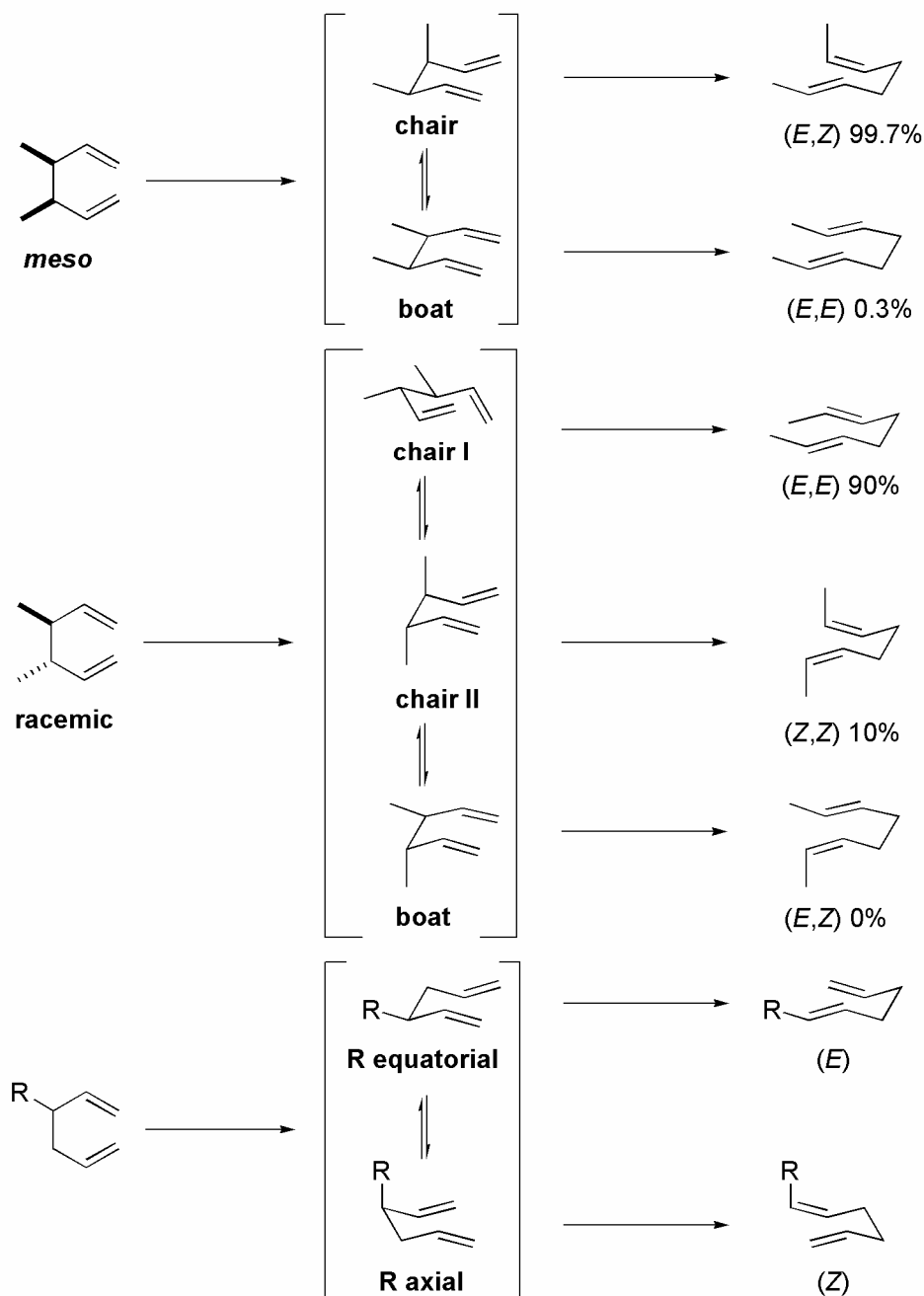


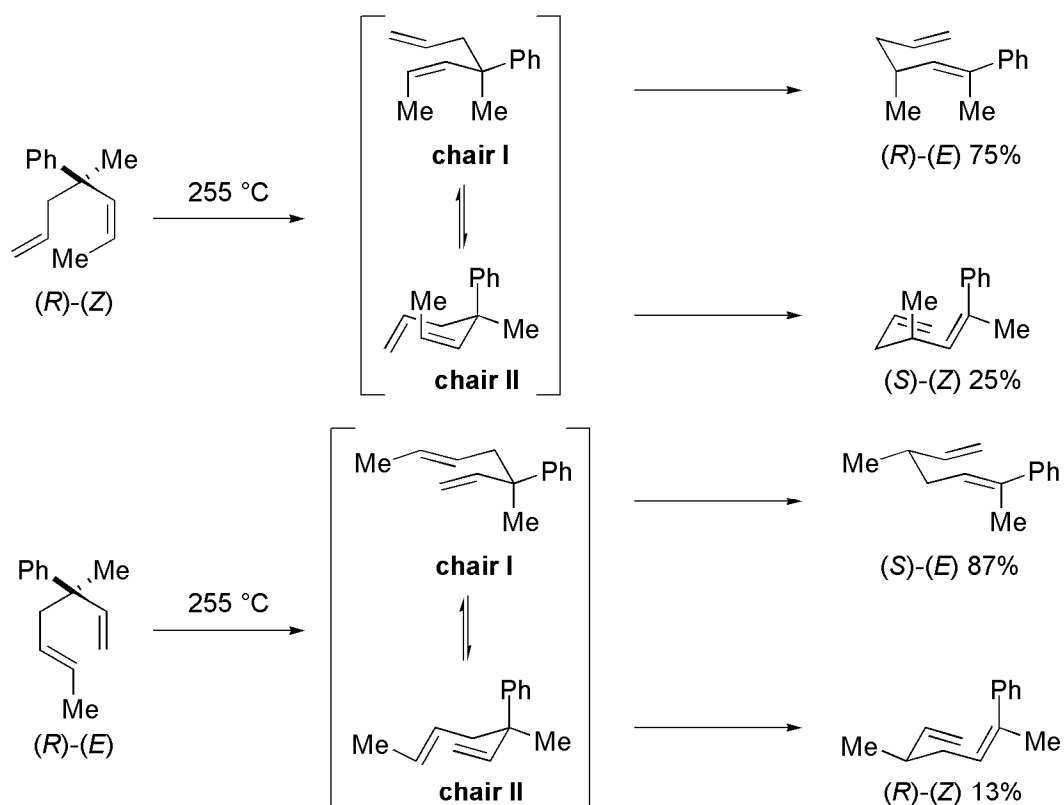
Diastereoselective Sigmatropic Rearrangements

1. [3,3] Sigmatropic Rearrangement: Transition State

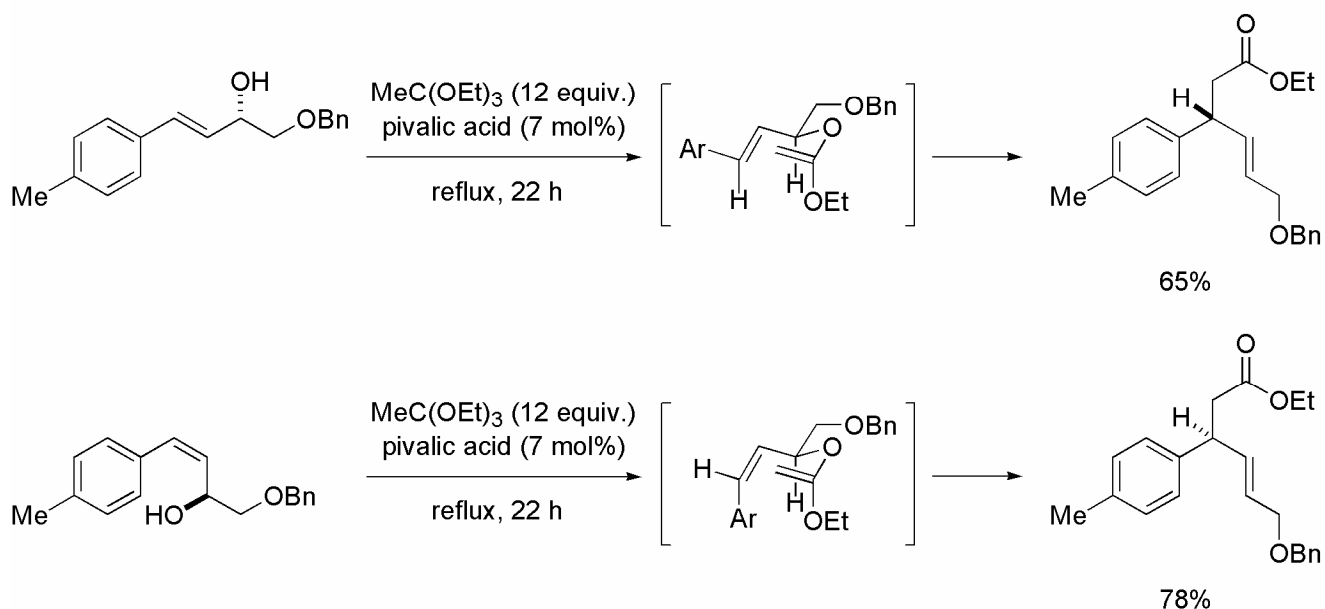


- Two transition states are possible: chair and boat
- The boat transition state for acyclic systems is about 5 kcal/mol higher in energy than the chair transition state
- The chair transition state with the substituent at the sp^3 center in equatorial position is preferred: this generally leads to high (*E*)-selectivity for the formed double bond
- Introduction of hetero atoms (e. g. O (Claisen)) does not change this analysis qualitatively but the quantitative energy difference is different (e.g. Claisen: chair/boat energy difference: 3 kcal/mol)

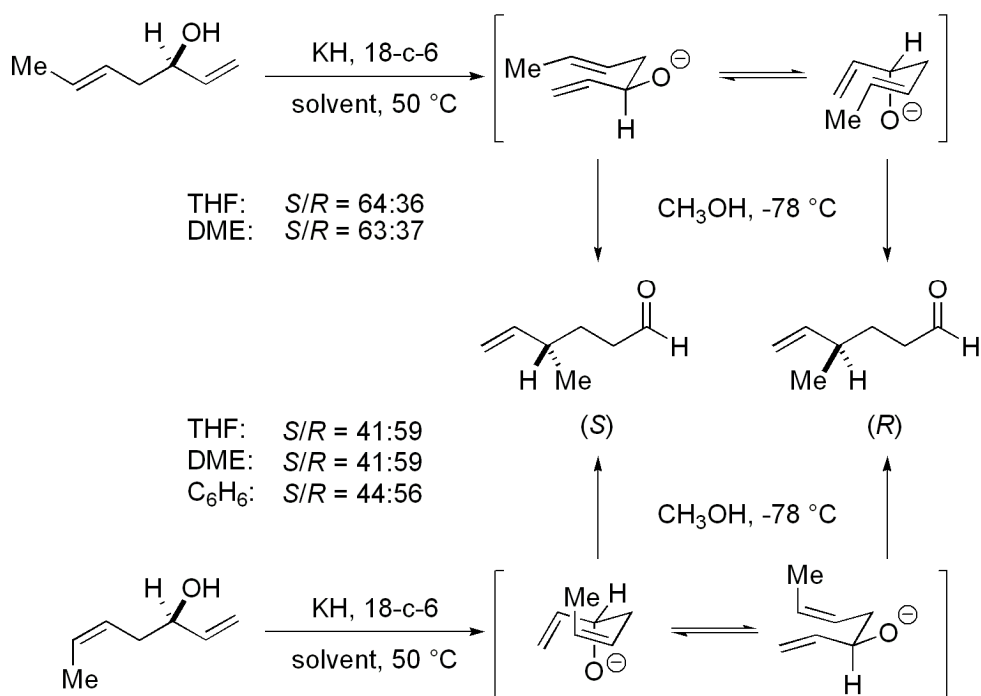
1.1. Transition State Analysis for Acyclic Systems



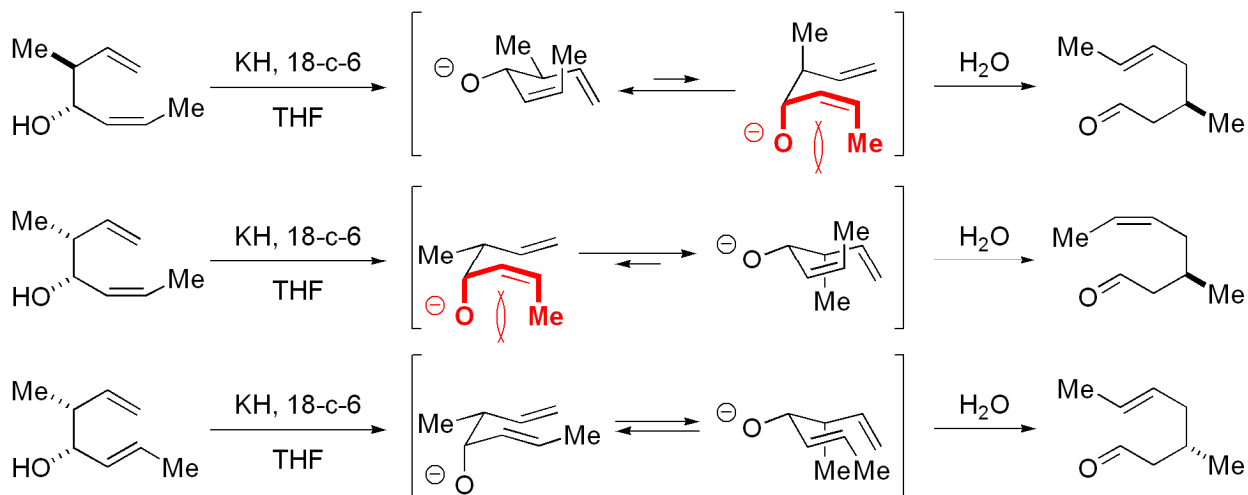
J. Chem. Soc. Chem. Commun. **1967**, 619.



Chem. Lett. **1989**, 1781.



J. Org. Chem. **1994**, *59*, 1444.

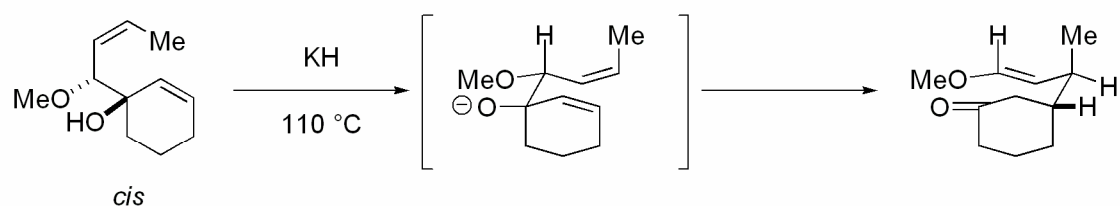
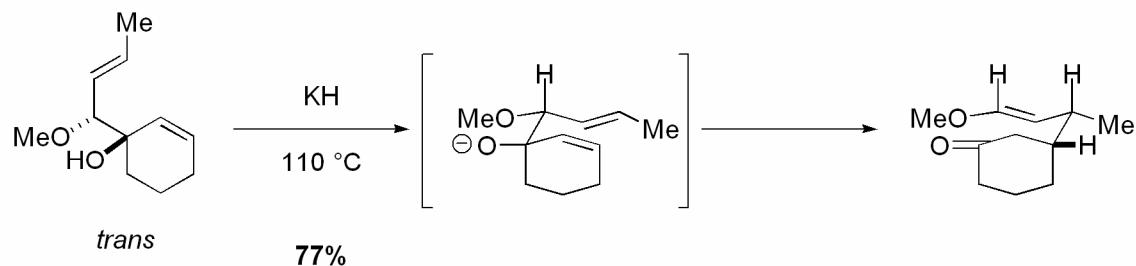


Tetrahedron **1993**, *49*, 1025.

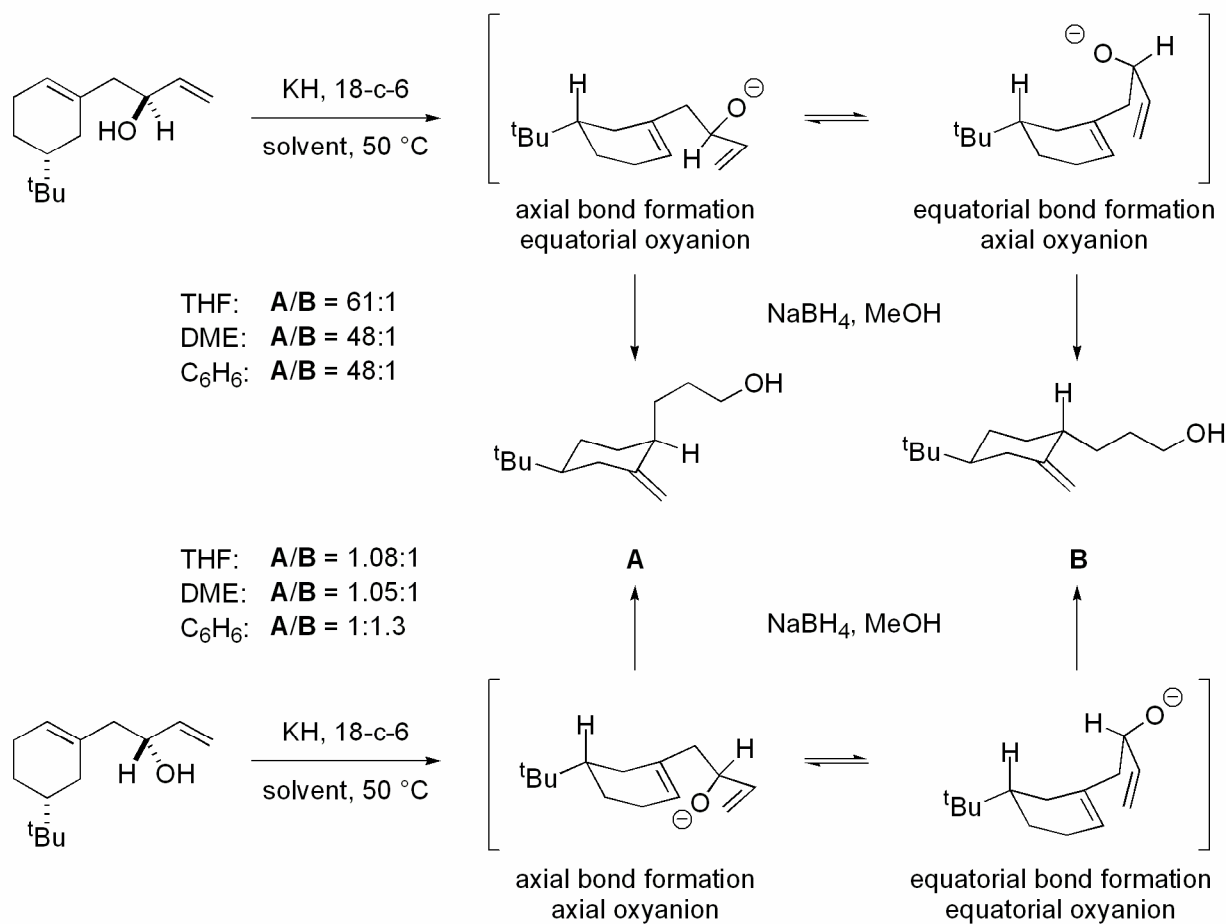
- The oxy-Cope rearrangement of enantiomerically pure secondary alcohols is not highly selective, as the two transition states are very close in energy.
- Introduction of a second stereocenter vicinal to the alcohol can lead to high selectivities.

1.2. Transition State Analysis for Cyclic Systems

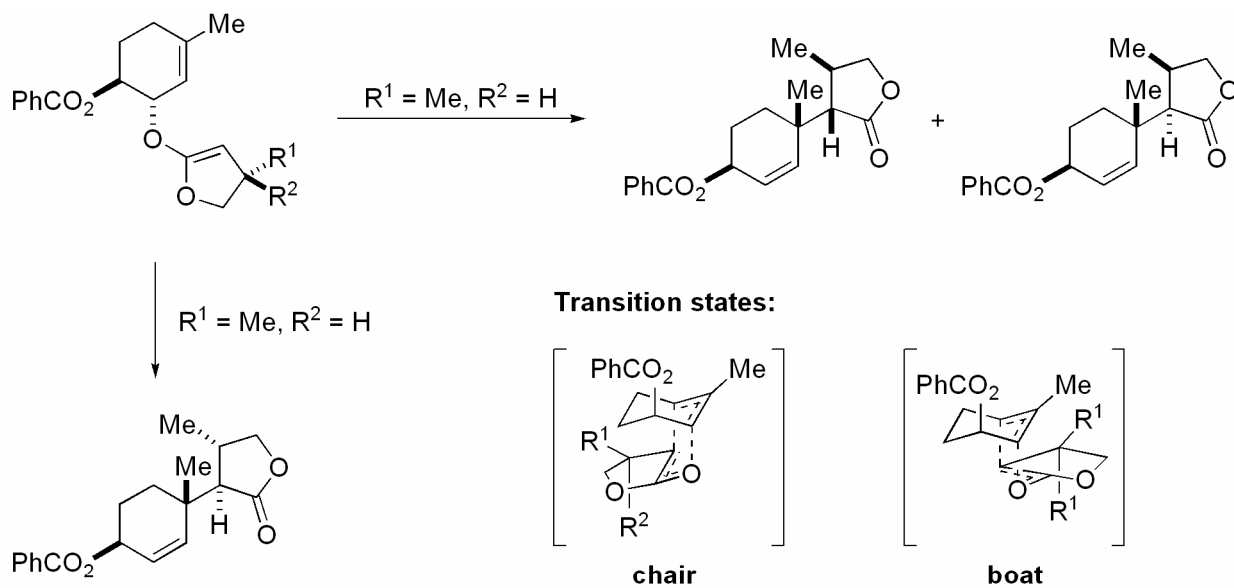
boat transition state can be preferred



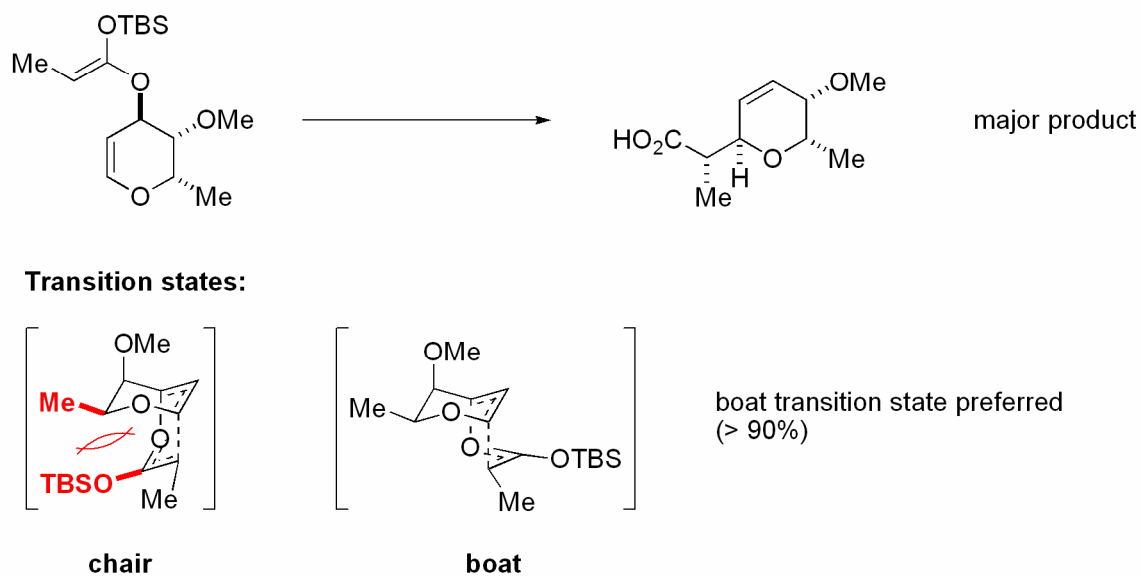
Evans *J. Am. Chem. Soc.* **1980**, *102*, 774.



Paquette *Angew. Chem. Int. Ed.* **1991**, *30*, 1368.
J. Am. Chem. Soc. **1992**, *114*, 5018.



J. Chem. Soc. Perkin Trans. 1 **1977**, 1211.



Ireland J. Org. Chem. **1980**, 45, 48.

For cyclic substrates, the steric interactions can override the preference for the chair transition state, and high boat selectivities can be observed.

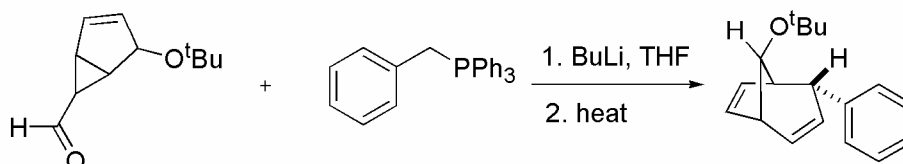
In general, predictions for cyclic substrates are more difficult and require a careful analysis of the conformation of the transition state and the existing ring.

2. Practical Applications of [3,3] Sigmatropic Rearrangements

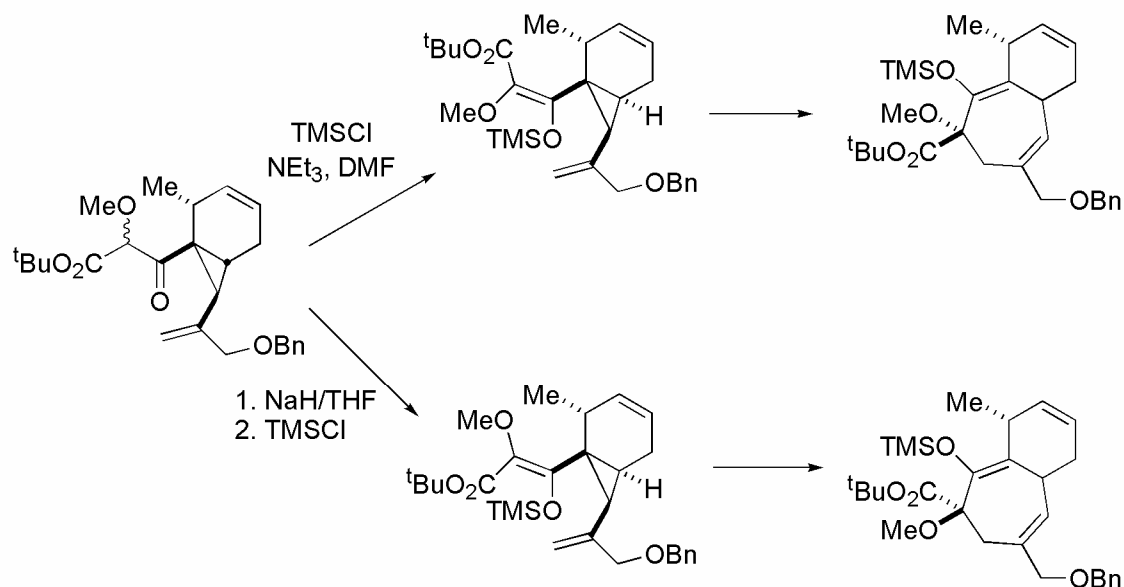
- Practical problem: the sigmatropic rearrangements are highly stereoselective, but suffer from high activation energy and often low thermodynamic driving forces, which can lead to mixtures of product and starting material
- Devised solutions:
 - charge acceleration
 - release of ring strain
 - highly reactive starting material (enolates)
 - stabilized products (formation of carbonyls)
 - metal mediated acceleration

2.1. Cope Rearrangement

Release of ring-strain, use of enolates

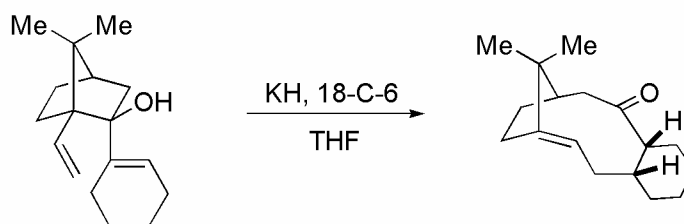


Danishefsky *Tetrahedron Lett.* **1998**, 39,767.



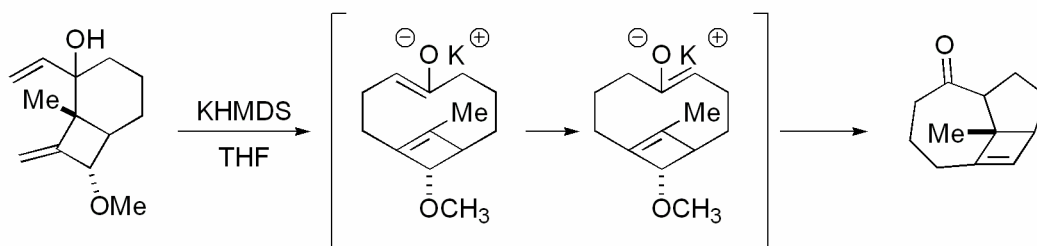
Wender *Tetrahedron Lett.* **1988**, 29, 6741.

Oxy-anion Cope: access to strained medium sized ring

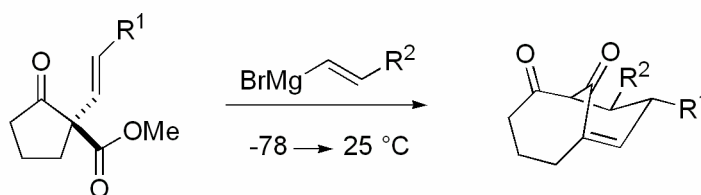


Paquette *J. Am. Chem. Soc.* **1990**, 112, 277.

Oxy-anion-Cope: trapping of formed enolate through electrophile

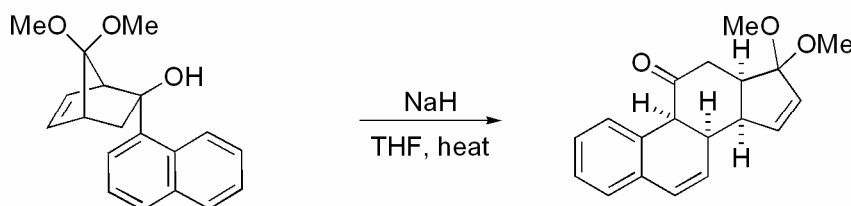


Paquette and Schreiber *J. Am. Chem. Soc.* **1989**, *111*, 2331.



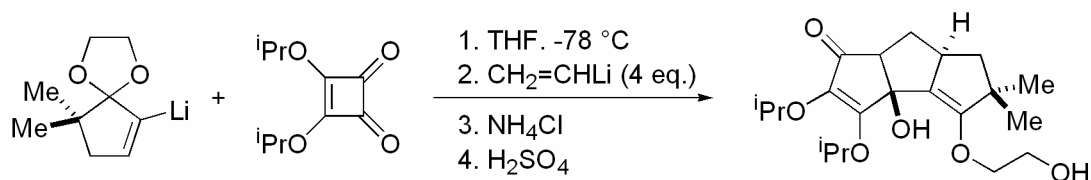
Shair *J. Am. Chem. Soc.* **1998**, *120*, 10784.

Oxy-anion-Cope: reaction of aromatic compounds



J. Am. Chem. Soc. **1978**, *100*, 4309.

Oxy-anion-Cope: reaction cascade

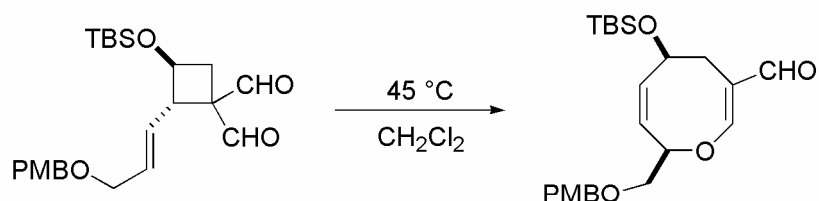


Paquette *Org. Lett.* **2002**, *4*, 71.

reaction cascade consisting of oxy-Cope rearrangement, elimination and aldol reaction, or of electrocyclic ring opening and closing, followed by elimination and aldol reaction

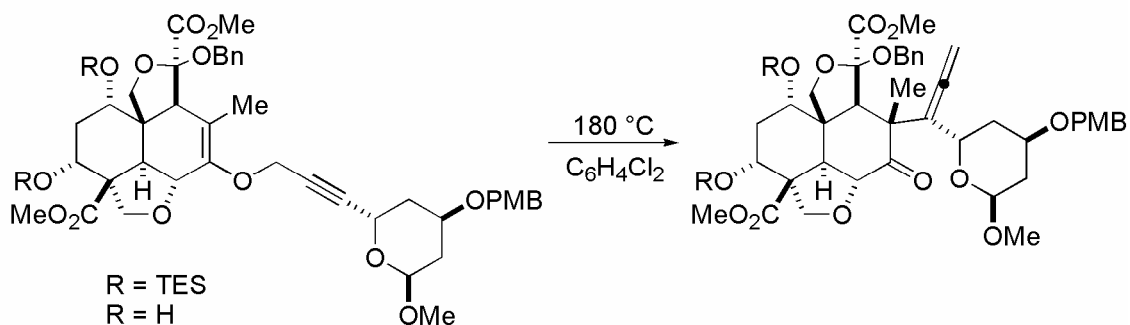
2.2. Claisen Rearrangement

Release of ring-strain: retro-Claisen is promoted!



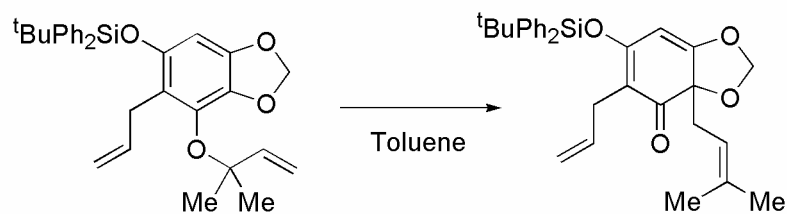
Boeckman Jr. *Org. Lett.* **2002**, *4*, 3891.

Claisen on triple bond: formation of allenes



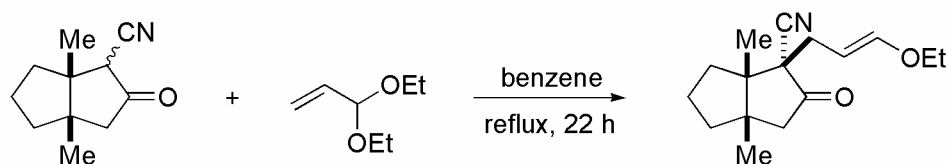
Ley *Org. Lett.* **2002**, *4*, 3847.

Claisen on aromatic compounds



Danishefsky *J. Am. Chem. Soc.* **1998**, *120*, 12684.

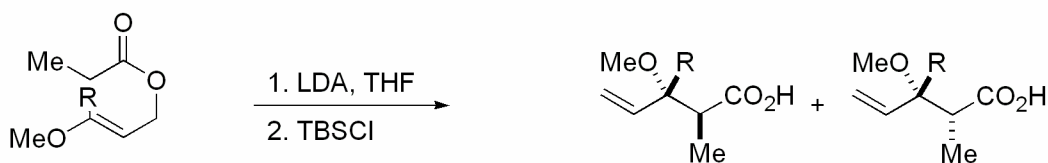
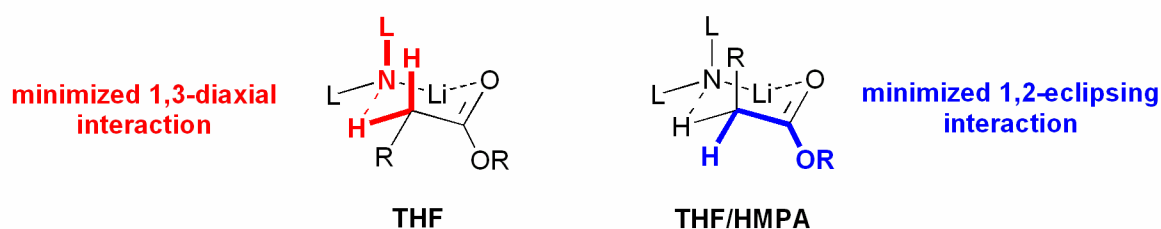
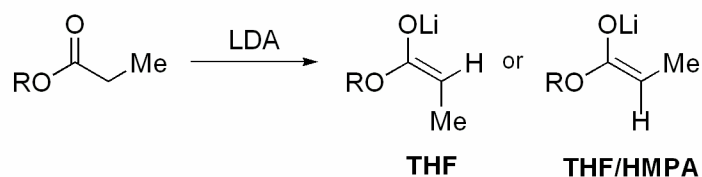
Claisen on cup-shaped substrates: highly selective



J. Am. Chem. Soc. **1982**, *104*, 2198.

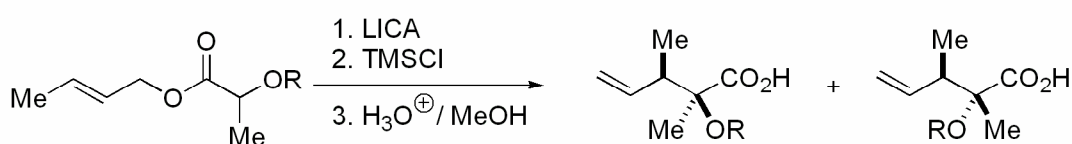
2.3. Claisen-Ireland Rearrangement

Acyclic substrates: selective enolate formation is crucial for high selectivities



Ireland *J. Am. Chem. Soc.* **1976**, 98, 2868.
Tetrahedron Lett. **1977**, 33, 2839.
 Ireland and Wipf *J. Org. Chem.* **1991**, 56, 650.

R	solvent	dr [%]
H	THF	82 : 18
H	THF/HMPA	20 : 80
Me	THF	83 : 17
Me	THF/HMPA	23 : 77

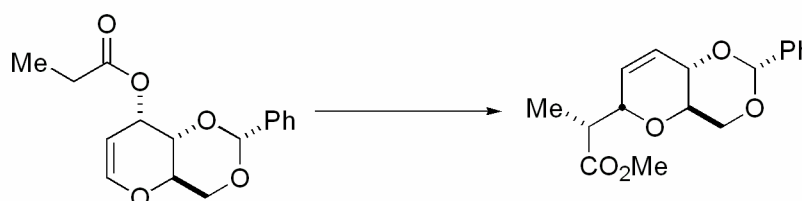


Bartlett *J. Org. Chem.* **1982**, 47, 3941.

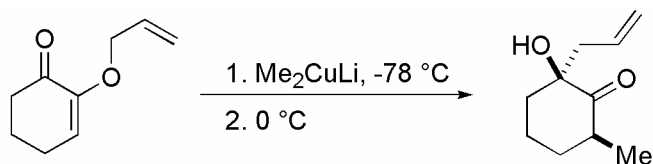
chelation effect

R	dr [%]
Bn	3 : 1
MgCl	10 : 1

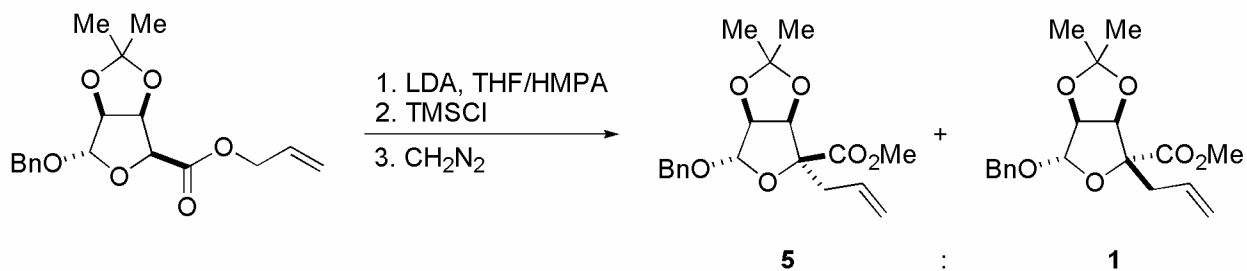
Ireland rearrangement: cyclic substrates



Ireland *J. Org. Chem.* **1981**, 46, 479.

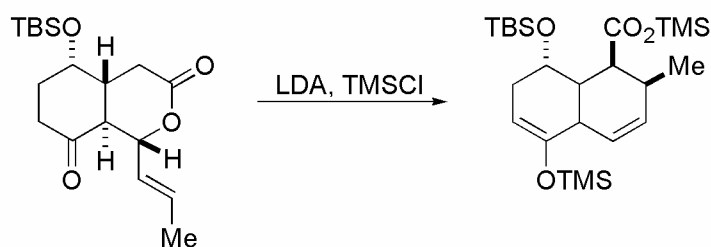


J. Am. Chem. Soc. **1985**, *107*, 5572.

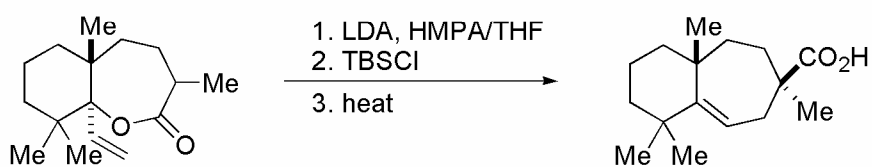


Tetrahedron Lett. **1994**, *35*, 923.

Rearrangement of bicyclic lactones

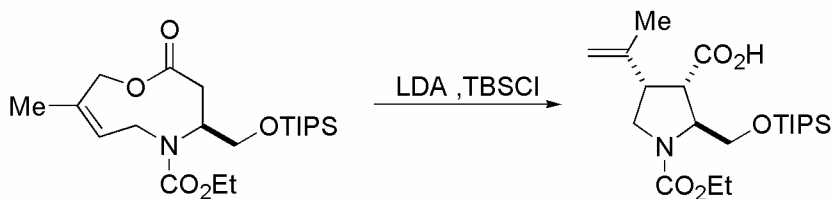


Danishefsky *J. Am. Chem. Soc.* **1989**, *111*, 2599.



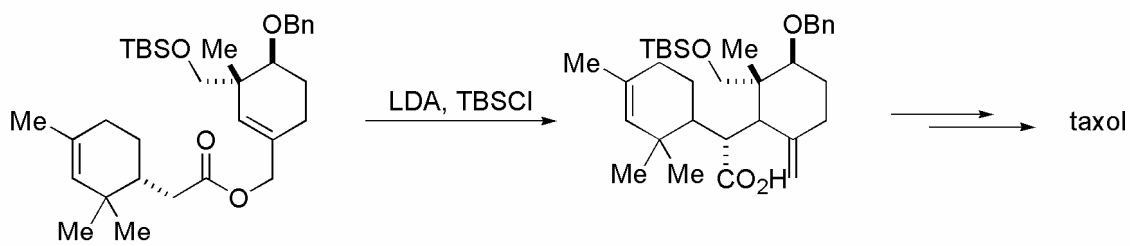
Danishefsky *J. Am. Chem. Soc.* **1980**, *102*, 6891.

Ring contraction of lactones



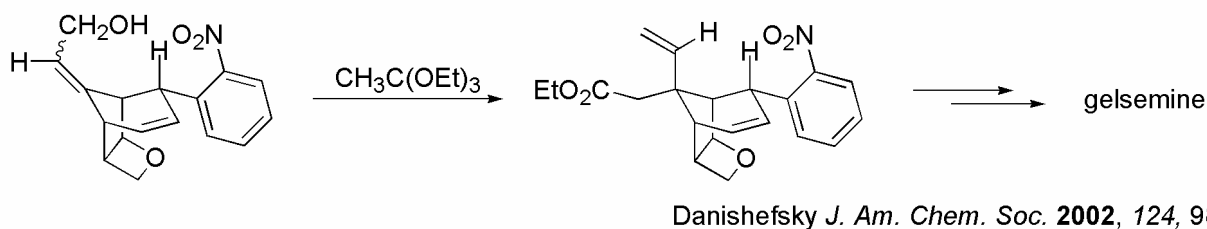
J. Chem. Soc. Perkin Trans. 1 **1992**, *5*, 553.

Magnus' approach towards taxol

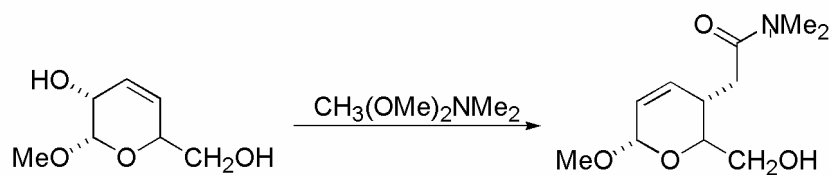


2.4. Other Claisen Rearrangements

2.4.1. Johnson-Claisen Rearrangement

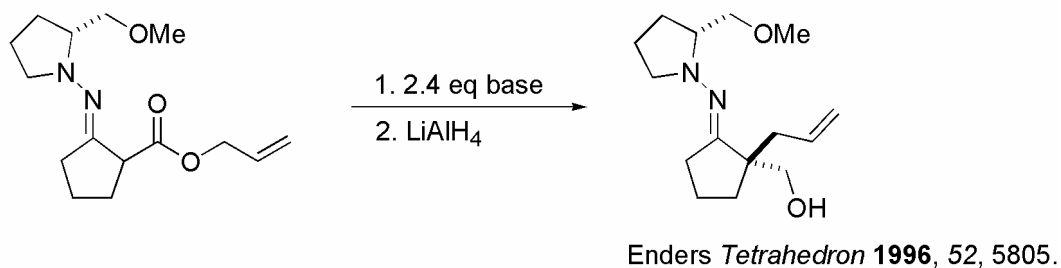


2.4.2. Eschenmoser-Claisen Rearrangement



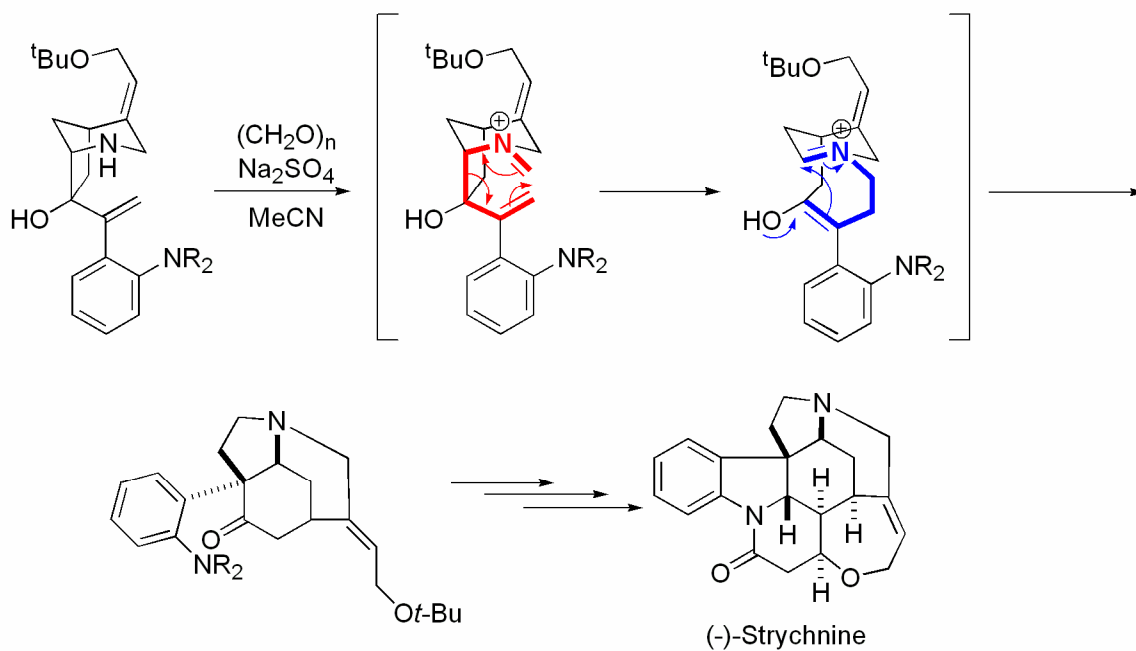
2.4.3. Carroll-Claisen Rearrangement

SAMP chiral auxiliary for the Carroll rearrangement

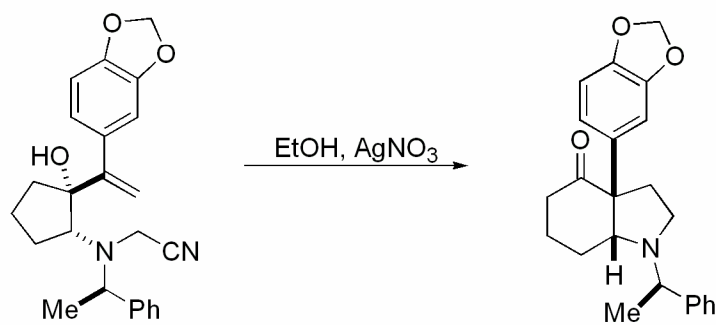


2.5. "Aza-Claisen" Rearrangement

The aza-Claisen-Mannich tandem reaction

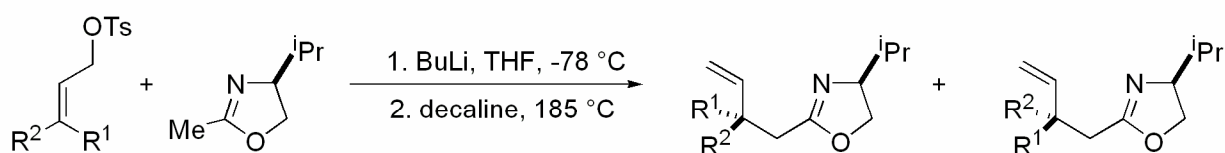


Overman *J. Am. Chem. Soc.* **1993**, *115*, 9293.



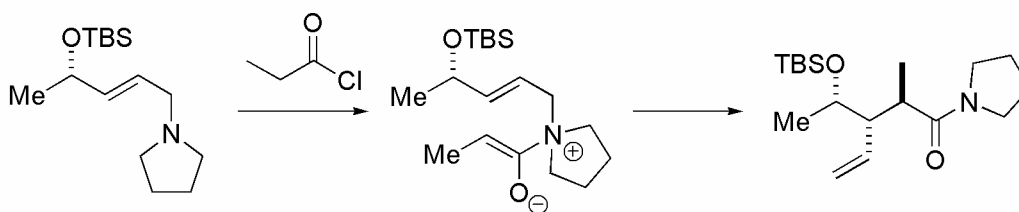
Overman *Helv. Chim. Acta* **1985**, *68*, 745.

Remote stereocontrol through chiral oxazolines

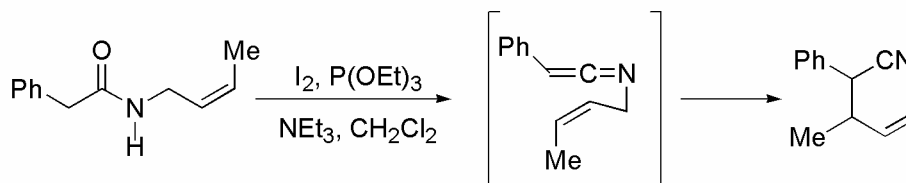


R ¹	R ²	dr [%]
Me	H	87 : 13
H	Me	81 : 19

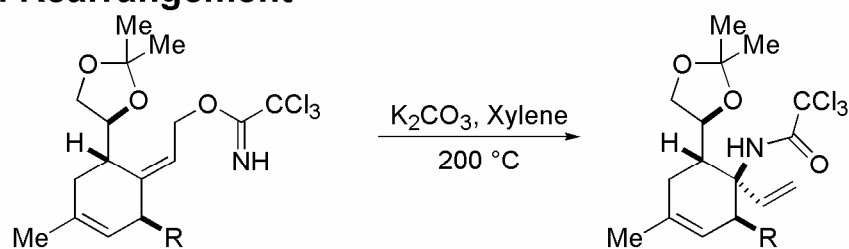
J. Org. Chem. **1985**, *50*, 5769.

Charge acceleration and remote stereocontrol

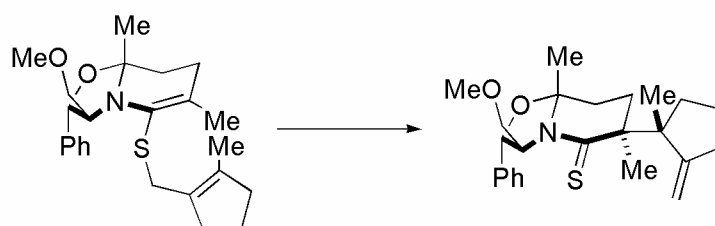
J. Org. Chem. **1995**, *60*, 3773.

Use of hetero-cumulene: access to nitriles

J. Org. Chem. **1994**, *59*, 2645.

2.6. Overman Rearrangement

J. Am. Chem. Soc. **2002**, *124*, 7847.

2.7. Thia-Claisen Rearrangement**Chiral auxiliary for the thia-Claisen rearrangement**

Meyers *J. Am. Chem. Soc.* **1998**, *120*, 5453.

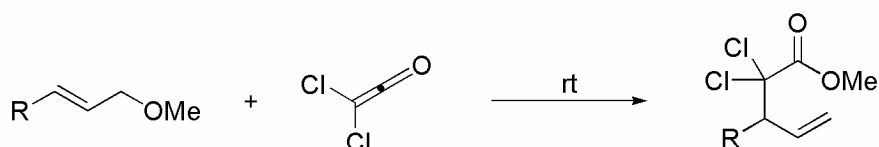
3. Metal Assisted Sigmatropic Rearrangements

By binding to hetero atoms, metals (often B, Al, Pd) can lower the activation energy, allowing to conduct the reaction at rt or lower temperature

Chiral metal complexes offer the opportunity to control the absolute stereochemistry of the product, but usually don't need extra steps to be introduced and removed as chiral auxiliaries do

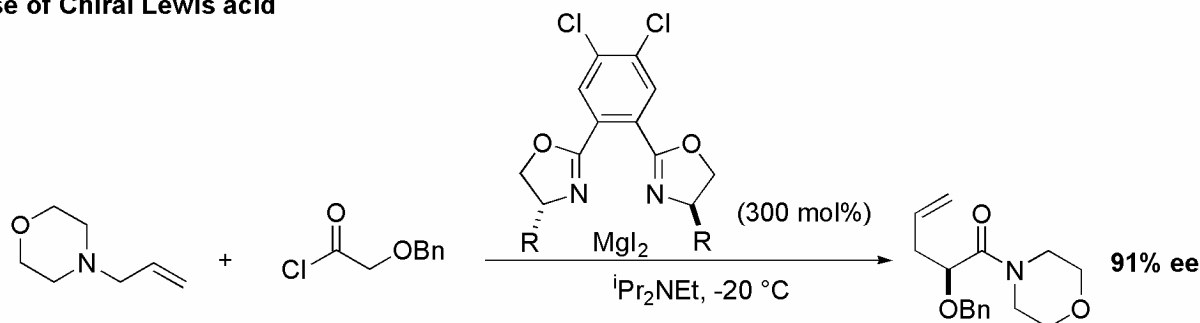
A severe limitation of this method is the use of stoichiometric amounts of metal complexes, as the product of the sigmatropic reaction usually binds the metal more tightly than the starting material. Progress towards catalytic sigmatropic reactions has been achieved only very recently.

Use of ketenes for [3,3] rearrangements



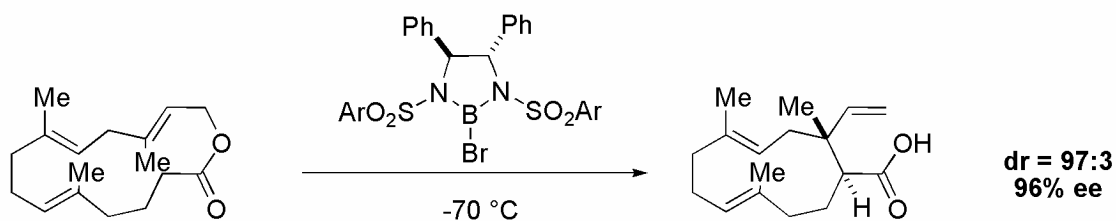
Bellus Helv. Chim. Acta **1978**, *61*, 3096.

Use of Chiral Lewis acid

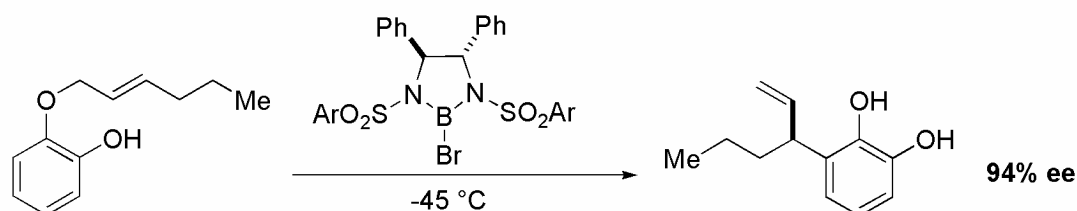


MacMillan J. Am. Chem. Soc. **2001**, *123*, 2911.

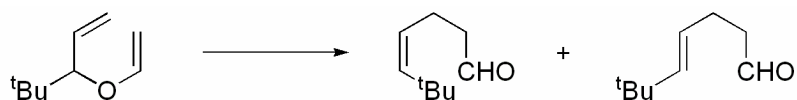
Use of chiral metal bound enolates or alcoholates



Corey J. Am. Chem. Soc. **1996**, *118*, 1229.

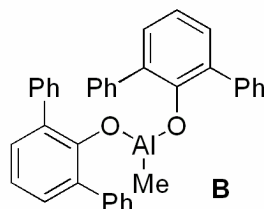
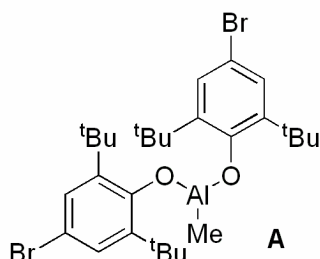


Tetrahedron Lett. **1997**, *38*, 4815.



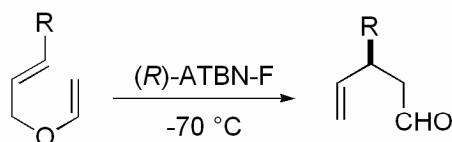
catalyst	conditions	dr [%]
A	-78 °C, 30 min	93 : 7
B	-20 °C, 20 min	7 : 93

Fine tuning of the ligand on Al promotes a change in transition state and reversed selectivity for double bond formation.



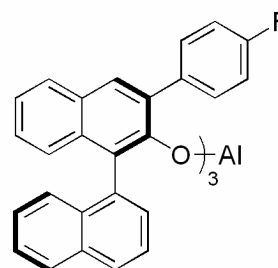
Yamamoto *J. Am. Chem. Soc.* **1988**, *110*, 7922.

Chiral Al-complex for enantioselective Claisen rearrangement:



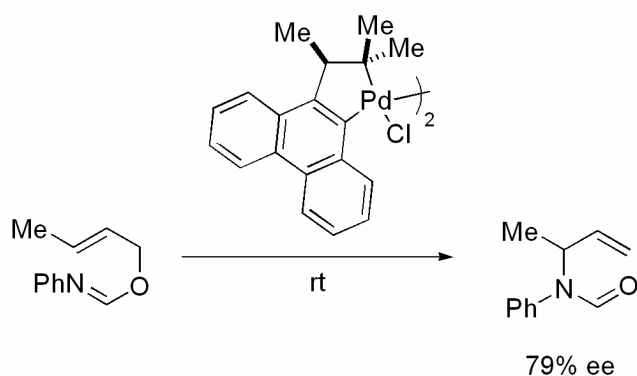
R	ee [%]
tBu	91
Ph	76
TMS	92

(R)-ATBN-F:



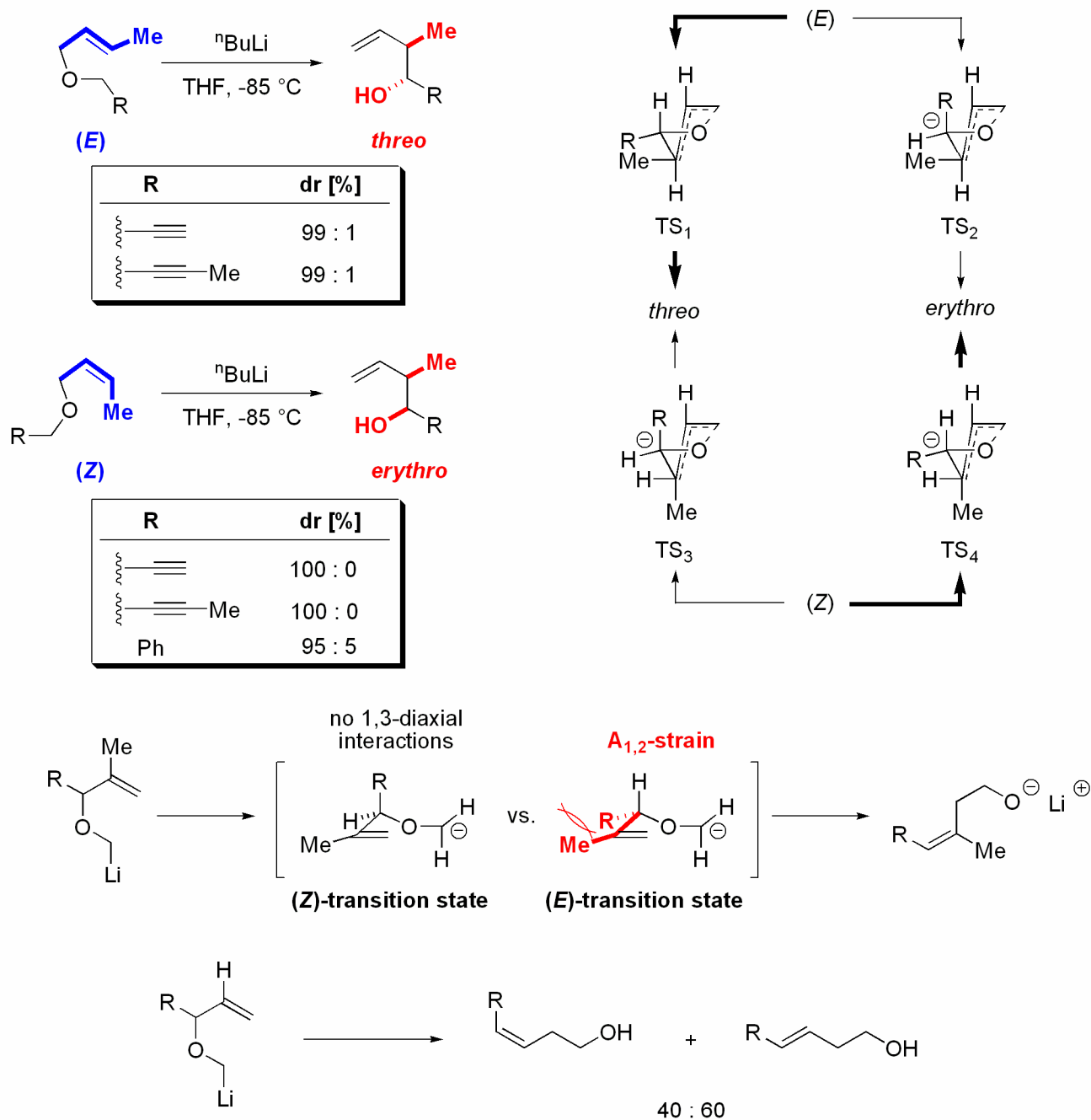
Yamamoto *J. Am. Chem. Soc.* **1995**, *117*, 1165.

Chiral Pd-complex for enantioselective hetero-Claisen rearrangement:



Chem. Commun. **1999**, 2435.

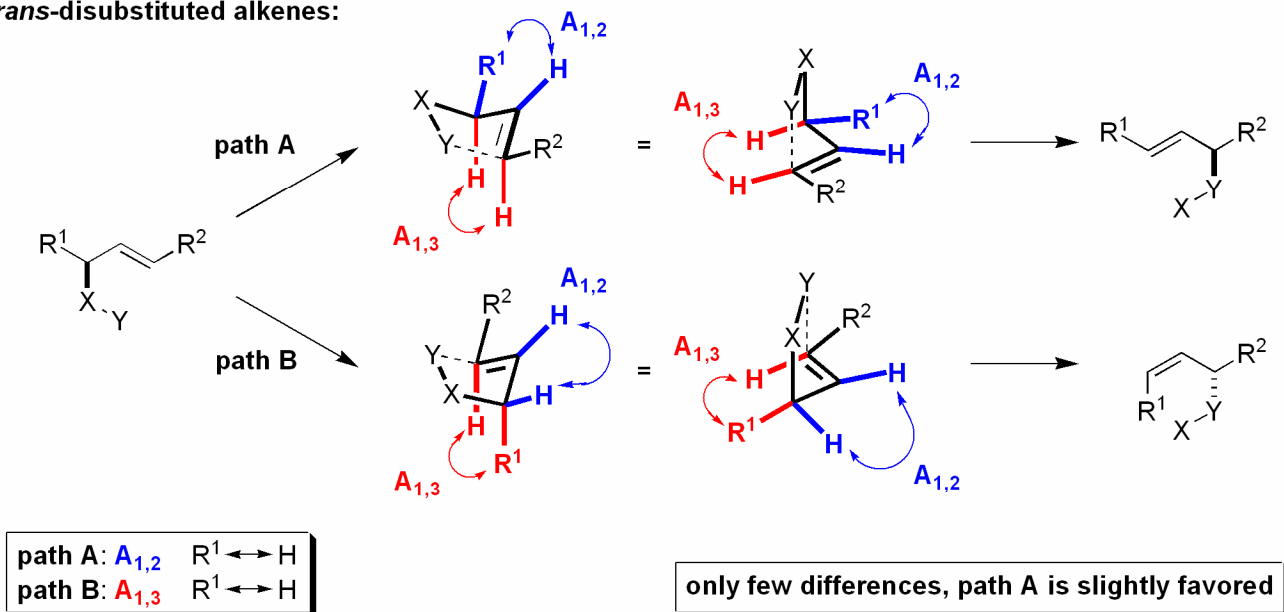
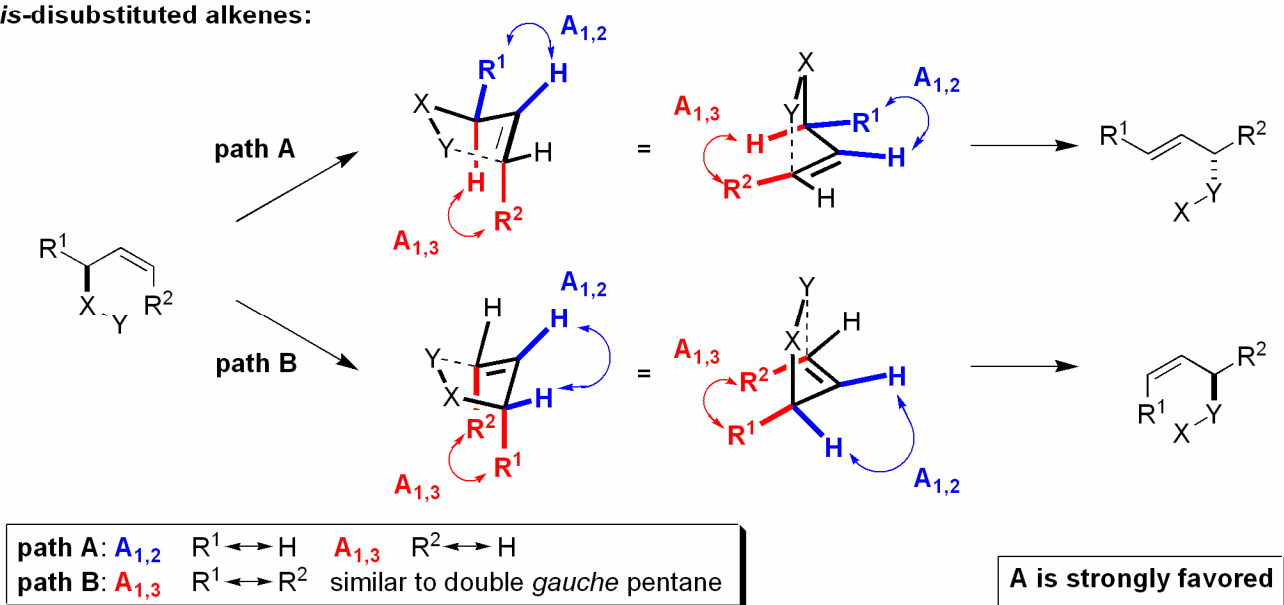
4. [2,3] Sigmatropic Rearrangement: the Wittig Reaction

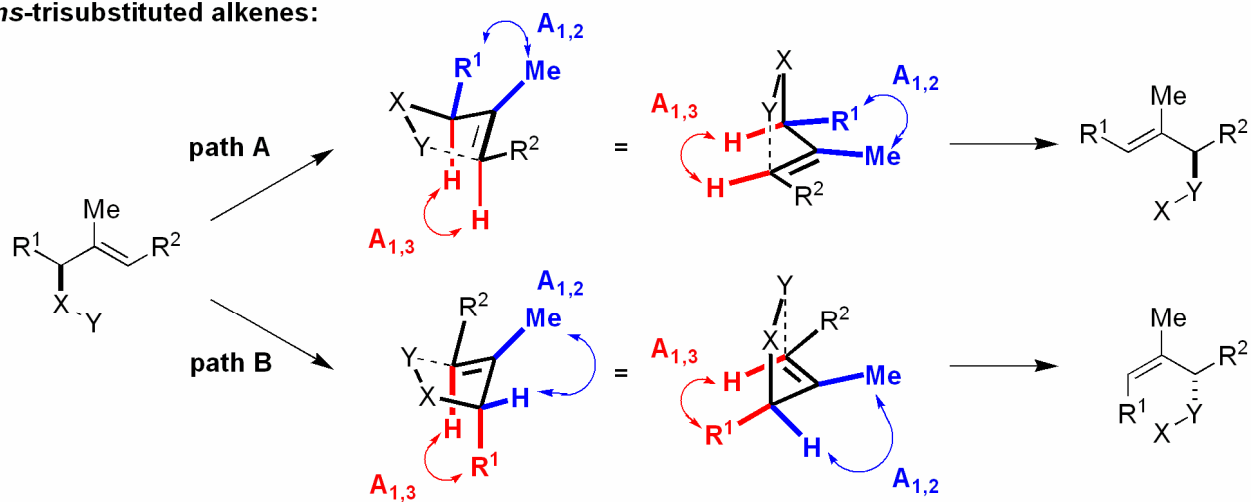


For the [2,3] sigmatropic rearrangement, the transition state is a more flexible envelope conformation. This makes transition state analysis more difficult, as different conformers can be used to explain the observed selectivity.

High selectivities are only achieved for special cases, in which clear steric interactions (e.g. A_{1,2}-strain) are encountered.

4.1. Wittig Rearrangement: Detailed Analysis

trans-disubstituted alkenes:*cis*-disubstituted alkenes:

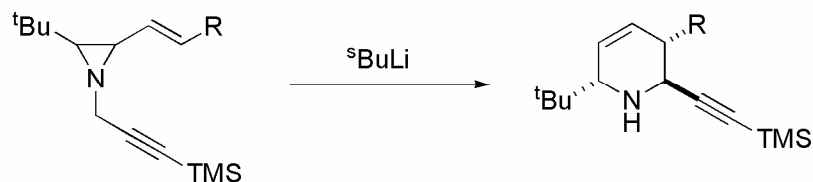
trans-trisubstituted alkenes:

path A:	A _{1,2}	R ¹ ↔ Me		
path B:	A _{1,2}	Me ↔ H	A _{1,3}	R ¹ ↔ H

path B is favored

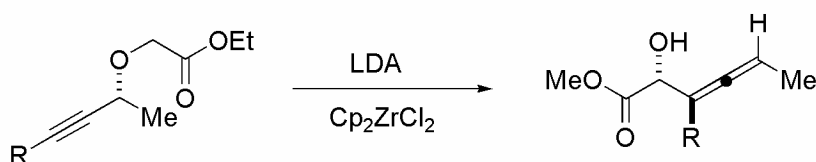
4.2. Practical Application of the Wittig Rearrangement

Release of ring strain as driving force:



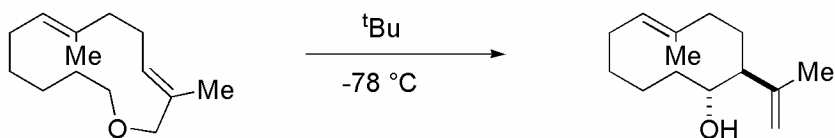
Somfai *Tetrahedron Lett.* **1996**, 37, 2495.

Stereoselective formation of allenes:



Marshall *J. Org. Chem.* **1991**, 56, 4913.

Use in natural products synthesis:



Tetrahedron **1989**, 43, 5499.