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5.37 Introduction to Organic Synthesis Laboratory
Spring 2009

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Massachusetts Institute of Technology
Chemistry 5.37
Professor Rick L. Danheiser

Lecture 5

**The Invention of
Cycloaddition and Annulation Strategies**

May 12, 2008

The Diels–Alder Reaction
Historical Background



Richard Willstätter

“ I consider the teaching and study of the historical development of science as indispensable Our textbooks fail in this respect ”

“ Science is not an abstract thing, but rather, as a product of human labor, is tightly bound in its development to the particularity and fate of the individuals who dedicate themselves to it.”



Emil Fischer

Discovery and Invention

Alternate Paths for the Development of New Synthetic Methods

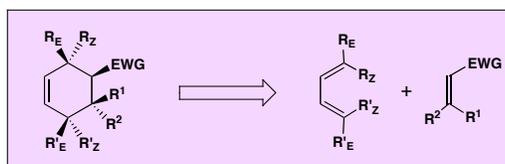
Discovery:

to find something not
previously known

Invention:

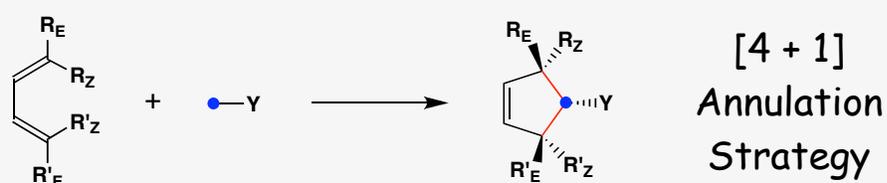
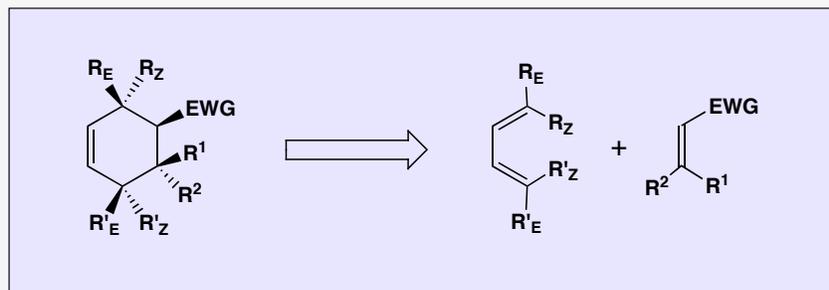
deriving from a deliberate attempt
to solve a problem

The Diels–Alder Reaction

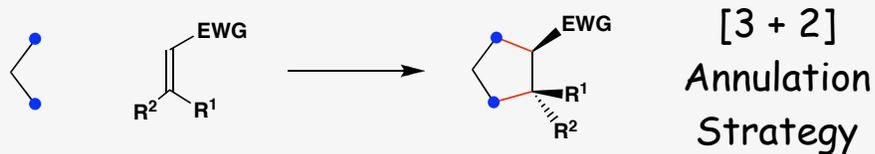
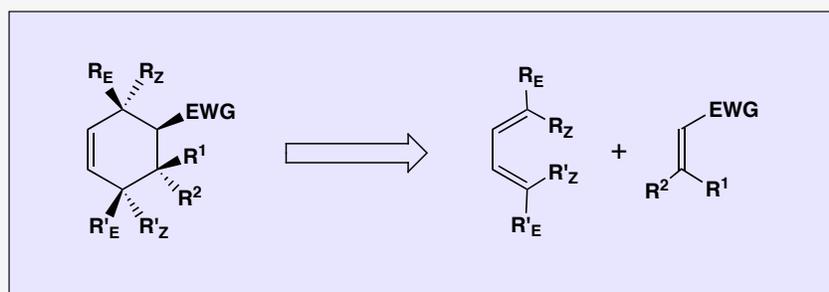


*The single most powerful ring-forming
reaction in the arsenal of organic
chemistry!*

Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

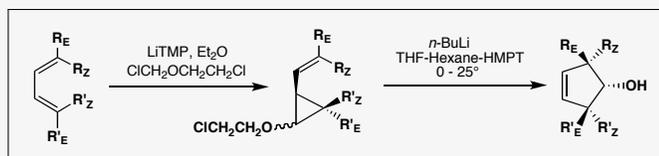


Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

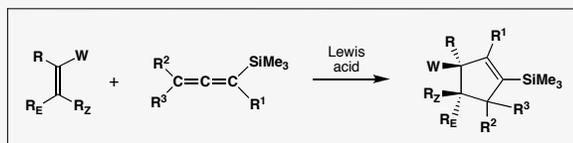


Annulation Strategies for the Synthesis of Carbocyclic and Heterocyclic Compounds

Annulation strategies previously developed in our laboratory



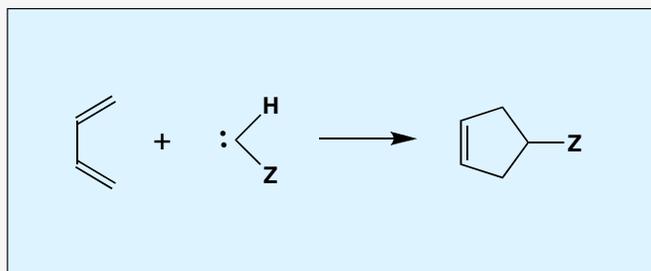
[4+1] Annulation Strategy
Stereocontrolled synthesis of five-membered carbocycles based on anion-accelerated vinylcyclopropane rearrangements



[3+2] Annulation Strategy
Stereocontrolled synthesis of five-membered carbocycles and heterocyclic compounds based on allenylsilanes and allylsilanes

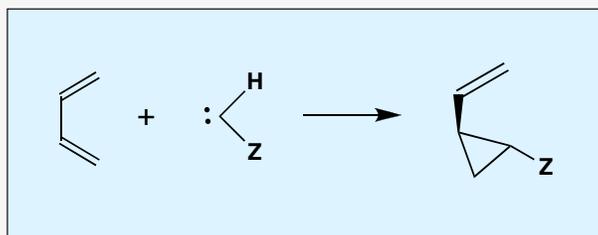
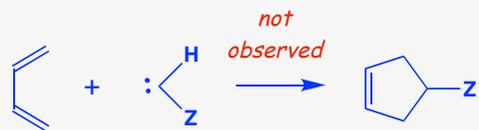
Reaction of Carbenes with 1,3-Dienes

Potential Basis for a [4 + 1] Annulation Strategy



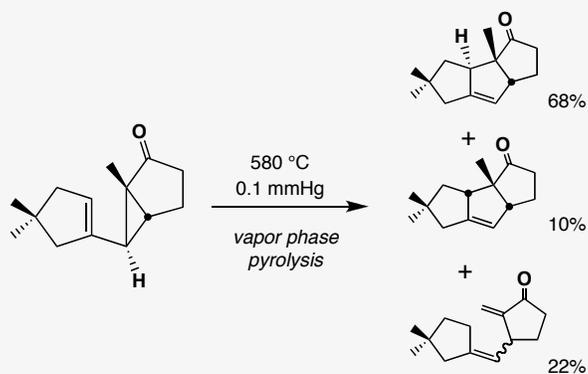
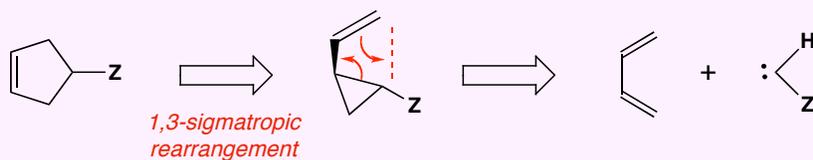
Reaction of Carbenes with 1,3-Dienes

Potential Basis for a [4 + 1] Annulation Strategy

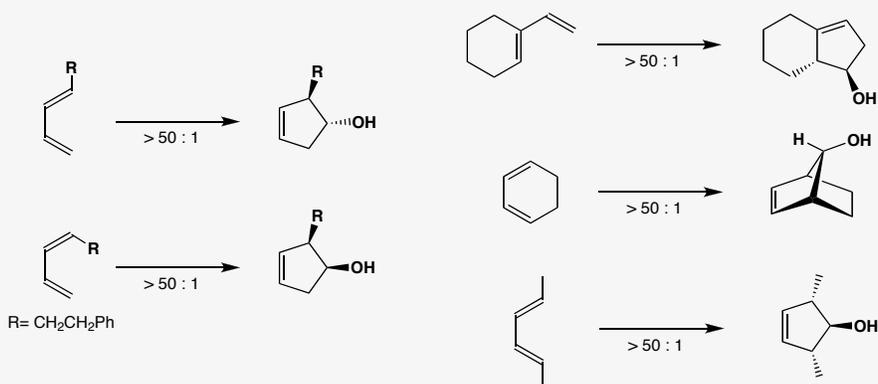
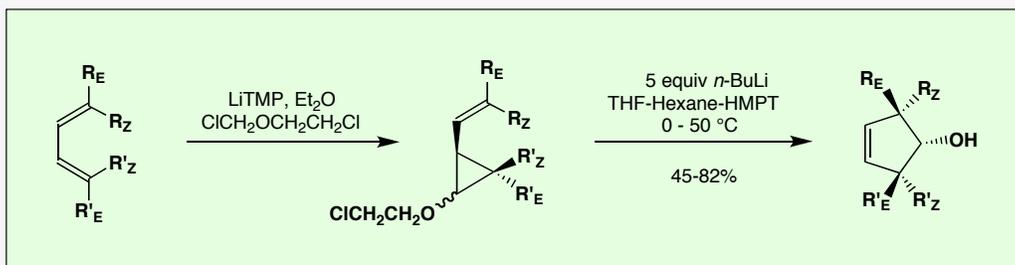


The Vinylcyclopropane Rearrangement

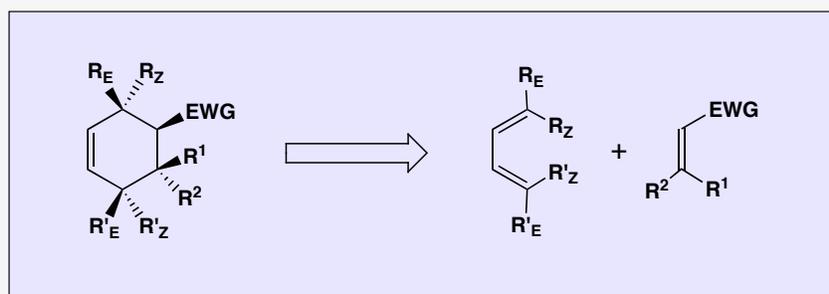
Potential Basis for a [4 + 1] Annulation Strategy



Stereocontrolled [4 + 1] Annulation Strategy Anion-accelerated Vinylcyclopropane Rearrangement

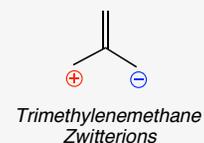
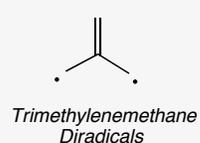
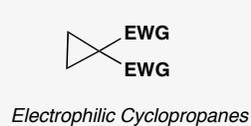
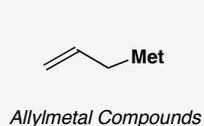
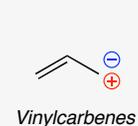
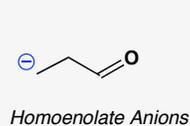
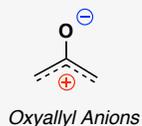
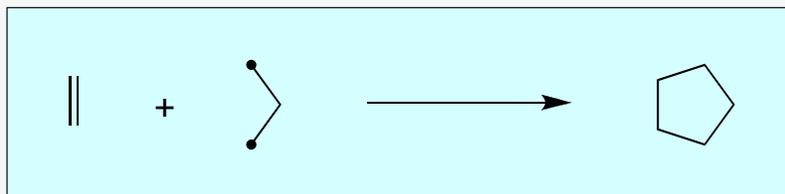


Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

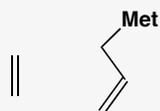
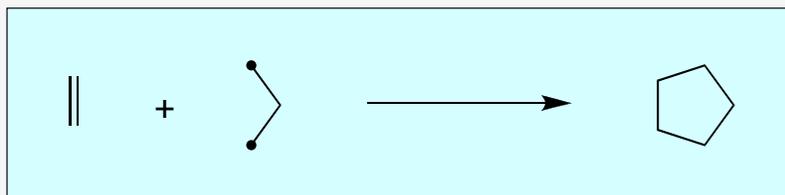


[3 + 2]
Annulation
Strategy

Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

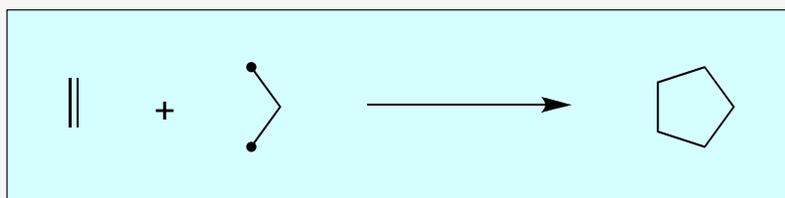


Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings



[3 + 2] Annulation Strategy Based on Allylmetal Compounds

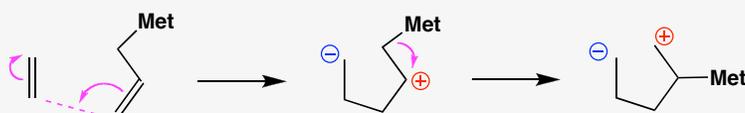
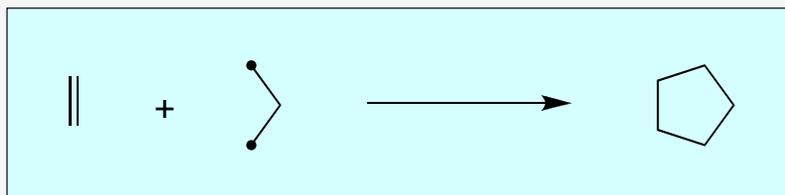
Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings



Electrophilic addition of alkyne to nucleophilic allylmetal compound

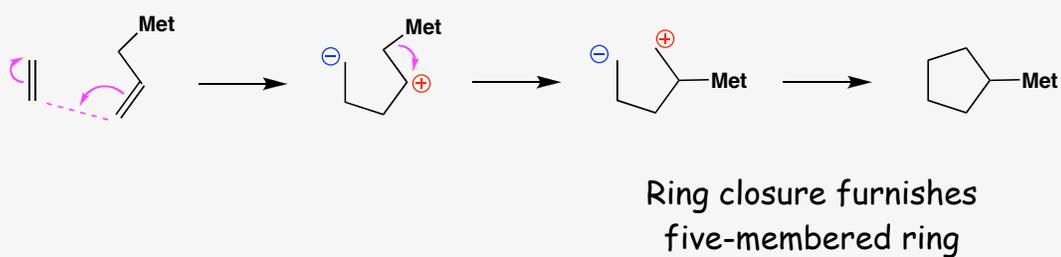
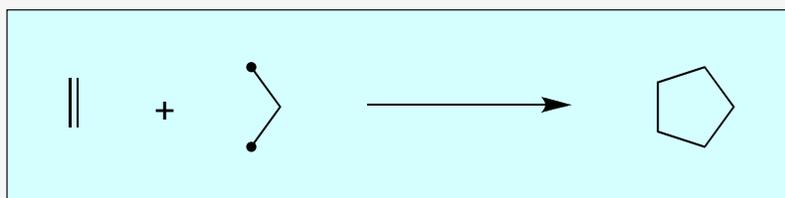
Carbocation stabilized by the β effect

Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

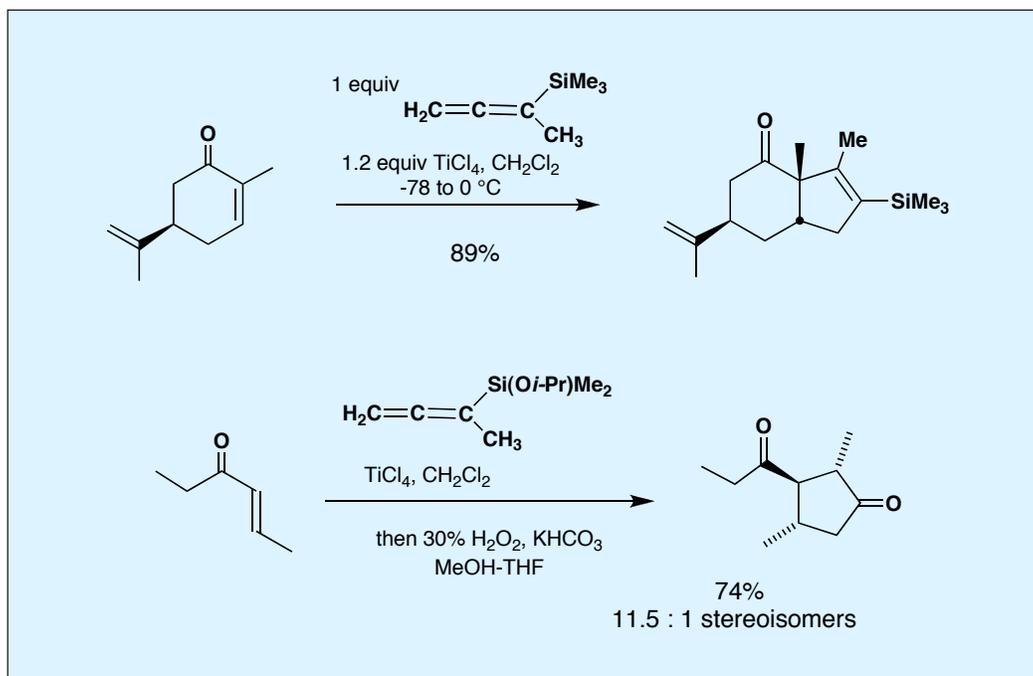


Reversible 1,2-shift of metal group

Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

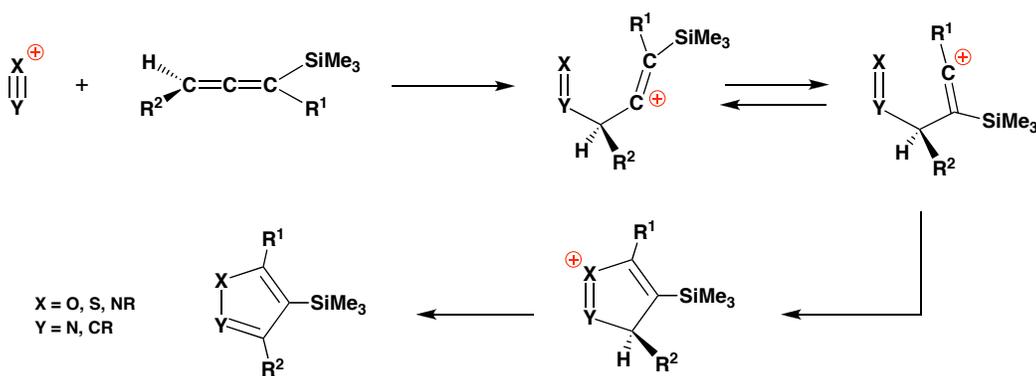


Stereocontrolled [3 + 2] Annulation Strategy



Stereocontrolled [3 + 2] Annulation Strategy

Application to the Synthesis of Five-Membered Heterocycles



Stereocontrolled [3 + 2] Annulation Strategy

Application to the Synthesis of Five-Membered Heterocycles

