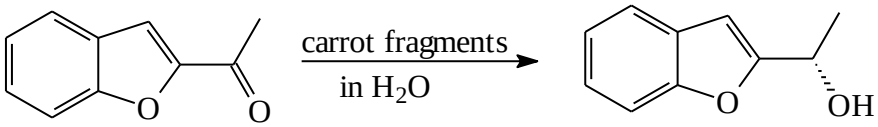
CHM 320 – Laboratory Projects
Spring, 2017

I. Enantioselective Reduction of Benzofuran-2-yl Methyl Ketone using Enzymes from Carrots.

Ravia, S.; Gamenara, D; Schapiro, V.; Bellomo, A.; Adum, J.; Seoane, G.; Gonzalez, D. *J. Chem. Educ.* **2006**, *83*, 1049-1051.
Strossmayer, J.J. *Croat. J. Food Sci. Technol.* **2014**, *6*, 51-60.

Typically, the reduction of an unsymmetrical, achiral ketone with a hydride reducing agent (*e.g.* $NaBH_4$) results in the production of a racemic mixture of secondary alcohols. This is due to the hydride having equal access to both faces of the planar carbonyl group. However, with a chiral reducing agent, a chiral alcohol can be obtained. Recently, biological organisms have been found to affect the reduction of a variety of prochiral ketones (upon reduction of the carbonyl group, a chiral center is formed) with remarkable enantioselectivity. This essentially mimics many of nature's synthetic processes. The most common microbial method is the reduction via microbes found in Baker's yeast. This method, although inexpensive, requires the use of large quantities of organic solvents.

Recently, new plant sources of enzymes have been shown to affect the reduction of prochiral ketones in an environmentally friendly way. Asymmetric reductions have been carried out using apples, carrots, cucumbers, onion, sweet potatoes and radishes with varying degrees of success. In this experiment, you will perform a reduction of benzofuran-2-yl methyl ketone using the enzymes found in carrots (**Scheme 1**). Although the setup is quite simple, the reaction may take several hours to complete. The reaction will be monitored by Thin Layer Chromatography (TLC).



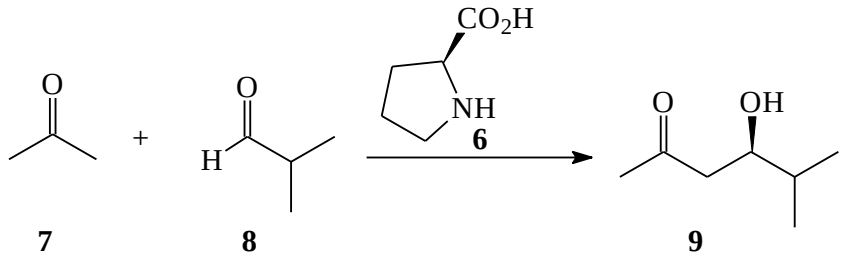
Scheme 1: Enatioselective reduction of benzofuran-2-yl methyl ketone using raw carrot fragments.

The enantioselectivity of this reaction (+/- ratio) will be determined by using polarimetry. You will need to find the $[\alpha]_D$ of the pure (-) enantiomer in the literature. What is the enantiomeric excess (e.e.) of this reaction?

II. 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, **6**), it can mimic an 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 (**7**) and isobutyraldehyde (**8**) using L-proline as a catalyst is shown in **Scheme 2**.



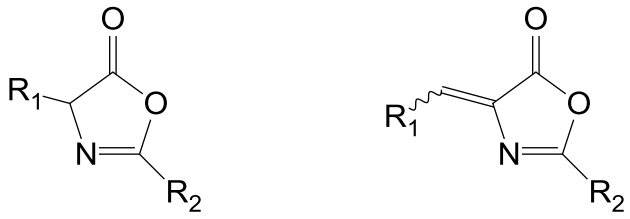
Scheme 2: Crossed aldol condensation to form (*R*)-4-hydroxy-5-methyl-2-hexanone (**9**)

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 NMR and IR spectroscopy and the enantiomeric excess determined using polarimetry.

III. Synthesis of a Biologically Active Oxazol-5-(4H)-one *via* an Erlenmeyer-Plöchl Reaction.

Rodrigues, C.A.B.; Martinho, J.M.G.; Alfonso, C.A.M. *J. Chem. Educ.* **2015**, *92*, 1543-1546.

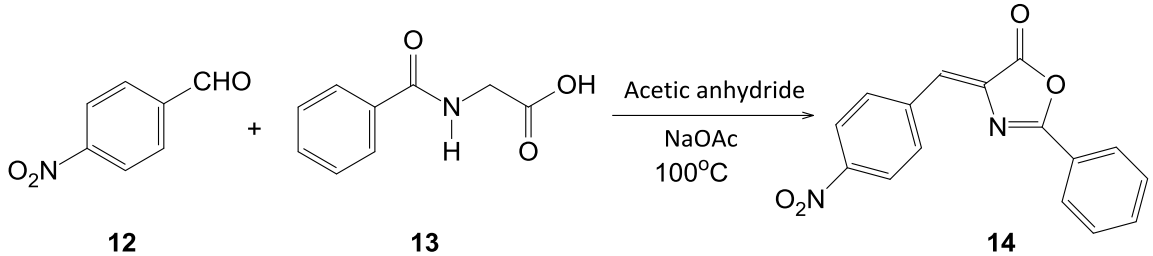
Oxazolones (general structure, **Figure 2**, compound **10**) are a ubiquitous functionality found in a wide variety of plant sources. With both an imine and an ester in the same five-membered ring, these compounds can react with both Lewis acids (electrophiles) and Lewis bases (nucleophiles) and thus are valuable synthetic intermediates. Interestingly, the presence of an exocyclic double bond between the carbonyl group and the nitrogen of the imine (compound **11**) not only provides more sites of reactivity, but also introduces a wide range of biological properties.



10 **11**

Figure 2: The general structure of an oxazolone (**10**) and an alkylidene oxazolone (**11**)

This project demonstrates a green Erlenmeyer-Plöchl condensation reaction between p-nitrobenzaldehyde (**12**) and hippuric acid (**13**) to form (Z)-4-(4-nitrobenzylidene)-2-phenyloxazol-5(4H)-one (compound **14**, **Scheme 3**).



12 **13** **14**

Scheme 3: Erlenmeyer-Plöchl Synthesis of (Z)-4-(4-nirobenzylidene)-2-phenyloxazol-5(4H)-one (**14**)

Reaction progress will be monitored by thin layer chromatography (TLC) and the product will be characterized using ^{1}H and ^{13}C-NMR spectroscopy. In addition to a melting point and percent yield, the "E-Factor" will be determined. Your discussion should include a detailed mechanism and a rationale and need for the nitro group in this synthesis (why do you need an electron-withdrawing group on the benzaldehyde?).

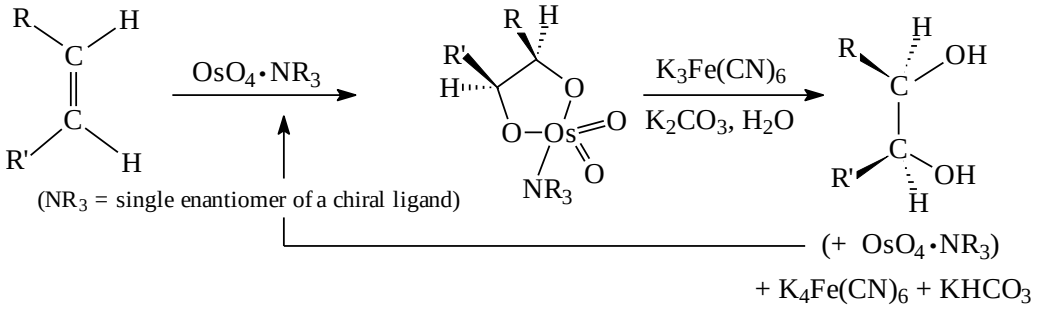
IV. Sharpless Asymmetric Dihydroxylation: Effect of Alkene Structure on Rates and Selectivity.

Spivey, A.C.; Hanson, R.; Scorah, N.; Thorpe, S.J. *J. Chem. Ed.* **1999**, *76*, 655-659.

Nichols, C.J.; Taylor, M.R. *J. Chem. Ed.*, **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 OsO_4 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.

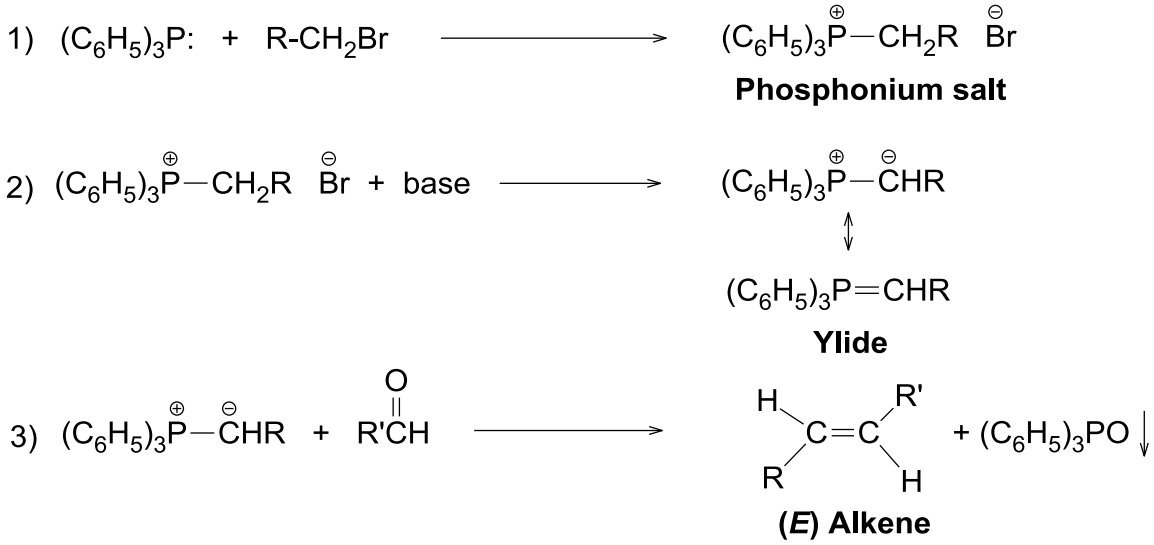
Your product will be characterized by ^{1}H NMR and Infrared spectroscopies; the specific rotation will be determined using polarimetry.

V. 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.

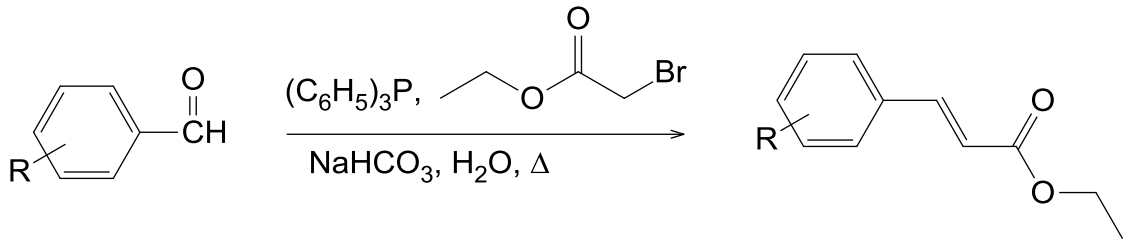
In the 1950s, Wittig discovered a very useful method for transforming aldehydes and ketones into alkenes. For this, he was awarded the Nobel Prize in Chemistry due to its general utility toward the syntheses of large numbers of pharmacologically active organic compounds.

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 1H and C-13 NMR spectroscopy as well as IR spectroscopy and mass spectrometry.

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 "In the Laboratory". 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.

An abstract for your project is due on Wednesday, March 1, 2017. 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 numbers of all chemicals that we need to purchase. If not available from ACROS, use Aldrich.

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, May 4, 2017 at 2:00 pm.**