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Asymmetric Allylboration Reactions with Soderquist's Chiral 10-Substituted-9-borabicyclo[3.3.2]decanes: A Theoretical Study

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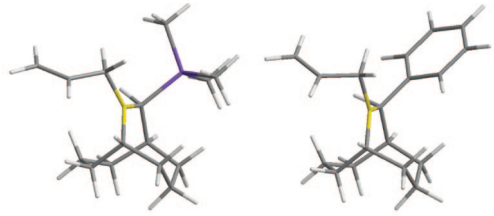
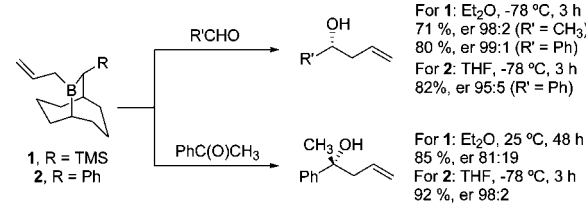


Chiral *B*-allyl-10-substituted-9-borabicyclo[3.3.2]decanes are highly efficient reagents for the enantioselective allylboration of adehydes and ketones. In this study, we use DFT calculations to rationalize the experimentally observed reactivity and selectivity. Calculations correctly reproduced the experimental reactivity trends and enantioselectivities. Our results suggest that the origin of the facial selectivity relies strongly on steric effects.

Stereocontrolled carbon−carbon bond forming reactions are of great importance in modern organic chemistry. Within this field, the asymmetric allylation of carbonyl compounds provides an excellent approach to nonracemic chiral homoallylic alcohols. Recently, Soderquist and co-workers reported the use of chiral 9-borabicyclo[3.3.2]decanes (BBDs) as effective and versatile chiral reagents for allyl- and crotylboration of carbonyl compounds.[1] This constitutes a key contribution to the progress of asymmetric synthesis since, aside from the excellent enantioselectivity achieved, the chiral source is stable, easily prepared in both enantiomeric forms, and recyclable. Also, the enantioselectivity diminishes slightly when the temperature is increased. The impact of the development of this novel system is evidenced by recent reports on the use of chiral BBDs in other asymmetric transformations[2] as well as on their application in synthesis.[3]

SCHEME 1. Allylboration Reactions with (−)-*B*-Allyl-10-TMS-9-BBD (1) and (−)-*B*-Allyl-10-Ph-9-BBD (2)



One of the main features of BBDs in allylboration reactions is that they can be strategically tuned by changing the substituent at C-10. As shown in Scheme 1, (−)-*B*-allyl-10-TMS-9-BBD (**1**) is highly effective for the allylation of aldehydes but much less reactive and selective when using ketones.[1b] On the other hand, (−)-*B*-allyl-10-Ph-9-BBD (**2**) displays excellent selectivities in the allylboration of ketones and lower selectivity in the case of aldehydes.[1c] To rationalize this experimental finding, the authors proposed that the interesting behavior of the BBD reagents relies mainly on the properties of the "chiral pocket" structure. Accordingly, in **1** the chair-boat (CB) conformation would be preferred providing a pocket that is receptive to aldehydic hydrogens, but it is too small to easily accommodate larger groups, thus failing to effectively allylate ketones. The replacement of the TMS group by a phenyl group is responsible for a preference toward the boat-chair (BC) conformation. The combination of a lesser steric bulk of the substituent and a chair form of the ring on the *cis* side in **2** provides an ideal pocket for methyl groups, leading to rapid and selective allylation of ketones.

In this study, we aimed to investigate the origin of the asymmetric induction by using DFT calculations. In addition, we wanted to rationalize one of the most remarkable features of these reactions, namely, the contrasting reactivity and selectivity of the 10-TMS and 10-Ph-substituted-9-BBD analogues in the allylation of aldehydes and ketones.

Computational Methods. Geometry optimizations were carried out with the B3LYP/6-31G* method,[4,5] using Gaussian 03.[6,7] Normal coordinate analyses were used to confirm the nature of the stationary points. All transition structures (TSs) were confirmed to have only one imaginary frequency corre-

(1) (a) Soderquist, J. A.; Matos, K.; Burgos, C. H.; Lai, C.; Vaquer, J.; Medina, J. R.; Huang, S. D. *A.C.S. Symp. Ser.* **2001**, *783*, 176–194. (b) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044–8049. (c) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573. (d) Soto-Cairoli, B.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 401–404.

(2) (a) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799–802. (b) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397–5400. (c) Hernandez, E.; Canales, E.; Gonzalez, E.; Soderquist, J. A. *Pure Appl. Chem.* **2006**, *78*, 1389–1395. (d) Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712–8713. (e) Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331–3334. (f) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091. (g) Canales, E.; Gonzalez, A. Z.; Soderquist, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 397–399. (h) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081–1084. (i) Román, J. G.; Soderquist, J. A. *J. Org. Chem.* **2007**, *72*, 9772–9775. (j) Gonzalez, A. Z.; Román, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 9218–9219.

(3) (a) Alexander, M. D.; Fontaine, S. D.; La Clair, J. J.; DiPasquale, A. G.; Rheingold, A. L.; Burkart, M. D. *Chem. Commun.* **2006**, *44*, 4602–4604. (b) Fürstner, A.; Bindl, M.; Jean, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 9275–9278. (c) Melancon, B. J.; Perl, N. R.; Taylor, R. E. *Org. Lett.* **2007**, *9*, 1425–1428.

(4) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

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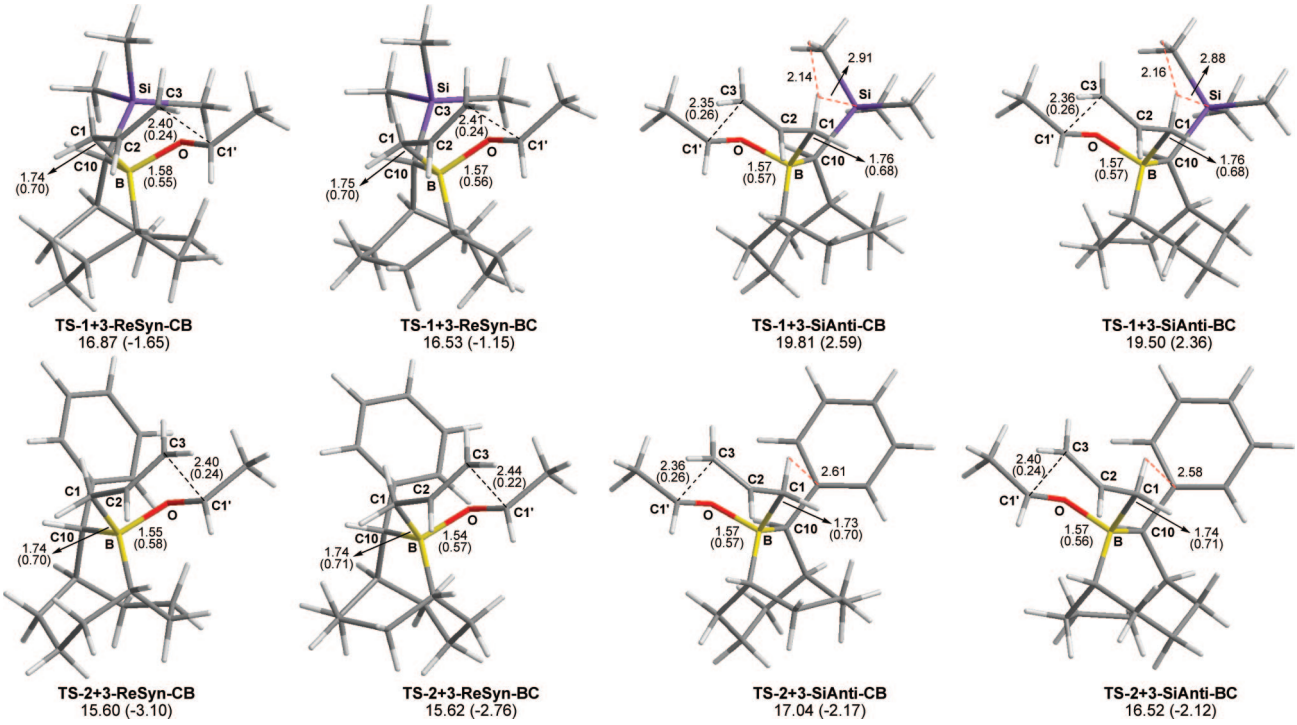
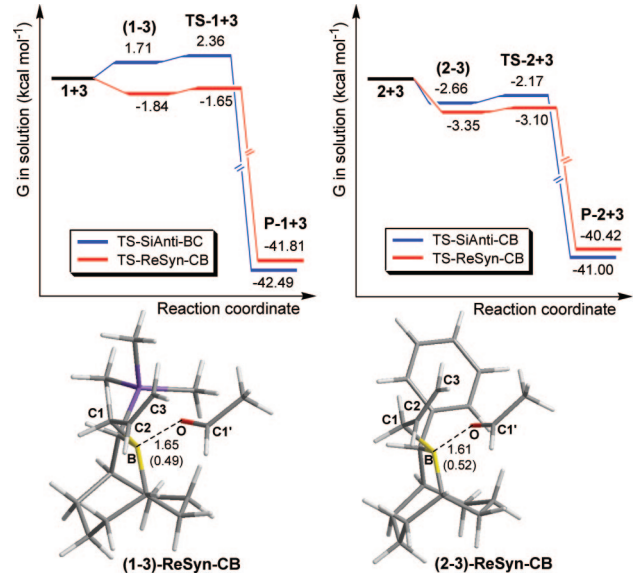


FIGURE 1. Optimized geometries for the TSs of the allylboration of acetaldehyde (**3**) with **1** and **2** with selected distances in Å and Wiberg bond indices in parentheses. Free energies relative to reactants in the gas phase and in solution (in parentheses) are shown in kcal mol^{-1}.

sponding to the formation of the expected bonds. Free energies in solution were computed on the structures optimized in the gas phase at the B3LYP/6-31G* level of theory with the polarizable continuum model (PCM),[8] using diethyl ether or THF as the solvent for the reactions of **1** and **2**, respectively.

Allylboration of Acetaldehyde. To begin our study, we first investigated the allylboration of acetaldehyde (**3**) with allylboranes **1** and **2**. Of all possible six-membered-ring chair-like TSs,[9] we found that for the *re* face approach the *syn* addition is far more stable than the *anti* addition, while the opposite situation is observed for the *si* face approach (Figure 1). Additionally, due to ring-flipping two stable conformations were found for each mode of addition, **TS-ReSyn-CB**, **TS-ReSyn-BC**, **TS-SiAnti-CB**, and **TS-SiAnti-BC**.[10] Inspection of the optimized geometries reveals that all transition structures are highly asynchronous with forming C1′−C3 bond distances of ∼2.40 Å and C1−B and B−O distances of ∼1.75 and ∼1.57 Å, respectively. The computed Gibbs free energy activation barriers for the **1** + **3** reaction suggest that *re* addition should be strongly favored, giving a *S*:*R* product ratio of >99:1 (Et_2O, −78 °C), which is in very good agreement with the experimentally observed enantiomeric ratio of 98:2.

SCHEME 2. Reaction Profiles of the Allylboration of 3 with 1 and 2 for the Most Stable TSs Corresponding to *re* and *si* Attack with Free Energies in Solution Relative to Reactants[a]



[a] Optimized geometries of the complexes with selected distances in Å and WBIs in parentheses are shown below the reaction profiles.

Interestingly, the computed energies for the **2** + **3** system reveal that the preference for *re*-face addition should be maintained but attenuated. The calculated *S*:*R* ratio is 89:11 (THF, −78 °C), which is consistent with the experimental value for benzaldehyde (95:5). It is important to point out that calculations suggest that the *re* selectivity observed with boranes **1** and **2** does not arise from the conformation adopted by the 9-BBD system, since the chair-boat and boat-chair TSs have

(5) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.

(6) Frisch, M. J. et al. *Gaussian 03*, revision C.02; Gaussian, Inc., Pittsburgh, PA, 2003.

(7) For full details of the calculations, see the Supporting Information.

(8) For a review on continuum solvation models, see: Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(9) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236–1240. (c) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692–10697. (d) Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519–12526.

(10) We located other conformations for some of the TSs, such as the chair−chair form, but they exhibited higher energies. See the Supporting Information.

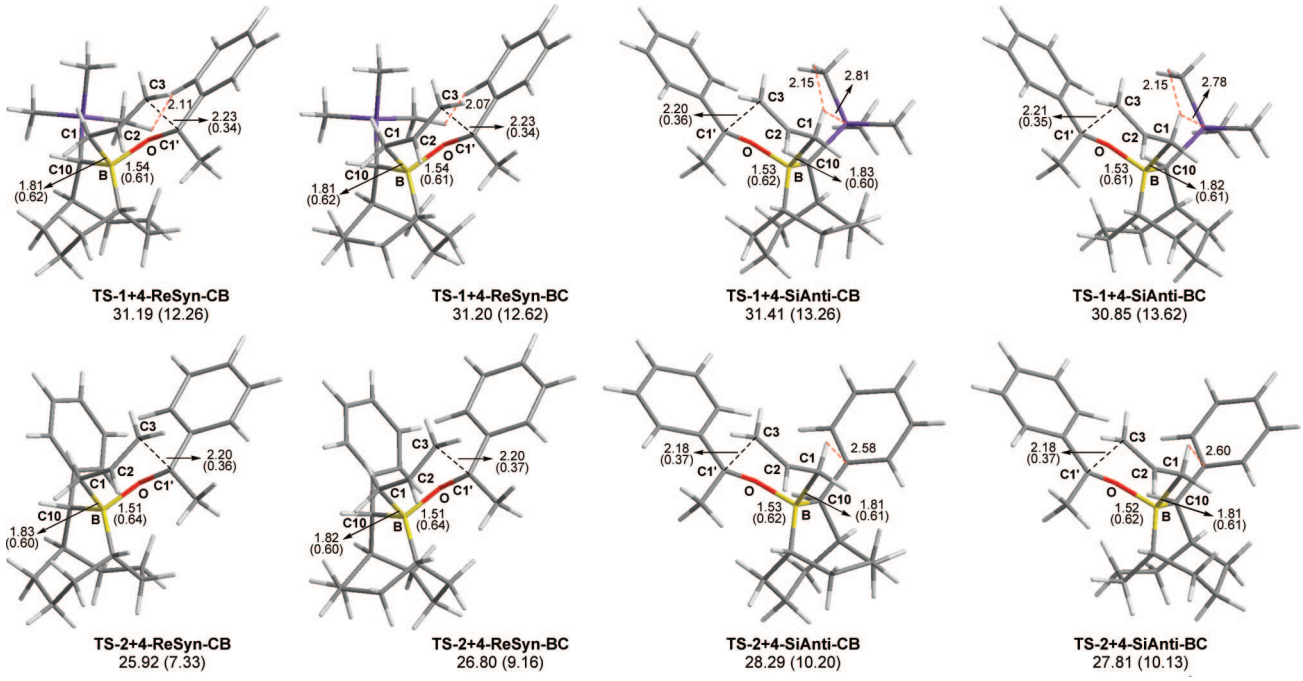


FIGURE 2. Optimized geometries for the TSs of the allylboration of acetophenone (**4**) with **1** and **2** with selected distances in Å and WBIs in parentheses. Free energies relative to reactants in the gas phase and in solution (in parentheses) are shown in kcal mol^{-1}.

similar energies and so both structures must be considered to compute the er.

Since all TSs show similar Wiberg bond indices (WBIs),[11] the destabilization of TSs arising from the attack of the *si* face needs to be explained in terms of steric interactions. In both **TS-1+3-SiAnti-CB** and **TS-1+3-SiAnti-BC** the allyl moiety lies on the same side of the TMS group, which results in close contacts between H−Si (∼2.90 Å) and H−H (∼2.15 Å), shown in red in Figure 1. Moreover, the calculated distance between the carbonyl oxygen and C10−H is 2.35 Å, less than the sum of van der Waals radii of both nuclei. In contrast, in **TS-1+3-ReSyn-CB** and **TS-1+3-ReSyn-BC** the allyl moiety lies on the opposite side, so most steric clashes are avoided despite the carbonyl oxygen being in close contact with the Si atom (3.08 Å). The calculations also suggest that the origin of the lower selectivity in the allylboration of aldehydes with borane **2** can be attributed mainly to steric reasons. Since a Ph group is less sterically demanding than a TMS, only two close contacts may cause destabilization of both **TS-2+3-SiAnti**: C_{ipso}−H (∼2.60 Å) and O−C10−H (∼2.40 Å).

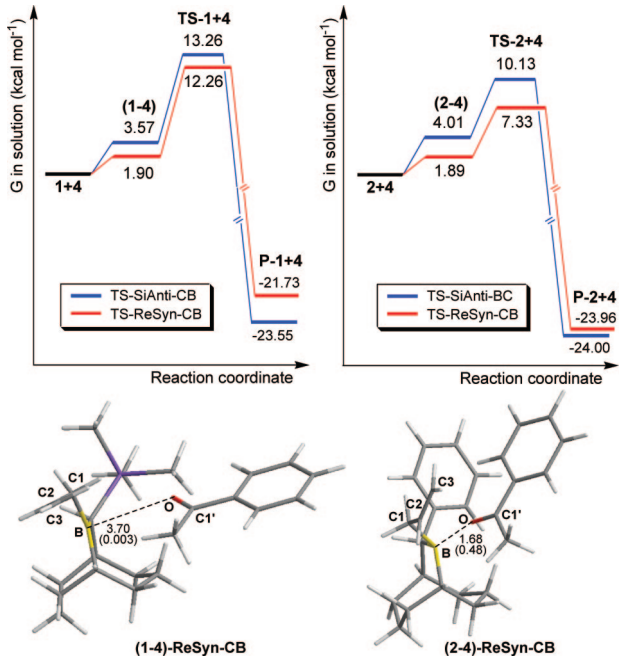
We then examined the reaction profiles of the allylboration of acetaldehyde (**3**) with **1** and **2** by performing intrinsic reaction coordinate (IRC) calculations starting from the optimized TSs (Scheme 2).

The TSs were found to be connected to strongly bound coordination complexes and to products, so once the complexes are formed, the formation of the C3−C1′ bond occurs in a concerted fashion with the breaking of the C1−B bond. The calculated B−O and C3−C1′ distances in the complexes are *ca.* 1.65 and 2.90 Å, respectively, suggesting that these species are well positioned for collapse to the expected chair-like TS. The computed B−O WBIs for the complexes are ∼0.50, slightly lower than those observed in the TSs. Furthermore, we found small WBIs between C3 and C1′ in these complexes (∼0.09), so they can be considered as pretransition state structures. Scheme 2 clearly demonstrates that both the kinetics and the thermodynamics of the allylboration are highly favorable. Due to the higher polarization of the complexes, the TSs, and the products as compared with the reactants, the inclusion of solvent effects in the calculations reduced the activation and reaction free energies by more than 10 kcal mol^{-1}.[7]

Allylboration of Acetophenone. We next studied the allylboration of acetophenone (**4**) (Figure 2). As expected, the most stable TSs were again the chair-boat (CB) and boat-chair (BC) conformations of both **TS-ReSyn** and **TS-SiAnti**. All TSs are asynchronous with forming C3−C1′ bond distances of ∼2.20 Å and C1−B and B−O distances of ∼1.82 and ∼1.53 Å. It is interesting to note that forming C3−C1′ bond distances are 0.2 Å shorter than those of the corresponding TSs for acetaldehyde, while C1−B are 0.1 Å higher. The calculated WBIs are nearly the same for all structures shown in Figure 2 (*ca.* 0.61 for B−O and C1−B and 0.35 for C3−C1′). The computed Gibbs free energy barriers for the system **1** + **4** suggest that *re* addition should be favored, giving an *R*:*S* product ratio of 84:16 (Et_2O, 25 °C), which is in very good agreement with the experimental enantiomeric ratio of 81:19. The computed activation free energies for the system **2** + **4** reveal that higher enantioselectivity should be expected. The calculated *re*/*si* selectivity is >99:1 (THF, −78 °C), which is consistent with the experimental data (98:2). The analysis of the TSs shown in Figure 2 suggested that the contribution of steric effects seems to be much more important than that of electronic effects in determining the enantioselectivity. Furthermore, for **TS-1+4-SiAnti** and **TS-2+4-SiAnti** we found similar close contact interactions as described before for **TS-1+3-SiAnti** and **TS-2+3-SiAnti**, respectively. However, in both **TS-1+4-ReSyn** we now found a close proximity between one of the aromatic hydrogens of acetophenone and the TMS group, as shown in red in Figure 2. These unfavorable interactions are responsible for the lower reactivity and selectivity observed in the reaction of acetophe-

(11) *NBO*, Version 3.1; Glendening, E. D., Reed, A. E., Carpenter, J. E., Weinhold, F.

SCHEME 3. Reaction Profiles of the Allylboration of 4 with 1 and 2 for the Most Stable TSs Corresponding to *re* and *si* Attack with Free Energies in Solution Relative to Reactants[a]



[a] Optimized geometries of the complexes with selected distances in Å and WBIs in parentheses are shown below the reaction profiles.

none with (−)-*B*-allyl-10-TMS-9-BBD (**1**). In contrast, the steric reasons that make (−)-*B*-allyl-10-Ph-9-BBD (**2**) less selective for the allylboration of aldehydes appear to be responsible for the much better performance, in terms of both reactivity and selectivity, when using ketones since **TS-2+4-ReSyn** do not exhibit any unfavorable interactions. These results indicate that the replacement of the TMS group by a phenyl group has a greater impact on the size rather than on the conformation of the chiral pocket of the 9-BBD system.

The reaction coordinates for the most stable TSs corresponding to *re* and *si* attack for the allylboration of acetophenone (**4**) with **1** and **2** are shown in Scheme 3. As expected, the computed energy barriers for the allylboration of acetophenone are higher than those for acetaldehyde (Scheme 2). In addition, the activation energy for **TS-1+4-ReSyn** is *ca.* 5 kcal mol^{-1} higher in energy than that for **TS-2+4-ReSyn**, which explains the experimental finding that the allylboration of acetophenone with **1** is slower than that with **2** (25 °C, 48 h *vs* −78 °C, 3 h). In this case, the calculated activation and reaction free energies in solution were 20 kcal mol^{-1} lower than those in the gas phase. In line with the results for the allylboration of acetaldehyde, transition structures **TS-2+4-ReSyn** were shown to be connected to coordination complexes **(2−4)-ReSyn**. However, all

TABLE 1. Calculated and Experimental *re/si* Facial Selectivities[a] for the Allylboration Reactions of Compounds 3 and 4 with Allylboranes 1 and 2

system	calcd *re/si* ratio from Δ*G* (complexes)	calcd *re/si* ratio from Δ*G* (TSs)	exptl *re/si* ratio
1 + **3**	>99:1	>99:1	98:2
2 + **3**	79:21	89:11	95:5[b]
1 + **4**	94:6	84:16	81:19
2 + **4**	26:74	>99:1	98:2

[a] Selectivity ratios calculated from the Boltzmann factors of four most stable TSs and corresponding complexes with use of Gibbs free energies in solution. [b] For benzaldehyde.

efforts to locate coordination complexes for **TS-1+4-ReSyn**, **TS-1+4-SiAnti**, and **TS-2+4-SiAnti** failed, which might be related to the higher steric hindrance of **1** and of the *si-anti* approach for **2**. Instead, loosely bound molecular complexes **(1−4)-ReSyn**, **(1−4)-SiAnti**, and **(2−4)-SiAnti** were found, in which the boron atom remains trigonal and is 3.3−4.4 Å from the carbonyl oxygen of the ketone. The calculated B−O WBIs in the molecular complexes vary in the range 0.002−0.016.

Finally, the product stereochemistry has been previously predicted through the relative stabilities of the pretransition state complexes.[1b,c] We thus compared the *re/si* facial selectivities computed based on the Gibbs free energies of the complexes and the TSs (Table 1). We observed a much better correlation when using the relative free energies of the TSs rather than those of the complexes. Moreover, a preference for addition to the *si* face was incorrectly predicted for the reaction of acetophenone with allylborane **2**. Therefore, care must be exercised when evaluating BBD reagents on the basis of complexes.

In conclusion, DFT calculations have shown that the enantioselectivity of the allylboration reactions with Soderquist's BBDs is mainly governed by steric interactions in the TSs. In addition, the BBD system adopts chair-boat and boat-chair conformations in the more contributing TSs and both have similar energies so they must be considered when computing enantiomeric ratios. Calculations based on Gibbs free energies of the competing TSs accurately reproduced the experimentally observed enantioselectivities.

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Supporting Information Available: Optimized geometries, Cartesian coordinates, and energies of all the stationary points; values of imaginary frequencies of all TSs; energies of the FMOs of the reactants; full ref 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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