

## Six Membered Rings

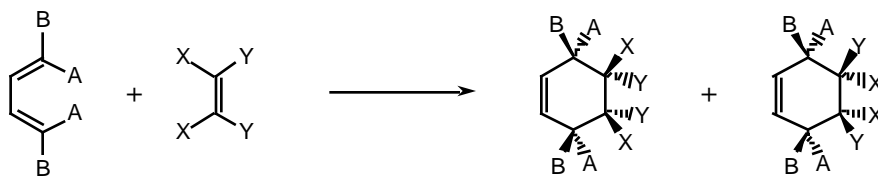
1. Diels-Alder Reaction
2. o-Quinodimethanes
3. Intramolecular ene reaction
4. Cation olefin cyclizations
5. Robinson annulation

### Diels-Alder Reaction

ACIEE **1984**, 23, 876; ACIEE **1977**, 16, 10; Organic Reactions **1984**, 32, 1

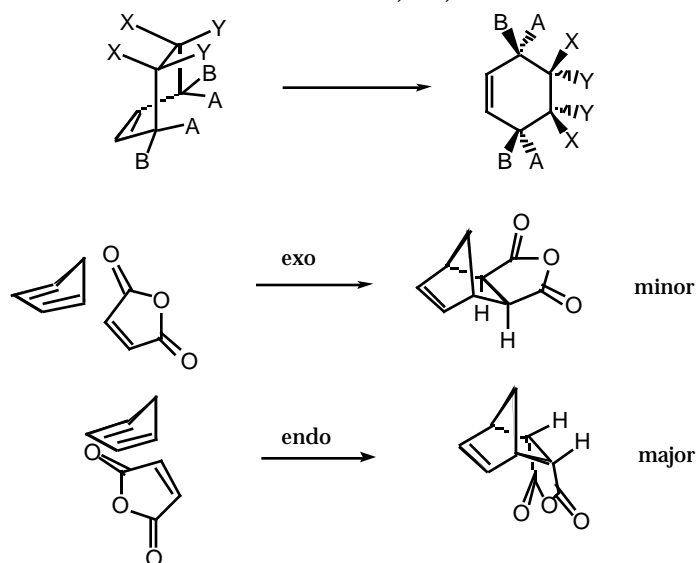
W. Carruthers *Cycloadditions Reactions in Organic Synthesis* (Pergamon Press, Oxford) **1990**

- reaction of a 1,3-diene with an olefin to give a cyclohexene.
- thermal symmetry allowed pericyclic reaction
- diene must react in an s-cis conformation
- highly stereocontrolled process- geometry of starting material is preserved in the product
- possible control of 4 contiguous stereocenters in one step

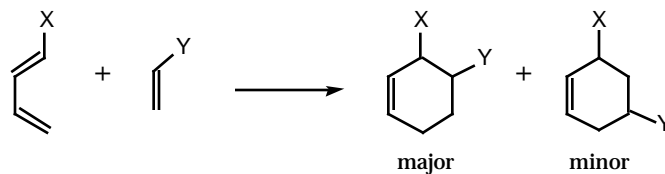


- Alder Endo Rule: In order to maximize secondary orbital interactions, the endo TS is favored in the D-A rxn.

*Tetrahedron* **1983**, 39, 2095

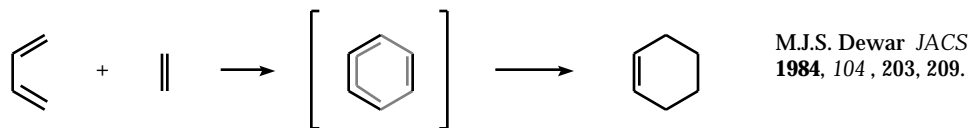


### Orientation Rules

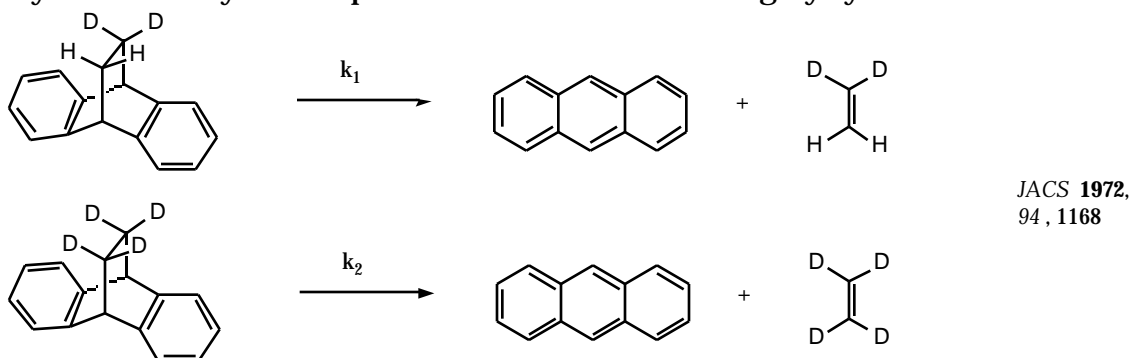




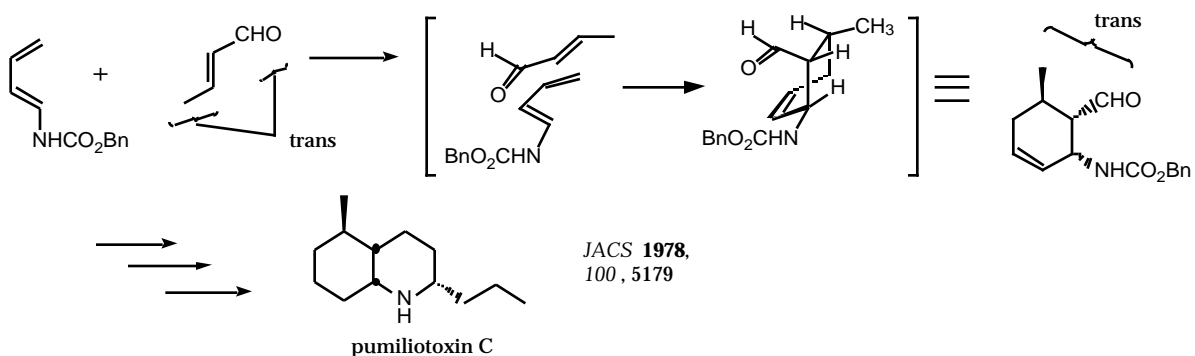
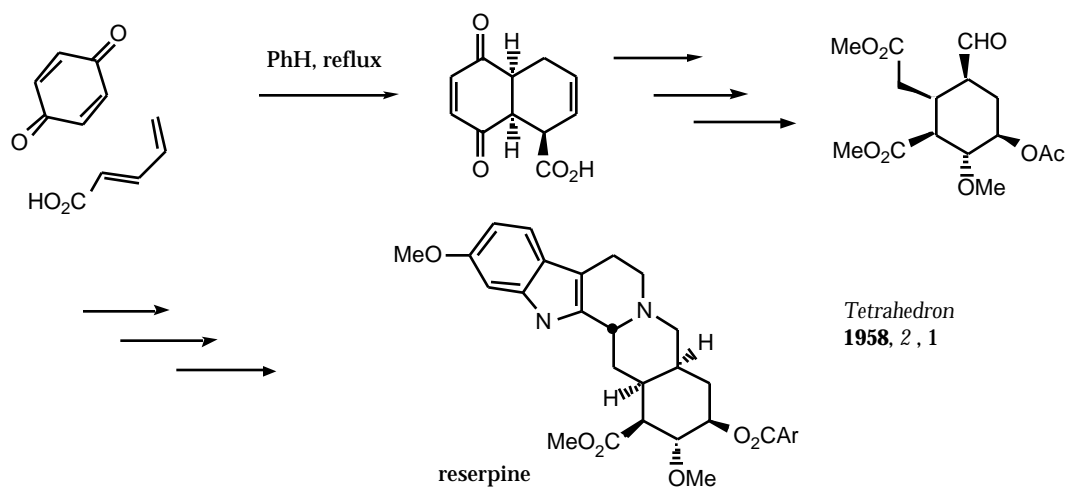
- The mechanism of the D-A rxn is believed to be a one-step, concerted, non-synchronous process.
- concerted- bond making and bond breaking processes take place in a single kinetic step (no dip in the transition state)
- synchronous- bond making and bond breaking take place at the same time and to the same extent.

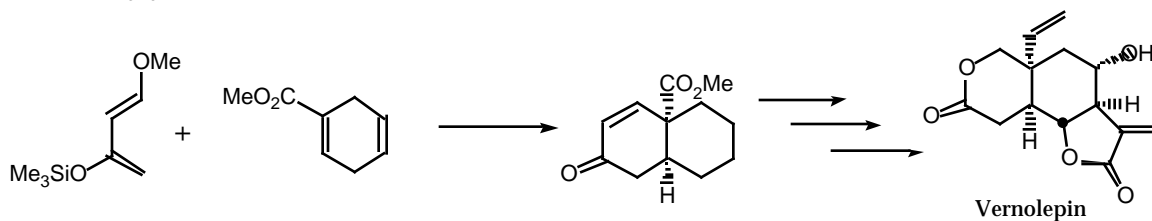
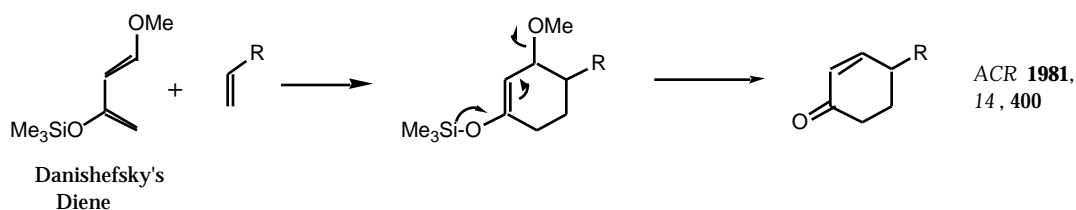
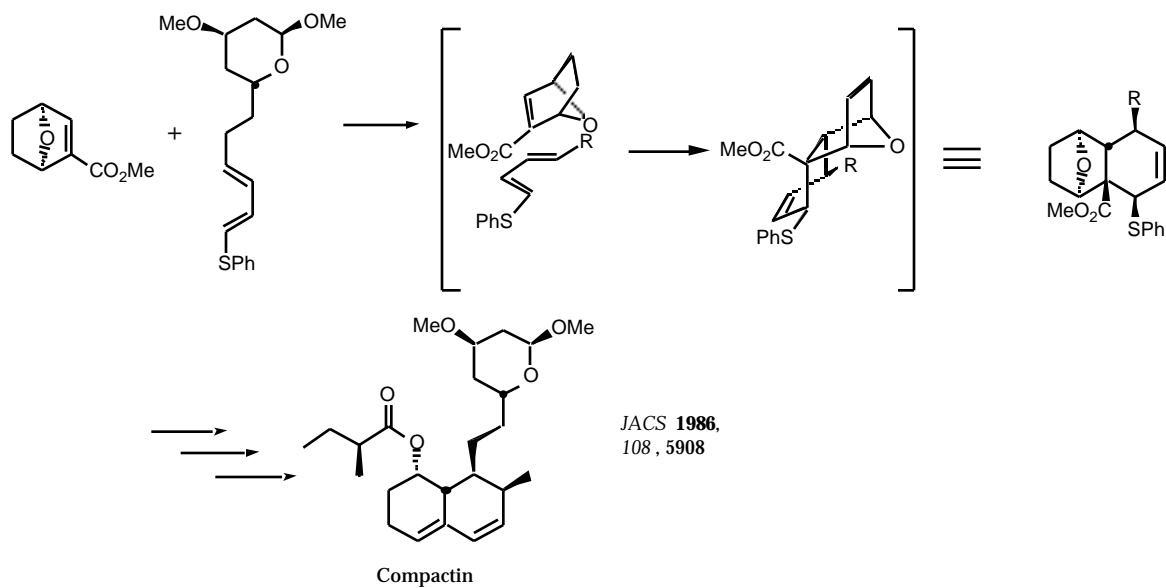


- study of secondary D-isotope effects have indicated a highly symmetrical T.S.

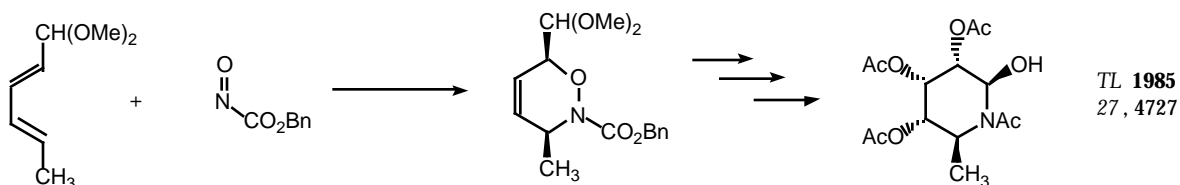
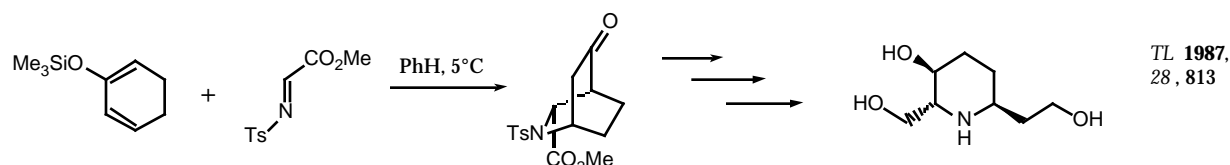
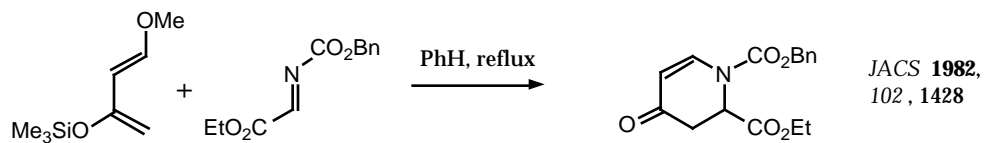


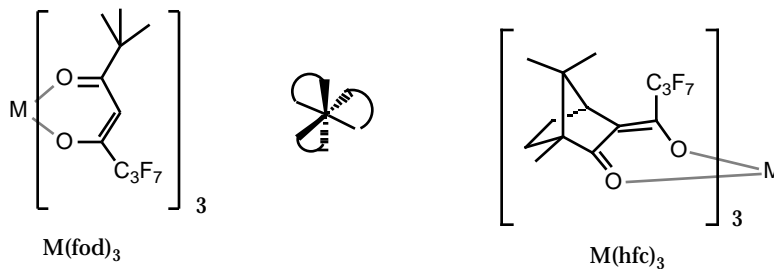
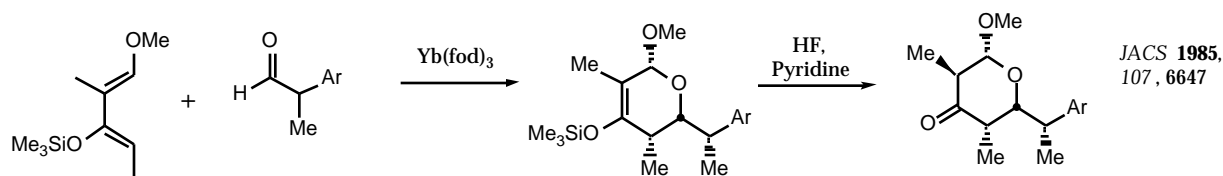
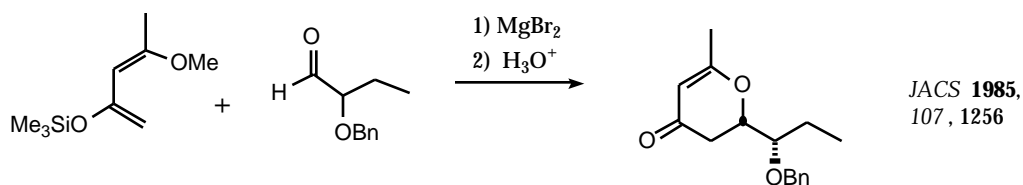
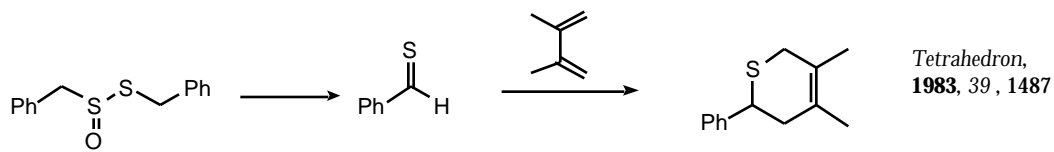
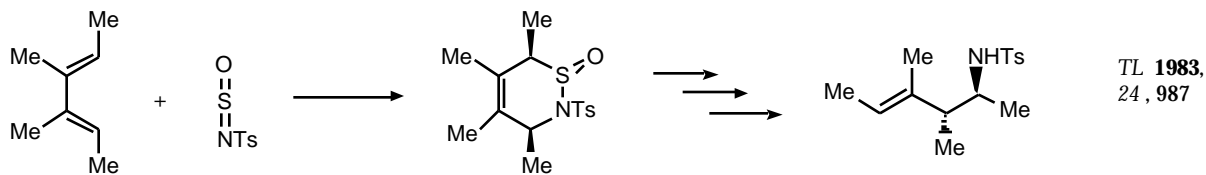
### Diels Alder Reactions:



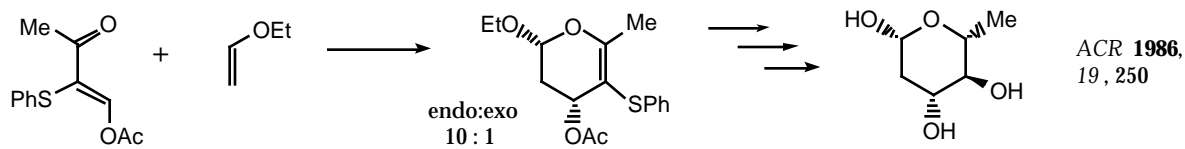
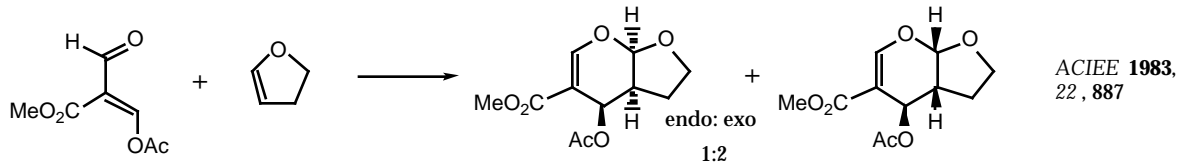


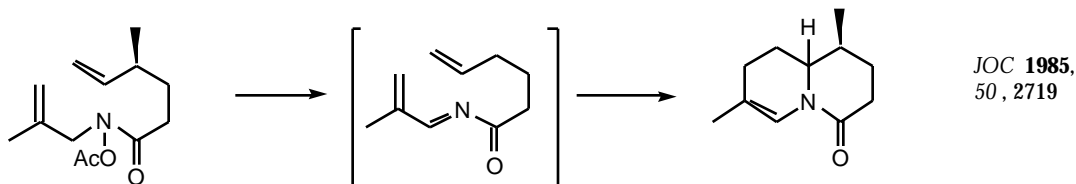
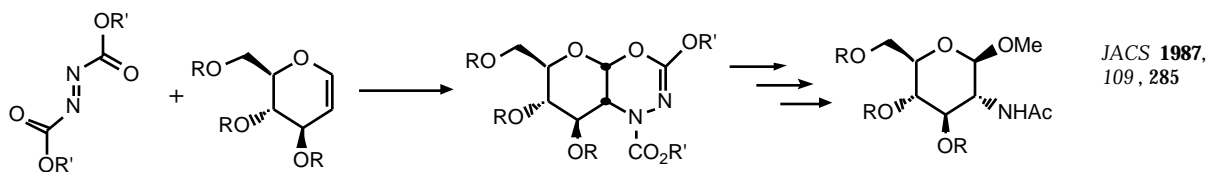
### Hetero Diels-Alder Reactions - Heterodienophiles





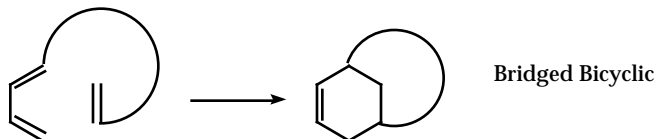
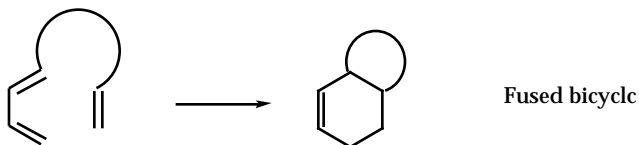
### - Heterodienes





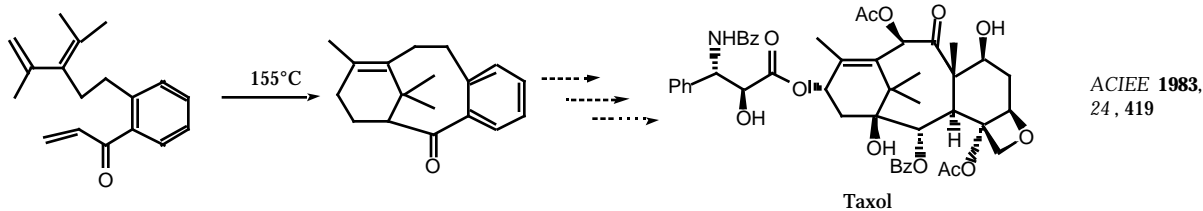
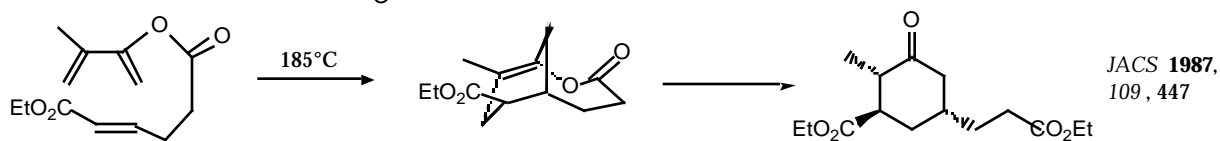
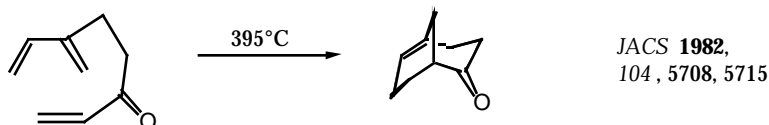
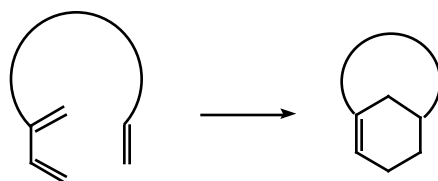
### Intramolecular Diels-Alder Reactions (IDA)

#### - Type I IDA rxns

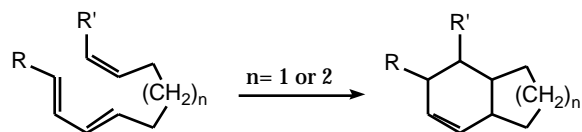


- Generally, for E-dienes, the fused product is observed unless the connecting chain is very long. For Z-dienes, either the fused or bicyclic products are possible.

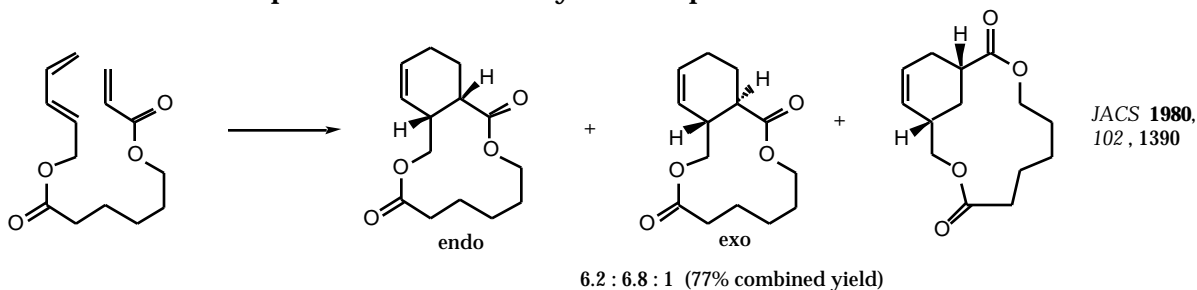
#### - Type II IDA rxns: gives bridgehead olefin



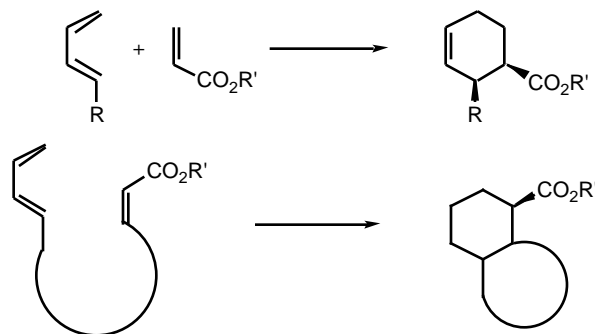
- IDA reactions to give fused 6•5 (hydroindene) and 6•6 (hydronaphthalene) ring systems are usually favorable reactions.



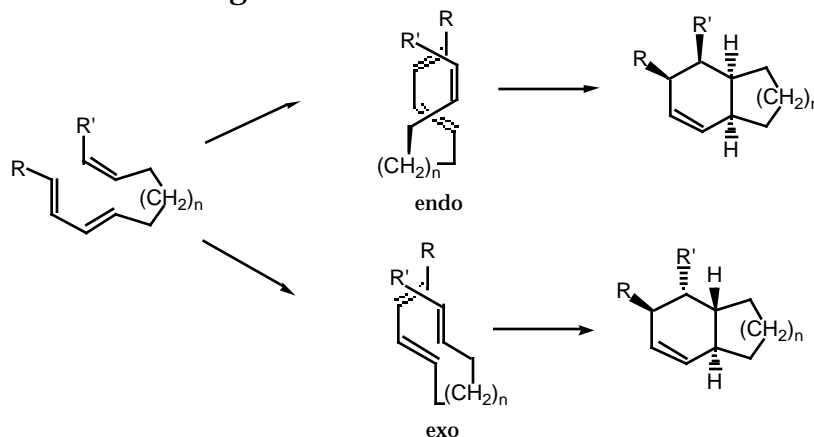
- Intramolecular D-A rxns that give medium sized rings (7,8,9, 10) are much less favorable.
- Intramolecular D-A rxn which form large rings are often favorable reactions with the diene and olefin portions act as if they were separate molecules



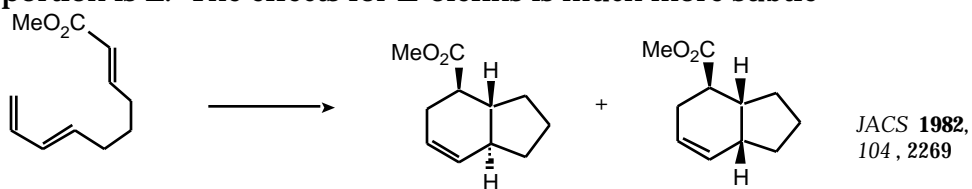
- Preference for endo or exo transition state depends on the substitution of the diene, dienophile and connecting chain.
- For intramolecular D-A rxns, geometric constraints can now reverse the normal regiochemistry of the addition as compared to the intermolecular rxn.



- for intramolecular D-A reactions, we will use endo and exo to describe the disposition of the connecting chain

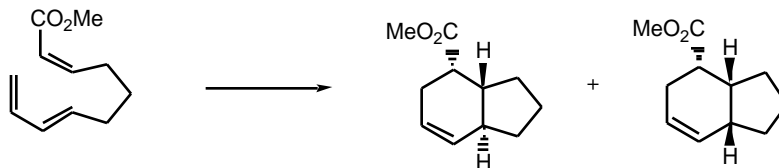


- Lewis acids can greatly effect the endo/exo ratio of IDA reactions especially when the olefin portion is E. The effects for Z-olefins is much more subtle



150°C  
(RO)<sub>2</sub>AlCl<sub>2</sub>, rt

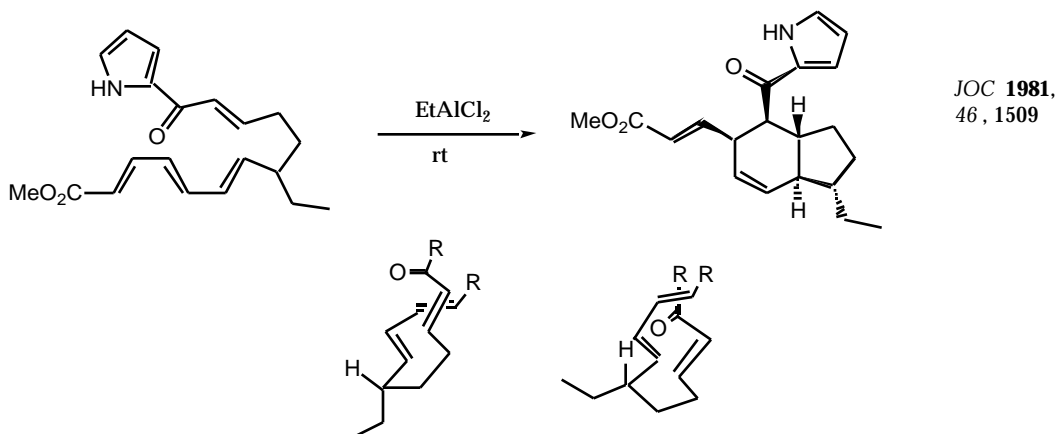
75 : 25	(75% combined yield)
100 : 0	(72% combined yield)



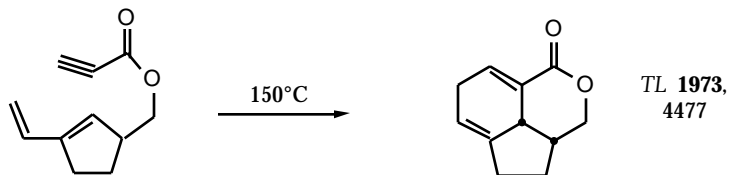
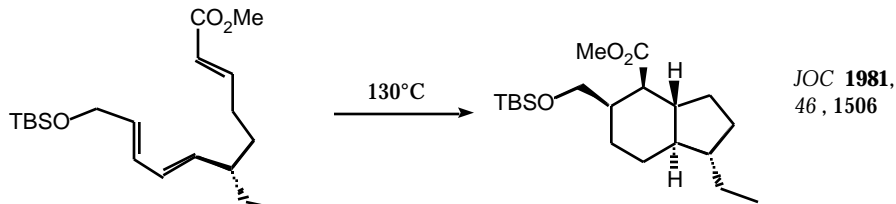
180°C  
EtAlCl<sub>2</sub>, rt

75 : 25	(74% combined yield)
63 : 37	(60% combined yield)

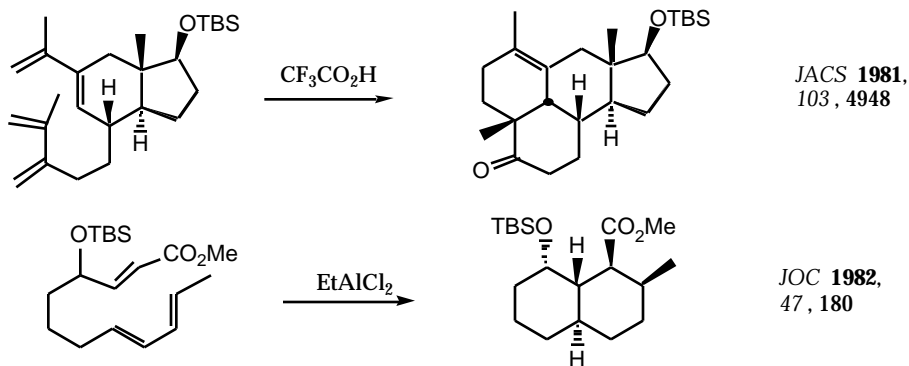
- the effect of substituents on the connecting chain can influence the stereochemical course of the IDA reaction



### Intramolecular Diels-Alder Reactions:

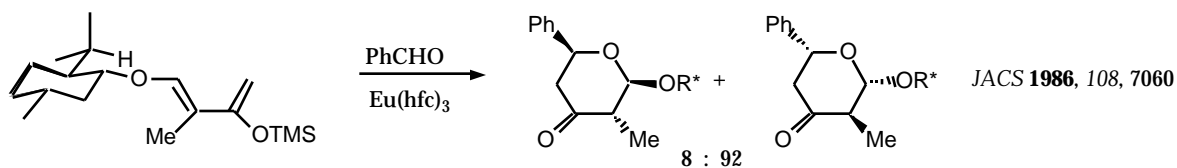
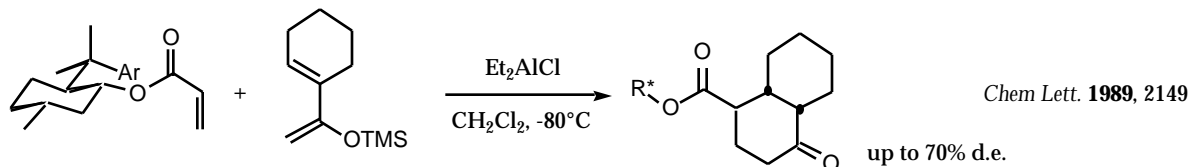
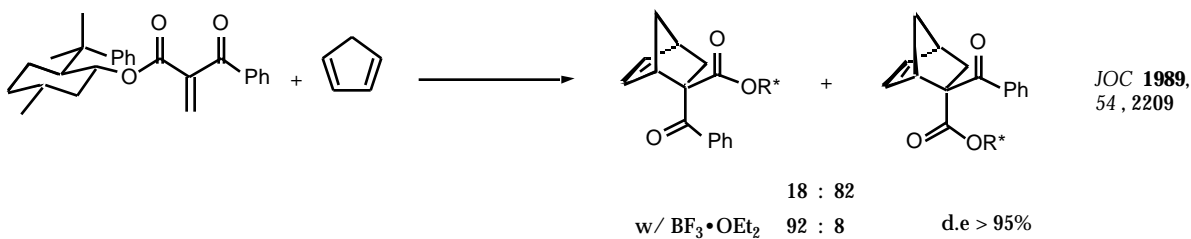
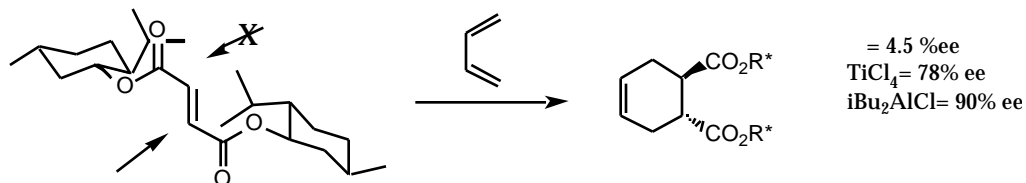
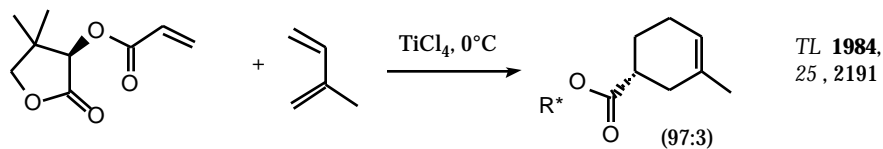
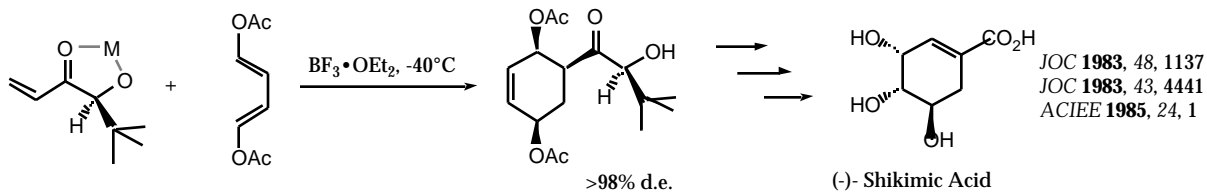


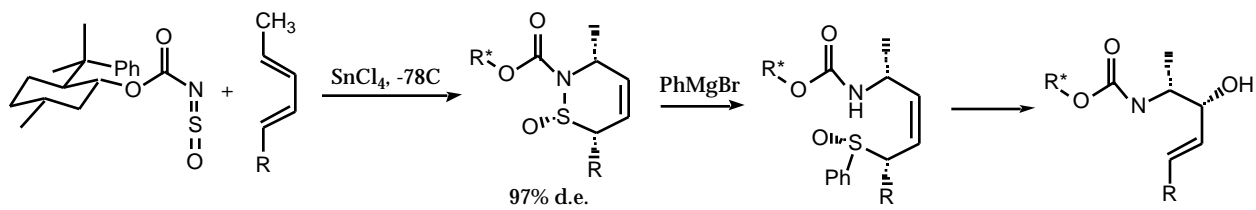




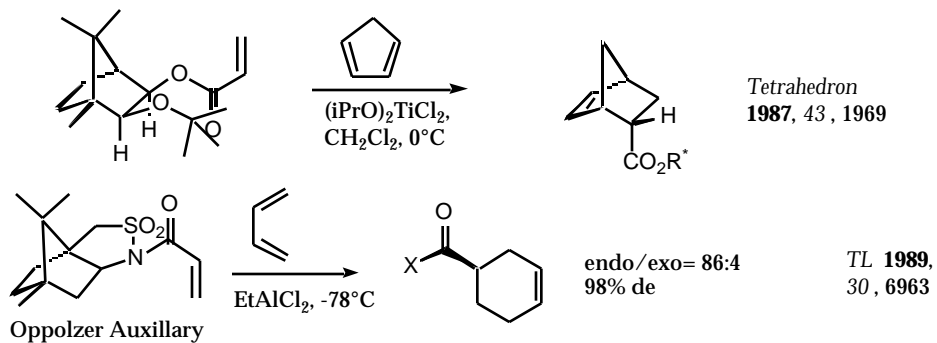
## Asymmetric Diels-Alder Reactions

## - Chiral Auxillaries

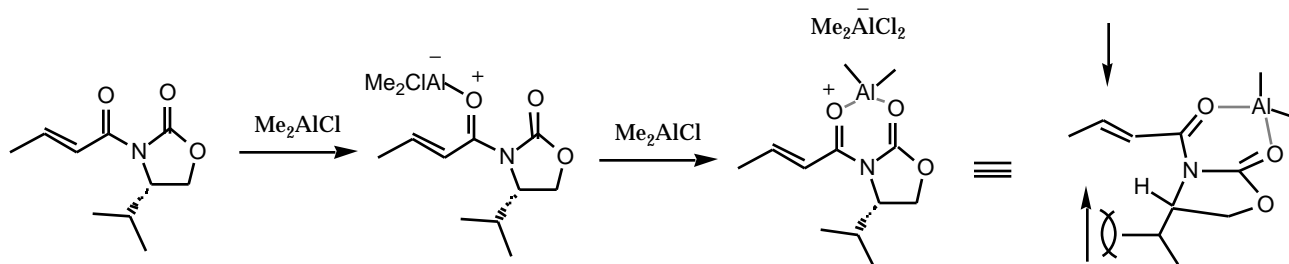
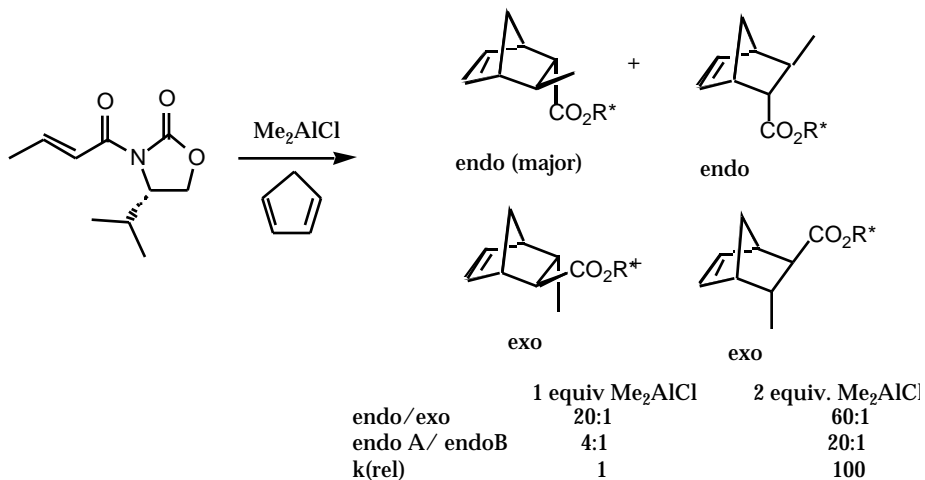
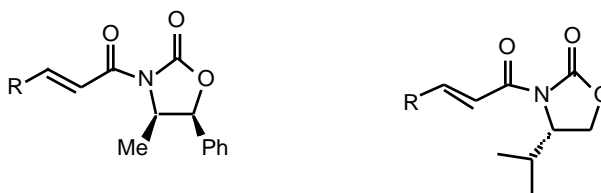
Chem. Rev. **1992**, 92, 953; Tetrahedron **1987**, 43, 1969

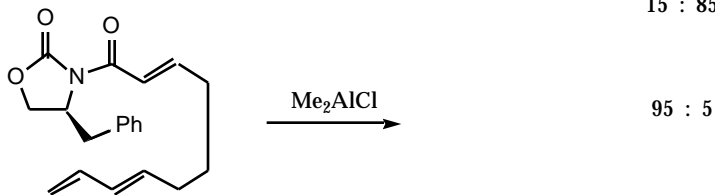
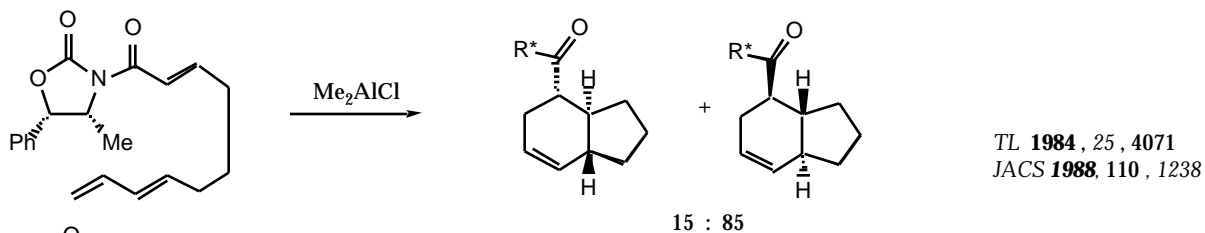
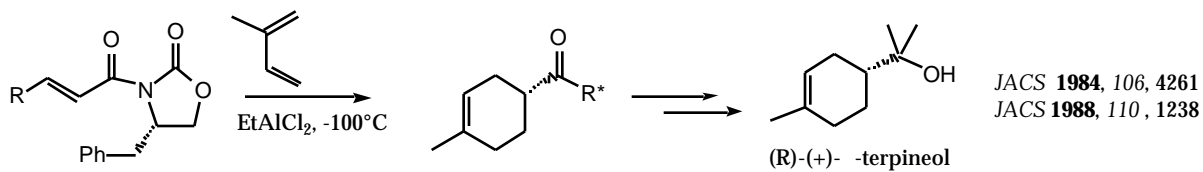


JCSCC, 1985, 1449  
TL 1986, 27, 1853

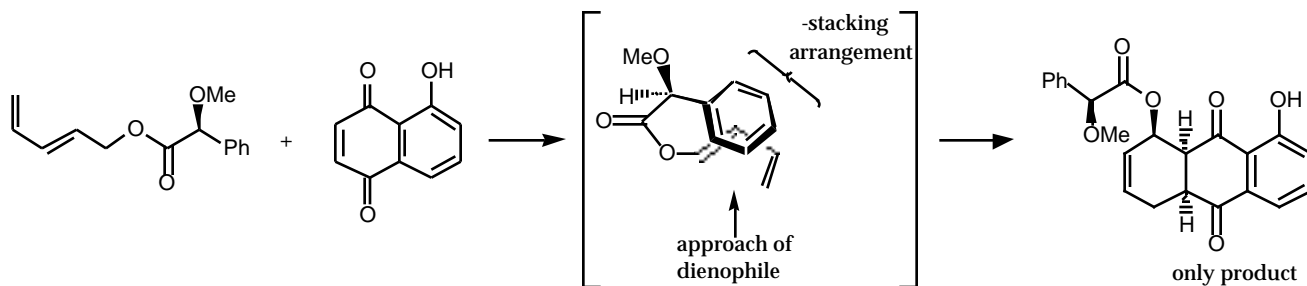
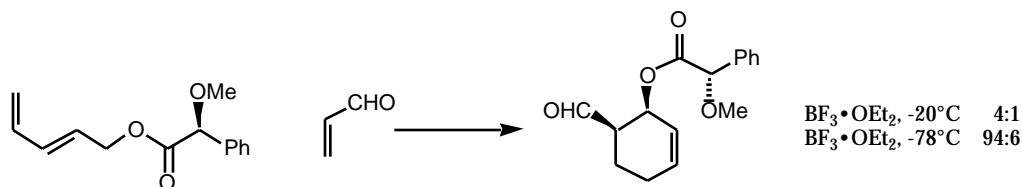
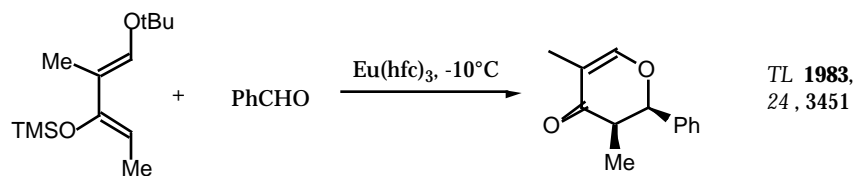
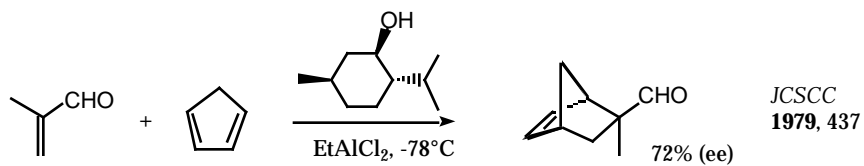


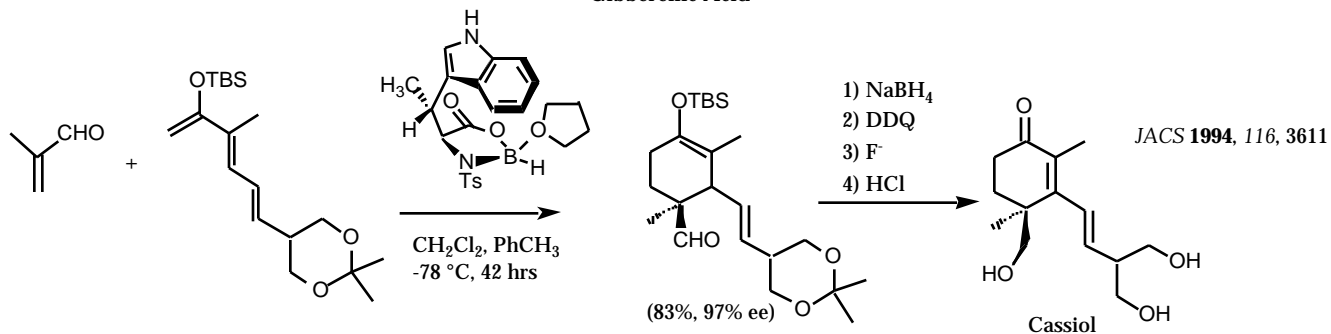
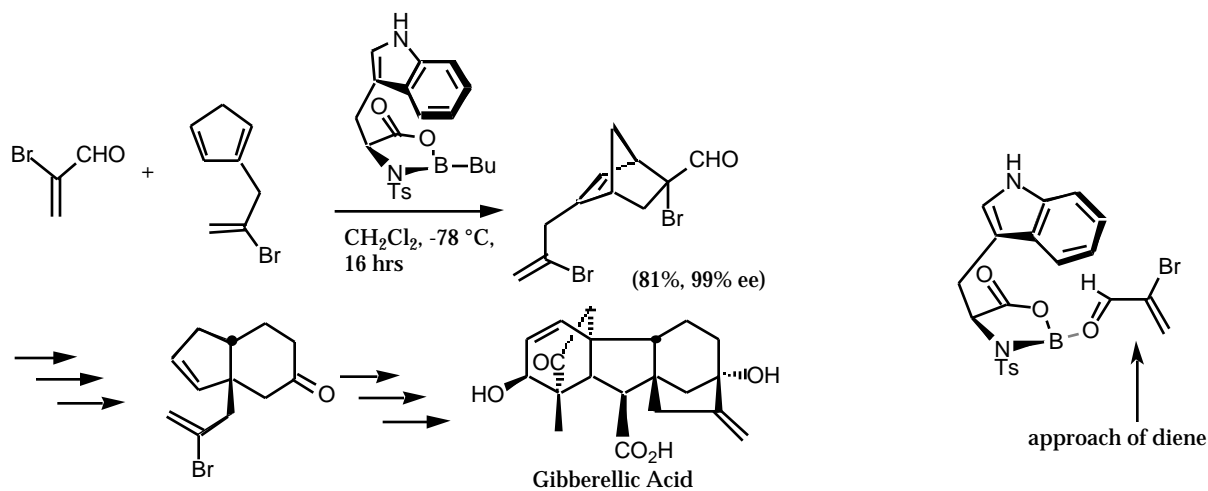
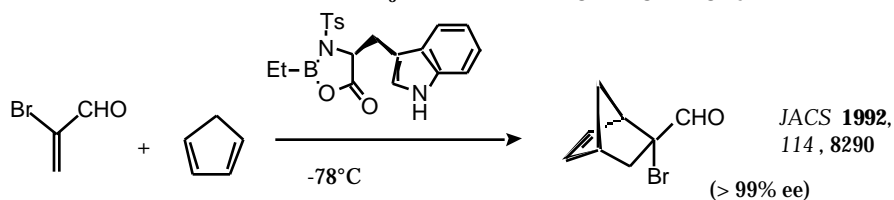
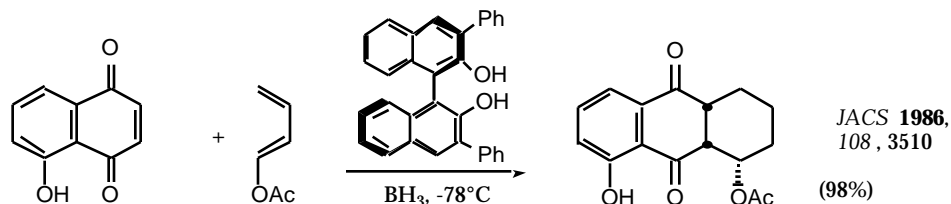
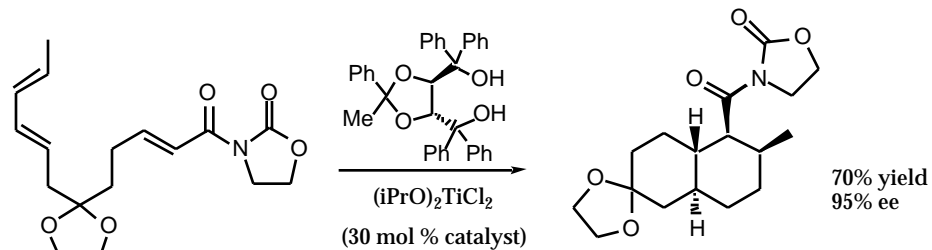
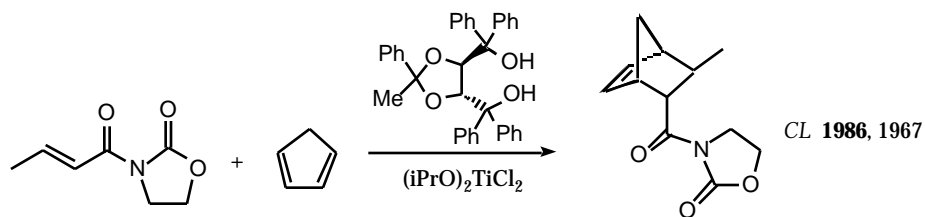
Evan's auxiliaries





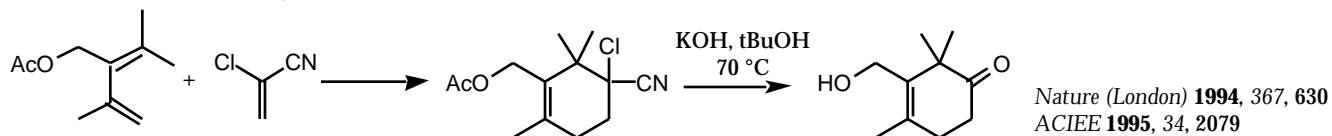
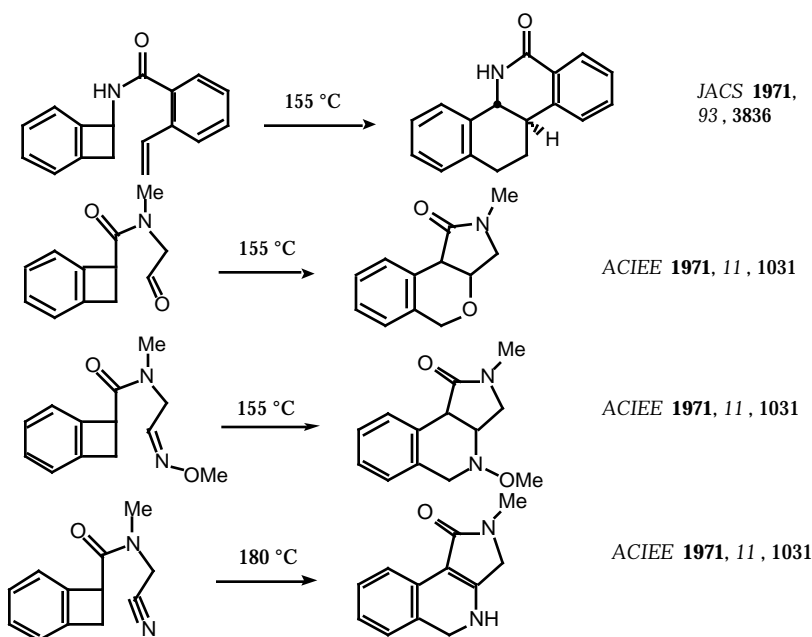
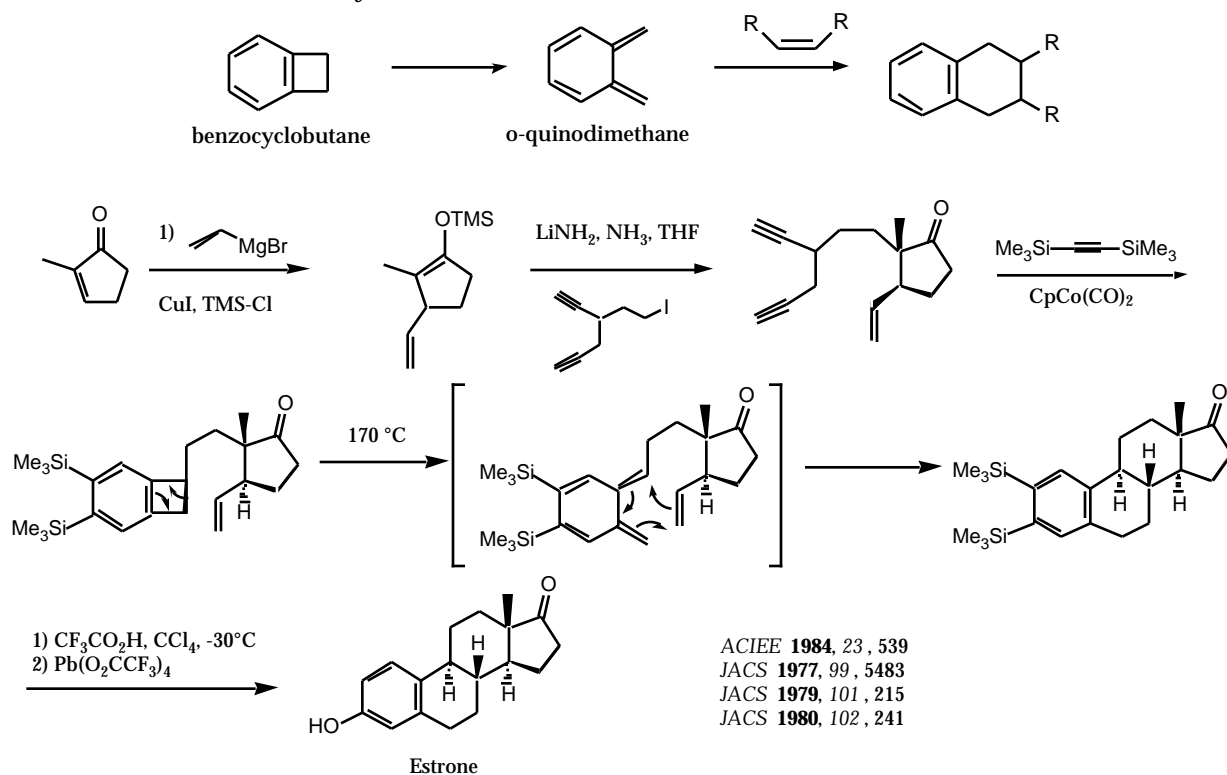
## - Chiral Dienes

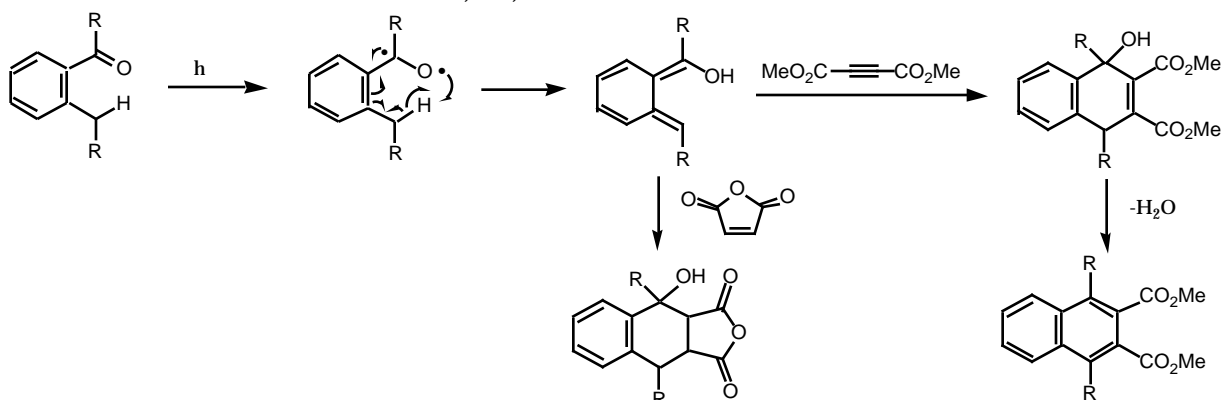
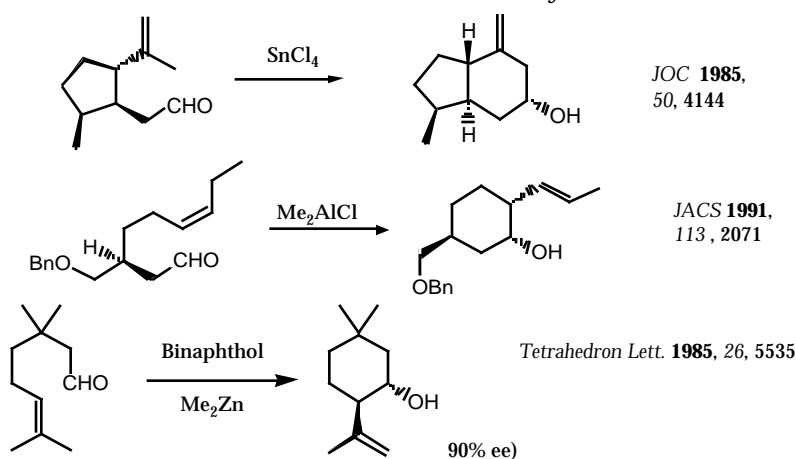
- Chiral Catalysts Chem. Rev. **1992**, 92, 1007; Synthesis **1991**, 1; OPPI **1994**, 26, 129-158



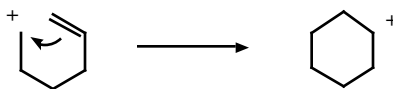
## Ketene Equivalents in the D-A reaction

- ketenes undergo thermal [2+2] cycloaddition with dienes to give vinyl cyclobutanones.
- 2-chloroacrylonitrile as a ketene equiv. for D-A rxns.

*ortho*-Quinodimathanes Synthesis **1978**, 793; *Tetrahedron* **1987**, 43, 2873

Photoenolization *Tetrahedron* **1976**, 22, 405Intramolecular Ene Reactions *ACIEE* **1984**, 23, 876, *Synthesis* **1991**, 1

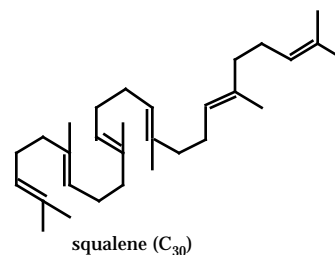
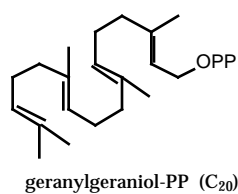
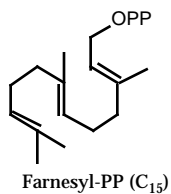
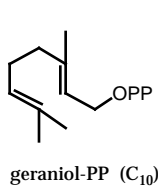
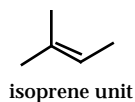
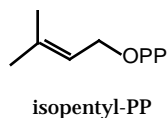
## Polyene Cyclization

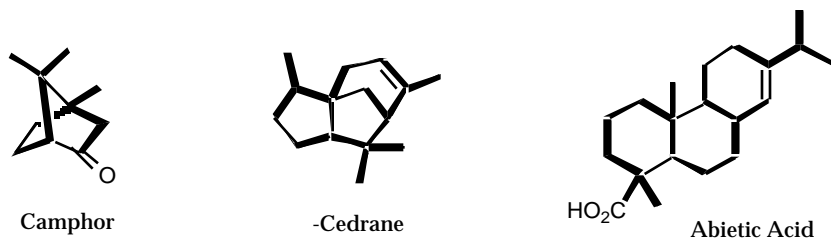


## Terpene Biosynthesis

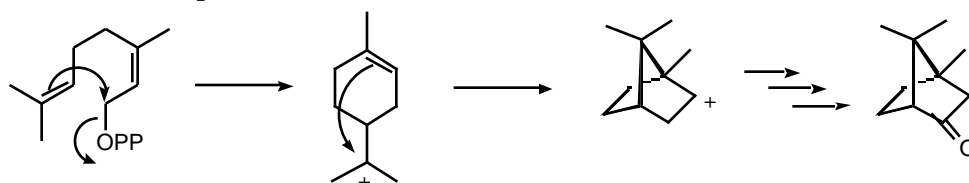
terpenes	C <sub>10</sub>	geraniol
sesquiterpenes	C <sub>15</sub>	farnesol
diterpenes	C <sub>20</sub>	geranylgeraniol
steroids	C <sub>30</sub>	squalene

- isoprene- basic building block

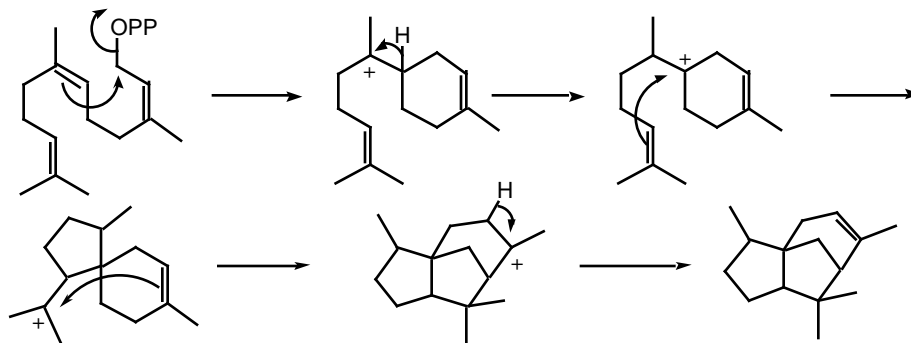




### Biosynthesis of camphor:

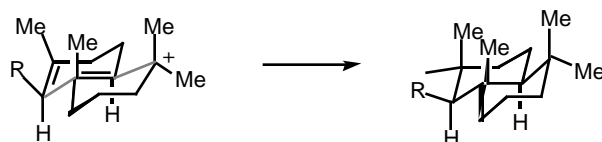


### Biosynthesis of cedrane:

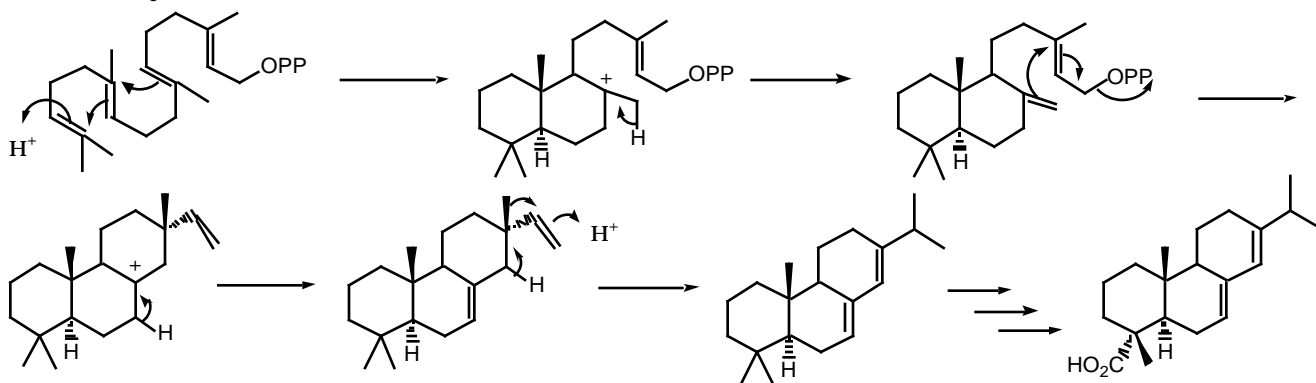


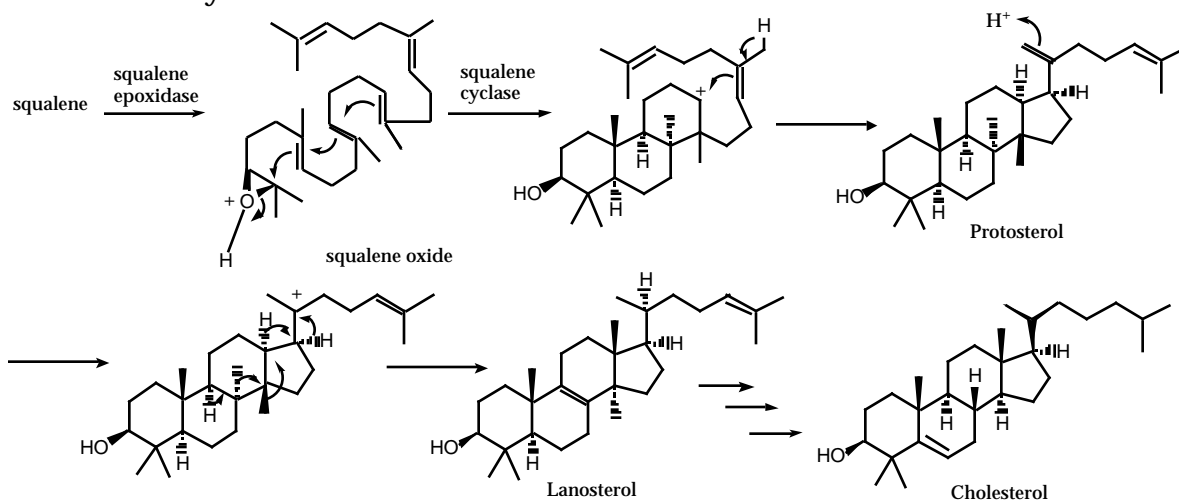
**Stork-Eschenmoser Hypothesis-** Olefin Geometry is preserved in the cyclization reaction, i.e. trans olefin leads to a trans fused ring junction

A. Eschenmoser *HCA* **1955**, 38, 1890; G. Stork *JACS* **1955**, 77, 5068

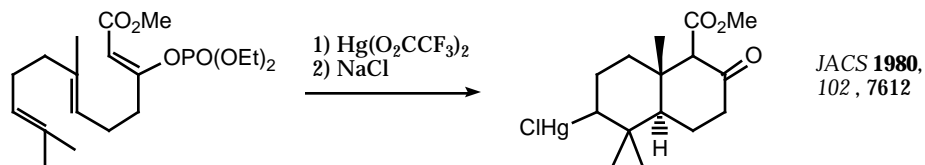
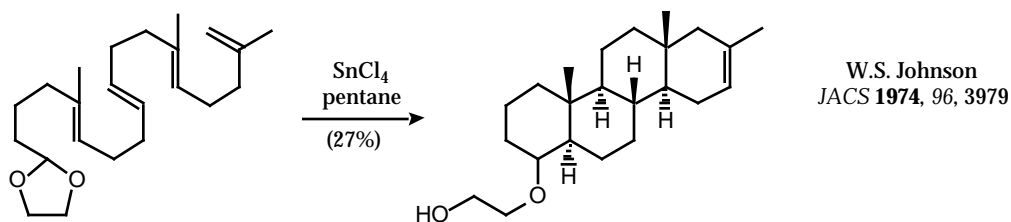
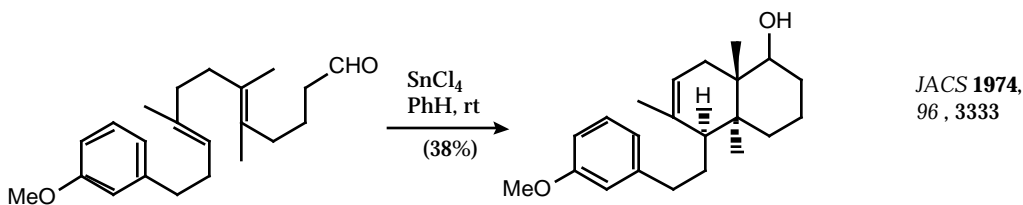
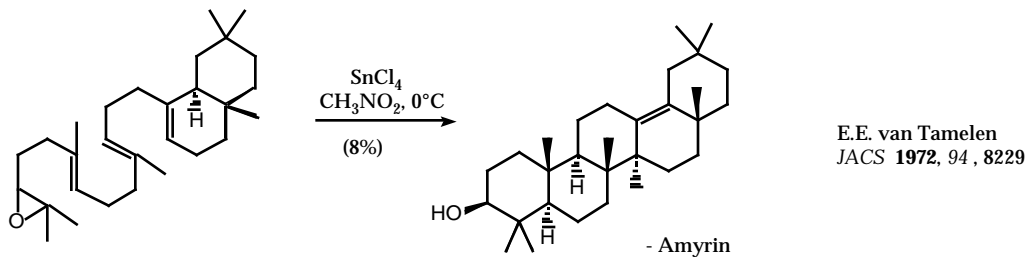


### Biosynthesis of Abietic acid:



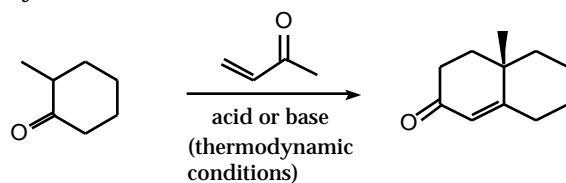
**-Steroid Biosynthesis:**

- Polyene cyclization in synthesis *ACR* **1968**, 1, 1; *Bioorg. Chem.* **1976**, 5, 51; *Asymmetric Synthesis* **1984**, 3, 341-409; *ACIEE* **1976**, 15, 9

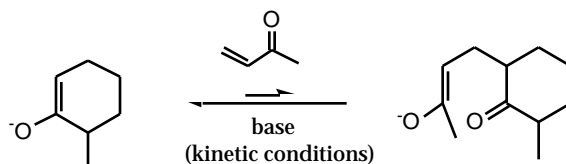




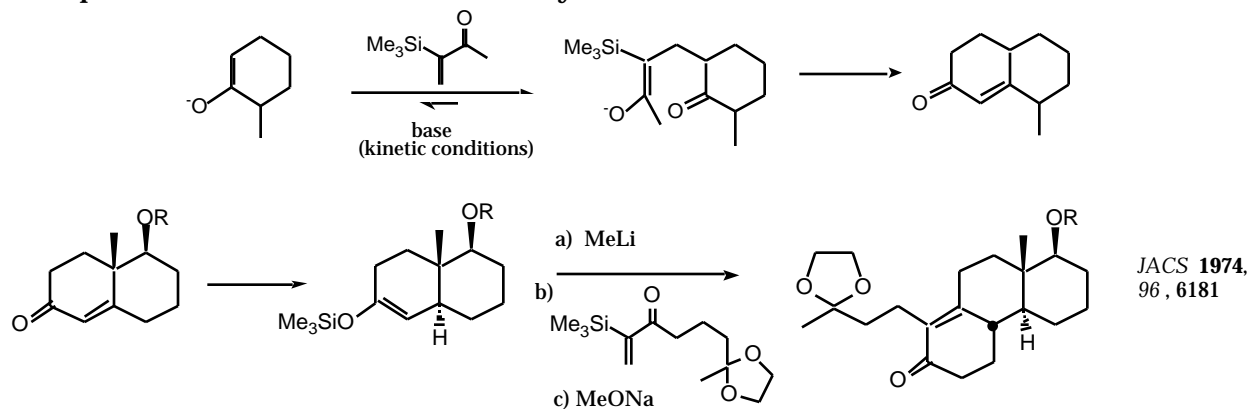
Robinson Annulation

Synthesis **1976**, 777; *Tetrahedron* **1976**, 32, 3.

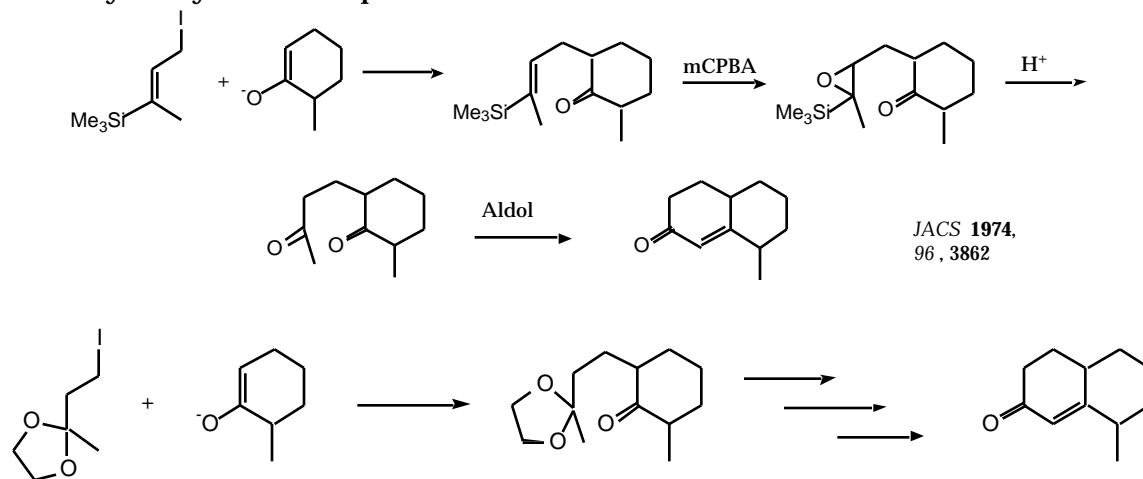
- unfavorable equilibrium for the Michael addition under kinetic conditions



- stabilizing the resulting enolate of the Michael Addition product can shift the equilibrium as in the case of the vinyl silane shown below

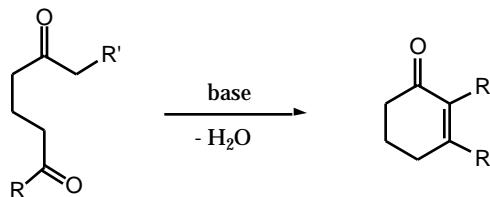


- Methyl Vinyl Ketone equivalents

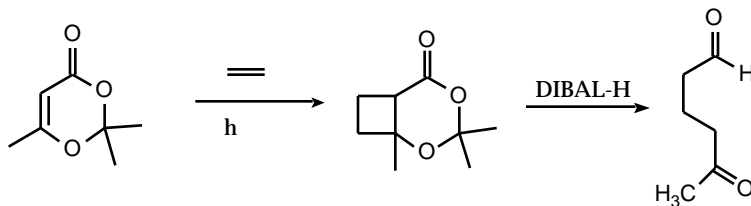


## Intramolecular Aldol Condensation of 1,5-Diketones

6-exo-trig; favored process



- DeMayo reaction to 1,5-diketones

Intramolecular Alkylations (S<sub>N</sub>2 reaction)

Radical Cyclizations

Acyloin Reaction

Birch Reduction *Organic Reactions* **1992**, 42, 1.

Aromatic Substitution (Carey &amp; Sundberg, Chapter 11)

Intramolecular Wittig Reaction

Sigmatropic Rearrangements