



## Abstract

Pd(0)-catalyzed trimethylenemethane (TMM) cycloaddition reactions have been used extensively to generate disubstituted 5-membered rings with high levels of regioselectivity, chemoselectivity, and stereoselectivity. We aim to improve upon existing methodologies by introducing an epoxide into the TMM precursor, which should yield more highly functionalized products. A three step synthesis of a TMM precursor has been achieved in 20% overall yield. Efforts are underway to determine the reactivity of this precursor in Pd<sup>0</sup>-catalyzed cycloaddition reactions with substituted alkenes.

## Background

- Natural products and pharmaceutical drug targets often contain rings of varying size and complexity.<sup>1-3</sup> Having methods for stereoselectively and regioselectively producing these rings is crucial to organic synthesis.

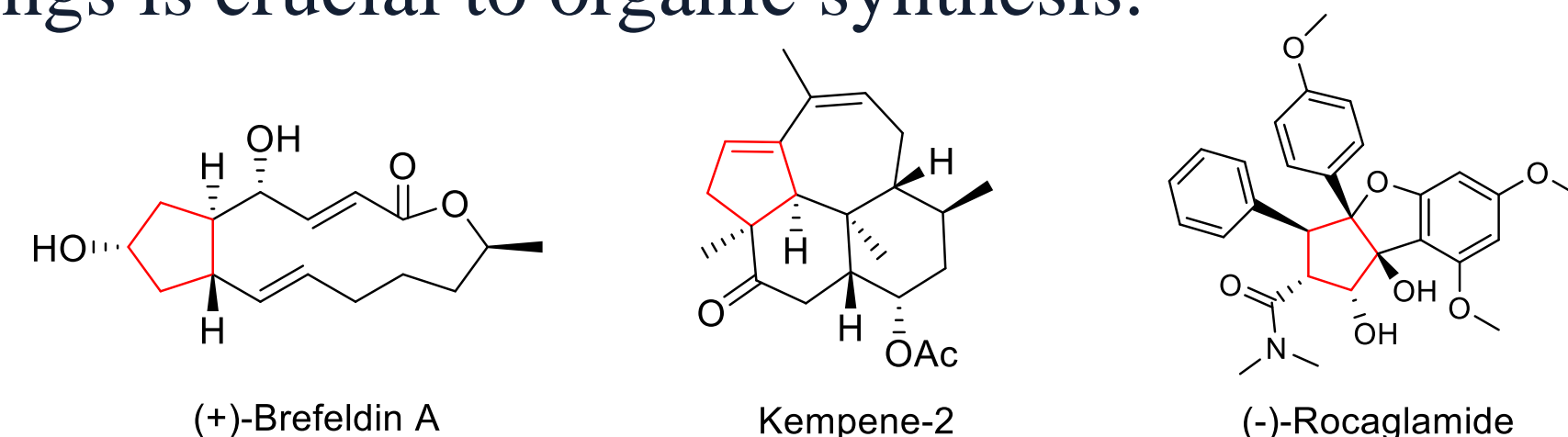


Figure 1. Compounds synthesized using Pd<sup>0</sup>-catalyzed TMM [3+2] cycloadditions.

- The Trost group at Stanford has studied Pd<sup>0</sup>-catalyzed TMM [3+2] cycloadditions rather extensively, successfully generating disubstituted cyclopentane structures.<sup>4</sup>

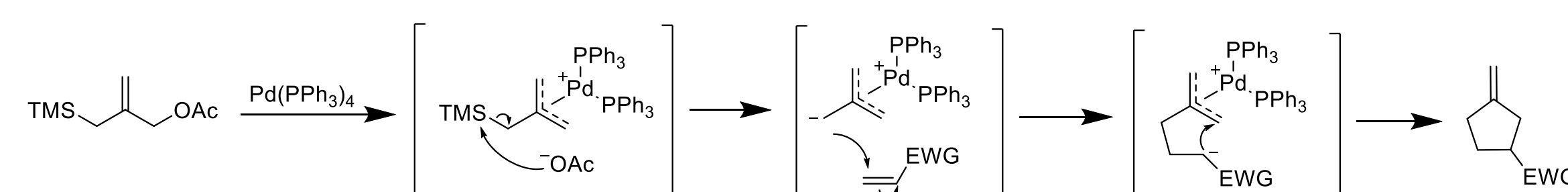


Figure 2. General mechanism of cycloadditions performed by the Trost group.

- Pd<sup>0</sup>-catalyzed  $\pi$ -allyl alkylations have been done successfully on epoxides<sup>5</sup>, but this approach has not yet been used in TMM cycloadditions.

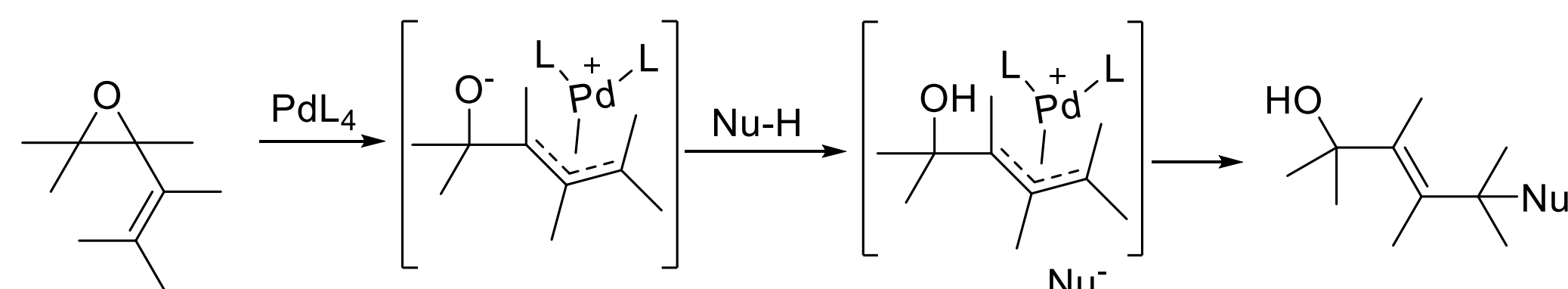


Figure 3. Pd<sup>0</sup>-catalyzed  $\pi$ -allyl alkylation mechanism with TMM epoxide precursor.

- We hypothesize that an epoxide-containing TMM precursor will go through a similar mechanistic pathway as in Figure 3 to yield a trisubstituted 5-membered ring, shown in Figure 4.

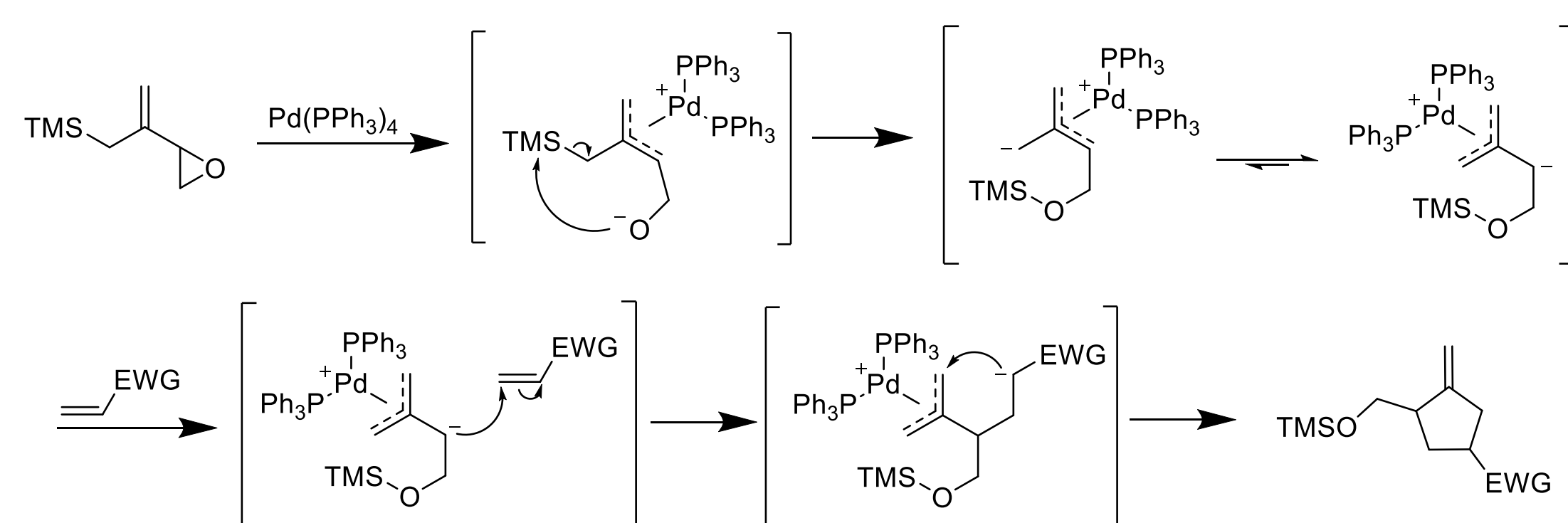
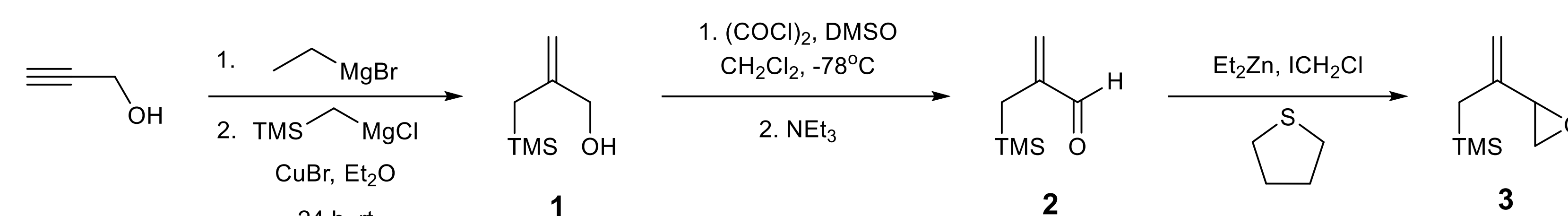


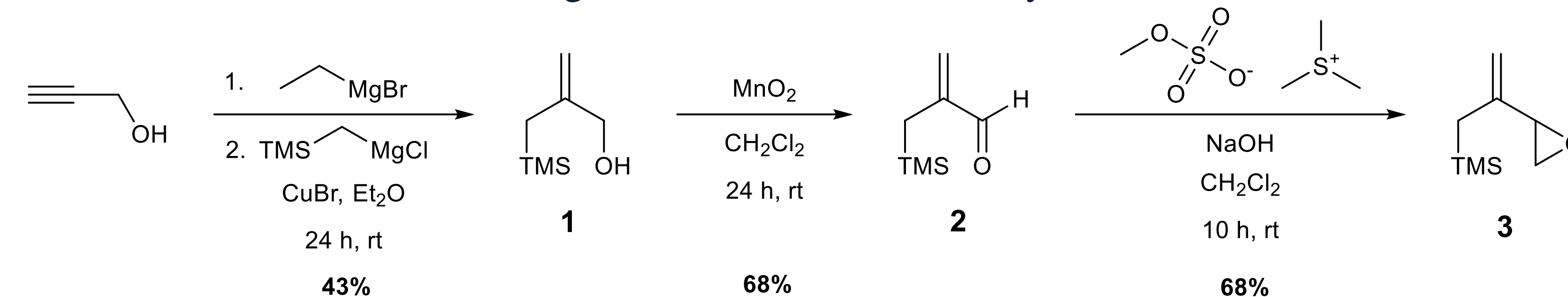
Figure 4. Proposed cycloaddition mechanism with epoxide TMM precursor.

## Optimization of TMM Precursor Synthesis



Scheme 1. Original synthesis of epoxide precursor.

- The preliminary focus of this research was to further optimize the synthesis shown in Scheme 1 that had been used previously in this project. The primary goals were time and cost efficiency, as well as minimizing the amount of hazardous waste.
- Optimization was guided by the goal for this synthesis to ultimately be used by an individual student in an undergraduate research laboratory.



Scheme 2. Optimized synthesis of epoxide precursor.

- Drying diethyl ether with Na<sup>0</sup> for the first synthetic step was determined to be unnecessary, as it improved the yield by a negligible amount when compared to ether that had not been dried.
- MnO<sub>2</sub> was found to be the best oxidant due to mild conditions, simple workup, and a reduced amount of hazardous waste.<sup>6</sup>
- A large excess (13-17 eq.) of MnO<sub>2</sub> used in each oxidation, but 10-12 eq. of activated MnO<sub>2</sub> was recovered from each reaction and could be used again in future oxidations.

Table 1. Optimization of carbocupration, producing 1.

Solvent	TMSCH <sub>2</sub> MgCl	Yield
Dry THF	1 equivalent	43%
Dry THF	1.5 equivalents	36%
Dry ether	1 equivalent	39%
Ether	1 equivalent	40%

Table 2. Optimization of the oxidation of 1 to 2.

Solvent	Time	Temperature	Yield
Pentane	2 h	RT	0%
Pentane	24 h	RT	12%
CH <sub>2</sub> Cl <sub>2</sub>	2 h	RT	12%
CH <sub>2</sub> Cl <sub>2</sub>	2 h	Reflux	43%
CH <sub>2</sub> Cl <sub>2</sub>	24 h	RT	68%
CH <sub>2</sub> Cl <sub>2</sub>	24 h	Reflux	11%

- A major benefit of this synthetic approach is that while the final epoxide precursor needed to be purified via distillation, no purification steps were required for the intermediate products, as shown by the <sup>1</sup>H NMR spectra in Figures 5 and 6 below.

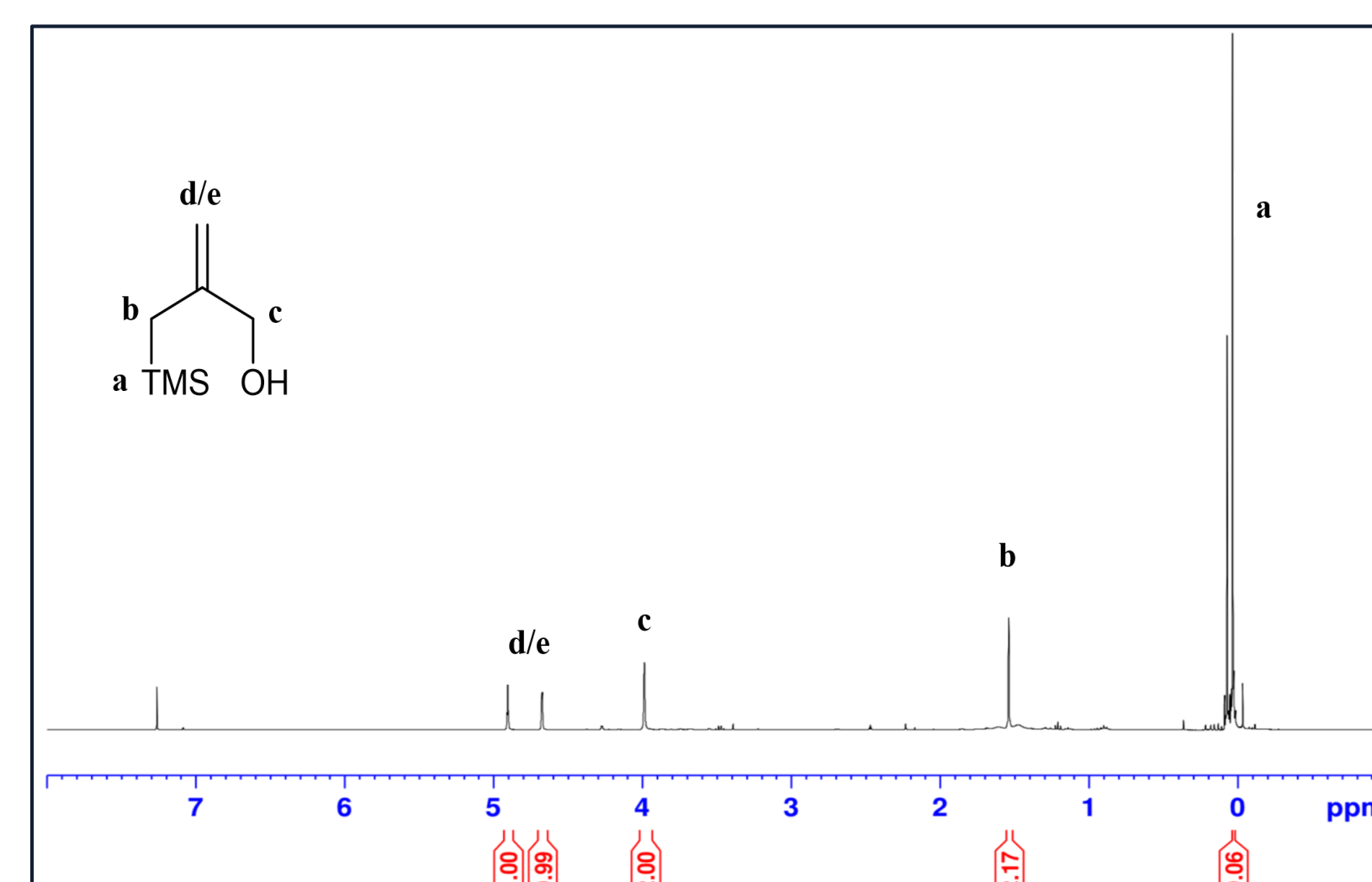


Figure 5. <sup>1</sup>H NMR spectrum of Compound 1.

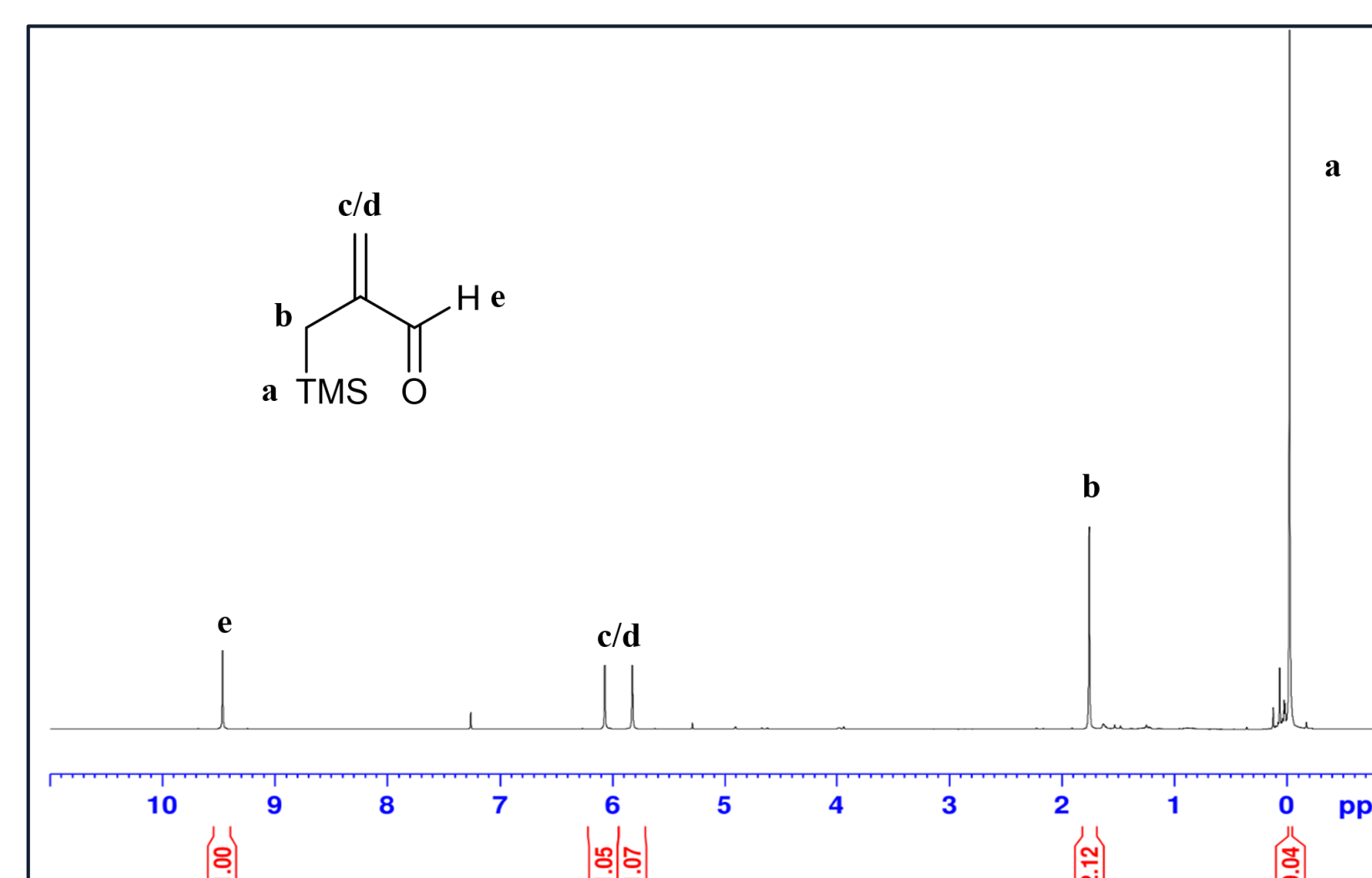


Figure 6. <sup>1</sup>H NMR spectrum of Compound 2.

Pd<sup>0</sup>-Catalyzed Cycloadditions

- Our epoxide-containing TMM precursor is currently being investigated for its reactivity with various electron-deficient alkenes.

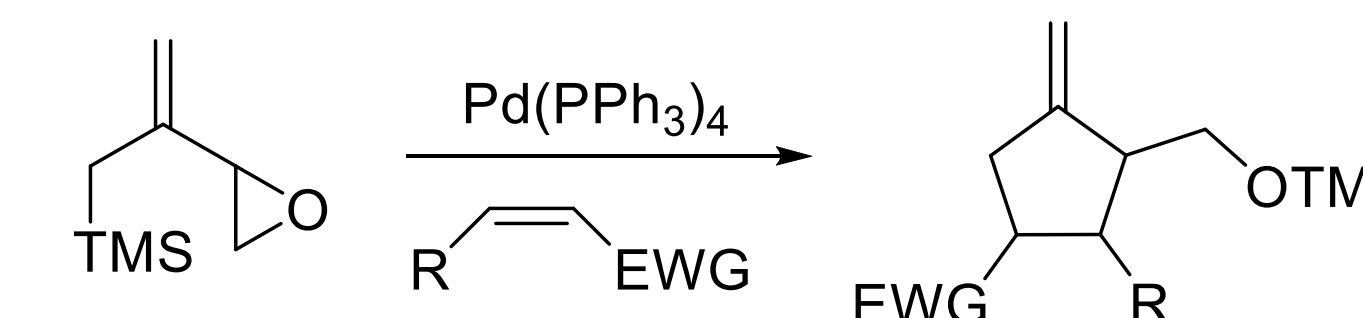


Figure 7. General proposed cycloaddition reaction with our novel TMM precursor.

- Alkenes were selected based on previous success in cycloaddition reactions performed using the model acetate-containing TMM precursor.<sup>7</sup>

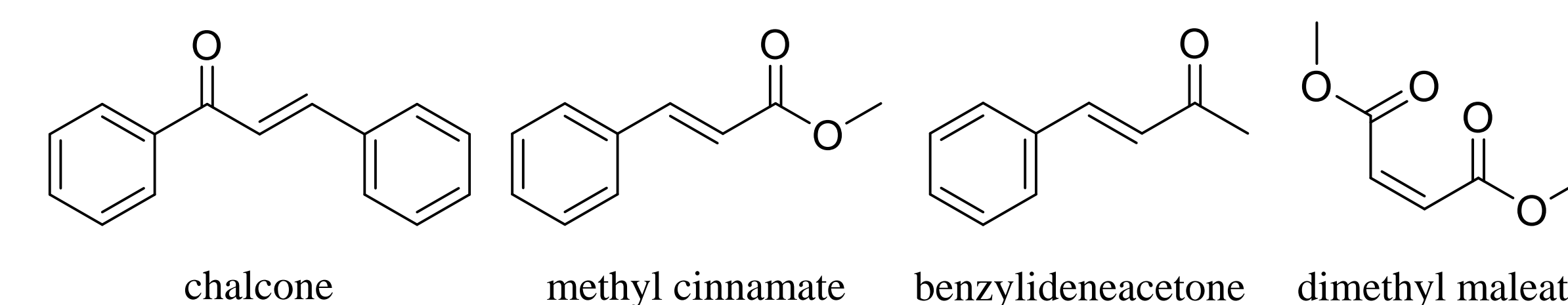


Figure 8. Alkenes currently being tested for reactivity in [3+2] cycloadditions.

## Future Work

- Continue screening alkenes and cycloaddition reaction conditions to determine if the predicted products are being formed
- Incorporate R groups into TMM precursor to determine the effects on regioselectivity and stereoselectivity
- Synthesize the aziridine equivalent TMM precursors and repeat cycloaddition reactions and analysis

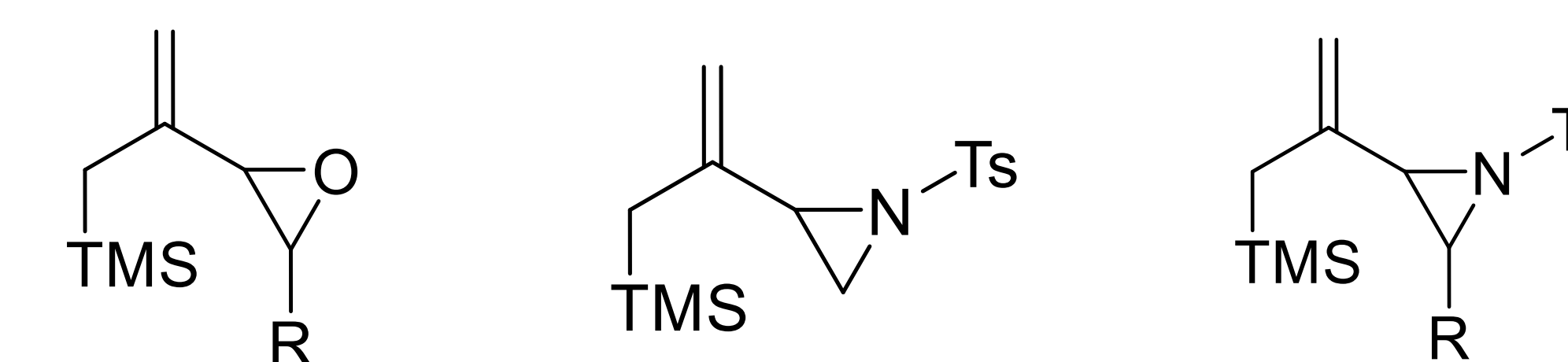


Figure 9. Substituted epoxide TMM precursor and aziridine TMM precursors with and without additional substitution.

## References

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