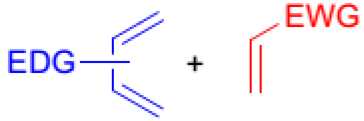
DIELS-ALDER CYCLOADDITION

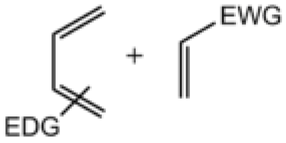
Diels-Alder topics to be covered

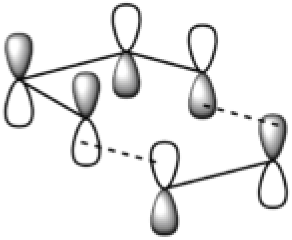
- 1. Reactivity: s-cis conformation, electronic effects
- 2. Regioselectivity (ortho/meta, para/meta)
- 3. Stereospecificity: cis-dienophilies go to cis cyclohexenes, trans-trans dienes go to cis-1,4-cyclohexenes
- 4. Stereoselectivity: Alder endo rule
- 5. Facial selectivity in diene and dienophile
- 6. Enantioselectivity - chiral auxiliaries and chiral catalysts
- 7. Inverse electron demand Diels-Alder reactions
- 8. Retro-Diels-Alder reactions

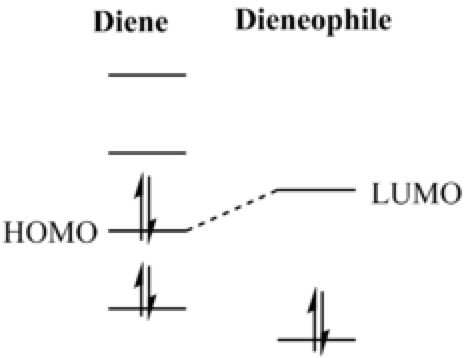
Mechanism

Normal Demand

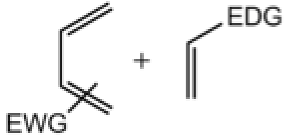


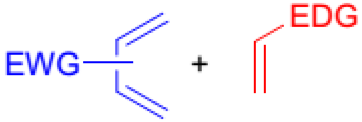


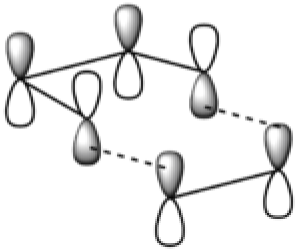


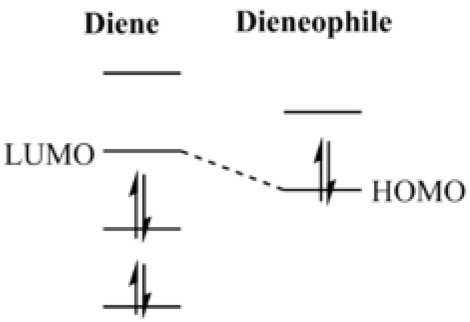


Inverse Demand

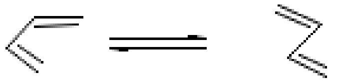




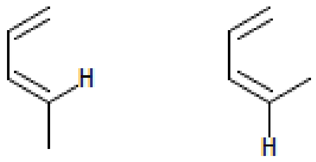




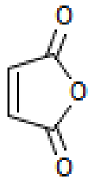
Reactivity-Conformation of Diene


s-cis
s-trans

Angew. Chem. Int. Ed. **1966**, *5*, 211; **1967**, *6*, 16.



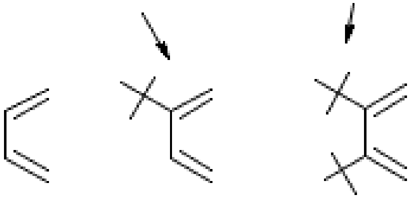
Reactivity towards ? 10^5 1



Maleic anhydride

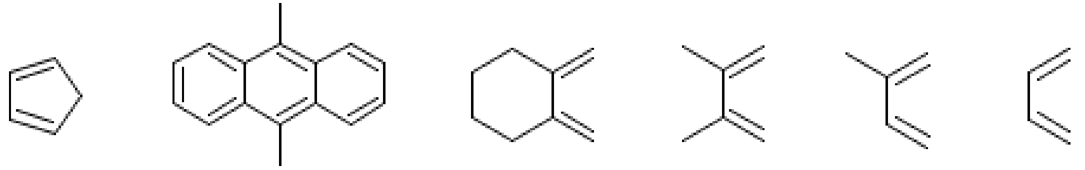
t-Butyl group favors s-cis conformation

Neither planar conformation possible



Reactivity towards maleic anhydride 1 27 no reaction

Dienes with an enforced coplanar s-cis conformation are exceptionally reactive (Sauer *Angew. Chem. Int. Ed.* **1962**, *1*, 268):

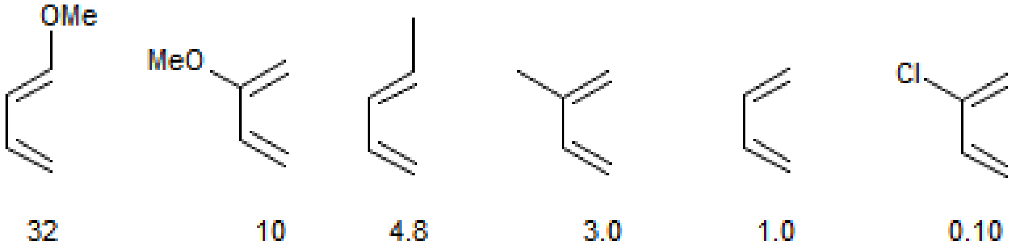


Reactivity towards maleic anhydride at 30 °C 1350 234 110 4.9 2.3 1.0

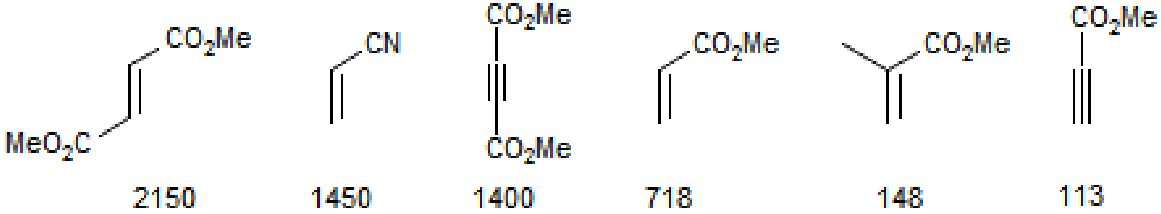
Reactivity-Electronic Effects

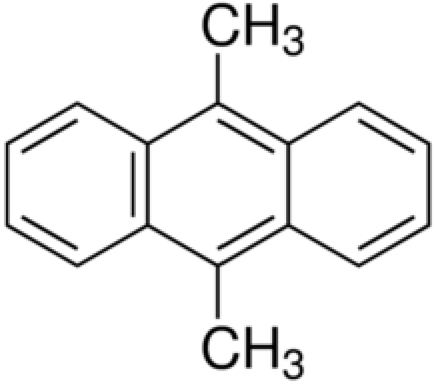
Fowler, *JACS* **1961**, *83*,2885

Diene reactivity towards maleic anhydride

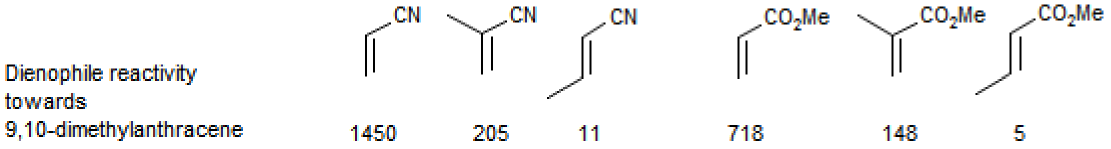


Dienophile reactivity towards 9,10-dimethylanthracene at 130 °C



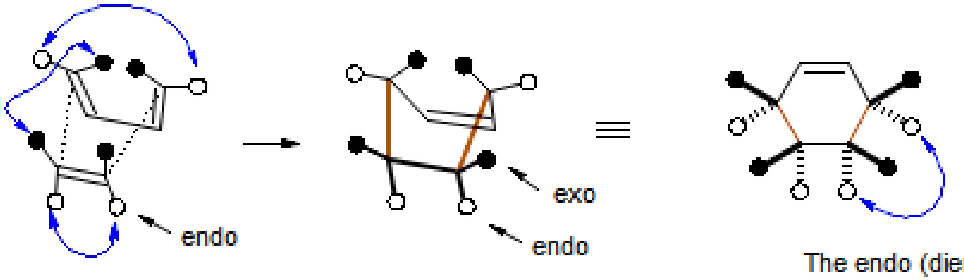


Reactivity-Steric Effects



Because of the compact cyclic nature of the Diels-Alder transition state, the reaction is very sensitive to steric effects at all positions except the two central positions on the diene. Alkyl groups on the dienophile are especially problematic because the electronic and steric effects are in the same direction

Stereospecificity



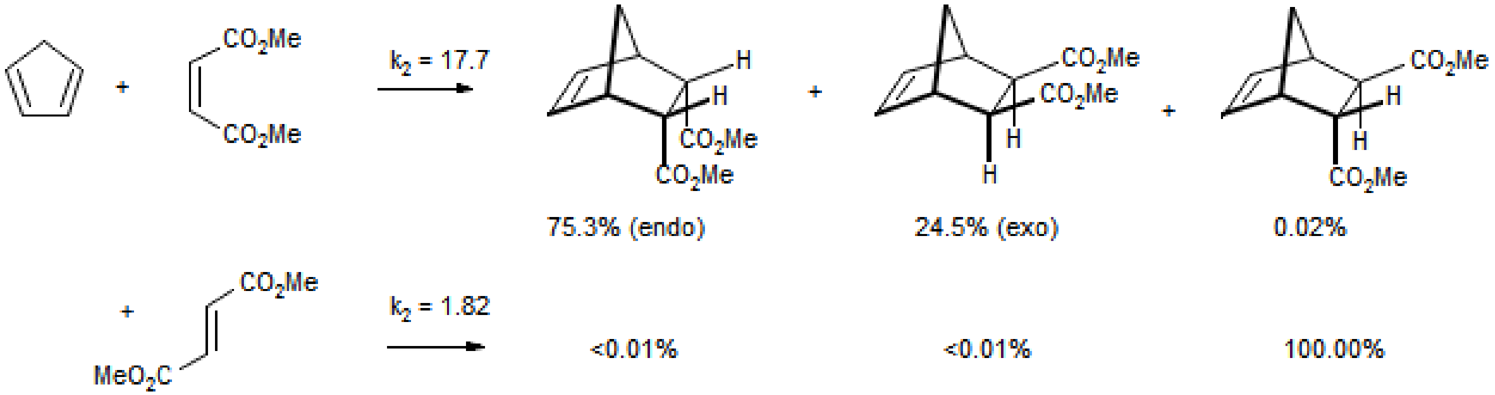
These two substituents will be cis in the product

These two substituents will be cis in the product

These two substituents will be cis in the product

The endo (dienophile) and trans (diene) substituents will be cis to each other

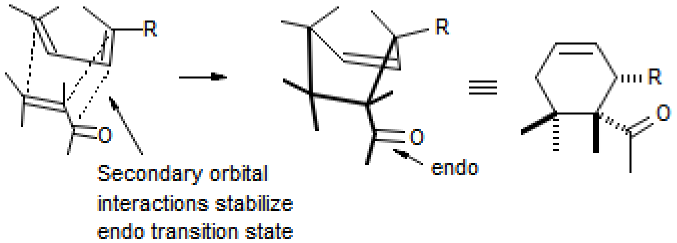
Tetrahedron Lett. **1982**, *23*, 1139

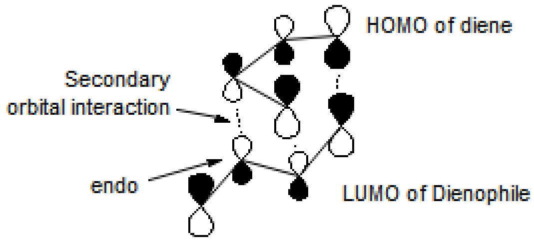


suprafacial

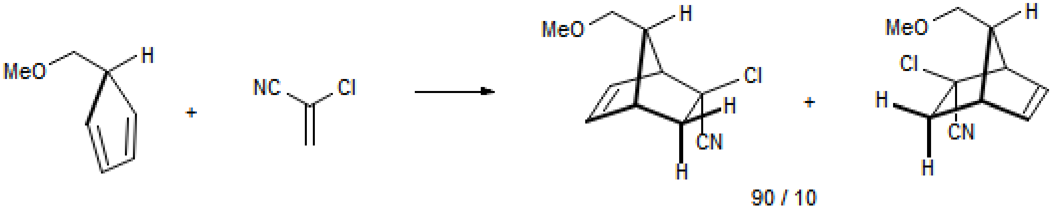
Stereoselectivity

The Alder Endo Rule: the unsaturated substituent on the dienophile generally prefers the endo position in the transition state. Since this is usually the more sterically crowded isomer, Diels-Alder reactions can show different endo/exo ratios under conditions of kinetic and thermodynamic control. The endo-selectivity is not usually very large, with values between 4:1 and 10:1 being common



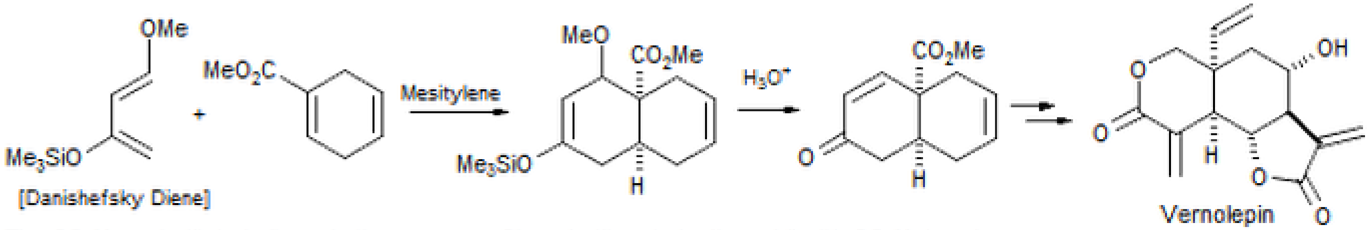


Facial Selectivity: If the diene or dienophile does not have planar symmetry, then there may be substantial face-selectivity in Diels-Alder reactions resulting from combinations of steric and electronic effects.Intermediate in prostaglandin synthesis: Corey, E. J. *J. Am. Chem. Soc.* **1969**, *91*, 5675.



Stereospecificity in Dienophile:

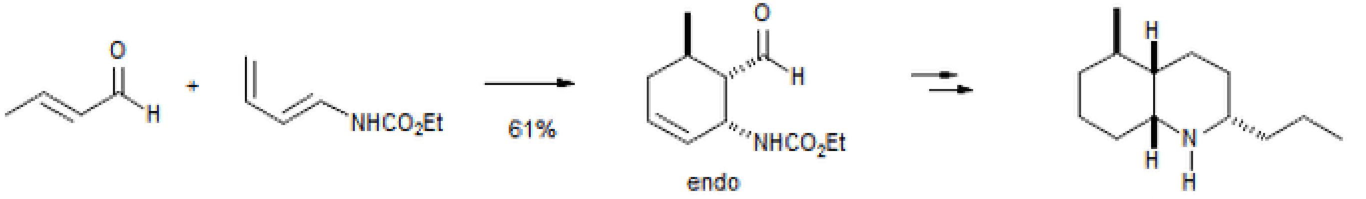
Vernolepin: Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 302



The CO$_2$Me-substituted alkene is the more reactive dienophile.

Cis-substituents in dienophile (H, CO$_2$Me) end up as cis substituents in cyclohexene adduct

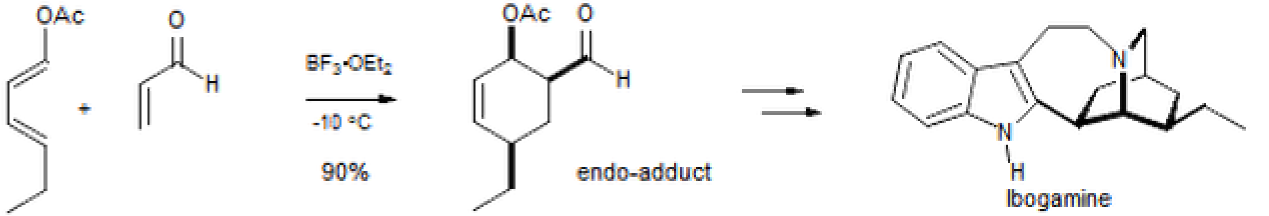
Pumiliotoxin: Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179



The *trans* relationship between the Me and CHO groups is a result of the stereospecificity of cycloaddition - these groups were *trans* in the dienophile. The *cis* relationship between the CHO and NHCO$_2$Et is the result of the Alder endo-rule.

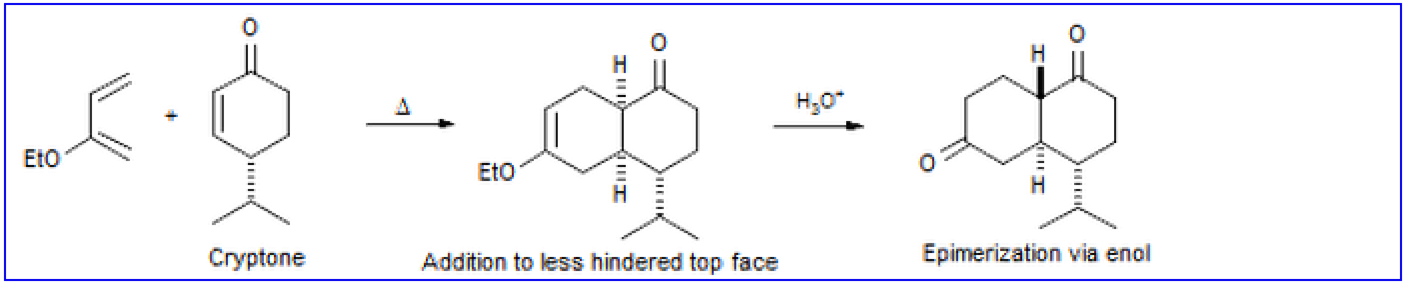
Stereospecificity in Diene:

Ibogamine: Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.*, **1978**, *100*, 3930.

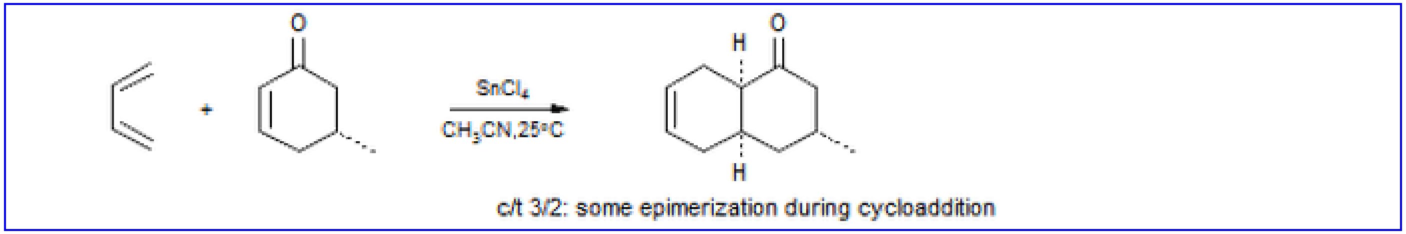


Facial Selectivity in Dienophile

Cadinene Dihydrochloride: Soffer, M. D.; Gunay, G. E.; Korman, O.; Adams, M. B. *Tetrahedron Lett.* **196**

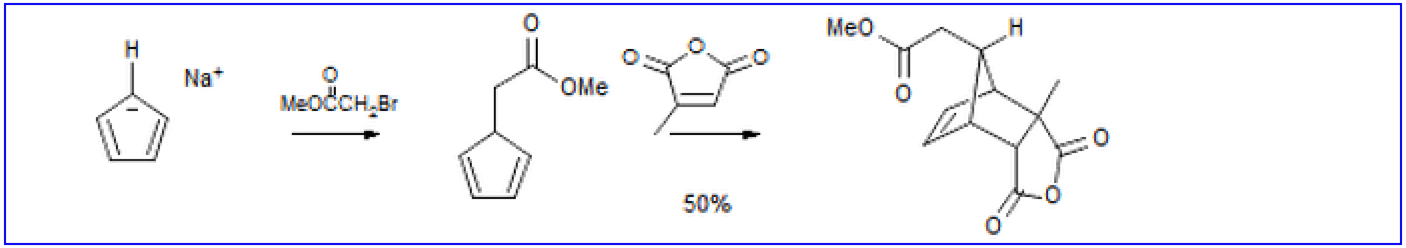


Luciduline: Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc*, **1976**, *98*, 6722

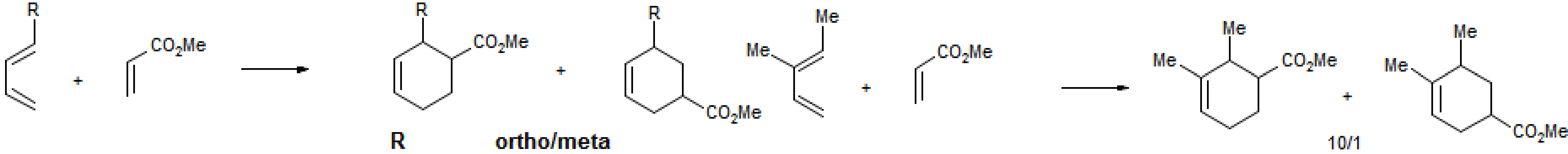


Facial Selectivity in Diene

Elenolate, Methyl: Kelly. R. C.; Schletter, I. *J. Am. Chem. Soc.* **1973**, *95*, 7156

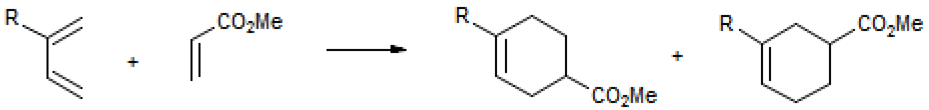


Regioselectivity

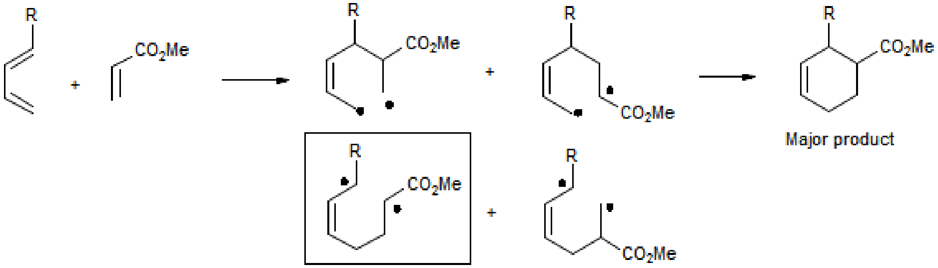


R	ortho/meta
Me	6.7/1
Ph	39/1
CN	"only" ortho
OMe	"only" ortho
NMe$_2$	"only" ortho

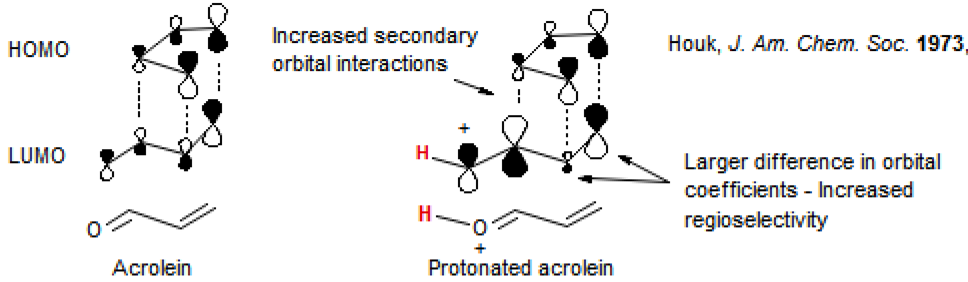
1-substituents generally have a larger directing effect than 2-substituents.



R	para/meta	
Me	2/1	
CH$_2$SiMe$_3$	5.3/1	TL-80-355
CH$_2$SnMe$_3$	10.1/1	TL-80-355
Ph	4.5/1	
Cl	8.3/1	
OMe	8/1	



Lewis Acid Catalysis

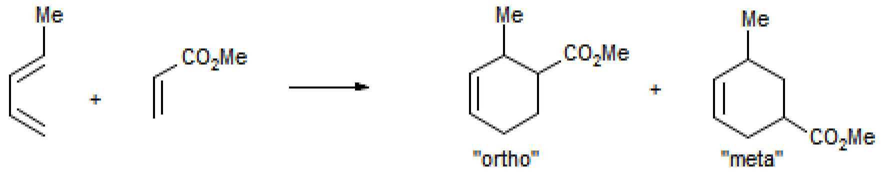


Increased secondary orbital interactions

Larger difference in orbital coefficients - Increased regioselectivity

Houk, *J. Am. Chem. Soc.* **1973**, *95*, 4094

Regioselectivity:

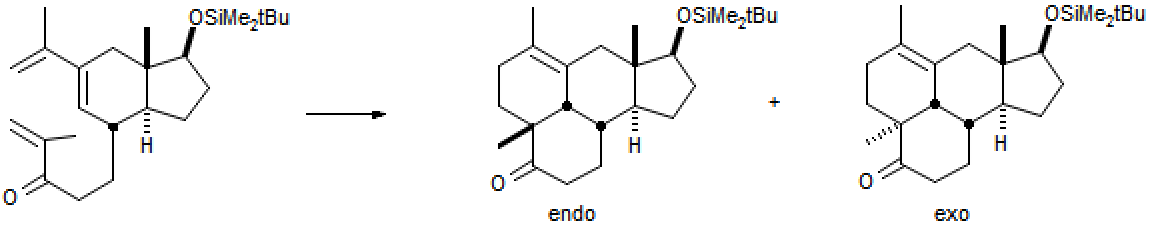


Thermal	90 / 10
$AlCl_3$ catalyzed	98 / 2

Exo-endo ratio:

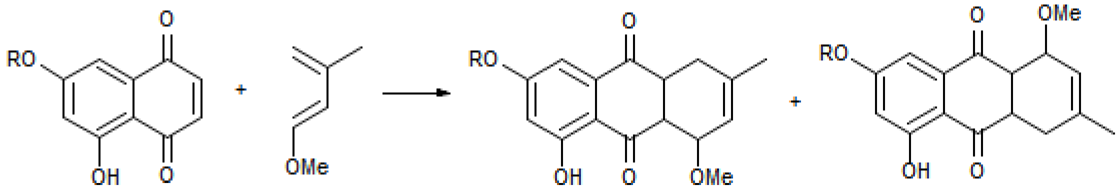
Thermal	82/18
$AlCl_3$ catalyzed	99 / 1

Steroid synthesis: Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1881**, *103*, 4948



Thermal (70 °C)	60 / 40	
CF_3CO_2H, -78 °C	96 / 4	70% yield

Changes in regioselectivity: "Lewis Acid-Catalyzed Diels-Alder Reactions of peri-Hydroxylated Naphthoquinones: A Regiochemical Divergence" Kelly, T. R.; Montury, M. Tetrahedron Lett. 1978, 19, 4311



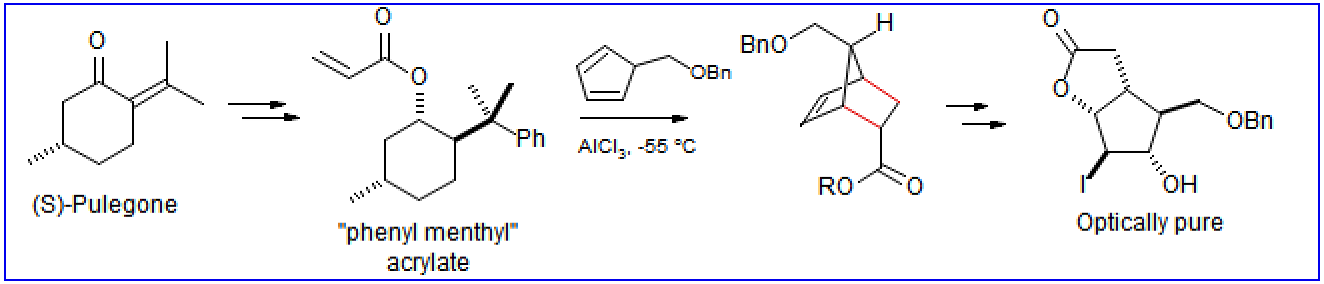
These changes in regiochemistry are not really understood mechanistically

R = Me	Thermal (25 °C)	40 / 60
R = Me	MgI_2, 0 °C	<5 / >95
R = H	Thermal (25 °C)	45 / 55
R = H	$B(OAc)_3$ or $BF_3 \cdot OEt_2$, 0 °C	>95 / <5

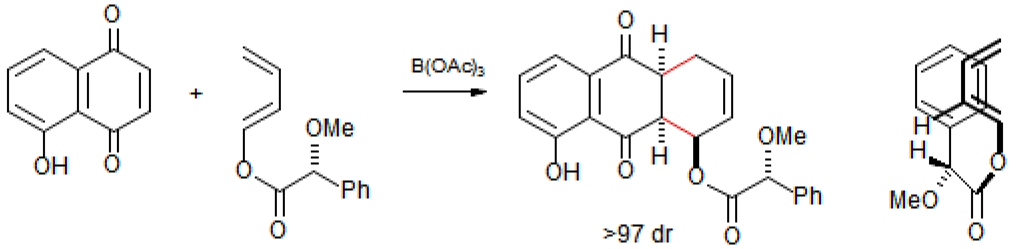
The Asymmetric Diels-Alder Reaction

Diels-Alder Chiral Auxiliaries

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



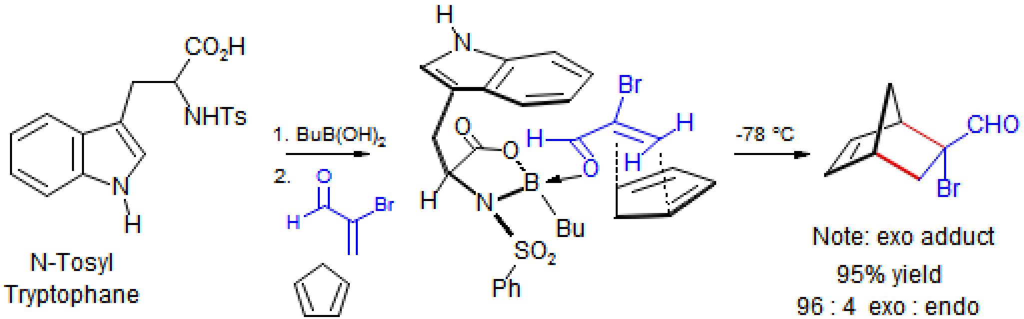
Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.



π-Stacking model -
dienophile approaches
from the top

Asymmetric Catalysis in Diels Alder Reactions

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



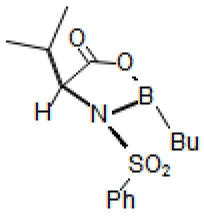
N-Tosyl Tryptophane

5 mol% catalyst

Note: exo adduct

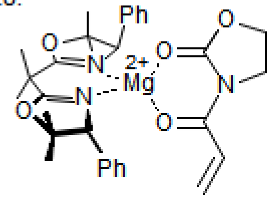
95% yield

96 : 4 exo : endo
200 : 1 R : S



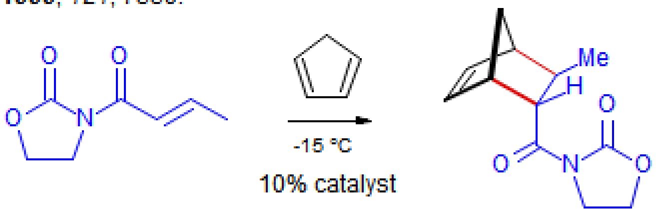
Gave **opposite** enantiomer, 70% ee thus postulate π-stacking interaction

Magnesium complex: Corey, E. J.; Ishihara, K. *Tet. Lett.*, **1992**, *33*, 6807. Similar Fe complex: Corey, *JACS*, **1991**, *113*, 728.



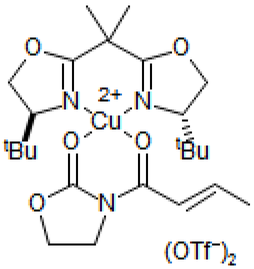
10% catalyst
Cyclopentadiene
92% ee
97/3 endo/exo
82% yield

The cupric salts are square planar, and give the opposite enantiomer: Evans, Miller, Lectka, von Matt *J. Am. Chem. Soc.* **1999**, *121*, 7559.



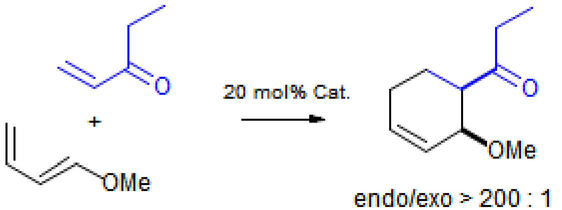
10% catalyst

97% ee
96/4 endo/exo



Chiral Organocatalysis of Diels-Alder Reactions

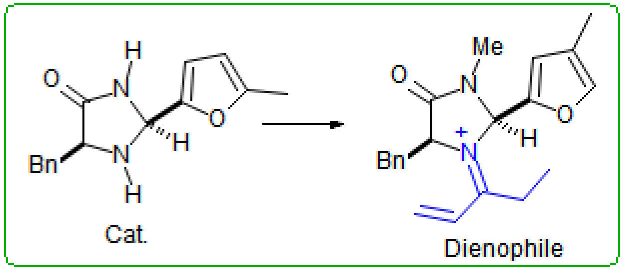
Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.



endo/exo > 200 : 1

88% yield

96% ee

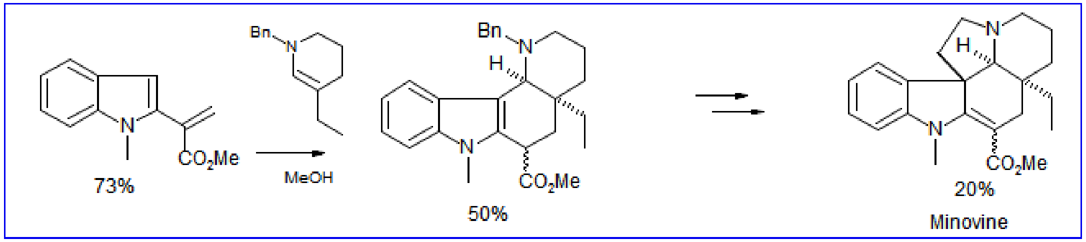


- Methyl and isopropyl ketones as well as cyclopentenone and cyclohexenone worked poorly
- Variety of dienes worked well
- Reactions can be run in aqueous or ethanolic media

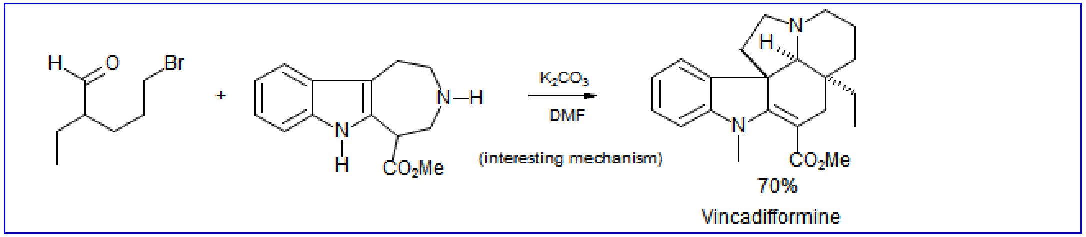
Inverse Electron Demand Diels-Alder Reactions

Minovine: Ziegler, F. E.; Spitzner, E. B.. *J. Am. Chem. Soc.* **1973**, *95*, 7146

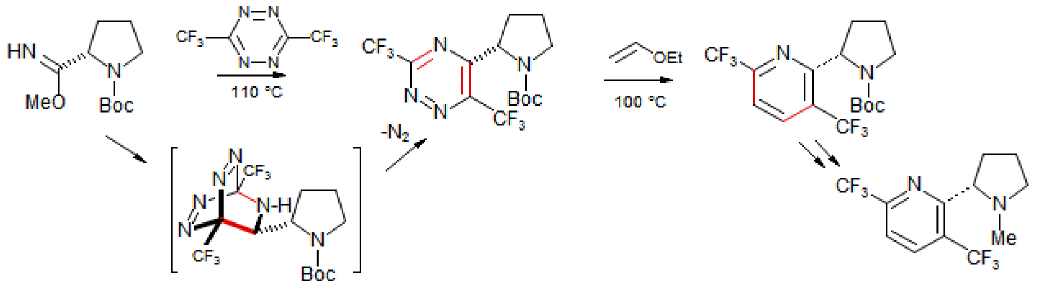
Minovine: Ziegler, F. E.; Spitzner, E. B.. *J. Am. Chem. Soc.* **1973**, *95*, 7146



Vincadifformine: Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705



Synthesis of a nicotine analog: Che, Siegl, Seitz *Tetrahedron Assym.* **1999**, 573.

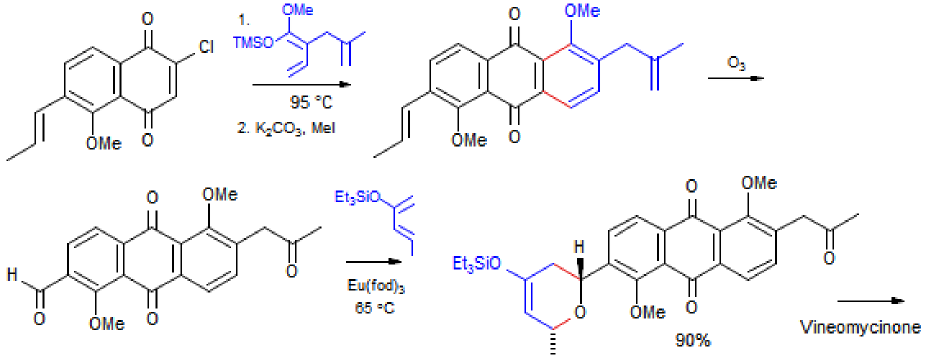


Nicotine Analog

Heterodienophiles and Heterodienes

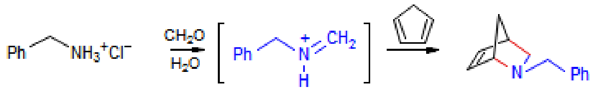
Aldehyde as dienophile:

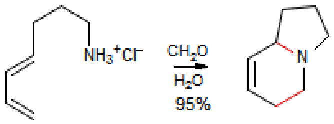
Danishefsky, JACS, ***1985****, 107, 1285*

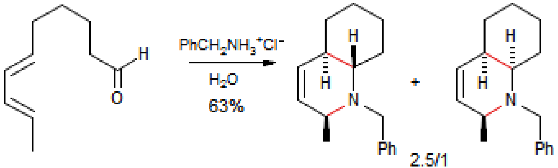


Iminium Salt Cycloaddition.

Grieco, J. Am. Chem. Soc., ***1985****, 107, 1768.*







Aldehydes work, but ketones don't.

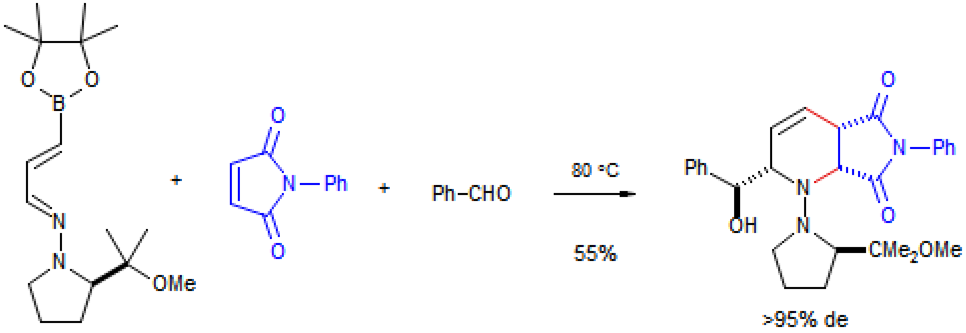
Azadiene

Tailor, Hall Org. Lett. ***2000****, 2, 3715*

Heterodienophiles and Heterodienes

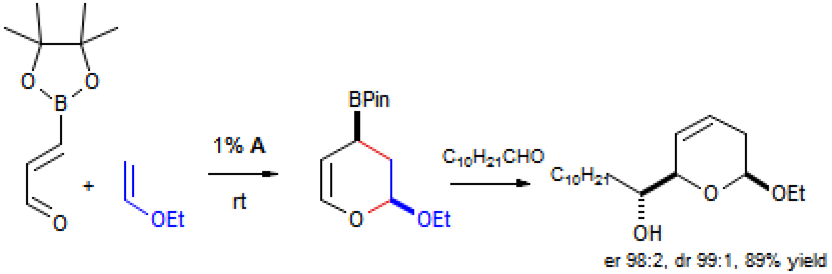
Azadiene

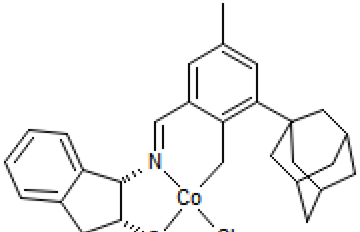
Tailor, Hall Org. Lett. ***2000****, 2, 3715*



Sequential Inverse Electron Demand Diels-Alder - Allylboration

Gao, X.; Hall, D. G. J. Am. Chem. Soc. ***2003****, 125, 9308-9309*

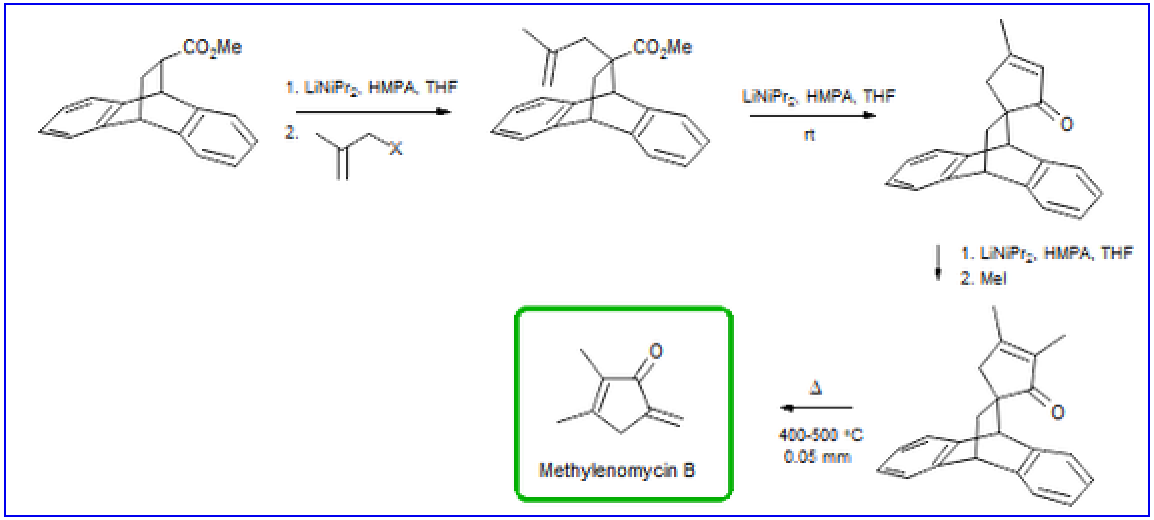




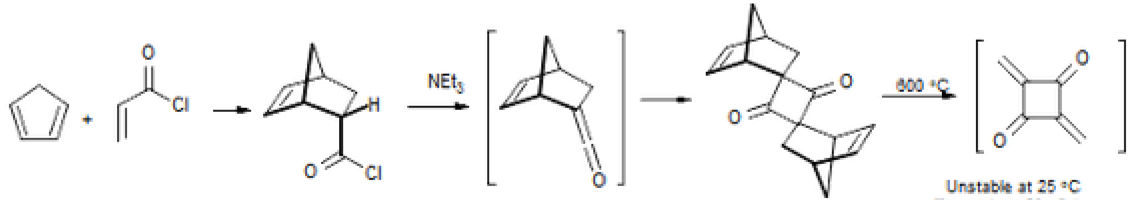
A

Retro-Diels-Alder Reactions

Methylenomycin B: Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598.



1,3-Bismethylene-1,3-cyclobutanedione: Ripol, J. -L.; Lasne, M. -C. *Tetrahedron Lett.* **1978**, 5201



Unstable at 25 °C
Trapped at -50 °C by
2,3-dimethylbutadiene as
bis-adduct

advantages

- potentially set four stereocenters in one step
- highly regioselective and stereospecific – unsymmetric synthesis:E-alkene→Trans; Z-alkene→Cis
- predominantly the “ortho” and “para” products over the “meta” product:
- stereochemical information (E or Z) in the diene is also transferred to the product
- the predominant product is the endo cycloadduct
- appropriate chiral catalysts
- multiple rings can be created in one step with defined stereochemistry