

Intramolecular Diels-Alder Reactions

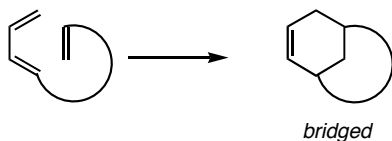
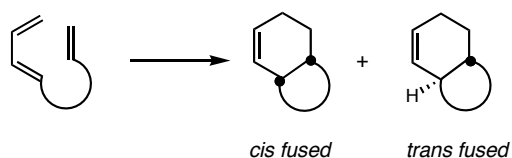
Rebecca Wilson
MacMillan Group Meeting
January 24, 2001

- I. Introduction
- II. Simple Diastereoselectivity
- III. Transfer of Stereochemistry
- IV. Heteroatoms
- V. Removable Tethers
- VI. Chiral Auxiliaries
- VII. Enantioselective Catalysis

Introduction: Intramolecular Diels Alder

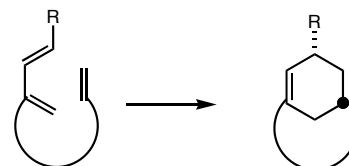
Type I vs. Type II

Type I: Tether is attached at 4- position of diene.



- Bridged products rarely observed (tether must be >9 atoms).
- Fused products usually have 3 or 4 atom tethers

Type II: Tether is attached at 3- position of diene.

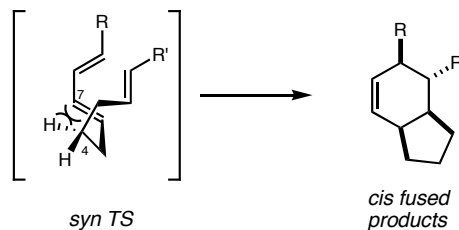
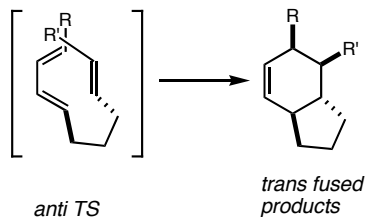


- Type II IMDA's always cyclize to syn product.
- References for Type II IMDA:

Shea, KJ *Tetrahedron Lett.* **1994**, 35, 7311.
Shea, KJ *J. Am. Chem. Soc.* **1988**, 110, 860.

Syn vs. Anti Transition State

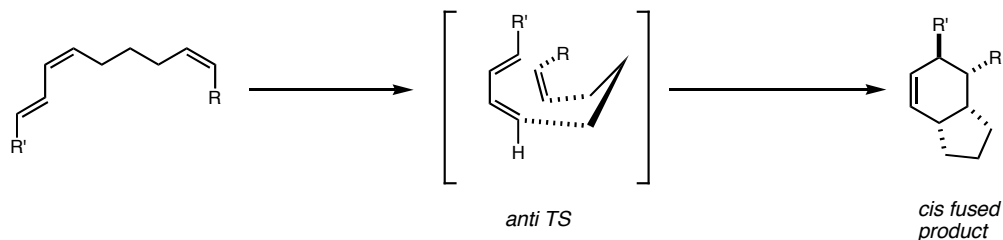
Representative Transition States for *E*- diene



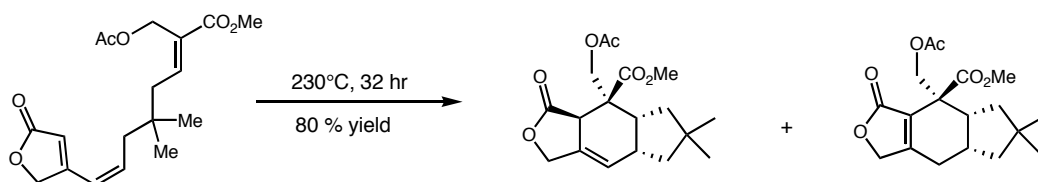
- With *E*- diene, *anti* TS is sterically favored. *Syn* TS experiences nonbonding interactions between C4-C7.
- A combination of steric and electronic factors determine IMDA stereochemistry.

Diastereoselectivity in the IMDA: Z - Dienes

Representative Transition State for Z-Diene.



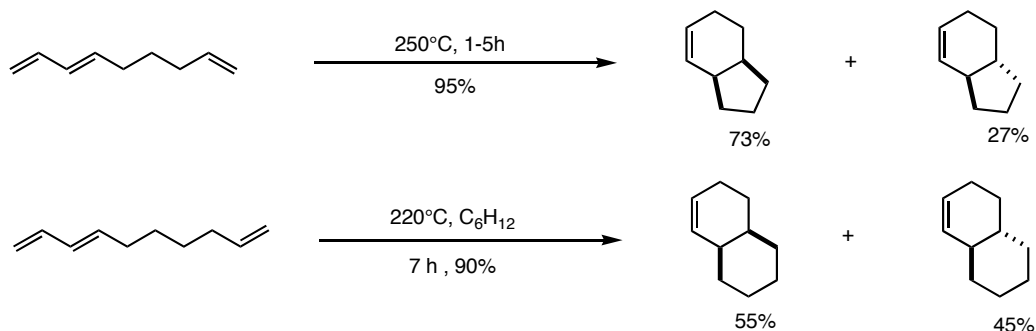
- Regardless of the length or nature of the tether, Z - dienes always cyclize to give cis- fused products



- Due to steric congestion, Z - dienes often cyclize more slowly than E - dienes.

Boeckman, RK *J. Am. Chem. Soc.* **1982**, 104, 3216.

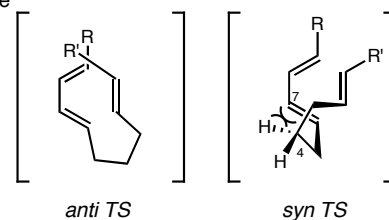
Diastereoselectivity in the IMDA: Unactivated trienes



- In both nonatriene and decatriene systems, there is a some preference for *cis* fused cycloadducts
- Product ratios can be enhanced or reversed through the use of substituents on the triene

Concept of Asynchronous Transition State and Twist Asynchronicity

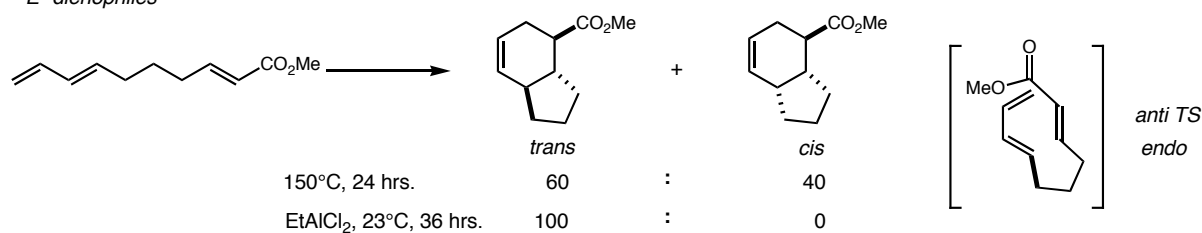
- Although the IMDA is concerted, bond formation is asynchronous in the transition state
- Internal bond formation is more advanced in the TS \Rightarrow *anti* TS, *trans* product
- External bond formation is more advanced in the TS \Rightarrow *syn* TS, *cis* product
- Effects of asynchronicity are less pronounced for decatriene systems



Diastereoselectivity in the IMDA

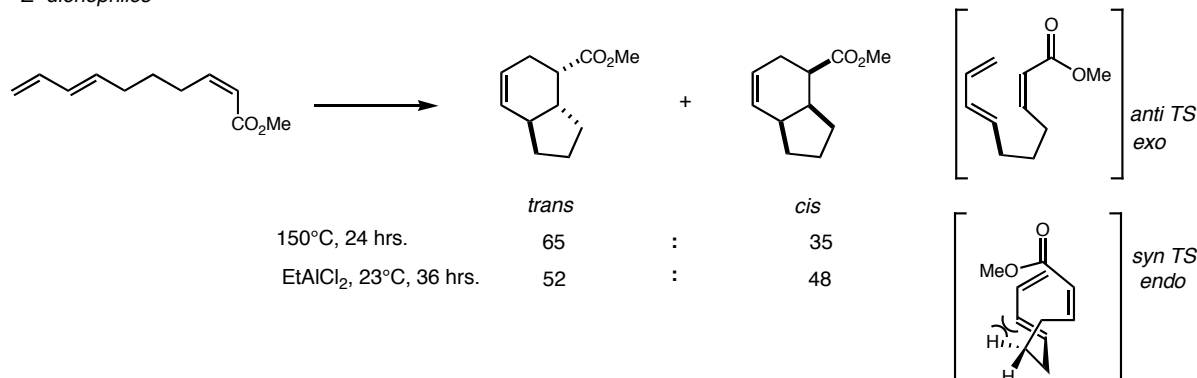
Terminally Activated Dienophiles- [4.3.0] Bicycles

E-dienophiles



■ *Trans* product is favored sterically and electronically with terminally activated *E*-dienophiles.

Z-dienophiles



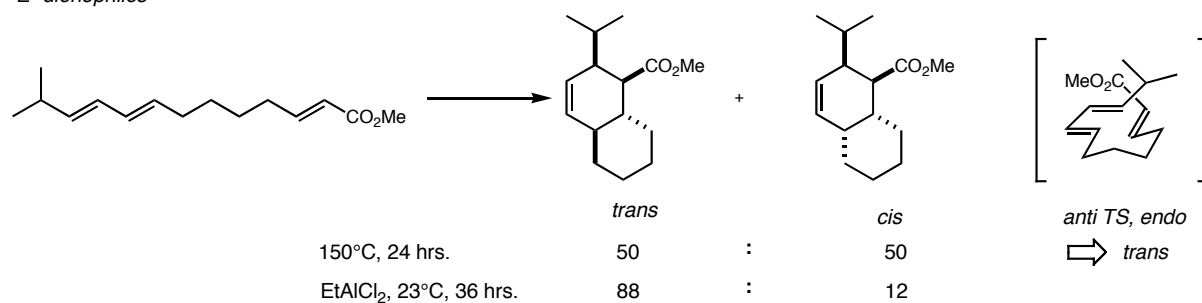
■ *Trans* product is favored sterically and *cis* product is favored electronically with terminally activated *Z*-dienophiles.

Roush, WR *J. Am. Chem. Soc.* **1982**, 104, 2269

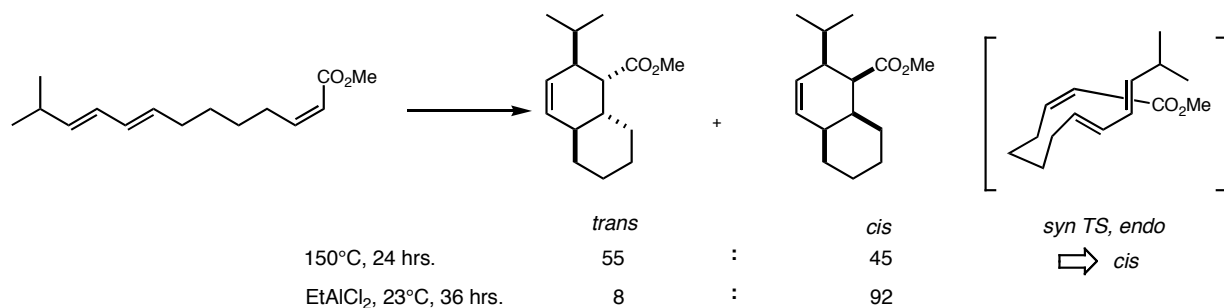
Diastereoselectivity in the IMDA

Terminally Activated Dienophiles- [4.4.0] Bicycles

E-dienophiles



Z-dienophiles

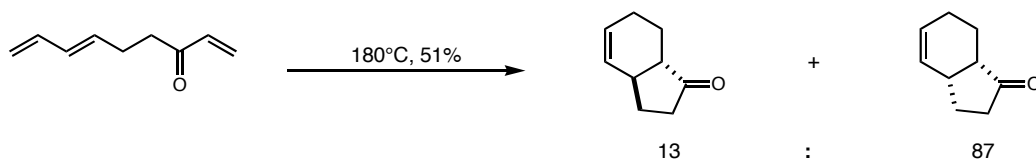


■ Lewis Acid- promoted terminally activated [6.4.0] IMDA's give endo product.

Roush, W.R. *J. Org. Chem.*, **1982**, 47, 4825.

Diastereoselectivity in the IMDA

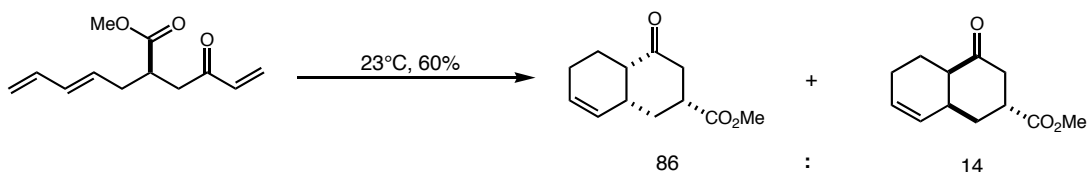
Internally Activated Dienophiles- [4.3.0] Bicycles



- Unless other steric factors intervene, internally activated trienes give cis-fused products.

Roush, W.R. *J. Am. Chem. Soc.* **1981**, *103*, 6896

Internally Activated Dienophiles- [4.4.0] Bicycles: Carbonyl Coplanarity Effect

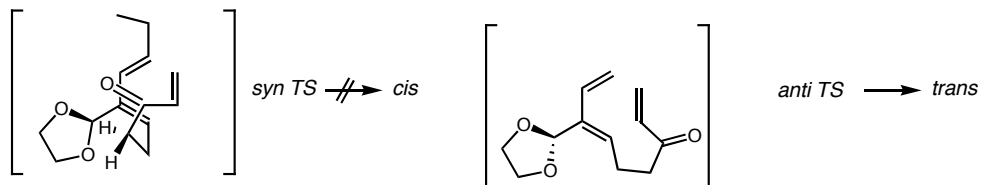
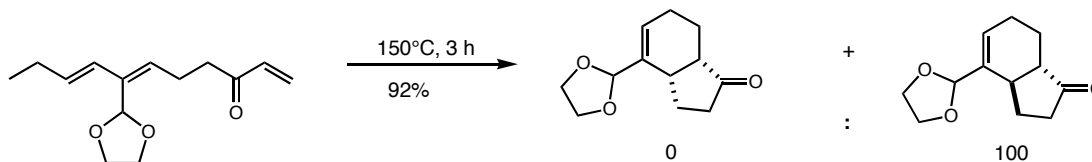


- Decatrienes with internal carbonyls adjacent to dienophile cyclize through boat TS to give cis-fused products.

Zschiesche, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1086.

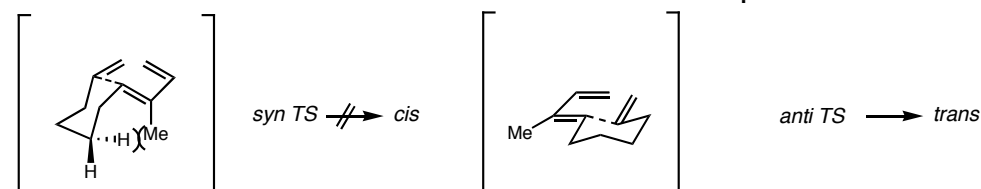
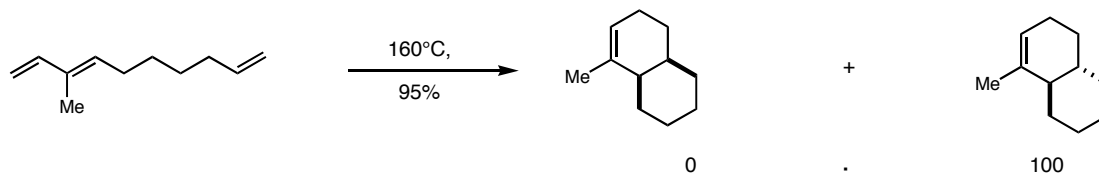
Diastereoselectivity in the IMDA

Internally Substituted Dienes- [4.3.0] Bicycles



Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353.

Internally Substituted Dienes- [4.4.0] Bicycles

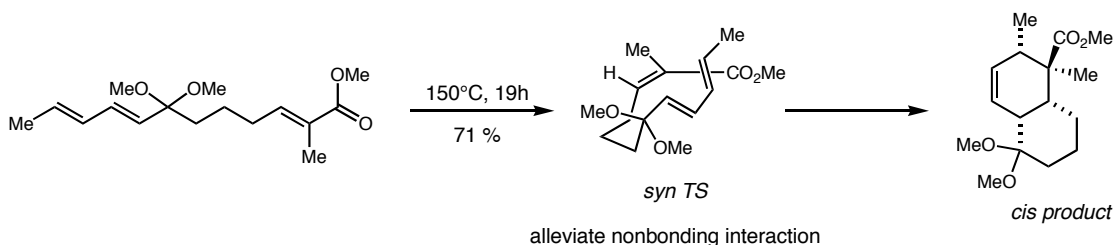
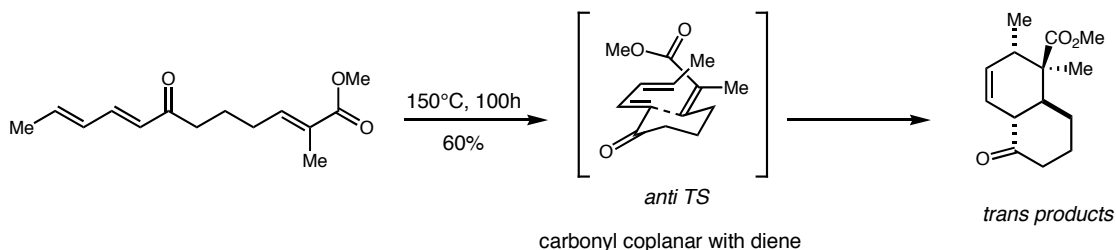


- Internally substituted dienes give trans fused products for steric reasons.

Wilson, S.R. *J. Am. Chem. Soc.* **1978**, *100*, 6289

Diastereoselectivity in the IMDA

Substitution adjacent to diene- [4.4.0] Bicycles



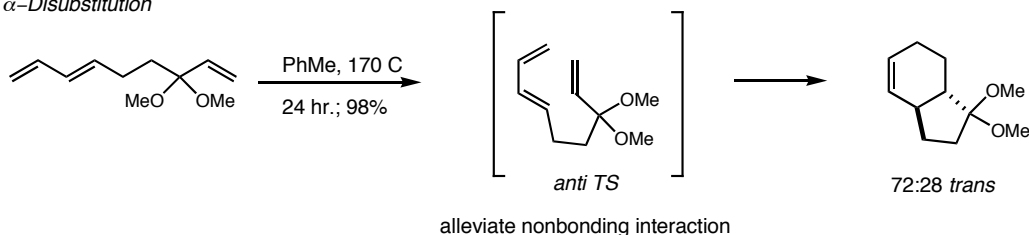
- If oxygenation is desired adjacent to diene, alter product stereochemistry by choosing between ketal and ketone.

Roush, WR *J. Am. Chem. Soc.* **1981**, 103, 5200.

Diastereoselectivity in the IMDA

Disubstitution on tether- [4.3.0] Bicycles

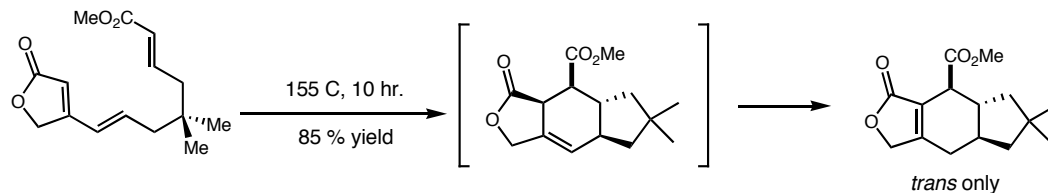
α-Disubstitution



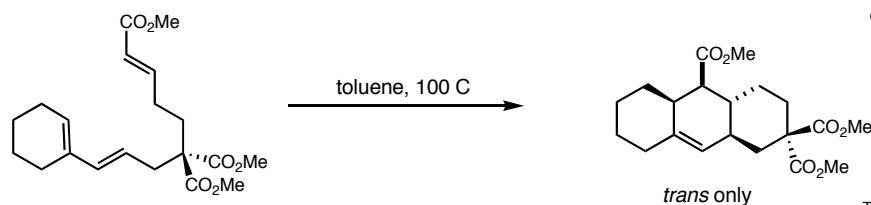
- Nonbonding interactions in syn TS give predominantly trans product

Jung, M.E. *Tetrahedron Lett.* **1981**, 22, 3929.

β-Disubstitution



Dialkyl Substitution on tether- [4.4.0] Bicycles



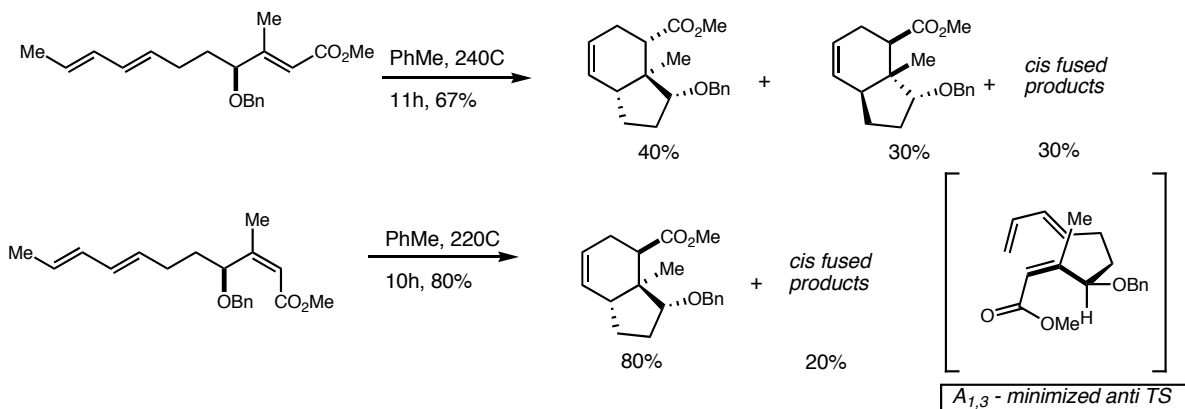
Oppolzer W. *Helv. Chim. Acta.* **1981**, 64, 2002.

- Thorpe-Ingold effect: Dialkyl Substitution gives enhanced reaction rates. IMDA products usually trans.

Trost, B.M.
J. Am. Chem. Soc.
1985, 106,
 7641.

Relay of Stereochemistry in the IMDA

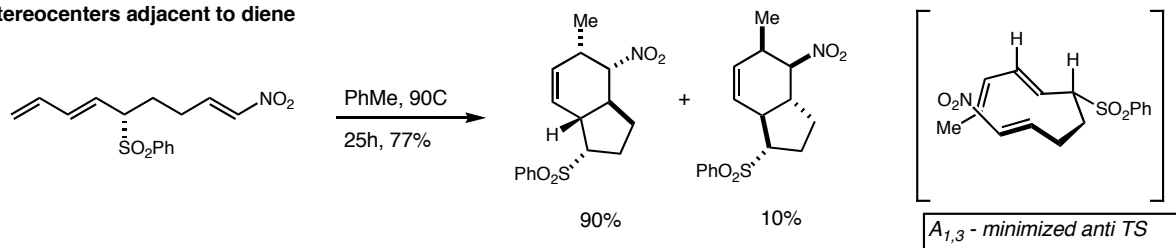
Stereocenters adjacent to dienophile



- Allylic strain dictates orientation of tether. Z-Dienophile experiences $A_{1,3}$ strain---products obtained with good diastereocontrol

Roush, WR *J. Am Chem. Soc.* **1981**, *103*, 6696.

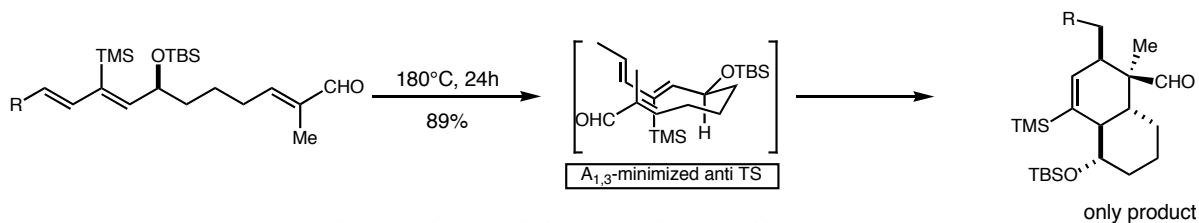
Stereocenters adjacent to diene



Oppolzer, W. *Helv. Chim. Acta* **1975**, *587*.

Relay of Stereochemistry in the IMDA

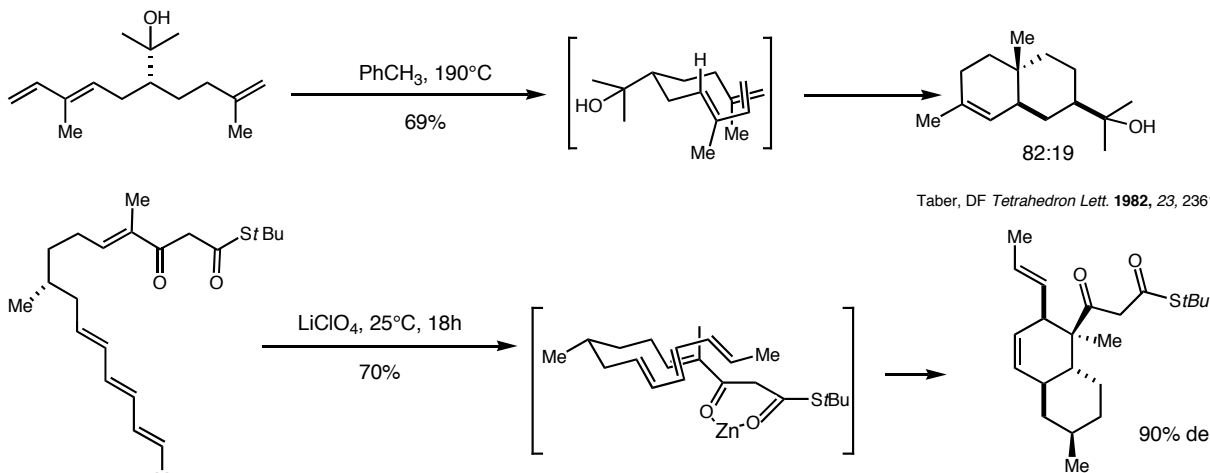
Stereocenters adjacent to diene: [4.4.0]



- Minimize $A_{1,3}$ strain in both syn and anti transition states

Boeckman, RK *J. Org. Chem.* **1985**, *50*, 3241.

Nonallylic tether stereocenters: [4.4.0]



Taber, DF *Tetrahedron Lett.* **1982**, *23*, 2361.

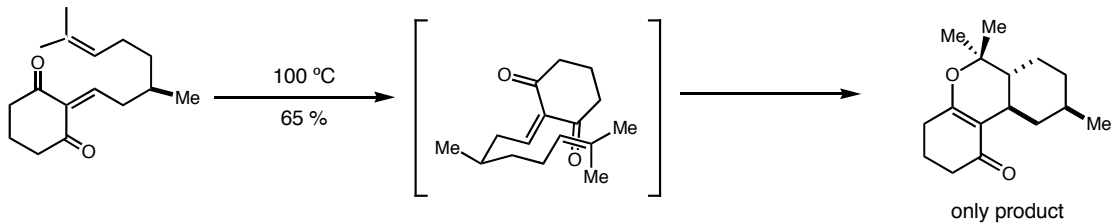
Dixon, D.J. *Org. Lett.* **2000**, *2*, 3611.

- Place stereocenter equatorial in chair transition state when not in conjugation

Heteroatoms in Diene

- Most substrates with diene heteroatoms cyclize according to the same rules of diastereoselectivity as all-carbon dienes.

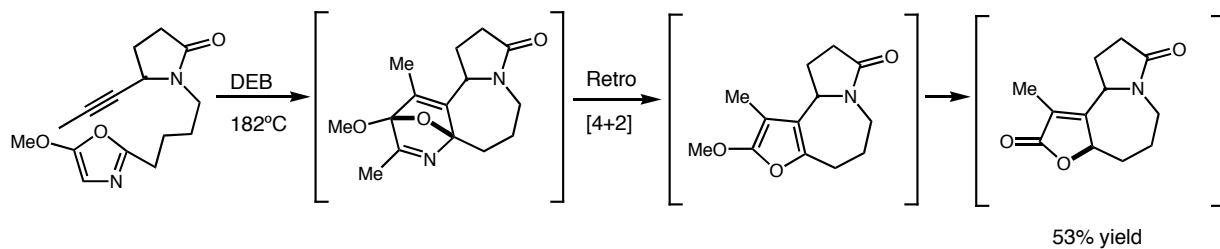
Enone Diene



- substituent in 3-position of diene promotes *anti* TS
- stereocenter placed equatorial in chair-like TS

Jung, ME *J. Org. Chem.* **1982**, 47, 1084

Oxazole Diene- Total Synthesis of (-)-Stemoamide



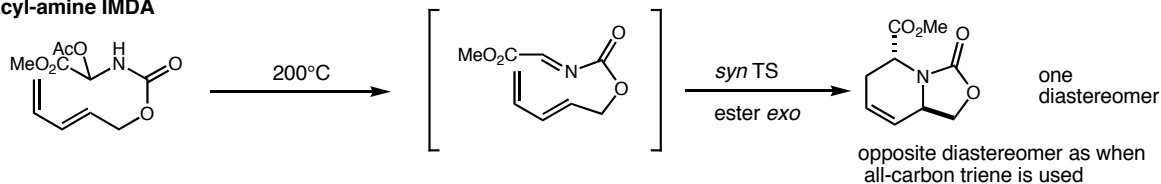
- Oxazoles are very reactive dienes. Retro [4+2]- eliminate MeCN and form furan

Jacobi, P.A. *J. Am. Chem. Soc.* **2000**, 122, 4295.

Heteroatoms in Dienophile

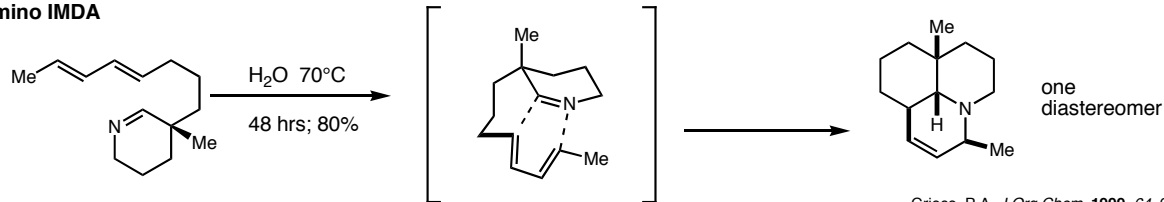
- Substrates with dienophile heteroatoms often have different electronic properties than all-carbon dienophiles. This can have large effects on stereoselectivity of IMDA

Acyl-amine IMDA



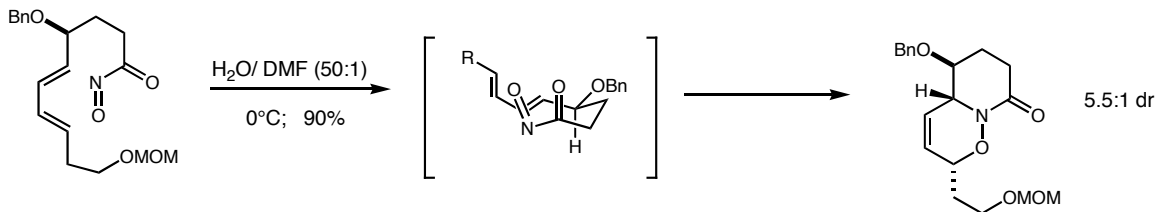
Weinreb, SM *J. Am. Chem. Soc.* **1981**, 103, 7573

Imino IMDA



Grieco, P.A. *J. Org. Chem.* **1999**, 64, 6041-8.

Acylnitroso IMDA



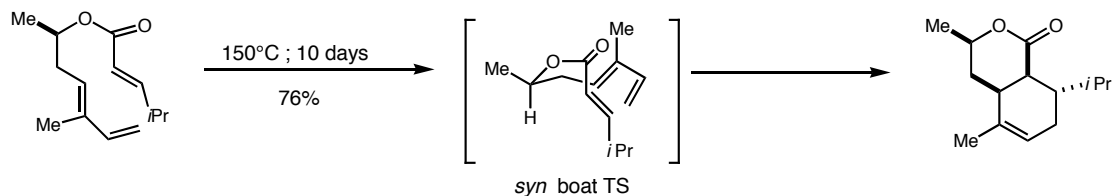
Kibayashi, C. *Org. Lett.* **2000**, 19, 2955-8.

Heteroatoms in Tether- Esters

Amines, ethers, and thioethers in the linker:

- Usually react to produce IMDA adducts with stereoselectivities similar to those seen in all-carbon tethers.

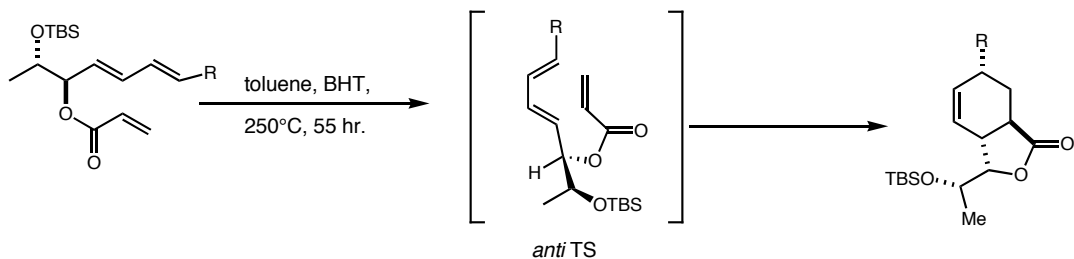
Ester conjugated to dienophile: [4.4.0]



- Carbonyl coplanarity effect: Ester reacts through boat TS to give [4.4.0] bicycles

Jung, M.E. *Org. Lett.* **2000**, *2*, 1835-7.
Kurth, M.J. *Org. Lett.* **2000**, *2*, 1831-4.

Ester conjugated to dienophile: [4.3.0]



- Sterically favored *trans* product predominates

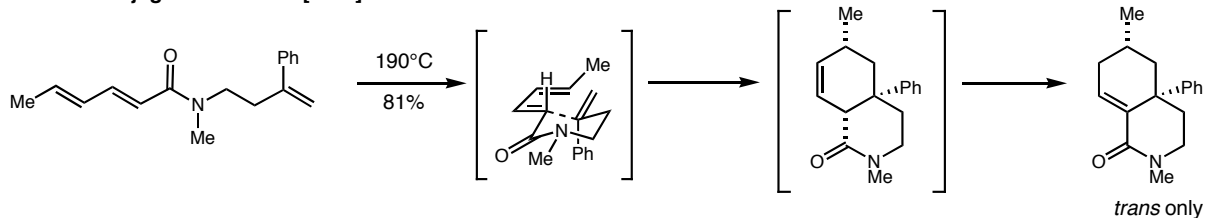
White, J.D. *Org. Lett.* **2000**, *2*, 3313-6

Esters not in conjugation with dienophile:

- Often exhibit low reactivity due to poor overlap of nonbonding ethereal electrons with carbonyl in TS

Heteroatoms in Tether- Amides

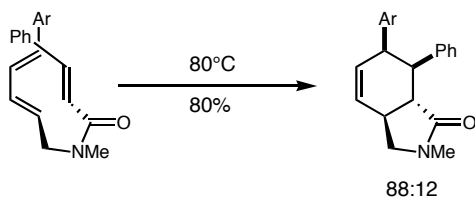
Amide conjugated to diene: [4.4.0]



- Carbonyl coplanarity: Amide reacts through chair TS when in conjugation with diene to give *trans* products
- Diastereoselectivity of IMDA for [4.4.0] Amides varies greatly, depending upon position/ orientation on chain.

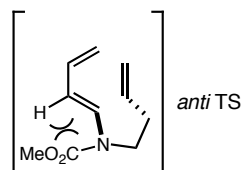
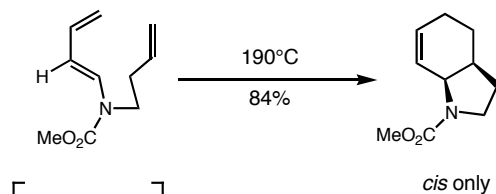
Handa, S. *J. Chem. Soc. Chem. Commun.* **1985**, 1362.

Amide conjugated to dienophile: [4.3.0]



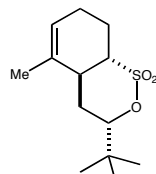
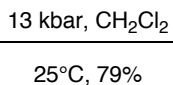
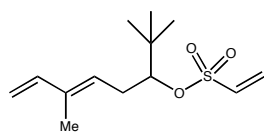
- Sterically favored *trans* product predominates

Amide conjugated to diene: [4.3.0]



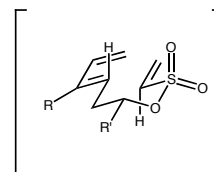
- Ester and C7-H experience eclipsing intrixns in *anti* TS

Removable Tethers for IMDA: Vinyl Sulfonates

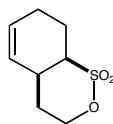
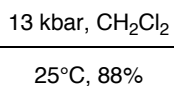
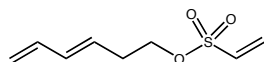


3.6:1 (anti)

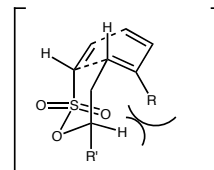
- *anti*-selective because of substitution on 3- position of diene.



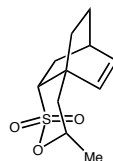
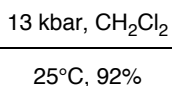
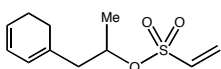
anti TS



2.3: 1 (syn)



syn TS

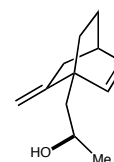
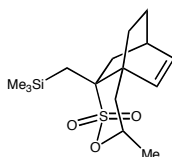
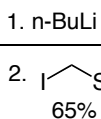
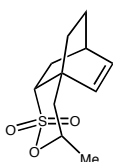


54.6:1 (syn)

- highly *syn*-selective because bridgehead methylenes experience nonbonding interactions in *anti* TS.

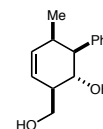
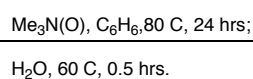
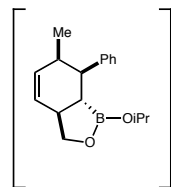
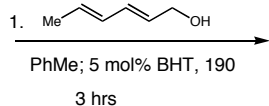
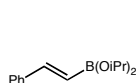
Metz, P. *Tetrahedron* **2000**, *56*, 873-9.
Metz, P. *Tetrahedron Lett.* **1996**, *22*, 3841-4.

Removal of sulfonate tether:



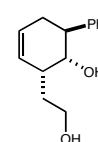
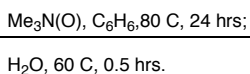
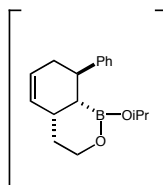
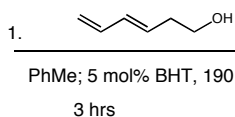
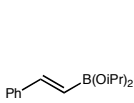
Removable Tethers for IMDA: Boron

Alkenyl Boronate Tethers (C-B-O)



90:10 (trans:cis)
83% yield

- When three-atom linker is used, *trans* fused product formed

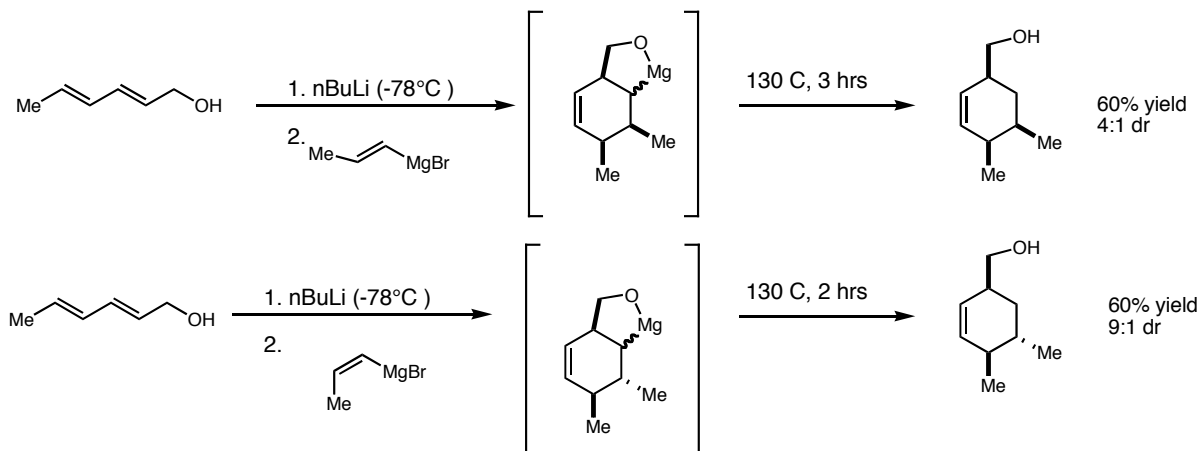


80:20 (cis:trans)
85% yield

- When four-atom linker is used, *cis* fused product formed

Removable Tethers for IMDA: Magnesium and Silicon

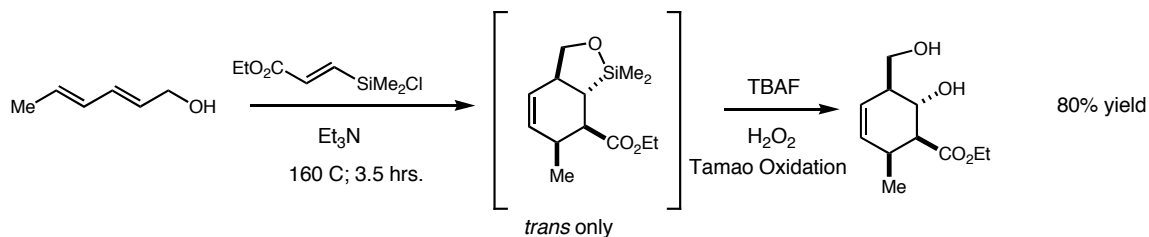
Magnesium Tethers (C-Mg-O)



- Stereochemistry of Diels-Alder adducts dependent upon geometry of vinyl magnesium bromide.

Silicon Tethers (C-Si-O)

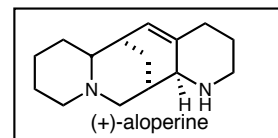
Stork, G. J. *Am. Chem. Soc.* **1995**, *117*, 6595-6.



- IMDA of silyl ethers gives *trans* fused products

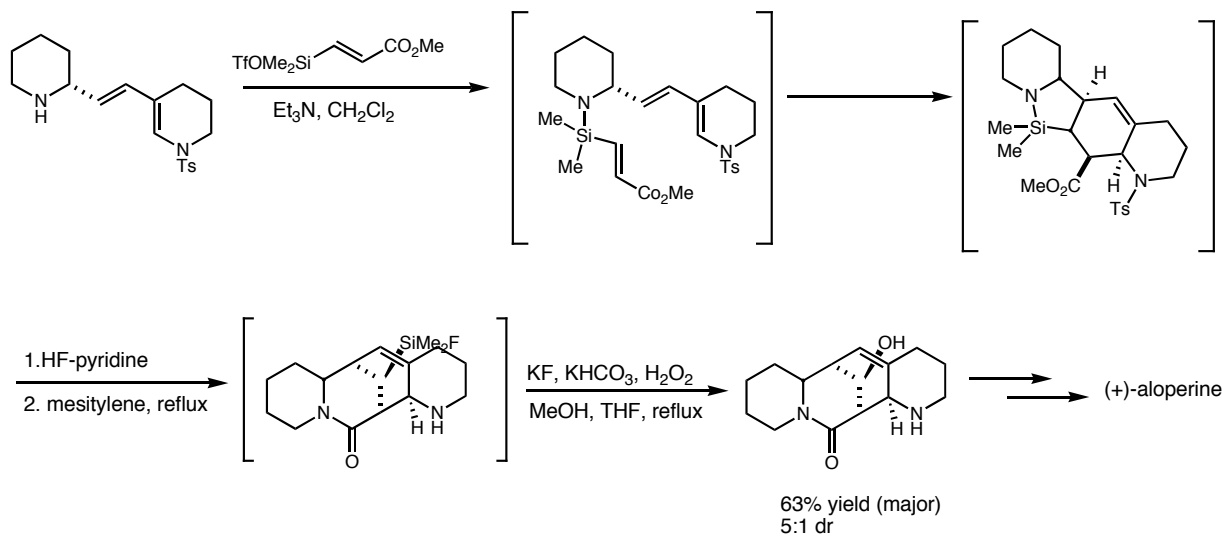
Stork, G. J. *Am. Chem. Soc.* **1992**, *114*, 7578-9.

Removable Tethers for IMDA: Silicon



Silicon Tethers (C-Si-N)

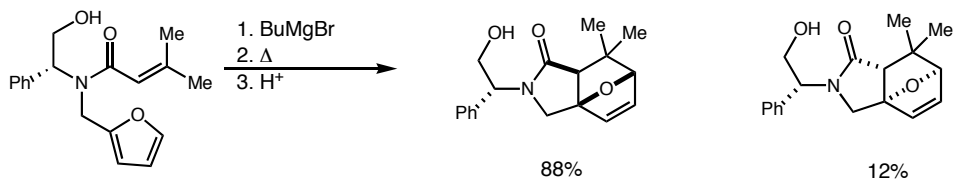
- First example of a diastereoselective nitrogen-silicon tethered IMDA



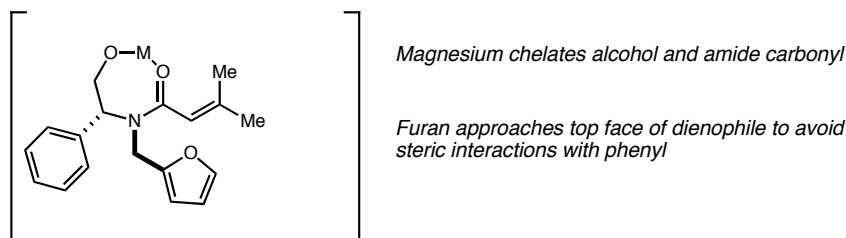
Overman, L.E. *J. Am. Chem. Soc.* **1999**, *121*, 700-9

Internal Chiral Auxiliaries: Chiral Amides

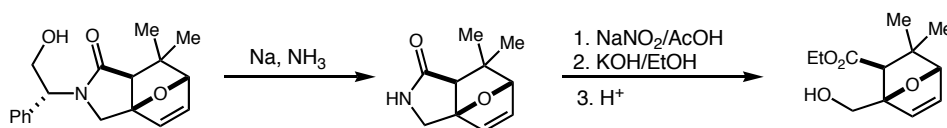
Phenylglycinol-Derived Carboxylic Amides



- Rationale for observed stereoselection:

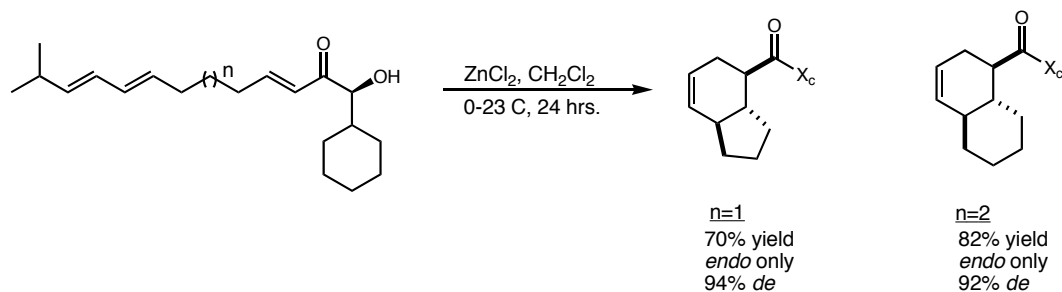


- Removal of Chiral Auxiliary

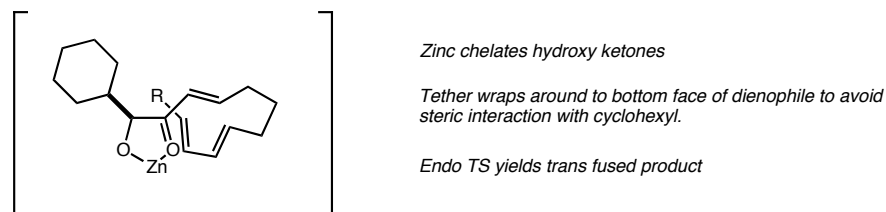


Mukaiyama, T. *Chem. Lett.* **1981**, 29-32.

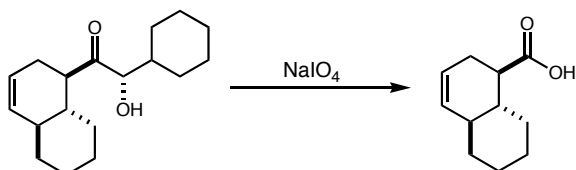
External Chiral Auxiliaries: α -Hydroxy Ketones



- Stereochemical Rationale:

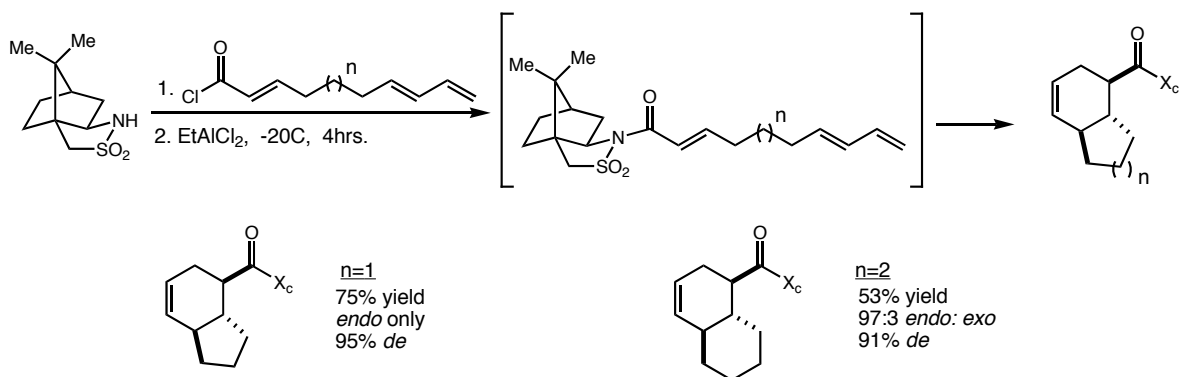


- Drawback of hydroxyketone is the harsh conditions required to remove the auxiliary.

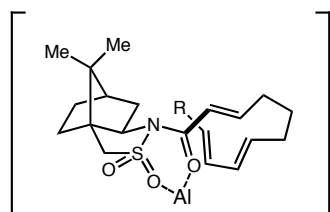


External Chiral Auxiliaries: Acyl Sultams

N-Acyl sultam gives trans-fused (endo) adducts with excellent diastereoselectivity and good yields.



▪ Stereochemical Rationale:



Aluminum chelates sulfonyl and carbonyl.

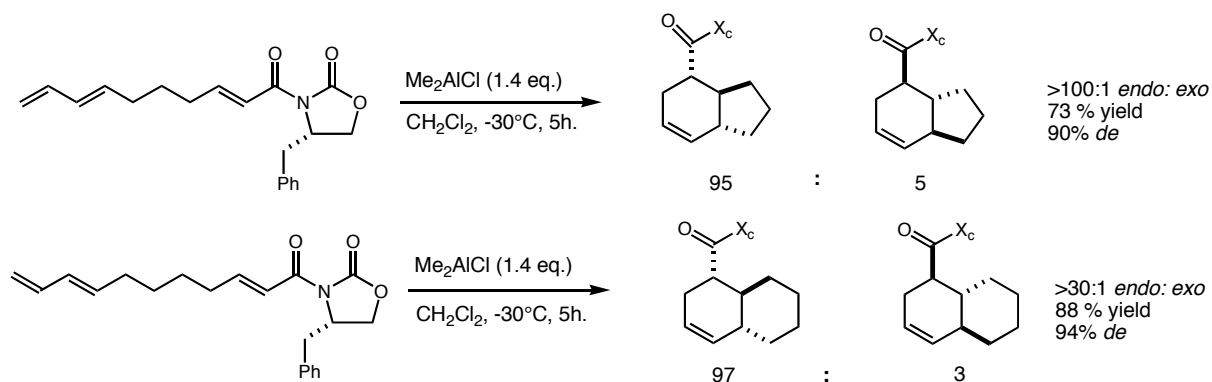
Tether wraps around to bottom face of dienophile to avoid steric interaction with camphor.

Endo TS yields fused product

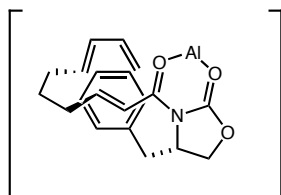
Oppolzer, W. *Tetrahedron Lett.* **1985**, 26, 5437-40.

External Chiral Auxiliaries: Oxazolidinones

Trienes with oxazolidinone auxiliary exhibit high reactivity and endo:exo selectivity



▪ Rationale for observed stereinduction:



Aluminum chelates imide carbonyls.

Pi- stacking interactions believed to exist with phenyl ring and dienophile.

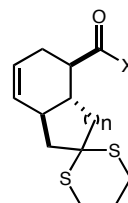
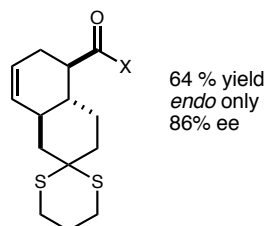
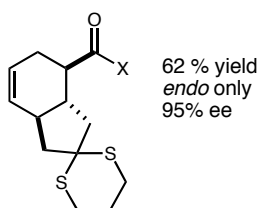
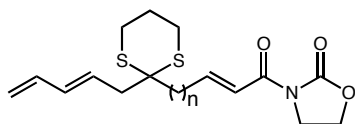
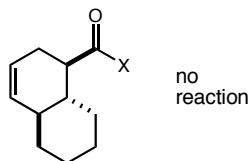
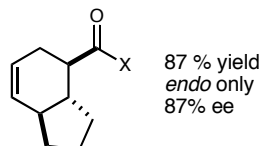
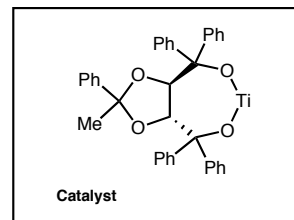
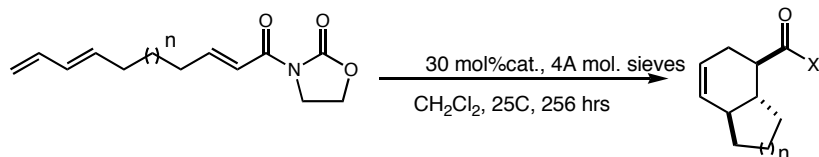
Diene approaches from top face to avoid steric interactions with phenyl

Endo transition state yields trans fused products

Evans, D.A., *Tetrahedron Lett.* **1984**, 25, 4071-4.
Evans, D.A., *J. Am. Chem. Soc.* **1988**, 110, 1238-56.
Evans, D.A., *J. Am. Chem. Soc.* **1984**, 106, 4261-3.

Enantioselective Catalysis: Ti-TADDOL

Narasaka's Titanium TADDOL Catalyst



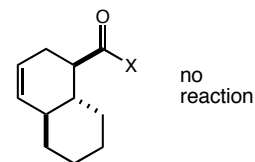
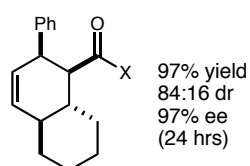
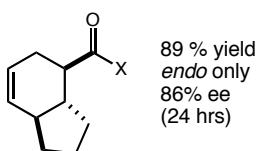
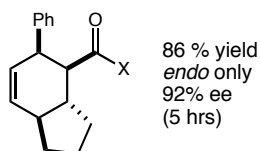
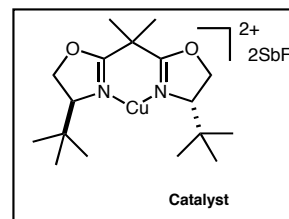
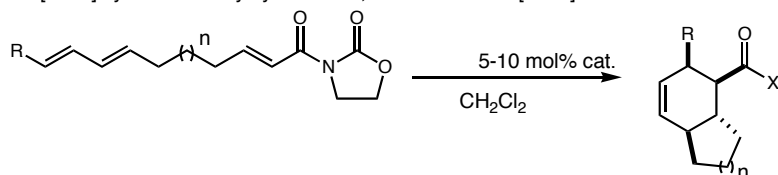
- Moderate reactivity: Geminal dialkyl substituents required for [6.4.0] bicycles.

Narasaka, K. *Chem. Lett.* **1989**, 62, 1947-50
Narasaka, K. *Tetrahedron: Asymm* **1991**, 12, 1305-18.

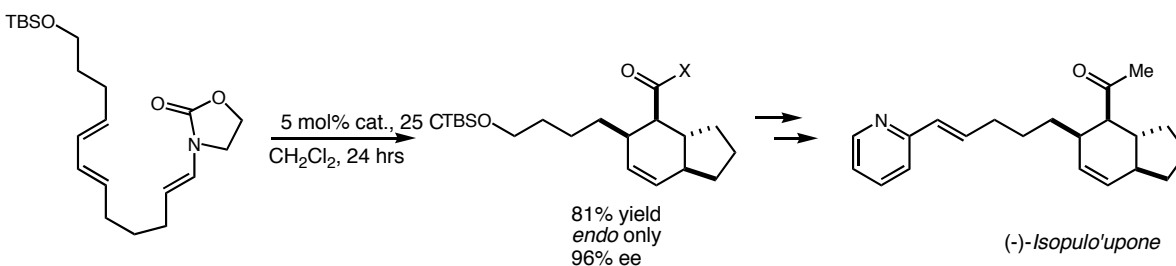
Enantioselective Catalysis: Bis(oxazoline)

Evans' C₂-symmetric Cu(II) *tert*-butylbis(oxazoline) catalyst:

- [4.3.0] systems readily synthesized, but unactivated [4.4.0] substrates are unreactive.



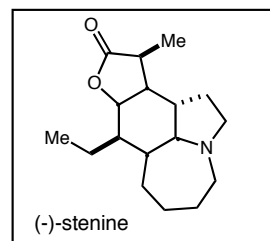
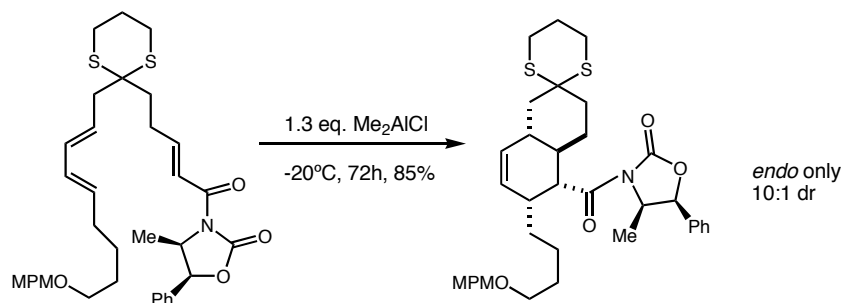
- Application towards the total synthesis of (-)-Isopulo'upone



Evans, D.A. *J. Org. Chem.* **1997**, 62, 786-7.

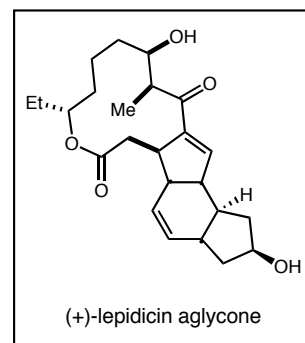
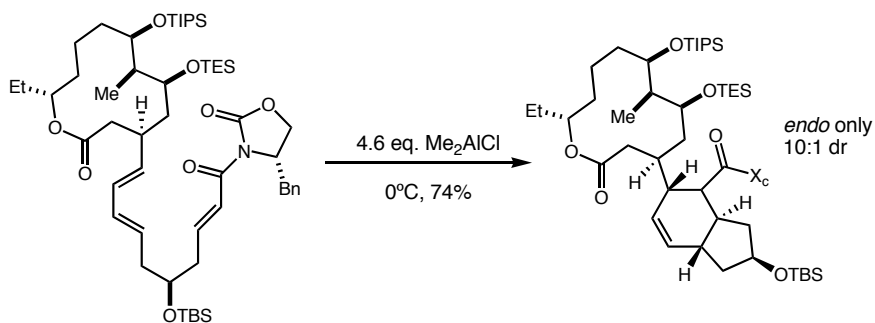
Application of Asymmetric IMDA: Evans Oxazolidinone

Total synthesis of (-)-Stenine



Morimoto, Y. *Ang. Chem. Int. Ed. Engl.* **1996**, 35, 904.

Total synthesis of (+)-Lepidicin A

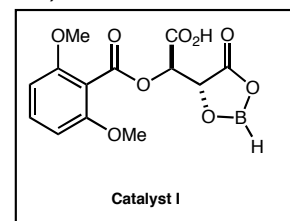
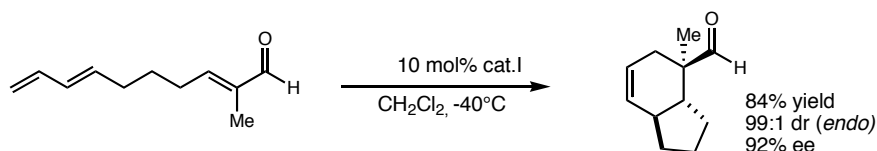


- Able to overcome inherent stereochemical bias for opposite *endo* stereoisomer

Evans, D.A.. *J. Am. Chem. Soc.* **1993**, 115, 4497

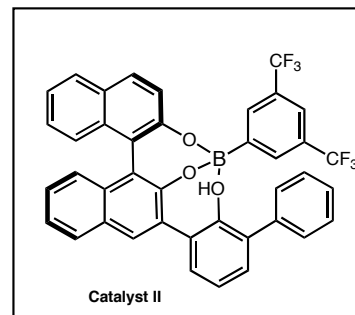
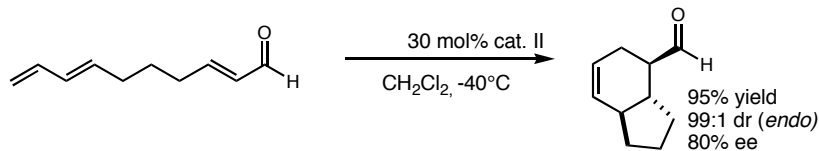
Enantioselective Catalysis: Chiral Acyloxyborane (CAB)

Yamamoto's First Generation CAB Catalyst:

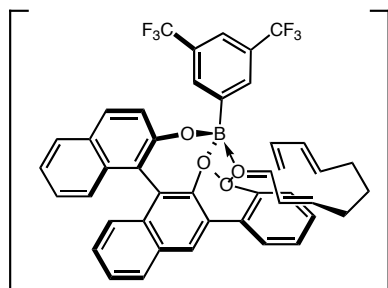


- First Generation Catalyst requires α -Substituent on dienophile

Yamamoto, H. *Tetrahedron Lett.* **1989**, 30, 7231-2.



- Second Generation Catalyst allows cycloaddition of non-substituted dienophiles.
- Proposed Mode of Stereoinduction:



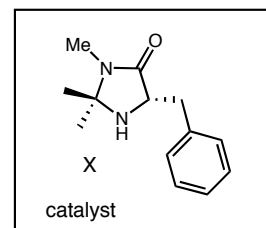
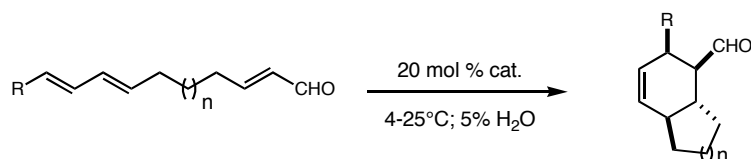
Aldehyde coordinates with boron.

Dienophile rests over phenyl, forcing chain to wrap around to top face.

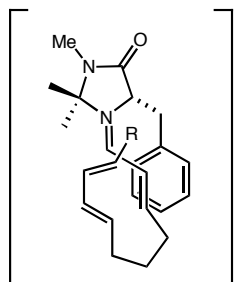
Anti TS \longrightarrow Trans Product

Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 3049-50.

Enantioselective Catalysis in the IMDA: MacMillan Imidazolidinone Catalyst



■ Stereochemical Rationale:



Iminium ion forms cis to benzyl group.

Tether wraps around to top face of dienophile to avoid steric interactions with phenyl.

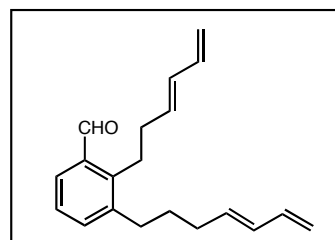
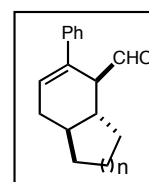
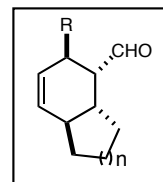
Reaction is endo-selective.

■ Challenges:

Diels-Alder adducts can epimerize under reaction conditions.

Less reactive substrates can polymerize or undergo amine-catalyzed *intermolecular* Diels-Alder/aromatization sequence.

When R=Ph, the olefin can isomerize into conjugation with phenyl.



Enantioselective Catalysis in the IMDA: MacMillan Imidazolidinone Catalyst

