

NARRATIVE PROGRES REPORT

PRF Grant Number: 57175-DNI1

Project Title: Dearomative Functionalization with Arenophiles

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The discovery and development of new processes for the conversion of simple chemicals to high-value compounds is a critical challenge to contemporary organic synthesis. Our group focuses specifically on dearomatization reactions, transformations that convert arenes into compounds of greater complexity and broader utility. We believe that this area is still largely underdeveloped, especially when compared to the arsenal of transformations that are available for olefin functionalization. Our long-term goal is to develop controlled, alkene-like dearomative functionalizations of readily available arenes, thus capitalizing on well-established olefin chemistry to expand the field of dearomative functionalization. Our working strategy is to use arenophiles, small heteroatom-containing molecules that can undergo visible-light-mediated para-photocycloadditions with arenes. Arenophiles simultaneously induce dearomatization, introduce functionality, create stereogenic centers, and enable further chemoselective *in situ* transformations of the resulting adducts. Subsequent transformations, based on olefin functionalizations or transition metal catalysis, followed by arenophile moiety manipulation, then provide selective access to the corresponding functionalized products. This arenophile-based dearomative strategy can be viewed as formally isolating π -bonds within the aromatic starting material, allowing standard alkene chemistry to be performed thereon.

Using the second half of funds provided by ACS PRF we have recently reported several new dearomative methods and syntheses. For example, we have completed a second-generation, enantioselective synthesis of lycoricidine and narciclasine (Bingham, et al. *JACS* 2019). Our strategy for accessing this unique class of natural products is based on the development of a Ni-catalyzed dearomative *trans*-1,2-carboamination of benzene. The effectiveness of this dearomatization approach is notable, as only two additional olefin functionalizations are needed to construct the fully decorated aminocyclitol cores of these alkaloids. Installation of the lactam ring has been achieved through several pathways and a direct interconversion between natural products was established via a late-stage C-7 cupration. Using this synthetic blueprint, we were able to produce natural products on a gram scale and provide tailored analogs with improved activity, solubility, and metabolic stability. Moreover, we have also completed synthesis of anticancer agent idarubicinone (Dennis, et al. *JACS* 2019), using a dearomative hydroboration, a unique transformation enabled by this grant. Thus, idarubicinone could be made in only a few steps from a polynuclear tetracene.

These funds were also used to sponsor methodology work. For instance, during the last funding period we reported dearomative deamination (Wertjes, et. al *JACS* 2019), carboamination (Tang, et al. *ACIE* 2019) and oxyamination (Tang, et al. *ACIE* 2019). These one-pot methods utilize arene–arenophile *para*-cycloadducts, that undergoes formal allylic substitution with amine, carbon, or oxygen nucleophiles under Pd-catalysis. The products are obtained with exclusive *syn*-1,4-selectivity; the procedures permit enantioselective desymmetrization, and the products could be elaborated to numerous further small, highly-functionalized molecules. Overall, these novel dearomative functionalization strategies offers rapid and straightforward access to complex building blocks, which are difficult to prepare otherwise, from simple arenes.

The current outcomes related to our 2nd year of ACS PRF funding are:

Palladium-Catalyzed Dearomative syn-1,4-Diamination

W. C. Wertjes, M. Okumura, and D. Sarlah, *J. Am. Chem. Soc.* **2019**, *141*, 163–167.

Enantioselective Synthesis of Isocarbostryril Alkaloids and Analogs Using Catalytic Dearomative Functionalization of Benzene

T. W. Bingham, L. W. Hernandez, D. G. Olson, R. L. Svec, P. J. Hergenrother, and D. Sarlah, *J. Am. Chem. Soc.* **2019**, *141*, 657–670.

Synthesis of (\pm)-Idarubicinone via Global Functionalization of Tetracene

D. G. Dennis, M. Okumura, D. Sarlah, *J. Am. Chem. Soc.* **2019**, *141*, 10193–10198.

Palladium-Catalyzed Dearomative syn-1,4-Carboamination with Grignard Reagents

C. Tang, M. Okumura, Y. Zhu, A. R. Hooper, Y. Zhou, Y.-H. Lee, D. Sarlah, *Angew. Chem. Int. Ed.* **2019**, *58*, 10245–10249.

Palladium-Catalyzed Dearomative syn-1,4-Oxyamination

C. Tang, M. Okumura, H. Deng, D. Sarlah, *Angew. Chem. Int. Ed.* Early View, DOI: 10.1002/anie.201909838

Impact on personnel:

This grant has been supporting several graduate students, as well as one postdoc. This resulted in many positive impacts. For example, postdoc funded by this grant made significant progress and was able to move to the new academic position. One graduate student received first-author paper while supported by PRF and is about to graduate. Another graduate student supported by this grant from the start date is spearheading a unique synthesis of aminoglycosides from benzene, which is anticipated to have significant impacts in medicinal chemistry.