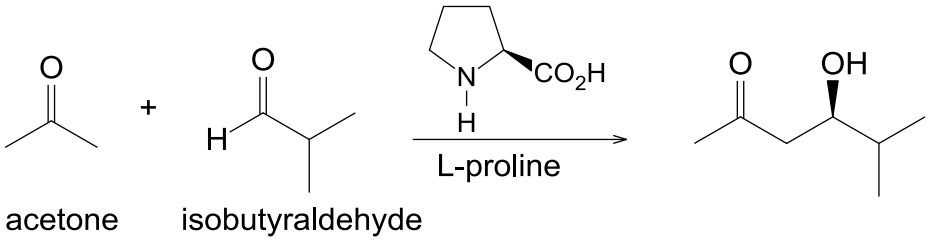
CHM 320 – Laboratory Projects
Spring, 2020

I. A Green Enantioselective Aldol Condensation for the Undergraduate Laboratory.

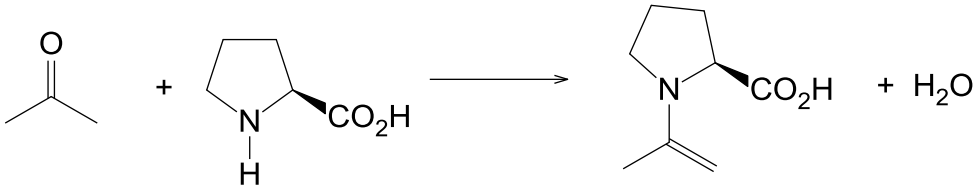
Bennett, G. D. *J. Chem. Educ.* **2006**, *83*, 1871-1872.

The aldol condensation between an aldehyde and a ketone is one of the most common carbon-carbon bond forming reactions known. These reactions usually create an asymmetric (chiral) center in racemic form. Typically these reactions are catalyzed by a base such as KOH or NaOH. However, when the base used is chiral (such as L-proline), it can mimic an aldolase I enzyme and will allow for the formation of one enantiomer in preference to the other (this is known as an *enantioselective* reaction). The reaction between acetone and isobutyraldehyde using L-proline as a catalyst is shown in **Scheme 1**.



Scheme 1: Crossed aldol condensation to form (*R*)-4-hydroxy-5-methyl-2-hexanone

The enantioselectivity in this reaction is due to the initial conversion of the ketone (acetone) into a chiral enamine (**Scheme 2**).



Scheme 2: Formation of chiral enamine

A hydrogen bond complex between the carboxylic acid portion of the chiral enamine and the isobutyraldehyde allows for delivery of the aldehyde to one face of the nucleophilic enamine. Hydrolysis of the product liberates the chiral β-hydroxyketone product.

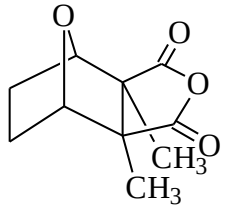
The ability to synthesize a compound with a specific chirality is crucial in modern organic synthesis. Since a majority of medicines are optically active (meaning the biologically active molecule has a (+) or (-) $[\alpha]_D$ (specific rotation)), methods that are enantioselective are quite valuable. This reaction has some green aspects and "not so green" aspects to it. Both should be articulated in your paper.

The product will be characterized using ^{1}H and ^{13}C NMR spectroscopy as well as IR spectroscopy; the enantiomeric excess will be determined using polarimetry.

II. Synthesis of a Norcantharidin Analogue: A Three-Step Synthesis of LS-16.

France, M.B.; Alty, L.T.; Earl, T.M. *J. Chem. Educ.* **1999**, *76*, 659-660.
Broshears, W.C.; Esteb, J.J.; Richter, J.; Wilson, A.M., *J. Chem. Educ*. **2004**, *81*, 1018-1019.
Walter, W.G., *J. Pharm. Sci.* **1989**, *78*, 66-67.

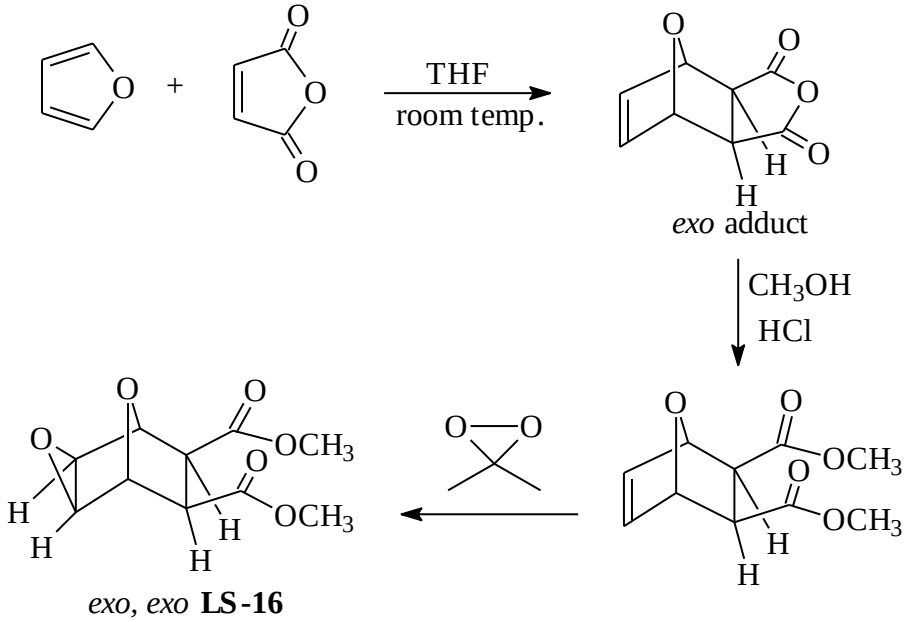
Cantharidin, a natural product from the Chinese blister beetle (*Mylabris phalerata*), has been used in China as a medicine for over 2000 years. It is one of several known protein phosphatase inhibitors that may facilitate DNA compaction in cancer cells.



Cantharidin

Cells whose DNA is tightly compacted about histone proteins are much more susceptible to cell death in the presence of gamma radiation. Although many healthy cells exist with this tightly wound DNA architecture (cells at mitosis e.g.), tumor cells are already particularly vulnerable to the effects of ionizing radiation. The working hypothesis is that Cantharidin would make the cells even more susceptible hence healthy cells would have a greater chance of survival. Preliminary studies have indeed shown this to be the case.

Bicyclic and tricyclic compounds that are demethylated, yet structurally related to cantharidin are currently being investigated. To date, 15 compounds of this type have been synthesized and have been tested as radiosensitizers. This project involves three-step preparation of a new cantharidin analogue (**LS-16, Scheme 3**).



Scheme 3: Synthetic scheme for the preparation of *exo*, *exo* **LS-16**

The first step involves a relatively simple Diels-Alder reaction ([4+2] cycloaddition) of furan and maleic anhydride. This is an interesting reaction that works well when the crystals of

the adduct are allowed to grow slowly, undisturbed, over a period of several days. The next step involves a methanolysis of the anhydride portion of the molecule. Finally, the epoxidation reaction is carried out using dimethyldioxirane, an oxidizing agent that is generated *in situ*; this is a relatively new and environmentally friendly method. The final epoxide will be purified using column chromatography. Monitoring of the reaction and the column will be done with thin layer chromatography using an anisaldehyde stain reagent to visualize.

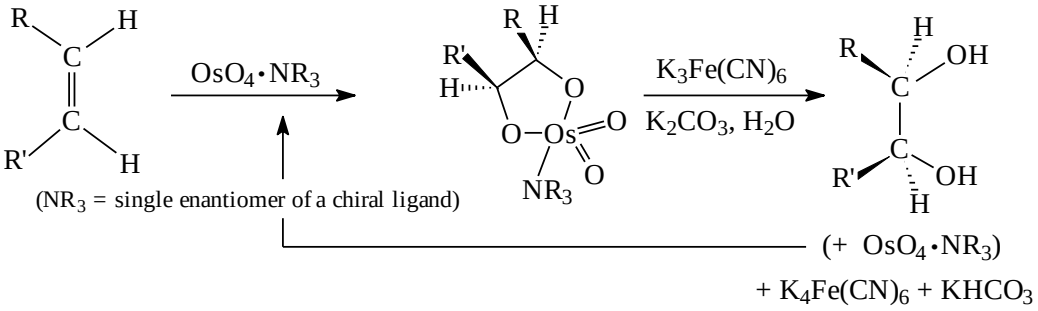
Diels-Alder reactions are clearly documented in the literature as cycloaddition processes that occur almost exclusively via *endo* addition. Hence, cantharidin has proven to be an elusive target for synthetic organic chemists. If the information in France's paper is true (exclusive *exo*-addition), we should have a rapid approach to our target compound. According to Wilson's paper, we should get exclusively *endo*-epoxidation. However, preliminary studies in our laboratory indicate the opposite to be true. How can one tell if the product is *exo*- or *endo*- at each position? Your report should discuss how all reactions work with mechanisms. All products will be characterized with m.p. and ^{1}H and ^{13}C NMR spectroscopy.

III. Sharpless Asymmetric Dihyroxylation: Effect of Alkene Structure on Rates and Selectivity

Spivey, A.C.; Hanson, R.; Scorah, N.; Thorpe, S.J. *J. Chem. Educ.* **1999**, *76*, 655-659.
Nichols, C.J.; Taylor, M.R. *J. Chem. Educ.* **2005**, *82*, 105-108.

Because of his contributions toward the catalytic syntheses of single enantiomeric products, K. Barry Sharpless won the Nobel Prize in Chemistry in 2001. One of the reactions he developed, the asymmetric dihydroxylation, is one of the most often utilized and most useful reactions of modern times. The importance of this reaction is that it incorporates two adjacent chirality centers in a molecule in a highly stereoselective fashion. This is significant as pharmaceutical companies must now often prepare medicines in their pure (+) or pure (-) forms and not as racemates. In this reaction, the oxidizing agent is OsO4 complexed to a chiral amine ligand. This makes the oxidizing agent chiral and thus the *syn* addition of the two -OH groups will occur on a specific face of the alkene.

Each group will have the option of choosing one of several alkenes as a substrate so we can compare differences in structure with the efficiency of the reaction (both reaction rate and enantioselectivity). The reaction is outlined in Scheme 4. The structure of the complex chiral ligand can be found in the lead reference. Another excellent source describing this reaction can be found at this link: http://www.organic-chemistry.org/namedreactions/sharpless-dihydroxylation.shtm



Scheme 4: A general schematic of the Sharpless dihydroxylation.

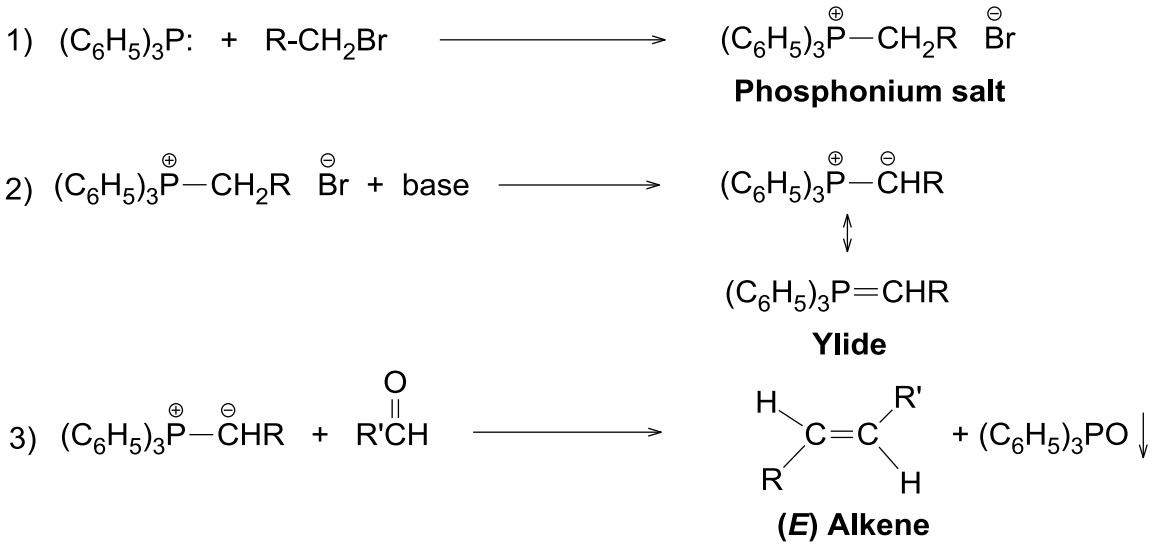
Your product will be characterized by ^{1}H and ^{13}C NMR and Infrared spectroscopies; the enantiomeric excess of the reaction will be determined by comparing the specific rotation of your product with the literature value.

IV. Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the *in situ* Formation of Stabilized Ylides.

Kelly, M.J.B.; Fallot, L.B.; Gustafson, J.L.; Bergdahl, B.M. *J. Chem. Educ.* **2016**, *93*, 1631-1636.

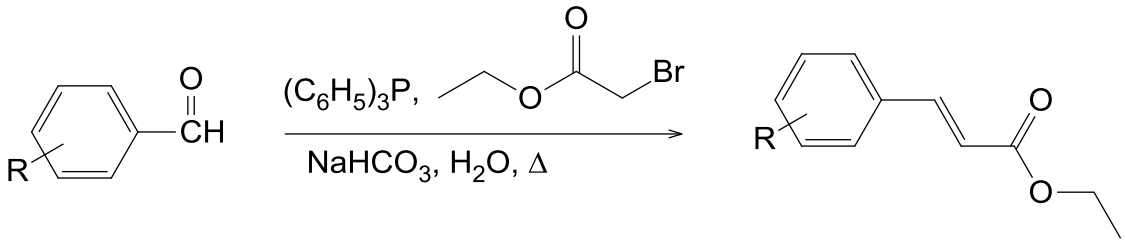
In the 1950s, Wittig discovered a very useful method for transforming aldehydes and ketones into alkenes. For this, he was awarded the Nobel Prize in Chemistry due to its general utility toward the syntheses of large numbers of pharmacologically active organic compounds.

Typically, the Wittig reaction involves three steps: 1) the initial preparation of a phosphonium salt; 2) the deprotonation of this salt to form a stabilized ylide; and 3) the reaction of the ylide with a ketone or aldehyde to form an olefin (alkene, see **Scheme 5**).



Scheme 5: The three steps of a Wittig Reaction

This particular version of the Wittig reaction is unique in that it is run "on water" (as opposed to "in water") to generate specifically an *E* alkene. The difference between a solvent and a "medium" is exemplified in this reaction as the reagents used appear to be insoluble throughout. Additionally, all three of the above steps will be carried out in rapid sequence in one flask. We will run this reaction on a variety of aromatic aldehydes with ethyl bromoacetate as your primary alkyl bromide (**Scheme 6**).



Scheme 6: Wittig reaction to be run by class; R = a variety of *para*, *meta* and *ortho* substituents.

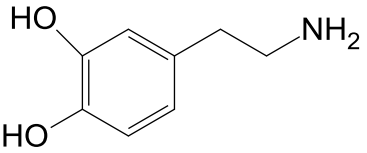
The final product will be purified with column chromatography and characterized using ^{1}H and ^{13}C NMR spectroscopy as well as IR spectroscopy and mass spectrometry.

V. Synthesis of a Parkinson's Disease Treatment Drug, the *R*,*R*-Tartrate Salt of *R*-Rasagiline

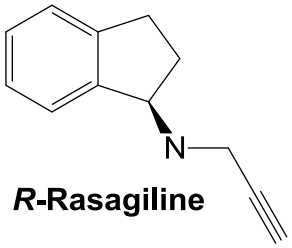
Aguilar, N.; Garcia, B.; Cunningham, M.; David, S. *J. Chem. Educ.* **2016**, *93*, 937-940.

Parkinson's disease is a neurological disorder that is in part, due to the inability to generate dopamine (3,4-**d**ihydr**o**xy**p**henethyl**amine**) in the brain. This neurotransmitter is essential for proper muscle function. Although there is no cure to date, the alleviation of symptoms of compromised motor and speech function can lead to a relatively normal existence.

Enzymes that specifically oxidize dopamine, necessarily decrease the concentration in cells. To prevent this decrease in dopamine levels, monoamine oxidase-B (MAO-B) inhibitors are often used as ways of maintaining dopamine levels in the brain. *R*-Rasagiline has been shown to be a MAO-B inhibitor.

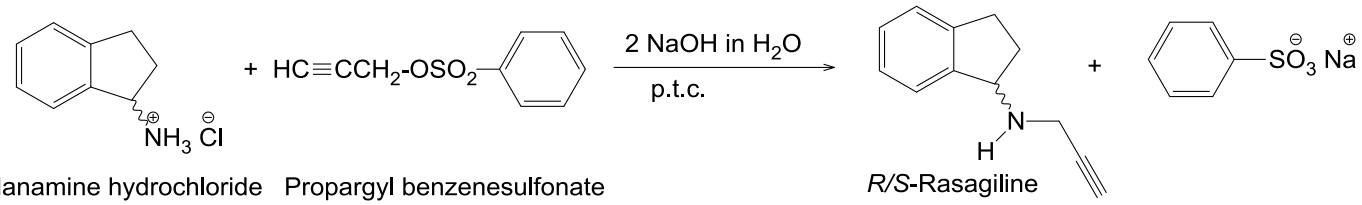


Dopamine



***R*-Rasagiline**

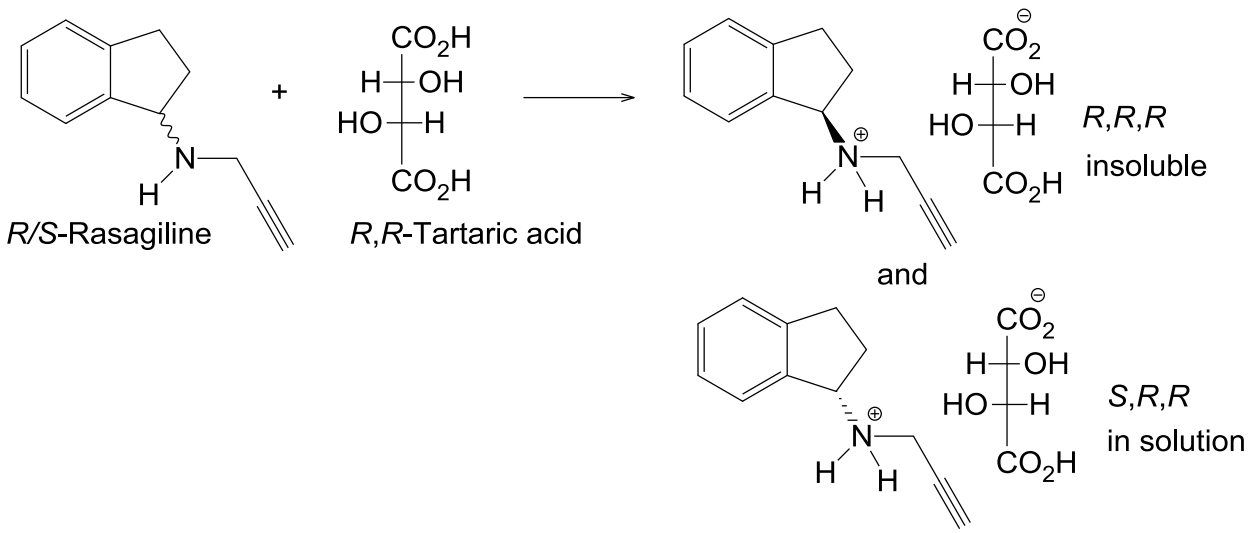
This project involves the synthesis of racemic rasagiline, followed by the chemical resolution of the 50/50 mixture of enantiomers into a pure *R*-rasagiline salt. The synthesis is shown in **Scheme 7** below.



Indanamine hydrochloride Propargyl benzenesulfonate *R/S*-Rasagiline

Scheme 7: S_N2 reaction between indanamine hydrochloride and propargyl benzenesulfonate to form racemic rasagiline

Optical resolution of the racemic mixture is a seemingly simple acid/base reaction between *R*,*R*-tartaric acid and the rasagiline oil. Since the two salts that form (*R,R*,*R*-rasagiline tartrate and *S*,*R*,*R*-rasagiline tartrate) are diastereomers, they have different properties and can be separated by crystallization and recrystallization (**Scheme 8**). The salt derived from the *R*-rasagiline is considerably less soluble than the one derived from the *S* enantiomer.



Scheme 8: Optical resolution of racemic rasagiline with R,R-tartaric acid

The racemic rasagiline will be characterized using ^{1}H, ^{13}C NMR and IR spectroscopies as well as mass spectrometry. The tartrate salt will be further characterized with polarimetry and melting point.

VI. Independent Project

For the sixth laboratory project, you have the opportunity to carry out an experiment that complements the previous five. This project should introduce a unique reaction and/or technique and present a challenge. In each issue of the *Journal of Chemical Education*, there is a section entitled "Laboratory Experiments" or "In the Laboratory" in earlier issues. Typically there are two or three good advanced organic laboratory experiments each month but you certainly do not need to limit yourself to that journal. This project should introduce a new type of reaction that has not otherwise been covered in your three semesters of Organic Chemistry.

An abstract for your project is due on Wednesday, March 4, 2020. In this brief proposal, you should include the cover sheet from the link on our site that includes:

I) Name of students carrying out the work.

II) Title of the project.

III) Reference of primary article used in proposal (attach a copy of the article including experimental sections).

IV) Novel techniques/reactions utilized in this project.

V) Approximate timetable for project.

VI) Budget and chemicals needed: include amounts and ACROS or Sigma-Aldrich numbers of all chemicals that we need to purchase.

VII) Equipment needed: includes glassware, dry ice, and gases (argon or nitrogen). If unavailable, supply a vendor.

Upon approval, your chemicals will be ordered – we will try to limit each group to a budget of $75 to $100 for this project. The report for this laboratory project will be submitted in the form of a *15 minute talk* (with slides) and weekly details will be kept in a notebook. Details on the make-up and design and number of slides for your seminar are forthcoming. **The dissemination seminars will be held on Thursday, April 30, 2020 at 2:00 pm.**