

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

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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 tetrazines and azides. Our studies clearly 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.

Specific, we have identified that nine-membered ring cycloallenes substituted with an adjacent oxygen group (oxy allenes) undergo inverse-electron demand Diels Alder reactions with mono substituted tetrazines at rate constants at least two orders of magnitude faster than analogous acyclic systems. Molecules of this type can be prepared in six synthetic steps from simple petroleum derived feedstocks, such as cyclic ketones. The key transformations towards preparing the oxy-cycloallene involves the careful elimination of acetate from a cyclic acetoxy ketal, generating a cyclic vinyl ether, followed by olefin dibromocyclopropanation and Skattøbol rearrangement by treatment with MeLi yields the desired oxy-allene target (Fig 1). These steps required significant optimization to enable the preparation of large enough quantities of material to test stability and reactivity. To the best of our knowledge, structures of this type have not been reported in the literature. We now can provide a robust and reproducible protocol for the generation of oxygen-substituted cycloallenes. Modification of the allene backbone (incorporation of heteroatoms or linker groups) should be straight-forward by accessing the requisite 7-membered ring ketone. These oxy-cycloallene are stable at room temperature for days, and in methanol/water mixtures over several hours at neutral pH, although are prone to acid-promoted ring opening.

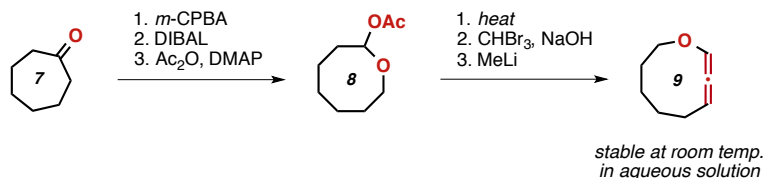


Fig. 1 Overview of the synthetic route towards a medium-ring oxy-cycloallene.

We have benchmarked this and other allene-containing molecules with the state-of-the-art reagents for strain-promoted cycloaddition reactions. In these studies, the comparative rate of cycloaddition is significantly influenced by the substitution of the tetrazine unit. Mono-substituted tetrazines, which are less sterically encumbered, undergo fast ligation with cyclic allenes, while 1,4-disubstituted tetrazines react much slower (Fig 2). This is the case even with tetrazines substituted with electronically-activating electron-withdrawing groups. The twisted nature of the cyclic structure due to the orthogonal π -systems of the allene unit are likely the reason for the high degree of steric sensitivity. This trend counters that which is typically observed with cyclooctene or norbornene derived reagents, suggesting cycloallene species might serve as chemoselective ligation species in “click-type” transformations. In all examined cases, reactivity with aryl or alkyl azides, or nitrones is comparatively poor.

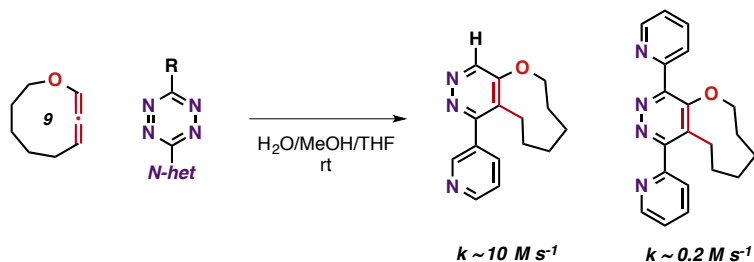


Fig. 2 Second order rate constant comparison for the inverse-electron demand Diels Alder reaction of an oxy-cycloallene and substituted tetrazines.

We have started to develop structure/reactivity relationships for strain/electronic promoted inverse-electron demand Diels Alder reactions (Fig 3). The oxy-cycloallene depicted in Fig 1 and 2 represents the most reactive species we have prepared that is isolable under normal laboratory conditions and stable for a long enough period of time to be considered a “bottleable” reagent (minimal decomposition for hours at room temperature, or weeks in at -15 °C). The origin of reactivity is both strain promoted and derived from the increased electron density of the π -system compared to carbocyclic allenes. These observations are in agreement with the general conclusion drawn by Houk and Fox concerning the IEDDA reactions of cycloalkenes.

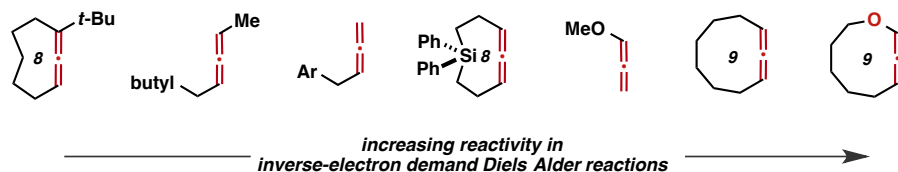


Fig. 3 Overview of structure/reactivity relationships in the IEDDA reaction of allenes with tetrazines.

This research has allowed our group to branch off from our studies in more traditional synthetic methodology development. The data generated to date clearly demonstrate the ability of medium-ring allenes to be both fundamentally interesting species and those which may compliment the current arsenal of unsaturated molecules for strain-promoted ligation reactions. We believe this will lead to high impact publications and sustained funding for the project. Each aspect of this project has enabled the researchers involved to develop skills and understanding of physical and synthetic organic chemistry.