

Fundamental Structure-Reactivity Relationships of Isolable Distorted Cycloallenes: New Petroleum Derived Reagents for Rapid, Strain Promoted Cycloaddition Chemistry

Rylan Lundgren, University of Alberta

Research Progress

Through the support of the ACS PRF, we have synthesized a diverse array of medium-ring cycloallene structures and examined their reactivity in strain-promoted cycloaddition reactions with potential reactive small molecules (azides, nitrones, tetrazines). Our studies demonstrate that properly constructed cycloallenes can be both stable under ambient conditions and undergo rapid inverse-electron demand Diels Alder (IEDDA) reactions with tetrazine derivatives. Preliminary kinetic and stability studies suggest medium ring cycloallenes are a promising new class of π -systems for strain-promoted cycloaddition type ligations.

A primary goal of this project was to provide complementary IEDDA reactivity to established alkene systems. Towards this end, we conducted a series of detailed benchmarking UV-vis and NMR-based kinetic studies to compare the relative second order rate constants of alkenes and allenes with differentially substituted tetrazines (Figure 1). Broadly speaking, strained cyclooxyallenes undergo IEDDA reactions with monosubstituted tetrazines with rate constants larger than norbornenes but smaller than that of *trans*-cyclooctenes. We confirmed literature reports that for both cyclic and acyclic alkenes, more electronic-deficient 2,5-heteroaromatic disubstituted tetrazines (Tz1) undergo IEDDA \sim 3-5 times faster than monosubstituted tetrazines (Tz2). Conversely, both cyclic and cyclic allenes react with rate constants \sim 3 times faster with monosubstituted tetrazines. This observation holds for both aliphatic allenes and α -oxyallenes. We believe the origin of this difference in behavior lies in the different steric environment about the reacting allene π -system, where the flanking C_{sp^2} carbon units are nearly orthogonal to each other and can block access from the incoming tetrazine. Thus, sterics in IEDDA reactions of allenes appear to override electronic factors. We hope to take advantage of these reactivity principles to enable cross-selectivity in click-type reactions between tetrazines and dienophiles.

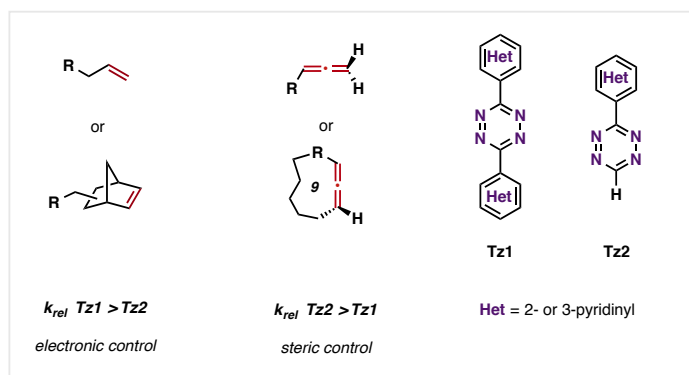


Figure 1. Comparison of relative rates for alkenes and allenes with mono- and disubstituted tetrazines in the inverse electron-demand Diels-Alder reaction.

We have begun to understand how allene structure and reaction conditions impacts the end products of IEDDA reactions with tetrazines (Figure 2). Initial 4+2 cycloaddition gives a bicyclic intermediate that rapidly loses N_2 to generate a diazine with an exocyclic olefin unit. Driven by the regeneration of aromaticity, this species converts to two products. One is generated by tautomerization, a second product is generated by allylic oxidation. We are investigating reaction conditions to enable the selective generation of either product.

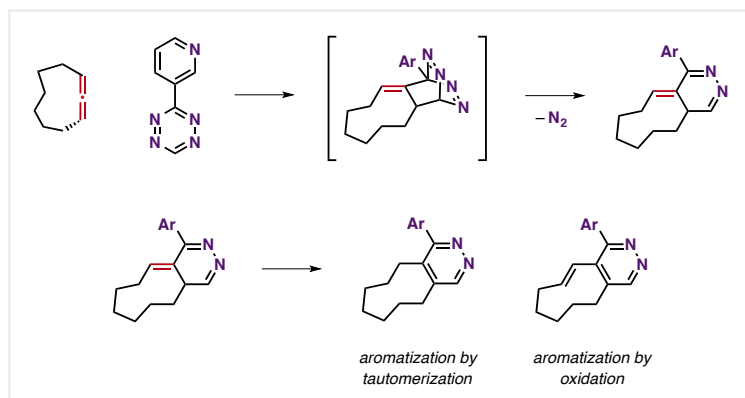


Figure 2. Products generated from IEDDA reactions of a cyclic allene and a monosubstituted tetrazine.

Our long-term goal remains to develop “bottleable” reagents for tetrazine ligation applications. This will ultimately involve the preparation of cycloxyallenes with backbone functionalization (hydroxyl, carboxylic acid, or N-hydroxysuccinimide ester). Our current synthetic route involves six steps from cycloheptanone (Figure 3a). The challenging step in the sequence is the generation of the eight-member ring cyclic vinyl ether by the elimination of acetic acid from a cyclic α -acetoxyether (Figure 3b). To date, only thermal eliminations at $\sim 130^\circ\text{C}$ have proven viable to generate product in $\sim 30\%$ yield. Addition of base to promote elimination or the use of more mild conditions are not productive. We are currently exploring alternative elimination protocols and substrates in order to improve the efficiency of the synthesis of addressable cycloxyallenes.

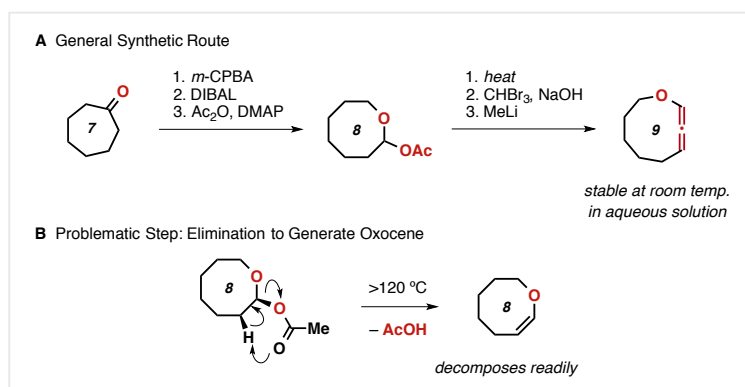


Figure 3. Overview of the synthetic route towards a medium-ring oxycycloallene and the challenging elimination step to prepare the key sensitive cyclic vinyl ether intermediate.

Support from the ACS PRF has been essential to conduct this research, all students and postdocs taking part in the project have received (at least partial) support from the grant. This project has enabled my lab to explore a new area that is significantly different from the transition metal catalysis/synthetic methodology areas we have more experience in. The project has been fantastic training platform, as it combines aspects of synthetic and physical organic chemistry. We believe this will lead to publications and sustained funding for the project, particularly once we have disclosed the reactivity of our “first generation” cycloxyallene reagents.