PRF# 56505-DNI1
Chiral α,α-Disubstituted Amines via the Allylic Azide Rearrangement

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OVERVIEW: Research in the Topczewski lab is focused on developing new synthetic methods to enable efficient and sustainable chemical syntheses. The funded work aims to develop more efficient synthetic methods for the synthesis of sterically congested chiral amines. To accomplish this goal, we proposed developing methods capable of resolving equilibrium mixtures of allylic azides. This proposal specifically focused on identifying reagents and pathways that could selectively functionalize the allylic azide's alkene.

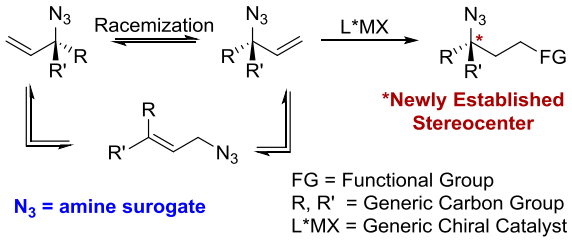
IMPACT: The funds from this award have supported several graduate and undergraduate students in the lab, either directly through salary or indirectly by providing supplies. There are a total of seven papers published that acknowledge the support from this award, including two communications in the *Journal of the American Chemical Society*, an *Organic Letters* publication, and a full article in the *Journal of Organic Chemistry*, which are all ACS journals. At least two additional publications are likely in the near future. These publications feature fourteen different authors and include a high school student, five different undergraduates, and four different graduate students.

The recognition of these publications allowed a co-author to be awarded an excellence fellowship (A.A.O.), to gain national recognition as a Goldwater Scholar (J.H.C.), and to launch a career in the chemical industry (V.P.S. at Phillips 66). Several of the students have or will present their work at ACS meetings. Three students presented at the 2017 ACS National Organic Symposium, where one (M.R.P.) was recognized with an award for his poster presentation. Many of the students have submitted abstracts for the 2018 Midwest regional ACS meeting.

The impact of this award on the PI's career is also notable. The preliminary data gained from this award's support was used in a grant application to the National Institutes of Health. The PI obtained the Maximizing Investigators' Research Award (R35GM124718), which constitutes a major federal grant. The PIs publication track record, which is supported by this award, is on track to meet the UMN tenure requirement guidelines and suggests a positive career trajectory.

ACCOMPLISHED RESEARCH: Over the last two years, we have made significant progress towards the goals outlined in the PRF proposal. Our primary goal was to use allylic azides in a dynamic kinetic resolution to enable the direct, catalytic, and stereospecific synthesis of chiral amines or chiral amine building blocks. A generic outline of this process is provided in Figure 1. We can categorize the accomplishments broadly into two categories i) Fundamental Understanding, and ii) Methods Development.

Figure 1. Dynamic Kinetic Resolution of Allylic Azide



FUNDAMENTAL UNDERSTANDING: When we initiated this project, very few systematic studies had been conducted on allylic azides. We sought to i) define parameters that controlled the equilibrium and ii) understand the mechanism and selectivity of the rearrangement. Each of these goals has been accomplished. In an initial publication, we described how proximal functionality biases the equilibrium concentration of various azide isomers (Figure 2). This work allowed us to

design substrates with biased equilibrium concentrations that could be used in a dynamic cyclization (below).

Figure 2. Understanding the Equilibrium

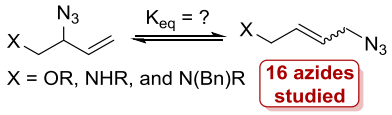
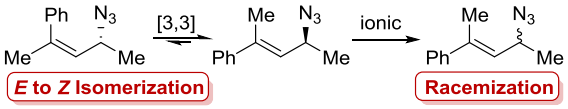
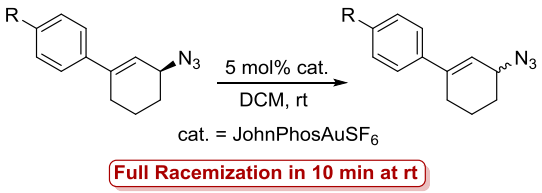


Figure 3. Understanding the Mechanism



In a second study, we were able to address several questions regarding the mechanism of the allylic azide isomerization (Figure 3). In this study, we conducted several classical mechanistic experiments that revealed an unexpected ionic pathway. This observation made during our fundamental studies lead us to identify a catalyst for the process (Figure 4, not yet published). The catalytic racemization of an allylic azide was unexpected and will enable dynamic kinetic resolutions as part of our methods development.

Figure 4. Catalytic Azide Racemization



METHODS DEVELOPMENT: The fundamental studies enabled us to develop reactions that utilize allylic azides. Our first report describes a direct synthesis of these azide starting materials, which has expedited our synthetic efforts (Figure 5). Subsequent work demonstrated that we can accomplish stereoselective syntheses from allylic azides. The proof-of-concept report describes the enantioselectve synthesis of densely functionalize azido-alcohols by coupling the azide equilibration with a Sharpless Asymmetric Dihydroxylation (SAD) to facilitate the dynamic kinetic resolution (DKR, Figure 6). A subsequent dynamic cylization reaction borrowed knowledge from our fundamental studies and led to a general synthesis of 3-azido-tetralins, -chromanes, and –tetrahydroquinolines (Figure 7). Another report describes a highly regioselective Wacker oxidation of allylic azides, providing expedited access to valuable β-azido ketone building blocks.

Figure 5. Direct Azide Synthesis

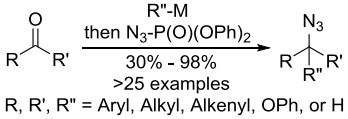


Figure 6. DKR of Azides by SAD

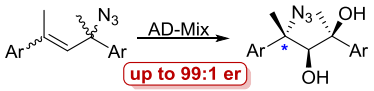


Figure 7. Tandem Cyclization Reaction

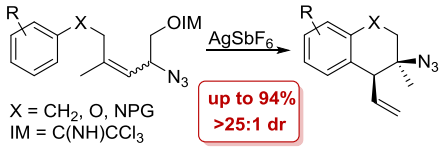
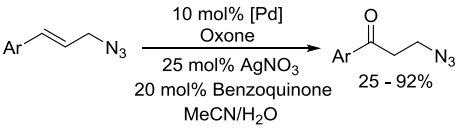


Figure 8. Wacker Oxidation of Allylic Azides



We are continuing to develop unique methods with our DKR approach and will disclose the first enantioselective CuAAC “click” reaction that proceeds by DKR. We are excited about these findings because of the numerous applications of the click reaction.

CONCLUSIONS: The ACS-PRF-DNI grant has been instrumental in building the PI’s research program and has significantly impacted the students involved in the project. Much research has been accomplished that acknowledges support from this award and several more works are in progress.