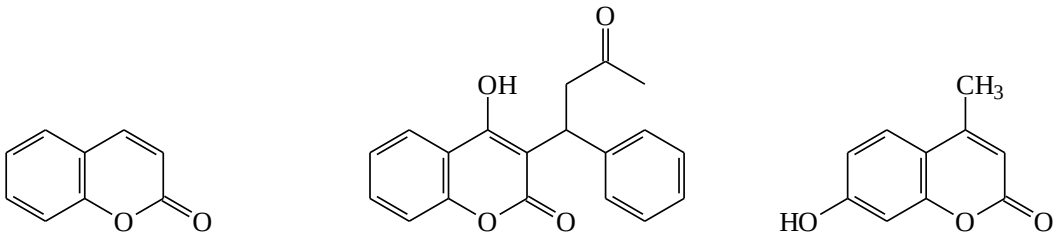
CHM 320 – Laboratory Projects
Spring, 2015

I. Green Synthesis of a Fluorescent Natural Product.

Young, D.M.; Welker, J.J.C.; Doxsee, K.M. *J. Chem. Educ.* **2011**, *88*, 319-321.

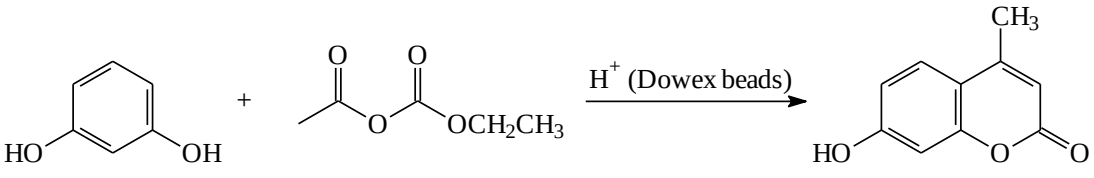
This project involves a synthesis of a compound that is classified as a "coumarin". Coumarins are bicyclic oxygen-containing heterocycles that are extremely common in nature. The coumarin template (compound **1, Figure 1**) is found in a wide variety of natural products from plants, and has applications found in synthetic analogues ranging from anti-coagulants (blood thinners, e.g. Coumadin® (**2**)) to spices (Figure 1). Our target molecule, 4-methylumbelliferone (**3**) is found in parsley and carrots and has a large variety of potential uses.



1 **2** **3**

Figure 1. Coumarin (**1**), Coumadin® (**2**), 4-methylumbelliferone (**3**)

One theme in the projects that we will carry out this semester is to explore carbon-carbon bond forming reactions. Without readily accessible reactions of this type, organic synthesis is not possible. The Pechman condensation used to synthesize compound **3** involves three successive acid catalyzed reactions in one "pot". **Scheme 1** shows the reaction between resorcinol (**4**) and ethyl acetoacetate (**5**) to form compound **3**.



4 **5** **3**

Scheme 1: Pechman Condensation to form 4-Methylumbelliferone (**3**)

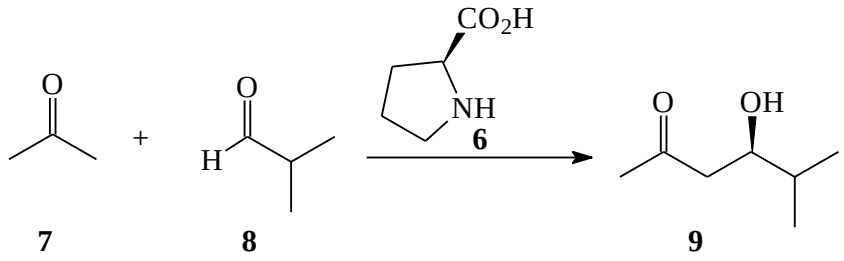
The lack of solvent in this reaction together with the fact that the acid catalyst used is recyclable (imbedded on a polymer bead) adds to the environmentally friendly conditions.

The product displays a pH-dependent fluorescence which will be investigated together with a complete characterization using NMR spectroscopy.

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**.



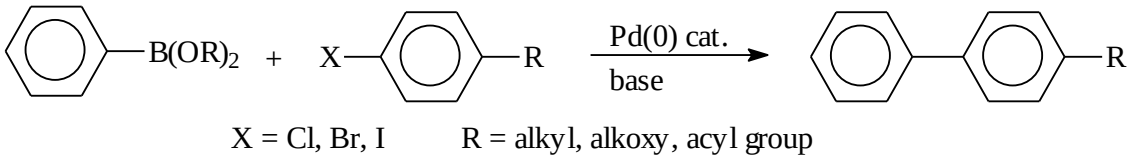
Scheme 2: Crossed aldol condensation to form (*R*)-4-hydroxy-5-methyl-2-hexanone (**9**)

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. "Greening Up" the Suzuki Reaction. Pd(0) Catalyzed Aqueous Reactions.

Aktoudianakis, E.; Chan, E.; Edward, A.R.; Jarosz, I.; Lee, V.; Mui, L.; Thatipamala, S.S.; Dicks, A.P. *J. Chem. Educ.* **2008**, *85*, 555-557.

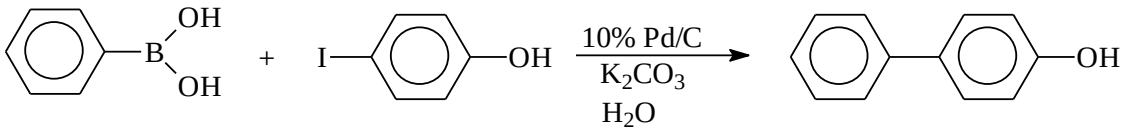
The Suzuki cross-coupling reaction is about 30 years old and represents a smooth method for creating carbon-carbon bonds. Typically, in the Suzuki reaction aryl halides are combined with an aryl boronic acid or boronic ester in the presence of a Pd(0) catalyst and base to afford a variety of biaryl compounds (**Scheme 1**). These biphenyl templates are very common in non-steroidal anti-inflammatory drugs (NSAIDs).



Scheme 3: Suzuki reaction to form biphenyl molecules

Strides have been made recently to make the reaction more environmentally friendly by using less organic solvent and lower heating times. Conventional organic reactions involve significant quantities of non-aqueous solvents and substantial heating times. For example, one improvement on the Suzuki reaction involves the use of microwaves; this has become more popular due to the lower amounts of solvent needed and dramatically shorter reaction times.

Another way of "greening" the Suzuki cross-coupling reaction is by using water as the only solvent with an inexpensive 10% palladium on carbon catalyst. In this reaction, the preparation of 4-hydroxy biphenyl will be carried out (**Scheme 2**) and the concept of a catalytic reaction cycle will be introduced as a new mechanistic thought process.



Scheme 4: Suzuki reaction between phenyl boronic acid and 4-iodophenol

The product will be characterized by ^{1}H and C-13 NMR spectroscopic methods. The report should include a complete mechanism showing the catalytic nature of the Pd catalyst.

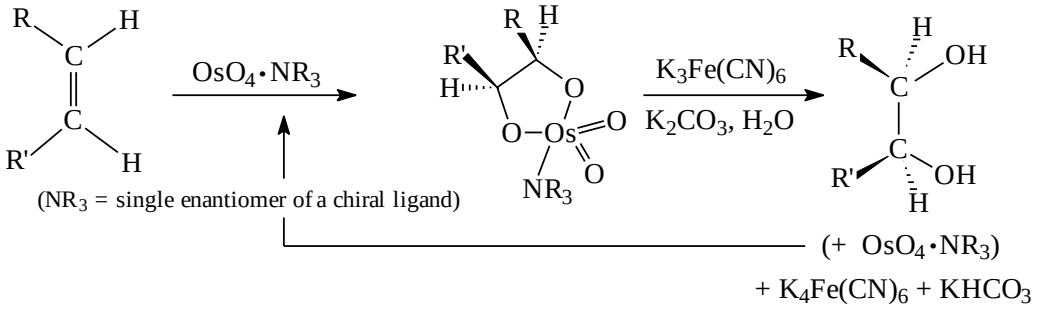
IV. Sharpless Asymmetric Dihydroxylation: Effect of Alkene Structure on Rates and Selectivity.

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 5**. 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

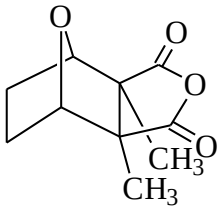


Scheme 5: A general schematic of the Sharpless dihydroxylation.

V. 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. Ed.*, **2004**, *81*, 1018-1019.
Walter, W.G., *J. Pharm. Sci.* **1989**, *78*, 66-67.

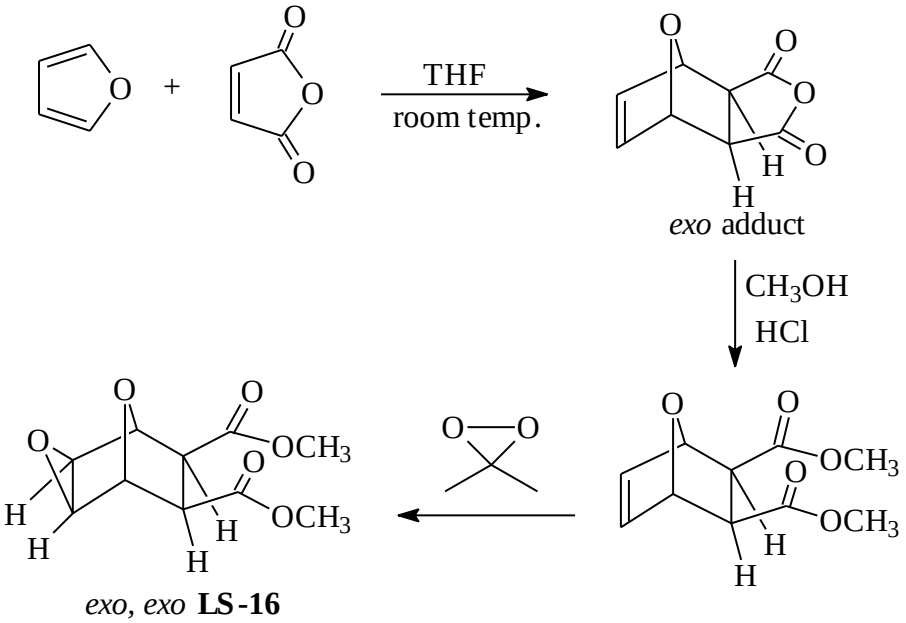
Cantharidin, a natural product from the Chinese blister beetle (*Mylabris phalerata*), has been used in China as a medicine for over 2000 years. It is one of several known protein phosphatase inhibitors that may facilitate DNA compaction in cancer cells.



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 6**).



Scheme 6: 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. The next step involves a methanolysis of the anhydride portion of the molecule. Finally, the epoxidation reaction is going to be 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.

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.

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 February 19, 2015. 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. 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 seminar will be held on Thursday, April 30, 2015.**