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5.37 Introduction to Organic Synthesis Laboratory

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MASSACHUSETTS INSTITUTE OF TECHNOLOGY
DEPARTMENT OF CHEMISTRY

Chemistry 5.37

Module 7: Introduction to Organic Synthesis

Catalytic Asymmetric Cycloadditions

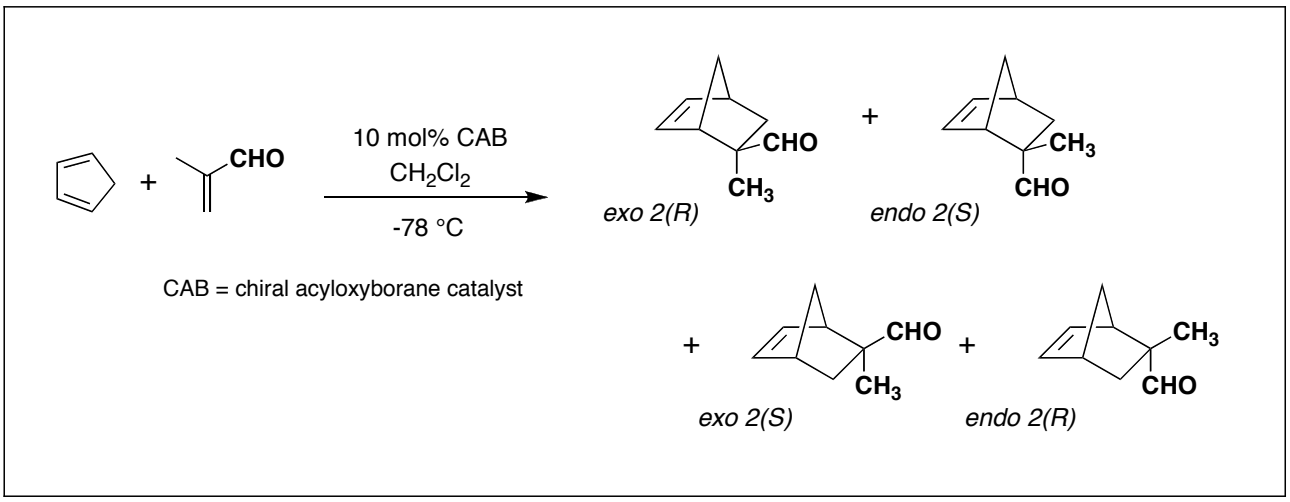
Version 2009.2 Prepared by Professor Rick L. Danheiser, March 2008

Contents

I. Introduction

The goal of Module 7 is to provide you with experience with techniques employed in synthetic organic chemistry and to introduce you to the exciting research area of catalytic asymmetric organic synthesis. This research-inspired experiment is based on a useful class of chiral catalysts developed by Professor Hisashi Yamamoto of the University of Chicago (the original work was performed at Nagoya University). The procedures in the experiment are somewhat modified versions of the procedures described in a publication by Professor Yamamoto in *Organic Syntheses* (*Org. Synth.* **1995**, *72*, 86). This chemistry was originally adapted for the Chemistry 5.32 laboratory course by Dr. Mircea Gheorghiu and the current version of Module 7 is a modification of that Chemistry 5.32 experiment.

The key reaction in the experiment is the asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein. As shown below, in principle four stereoisomeric [4 + 2] cycloaddition products can result from this reaction: an *endo* cycloadduct and an *exo* cycloadduct, each of which in turn can be



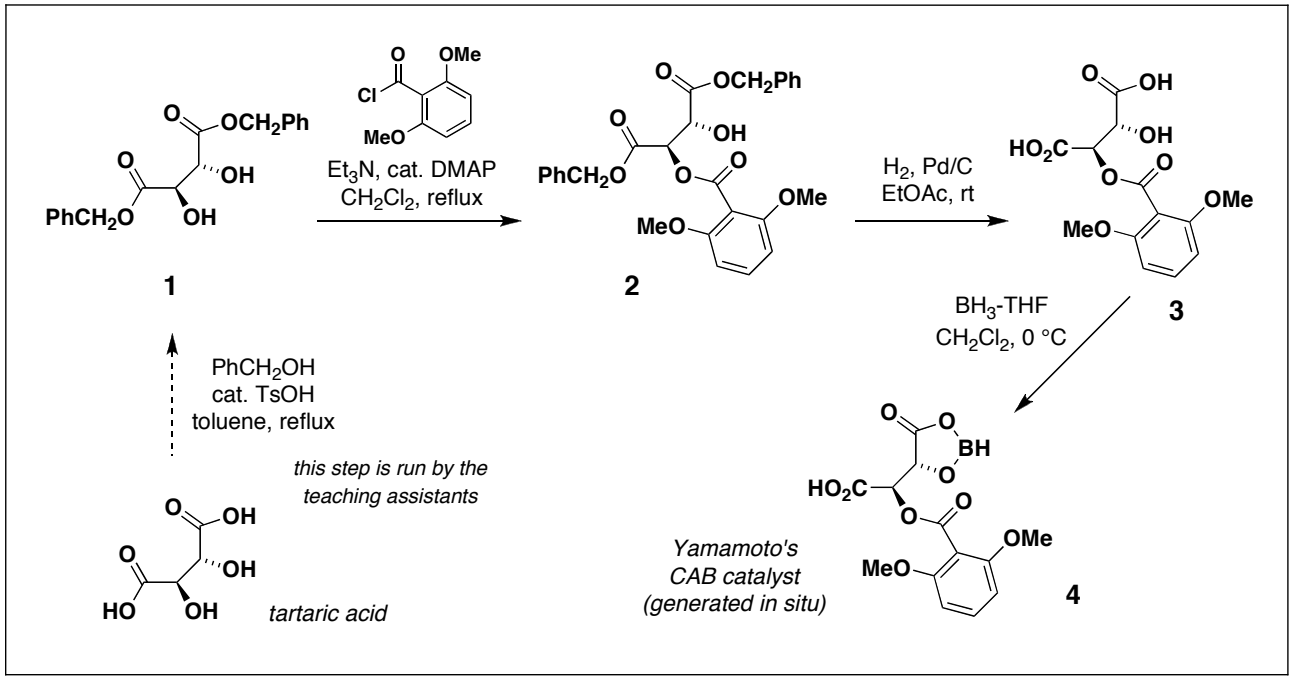
produced in two enantiomeric forms. Two varieties of stereocontrol thus are involved in determining the outcome of this reaction: *diastereoselectivity* and *enantioselectivity*. The diastereoselectivity of the cycloaddition refers to the ratio of endo and exo products and is influenced by steric factors and secondary orbital interactions. The enantioselectivity refers to the ratio of the enantiomeric forms of each diastereomeric product. The factors that control the stereochemical outcome of Diels-Alder cycloadditions will be discussed further in 5.37 lectures by Professor Danheiser.

In the late 1980s, Hisashi Yamamoto and his coworkers reported that a class of chiral Lewis acid catalysts that was under development in their laboratory has the ability to promote highly enantioselective Diels-Alder reactions. The mechanism of this reaction will be discussed by Professor Danheiser in 5.37 lectures. In this URIECA module, we will prepare one of the Yamamoto "chiral acyloxyborane (CAB)" catalysts (**4**) and employ it for the asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein.

The CAB catalyst will be generated in situ for the Diels-Alder reaction by addition of borane to a tartaric acid derivative, which will itself be synthesized in two steps from dibenzyl tartrate as outlined in the scheme below. The synthesis of the catalyst precursor **3** requires the monoacylation of one hydroxyl group of tartaric acid with 2,6-dimethoxybenzoyl chloride. To accomplish this, first the carboxylic acid groups of tartaric acid must be protected as esters so that they do not interfere with the acylation reaction. The esters chosen for this protection must subsequently be cleavable in the presence of the newly formed benzoate ester. This rules out the use of standard saponification conditions, since under those conditions (e.g., aqueous sodium hydroxide) cleavage of the benzoate ester would take place as well. However, benzyl esters can be cleaved selectively by the process known as *hydrogenolysis*, the reductive cleavage of benzylic bonds under the conditions of catalytic hydrogenation.

Dibenzyl tartrate (**1**) will be prepared by the teaching assistants via esterification of tartaric acid with benzyl alcohol and will be provided to you as a "crude" product requiring further purification by trituration and recrystallization. Esterification of dibenzyl tartrate to afford **2** will then be carried out by heating the diol overnight with 1 equiv of 2,6-dimethoxybenzoyl chloride in the presence of a catalytic amount of 4-dimethylaminopyridine ("DMAP"). For a review of the use of DMAP as an

acylation catalyst, see Hoefle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569. The product of the esterification reaction (**2**) will be purified by column chromatography.



Hydrogenolysis to cleave the benzyl esters will be achieved by hydrogenation using 10% palladium on carbon as the catalyst in ethyl acetate at room temperature to furnish the desired precursor (**3**) to the CAB catalyst. This product should be of sufficient purity for use in the next step without further purification. For the asymmetric Diels-Alder reaction, the chiral Lewis acid catalyst (**4**) is generated in situ and the cycloaddition is carried out at -78 °C in dichloromethane. The product is purified by column chromatography and analyzed by NMR spectroscopy and chiral gas chromatography.

Further discussion of strategies for asymmetric synthesis and enantioselective Diels-Alder reactions will be presented by Professor Danheiser in lectures during Module 7.

II. Overview of the Experiment

The experimental component of this URIECA module is designed to be completed in nine laboratory periods plus 1-2 additional days for analysis of the products as outlined below. A total of 11 days are allocated for the experiment (including check-out) to ensure that you have adequate time to complete the work. Students will carry out the experiment in groups of two.

Be sure to read ahead in the experimental procedure to be aware of what is going to be done during the next laboratory period. In some cases it is necessary to place glassware in the drying oven for at least 24 h, and you will need to do that during the lab period prior to the day that the equipment is needed.

Day 1: Dry and purify triethylamine by distillation and purify dibenzyl tartrate by trituration and recrystallization.

Day 2: Set up esterification of dibenzyl tartrate with 2,6-dimethoxybenzoyl chloride which then runs overnight at reflux. The teaching assistants will turn off the heat the following day for you and the reaction will be allowed to proceed at room temperature until the next laboratory period of your group.

Day 3: Work up the esterification reaction.

Day 4: Purify the product of the esterification reaction by column chromatography. Analysis of the product by proton NMR spectroscopy (spectrum can be run at the beginning of Day 5 if necessary).

Day 5: Set up the hydrogenolysis reaction which will then run over the weekend at room temperature. If necessary, the teaching assistants will add more hydrogen to your balloons on the day after you set up the reaction.

Day 6: Filter and concentrate the hydrogenolysis reaction mixture, and set up overnight drying of the diacid product under vacuum. The measurement of the melting point of the product and NMR analysis can be performed either at the beginning of Day 7 or on an "off day" for your group between Days 6 and 7.

Day 7: Generate the chiral CAB Lewis acid catalyst in situ and set up the Diels-Alder reaction to run overnight at low temperature. The teaching assistants will add additional dry ice to your cooling bath during the evening to extend the time that the reaction remains below -70 °C.

Day 8: Work up the Diels-Alder reaction and analyze the crude product by TLC and proton NMR spectroscopy.

Day 9: Purify the Diels-Alder product by column chromatography and separate the endo and exo cycloadducts.

Day 10: Analyze the Diels-Alder product by proton NMR spectroscopy and determine the enantiomeric ratio for the exo isomer by gas chromatography using a chiral GC column. This characterization can be completed on Day 11 if necessary.

Day 11: Extra time for completion of the experiment and checkout.

III. Reports and Grading

Your grade for this experiment will be based on a total of 100 points assigned as follows.

Oral quiz	10 points
Lab notebook	20 points
Experimental results and technique	30 points
Waste inventory sheet	5 points
Analysis, conclusions, and final report	35 points

It is essential for you to carefully study the instructions for the module, complete the reading assignment, and to watch the relevant sections of the Digital Techniques Manual prior to beginning work on the experiment. A short **oral quiz** covering all *experimental aspects* of the module will be given to each student by their TA sometime during the first four lab sessions to ensure that you are prepared to work on the module. You will not be informed in advance by your TA as to which day your exam will be scheduled. You will be graded A, B, C, or F based on whether your familiarity and understanding of the experimental techniques is "superior", "good", "acceptable", or unsatisfactory, and this score will contribute 10% toward your final grade for the module. The oral quiz will be based on the reading assigned in Mohrig, Hammond, and Schatz on experimental techniques in Chapters 5-11 and 14-17, as well as the information in the assigned videos from the Digital Techniques Manual. The quiz will *not* include questions on asymmetric synthesis and the Diels-Alder reaction, but rather will focus on the theory and practice of the experimental techniques that are employed in Module 7.

"**Prelab writeups**" are required prior to each lab session and will comprise 10 points of the **lab notebook** portion of the total grade. These writeups should be concise outlines (one page or less) describing what you propose to carry out in that lab session. The purpose of preparing these outlines is to ensure that you mentally think through what you intend to carry out in the lab beforehand. The carbon copy of the prelab outline should be submitted to your TA at the beginning of each lab session. The remainder of the lab notebook portion of the grade (10 points) will be based on the organization, completeness, and clarity of your record of your experimental results. Guidelines are provided below in the Experimental Procedure section for recording data in specific sections of the module.

Experimental results and technique will comprise 30 points of the total grade. This portion of the grade will be based principally on your experimental results, including the yields you obtain for reactions in various sections of the experiment, the success and efficiency of your separations and purifications, and the quality of the spectra you obtain for your products.

Students must prepare a **waste inventory sheet** and 5 points of the grade will be awarded based on this. Copies of blank waste inventory sheets can be downloaded from the Experiments page of the 5.37 website or copied from Appendix I of this writeup.

The final 35 points of the grade will be determined by your **analysis of results and conclusions** (i.e., your interpretation of spectra and conclusions) and your **final written report**, including your "mini-review" profiling an alternative asymmetric Diels-Alder strategy. More information on the written report is provided in Section VII below.

IV. References

(1) References on Experimental Methods

The **Digital Techniques Manual** provides detailed instructions concerning most of the experimental techniques employed in this module. The DTM can be accessed via the following url (which is also linked to the 5.37 website):

http://ocw.mit.edu/ans7870/resources/chemvideo/index.htm

The specific DTM videos that are relevant to this module are indicated in each section of Part V (Experimental Procedure) below. Additional discussion of experimental techniques is contained in the required reading in the following chapters of the course text *"Techniques in Organic Chemistry"*, Second Edition, Jerry R. Mohrig, Christina Noring Hammond, and Paul F. Schatz, W. H. Freeman, New York, 2006. Note that you should already be familiar with many of these sections (marked with an asterisk) as they were previously assigned in connection with Module 6.

Chapter 5*	Measuring Mass and Volume
Chapter 6	Heating and Cooling Methods
Chapter 7*	Assembly of Reaction Apparatus and Planning a Chemical Reaction
Chapter 8*	Extraction and Drying Organic Liquids
Chapter 9	Recrystallization
Chapter 10	Melting Points and Melting Ranges
Chapter 11	Boiling Points and Distillation
Chapter 14	Optical Activity and Enantiomeric Analysis
Chapter 15*	Thin Layer Chromatography
Chapter 16	Gas-Liquid Chromatography
Chapter 17*	Liquid Chromatography
Chapter 18*	Infrared Spectroscopy
Chapter 19*	Nuclear Magnetic Resonance Spectroscopy

Also useful in connection with the interpretation of IR and NMR spectra is *Spectrometric Identification of Organic Compounds* (Seventh Edition) by R. M. Silverstein, F. X. Webster, and D. J. Kiemle (Wiley, 2005) ISBN 0-471-39362-2.

(2) Background Reading on the Diels-Alder Reaction and Asymmetric Synthesis

For general background on the Diels-Alder reaction, including asymmetric variants, please consult the following organic chemistry texts which are on reserve in the Science Library (this reading is optional).

(1) "Advanced Organic Chemistry, Part A: Structure and Mechanisms", Fifth Edition, by F. A. Carey and R. J. Sundberg, Springer, 2007, Chapter 10 ("Concerted Pericyclic Reactions"), pp 833-873.

(2) "Advanced Organic Chemistry, Part B: Reactions and Synthesis", Fifth Edition, by F. A. Carey and R. J. Sundberg, Springer, 2007, Chapter 6 ("Concerted Cycloadditions, Unimolecular Rearrangements, and Thermal Eliminations"), pp 473-526.

(3) "Organic Chemistry" by J. Clayden, N. Greeves, S. Warren, and P. Wothers, Oxford University Press, 2001, Chapter 35 ("Pericyclic Reactions I: Cycloadditions"), pp 905-924 and Chapter 45 ("Asymmetric Synthesis"), pp 1217-1232.

Chiral Acyloxyboranes as Catalysts for Asymmetric Diels-Alder Reactions

Please read these three papers carefully; this experiment is based on the chemistry described in these publications. These articles can be accessed via the MIT Library website.

(1) Furuta, K.; Gao, Q.-Z.; Yamamoto, H. *Org. Synth.* **1995**, *72*, 86.

(2) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

(3) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.

Review of Yamamoto's Work on Chiral Acid Catalysts

Optional further reading on Yamamoto's chiral acid catalysts:

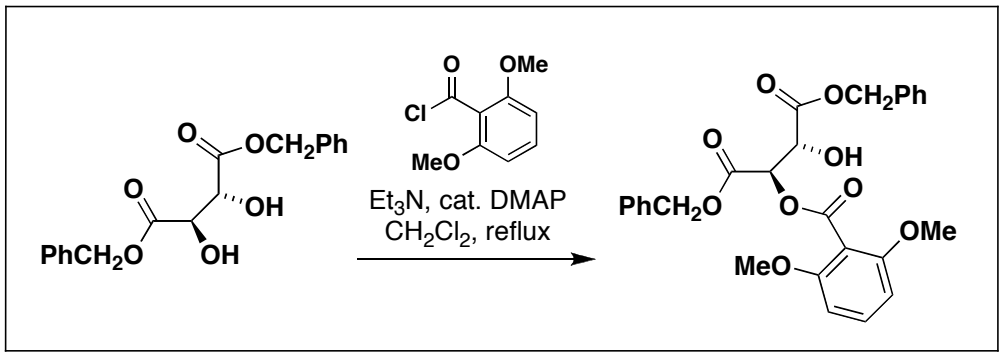
(1) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

V. Experimental Procedure

As was the case with Module 6, it is important to watch the assigned videos in the Digital Techniques Manual and to read the assigned sections of Mohrig, Hammond, & Schatz in advance to obtain detailed guidance as to how to carry out the experimental operations referred to in the experimental procedure below. You may wish to view sections of some of the DTM videos several times to be sure that you fully understand how to carry out these operations. You should also carefully read the relevant assigned sections of the text (*Mohrig, Hammond, & Schatz*) which provide additional useful instructions on these techniques and which also include background on the theory behind techniques such as extraction and chromatography. The oral quiz which contributes 10% of your grade on this module will be based on the assigned reading in Mohrig et al. and on the DTM videos assigned for the experiment. Although the quizzes will be carried out on Day 1, 2, 3 or 4 of the module, they will include questions covering all of the reading and the assigned videos for the entire experiment.

Part VI describes special safety considerations associated with each phase of the experiment. Be sure to study the appropriate sections of Part VI carefully before carrying out each operation. If you have any questions concerning safety practices, please consult with a teaching assistant, Professor Danheiser, or Dr. Gheorghiu.

Days 1-4 Monoesterification of Dibenzyl Tartrate with 2,6-Dimethoxybenzoyl Chloride



Day 1: Purification of Reactants for the Esterification Reaction

Digital Techniques Manual: TLC-The Basics and TLC-Advanced, Distillation I, Recrystallization, Filtration, Melting Point Determination

Mohrig, Hammond, & Schatz: Chapter 6 (Heating and Cooling Methods), Chapter 11 (Boiling Points and Distillation), Chapter 15 (Thin-Layer Chromatography), Chapter 5 (Measuring Mass and Volume), Chapter 9 (Recrystallization), and Chapter 10 (Melting Points and Melting Ranges).

Equipment: Glass-backed silica TLC plates, glass capillary TLC spotters, three TLC chambers with filter paper, TLC developing stock solutions (ceric ammonium molybdenate, phosphomolybdic acid, and p-anisaldehyde), small vials, disposable glass pipettes and pipette bulbs. For distillation: short path distillation head, distillation cow, three 10-mL round-bottomed flasks, 25-mL round-bottomed flask, glass stoppers. For trituration: 250-mL Erlenmeyer flask, spatula, glass rod, Buchner funnel, 500-mL Erlenmeyer filter flask, 100-mL graduated cylinder. For recrystallization: 250-mL Erlenmeyer flask, 50-mL round bottomed flask, 500-mL beaker, vials, filter funnel. Chemicals: diethyl ether, ethyl acetate, hexanes, triethylamine, and calcium hydride.

For optimal results it is necessary to purify the triethylamine that is used as an HCl scavenger in the esterification reaction. In particular, if any water is present in the triethylamine, then it can hydrolyze the acyl chloride faster than your alcohol reacts, and thus reduce the yield of the desired ester product. Triethylamine can be dried by stirring it over calcium hydride and then distilling it into a dry flask at atmospheric pressure under nitrogen.

Transfer 10-15 mL of triethylamine into a 25-mL round-bottomed flask by dispo pipette. Add a magnetic stirbar and ca. 0.5 g of calcium hydride. Attach a short-path distillation head equipped with a thermometer to the distillation flask and equip the still head with an oven-dried cow attached to your nitrogen line via a T connector. Be sure to connect the condenser of the still head to your water line. The third branch of the T connector should be linked to an oil bubbler via Tygon tubing.

The cow should be equipped with three oven-dried, 10-mL, round-bottomed flasks. Stir the triethylamine over calcium hydride for at least 1.5 h. Distill the triethylamine at atmospheric pressure by heating the flask in a sand bath; the boiling point of triethylamine is 89 °C. Collect at least 5 mL of dry triethylamine. Seal the flask containing the distilled triethylamine with a glass stopper. Any other triethylamine that you distill over can be returned to the original bottle. The calcium hydride remaining in the distillation flask should be quenched according to the procedure described in Part VI.

Photo of distillation setup here

The following purification of dibenzyl tartrate should be started while the triethylamine is stirring over calcium hydride. The sample of dibenzyl tartrate you will be given is the crude product from a reaction of benzyl alcohol and tartaric acid that was run by the teaching assistants. The sample of diester is impure and contains a small amount of unreacted benzyl alcohol. Separation of the benzyl alcohol impurity from the diester by chromatography would be difficult, and can be accomplished more easily on a large scale by trituration followed by recrystallization according to the procedure described below.

First, check the purity of your sample of dibenzyl tartrate by TLC analysis on silica gel using the techniques introduced in Module 6. A sample of benzyl alcohol can be obtained for reference from your teaching assistant. For eluant, begin by trying 25% ethyl acetate-hexane, but you may wish to examine other solvent systems. Visualization should be carried out by UV and PMA.

The first step in the purification of the crude dibenzyl tartrate is trituration. Trituration is the process in which a solid is treated with a solvent in which it is not soluble but which does dissolve some of the impurities present. You will be given ca. 10 g of crude dibenzyl tartrate in a 250-mL Erlenmeyer flask. Trituration of your dibenzyl tartrate (the crude material is a gummy solid) is carried out by adding 200 mL of hexane and 10 mL of diethyl ether to the diester in the 250-mL Erlenmeyer. Rub and grind the solid material with a glass rod and metal spatula for 5-10 min to break up clumps and to thoroughly mix the solid with the solvent. Next, add a magnetic stirbar to the flask and stir the mixture for 10 min. Filter the resulting mixture through a filter paper disk on a Buchner funnel into a 500-mL Erlenmeyer filter flask, washing the solid that you collect with three 15-mL portions of

20:1 hexane-ether. Transfer the solid to a tared 250-mL Erlenmeyer flask and record the weight of dibenzyl tartrate (you should have at least 9 g at this stage of the purification).

Recrystallize your dibenzyl tartrate from a mixture of hexane and ethyl acetate according to the following procedure. First, add the *minimum* amount of ethyl acetate to the solid required to dissolve it. Add ethyl acetate in small portions and thoroughly stir the mixture before adding the next portion. A total of approximately 30 mL of ethyl acetate will be needed. Next, add hexane in small portions (ca. 5-10 mL at a time) until the solution just begins to become cloudy. Approximately 50 mL of hexane will be required. Finally, add ethyl acetate again dropwise until the mixture just again becomes clear. At this point, cool the Erlenmeyer flask in an ice-water bath. Dibenzyl tartrate will crystallize and cooling should be continued until no further solid appears (ca. 20 min). Collect the solid by filtration through a filter paper disk on a Buchner funnel into a 500-mL Erlenmeyer filter flask, washing the solid that you collect with three 10-mL portions of cold hexane. Transfer the solid to a tared 500-mL beaker and record the weight of pure dibenzyl tartrate (you should have 8-9 g). Carry out TLC analysis of the product to confirm that no benzyl alcohol is present. Next, dry the solid by spreading it out on the bottom of the beaker, covering the top of the beaker with a Kimwipe secured with a rubber band (to keep out dust), and allowing it to stand exposed to air until your next laboratory period.

Day 2: Setting Up the Esterification Reaction

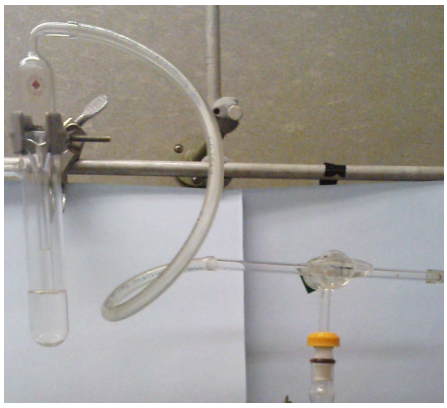
Digital Techniques Manual: Refluxing a Reaction

Mohrig, Hammond, & Schatz: Chapter 5 (Measuring Mass and Volume), and Chapter 7 (Assembly of Reaction Apparatus and Planning a Chemical Reaction)

Equipment: Disposable glass pipettes and pipette bulbs, sand bath, 250-mL three-necked round-bottomed flask, reflux condenser, three-way stopcock with inlet adapter, magnetic stirbar, oil bubbler, 2 glass stoppers, 100-mL graduated cylinder, 5-mL syringe, heating mantle, dichloromethane, 4-dimethylaminopyridine.

Measure the melting point of your dried dibenzyl tartrate (the mp of pure diester is 49-50 °C). You will need 6.1 g for the esterification reaction that you will set up on this day of Module 7.

The esterification will be carried out in an oven-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar. The center neck of the flask should be fitted with a reflux condenser topped with a inlet adapter connected to a three-way stopcock. One branch of the stopcock is connected by tygon tubing to the nitrogen source, and the other branch to an oil bubbler to allow for the monitoring of the nitrogen flow rate. The two side necks of the reaction flask are capped with glass stoppers. A photograph of the reaction setup is shown in Figure 1 below.



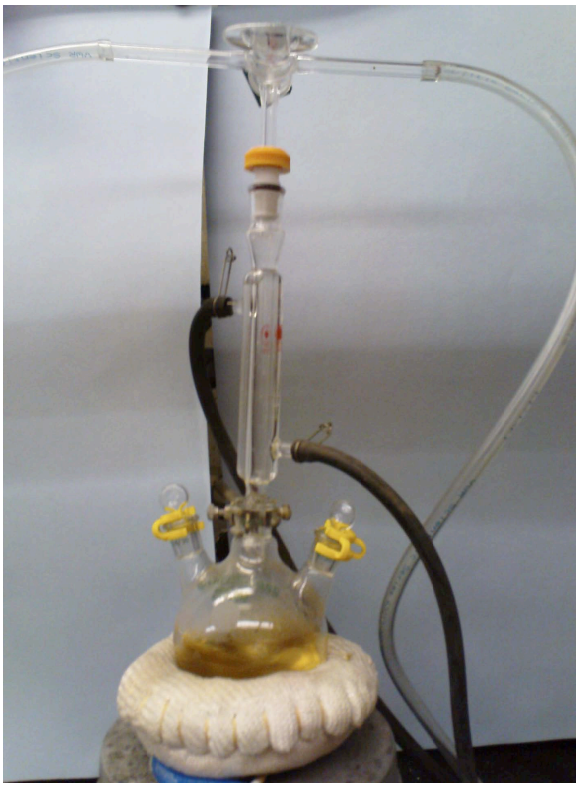


Figure 1. Reaction setup for the esterification reaction.

Remove the flask from the oven and quickly assemble it and begin the flow of nitrogen while it is still hot. The reaction flask is flushed with nitrogen for 5 min by turning the three-way stopcock so as to temporarily cut off flow to the bubbler and to direct nitrogen into the flask while a glass stopper is removed from one of the side necks. With the flow of nitrogen continuing, the flask is then charged via the open side neck with 6.1 g (18.5 mmol, 1.02 equiv) of dibenzyl tartrate (a solid) and then 100 mL of dichloromethane (previously dried over 4A molecular sieves) is added in one portion. Triethylamine (4 mL, 28.8 mmol, 1.58 equiv), previously distilled from calcium hydride, is then added with a 5 mL syringe followed by 4-dimethylaminopyridine (0.050 g, 0.4 mmol, 0.02 equiv). 4-Dimethylaminopyridine is a solid with mp 112-114 °C. The side neck is capped with a glass stopper, the three-way stopcock is adjusted so that it is open to the nitrogen source, flask, and the bubbler, and the reaction mixture is cooled in an ice-water bath. Once the reaction mixture has reached ca. 0 °C, the first portion of 2,6-dimethoxybenzoyl chloride is added by momentarily opening a side neck and adding the acyl chloride. Commerically available 2,6-dimethoxybenzoyl chloride is only 80% pure, so a total of 4.65 g of this material must be used in order to have 18.2 mmol (1.0 equiv) of acyl chloride. Note that 2,6-dimethoxybenzoyl chloride is a solid with mp 64-66 °C. The acyl chloride is added in five portions at ca. 10-min intervals. After the last portion is added, the ice bath is replaced with a heating mantle and the reaction mixture is heated at a gentle reflux (the boiling point of dichloromethane is 40 °C). Place a tag on your flask with your name and indicating the time that reflux was begun. A teaching assistant will shut off the heat 24 h after the time you indicate on the tag and the reaction will be allowed to run at room temperature until your next laboratory period.

Day 3: Workup of the Esterification Reaction

Digital Techniques Manual: Reaction Workup I and II

Mohrig, Hammond, & Schatz: Chapter 8 (Extraction and Drying Organic Liquids.

Equipment: Disposable glass pipettes and pipette bulbs, 100-mL graduated cylinder, 500-mL separatory funnel, 1-L Erlenmeyer, two 500-mL Erlenmeyers, 250-mL round-bottomed flask, 50-mL round-bottomed flask, filter funnel, fluted filter paper, dichloromethane, saturated sodium bicarbonate solution, saturated NaCl solution, anhydrous sodium sulfate.

Confirm that the esterification reaction is complete by performing TLC analysis on a sample of the reaction mixture withdrawn from the flask through a side neck with your TLC spotter. If TLC indicates that substantial starting material remains, consult with your teaching assistant.

The workup outlined below is designed to remove any carboxylic acid impurities; the excess triethylamine (bp 89 °C) will be removed after the workup by rotary evaporation. First, transfer the reaction mixture to a 500-mL separatory funnel, rinsing the flask with a small amount of dichloromethane and water to ensure complete transfer of the contents of the flask. Extract the organic solution with 100 mL of water, and then back-extract the aqueous phase with 50 mL of dichloromethane. Extract the combined organic phases with three 75-mL portions of saturated sodium bicarbonate solution and then 75 mL of water. Transfer the organic solution to a 500-mL Erlenmeyer flask and dry it over anhydrous sodium sulfate. Filter the solution into a 250-mL round-bottomed flask and concentrate it by rotary evaporation at ca. 20 Torr and 40 °C to remove the dichloromethane and triethylamine. Transfer the product to a tared 50-mL round-bottomed flask using a small amount of dichloromethane and again concentrate the solution. Record the weight of your "crude product" and check it by TLC analysis using 3:1:5 hexane-diethyl ether-dichloromethane as eluant. You should obtain ca. 9 g of crude esterification product as a gold or brown-colored viscous liquid.

Day 4: Purification of the Esterification Product

Digital Techniques Manual: Column Chromatography

Mohrig, Hammond, & Schatz: Chapter 17 (Liquid Chromatography) and Chapter 19 pp 269-276 (NMR Instrumentation and Sample Preparation)

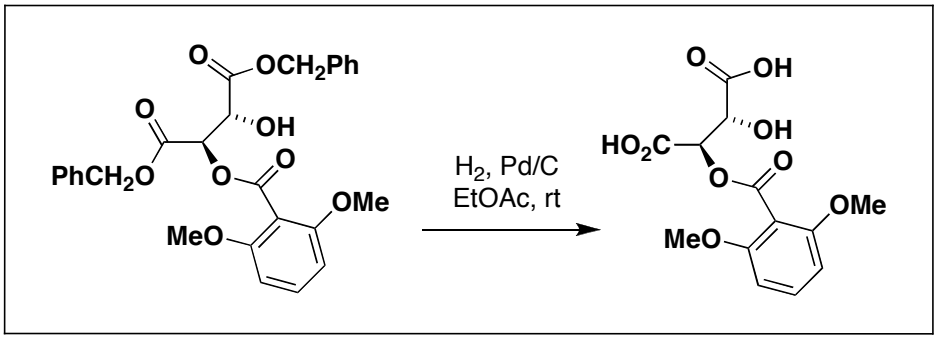
Equipment: Chromatography column (67 cm length, 55 mm width) with adapter and tubing for top of column for applying pressure, funnel, 100-mL graduated cylinder, 230-400 mesh silica gel 60, sand, 18 x 150-mm test tubes, test tube racks, round-bottomed flasks (50 and 500 mL), 1-L beaker, NMR tube, hexanes, diethyl ether, dichloromethane, and $CDCl_3$.

Purify your crude esterification product by flash column chromatography on 200 g of silica gel. Weigh out the silica gel in a 1-L beaker (200 g will come to about the 450-mL mark). Prepare the

column using a 3:1:5 mixture of hexanes-diethyl ether-dichloromethane and then elute with the same solvent system. For general guidance, refer to the Digital Techniques Manual, Chapter 17 of Mohrig et al., and your experience with column chromatography from Module 6. Be sure to save a small sample of the crude reaction product to use as a TLC reference sample; this should be spotted in lane 1 on each plate as you monitor the fractions obtained in your chromatography. Collect 20-mL fractions in test tubes and identify the fractions containing your esterification product by TLC analysis (remember that it is usually not necessary to perform TLC analysis of every fraction). Combine the desired fractions in a 500-mL round-bottomed flask and concentrate by rotary evaporation to remove all of the solvent. Transfer the product to a tared 50-mL round-bottomed flask using dichloromethane and again remove all of the solvent by rotary evaporation. Record the weight of your purified esterification product and record the results of all TLC analyses and the details of your chromatographic purification following the same guidelines described in Module 6. The *Organic Syntheses* procedure reports obtaining 7.1-7.5 g (78-82% yield) of esterification product; you will need at least 3 g to go on to the next step in the synthesis. Be sure that your notebook record of the chromatographic purification is detailed and complete. Record the amount of silica gel used, and for each fraction collected indicate the volume and the eluant. Draw TLC plates (using the format described in Module 6) showing all of the fractions that were monitored by TLC analysis.

Obtain a proton NMR spectrum of a small sample of your purified product in $CDCl_3$. Note that if solvent (e.g., ether, hexanes, or dichloromethane) appears in your spectrum, you will have to concentrate your product further by rotary evaporation, record the new (solvent-free) weight of product, and run another NMR spectrum to confirm the purity of your material. If necessary, the NMR spectrum can be run on an "off-day" for your group or at the beginning of Day 5 of the module. NMR data for dibenzyl mono(2,6-dimethoxybenzoyl)tartrate can be found in the *Organic Syntheses* paper by Yamamoto et al.
Submit a copy of the NMR spectrum to your TA who must approve it before you proceed to the next phase of the experiment. Also report the weight of your purified product to your TA.

Days 5-6 Deprotection of Benzyl Esters by Hydrogenolysis



Day 5: Setting Up the Hydrogenation Reaction

Equipment: Disposable glass pipettes and pipette bulbs, balloons, 250-mL three-necked round-bottomed flask, reflux condenser, three-way stopcock with inlet adapter, magnetic stirbar, oil bubbler, 2 glass stoppers, 100-mL graduated cylinder, ethyl acetate, palladium on carbon.

Equip a 250-mL, three-necked, round-bottomed flask with a magnetic stirbar, two glass stoppers in the side necks, and a reflux condenser in the center neck. The condenser simply functions as a "spacer" and is not connected to a water line. The top of the condenser is fitted with an inlet adapter connected to a three-way stopcock. One branch of the stopcock is connected by tygon tubing to the nitrogen line, and the other branch to an oil bubbler to allow for the monitoring of the nitrogen flow rate. Flush the reaction flask with nitrogen for 5 min by closing the bubbler off at the three-way stopcock and opening one of the side necks of the flask as an outlet for the nitrogen. After 5 min, charge the flask with 10% palladium on carbon (10% by weight to the amount of dibenzyl ester that you will be using). Next, add 90 mL of ethyl acetate carefully, washing any palladium on carbon off the walls of the inside of the flask so that all of the catalyst is under the surface of the solvent. Finally, add the dibenzyl ester via dispo pipette, using 10 mL of ethyl acetate to rinse the flask and pipette used for the transfer. Continue flushing the flask with nitrogen for 3-4 min and then seal the side neck with a glass stopper.

Prepare two "hydrogen balloons" by connecting each balloon to a 5-cm length of tygon tubing and securing the balloon to the tubing using copper wire. Wrap the connection with electrical tape to further ensure a tight seal. Turn the stopcock on your flask so that it is open to the nitrogen line and flask, and closed off from the oil bubbler. Detach from the stopcock the tygon tubing leading to the bubbler, and replace it on the stopcock with a balloon filled with hydrogen. Turn the stopcock so as to close off the nitrogen line and to open the flask to the hydrogen balloon, simultaneously loosening a glass stopper on a side neck so as to allow the flask to be flushed with hydrogen. Next, turn the stopcock to close off the balloon, remove and refill the balloon with hydrogen, and flush the flask with hydrogen a second time. Close the side neck tightly with the glass stopper, remove and refill the balloon with hydrogen as described above, and replace the freshly filled balloon on the stopcock. Attach a a second balloon filled with hydrogen to the other branch of the stopcock in place of the nitrogen line. The stopcock should then be turned so that both balloons are open to the flask and the reaction mixture is stirring under an atmosphere of hydrogen. A photograph of a typical reaction

setup is shown in Figure 2 below. After 24 h, it will be necessary to refill the balloons with hydrogen which may be lost by diffusion. The hydrogenolysis reaction will be allowed to run until your next laboratory period.

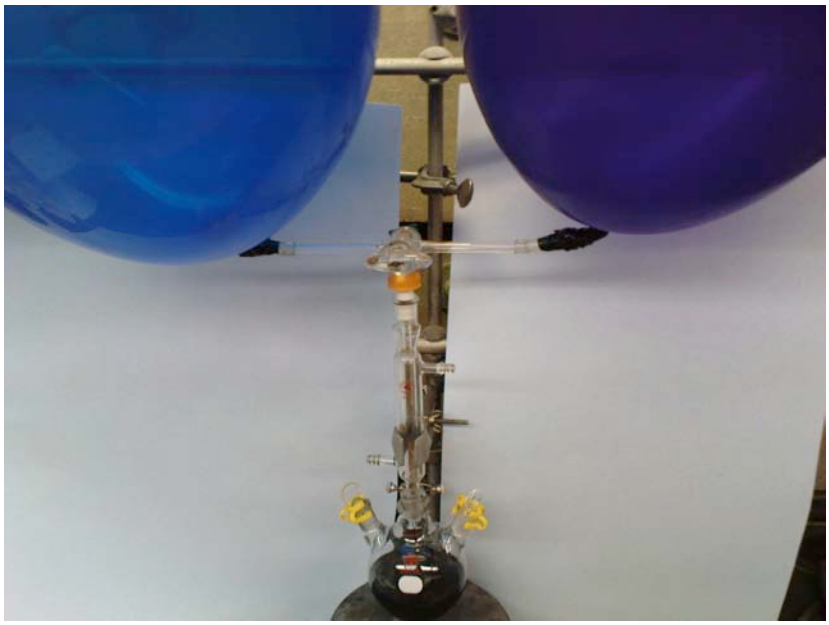


Figure 2. Hydrogenolysis reaction setup.

Day 6: Workup of the Hydrogenation Reaction

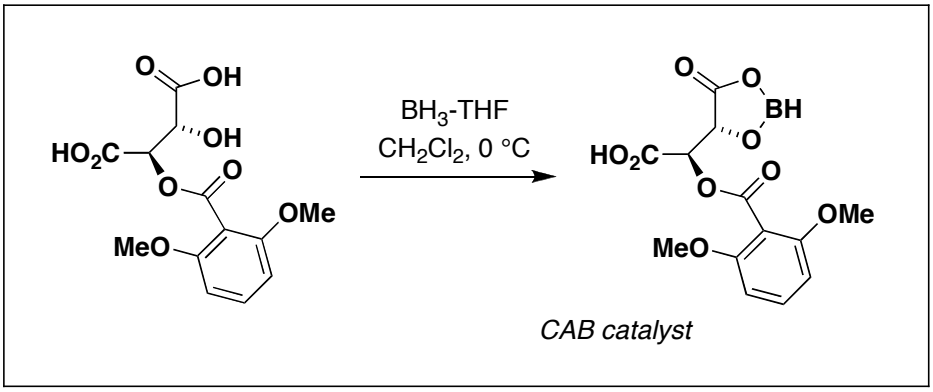
Equipment: Glass-backed silica TLC plates, glass capillary TLC spotters, TLC chambers with filter paper, TLC developing stock solutions (ceric ammonium molybdenate, phosphomolybdic acid, and p-anisaldehyde), small vials, disposable glass pipettes and pipette bulbs, sand bath, 100-mL graduated cylinder, Buchner funnel, 500-mL Erlenmeyer filter flask, round-bottomed flasks (100 and 250 mL), inlet adapter, Celite.

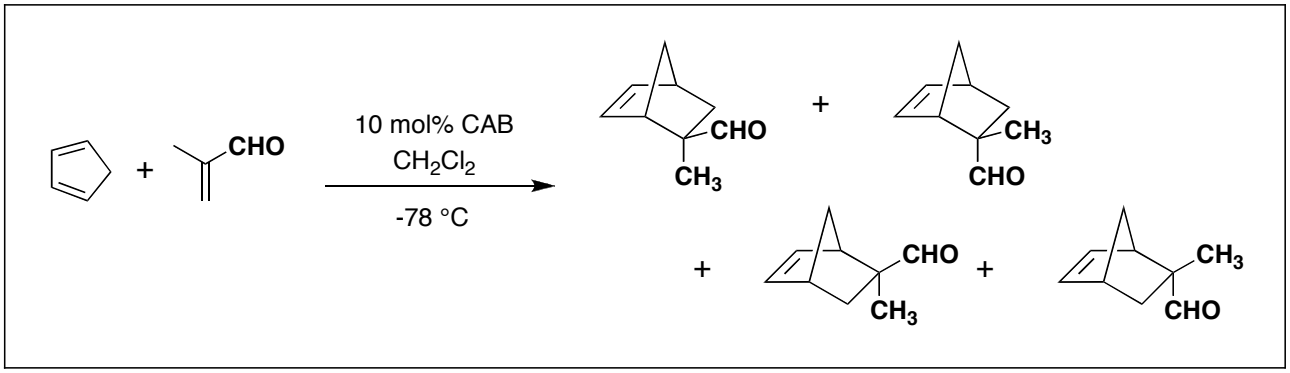
Confirm that the hydrogenolysis is complete by TLC analysis of a sample of the reaction mixture withdrawn via a side neck with your TLC spotter (close off the balloons before opening the neck!). Use 3:1:5 hexane-ether-dichloromethane as eluant for the TLC analysis. Suction filter the reaction mixture through a 1.5-cm pad of Celite in a Buchner funnel into a 250-mL Erlenmeyer filter flask. Before filtering your mixture, run some ethyl acetate through the Celite and then pack it down in the funnel using a stopper or the bottom of a small vial. Be sure to wash the solid thoroughly with three 20-mL portions of ethyl acetate. Do not allow the solid to become dry as it may ignite! Leave the solid damp after the third wash and transfer the material immediately to the special palladium waste container as described in Section VI.

Transfer the filtrate to a tared, 250-mL, round-bottomed flask (using a small amount of dichloromethane to rinse the Erlenmeyer) and concentrate the filtrate by rotary evaporation. Transfer the resulting material to a 100-mL round-bottomed flask using methanol. Concentrate this

solution and record the weight of your crude product. Equip the flask with an inlet adapter and attach it by rubber tubing to a vacuum pump. Dry the crude product for 24-48 h under vacuum (less than 1 Torr) at 80 °C in a sand bath. It is important to thoroughly dry the product as residual organic solvent will result in diminished enantioselectivity in the asymmetric Diels-Alder reaction. Record the weight of the dried product; you should obtain 3.0-3.5 g of the diacid. This can be performed on the "off day"for your group between Day 6 and Day 7 of the experiment, or can be postponed until the beginning of Day 7.

Days 7-11 Catalytic Asymmetric Diels-Alder Reaction





Day 7: Setting Up the Diels-Alder Reaction

Equipment: Disposable glass pipettes and pipette bulbs, 125-mL three-necked round-bottomed flask, reflux condenser, three-way stopcock with inlet adapter, magnetic stirbar, oil bubbler, 2 glass stoppers, 5-mL and two 10-mL syringes with needles, 100-mL graduated cylinder, two cooling baths, methacrolein, cyclopentadiene, dichloromethane, borane-THF solution, acetone, dry ice.

Before carrying out the Diels-Alder reaction you will need to confirm that the hydrogenolysis has proceeded successfully. Measure the melting point of the dried product (in the *Organic Syntheses* paper Yamamoto et al. report mp 184-186 °C) and confirm that no starting material remains by TLC analysis. A proton NMR spectrum should also be obtained for the product but this can be run after the Diels-Alder reaction has been started unless there is some concern about the purity of your

material. NMR data for the hydrogenolysis product can be found in the *Organic Syntheses* paper by Yamamoto et al.

An oven-dried, 125-mL, tapered flask with two 14/20 ground glass necks and a thermometer inlet is equipped with a magnetic stirbar, a rubber septum in the side neck, a low-temperature thermometer, and a reflux condenser in the center neck. The condenser simply functions as a "spacer" and is not connected to a water line. The top of the condenser is fitted with an inlet adapter connected to a three-way stopcock. One branch of the stopcock is connected by tygon tubing to the nitrogen line, and the other branch to an oil bubbler to allow for the monitoring of the nitrogen flow rate. Flush the reaction flask with nitrogen for 8 min by closing the bubbler off at the three-way stopcock and venting the flask with a short syringe needle throught the rubber septum as an outlet for the nitrogen. Figure 3 below shows the setup for the generation of the CAB catalyst and Diels-Alder reaction.

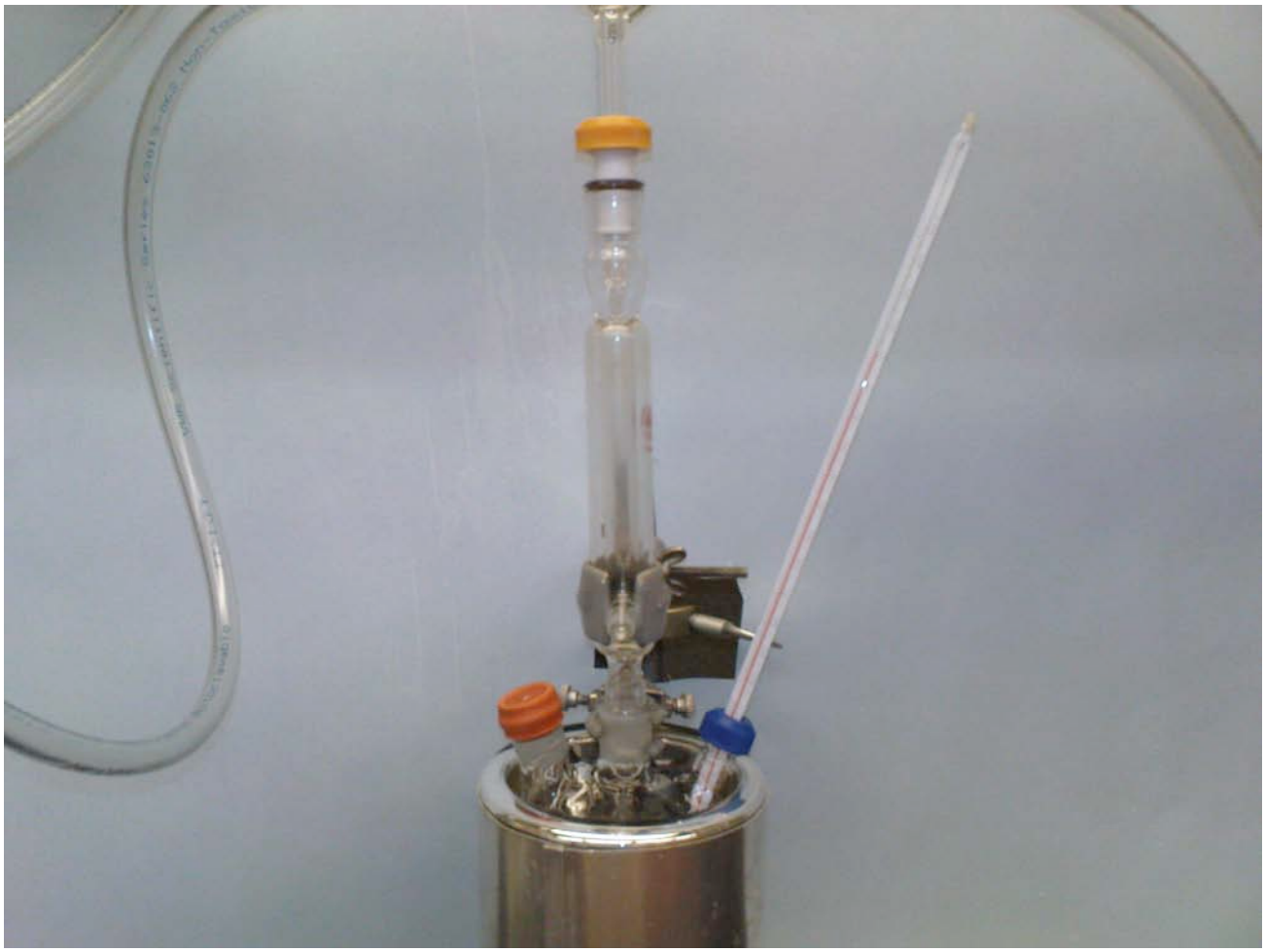


Figure 3. Set up for the in situ generation of the CAB catalyst and Diels-Alder reaction.

With a strong flow of nitrogen continuing, temporarily open the side neck of the flask by removing the septum and charge the flask with mono(2,6-dimethoxybenzoyl)tartaric acid (1.57 g, 5.00 mmol, 0.1 equiv) and 50 mL of dichloromethane (previously dried over 4A molecular sieves). Replace the

septum and cool the reaction flask in an ice-water bath. Once the temperature of the reaction mixture has reached 0-5 °C, add borane-THF solution (1.0 M, 5.0 mL, 5.0 mmol, 0.1 equiv) dropwise via a 10-mL syringe through the rubber septum over a period of ca. 30 min. Vigorous evolution of hydrogen will occur during the addition. The rate of gas evolution can be observed by *temporarily* turning the stopcock so that the nitrogen source is closed off and the stopcock is open only to the flask and the bubbler. After the addition of borane is complete, continue stirring the reaction mixture for 15 min at 0 °C, and then remove the ice-water bath and replace it immediately with a Dewar cooling bath containing a mixture of dry ice-acetone at -78 °C. Once the internal temperature of the reaction mixture has reached -75 to -78 °C, add methacrolein (4.14 mL, 50 mmol, 1.0 equiv) dropwise via a 5-mL syringe over several min. The methacrolein will have previously been distilled earlier in the day for you by the teaching assistants. Immediately after adding the methacrolein, add cyclopentadiene (5 mL, 60 mmol, 1.2 equiv) dropwise via a 10-mL syringe over a period of several min.

The Diels-Alder reaction will be allowed to proceed until the next laboratory period. For best results, it is critical that the reaction mixture remain below -70 °C for as long as possible. Before leaving the reaction to run overnight, add fresh dry ice to your Dewar cooling bath. The teaching assistants will return to the lab later that evening to add additional dry ice to your bath so that the total time below -70 °C will be at least 5 h.

Day 8: Workup of the Diels-Alder Reaction

Equipment: Disposable glass pipettes and pipette bulbs, glass-backed silica TLC plates, glass capillary TLC spotters, TLC chambers with filter paper, TLC developing stock solutions, small vials, 100-mL graduated cylinder, 1000-mL separatory funnel with glass stopper, 1-L Erlenmeyer, two 500-mL Erlenmeyers, 500-mL round-bottomed flask, 25-mL round-bottomed flask, filter funnel, fluted filter paper, NMR tube, ethyl acetate, hexanes, dichloromethane, saturated sodium bicarbonate solution, saturated NaCl solution, anhydrous magnesium sulfate, $CDCl_3$.

Confirm that the Diels-Alder reaction has taken place by performing TLC analysis of a sample of the reaction mixture withdrawn via a side neck with your TLC spotter. Use 10% ethyl acetate-hexanes for elution and UV and PMA for visualization. Pour the reaction mixture into a 1-L separatory funnel containing 150 mL of ice-cold saturated sodium bicarbonate solution. Be careful to release any gas that builds up during the extraction by venting the funnel after shaking for only a brief period at a time. Separate the layers and back-extract the aqueous phase with three 100-mL portions of hexane. The combined organic phases are then washed with two 200-mL portions of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered into a 500-mL round-bottomed flask, and concentrated by rotary evaporation at room temperature. Dissolve the residue in dichloromethane and transfer the solution to a tared 25-mL round-bottomed flask. Concentrate the solution and record the weight of your crude Diels-Alder product. Obtain a proton NMR spectrum of this material in $CDCl_3$. Determine the ratio of endo and exo Diels-Alder adducts by integration of the NMR spectrum. Yamamoto has reported NMR data for the Diels-Alder adducts (prepared using a different catalyst system) in Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920:

exo-2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (d, J = 12.0 Hz, 1H), 1.01 (s, 3H), 1.38-1.40 (m, 2H), 2.25 (dd, J = 3.8, 12.0 Hz, 1H), 2.82 (br s, 1H), 2.90 (br s, 1H), 6.11 (dd, J = 3.0, 5.7 Hz, 1H), 6.30 (dd, J = 3.0, 5.7 Hz, 1H), 9.69 (s, 1H).

endo-2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: ^{1}H NMR ($CDCl_3$, 300 MHz) formyl resonance is observed at 9.40 (s, 1H).

Day 9: Purification of the Diels-Alder Reaction Product

Equipment: Glass-backed silica TLC plates, glass capillary TLC spotters, TLC chambers with filter paper, TLC developing stock solutions (ceric ammonium molybdenate, phosphomolybdic acid, and p-anisaldehyde), small vials, disposable glass pipettes and pipette bulbs, chromatography column (xx cm length, xx mm width) with adapter and tubing for top of column for applying pressure, funnel, 100-mL graduated cylinder, 230-400 mesh silica gel 60, sand, 13x100-mm test tubes, test tube rack, round-bottomed flasks (25, 100, and 500 mL), NMR tube, hexanes, ethyl acetate, dichloromethane, and $CDCl_3$.

A 500-mg sample of your crude product will be purified by column chromatography on silica gel. The main goal of this chromatographic purification is to separate the endo and exo cycloadducts. This is a very challenging separation, but can be achieved by using a high ratio of silica gel to compound. In order to achieve optimal resolution, it is necessary to apply your compound to the column deposited on a small amount of silica gel. This technique allows you to begin the column with your compound in a much narrower band of silica gel than would be possible if the compound was applied to the column as a neat liquid or in solution.

Prepare a column containing 100 g of silica gel using hexanes as solvent and run the solvent level down so that it is just very slightly below the level of the top of the silica gel (do not add sand at the top of the column yet). Make sure that the inside of the glass column above the level of the silica gel is dry of solvent. If necessary, dry the glass with a stream of nitrogen introduced via a dispo pipette attached to the end of tygon tubing hooked up to your nitrogen line. Meanwhile, weigh out 0.500 g of your crude Diels-Alder product in a tared 100-mL flask and dissolve it in 20 mL of dichloromethane. Add 1 g of silica gel to the flask and concentrate the mixture at room temperature on the rotary evaporator. Make sure that the rotary trap is clean before you begin in case the silica gel "bumps" and you have to recover it from the trap. Evaporation of the dichloromethane in this fashion will leave you with silica gel on which your compound has been adsorbed. The silica gel should be dry and free flowing. Add this material to the top of the silica gel column, tapping the glass column gently to help dislodge any silica gel that adheres to the glass above the level of the silica gel column. If necessary, wash adhering silica gel off the walls using a minimum amount of hexane. Add 10 mL of dichloromethane to the 100-mL round bottomed flask followed by 0.5 g of additional silica gel. Concentrate this mixture and add the resulting dry silica gel to the top of your column. This serves as a "wash" to ensure that all of the compound originally in the flask is deposited on silica gel and added to the column. Add a thin layer of sand to the top of the silica gel column and then carefully add hexanes and begin elution.

Use a gradient of 1-5% ethyl acetate-hexanes to elute your compounds from the column. Be sure to save a small sample of the crude reaction product to use as a TLC reference sample; this should be spotted in lane 1 on each plate as you monitor the fractions obtained in your chromatography. Collect 10-mL fractions in test tubes and identify the fractions containing your desired exo product by TLC analysis (remember that it is usually not necessary to perform TLC analysis of every fraction). Combine the desired fractions in a 500-mL or 1-L flask and concentrate by rotary evaporation to remove all of the solvent. Transfer the product to a tared 25-mL round-bottomed flask using dichloromethane and again remove all of the solvent by rotary evaporation. Record the weight of your purified exo Diels-Alder product and record the results of all TLC analyses and the details of your chromatographic purification following the guidelines described in Module 6.

If "mixed fractions" containing your desired product and impurities are obtained, these fractions should be combined, concentrated, weighed, and analyzed by TLC and proton NMR spectroscopy. Consult with your teaching assistant to decide whether a second column should be run on this material to obtain additional pure compound.

To prevent decomposition of the Diels-Alder product, it is necessary to store it in the cold, in solution, and in the absence of air since like most aldehydes, this compound is sensitive to autoxidation. Dissolve your product in dichloromethane and degass the solution by bubbling nitrogen through the solution for 5 minutes. The nitrogen should be introduced via a dispo pipette attached to rubber tubing from the nitrogen source. Seal the flask and store in the refrigerator. During the course of analyses try to keep the flask closed whenever possible and minimize the time the "neat" compound is exposed to air.

Days 10-11: Analysis of the Diels-Alder Reaction Product

Mohrig, Hammond, & Schatz: Chapter 16 (Gas-Liquid Chromatography)

Equipment: NMR tube, $CDCl_3$.

Obtain a proton NMR spectrum of your purified Diels-Alder product, and also an infrared spectrum. Optional: if time permits, you may wish to obtain a carbon NMR spectrum of the compound as well. After confirming that your material is pure exo isomer, measure the enantiomeric ratio of cycloadducts using gas-liquid chromatography on a chiral GC column. Instructions for the use of the chiral GC will be provided separately prior to Day 10 of the experiment.

VI. Special Safety Considerations

This section provides some specific safety information for the Module 7 experiment. In particular, this section discusses chemicals that you may not have encountered previously in the undergraduate laboratory. Note that this summary is only intended to supplement the safety training provided at the beginning of the URIECA lab courses and does not replace the general practices described in that training which should be followed at all times. For example, students should practice "zero contact" with chemicals by always wearing gloves while working with all organic chemicals so as to avoid all contact with the skin.

General: Working with Flammable Solvents

Several solvents employed in Module 7 are highly flammable and care should be taken to avoid spills. Diethyl ether (flash point -45 °C), acetone (flash point -18 °C), ethyl acetate (flash point -4 °C), and hexane (flash point -22 °C) are of particular concern. Be sure that you are aware of the location of "solvent pillows" in the laboratory so that in the event of a spill you are prepared to immediately absorb the spilled solvent before a highly flammable cloud of solvent vapor can form.

Day 1

Triethylamine is flammable (flash point -9 °C) and relatively volatile (bp 89 °C). With an LD50 (oral, rat) of 460 mg/kg it is classified as "moderately toxic". Triethylamine should be handled in the hood so as to avoid inhalation of its vapors and all contact with the skin should be avoided by wearing impermeable gloves.

Calcium hydride reacts vigorously with water with the formation of hydrogen gas which is highly flammable and in mixture with air can even be explosive. Do not handle calcium hydride in areas where there is any quantity of water (e.g, spill) present. Avoid all skin contact with calcium hydride since it will react with moisture to form highly basic and corrosive calcium hydroxide. In the event of a spill, dilute the calcium hydride with an inert solid such as dry sand and transfer to an empty waste container.

The following procedure should be employed for the disposal of the "pot residue" left after the distillation of triethylamine. Working in the fume hood, carefully dilute the residual slurry of triethylamine and calcium hydride with acetone until the round-bottomed flask is approximately half full. Add the acetone a few drops at a time at first to be sure that no vigorous reaction occurs. Next, add water dropwise, allowing the mixture to stir (magnetic stirring) until no significant evolution of hydrogen is evident. Continue adding water until no further reaction is observed. Pour the contents of the flask into a large beaker and add additional water (carefully at first) to confirm that no "active" calcium hydride remains. Transfer the resulting mixture to the waste container designated for calcium hydride waste.

Day 2

2,6-Dimethoxybenzoyl chloride will hydrolyze upon exposure to moisture in the air with the formation of highly corrosive HCl. Be careful to avoid all skin contact with this acyl chloride and handle it only in a fume hood.

4-Dimethylaminopyridine is toxic and can cause burns and should therefore be handled in a fume hood and all skin contact should be avoided by wearing impermeable gloves.

Day 4

Silica gel dust can be irritating to the respiratory tract and any manipulations that have the potential to create dust in the air should be carried out in a fume hood.

Day 5

Hydrogen is not toxic and the main hazard associated with its use is due to its flammability. Hydrogen is a highly flammable gas which forms explosive mixtures with air over a wide range of concentrations (from 4 to 75% by volume). The ignition energy for hydrogen is very low, about 1/10 that required for gasoline! Pure hydrogen burns with a nearly invisible bluish flame and the temperature for hydrogen burning in air is extremely high (3713 °F)

Palladium on carbon presents a fire hazard. The dry catalyst should never be added to an organic solvent in the presence of air; instead, the organic solvent should be carefully added to the catalyst which must be under an inert atmosphere of argon or nitrogen. Palladium with adsorbed hydrogen is particularly hazardous (see Day 6 for precautions).

Day 6

Care must be taken while filtering the finely divided **palladium on carbon** catalyst at the end of the hydrogenolysis reaction since it is saturated with adsorbed hydrogen and readily may ignite on exposure to air. Be sure that the solid remains damp while filtering it and do not allow it to become dry at any time. Transfer the damp material with the aid of water to the special waste container designated for palladium catalyst waste.

Day 7

Borane-THF solution should be regarded as toxic and should be handled in a fume hood and all skin contact should be avoided.

Methacrolein poses a flammability hazard (flash point -15 °C) and is relatively volatile (bp 68 °C). Methacrolein should be handled as if it is highly toxic by analogy to acrolein which has an LD50 (oral, rat) of only 46 mg/kg. Methacrolein must be handled exclusively in a fume hood. Strict precautions must be taken to avoid all skin contact and inhalation of this compound.

Cyclopentadiene is quite volatile (bp 42 °C) and is flammable. Avoid skin contact and inhalation by working in a fume hood and wearing appropriate impermeable gloves.

VII. Final Report

A final written report must be submitted by May 15 (the last day of classes). Unfortunately, MIT end-of-term regulations require that no assignment can be due later than that day. It should be possible for you to complete most of your report prior to the last week to avoid a last-minute crunch. The final report must include the following sections.

I. **Introduction** – a concise outline of the aims of the experiment, a description of the reactions (use equations), and references to the relevant literature (all references must follow the style of the *Journal of the American Chemical Society*; for instructions, see *The ACS Style Guide* or refer to recent articles in *JACS*). This section should be 1-2 pages (single-spaced) in length.

2. **Experimental Procedure** – prepare a detailed experimental procedure for your reactions. Follow the style guidelines currently used in *Organic Syntheses* which are described in detail in the *Organic Syntheses* "Instructions to Authors". A pdf file of this document can be downloaded from the "Info for Authors" section of the *Organic Syntheses* website http://www.orgsyn.org/.

3. **Spectroscopic Characterization** – present the proton NMR data (and optional carbon, if run), and IR data for each of your products in table form. For the NMR data, for each resonance provide the chemical shift, integration, multiplicity, and coupling constant. Show the assignment of all resonances in the spectrum.

4. **Discussion** – discuss your results including any problems encountered. The Discussion Section should also include a 2-3 page "mini-review" of an alternative strategy for asymmetric Diels-Alder reactions. Detailed instructions for this part of the report will be provided during a 5.37 lecture.

5. **Appendices** – should include your waste inventory sheet and the actual copies of all spectra.

Massachusetts Institute of Technology
Department of Chemistry

Chemistry 5.37

Module 7: Introduction to Organic Synthesis

Waste Inventory Sheet

Description (Content)	Approximate amount	Disposition

Suggestions For Waste Reduction

Name:_____ **Lab Group**_____

T.A. Initials:_____