PRF grant #: 57440-ND1

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

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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.

David has graduated since last progress report, but before he trained two new graduate students (Nick Lauta and Ryan Williams) who are now leading this project forward. Not surprisingly, having this important project being led by a productive talented 5th year student, to now being led by two excellent first year student progress has slowed down momentarily. Ryan and Nick are doing phenomenally well, and I am very proud of their progress to date.

We expect, based on outstanding work by David, Ryan and Nick, to submit our 2nd ACS-PRF ND supported publication in the next two months. This work details a new oxidative dearomatization based reaction to form indoles from simple building blocks. Extensive substrates scope has already been established and characterization of new structures as well as detailed mechanistic efforts are currently underway. We plan to submit these new exciting results to Angewandte Chemie or J. Am. Chem. Soc.

Concurrently with these efforts, we have been investing thoroughly *ortho*-keto phenoxonium ions, and the selective introduction of matched nucleophiles in their *para*-positions. My students are making great progress, and it is our goal to be able to publish additional papers before the end of the no-cost extension grant period (August 2020).

I am pleased to report that results emanating from ACS-PRF investigations were used to submit a NIH RO1 grant application early this year. This NIH grant was not funded, but it was clear based on feedback and comments that more results would aid in re-submission efforts, which is one of the reasons (along with David graduating) why we requested a no-cost extension.

Our new indole results, and publication, in addition to para-selective addition results we expect will prove instrumental in helping us land federal funding.

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) approaches, we are investigating, promise to be useful new reactions to functionalize aromatic rings selectively, and as such will find applications for small and complex molecule synthetic planning and to streamline synthesis of commodity chemicals. Furthermore, as we learn

more about these oxidative dearomitzation/rearomatization reactions new unanticipated exciting research directions are expected to emerge as is often the case in underexplored areas of research.

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 significant as it has enabled the PI to pursue a new path of investigation that will allow the generation of enough data, publications and proof-of-principle results to competitively pursue new federal grants (NIH, NSF etc.). The PI is grateful to the ACS-PRF ND program for their generous support and for the opportunity they have provided to expand the PIs research program.

Student-Career Impact: My graduate (David, Nick and Ryan) and undergraduate students have greatly benefitted professionally from their participation in this new research direction enabled by ACS-PRF ND funds, which has to date resulted in one peer-reviewed high impact publication with many more on the horizon. These students have additionally been part of assembling and submitting a federal grant application and as such learned what it takes to make the case for funding of a research project, as well as writing a manuscript and present their research as part of oral presentations. I am delighted to report, that during David's time on this project he received all the highest honors bestowed on a graduate student in our department, including the highest award (Marvel award). This past summer, Nick was awarded one of the department's early excellence award recognition. These wonderful students have learned how a) to initiate a new project and advance it to , b) to assemble and write a manuscript and supplementary section, c) enjoyable unanticipated discoveries are, d) to write a grant application and e) to go about cracking a reaction mechanism. Beyond the specific students associated with this project, other Njardarson group members have also been 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.