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Supplementary Material Available: Summary of the reduction of chiral ketones with *R,R* and *S,S* reagent I (2 pages). Ordering information is given on any current masthead page.

Organoboron Compounds in Organic Synthesis. 3. Mechanism of Asymmetric Reduction of Dialkyl Ketones with (*R,R*)-2,5-Dimethylborolane

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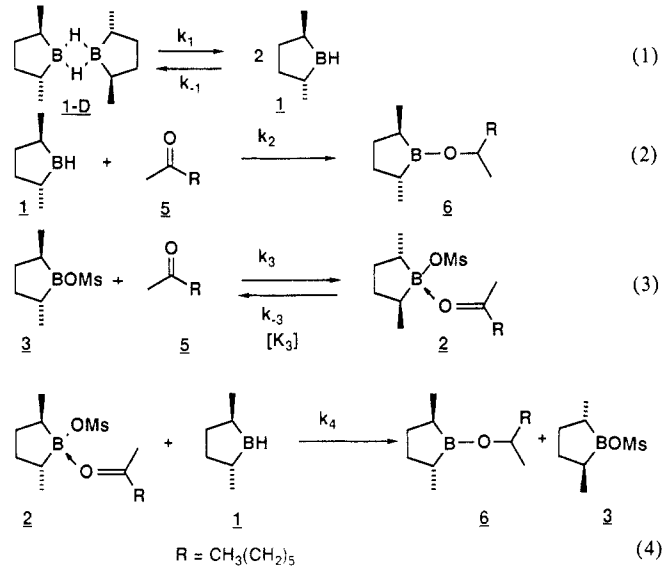
The preceding paper describes the asymmetric reductions of prochiral dialkyl ketones: Reagent I which contains dimeric (*R,R*)-2,5-dimethylborolane (**1**-D) (see Scheme I for the structures) provides the *R* alcohols of high enantiomeric purity.[1] These results surprised us, mainly because dialkyl ketones are isostructural with the corresponding terminal (type I) alkenes which, with **1**-D, undergo hydroboration with insignificant asymmetric induction.[2] No reasonable explanation for this apparent anomaly was immediately available. The accumulated evidence described below indicates, however, a rationalization for the observed high asymmetric induction. We propose the following mechanism for this reaction: A ketone forms the complex **2** with (*R,R*)-2,5-dimethylborolanyl mesylate (**3**) (Scheme I, eq 3) which is present in reagent I and subsequently complex **2** reacts with monomeric **1** (eq 1 and 4). The transition state of the last crucial step is also proposed and its geometry is evaluated with the aid of a combination of ab initio and MM2 computations.

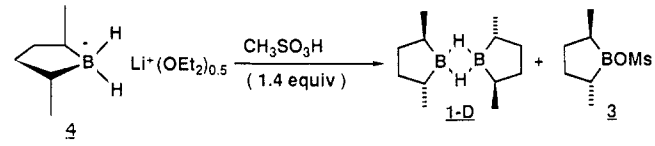
Experiment Set 1. Treatment of lithium dihydridoborate (**4**)[2] in hexane with dimethyl sulfate (1.2 equiv) provided **1**-D (^{11}B NMR δ 31.5) as the sole boron-containing species. Reduction of 2-octanone (**5**) with **1**-D, free from **3**, followed three-halves-order kinetics, first order in **5** and one-half order in **1**-D to provide (*S*)-2-octanol with 4% ee (cf. hydroboration of type I olefins).[2] The rate constant was $k_{3/2} = 7.0 \times 10^{-4}$ M$^{-1/2}$ at 29.9 °C.[3] Thus, this reduction (eq 1 and 2) proceeded in a manner expected from the reduction of **5** with dialkylboranes[4] and does not bring about high asymmetric induction (81% ee) observed in the reaction with reagent I.[1]

Set 2. Methanesulfonic acid (2 equiv) reacted with **4** to form mesylate **3** which was isolated and characterized (e.g., ^{11}B NMR δ 62.2). Thus, it was confirmed spectroscopically that reagent I prepared from **4** (1.2 equiv) and methanesulfonic acid (1.4 equiv)

Scheme I



Scheme II



contained **1**-D (1.0 equiv as monomer) and **3** (0.2 equiv) (Scheme II). Addition of ketone **5** (1 equiv) to **3** in hexane shifted its ^{11}B NMR signal to δ 44.5,[3] indicating **3**, a strong Lewis acid, formed complex **2** with **5**. Thus, at the initiation of the ketone reduction (1.0 equiv of **5** used), the solution contained **1**-D (1.0 equiv) and an equilibrium mixture of **2**, **3**, and **5** (eq 1 and 3).

Set 3. 2-Octanone was reduced at −10.0 °C with **1**-D in the presence of varying amounts of **3**. As the amount of **3** increased, the following trends were evident.[3] The reduction accelerated, the kinetic order changed from three-halves as observed in the absence of **3** to first order, and the percent ee of the product 2-octanol became higher. With 0.2 equiv of **3**, the first-order rate constant approximated $k_1 = 12.4 \times 10^{-4}$ s^{-1} and the ee of octanol was close to 80.4%, both being the highest values attainable at −10.0 °C.[3] With **1**-D (free from mesylate **3**) hydroboration of the highly reactive 1-decene and reduction of butyraldehyde (also highly reactive) proceeded with first-order rate constants of $k_1 = 12.1 \times 10^{-4}$ and 11.6×10^{-4} s^{-1} at −9.5 °C, respectively. These three values of k_1 agree well and should represent the rate constant of a step common to the three reactions (eq 1).

Proposed Mechanism and Transition State. Reduction of ketone **5** with **1**-D follows three-halves-order kinetics, typifying the behavior of a slow-reacting ketone toward a dialkylborane.[4] As shown in eq 1 and 2, an equilibrium dissociation of **1**-D is followed by a slow reaction of **1** with **5**. The change in kinetic order from three-halves to first order outlined in experiment set 3 demands the involvement of an "activated ketone" which reacts fast enough to render the dissociation of **1**-D into **1** rate-determining as observed in hydroboration and reduction of reactive substrates.[4] We propose this "activated ketone" is complex **2** in which the boron atom of **3** coordinates with the carbonyl group of **5** *syn to the (small) methyl group*.[5] With 0.2 equiv of **3**, **5** is no longer able to compete with **2** for monomeric **1**. The sum of eq 3 and 4 is equivalent to eq 2, thereby allowing **3** to play a catalytic role. Also note that the geometry of **2** is such that the incoming borolane **1** is oriented in the manner shown in **7**, reminiscent of the transition state involved in the highly enantioselective hydroboration of a trisubstituted alkene.[2]

(1) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S., preceding paper in this issue.
(2) Masamune, S.; Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549.
(3) Detailed in the supplementary material, the kinetic data were obtained with the aid of ^{11}B NMR spectrocopy (Varian XL-300).
(4) Brown, H. C.; Chandrasekharan, J.; Wang, K. K. *Pure Appl. Chem.* **1983**, *55*, 1387.
(5) Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymann, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

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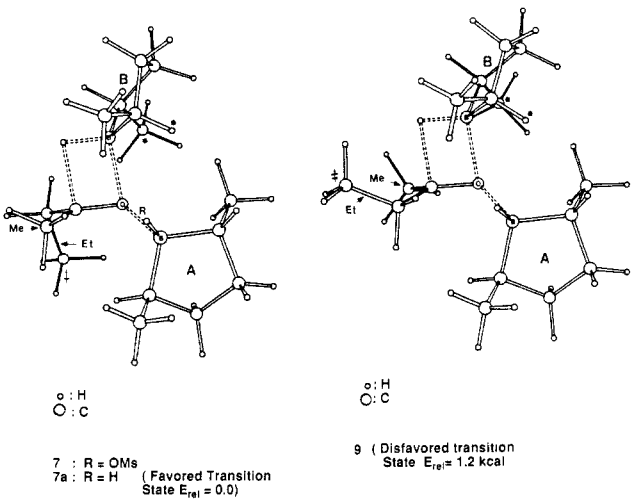

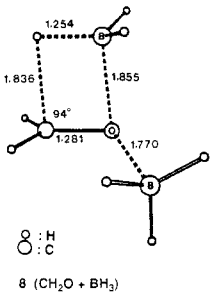

Computational Evaluation of 7. For the reaction of diborane with formaldehyde, ab initio calculations[6] were carried out to examine three different transition states,[7] one of which has one (mono)borane acting as a Lewis acid complexing with an oxygen lone-pair and the second (mono)borane undergoing a four-center addition. At the MP2/6-31G*/3-21G level this transition state (**8**) with the geometry shown is 26 kcal/mol above that of diborane plus formaldehyde.

Modified MM2 models[8,9] were devised to investigate the stereoselectivity expected in the reaction of two molecules of **1** with 2-butanone via **8**. The two models shown in **7a** and **9** lead to the formation of *R*- and *S*-2-butanol, respectively. The transition state **7a** is more stable than **9** by 1.2 kcal/mol which corresponds to 82% ee for this asymmetric reaction carried out at −9.5 °C (experimental ee 80.4%, see above).

Both **7a** and **9** have the nonreacting borane (A) coordinated on the side of the oxygen near the asterisked hydrogen projecting downward from the reacting borane (B), rather than near the asterisked methyl projecting downward. Transition states with the borane (A) on the other side of the carbonyl are 4–5 kcal/mol higher in energy. Therefore, the enantioselection of the reduction is correlated with the manner in which A is coordinated with 2-butanone. The favored transition state **7a** has the ethyl group in its preferred conformation with the methyl (dagger) anti to the forming bond.[10] The less favored transition state has the methyl (double dagger) in the disfavored "outside" conformation in order to avoid repulsion with the nonreacting borane.

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Supplementary Material Available: Detailed kinetic data including experimental procedures, tables of data, and graphs of data presented in tables (18 pages). Ordering information is given on any current masthead page.

(10) This preference is described in ref 9.

(6) Geometry optimizations were carried out with the 3-21G basis set, and energies were recomputed on these geometries at the MP2/6-31G* level. The GAUSSIAN 82 programs were used for these calculations: Binkley, J. S.; Frisch, M. J.; Defrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. GAUSSIAN 82; Carnegie-Mellon University: Pittsburgh, PA.

(7) The reaction of 2-butanone with 1-D via either one of the other two transition states exhibits no or low enantioselectivity. Details of these calculations will be described in a full paper.

(8) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Burkert, T.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. We use ab initio calculations to determine the "normal" position of atoms and devise force constants for bond stretching, angle bending, and torsions involving unusual transition-state atoms, in order to allow movement of all atoms.

(9) These models are developed in ways analogous to the many models described in: Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-d.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D. C.)* **1986**, *231*, 1108.

Site-Specifically Platinated DNA, a New Probe of the Biological Activity of Platinum Anticancer Drugs

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Platinum anticancer drugs, the prototype of which is *cis*-diamminedichloroplatinum(II) (*cis*-DDP), exhibit their biological activity by binding to DNA and inhibiting replication.[2] The principal adduct formed by *cis*-DDP in its reactions with DNA is an intrastrand cross-link in which the N(7) atoms of adjacent guanine bases have replaced the chloride ions in the platinum coordination sphere.[3] With the exception of short, synthetic oligonucleotides constructed to study the stereochemistry of *cis*-diammineplatinum(II) binding by NMR spectroscopy[4] and X-ray crystallography,[5] DNA platinated with *cis*-DDP has previously contained a variety of adducts, including d(GpG) and d(ApG) intrastrand cross-links and, at lower frequency, interstrand cross-links and monoadducts.[6] The heterogeneity of reaction products of these globally platinated DNAs has made it difficult to discern the effects of any one specific adduct upon the processing of DNA in vivo. In the present paper we report the design, synthesis, and preliminary characterization of a duplex bacteriophage M13 DNA containing a *cis*-[$Pt(NH_3)_2${d(GpG)}] cross-link at a unique, programmable site in the genome. The strategy used to construct this site-specifically platinated DNA should be generally applicable for building other chemically modified oligonucleotides into specific sites in DNA.

The chemically synthesized[7] dodecanucleotide d(TCTAGGCCTTCT) (9.4×10^{-4} M strand[8]) was allowed to

(1) (a) Department of Chemistry. (b) Department of Applied Biological Sciences.

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