

Chem 535-Synthetic Organic Chemistry

Ring Contraction Ideas for this lecture were taken from: The following sources:

1. Doyle, M. P. "Catalytic Methods for Metal Carbene Transformations." *Chem. Rev.* **1986**, 86, 919.
2. Ferraz, H. M. C.; Silva, L. F.; Vieira, T. D. "Thallium(III) in organic synthesis." *Synthesis* **1999**, 2001-2023.
3. Gill, G. B. "The Wolff Rearrangement." *In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 887.*
4. Mann, J. "The Favorskii Rearrangement." *In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 839.*

1. Ring contraction in organic synthesis often involves N and S in the target structures; I don't want to include these in the scope of this course.

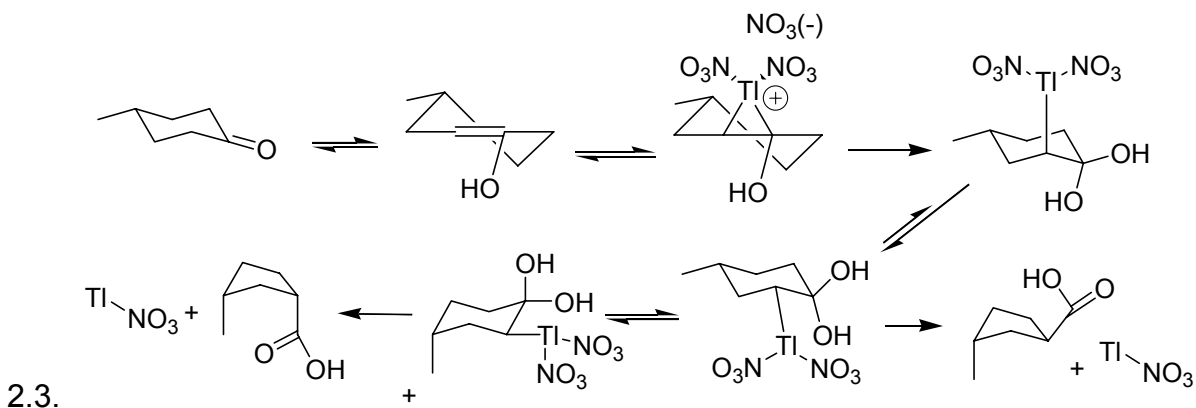
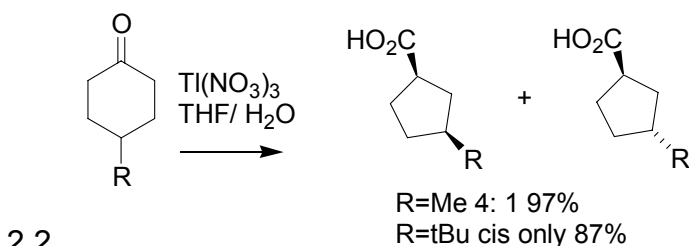
1.1. Synthetic targets that involve C, H and O are an appropriate and challenging basis for introduction of synthesis.

1.2. Below are some of the protocols that you can apply in the current course work.

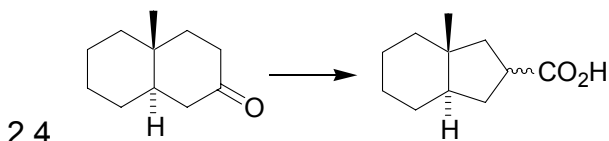
2. Tl(3+) salts effectively induce cyclic ketones to ring contract.

2.1. "Thallium reagents are used only sparingly by organic chemists. This is perhaps due to the over exaggerated toxicity of these compounds. Indeed, it is important to realize that thallium, in contrast to lead and mercury, is not a cumulative poison."

2.1.1. Markó et. al. *J. Am. Chem. Soc.* **1994**, 116, 371.



2.3.1. Mechanism.

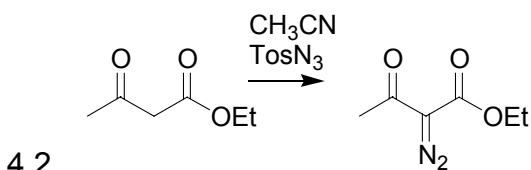
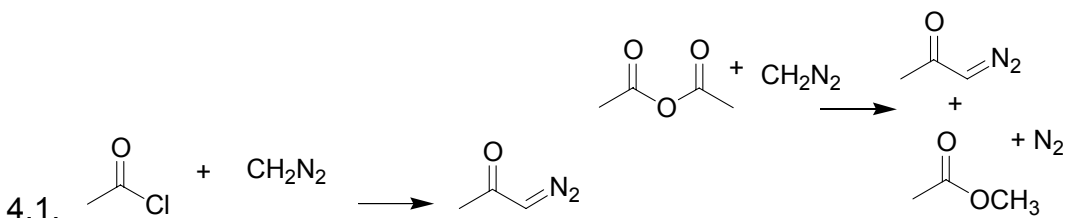


2.5. You can imagine a few methods to access the [4.4.0] bicycle, however the product [4.3.0] bicycle might be a little more challenging.

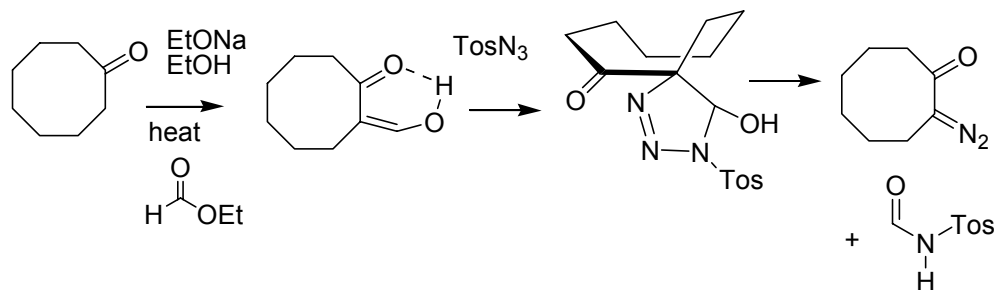
2.5.1. Ring contraction is a good method to consider here.

3. The Wolff Rearrangement, another common method to contract rings.

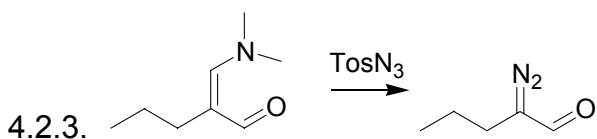
4. To perform this procedure you need to be able to synthesize α -diazoketones.



4.2.1. Carbonyl derivatives need to be doubly activated to use tosylazide. This is circumvented by simply starting from a ketoaldehyde or a ketoenamine (two examples below).



4.2.2.

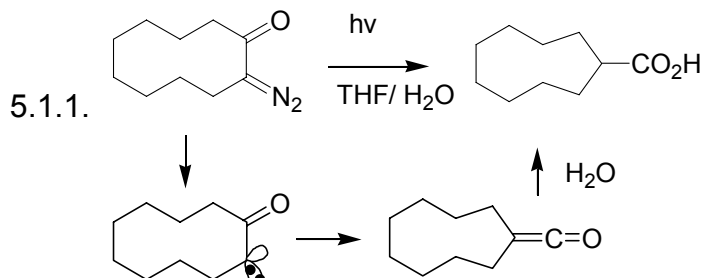


4.2.3.1. I have cautioned you about handling aldehydes excessively or expecting to do a lot with them. The above aldehydes are conjugated

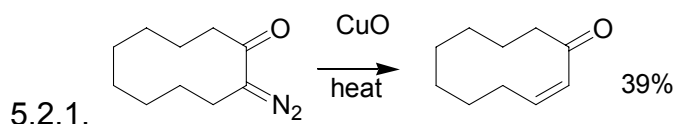
(resonance stabilized) thus more stability can be expected of them.

5. Diazocompounds are carbene precursors.

5.1. When unleashed the carbene can usually be coaxed to insert in the adjacent sigma bond and contract the ring.

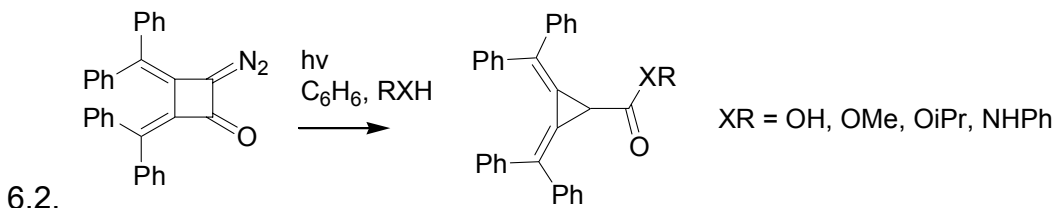
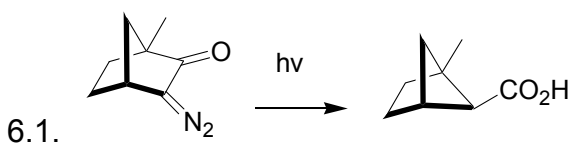


5.2. Below there is obviously a metal associated carbenoid and not a free carbene as a reaction intermediate when transition metals are used.

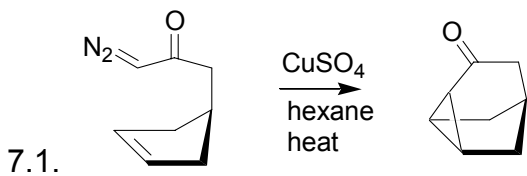


5.2.2. Compare this ten-membered ring product with the one above. What is the likely mechanism of the production of the ten-membered ring α,β -unsaturated ketone?

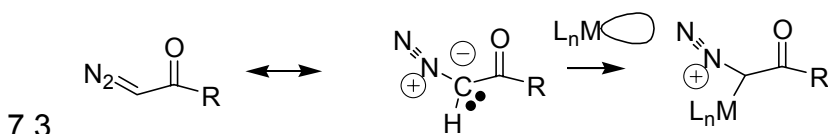
6. Three-membered rings and strained polycyclic systems can be made via the **Wolff Rearrangement**.



7. If given the opportunity the carbene/ carbenoid intermediates preferentially performs a lower energy processes than insertion between a C-C sigma bond.



7.2. A metal atom with an empty orbital allows for the formation of carbenoid species from diazoketones.



7.3.1. These metal-bound species behave differently than free carbenes.

7.3.2. They have the potential to perform the same reactions however.

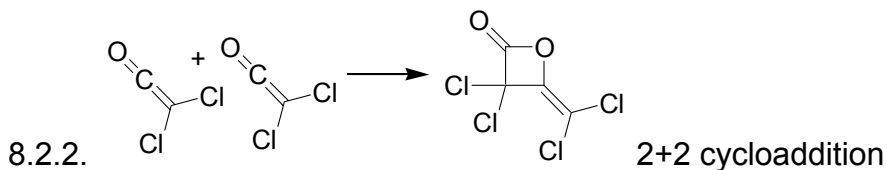
7.3.3. More about this later

8. A ketene is an intermediate in the Wolfe reaction.

8.1. When RXH is not included in the mix the ketene finds other things to do.

8.2. Ketenes undergo facile cycloaddition.

8.2.1. They dimerize by this route.



9. If HX is not included in the reaction mixture the ketene intermediate can do cycloaddition chemistry and sigmatropic rearrangements.

