5.37 Introduction to Organic Synthesis Laboratory
Spring 2009

Massachusetts Institute of Technology

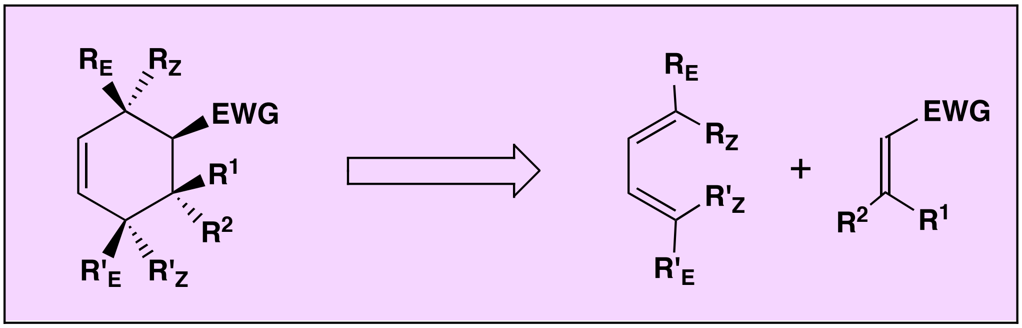
Organic Chemistry 5.37

April 25, 2008
Prof. Rick L. Danheiser

Lecture 4

Introduction to Organic Synthesis

The Diels-Alder Reaction, Part IV



Stereochemical Course of the Diels-Alder Reaction

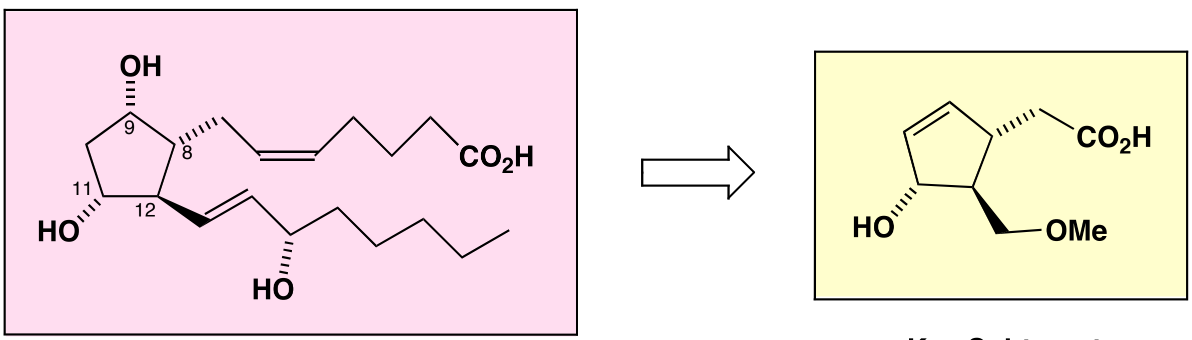
Intrinsic Stereoselectivity
- ★ Suprafacial with respect to the diene
- ★ Suprafacial with respect to the dienophile
- ★ Alder endo rule

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

Catalytic Asymmetric Cycloadditions

Case Study

Total Synthesis of Prostaglandins
Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675



Prostaglandin $F_{2\alpha}$

Key Subtarget

Controlling the Relative Stereochemistry

In the previous lecture, we saw how Corey's synthesis of **prostaglandin $F_{2\alpha}$** exploits two of the stereochemical features of the Diels-Alder reaction:
- ★ the intrinsic stereoselectivity (suprafacial addition with respect to the diene)
- ★ asymmetric induction (substrate control by the diene)

Controlling the Absolute Stereochemistry

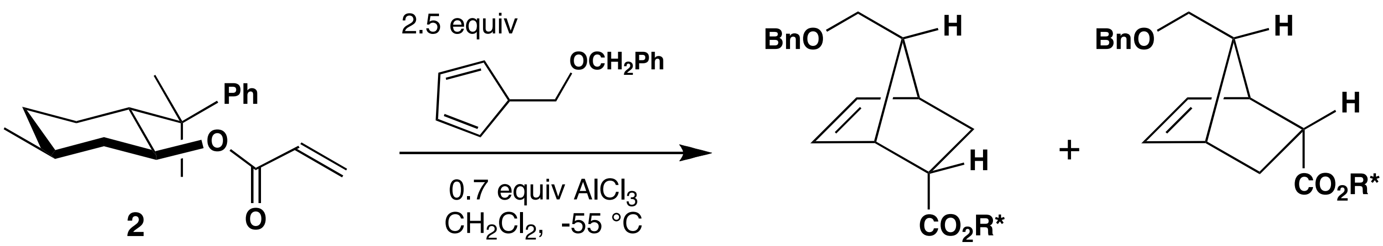
✱ Approach I: Resolution

Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397

Controlling the Absolute Stereochemistry

Approach II: Chiral Auxiliaries

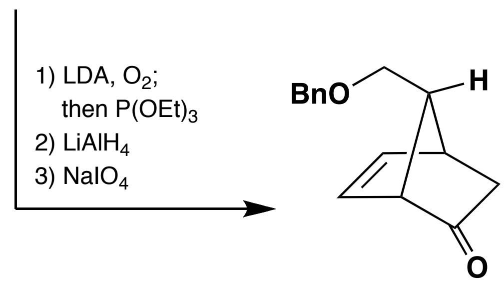
Corey, E. J.; Ensley, H. E.
J. Am. Chem. Soc. **1975**, *97*, 6908



prepared in 4 steps from (-)-pulegone

97:3 ratio
major cycloadduct isolated in 89% yield
also obtained 7% exo cycloadducts

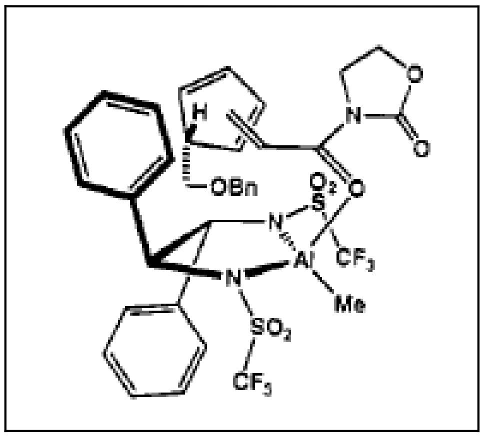
Peppermint
"The Worlds's Oldest Medicine"

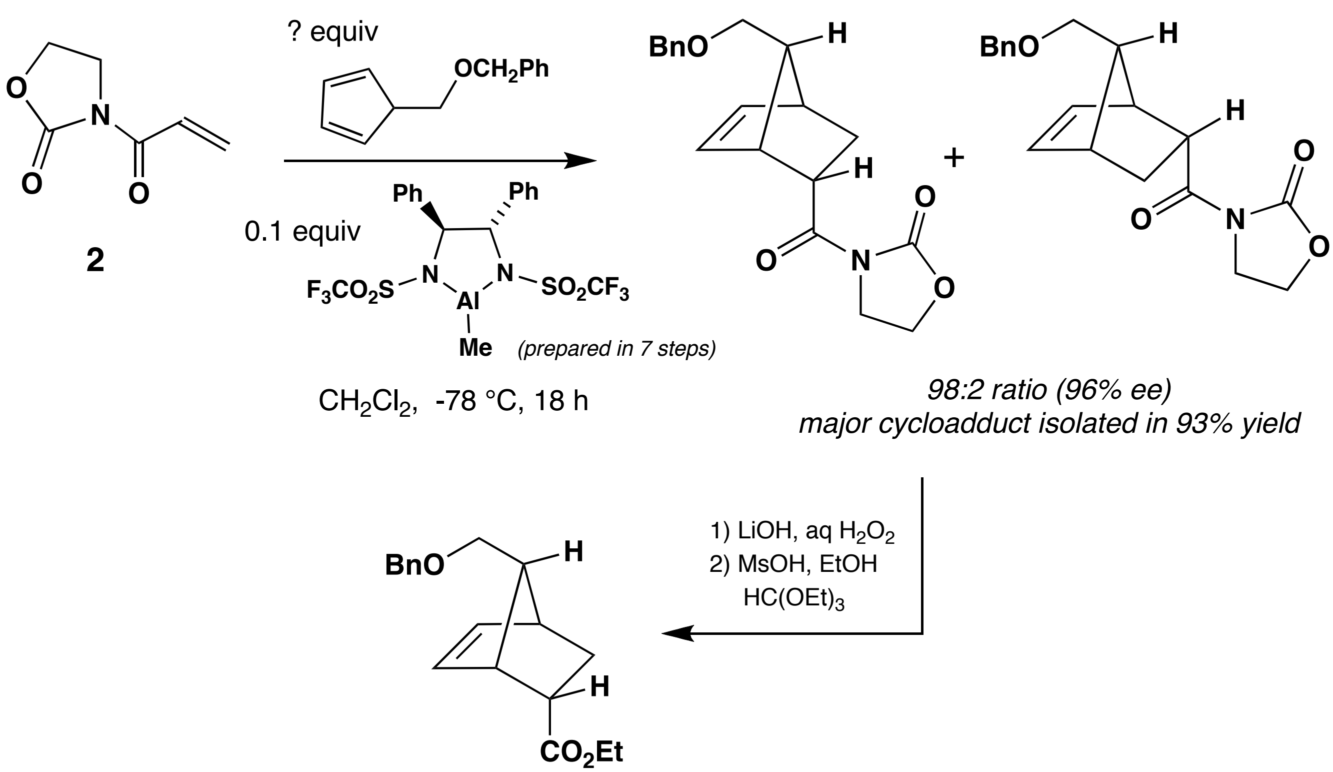


Approach III: Catalytic Asymmetric Diels-Alder Reactions

Example 1: Corey's "Stein" ("Stilbene Diamine") Catalyst

Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493
Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991**, *32*, 7517
Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938

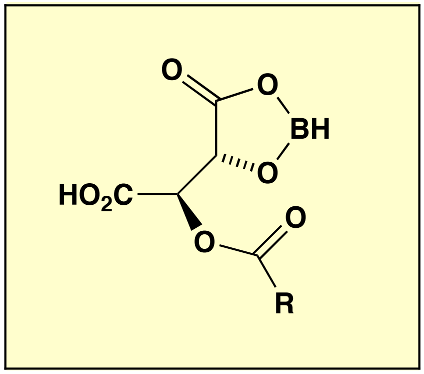


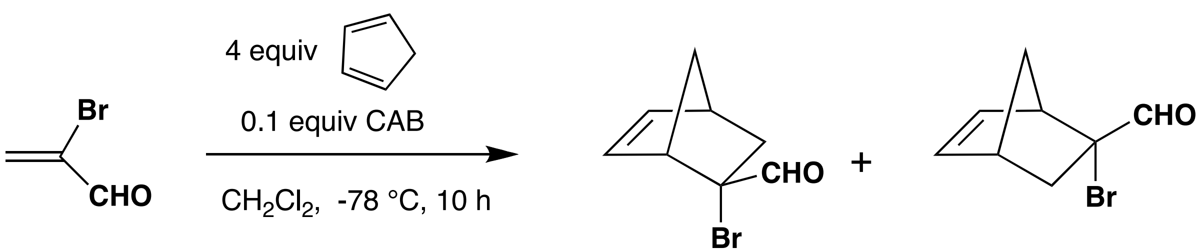


Approach III: Catalytic Asymmetric Diels-Alder Reactions

Example 2: Yamamoto's "CAB" ("Chiral Acyloxy Borane") Catalyst

Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917
Furuta, K.; Gao, Q.-Z.; Yamamoto, H. *Org. Synth*. **1995**, *72*, 86
Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54,* 1481
Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1988**, *110*, 6254





97.5:2.5 ratio (95% ee)
100% yield
94:6 exo/endo cycloadducts

Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc*. **1991**, *113*, 8966