



Synthesis of Sultams from Vinyl Aziridines and 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide)

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ABSTRACT

Sultams are an important functional group found in medicinal compounds with anticancer and enzyme inhibition activity. Traditional methods for sultam synthesis often require harsh conditions and have limited substrate scope. This research focuses on developing a novel methodology for the production of sultams using DABSO (1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide)) and vinylic aziridines. Our synthetic strategy starts with a Corey-Chaykovsky epoxidation of cinnamaldehyde, followed by an epoxide-opening using sodium azide. The final vinylic aziridine is synthesized by mesylation and Staudinger reduction of the resulting azido alcohol. Reaction of this vinyl aziridine with DABSO may provide a new strategy for synthesizing sultams. Following this strategy, we have thus far synthesized the penultimate mesylate in 17% yield over 3 steps.

INTRODUCTION

- Sultams are cyclic sulfonamides that are widely utilized in commercial drugs for its bioactivity and function in enzyme inhibition, cancer, and treatment for inflammatory disease,¹ as shown in Figure 1

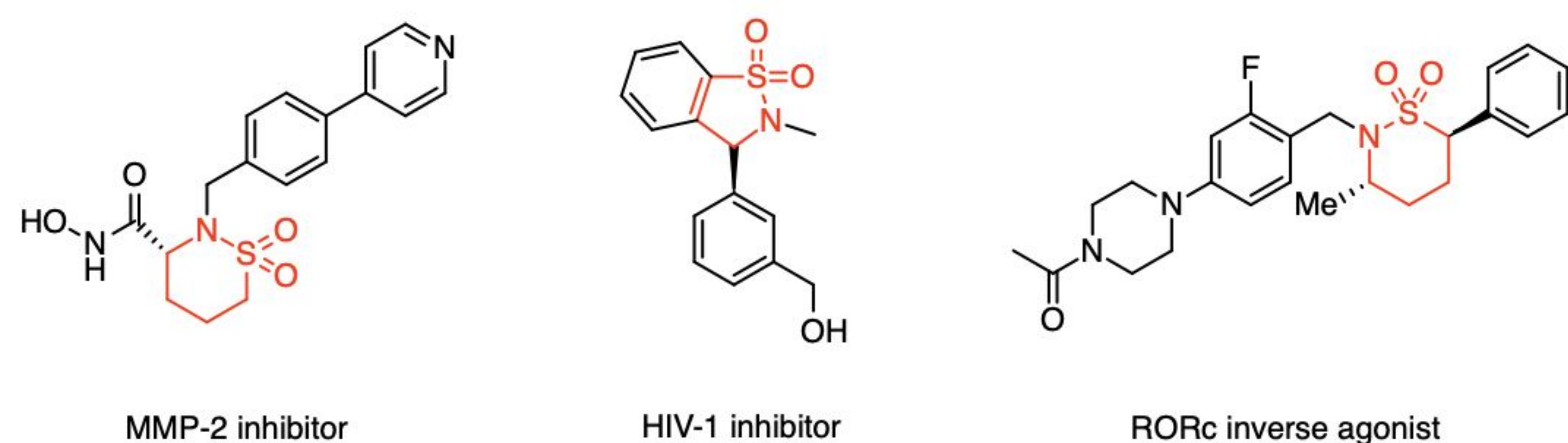
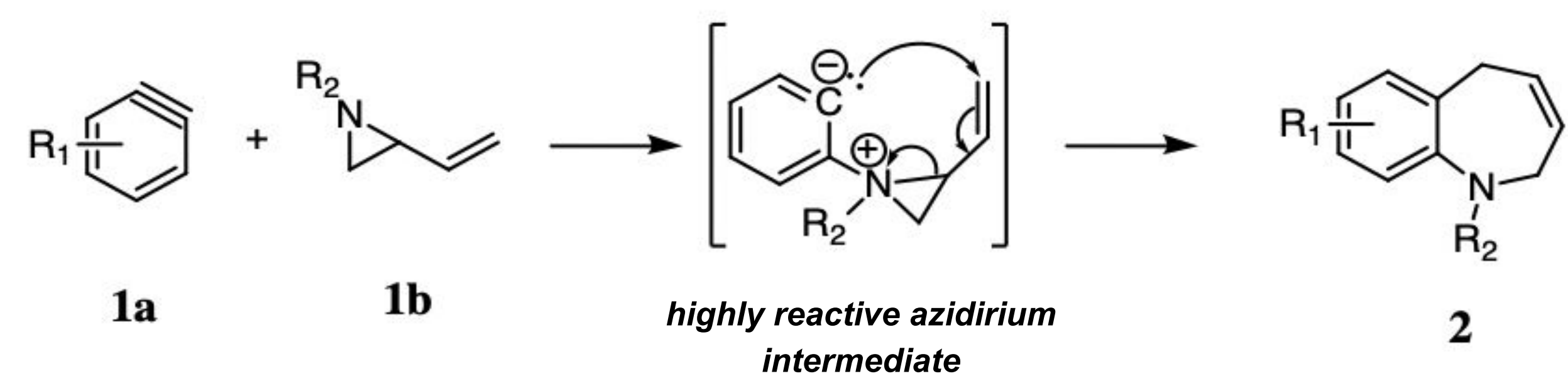


Figure 1. Bioactive molecules containing a sultam (indicated in red)

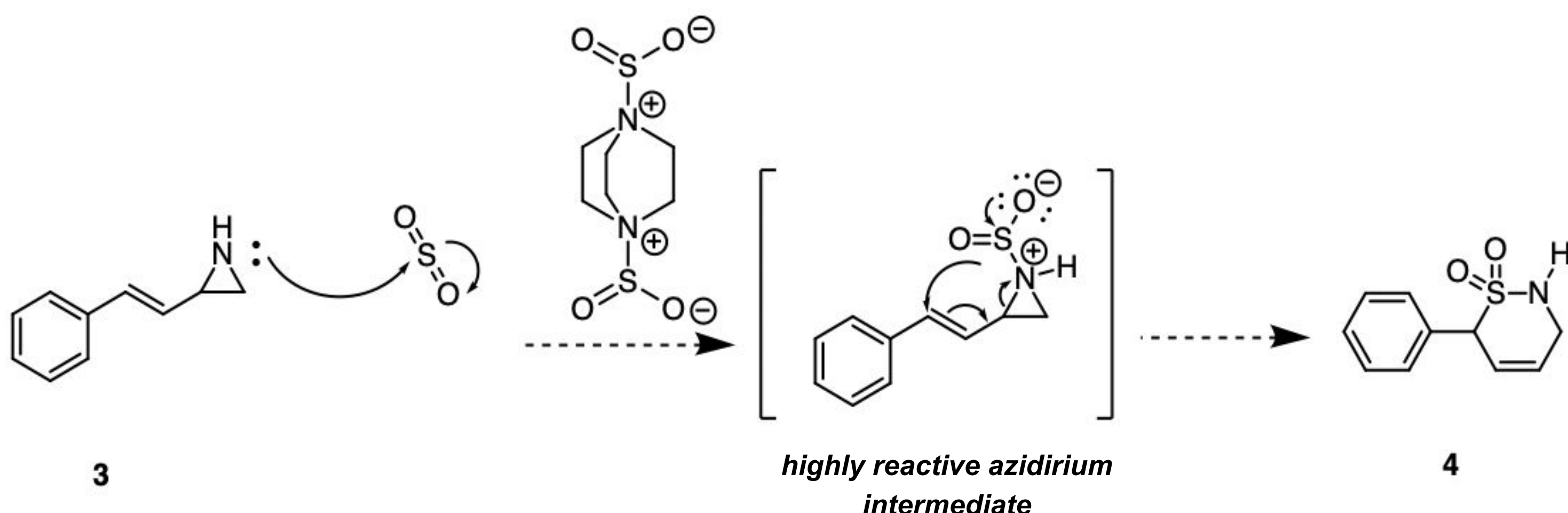
- The large presence of sultam cores found in commercial drugs have resulted in synthetic developments of sultams²
- Following the paper by Studer et al.,³ we are hopeful to synthesize a sultam from a vinyl aziridine due to the formation of the highly reactive aziridium intermediate, as shown in Scheme 1 below

Scheme 1. Intramolecular reaction to form a closed ring from a vinyl aziridine



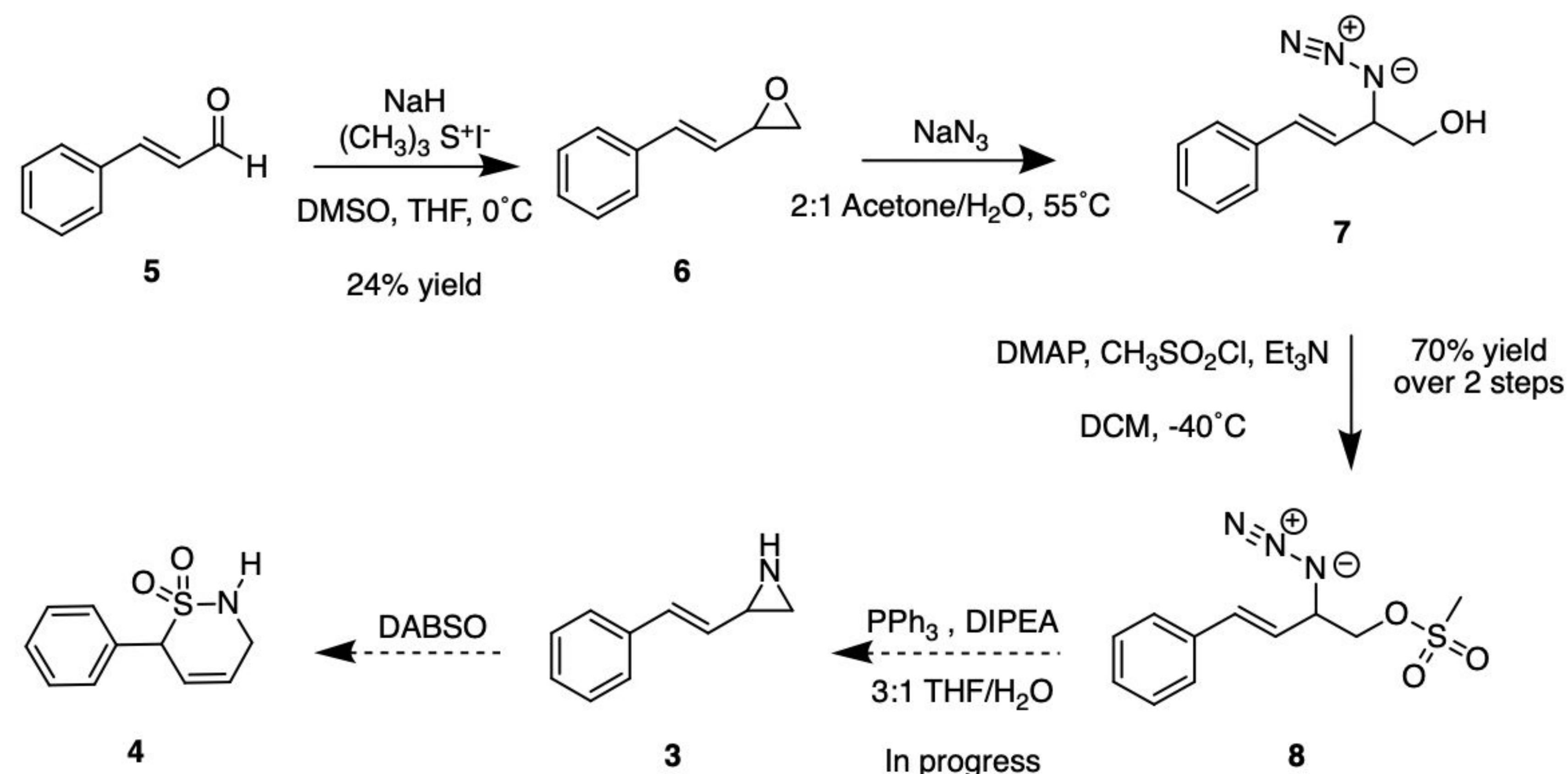
- The proposed mechanism from a vinyl aziridine may provide a new method for synthesizing a sultam as shown in Scheme 2 below

Scheme 2. The proposed mechanism for synthesis of sultam using DABSO



RESULTS

Scheme 3. The synthetic scheme to synthesize a sultam from starting conditions



Johnson Corey-Chaykovsky Mechanism

Scheme 4. The mechanism to form a vinyl epoxide under basic conditions from cinnamaldehyde

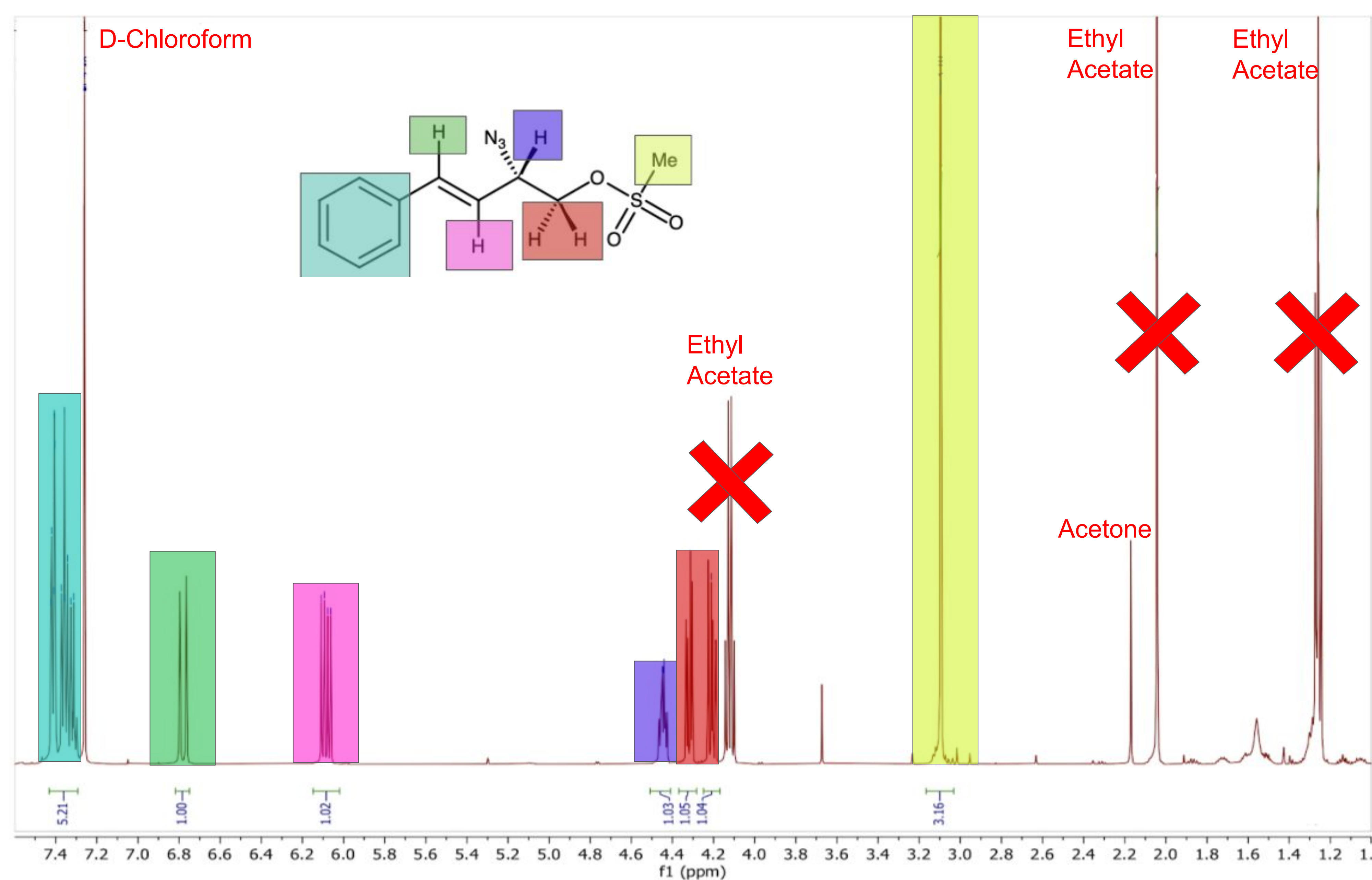
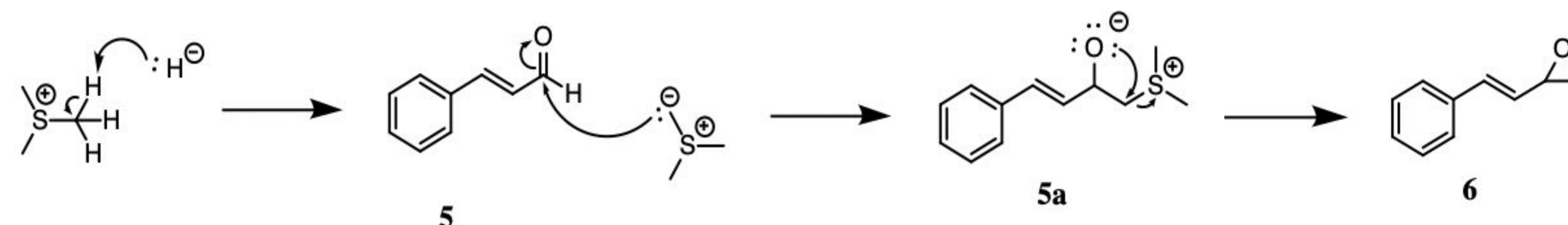
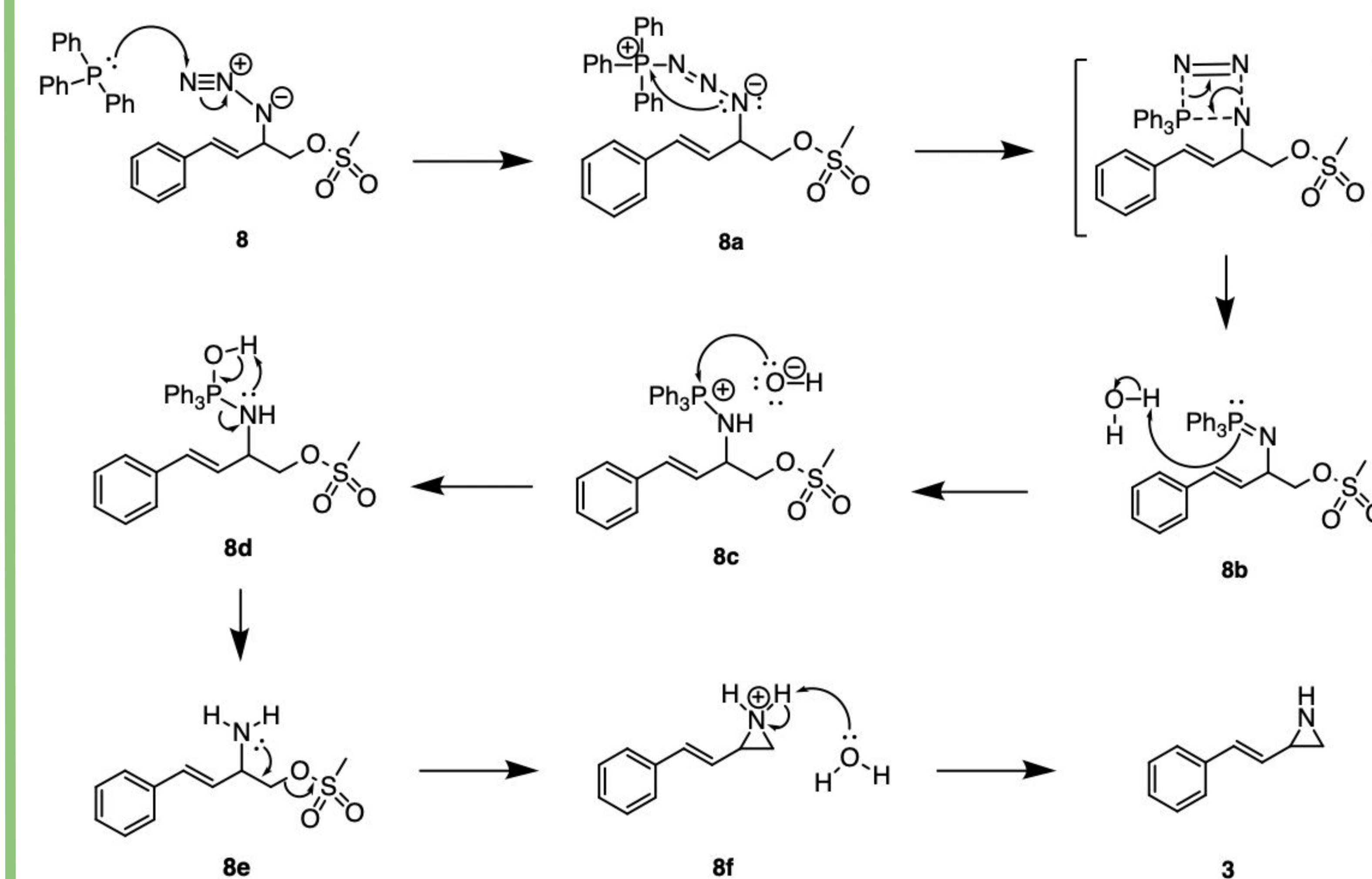


Figure 2. ¹H NMR spectrum of mesylated azido alcohol

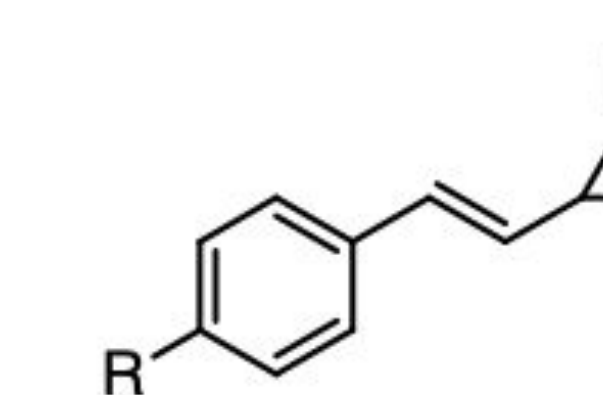
Staudinger Reduction Mechanism

Scheme 5. The mechanism to form a vinyl aziridine under basic conditions



FUTURE WORK

- Finish synthesizing and analyzing the formation of sultams from vinyl aziridines and DABSO
- Optimize conditions to increase yields
- Synthesize vinyl aziridines with various substitution on the phenyl ring to test compatibility of the reaction with various functional groups



R = OCH₃ R = NO₂
R = OH R = CN
R = NH₂ R = Cl

Figure 3. The R groups colored in red are activators, and the R groups colored in blue are deactivators

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