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5.37 Introduction to Organic Synthesis Laboratory
Spring 2009

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Massachusetts Institute of Technology

Chemistry 5.37

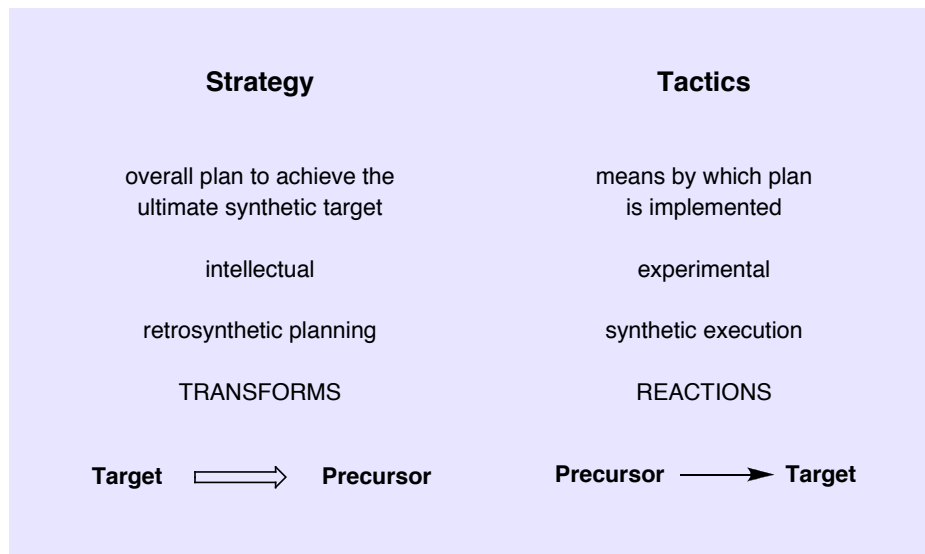
Professor Timothy M. Swager



The Diels-Alder Reaction
(Adapted from 2008 Lecture Given by
Professor Rick Danheiser)

April 7, 2009

Strategies and Tactics in Organic Synthesis



Efficiency and Selectivity in Organic Synthesis

Selectivity

- ★ Stereoselectivity
- ★ Regioselectivity
- ★ Chemoselectivity

Efficiency

Tactical Efficiency

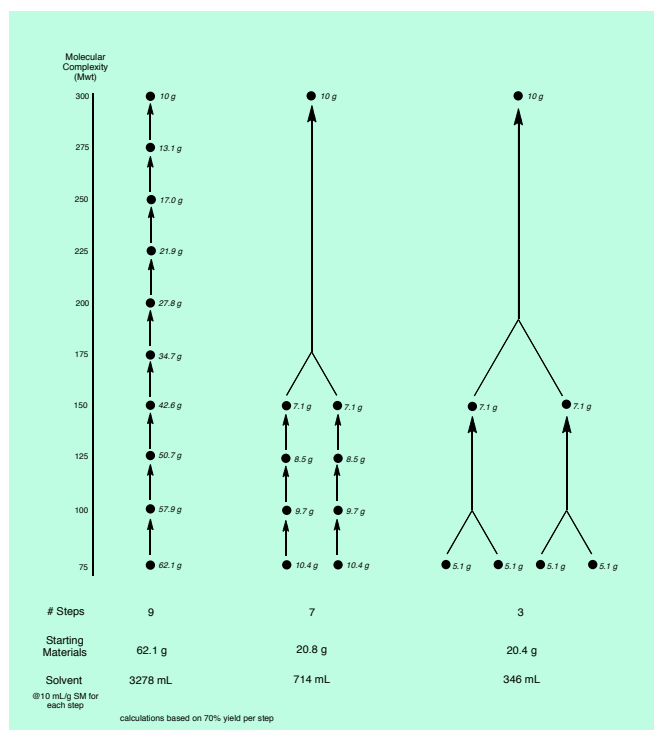
- ★ High Yield
- ★ Atom Economy

Strategic Efficiency

- ★ Minimum # Steps
- ★ Convergence

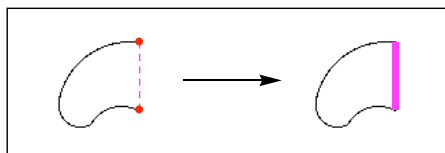
Efficiency and Selectivity in Organic Synthesis

The Power of Convergent Synthesis

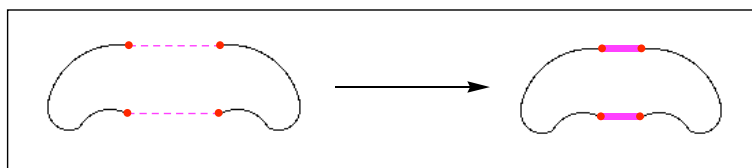


Strategies for the Assembly of Cyclic Compounds

Cyclization



Annulation



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

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

Efficiency and Selectivity in Organic Synthesis

**Cycloaddition
and
Annulation
Strategies**

Efficiency

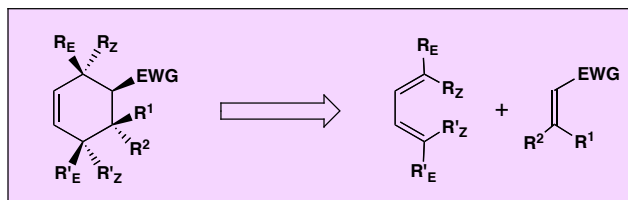
Strategic Efficiency

- ★ Minimum # Steps
- ★ Convergence

Tactical Efficiency

- ★ High Yield
- ★ Atom Economy

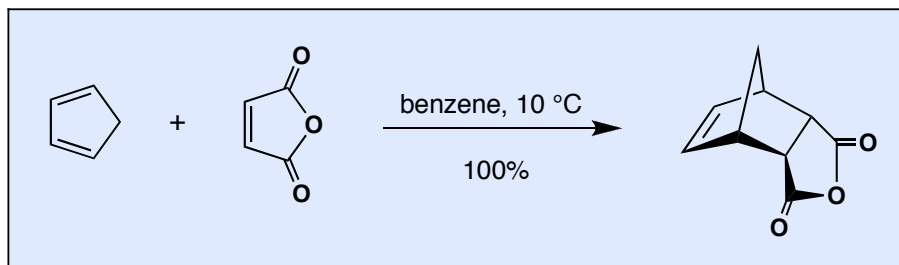
The Diels-Alder Reaction



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

The Diels-Alder Reaction

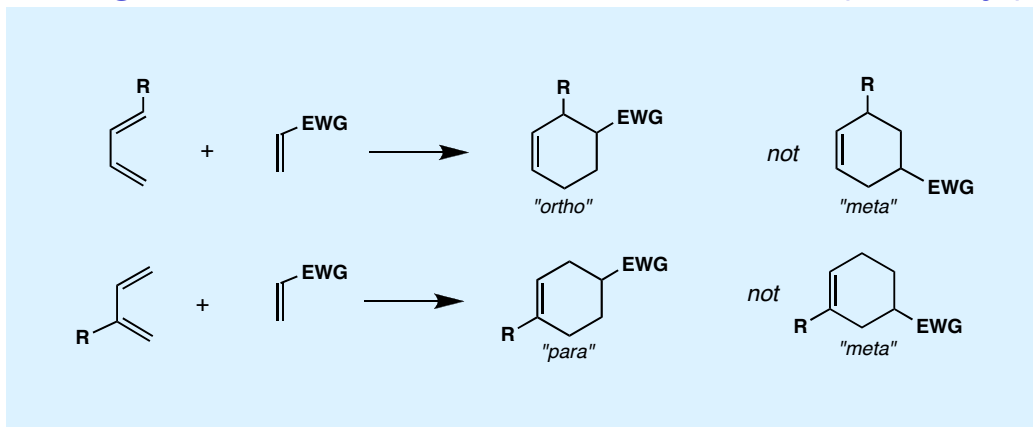
Reaction Conditions



"Tragt man in eine Suspension von 1 Mol. Maleinsäure-anhydrid in der 5 fachen Menge von reinem Benzol unter Kühlung allmahlich 1 Mol. Cyclopentadien ein, so reagieren die Komponenten augenblicklich unter starker Warmentwicklung. Das Maleinsäure-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."

The Diels-Alder Reaction

Regiochemical Course of the Reaction (R= alkyl)



The Diels-Alder Reaction

Stereochemical Course of the Reaction

Intrinsic Stereoselectivity

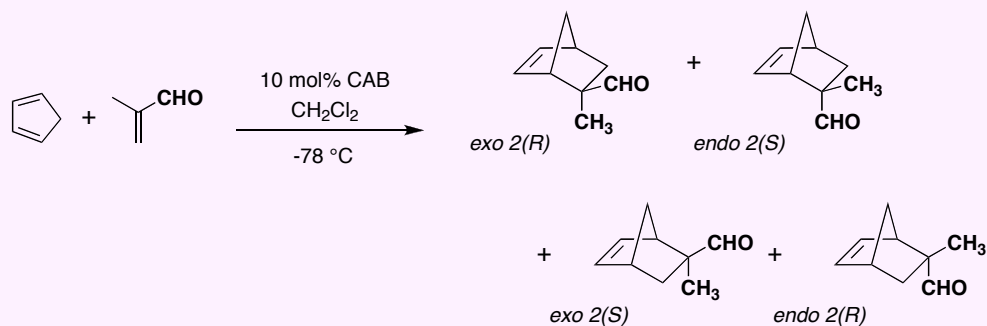
- ★ Suprafacial with respect to the diene
- ★ Suprafacial with respect to the dienophile
- ★ Alder endo rule

Asymmetric Induction

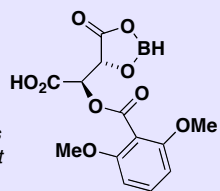
- ★ Substrate control by chiral dienophiles
- ★ Substrate control by chiral dienes
- ★ Stereocontrol via chiral auxiliaries

Catalytic Asymmetric Cycloadditions

Module 7 Catalytic Asymmetric Diels-Alder Reaction



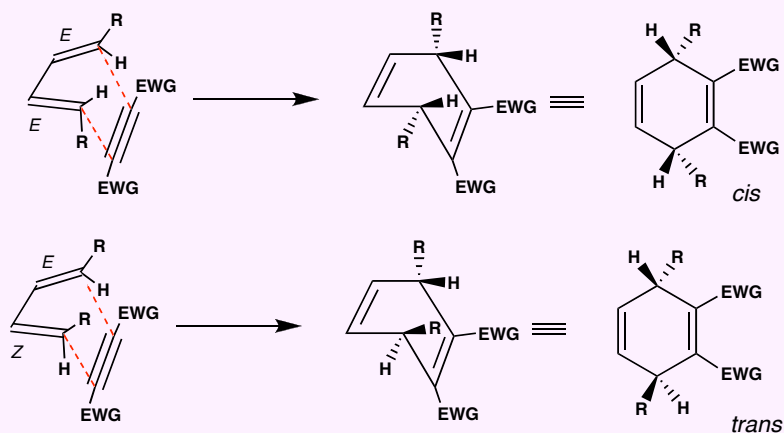
Yamamoto's
CAB catalyst



The Diels-Alder Reaction

Stereochemical Course of the Reaction

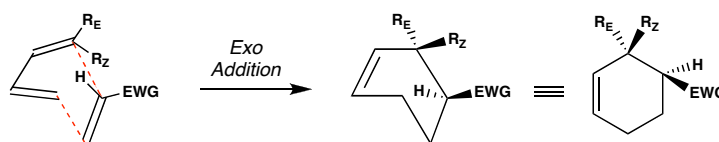
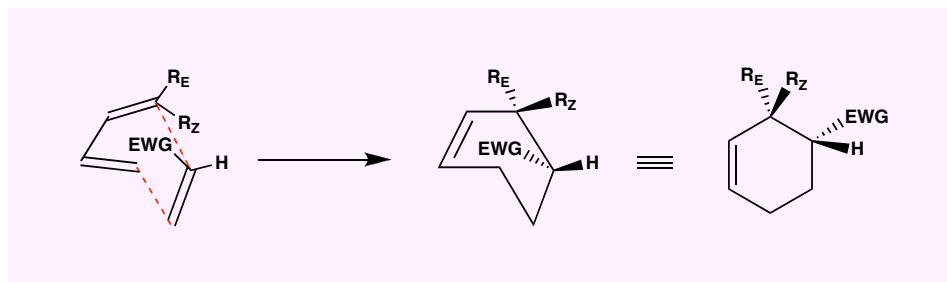
Suprafacial with respect to the diene component



The Diels-Alder Reaction

Stereochemical Course of the Reaction

The Alder Endo Rule

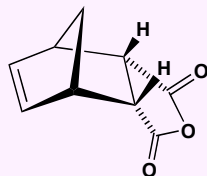
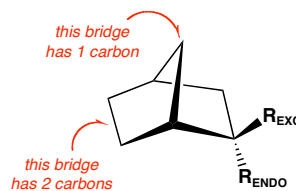


The Diels-Alder Reaction

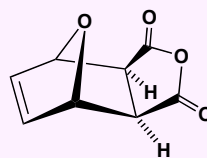
Stereochemical Course of the Reaction

The Alder Endo Rule

The term "**endo**" originates in the terminology used to describe the stereochemistry of substituents on bicyclic ring systems. A substituent is said to be **endo** when it is *trans* to the smaller of the two bridges; an **exo** substituent is *cis* to the smaller bridge.



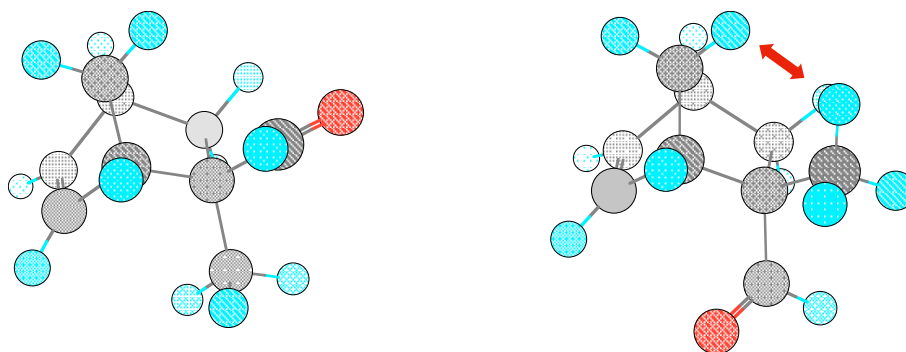
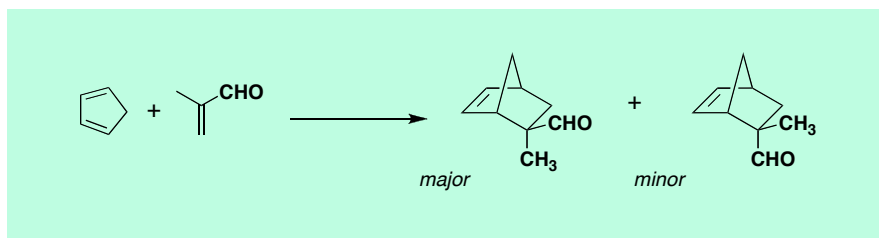
This is an endo Diels-Alder adduct



This is an exo Diels-Alder adduct

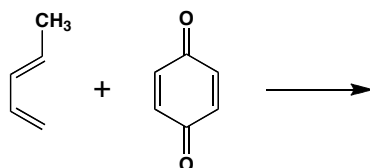
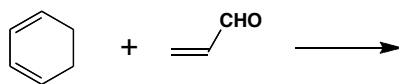
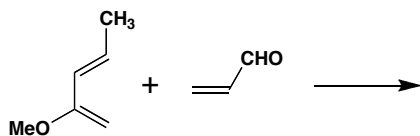
The Diels-Alder Reaction

Exceptions to the Alder Endo Rule



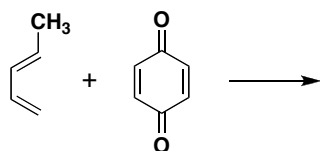
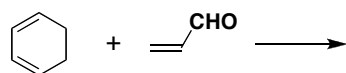
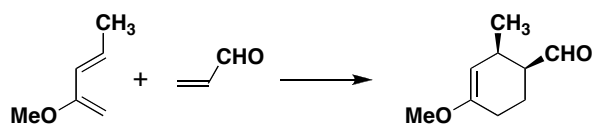
The Diels-Alder Reaction

Intrinsic Stereoselectivity

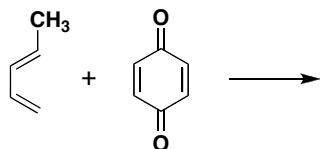
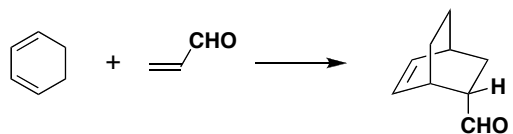
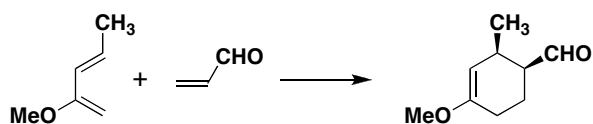


Predict the products
of these
Diels-Alder
cycloadditions

The Diels-Alder Reaction Intrinsic Stereoselectivity

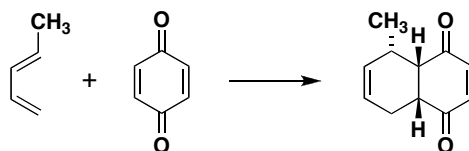
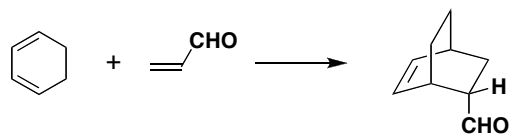
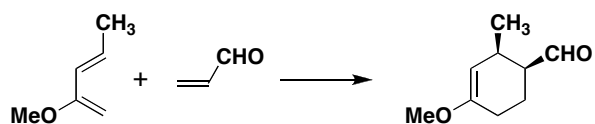


The Diels-Alder Reaction Intrinsic Stereoselectivity



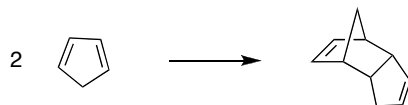
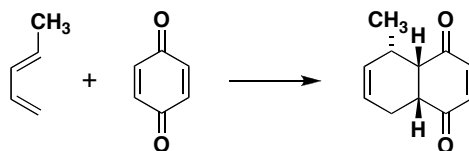
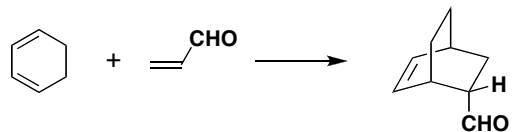
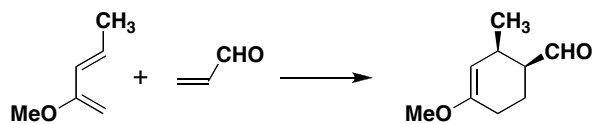
The Diels-Alder Reaction

Intrinsic Stereoselectivity



The Diels-Alder Reaction

Intrinsic Stereoselectivity



The Diels-Alder Reaction

Stereochemical Course of the Reaction

Intrinsic Stereoselectivity

- ★ Suprafacial with respect to the diene
- ★ Suprafacial with respect to the dienophile
- ★ Alder endo rule

Asymmetric Induction

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Catalytic Asymmetric Cycloadditions