Synthesis of cis-1,5-Cyclooctanediol

(Developed by R. Minard and Denise Lindenmuth, Penn State, 1991.)

**Introduction:**
In this experiment the B-H bond of borane (BH₃) is added to the double bonds of 1,5 cyclooctadiene yielding an organoborane. This process is called a hydroboration reaction, a very useful alkene addition first reported by H.C. Brown in 1959. The very reactive remaining B-H hydride hydrogen is then replaced by -OC₂H₅ by reaction with ethanol and hydrogen gas is evolved. When a basic solution of hydrogen peroxide is added, oxidation occurs breaking the two C-B bonds. Two hydroxyl groups are added forming the final product, cis-1,5-cyclooctanediol.

\[
\text{Boron ring} + H_3B:THF \xrightarrow{\text{THF, 0°C}} \left[ \begin{array}{c} 1,4- \\ 1,5- \end{array} \right] \xrightarrow{\text{THF}} \text{HB} \\
\]

\[
\text{BH} + C_2H_5OH \xrightarrow{\text{THF, 25°C}} BOC_2H_5 + H_2 \\
\]

\[
BOC_2H_5 + 2H_2O_2 + \text{NaOH} \xrightarrow{\text{THF-EtOH, 40-50°C}} \rightarrow \text{product} + C_2H_5OH + \text{NaB(OH)₄} \\
\]

Borane, BH₃, actually exists as a hydrogen bridged dimer, B₂H₆, a very difficult material to work with because it ignites spontaneously in air. The Lewis acid/base complex, BH₃:THF, however is considerably less reactive and therefore can be handled with greater ease. Never-the-less, it still decomposes rapidly on contact with oxygen and moisture in the atmosphere, and therefore, must be handled and reacted under an inert atmosphere of nitrogen or argon. Many clever methods for handling air-sensitive materials were developed in the 40's by Schlenk and because of this, the gas/vacuum manifold and flasks developed by him are called "Schlenk lines" (see diagram) and "Schlenk flasks" (see below), respectively and the techniques are often called "Schlenk techniques". The Schlenk line allows the rapid flushing of air from systems connected to it by vacuum tubing. Reactions are typically run in Schlenk flasks that have glass or teflon stopcocks which are connected to the Schlenk line and through which a vacuum can be drawn or an inert gas introduced. Highly reactive reagents, such as borane:THF, are transferred using syringes inserted through septa in the reagent bottle and in the Schlenk flask, thus avoiding pouring highly reactive materials in the open air.
Before you actually carry out the reaction using borane:THF, you should practice the whole Schlenk line procedure by transferring ether from a septum stoppered supply bottle to a Schlenk flask attached to the manifold, all transfers taking place under an inert atmosphere. Only after you have mastered the solution transfer technique so that the ether is transferred without squirting or dripping from the syringe should you consider running the hydroboration reaction. Don't hesitate to ask an instructor for help.

**CAUTION:** BH₃:THF is very moisture sensitive and can explode upon contact with water. It is also a very flammable solution so handle it very carefully and of course wear goggles and gloves when handling it.

**Experimental Procedure:**

**Hot water bath:**

Before starting the reaction, prepare a hot water bath using a half-filled 400-mL crystallizing dish on a combination magnetic stirrer/hot plate (available from the stock room). After the water gets to about 40°C, turn down the heating control dial. Continue to adjust the heating control to maintain the temperature of the water between 40 and 50°C.

**Oven drying equipment:**

Remove the teflon valve from a 100 to 200-mL Schlenk flask and place a 1" magnetic stirring bar in it. Place the flask and the separated plunger and barrel of a 10 to 25 mL glass gas-tight syringe fitted with a 12 inch needle in an oven and heat at 100 to 120°C for at least two hours to drive off all traces of moisture. After removing the dried equipment from the oven, allow the Schlenk flask to cool two or three minutes and then screw in the teflon valve carefully, being careful to thread it in properly. Don't close the valve completely.

While the flask is still warm, put a septum in its 14/20 opening, attach it to the Schlenk line via the vacuum tubing as shown below and clamp the flask to the vacuum rack. **Make sure the traps are clean and dry** and then turn on the vacuum pump and turn the two way stopcock of the Schlenk line so that the air is evacuated from the flask. Make sure the teflon valve is open. Since no volatile solvents will be removed by the vacuum, you don't need to fill the vacuum traps with dry ice for this experiment.

While the Schlenk flask is cooling under vacuum, remove the 1.0 M BH₃:THF solution from the refrigerator and desiccator jar and allow to warm to room temperature.

Start the flow of nitrogen through the nitrogen manifold as follows (refer to diagram): At the bottom of the nitrogen regulator, close the flow control valve completely (turn clockwise) and open the main tank valve at the top of the nitrogen tank (counterclockwise). The pressure on
the low pressure gauge of the nitrogen regulator should not be more than 5 to 10 PSI. If it is, regulate the pressure lower by turning the pressure controlling screw counterclockwise (just the opposite of your intuition!). Open the flow control valve slowly, watching the bubbler at the other end of the Schlenk line to be sure the nitrogen isn’t going through at a rate faster than a continuous stream of discreet bubbles. Once the Schlenk flask is completely cool, turn the two way stockcock slowly so that the flask is filled with nitrogen. If the switch from vacuum to nitrogen is too fast, the pressure in the nitrogen manifold will drop so low that air will be drawn into it through the bubbler, which is not good.

Immerse the Schlenk flask in an crystallizing dish ice bath setting on a magnetic stirrer resting on a lab jack.

Transfering the air-sensitive borane solution:

Cut a 1-mL plastic syringe in the middle, insert the lower part into one of the Schlenk line tubes, and attach a needle to it. Open the two way stopcock so that nitrogen is flowing out through the needle and purge the tubing for 5 min. Then insert the needle through the septum of the Aldrich "Sure-Seal" bottle of 1M BH₃:THF solution as shown in the diagram. (The borane solution bottle should be clamped.) This maintains a nitrogen atmosphere in the reagent bottle and makes it easier to draw solution from the bottle with a syringe. Incidentally, the "Sure-Seal" will last longer if you try to puncture it at the same puncture points made by the last user.

Grasp the oven-dried long (10-12") needle near its tip and push it about an inch through the "Sure-Seal" so that it is well above the liquid level. Attach the oven-dried gast-tight 10 mL syringe, if it is not already, and fill it with nitrogen gas, not solution, by drawing back the plunger the whole way. Detach the syringe from the needle and push the plunger all the way in to expel the nitrogen. Immediately reattach the syringe to the needle.

Now push the long needle into the bottle so that it is below the liquid level of the bottle. Keeping the syringe in a downward position as shown, draw 10 mL of 1M BH₃:THF solution into the syringe. Then withdraw the needle slightly so that it is again above the liquid level, but still in the bottle, and draw in about a half mL of nitrogen gas. Keeping the syringe in the downward position, withdraw the long needle from the reagent bottle and insert it through the septum on the Schlenk flask, turn the syringe upward and inject the solution into the Schlenk flask.

Close the stopcock supplying nitrogen to the reagent bottle (¼ turn), withdraw the needle from the "Sure-Seal", cap the bottle, and return it to the refrigerator in its dessicator jar.

Adding other reagents; completing the reaction:

Place a crystallizing dish containing ice and a magnetic stirrer under the Schlenk flask. Next, add 5 mL of a 2.0 M solution of 1,5 cyclooctadiene in anhydrous THF dropwise over 5 minutes using a clean 10 mL plastic syringe (obtained from the stockroom). This solution is added while maintaining the temperature of the rapidly stirred solution of BH₃:THF at approximately 0°C with the ice bath.

Finally, 5 mL of anhydrous THF is added dropwise to the Schlenk flask using the same plastic syringe. After complete addition the magnetic stirrer/cooling bath is replaced by a combination magnetic stirrer/plate/hot water bath and the reaction mixture is heated and stirred at 40 to 50 °C for one hour.

Turn off the nitrogen flow and detach the Schlenk flask from the Schlenk line tubing. Clamp the flask to a ring stand in the hood. The septum is removed and 1 mL of ethanol is added while stirring magnetically. After hydrogen evolution has ceased, 5 mL of 3 M NaOH is
added. The flask is immersed in an ice-water bath and 2.5 mL of 30% hydrogen peroxide is
added dropwise using a pipet, maintaining the temperature below 40°C. When all of the
H₂O₂ has been added, the reaction mixture is then stirred at 40 to 50 °C in a hot water bath
for one hour.

**Isolation and Purification:**
After one hour, the resulting two phase system is separated using a separatory funnel. Solid
anhydrous potassium carbonate is added to the organic layer to saturate any aqueous layer
left, thus drying the THF phase. The THF is removed by rotary evaporation. GC analysis is
used to confirm the production of cis-1,5-cyclooctanediol in significant yield. If good yields
are evidenced, recrystallization from ether should yield solid cis-1,5-cyclooctanediol.

**Cleaning Up:**
The aqueous layer can be flushed down the drain with water. The potassium carbonate can
be left to dry in the hood on filter paper. When dry it can be placed in the paper waste
container.

**Questions:**
1. How many millimeters of 99% 1,5 cyclooctadiene is used to make a 2.0 M solution of 1,5
cyclooctadiene?
2. Show how THF is complexed to BH₃.
3. Why is it necessary to carry out this reaction under a nitrogen atmosphere? What would
be the decomposition products of the reactive reagents?