

Laboratories and Demonstrations

Asymmetric Reduction of Acetophenone  
with (-)- $\beta$ -chlorodiisopinocampheylborane,  
and Derivatization with (-)-Menthyl  
Chloroformate.

An Undergraduate Organic Synthesis, GC  
Analysis, and Molecular Modeling Project.

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*...we have  
developed a  
combined  
molecular  
modeling and  
enantioselective  
laboratory  
experiment...*

A set of experiments is described for the sophomore level organic chemistry laboratory in which students investigate an enantioselective reduction both in the wet laboratory and theoretically, using desktop molecular modeling techniques. In the wet laboratory, students carry out an enantioselective reduction of an asymmetric ketone using (-)- $\beta$ -chlorodiisopinocampheylborane. After workup, the chiral alcohol is derivatized with enantiomerically pure (-)-menthyl chloroformate to provide a diastereomeric mixture of carbonates derived from the *R* and *S* alcohols. The products are isolated, and purified by silica gel column chromatography. Two reference samples are prepared in a similar manner: derivatization of both racemic and enantiomerically pure alcohols. Each of the three products is analyzed by capillary gas chromatography to determine the absolute stereochemistry of the reduction products and to

quantitate the extent of enantioselectivity in the reduction. Students also investigate the reaction using desktop molecular modeling techniques. They construct the model of the chiral borane–ketone complex and search conformational space in two dimensions to determine an overall energy minimum. Then they find, or approximate, the transition-state geometries of two possible diastereomers and compare heats of formation. In this manner they can predict the stereochemical outcome of the reaction, at least in a qualitative sense, and compare their results to the laboratory experiment. The complete laboratory exercise can be accomplished in three 4-hour laboratory periods.

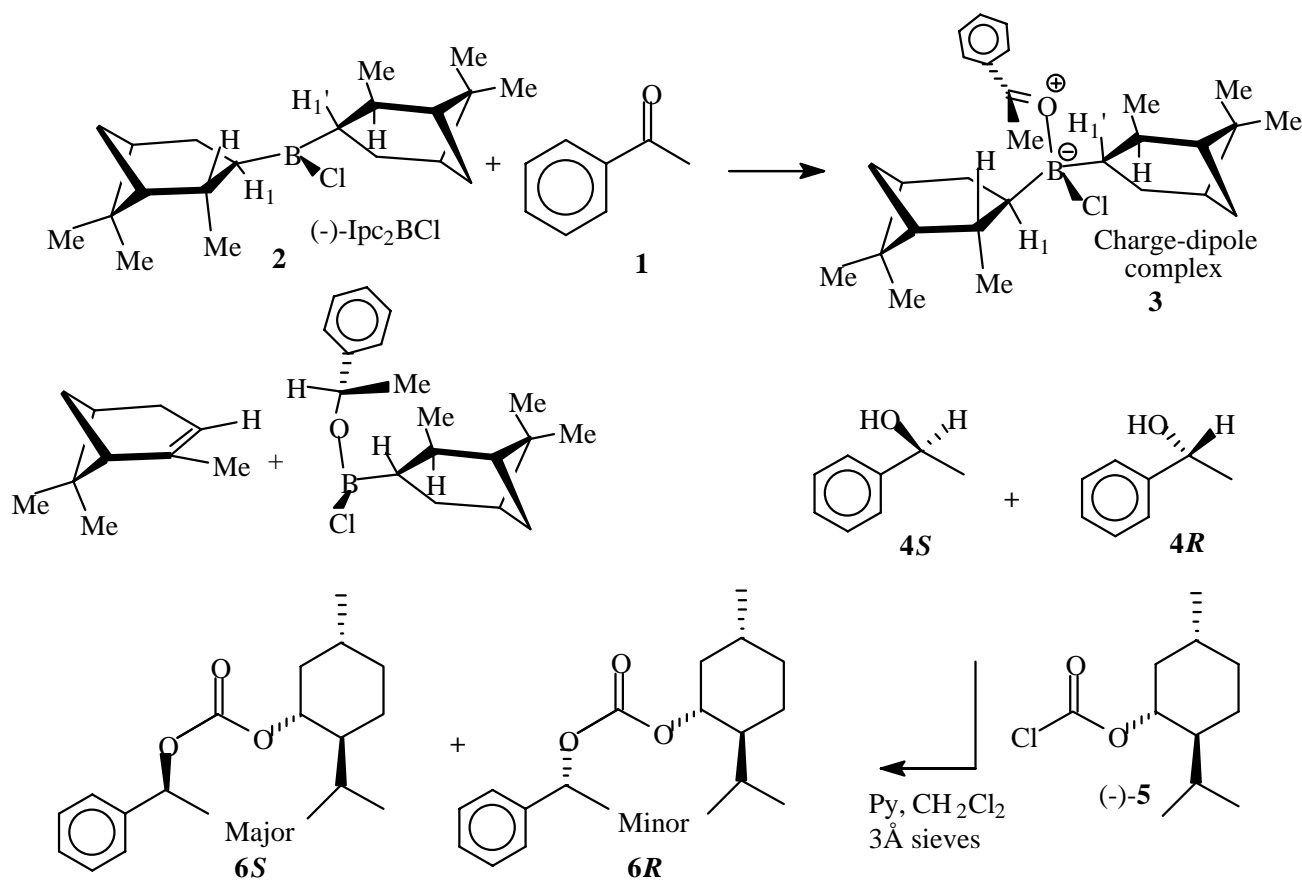
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## Introduction

Enantioselective reactions have become an increasingly important part of organic synthesis [1], yet instructional laboratory experiments for the undergraduate laboratory have only recently started to appear [2]. Students usually learn about stereochemical principles in lecture. They may build plastic models to investigate the geometries of enantiomers and diastereomers, but rarely do they have opportunities to synthesize chiral compounds, or to compare enantiomers or diastereomers in a laboratory setting. With the recent development of desktop molecular modeling software, students can have better opportunities to study properties of chiral molecules with molecular modeling techniques. With the availability of microscale experiments, they now have the chance to investigate the 3-dimensional properties of a chiral system and actually carry out wet laboratory experiments as well, at a reasonable cost.

To address this deficiency, we have developed a combined molecular modeling and enantioselective laboratory experiment in which acetophenone, **1**, is enantioselectively reduced with the chiral reducing agent (-)- $\beta$ -chlorodiisopinocampheylborane ( $\text{Ipc}_2\text{BCl}$ ), **2**, via the borane–ketone charge–dipole complex **3**, to *sec*-phenethyl alcohol, **4**. Chiral organoborane chemistry has been reported in many aspects of the preparation of chiral compounds [3].

In the wet laboratory, students carry out a total of four reactions. First, reduction of **1** with (-)- $\text{Ipc}_2\text{BCl}$  forms a borane–ketone complex **3**, which further reacts to produce (*S*)-*sec*-phenethyl alcohol as the predominant enantiomer. Second, derivatization of the alcohol mixture **4** with (-)-menthyl chloroformate, **5**, produces a diastereomeric



SCHEME 1

mixture of carbonates **6**. In an analogous manner, for the third reaction **4<sub>R</sub>** is derivatized to produce the carbonate **6<sub>R</sub>**, which is used as a GC standard for determining the absolute stereochemistry of the product from previous reaction. For the fourth reaction, a racemic mixture of the alcohol **4** is derivatized to provide a 1:1 mixture of diastereomers **6<sub>R</sub>** and **6<sub>S</sub>**, which are also used as a GC standard. Following this, students analyze each of their three carbonate products by capillary GC, and from this determine the enantioselectivity of the reaction. The reactions are outlined in Scheme 1.

In the molecular modeling laboratory, students construct the borane–ketone complex **3** using the desktop molecular modeling program MacSPARTAN Plus or PC SPARTAN Plus [4]. They construct a conformational energy map of the borane complex to determine the global energy minimum using a molecular mechanics force field. The reduction reaction courses leading to both the *R* and *S* enantiomers are studied by

analyzing the pathway of the hydride transfer from the structure they previously calculated. Their theoretical predictions are compared to the laboratory results.

## Background on Chiral-Borane–Mediated Ketone Reductions

Chiral borane reductions were first reported by H. C. Brown [5]. Since then, the chiral reducing agent (-)- $\beta$ -chlorodiisopinocampheylborane [(-)-DIP-Chloride<sup>TM</sup> or Ipc<sub>2</sub>Cl] has been introduced. This reduces a wide variety of asymmetric ketones, including acetophenone, to optically active secondary alcohols [6]. Stereochemical analysis is often carried out by derivatization with the expensive Mosher's reagent [7] followed by NMR and GC analysis. In our case, we have found that a much less expensive chiral derivatizing reagent, (-)-menthyl chloroformate, **5** [8], can be used to analyze enantiomeric purity by GC analysis. Absolute stereochemistries can be determined by comparison by GC to commercially available (*R*)-*sec*-phenethyl alcohol that has been appropriately derivatized. The racemic alcohol is also derivatized so that relative detector responses can be quantified and each diastereomer unambiguously identified.

The mechanism of reduction by these chiral boranes involves the transfer of a hydrogen  $\beta$  to the boron and elimination of the Ipc group, and proceeds through a 6-membered cyclic transition state [9] that can be readily investigated and modeled using molecular mechanics and semiempirical modeling techniques.

## Experimental

### *Safety*

This experiment uses diethyl ether; appropriate precautions need to be observed when using flammable solvents. We recommend that the water-sensitive borane be prepared by stockroom personnel as a solution in ether. If syringes are used, students need to be instructed on the use and dangers of using sharp implements. As with all chemistry experiments, it is absolutely essential that proper eye protection is worn at all times and that adequate ventilation in is maintained in the laboratory. Disposal of all wastes should, as always, be in accordance with state and local regulations.

### *General*

All reagents can be purchased from Aldrich and used as received, except as noted below. Anhydrous diethyl ether can be used as received. Dichloromethane was

distilled from  $\text{CaH}_2$  within 1 day of use. All reactions were carried out under dry nitrogen. Infrared spectra were obtained on a Bio-Rad FTS-7 FTIR spectrometer and  $^1\text{H-NMR}$  spectra on a Hitachi R-1500 60-MHz FT-NMR spectrometer. GC analyses were conducted using a Shimadzu GC-14A capillary GC using flame ionization detection and fitted with an Alltech AT-Wax 30-m  $\times$  0.25-mm capillary column. GC data were collected using a Labworks II AD data acquisition board [10] and analyzed using KaleidaGraph graphing software [11].

#### *Preparation of (S)-sec-Phenethyl Alcohol, 4S.*

(-)- $\beta$ -Chlorodiisopinocampheylborane, **2**, provided as a 0.50 M solution in anhydrous ether (0.92 mL, 0.46 mmol). is added to an oven-dried 25-mL round-bottom flask. Anhydrous  $\text{Et}_2\text{O}$  (2 mL) is added via pipet, the vessel purged with nitrogen, and capped with a septum. After fitting the vessel with a nitrogen-filled balloon and needle, it is cooled in an ice-water bath. Acetophenone, **1**, (50 mg, 0.42 mmol) is dissolved in  $\text{Et}_2\text{O}$  (1 mL) and added dropwise via syringe to the magnetically stirred solution. The reaction is stirred at 0 °C for 3 hours and allowed to come to room temperature over 30 additional minutes. Workup of the reaction is initiated by the addition of 2 M NaOH (2 mL). The two layers are shaken, then separated. The ether layer is washed successively with 2 M HCl, 2 M NaOH, water, saturated aqueous NaCl (brine), and dried over  $\text{MgSO}_4$ . Filtration and evaporation of the volatile components under reduced pressure, or by small-scale distillation (heating with a water bath), yields a clear colorless liquid, **4**, which can be used without further purification.

#### *Carbonate Formation*

Pyridine, which can be provided as a 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , (0.84 mL of solution, 0.84 mmol) is added to the crude **4** in the same flask, followed by a small amount of powdered, activated 3-Å molecular sieves. A solution of (-)-menthyl chloroformate, **5**, in  $\text{CH}_2\text{Cl}_2$  (1.0 M, 0.46 mL, 0.46 mmol) is added, followed by 2 mL of  $\text{CH}_2\text{Cl}_2$ . The vessel is purged with  $\text{N}_2$  and fitted with a septum and balloon as previously described. The reaction is stirred for 2–3 hours at room temperature. The solvent is removed by distillation and the residue is dissolved in  $\text{Et}_2\text{O}$ . Washing successively with 1 M HCl, 5%  $\text{NaHCO}_3$ , and brine, followed by drying over  $\text{MgSO}_4$  and removal of the solvent provide a light yellow oil. Passage of the material through a small silica gel column (95:5 hexane/ethyl acetate) provides a clear colorless oil. GC analysis reveals a 98.5:1 ratio of **6S** to **6R**.

### Preparation of the (-)-Menthyl Carbonate of Racemic *sec*-Phenethyl Alcohol (**6**)

Racemic *sec*-phenethyl alcohol (100 mg, 0.82 mmol) is reacted with (-)-menthyl chloroformate (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.84 mL, 0.84 mmol) in the presence of pyridine (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.68 mL, 1.68 mmol) and 2 mL of additional CH<sub>2</sub>Cl<sub>2</sub>, as described above, to yield a clear colorless oil. This is filtered through a small column of silica gel (95:5 hexane/ethyl acetate, (TLC<sup>1</sup> R<sub>f</sub> 0.33) to yield a clear colorless oil (200 mg, 80%). Capillary GC analysis indicates a 1:1 mixture of diastereomers (retention times 15.92 and 16.50 min). FTIR (neat, AgCl, cm<sup>-1</sup>): 2958, 2866, 1779, 1738, 1450, 1369, 1256, 1157, 941, 833, 696. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>, δ): 7.33 (m, 5H), 5.70, (q, *J* = 6.4, 1H), 4.32 (m, 1 H), 1.5–0.5 (m, 21 H).

### Preparation of the (-)-Menthyl Carbonate of (*R*)-*sec*-Phenethyl Alcohol (**6R**)

(-)-(*R*)-*sec*-phenethyl alcohol (0.50 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.32 mL, 0.16 mmol) is reacted with (-)-menthyl chloroformate (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.17 mL, 0.17 mmol) in the presence of pyridine (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.34 mL, 0.34 mmol) and 2 mL additional CH<sub>2</sub>Cl<sub>2</sub> as described above to yield a clear colorless oil (42 mg, 81%). The product appears identical to the equimolar mixture of **6R** and **6S** (produced above) when analyzed by FTIR, TLC (95:5 hexane/ethyl acetate, R<sub>f</sub> 0.33), and <sup>1</sup>H NMR (60 MHz). GC analysis indicates a 97.3% excess of **6R** to **6S**.

#### GC Separation

Samples in CH<sub>2</sub>Cl<sub>2</sub> are injected (0.5–1.0 μL) using a split injection technique (20:1) onto an Alltech AT-Wax 30-m × 0.25-mm capillary column [12]. The initial column temperature (100 °C) is held for 2 min, then increased at 15 °C/min to 240 °C and held for 15 min. (-)-Menthyl carbonate **6S** elutes first (15.92 min) followed by **6R** (16.50 min), with a relative response ratio of approximately 1:1. Instrument parameters: Injector temperature, 250 °C; detector temperature, 275 °C; flow rate (He), 0.8 mL/min, with He as the make-up gas.

## Results and Discussion

### Synthesis Experiments

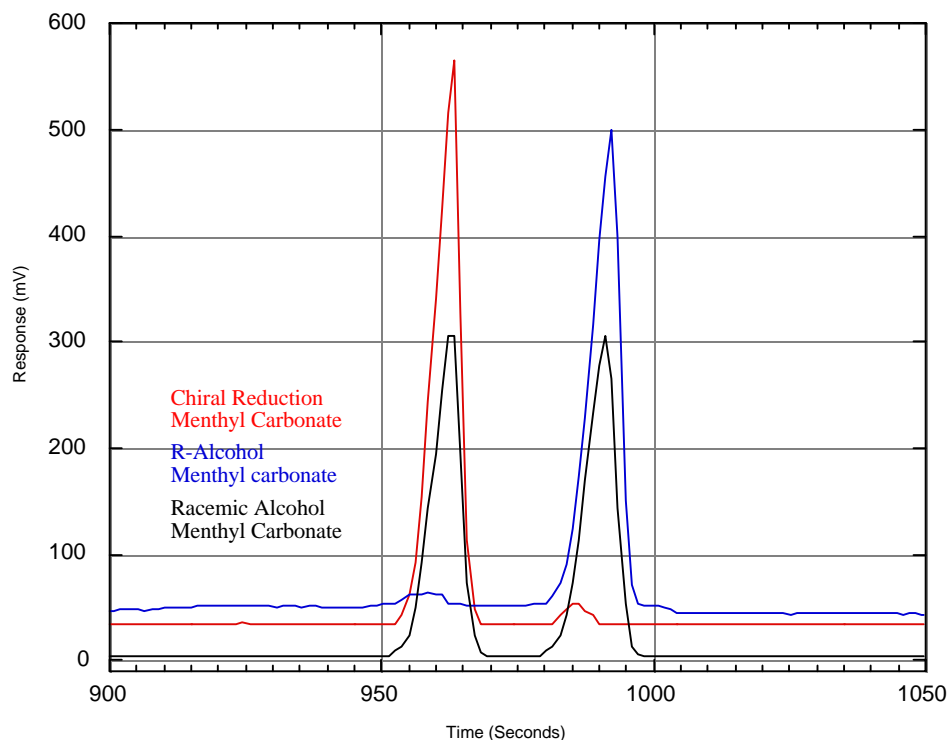
Students can work efficiently in pairs for both the synthetic and modeling portions of

<sup>1</sup> TLC plates are the normal 0.25 mm aluminum backed analytical tlc plates, 6.7 × 2 cm.

this experiment. Students are asked to first carry out the enantioselective reduction reaction between  $\text{Ipc}_2\text{BCl}$  and acetophenone. Acetophenone, **1**, reacts with (-)- $\text{Ipc}_2\text{BCl}$ , **2**, at 0 °C to first provide a charge–dipole complex **3**, which is followed by hydride transfer to the carbonyl and elimination of one Ipc group from the complex. Hydrolysis of the borane complex yields *sec*-phenethyl alcohol **4R** and **4S**, in 70–75% yield and in 95–98% ee (**4S** predominates) [6].

We have found it more convenient to prepare a 0.5 M solution of the chiral reducing agent. We have also found that disposable 1- or 2-mL tuberculin syringes equipped with 1.5-in. 20-gauge Luer lock needles work very well for measuring out volumes as small as 50  $\mu\text{L}$ . As the reactions should be carried out under a dry  $\text{N}_2$  atmosphere, we use a balloon attached with wax film to the end of a 5-mL plastic-needle–equipped disposable syringe (with the end and plunger removed) as the  $\text{N}_2$  reservoir. The reaction is cooled with an ice–water bath and stirred with a magnetic stirrer. After the reaction is worked up and dried, the ether can be removed by a small-scale distillation using a water bath as a heating device. If desired, the crude reaction can be stoppered and left for the next laboratory period.

The crude alcohol mixture is derivatized with (-)-menthyl chloroformate, **5**, in the presence of pyridine to yield two diastereomers, **6R** and **6S**. Reaction of racemic *sec*-phenethyl alcohol, or (*R*)-(+)-*sec*-phenethyl alcohol, **4R**, under the same conditions provides an equimolar mixture of the two diastereomers and a single diastereomer, respectively, in 75–90% yield. The structures of **6R** and **6S** are confirmed by  $^1\text{H-NMR}$  analysis. At 60 MHz, no differences in the proton NMR spectra can be detected. As in the first reaction it is convenient, but not necessary, for students to have available a 1.0 M solution of the menthyl chloroformate in dichloromethane. The powdered molecular sieves increase the yield of the reaction dramatically by removing residual water that may have been adsorbed by the glassware during the wait between laboratory periods. Students can prepare one or both of the racemic or (*R*)-*sec*-phenethyl alcohol derivatives while the reduction reaction is being carried out. During the second period, while the menthyl carbonate of their reduction product is being prepared, students can be collecting GC and spectroscopic data on the menthyl carbonate standards previously prepared. We are using the Labworks II data acquisition board [10] for data collection. Students are required to collect the data, import their files into a graphical analysis program (we use KaleidaGraph [11]), and report retention times and relative



**FIGURE 1.** GAS CHROMATOGRAMS OF MENTHYL CARBONATES OF *SEC*-PHENETHYL ALCOHOL. IPC<sub>2</sub>BCL REDUCTION OF ACETOPHENONE (RED), (*R*)-*SEC*-PHENETHYL ALCOHOL (BLUE), AND RACEMIC *SEC*-PHENETHYL ALCOHOL (BLACK).

peak areas for each product. Absolute stereochemistries are determined by coelution of the known *R* derivative with the racemic mixture on a capillary GC column (Alltech AT-Wax). Gas chromatograms of the three reactions are shown in Figure 1. Retention times and the relative areas of each peak are given in Table 1.

If available GC time is limited, students can be required to analyze only their chiral reduction derivatives and compare these data to chromatograms of the racemic and chiral reference carbonates.

### *Molecular Modeling Studies*

Molecular modeling experiments are used to investigate the geometries and energies responsible for the enantioselectivity of the reaction. The complexes leading to the *R* and *S* alcohols are constructed using MacSPARTAN Plus or PC SPARTAN Plus [4]. (PC and MacSPARTAN users do not have boron available, so a workaround solution

**Table 1.** Retention times and percent composition of chiral menthyl carbonates of the three reactions.

(-)-Menthyl carbonates of:	S ret. time	%S	R ret. time	%R
Racemic <i>sec</i> -phenethyl alcohol	15.92	49.1	16.50	50.9
( <i>R</i> )- <i>sec</i> -phenethyl alcohol	15.92	2.70	16.50	97.3
Enantioselective reduction (( <i>S</i> )- <i>sec</i> -phenethyl alcohol)	15.92	97.7	16.50	3.33

would be to replace the boron of **3** with carbon, and the carbonyl oxygen with nitrogen. The relative energies will yield the same stereochemical predictions, although the relative and absolute values will not be of much utility.) In our teaching laboratories we have found that a 1-hour prelaboratory tutorial is adequate to introduce the experiment, explain the mechanism and stereochemical concepts, and describe the molecular modeling requirements for the hydride transfer. Since the synthetic portion of the experiment has a significant amount of idle time, we have found that students, particularly during the second and third lab periods, can accomplish most, if not all, of the modeling during this time. We have typically 24 students per section, and utilize six computers and one GC. Students are encouraged to work on their modeling outside of laboratory time; our computer laboratories are available daily.

In the computer laboratory, the molecule is constructed as a demonstration and the methodology for defining and setting bond-length and dihedral-angle constraints is outlined. This tutorial can reasonably be accomplished in 30 minutes.

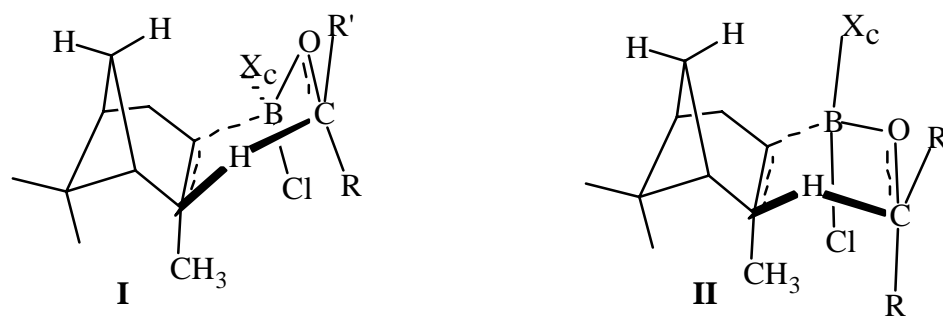
Students first construct complex **3** (Scheme 1) and minimize its energy using the SYBYL minimizer in the SPARTAN builder interface. Individual atomic charges need not be assigned, as the overall charge of the complex is set as zero by the software when the minimization job is submitted. Particular care must be taken to be certain that the absolute stereochemistry is correct in all cases. Students are encouraged to build plastic models of at least one of the bicyclic rings to help in their visualizations.

Both chiral auxiliaries of **3** can transfer a hydride, yielding a number of possible transition states. However, if only the one side is considered and the lowest energy conformation is the starting point, then realistic *R* and *S* transition structures can be considered and the experiment is greatly simplified. Thus, this experiment considers only the hydride transfer from one side of the molecule: the left side of **3** as portrayed in Scheme 1.

The modeling exercises are carried out in the following stages. After the molecule is constructed, two dihedrals are defined about the B–C bonds. The molecule is arranged so that the B–C1 bond is coming out of the screen and the ketone is up. The ring carbon on the left attached to the boron is defined as C1. The other ring carbon, on the right, is C1'. Dihedral angle **a** is defined as O–B–C1–H1 and dihedral angle **b** as O–B–C1'–H1'. A further dihedral angle, **c**, is defined as C1–B–C–O, and dihedral angle **d** is defined as B–O–C–C<sub>phenyl</sub>. Students will need to manipulate only these dihedral angles for all aspects of the experiment.

Introductory students will begin by considering the reaction mechanism. In this case, both the *R* and *S* alcohols can be generated by rotating 180° about the axis of the carbonyl bond (dihedral angle **d**). Consequently, there are only two geometries possible that can lead to a hydride transfer from the left side to the carbonyl for a particular enantiomer [13]. These two conformations correspond to the two lowest energy structures of the nine calculated in the conformational search (vide infra). The structures resulting from each of these conformations are termed **3**<sub>axial</sub> (angle **a** = 180°, O and H anti) and **3**<sub>equatorial</sub> (angle **a** = 60°, O and H gauche) and are shown in Figure 2. Complex **3**<sub>axial</sub> can be considered to be a chairlike structure, while **3**<sub>equatorial</sub> can be considered a boatlike structure. The relative steric energies of the two ground-state structures are 108.88 (axial) and 112.38 (equatorial) kcal/mol respectively. In the sophomore-level class, students are asked to further consider only the lowest energy structure, which leads to the lowest energy transition state, **3**-axial.

The next step is to investigate the starting conformations of **3**<sub>axial</sub> leading to the *R*, and *S* alcohols. Accordingly, both complexes are generated beginning from **3**<sub>axial</sub>. This can be done simply by rotating the carbonyl (C=O) dihedral 180°. Students are instructed to set angle **a** to 180°, angle **b** to –60°, angle **c** to –15°, and angle **d** to 0° (*R*), or 180° (*S*). Students minimize each structure using two levels of theory: molecular mechanics and AM1 semiempirical calculations. The steric energies calculated for

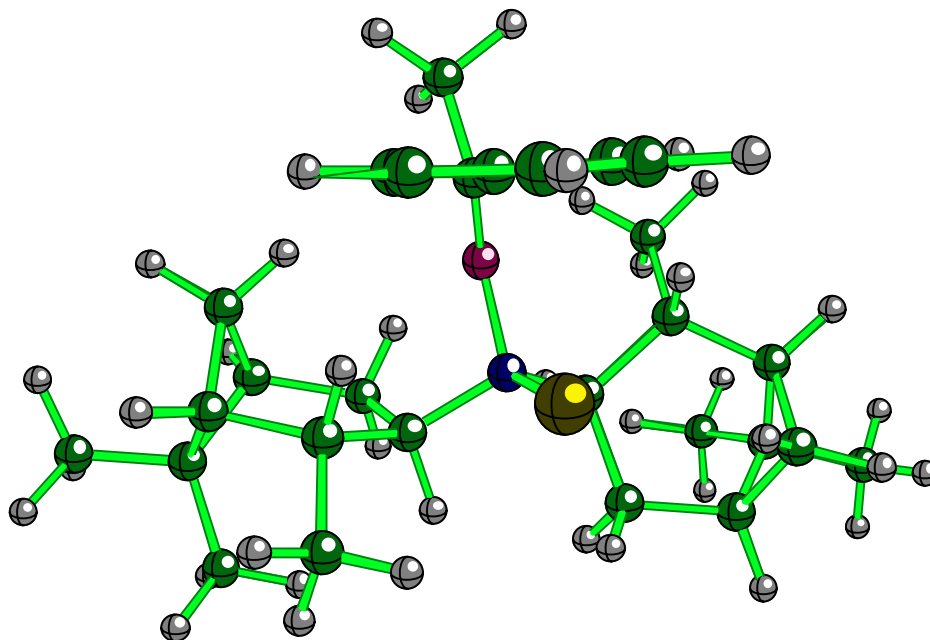


**FIGURE 2.** POSSIBLE CONFORMATIONS OF THE TRANSITION-STATE STRUCTURE. I =  $3_{\text{AXIAL}}$ , CARBON-BORON BOND AXIAL. II =  $3_{\text{EQUATORIAL}}$ , CARBON-BORON BOND EQUATORIAL

each molecule are almost identical, (108.88 vs 108.89 kcal/mol). On the other hand, semiempirical (AM1) calculations reveal a difference of 2.37 kcal/mol, with the *S* isomer lowest in energy (−45.92 and −43.55 kcal/mol for *S* and *R* respectively). The preferred conformations for each of the two energy-minimized starting complexes, leading to the *R* or the *S* alcohol, are shown in Figure 3.

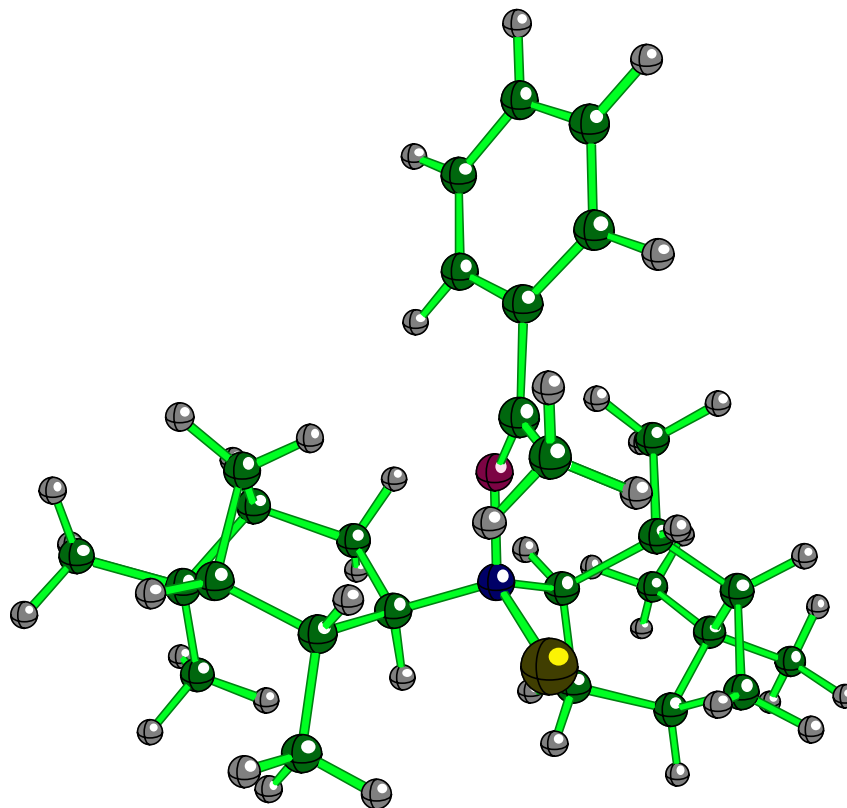
With the ground-state complexes generated and minimized, approaches to the analysis of the transition states can be accomplished. In this case only semiempirical calculations at the AM1 level are useful for energy and geometry analyses.

At the introductory organic chemistry level, a qualitative approach can be taken. The carbonyl carbon and approaching hydrogen can be constrained to a distance of 1.30 Å, which is close to the transition state, yet will yield a structure that can be minimized at the AM1 level. In each case, a chairlike, six-membered-ring-like structure develops as the transition state is approached. First, the 1.30-Å constraint is applied and the structure minimized at the SYBYL level. Energy minimization can be done directly at the AM1 level, but we have found that the intermediate minimization significantly reduces computational time. Then, the structure (with the constraint) is minimized at the AM1 level. Students can clearly see the hybridization of the carbonyl carbon change from  $sp^2$  to  $sp^3$  as the hydride approaches. In order to evaluate steric interactions as reasons for diastereomeric energy differences, the closest approach of nonbonded atoms can be measured. The closest nonbonding interactions are between the bridging methylene on the left ring and the methyl group (*R*) or the phenyl group (*S*) of acetophenone as the transition state is approached. However, the steric interactions are not readily apparent, which highlights the utility of carrying out



**FIGURE 3R.** IPC<sub>2</sub>BCL COMPLEX LEADING TO (*R*)-SEC-PHENETHYL ALCOHOL.

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**FIGURE 3S.** IPC<sub>2</sub>BCL COMPLEX LEADING TO (*S*)-SEC-PHENETHYL ALCOHOL.

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**Table 2.** Energies and selected interatomic distances of *R* and *S* complexes and transition states.

Molecule	Energy (AM1) (kcal/mol)	Energy (Sybyl) (kcal/mol)	H-C(O) distance (Å)	C-H X distance (Å)	Imaginary frequency (cm <sup>-1</sup> )
<b>(S)-complex</b>					
Ground-state	-45.92	108.89	3.11	2.41(H-C <sub>1</sub> Ar)	
1.3-Å-Constrained	-12.163		1.300	2.57	
Transition state	-10.95		1.27	1.27	-783.7
<b>(R)-complex</b>					
Ground-state	-43.55	108.88	3.02	2.87(CH <sub>3</sub> -H <sub>1</sub> )	
1.3-Å-Constrained	-10.41		1.300	2.06	
Transition state	-9.44		1.28	2.02	-804.4

quantitative calculations in order to be able to predict relative reaction rates. Comparing the two methods of calculating the ground-state energies (molecular mechanics and semiempirical) illustrates the limitations of the simpler mechanics method, and demonstrates the importance of using appropriate tools for reaction pathway analysis.

Bond distances and energies of the ground-state complexes, the 1.3-Å-constrained complexes, and the geometries of the two calculated transition-state structures are summarized in Table 2.

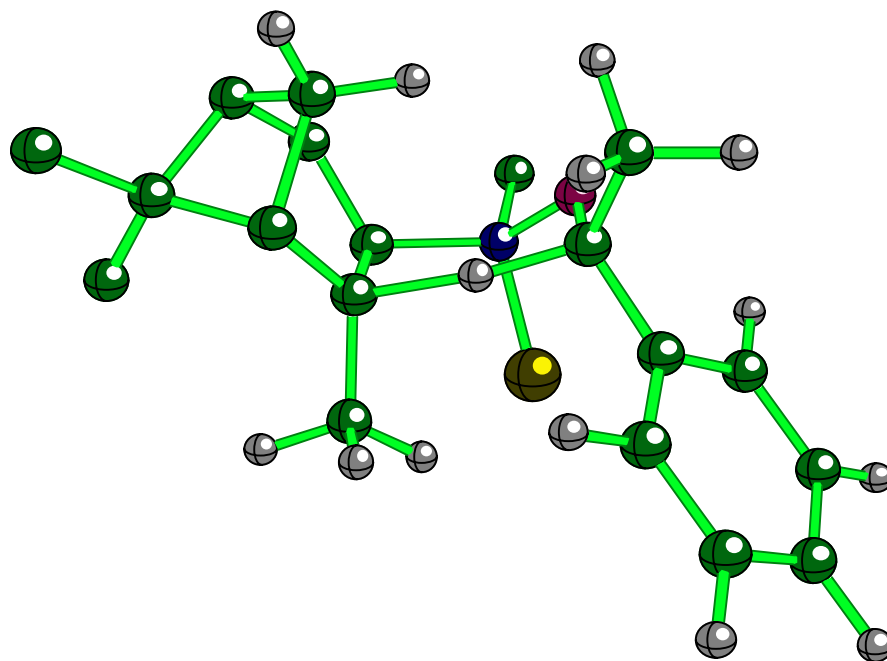
For a more advanced class, all possible staggered conformations of the ground-state complex **3** can be generated sequentially and minimized using the SYBYL molecular mechanics force field. Final dihedral angles and energies are tabulated in Table 3. In addition, students could calculate and compare AM1-calculated energies with the SYBYL-calculated relative values. We have only reported the SYBYL-calculated values.

The next step is to calculate the transition-state geometries and energies of each of the two stereoisomers. This can be accomplished in one of two ways. A simple method is to generate both the starting and ending geometries, and carry out a transition-state

**Table 3.** Relative energies (SYBYL) and dihedral angles of charge–dipole complex. Dihedral angle **a** = O–B–C1–H1. Dihedral angle **b** = O–B–C1'–H1'.

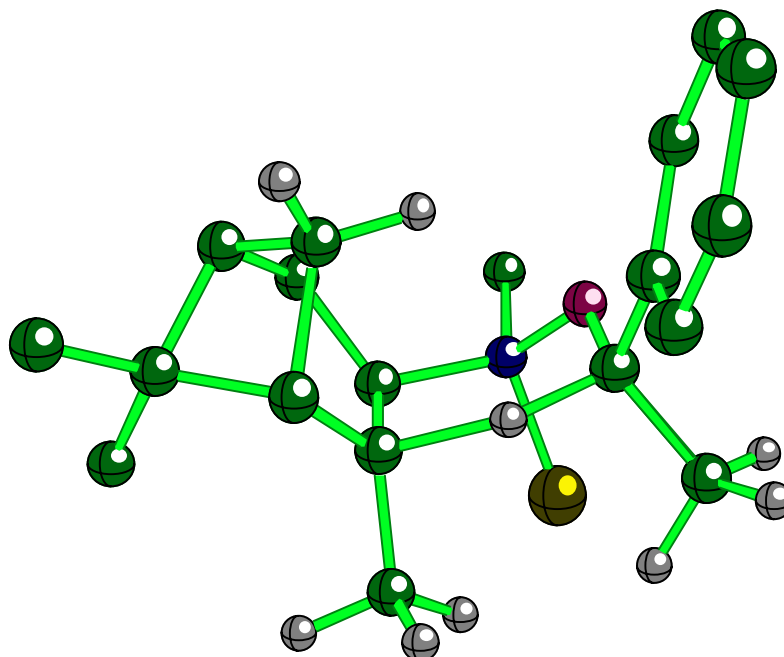
Initial angle <b>a</b> →	60° Energy (kcal/mol)	180°	–60° <i>R</i>
Initial angle <b>b</b> ↓	(angle <b>a</b> , angle <b>b</b> )		
60°	118.31 (72.66°, 67.57°)	116.39 (140.34°, 61.52°)	119.49 (–49.18°, 79.85°)
180°	112.38 (67.60°, –169.92°)	114.06 (157.14°, –179.31°)	119.49 (–57.75°, 176.86°)
–60°	112.75 (54.64°, –72.51°)	108.89, (164.4°, –63.5°)	115.36 (–61.34°, –82.44°)

search, as provided in the MacSPARTAN Plus package. However, we find that this approach is very sensitive to the geometries of the starting and ending structures and often does not lead to realistic transition-state structures. In our hands, a more consistently successful approach is to generate a series of structures beginning with the ground-state structures. The distance between approaching hydride and the carbonyl is constrained to successively shorter distances, between 2.00 and 1.20 Å in 0.1-Å increments, and each structure (with constraints) minimized at the AM1 level of theory. After the transition state is reached, the molecule dissociates, leading to a sudden decrease in energy. A map of distance versus energy enables a selection of a likely candidate structure for a transition-state-structure calculation. Exact transition-state structures can be calculated by conducting a transition-state-structure calculation on a minimized structure close to, and still approaching, the transition state. In our case we used structures with the carbonyl–hydride distance constrained at 1.28 Å (for both the *R* and *S* isomers), which were optimized for transition-state-structure analysis. Two transition-state structures can be generated and confirmed by vibrational frequency analysis. A single imaginary frequency is found for each transition-state structure, verifying that each is reasonable. In both isomers, a chairlike transition-state structure is produced. The relative heats of formation of the *R* and *S* transition-state structures are –9.44 and –10.95 kcal/mol, respectively; these structures are shown in Figures 4*R* and 4*S*. From these data, relative reaction rates at various temperatures could be calculated. A bond-distance-driving feature is most useful for this experiment, and is found in MOPAC, HyperChem, and the Unix version of SPARTAN. However, the MacSPARTAN Plus and PC SPARTAN Plus versions do



**FIGURE 4R.** *R*-COMPLEX TRANSITION STATE (ONE IPC GROUP AND SOME HYDROGENS REMOVED FOR CLARITY) ( $\Delta H_f$ , -9.44 KCAL/MOL, C(O)-H = 1.2688 Å;  $\Delta H_s$ , -10.41 KCAL/MOL, C(O)-H = 1.3 Å).

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**FIGURE 4S.** (*S*)-COMPLEX TRANSITION STATE (ONE IPC GROUP AND SOME HYDROGENS REMOVED FOR CLARITY) ( $\Delta H_f$ , -10.95 KCAL/MOL, C(O)-H = 1.27 Å;  $\Delta H_s$ , -12.16 KCAL/MOL, C(O)-H = 1.30 Å).

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not support this option and so it is more tedious for students to find a structure close enough to the transition state to be successful.

## Conclusion

Texas A&M University-Commerce's facilities and class sizes make this set of experiments easy to accomplish because our PC and Macintosh laboratories are available for student use most of the time. We find that it also works if students must carry out calculations only during a 3- or 4-hour laboratory period. The laboratory portion can be accomplished in two 4-hour periods, but could be done in more sessions with shorter time periods as well. The synthesis experiments are reasonably straightforward and are similar to experiments described in laboratory textbooks and manuals. The only unusual part of the experiment is the use of a nitrogen atmosphere. This provides a good opportunity to introduce rudimentary techniques for carrying out reactions under an inert atmosphere and only requires a septum, disposable syringe, and a balloon to maintain the atmosphere. Analysis of the products requires a gas chromatograph. While we have described this as a microscale synthesis and gas chromatography experiment, the experiment can easily be adapted to include spectroscopic analyses such as FTIR, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR. This would require that a larger silica gel column be used in order to obtain pure samples. In this case, students could measure optical rotations, which we have not measured.

Molecular modeling using the combination of force-field and semiempirical methodologies provides an effective way to investigate the mechanistic details of the reaction, and effectively illustrates the importance of quantitative energy calculations in determining the relative energies of two diastereomeric transition states. In this laboratory exercise, concepts of chirality are explored and studied in a detailed manner, and then are examined experimentally. Undergraduate students at the sophomore or junior level can participate in the exploration of both experimental and computational problems, and can begin to understand the importance of using theoretical models to explore reactivity and enantioselectivity.

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