

PRF grant #: 57440-ND1

Project Title: Development of an Aromatic C-H Bond Substitution Approach

PI Name, Affiliation: Professor Jon T. Njardarson, University of Arizona
Department of Chemistry and Biochemistry, Tucson, AZ 85721, USA

The thesis of this grant is focused on realizing in situ polarity reversal of catechol type structures by generating highly reactive phenoxonium ions, through dearomatization (*DeA*) approaches, which can then be selectively captured with heteroatom and carbon nucleophiles before being rearomatized (*ReA*) in the same pot. The net result is strategically selective substitution of aromatic C-H bonds with C-C or C-X (X = O, S, N etc.) without use of pre-installed functional groups, precious transition metals or complex directing groups.

Progress to date has been excellent, and we are pleased to report that we have published, with support from this ACS-PRF ND grant, our first publication (Smith, D. T.; Vitaku, E.; Njardarson, J. T. "Dearomatization Approach to 2-Trifluoromethylated Benzofuran and Dihydrobenzofuran Products" *Org. Lett.* **2017**, *19*, 3508-3511). In this paper, we demonstrated how in situ generated phenoxonium ions could be captured by a designer fluorinated nucleophile, which following substitution formed a hemiacetal with the resulting rearomatized phenol. Optimizations were challenging, but through fantastic effort by David (one of the top graduate students in our program who is also a veteran) we were finally able to identify the right solvent, stoichiometry, order of addition to achieve success. Wonderfully, David took the initiative and learned about Design of Experiment (DoE) approaches to optimizations and used these principles and a computer program to guide his optimization efforts. The products turned out to be unstable, and as part of this effort we designed work-up procedures and in situ transformations to enable us to deliver both fluorinated dihydrobenzofuran and benzofuran products.

Concurrently with these efforts, we have been studying in great detail the corresponding *ortho*-keto phenoxonium ions, and the selective introduction of matched nucleophiles in their *para*-positions. My students are making wonderful progress and it is our goal to be able to publish two additional papers before the end of the ACS-PRF ND grant period at which point it is our intention to use these publications and other preliminary results as a strong foundation for us to pursue federal funding. Toward that goal, we are delighted to report that Professor Paul Cheong (Oregon State University) has agreed to support our investigative effort as our computational partner. Paul and his student will propose

The impact of this ACS-PRF ND grant is on multiple fronts including new exciting research contributions, my student careers and experiences as well as my own. Let me elaborate more about each one of these Impact categories.

Research Impact: The dearomatization-rearomatization (DeA-ReA) approach we are investigating and establishing promises to be an impactful new method to functionalize aromatic rings selectively in a way that is currently very difficult for the substrate classes under investigation. Once developed and mature this approach will be useful for small and complex molecule synthetic planning and to streamline synthesis of commodity chemicals as well as transform simple commercial catechol type chemicals into higher value products. Furthermore, as we learn more about this reaction, how to control it and its nuances we are realizing the birth of new unanticipated exciting research directions.

PI-Career Impact: One of the challenges with funding these days is that it is very difficult to find funding to start a new research direction as most federal grants are challenging to land without significant preliminary results and ideally a publication or two. This is why the ACS-PRF ND grant mechanism is so wonderful and why it has benefitted the PI so greatly as it has enabled the PI to launch and pursue a new path of investigation that will allow the generation of enough data, publications and proof-of-principle results to at the end of the ACS-PRF ND grant period (Fall 2019) to be able to competitively pursue new federal grants from agencies such as the National Science Foundation (NSF) and National Institute of Health (NIH). The PI is grateful to the ACS-PRF ND program for their generosity and opportunity they have provided.

Student-Career Impact: My students have greatly benefitted professionally from being part of this new and exciting project, which has been rewarded to date with one peer-reviewed publication and exciting results that we are presently advancing and hope to publish next year. It is our hope, that by the end of the grant period (Fall 2019) that the students that are part of this project will not only have two additional publications but will also have been part of seeing their scientific successes being used to put together a competitive federal grant application. During this time one undergraduate student was part of the team, and was mentored by me and the lead graduate student. In summary, the students associated with this project have learned a) how to start a new project from scratch and advance it to a successful first deliverable (publication), b) learned how to put a publication together, including perfecting characterization, writing the manuscript and supplementary section, c) have learned about the joys of unintended exciting discoveries (the greatest part of science) through their experiences, and d) soon will be part of writing a grant application based on their successes. Beyond the specific students that have and are working on this exciting project, the rest of my research group (graduate and undergraduate students) are also positively impacted as they get to learn about a new science direction and follow their peers progress and synthetic challenges they need to overcome along the way in a different synthetic context than existing group projects.