

56603-DNII

(Poly)cationic Nitrogen Substituted λ^3 -Iodanes for the Functionalization of Chemical Feedstocks
Sarah Wengryniuk, Temple University**Research Period Summary:**

This DNI award aimed to advance (poly)cationic hypervalent iodine reagents, possessing heterocyclic nitrogen-ligands (*N*-HVI) (Figure 1), as a novel and powerful class of synthetic reagents. This overarching goal was approached through three specific aims involving focused reagent development as well as synthetic derivatizations of chemical feedstocks. Building on our significant discoveries from the first year of funding, the project saw excellent progress during the final year of support. Research into reagent development has led to an expanded library of >25 λ^3 *N*-HVIs and a deeper understanding of their stability and reactivity. Additionally, we expanded the oxidation state of these compounds to include a λ^5 -iodanes, possessing bidentate nitrogen ligands, with enhanced reactivity and superior safety profiles (Aim 2). These reagents have been found to be one of the only means to oxidize challenging electron-deficient phenols to *o*-quinones (Aim 3). In other efforts towards oxidative transformations, we explored the application of *N*-HVIs in high valent nickel chemistry, and developed a tunable platform to access either Ni(III) or Ni(IV) species depending on the oxidant used (Aim 3, not pictured). Furthermore, advancements in reaction discovery included the oxidative ring expansion of aliphatic secondary alcohols as well as a simple alcohol oxidation protocol with λ^3 -iodanes facilitated by Lewis base activation (Aim 1). The alcohol oxidation protocol included a method for the *in situ* generation of *N*-HVIs, a significant advancement of the practical application of these compounds. These works have led to two published manuscripts and three additional which are under preparation. The support of the PRF has facilitated foundational discoveries in our group's work with *N*-HVIs, from which our research program will continue to grow and expand for years to come.

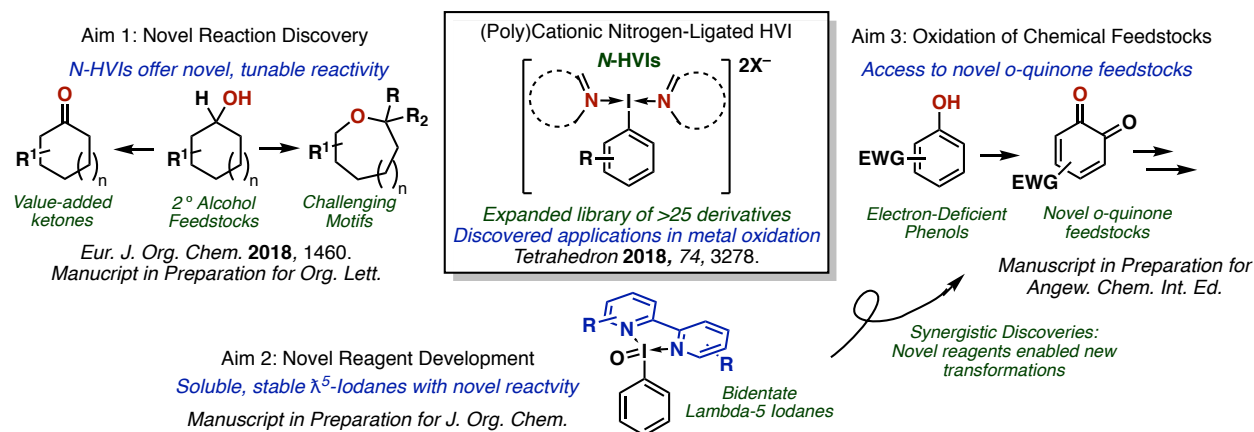


Figure 1. Summary of key discoveries across three proposal aims. Development of novel class of (poly)cationic *N*-HVI reagents and exploration of their applications in organic synthesis.

- **Aim 1 Progress:** Our novel electrophilic alcohol ring expansion was extended to secondary aliphatic alcohols. Through this effort our existing library of *N*-HVI reagents has expanded and the effect of reagent sterics and electronics on reactivity has become more clearly understood. Additionally, this work led to the development of a complimentary, simple approach to direct alcohol oxidation with *in situ* generated *N*-HVIs. This method for *in situ* *N*-HVI generation will also address limitations of reagent bench stability and expand the potential applications of our chemistry.
 - **Products:** This work resulted in a publication in *Eur. J. Org. Chem* as well as a manuscript in preparation for *Organic Letters*.
- **Aim 2 Progress:** Lambda-3 *N*-HVIs: Supported by both targeted efforts as well as our parallel research programs in reaction development, our library of lambda-3 *N*-HVIs has expanded to include >25 derivatives. Using this diverse reagent set, efforts to fully understand the effects of ligands on stability and reactivity are ongoing. Lambda-5 *N*-HVIs: Attempts to synthesize reactive, chiral lambda-3 derivatives, as outlined in the original proposal, were plagued by lengthy syntheses and low reactivity. Therefore, we turned our attention to the higher oxidation lambda-5 scaffolds, which are more reactive and therefore allow access to a broader set of transformations. In this case, structural differences allowed for bidentate ligands to be employed which hold

promise for future chiral reagent development. We directed our initial efforts toward developing a robust synthesis and understanding their reactivity as only one extremely limited report on reagents of this type existed at the outset of our efforts. Key accomplishments to date include the synthesis and reactivity profiling of a library of 10 diverse reagents. Significantly, these reagents address many of the central limitations of existing lambda-5 iodanes, offering high reactivity, excellent solubility, and favorable safety profiles, making them a very appealing option for broad synthetic application. These reagents were also uniquely able to achieve the reactions described in Aim 3.

- **Products:** *This work is currently being prepared for publication in J. Org. Chem..*
 - **Future Directions:** With a strong understanding of reactivity and synthesis, we will turn our attentions to developing chiral derivatives for asymmetric dearomatization reactions as well as catalysis manifolds.
- **Aim 3 Progress: Phenol Oxidation:** Due to the shift in Aim 2, we focused our efforts in phenol oxidation to the oxidation of electron-deficient phenols to *o*-quinones using the highly reactive lambda-5 *N*-HVI's we had developed. This represents the first time that a synthetically useful oxidation of electron-deficient phenols has been reported. This results in a greatly expanded library of feedstock *o*-quinones with varied electronic properties and the downstream application of these compounds is under investigation. Their potential applications include monomer synthesis, ligands for transition metal catalysis, novel boronic esters for cross couplings, and novel sensors and materials.
- Transition Metal Oxidation:** Lambda-3 *N*-HVI's were explored for their ability to act as oxidants in high-valent transition metal chemistry. Specifically, we focused on the ability to access either Ni(III) vs Ni(IV) species by tuning the oxidant being used. We found that both the oxidation state as well as the reaction pathway were dependent on the oxidant being used.
- **Products:** *The phenol oxidation work is currently being written up for publication in Angew. Chem. Int. Ed. Engl. and the process is being patented. The high-valent nickel chemistry was published in Tetrahedron, 2018, 74, 3278.*
 - **Future Directions:** *The development of chiral analogues in Aim 2 will then lead to efforts in asymmetric dearomatization of electron-deficient phenols.*

Research Impacts: The progress outlined above has had broad reaching impacts in both the success of our young research laboratory as well as student education.

- **Federal Funding:** Results obtained during DNI-56603 were crucial preliminary findings that were included in a successful NSF CAREER proposal (NSF CAREER 1752244).
- **Publications:** As specifically highlighted in the above sections, the work of this funding period has already resulted in two peer reviewed publications in which the PRF was acknowledged (*Eur. J. Org. Chem.* **2018**, 1460.; *Tetrahedron*, **2018**, 74, 3278.) and 3 additional manuscripts in preparation. In total, this PRF grant will have resulted in a total of **six peer-reviewed publications**.
- **Presentations:** The work has been presented at national and regional meetings by the PI, graduate students, undergraduates and postdoctoral fellows. This includes national ACS meetings (PI; Oral presentation), Gordon Research Conferences (PI, Graduate Student; Oral and Poster presentations), 2018 Florida Heterocyclic Chemistry Conference (PI, Graduate Student, Postdoc; Oral and Poster presentations), the International Conference on Hypervalent Iodine Chemistry (PI; Oral presentation), local undergraduate poster sessions, and internal Temple Research Symposia.
- **Student Support & Training:** The research funding provided student support for two female graduate students and one international student. These students had critical opportunities for professional development and technical training throughout their support. Each graduate student was also paired as a mentor with an undergraduate researcher. In addition to the undergraduates directly supported, numerous undergraduates as well as additional postdoctoral researchers collaborated on this work. Two undergraduates were selected for medicinal chemistry fellowships at BMS, three were poster session winners at the Temple Undergraduate Research Symposium, and one has been accepted to several top graduate programs for next fall. The postdoctoral fellow involved in research and student mentorship on these projects has just accepted a tenure-track position at a top-tier PUI.
- **Young Faculty Development:** As a young, pre-tenured faculty, this PRF DNI grant provided an absolutely critical foundation to launch my research program and I am deeply indebted to this program for their support. In addition to providing initial funds to support my graduate students and purchase critical supplies, the results obtained from this grant were central to obtaining federal funding. The findings were used as preliminary results to obtaining both an NIH R01, a subsequent NIH Supplemental Award and NSF CAREER grant, amounting to almost \$1.5 million in funding, during the two years of support. The travel funds supported the dissemination of the findings at high profile conferences and provided critical professional development opportunities for the students.