

Ab Initio Investigation of the Transition State for Asymmetric Synthesis with Boronic Esters

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The transition state for the Lewis acid-assisted migration of an alkyl group from boron to an α -dichlorocarbon in a nonracemic boronic ester, $\text{RB}(\text{OR})_2$ (Matteson homologation), has been investigated using ab initio calculations. It has been postulated that the reaction involves a complexation of a Lewis acid with one of the two oxygens of the boronic ester and that the Lewis acid then assists one of the two prochiral chlorine atoms in leaving.¹ The results of the calculations are contrary to the previously postulated transition state¹ in that they suggest that the Lewis acid should be placed on the opposite oxygen of the boronic ester.²

A widely used process in organoborane chemistry is the construction of bonds via migration of a group from a tetracoordinated boron atom to an adjacent atom bearing a leaving group. One example is the asymmetric construction of carbon–carbon bonds by treatment of a nonracemic boronic ester ($\text{R}'\text{B}(\text{OR})_2$) with (dichloromethyl)lithium.³ The use of diols such as pinanediol,⁴ 1,2-diisopropylethanediol,⁵ 1,2-dicyclohexylethanediol,⁶ and 2,3-butanediol⁷ can lead to diastereomeric purities of greater than 100:1. The required borate intermediate⁸ may be prepared by either treating an alkylboronic ester with (dichloromethyl)lithium or treating a (dichloromethyl)boronic ester with an alkyl lithium reagent as shown in Scheme 1.

The process is facilitated by a Lewis acid such as zinc chloride. Selectivities are much lower without the Lewis acid.

The overall process involves two migrations of alkyl groups from boron to an adjacent chlorine-bearing carbon atom. It is known that the migration of an alkyl group from boron to an adjacent halogen-bearing carbon atom proceeds with inversion of configuration at the migration terminus.⁹ Therefore, the stereochemistry of the process must be set when one of the two prochiral chlorine atoms leaves during the first migration. From the absolute configuration of the final product it can be deduced that the reaction proceeds as depicted in Scheme 2.

However, a rational explanation for this selectivity has been lacking.

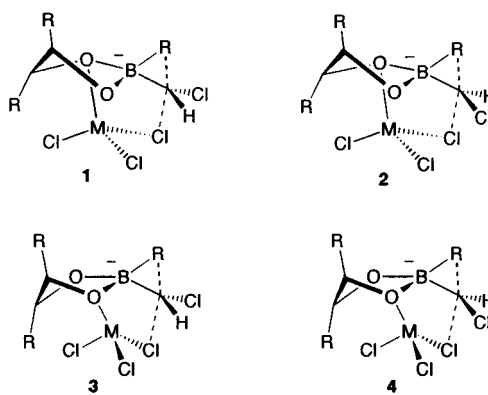
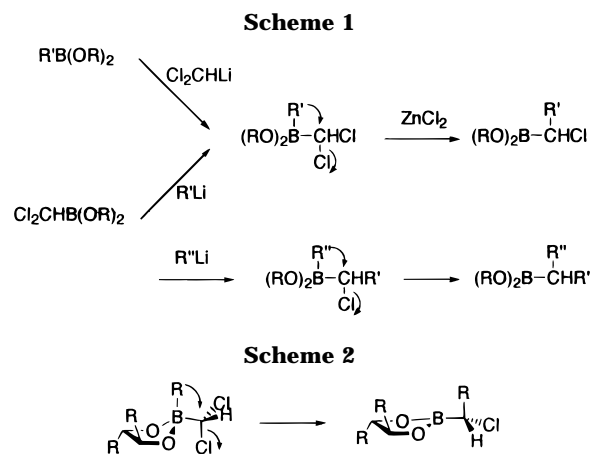


Figure 1.



To rationalize the selectivity, model Lewis acid complexes were examined using molecular mechanics.¹ There are four probable transition state complexes that are depicted in Figure 1.

It was found that structure **1** was about 1 kcal/mol more stable than **2**. Structures **3** and **4** were not reported.¹⁰ Structure **1** leads to the correct product as does **3**. The results seemed to place the metal in a congested environment, being close to the R group of the diol and to the nonparticipating chloride atom. Molecular mechanics programs are not well parametrized for structures of this type. Therefore, we investigated this reaction using ab initio methods.

Transition-state optimizations were performed using Gaussian 94¹¹ on structures **1–4** where $\text{R} = \text{CH}_3$ and $\text{M} = \text{Mg}$.¹² At the RHF/3-21G level, structures **1** and **4**, in which

(1) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995; pp 187–189.

(2) Professor E. J. Corey has also proposed that the transition state is incorrect and has suggested that the major product arises from a transition state that is similar to ours. Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Asymmetry* **1997**, *8*, 3711. We thank Professor Corey for a preprint of his manuscript.

(3) For reviews, see: (a) Reference 1, Chapter 5. (b) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. (c) Matteson, D. S. *Pure Appl. Chem.* **1991**, *63*, 339. (d) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (e) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294.

(4) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077.

(5) Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200.

(6) Ditrich, K.; Bube, T.; Stürmer, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028.

(7) Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804.

(8) For an alternative route to the nonracemic α -halo boronic esters using a chiral Lewis acid, see: Jadhav, P. K.; Man, H.-W. *J. Am. Chem. Soc.* **1997**, *119*, 846.

(9) Midland, M. M.; Zolopa, A. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 248.

(10) Structures **3** and **4** proved to be difficult to minimize. (Matteson, D. S. Personal communication.)

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, P.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision E.1*, Gaussian, Inc.: Pittsburgh, PA, 1995.

(12) Magnesium was used in place of zinc to facilitate the calculations. Magnesium salts have been used for the reaction but they have not been fully investigated. (Matteson, D. S. personal communication.)

(13) Transition states were located using the QST3 keyword and were confirmed by the presence of a single negative vibration. This vibration corresponded to the migration of the methyl group from boron to the adjacent carbon and loss of chlorine. The vibrations were visualized using PCVIB from Serena Software. The energies are corrected for the zero point energy.

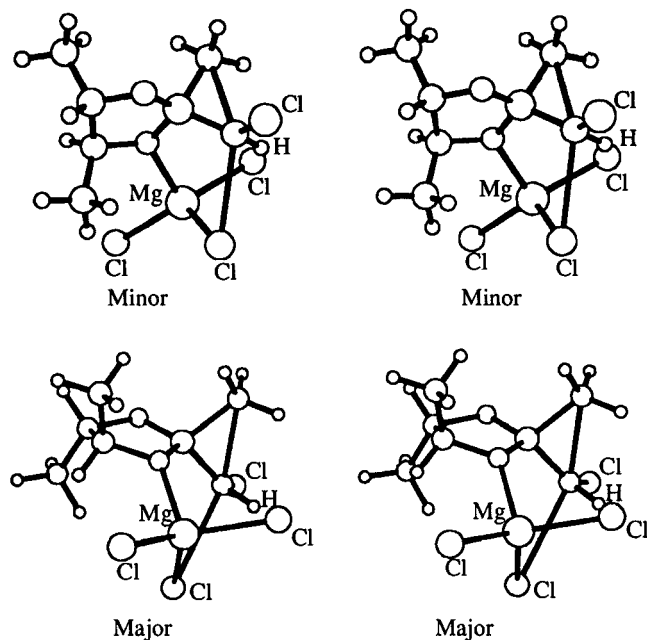


Figure 2.

the nonparticipating chlorine atom is syn to the metal, were 16.9 and 12.6 kcal/mol higher in energy than the lowest structure, **3**, and were therefore not considered further. At the RHF/6-31G* level, structure **2** was 4.7 kcal/mol higher than structure **3**.¹³ The lowest energy transition state, **3**, is in agreement with the experimentally observed relative configuration. The relative difference in energy between **2**

and **3** is in agreement with the high selectivity observed for these reactions but may exaggerate the selectivity.¹⁴ Stereoviews of the calculated transition states are given in Figure 2.

The calculated transition-state structure for the major product indicates that there is considerable loss of bonding between carbon and the leaving halogen (C–Cl distance 2.9 Å). Also, the new carbon–carbon bond is poorly formed (C–C distance 2.29 Å), while the migrating methyl group has not departed very far from the boron atom (C–B distance 1.7 Å). The carbon–boron–carbon angle is 88.1°. These measurements suggest that the Lewis acid assists the halogen in leaving before the alkyl group migrates. Surprisingly, the methyl groups of the diol are pseudoaxial.

The calculated transition state is in accord with the experimental results. It is important to have the nonparticipating chlorine atom anti to the metal (**2** and **3**). This is the opposite of what was previously suggested.¹ The stereoselectivity is then dictated by placing the metal on the least hindered side of the oxygen, trans to the R group of the ester. This combination places the Lewis acid in the least sterically hindered position. Thus, the proposed transition state provides a more rational explanation of the stereoselectivities observed in the Matteson homologation reaction.

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(14) There is some uncertainty in the selectivity with 2,3-butanediol (90% de, ref 7) because of uncertainties with analytical methods and the purity of the starting diol (ref 3e).