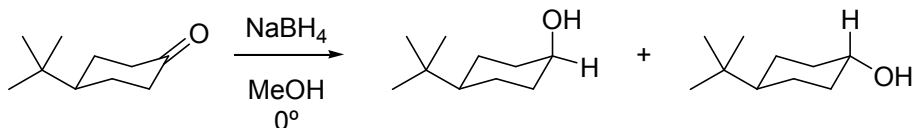


## Hydride Reduction

### Overall Reaction



### Purpose

This experiment has the following goals:

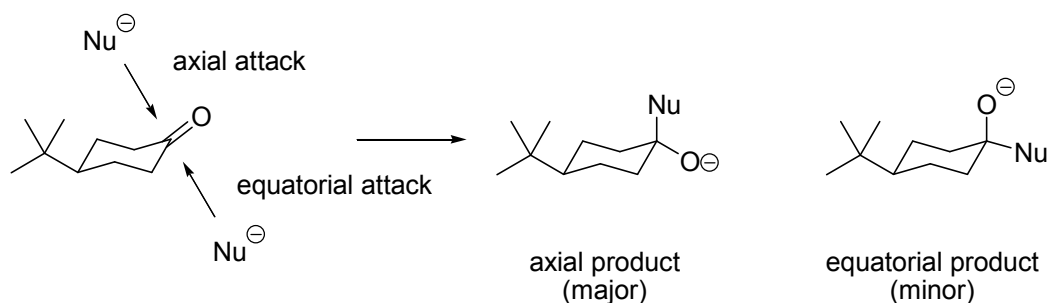
- (1) demonstrate a stereoselective reaction
- (2) show a nucleophilic addition
- (3) require a challenging separation by column chromatography.

### Background

Nucleophilic additions onto carbonyls are everywhere in organic chemistry. The carbonyl is a natural electrophile and a very easy functional group to prepare. Nucleophiles that attack a carbonyl can be broken up into two categories – reversible and irreversible. The reversible nucleophiles include functional groups like alcohols, amines, and enolates. The irreversible nucleophiles include organometallic reagents and hydride sources. From the standpoint of our laboratory constraints, hydride reagents like  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  are more attractive than Grignards and organolithium reagents.  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  are available in pure form, which makes them easier to handle. While many organometallics can be purchased, they are sold as solutions of questionable concentration. Furthermore, making an organometallic reagent is not always predictable (though they generally work – eventually).

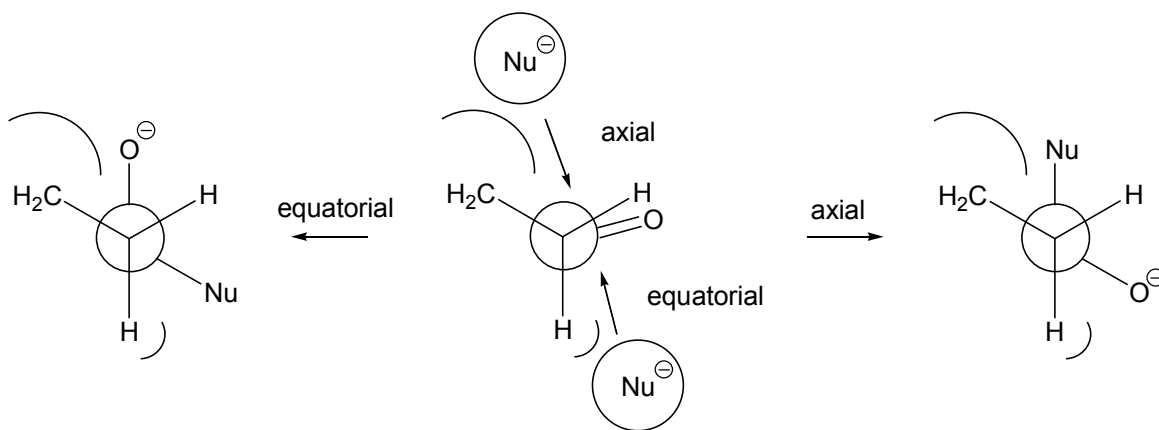
When a nucleophile attacks a carbonyl, a tetrahedral intermediate is formed. Protonation of the anionic intermediate gives an alcohol. In most cases, the alcohol carbon is a new stereocenter. If the product contains no other stereocenters, the stereoisomeric alcohols will be enantiomers. Unless there is some other source of chirality in the reaction, the two enantiomeric products will be formed in a 1:1 ratio to make a racemic mixture. If another stereocenter is present in the molecule, then the products will be diastereomers. Normally, reactions do not show 1:1 diastereoselectivity because the pre-existing stereocenter exerts influence on the incoming nucleophile. Many chemists have dedicated their careers to understanding the diastereoselectivity of nucleophilic additions to carbonyls.

The addition of a hydride to the carbonyl of 4-*tert*-butylcyclohexanone is an example of an addition that generates two diastereomeric alcohol products (Scheme 1). (Terminology is a bit dicey here because both the starting material and products are achiral.) The two  $\pi$ -faces of the carbonyl are not equivalent, and they therefore do not react in a 1:1 ratio. This reaction, therefore, shows diastereoselectivity for one of the products. The major product results from the hydride approaching from the top face of the carbonyl. This is called *axial attack* because the hydride will occupy the axial position of the alcohol carbon. The minor product arises from *equatorial attack*. In general, when cyclohexanones undergo nucleophilic addition, axial attack is favored.



Scheme 1. Facial selectivity in cyclohexanone additions

Diastereoselectivity in addition reactions is normally attributed to either steric or electronic effects. Because this molecule is fairly bland in terms of functionality, steric effects would seem to be somehow influencing the stereochemical outcome of the reaction. When examining the starting ketone as a Newman-type projection, the axial approach seems more hindered (Scheme 2). (The point of view for this picture is looking at the  $\alpha$ -carbon with the carbonyl carbon behind.) This is the exact opposite of what we would have predicted. As it turns out, the diastereoselectivity of this reaction is best explained by a *torsional effect*. If the nucleophile approaches from the equatorial face, the oxygen, in its movement to occupy the axial position, will be forced to sweep across and eclipse the equatorial hydrogen on the  $\alpha$ -carbon. In the axial attack, this eclipsing interaction is unnecessary. With groups as small as a hydrogen and oxygen, the eclipsing interaction is considered to be torsional strain (electrostatic repulsion of the filled  $\sigma$ -bonds) rather than steric (overlapping of van der Waal radii of two groups).



Scheme 2. Newman projections of the ketone and alcohols

The diastereomeric alcohols from the hydride reduction have different  $R_f$  values by TLC and are at least somewhat separable by column chromatography. Once purified, the two diastereomers will have one characteristic signal by  $^1\text{H}$  NMR – the hydrogen on the alcohol carbon. In both products, this hydrogen will have two pairs of equivalent neighbors. One pair will be the axial hydrogens on the  $\alpha$ -carbons, and the other will be the equatorial hydrogens on the  $\alpha$ -carbons (Figure 1). Therefore, in both products, the key hydrogen will theoretically appear as a triplet of triplets. In the major product, the key hydrogen will be axial. Its dihedral angles ( $\varphi$ ) to the  $\alpha$ -hydrogens will be approximately  $60^\circ$  and  $180^\circ$ . In the minor product, all the dihedral angles will be approximately  $60^\circ$ . So, based on the Karplus equation (eq. 1), the key proton in each product

should show a very different splitting pattern. We will be able to use this information to assign our structures.

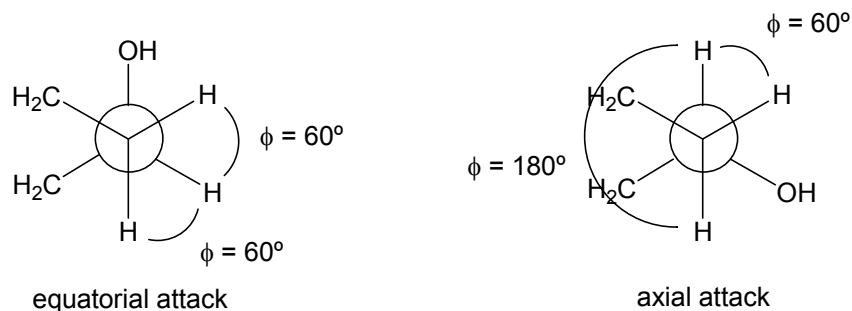


Figure 1. Dihedral angles of the diastereomeric products

$$J_{HH'} = 1.6 - 1.7 \cos \phi + 7.6 \cos^2 \phi \quad (1)$$

**Experiment** (procedure modified from Garner, C. M. *Techniques and Experiments for Advance Organic Laboratory*; Wiley: New York, 1997; pp. 71-74)

Monday/Wednesday: Dissolve 4-*tert*-butylcyclohexanone (2 mmol) into MeOH (1 mL) in a large test tube (150×15mm) equipped with a baby stir bar. Cool the mixture to 0°. Add NaBH<sub>4</sub> (1.5 mmol) in one portion (fizzing). After 10 min check the reaction by TLC (25% EtOAc/75% Hex) using a phosphomolybdic acid stain. If the starting material has been consumed, add H<sub>2</sub>O (4 mL) and EtOAc (5 mL). Thoroughly mix the reaction with a pipet. With a pipet, carefully remove the top layer of the biphasic mixture. Add EtOAc (4 mL) to the test tube, mix, and remove the top layer. Repeat once. Combine the organic layers in a 50 mL flask, dry them over MgSO<sub>4</sub>, and filter the mixture through a pipet with cotton plug into a tared 50 mL round-bottom flask. Concentrate the solution and determine the crude recovery. Obtain a crude <sup>1</sup>H NMR spectrum and be sure to integrate the protons on the alcohol carbon (for determining product ratio). Seal the flask and let the mixture stand for a week.

Monday/Wednesday: Chromatograph the crude product on a column (2 cm i.d.) loaded with 4-5" silica gel. The product should be dry loaded (dissolve in CH<sub>2</sub>Cl<sub>2</sub>, add silica gel, and concentrate solvent). Elute the column with 25 mL (0% EtOAc/100% Hex), 50 mL (5% EtOAc/95% Hex), 100 mL (10% EtOAc/90% Hex), and 200 mL (15% EtOAc/85% Hex). Collect the

fractions in test tubes (100×13mm). Combine the clean fractions of each diastereomer, concentrate, and weigh them. Collect full  $^1\text{H}$  NMR spectra for each clean diastereomer with expansion plots for the relevant peaks.

### Lab Report

Aside from the standard lab report items, your report should include the following items in the Discussion Section.

- Model the starting ketone and both alcohol products using Spartan (AM1 calculation). Assuming the calculate  $H_f$  for each isomer is equal to its  $G_f$  (inaccurate but OK for our  $\Delta G$  determination), what is the  $\Delta G$  between the two isomers? *If this reaction were reversible*, what should the ratio of the two diastereomeric products be? What was your observed ratio based on the crude  $^1\text{H}$  NMR spectrum? (The fact that the two ratios are not identical does not prove that the hydride reduction is irreversible. It is theoretically possible – wrong in this reaction – that the products were isolated before they reached equilibrium.)
- For the ketone, determine the dihedral angle between the equatorial  $\alpha$ -hydrogen and the carbonyl oxygen. The carbonyl oxygen should be tilted slightly toward what will become the equatorial position or else the entire torsional argument is not valid. (This tilt is cause by the  $sp^2$  hybridized carbonyl carbon, which flattens the ring from the ideal chair conformation.)
- Determine the dihedral angles of the alcohol carbon proton to its neighboring hydrogens. They should be approximately 60 and 180°. Use the Karplus equation (eq. 1) to predict the coupling constants of the products. From the clean  $^1\text{H}$  NMR spectra of the two alcohols, determine as many of the coupling constants as you can. Assuming the predicted values are legitimate, how close are your numbers?