# Developing a Passion for Science

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In March 2010, as a graduating high-school student, I was fortunate to publish an article in the Nucleus[1] describing my career aspirations, and how my progressive research internships helped guide my interests and passion for science. I am extremely grateful for an opportunity to write a follow-up article detailing my experiences since that time, and how I have continually sought out opportunities to conduct research and work towards bringing my goal of being admitted to an M.D./Ph.D. degree program to fruition. I was thrilled to work with several extraordinarily distinguished scientists, and I was struck by how remarkably well they mentored, guided and inspired their students.

I am currently a senior majoring in chemistry with a minor in biomedical engineering at Carnegie Mellon University. I strive to ultimately pursue a career in academic medicine. This aspiration was instilled in me at a very young age, fueled by a love and passion for sports, science and medicine, and a desire to help people. To complement my determination and excitement at the prospect of advancing science, an entrepreneurial mindset was essential in seeking out opportunities for conducting research.

For my first laboratory experience, I was fortunate to secure a research appointment at the California Institute of Technology under Professor Robert Grubbs. Working under a Nobel Laureate was truly an inspiring experience. I studied olefin metathesis by the Grubbs catalyst and performed chiral reductions with menthol as an auxiliary[2]. This opportunity developed my technical skills and introduced me to the problem-solving mindset necessary to carry out scientific research. From my first experience in a chemical laboratory, I was hooked. I loved research, and I knew that solving problems using precise scientific methodology would be instrumental in reaching my ultimate goal of becoming a physician.

Next I secured a research appointment at the Beth Israel Deaconess Medical Center, under the mentorship of Dr. Vikas Sukhatme, Chief Academic Officer. In my first exposure to cell culture work, I treated cancerous A549 cells with combinations of anticancer drugs to determine their synergistic efficiency in blocking mitochondrial function and causing selective apoptosis. This incredible experience, allowed me to work with a living organism, and directly see the benefits of advancing science at the cellular level.

I then worked in the field of organic chemistry at Harvard University under the supervision of Professor Eric Jacobsen. The Massachusetts Life Sciences Center awarded me a highly competitive internship in the “Internship Challenge”. I designed and implemented thiourea catalysts for enantioselective synthesis. This project allowed me to delve into mechanistic studies of reactions, promising to give me a greater insight into the molecular basis of medicine.

During a study abroad semester at the University of Cambridge, I worked in flow chemistry under the mentorship of Professor Steven Ley. This was truly an amazing experience to learn both the science and culture of England and life in the hallowed halls of Trinity College. I worked to optimize the Oppenauer oxidation and Meerwein-Ponndorf-Verley reduction using hydrous zirconia catalysts.

Oxidation is an extremely important step used in the synthesis of numerous commercial pharmaceutical drugs. However, there is currently no perfect method to perform oxidation without the use of expensive heavy metals, toxic reagents, or harsh conditions. My goal was to develop a faster, cheaper, safer system to perform Oppenauer oxidations in a more sustainable manner, using green solvents, less toxic reagents, and mild conditions[3].

Hydrous zirconia was chosen as a catalyst because it is cheap, recyclable, stable to high temperatures, and was shown to work well in MPV reductions. The hydrous zirconia catalyst was calcinated at different temperatures to increase its active surface area. Below, Figure 1 shows the ketone products of benzylic alcohols obtained through the use of acetone as an oxidant at 80 °C.

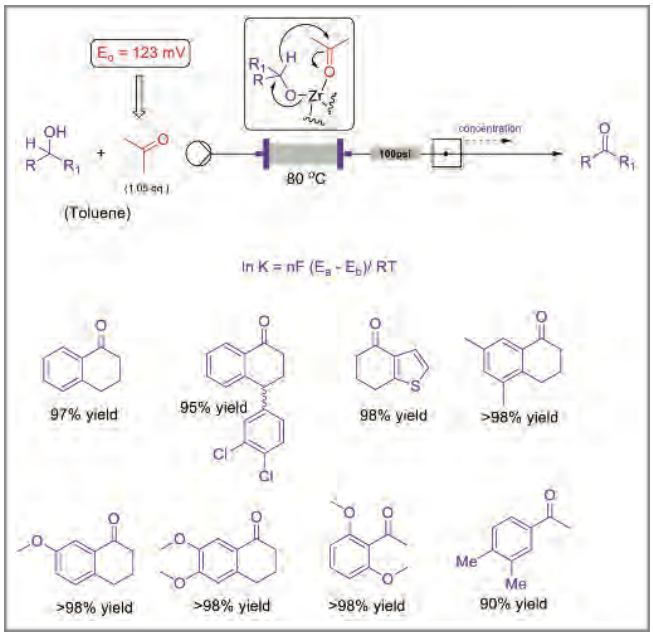


Figure 1: Oxidation products using acetone as oxidant[3]

With acetone used as the oxidant, the above products were obtained in high yield, with very few aldol condensation side products. These products had relatively low oxidation potentials, and, due to their relatively flat, fixed geometries, they were readily able to bind to the catalyst in the proper conformation to carry out the electron-transfer mechanism. However, to oxidize alcohols with higher oxidation potentials, a large excess of acetone would be needed, which would result in greater aldol side product condensation and a lower yield. Hence cyclohexanone and

trimethylacetealdehyde were used as oxidants in the oxidation of alcohols with higher oxidation potentials. Below, Figures 2 and 3 show the products obtained using cyclohexanone and trimethylacetaldehyde, respectively, as oxidants over a temperature range of 40-80 °C.

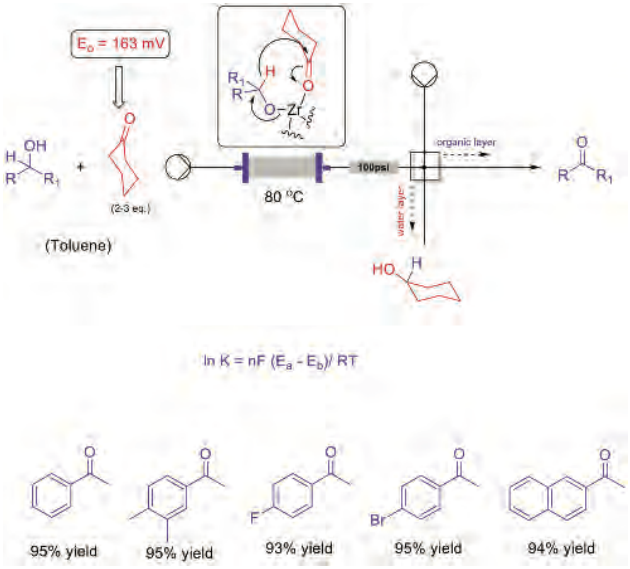


Figure 2: Oxidation products obtained using cyclohexanone as oxidant[3]

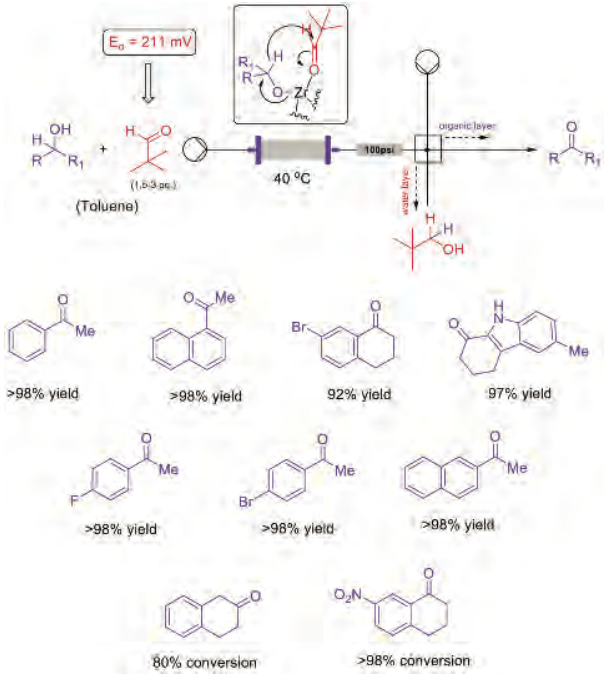


Figure 3: Oxidation products obtained using trimethylacetaldehyde as oxidant[3]

This Oppenauer oxidation method proved to be extremely effective and offered the advantages of being extremely cheap, using mild conditions and less toxic reagents, allowing for fast delivery of products, (within 8-25 minutes) and causing a reduced downstream work-up process.[3] In addition to this project, I conducted cerium oxide enhanced Sonogashira reactions by perovskite catalysts.[4] A flow procedure was chosen to contain the heterogeneous catalyst, reduce downstream processing, and deposit the catalyst onto the solid support surface. The perovskite catalysts were previously used by the Ley group for Sonogashira and Suzuki reactions in batch, and were very attractive due to extremely low level palladium loading and high ability for reuse without loss of turnover. A solid support was necessary to both contain the catalyst and help prevent the leaching of palladium from the catalyst. Cerium oxide is commonly used in the water gas shift reaction, and cerium oxide-supported nanoparticles have shown high stability and catalytic turnover. Although the perovskite catalysts contained extremely low levels of palladium and iron, it was shown that they were effective in catalyzing Sonogashira reactions using different substrates with varying electronic effects at high yield. In addition, it was shown that as the level of cerium oxide was increased the yield of the reaction increased, demonstrating a synergistic effect from the cerium oxide. This method showed the advantages of being extremely cheap, using an extremely low level of palladium, allowing for fast delivery of products, and a high potential for reuse without a loss of catalytic turnover. Below, Figure 4 shows the products of Sonogashira reactions obtained through this method.

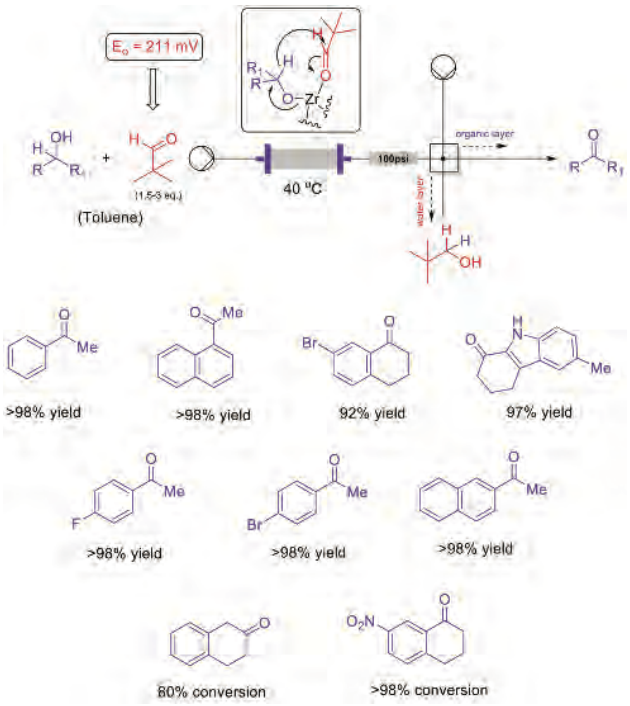


Figure 4: Sonogashira products using perovskite catalysts[4]

Currently, I am working under Professor Danith Ly at Carnegie Mellon University, synthesizing guanidinium-rich peptide nucleic acids (PNAs) for use in gene correction. I am continually working to further develop my technical and analytical skills, and to gain a greater understanding of the mechanism of medicine at the molecular level. This research has helped me grow tremendously as a researcher, and is allowing me to use chemistry knowledge and skills to attempt to ultimately provide a useful treatment to help save lives. This experience is extremely rewarding to me, and provides me further motivation to apply knowledge of chemistry towards a medical career.

These numerous laboratory-based research experiences were extremely inspiring and motivating and they helped bolster my desire to actively use research as a means for advancing clinical practice. To gain a greater understanding of how medicine is administered in a clinical setting, I con- ducted research at Massachusetts General Hospital under Dr. Ravi Thadhani. I recruited patients, collected blood samples, and performed statistical analysis for "Predictive Bio- logical Markers for Hepatorenal Syndrome" and "Perceptions of CVVH" observational clinical trials. Work- ing in a hospital setting was awe-inspiring and extremely humbling. I was given the opportunity to directly interact with patients every day in the intensive care unit, and I learned the importance of effective communication skills. Working with extremely sick patients was initially very jar- ring, but provided further motivation for me to work tirelessly to improve their lives.

Late last summer, I was honored to be offered an advisory position with Empiriko. The central theme of Empiriko is to connect drug discovery to patient outcomes, so the right therapies are developed for the right subpopulation, and physicians are able to treat patients more effectively. Led by my father, Dr. Mukund Chorghade, scientists are progressing in the design and development of proprietary oxidative catalysts to conduct and predict metabolic profiling of drugs, both in vitro and ex vivo, using chemosynthetic livers rather than human liver cells.[5]

These catalysts (commercialized under the name BiomimiksTM) work to mimic the function of Cytochrome P450. With this technology, drug discovery scientists can quickly screen a series of compounds by reacting them with permutations of the patented oxidative catalysts, co-oxidants and non-aqueous solvents. This powerful combination serves as an "in vitro cocktail" that reduces the elapsed time for drug screening from several days to a matter of hours[5]. In addition, BiomimiksTM can be used by clinicians to dynamically measure a patient's response (drug-to-drug interactions, dosing levels and regimens) to a spectrum of drugs and incorporate the results into more effective diagnosis and patient treatment. The long-term strategy is to continuously enhance the BiomimiksTM platform by developing a "Chemosynthetic-liver-on-a-chip" and other future applications (e.g., defining CYP-specific reactions and delineating bioequivalence among species, liver dialysis). Currently, I am involved in performing soft-spot analysis of drug molecules, predicting metabolism pathways and profiles and correlating mass spectrometry data to potential metabolites.

The accountability, responsibility, and leadership and critical thinking skills I learned from these research experiences make me a perfect fit in the highly collaborative and motivated

environment within a medical team. I aim to use my extensive research experience to secure an M.D./Ph.D. degree, and discover causative and curative factors in sports medicine. Receiving this joint training is essential to further understanding medicine at the molecular level. It will allow me to use this research-based problem-solving approach, coupled with knowledge of anatomy and physiology, to develop novel treatments to save and improve lives.

**References:**


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