

NARRATIVE PROGRESS REPORT YEAR 1

1. PRF # 58487-DNI1

2. **Project Title:** Synthetic Utility of Cascade Reactions Involving Diazo Synthons

3. **P.I. Name, Affiliation:** Indrajeet Sharma, Department of Chemistry and Biochemistry, University of Oklahoma

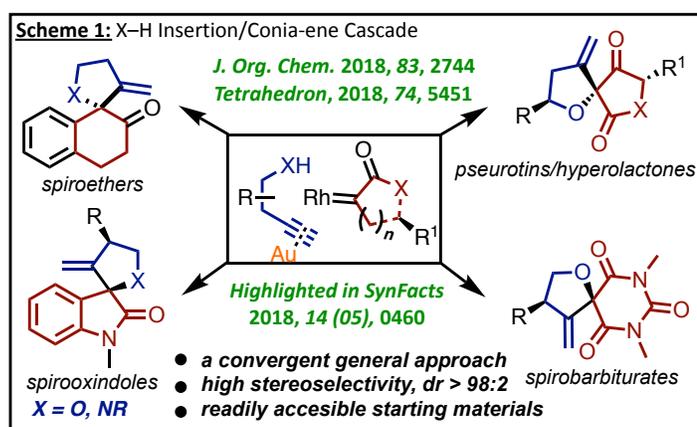
4. Co-PI (if any), Affiliation: Not Applicable

We are pleased to report excellent progress in our first report. The ACS-PRF grant has not only enabled peer-reviewed publications but also helped our research group to secure federal funding. The research work has also been highlighted in SynFacts and led to several collaborative projects.

1. Contributions to stereoselective synthesis of spirocycles: We have developed a convergent cascade approach to the stereoselective synthesis of spirocycles using readily accessible starting materials derived from petroleum feedstock. Spirocycles are valuable products as they are used as chiral catalysts in asymmetric synthesis. The cascade approach involves stereoselective trapping of rhodium carbenoids with functionalized alkynes for the construction of challenging quaternary as well as spiro centers.

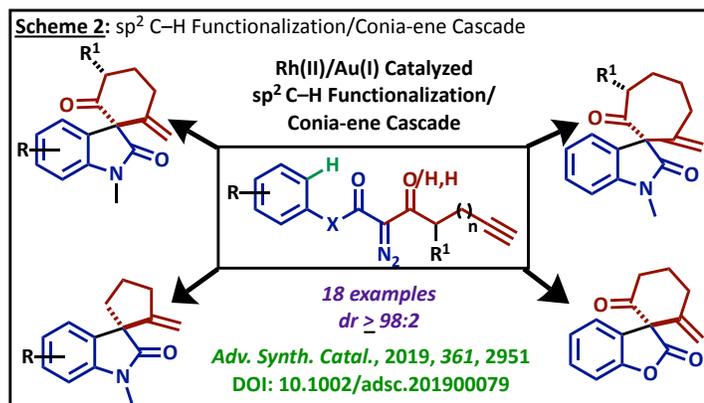
1.1: Stereoselective synthesis of diverse spiroheterocycles:

Stereoselective synthesis of diverse spiroheterocycles: We have developed a convergent approach for the synthesis of diverse spiroheterocycles using a synergistic Rh(II)/Au(I) catalytic system (Scheme 1). The reaction involves trapping of diazo-derived rhodium carbenoids with gold activated alkynes and accommodates both the donor/acceptor (D/A) as well as acceptor/acceptor (A/A) diazocarbonyls. Deuterium-labeling mechanistic experiments suggest the possibility of a gold-acetylide as a reactive intermediate that is in equilibrium with an alkyne π -complex with gold. A plausible mechanism involves rhodium-catalyzed decomposition of diazo compound to form a Rh(II)-carbene that undergoes heteroatom addition to provide a zwitterionic intermediate, which undergoes a Conia-ene cyclization in presence of a gold activated alkyne complex. This work has resulted in two peer-reviewed publications and has been highlighted in SynFacts.



1.2: Stereoselective synthesis of diverse spirocarbocycles:

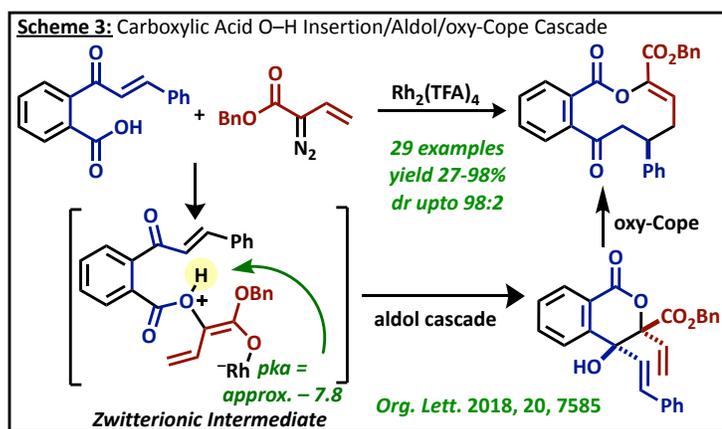
Stereoselective synthesis of diverse spirocarbocycles: We have also completed a Rh(II)/Au(I) catalyzed carbene cascade approach for the stereoselective synthesis of diverse spirocarbocycles (Scheme 2). The cascade reaction accommodates a variety of aryl substituents as well as ring sizes and proceeds in high diastereoselectivity providing access to 5-, 6-, and 7-membered spirocarbocycles. Mechanistically, the diazo is decomposed by dirhodium carboxylate to form a rhodium carbenoid that undergoes sp^2 C-H functionalization to provide the oxindole, which then sets the stage for a Au(I) activated enolendo-*exo*-dig Conia-ene cyclization of the enol tautomer to provide the desired spirocarbocycle.



2. Contributions to stereoselective synthesis of medium sized rings: Synthesis of medium-sized-rings (8 to 12 atoms) is a subject of continuing interest to chemists, as they are the core structure of several value-added products. The construction of medium sized rings through intramolecular cyclization is not straightforward. The cyclization

step in the ring-closing strategies, such as lactonization and ring-closing metathesis, pose challenges due to entropic/enthalpy barriers, and usually require high dilution conditions to minimize polymerization. Ring expansion reactions that are insensitive to substrate conformational effects provide an alternative to conventional cyclization approach. However, the synthesis of appropriate precursors for ring expansion reactions often requires multiple steps, and limits the synthetic utility. To address this synthetic challenge, we have developed a convergent approach, which allows the simultaneous formation and expansion of small rings for direct access to medium-sized rings.

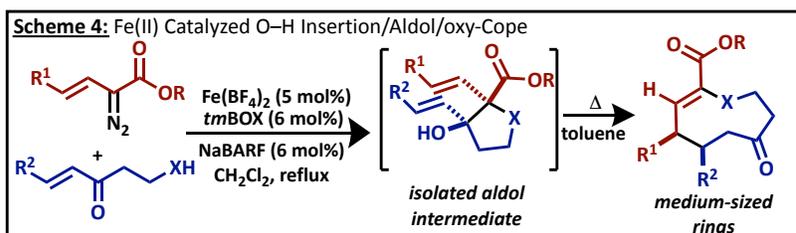
Building upon our previously developed diazo-heteroatom insertion/aldol/oxy-Cope cascade sequence (*Org. Lett.* **2016**, *18*, 6340, *Chem. Commun.* **2017**, *53*, 12205), we have developed a convergent cascade approach for the stereoselective synthesis of diverse lactones (Scheme 3). The Rh₂(TFA)₄-catalyzed cascade reaction proceeds via a carboxylic acid O–H insertion/aldol cyclization with high chemo-, regio-, and diastereoselectivity. The cascade reaction provides quick access to highly functionalized γ -butyrolactones and δ -valerolactones from readily accessible ketoacids and diazo synthons. To demonstrate the utility of this approach, a thermally induced oxy-Cope ring-expansion strategy has been incorporated in the cascade sequence to access medium-sized lactones.



3. Future Directions: Enantioselective variants and use of earth-abundant metal. In year 1 we have begun to

take the initial steps toward replacing expensive rhodium with earth abundant iron as a sustainable catalyst in our heteroatom insertion/aldol/oxy-Cope cascade reaction for accessing medium-sized rings. Iron is the most abundant metal in the Earth's crust after aluminum and its salts are readily

available, cheap, and relatively non-toxic. Iron carbenes have been underexplored in cascade reactions; therefore our identification of this new catalytic system will be of great value to the chemical community (Scheme 4). We are also developing copper-catalyzed asymmetric Conia-ene cyclization for the synthesis of diverse heterocycles.



4. Impact on the PI and students career: The chemistry developed in this proposal is convergent and transformative in nature, and is having an impact on our collaborative projects. For example, in collaboration with the OU Health Sciences center, a medium-sized 10 membered lactone SRG-025 has been identified as a potent Bax/Bak inhibitors for developing neuroprotective agents. The grant has also yielded the data, which helped the PI to apply for a NIGMS-MIRA-R35 grant. The PI has also been selected to present his research work at the ACS-DOC Young Academic Investigator Symposium in the Fall 2019 National meeting. This project also partially supported 2 postdoctoral fellows at OU. The first postdoc (Kiran Chinthapally) is now working as a research scientist at the Warren Center for Drug Discovery at the University of Notre Dame. Two graduate students, and 1 undergraduate also participated in this project. One of the graduate students Arianne Hunter, who was a DoD SMART Scholarship recipient, completed her PhD thesis in the Spring 2019, and has joined the DOD Department of Forensic Science Center in Atlanta. Arianne also won the Three Minute Thesis (3MT) Competition Runner-Up and People's Choice Award among 80 applicants. She was selected among top 30 PhD and postdoctoral researchers by the CAS Future Leaders Program. Arianne also won the 2019 Belle W. Goodman Research Award, which is the most prestigious premier research award from the department to a student for the exceptional performance in research. Another graduate student Nicholas Massaro, who defended his PhD thesis, is working as a postdoc at the NC State University. Nick was selected among top 50 4th year graduate students to present his research at the 2018 ACS-Division of Organic Chemistry symposium held at the Indian University. The undergraduate student Ibikari was selected to represent the University of Oklahoma for the 2019 research day at the Oklahoma State Capitol.