**SUMMER 2018 RESEARCH PROGRAM**
**CARLETON CHEMISTRY DEPARTMENT**

This summer the Carleton Chemistry Department will offer another year of its continuing summer research program for Carleton students. We expect to offer research positions to up to **10-15** new students. Most of the new student researchers will come from the sophomore and junior classes. Professors Alberg/Hofmeister, Calderone, Chihade, Gross, and Whited will offer projects that are described at the end of this document.

A summer research recruiting seminar will be held on **Friday, January 12th in Olin 149 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 11th, through Friday, August 17th, for a total of 10 weeks. Each student will arrange starting and ending dates and summer vacation with his or her professor; these dates can be flexible.

**Stipend**: $4,600 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 (https://www.surveymonkey.com/r/ChemSummerResearch2018) is available now. 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 take a student into their research group unless the student has taken the time to stop by, meet the professor, and discuss the research project. Others may also want additional topics addressed in your application, such as relevant courses and experiences you've had outside of the department. Applications are due at **midnight on Monday, February 12, 2018**.

Offers will go out on **Friday, March 2** in campus mail. We will ask for your decision on our offer by **Friday, March 9** (the last day of class).

**Reasons for Participating in the Summer Research Program**

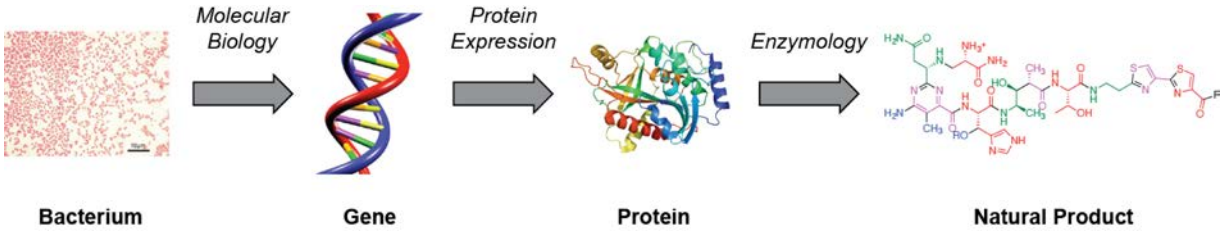
Research is considered by many to be at the pinnacle of intellectual endeavors as it is the main vehicle by which new knowledge is created. Research requires a demanding combination of intellect, creativity, endurance, and curiosity. Many valuable skills are developed in the research laboratory. Some 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 get to know your professors much better. In addition, you 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, your research project can be continued as appropriate through 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 outings, with canoe trips, baseball games, Valley Fair, and tubing having been popular choices in the past.

**Professor Chris Calderone: Enzymology of Natural Product Biosynthesis**

*Positions for 4 students*




The Calderone lab is interested in deciphering the enzymatic logic of *natural product biosynthesis*. Natural products are molecules that are produced by bacteria, fungi, and plants with a wide range of biochemical functions: some natural products serve as toxins, others are signaling molecules, and many have unknown function. Many natural products, 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 natural products in nature. Ultimately, this work can have several impacts on our understanding of biochemistry: (1) Many natural products are extremely structurally complex. Understanding how they are produced may allow us to produce clinically valuable natural products more efficiently using enzymatic, as opposed to synthetic, strategies. (2) In many cases, the production of natural products 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 natural product-producing enzymes, we can actually use this information to probe genome sequences for genes encoding related enzymes, and thereby potentially discover new natural products that could have therapeutic use.

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 characterizing a novel class of dehydratase enzymes we believe we have recently identified.

**A novel dehydratase?** An important class of natural product is the *non-ribosomal peptides*, which are biosynthesized by phenomenally complex assembly line-like megaenzymes known as *non-ribosomal peptide synthetases* (NRPS). Importantly, we can break NRPS into individual domains, each with a specific biochemical role, and these domains act in the order that they occur in the NRPS assembly line. As a result, simply by looking at the sequence of domains in an NRPS assembly line, we can predict what the non-ribosomal peptide product will be.

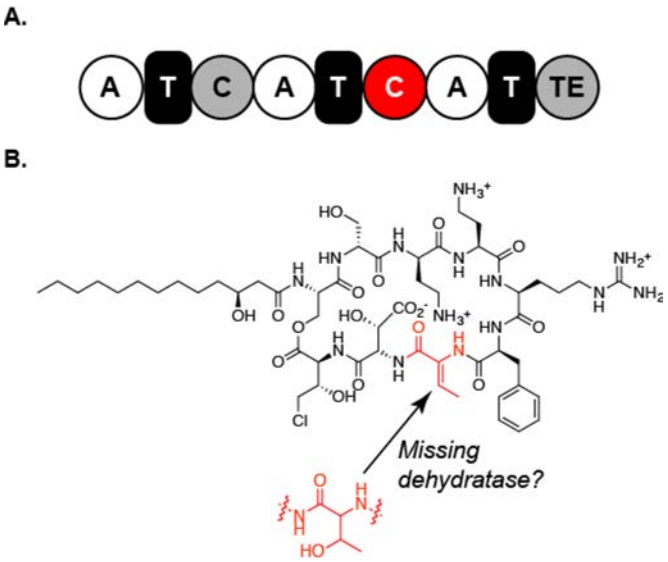



**Figure 1.** (a) Typical NRPS assembly-line organization, with domains indicated. The unusual C-variant is highlighted in red. (b) Syringomycin, an example of a natural product with a "missing dehydratase;" we hypothesize that the dehydration is catalyzed by a novel dehydrating C-domain.

Despite this linkage of NRPS domain sequence with non-ribosomal peptide structure, there are several non-ribosomal peptides whose structures do not match up with domains in the corresponding NRPS assembly lines (Figure 1). In one class of non-ribosomal peptides, it appears that dehydration has occurred at some point during the biosynthesis, but there is no "dehydratase" domain in the assembly line to catalyze the reaction. Interestingly, when we compare these "missing dehydratase" NRPS assembly lines, there appears to be a variant of a "normal" NRPS domain known as a C domain; though C domains have never been shown to catalyze dehydration, bioinformatic analysis of this particular set of C domain variants suggest that they may in fact have this never-before observed. A key focus of the lab's work this summer will be to clone, express, and purify several of these C domains, in hopes of proving their ability to catalyze dehydration.

**LearningWorks outreach.** In addition, there are opportunities for two students to participate in the LearningWorks program located in downtown Minneapolis. LearningWorks is a college preparatory program for middle-school students from traditionally underserved populations (http://www.blakeschool.org/page.cfm?p=515). The roles of these students will be determined based on interest and needs, and could include serving as summer science faculty at LearningWorks or working at Carleton, designing a set of experiments that can be utilized by students at LearningWorks. These positions are funded by a recent grant supporting our explorations of the dehydratase enzymes described above, and are designed to bring laboratory experiences inspired by the authentic research going on in the lab to LearningWorks students.

**How to apply.** The research and outreach positions have separate applications. Applicants for the research positions should have taken Chem 234 before beginning work in the lab this summer and should plan to enroll in an independent study (Chem 394) in Spring 2018. For at least one of the research openings, preference will be given to those with interest in continuing their work in the lab into summer 2019. There are no course prerequisites for the outreach position. However, for either position, you *must* meet with me to discuss your interest and background.

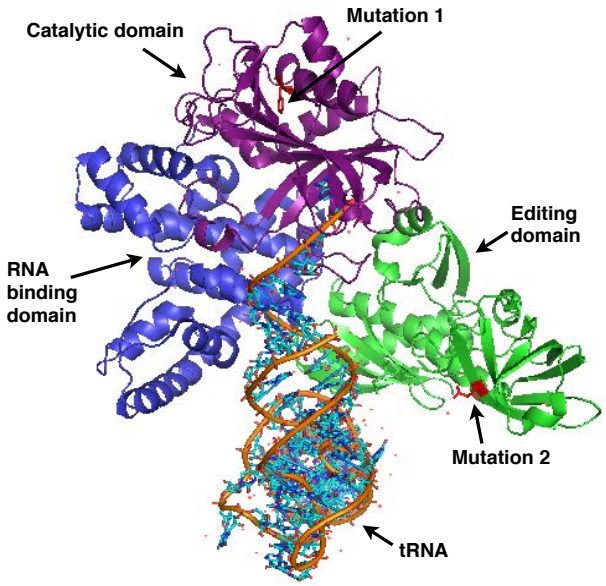
**Professor Joe Chihade**

*Positions for 1-3 students*

Converting the information stored in DNA into functional proteins requires a set of enzymes that are common to all organisms, from bacteria to humans. Among the most important of these enzymes are the aminoacyl-tRNA synthetases (aaRSs). aaRSs enforce the genetic code by catalyzing the formation of ester linkages between amino acids and particular transfer RNAs (tRNAs), so that each of the twenty amino acids is only linked to the tRNAs that match the corresponding DNA codons. So, for example, alanine is only linked to tRNAs that match the codons GCU, GCC, GCA, and GCG. In most organisms, there are twenty aaRSs, one for each amino acid. Each one of these enzymes must differentiate between several potential amino acid and tRNA substrates, recognizing subtle differences between them. Some of the enzymes use error-correcting "editing" domains to ensure that only correctly aminoacylated tRNAs are produced.

| First position | Second position: U | Second position: C | Second position: A | Second position: G | Third position |
|---|---|---|---|---|---|
| U | Phenylalanine | Serine | Tyrosine | Cysteine | U |
| | Leucine | | STOP | STOP | C |
| | | | | Tryptophan | A |
| | | | | | G |
| C | Leucine | Proline | Histidine | Arginine | U |
| | | | Glutamine | | C |
| | | | | | A |
| | | | | | G |
| A | Isoleucine | Threonine | Asparagine | Serine | U |
| | | | Lysine | Arginine | C |
| | Methionine | | | | A |
| | | | | | G |
| G | Valine | Alanine | Aspartic Acid | Glycine | U |
| | | | Glutamic Acid | | C |
| | | | | | A |
| | | | | | G |

For the several years, students in my lab have worked on understanding one particular aaRS, the enzyme that links alanine to its corresponding tRNA in human mitochondria. This enzyme, human mitochondrial alanyl-tRNA synthetase, is of interest because even though it is quite similar to alanyl-tRNA synthetases from other organisms, it recognizes and binds to its tRNA substrate in a very unique way. By making a series of changes to the tRNA substrate and seeing how they affect the rate of aminoacylation, we try to understand how this tRNA recognition works.




A few years ago, researchers in Finland discovered that two mutations in the human mitochondrial alanyl-tRNA synthetase cause severe infantile cardiomyopathy and early death. (Götz, *et al.*, *Am. J. Hum. Genet.* 88, 635, 2011). Since then several additional pathogenic mutations have been discovered. We have begun to characterize these mutations at the molecular level. Some mutations appear to cause protein misfolding, which results in a completely non-functional and mostly insoluble enzyme, others do not appear to disrupt protein folding and do not even affect aminoacylation rates much. This summer we will continue to try to understand

the lethal phenotypes of these mutations using other biochemical assays.

Work in my lab involves protein purification, *in vitro* transcription of tRNAs, creation of new RNA and protein mutants using site-directed mutagenesis and other molecular biology techniques, enzymatic assays to measure charging ability, and probing of tRNA structures to determine regions of protein-RNA interactions. This year we will also work to develop a new set of assays to follow the aminoacylation reaction without using radioactivity. I plan to take one to three new students in my lab this summer.

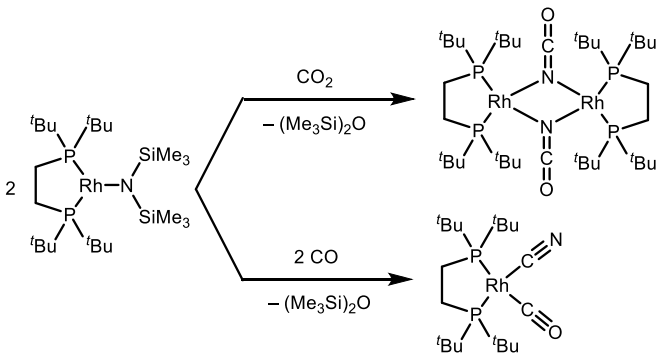
## Professor Matt Whited: Synthetic Inorganic Chemistry and Catalysis

*Positions for up to 4 new students*

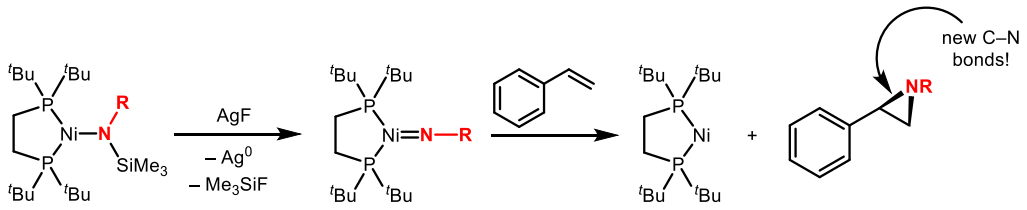
Research in my laboratory addresses problems related to energy and organic synthesis by focusing on reaction chemistry of late transition metals (Group 8–10). We are "inorganometallic" chemists, shamelessly exploiting the whole periodic table (especially silicon) for our purposes! This summer, research 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** *(supported by ACS-PRF)*

Over the past 3 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 continue to transition 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. One possible reaction is shown below, but there are many directions to pursue this research!

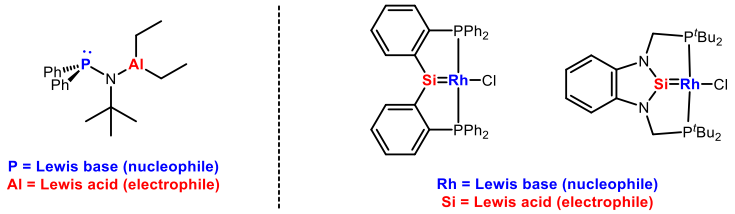



[1] Whited, M. T.; Kosanovich, A. J.; Janzen, D. E. "Synthesis and Reactivity of Three-Coordinate (dtbpe)Rh Silylamides: $CO_2$ Bond Cleavage by a Rh(I) Disilylamide" *Organometallics* **2014**, *33*, 1416–1422.

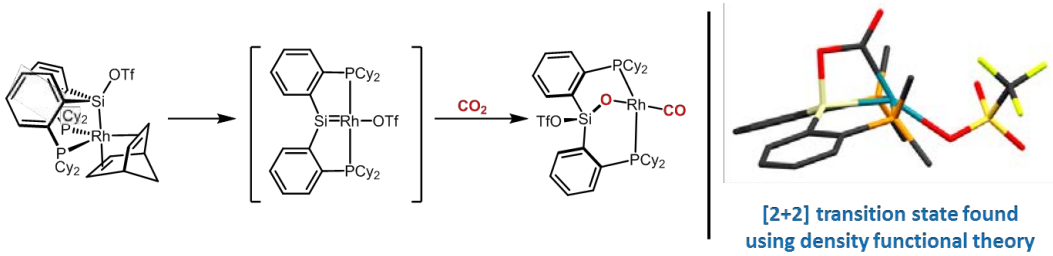
[2] Whited, M. T.; Qiu, L.; Kosanovich, A. J.; Janzen, D. E. "Atom and Group Transfer from Heteroallenes and Carbon Monoxide at a Three-Coordinate Rh(I) Disilylamide", *Inorg. Chem.* **2015**, *54*, 3670–3679.

**Ambiphilic Metal Complexes for Cooperative Small-Molecule Activation** *(supported by NSF)*

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 Si=Rh double-bonded species such as the ones shown above,[3] a surprising and exciting finding. More recently, we have been examining stoichiometric and catalytic reactions, especially transformations of carbon dioxide, that involve Si=M double-bonded intermediates.[4,5]




**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 and 2-dimensional NMR and X-ray crystallography will be our primary characterization techniques, but we will also use IR and UV-Vis spectroscopies and GC-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.

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[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.

[4] Whited, M. T.; Deetz, A. M.; Donnell, T. M.; Janzen, D. E. "Examining the Role of Rh/Si Cooperation in Alkene Hydrogenation by a Pincer-Type [$P_2$Si]Rh Complex" *Dalton Trans*. **2016**, *45*, 9758–9761.

[5] Whited, M. T.; Zhang, J.; Ma, S.; Nguyen, B. D.; Janzen, D. E. "Silylene-Assisted Hydride Transfer to $CO_2$ and $CS_2$ at a [$P_2$Si]Ru Pincer-Type Complex" *Dalton Trans*. **2017**, *46*, 14757–14761.

**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 or come to an open session (times to be announced).**
- **Talk with one (or more) of the students who have recently worked in my lab: Jim Zhang and Paul Peterson (summer); Madeline Chosy, Jason Ma, Ben Byun, Kitty Miao, Isaac Martinez, and Joseph Luther (academic year).**

**Professors Dave Alberg and Gretchen Hofmeister.**
**Organocatalysis: Synthetic Methodology and Structural and Computational Studies of Catalyst-Transtion State Complexes.**

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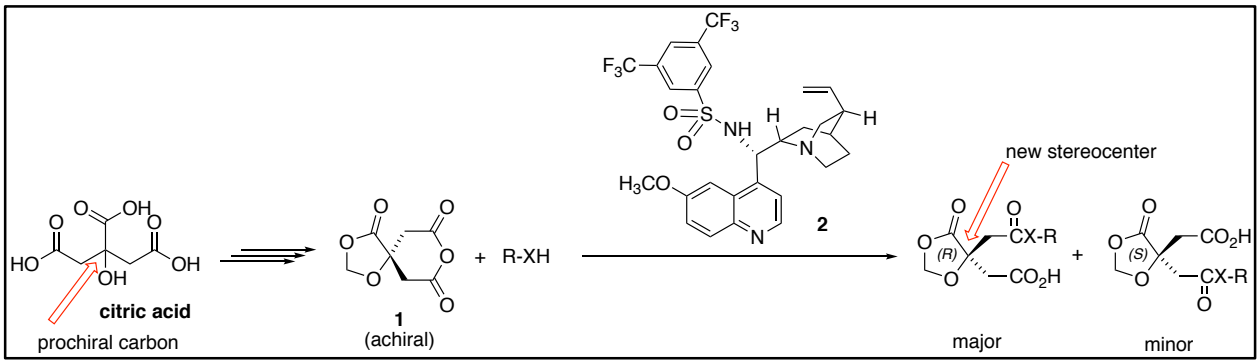
*Positions for 2 new students*

We are looking for two new students to join our studies on a class of organocatalytic reactions. Organocatalysis involves the use of small organic molecules to catalyze reactions that are valuable in synthesis. Our primary interest is to understand how chiral organocatalysts convert achiral reactants into enantio-enriched chiral products.

One of our projects involves the desymmetrization of anhydride **1**, a derivative of the pro-chiral citric acid. The desymmetrization of the citrate-derived anhydride **1** with nucleophiles (R-XH), mediated by quinine-derived catalyst **2**, is shown below.

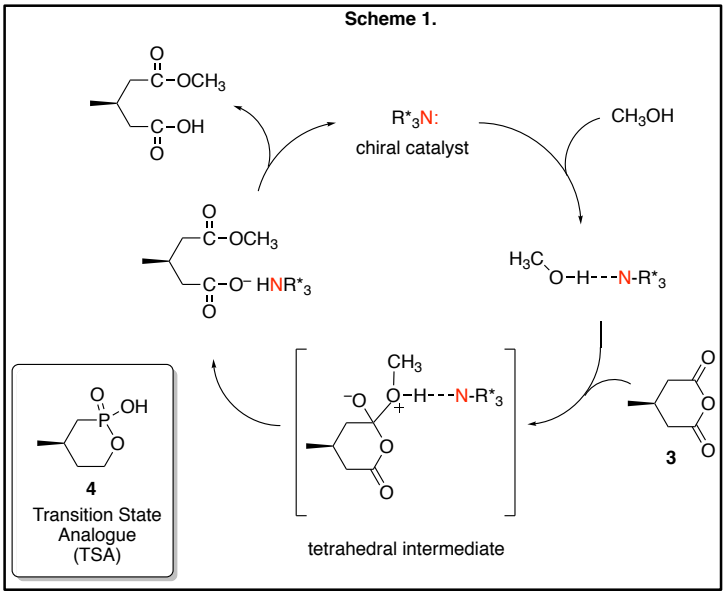



We have explored this reaction with a number of nucleophiles, including a series of substituted phenols. Our work with the phenols revealed an interesting dependence of the enantioselecitivity of the reaction on the electronic nature of the phenols, with electron-rich phenols providing better enantioselectivity in the reaction than their electron-poor counterparts. In order to understand what this says about the mechanism of the reaction, we need to complete several experiments to explore the nature of the trends we observe. Among other work, this project will involve synthesis, enantiomer resolution by traditional fractional crystallization, and running and analyzing (by chiral HPLC) variations of the desymmetrization reaction shown above.

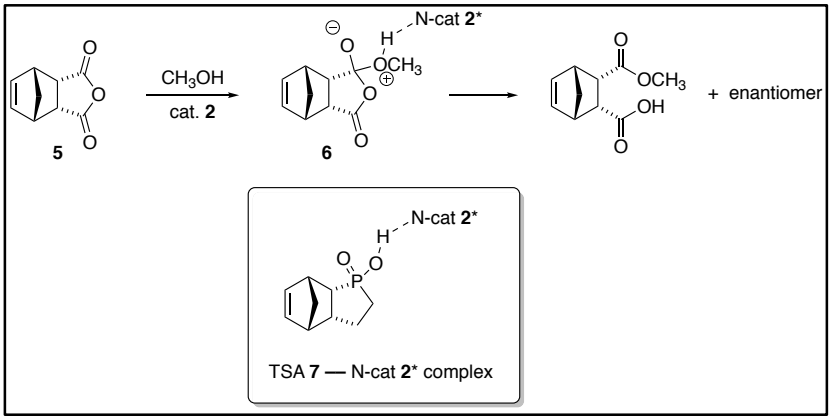
Our other project is aimed at identifying the molecular interactions between the catalyst and substrates that account for the enantioselectivities in these desymmetrization reactions. Our studies involve both experimental work, as well as computational efforts, carried out in collaboration with a theoretical chemist, Dani Kohen.

Our approach involves the synthesis of stable mimics of the putative transition state (TS) for the anhydride substrate and studies of the interaction of these transition state analogues (TSAs) with the catalyst by computational and experimental methods. Scheme 1 shows the catalytic cycle for the reaction of anhydride **3** with methanol. The important TS that determines the enantioselectivity of the transformation results from the reaction of the catalyst-activated methanol with the anhydride, to form the tetrahedral intermediate (by the Hammond postulate,

the TS should be very similar to this intermediate.) We have synthesized TSA **4** to mimic this TS shown in Scheme 1. Likewise, we have also prepared TSA **7**, corresponding to TS **6** in the desymmetrization reaction of anhydride **5**.




The student working on this project would split time between experimental work and computations. Among our goals in the lab are to determine the absolute configurations of our resolved enantiomers of **7**, and to crystalize TSA-catalyst complexes and investigate their structures by X-ray crystallography. We will also examine these complexes by computational methods and we will compare our experimental findings with the computational results.




## More Information and Applying:

Students who want to hear more about the research projects should attend one of the following two scheduled meetings to be held in the Old Music Hall 107:

- Friday, February 2 at 8:00-9:00am
- Wednesday, February 7 at 8:00-9:00am

Applicants for our research positions should complete Organic Chemistry II (CHEM 234) before beginning work in the lab this summer and should plan to enroll in an independent study (CHEM 394) in Spring 2018.

***DEBORAH GROSS: THE CHEMISTRY OF ATMOSPHERIC AEROSOL PARTICLES***
*Positions for 1-2 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.

**Figure 1. One of the Carleton College ATOFMS instruments.**

I hope to have <u>two students</u> work with me this summer. Students will work collaboratively on bringing the instrument "Wallace" back to working order, following up on the work done by last summer's group, and will divide up and take on a variety of projects, with the following possibilities available: 1) Continuing to develop data analysis methods to help us identify particle sources from the ATOFMS data signatures; 2) Collecting and analyzing ambient data collected in Northfield and testing methods to convert the number concentration to speciated mass concentration; 3) Characterizing the particles emitted by "clean" cookstoves in the indoor environment, especially relevant to Ethiopian style cooking techniques (see Figure 2); and 4) Developing methods to analyze light emitted in the ion source, which can provide elemental information. Students' interests will drive selection of the projects.

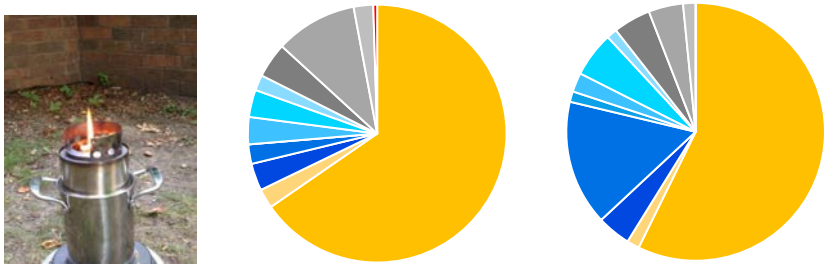


**Figure 2. Fraction of particles of various types emitted from a prototype clean cookstove (left) during a water boiling test (middle) and cooking lentils (right). Colors correspond to different particle types, with yellows being elemental carbon, blues being organic carbon, grays being ash, and red being ambient.**

***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 instruments. Email to make an appointment or attend the open meeting scheduled on Jan. 30 from noon – 1pm in Old Music Hall 313. It's a requirement for applying that we've talked, either individually or at the open meeting!
- Plan to enroll in an independent study in Spring, 2018, to prepare for the summer.