The Diels-Alder Reaction

Lecture Notes

Key Reviews:

Total Synthesis
K.C. Nicolaou, S.A. Snyder, T. Montagnon, G. Vasillikogiannakis, Angew. Chem. Int. Ed. 2002, 41, 1668.

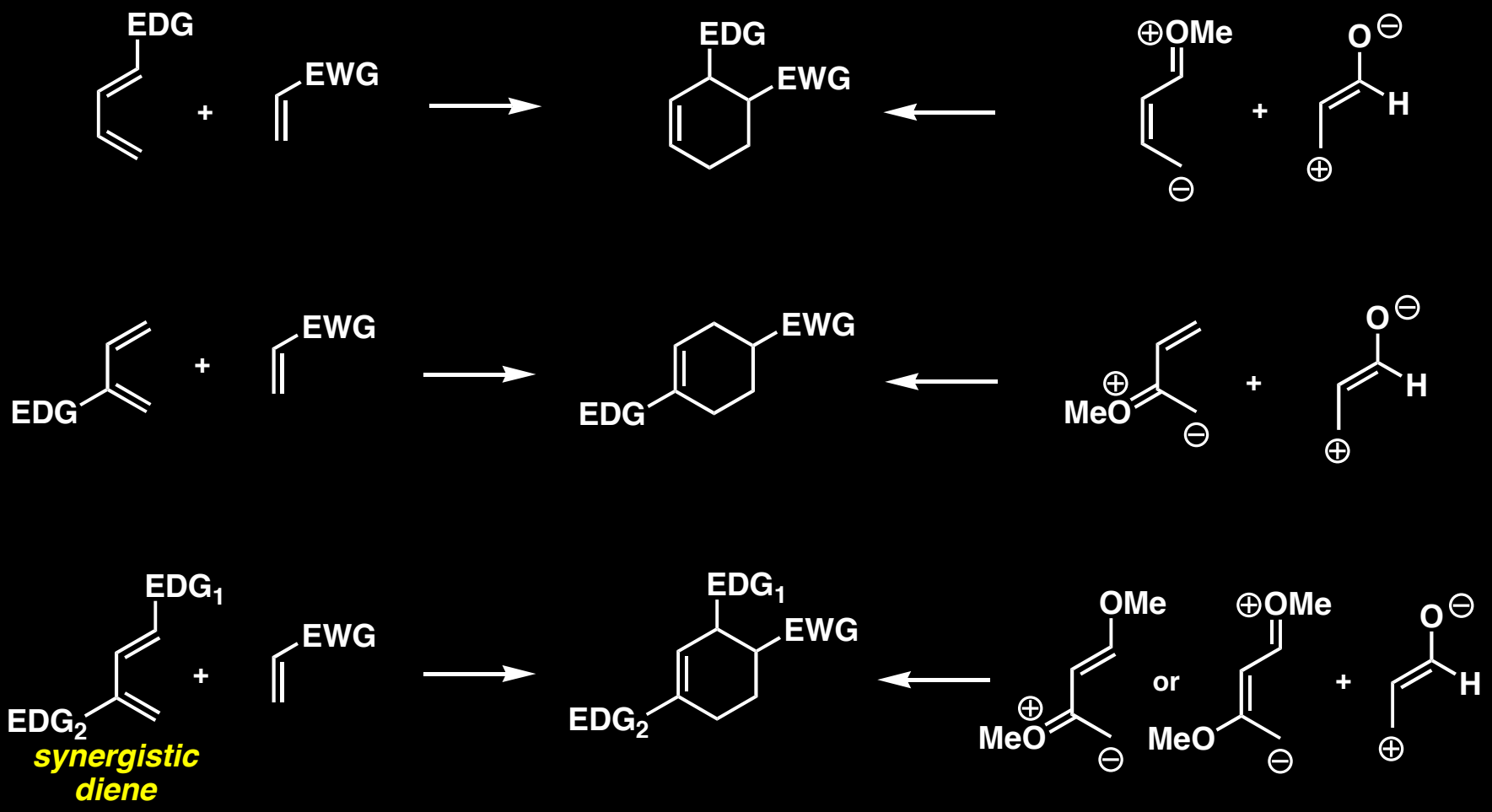
Asymmetric
E.J. Corey, Angew. Chem. Int. Ed. 2002, 41, 1650.

Hetero
D. L. Boger, Comprehensive Organic Synthesis, Vol. 5., 1991, p. 451-512.

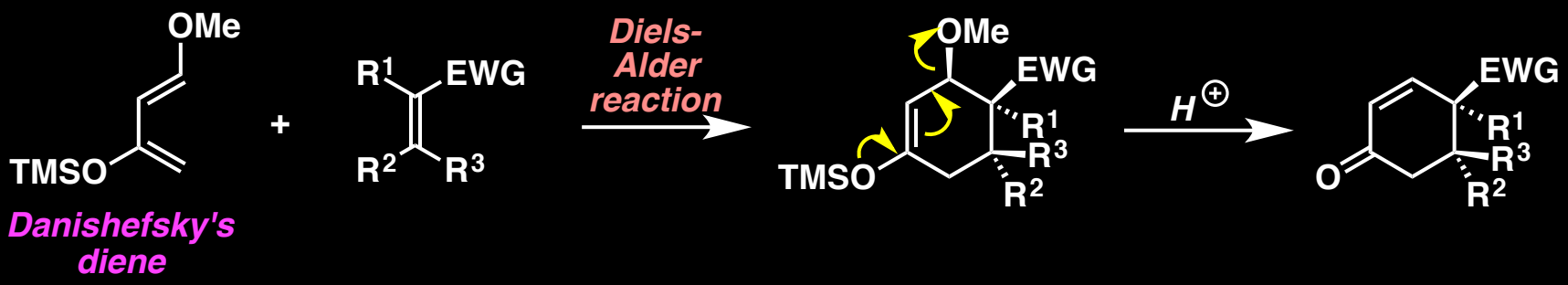
Biomimetic
E. M. Stocking, R. M. Williams, Angew. Chem. Int. Ed. 2003, 42, 3078.

Transannular
P. Deslongchamps, Tetrahedron 2001, 57, 4243.

The Diels-Alder Reaction: Regioselectivity



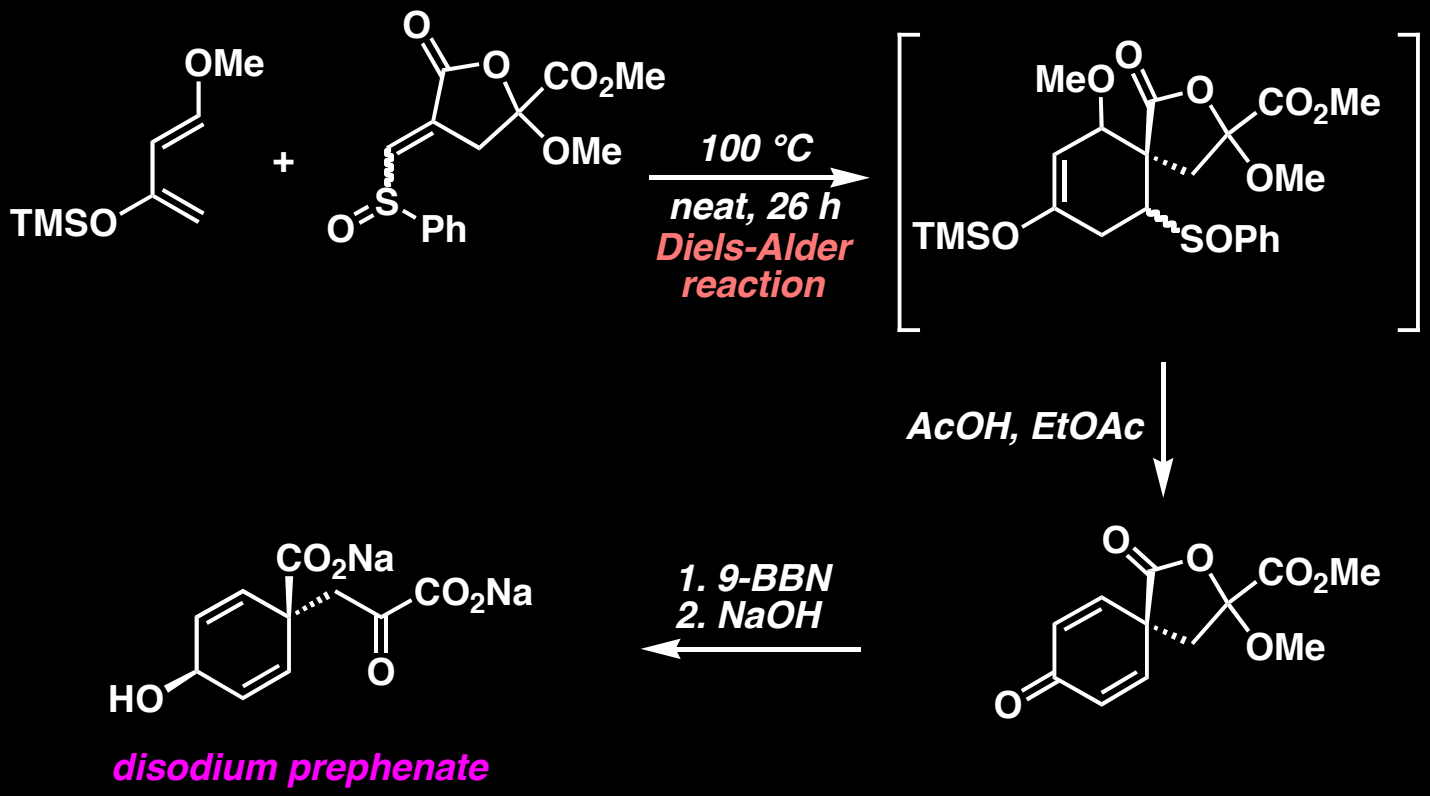
Regioselective Diels-Alder Reactions: Danishefsky's Diene



***Synergistic diene**: the methoxy and silyloxy substituents reinforce each other in terms of regioselectivity and provide sufficient electron density on the diene subunit that most Diels-Alder reactions proceed with good dienophiles at low temperature (without the need for Lewis acid catalysis) with incredible regioselectivity.*

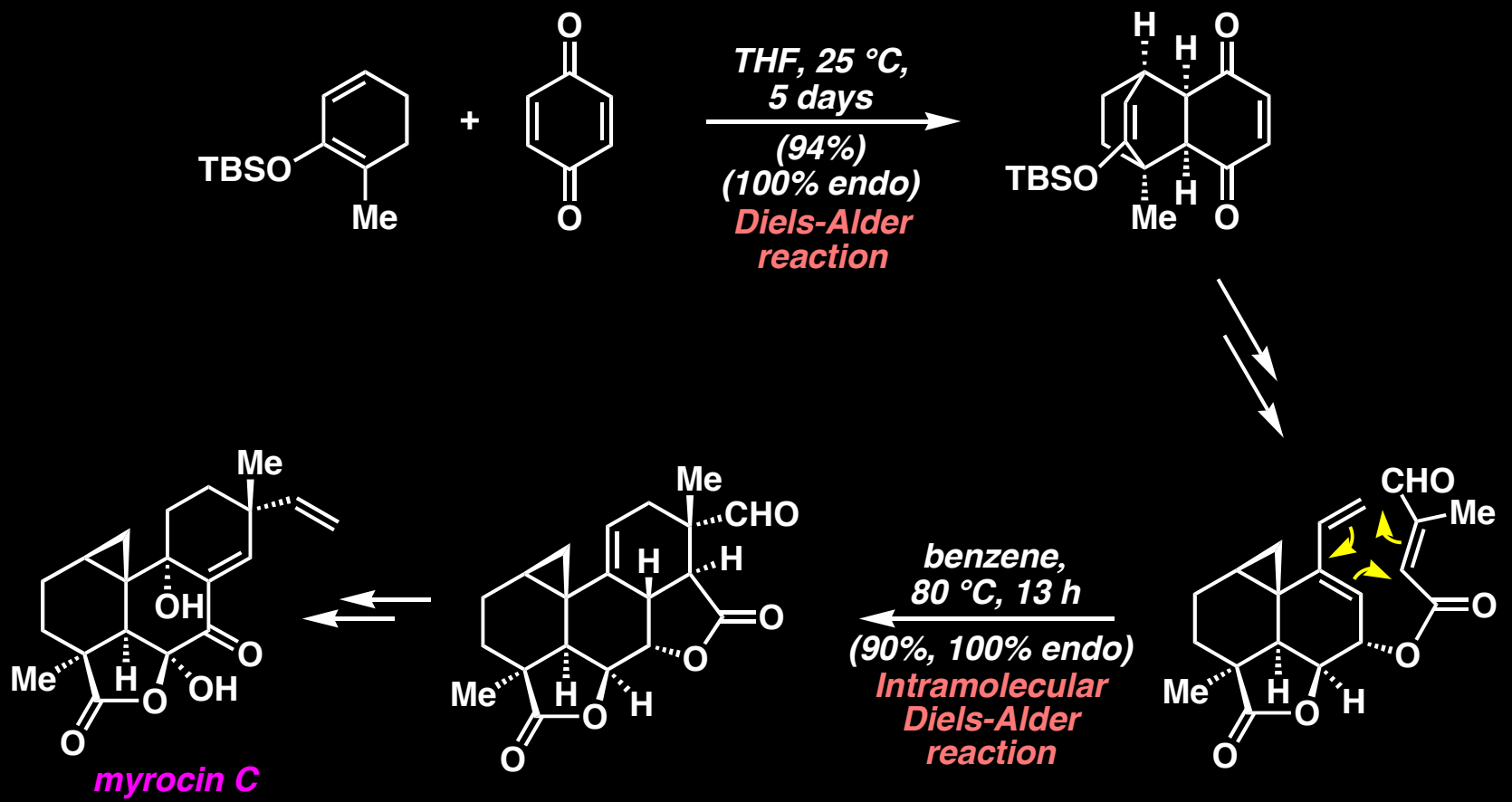
S. J. Danishefsky, T. Kitahara, J. Am. Chem. Soc. 1974, 96, 7808.
S. J. Danishefsky, Acc. Chem. Res. 1981, 14, 400.

Regioselective Diels-Alder Reactions: Danishefsky's Diene



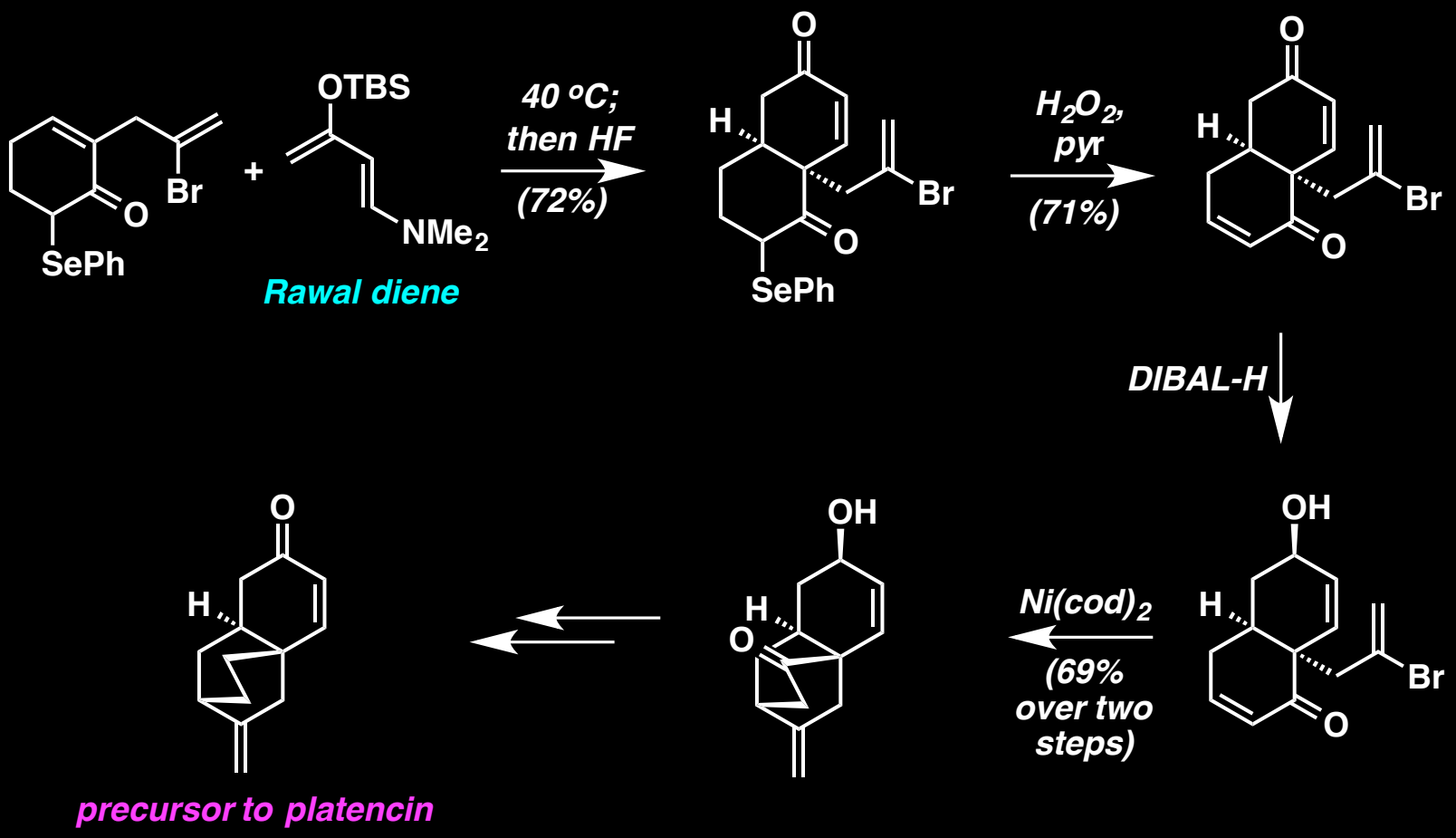
S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 1979, 101, 7013.

Regioselective Diels-Alder Reactions: Danishefsky's Diene



S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 1992, 114, 8883.
S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 1994, 116, 11213.

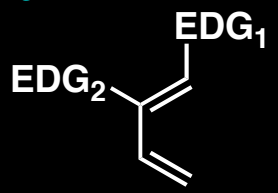
The Rawal Diene - Another Synergistic Diene

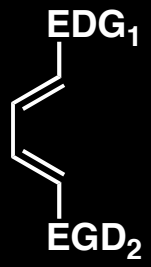


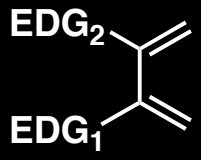
J. Hayashida, V. Rawal, Angew. Chem. Int. Ed. 2008, 47, 4373.

The Diels-Alder Reaction: General Principles

However . . .



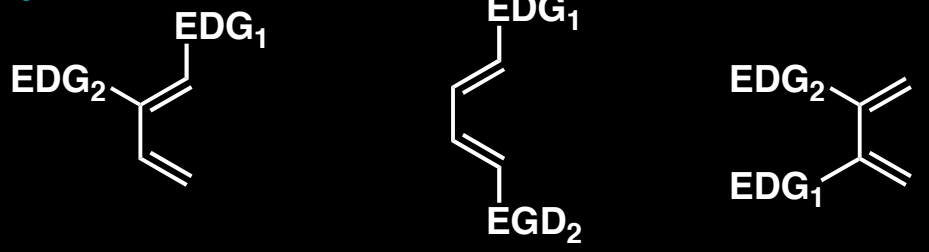




Predictions are hard since these groups are battling each other for control

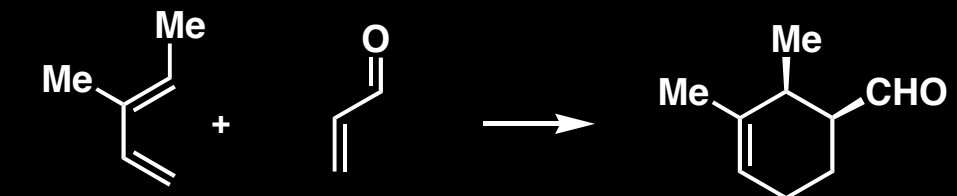
The Diels-Alder Reaction: General Principles

However . . .

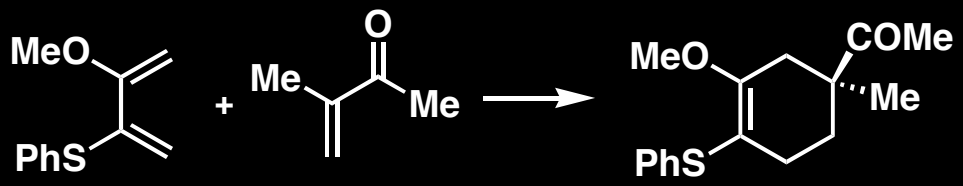


Predictions are hard since these groups are battling each other for control

What Determines Who Wins? Both position and electronics matter



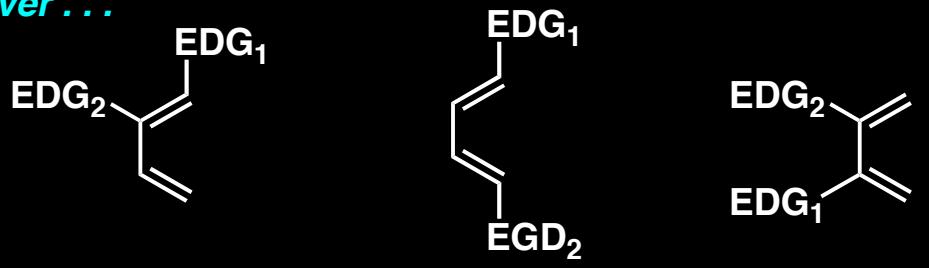
The C-1 methyl group dominates the reaction



$NHCO_2R$ > SR > OR > alkyl

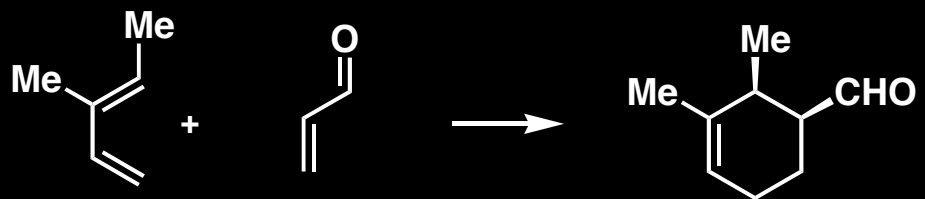
The Diels-Alder Reaction: General Principles

However . . .

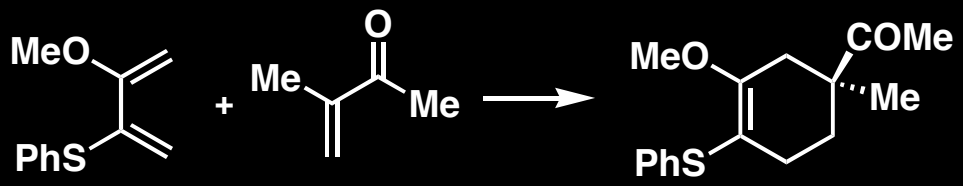


Predictions are hard since these groups are battling each other for control

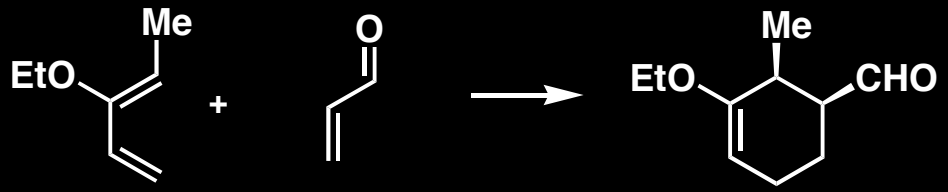
What Determines Who Wins? Both position and electronics matter



The C-1 methyl group dominates the reaction

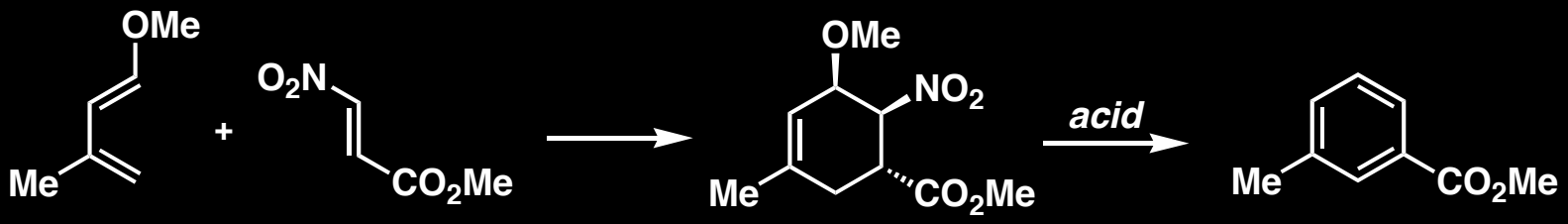


$NHCO_2R$ > SR > OR > alkyl

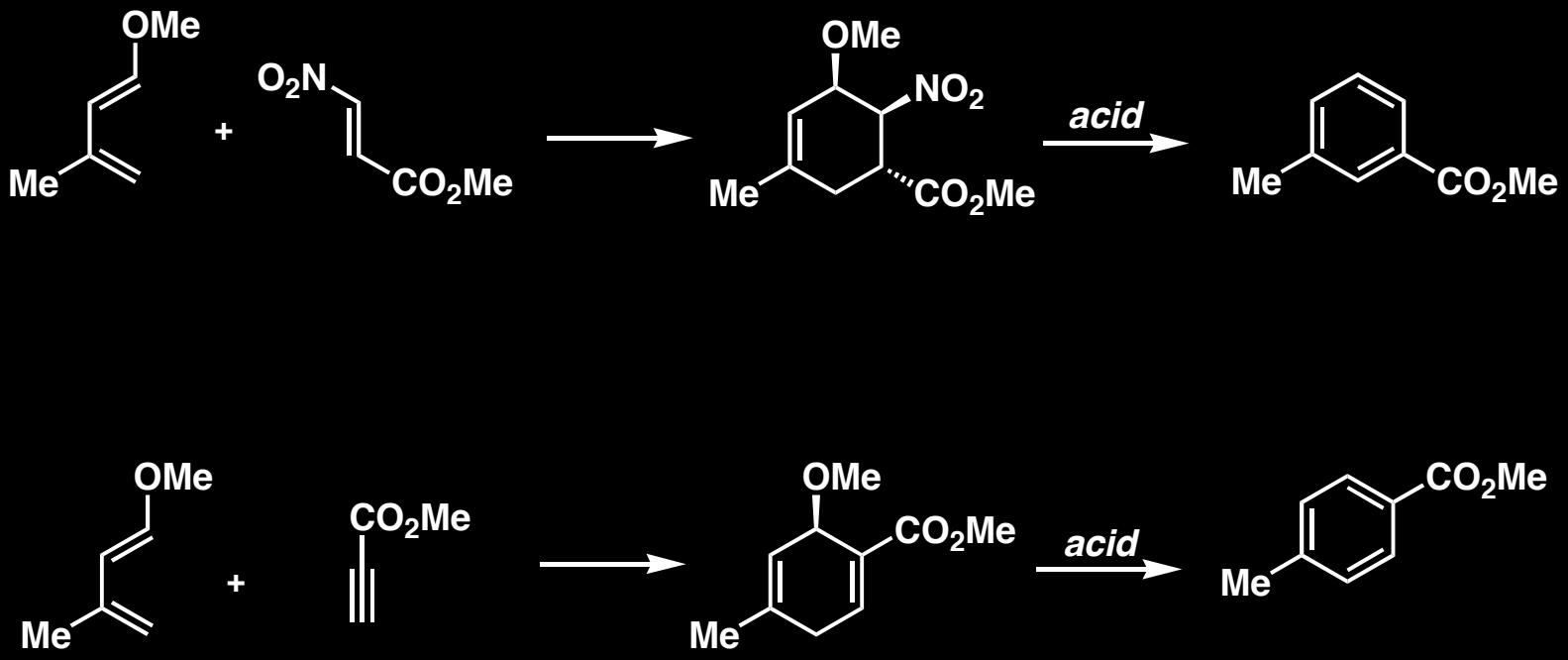


When a group is at C-1, it tends to win even if the C-2 group is a better donor

The Diels-Alder Reaction: General Principles

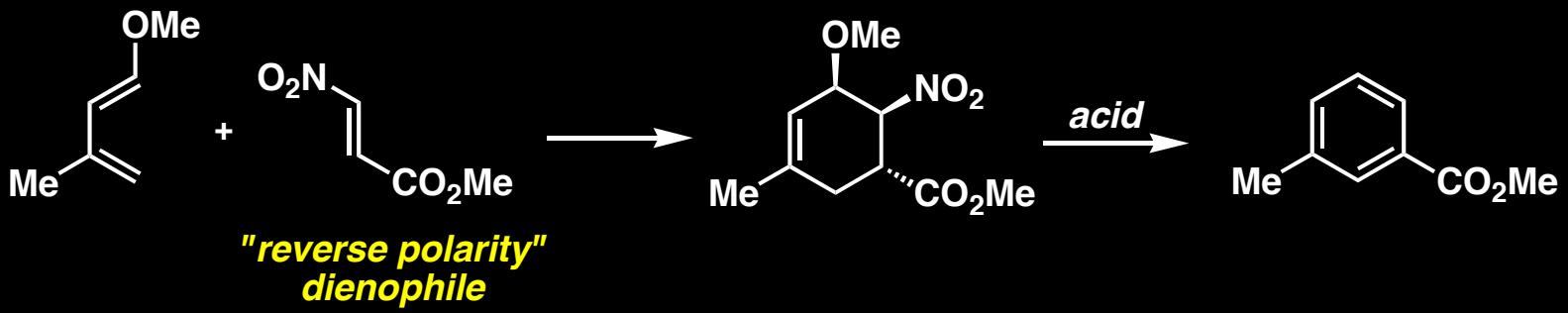


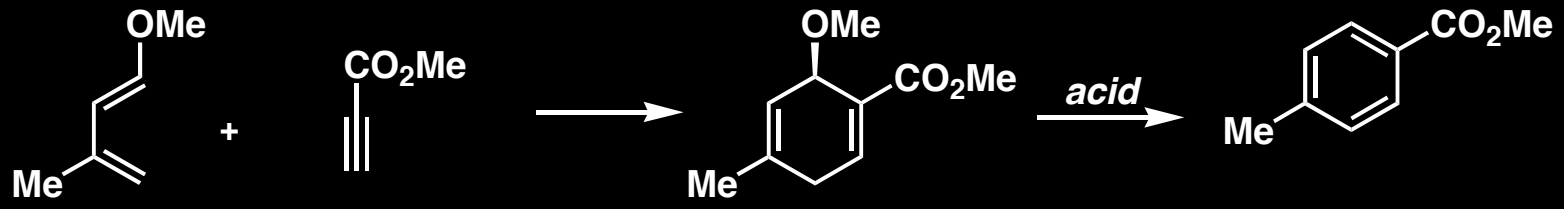
The Diels-Alder Reaction: General Principles



These contrasting outcomes are quite striking

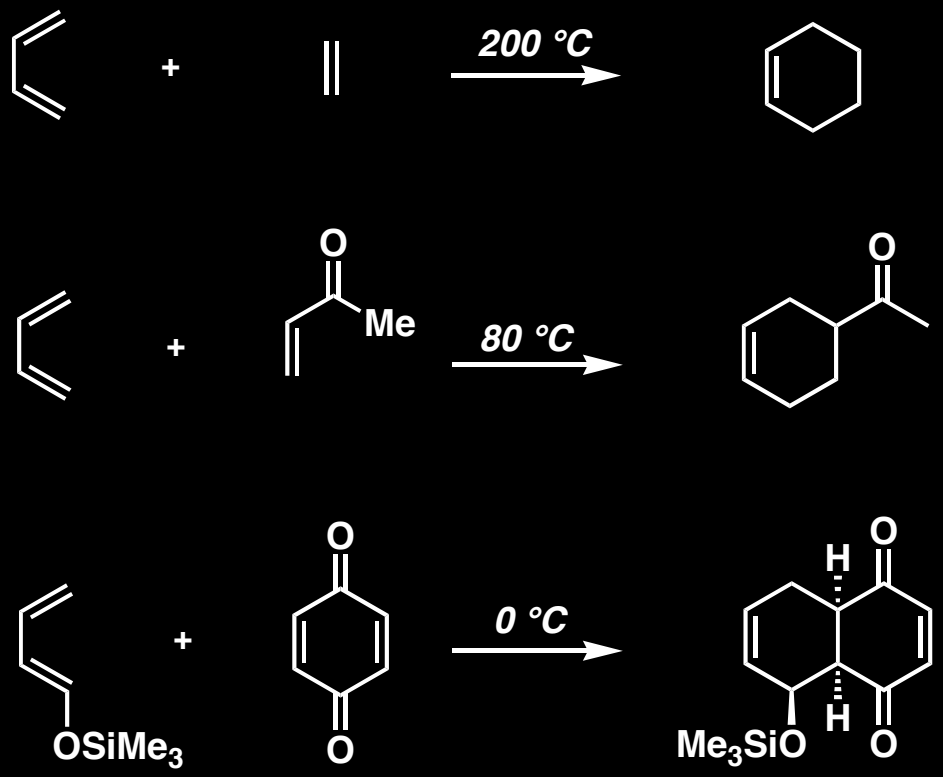
The Diels-Alder Reaction: General Principles



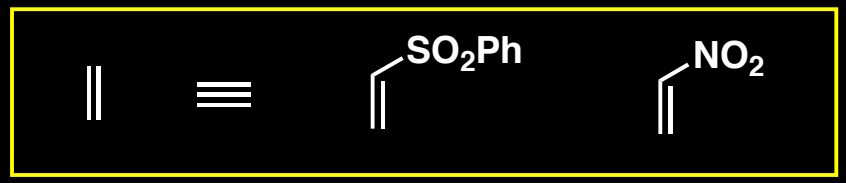


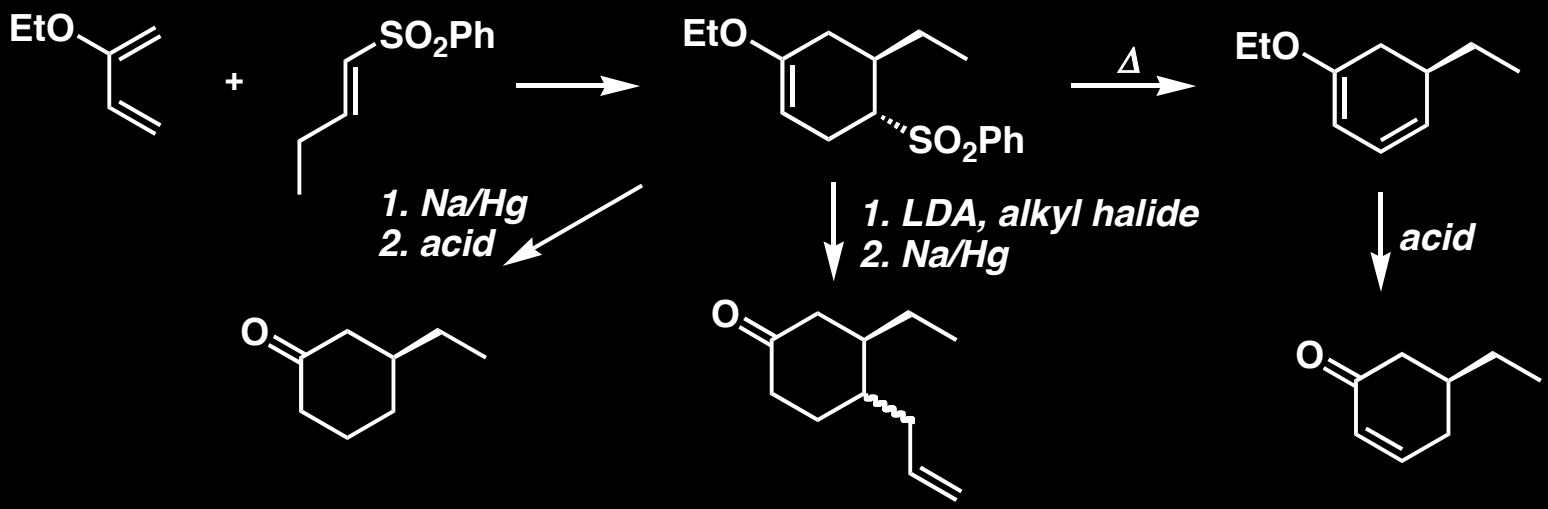
These contrasting outcomes are quite striking

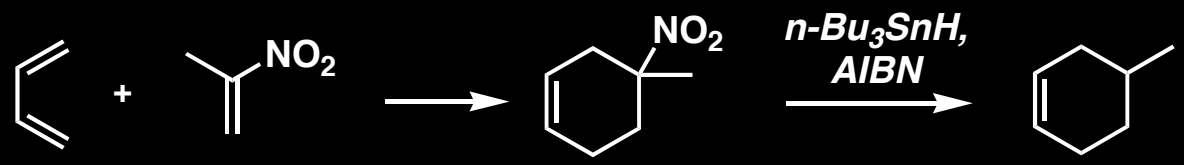
The Diels-Alder Reaction: General Principles



Synthetic Equivalence: Alternate Forms of "Impossible" Dienes/Dienophiles

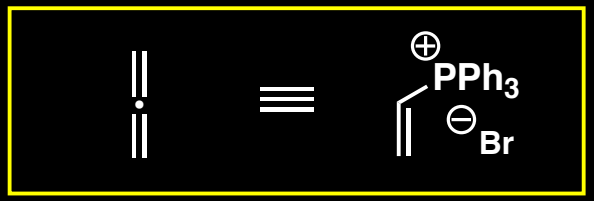


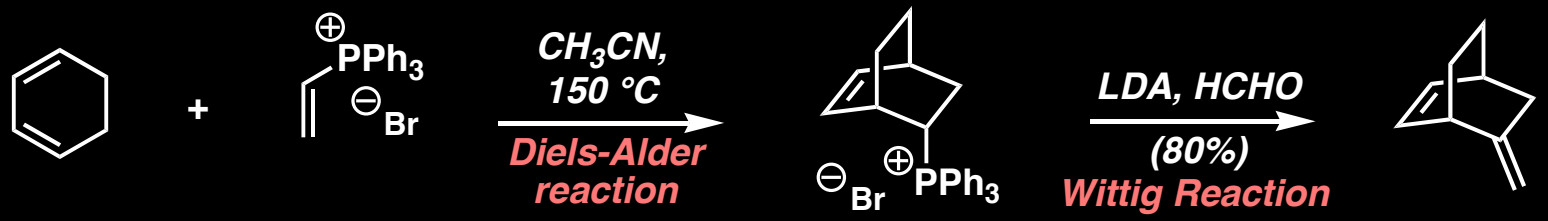




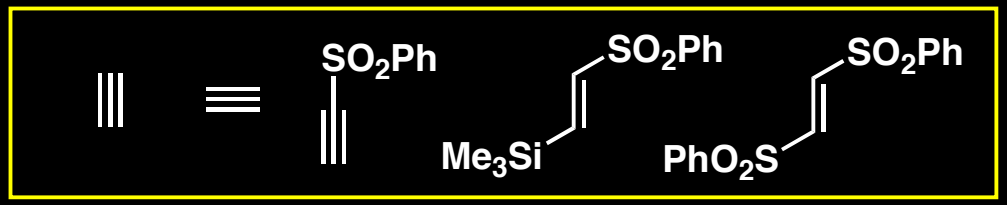
2°, 3°, allylic, benzylic nitro only

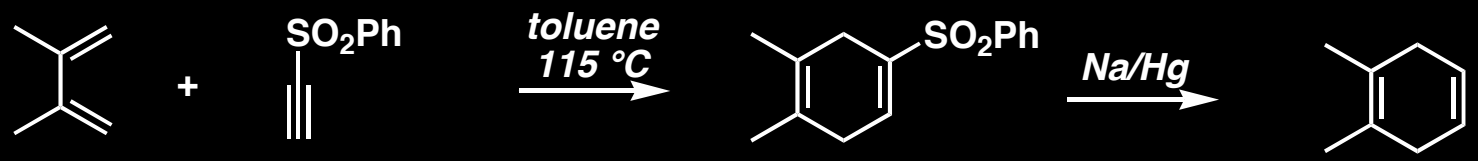
Synthetic Equivalence: Alternate Forms of "Impossible" Dienes/Dienophiles

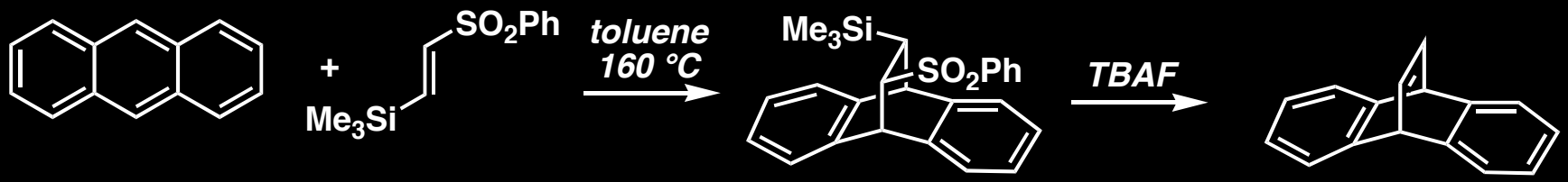


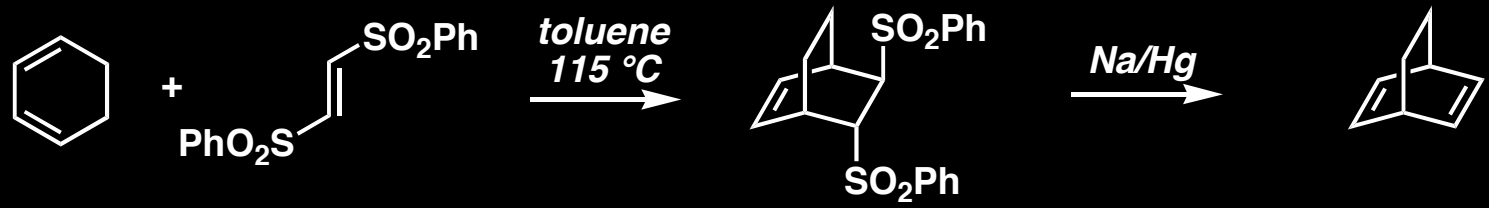


Synthetic Equivalence: Alternate Forms of "Impossible" Dienes/Dienophiles



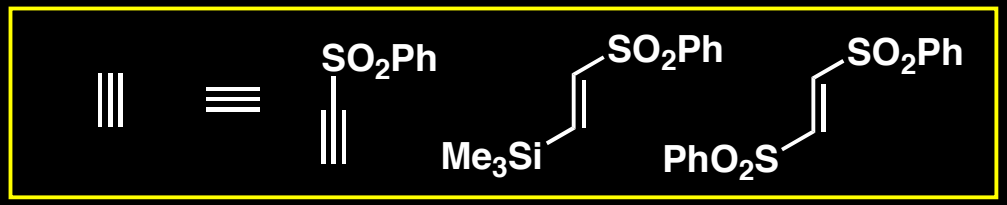


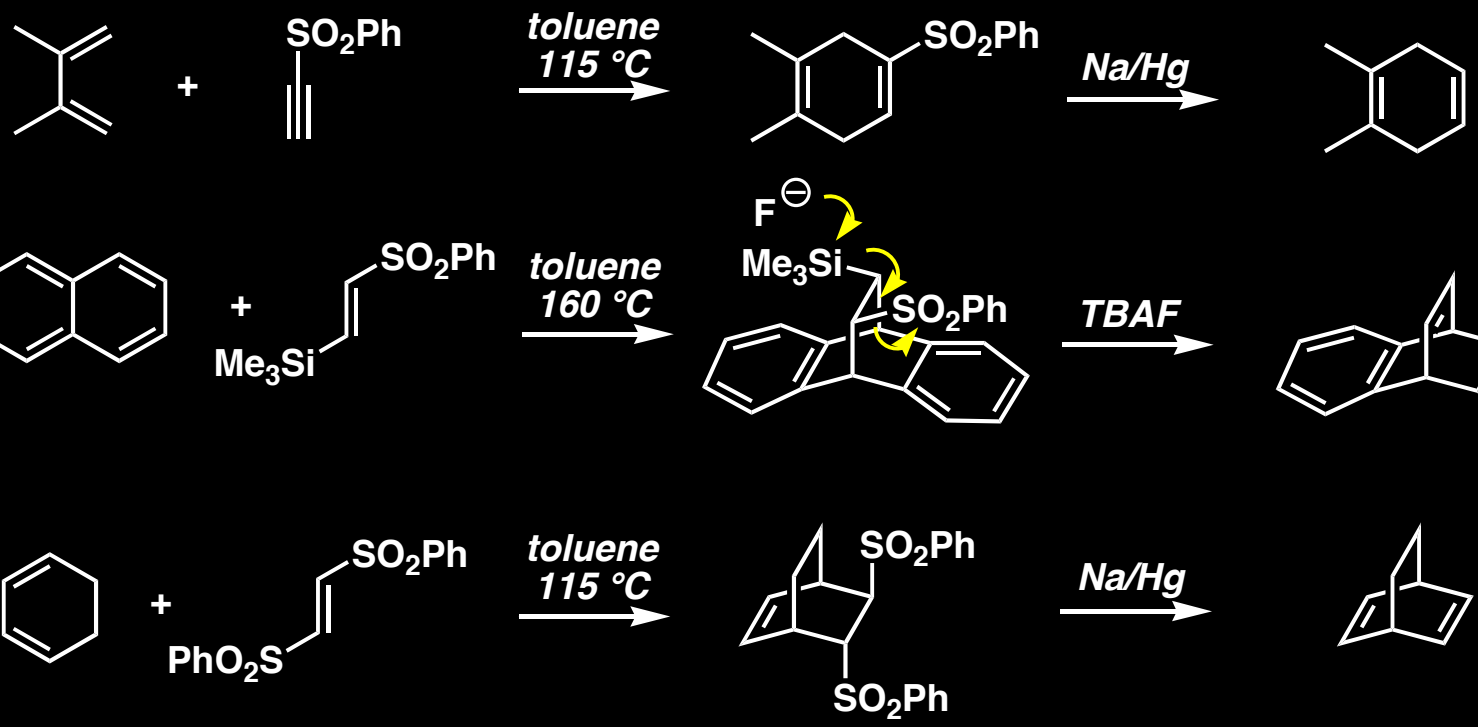




For a review, see: O. De Lucchi, G. Modena, Tetrahedron 1984, 40, 2585.

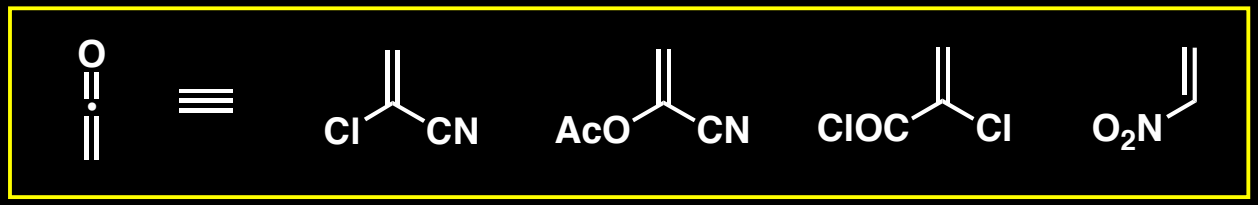
Synthetic Equivalence: Alternate Forms of "Impossible" Dienes/Dienophiles

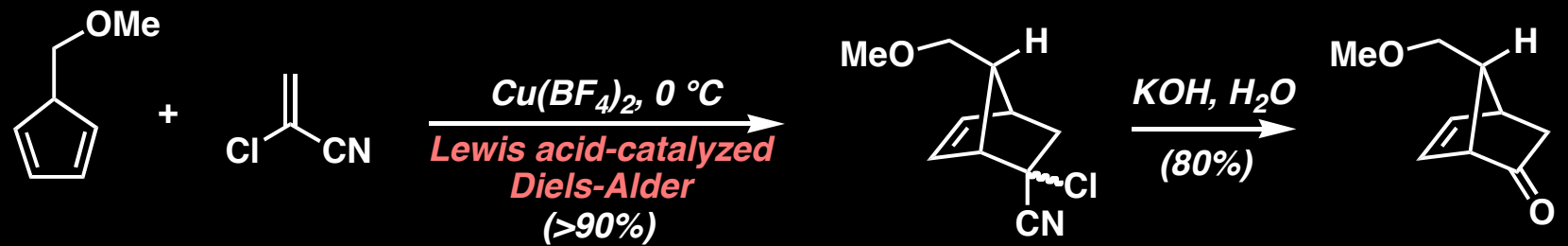


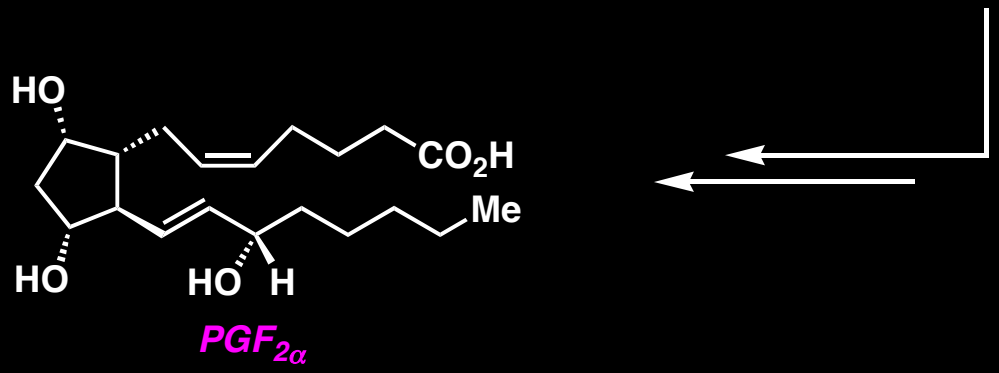


For a review, see: O. De Lucchi, G. Modena, Tetrahedron 1984, 40, 2585.

Synthetic Equivalence: Alternate Forms of "Impossible" Dienes/Dienophiles







E. J. Corey and co-workers, J. Am. Chem. Soc. 1969, 91, 5675.

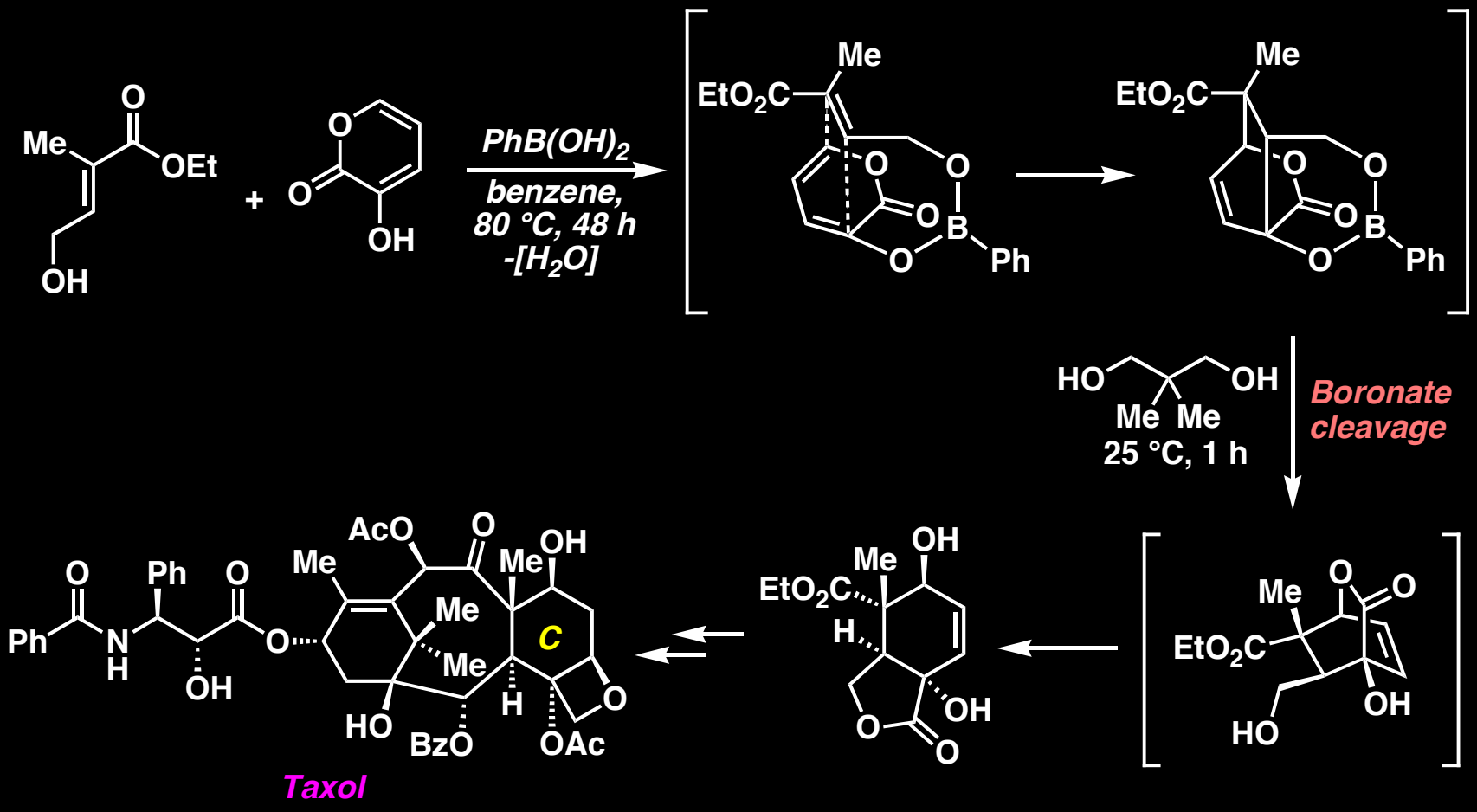
Words of Wisdom from Our Synthetic Elders

Albert Eschenmoser

Whenever in the synthesis of organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly.

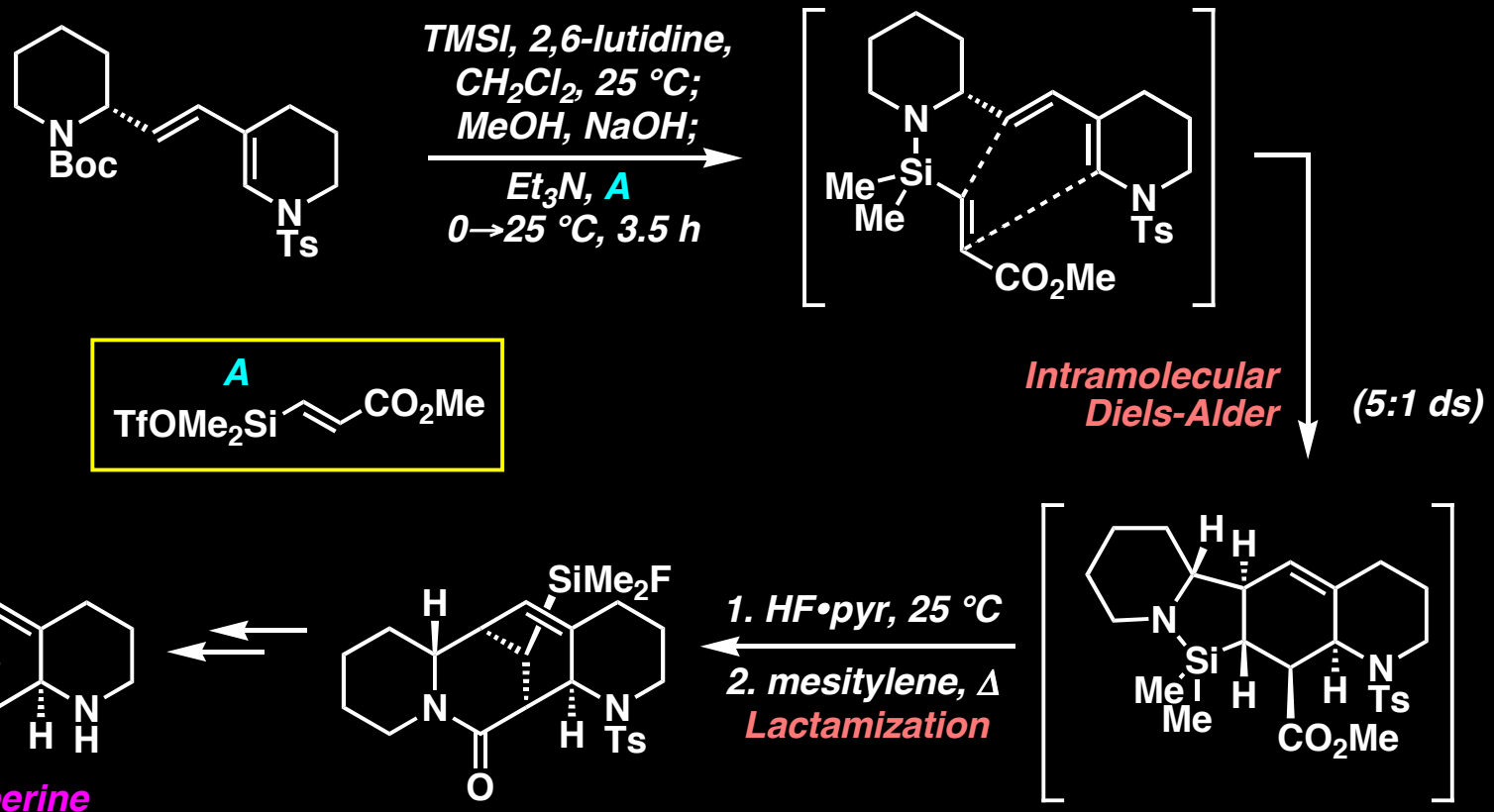
A. Eschenmoser, Quart. Rev. 1970, 24, 366.

Improving Diels-Alder Reactivity: Intramolecular Reactions Via Temporary Tethers



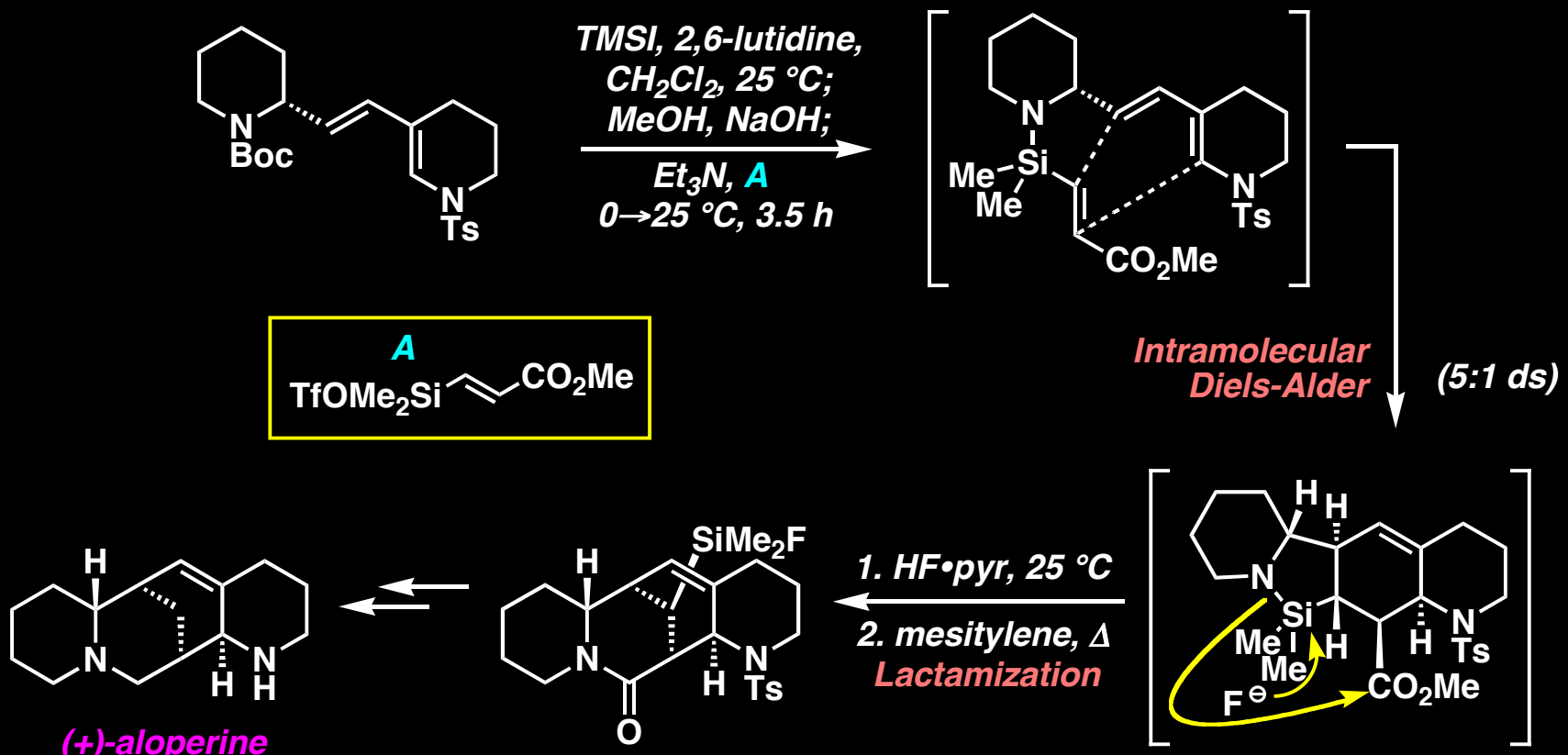
K. C. Nicolaou and co-workers, Nature 1994, 367, 630.

Improving Diels-Alder Reactivity: Intramolecular Reactions Via Temporary Tethers



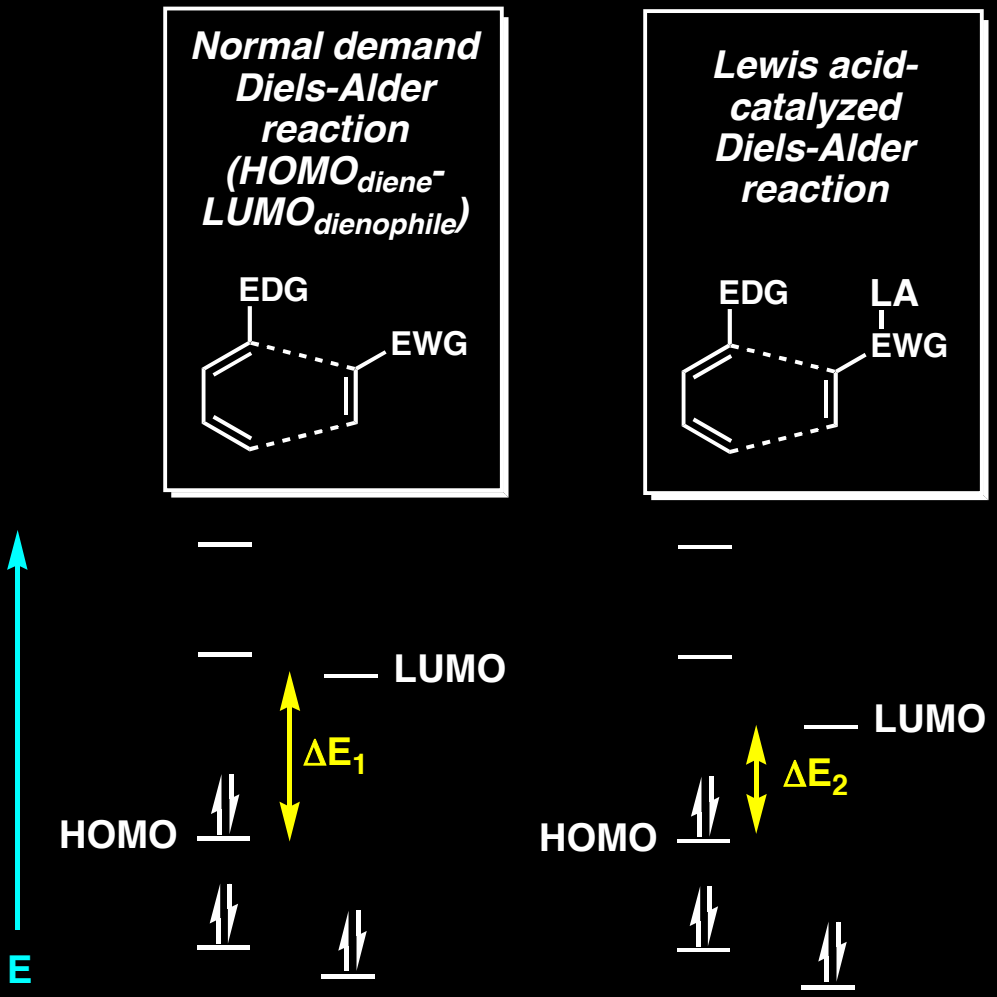
A. D. Brosius, L. E. Overman, L. Schwink, J. Am. Chem. Soc. 1999, 121, 700.

Improving Diels-Alder Reactivity: Intramolecular Reactions Via Temporary Tethers



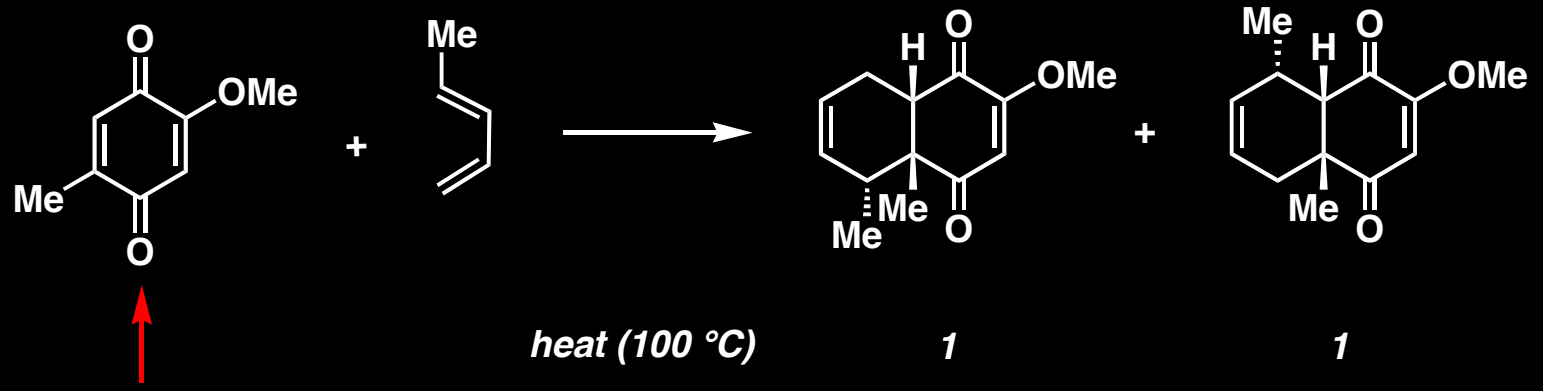
A. D. Brosius, L. E. Overman, L. Schwink, J. Am. Chem. Soc. 1999, 121, 700.

Lewis Acid Complexation: A Way to Improve Reaction Conditions and Endo Selectivity



- *Lewis acid complexation lowers the energy of the LUMO of the diene.*
- *Consequently, reactions occur at lower temperature and are more endo selective since they are better under kinetic control.*

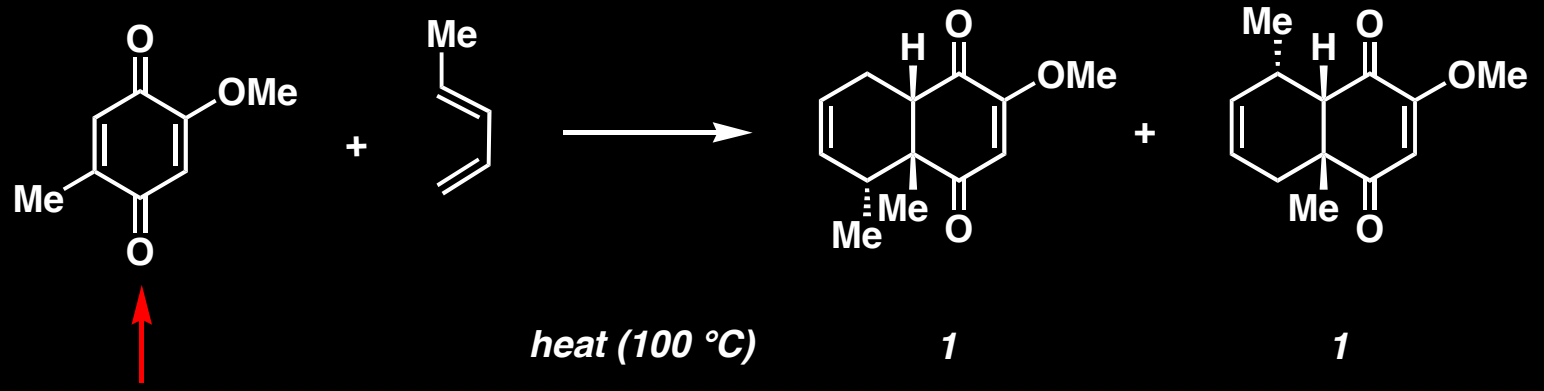
Regioselective Diels-Alder Reactions: Using Lewis Acid Catalysis



most Lewis basic carbonyl

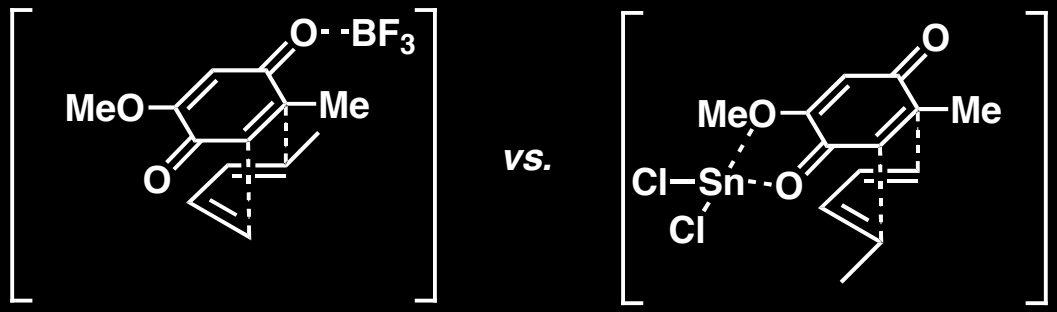
heat (100 °C)	*1*	*1*
$BF_3 \cdot OEt_2$ (-16 °C)	*4*	*1*
$SnCl_4$ (-16 °C)	*1*	*20*

Regioselective Diels-Alder Reactions: Using Lewis Acid Catalysis

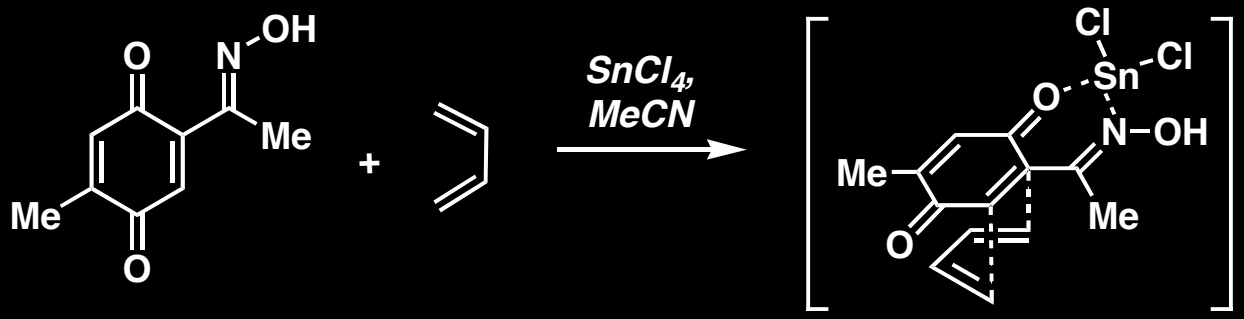


most Lewis basic carbonyl

heat (100 °C)	*1*	*1*
BF_3·OEt_2 (-16 °C)	*4*	*1*
$SnCl_4$ (-16 °C)	*1*	*20*

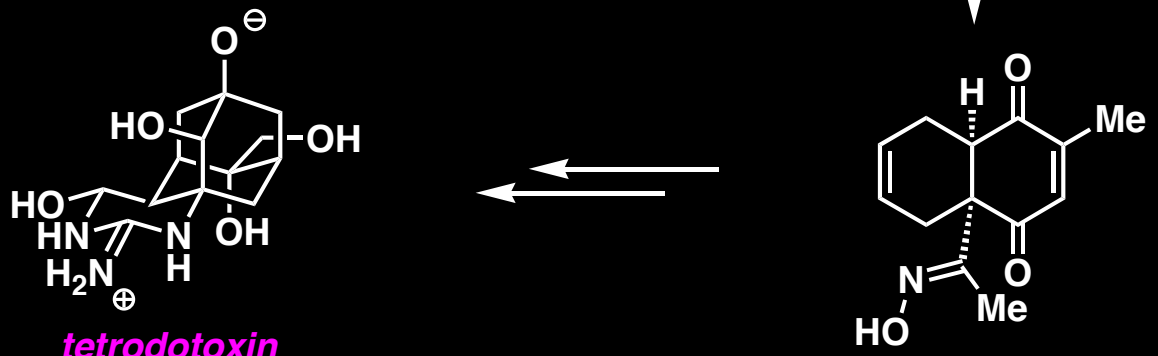


Regioselective Diels-Alder Reactions: Using Lewis Acid Catalysis



In the absence of this Lewis acid, 1,3-butadiene engages the other olefin of the quinone exclusively!

Lewis acid-catalyzed intermolecular Diels-Alder reaction (83%)

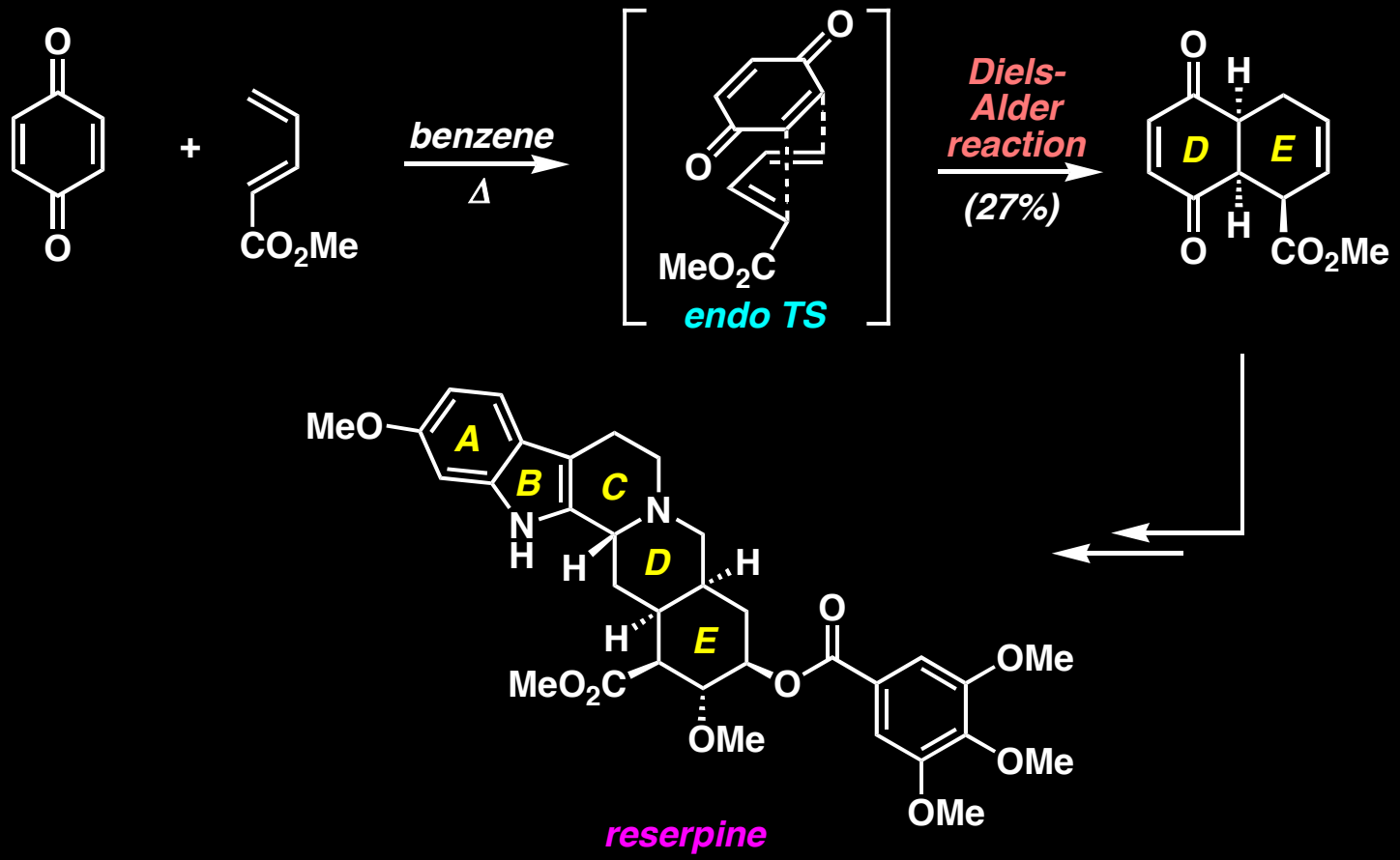


tetrodotoxin

For first LA catalyzed D-A reaction, see: P. Yates, P. Eaton, J. Am. Chem. Soc. 1960, 82, 4436.

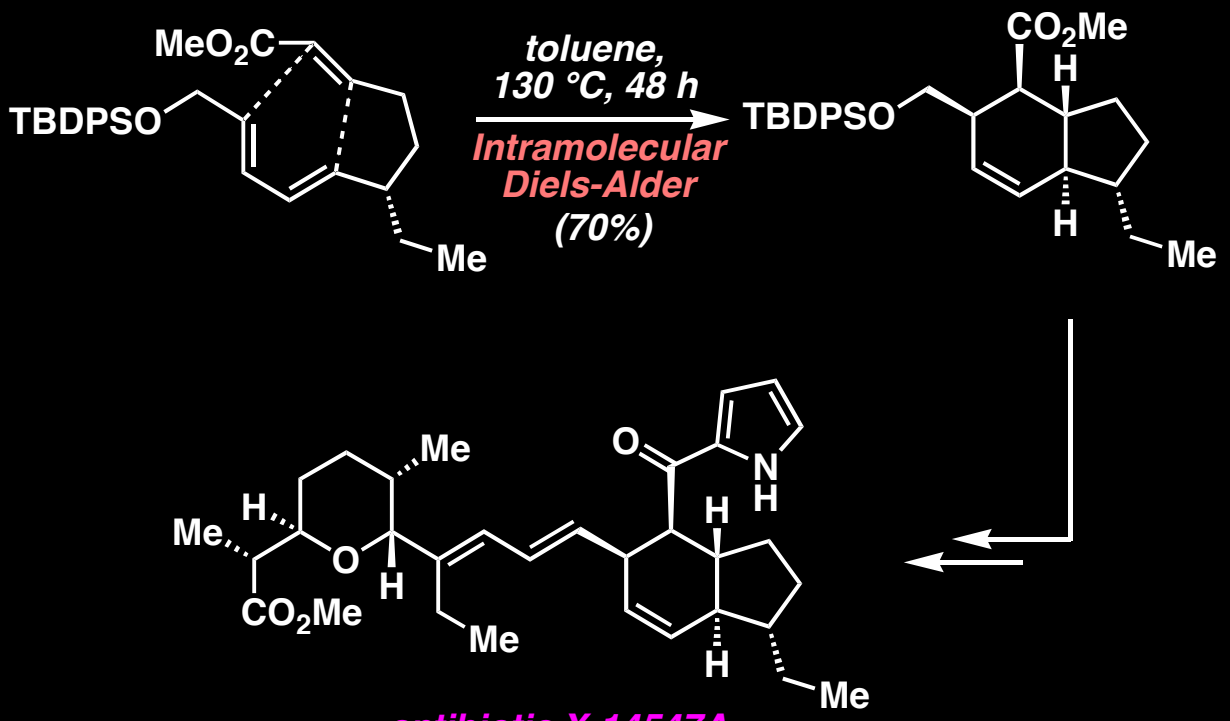
Y. Kishi and co-workers, J. Am. Chem. Soc. 1972, 94, 9217.
Y. Kishi and co-workers, J. Am. Chem. Soc. 1972, 94, 9219.

Regioselective Diels-Alder Reactions: Early Examples



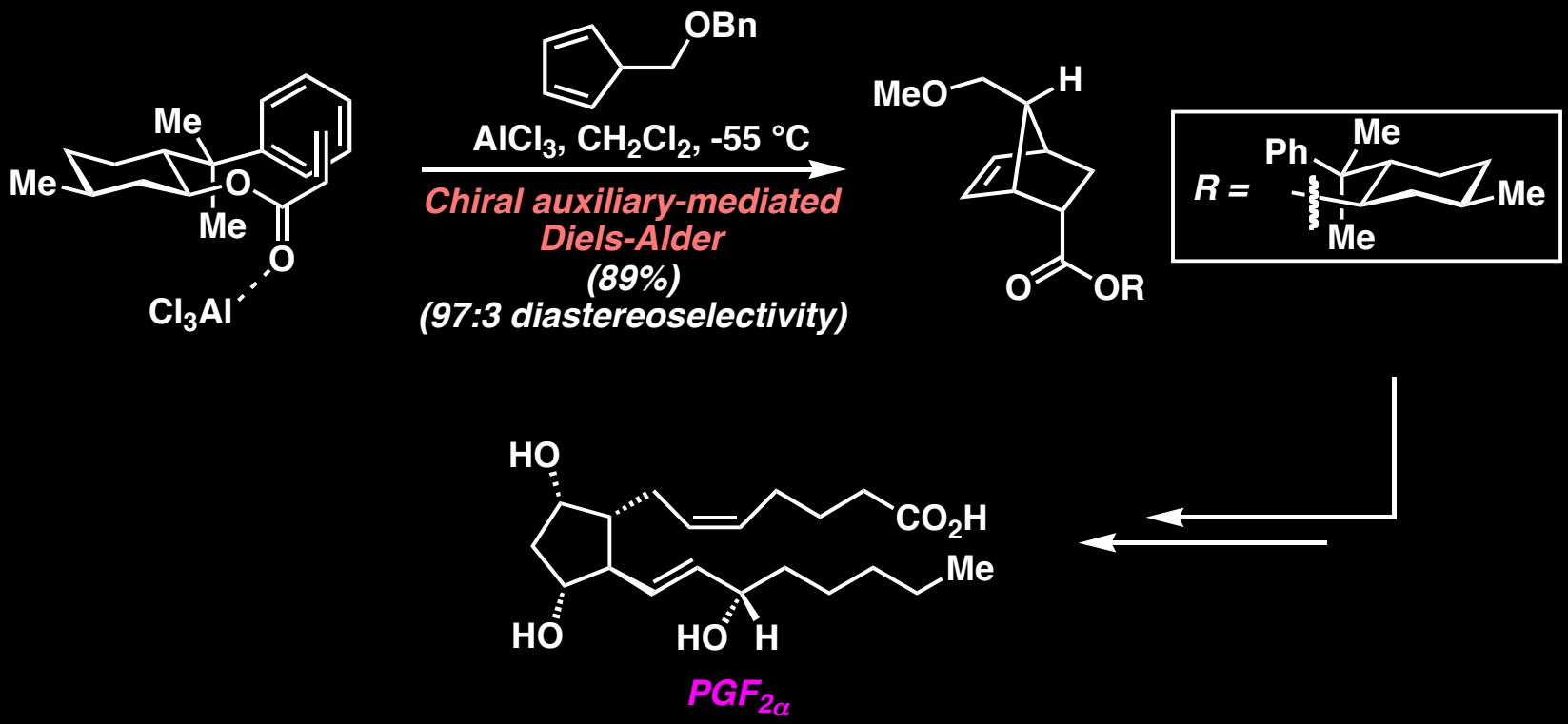
R. B, Woodward and co-workers, J. Am. Chem. Soc. 1956, 78, 2023.
R. B, Woodward and co-workers, Tetrahedron 1958, 2, 1.

Asymmetric Diels-Alder Reactions: Diastereoselective



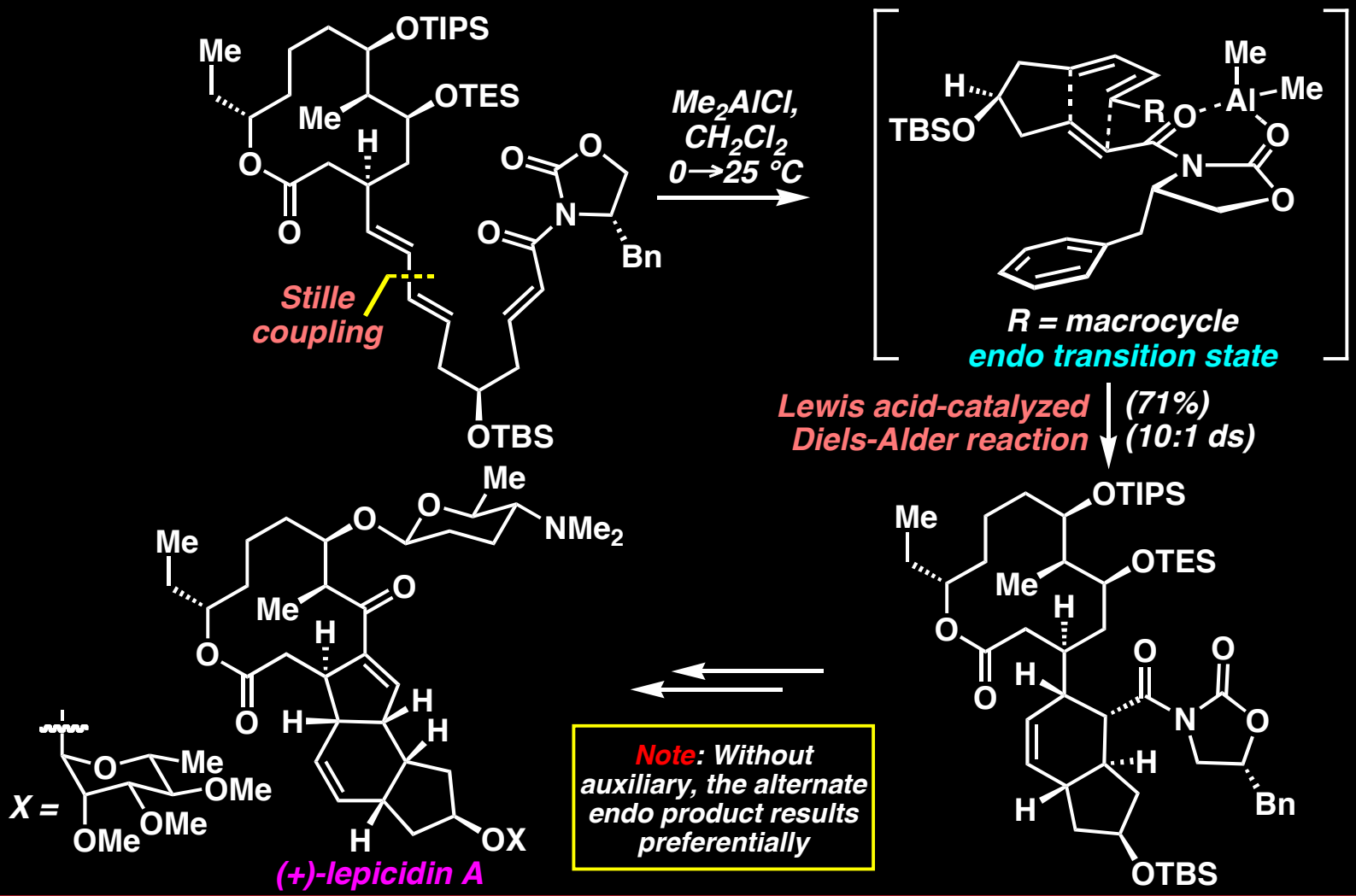
K. C. Nicolaou and co-workers, J. Org. Chem. 1985, 50, 1440.

Asymmetric Diels-Alder Reactions: Diastereoselective



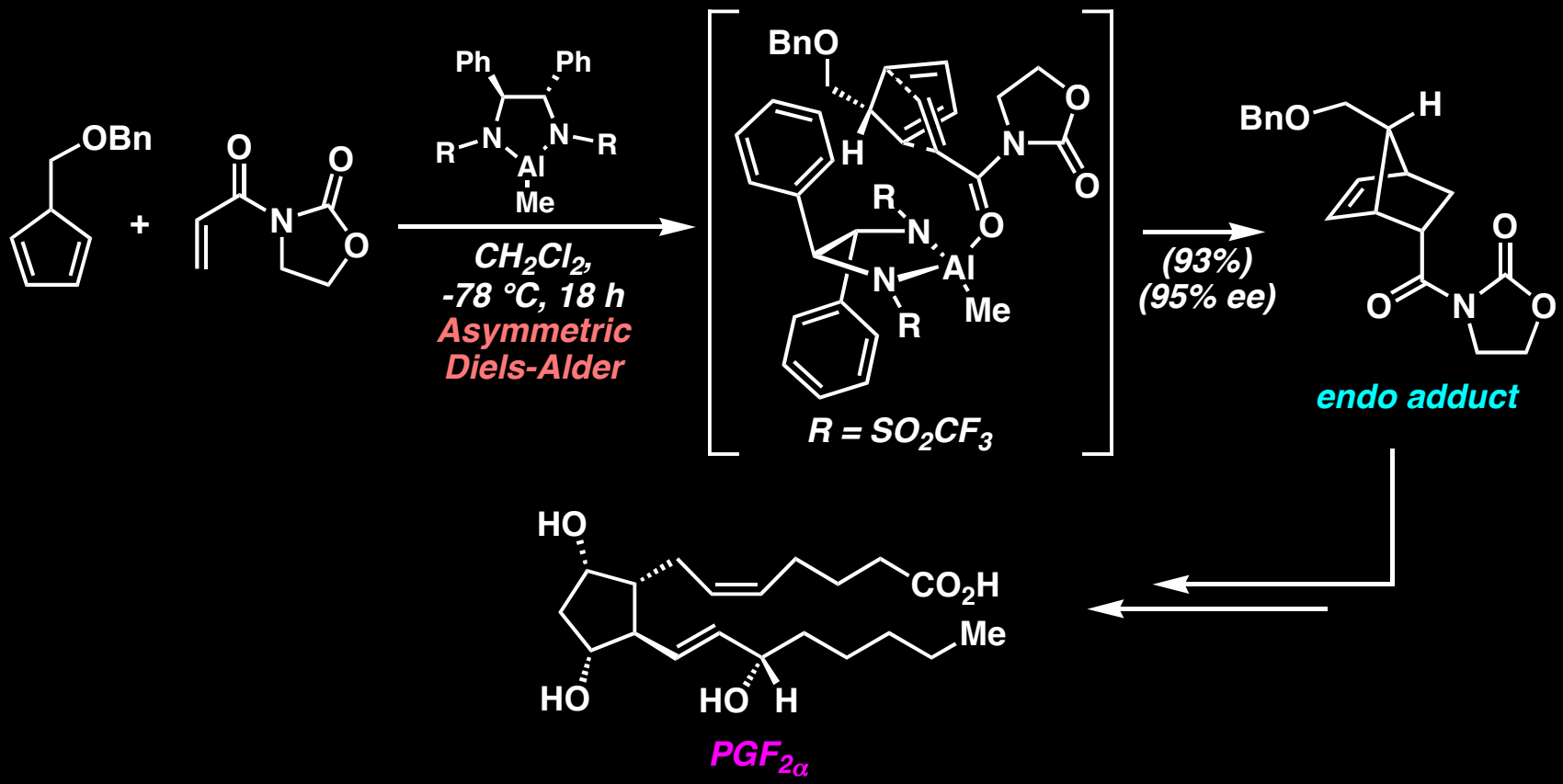
E. J. Corey and co-workers, J. Am. Chem. Soc. 1975, 97, 6908.

Diastereoselective Diels-Alder Reactions: Using Implanted Auxiliaries



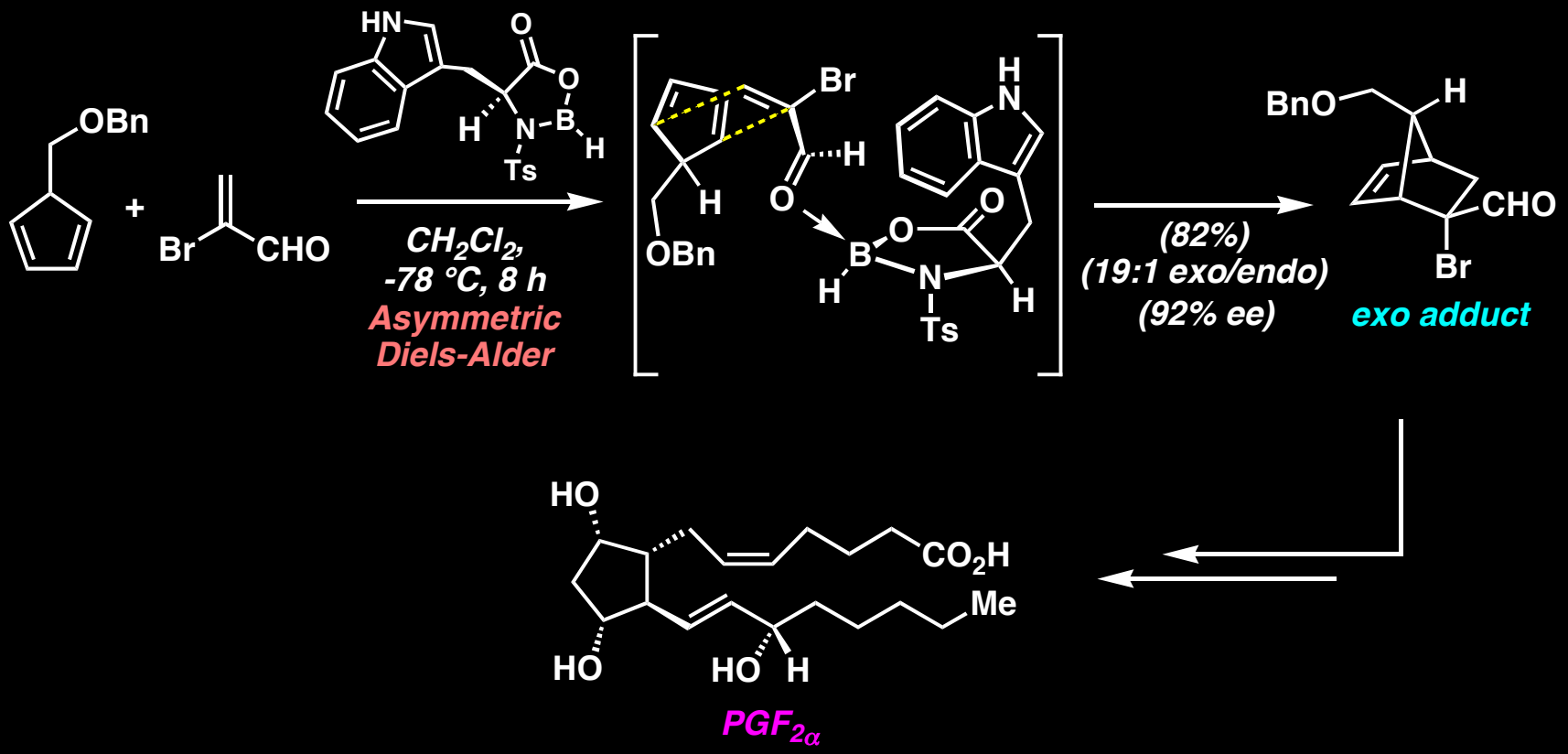
D. A. Evans, W. C. Black, J. Am. Chem. Soc. 1993, 115, 4497.

Asymmetric Diels-Alder Reactions: Enantioselective



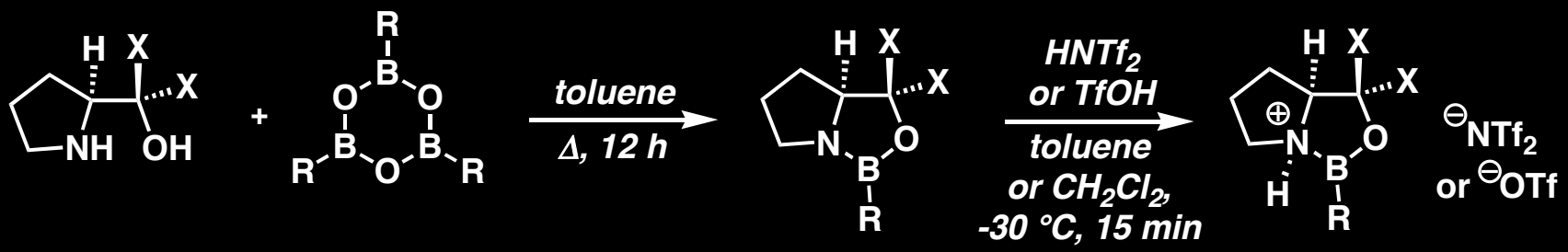
E. J. Corey and co-workers, J. Am. Chem. Soc. 1989, 111, 5493.

Asymmetric Diels-Alder Reactions: Enantioselective



E. J. Corey and co-workers, J. Am. Chem. Soc. 1992, 114, 8290.

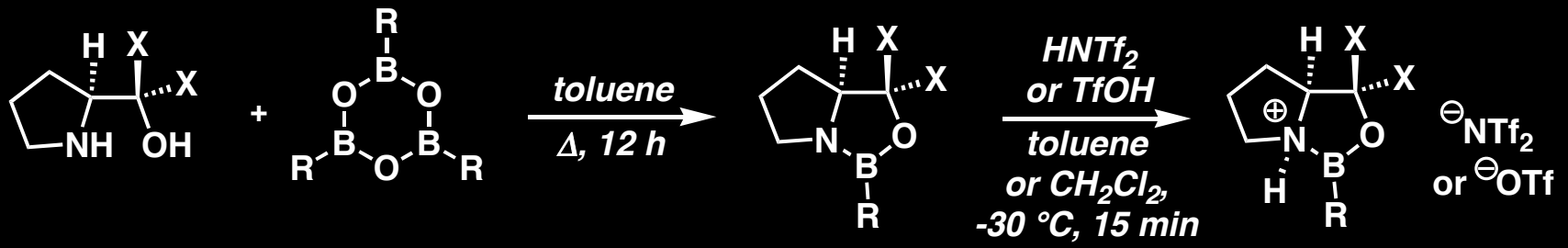
Enantioselective Diels-Alder Reactions Using Chiral Oxaborolidinium Cations

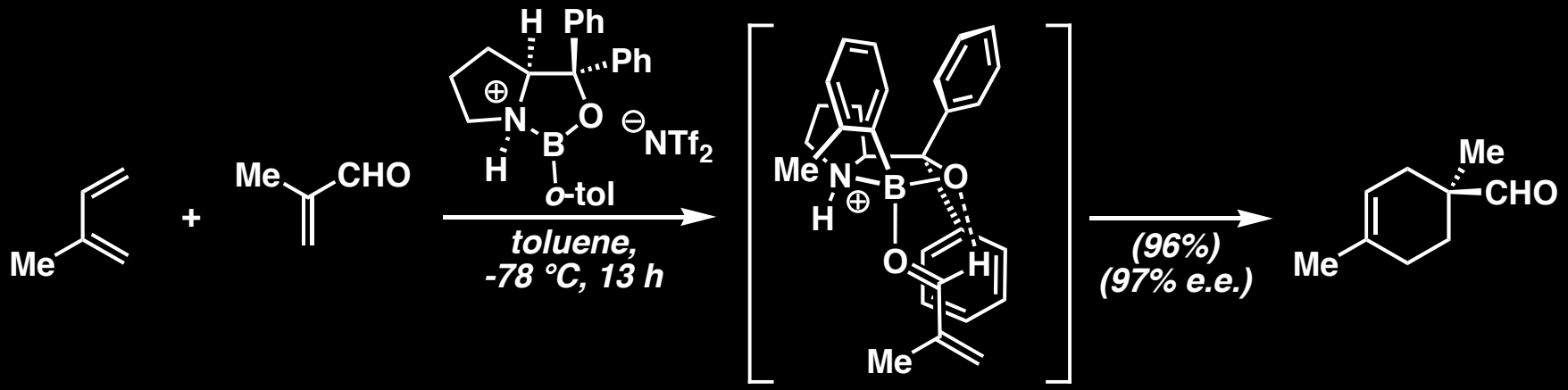


For a review on enantioselective Diels-Alder reactions, see:
E.J. Corey, Angew. Chem. Int. Ed. 2002, 41, 1650.

E.J. Corey, T. Shibata, T.W. Lee, J. Am. Chem. Soc. 2002, 124, 3808.
D.H. Ryu, T.W. Lee, E.J. Corey, J. Am. Chem. Soc. 2002, 124, 9992.

Enantioselective Diels-Alder Reactions Using Chiral Oxaborolidinium Cations

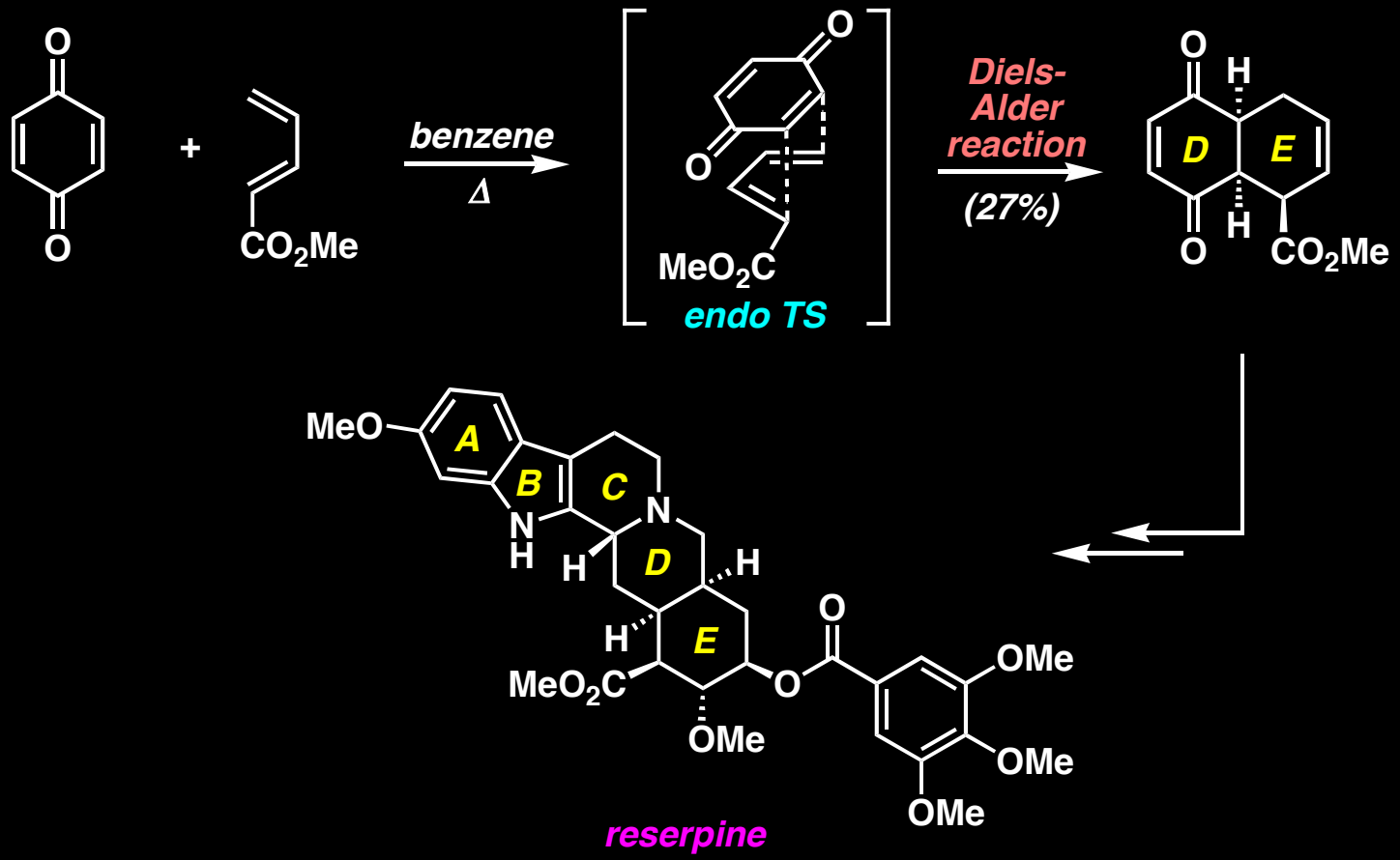




For a review on enantioselective Diels-Alder reactions, see:
E.J. Corey, Angew. Chem. Int. Ed. 2002, 41, 1650.

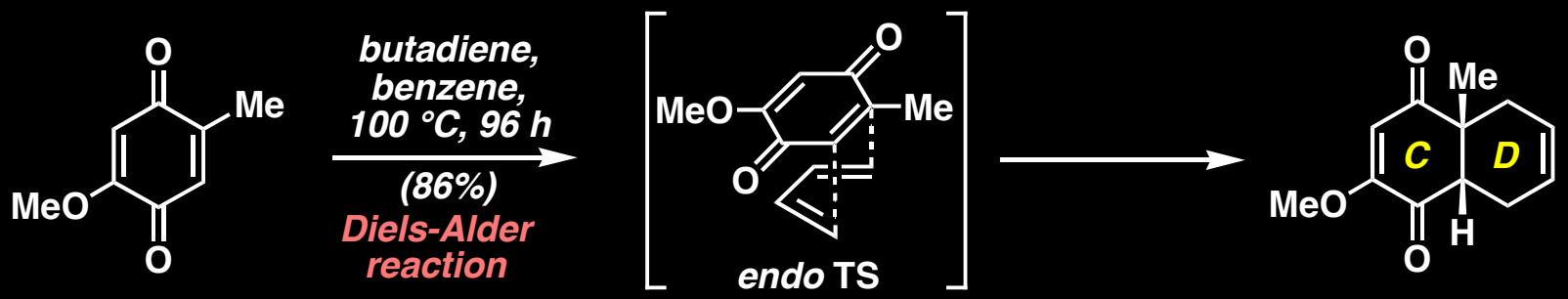
E.J. Corey, T. Shibata, T.W. Lee, J. Am. Chem. Soc. 2002, 124, 3808.
D.H. Ryu, T.W. Lee, E.J. Corey, J. Am. Chem. Soc. 2002, 124, 9992.

Regioselective Diels-Alder Reactions: Early Examples



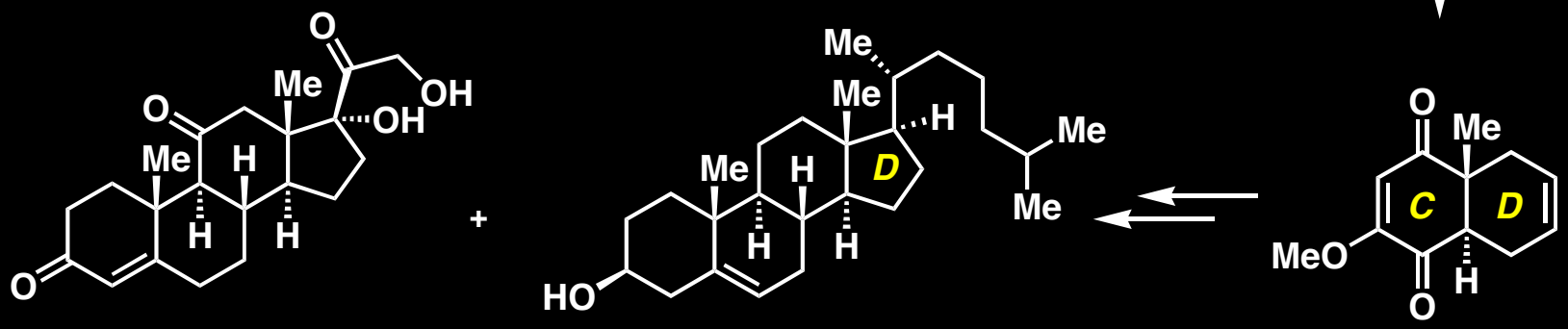
R. B, Woodward and co-workers, J. Am. Chem. Soc. 1956, 78, 2023.
R. B, Woodward and co-workers, Tetrahedron 1958, 2, 1.

Regioselective Diels-Alder Reactions: Early Examples



Note the regioselectivity in this reaction

aq. NaOH, dioxane;
then 1 N aq. HCl
[epimerization]

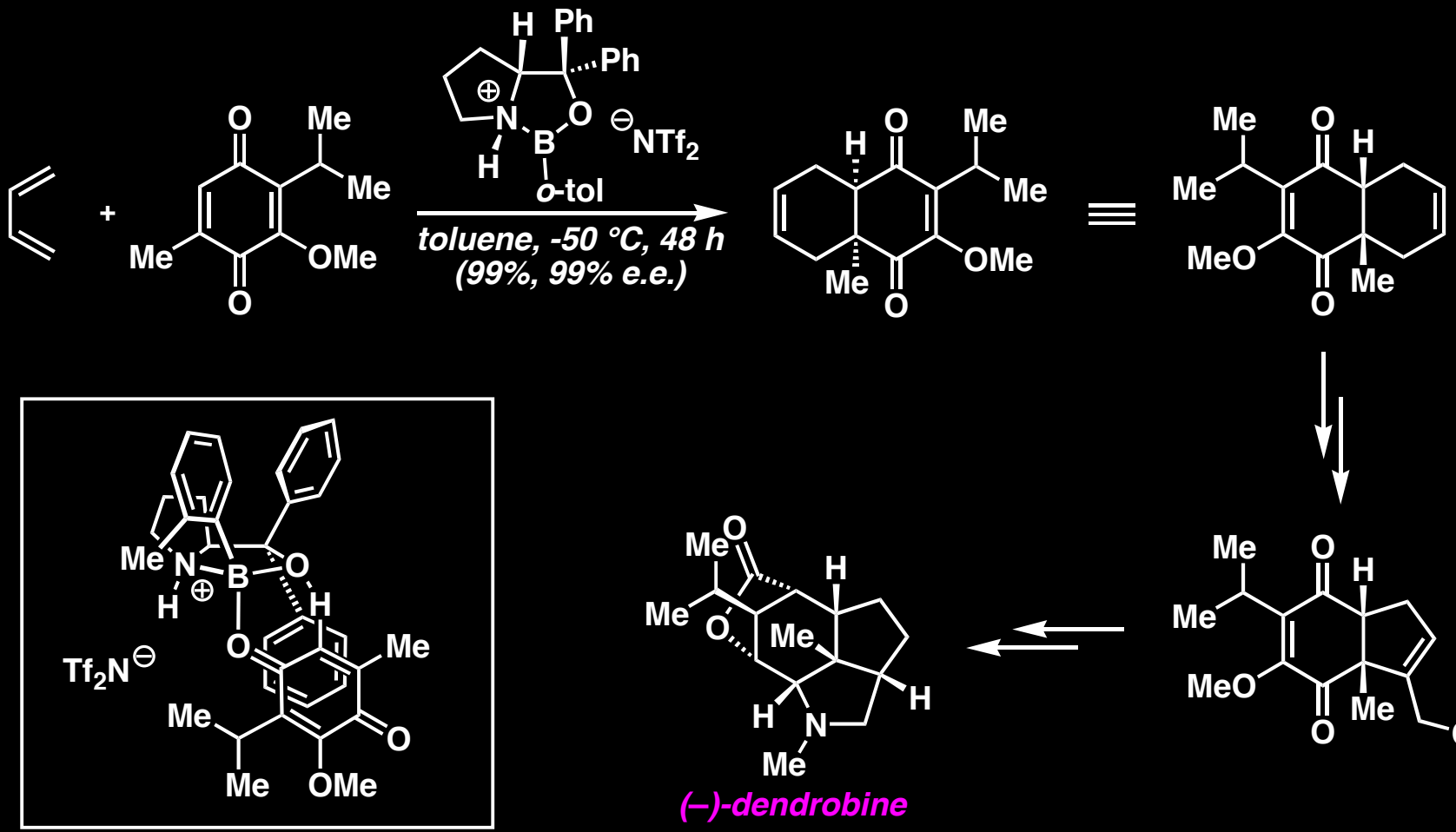


cortisone

cholesterol

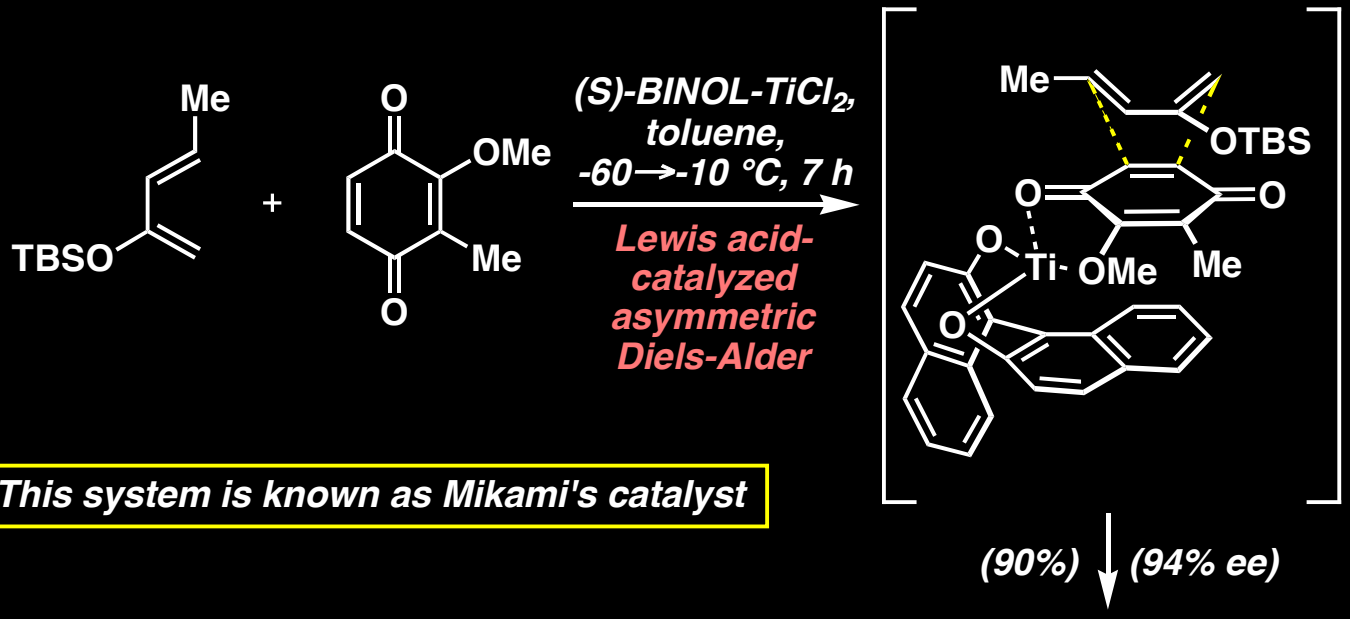
R. B. Woodward and co-workers, J. Am. Chem. Soc. 1952, 74, 4223.

Enantioselective Diels-Alder Reactions Using Chiral Oxaborolidinium Cations

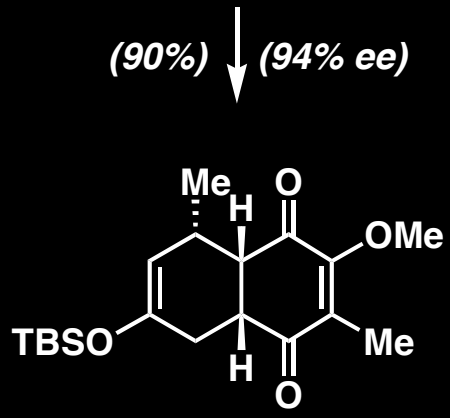


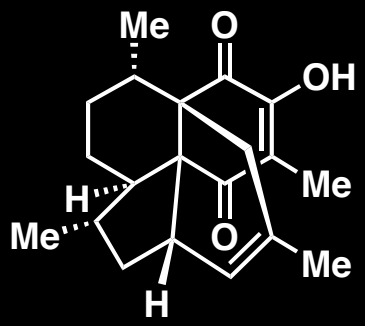
Q.-Y. Hu, G. Zhou, E.J. Corey, J. Am. Chem. Soc. 2004, 126, 13708.
Original dendrobine synthesis: A.S. Kende, T.J. Bentley, J. Am. Chem. Soc. 1974, 96, 4332.

Asymmetric Diels-Alder Reactions: Enantioselective



This system is known as Mikami's catalyst

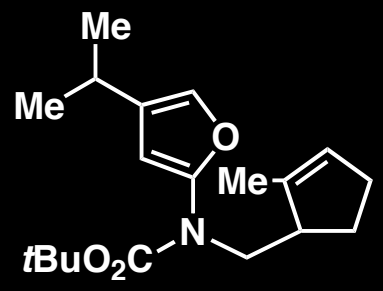




(–)-colombiasin A

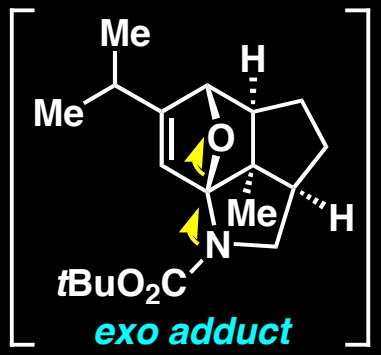
K. C. Nicolaou and co-workers, Chem. Eur. J. 2001, 7, 5359.

Hetero Diels-Alder Reactions: Furans as Diene Components



toluene,
165 °C, 15 h

Intramolecular
Diels-Alder

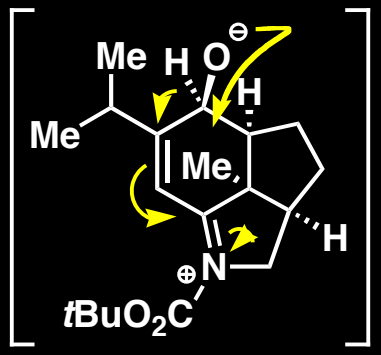


exo adduct

Furans are normally poor dienes; retro Diels-Alder reactions occur with equal facility as Diels-Alder reactions

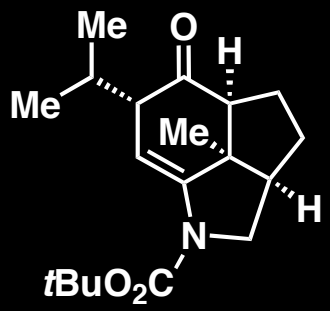
Note: Thiophene and pyrrole are not viable dienes

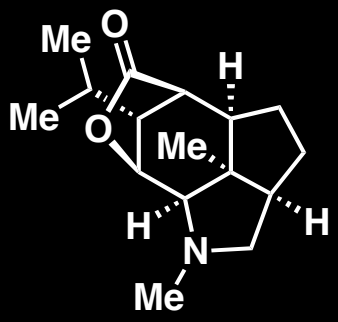
Ring opening



(74%)

Hydride shift

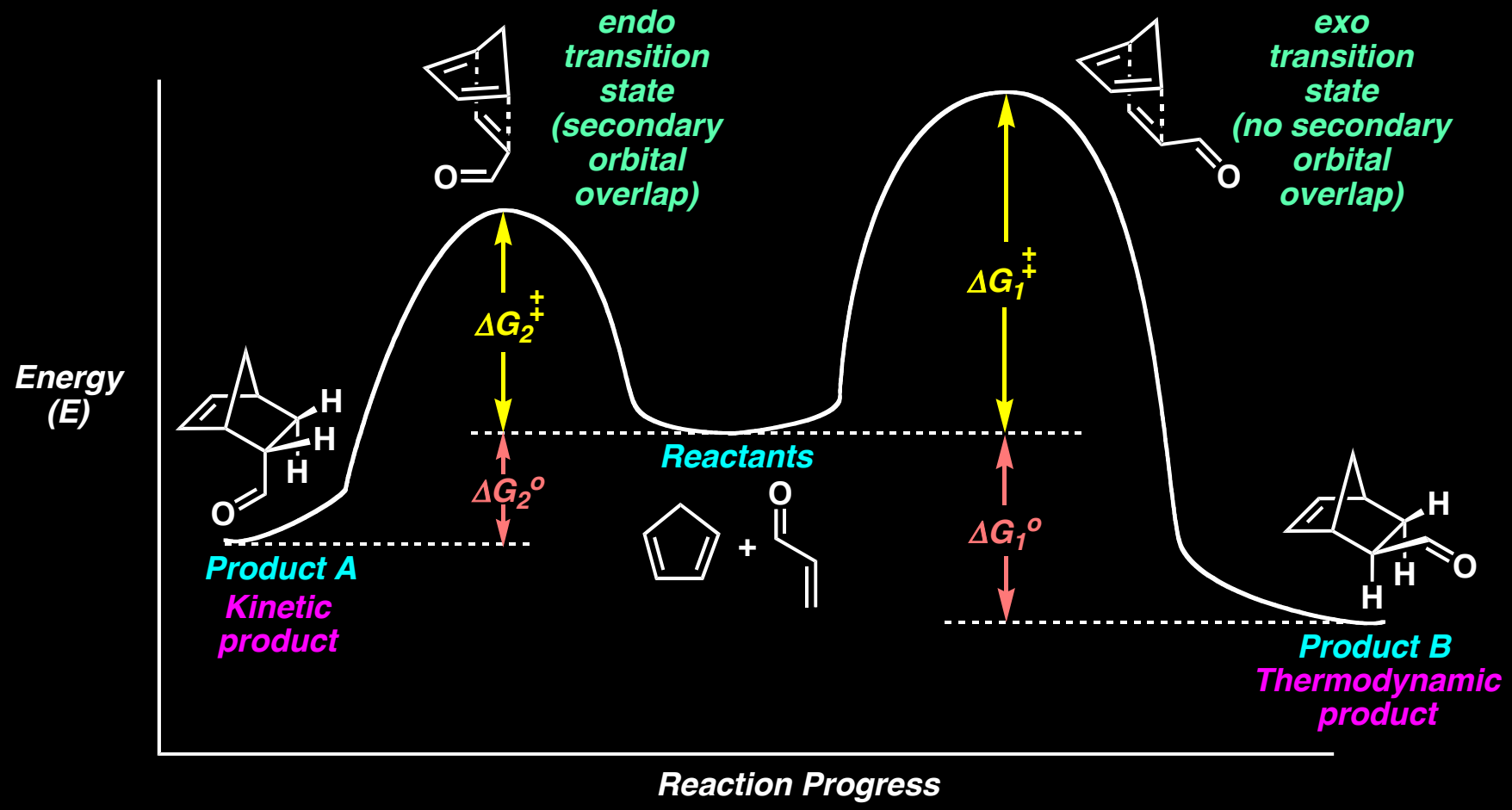




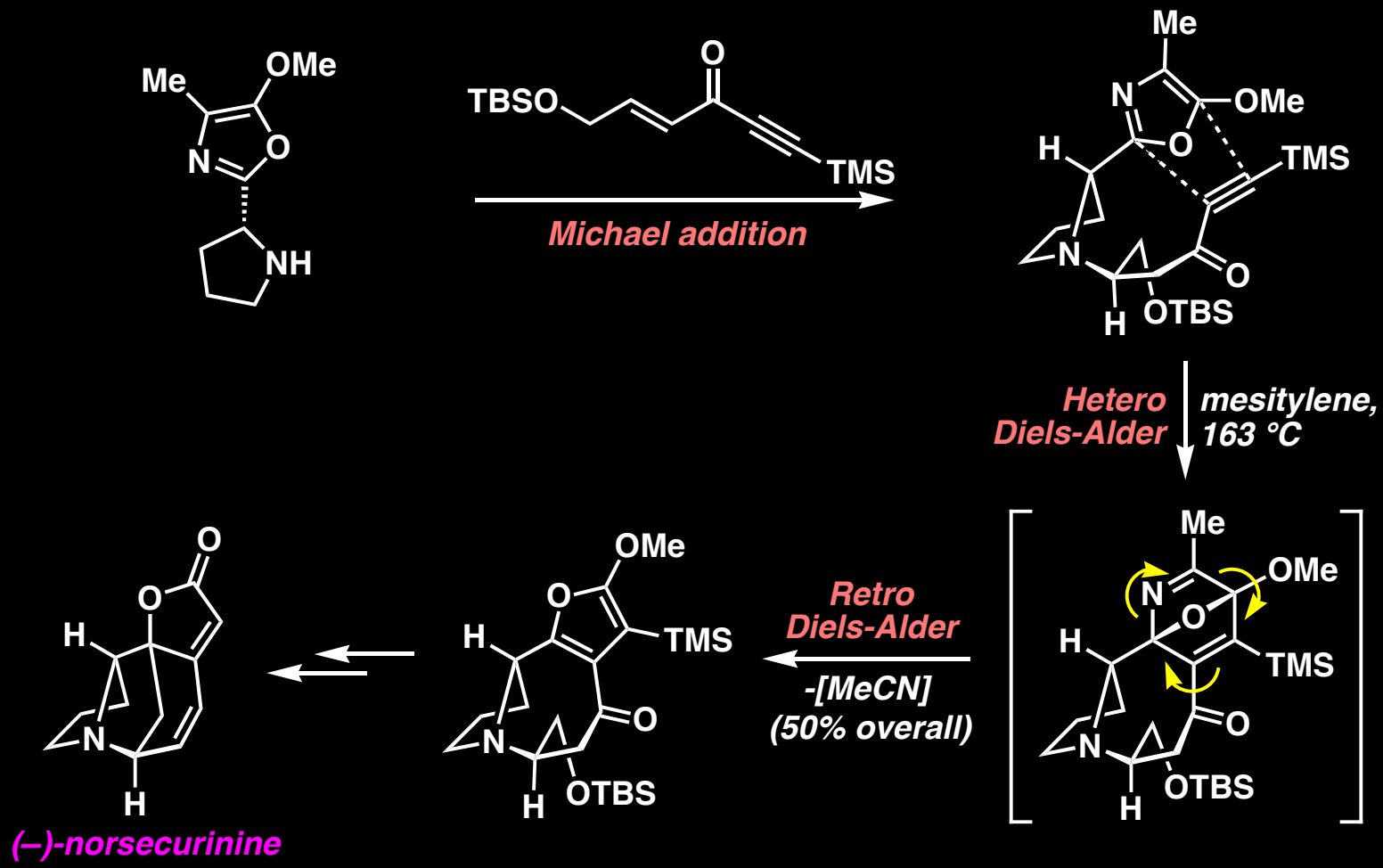
dendrobine

For a review, see: D. L. Boger, Comprehensive Organic Synthesis, Vol. 5., 1991, p. 451-512.

Reaction Energy Diagrams: Kinetic and Thermodynamic Products

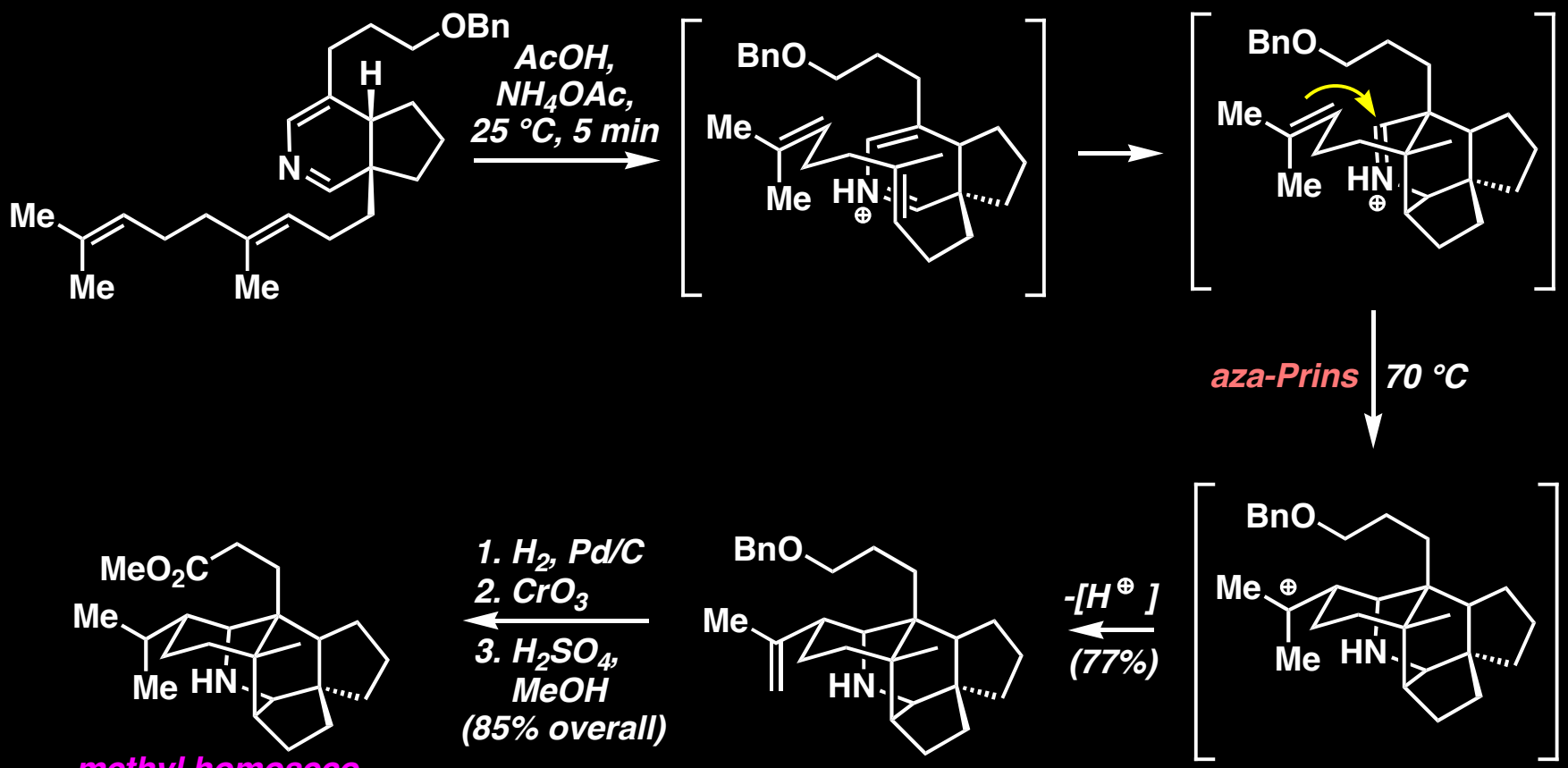


Hetero Diels-Alder Reactions: Oxazoles as Diene Components



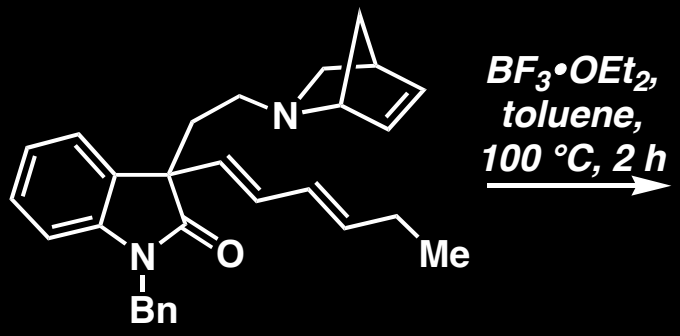
P. A. Jacobi and co-workers, Tetrahedron Lett. 1989, 30, 7173.

Hetero Diels-Alder Reactions: Imines/Iminium Ions as Diene Components



C. H. Heathcock, Angew. Chem. Int. Ed. Engl. 1992, 31, 665.
C. H. Heathcock, Proc. Natl. Acad. Sci. 1996, 93, 14323.

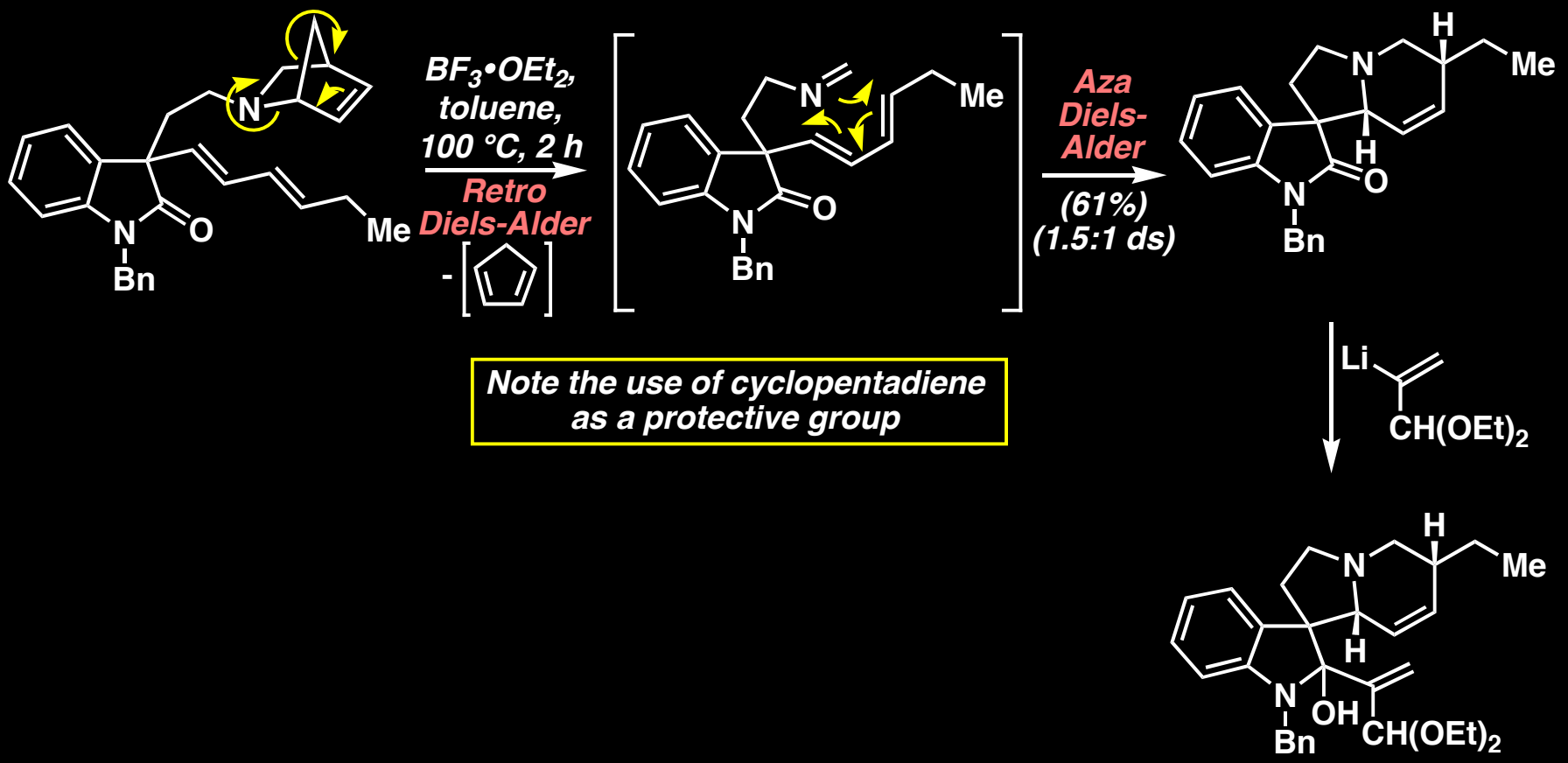
Hetero Diels-Alder Reactions: Imines/Iminium Ions as Diene Components



$BF_3 \bullet OEt_2$,
toluene,
100 °C, 2 h

P. A. Grieco, A. Bahsas, J. Org. Chem. 1987, 52, 5746.

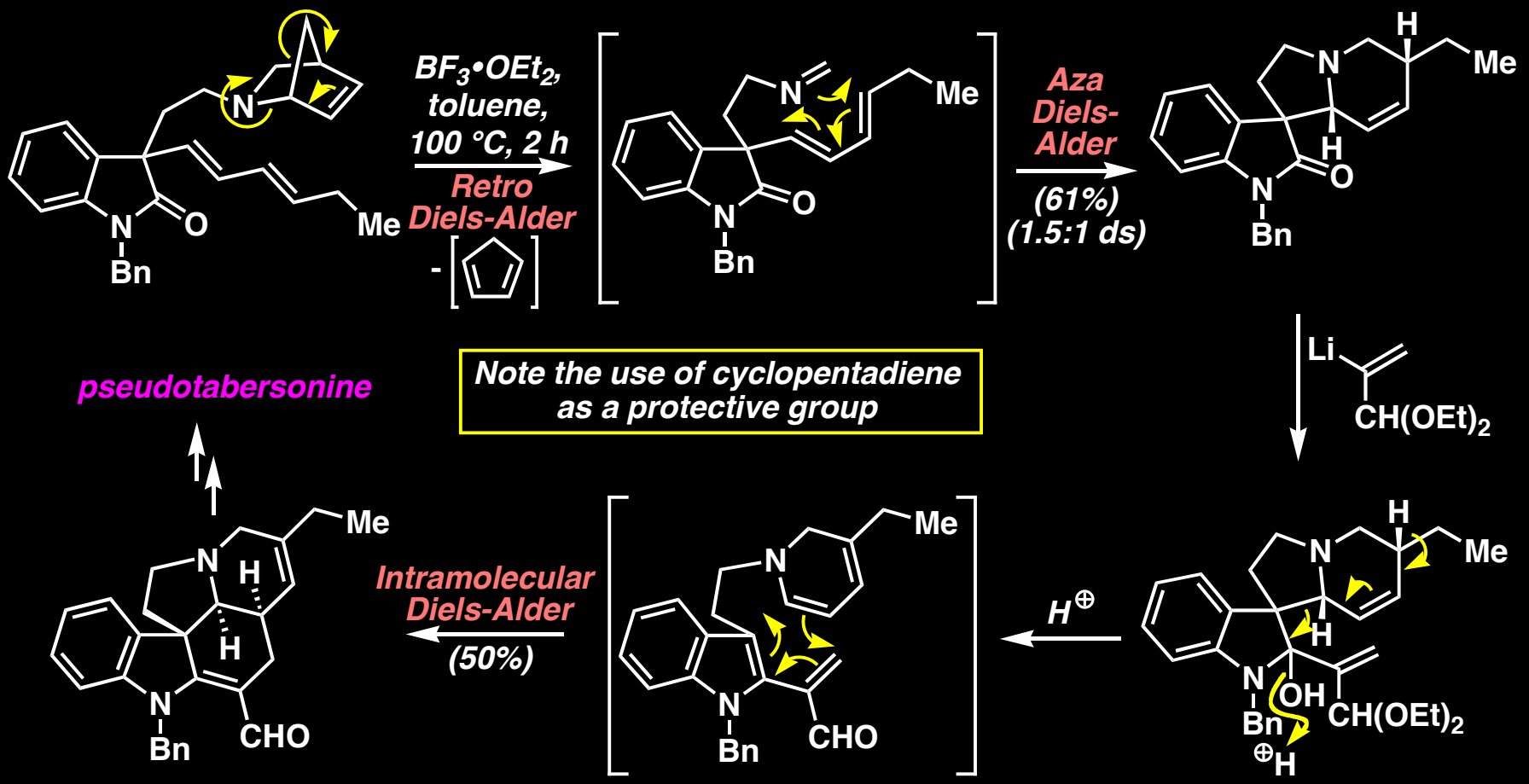
Hetero Diels-Alder Reactions: Imines/Iminium Ions as Diene Components



Note the use of cyclopentadiene as a protective group

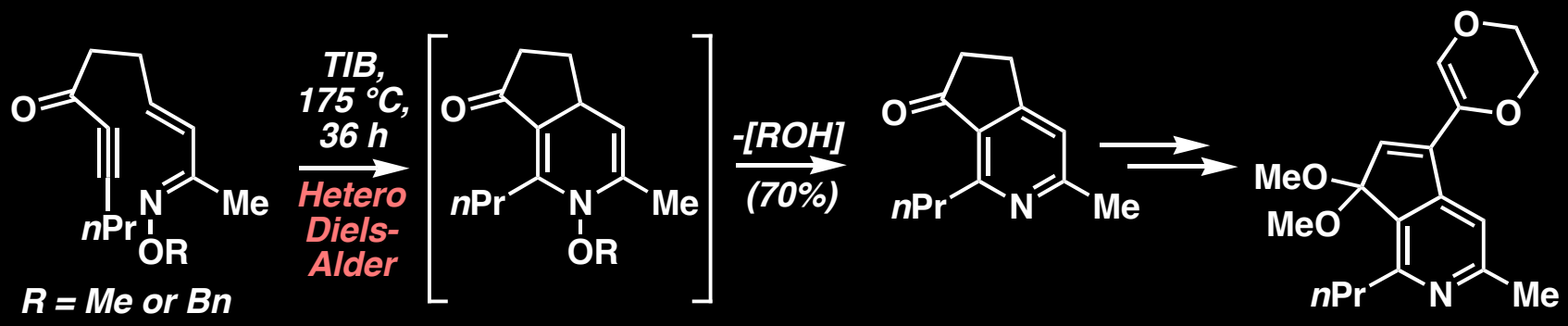
P. A. Grieco, A. Bahsas, J. Org. Chem. 1987, 52, 5746.

Hetero Diels-Alder Reactions: Imines/Iminium Ions as Diene Components



P. A. Grieco, A. Bahsas, J. Org. Chem. 1987, 52, 5746.

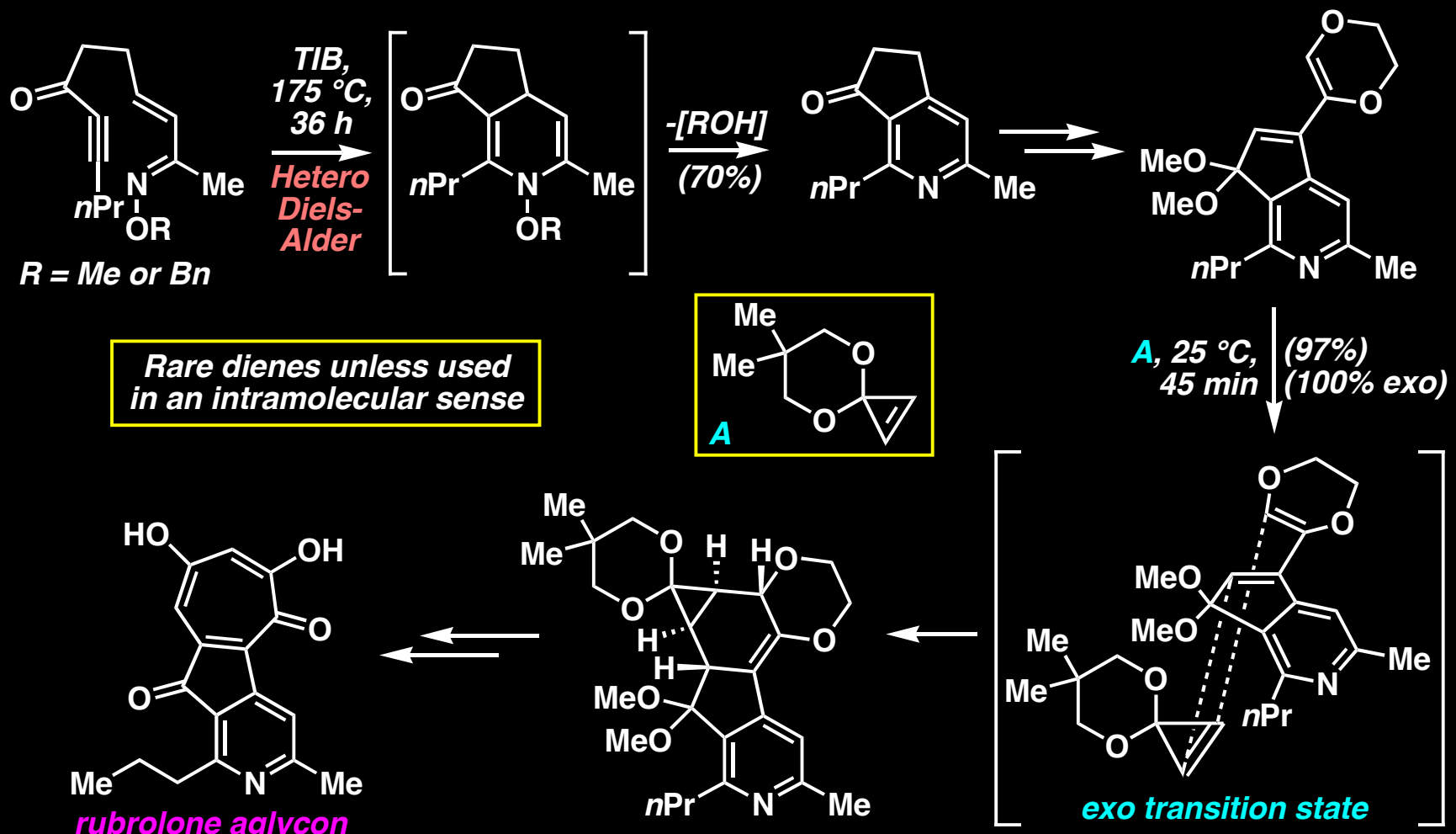
Hetero Diels-Alder Reactions: Oxime Ethers as Diene Components



Rare dienes unless used in an intramolecular sense

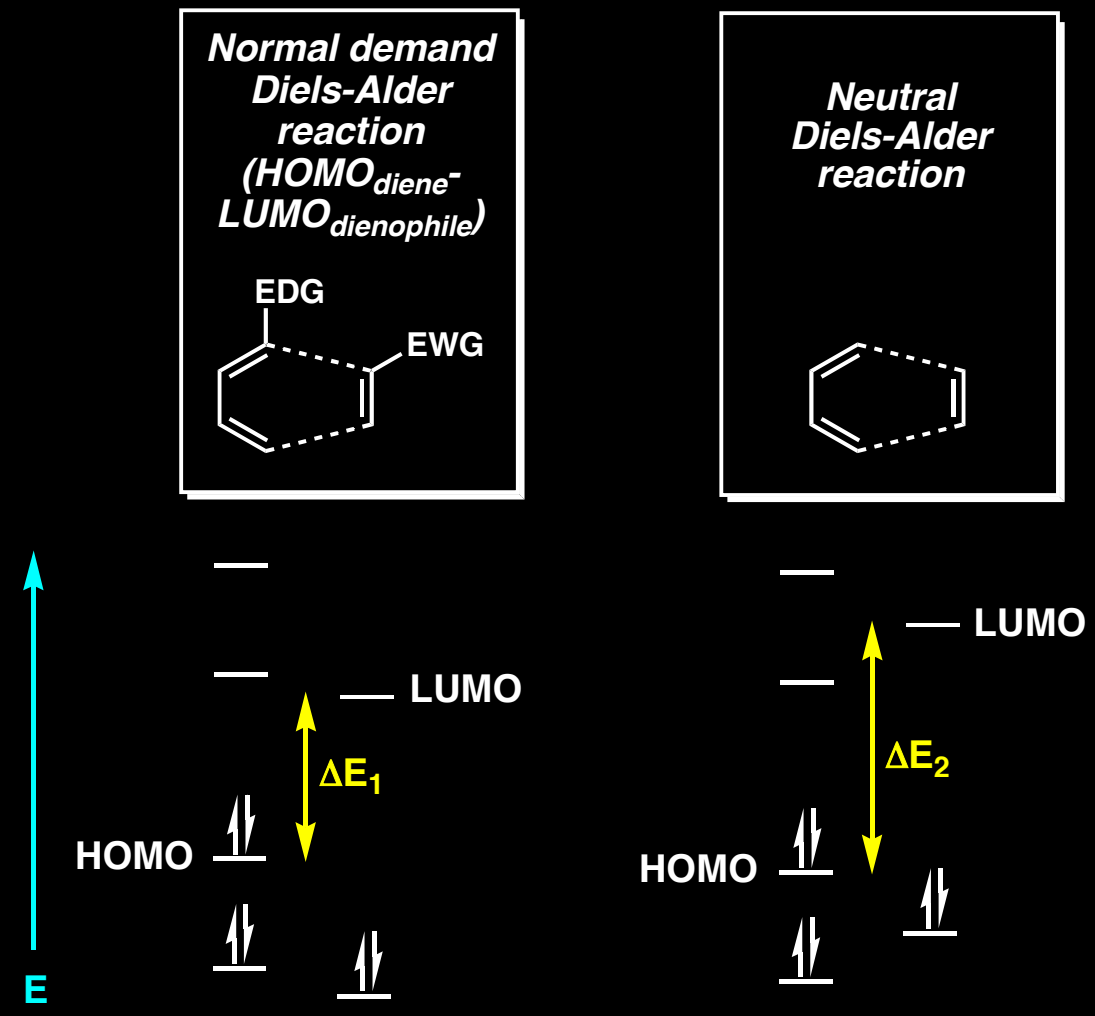
D. L. Boger, S. Ichikawa, H. Jiang, J. Am. Chem. Soc. 2000, 122, 12169.

Hetero Diels-Alder Reactions: Oxime Ethers as Diene Components



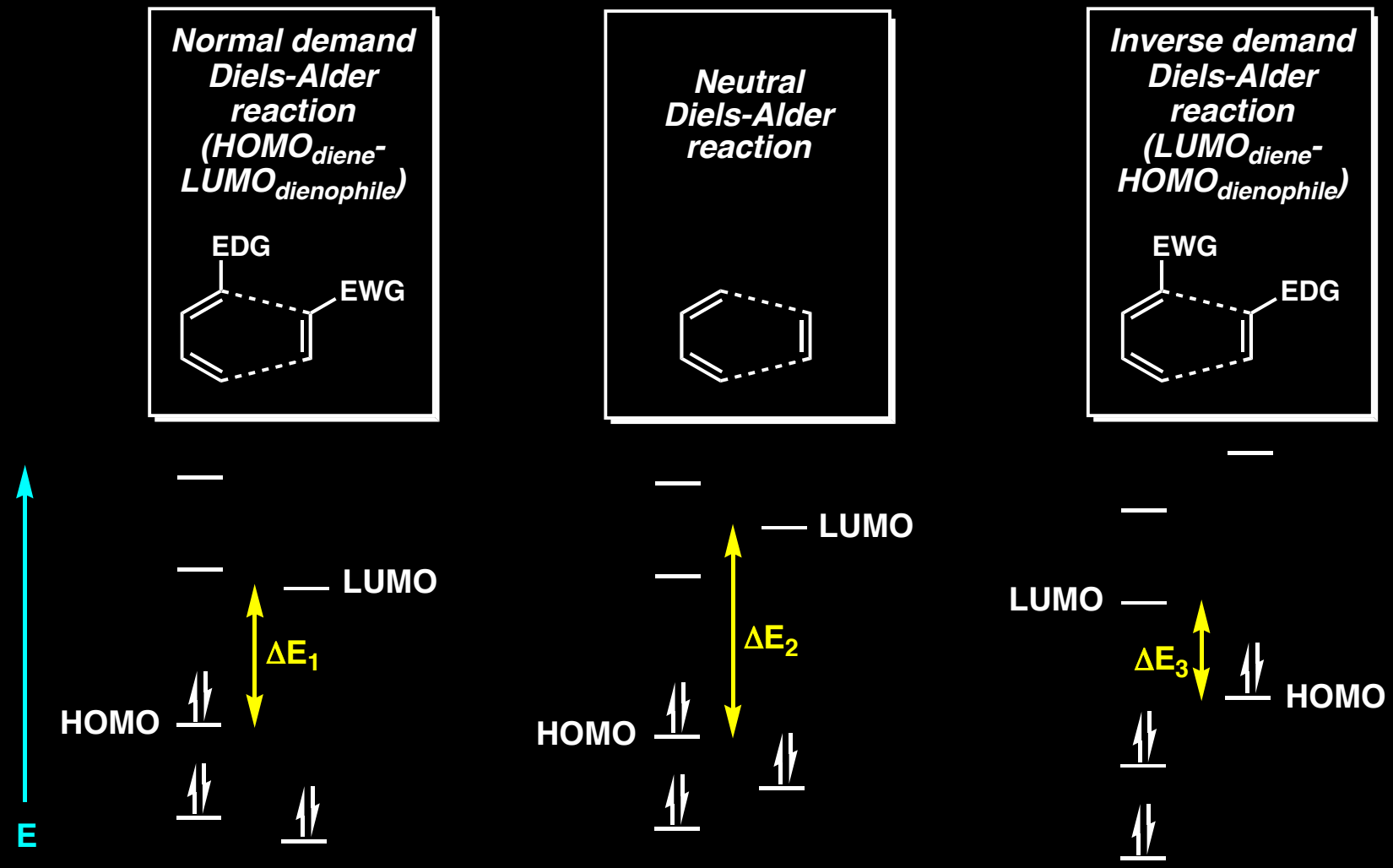
D. L. Boger, S. Ichikawa, H. Jiang, J. Am. Chem. Soc. 2000, 122, 12169.

Hetero Diels-Alder Reactions: Often an Inverse Electron Demand Scenario



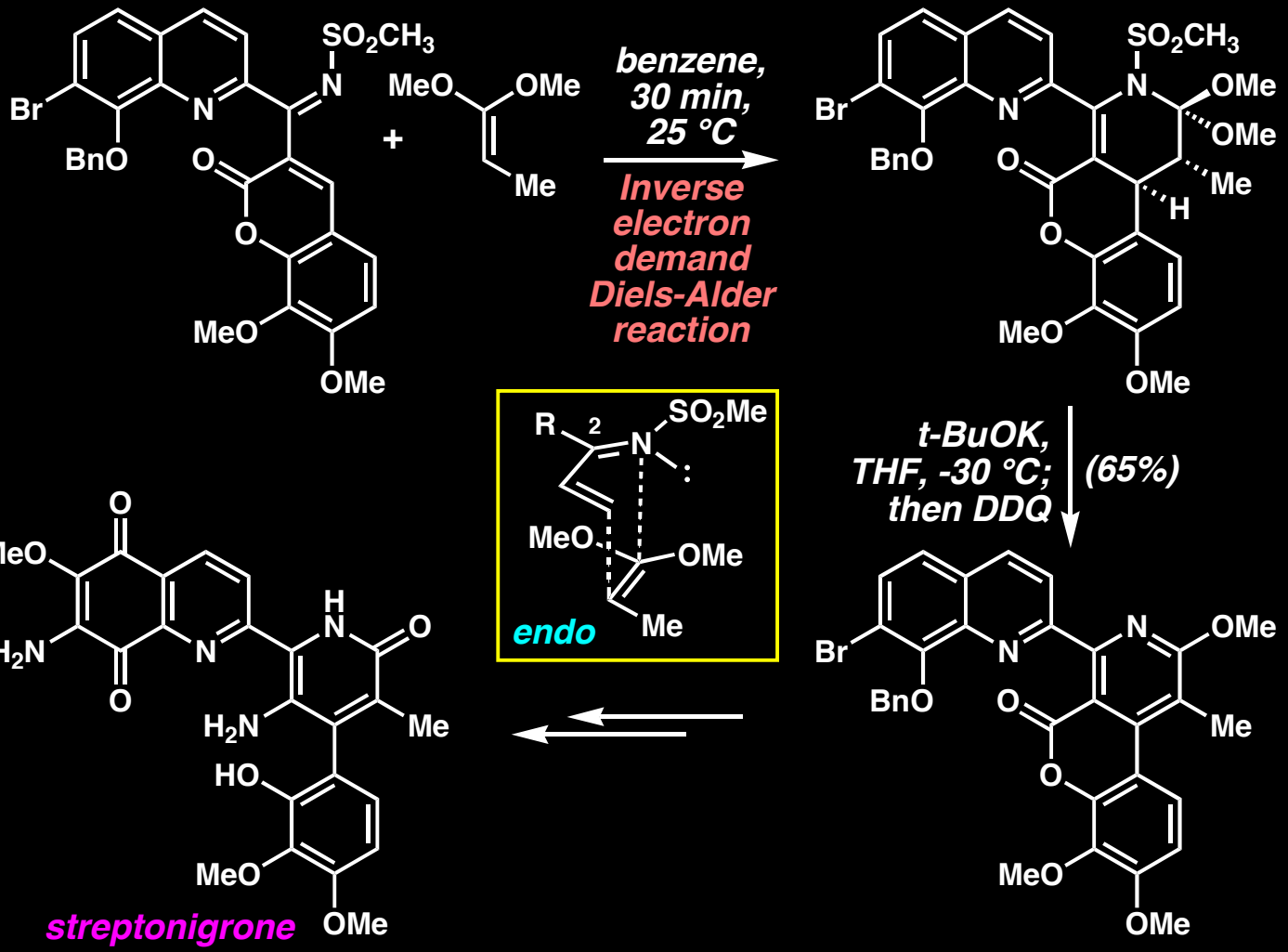
For a review, see: D. L. Boger, Comprehensive Organic Synthesis, Vol. 5., 1991, p. 451-512.

Hetero Diels-Alder Reactions: Often an Inverse Electron Demand Scenario



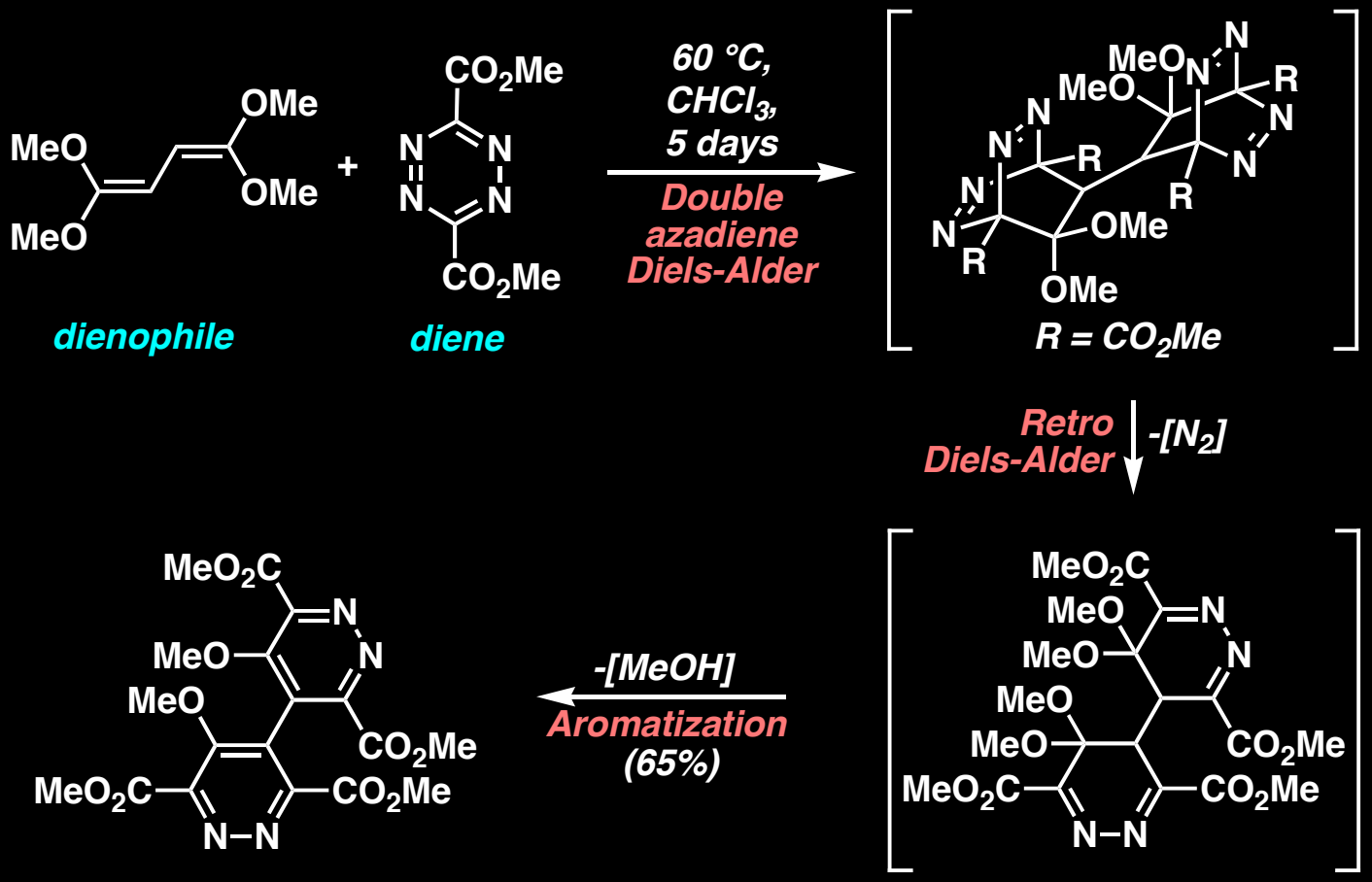
For a review, see: D. L. Boger, Comprehensive Organic Synthesis, Vol. 5., 1991, p. 451-512.

Hetero Diels-Alder Reactions: Azadienes as Diene Components



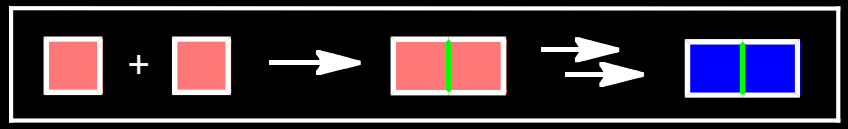
D. L. Boger, K. C. Cassidy, S. Nakahara, J. Am. Chem. Soc. 1993, 115, 10733.

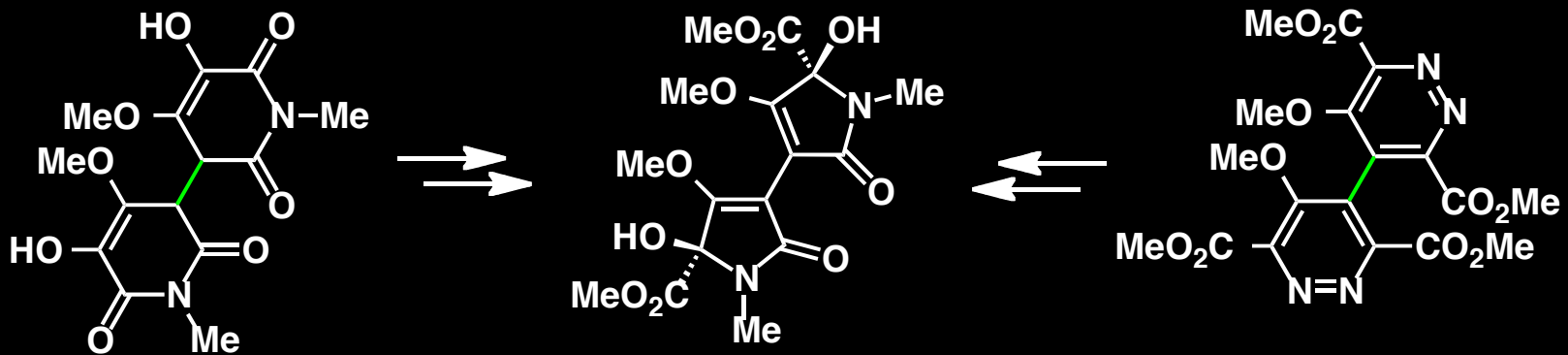
Hetero Diels-Alder Reactions: Azadienes as Diene Components



D. L. Boger, C. Baldino, J. Am. Chem. Soc. 1993, 115, 11418.
For a review, see: Classics in Total Synthesis II, Chapter 2.

Early-Stage Dimerization and Elaboration to Final Target

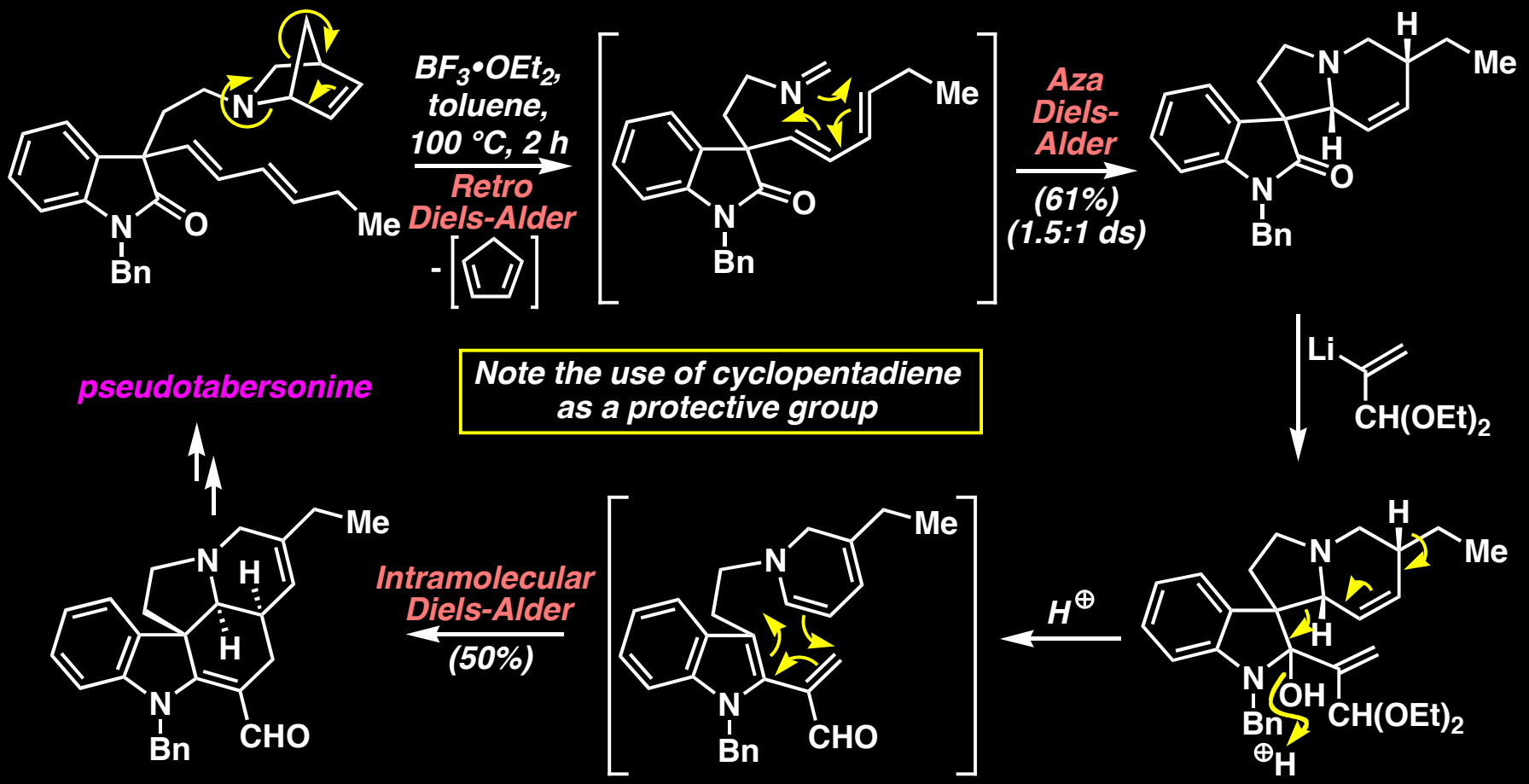




meso-isochrysohermidin

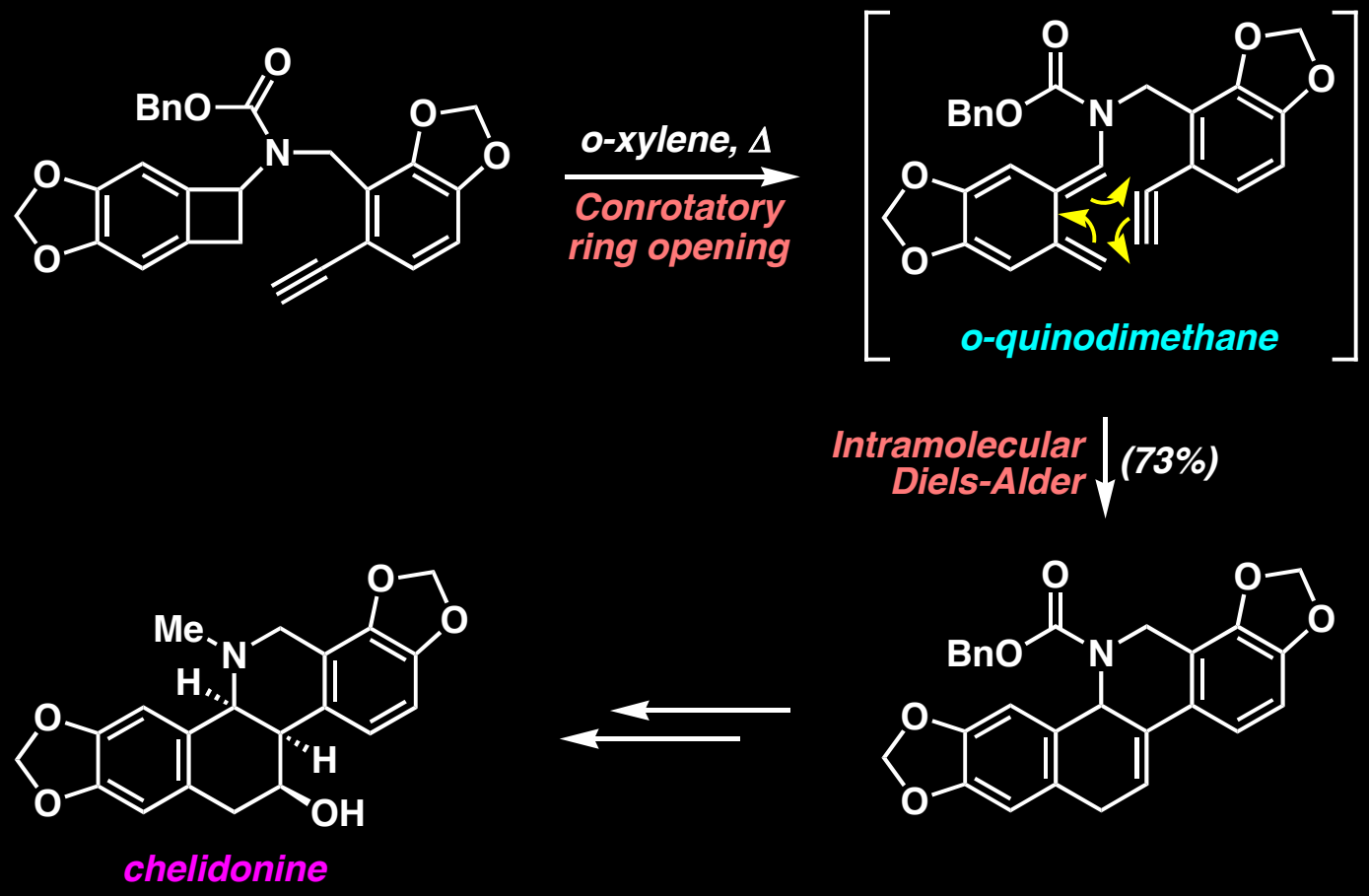
D. L Boger, C. M. Baldino, J. Am. Chem. Soc. 1993, 115, 11418.

Hetero Diels-Alder Reactions: Imines/Iminium Ions as Diene Components



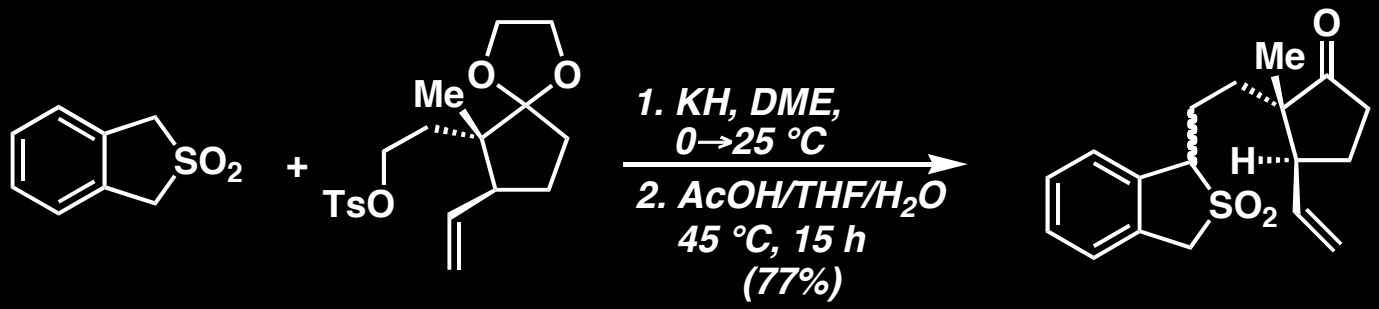
P. A. Grieco, A. Bahsas, J. Org. Chem. 1987, 52, 5746.

Masked Dienes/Dienophiles



W. Oppolzer, C. Robbiani, Helv. Chim. Acta 1983, 66, 1119.

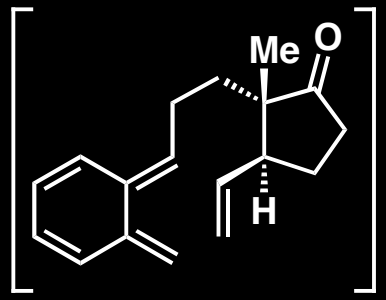
Masked Dienes/Dienophiles



DBP = di-n-butyl phthalate

Cheletropic elimination of SO_2

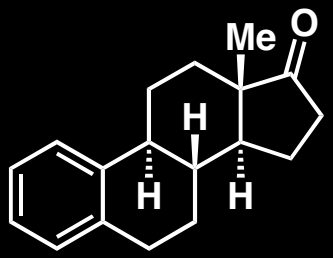
DBP, 210 °C, 8 h



o-quinodimethane

Intramolecular Diels-Alder

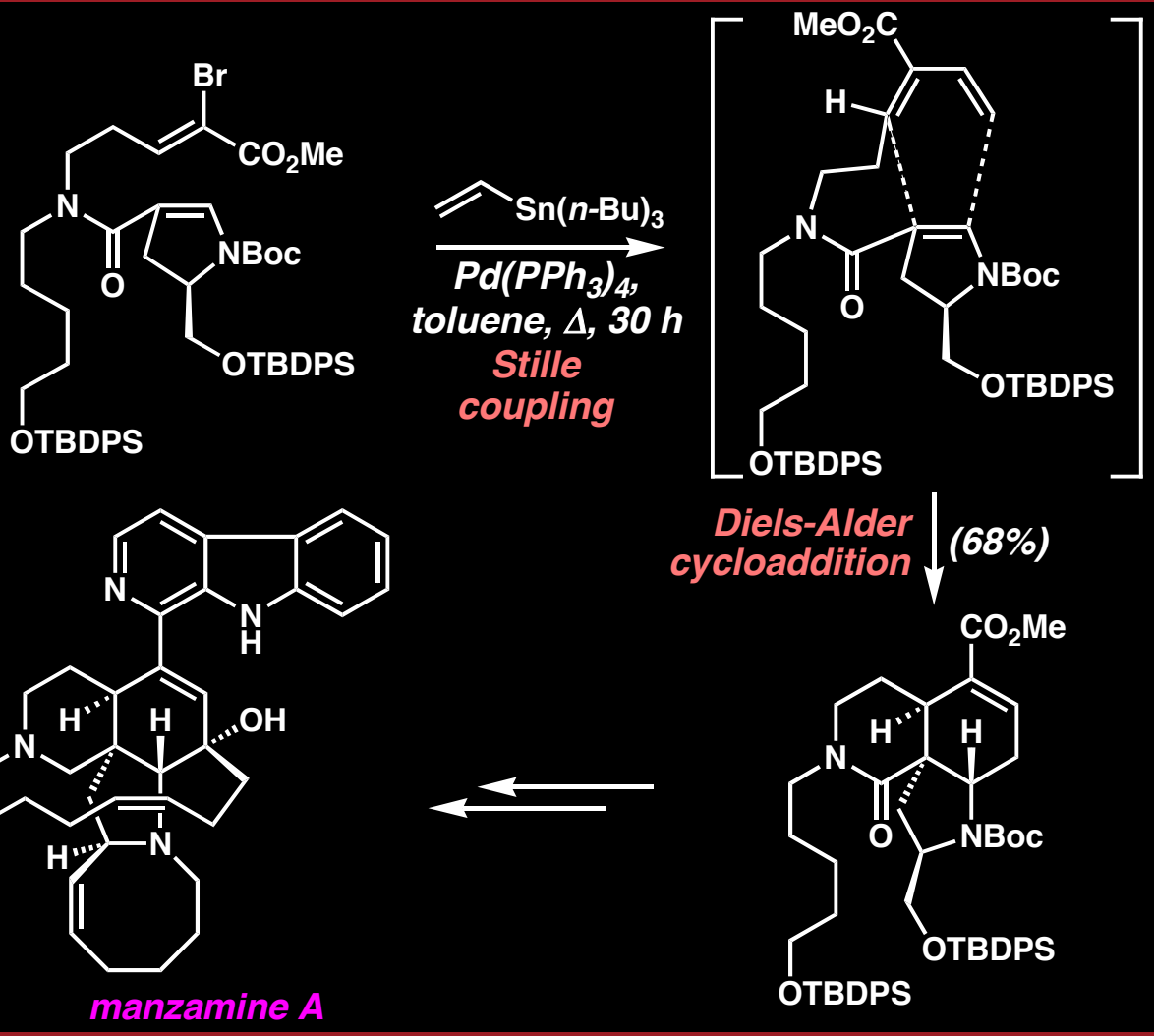
(85%)



estra-1,3,5(10)-trien-17-one

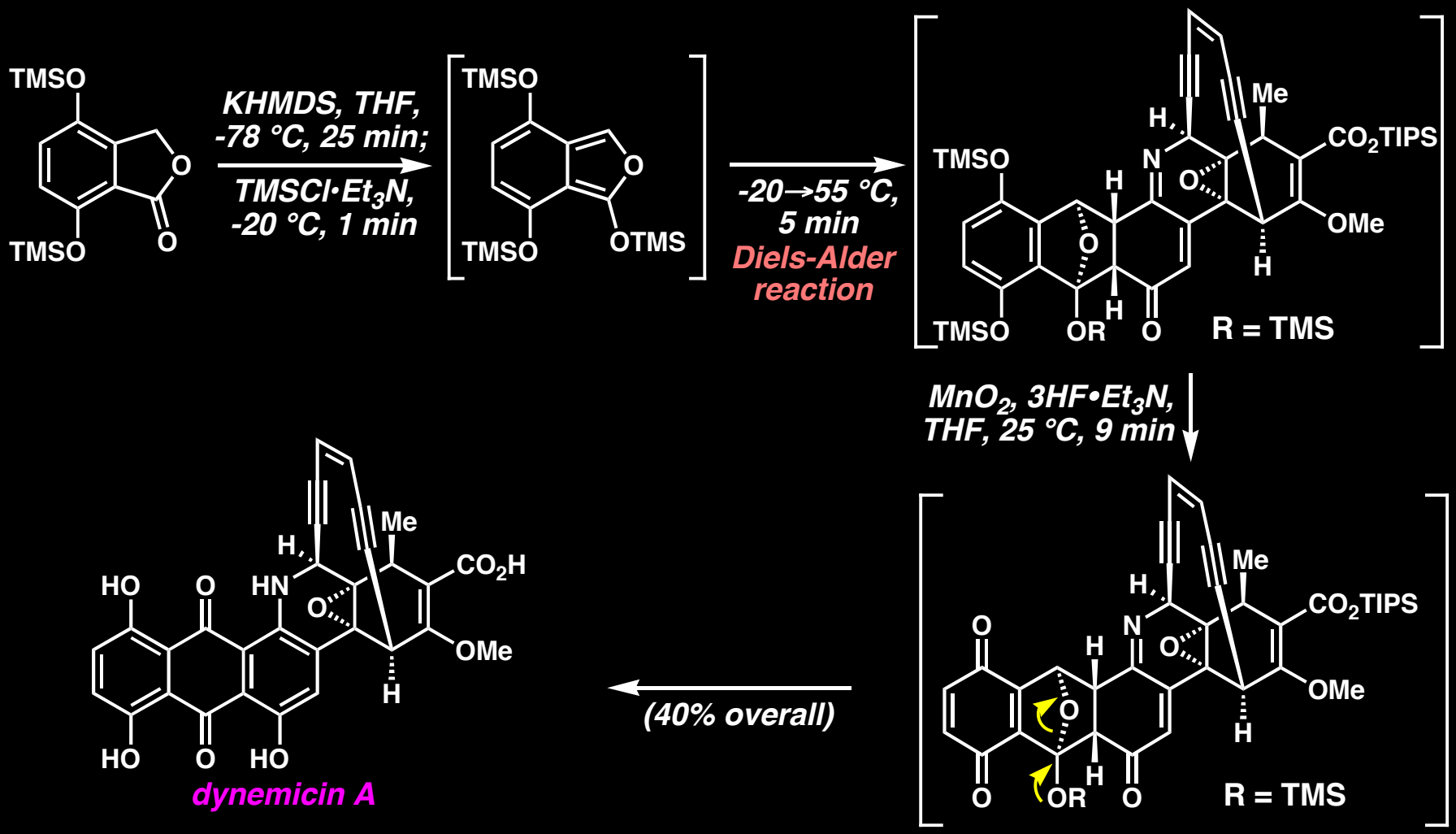
K. C. Nicolaou, W. E. Barnette, J. Chem. Soc., Chem. Commun. 1979, 1119.

Cascade Reactions: Diels-Alder Reactions Set-up by Prior Events



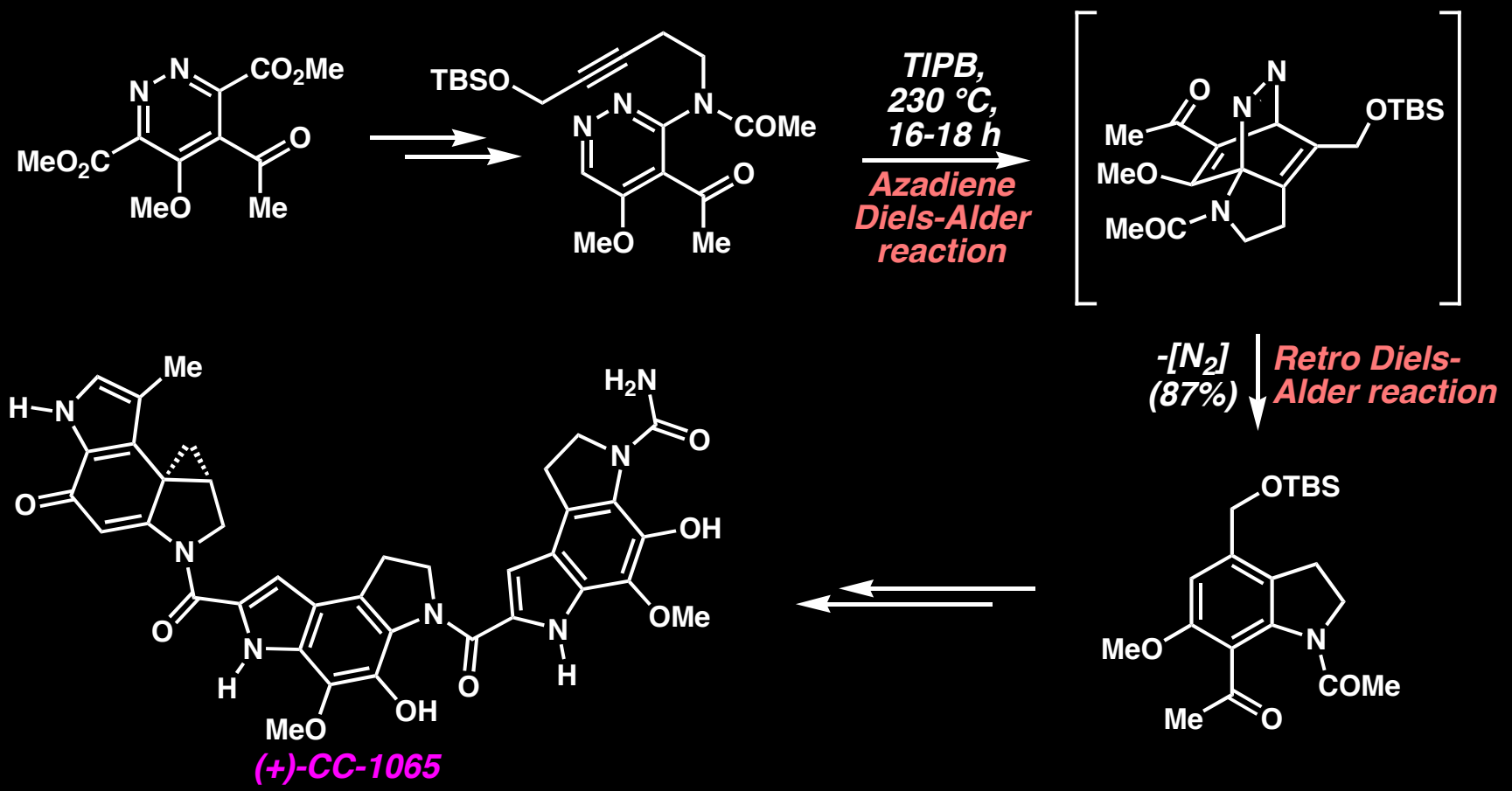
S. F. Martin and co-workers, J. Am. Chem. Soc. 1999, 121, 866.
For a review, see: Classics in Total Synthesis II, Chapter 8.

Non-Obvious Diels-Alder Products



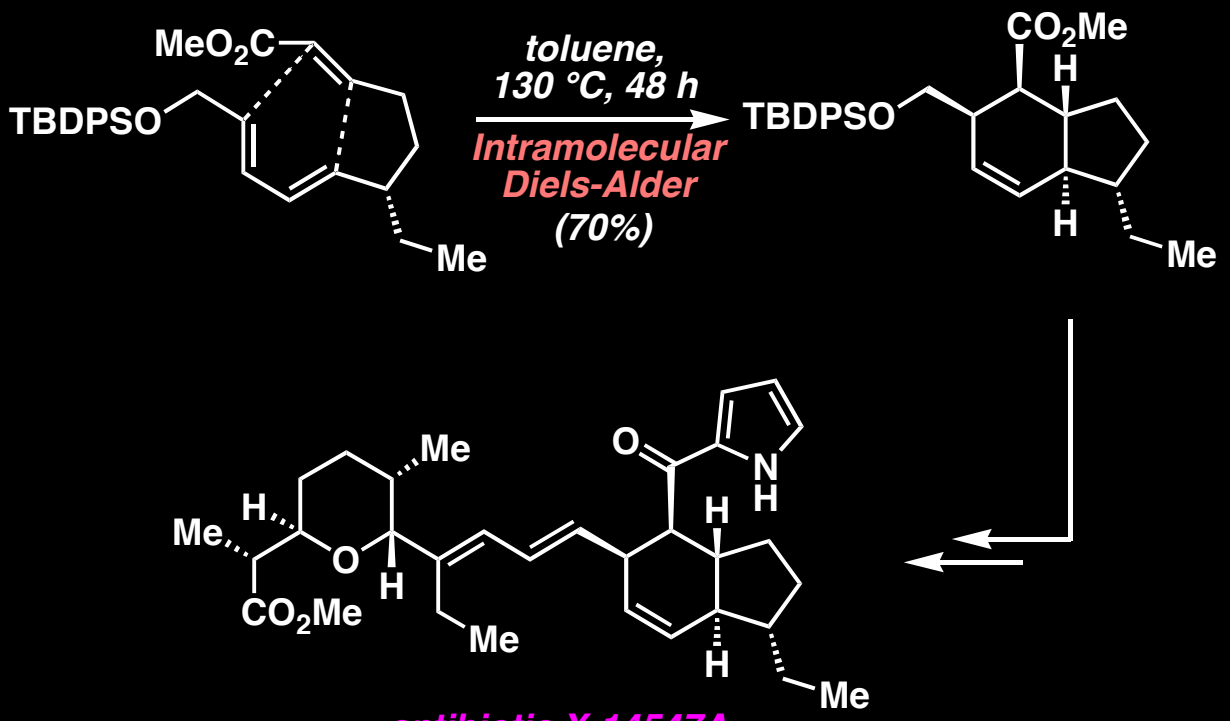
A. G. Myers and co-workers, J. Am. Chem. Soc. 1997, 119, 6072.
For a review, see: Classics in Total Synthesis II, Chapter 4.

Non-Obvious Diels-Alder Products



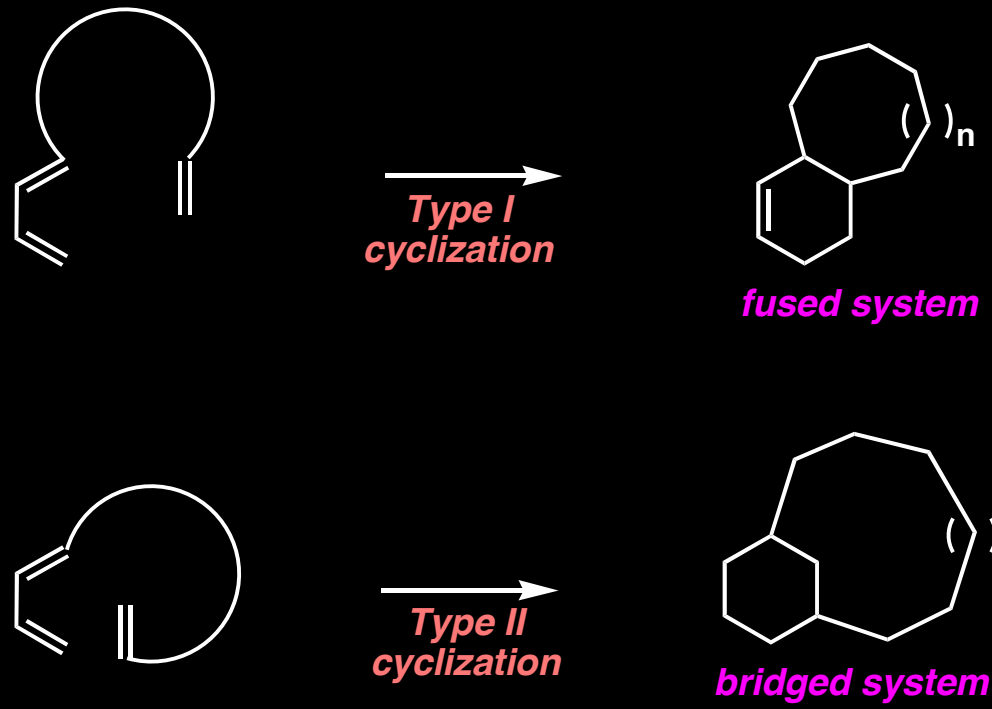
D. L. Boger and co-workers, J. Org. Chem. 1988, 53, 1415.
D. L. Boger and co-workers, J. Am. Chem. Soc. 1988, 110, 4796.

Asymmetric Diels-Alder Reactions: Diastereoselective



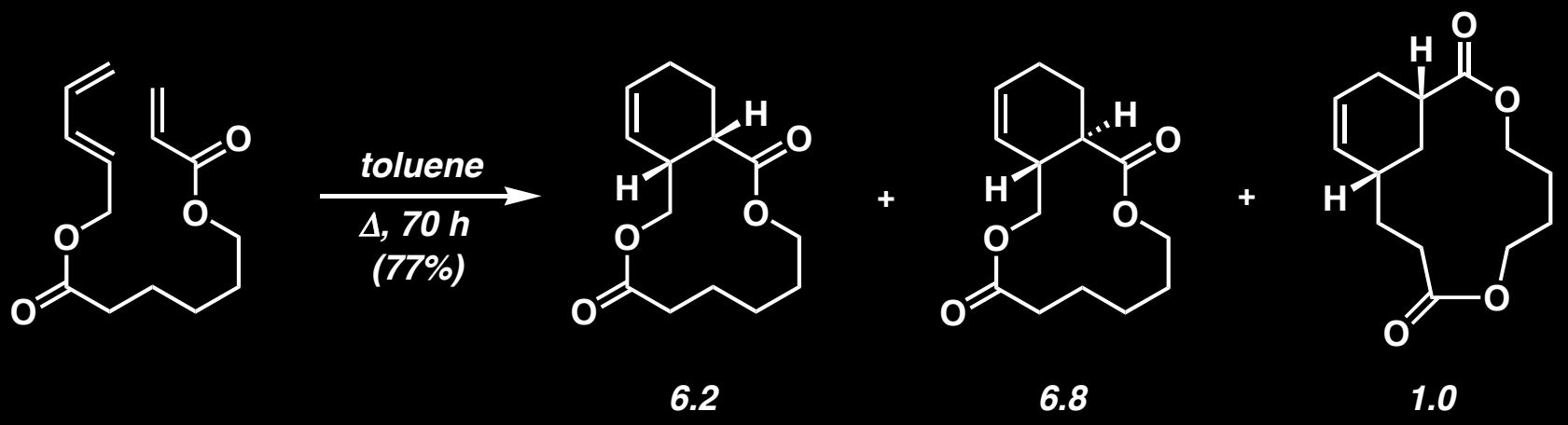
K. C. Nicolaou and co-workers, J. Org. Chem. 1985, 50, 1440.

Diels-Alder Reactions Leading to Macrocyclic Rings: Possible Modes of Cyclization



Most reactions of this kind furnish fused ring systems, though bridged systems may form if the connecting chain is of sufficient length.

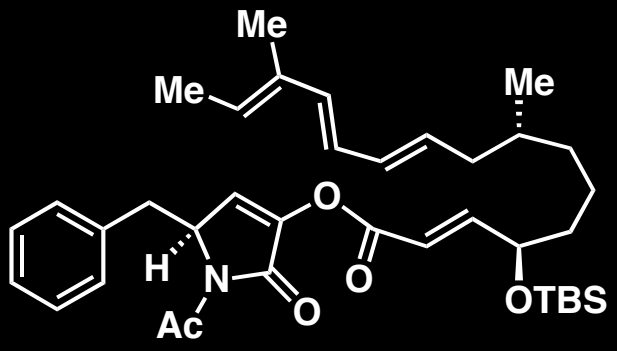
Macrocyclization With the Diels-Alder Reaction: The First Proof of Principle



6.2 *6.8* *1.0*

E.J. Corey, M. Petrzilka, Tetrahedron Lett. 1975, 16, 2537.

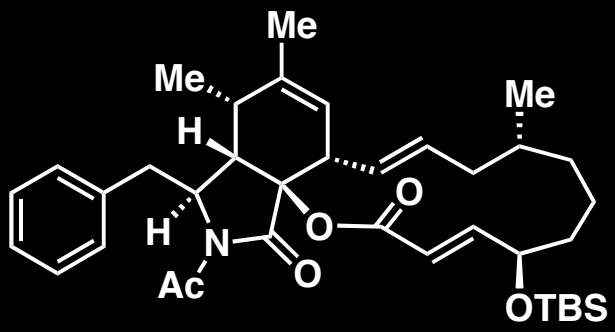
Diels-Alder Reactions Leading to Macrocyclic Rings: The 14-Membered Ring of Cytochalasin D

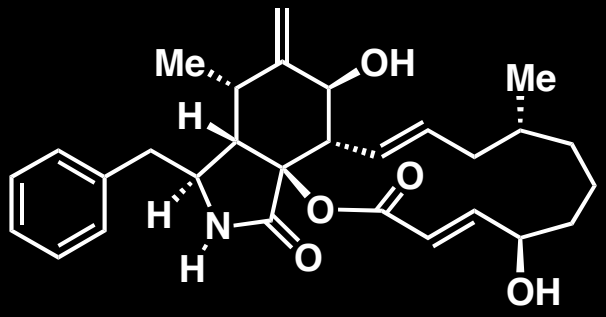


mesitylene, 180-190 °C, 6 days

(35%)

Intramolecular Diels-Alder reaction

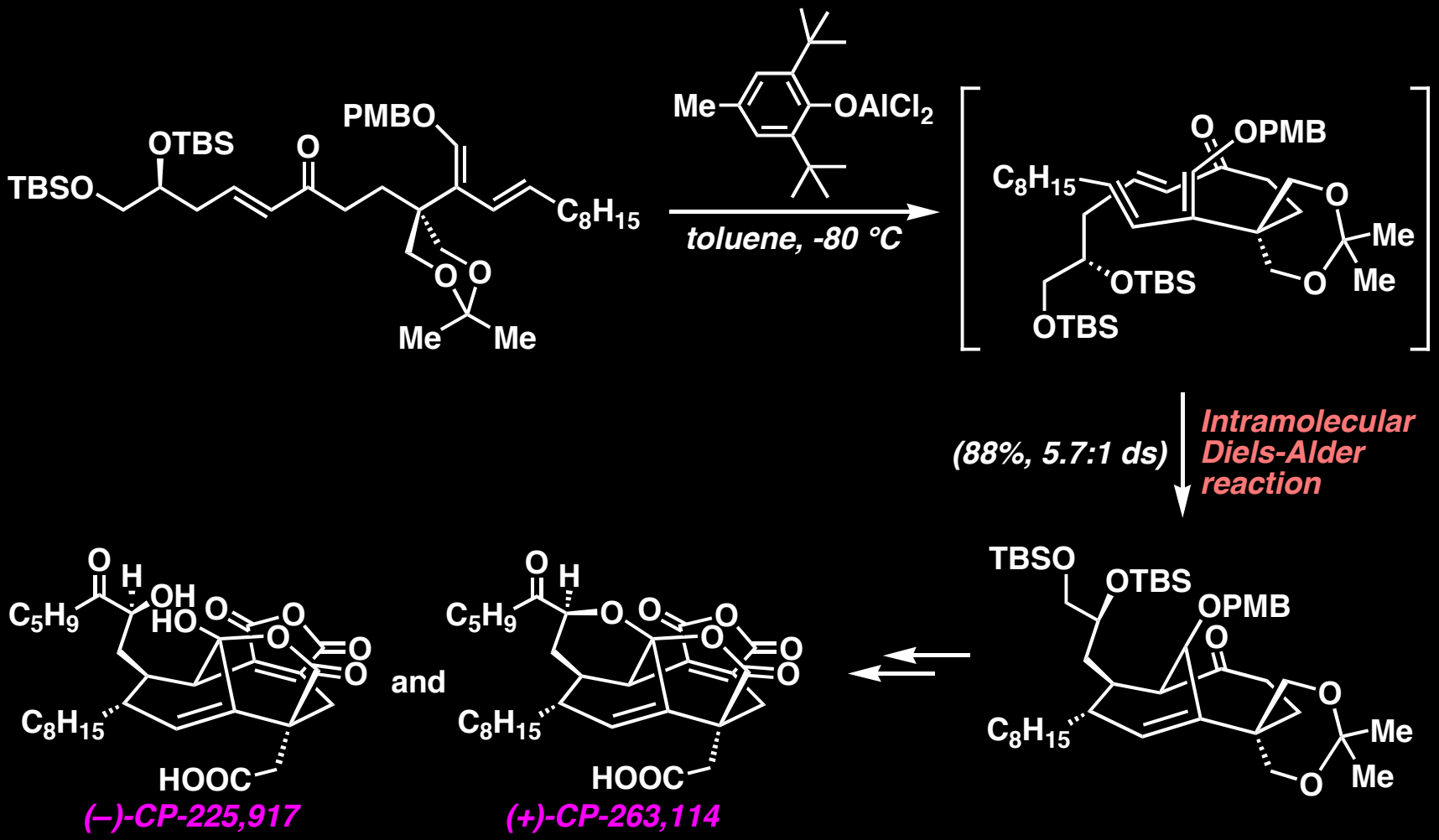




cytochalasin D

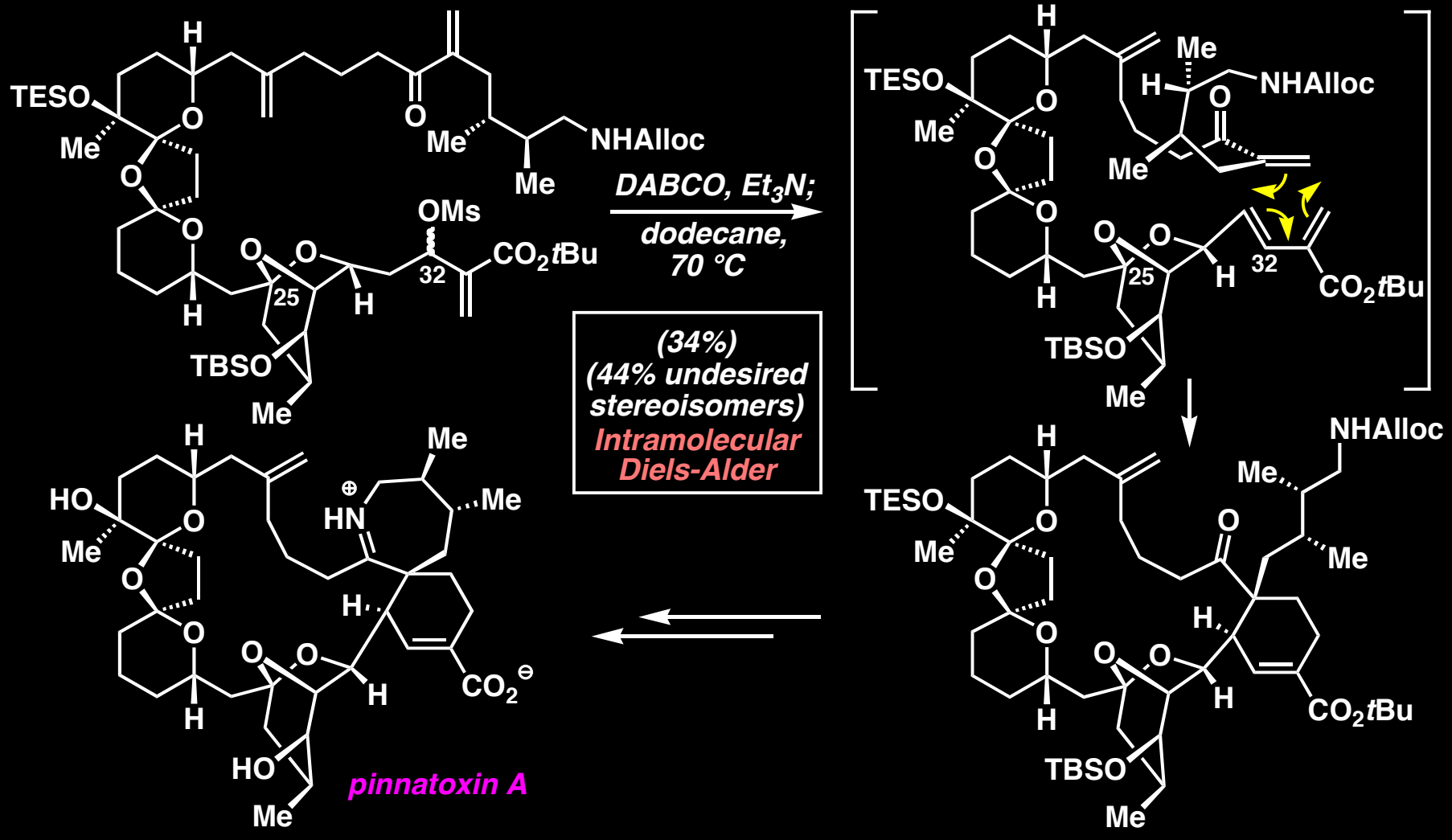
G. Stork, E. Nakamura, J. Am. Chem. Soc. 1983, 105, 5510.

Diels-Alder Reactions Leading to Macrocyclic Rings: The 9-Membered Ring of the CP-Molecules



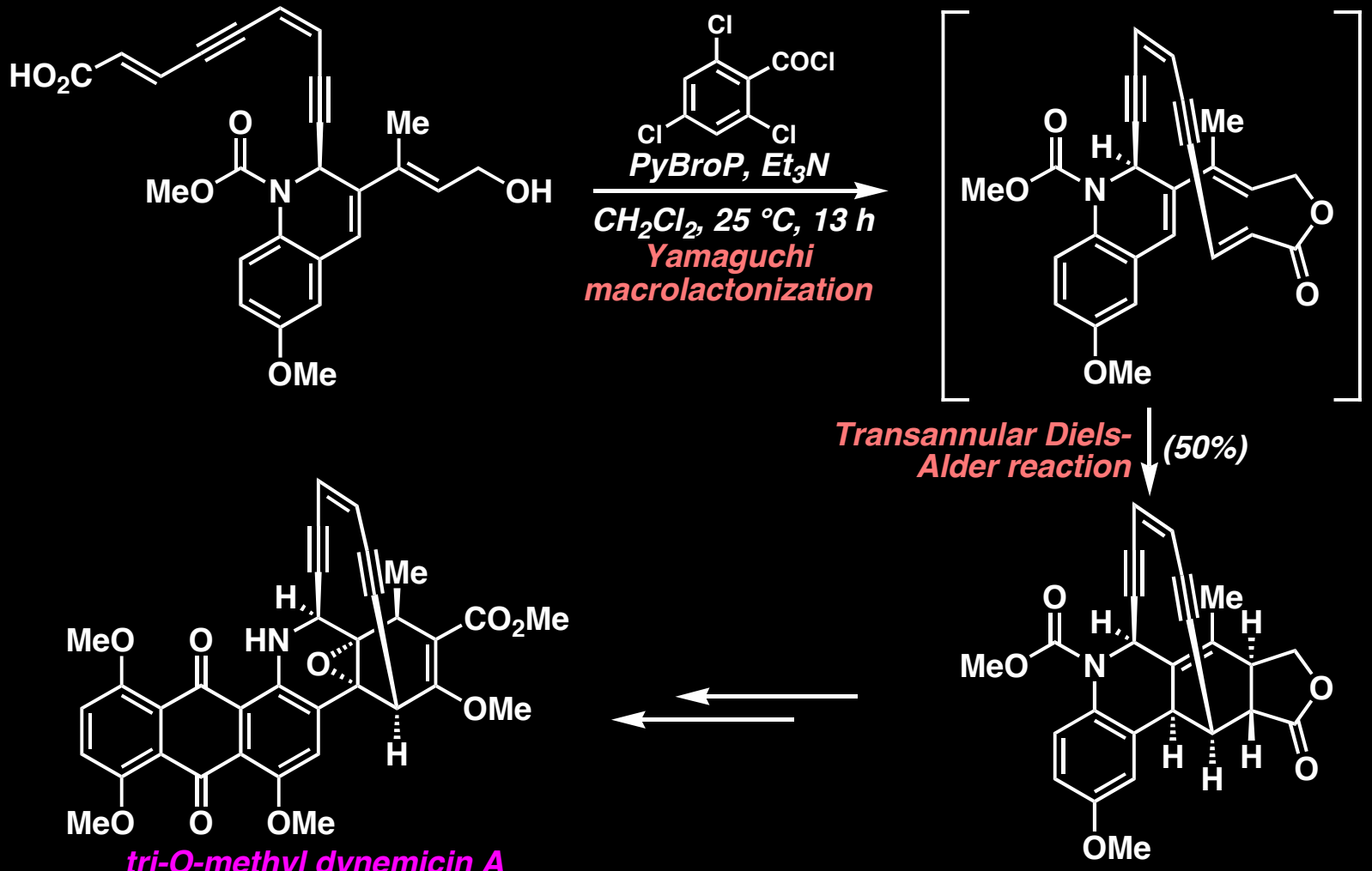
K.C. Nicolaou, P.S. Baran, Angew. Chem. Int. Ed. 2002, 41, 2678.

The Diels-Alder Reaction To Make Macrocyclic Systems: A Provocative Example



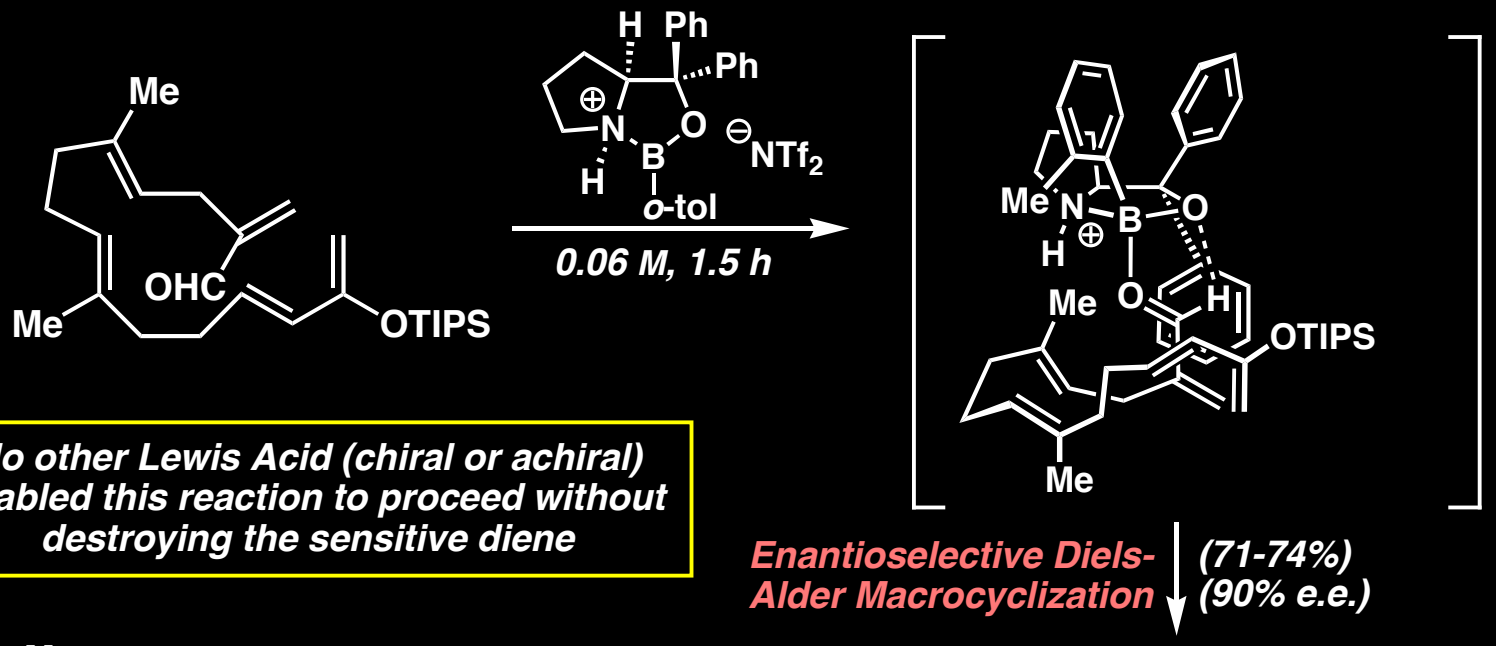
Y. Kishi and co-workers, J. Am. Chem. Soc. 1998, 120, 7647.

Diels-Alder Reactions Leading to Macrocyclic Rings: The 10-Membered Ring of Dynemicin A



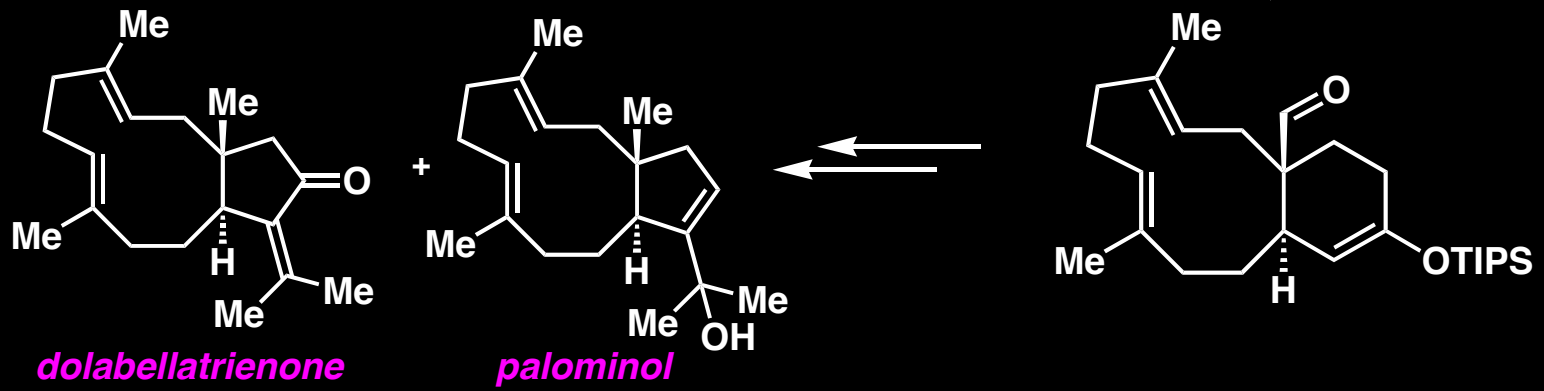
J. Taunton, J. L. Wood, S. L. Schreiber, J. Am. Chem. Soc. 1993, 115, 10378.

Macrocyclization With the Diels-Alder Reaction: The First Enantioselective Reaction



No other Lewis Acid (chiral or achiral) enabled this reaction to proceed without destroying the sensitive diene

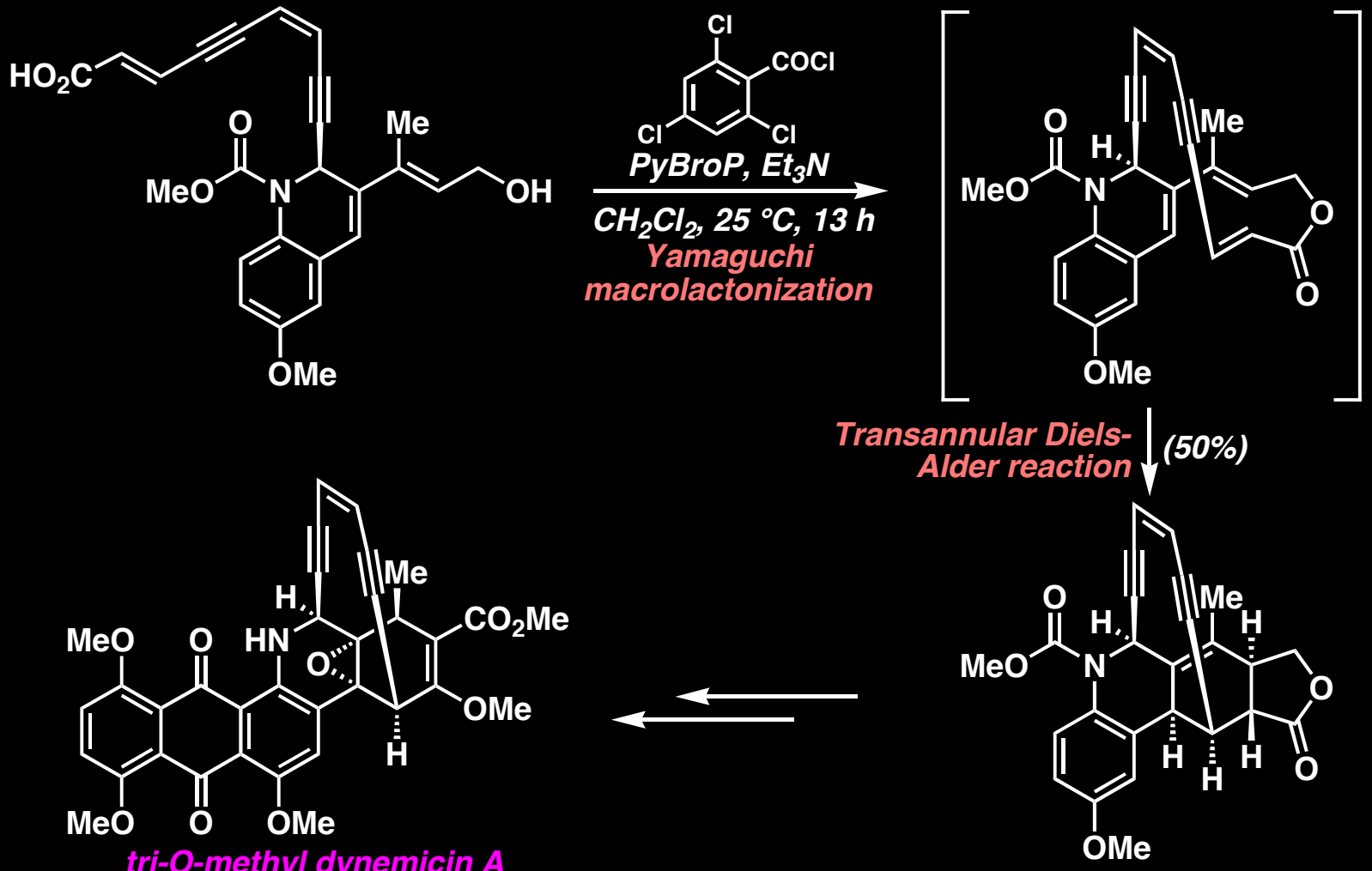
Enantioselective Diels-Alder Macrocyclization ***(71-74%) (90% e.e.)***



dolabellatrienone ***palominol***

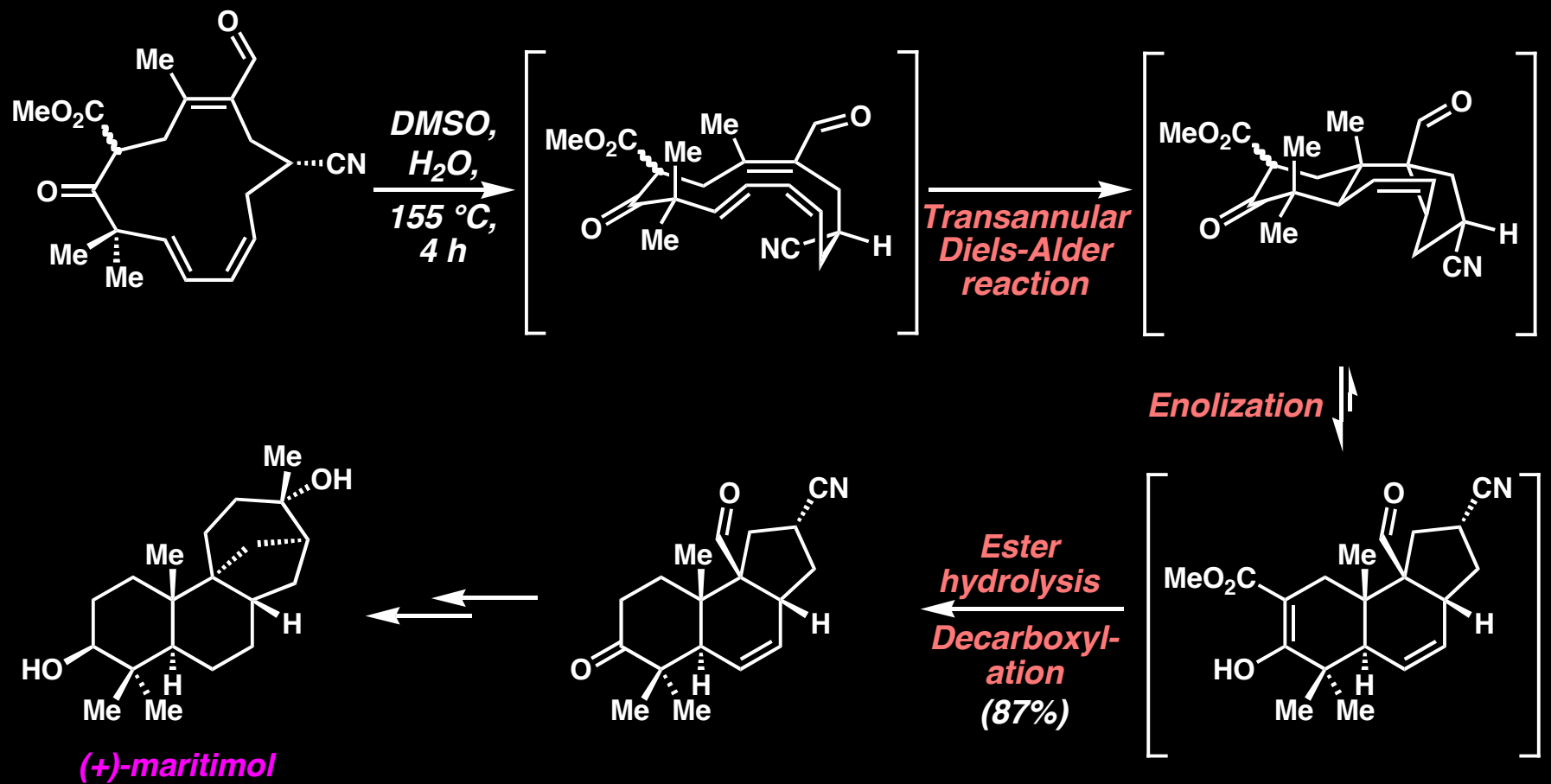
S.A. Snyder, E.J. Corey, J. Am. Chem. Soc. 2006, 128, 740.

Diels-Alder Reactions Leading to Macrocyclic Rings: The 10-Membered Ring of Dynemicin A



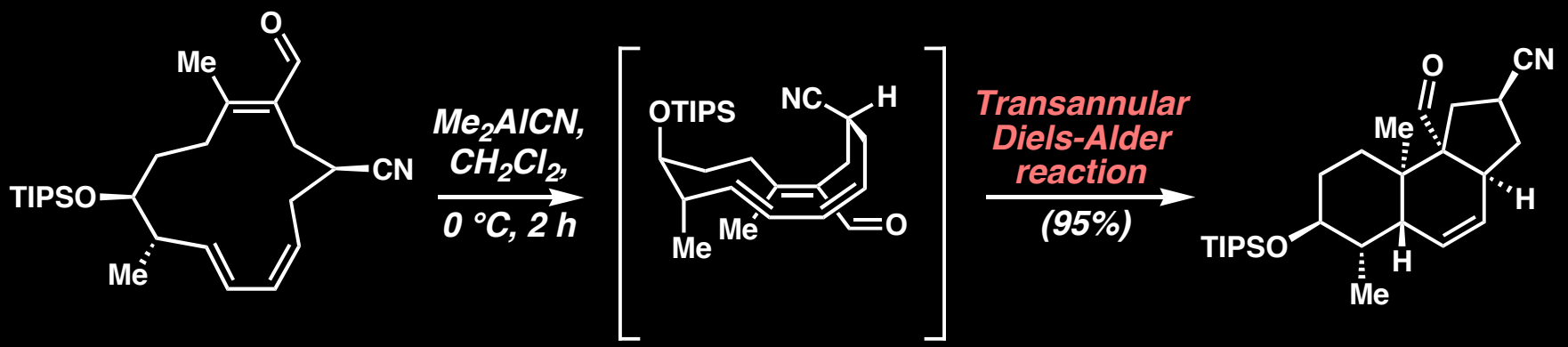
J. Taunton, J. L. Wood, S. L. Schreiber, J. Am. Chem. Soc. 1993, 115, 10378.

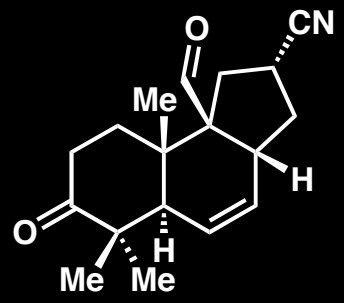
The Diels-Alder Reaction Within Rings: Transannular Cycloadditions



A. Toro, P. Nowak, P. Deslongchamps, J. Am. Chem. Soc. 2000, 122, 4526.
For a review, see: P. Deslongchamps and co-workers, Tetrahedron 2001, 57, 4243.

The Diels-Alder Reaction Within Rings: Transannular Cycloadditions





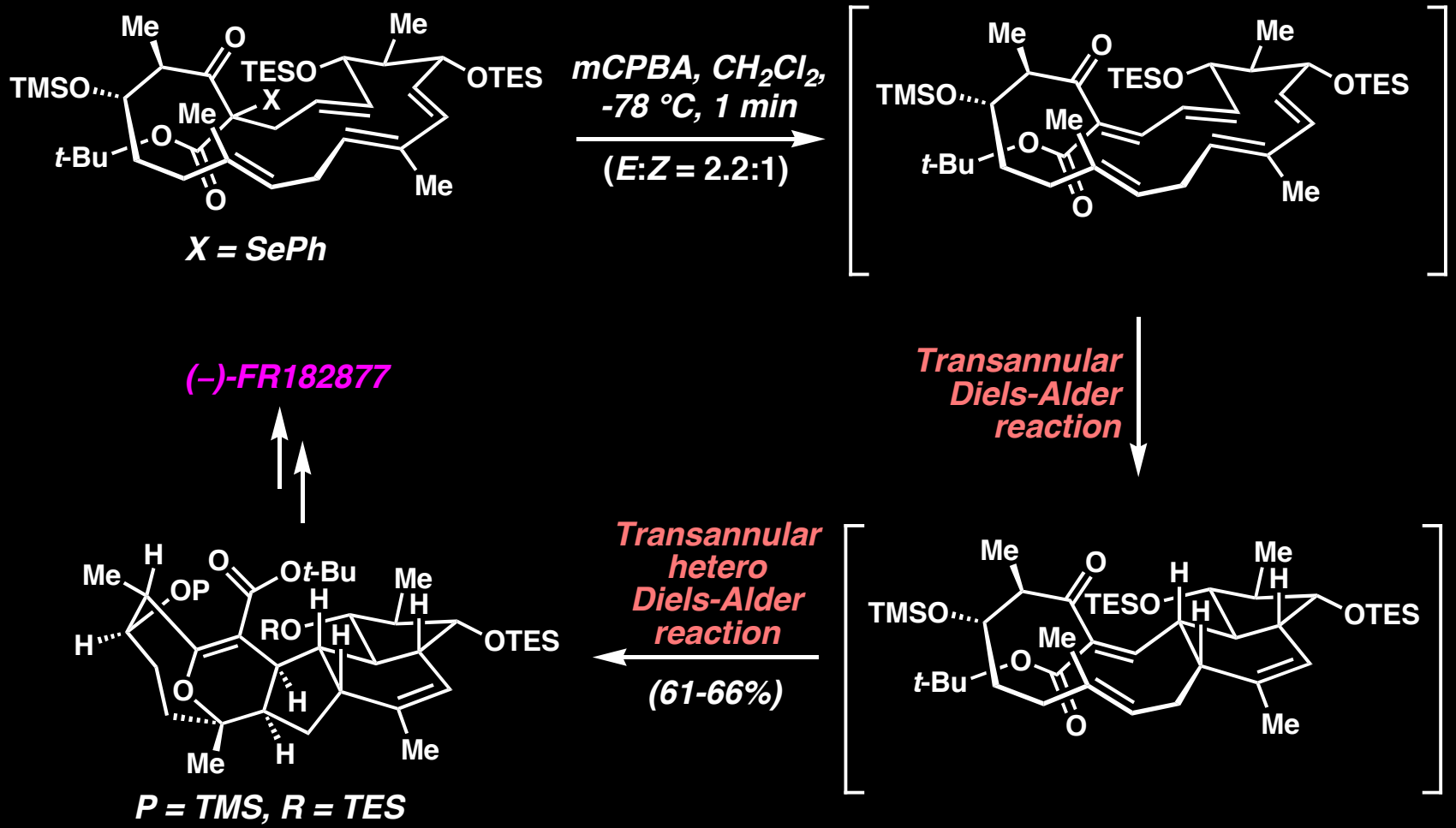
Product from previous slide

This example reveals how subtle stereochemical effects within the intervening carbogenic chain can influence the outcome of Diels-Alder reactions.

These effects are often impossible to predict prior to experimentation.

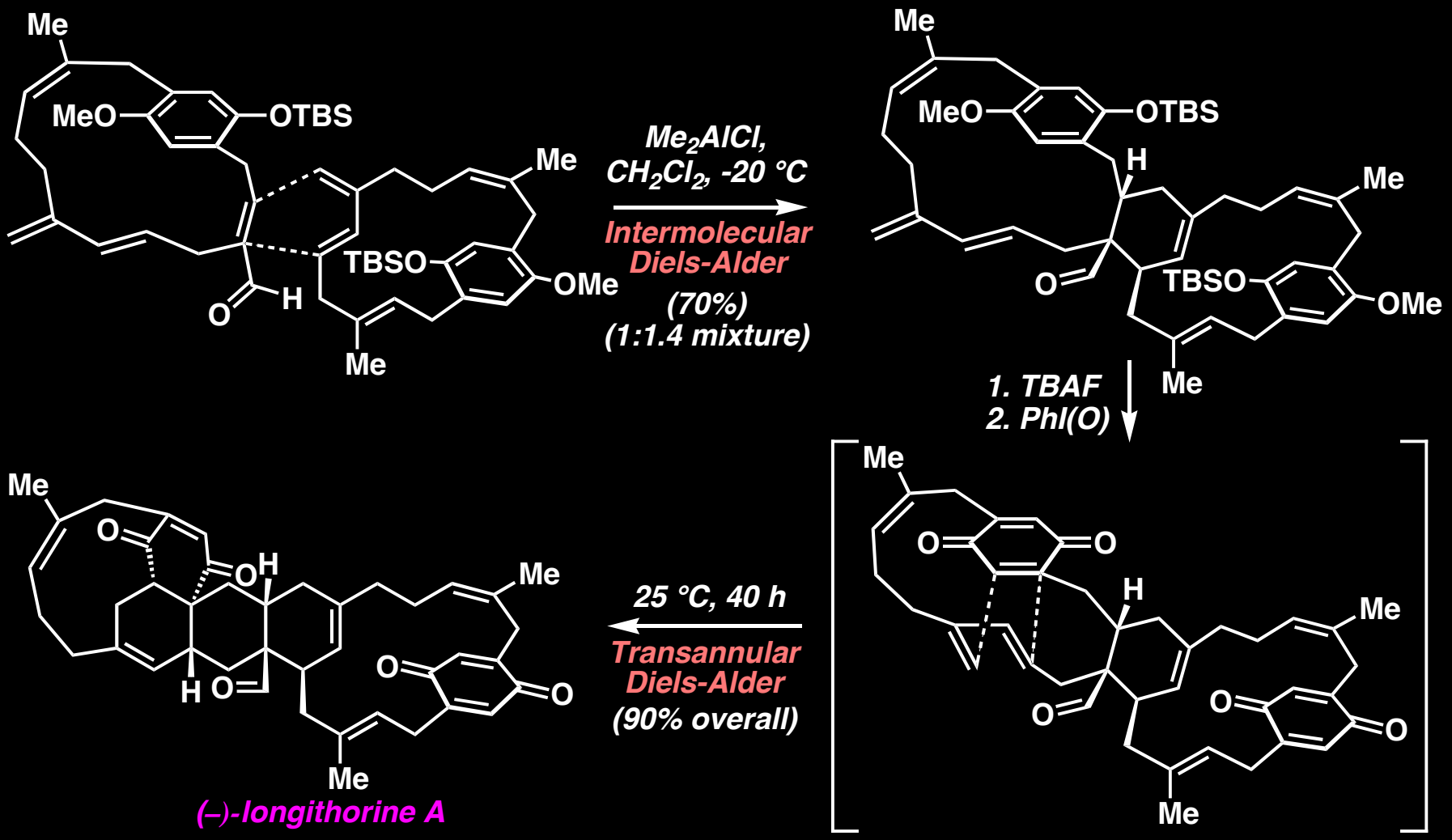
A. Toro, P. Nowak, P. Deslongchamps, J. Am. Chem. Soc. 2000, 122, 4526.
For a review, see: P. Deslongchamps and co-workers, Tetrahedron 2001, 57, 4243.

The Diels-Alder Reaction in Nature? Some Provocative Examples



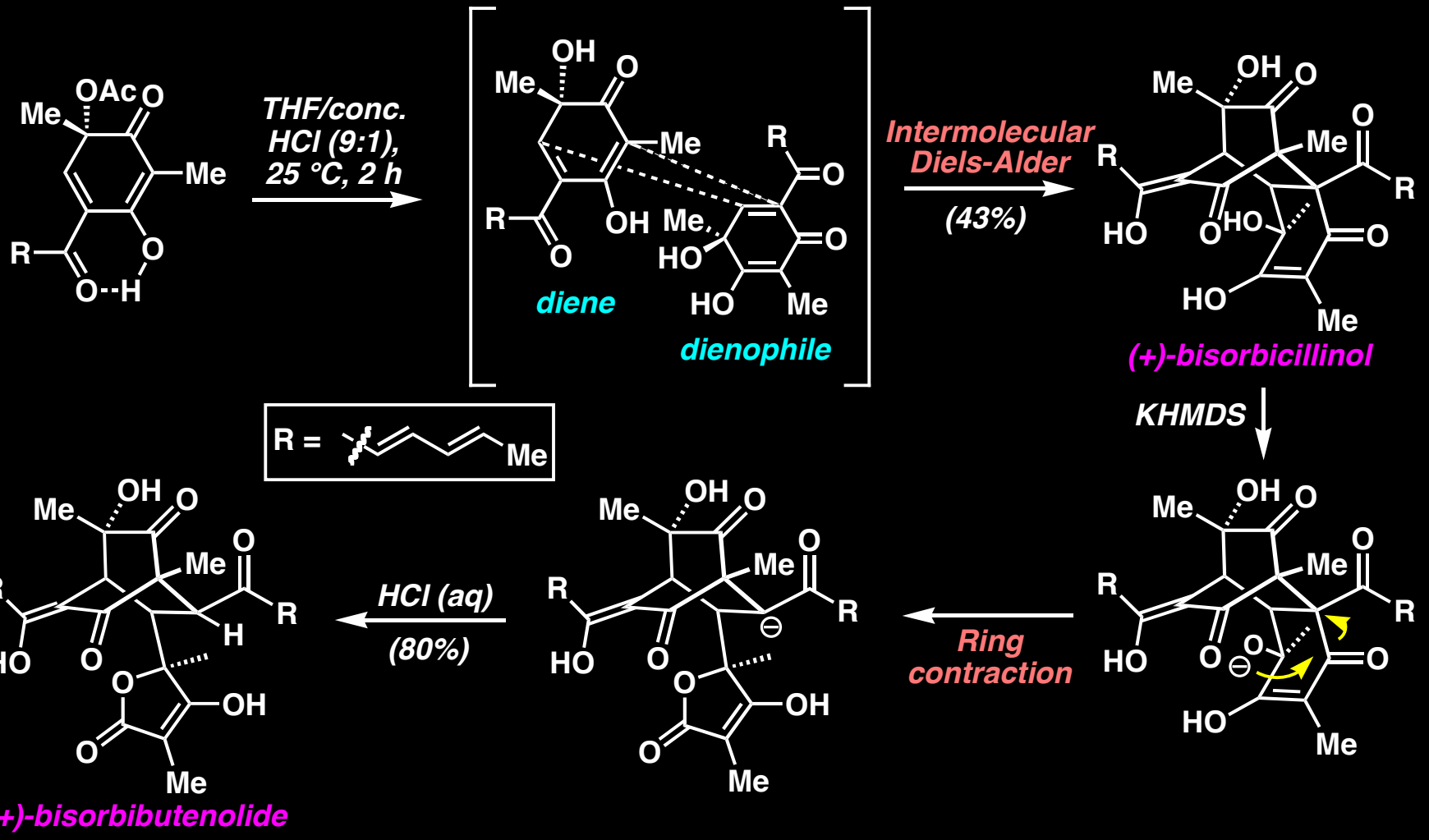
E. J. Sorensen and co-workers, J. Am. Chem. Soc. 2002, 124, 4552.
For a review, see: Classics in Total Synthesis II, Chapter 17

The Diels-Alder Reaction in Nature? Some Provocative Examples



M. E. Layton, C. A. Morales, M. D. Shair, J. Am. Chem. Soc. 2002, 124, 773.

The Diels-Alder Reaction in Nature? Some Provocative Examples



K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 2000, 122, 3071.