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Mechanistic Insights into the Catalytic Asymmetric Allylboration of Ketones: Brønsted or Lewis Acid Activation?

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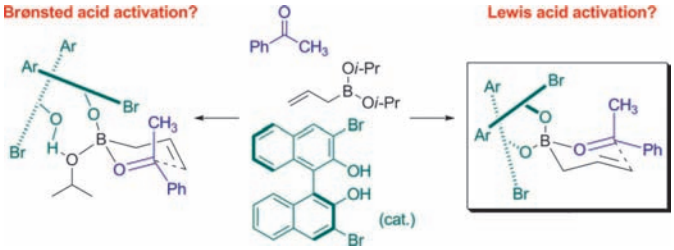
ABSTRACT



Binaphthol ligands promote the enantioselective addition of allylboronates to ketones. In this study, we use DFT calculations to establish the identity of the reacting chiral species. Our results show that a cyclic Lewis acid-activated boronate is the most reactive species on the basis of calculated energy barriers, and it is only this species that leads to the correct enantiomer. The stereoinduction can be rationalized in terms of the competing chairlike transition structures.

The asymmetric allylation is a valuable synthetic method for preparing chiral homoallylic alcohols. In 2004, Chong and co-workers reported that the allylboration of both aldehydes and ketones with the (*S*)-3,3′-$(CF_3)_2$-binaphthol-derived allylboronate occurs in high yields and enantioselectivities.[1] More recently, Schaus and co-workers developed a closely related and highly enantioselective ligand-accelerated protocol for the catalytic asymmetric allylboration of ketones.[2,3] To develop this challenging reaction, the authors relied on the facility with which acyclic boronates undergo ligand exchange and also on the rate acceleration produced by the use of Lewis acids[4] or strong Brønsted acids[5] in the addition of allylboronates to aldehydes. They suggested that chiral diols could catalyze asymmetric allylboration reactions by acting as exchangeable chiral ligands with Brønsted acid properties. To investigate this concept, several chiral diols were tested, and (*S*)-3,3′-Br_2-BINOL was shown to be the catalyst of choice. The reaction of ketones with B-1-allyldiisopropylboronate (**2**) catalyzed by (*S*)-3,3′-Br_2-BINOL (**3a**) gave the chiral tertiary homoallylic alcohols with excellent yields and enantioselectivities (Scheme 1). Under optimized reaction conditions, the allylation of acetophenone (**1**) afforded the (*S*)-homoallylic alcohol **4** in 83% yield and

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(1) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.

(2) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

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(4) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Miyaura, N.; Ahiko, T.; Ishiyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (d) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (e) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412. (f) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.

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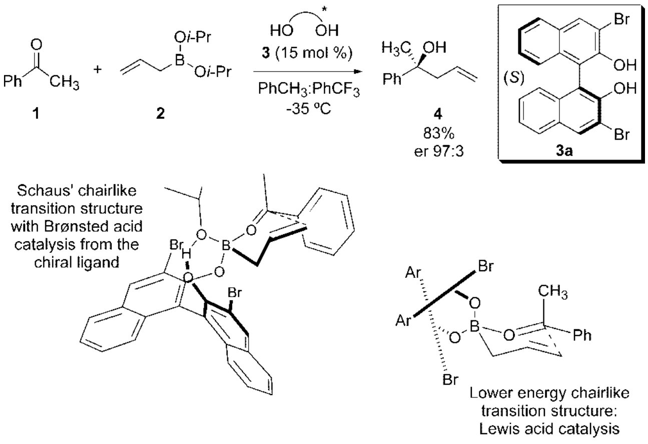
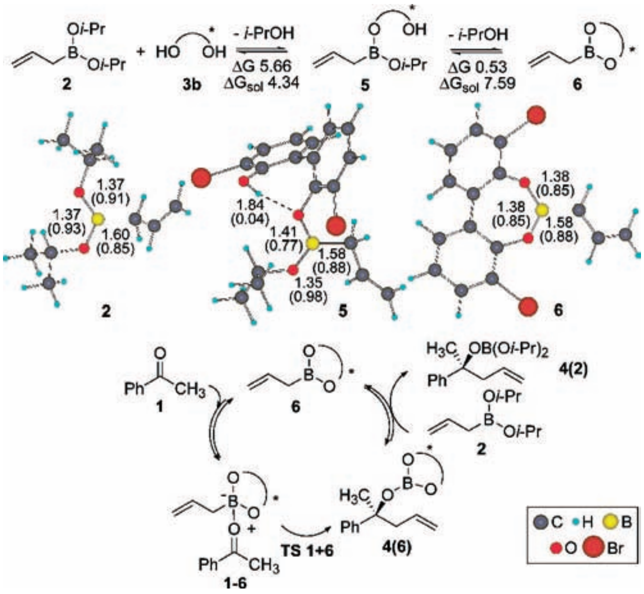
Scheme 1. Catalytic Asymmetric Allylboration of Ketones



97:3 er. The reactions of **1** with (*E*)- and (*Z*)-crotylboronates were also highly enantio- and diastereoselective, giving the *anti* and *syn* products, respectively. On the basis of preliminary kinetic and ^{1}H NMR mechanistic experiments, it was proposed that **2** exchanges one isopropoxy ligand to give a binaphthol-associated boronate. A hydrogen-bonding interaction between the catalyst and the remaining alkoxy ligand leads to the preferential attack of the ketone *Si* face in the proposed chairlike allylboration transition structure (TS). Here we report the results of DFT calculations that point to an alternative mechanistic hypothesis: Lewis acid catalysis (Scheme 1).

We studied the reaction of acetophenone (**1**) with allyl diisopropylboronate (**2**) using (*S*)-3,3′-dibromo-1,1-biphenyl-2,2-diol (**3b**) as a model for catalyst **3a**. Calculations were performed at the B3LYP/6-31G* level of theory with Gaussian 03.[6] The choice of this level of theory for the present investigation was based on our previous experience on the study of reactions of organoboranes.[7] 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) as implemented in Gaussian 03 using dichloromethane as the solvent, which has a dielectric constant similar to that of trifluorotoluene.[8] We have investigated the competing allylboration reactions of **1** with boronates **2**, **5**, and **6**, in which the isopropoxy groups are sequentially displaced by the chiral ligand. Scheme 2 shows the energetics for ligand exchange, the optimized geometries of the boronates, and our proposed catalytic cycle for **6**. Scheme 3 depicts the reaction coordinates for the most favorable transition structures and gathers the geometries of the complexes.[9]

Scheme 2. Ligand Exchange: Optimized Geometries of **2**, **5**, and **6** with Selected Distances, in Å, and Bond Indices (In Parentheses) and Catalytic Cycle for **6**[a]



[a] Free energies are shown in kcal mol^{-1}.

It is interesting to point out that complexation and allylboration are calculated to be more favorable in solution than in the gas phase. In addition, activation barriers in the gas phase are much higher than those in solution. This can be attributed to the greater stabilization of the more polarized intermediates and transition structures relative to starting materials in solution. However, the reaction and activation free energies computed with both methods follow the same trends.

In agreement with the results of NMR experiments, our calculations suggest that **5** is the predominant chiral boronate in the reaction mixture. Crucially, however, although boronate **6** is present in smaller amounts, it is predicted to be the *most reactive* species. In line with our previous theoretical

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(5) (a) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981. (b) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (c) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (d) Elford, T. G.; Arimura, Y.; Siu, H. Y.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276.

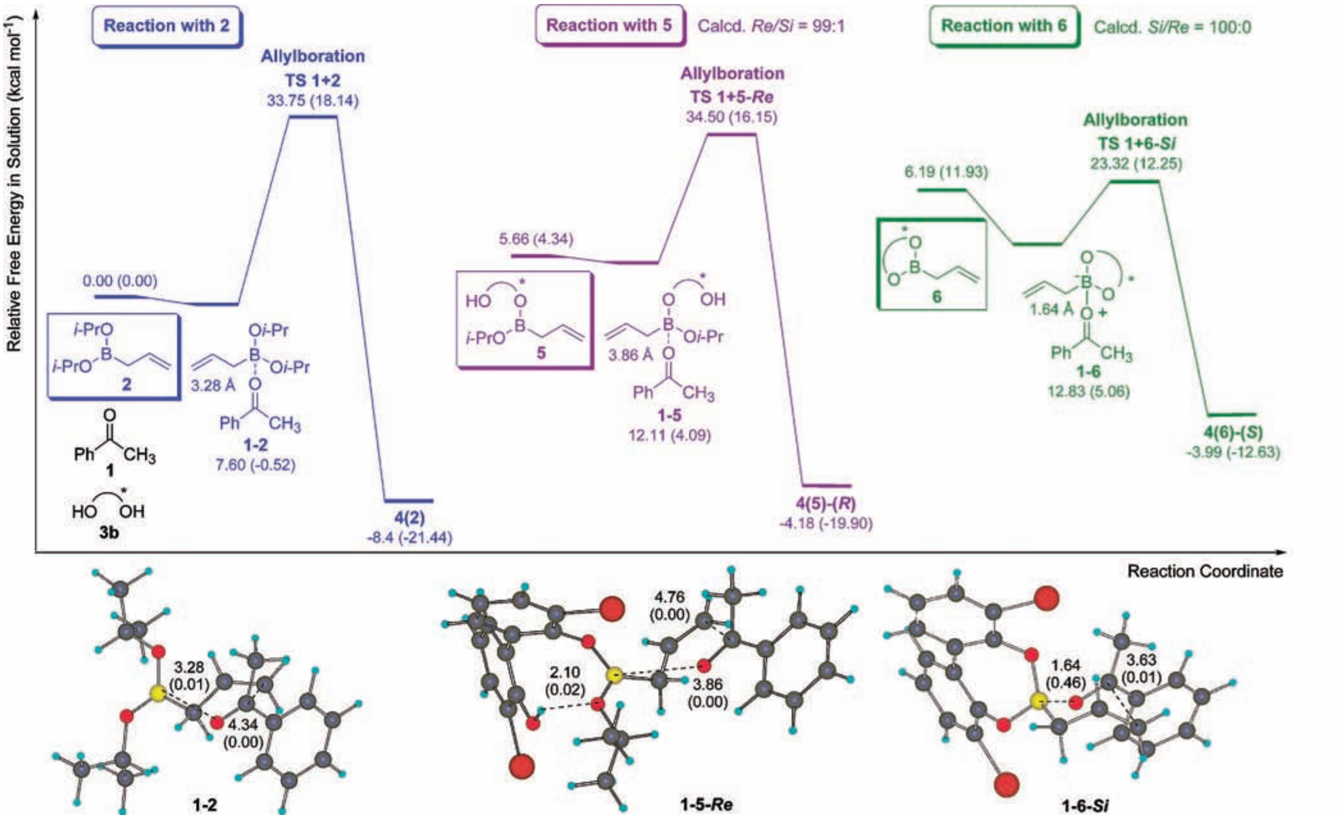
(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford CT, 2004.

(7) For example, see: (a) Pellegrinet, S. C.; Silva, M. A.; Goodman, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 8832. (b) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2002**, *67*, 8203. (c) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2003**, *68*, 4059. (d) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *Arkivoc* **2003**, *X*, 556.

(8) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117. (b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.

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

Scheme 3. Reaction Profiles in Solution for the Allylboration of **1** with **2**, **5**, and **6**: Free Energies Relative to Reactants in the Gas Phase and in Solution (in Parentheses); Optimized Geometries of the Complexes (Below the Reaction Profiles) with Selected Distances in Å and Bond Indices in Parentheses



results for related reactions,[10] calculations predict that the pathway for **6** is more favorable than that of **5**, which, in turn, is more favorable than the background reaction for **2**. The cyclic allylboronate **6** is nonplanar so the oxygen lone pairs cannot delocalize into the vacant boron orbital, enhancing its Lewis acidity. Consequently, **6** readily forms a coordination complex with ketone **1** and the activation energy of the subsequent addition step is lowered. In contrast, diisopropylboronate **2** and Brønsted acid activated boronate **5** both allow the oxygen lone pairs to delocalize into the vacant boron orbital and so are less able to coordinate to the ketone. Ultimately, this leads to higher allylboration energy barriers.

The argument that cyclic boronate **6** is the reacting species is strengthened further by considering the calculated enantioselectivities.[11] The computed *Re* facial selectivity for **5** (*Re*/*Si* 99:1, Brønsted acid) is at odds with experiment, while the *Si* selectivity for **6** (*Si*/*Re* 100:0, Lewis acid) agrees both qualitatively and quantitatively with the experimental value (*Si*/*Re* 97:3). It may be argued that the differences between the calculations and the experiment could arise from the use of biphenol **3b** as a model for the binaphthol catalyst **3a**. However, Jaguar[12] calculations with the compound used in the experiments (**3a**) demonstrate that the higher reactivity computed for boronate **6** and the opposite *Re* versus *Si* facial selectivity for **5** and **6**, respectively, are maintained. This indicates that the inclusion of the additional aromatic rings in the transition structures does not alter the results obtained with **3b**, which supports the use of this model for performing the calculations.

We note that the calculations suggest that the isopropoxy group in the transition structures corresponding to the reaction of **5** prefers to be equatorial (Figure 1) and not axial, as Schaus suggested (Scheme 1), and this may account for the reverse in selectivity from his suggested transition structure. For cyclic boronate **6**, a close contact exits between a bromine atom in the ligand and the axial methyl group in the six-membered chairlike TS leading to attack of the *Re* face of the ketone (**TS 1 + 6-*Re***), which explains the observed *Si* facial selectivity (Figure 1). The transition structures for allylboronate **5a** are more crowded, especially **TS 1 + 5-*Si***, which shows an unfavorable steric interaction between the allylic methylene and one of the bromines. In Scheme 4, we represent the chiral ligand in the same way as our earlier studies of binaphthol-derived catalysts.[13]

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[10] (a) Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3116. (b) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *J. Org. Chem.* **2008**, *73*, 5078.

[11] Ratios were computed using Boltzmann factors based on activation free energies.

[12] *Jaguar, version 6.5*, Schrodinger, LLC: New York, NY, 2005.

[13] Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.

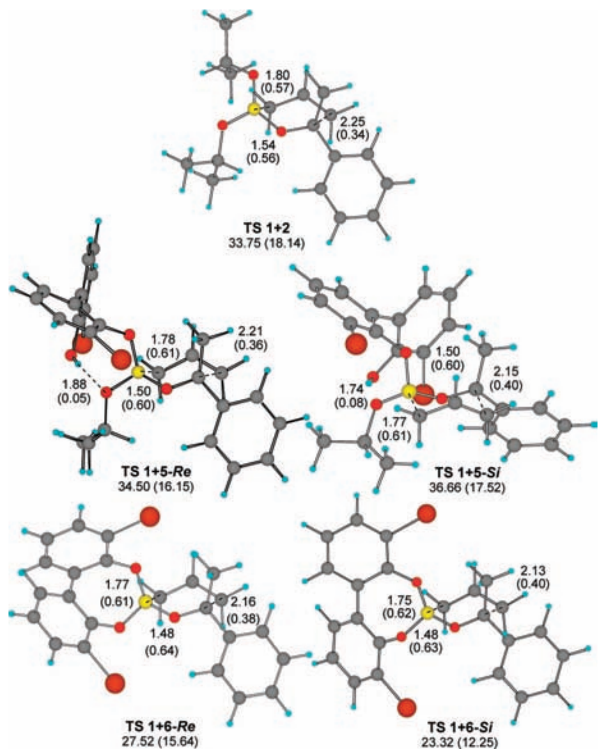
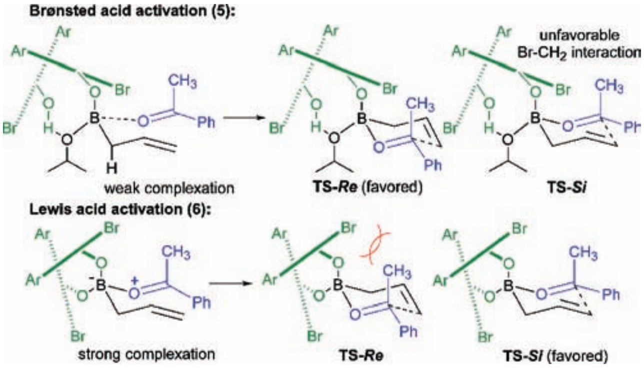


Figure 1. Optimized geometries of the transition structures with selected distances in Å and bond indices in parentheses and free energies (in kcal mol^{-1}) relative to reactants in the gas phase and in solution (in parentheses).

Scheme 4. Brønsted Acid versus Lewis Acid Activation



The 6-31G* basis set may treat structures such as **2** and **6** well. However, the lack of polarization or diffuse functions on hydrogen may lead to a poor treatment of the hydrogen bonding observed in **5**. To validate the use of the 6-31G* basis set, we ran single-point calculations for the reagents and the transition structures corresponding to boronates **5** and **6** with the 6-311++G** basis set.[14] These demonstrated that the relative activation energies are consistent with both basis sets.

In conclusion, DFT calculations have shown that the binaphthol-catalyzed allylboration reaction operates by Lewis acid activation rather than Brønsted acid activation. The activation proceeds via the formation of a reactive cyclic boronate intermediate. This mechanism contrasts with the originally proposed pathway via a Brønsted acid activated mixed boronate, which was found to possess a higher energy barrier for allylboration and to give the wrong sense of stereoinduction. The cyclic binaphthol-derived boronate is predicted to impart stereoselectivity in the allylboration by minimizing the steric interactions between a bromine atom and the methyl of the ketone, and the calculated enantioselectivity agrees closely with the experiment. These findings should aid the design of new ligand-accelerated boron reactions. More calculations on related allylboration reactions, such as the catalytic asymmetric allylboration of acyl imines,[15] are in progress and will be reported in due course.

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Supporting Information Available: Cartesian coordinates and energies of all the stationary points reported in the paper; values of imaginary frequencies of all TSs; optimized geometries not included in the paper; energies of the FMOs of the reactants. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802270U

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(14) The size of the systems under study makes geometry optimizations at this level of theory extremely expensive in CPU time.

(15) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.