

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 funds provided by ACS PRF we have recently reported several new dearomative methods and syntheses. For example, we have completed the synthesis of lycoricidine (Figure 1, Southgate *et al.*, *Angew. Chem. Int. Ed.* 2017). Salient features of this synthesis are an arenophile-mediated dearomative dihydroxylation of bromobenzene under Narasaka-Sharpless conditions and subsequent transpositive Suzuki coupling. Moreover, we have demonstrated the general applicability of this strategy by preparing nine different dihydroxylated biphenyls. Finally, by employing a late-stage hydroxylation of position 7, we were able to develop a direct synthetic connection between lycoricidine and narciclasine.

Moreover, by applying this new dearomative protocol, we have recently completed a second-generation, enantioselective synthesis of lycoricidine and narciclasine (Bingham, *et al.* *JACS* 2019) unpublished results). 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.

These funds were also used to sponsor methodology work. For instance, we recently reported dearomative deamination (Wertjes, *JACS* 2019). This one-pot method utilizes arene-arenophile para-cycloadducts, that undergoes formal allylic substitution with amine nucleophiles under Pd-catalysis. The products are obtained with exclusive *syn*-1,4-selectivity; the method permits enantioselective desymmetrization, as well as elaborations of amine-containing drug molecules. Furthermore, the resulting unsaturated products are amenable to numerous options for diversification. Overall, this novel dearomative functionalization strategy offers rapid and straightforward access to complex building blocks, which are difficult to prepare otherwise, from simple arenes.

In addition to research, this funding enabled PI a ½ month summer salary during which he devised new research projects and also wrote a perspective on this work (Okumura and Sarlah, *Synthesis*, 2018).

Finally, we are actively developing additional methodologies and synthetic applications, which will be reported soon.

The current outcomes related to our 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.

Arenophile-Mediated Dearomative Functionalization Strategies

M. Okumura, D. Sarlah, *Synlett* **2018**, *29*, 845–855.

Total Synthesis of Lycoricidine and Narciclasine by Chemical Dearomatization of Bromobenzene

E. H. Southgate, D. Holycross, D. Sarlah, *Angew. Chem. Int. Ed.* **2017**, *56*, 15049–15052.

Impact on personnel:

This grant has been supporting several graduate students, a PI (1/2 summer month), as well as one postdoc. This resulted in many positive impacts. For example, postdoc funded by this grant made significant progress (unpublished) and was able to move to the new academic position in China. One graduate student received first-author paper while supported by PRF and also graduated. 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. The PI, while supported by PRF, was able to write a review article as well as two manuscripts.