

Chiral Compounds and Green Chemistry: Reduction of a ketone by sodium borohydride and baker's yeast (Introduction)

Adapted and Revised from J.Chem.Ed., 79, 6, 727 (June 2002)

Nicola Pohl, Allen Clague, and Kimberly Schwarz
Iowa State University, Department of Chemistry

PURPOSE

Examining traditional achiral borohydride reduction and chiral syntheses of ethyl beta-hydroxybutyrate from ethyl acetoacetate using three different methods. The various procedures are to be related in general to chiral catalysis and green chemistry.

BACKGROUND RESEARCH / READING / REVIEW

- Reductions using sodium borohydride
 - Biological reactions & Applications
 - Column chromatography
 - Polarimetry
 - Stereochemistry
-

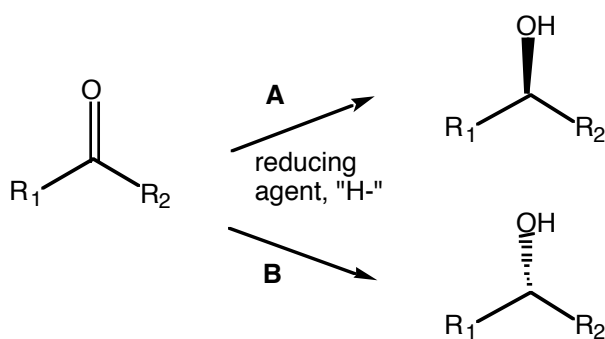
INTRODUCTION

The importance of chiral compounds. As you have seen, the biological world has an enormous number of chiral molecules—molecules with a handedness to their structure. Therefore, molecular and synthetic designs that can specifically interact with biological targets most often result in benefits from the inclusion of stereogenic centers. Many important therapeutics such as β -lactams and vancomycin antibiotics, and corticosteroids contain one or more stereogenic carbons. The handedness of a drug is so critical to its biological activity that the Food and Drug Administration requires drugs to be sold as single enantiomers unless each enantiomer is tested separately and shown to be safe. This regulation has been a large driving force in designing chiral syntheses and developing chiral separation techniques. Chiral separation technologies, chiral catalysts, enzymatic technologies, and bioengineered synthetic pathways to produce chiral starting materials and products are extremely active areas of research around the world in both academic and corporate labs.

Green chemistry. Another extremely active area of research that overlaps with the study of chiral compounds is “green” chemistry. Green chemistry is chemistry that looks at an entire process with an eye toward minimizing negative environmental impacts. (See attachment.) To this end, green chemists try to 1) minimize waste, 2) design safe (nontoxic, nonexplosive, etc.) chemical syntheses, 3) explore alternative reagents and solvents, 4) minimize energy usage, 5) utilize renewable resources whenever possible, 6) design products that break down after disposal into safe nonpersistent by-products, and 7) discover reactions that require catalytic rather than stoichiometric reagents.¹ Chemists are constantly trying to invent and discover new reactions and methods that improve on known reactions, avoiding hazards or circumventing a harmful process entirely. However, the perfect process has not yet been found. Therein lies the challenge.

How can chiral compounds be made from achiral compounds and apply one or more of the principles of green chemistry? Mimicking Nature offers enormous opportunities. Chemists can utilize living organisms or “borrow” their enzymes and screen their ability to catalyze new reactions, or use genetics and bio-engineering to design new optimal protein catalysts for a particular reaction.² These enzymes can then be used either in a less stable purified form or, if substrate access is not a problem, enzymes can be used while still contained in the cell that made the enzyme (protein). An alternative method is to use chiral compounds, such as glucose or malic acid, available from such processes in the design of a chemical

reaction. The chiral compound can either be covalently or noncovalently attached to the starting material, thereby biasing the resulting reaction in favor of a desired enantiomer, or be attached to a reagent, thereby biasing its reaction with the achiral substrate.



The chemical reduction of ketones to alcohols. The reduction of a ketone to an alcohol is a classic example of a reaction that has the potential to produce a chiral compound from an achiral starting material. Currently the most common way of accomplishing this transformation chemically is to use a metal hydride reducing agent such as sodium borohydride ($NaBH_4$) or lithium aluminum hydride ($LiAlH_4$). Ketones (pictured on the left) in which R_1 and R_2 are identical will produce an alcohol that is achiral. However, if R_1 and R_2 are different and

achiral, the resulting alcohols will be chiral. Because sodium borohydride and lithium aluminium hydride are not chiral reagents, the alcohol that is produced in reactions with those reagents will always be racemic. The transition states leading to each isomer of the alcohol are enantiomeric and of equal energy. This means that the activation energy for reaction pathways A and B will be identical. The two enantiomers will form at the same rate yielding a racemic product (a 1:1 mixture of each enantiomer).

The reduction of ketones to form nonracemic alcohols. If a source of chirality is introduced into the system then the transition states leading to the two isomers of the alcohol become diastereomeric and of different energy. Reaction pathways A and B will no longer be identical. Therefore, different amounts of the two stereoisomers of the alcohol can be formed. A source of chirality can be introduced into the reaction mixture in many ways. For example, a chiral reducing agent or a chiral solvent can be employed in the reaction. Chemists in recent years have devised a number of chiral reducing agents and much research is in progress to optimize chiral reductions using new combinations of ligands, solvents, and reducing agents. For ultimate practicality, the principles of green chemistry have to be kept in mind, too. Two experiments below describe the chemical reduction of a ketone both in the presence and the absence of a chiral compound.

The enzymatic reduction of ketones to alcohols. Biocatalysis is often thought of as an environmentally friendly alternative to the use of harsher chemicals. Chemists in recent years have devised a number of chiral reducing agents, but few of them are as efficient as the enzymatic reducing agents found in nature. One experiment will introduce you to the methods of using a benign organism—Baker's yeast—to carry out a synthetic organic transformation. Enzymes, which are protein catalysts, can also be isolated from organisms such as yeast and used directly to carry out a desired reaction. The use of whole organisms or individual enzymes is desirable as the chemical reactions happen at ambient temperature and pressure, but they also usually require large amounts of water that must be properly disposed as waste.

For this series of experiments, the reduction of a ketoester with and without the use of a chiral additive will be investigated. Two chiral reagents will be examined to compare the procedures: an enzyme contained within Baker's yeast³ and a chiral tartaric acid ligand complexed to sodium borohydride.⁴ Afterwards the reaction yield will be determined along with the enantiomeric excess and absolute configuration of the alcohols that are formed. Which method most closely achieves the "green" ideal?

TIMETABLE FOR THE EXPERIMENTS

In order to complete this series of experiments, your research group will need to plan the available time very carefully. The following timetable should be followed as closely as possible and matched to the deadlines found in the course calendar. Your research group will examine three different experimental methods and compare the resulting products. Each group is to choose how to best divide the overall tasks. Group members will confidentially rate the contribution of each member at the experiment's end.

Lab 1 (full lab period)	Initial briefing. (Dr. R.) Pre-lab; Set up the following reductions: <i>Method 1:</i> Sodium borohydride (NaBH_4) reduction of ethyl acetoacetate. (Can be moved to Lab 2.) <i>Method 2:</i> Yeast-catalyzed reduction of ethyl acetoacetate. (MUST be started.)
Lab 2 (full lab period)	<i>Method 1:</i> Work up & analysis of NaBH_4 reduction. <i>Method 2:</i> Yeast-catalyzed reduction (continued). <i>Method 3:</i> Sodium borohydride chiral reduction using chiral ligand.
Lab 3: (full lab period)	<i>Method 2:</i> Work-up and isolation of the yeast reduction product(s). <i>Method 3:</i> Work-up and isolation of the chiral reduction product(s).
Lab 4: (Concurrent with other, different lab experiment.)	<i>Methods 2 and 3:</i> Characterization of the yeast and chiral sodium borohydride reduction product(s). Comparing enantiomeric excesses.
	Final Report Due

CAUTION:

As with any hydride reaction, hydrogen gas is evolved during the course of the reaction. Hydrogen must be kept away from ignition sources to avoid explosions. The organic solvents are all flammable. Tetrahydrofuran is an irritant. Deuterated chloroform used to make samples for NMR is highly toxic and a cancer suspect agent. Hydrochloric acid and sodium borohydride are corrosive and tartaric acid is an irritant. Standard chemical safety precautions should be practiced at all times.

PRELAB:

Prior to the initial briefing, select one student who is to be responsible for the overall management of time and tasks. Each of the remaining student team members is to write a prelab for one of the experimental procedures in their lab notebook following the required format as outlined in the course syllabus and lab textbook. Complete the prelab questions and turn in on the prelab group form.

PRELAB QUESTIONS: (ANSWER ON GROUP FORM.)

- 1) Draw line or condensed structures (3d where appropriate) of: ethyl acetoacetate, (L)-tartaric acid, (R)-ethyl-3-hydroxybutyrate, and (S)-ethyl 3-hydroxybutanoate.
- 2) *The addition of acetic acid to sodium borohydride will cause the displacement of one or more hydrides from each boron atom with an acetate ion. The resulting borohydride reducing agent is less reactive than the parent sodium borohydride. What does tartaric acid do in the sodium borohydride reduction to cause a chiral reaction environment for the ketone reduction reaction? Illustrate with a structure.*
- 3) What are the specific rotations of pure (R)-ethyl 3-hydroxybutanoate, (S)-ethyl 3-hydroxybutanoate and (L)-tartaric acid?
- 4) Data indicated that procedure #3 converted 80% of the starting material, ethyl acetoacetate, to give a product mixture of (R)-ethyl-3-hydroxybutyrate and (S)-ethyl-3-hydroxybutyrate. Using a 1 dm long polarimeter cell, the optical rotation of the reaction mixture, which includes unreacted ethyl acetoacetate to be $+10.5^\circ$. The concentration is 0.5 g/mL (total material, not just product). Find the TOTAL percent of the enantiomer that is in excess.
- 5) Could you use LiAlH_4 for the reduction of ethyl acetoacetate rather than NaBH_4 and obtain the same products?

Green Chemistry: Science and Politics of Change

Martyn Poliakoff, J. Michael Fitzpatrick, Trevor R. Farren, Paul T. Anastas
Science, Volume 297, Number 5582, Issue of 2 Aug 2002, pp. 807-810.

Green Chemistry Principles

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g., solvents, separation agents, and so forth) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control before the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.