finding that their addition to boranes is, in fact, reversible.

Results and discussion

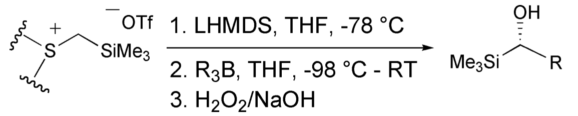
The required sulfonium salts (**5**, **6**) were easily prepared by reaction of the appropriate sulfides with the commercially available triflate (Scheme 4).[10] Reactions of the salts **5** and **6** with LHMDS and two different boranes (Ph_3B and Bu_3B) furnished the silylcarbinols in moderate yield after oxidative work up (Table 1). However, we were surprised and disappointed at the low enantioselectivity obtained with the chiral sulfonium salt **6** in both cases (entry 2,4), and so further optimisation of yield was not conducted.

We considered two possible reasons for the low enantioselectivity. Our first consideration was that the two ylide conformers might react with vastly different rates—the major conformer reacting much slower than the minor conformer (an example of the Curtin–Hammett principle[11]), since in the TS the bulky Me_3Si group is pushed toward the bulky camphor moiety (Scheme 5). Indeed, DFT calculation of the phenyl stabilised ylide–borane reaction and the corresponding ylide-aldehyde reaction revealed that there is substantially greater pyramidalisation in the TS of the former reaction.[1c] The greater degree of pyramidalisation in the TS of the ylide–borane reaction compared to the epoxidation reaction results in the ylide substituents being pushed further towards 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.



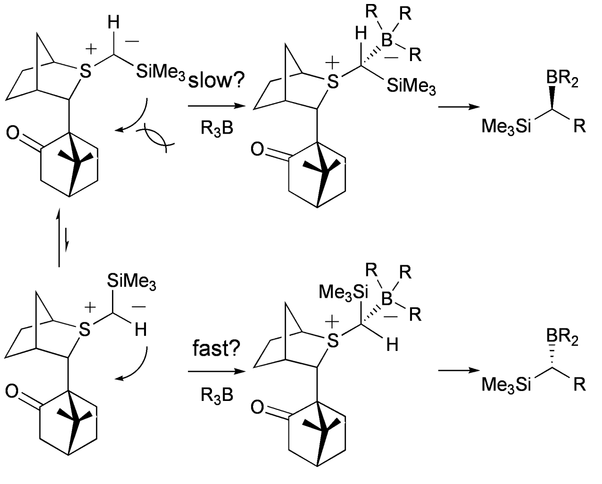
Scheme 4 Synthesis of sulfonium salts.

Table 1 Reaction of silyl-stabilised ylides with organoboranes



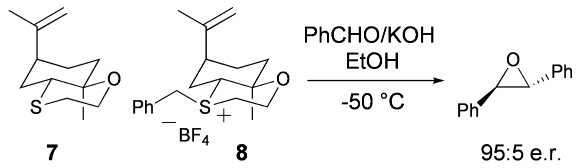
Entry	Salt	R	Yield (%)	Er (%)
1	**5**	Bu	63	—
2	**6**	Bu	72	60 : 40[a]
3	**5**	Ph	61	—
4	**6**	Ph	66	71 : 29[b]
5	**9**	Ph	41	57 : 43[b]

[a] The enantiomeric ratio was determined by formation of the Mosher's ester. [b] The enantiomeric ratio was determined by chiral HPLC using chiracel OD column under the following conditions: 5% IPA in hexane, 1 ml min^{-1}. Retention time: minor, 6.96 min; major, 10.53 min.



Scheme 5 Potential origin of low enantioselectivity in ylide reaction.

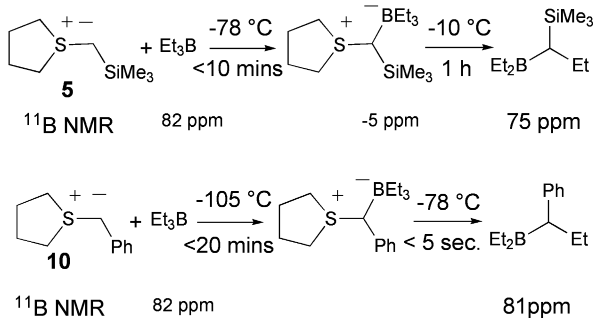
Although difficult to prove, we tested this proposition by using an alternative chiral sulfide **7** for which we had previously established good control over ylide conformation and face selectivity (Scheme 6: the phenyl stabilised ylide **8** gave 95 : 5 er in epoxidation[12]). In this case however, there is less steric encumbrance around the ylidic carbon and so the rates of reactions of the two ylide conformers can be expected to be more equal. However, in the event even lower enantioselectivity was observed in reaction of the silyl-stabilised ylide **9** with Ph_3B (entry 5). These results suggest that the origin of the low enantioselectivity is unlikely to originate from the major ylide conformer reacting more slowly than the minor ylide conformer.



Scheme 6 Demonstration of control of ylide conformation and face selectivity through epoxidation.

A second possibility was that the addition of the silyl-stabilised ylide onto the borane was reversible and that the two diastereomers of the ate complex underwent migration at similar rates. Although a reversibility of the addition did not seem that likely since Me_3Si is slightly less able to stabilise a carbanion than a Ph group[5,13] (so reversal of ate complex formation should be less favoured) it could be easily tested by cross-over experiments. The experiment would entail addition of borane A to an ylide at low temperature and after complete consumption of the ylide addition of a second borane B. If ate complex formation is non-reversible this should furnish the product derived solely from borane A but if ate complex formation is reversible a mixture of products derived from boranes A and B would be produced.

To establish the temperature and time required for the ylide to react with the borane, the reaction of ylides **5** and **10** with Et$_3$B was monitored by ^{11}B NMR (Scheme 7). In fact, within 10 minutes at −78 °C ate complex formation from the reaction of ylide **5** with Et$_3$B was essentially complete although rearrangement only took place upon warming to −10 °C. In contrast, the reaction of the phenyl-stabilised ylide **10** could not be monitored effectively. At −78 °C substantial migration had already occurred and it was difficult practically to monitor the reaction at lower temperature. Circumstantial evidence suggested to us that ate complex formation was very fast at −105 °C but that no significant migration occurred at that temperature: when we conducted reactions of ylide **10** with Et$_3$B/Ph$_3$B at this temperature, no products derived from a second homologation were observed whereas at −78 °C approximately 10% yield of the second homologation adducts were obtained.

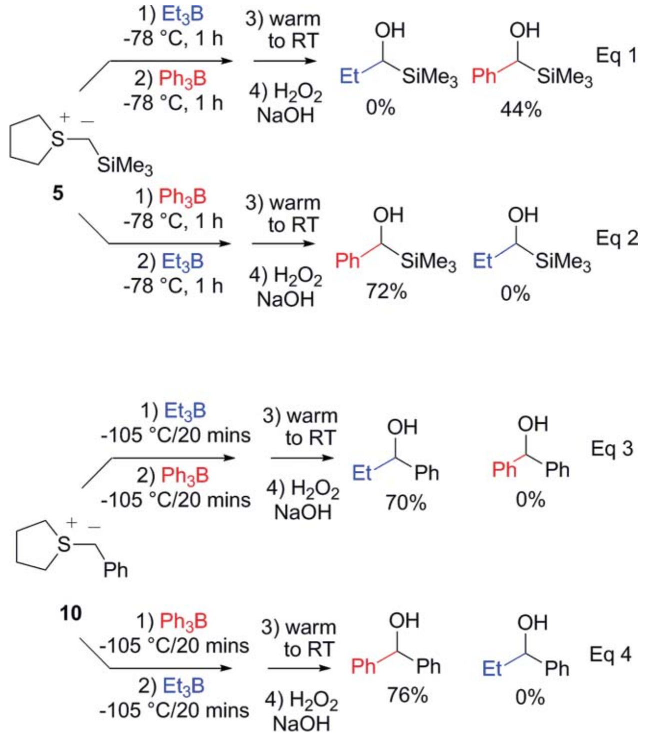


Scheme 7 Establishing reactivity of sulfur ylides with boranes.

In the event reaction of the phenyl-stabilised ylide with Et$_3$B followed by Ph$_3$B only furnished the product from Et$_3$B whilst under the same conditions the silyl-stabilised ylide only furnished the product from Ph$_3$B (Scheme 8, equations 3 and 1). Changing the order of addition of the two boranes resulted in the phenyl-stabilised ylide trapping the BPh$_3$ and the silyl-stabilised ylide again trapping the Ph$_3$B (Ph$_3$B is evidently considerably more reactive than Et$_3$B). This indicated that the phenyl-stabilised ylide added non-reversibly to Et$_3$B whilst the silyl-stabilised ylide reacted reversibly.

This means that in the reaction of silyl-stabilised ylides with organoboranes, addition may well occur faster for one conformer of the ylide (see Scheme 5), as for phenyl-stabilised ylide, but since this step is reversible the two diastereomers of the ate complex are accessible and the selectivity-determining step is the 1,2-migration. The low enantioselectivity observed in these cases must therefore result from a similar rate of migration in the two diastereomers of the ate complex.

We were intrigued as to why the silyl-stabilised ylide should add reversibly to the borane whilst the phenyl-stabilised ylide reacts non-reversibly because the silyl-stabilised ylide is expected to be a slightly poorer leaving group (since it has a lower pK_b[5]) than the phenyl-stabilised ylide. Clearly, in the case of the silyl-substituted ylide, either the barrier to alkyl/aryl group migration must be raised or the barrier to reversion is lowered, or both. In order to distinguish between these possibilities and to understand why there should be such differences in the reactions we carried out calculations to try to shed light on this unusual situation.



Scheme 8 Cross-over experiments of sulfur ylides with boranes.

In a previous study, we have studied the reaction of non-substituted and phenyl-substituted ylides with BMe$_3$.[14] These calculations revealed a high exothermicity of the ate complex formation (≈30 kcal mol^{-1}), which occurred without enthalpic barrier, and a low barrier to migration (12–15 kcal mol^{-1}). This accounts for the non-reversibility of the addition step in these cases. This study showed also that the MP2/6-311+G**//B3LYP/6-31G* method was the more adequate to describe these systems. It is however important to make the point that at this level of theory the energy of reactants (and hence exothermicity of ate complex formation) is overestimated by *ca.* 10 kcal mol^{-1} (see SI of ref. 14).

The computed energy profile for the reaction of silyl-substituted ylide is reported in Fig. 1. Calculations are in good agreement with cross-over experiments, supporting a reversibility of ate complex formation (if one takes into account the error involved in the method). Examination of the profile shows that the reason for this reversibility is a combination of a decrease in exothermicity of ate complex formation and an increase (as compared to phenyl-stabilised ylide) in barrier to alkyl migration (Table 2).

The fact that the Me$_3$Si group (unlike Ph) has no effect on methyl migration barrier (barriers with R = H and Me$_3$Si are comparable) is unexpected given that Me$_3$Si group is reported to activate S$_N$2 reaction at an α-carbon.[15] However, an electronic analysis reveals the development of a positive charge on the ylidic carbon at the TS (δ charge on the carbon is 0.29 a.u. in non-substituted case; see Supporting Information). This indicates a significant S$_N$1 character of the reaction which can explain the

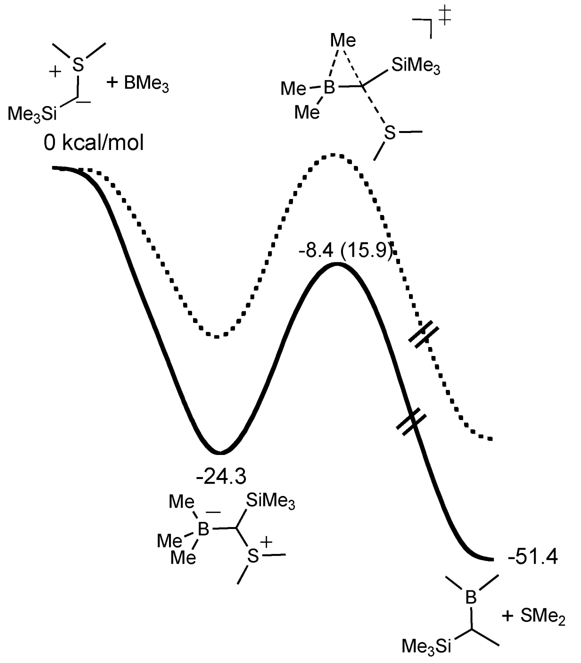
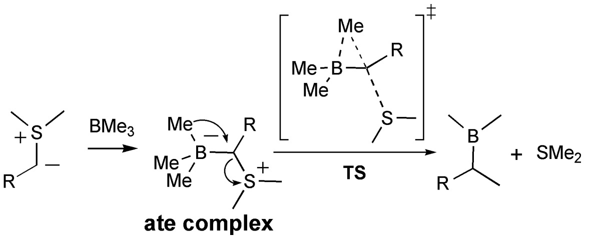


Fig. 1 Computational potential energy surface (relative energies in kcal mol^{-1}) for the reaction of Me_3B with $Me_3SiCHSMe_2$ (the dotted curve corresponds to qualitative energy profile taking into account the estimated error in the method).

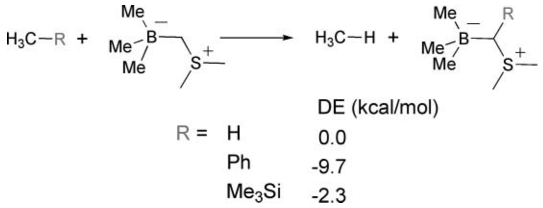
Table 2 Influence of substitution on the energy profile[a]



R	Reactants	Ate complex	TS(barrier)	Product
H	0.0	−34.6	−19.2(15.4)	−57.9
Ph	0.0	−34.6	−22.1(12.5)	−54.5
TMS	0.0	−24.3	−8.4(15.9)	−51.4

[a] Energies are obtained at the MP2/6-311+G**//B3LYP/6-31G* level of theory and are given in kcal mol^{-1} respective to reactants.

absence of activation by the Me_3Si group (Me_3Si has been shown to have little effect on S_N1 reactions[15c]).



Scheme 9 Computational analysis of the isodesmic reaction to probe stability of ate complex.

The substantial decrease in exothermicity of ate complex formation is even more surprising. Indeed, based on the slightly lower stabilisation of the silyl-stabilised ylide compared to the phenyl-stabilised ylide, and the similar steric encumbrance of the two groups (*vide supra*), one would expect, if anything, the opposite trend. A detailed analysis (see Supporting Information) shows that ate complex formation is highly exothermic in the case of phenyl-stabilised ylide because the phenyl group is able to stabilise the ate complex (hyperconjugation) to a similar extent as the ylide. This stabilisation of the ate complex can be illustrated by the energy of the isodesmic reaction reported in Scheme 9. For the silyl-substituted ylide the isodesmic reaction indicates a much lower stabilisation of the ate complex, probably due to destabilising geminal effects (strong donor and strong acceptor orbitals cause the greatest antibonding geminal destabilising interactions)[15] and vicinal steric interactions. Stabilisation of the ylide is thus not counter-balanced by a stabilisation of the ate complex in this case, which accounts for the decrease in exothermicity of ate complex formation.

In summary, in the case of phenyl-substituted ylide, a large stabilisation of the ate complex, which counter-balances stabilisation of the ylide, along with the activation of the migration step make the addition onto the organoborane non-reversible. For silyl-stabilised ylide, a combination of a decrease in exothermicity of ate complex formation, due to low stabilisation of the ate complex, and an absence of activation of the migration step, due to a significant S_N1 character of the 1,2-migration reaction, renders the addition of the ylide to the borane reversible.

Conclusions

In conclusion, it has been found that in contrast to aryl-stabilised ylides which react with boranes to give homologated products with very high enantioselectivity, silyl-stabilised ylides only give low enantioselectivity. Through cross-over experiments it has been shown that the two classes of ylides show quite different reactivity with boranes. Aryl-stabilised ylides react with boranes non-reversibly to give intermediate ate complexes which undergo stereospecific 1,2-metallate rearrangement leading to homologated boranes with high enantioselectivity. However, silyl-stabilised ylides react with boranes reversibly and so now selectivity is determined by the equilibrium ratio of diastereomeric ate complexes that are formed and their relative rates of subsequent 1,2-migration. The origin of the difference in reactivity and change in the selectivity-determining step has been analysed computationally. The main factors responsible for the silyl-stabilised ylide reacting reversibly with the borane are a reduction in exothermicity of ate complex formation and an increase in the activation barrier to migration of the borane substituent.

Computational details

The MP2/6-311+G**//B3LYP/6-31G* method has been selected to be the more adequate for the studied system after investigation of the model reaction of BMe_3 with CH_2SMe_2 at a variety of different levels of theory, including QCISD(T)/6-31G* and G3(MP2)//B3LYP methods (see reference 14).

All species have been fully geometry optimised using the Jaguar 6.0 pseudospectral program package.[16] Geometry optimisation and NBO analysis were carried out using the well established B3LYP hybrid density functional and the standard split valence polarised 6-31G* basis set.

Single point calculations at the MP2/6-311+G** level have been carried out on every transition state structure using the Gaussian 03 program package.[17]

Frequency calculations have been carried out on every transition state structure in order to check the correct nature of the point on the potential energy surface.

Acknowledgements

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