5.37 Introduction to Organic Synthesis Laboratory

Spring 2009

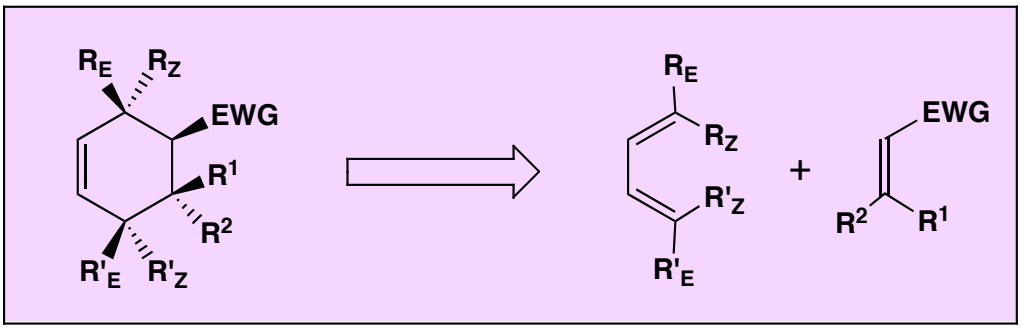
Massachusetts Institute of Technology

Organic Chemistry 5.37

April 16, 2008
Prof. Rick L. Danheiser

Lecture 1

Introduction to Organic Synthesis
The Diels–Alder Reaction



Otto Diels

Our results will play a role not only in the discussion of theoretically interesting questions . . . . but probably also will yield greater significance in a practical sense. Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect. . . . . We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems.

Otto Diels and Kurt Alder *Justus Liebigs Annalen der Chemie* **460,** 98 (1928)

Kurt Alder

For Additional Reading . . . .

(1) "Advanced Organic Chemistry, Part A: Structure and Mechanisms", Fifth Edition, by F. A. Carey and R. J. Sundberg, Springer, 2007, Chapter 10 ("Concerted Pericyclic Reactions"), pp 833-873.

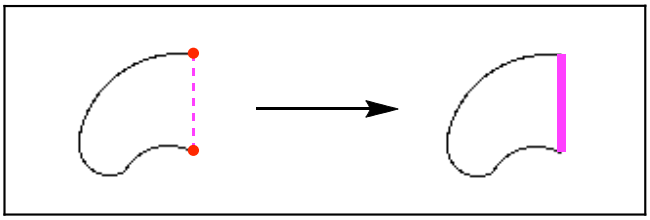
(2) "Advanced Organic Chemistry, Part B: Reactions and Synthesis", Fifth Edition, by F. A. Carey and R. J. Sundberg, Springer, 2007, Chapter 6 ("Concerted Cycloadditions, Unimolecular Rearrangements, and Thermal Eliminations"), pp 473-526.

(3) "Organic Chemistry" by J. Clayden, N. Greeves, S. Warren, and P. Wothers, Oxford University Press, 2001, Chapter 35 ("Pericyclic Reactions I: Cycloadditions"), pp 905-924 and Chapter 45 ("Asymmetric Synthesis"), pp 1217-1232.

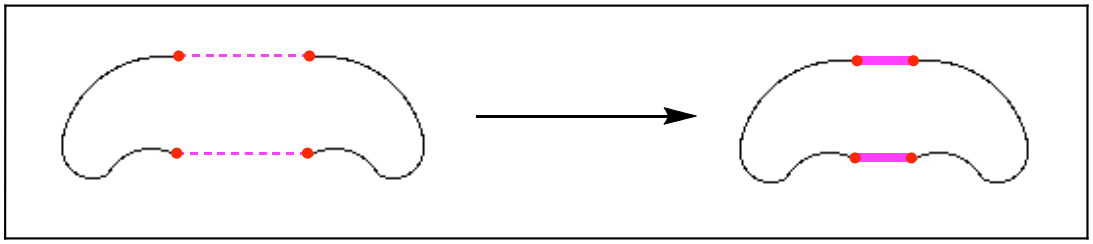
Strategy	Tactics
overall plan to achieve the ultimate synthetic target	means by which plan is implemented
intellectual	experimental
retrosynthetic planning	synthetic execution
TRANSFORMS	REACTIONS
Target ⟹ **Precursor**	**Precursor** → **Target**

Strategies for the Assembly of Cyclic Compounds

Cyclization



Annulation

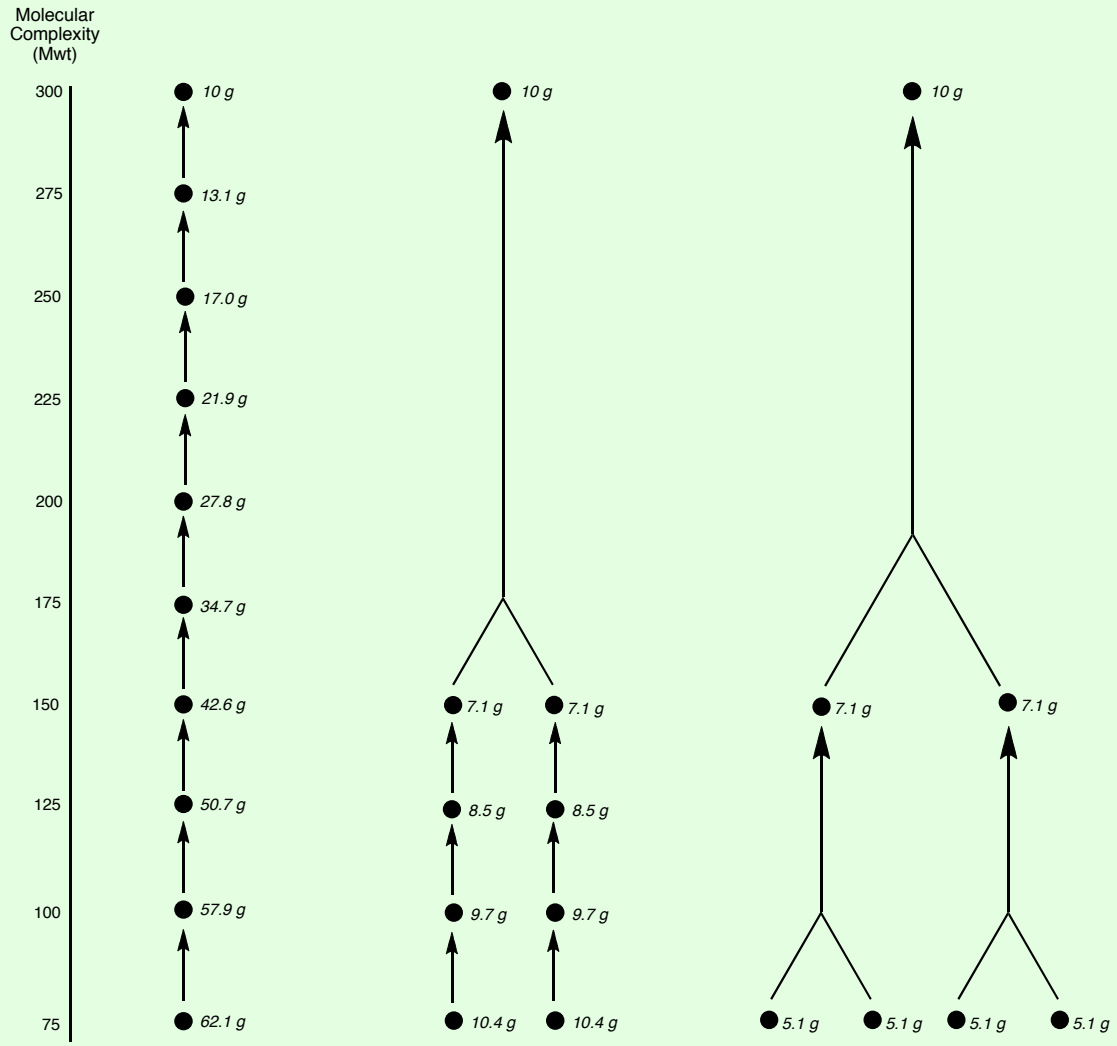


Concerted Cycloadditions
Non-Concerted "Single-Operation" Annulations
Multistep Annulation Strategies

★ General Principles of Retrosynthetic Analysis ★

The first principle of retrosynthetic planning: **convergent strategies** are the most efficient strategies for the assembly of complex molecules

The Power of Convergent Synthesis



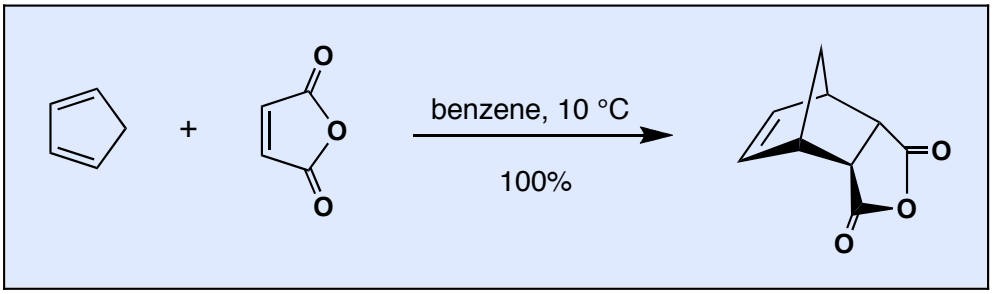
# Steps	9	7	3
Starting Materials	62.1 g	20.8 g	20.4 g
Solvent @10 mL/g SM for each step	3278 mL	714 mL	346 mL

calculations based on 70% yield per step

The "Discovery" of the Diels- Alder Reaction

"Tragt man in eine Suspension von 1 Mol. Maleinsaure-anhydrid in der 5 fachen Menge von reinem Benzol unter Kuhlung allmahlich 1 Mol. Cyclopentadien ein, so reagieren die Komponenten augenblicklich unter starker Warmentwicklung. Das Maleinsaure-anhydrid geht in Losung, und schon wahrend des Prozesses scheidet sich das Anhydrid der neuen Saure in schneeweissen, glanzenden Krystallen ab. Die Ausbeute ist nahezu quantitativ."

Otto Diels and Kurt Alder *Justus Liebigs Annalen der Chemie* **460,** 98 (1928)



R. B. Woodward
1917-1979
MIT B.S. 1936
MIT Ph.D. 1937