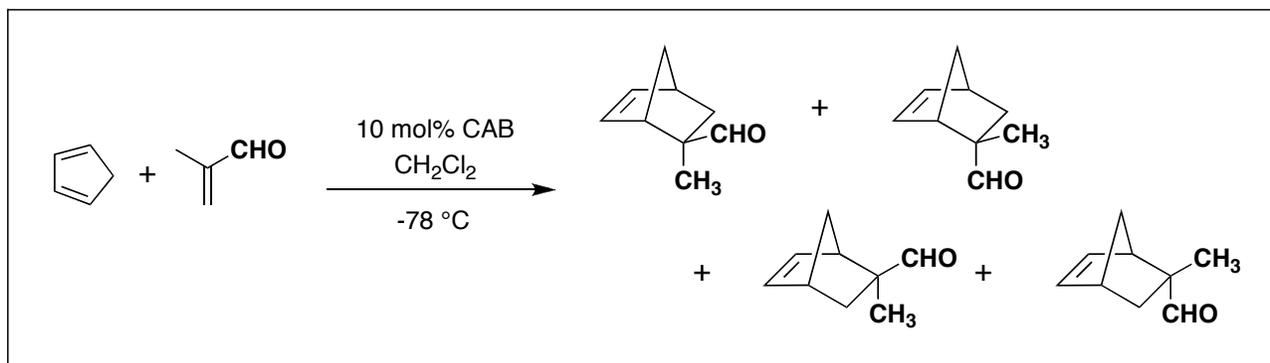
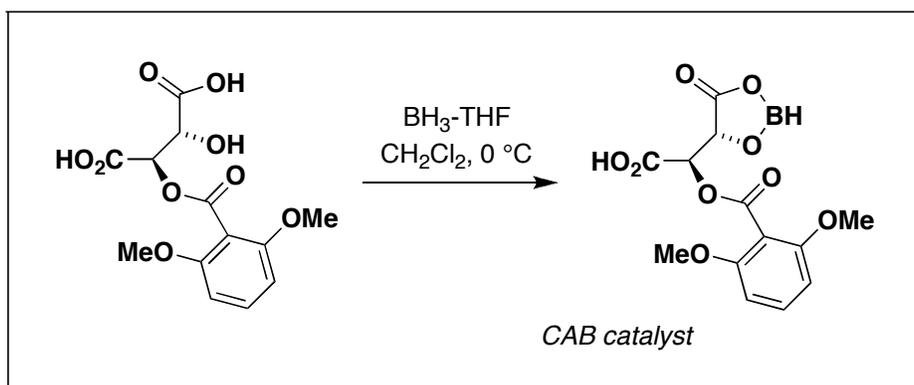


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Days 7-11 Catalytic Asymmetric Diels-Alder Reaction



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 through 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: ^1H 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: ^1H 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, CDCl₃.

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.