

SUMMER 2015 RESEARCH PROGRAM CARLETON CHEMISTRY DEPARTMENT

This summer the Carleton Chemistry Department will offer its continuing summer research program for Carleton students. We expect to offer research positions to up to 15 new students. For the most part, the new student researchers will come from the sophomore and junior classes. Professors Alberg/Hofmeister (jointly), Calderone, Gross, Hollingsworth, Steed, and Whited will offer projects that reflect their research interests. The research projects offered by each faculty member are described at the end of this document. In addition, a summer research recruiting seminar will be offered on **Friday, January 23 in Olin 04 at 3:30 pm**. General information on summer research in the chemistry department will be presented along with brief introductions to the science each research group is pursuing.

Dates of the Program: Monday, June 15, through Friday, August 21, for a total of 10 weeks. Each student will arrange starting and ending dates and summer vacation with his or her professor; these dates are usually flexible.

Stipend: \$4,300 for 10 weeks.

Expectations of Students by the Chemistry Department:

A research position in our summer research program is a full-time position. You should not plan on taking a second job during the same period.

Each week you will be expected to attend a research conference with all of our summer researchers. Each student will give an oral presentation on his or her project at this weekly research conference. You may have the opportunity to give a presentation on your research at a state or national research meeting. Following the summer of research, you will prepare a comprehensive written report and give a poster on your research at the fall Research Celebration at Carleton.

Deadlines and How to Apply: The application is available electronically at <https://www.surveymonkey.com/s/ChemSummerResearch2015>. Follow the directions on the electronic application form and rank order your preferences for research projects. Also tell us how strong your preferences are and how flexible you are in accepting a position in the other research groups you list. Before submitting your application, you should talk to individual professors in order to explore your interest in their research project. Keep in mind that some professors will not invite a student to join their research group unless the student has taken the time to stop by, meet the professor, and discuss the research project. Applications are due at midnight on Monday, February 16, 2015.

On Wednesday, March 4, offers will go out to individual students in campus mail. We will ask for your decision on our offer by Wednesday, March 11. If you have any questions about the mechanics of the application process, contact Chris Calderone (ccalderone@carleton.edu); for questions about specific labs, contact the appropriate faculty member.

Reasons to Participate in the Summer Research Program: Research is considered by many to be at the pinnacle of intellectual endeavors as it is the main vehicle by which new knowledge is created. Research requires a demanding combination of intellect, creativity, endurance, and curiosity. Many valuable skills are developed in the research

laboratory. Some examples include the ability to work as a member of a team, to operate sophisticated instrumentation, and to use available resources to become a life-long learner. Research is also excellent preparation for graduate school, a career in the medical sciences, or a career in other scientific or quantitative fields.

Choosing to do research at Carleton offers a number of advantages. First of all, you will have the chance to get to know your professors much better. In addition, you can start preparing for your summer research experience during spring term. This additional preparation will improve the quality of the research you can perform during the short ten-week summer. Furthermore, if you wish, your research project can be continued as an independent study during the following academic year. Some students at Carleton who have had the most positive research experiences have worked on their research projects over the course of two years. Unlike the experience at a larger institution, colleges like Carleton offer research opportunities exclusively for undergraduate students. At a larger institution, you would probably work most directly with a graduate student or post-doc, which is a good, yet different kind of experience. At Carleton you are guaranteed to work closely with a professor and to have your peers as research colleagues.

Life at Carleton and in Northfield is different during the summer than during the academic year. You will be surprised by the pace, and you will be pleased to know that you will not need your down jacket and warm hat (you may want to buy a fan). Many of the facilities (such as the gym, pools, weekly movies, etc.) at Carleton are open for summer programs. We will have at least two expeditions; canoe trips, baseball games, Valley Fair, and tubing have been popular choices in the past.

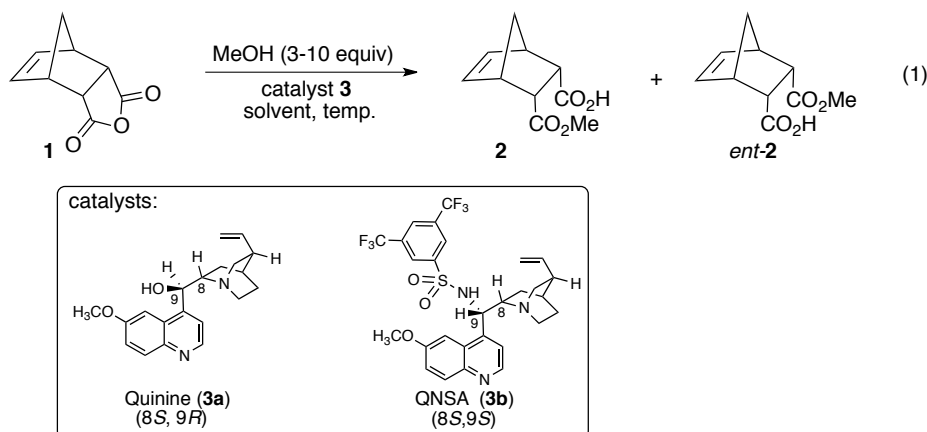
Professors Dave Alberg and Gretchen Hofmeister: Organic Synthesis and Mechanistic Studies

Positions for 2-3 new students

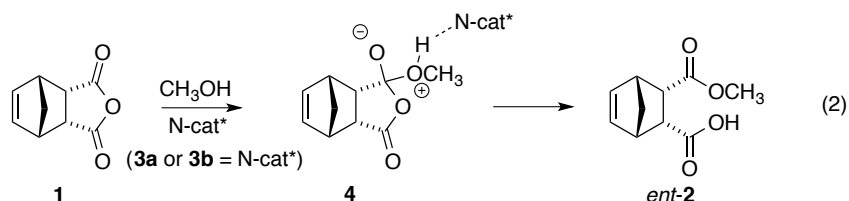
These students would continue ongoing projects in organocatalysis. Organocatalysis uses small organic molecules as catalysts for transformations that are valuable in synthesis, such as the introduction of chirality into achiral compounds. The primary motive in our research is to understand how organocatalysts control the stereochemical outcome of asymmetric reactions.

Transition State Analogs of Asymmetric Desymmetrization Reactions

We are preparing stable transition state analogs (TSAs) of the likely transition state for asymmetric desymmetrization reactions, as shown in eq 1 below, and we are using NMR to study their interactions with the chiral catalysts for this reaction.



This reaction is catalyzed by derivatives of cinchona alkaloids and the catalyst (e.g. **3a**, **3b**) is thought to act as a general base by hydrogen-bonding to the alcohol, activating it for nucleophilic attack on the anhydride (eq 2). The rate-limiting step in this mechanism is expected to involve formation of a tetrahedral species, such as **4**. The Hammond postulate suggests that the transition state for this step should resemble the intermediate, and we plan to mimic this tetrahedral transition state with stable tetrahedral phosphorus derivatives, as TSAs.



Under the conditions employed in the catalytic desymmetrization reactions, TSAs such as **5** (Fig. 1) will form a complex with the alkaloid catalyst. The solution conformations and

interactions of the resultant alkaloid-TSA complexes can be evaluated by NMR spectroscopy. We are preparing TSAs related to **5**, in both enantiomeric forms. After separating them into pure enantiomers, we will investigate each enantiomer's interactions with the catalyst separately by NMR

spectroscopy. Differences in these interactions can provide insight into the mechanism by which these alkaloids achieve their impressive enantioselective catalysis. Furthermore, they may enable us to corroborate the stereochemical biases of the reactions, thereby providing a means for evaluating the TSAs as suitable models of the transition state.

The students working on this project will gain expertise in synthesis, resolution of the chiral TSAs into pure enantiomers, and NMR spectroscopic investigations of the catalyst-TSA complexes. This provides excellent experience for future work in synthetic chemistry.

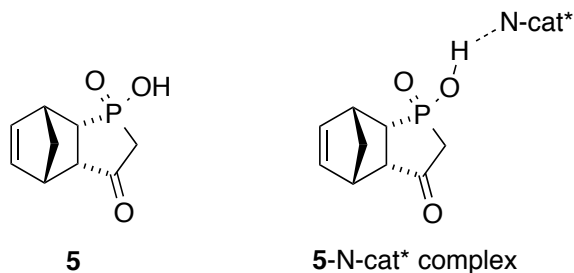


Figure 1. TSA **5** and its complex with catalyst.

Professor Chris Calderone: Enzymology of Secondary Metabolism

Positions for 1-2 students

The Calderone lab is interested in deciphering the enzymatic logic of *secondary metabolite biosynthesis*. Secondary metabolites are molecules that are produced by bacteria, fungi, and plants with a wide range of biochemical functions: some secondary metabolites serve as toxins, others are signaling molecules, and many have unknown function. Many secondary metabolites, including the antibiotics penicillin and erythromycin, the anticancer drug paclitaxel (licensed as Taxol), and the cholesterol-lowering drug lovastatin (licensed as Mevacor) have found value in the clinic.

The focus of the Calderone lab is on understanding the enzymes that produce secondary metabolites in nature. Ultimately, this work can have several impacts on our understanding of biochemistry: (1) Many secondary metabolites are extremely structurally complex. Understanding how they are produced may allow us to produce clinically valuable secondary metabolites more efficiently using enzymatic, as opposed to synthetic, strategies. (2) In many cases, the production of secondary metabolites involves biochemical reactions that have not previously been observed; thus, there is great opportunity to discover completely new enzymatic reactions and biochemistry. (3) As we characterize more and more secondary metabolite-producing enzymes, we can actually use this information to probe genome sequences for genes encoding related enzymes, and thereby potentially discover new secondary metabolites.

In general, our work on a particular enzyme comprises several phases. First, we use molecular biology techniques (PCR, gene cloning) to generate a DNA *plasmid* encoding the enzyme of interest; then, we use this plasmid to produce and isolate large amounts of this enzyme; finally, we characterize the enzyme's activity and mechanism using a variety of analytical techniques. Thus, students are exposed to several techniques over the course of a project and see how multiple experimental strategies can be brought to bear on a single scientific question. The lab's work this summer will focus on the production of the molecules tabtoxin and ECO-0501.

I. Tabtoxin. Tabtoxin is a phytotoxin produced by *Pseudomonas syringae*. Tabtoxin includes an unusual—and synthetically extremely challenging—four-membered ring (Figure 1); our goal is to decipher the phenomenally complex sequence of biochemical events, involving at least

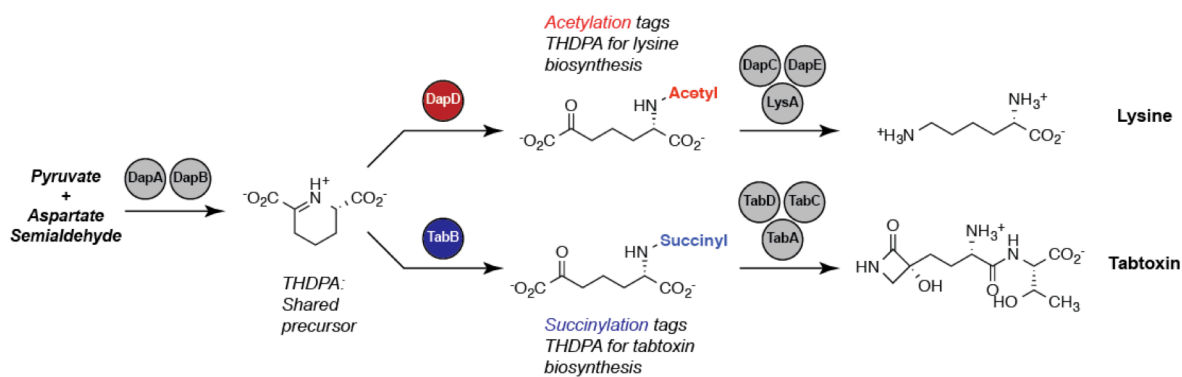


Figure 1. Branching biosynthetic pathways to lysine and tabtoxin production.

twelve proteins all acting in concert, that leads to the production of tabtoxin. Our first efforts in this project are driven by the hypothesis that one of the starting materials for tabtoxin is a molecule known as THDPA. Interestingly, THDPA is also a starting material for the production of the amino acid lysine, raising the question of how *P. syringae* is able to “direct traffic” to allocate THDPA toward lysine or tabtoxin. We have made significant progress on this question, obtaining evidence that the two enzymes DapD and TabB both process THDPA, but selectively divert THDPA toward lysine and tabtoxin production, respectively. Our goal for this summer is to nail down the activities of DapD and TabB, and prove that they are in fact the lysine/tabtoxin branchpoint.

II. ECO-0501. ECO-0501 is a secondary metabolite isolated from *Amycolatopsis orientalis*, which also produces the crucially important “antibiotic of last resort,” vancomycin. One of the enzymes that act in the ECO-0501 biosynthesis is ORF7, relatives of which were recently shown to catalyze a mechanistically complex and little-understood oxidative decarboxylation reaction. It is thought that ORF7 catalyzes oxidative decarboxylation of N-methylarginine (Figure 2), but we made the important discovery last summer that when ORF7 utilizes arginine as a substrate it is only able to catalyze the first few steps of the decarboxylation reaction before the mechanism is “derailed”. This observation is important because it allows us to probe individual steps in the reaction mechanism that have to date been impossible to study, ultimately allowing us to unravel exactly how this mysterious but widespread reaction occurs in biology. Work this summer will focus on continuing experiments to confirm individual mechanistic steps within this reaction.

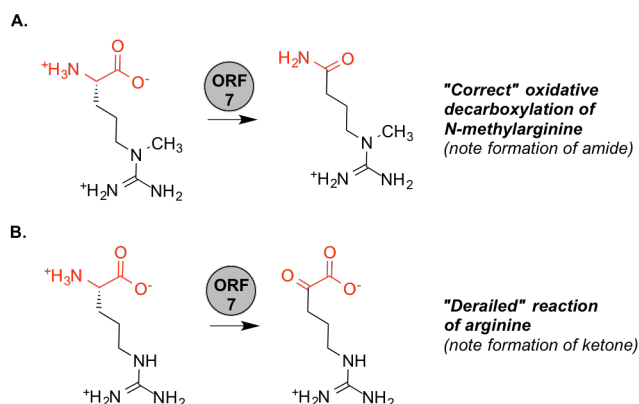


Figure 2. “Correct” (a) and “derailed” (b) oxidative decarboxylations catalyzed by ORF7 during ECO-0501 biosynthesis.

How to apply:

Applicants should have taken Chem 234 prior to this summer and should plan to enroll in an independent study (Chem 394) in Spring 2014 to prepare for research in the lab. For at least one of the openings, preference will be given to those with interest in continuing their work in the lab into summer 2016. If you wish to apply to work in my lab, you *must* meet with me to discuss your interest and background.

Deborah Gross: The Chemistry of Atmospheric Aerosol Particles

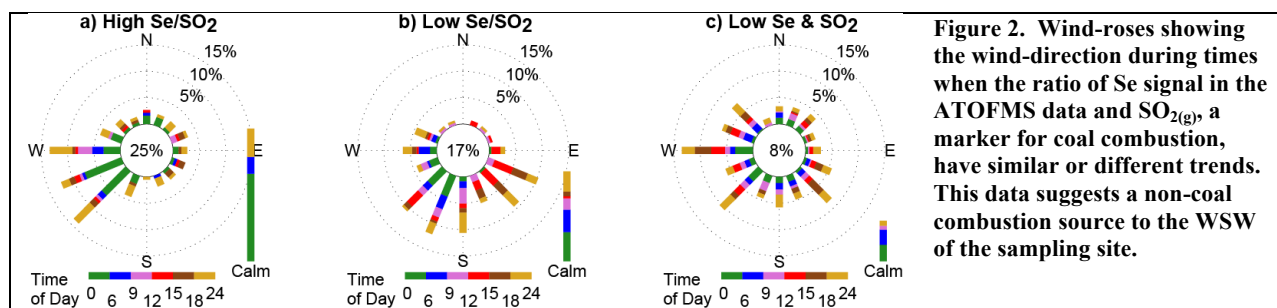
Positions for 2-3 new students

The air around us is full of aerosol particles (small droplets or chunks of solids), which impact our lives in many ways. These particles come from natural as well as anthropogenic (human) sources. They nucleate cloud droplets, they decrease visibility by scattering sunlight, and they impact our health when we inhale them. Our research group works with Aerosol Time-of-Flight Mass Spectrometers (ATOFMS) to obtain size and chemical composition information about the aerosol population in real time. With this data, we hope to try to increase our understanding of some of the complex issues in the atmosphere.



I hope to have two to three students work with me this summer. The first order of business will be to travel to China for 1 – 2 weeks, to develop some projects with collaborators there. All the students in the group will participate in this trip. Upon our return, students will work collaboratively on bringing the instrument “Wallace” back to working order and will divide up and take on a variety of projects, with the following possibilities available: 1) Developing data analysis methods to help us identify particle sources from the ATOFMS data signatures (Figure 2 shows an example); 2) Developing a new aerosol collection/ionization

source for use with any mass spectrometer, in collaboration with researchers at the U of MN and MSP Corporation; 3) Analyzing ambient data collected in Northfield and, hopefully, during our trip to China; 4) Characterizing the particles emitted by air fresheners in the indoor environment; and 5) Developing methods to analyze light emitted in the ion source, which can provide elemental information. Students’ interests will drive selection of the projects.



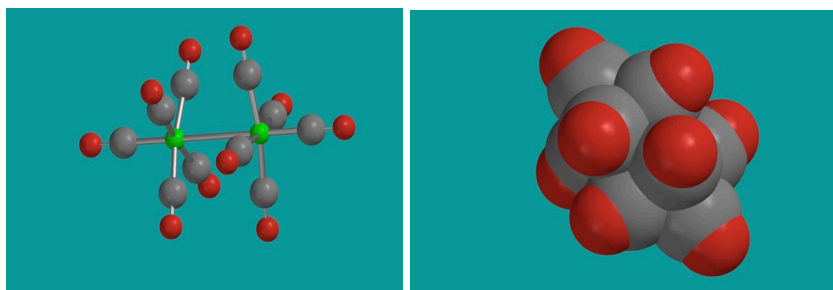
IF YOU ARE INTERESTED IN JOINING THESE PROJECTS, YOU SHOULD DO ALL OF THE FOLLOWING THINGS:

- Come talk to me as soon as possible, to discuss the details of the research and to see the ATOFMS instrument. Email to make an appointment. I won't accept anyone into the group unless we've talked about your interests, the projects, *etc.*, and I will set up some group meeting times.
- Plan to enroll in an independent study in Spring, 2015, to prepare for the summer.

Will Hollingsworth: Multiphoton Ionization of Gas-phase Metal-containing Molecules

We explore the fundamental fragmentation pathways that isolated molecules follow as they absorb the energy of many photons from a pulsed laser operating in the visible or near ultraviolet, through what is called a multiphoton process. In a single laser shot, all of the different ionic fragments are distinguished by their arrival times in a time-of-flight mass spectrometer (TOFMS)—see the end for a few pictures of the set-up. The general dissociative pathway a molecule follows is determined by the nature of its electronic excited states and metal carbonyls are known to follow neutral channels, only being ionized in the final step. This forms the basis of the direct research question—namely, how do metal-metal bonds compete with metal-ligand bonds in the breakup?

Consider manganese decacarbonyl, $\text{Mn}_2(\text{CO})_{10}$. Two representations of its structure from Spartan are shown—the metal-metal bond is formally a single bond. Evidence in literature is settling



on $\text{Mn}_2(\text{CO})_9$ and $\text{Mn}(\text{CO})_5$ as the initial photofragments of $\text{Mn}_2(\text{CO})_{10}$. However, the pattern of quantum yields determined in solution at different discrete wavelengths remains inconclusive.¹ With the correct amount of averaging, we are finding that we can do careful assessments of the wavelength dependence in the relative abundances of different fragments. In recent work, an anomalous pattern in fragmentation around 300nm was discovered, and it will be important to confirm and extend this finding by shifting to a different laser dye where the laser power can be more carefully controlled.

I'd like to work with two students this summer. In addition to seven weeks of research, three weeks will be dedicated to being TAs for my CSSI section on environmental chemistry, so it will be important to be able to devote time in the spring in preparation. The best way to see if this research could be right for you is to set up a time to come by and see the lab—beyond laser, vacuum, and mass-spectrometric techniques, there are also an array of electronic components such as oscilloscopes, box-car averagers and photodetectors, LabView software, and a chance to think a lot about molecular orbitals.

Types of Lasers in Use

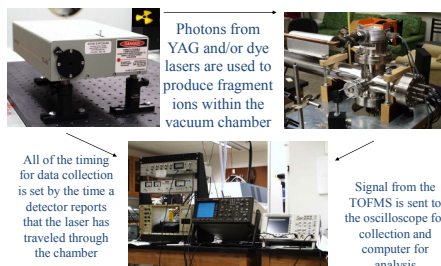
YAG laser—provides light fixed at 532, 355, or 266 nm



Dye laser (pumped by YAG at 532 nm)—provides tunable light



Overview of Basic Experiment



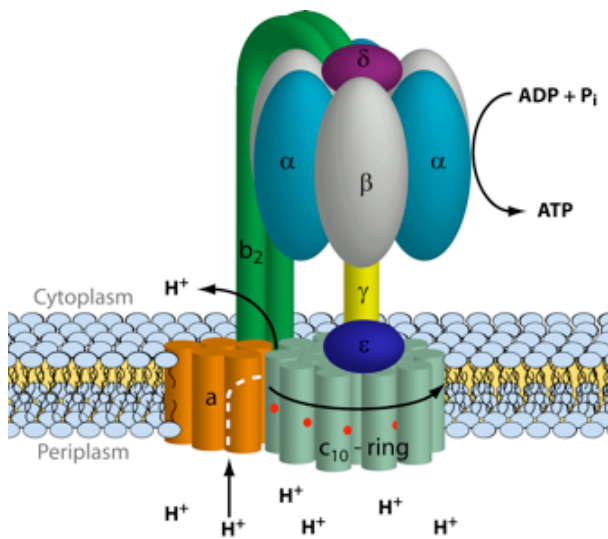
¹ Sarakha, M.; Ferraudi, G. *Inorganic Chemistry* **1999**, *38*, 4605-4607.

Ryan Steed

Structure and Function of ATP Synthase and CSSI Teaching

Likely funding for two students for 5 weeks of research and 3 weeks of CSSI teaching

ATP synthase is a fascinating biological nanomachine responsible for the conversion of electrochemical potential into mechanical energy and then chemical energy in cells. This massive protein complex consists of a membrane-embedded, ion-driven rotary motor (F_0) coupled to a soluble, ATP-driven rotary motor (F_1). In the presence of an electrochemical gradient, ion transport through subunit a , and via the a - c interface, drives the rotation of a ring of 8-15 c subunits. The rotation of this ring is coupled to the rotation of the γ subunit stalk within the $\alpha\beta$ hexamer, which contains three active sites responsible for the interconversion of ADP and ATP. Rotation of the stalk forces sequential conformational changes in the active sites resulting in the synthesis of ATP, the high-energy compound that serves as the universal chemical currency of the cell. The F_1F_0 complex can also operate in reverse, hydrolyzing ATP to generate an electrochemical gradient. The operation of this machine has been the past subject of intensive investigation, and multiple Nobel prizes have been awarded for work on its mechanism.



Despite the interest in this fundamental process of life, some questions remain unanswered, especially the mechanism by which ion translocation through membrane-embedded subunits a and c drives rotation of the c -ring. In order to understand how ion translocation is providing energy to do the work of rotation, we need to know the structures of subunits a and c , the parts of these subunits involved in the ion translocation pathway, and how the ion translocation process affects protein structure. My research addresses these questions focusing on the membrane-embedded F_0 sector of *E. coli* ATP synthase. Previous work mapped the complete pathway taken by protons through the membrane-embedded sector and established functional roles for some regions in subunits a and c . My current goals are to 1) determine the location and role of transmembrane helix 1 in subunit a , 2) determine the functional significance of an enigmatic set of amino acid residues at the subunit a - c interface, and 3) determine the structural dynamics of transmembrane helices and cytoplasmic loops of subunit a .

The students in my lab this summer will use chemical crosslinking of genetically-introduced cysteine amino acids to determine whether helix 1 of subunit a is in contact with the subunit c ring. The project will involve site-directed mutagenesis, isolation of cell membranes of mutant *E. coli* strains, chemical crosslinking, and Western blotting. Additionally, function of mutant F_1F_0 complexes will be probed using a fluorescent ATP-

driven H⁺-pumping assay. During the final 3 weeks, students will be my TAs the CSSI program for high school students. Being a TA involves assisting in a class on protein molecular machines and helping supervise students working in the lab on a similar project.

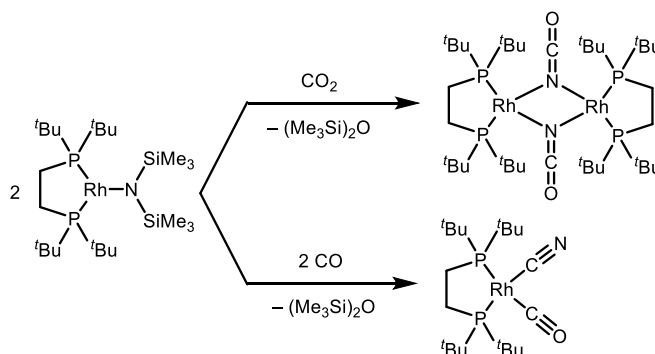
Professor Matt Whited: Synthetic Inorganic Chemistry and Catalysis

Positions for 2–5 students

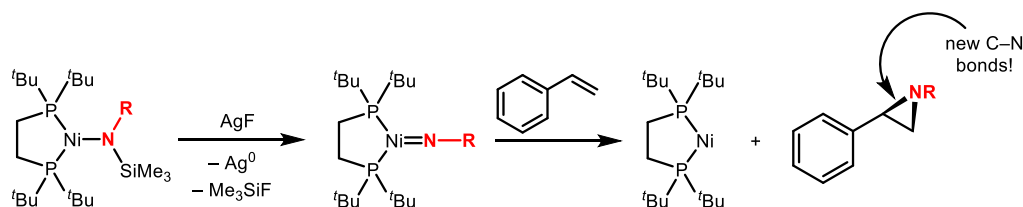
Research in my laboratory addresses problems related to energy and organic synthesis by focusing on reaction chemistry of late transition metals (Group 8–10). All of the projects look for new ways to generate and utilize highly reactive complexes containing metal–element single, double, or even triple bonds (where element = carbon, nitrogen, silicon, boron, oxygen). This summer, research projects in the Whited lab will be split into 2 subgroups, which use similar techniques but address different problems, as described below.

Delivering Reactive Nitrogen Fragments by Breaking N–Si Bonds

Over the past 2 years, my group has uncovered a rich set of reactivity from silylamide complexes of transition metals (a metal amide has a single M–N bond, and a silylamide is a metal amide with a silicon group on nitrogen).^{1,2} For instance, my students have shown that rhodium disilylamides can break the exceptionally strong C=O and C≡O bonds of carbon dioxide and carbon monoxide, forming new C–N and O–Si bonds in the process. We are always very interested in mechanism, and the mechanisms of these transformations have been thoroughly explored.



Reactions like those shown above clearly have potential to help us understand new ways to use normally inert molecules like carbon dioxide in chemical synthesis. This summer, we will be looking to expand our substrate scope for these rhodium reactions somewhat (for instance, looking at other unsaturated small molecules like ketones/aldehydes, isocyanates, sulfur dioxide, and others). We will also be transitioning this project to look at whether metal silylamides can be used in combination with chemical or electrochemical oxidation to install nitrogen-containing groups in organic molecules, as shown below (this last piece is the subject of a recently submitted grant proposal). One possible reaction is shown below, but there are many directions to pursue this research!

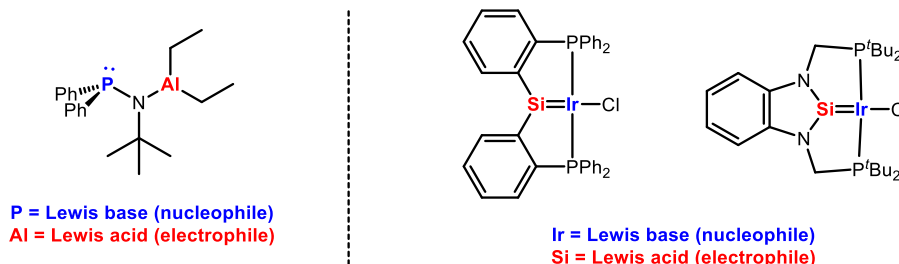


¹ Whited, M. T.; Kosanovich, A. J.; Janzen, D. E. "Synthesis and Reactivity of Three-Coordinate (dtbpe)Rh Silylamides: CO_2 Bond Cleavage by a Rh(I) Disilylamide" *Organometallics* **2014**, 33, 1416–1422.

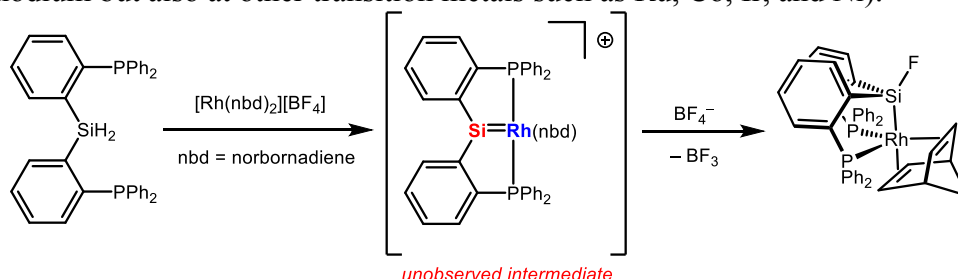
² Whited, M. T.; Qiu, L.; Kosanovich, A. J.; Janzen, D. E. "Atom and Group Transfer from Heteroallenes and Carbon Monoxide at a Three-Coordinate Rh(I) Disilylamide", in preparation for *Inorg. Chem.*

Ambiphilic Metal Complexes for Cooperative Small-Molecule Activation

Ambiphilic molecules are ones that have both Lewis acidic and Lewis basic sites, such as the (aluminoamino)phosphine shown at the left in the figure below (phosphorus has a nucleophilic lone pair and aluminum is electrophilic since it only has 6 valence electrons). These sorts of molecules are quite useful for activating molecules that are relevant to energy science (such as H_2 , CO , and CO_2).



We are interested in extending the idea of “ambiphilicity” to metal complexes, such as the two shown at right above, containing bonds between electron-rich transition metals and electropositive main-group elements such as silicon, carbon, and boron. Last year, we published preliminary results with suggesting that we can indeed form $\text{Si}=\text{Rh}$ double-bonded species such as the ones shown above,³ as surprising and exciting finding. More recently, we have demonstrated that $\text{Si}=\text{Rh}$ double bonds are extraordinarily reactive (one example shown below, where fluoride is extracted from the stable tetrafluoroborate anion), opening up an almost endless variety of new reactions that we can develop (not only at rhodium but also at other transition metals such as Ru, Co, Ir, and Ni).



What Will You Do?

Both projects involve some amount of organic synthesis in order to prepare the desired ligands. You will also become (intimately) familiar with methods for manipulation of air-sensitive organic and inorganic compounds in our inert-atmosphere glove box and Schlenk manifold.

Multinuclear NMR (^1H , ^{11}B , ^{13}C , ^{15}N , ^{29}Si , and ^{31}P) and X-ray crystallography will be our primary characterization techniques, though we will also use IR and UV-Vis spectroscopies and GC or LC/MS.

NOTE: You do not need a background in inorganic chemistry to work on these projects. Familiarity with organic chemistry (through Chem 234) is sufficient, and we'll cover the rest as we go.

If you are interested in working in my laboratory, please do the following:

- Set up an appointment to meet with me and discuss my research.
- Plan to enroll in an independent study in Spring 2015 in order to do some background work to prepare for your research project.
- Talk with one (or more) of the students who have recently worked in my lab: Christian Olivares, Lisa Qiu, Binh Nguyen, and Zander Deetz.

³ Whited, M. T.; Deetz, A. M.; Boerma, J. W.; DeRosha, D. E.; Janzen, D. E. "Formation of Chlorosilyl Pincer-Type Rhodium Complexes by Multiple Si-H Activations of Bis(phosphino)/Dihydrosilyl Ligands" *Organometallics* **2014**, 33, 5070–5073.