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Organic Chemistry Laboratory Experiments

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The asymmetric aldol reaction

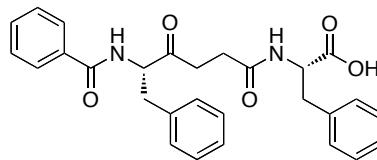
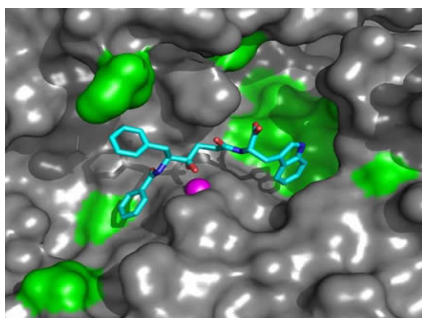
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The Asymmetric Aldol Reaction

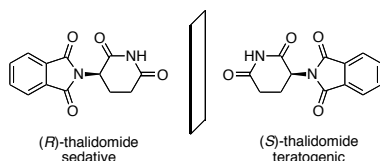
Introduction:

The controlled creation of new stereogenic centers is of paramount importance in organic synthesis. Many small molecule pharmaceuticals in use today are not simply linear or planar, but have a unique three-dimensional arrangement of functional groups that gives them a shape that is critical to their activity. It is this stereochemical display that forms the basis for drug-target interactions. Hydrogen bonding, dipole-dipole interactions, van der Waals forces, and electrostatic attraction between a drug and its enzyme or receptor target occur because certain groups are placed into close proximity with one another in space in a “snug fit”. Using x-ray crystallography, chemists are now able to even “see” the interactions that take place between a drug and its target and make modifications that enhance drug efficacy, as is the case with the following angiotensin-converting enzyme (ACE) inhibitor. In this illustration, the amino acids highlighted in green are those on the enzyme which make significant contact with the inhibitor, ensuring the proper binding.



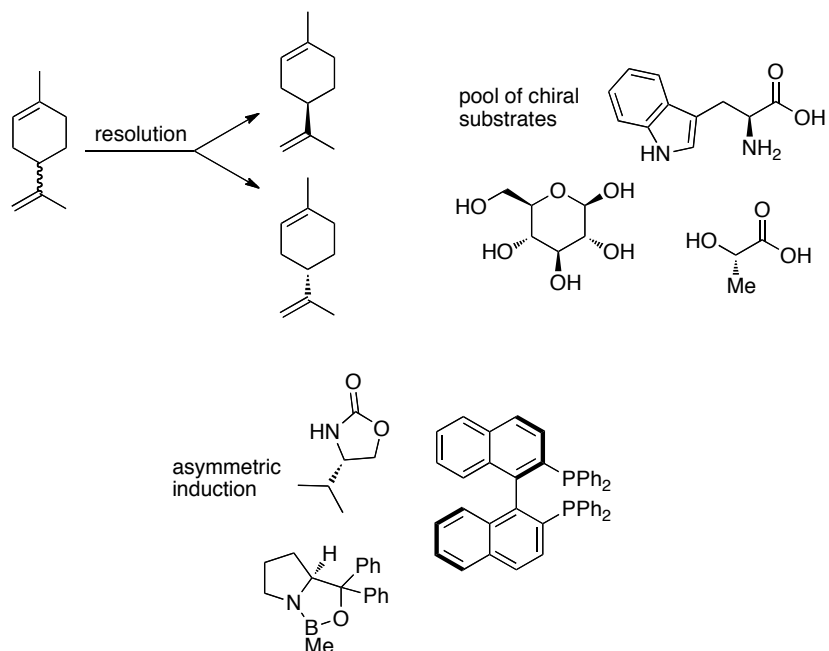
<http://www.iidmm.uct.ac.za/sturrock/images/ace-inhibitor>

In drug discovery, synthesizing a new chemical entity with the correct stereochemistry is important because biomolecules like proteins and nucleic acids have evolved with a certain “handedness.” For example, most of the amino acids are of the *S* configuration. This unique spatial arrangement is what makes the events of life possible. All too often, it can also be the reason for disease, drug resistance, speciation, and other events we wish to inhibit. In the context of the treatment of disease, binding of a drug to an active enzyme site or to a receptor requires a specific orientation. That is to say, one stereoisomer will likely be mismatched to the target and bind poorly while another stereoisomer will bind tightly and elicit a response. This interplay, if not optimized, can have strikingly fatal consequences, as was the case in the 1950’s with the two enantiomers of thalidomide. Thalidomide was sold as a racemic mixture in several countries (though never approved by the FDA in the United States, it was in clinical trials) as a sedative to relieve morning sickness in the late 1950’s. A tragic consequence was the teratogenicity (causing birth defects) of the otherwise “inactive” (*S*)-enantiomer. Today, thalidomide is being reinvestigated as a possible drug for use against leprosy and multiple myeloma.

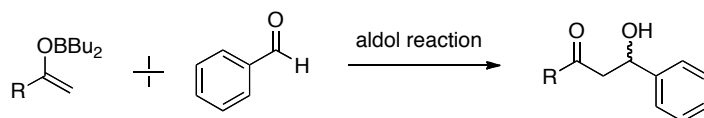


Today, pharmaceutical candidates are typically prepared in stereochemically-pure form before they are marketed. To market mixtures, each component must be purified and independently demonstrated to have no toxicological or other side effects, a prohibitively expensive process. To help realize this goal, organic chemists have tried to mimic Nature in constructing asymmetric carbon centers with exclusive selectivity. Concurrently, methods in purification have also greatly advanced to eliminate contamination from unwanted stereoisomers. While Nature is far better at stereoselective synthesis, a feature that has been perfected over millions of years of evolution, only recently have organic chemists been able to use the tools of synthesis to create stereogenic centers *de novo*. The field of asymmetric synthesis is a division of organic chemistry concerned with the construction of carbon-based stereogenic (chiral) centers, specifically those that are enantio- and diastereoenriched.

There are three ways to obtain stereochemically-pure material, each with their own advantages and pitfalls: (1) resolution of stereoisomers, (2) choosing from a collection of readily available, enantiomerically pure chiral substrates (the so-called “pool of chiral substrates”), and (3) by performing asymmetric induction on chirality-inducing reactions through use of a chiral auxiliary, reagent, or catalyst. Resolution of a racemic mixture (see figure below) can be performed using chiral chromatography or, when possible, by recrystallization as a diastereomeric salt. This method of obtaining enantiopure material is advantageous when both isomers are desired, but only results in a maximum of 50% yield when only a single enantiomer is the target (as is usually the case) and is therefore inefficient, wasteful, and seldom used on large scales. Choosing from the pool of chiral substrates (see figure below) is advantageous since many substances found in Nature are already themselves chiral. However, since Nature has evolved with “handedness,” the availability of a specific isomer may be limited and the stereoselective construction of contiguous stereocenters can be difficult. Asymmetric induction has received considerable attention since it allows one to induce a desired stereochemical outcome using cheap, readily available chiral material. Attachment of a temporary chiral auxiliary, use of a chiral reagent, or performing a catalytic reaction with a chirality controlling agent are all forms of asymmetric induction (see figure below). In this experiment, we will perform an asymmetric induction using a chiral auxiliary.

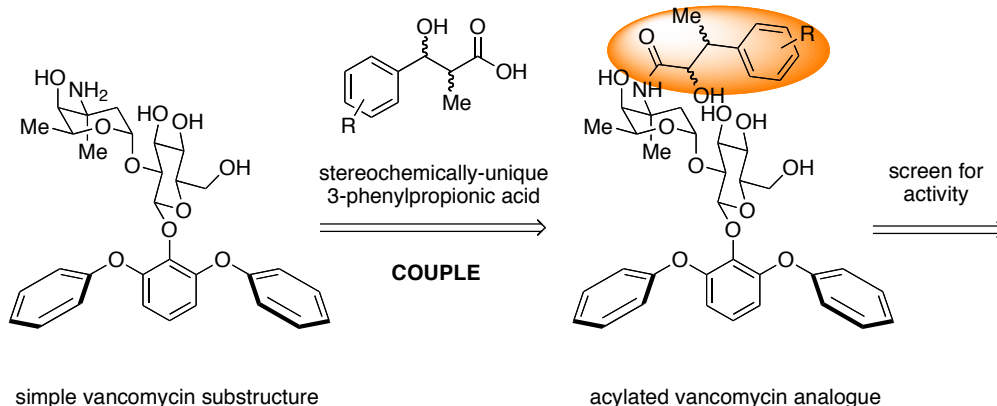
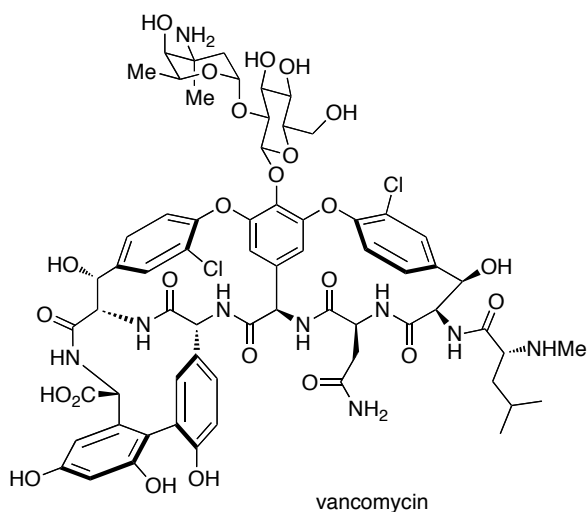


Temporary use of a chiral auxiliary is a rather mature field in asymmetric synthesis and often the stereochemical outcome of these reactions follows a series of predictable rules. Once a stereocenter has been created, the auxiliary can be easily removed, providing a convenient method to generate stereogenic centers. Pioneering work in this area was performed by David Evans at Harvard University nearly 30 years ago. Evans' oxazolidinones, as they are called, are chiral auxiliaries that can be easily prepared from readily available, homochiral amino acid starting materials, can be attached to organic substrates under mild conditions, and can be removed quickly after the reaction is complete. Moreover, these auxiliaries have been shown to be compatible (inert) to the desired transformations of other functional groups. Since the chiral auxiliaries contain a stereocenter, the products they generate upon asymmetric induction are diastereomers, and thus can be resolved by standard column chromatographic techniques. In this experiment, we will explore the asymmetric induction of an Evans' auxiliary in the reaction between a boron enolate and a substituted benzaldehyde, also known as the aldol reaction (racemic version below).



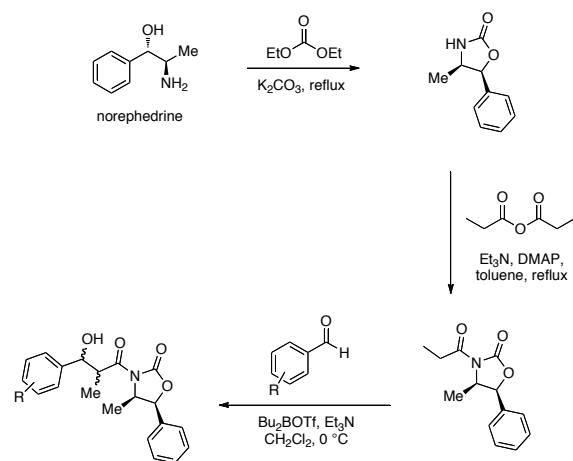
Consider the following scenario for this experiment:

You are a graduate student who is trying to modify chemically the drug vancomycin – an antibiotic of last resort – by acylating an aminosugar residue important to its activity. You want to create a library of stereochemically-unique 3-phenylpropionic acids that can be attached to a simple vancomycin substructure so that it can be collectively screened for antibiotic activity. You have settled on α -methyl- β -hydroxy 3-phenylpropionic acids as your acyl course because of their ease of synthesis.



Upon researching the best methods to synthesize these substrates, you decide to perform an asymmetric aldol reaction using an Evans chiral auxiliary, but since you desire single enantiomers, you are curious whether or not the electronic and steric environment of the reacting aldehyde plays a role in the observed aldol stereoselectivity.

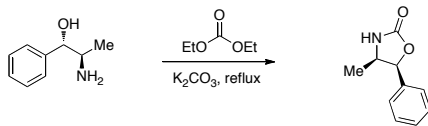
In this experiment, you will perform a multi-step synthesis to answer this question. A commercially-available enantioenriched amino alcohol will be used to construct a chiral auxiliary and you will be given one of several substituted benzaldehydes for the asymmetric aldol reaction with a boron enolate. Your task will be to carry out the asymmetric aldol, then determine the stereochemistry of your aldol product and use this information to form conclusions about the role of the reacting benzaldehyde in the observed diastereoselectivity.



References:

1. *Biochemistry* **2008**, *47*, 5942.
2. <http://en.wikipedia.org/wiki/Thalidomide>
3. *Chem. Asian J.* **2006**, *1*, 445.
4. *Aldrichimica Acta* **1982**, *15*, 23.

Week 1: Synthesis of a Chiral Auxiliary



Equipment:

Microscale glassware kit
Vacuum tubing
HPLC vials
NMR tubes and caps
TLC plates (small)
White-capped vials
1 mL syringes and needles
20 mL syringes and needles

Chemicals:

(1S,2R)-(+)-Norephedrine – provided as 1 g samples in a vial
Diethyl carbonate
Potassium carbonate
Methylene chloride – 200 mL
Anhydrous sodium sulfate
Hexanes:Ethyl acetate (1:2) – 500 mL
Hexanes – 100 mL
Ethyl acetate – 100 mL
Deionized water
Brine
Methanol
CDCl₃

Procedure: adapted from *Org. Synth.* **1990**, 68, 77.

Synthesis: Transfer 1 g of (1S,2R)-(+)-norephedrine into a 5 mL conical vial containing a spin vane. Use any remaining solid as your TLC standard. Add 0.1 equivalents of potassium carbonate followed by 2.0 equivalents of diethyl carbonate. Place a Hickman head on the conical flask followed by a water condenser. Heat the reaction mixture to reflux (internal temperature of collecting vapor should not exceed 85 °C). Ethanol will condense in the Hickman head. Remove ethanol occasionally and measure its weight so that you know when your reaction is complete. Pay attention to the volume in the conical vial and do NOT let it boil dry (add more diethyl carbonate if necessary). Monitor your reaction by TLC and after ~1 hour (or when ethanol evolution ceases and your TLC shows that the reaction is complete), allow the reaction mixture to cool to room temperature. Develop your TLC in 100% ethyl acetate as eluent.

Workup: Dilute the resulting light yellow product mixture with ~2 mL methylene chloride and transfer to a Falcon tube. Rinse the vial with ~1 mL methylene chloride and wash the organic layer with an equal amount of brine (centrifuge if needed). Dry the

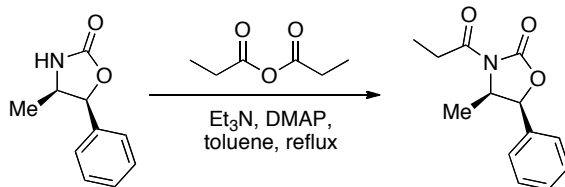
organic phase with sodium sulfate and filter into a clean, tared white vial. Concentrate the solution under vacuum on a rotary evaporator. If time permits, the product can be recrystallized from hot 1:2 hexanes–ethyl acetate and collected by vacuum filtration.

Analysis: Obtain a yield of your chiral auxiliary, in addition to ^1H NMR and IR spectra, and UPLC/MS analysis. Save your product in a labeled, white-capped vial at low temperature until the next laboratory session.

Pre-Lab Questions:

1. Draw a mechanism for the formation of your chiral auxiliary.
2. Propose a synthesis of norephedrine from the amino acid alanine.
3. Why is it necessary to remove ethanol from the Hickman head during the reaction?
4. What is the role of potassium carbonate in the reaction?
5. Why is it necessary to heat the stir plate higher than 85 °C to distill the ethanol into the Hickman head?
6. At what temperature would you expect ethanol to collect? Approximately how much ethanol do you expect to collect?
7. Do you expect your product to be more or less polar than your starting material?

Week 2: Preparation of the Aldol Substrate



Equipment:

Microscale glassware kit
Vacuum tubing
HPLC vials
NMR tubes and caps
TLC plates (small)
White-capped vials
1 mL syringes and needles
20 mL syringes and needles
Thermowells

Chemicals:

Propionic anhydride
N,N-Dimethylaminopyridine
Triethylamine
Toluene – 100 mL
Diethyl ether – 200 mL
2 N HCl – 200 mL
2 N NaOH – 200 mL
Brine (saturated sodium chloride) – 200 mL
Anhydrous sodium sulfate
Hexanes:Ethyl acetate (2:1) – 100 mL
Hexanes – 100 mL
Ethyl acetate – 100 mL
Deionized water
Methanol
 CDCl_3

Procedure: adapted from *J. Chem. Ed.* **2008**, 85, 695 and *Synthesis*, **1996**, 1283.

Synthesis: Pre-heat your Thermowell to 115 °C. Transfer your chiral auxiliary from Week 1 into a round bottom flask and dissolve in 2.5 mL dry toluene (note the concentration of this solution). Add a stir bar to your flask and use any remaining residual chiral auxiliary as your TLC standard. Add DMAP (0.1 equiv.) and triethylamine (1.6 equiv.) to your flask, then add 2.0 equiv. propionic anhydride to your flask dropwise over 2 min. Heat the solution to reflux (115 °C) and monitor by TLC. After 30 min. of reflux, allow the reaction mixture to cool to reaction mixture to room temperature. Add 1.0 mL

water to the mixture and continue heating for 10 min. Allow the mixture to cool to room temperature and monitor by TLC.

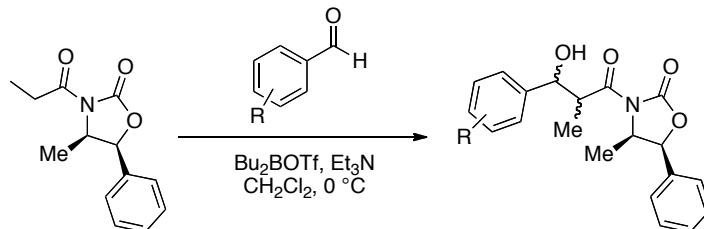
Workup: Transfer the product mixture to a Falcon tube. Add ~3 mL diethyl ether and separate the layers. Wash the organic phase sequentially with ~3 mL of each of the following: 2 N HCl (aq.), 2 N NaOH (aq.), and brine. Transfer the organic phase to a flask and dry over sodium sulfate. Filter into a tared, labeled, white-capped vial and concentrate under reduced pressure on a rotary evaporator.

Analysis: Obtain a yield of your aldol substrate, in addition to a ^1H NMR, IR, and UPLC/MS. Save your product in a labeled, capped vial at low temperature until the next laboratory session.

Pre-Lab Questions:

1. Why is it important to add propionic anhydride dropwise?
2. Why is it necessary to add water at the end of the reaction and continue to reflux for 10 min.?
3. What role does DMAP play in this reaction?
4. Why is it important to wash the organic phase with both acid and base during workup?
5. What three factors control the rate of distillation of your solvent in a rotary evaporator?
6. Draw a mechanism for the formation of the aldol substrate.

Week 3: The Asymmetric Aldol Reaction



Equipment:

Microscale glassware kit
Vacuum tubing
HPLC vials
NMR tubes and caps
TLC plates (small)
White-capped vials
1 mL syringes and needles
20 mL syringes and needles
5 mL syringes and needles
2 Balloons
Long needle

Chemicals:

Various benzaldehydes (H, 4-Br, 4-Cl, 4-OMe, 3-NO₂)
Dibutylboryl triflate (1.0 M in CH₂Cl₂)
Triethylamine
Ammonium chloride
0.01 M HCl – 200 mL
30% Aqueous hydrogen peroxide solution
Anhydrous methylene chloride – 200 mL
Anhydrous sodium sulfate
Hexanes – 1000 mL
Ethyl acetate – 1000 mL
Deionized water
Methylene chloride – 200 mL
Methanol
CDCl₃

Procedure: adapted from *J. Chem. Ed.* **2008**, 85, 695, *J. Chem. Ed.* **2006**, 83, 1333, and *Acc. Chem. Res.*, **2004**, 37, 387.

Synthesis: Dissolve your aldol substrate from Week 2 in 2.0 mL dry methylene chloride (note the concentration of this solution). Transfer to a 10 mL round bottom flask containing a stir bar. Use any remaining substrate as your TLC standard. Cap and cool the solution to 0 °C. Add 1.3 equiv. dibutylboryl triflate solution (1.0 M in methylene chloride) dropwise at 0 °C via syringe. Note any color change, then add 3.7 equiv.

triethylamine after 5 min. After stirring for 15 min., add 1.3 equiv. of your assigned substituted benzaldehyde. Stir for 5 minutes at 0 °C and then allow the reaction mixture to warm to rt and heat gently to 40 °C for 1 hour. Monitor the reaction by TLC (3:1 EtOAc:hexanes).

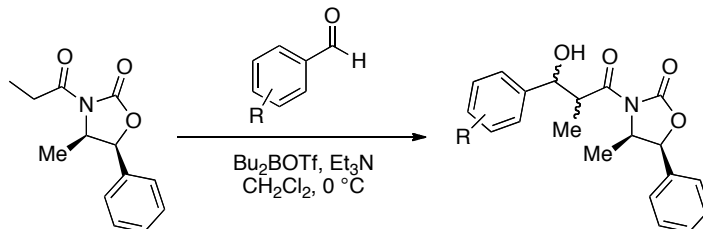
Workup: Allow the reaction mixture to cool to room temperature, then add 5 mL sat. aq. ammonium chloride solution carefully. Transfer the mixture to a Falcon tube, rinse the flask with 3 mL methylene chloride, and wash with 3 mL of 0.01 M HCl (aq.). Separate the layers and dry the organic phase with sodium sulfate. Filter the solution into a tared, labeled white-capped vial and concentrate under reduced pressure.

Analysis: Save your aldol product in a labeled, capped vial at low temperature (refrigerator) until the next laboratory session.

Pre-Lab Questions:

1. Look up the MSDS for hydrogen peroxide. What safety precautions should be taken when using this chemical?
2. Why is it important to maintain the temperature of this reaction at 0 °C throughout? What would you expect if the reaction was run at room temperature?
3. Dibutylboryl triflate is a strong Lewis Acid. What makes it so strong? What does this tell you about why it comes as a solution in methylene chloride?
4. Why is it necessary to stir the solution in triethylamine before adding your aldehyde?
5. What is the role of ammonium chloride in this reaction?
6. Draw a mechanism for the formation of the aldol product.

Week 4: Purification and Analysis



Equipment:

Microscale glassware kit
Teledyne Isco RediSepR_f 12 gram Silica Flash Columns
HPLC vials
NMR tubes and caps
TLC plates (small)
White-capped vials
1 mL syringes and needles
20 mL syringes and needles

Chemicals:

Hexanes – 2 L
Ethyl acetate – 2 L
Methanol
 CDCl_3

Procedure: adapted from *J. Chem. Ed.* **2008**, 85, 695, *J. Chem. Ed.* **2006**, 83, 1333, and *Acc. Chem. Res.*, **2004**, 37, 387.

Purification: Prepare a pre-packed flash column by eluting with hexanes using a 50 mL syringe to equilibrate the column. Dissolve your crude aldol product in 0.5 mL methylene chloride and load onto the column with a 1 mL syringe. Be sure to save a small sample as a TLC standard. Rinse the vial with methylene chloride and load onto the column. Via 50 mL syringe, elute with a dead volume of 20 mL hexanes first followed by increasing amounts of ethyl acetate in 20 mL portions until the ratio reaches 75% hexanes–ethyl acetate (3–4 steps). Collect your eluent in labeled test tubes. Determine the contents of each fraction by TLC analysis. Combine the appropriate fractions in a tared, labeled vial and concentrate under vacuum.

Analysis: Obtain a yield of your aldol product, in addition to ^1H NMR and IR spectra, and UPLC/MS analysis. If time permits, submit your sample for a COSY and/or NOESY experiment overnight. Determine the diastereomeric ratio of your products before the next Pre-Lab Lecture, where you will share your data with your classmates.

Pre-Lab Questions:

1. When performing column chromatography, why does the column need to be equilibrated before loading a sample?

2. There are two main types of elution: isocratic and gradient. What is the difference between these two techniques and which one will you use in your experiment?
3. How will you know which fractions contain the same compound?
4. Will diastereomers have the same or different R_f 's on a TLC plate? What about enantiomers?
5. Do you expect diastereomers to have the same ^1H NMR spectrum? How can you distinguish between them?

Full Lab Report Additional Questions: (not necessarily in this order)

1. Is the asymmetric aldol reaction stereospecific or stereoselective? How many possible products could form in this reaction? Draw their structures.
2. What is the diastereomeric ratio of your aldol reaction? What is the structure of the major isomer? Minor isomer? What spectroscopic techniques allowed you to make this assignment?
3. Provide a mechanistic rationale for your observed diastereoselectivity (a perspective drawing may be helpful). What controls the observed relative stereochemistry? What controls the observed absolute stereochemistry?
4. How would you increase the stereoselectivity of your aldol reaction? How would you assign the absolute stereochemistry of the aldol product? What if the chiral auxiliary was subsequently removed?
5. What role does the electronic nature of substituted benzaldehydes play in the observed diastereoselectivity? What is the role of the steric environment of these benzaldehydes on the observed diastereoselectivity?