

Stereochemistry and stereocontrolled synthesis (OC 8)

A lecture from Prof. Paul Knochel,
Ludwig-Maximilians-Universität München
WS 2015-16

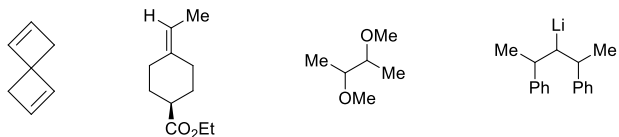
Wichtig!

- Prüfung Stereochemistry
02. Februar 2016
8:00 – 10:00
Willstätter-HS
- Nachholklausur Stereochemistry
5. April 2016
9:00 – 11:00
Willstätter-HS

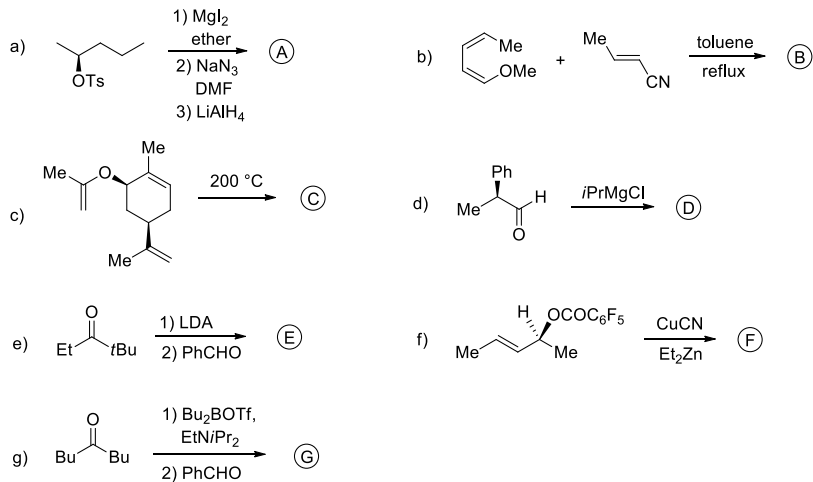
Problem set part I

First Problem Set for OC I Part I Prof. Paul Knochel

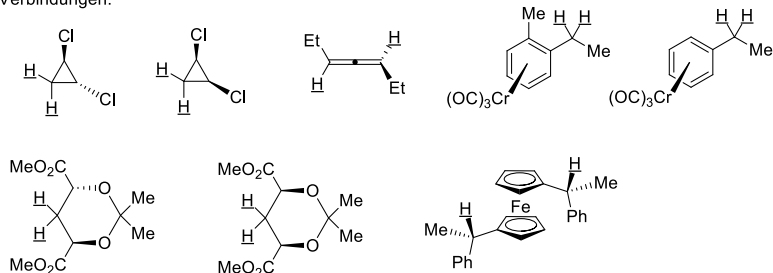
- 1) Geben Sie die Anzahl von Stereoisomeren sowie ihre stereochemische Bezeichnung (Enantiomer, Diastereoisomer) der folgenden Verbindungen:



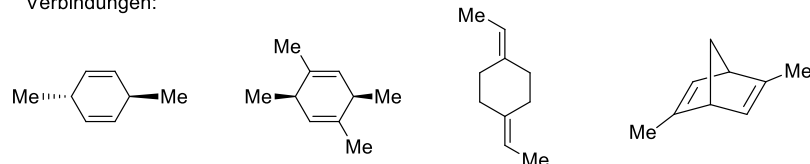
- 2) Geben Sie das Produkt der folgenden Umsetzungen:



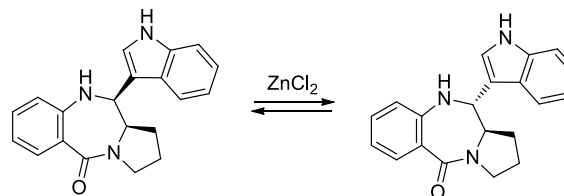
- 3) Klassifizieren Sie die markierten prochiralen Protonen (homotop, enantiotop, diastereotop) der folgenden Verbindungen:



- 4) Geben Sie die Anzahl und stereochemische Bezeichnung der Mono-Epoxidierungsprodukte folgender Verbindungen:



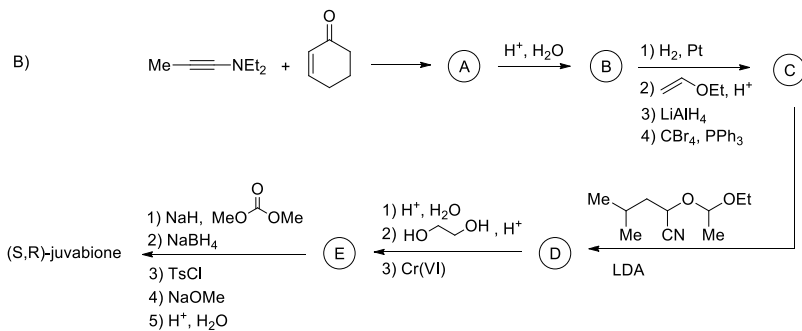
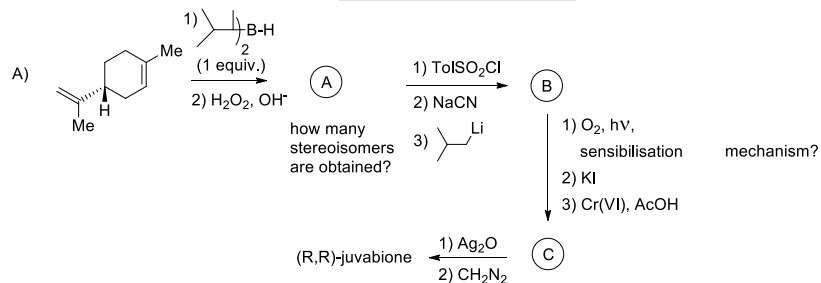
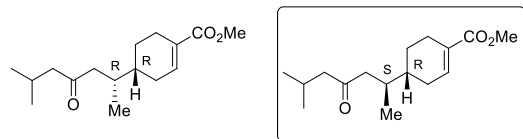
- 5) Durch Zugabe von ZnCl_2 wird das hier vorliegende Molekül epimerisiert, d. h. es entstehen zwei Diastereoisomere. Geben Sie einen möglichen Mechanismus für die Epimerisierung an:



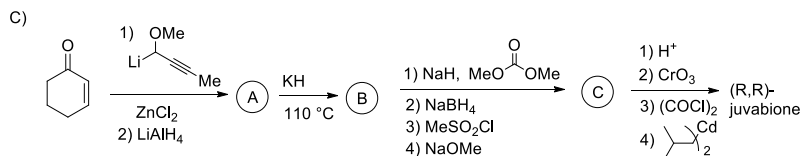
Problem set part II

First Problem Set for OC I part II Prof. Paul Knochel

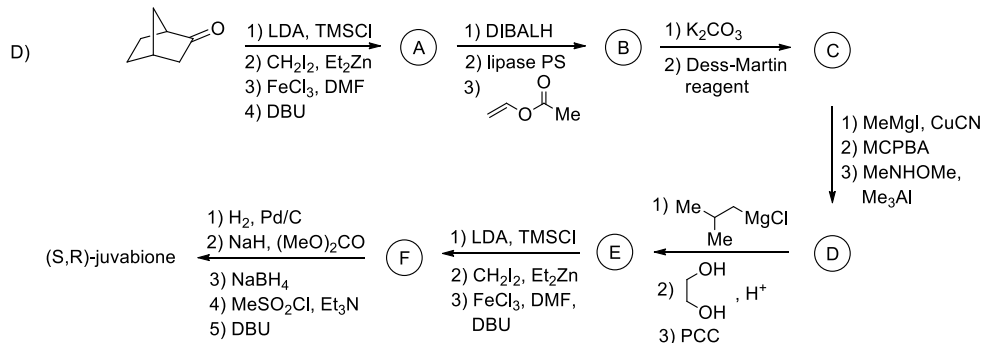
Stereoselective synthesis of (R,R) or (S,R)-juvabione



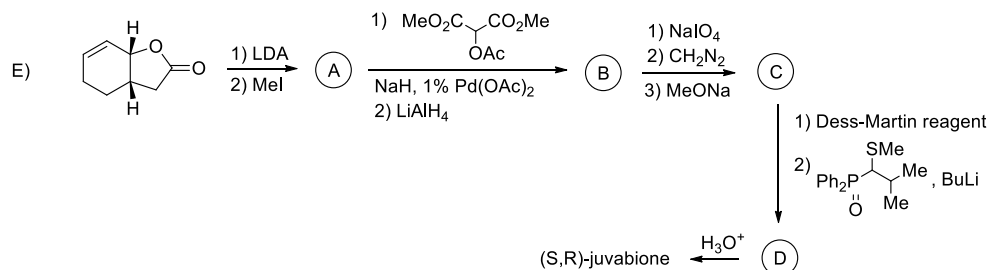
J. Ficini, *J. Am. Chem. Soc.* **1974**, 96, 1213



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



K. Ogasawara, *Tetrahedron Lett.* **1999**, 40, 4207



G. Helmchen, *J. Org. Chem.* **2000**, 65, 5072

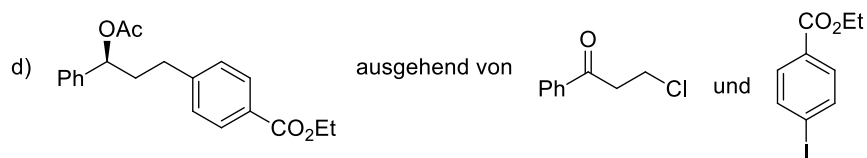
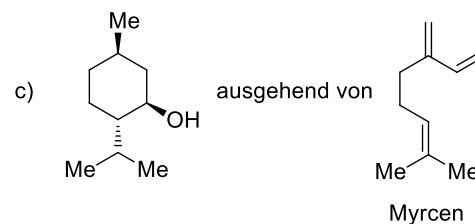
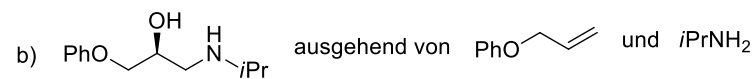
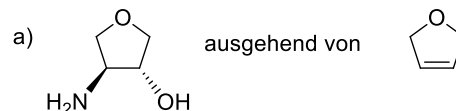
Problem set part III

First Problem Set for OC I part III Prof. Paul Knochel

1) Geben Sie das Produkt der folgenden Reaktionen:

- 1) CC(=O)Cc1ccccc1 $\xrightarrow[\text{THF, -78 } ^\circ\text{C}]{\text{LDA}}$ CC(=O)Cc1ccccc1 $\xrightarrow{\text{PhCH}_2\text{Br}}$ (A) $\xrightarrow[\text{NaBH}_4]{\text{Me}_2\text{NH}}$ (B)
- 2) CC(=O)Cc1ccccc1 $\xrightarrow[\text{THF, 25 } ^\circ\text{C}]{\text{NaH}}$ CC(=O)Cc1ccccc1 $\xrightarrow{\text{PhCH}_2\text{Br}}$ (C) $\xrightarrow[2) \text{Raney-Ni}]{1) \text{HS-CH}_2\text{CH}_2\text{SH}}$ (D)
- 3) CC(=O)C(C)C $\xrightarrow[\text{THF, -78 } ^\circ\text{C}]{\text{LDA}}$ CC(=O)C(C)C $\xrightarrow{\text{BuCHO}}$ (E)
- 4) CC(=O)CC(C)(C)C $\xrightarrow[\text{THF, -78 } ^\circ\text{C}]{\text{LDA}}$ CC(=O)CC(C)(C)C $\xrightarrow{\text{BuCHO}}$ (F)
- 5) CC(=O)C1CCCCC1 $\xrightarrow[2) \text{cyclohexanecarbaldehyde}]{1) \text{LDA, THF, -78 } ^\circ\text{C}}$ CC(=O)C1CCCCC1 $\xrightarrow[25 ^\circ\text{C}]{\text{MgBr}_2}$ (G)
- 6) CC(=O)CC(C)C $\xrightarrow[\text{iPr}_2\text{NEt}]{\text{Bu}_2\text{BOTf}}$ CC(=O)CC(C)C $\xrightarrow{\text{MeCHO}}$ (H)
- 7) CC(=O)N1C(=O)OCC1Cc1ccccc1 $\xrightarrow[\text{TiCl}_4]{\text{iPr}_2\text{NEt}}$ CC(=O)N1C(=O)OCC1Cc1ccccc1 $\xrightarrow{\text{MeCHO}}$ $\xrightarrow[\text{MeOH}]{\text{LiOMe}}$ (I)
- 8) CC(=O)C(C)C $\xrightarrow[3) \text{Me}_2\text{tBuSiCl, -78 } ^\circ\text{C}]{1) \text{MeCH}_2\text{COCl, 2) LDA, DMPU, -78 } ^\circ\text{C}}$ (J) $\xrightarrow[-78 ^\circ\text{C to 25 } ^\circ\text{C}]{\text{H}_3\text{O}^+}$ (K)
- 9) CC1CCCCC1O $\xrightarrow[25 ^\circ\text{C, 4 h}]{\text{Br}_2/\text{Ti}(\text{OiPr})_4}$ (L)
- 10) CC(C)C(C)C(C)C $\xrightarrow{\text{Bu}_2\text{CuLi}}$ (M)

2) Wie können Sie folgende chirale Verbindungen herstellen?

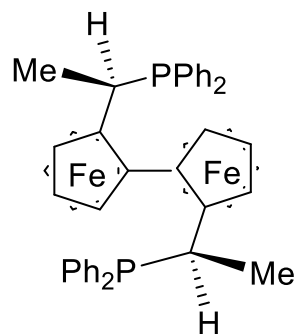


Recommended Literature

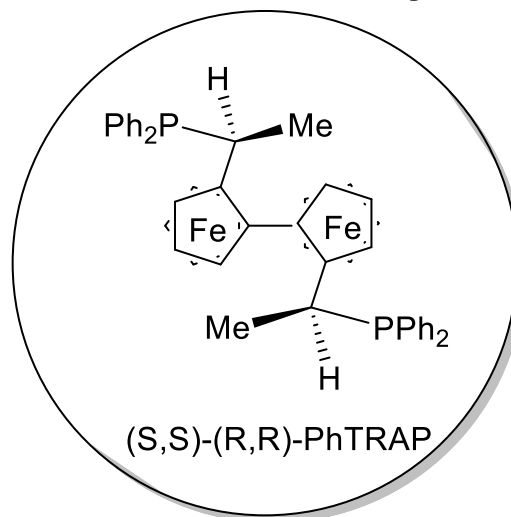
- E. Juaristi, Stereochemistry and Conformational Analysis, Wiley, 1991.
- E. Eliel, Stereochemistry of Organic Compounds, Wiley, 1994.
- A. Koskinen, Asymmetric Synthesis of Natural Products, Wiley, 1993.
- R. Noyori, Asymmetric Catalysis, Wiley, 1994.
- F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry, 5th Edition, Springer, 2007.
- A. N. Collins, G. N. Sheldrake, J. Crosby, Chirality in Industrie, Vol. I and II, Wiley, 1995 and 1997.
- G.Q. Lin, Y.-M. Li, A.S.C. Chan, Asymmetric Synthesis, 2001, ISBN 0-471-40027-0.
- P. Deslongchamps, Stereoelectronic Effects in Organic Chemistry, Pergamon, 1983.
- M. Nogradi, Stereoselective Synthesis, VCH, 1995.
- E. Winterfeldt, Stereoselective Synthese, Vieweg, 1988.
- R. Mahrwald (Ed.), Modern Aldol Reactions, Vol. I and II, Wiley, 2004.
- C. Wolf, Dynamic Stereochemistry of Chiral Compounds, RSC Publishing, 2008.
- A. Berkessel, H. Gröger, Asymmetric Organocatalysis, Wiley-VCH, 2005.
- J. Christoffers, A. Baro (Eds.), Quaternary Stereocenters, Wiley-VCH, 2005.
- Catalytic Asymmetric Synthesis, I. Oshima (Ed.), Wiley, 2010.

Recent advances of asymmetric catalysis

Asymmetric Hydrogenation of Heterocyclic Compounds

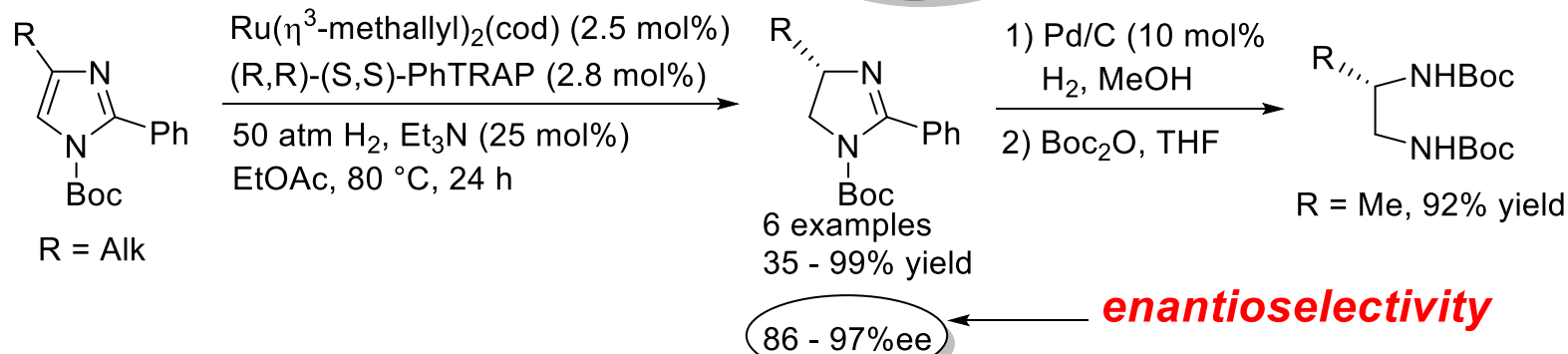


(R,R)-(S,S)-PhTRAP

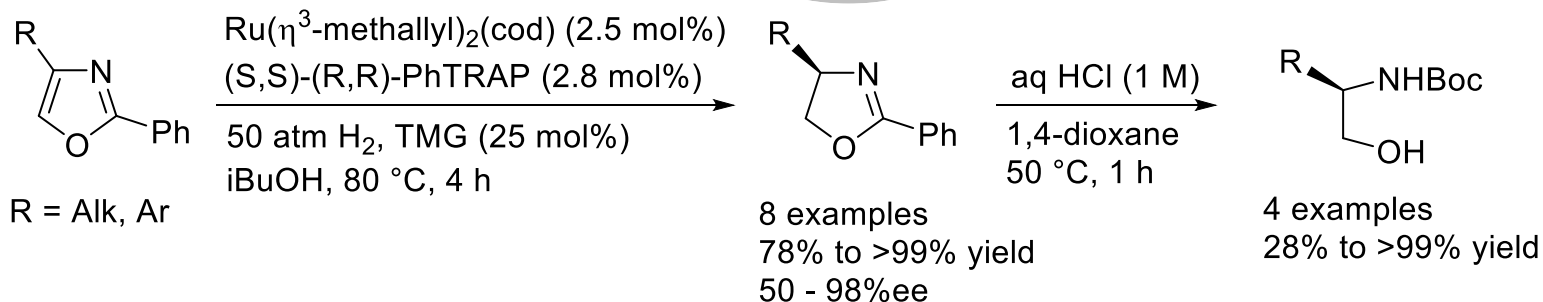


(S,S)-(R,R)-PhTRAP

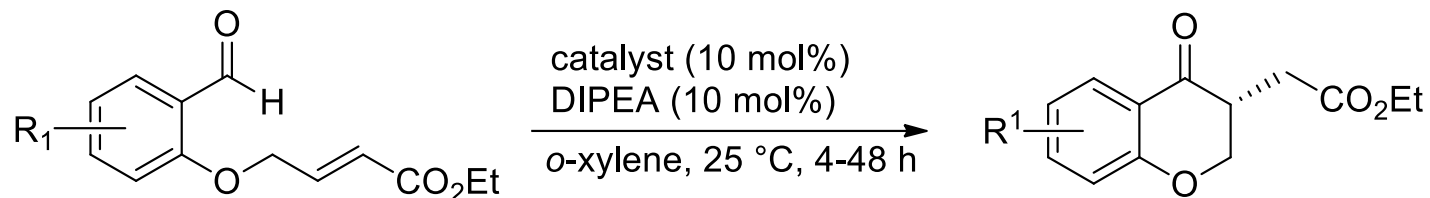
chiral ligand



enantioselectivity

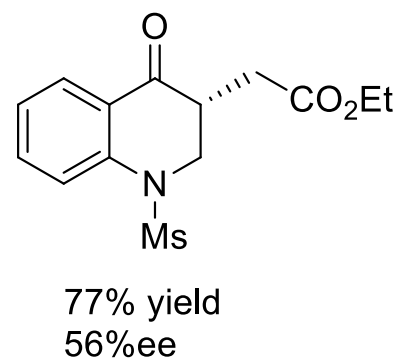
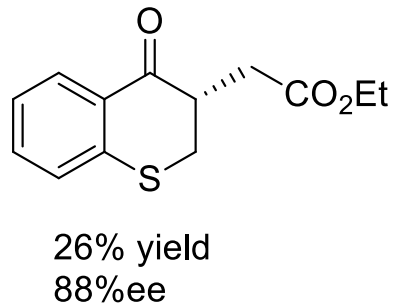
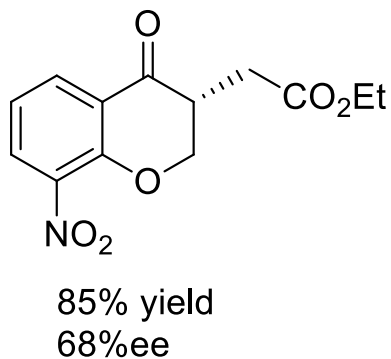
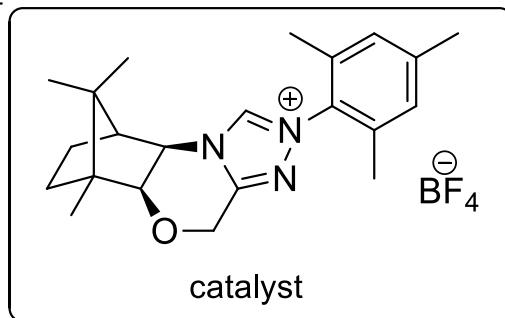


Camphor-Derived Organocatalytic Synthesis of Chromanones



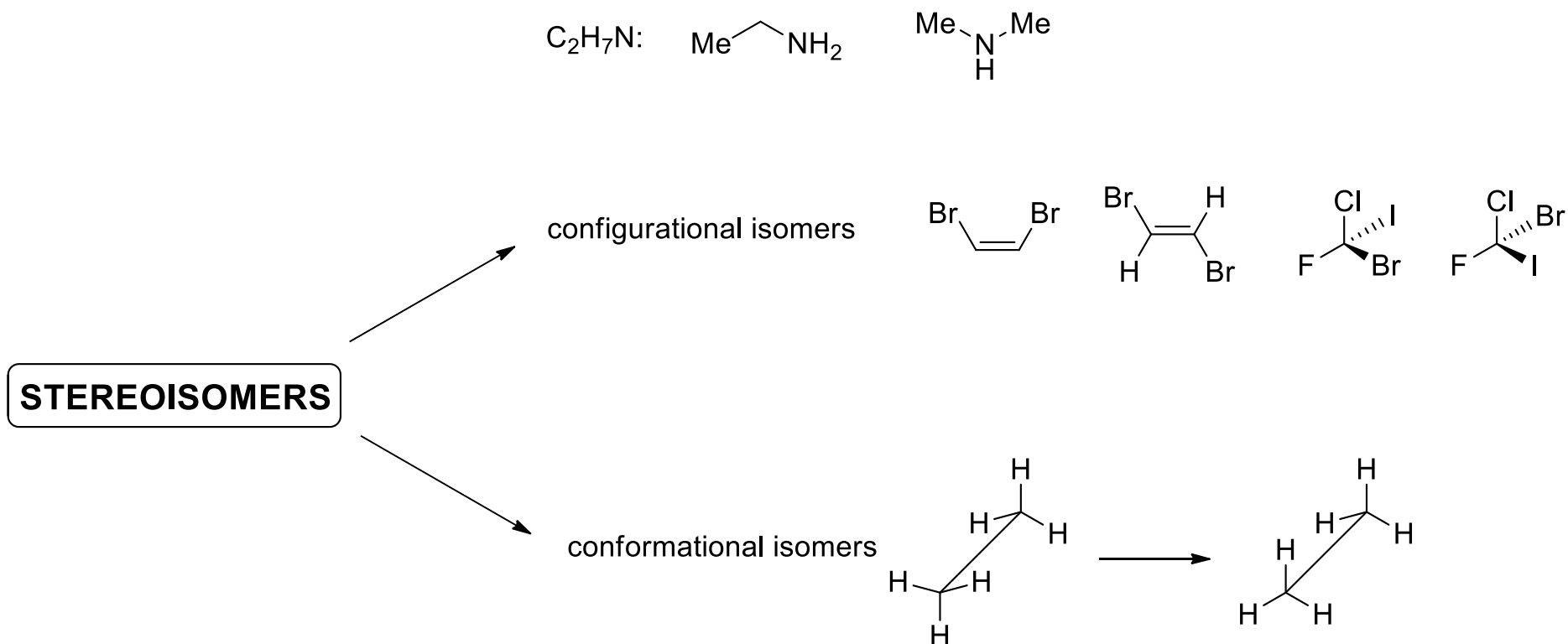
$\text{R}^1 = \text{H, 3-Me, 5-Me, 3-OMe, 4-OMe, 5-OMe, 5-Cl, 5-Br, 4-NEt}_2$

9 examples
 89 - 97% yield
 93 - 97%ee



Stereochemical principles - introduction and definitions

- Isomers are molecules having the same composition
- Structural isomers have different connectivities:



Classification of stereoisomers

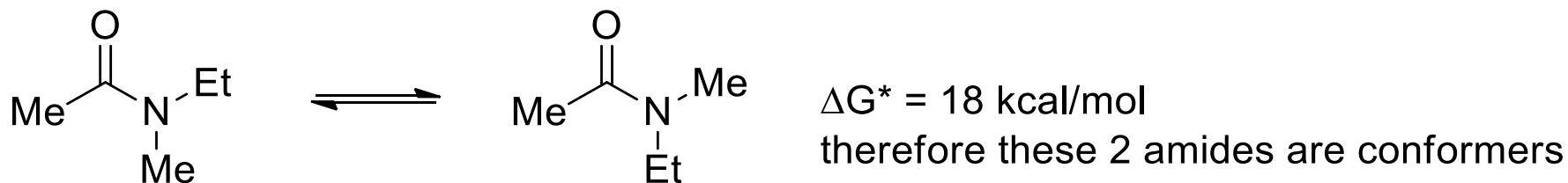
Enantiomers are two stereoisomers which are mirror images

Diastereomers are stereoisomers which are not enantiomers

Configuration isomers:



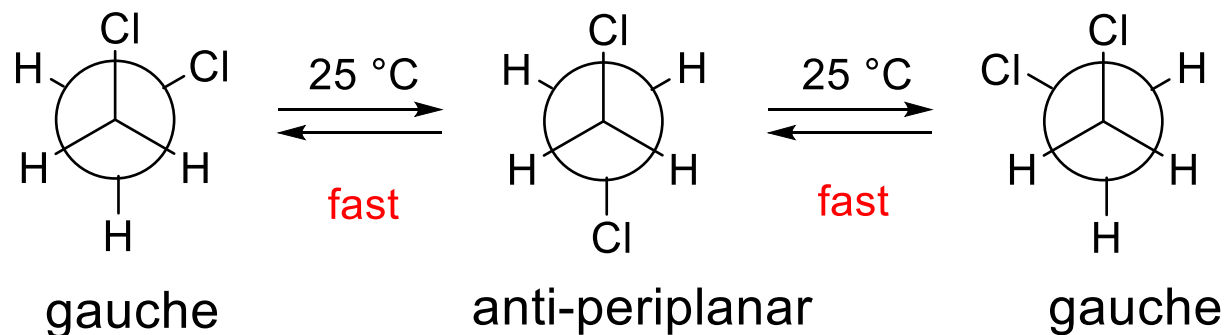
Conformation isomers:



The energy barrier has to be over 25 kcal/mol in order to speak of configurational isomers.

Introduction: classification of stereoisomers

- Conformation isomers:

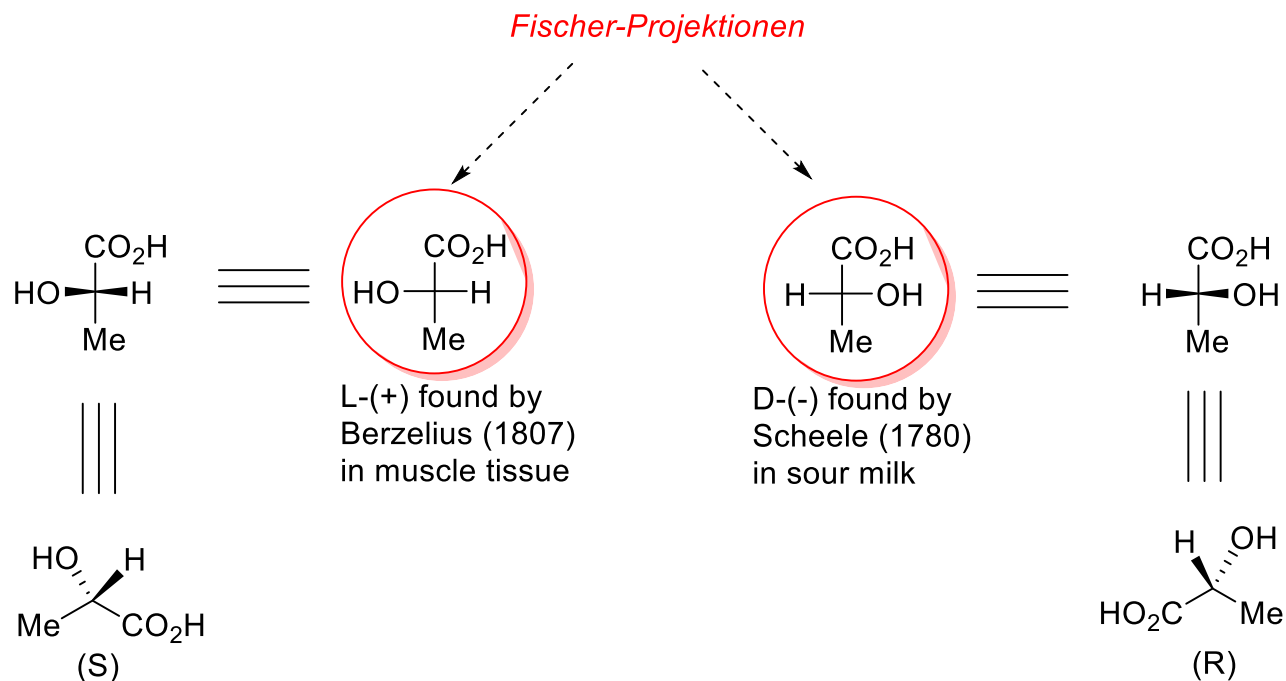


$$\Delta E^* = 3\text{-}5 \text{ Kcal/mol}$$

All processes having an energetic barrier (activation energy ΔE^*) lower than 19 Kcal/mol proceed at 25 °C

Introduction: classification of stereoisomers

Lactic acid as example



1874 suggestion by Van't Hoff; LeBel

The tetrahedral arrangement of substituents at Csp³ carbon centers.

Definitions

Chirality: A molecule is chiral if it is not identical with its mirror image.

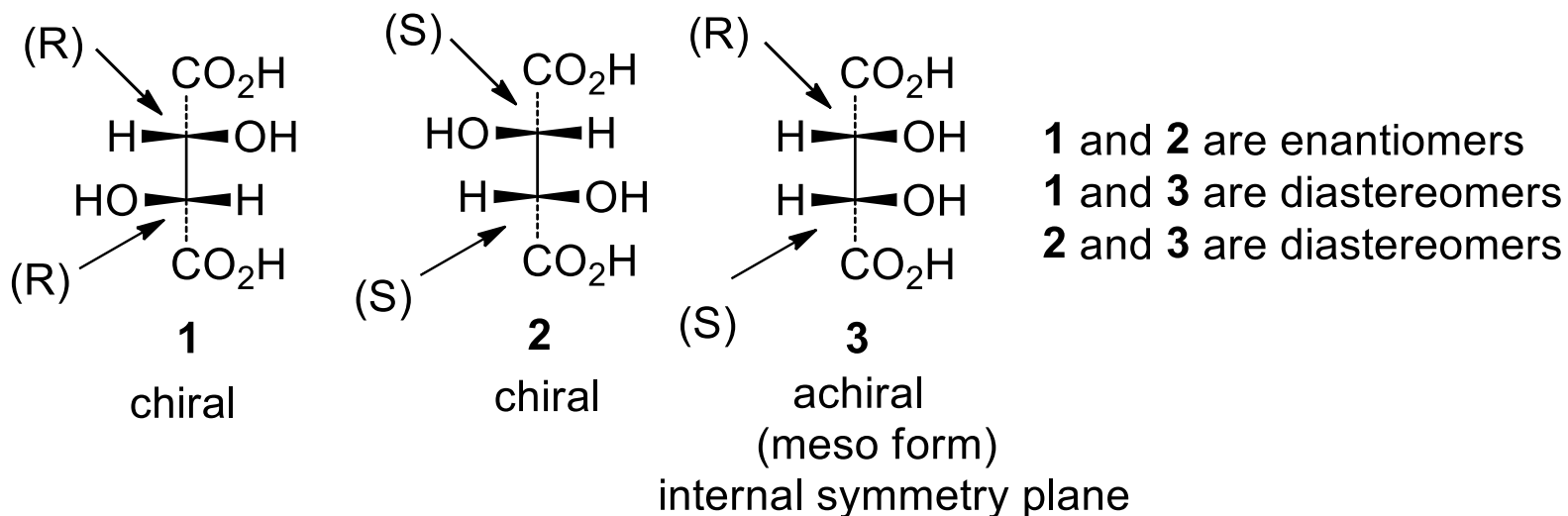
A chiral carbon-center bears 4 different substituents.

An organic molecule with n chiral centers has 2^n stereoisomers, if no additional symmetry element is present in this molecule.

A molecule is **achiral** if it contains a plane of symmetry or a center of inversion or a S_n symmetry element.

A **chiral** molecule may contain only C_n symmetry element and *identity* (E)

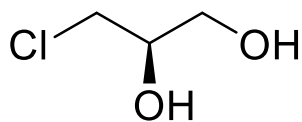
Tartaric acid exists only as 3 different stereoisomers:



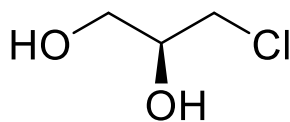
Properties of enantiomers

Two enantiomers have identical physical properties but show the opposite rotation of polarized light in a polarimeter.

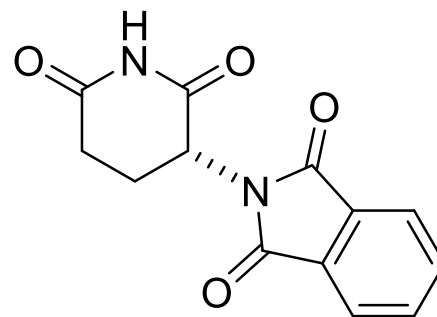
Importantly, the biological properties of enantiomers are different!



poison



useful pharmaceutical

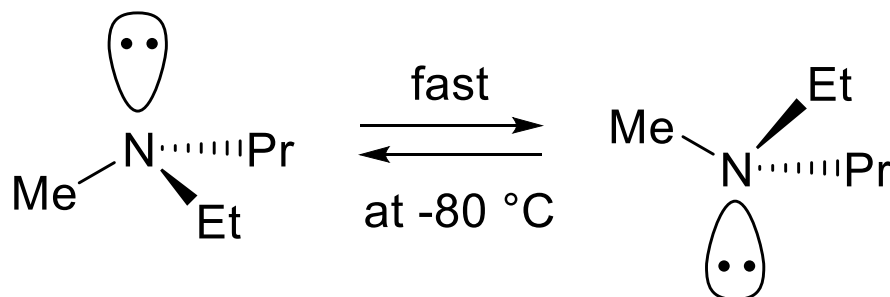
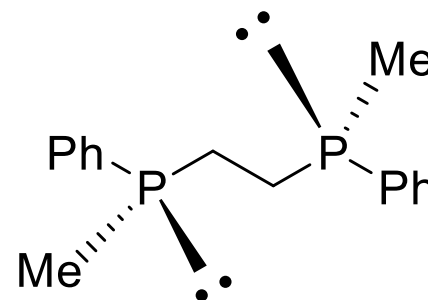
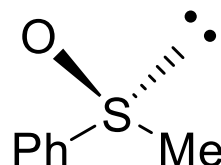
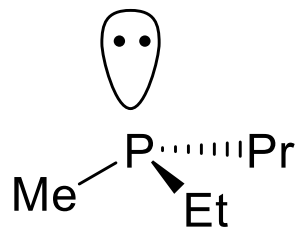
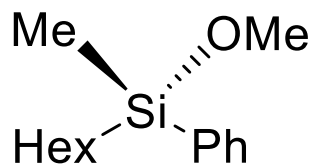


potent hypnotic

the enantiomer is teratogenic!

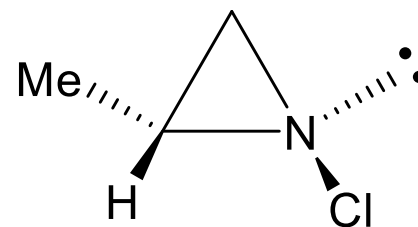
95% of all drugs are chiral, therefore the enantioselective synthesis of organic molecules is of key importance.

Chiral molecules not centered at carbon



$$\Delta E^* = 5 \text{ Kcal/mol}$$

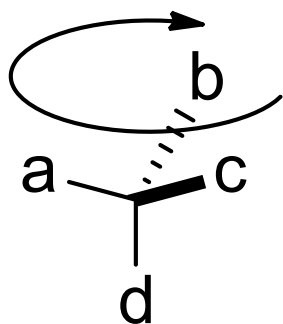
2×10^{11} inversions every second!



configurationally
stereoisomer

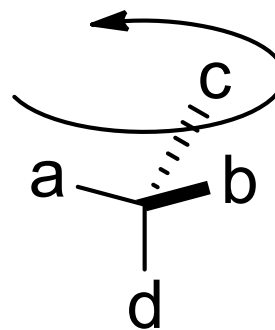
Nomenclature of stereoisomers

The Cahn-Ingold-Prelog rules (**CIP** rules)



(R)

clockwise



(S)

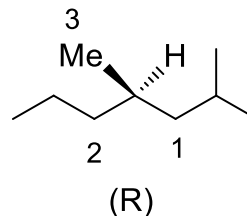
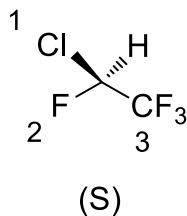
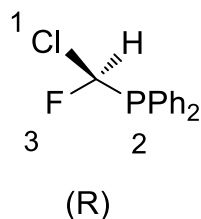
anti-clockwise

Nomenclature of stereoisomers

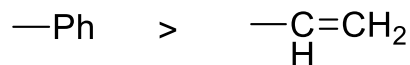
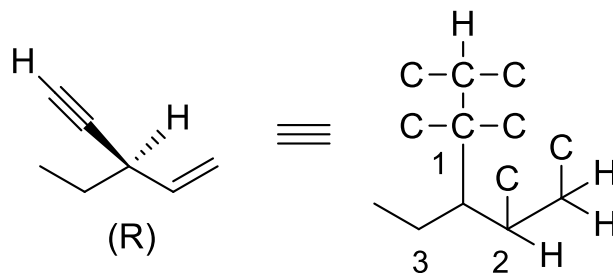
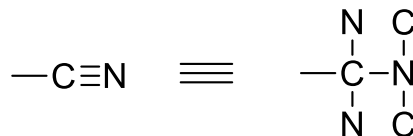
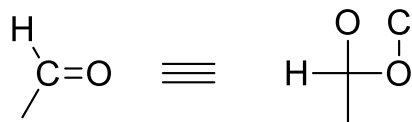
1. Highest atomic number: $I > Br > Cl$; $D > H$

2. $CH_2Br > CH_2Cl > CH_2OH > CH_2CH_3 > CH_3$

$CH_2Br > CCl_3$!



3. The case of multiple bonds



Nomenclature of stereoisomers

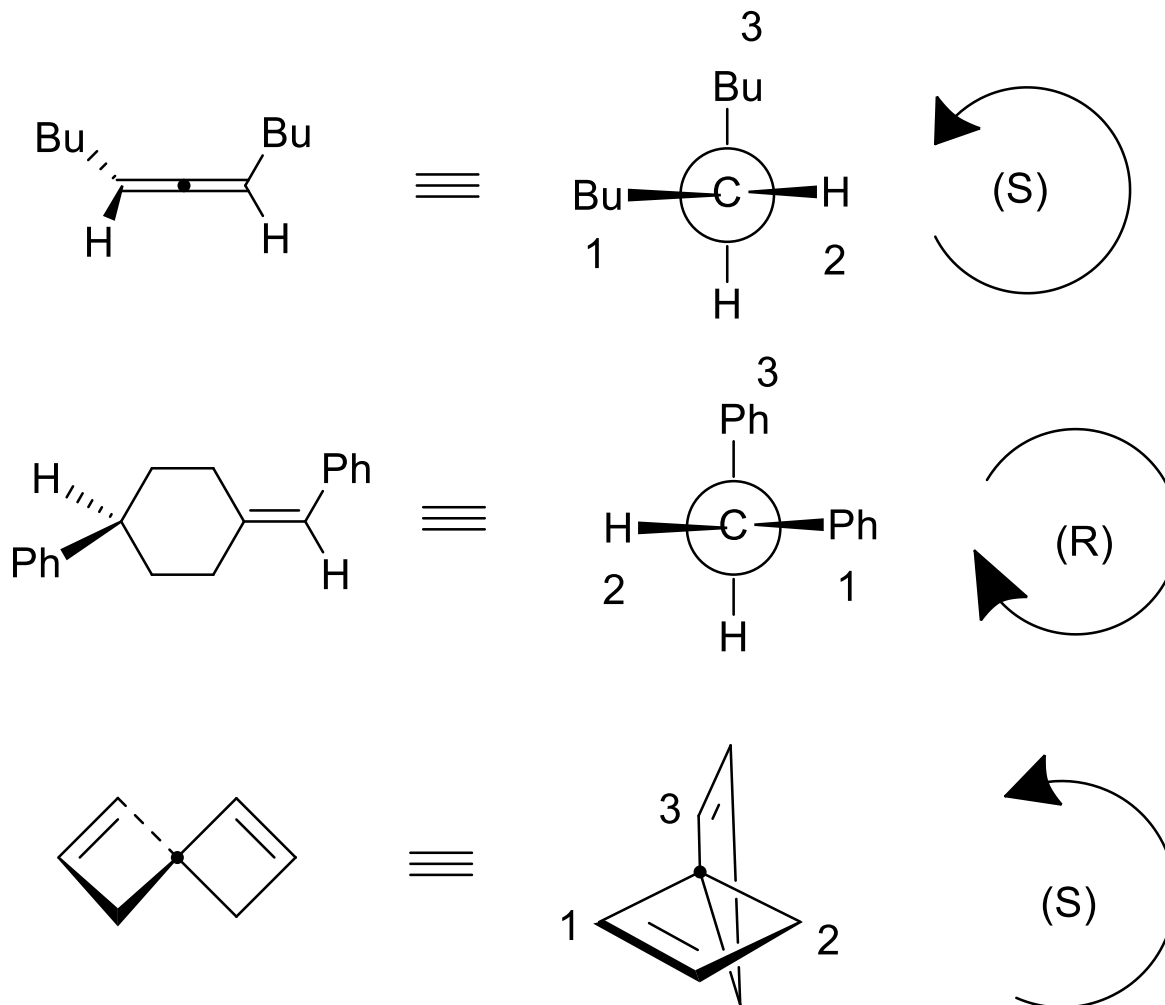
Ascending Order of Priority of Some Common Groups, According to the Sequence Rules

1. Electronic pair	21. $-\text{C}\equiv\text{CH}$	41. $-\text{NHCH}_3$
2. $-\text{H}$	22. $-\text{C}_6\text{H}_5$	42. $-\text{NHCH}_2\text{CH}_3$
3. $-\text{D}$	23. $-\text{C}_6\text{H}_4\text{CH}_3$ - <i>p</i>	43. $-\text{NHCOCH}_3$
4. $-\text{T}$	24. $-\text{C}_6\text{H}_4\text{NO}_2$ - <i>p</i>	44. $-\text{NHCOC}_6\text{H}_5$
5. $-\text{CH}_3$	25. $-\text{C}_6\text{H}_4\text{CH}_3$ - <i>m</i>	45. $-\text{N}(\text{CH}_3)_3$
6. $-\text{CD}_3$	26. $-\text{C}_6\text{H}_4\text{NO}_2$ - <i>m</i>	46. $-\text{N}^+(\text{CH}_3)_3$
7. $-\text{CH}_2\text{CH}_2\text{CH}_3$	27. $-\text{C}\equiv\text{C}-\text{CH}_3$	47. $-\text{N}=\text{O}$
8. $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	28. $-\text{C}_6\text{H}_4\text{CH}_3$ - <i>o</i>	48. $-\text{NO}_2$
9. $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	29. $-\text{C}_6\text{H}_4\text{NO}_2$ - <i>o</i>	49. $-\text{OH}$
10. $-\text{CH}_2\text{CH}(\text{CH}_3)_2$	30. $-\text{C}_6\text{H}_3(\text{NO}_2)_2$	50. $-\text{OMe}$
11. $-\text{CH}_2\text{CH}=\text{CH}_2$	31. $-\text{CHO}$	51. $-\text{OCOCH}_3$
12. $-\text{CH}_2\text{C}(\text{CH}_3)_3$	32. $-\text{COCH}_3$	52. $-\text{OSO}_2\text{CH}_3$
13. $-\text{CH}_2\text{C}\equiv\text{CH}$	33. $-\text{COC}_6\text{H}_5$	53. $-\text{F}$
14. $-\text{CH}_2\text{C}_6\text{H}_5$	34. $-\text{CO}_2\text{H}$	54. $-\text{SH}$
15. $-\text{CH}(\text{CH}_3)_2$	35. $-\text{CO}_2\text{CH}_3$	55. $-\text{SCH}_3$
16. $-\text{CH}=\text{CH}_2$	36. $-\text{CO}_2\text{CH}_2\text{CH}_3$	56. $-\text{S}(\text{O})\text{CH}_3$
17. $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	37. $-\text{CO}_2\text{C}_6\text{H}_5$	57. $-\text{SO}_2\text{CH}_3$
18. $-\text{C}_6\text{H}_{11}$ - <i>c</i>	38. $-\text{CO}_2\text{C}(\text{CH}_3)_3$	58. $-\text{Cl}$
19. $-\text{CH}=\text{CH}-\text{CH}_3$	39. $-\text{NH}_2$	59. $-\text{Br}$
20. $-\text{C}(\text{CH}_3)_3$	40. $-\text{NH}_3^+$	60. $-\text{I}$

Nomenclature of stereoisomers

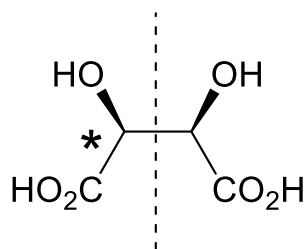
4. R,S-nomenclature for compounds with an axial chirality

allenes:



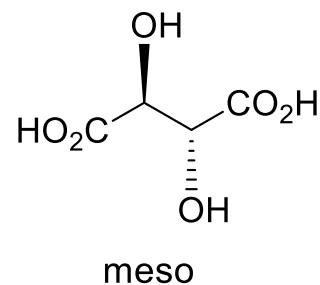
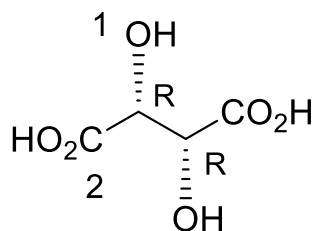
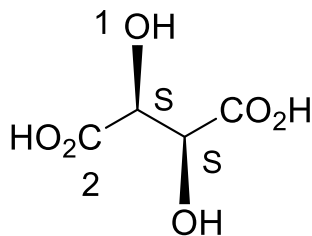
Prochirality: homotopicity, enantiotopicity, diastereotopicity

Relevance of symmetry:

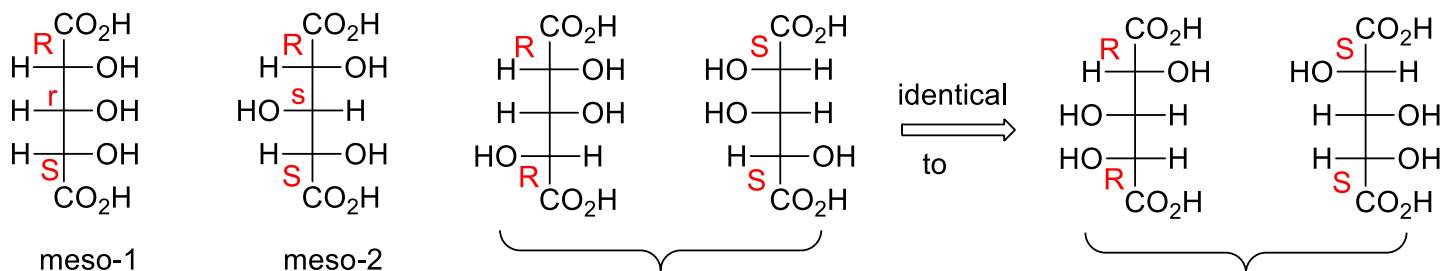


σ_h

2 stereocenters but only 3 stereoisomers

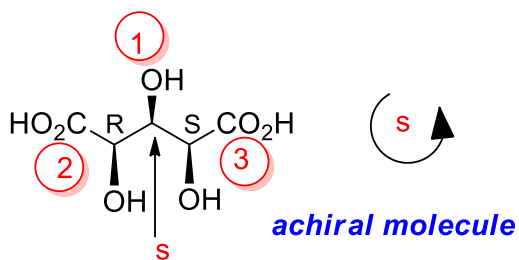


Fischer-Projection



2 enantiomeric chiral molecules
with a chirotopic center

chiral molecules
with a chirotopic center

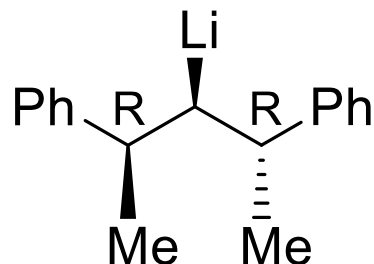


$$\begin{array}{c}
 \text{OH} \\
 | \\
 \text{HO}_2\text{C}-\text{R}-\text{C}-\text{R}-\text{CO}_2\text{H} \\
 | \quad \quad | \\
 \text{OH} \quad \quad \text{OH}
 \end{array}$$
chiral molecule

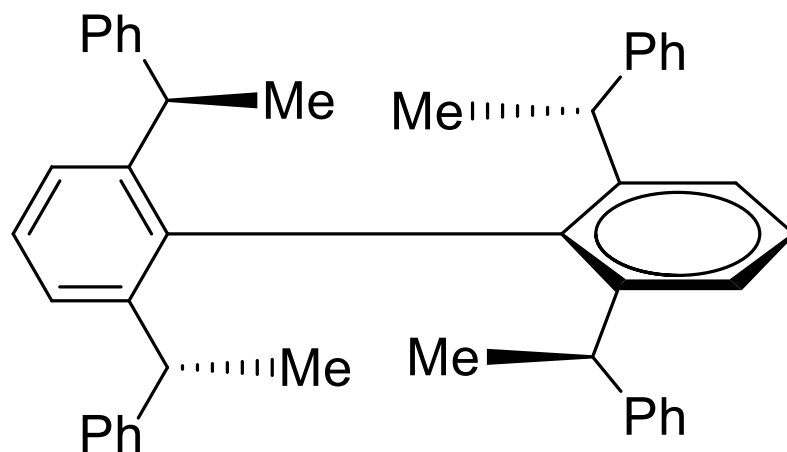
a chirotopic center is a non-stereogenic center in a chiral environment

a chiral center requires a chiral environment
and to be stereogenic (surrounded by 4 different substituents)
a **chirotopic center** or a **pseudo-asymmetric center** are not a chiral center

Molecules with a chirotopic center or a chirotopic center



chiral configurational stable molecule

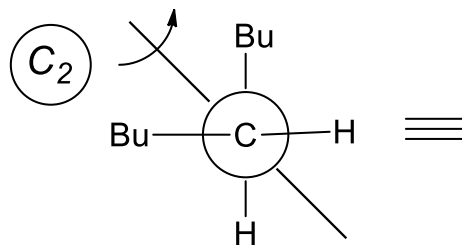
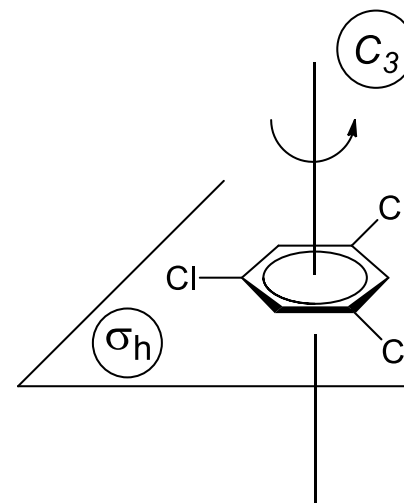
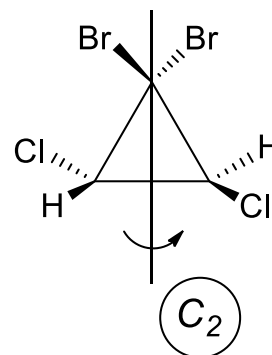
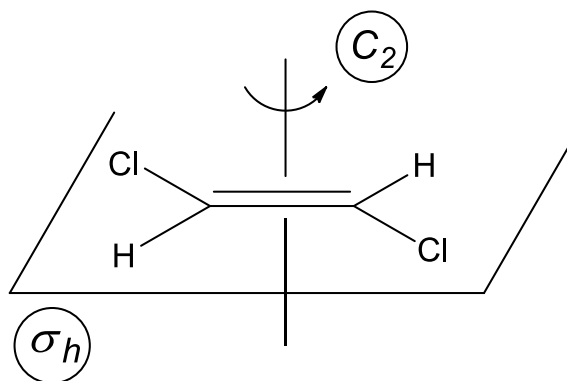
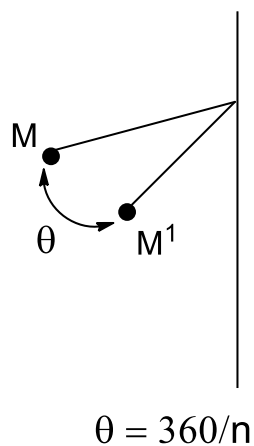


chirotopic chirality axis

Symmetry and stereochemistry

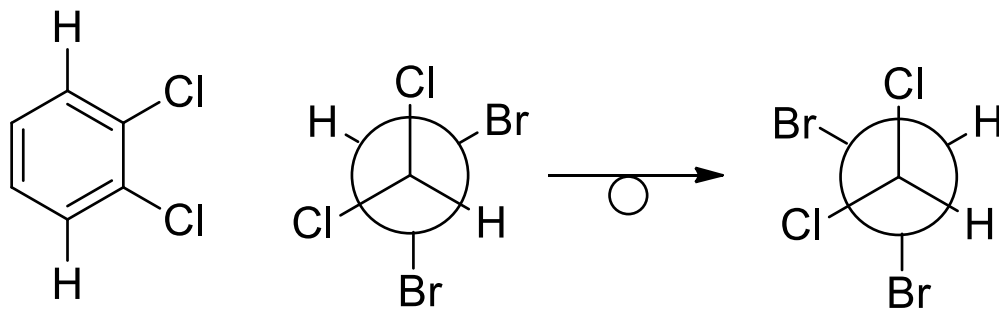
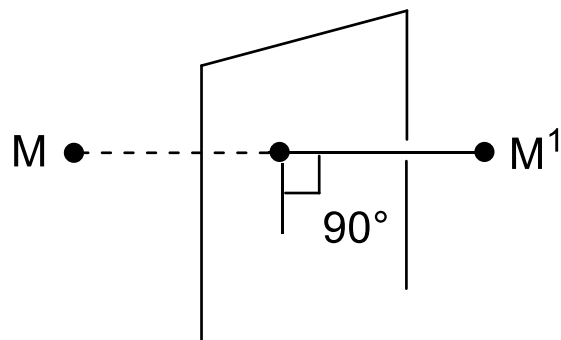
Symmetric operations:

1. C_n : n-fold rotation axes: rotation by an angle $360^\circ/n$



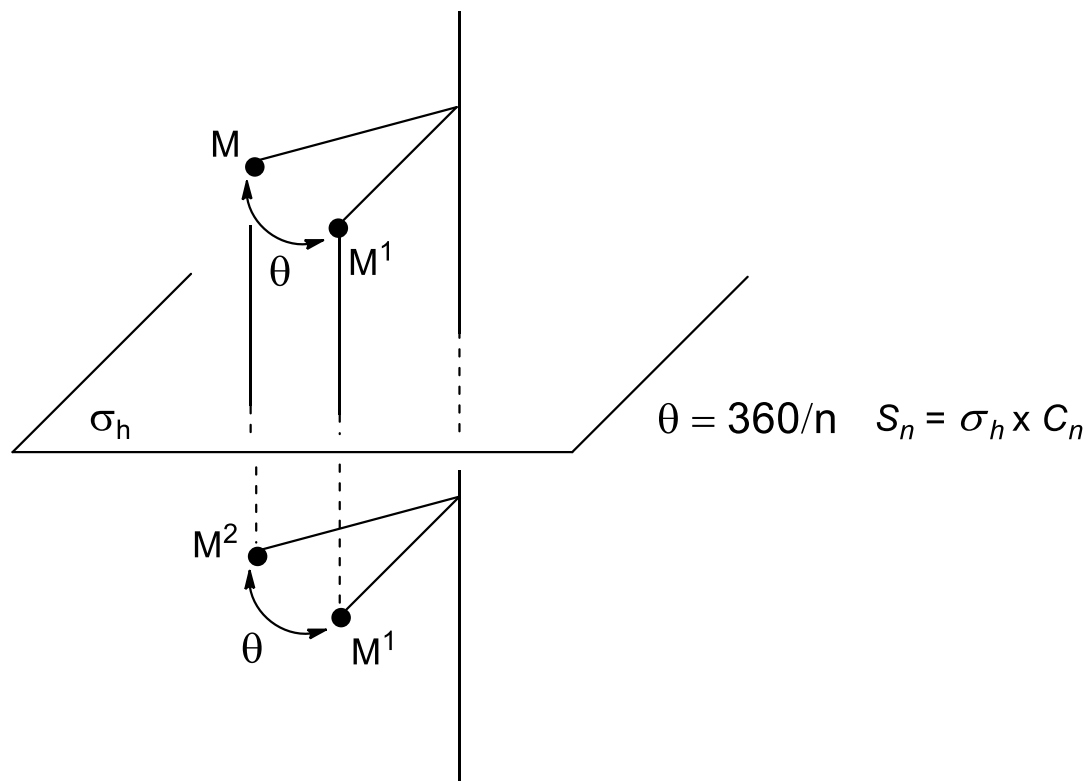
Symmetry and stereochemistry

2. σ_h : mirror plane



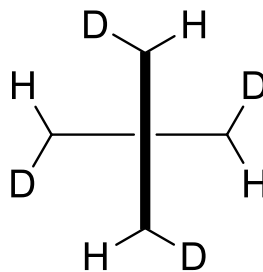
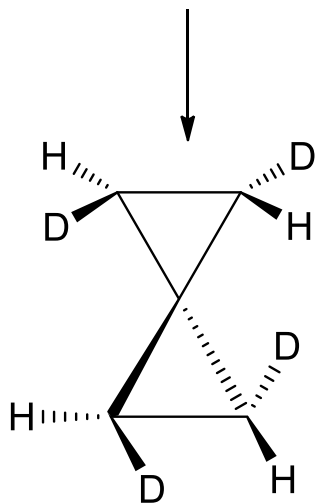
Symmetry and stereochemistry

3. Rotating mirror axis



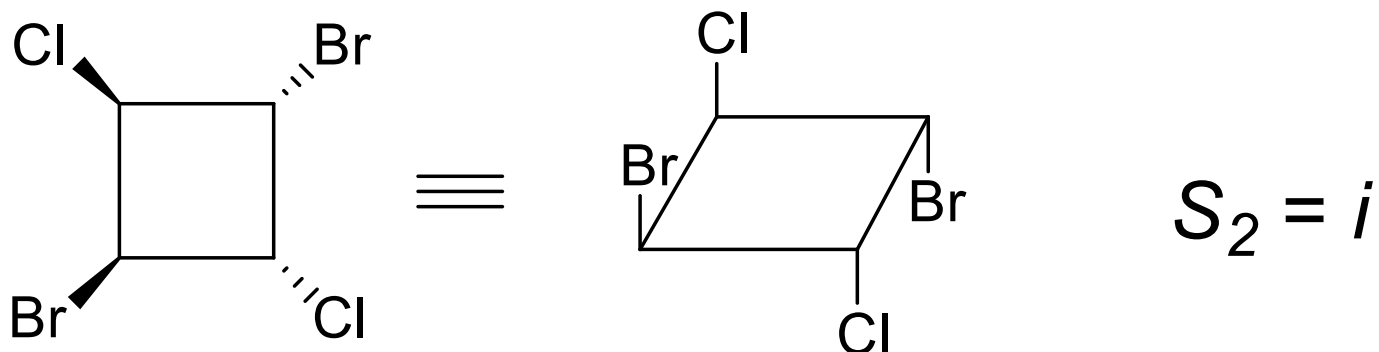
Symmetry and stereochemistry

Rotating mirror axis



$$S_4 = C_4 \times \sigma_h$$

Symmetry and stereochemistry

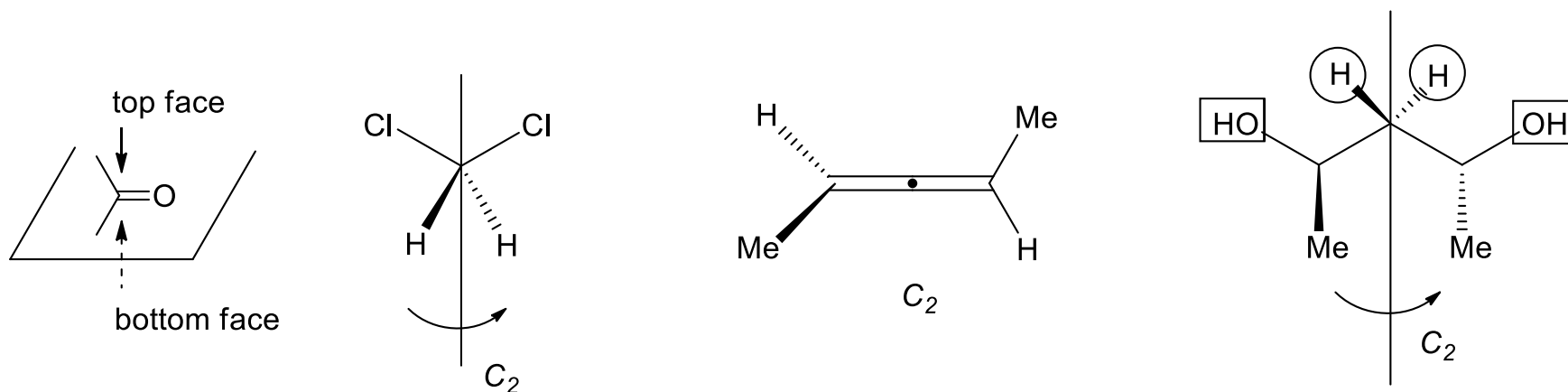


- molecules possessing C_n symmetry operations are chiral
- molecules possessing σ_h or S_n symmetry operations are achiral

Heterotopic groups and faces (Prochirality)

Two identical groups in one molecule can be either **homotopic**, **enantiotopic** or **diastereotopic** and show the corresponding properties.

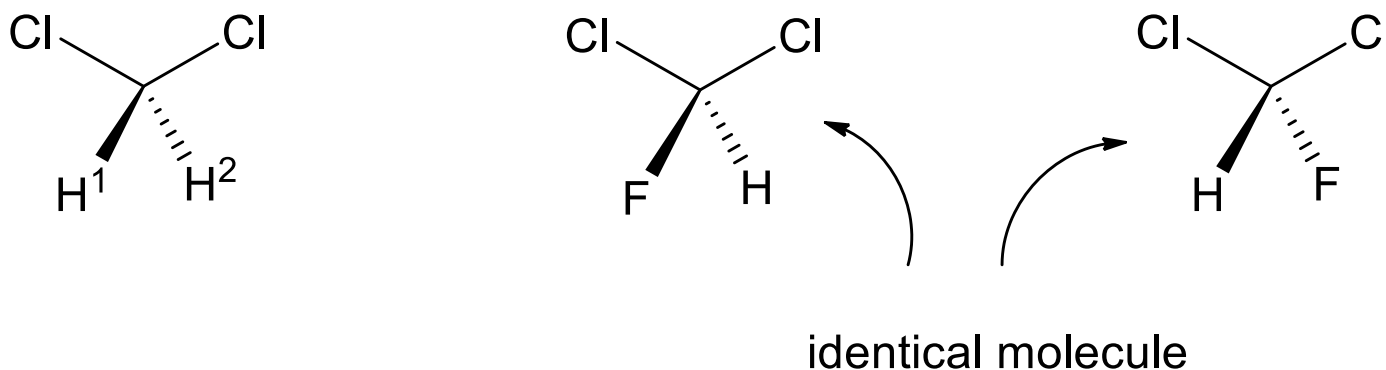
Definition: The groups are **homotopic** if there can be transformed into each other by a symmetry operation C_n



The reactivity of homotopic groups is the same towards all reagents. It is not possible to make a chemical distinction between homotopic groups.

Homotopic groups and faces

Substitution test: The substitution of an homotopic group by another group leads to the same molecule

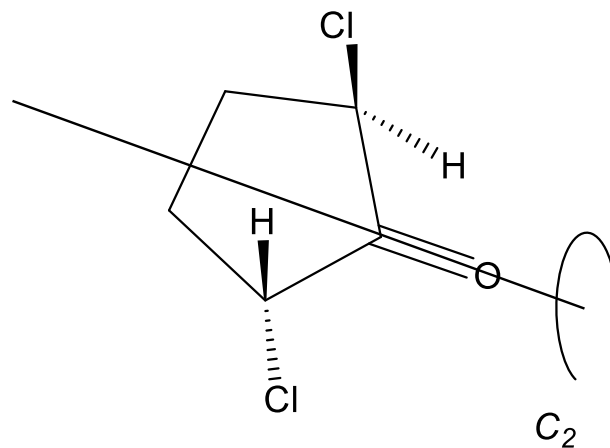
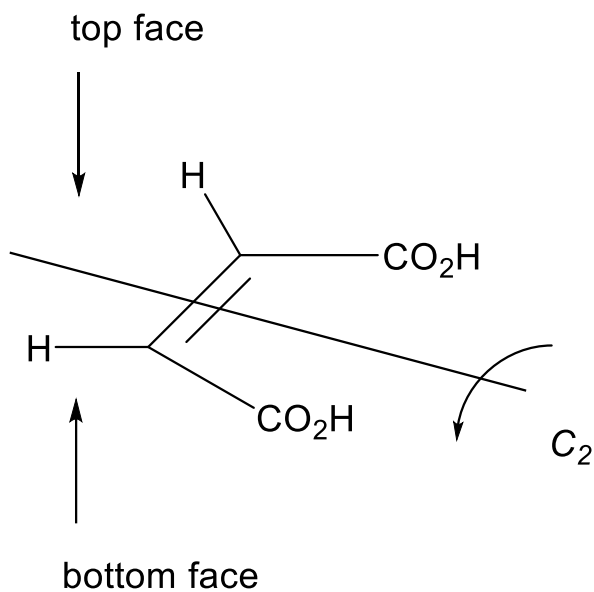


Feature: Homotopic groups and faces cannot be distinguished by any reagent.

The same chemical behaviour towards all reagents is observed.

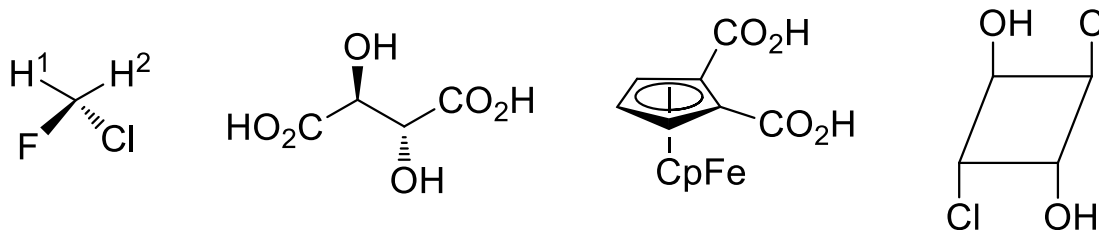
Homotopic faces of a molecule

Homotopic faces: two faces are homotopic, if the plane defined by the two faces contains a C_2 axis.

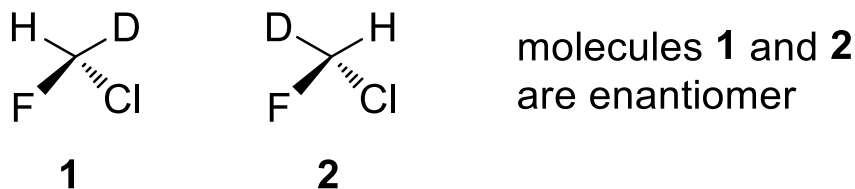


Enantiotopic groups and faces

Definition: The two groups in a molecule are enantiotopic, if they can be converted into one another by a S_n -or σ_h -operation.



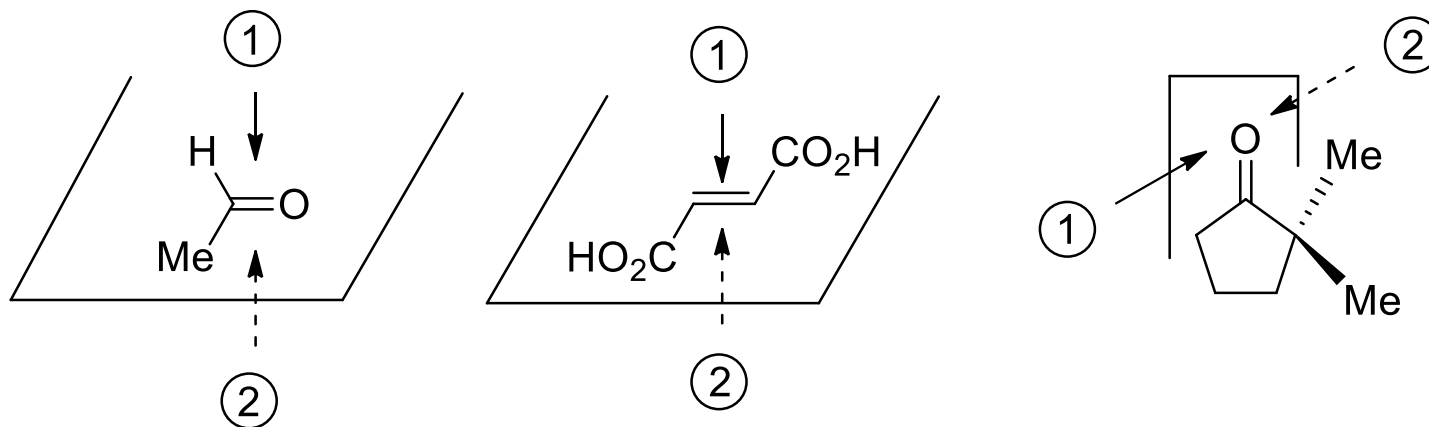
Enantiotopic groups are always found in achiral molecules.



Substitution test: The substitution of one group of two enantiotopic groups gives two enantiomeric compounds.

Enantiotopic groups and faces

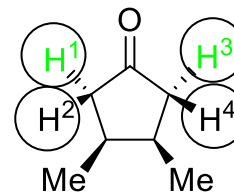
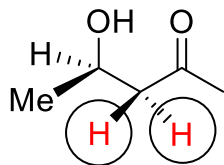
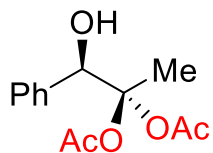
Enantiotopic faces are 2 faces that are defined by a plane of symmetry.



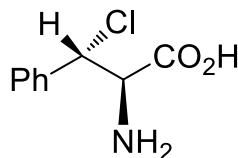
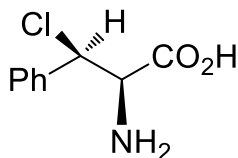
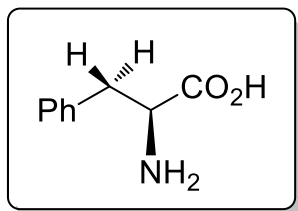
Features: Only chiral reagents can distinguish between enantiotopic groups.
Achiral reagents can not differentiate between enantiotopic groups and faces.

Diastereotopic groups and faces

Diastereomeric groups can be transformed into one another only by the identity symmetry operation.



H¹ and H³ (or H² and H⁴) are enantiotopic groups
H¹ and H² (or H³ and H⁴) are diastereotopic groups



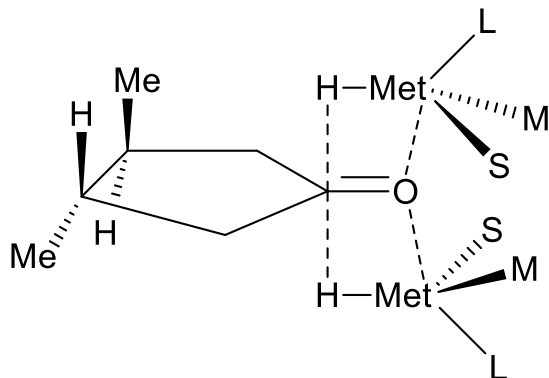
Substitution test:
provides two diastereoisomers.

Features: 2 diastereotopic groups and faces are distinguished by any reagent.

Diastereotopic faces are defined by a plane which is not a symmetry plane.

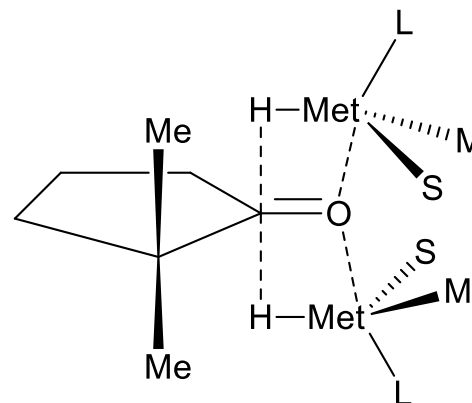
Additions to homotopic and enantiotopic faces

molecule with homotopic faces



identical transition states
the same activation energy

molecule with enantiotopic faces



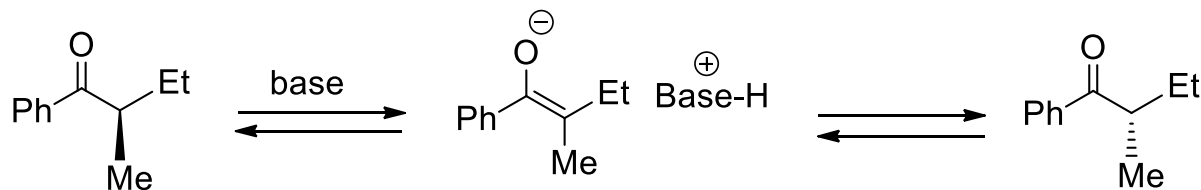
diastereomeric transition states
leads to activation energy

Topicity	Groups	Faces	Reactivity
Homotopic groups and faces	C_n	C_2	no differentiation possible
Enantiotopic groups and faces	σ_h or S_n	σ_h	differentiation by chiral reagents (or catalysts)
Diastereotopic groups and faces	none	$\neq \sigma_h$	differentiation by any reagent

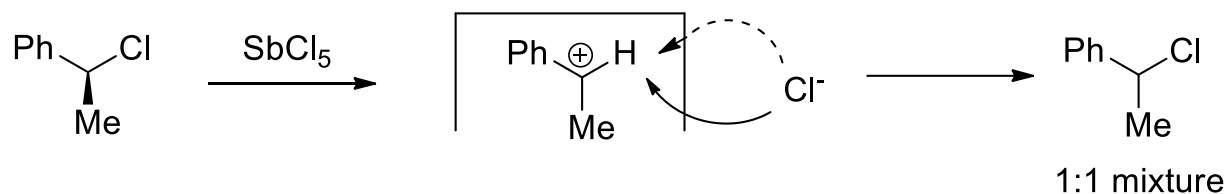
Enantiomers and racemates

Racemization: Processes which convert a pure enantiomer into a 1:1 mixture of enantiomers

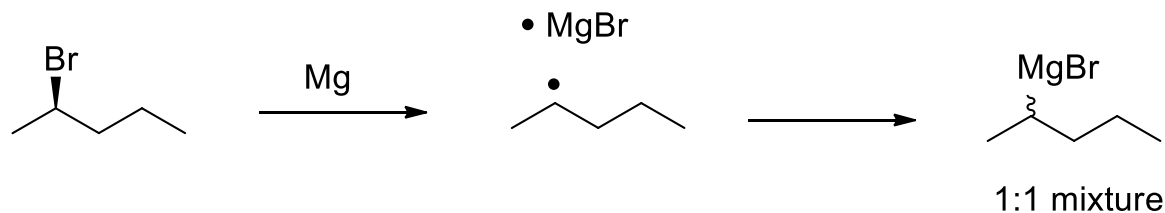
racemization under
basic conditions



racemization under
acidic conditions:



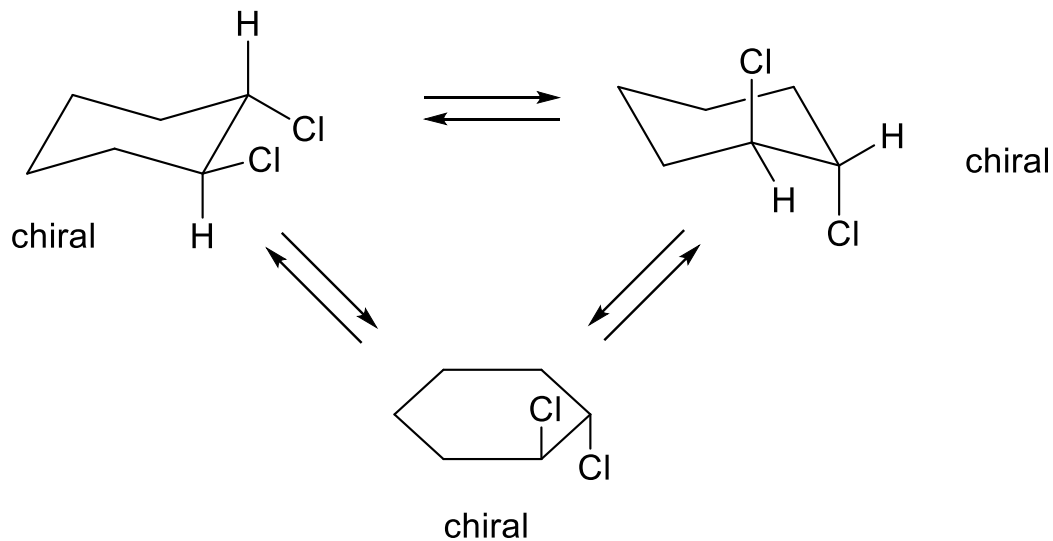
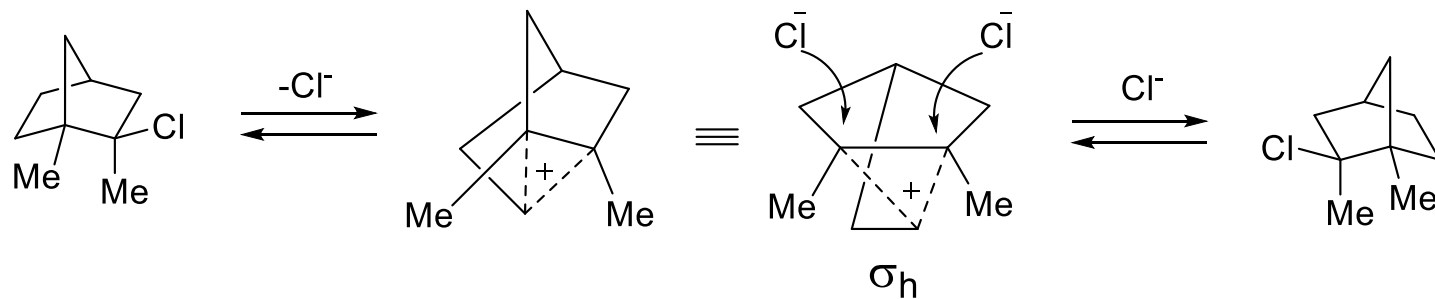
racemization under
radical conditions:



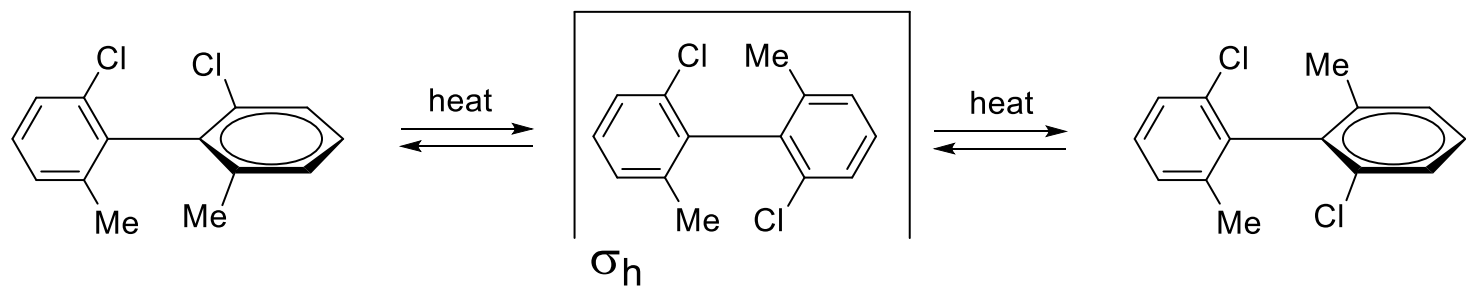
Racemization

Process which convert a pure enantiomer into the racemate

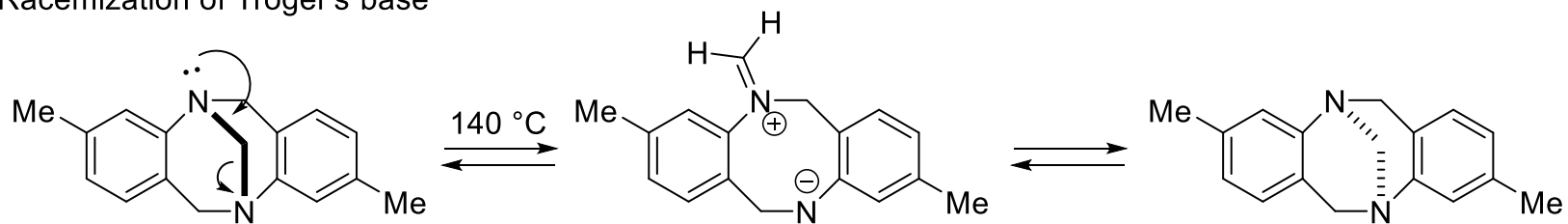
A racemization – process implies an achiral intermediate



Racemization

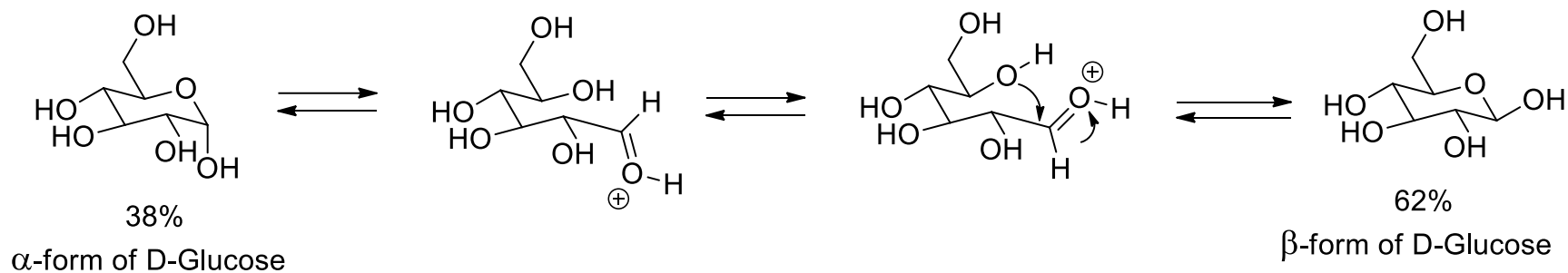
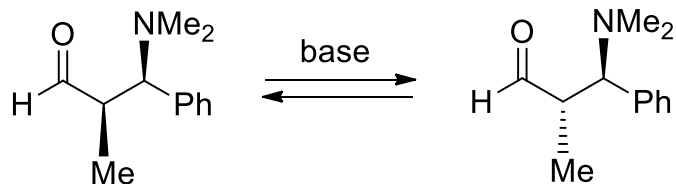


Racemization of Tröger's base



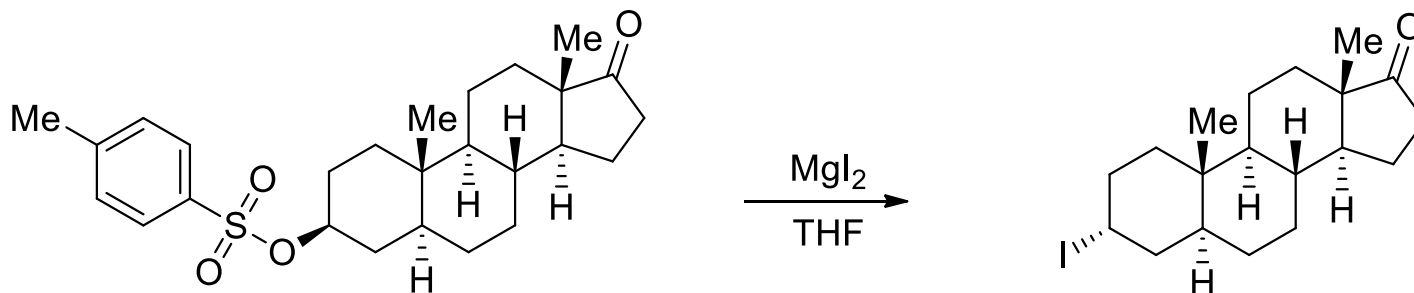
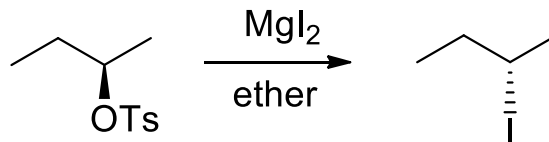
Epimerization of diastereoisomers

Epimerization: racemization of only one from several chiral centers.

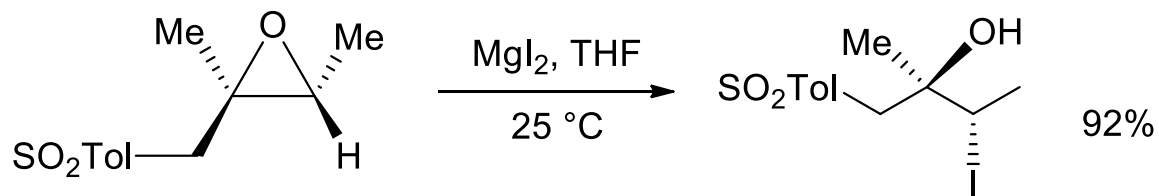


Selective inversion of the configuration at Csp³-centers

S_N2-substitutions :

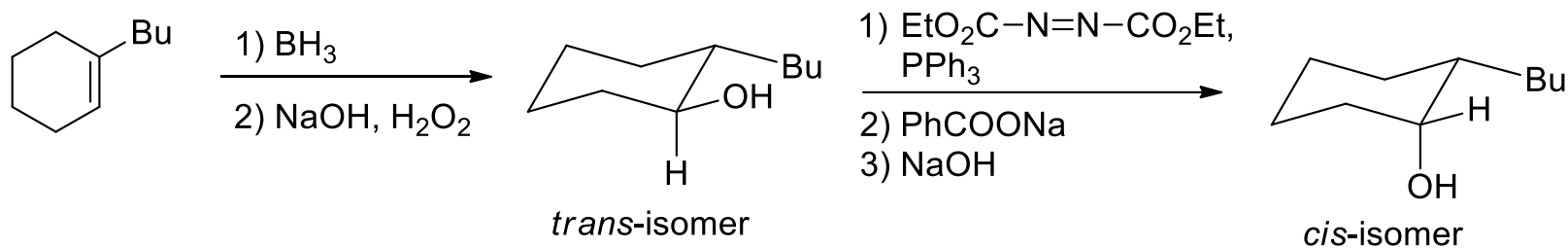


H.-J. Schneider, U. Buchheit, N. Becker, G. Schmidt, U. Siehl, *J. Am. Chem. Soc.* **1985**, 107, 1021-1039.



C. Banini, G. Righi, G. Sothiu, *J. Org. Chem.* **1991**, 56, 6206.

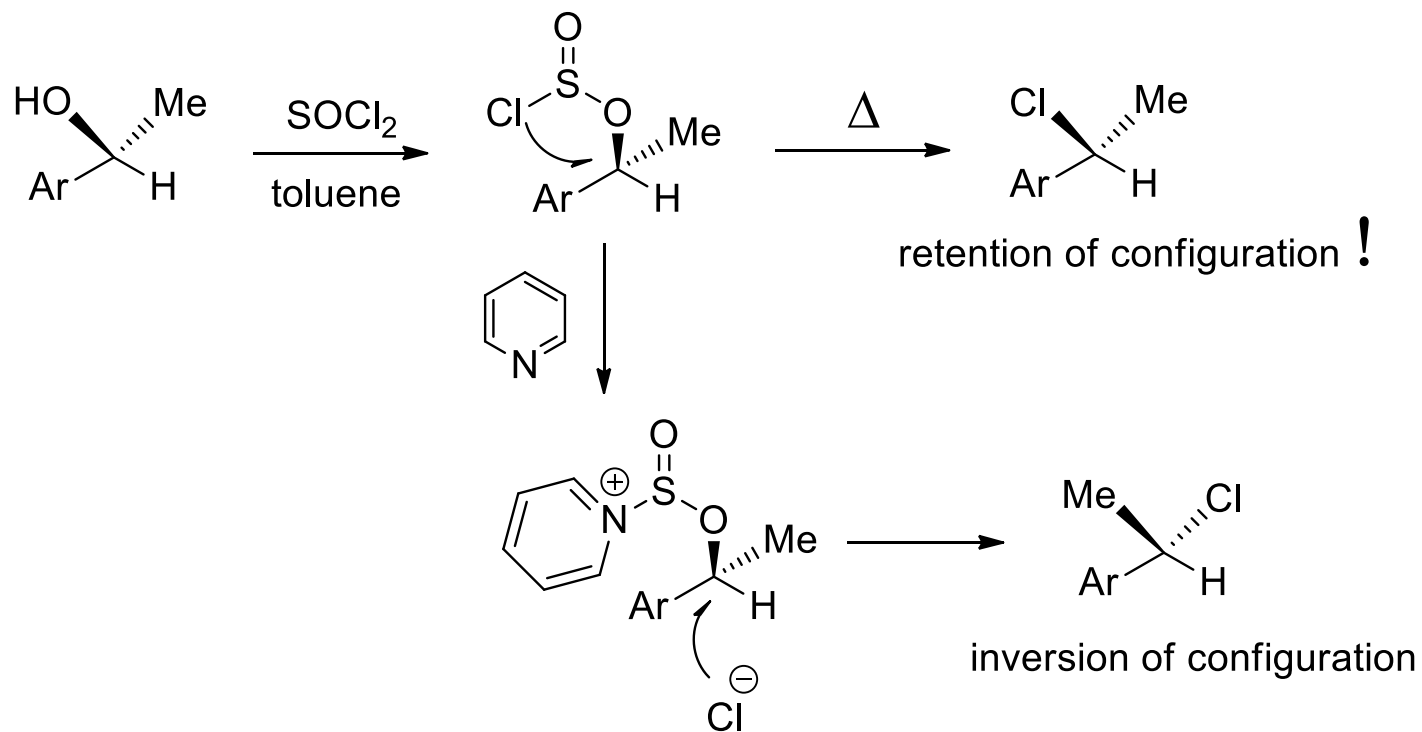
Inversion of alcohols: Mitsunobu reaction



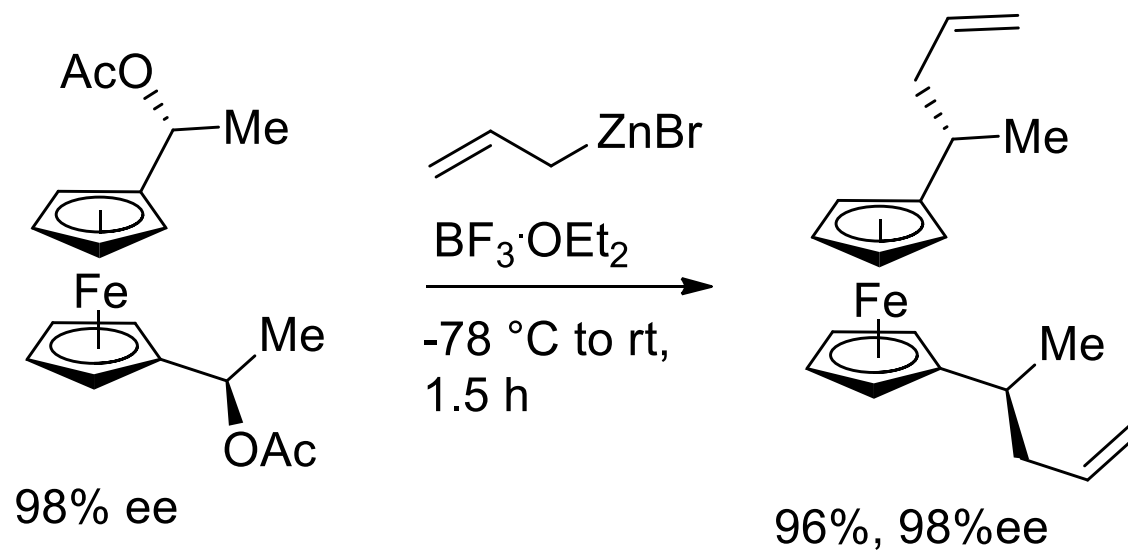
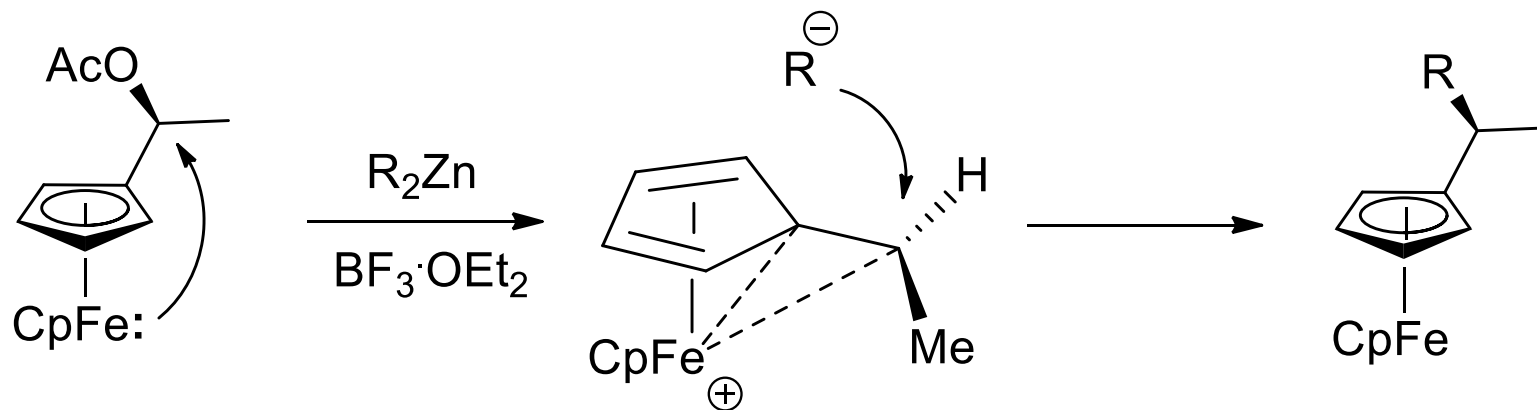
Mitsunobu reaction: D. L. Hughes, *Org. React.* **1992**, 42, 335-656.

S_Ni -reaction

S_Ni reaction



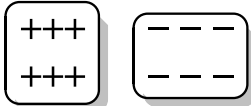
Substitution with retention of configuration

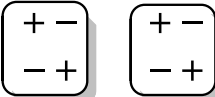


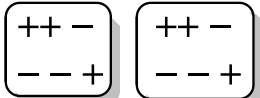
J. J. Almena Perea, T. Ireland, P. Knochel, *Tetrahedron Lett.* **1997**, 38, 5961-5964.

Methods for Racemate Resolution

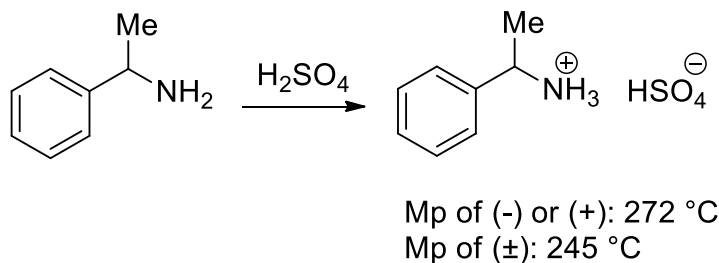
Separation of enantiomers

Conglomerates:  20% of all racemates

Racemates: 

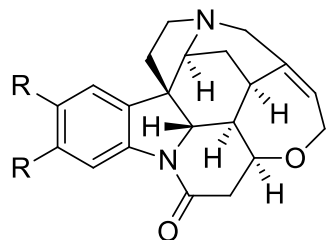
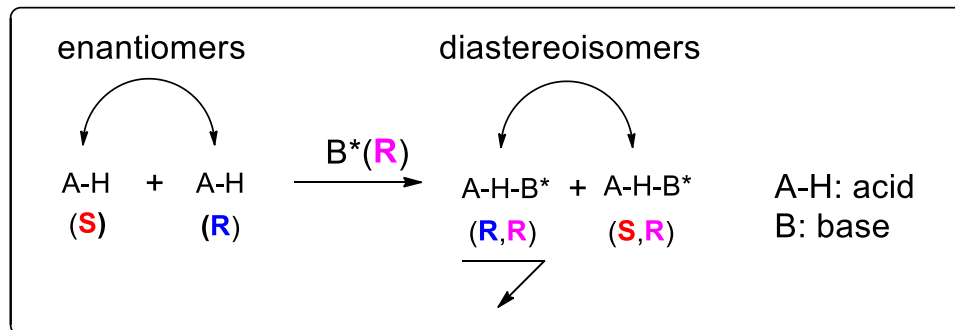
Pseudoracemates:  unordered crystals

- 1) Separation based on the crystal shape. Pasteur (1845): crystal picking. Triage
- 2) Selective crystallization using a seed crystal
Example: (+)-tartaric acid is easily crystallized by the addition of (-)-asparagine

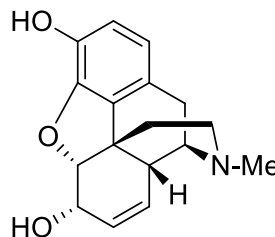


Resolution via separation of diastereomers

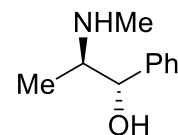
(±)-acids can be separated using chiral bases such as alkaloids: quinine, brucine, morphine.



R = H : strychnine
R = OMe : brucine

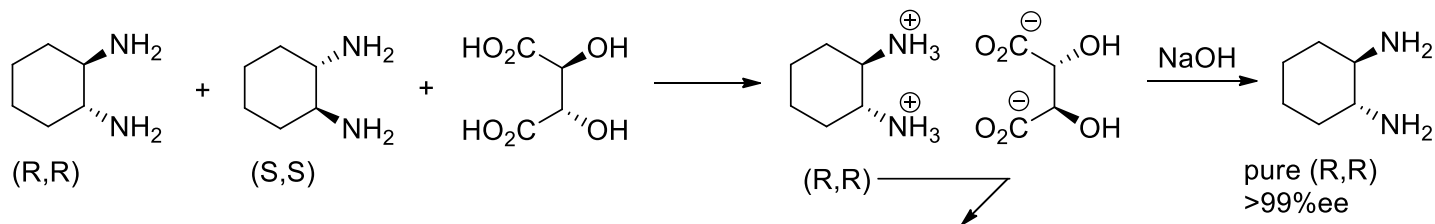


morphine

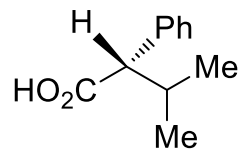
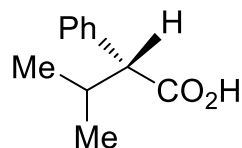


ephedrine

further example:



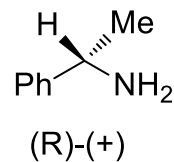
Resolution of 3-methyl-2-phenylbutanoic acid



racemic mixture: 461 g



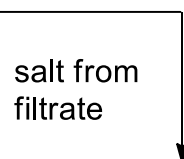
form salt with



mixture of 353 g of diastereomeric ammonium carboxylate salts recrystallized from ethanol-water



recrystallized product



salt from filtrate

R,R-salt, 272 g Mp 198-200 °C

enriched in S,R-salt



acidify



acidify

R-(-) acid, 153 g

partially resolved

Mp 50.5-51.5 °C

S-(+) acid, 261 g

$[\alpha]_D = -62.4^\circ$; >99%ee

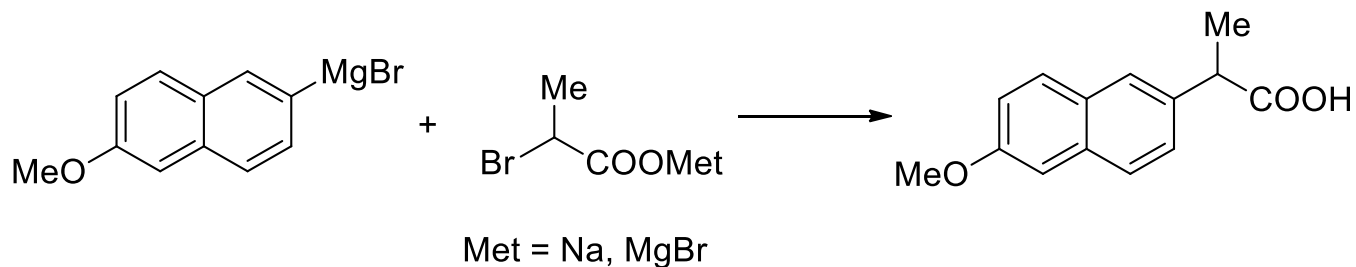
$[\alpha]_D = +36^\circ$

Resolution *via* separation of diastereomers

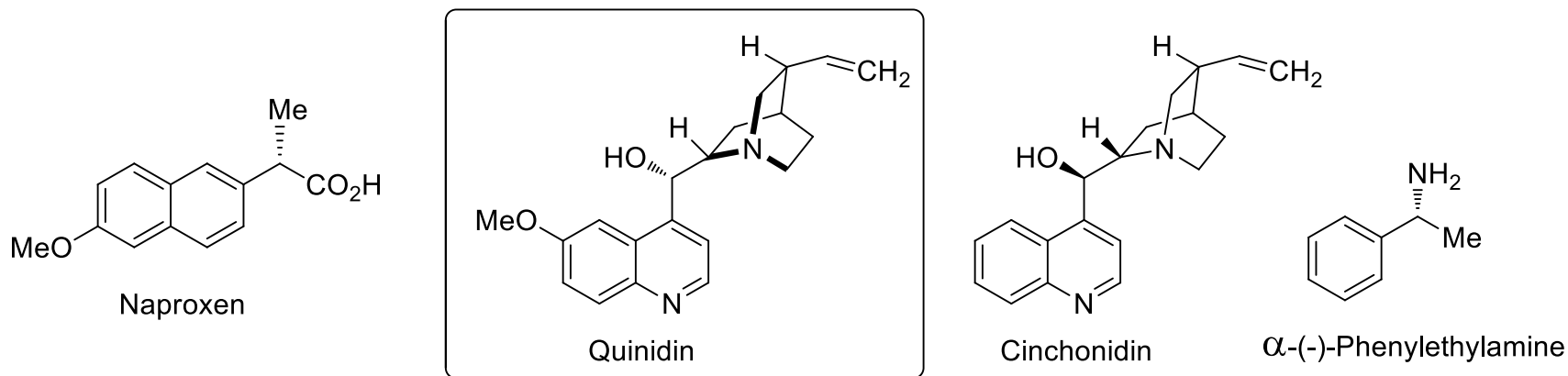
Commonly used resolving agents

For acids	For bases
α -Methylbenzylamine α -Methyl- <i>p</i> -nitrobenzylamine α -Methyl- <i>p</i> -bromobenzylamine 2-Aminobutane <i>N</i> -Methylglucamine Dehydroabietylamine α -(1-Naphthyl)ethylamine <i>threo</i> -2-amino-1-(<i>p</i> -nitrophenyl)-propane-1,3-diol Cinchonine Cinchonidine Quinine Ephedrine	1-Camphor-10-sulphonic acid Malic acid Mandelic acid α -Methoxyphenylacetic acid α -Methoxy- α -trifluoromethylphenylacetic acid 2-Pyrrolidone-5-carboxylic acid Tartaric acid

Separation of enantiomers



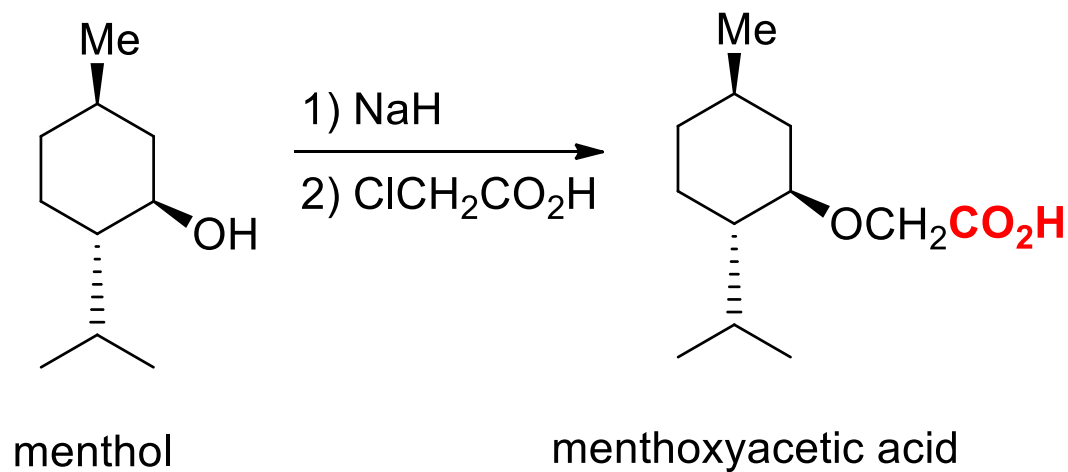
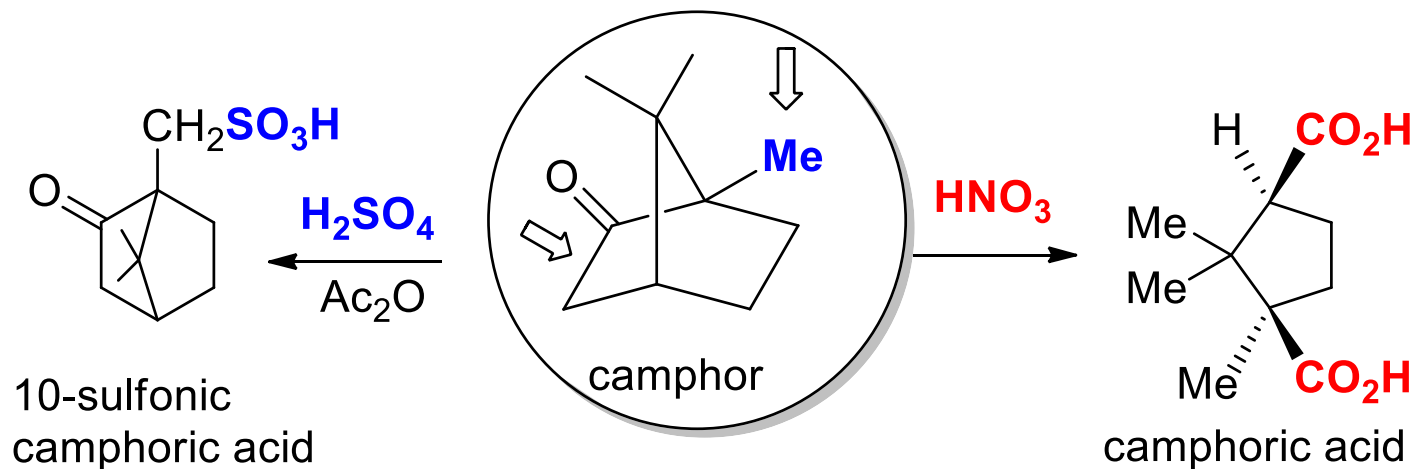
The resolution of enantiomers by preferential crystallization is the most common method used in industry:



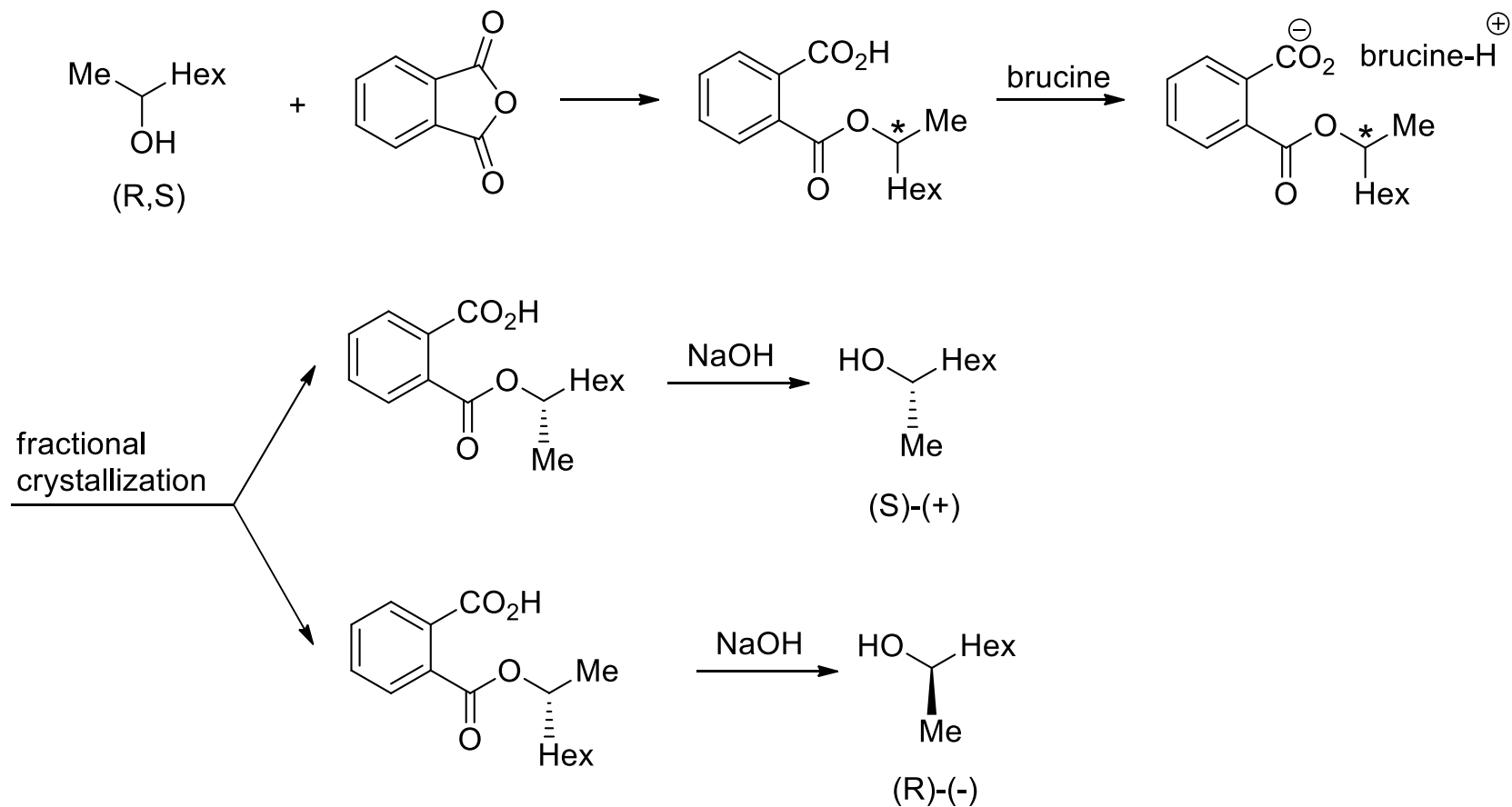
Resolution of Naproxen using Quinidine

C. G. M. Villa and S. Panossian, Chirality in industry, **1992**, Vol. 1, 303.

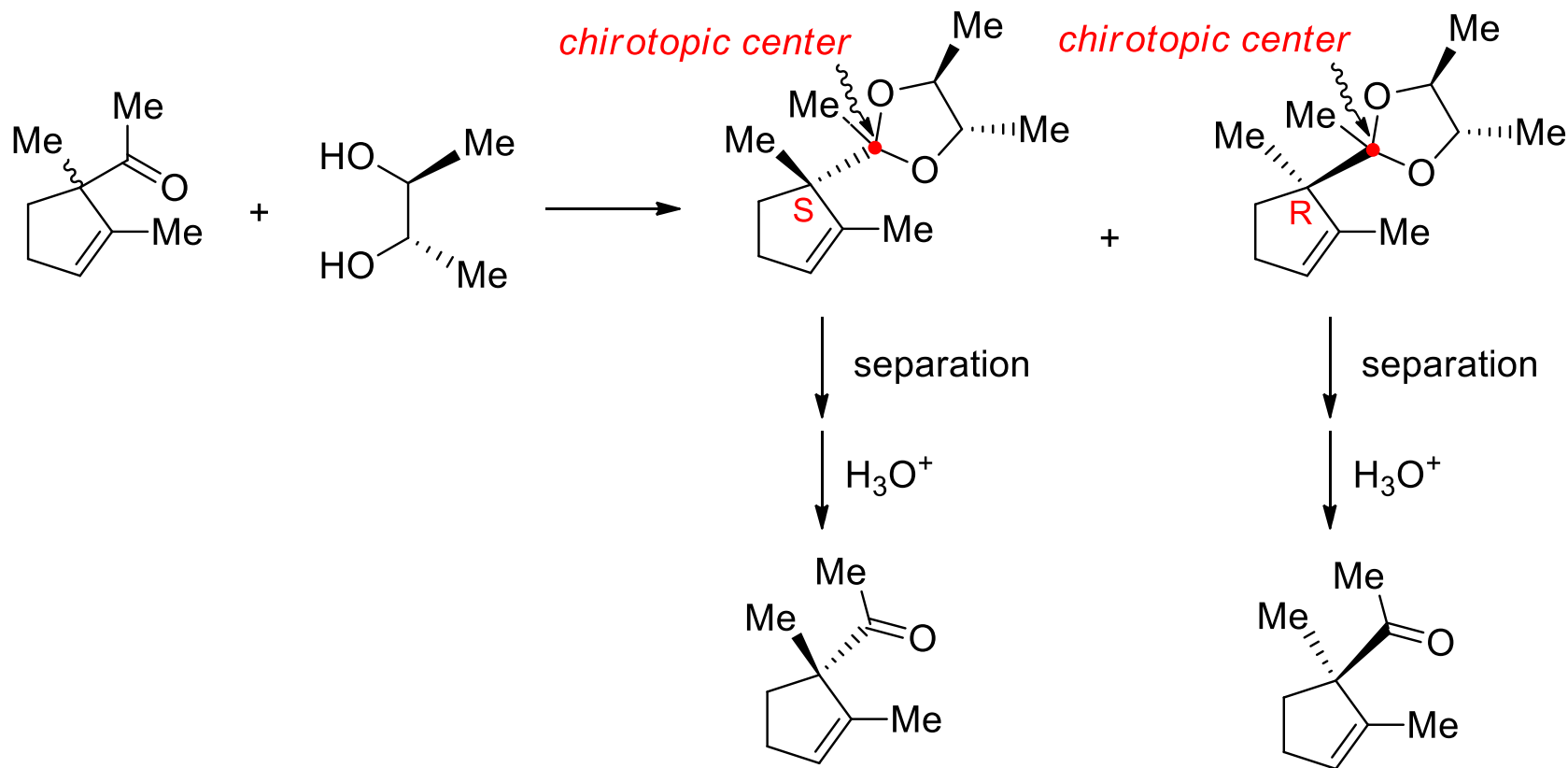
Preparation of acidic resolution agents



Extension to the resolution of alcohols



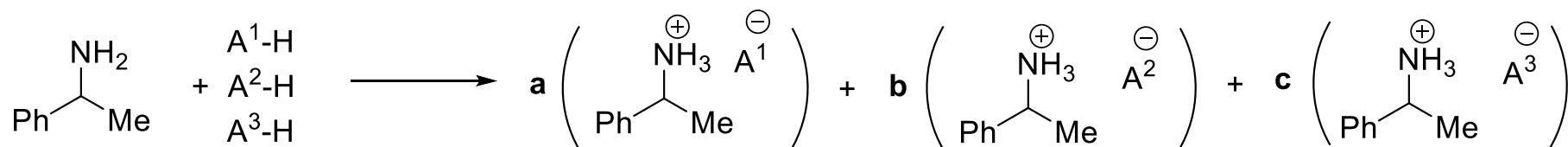
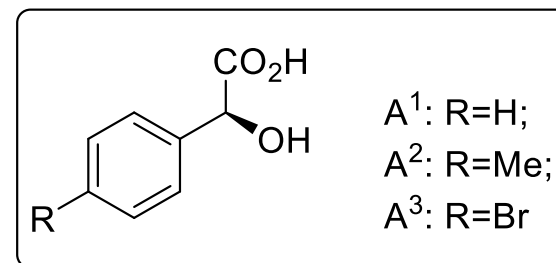
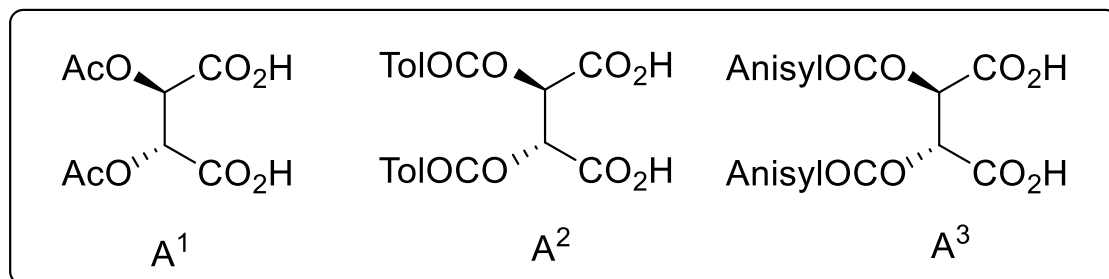
Resolution of ketones by the formation of diastereoisomers



The diastereomeric ketals are separated by chromatography and hydrolyzed leading to the pure enantiomers

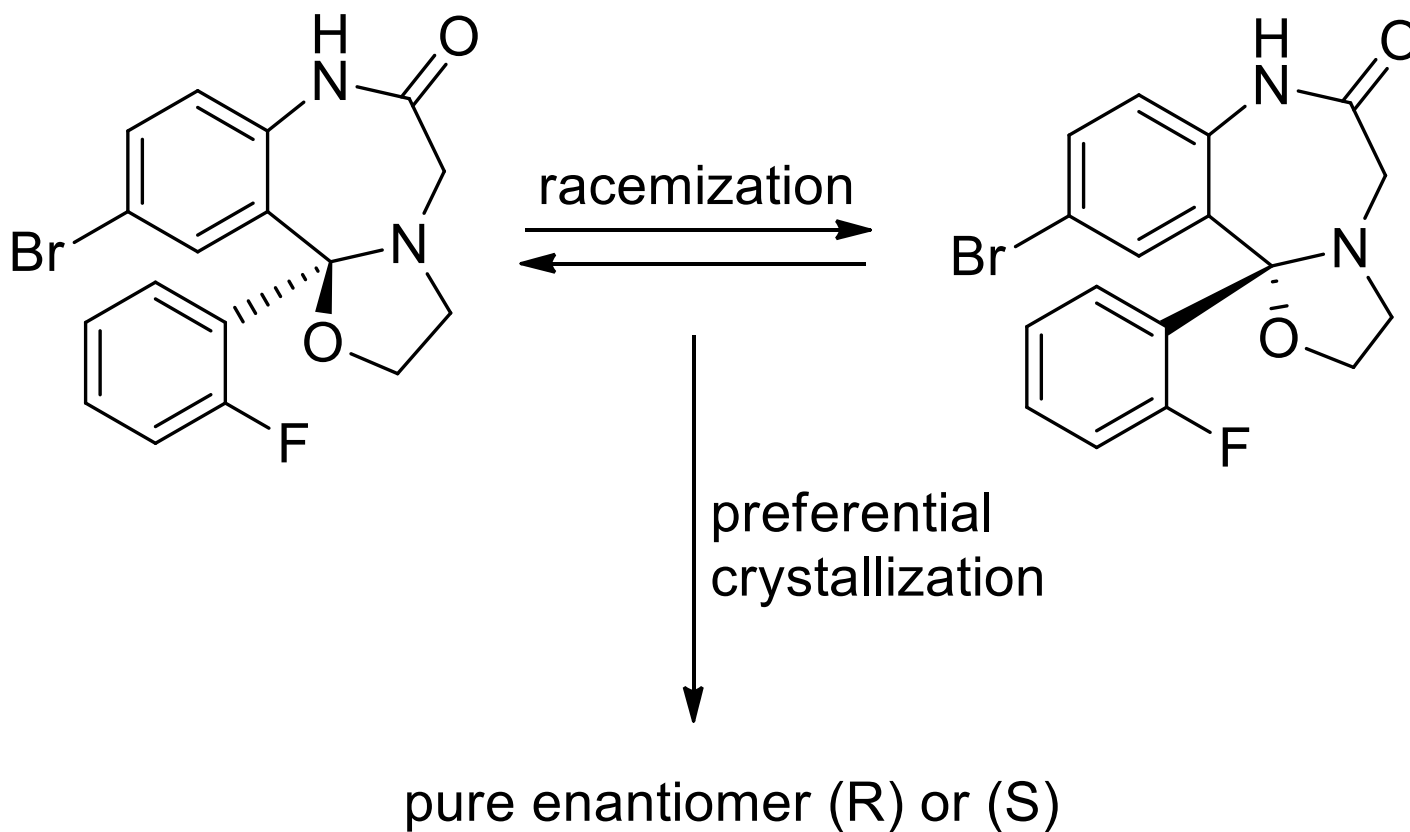
Improved resolution procedure: the method of Wynberg

Racemate resolution through the formation of two diastereoisomers (salts).



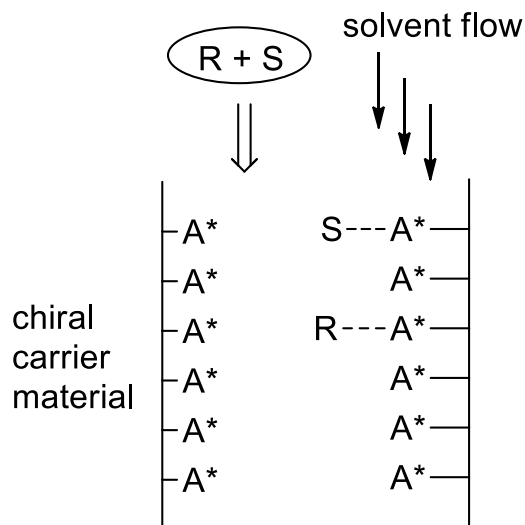
T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra *Angew. Chem.* **1998**, *110*, 2491; *Angew. Chem. Int. Ed.* **1998**, *37*, 2349.

Resolution with *in situ* racemization

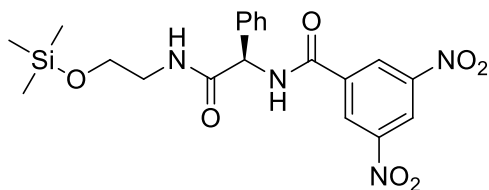
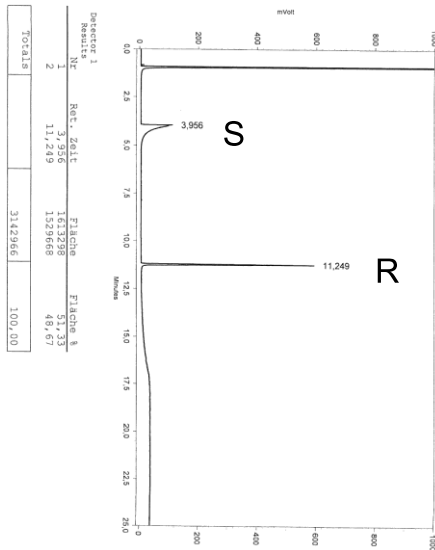


Y. Okada, T. Takebayashi, *Chem. Pharm. Bull.* **1988**, **36**, 3787.

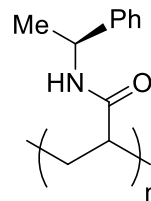
Separation using a chiral chromatographic columns



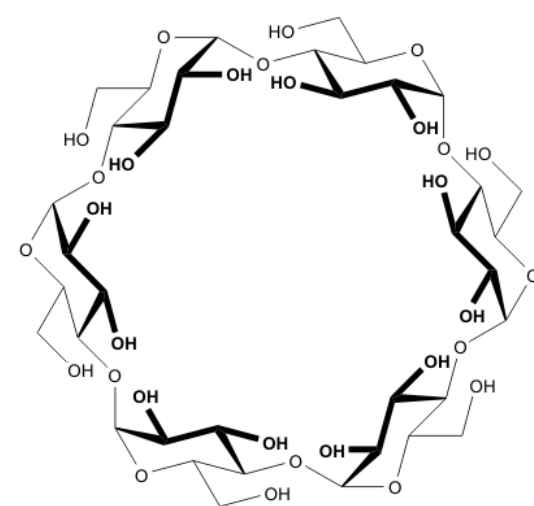
- Gas chromatography: the solvent is a gas
- HPLC (High Pressure Liquid Chromatography): the solvent is a mixture of liquids



Chiral phases

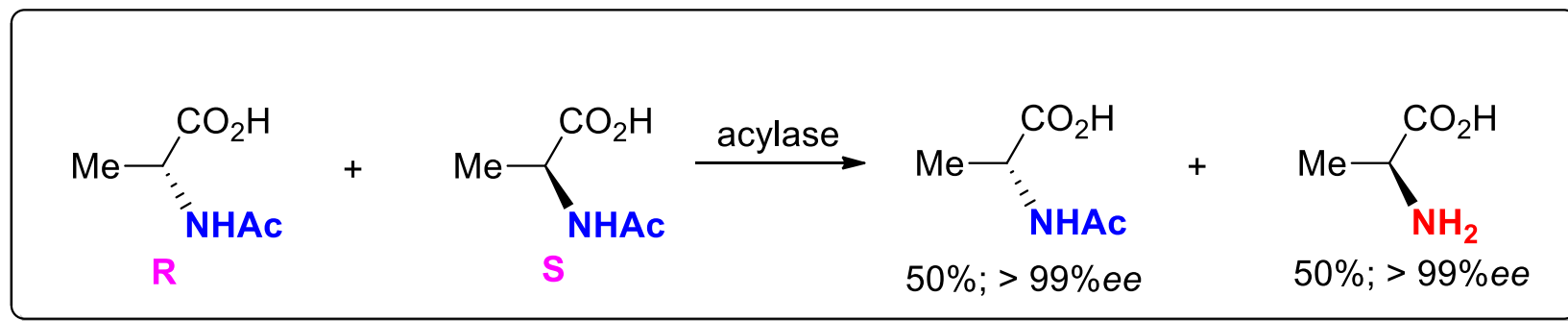
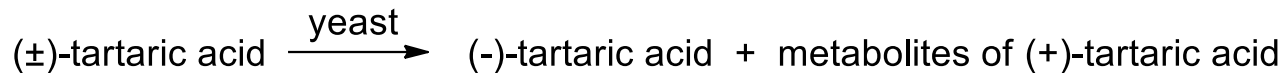


polysaccharides (α -Cyclodextrin)



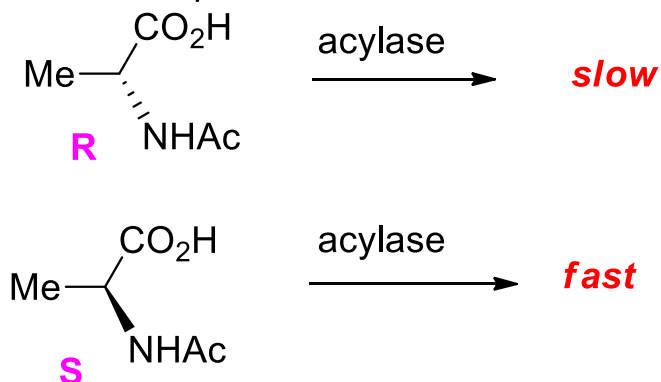
Enzymatic resolution: an example of kinetic resolution

Pasteur:



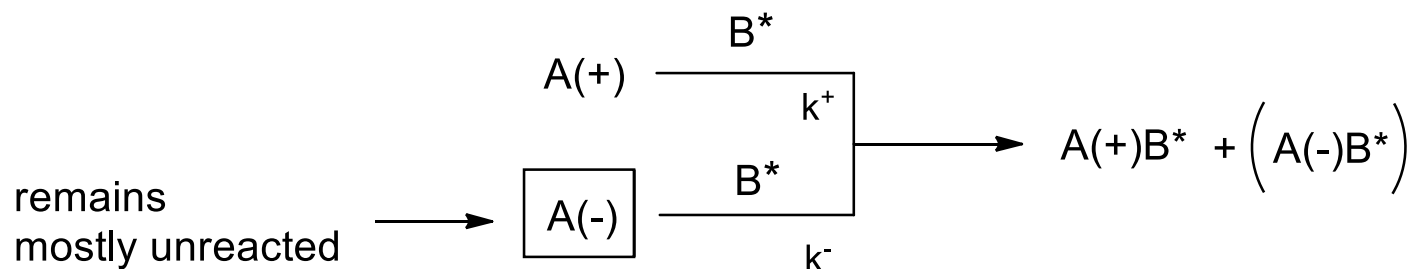
The two enantiomers react with different rates.

This differentiation is possible because a chiral reagent is used (an enzyme)



Application : Industrial use for the production of (D) - and (L)-amino acids

Kinetic resolution



$$k^+ > k^-$$

$$S = \text{selectivity factor} = k^+/k^-$$

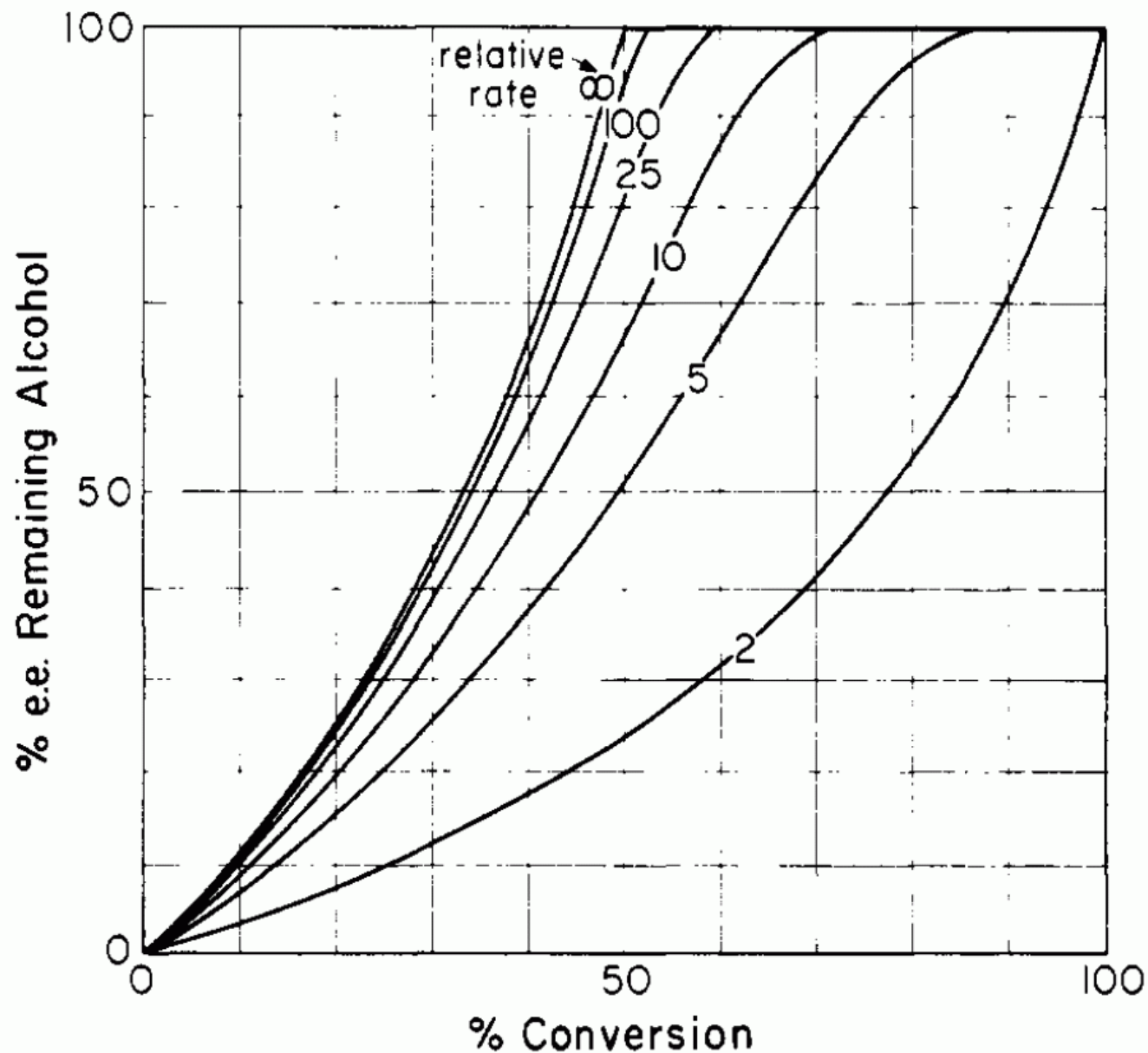
The kinetic resolution is only useful if the reaction rates of the two reactions are very different.

For example for a given conversion:

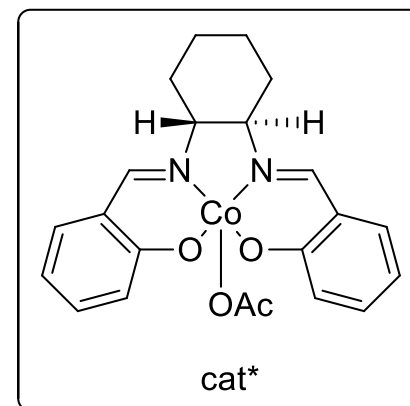
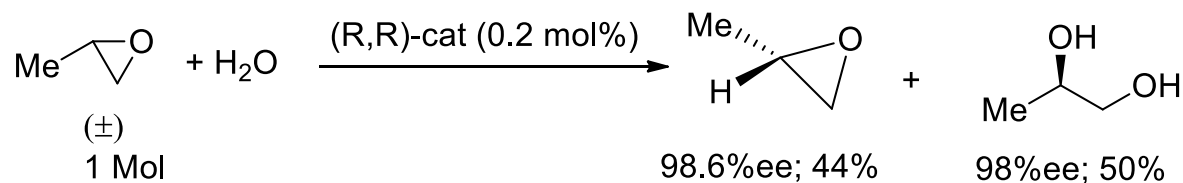
83%ee of the unreacted starting material is obtained if $k^+/k^- = S = 25$

93%ee of the unreacted starting material is obtained if $k^+/k^- = S = 100$

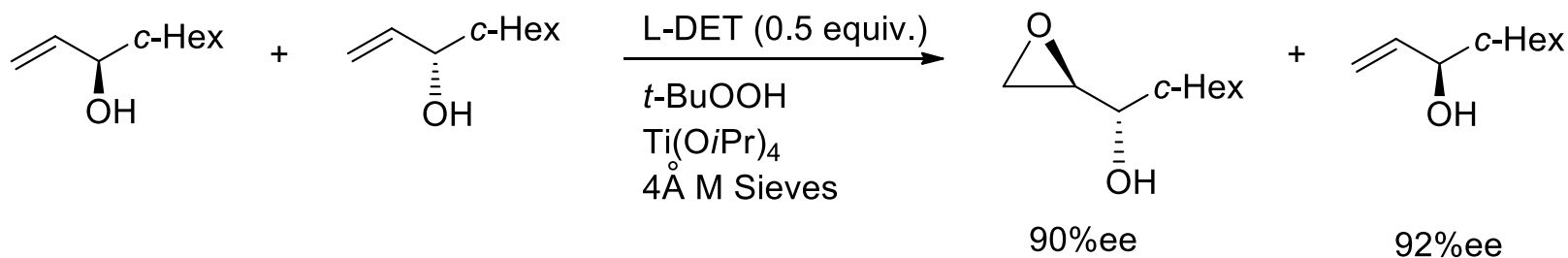
Dependence of enantiomeric excess on relative rate of reaction



Kinetic resolution



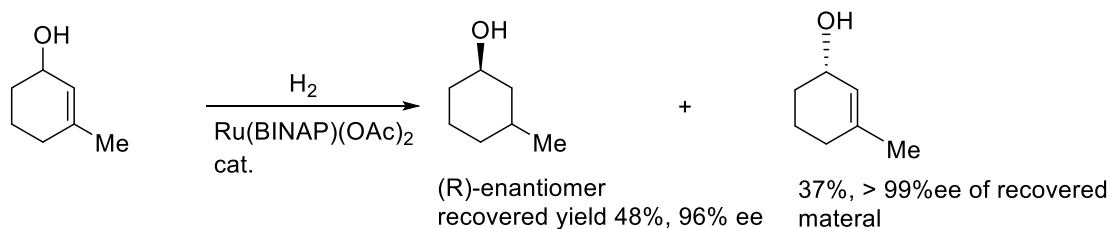
M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, 277, 936.



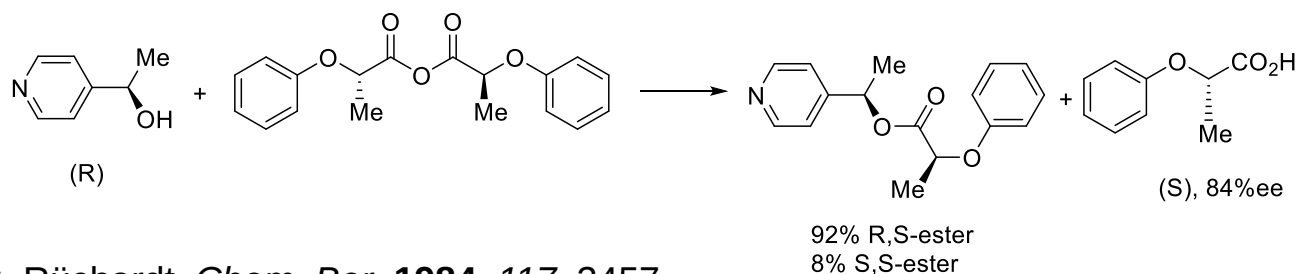
B. E. Rossiter, T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, 103, 464.

P. R. Carlier, W. S. Mungall, G. Schroder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, 110, 2978.

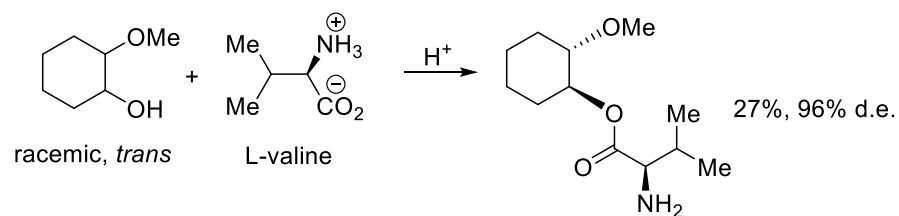
Examples of kinetic resolution



M. Kimura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem.* **1988**, 53, 708.



U. Salz, C. Rüchardt, *Chem. Ber.* **1984**, 117, 3457.

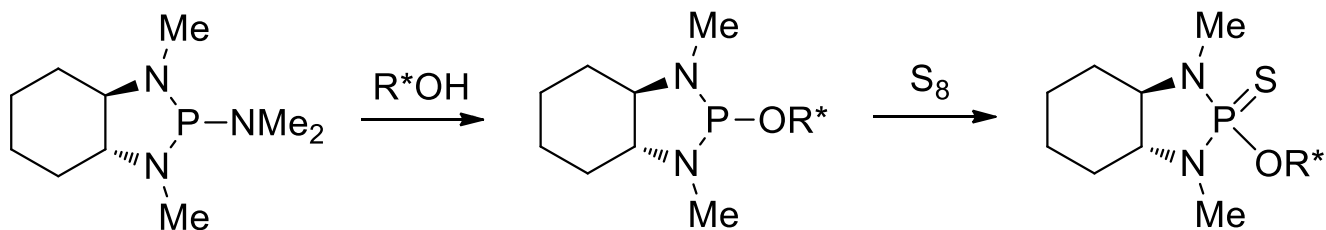
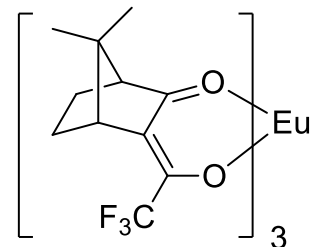


P. Stead, H. Marley, M. Mahmoudoan, G. Webb, D. Noble, Y. T. Ip, E. Piga, S. Roberts, M. J. Dawson, *Tetrahedron: Asymmetry* **1996**, 7, 2247.

Determination of the enantiomeric purity by NMR methods

Use of chiral shifts reagents:

C. C. Hinckley, *J. Am. Chem. Soc.* **1969**, *91*, 5160.



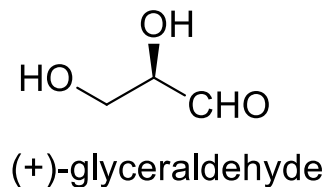
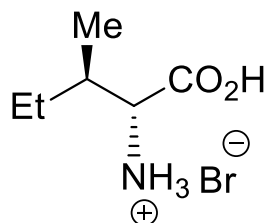
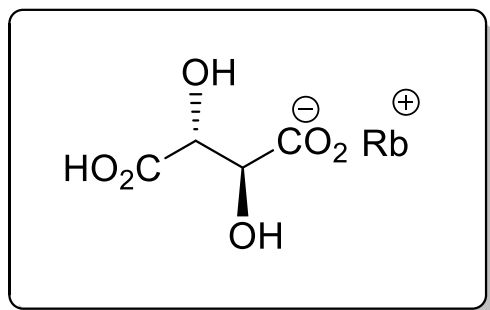
A. Alexakis, J. C. Frutos, S. Mutti, P. Mangeney, *J. Org. Chem.* **1994**, *59*, 3326.

Determination of ee% by NMR Methods: review article D. Parker *Chem. Rev.* **1991**, *91*, 1441

Determination of the absolute configuration

Classical X-ray analysis does not allow to distinguish between two enantiomeric structures.

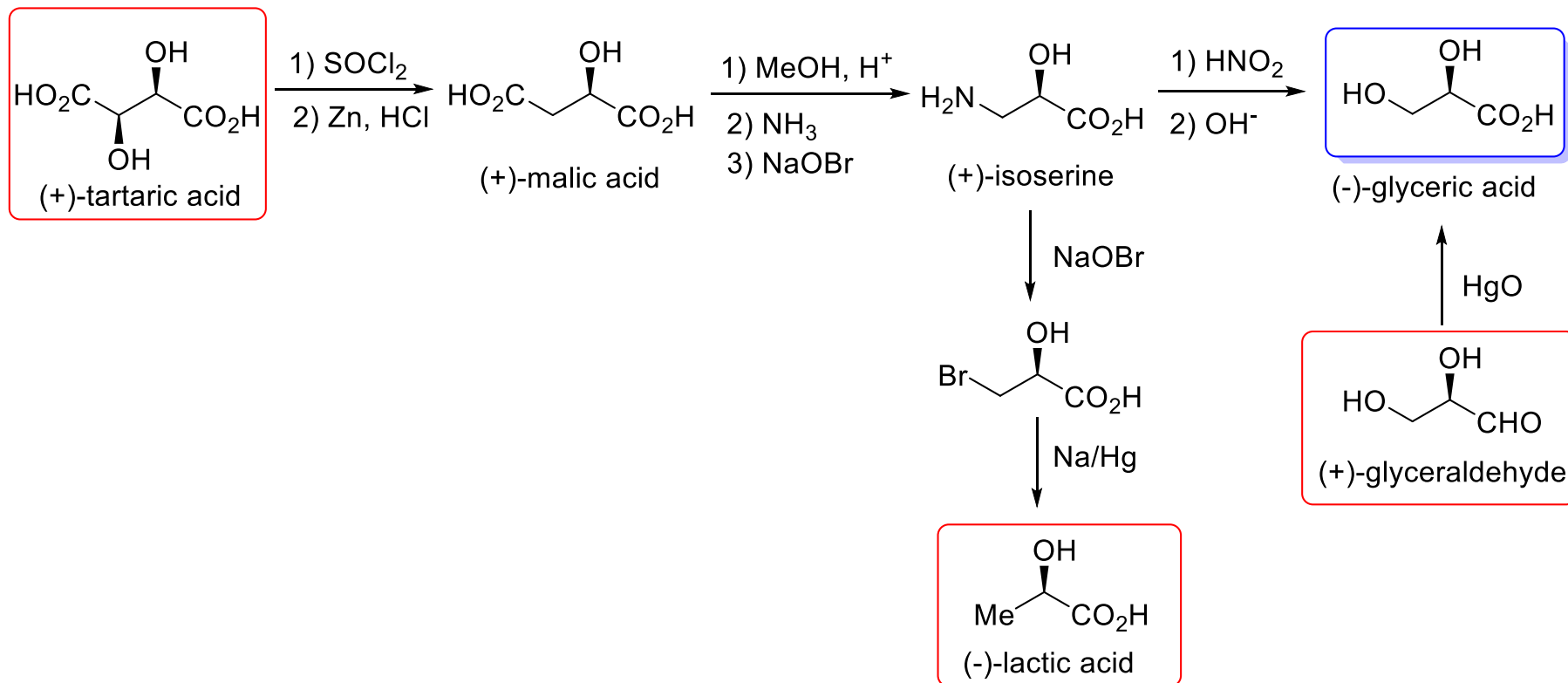
The method of Bijvoet (1951) uses heavy metal salts and allows the determination of the absolute configuration of molecules.



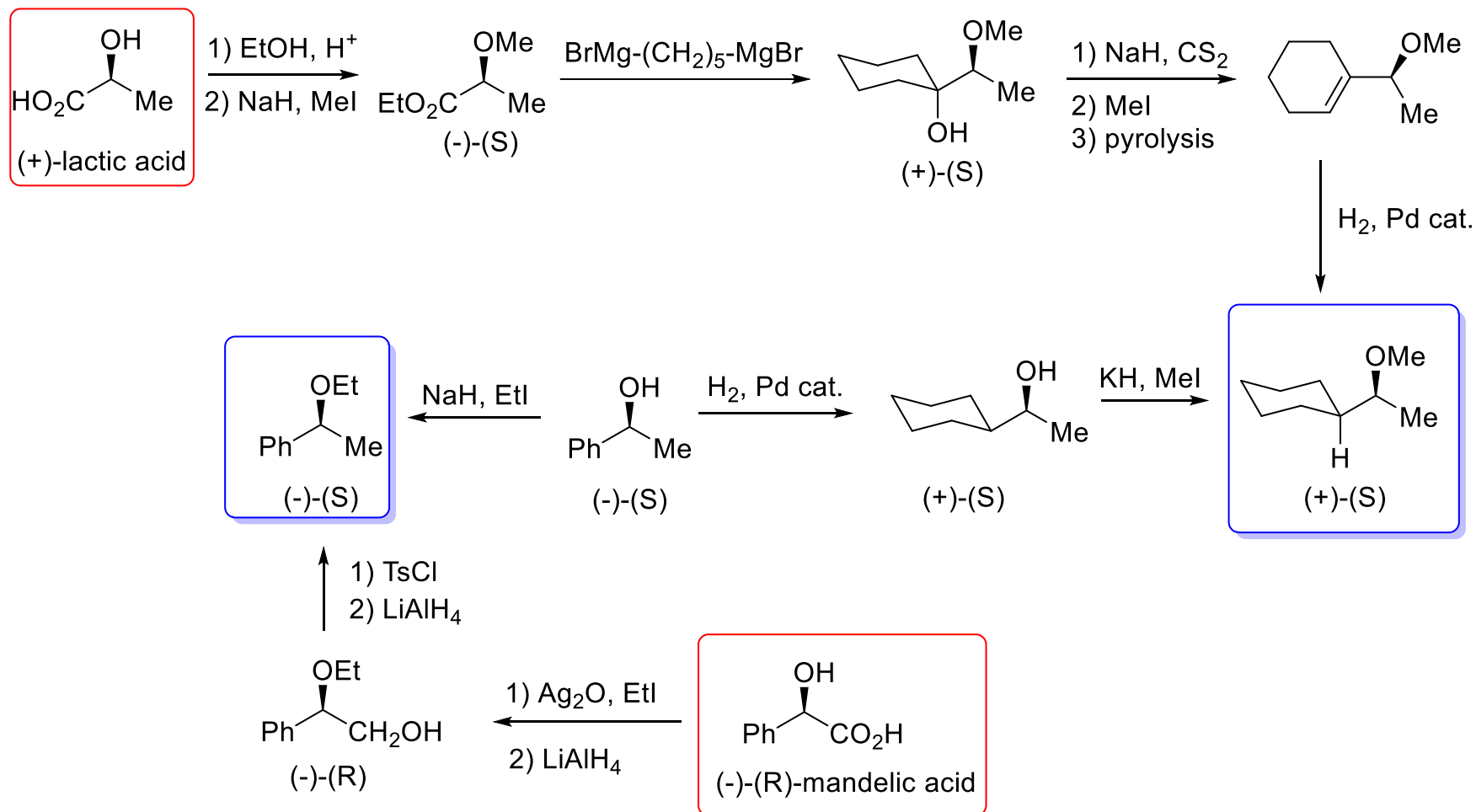
* The absolute configuration of (+)-glyceraldehyde was correct

J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature*, **1951**, 168, 271.

Chemical correlation (1)

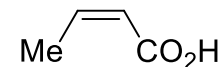
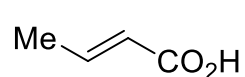


Chemical correlation (2)



Determination of the relative stereochemistry by NMR methods

Diastereoisomers have different properties: compare with

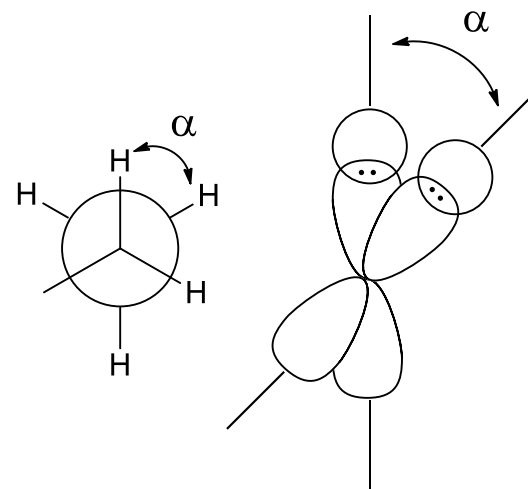
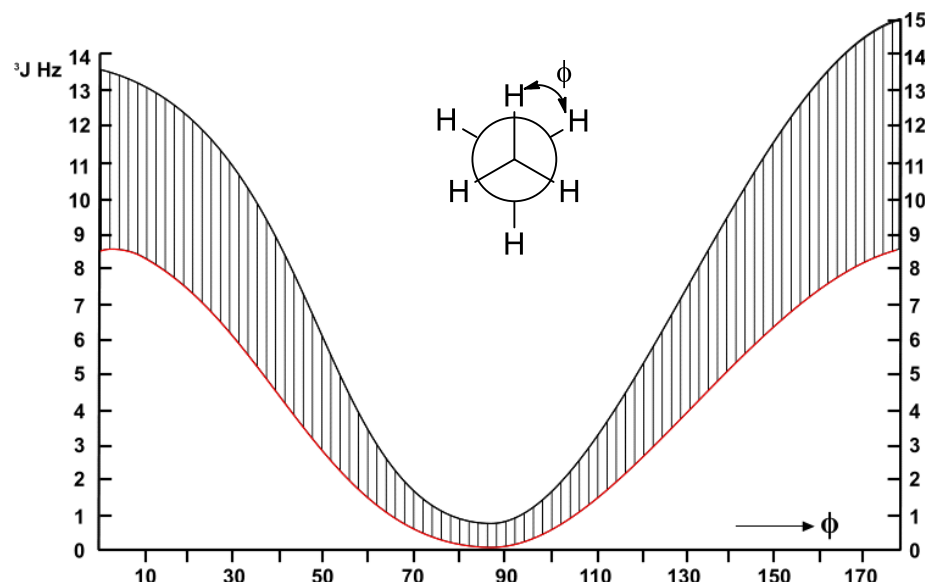


melting point: 72 °C

melting point: 15 °C

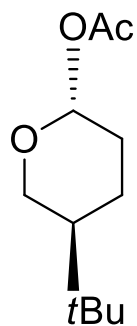
In general - ^1H and ^{13}C NMR analysis allows to differentiate diastereoisomers

Karplus Rules

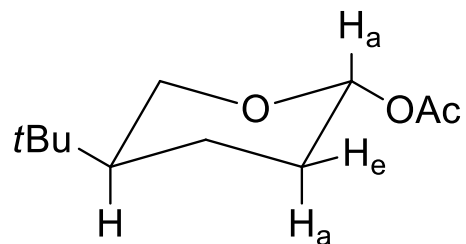


α small $\gg$ large overlapping $\gg$
large coupling constant

Determination of the relative stereochemistry by NMR methods

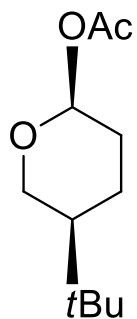
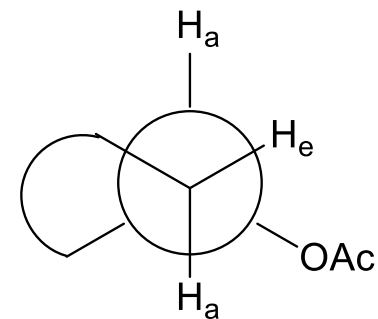


trans

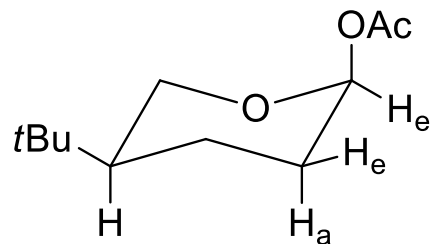


$$J_{aa} = 11 \text{ Hz}$$

$$J_{ae} = 4 \text{ Hz}$$

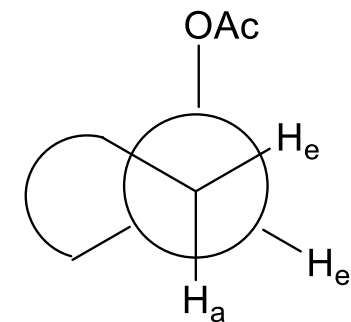


cis

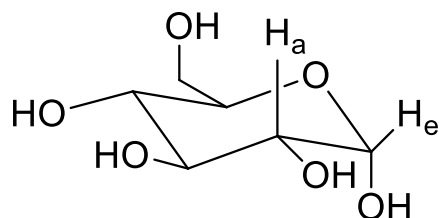


$$J_{ee} = 3 \text{ Hz}$$

$$J_{ea} = 3 \text{ Hz}$$

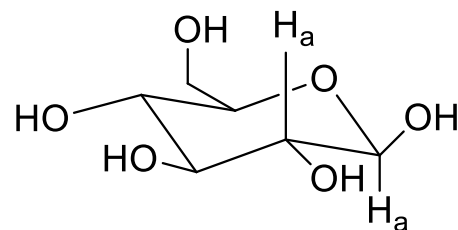


Determination of the configuration of the anomeric center of sugar



α -form of D-glucose

$$J_{ae} = 3 \text{ Hz}$$



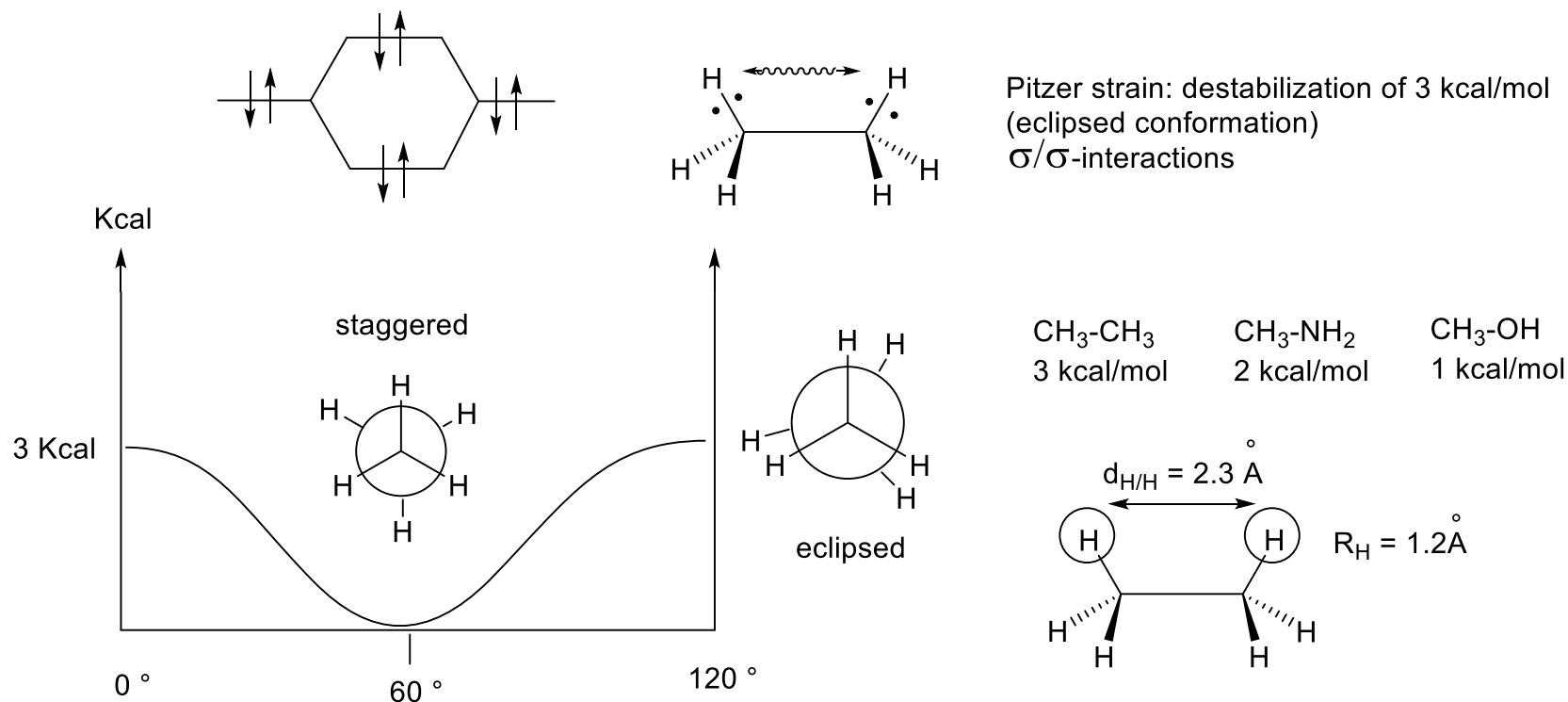
β -form of D-glucose

$$J_{aa} = 7.5 \text{ Hz}$$

Conformational analysis

1943: X-Ray analysis shows a chair conformation for cyclohexane derivatives

1950: Barton shows the difference between axial and equatorial positions in cyclohexane derivatives



Conformational analysis

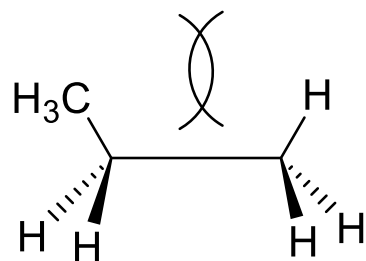
$$\Delta G^\circ = -3.0 \text{ Kcal} \implies K = e^{\frac{-\Delta G^\circ}{RT}} = \text{ca. } 100$$

$\implies$ 99% of ethane molecules exist in a staggered conformation

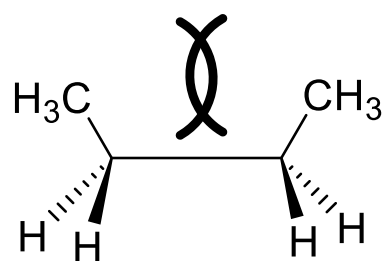
Isomeric ratios at equilibrium (T = 25 °C)

percent of more stable isomer	K	$\Delta G^\circ_{25^\circ\text{C}}$ (Kcal/mol)
50	1.0	0.0
55	1.22	0.12
60	1.50	0.24
70	2.33	0.50
75	3.0	0.65
85	5.67	1.03
90	9.0	1.30
95	19.0	1.75
99	99.0	2.72
99.9	999.0	4.09

Conformational analysis



4 kcal/mol

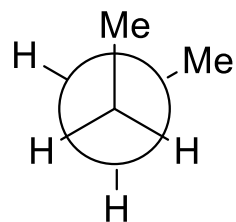
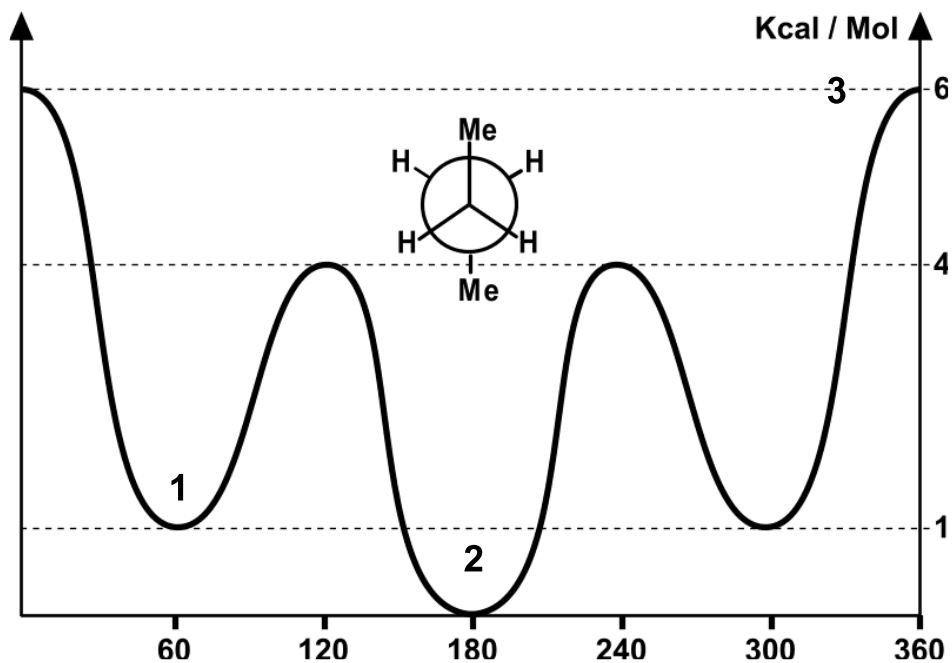


Pitzer strain

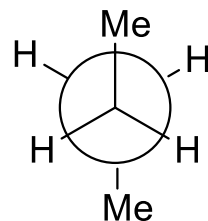
van der Waals
interactions

6 kcal/mol = ca. 3 kcal/mol + 3 kcal/mol

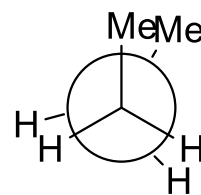
Conformational analysis of butane



1: gauche



2: antiperiplanar

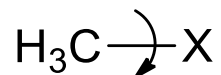


3: synperiplanar

70:30 mixture of antiperiplanar and gauche conformations

Conformational analysis

Rotational barriers of compounds of type $\text{CH}_3\text{-X}$

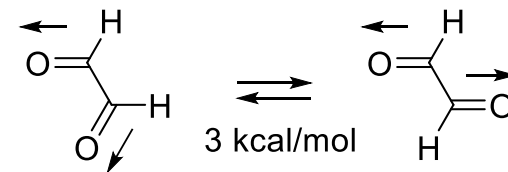
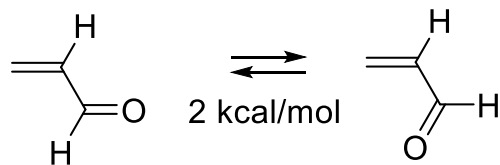
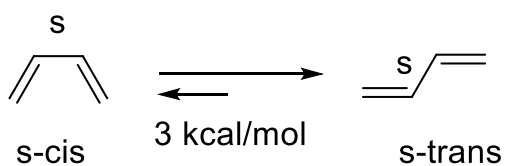
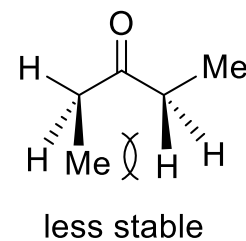
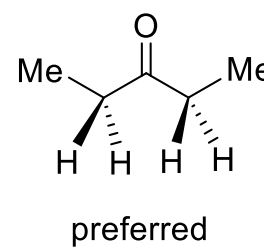
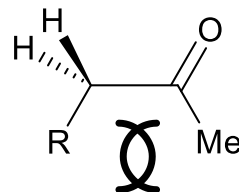
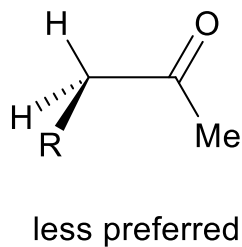
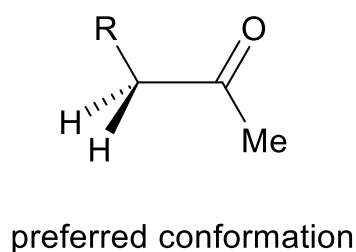
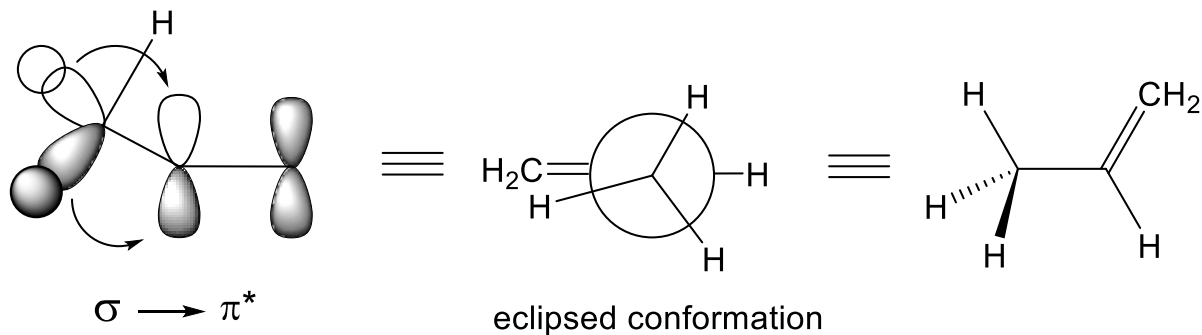


Alkanes	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
$\text{CH}_3\text{-CH}_3$	2.9	$\text{CH}_3\text{-NH}_2$	2.0
$\text{CH}_3\text{-CH}_2\text{CH}_3$	3.4	$\text{CH}_3\text{-NHCH}_3$	3.0
$\text{CH}_3\text{-CH}(\text{CH}_3)_2$	3.9	$\text{CH}_3\text{-N}(\text{CH}_3)_2$	4.4
$\text{CH}_3\text{-C}(\text{CH}_3)_3$	4.7	$\text{CH}_3\text{-OH}$	1.1
$(\text{CH}_3)_3\text{C-C}(\text{CH}_3)_3$	8.4	$\text{CH}_3\text{-OCH}_3$	4.6

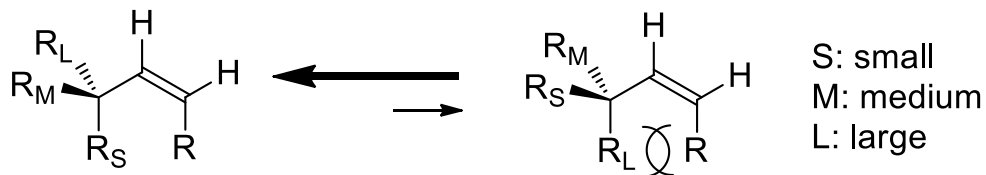
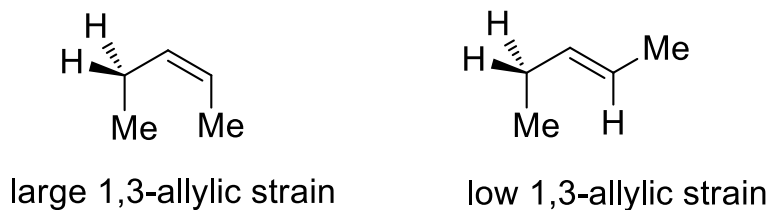
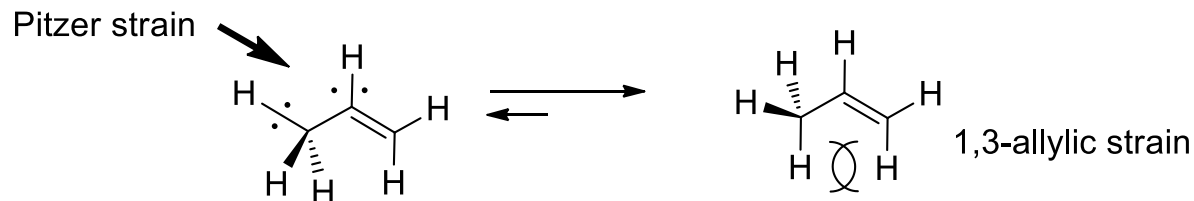
J. P. Lowe, *Prog. Phys. Org. Chem.* **1968**, 6, 1.

Conformational analysis of bonding between Csp² and Csp³

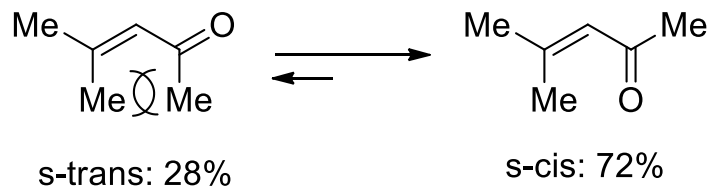
Propene: 2.7 kcal/mol stabilization effects of the Me-group ($n \longrightarrow \pi^*$)



1,3-Diaxial strain

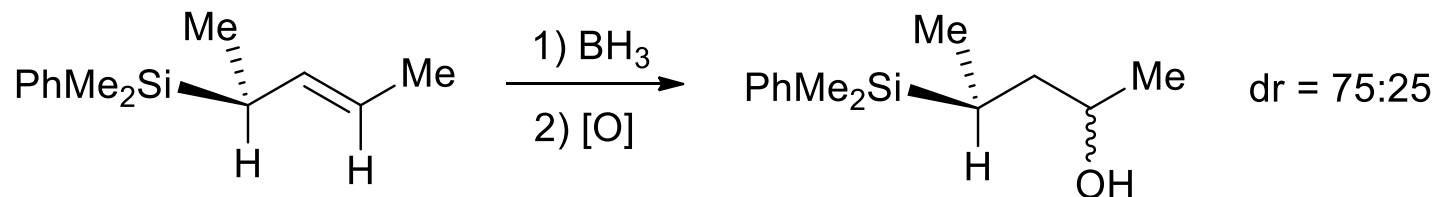


R. W. Hoffmann, *Chem. Rev.* **1989**, 89, 1841

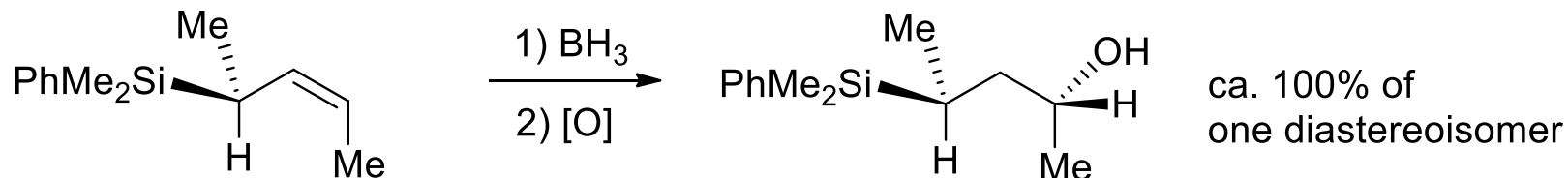


A. Bienvenue, *J. Am. Chem. Soc.* **1973**, 95, 7345

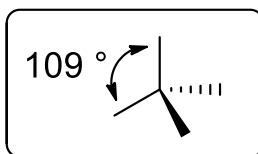
1,3-Diaxial strain



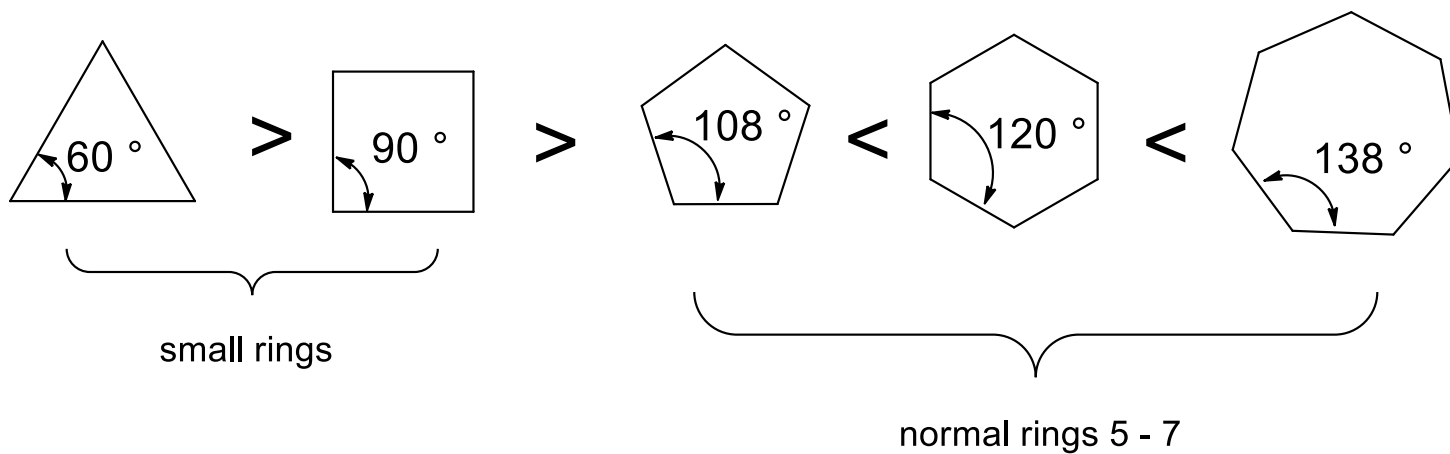
but



Conformational analysis of cyclic systems: Bayer strain



ideal tetrahedral angle



Classification of cyclic organic molecules

Cyclic molecules can be classified in 4 categories:

small rings: 3-4;

normal rings: 5-7;

medium-sized rings: 8 -12;

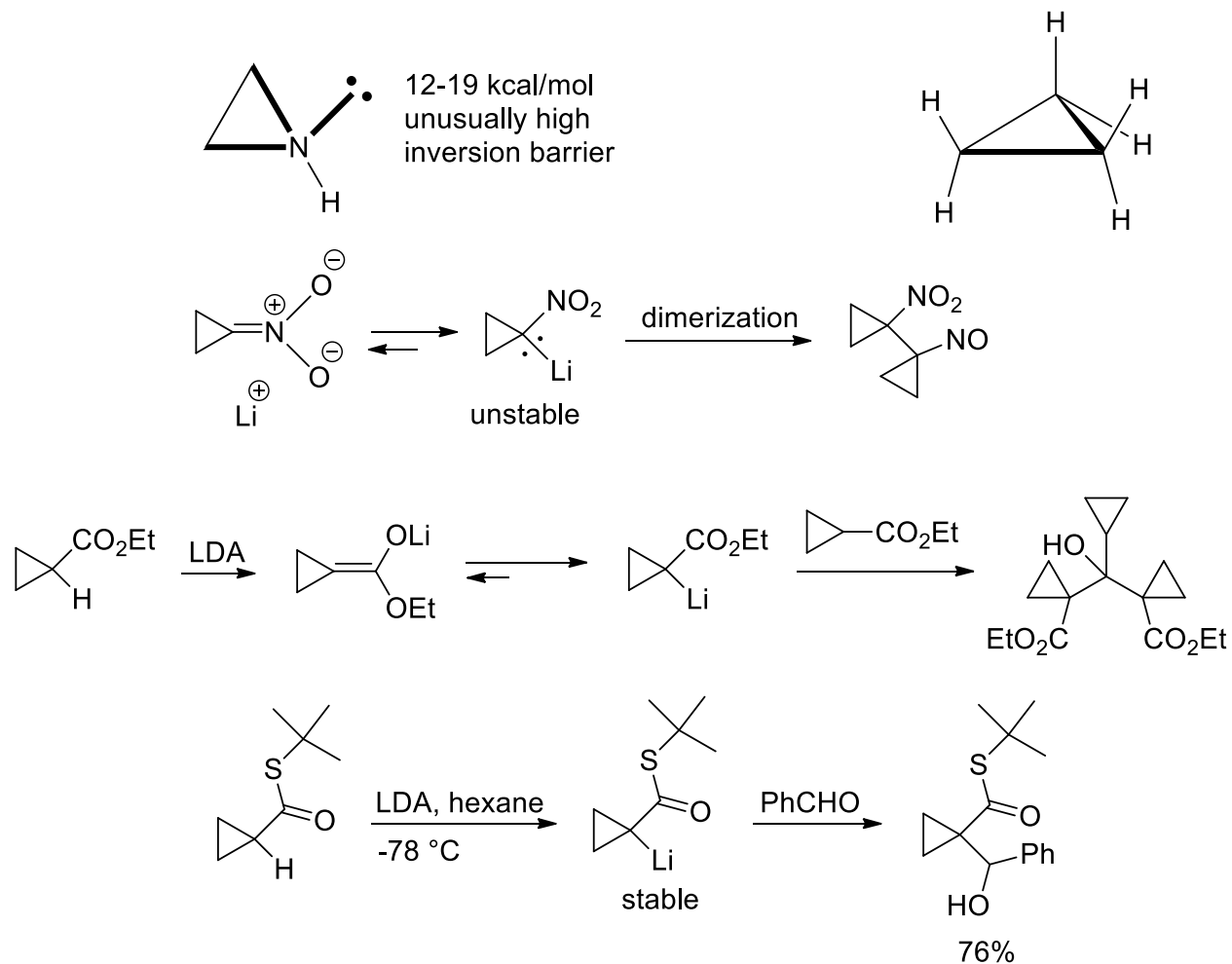
large rings: 13-membered rings and larger

	ring size	strain energy per methylene group	
small rings	{ 3 4	9 6.8	
normal rings	{ 5 6 7	1.4 0.2 1.1	
medium-sized rings	{ 8 9 10 11 12	1.4 1.6 1. 1.3 0.5	} transannular interaction

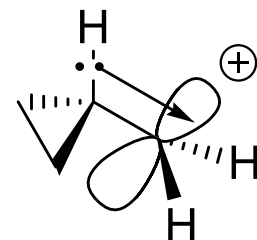
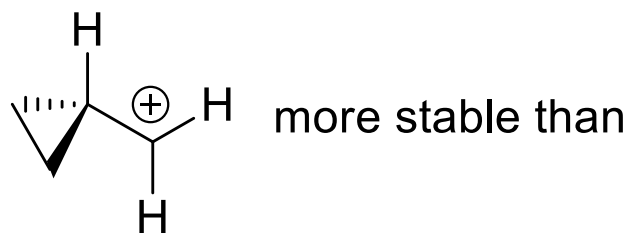
large rings behave like a per-chain systems

The cyclopropane ring

planar ring system: Pitzer strain 6 Kcal/mol

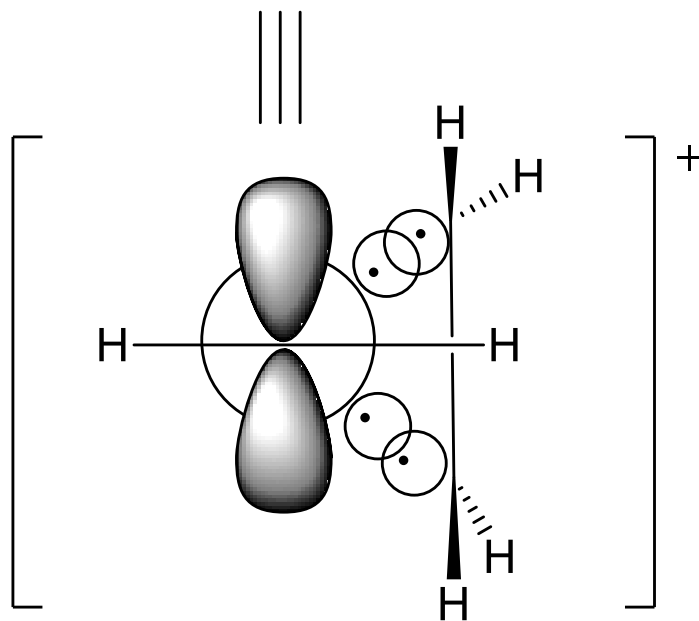


Conformation of the cyclopropylmethyl cation

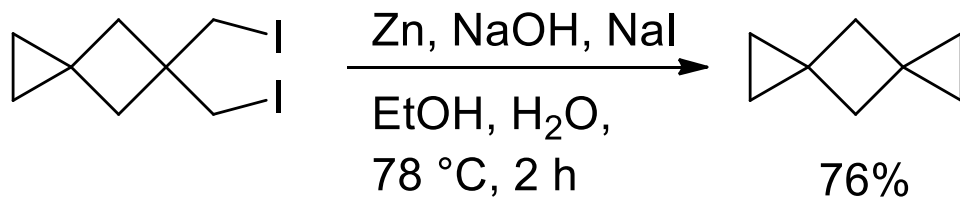


eclipsed
conformation

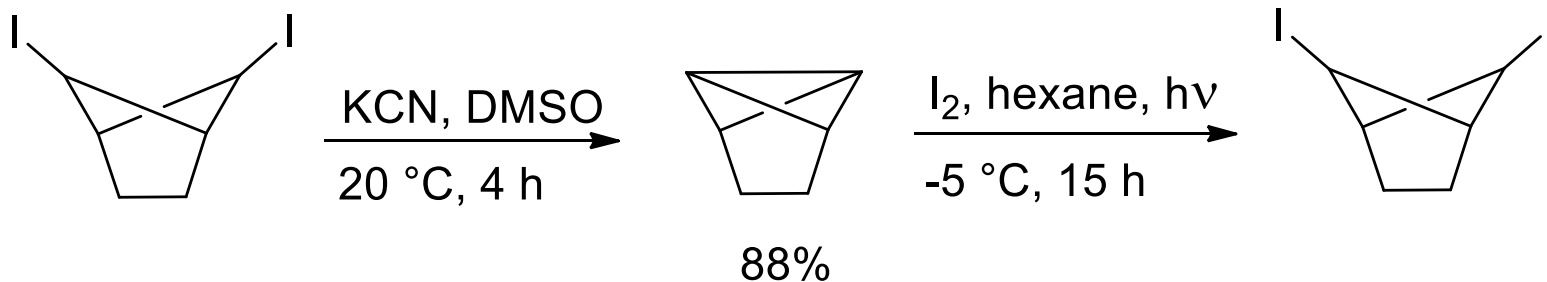
staggered
conformation



Synthesis of cyclopropanes

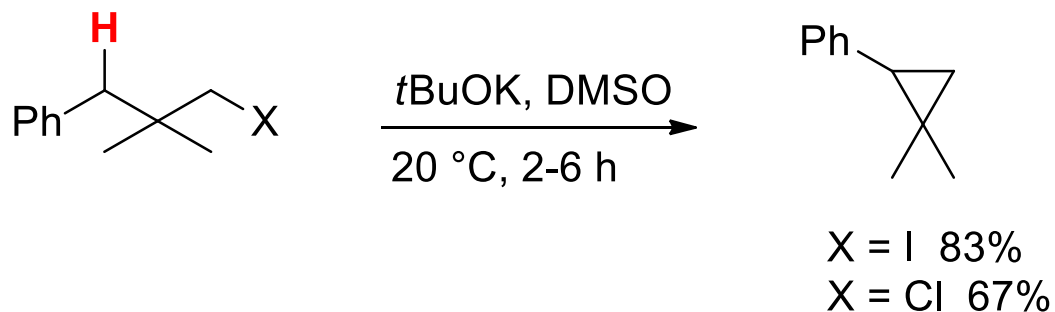


H.-D. Beckhaus, C. Rüchardt, S. I. Kozhushkov, V. N. Belov, S. P. Verevkin, A. de Meijere, *J. Am. Chem. Soc.* **1995**, *117*, 11854.

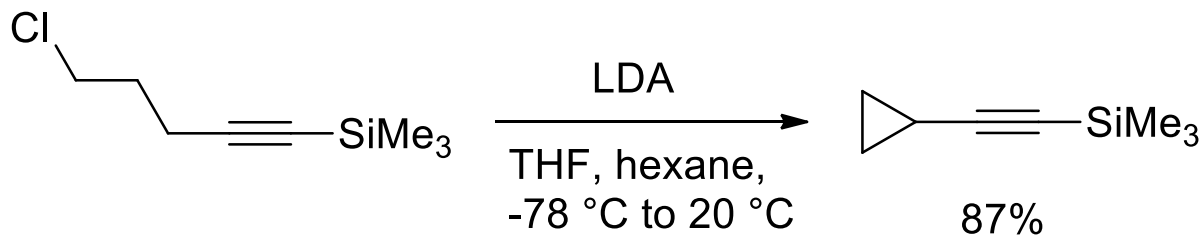


C. Mazal, O. Skarka, J. Kaleta, J. Michl, *Org. Lett.* **2006**, *8*, 749.

Synthesis of cyclopropanes

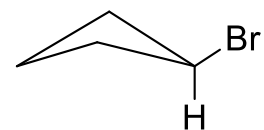
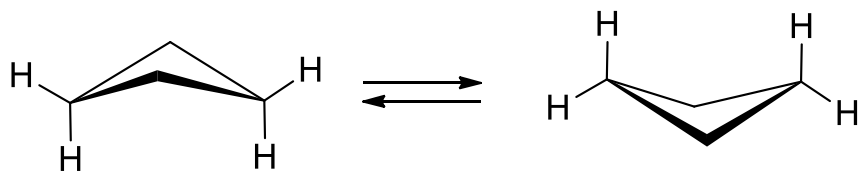


J. E. Argüello, A. B. Peñeñory, R. A. Rossi, *J. Org. Chem.* **1999**, 64, 6115.

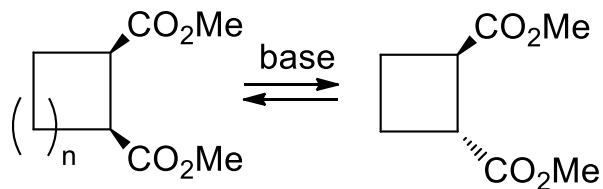


H.-C. Miltzer, S. Schömenauer, C. Otte, C. Puls, J. Hain, S. Bräse, A. de Meijere, *Synthesis* **1993**, 998.

The cyclobutane and cyclopentane systems

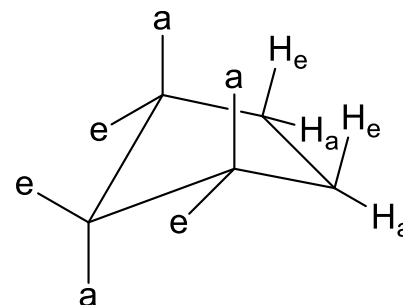


1.5 kcal/mol inversion barrier



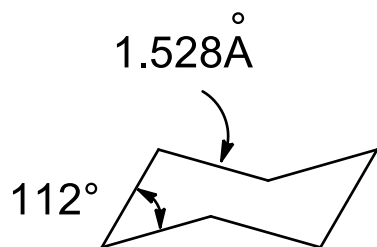
$n = 1$ 90:10

$n = 3$ 97(trans):3(cis)

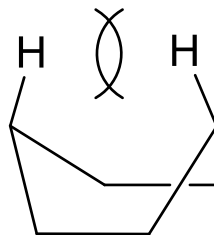


pseudo-axial

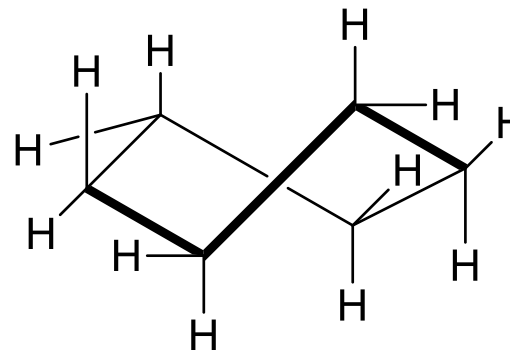
The conformations of cyclohexane



Chair form
0 kcal/mol



Boat form
7.1 kcal/mol



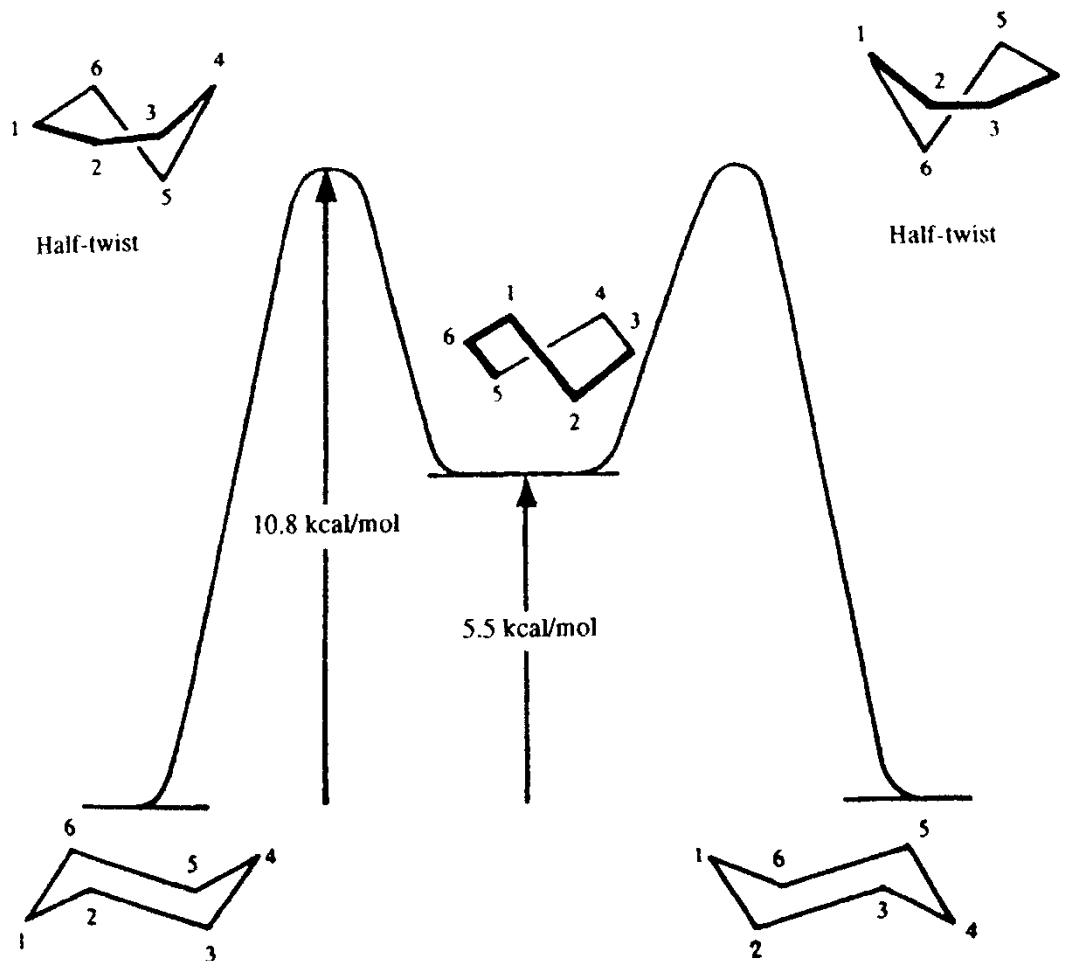
5.5 kcal/mol

inversion barrier of cyclohexane
ca. 10 kcal/mol

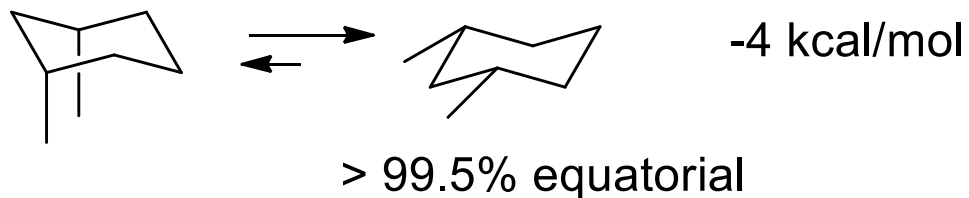
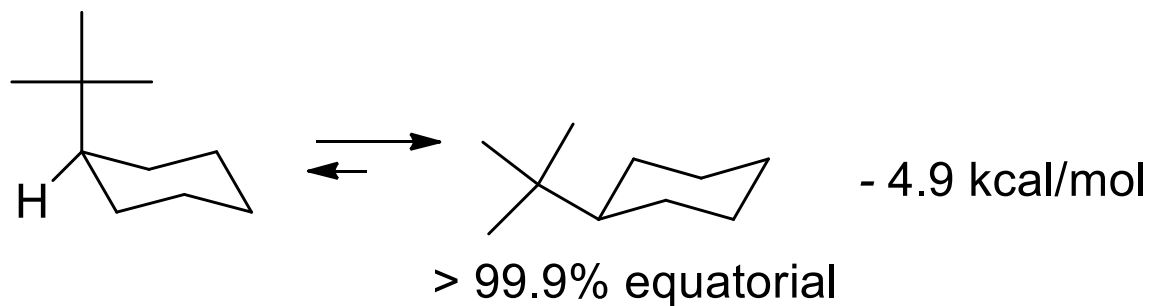
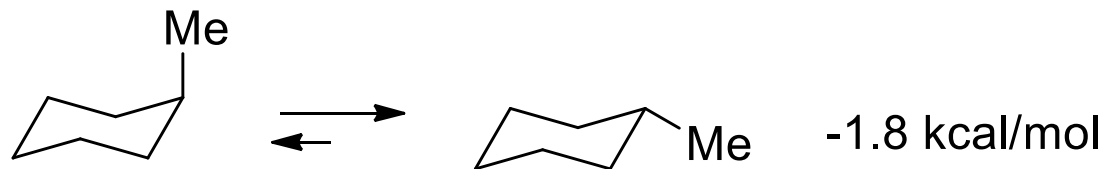


100 000 inversions/s
at 25 °C

Energy diagram for ring inversion of cyclohexane

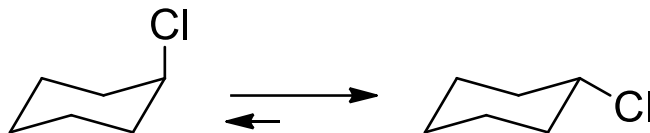


The conformation of substituted cyclohexane



For substituted cyclohexanes, a slow exchange is observed below -50 °C

Inversion of cyclohexane

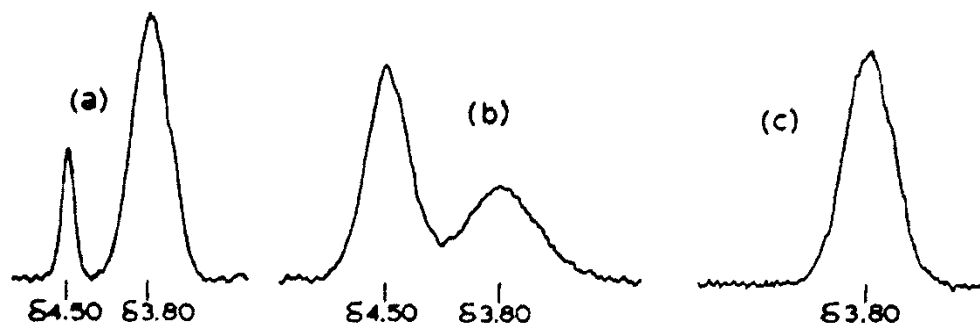


Half-life for conformation inversion of cyclohexane at various temperatures

T (°C)	Half-life
25	1.3×10^{-5} s
-60	0.03 s
-120	23 min
-160	22 years !

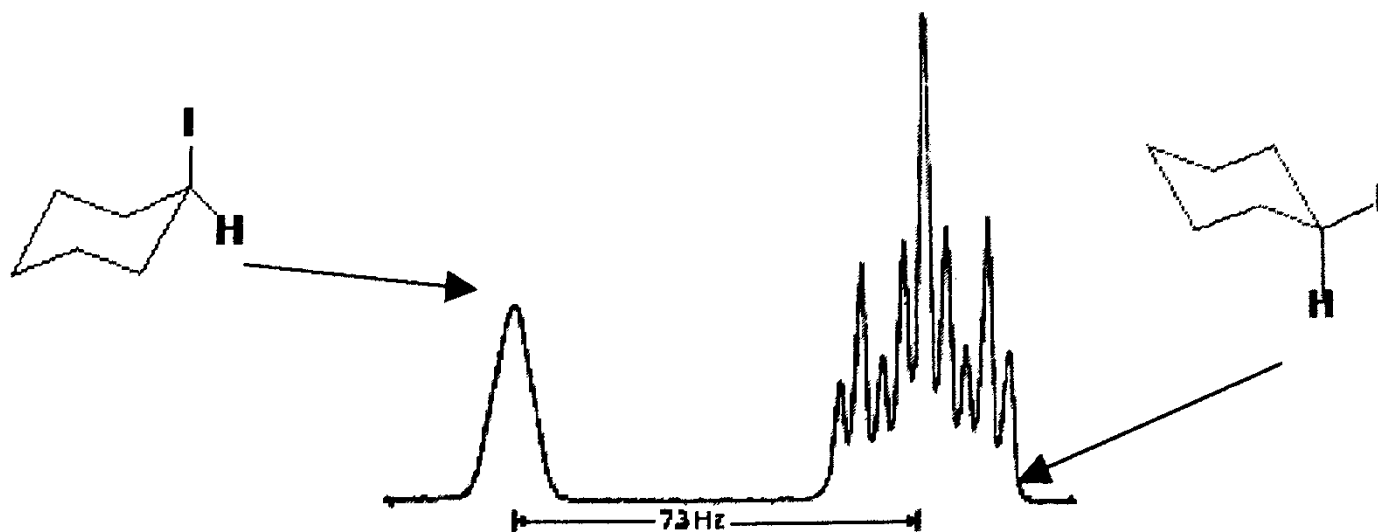
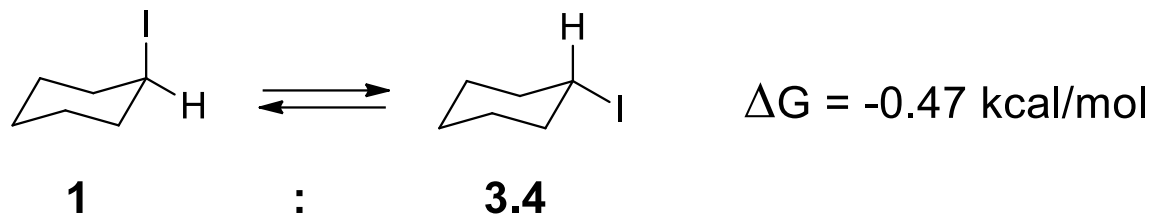
A crystallization of the equatorial isomer at -150 °C is possible

F. R. Jensen, *J. Am. Chem. Soc.* **1969**, 91, 3223.



60-MHz ^1H -NMR spectrum for the C(1)H in chlorocyclohexane. a) axial-equatorial equilibrium at -115 °C, b) axial enriched mixture at -150 °C, c) pure equatorial conformer at -150 °C

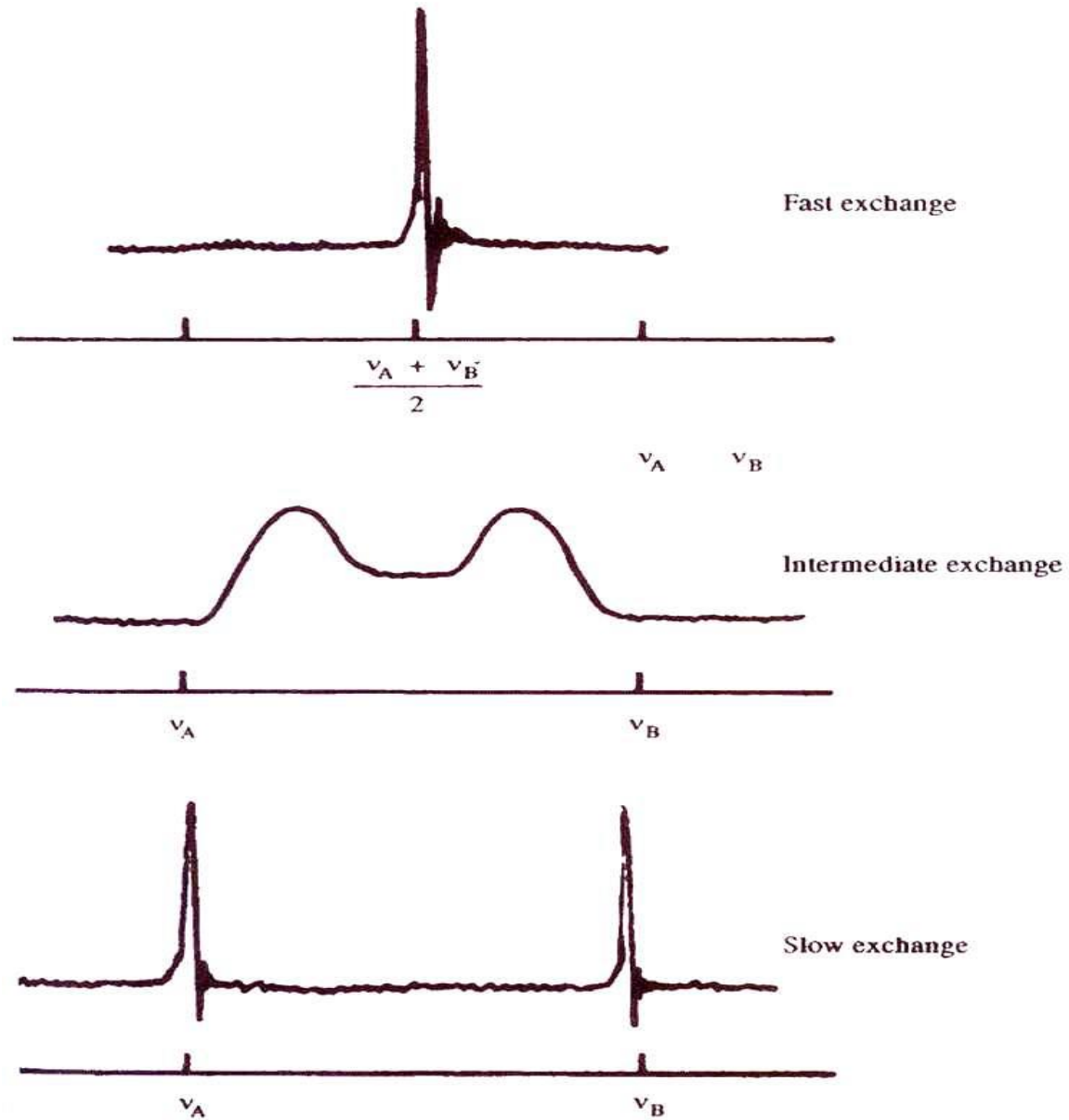
Cyclohexyl iodide



100 MHz ^1H -NMR spectrum of iodocyclohexane at -80°C . Only the low field C(1)H signal is shown.

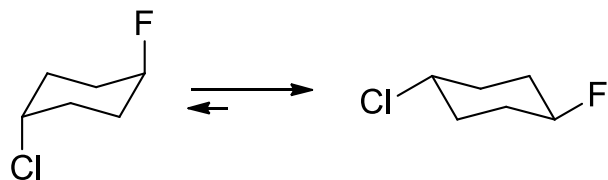
F. R. Jensen, *J. Am. Chem. Soc.* **1969**, 91, 344.

Temperature depending NMR-spectra / exchange rate of protons

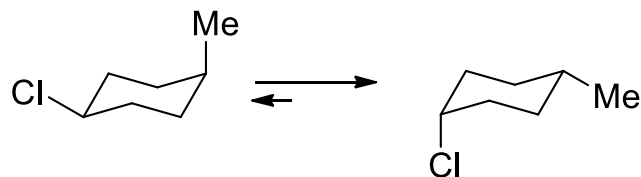


Conformational free energies ($-\Delta G$) for some substituents

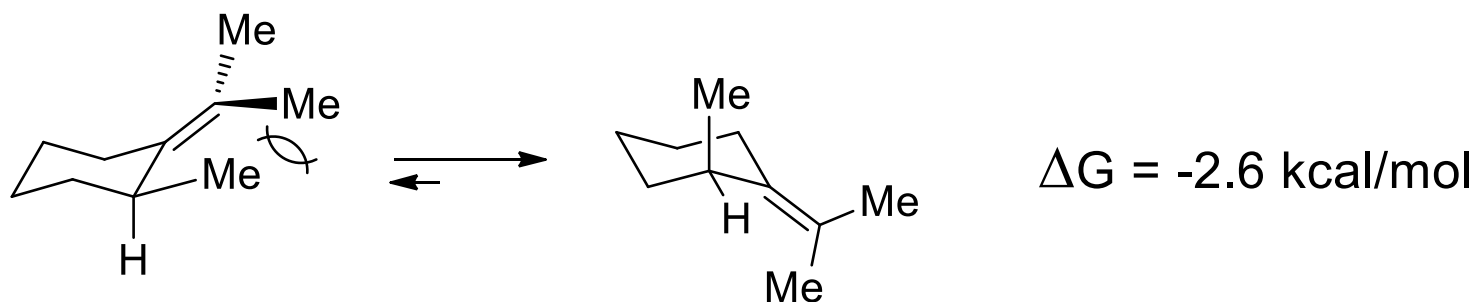
Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26	C ₆ H ₅	2.9
Cl	0.53	CN	0.2
I	0.47	CH ₃ CO ₂	0.71
CH ₃	1.8	HO ₂ C	1.35
CH ₃ CH ₂	1.8	C ₂ H ₅ O ₂ C	1.1-1.2
(CH ₃) ₂ CH	2.1	HO (aprotic solvent)	0.52
(CH ₃) ₃ C	>4.7	HO (protic solvent)	0.87
CH ₂ =CH	1.7	CH ₃ O	0.60
HC≡C	0.5	O ₂ N	1.16



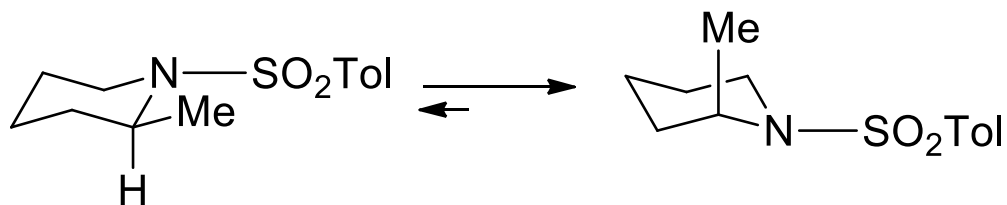
$$\Delta G = -(0.26 + 0.53) = -0.79 \text{ kcal/mol}$$



$$\Delta G = -(1.8 - 0.53) = -1.27 \text{ kcal/mol}$$

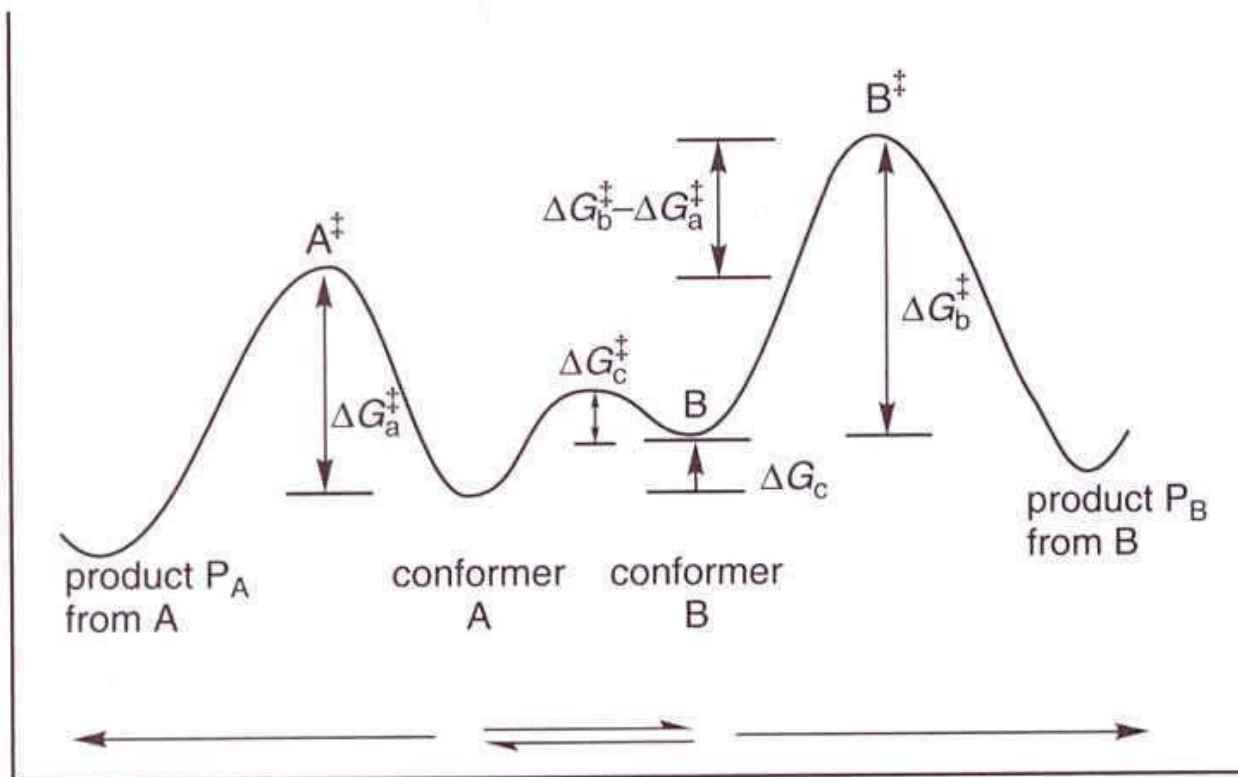
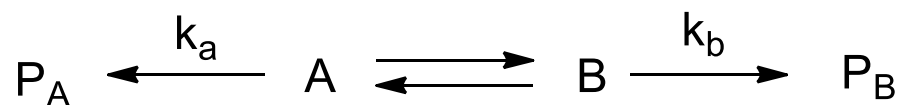


F. Johnson, *Chem. Rev.* **1968**, 68, 375



S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.*, **2011**, 133, 4774.

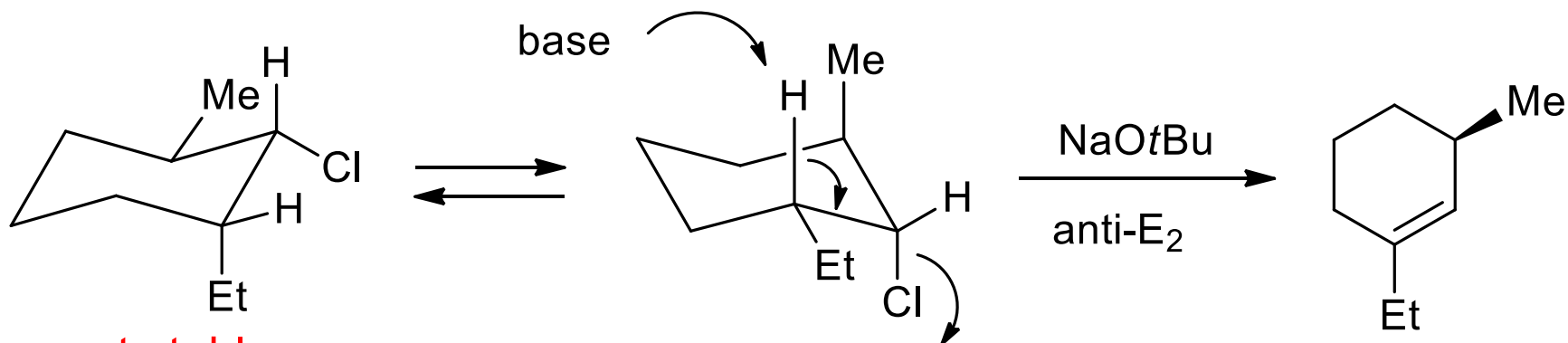
Stereoselective effects: Curtin-Hammett principle



According to the Curtin-Hammett principle, the position of the equilibrium between two molecules **A** and **B** cannot be used to predict the ratio between the products **P_A** and **P_B**, only the difference between the activation energies $\Delta G_B^\ddagger - \Delta G_A^\ddagger$ is relevant

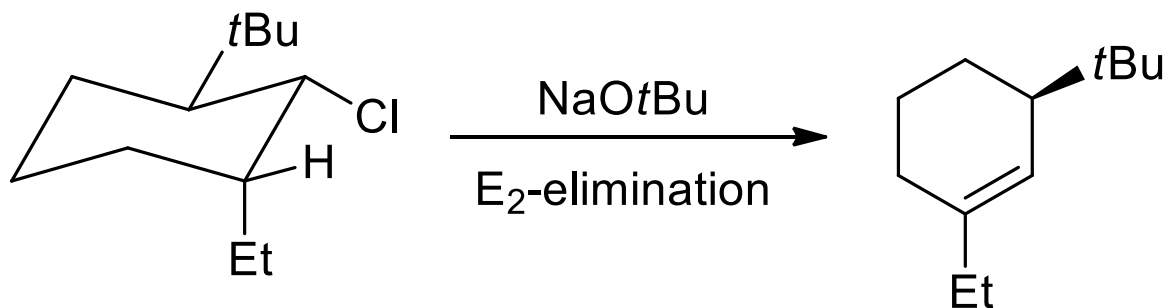
The Curtin-Hammett principle

Stereoselective E₂-elimination

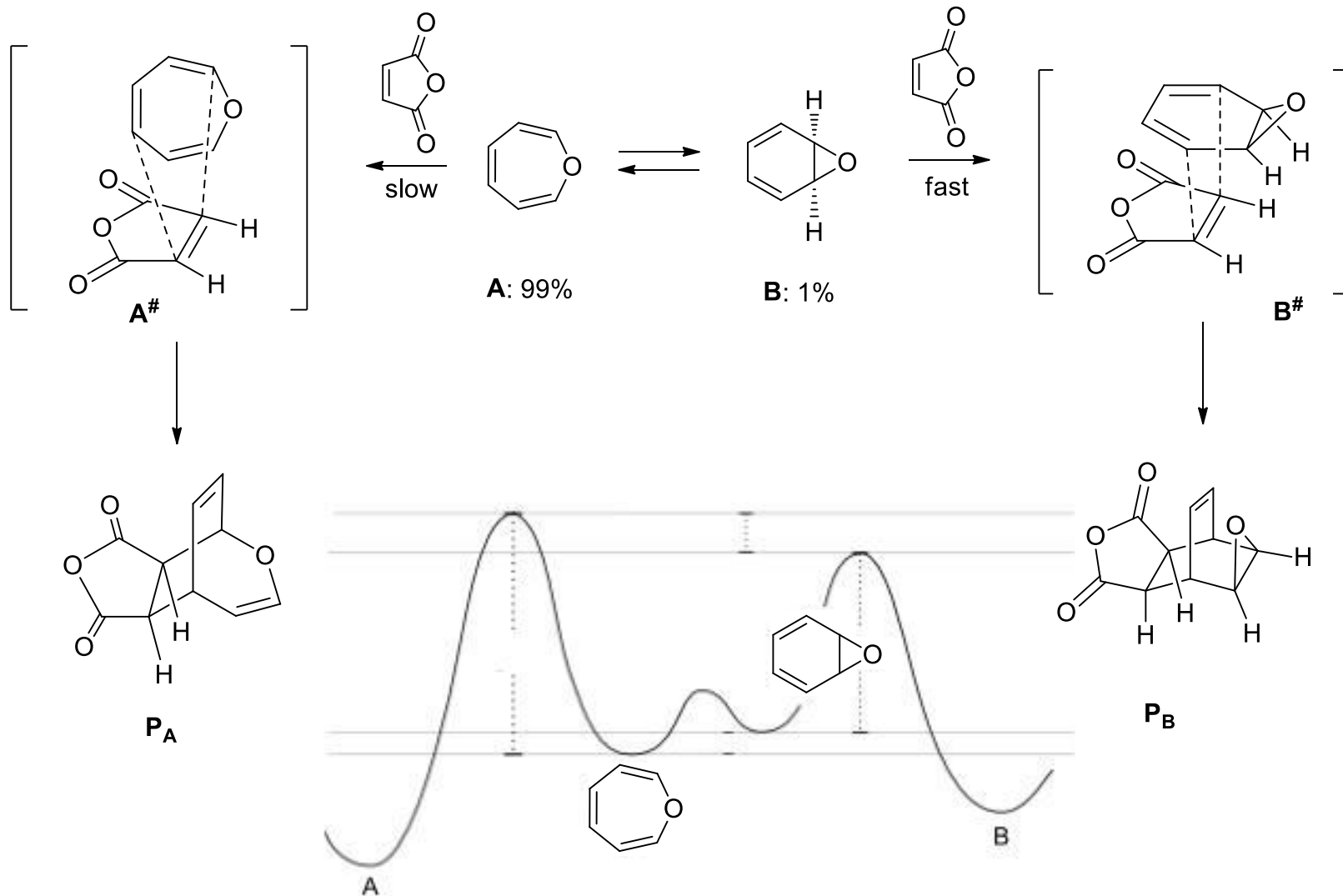


most stable
conformer but
unreactive for
an E₂-elimination

most reactive
conformer
(antiperiplanar arrangement
of the C-H and C-Cl bond)



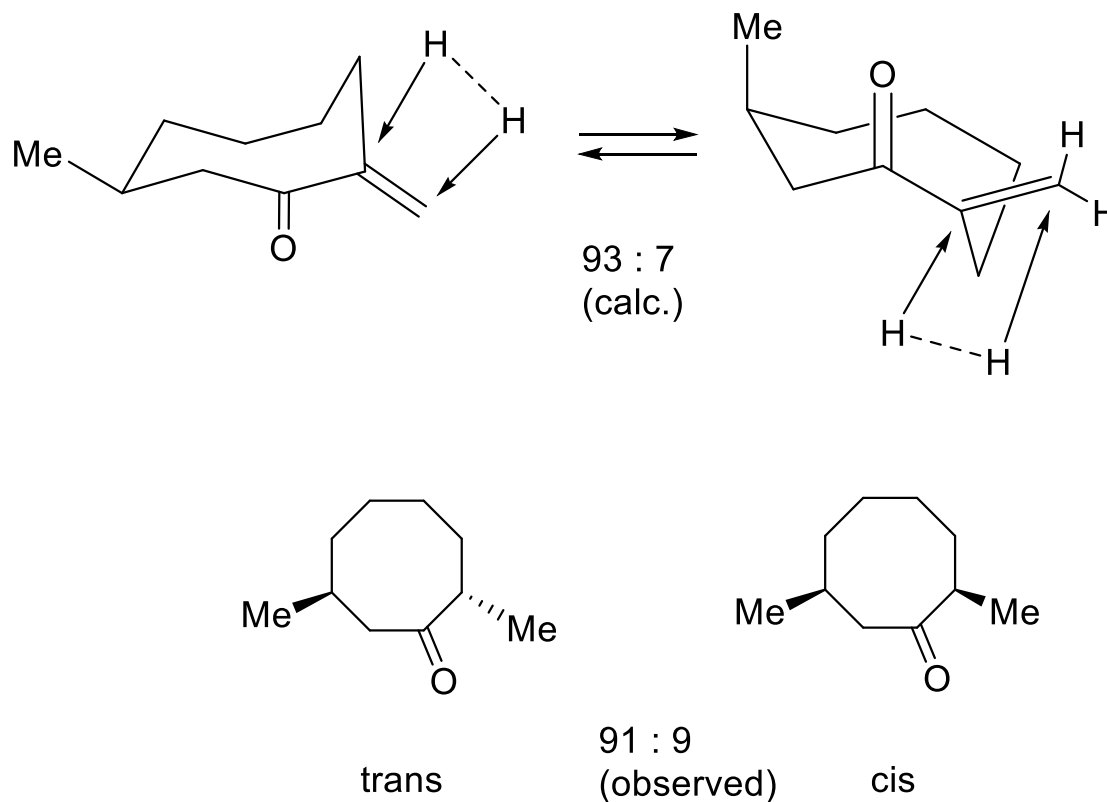
Example of the Curtin-Hammett principle



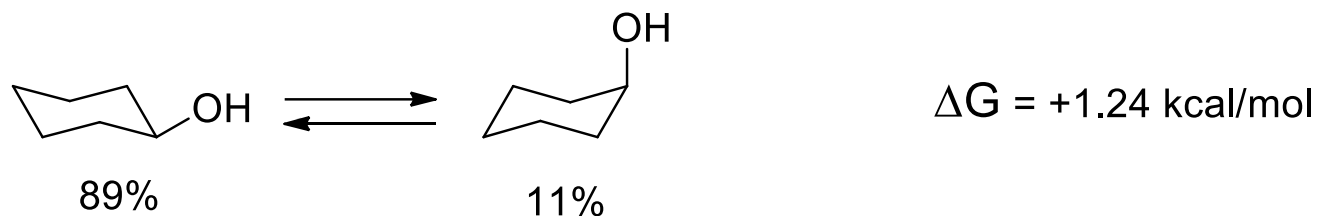
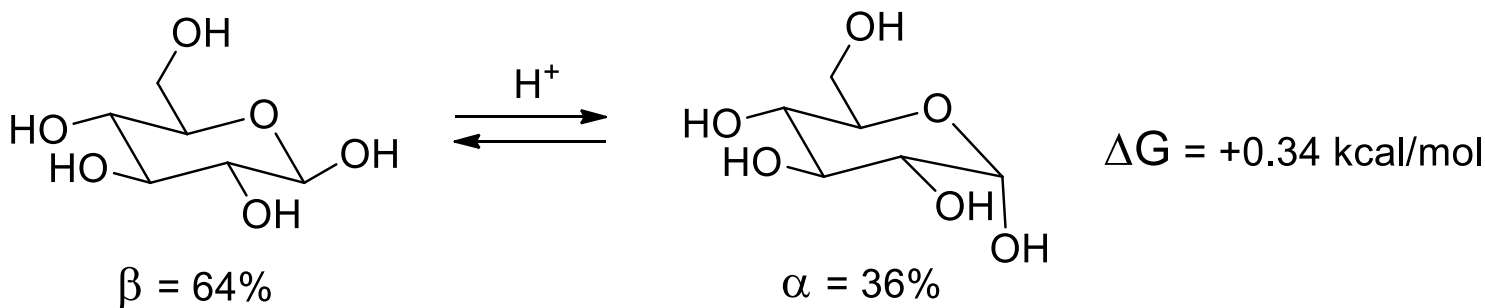
The Curtin-Hammett principle

According to the Curtin-Hammett principle, the position of the equilibrium between two molecules A and B cannot be used to predict the ratio between the products.

Exception: when the activation energy are very similar



The anomeric effect

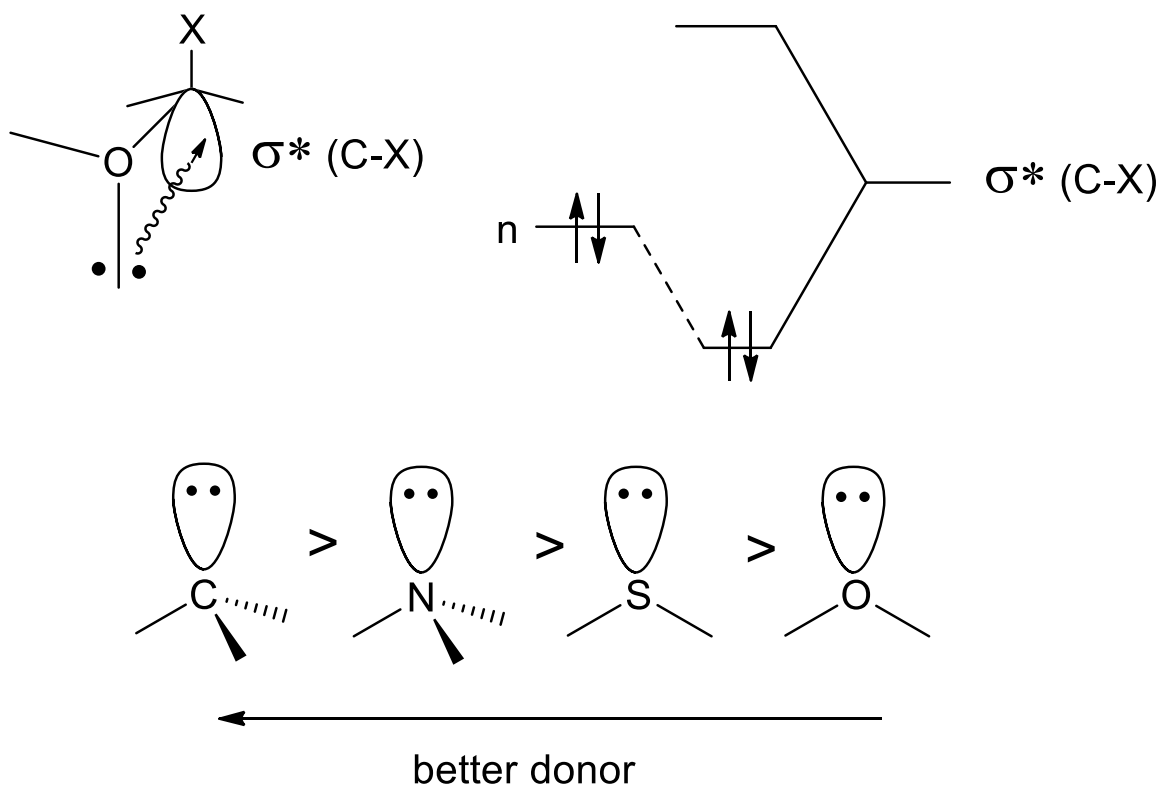


Anomeric effect: 0.9 kcal/mol

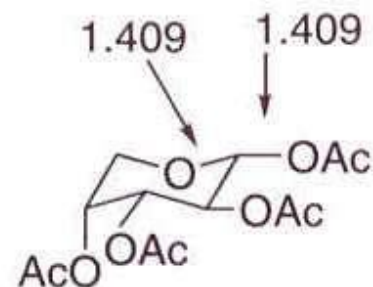
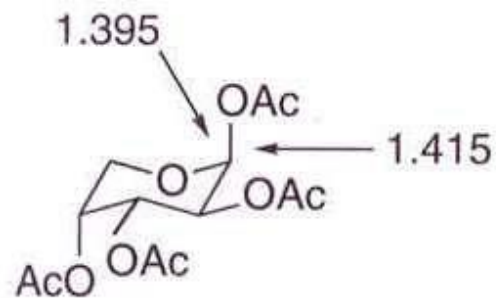
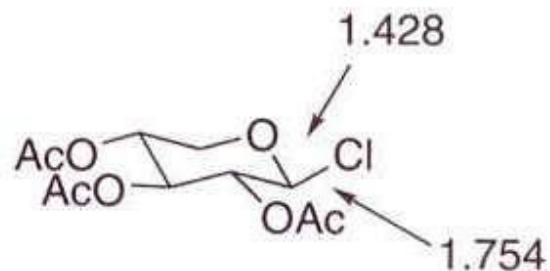
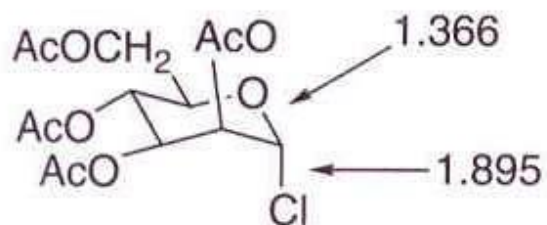
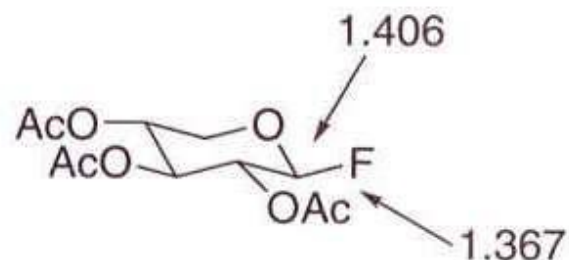
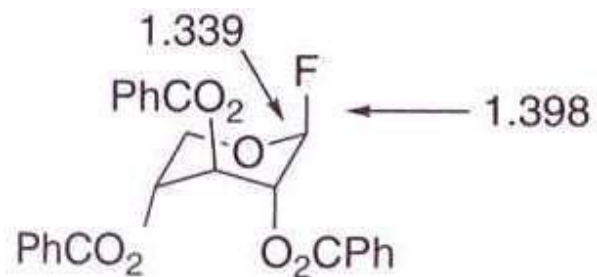
The tendency to prefer a substituent in an axial position increases with the electronegativity of the substituents. $X = \text{OAc}, \text{Cl}, \text{F}, \dots$

Origin of the anomeric effect

Most probable origin: hyperconjugation effect between electron lone pair of oxygen and the σ^* (C-X) bond

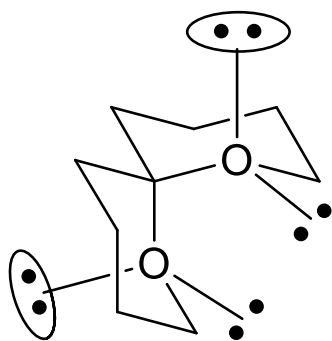
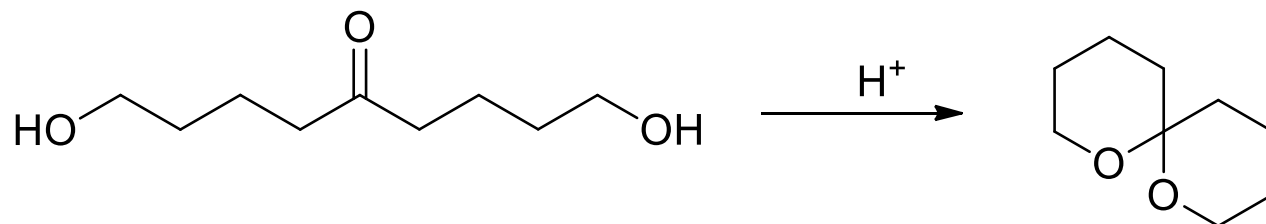


The anomeric effect

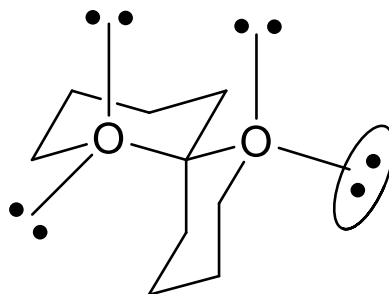


The anomeric effect

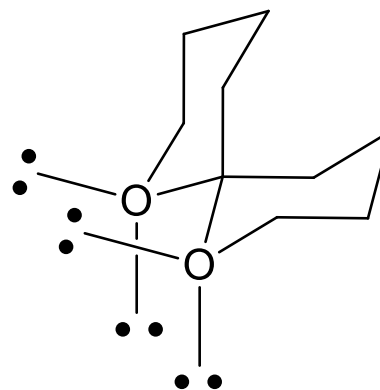
Application: Determination of the conformation of a ketal



2 anomeric effects



1 anomeric effect

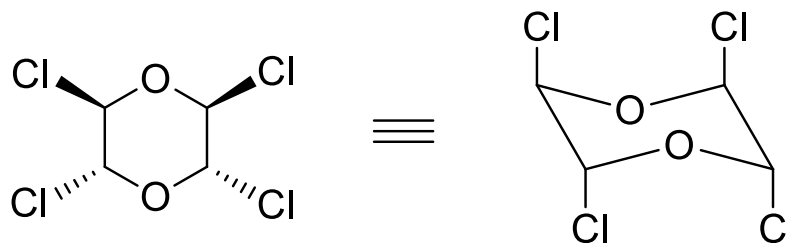


0 anomeric effect

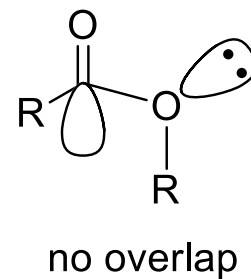
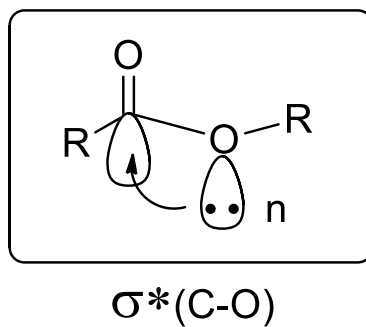
The anomeric effect

The anomeric effect allows to predict the preferred conformation of organic molecules:

Preferred conformation for

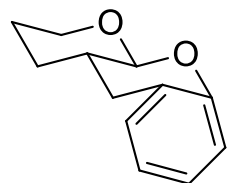
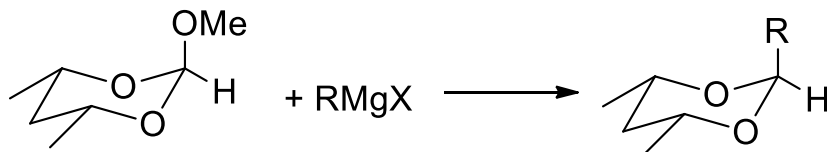


Preferred conformation of esters :

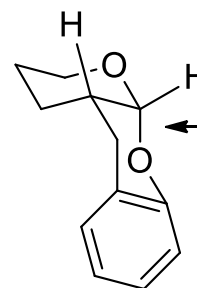


The kinetic anomeric effect

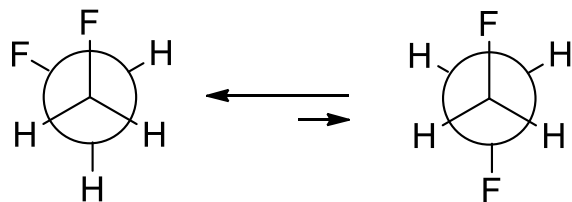
Kinetic effects:



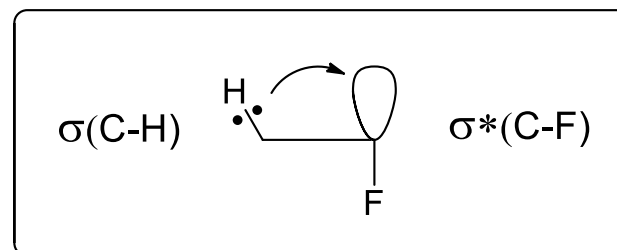
is hydrolyzed 3000 times slower than



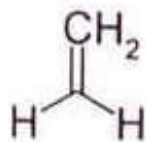
better leaving group



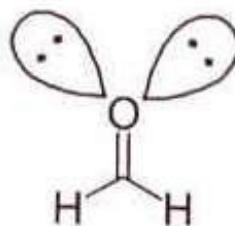
preferred gauche
conformation



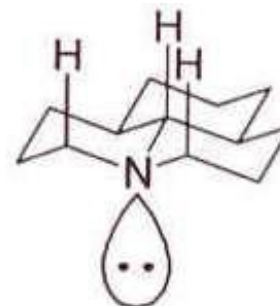
Effects on spectra and structure



$$\tilde{\nu} \text{C-H} = 3055 \text{ cm}^{-1}$$



$$\tilde{\nu} \text{C-H} = 2813 \text{ cm}^{-1}$$

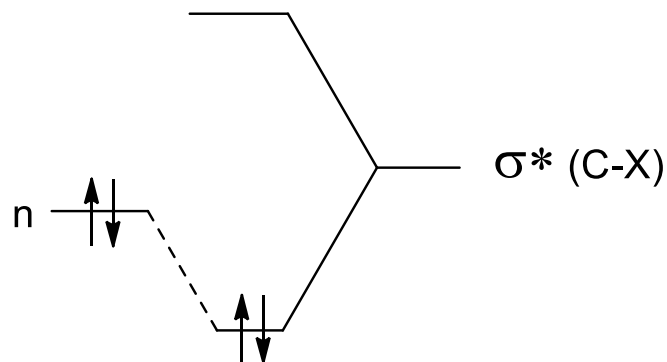
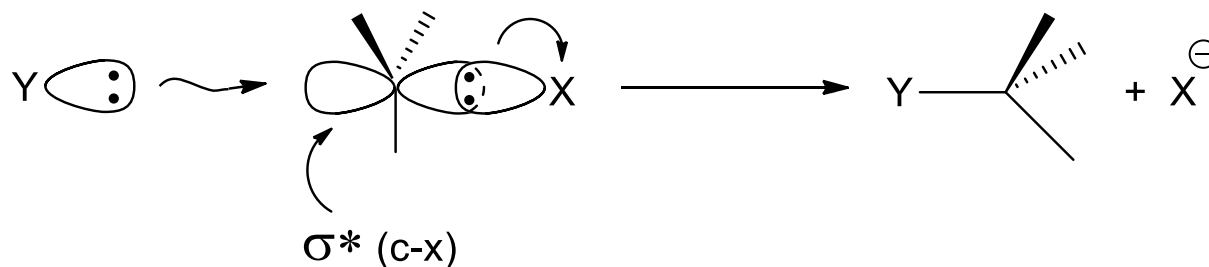


$$\tilde{\nu} \text{C-H} = 2800\text{--}2700 \text{ cm}^{-1}$$

Antiperiplanar lone pairs weaken C-H bonds and reduce their IR wavenumber

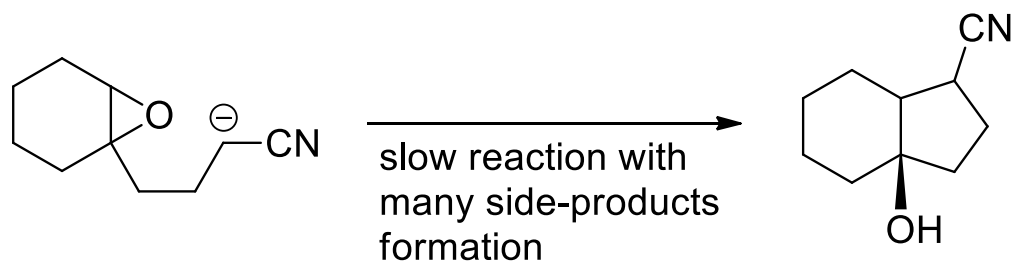
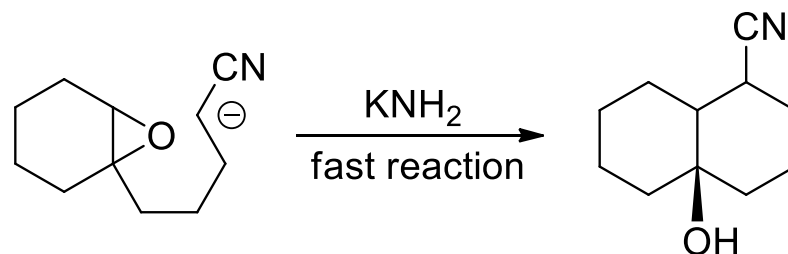
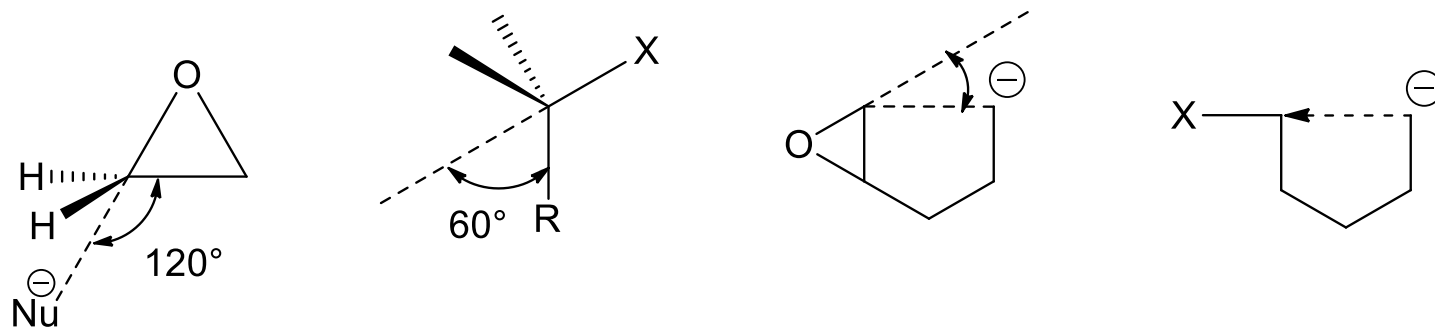
Stereoelectronic effects and the Baldwin rules

Stereochemical requirements for the S_N2 -substitution: linear arrangement between the leaving group and the entering nucleophile



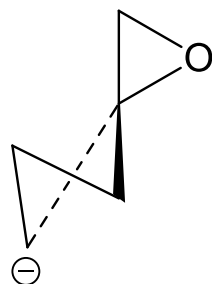
J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734-736.

Epoxide-opening

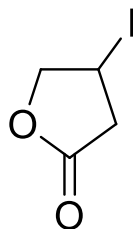
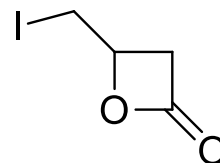
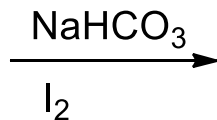
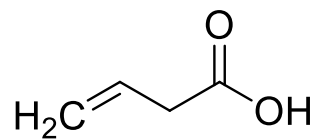
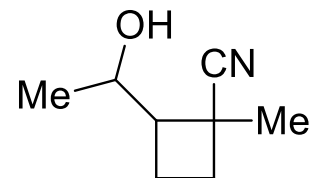
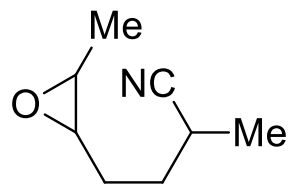


G. Stork, L. D. Cama, D. R. Coulson, *J. Am. Chem. Soc.* **1974**, 96, 5268.

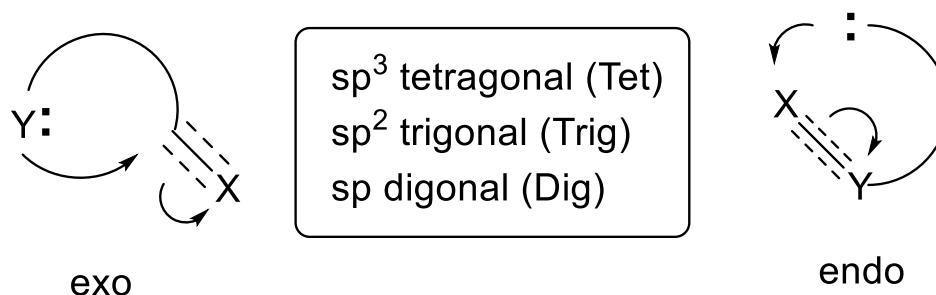
Epoxide-opening



preferred
conformation



Baldwin rules



Rule 1: ***Tetrahedral Systems***

3 to 7-*Exo-Tet* are all favoured processes
with many literature precedents
5 to 6-*Endo-Tet* are disfavoured

Rule 2: ***Trigonal Systems***

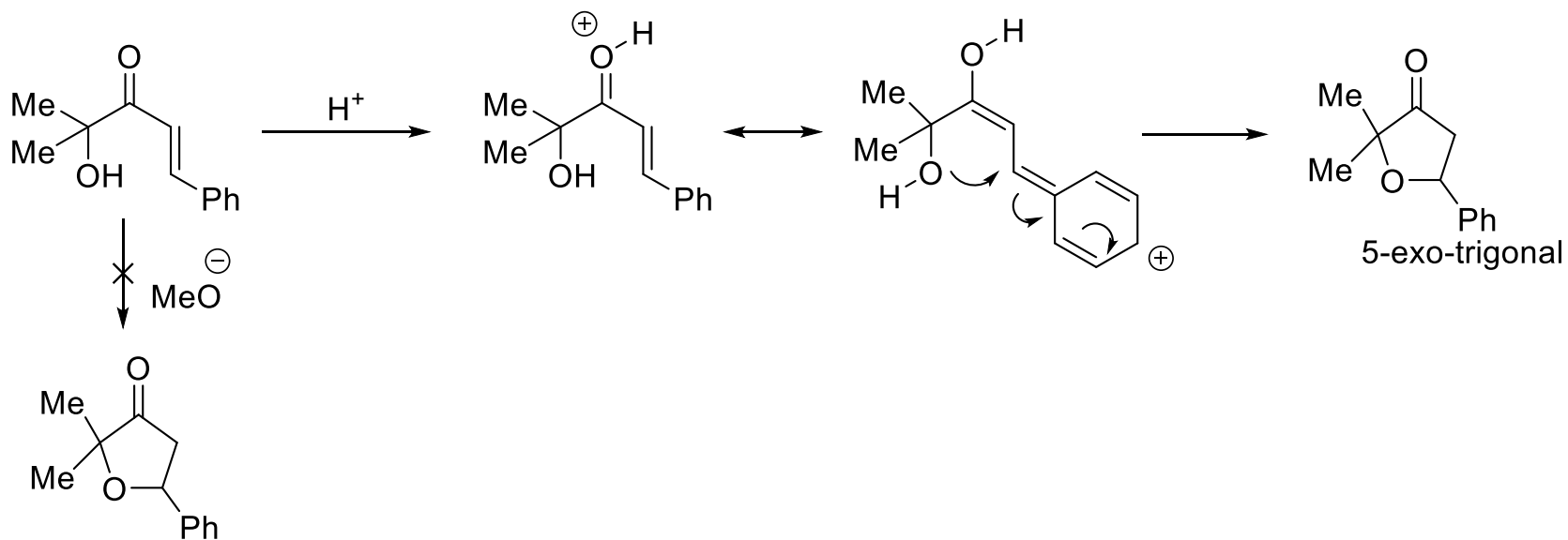
3 to 7-*Exo-Trig* are all favoured processes
with many literature precedents
3 to 5-*Endo-Trig* are disfavoured
6 to 7-*Endo-Trig* are favoured

Rule 3: ***Digonal Systems***

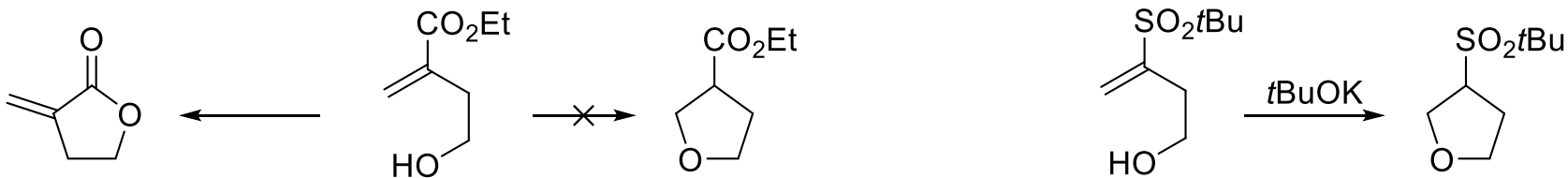
3 to 4-*Exo-Dig* are disfavoured processes
5 to 7-*Exo-Dig* are favoured
3 to 7-*Endo-Dig* are favoured

Stereoselective reactions

Examples:

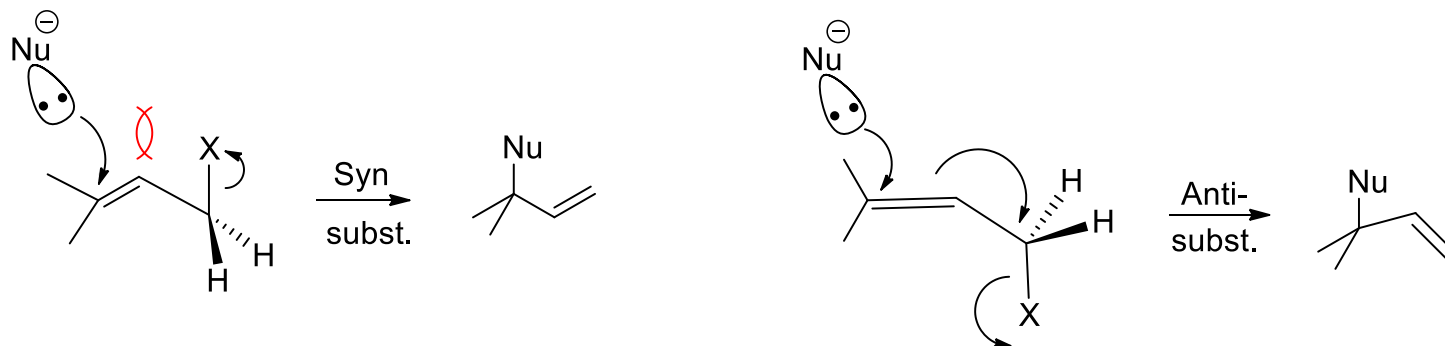


J. E. Baldwin, R. C. Thomas, L. I. Kruse, L. Silberman *J. Org. Chem.* **1977**, 42, 3846.

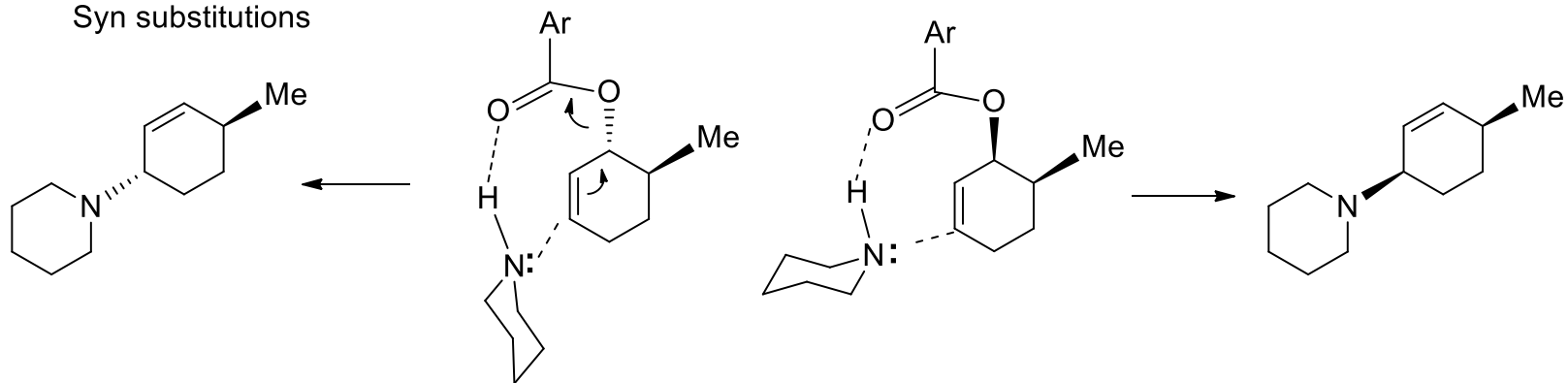


P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1985**, 26, 4455. 105

S_N2' -substitutions

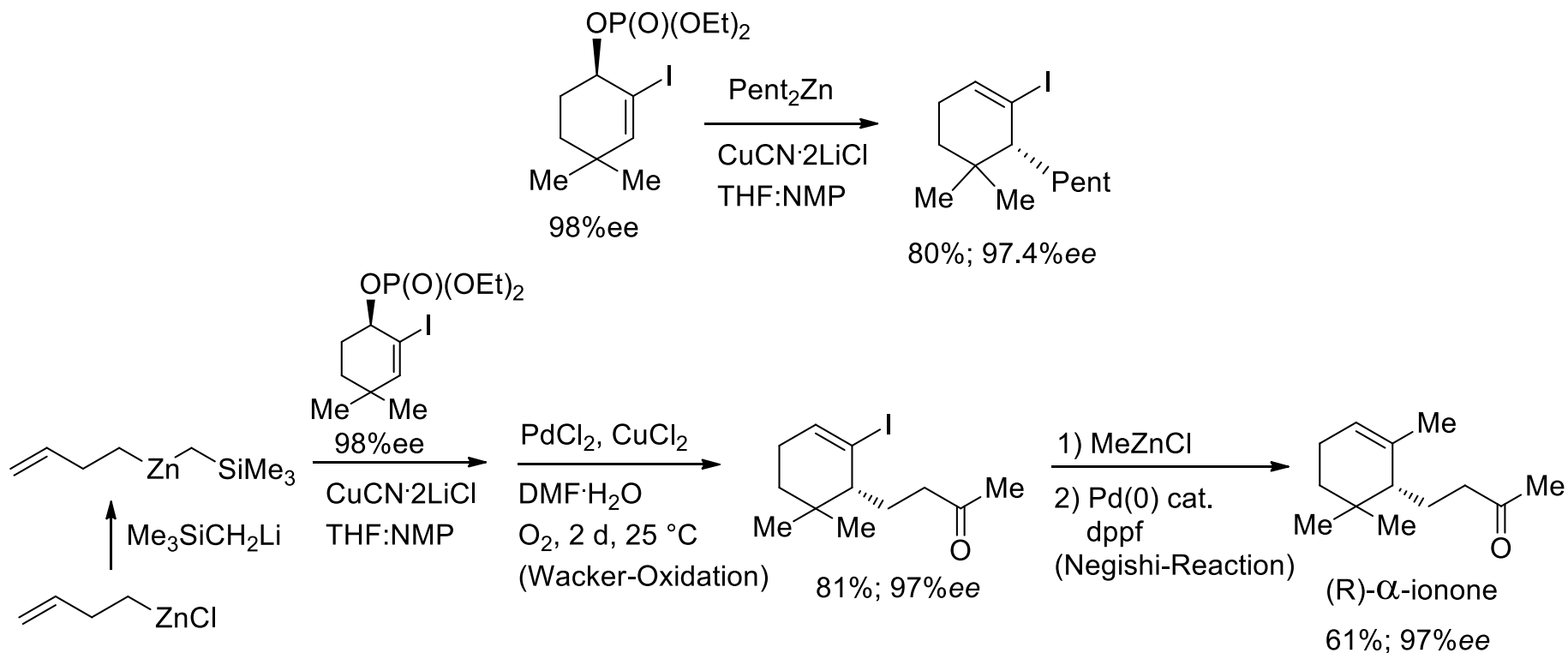


Syn substitutions



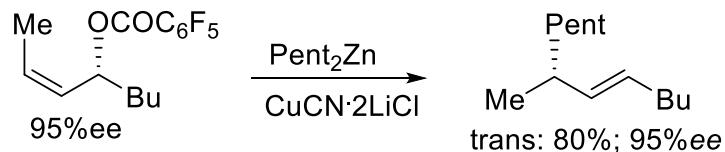
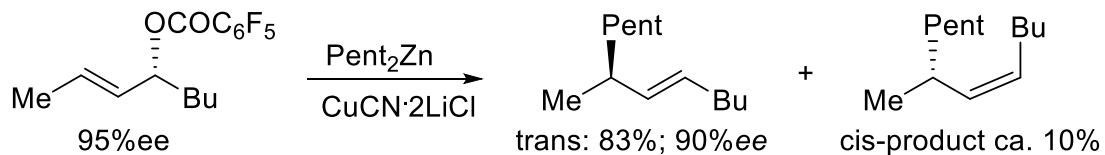
G. Stork, W. N. White, *J. Am. Chem. Soc.* **1956**, 78, 4609. For a review see: R. M. Magid, *Tetrahedron* **1980**, 36, 1901.

S_N2'-substitutions with organocopper

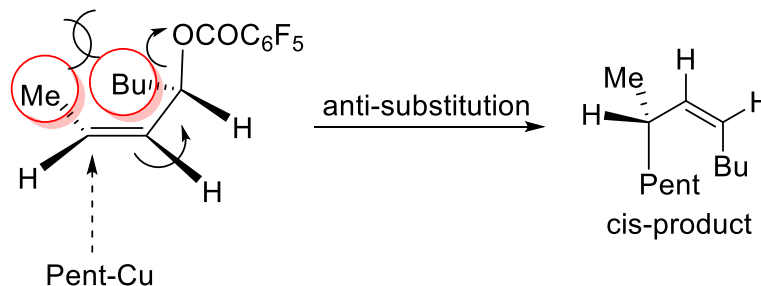
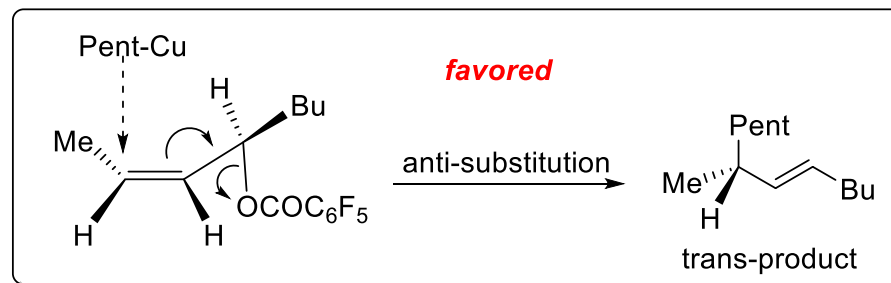


D. Soorukram, P. Knochel *Org. Lett.* **2004**, 6, 2409

Anti-S_N2'-substitutions with organocopper

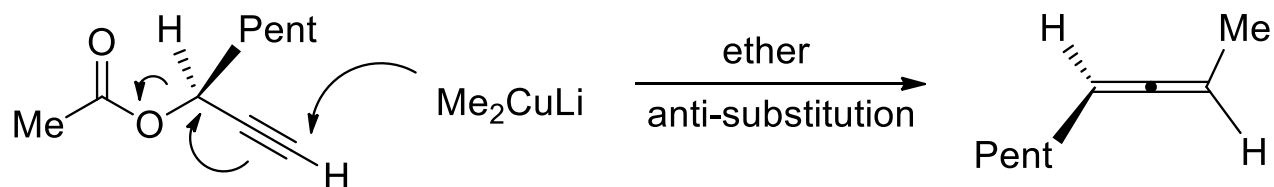


two anti-substitution
TS-structures
are possible:



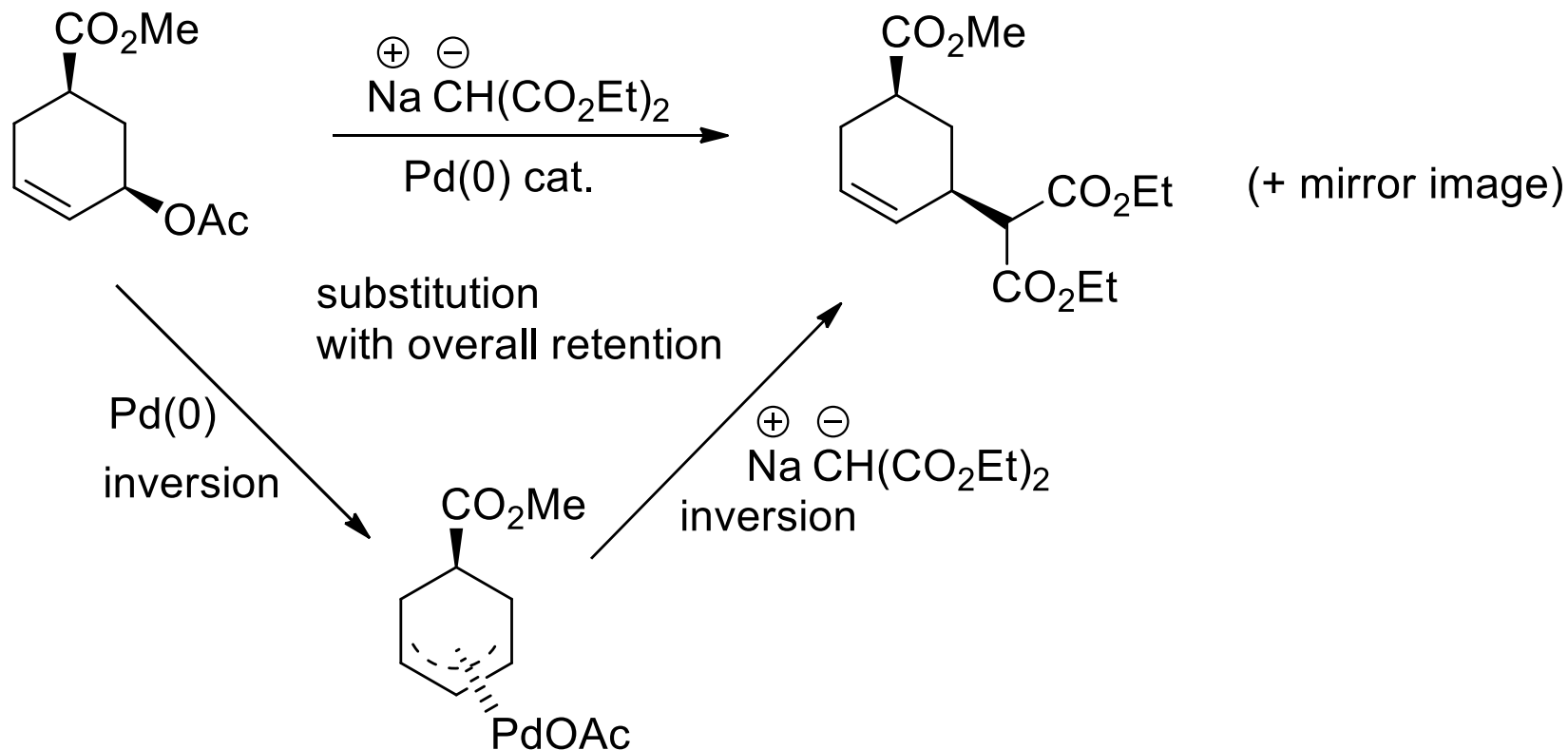
N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel,
Org. Lett., **2003**, 5, 2111

Anti-substitutions at propargylic systems



J.-M. Dollat, J.-L. Luche, P. Crabbe *J. Chem. Soc., Chem. Commun.*, **1977**, 761-762

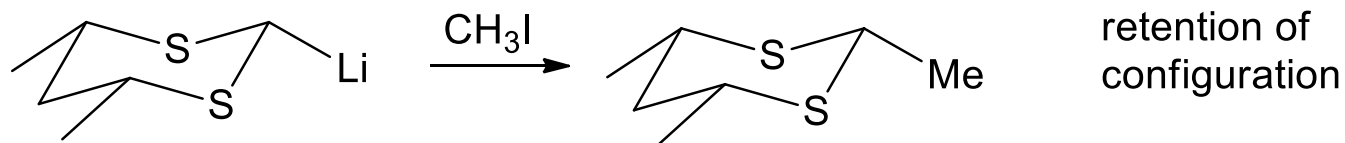
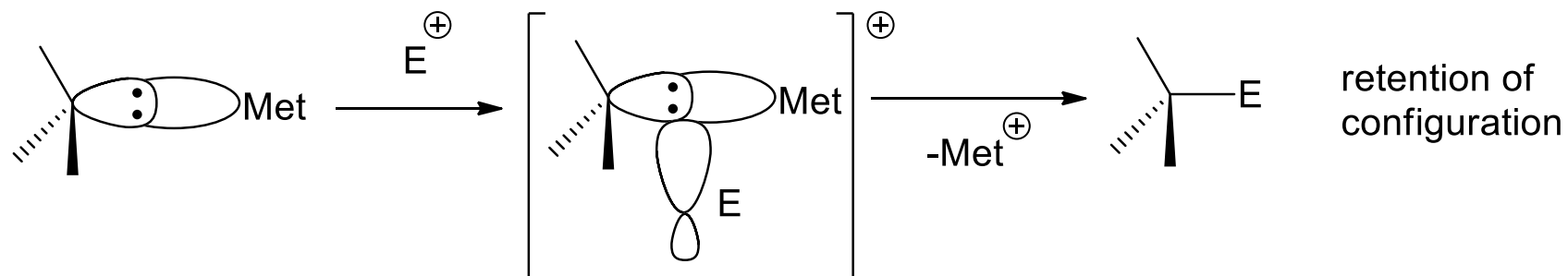
Stereoselective palladium-catalyzed allylic substitutions



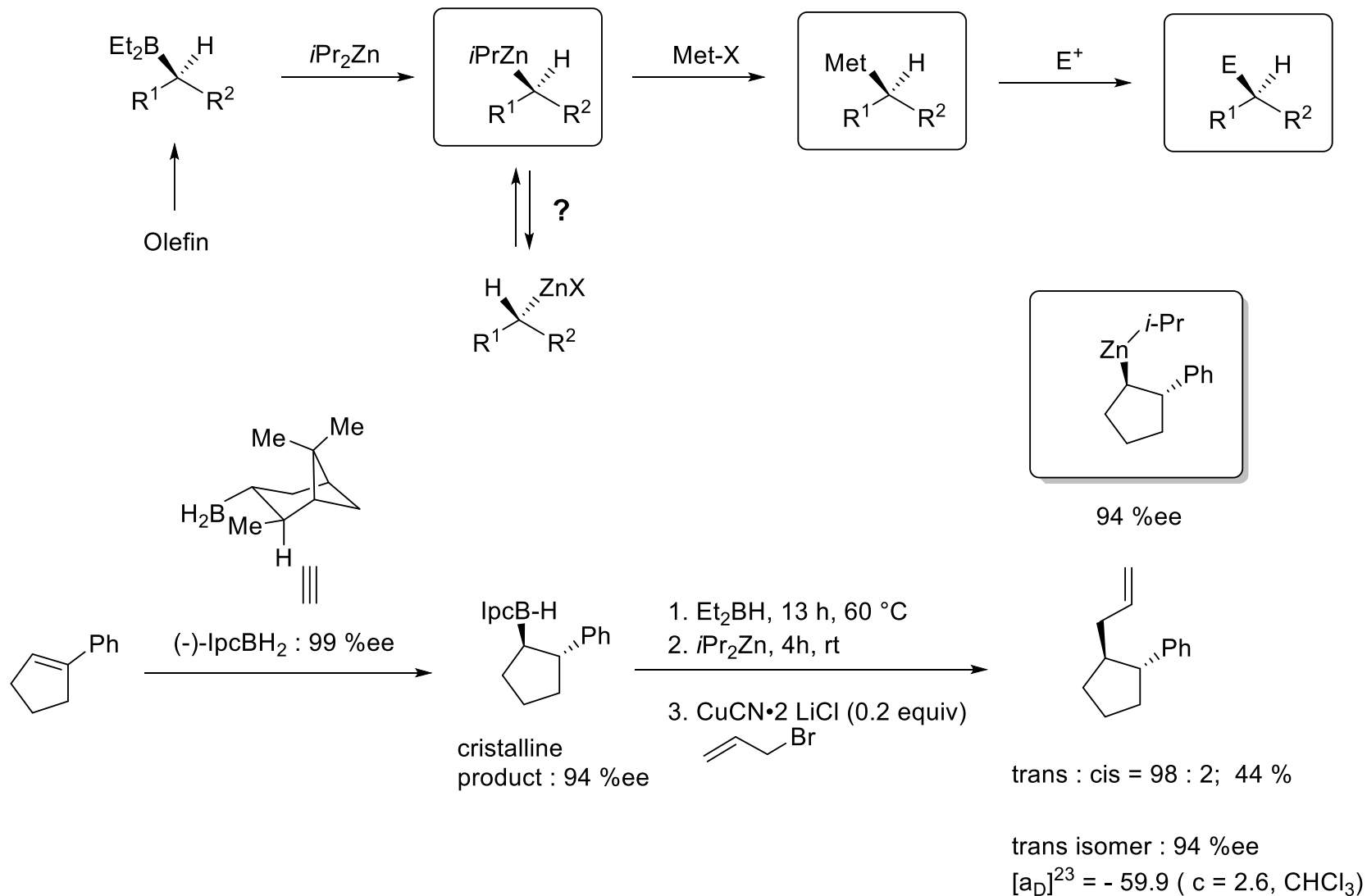
B. M. Trost, *Acc. Chem. Res.* **1980**, 13, 385.

Electrophilic substitutions

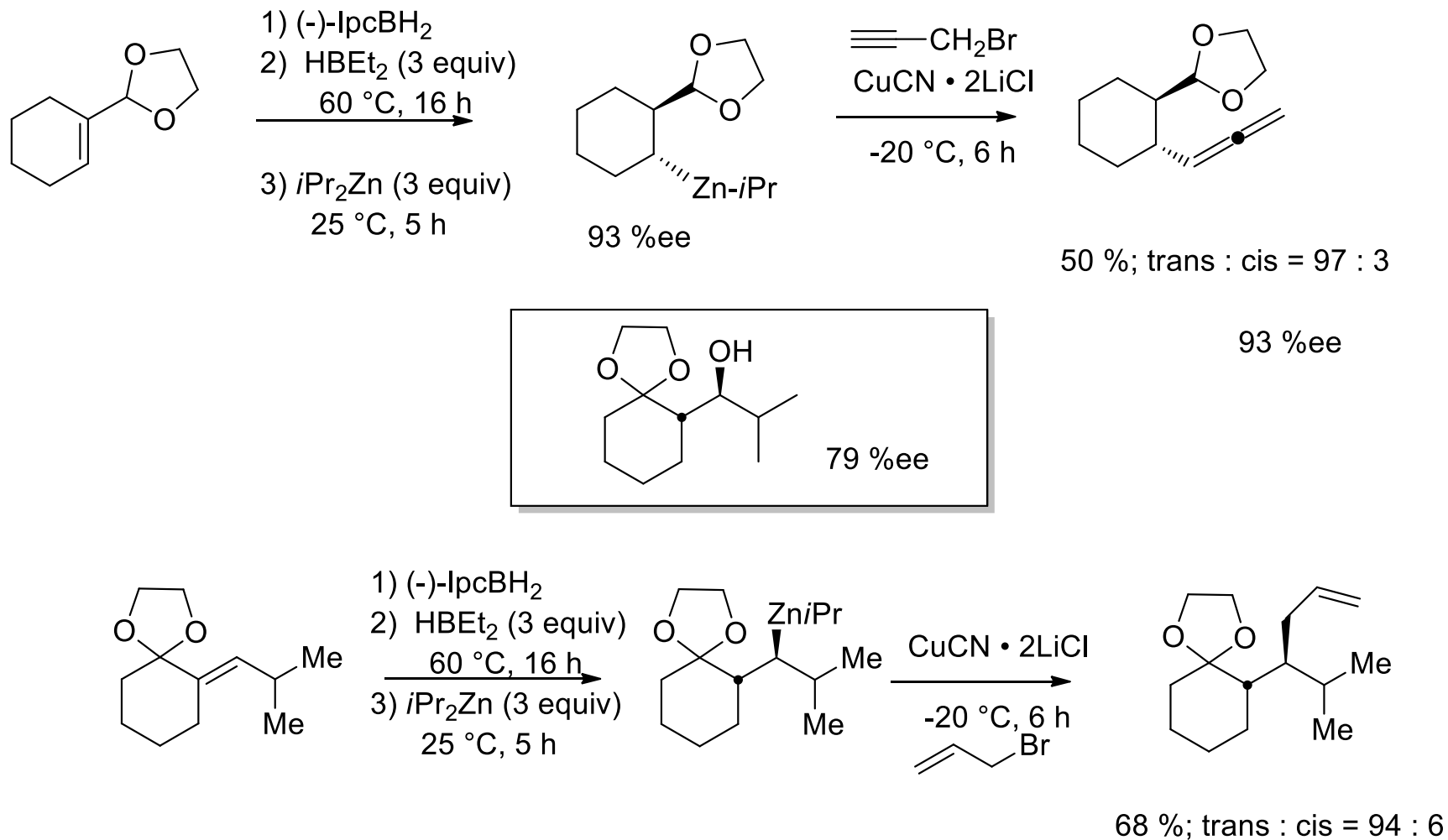
S_E2



First synthesis of an optically active zinc reagent

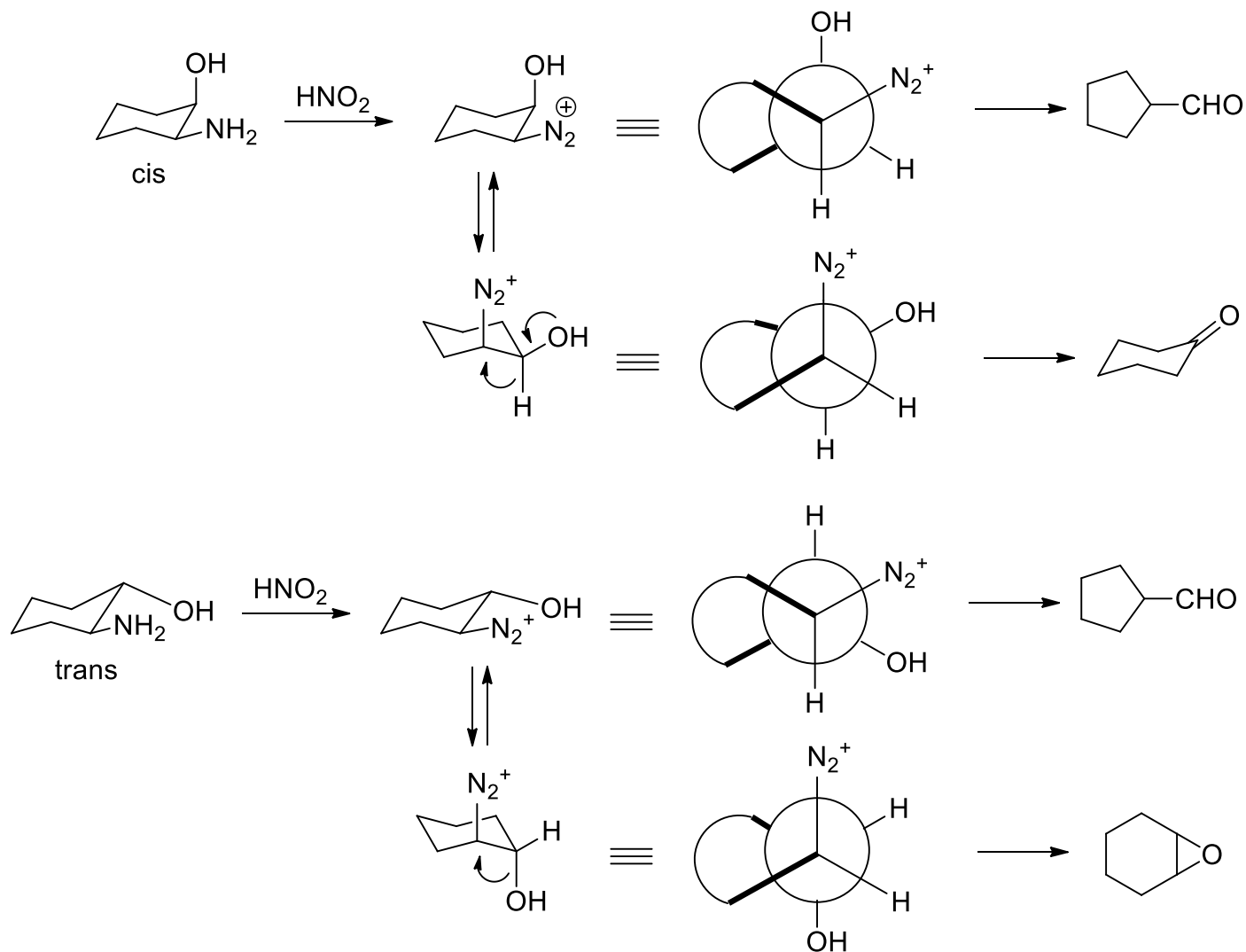


Preparation of chiral zinc reagents



E. Hupe, Knochel, P. *Angew. Chem. Int. Ed.* **2001**, 40, 3022

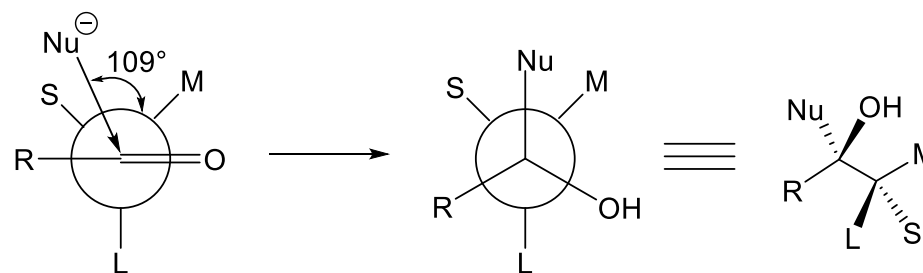
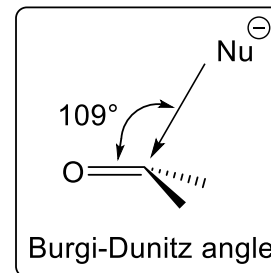
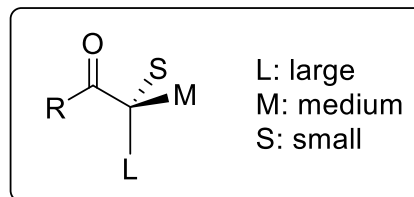
Stereoselective rearrangements



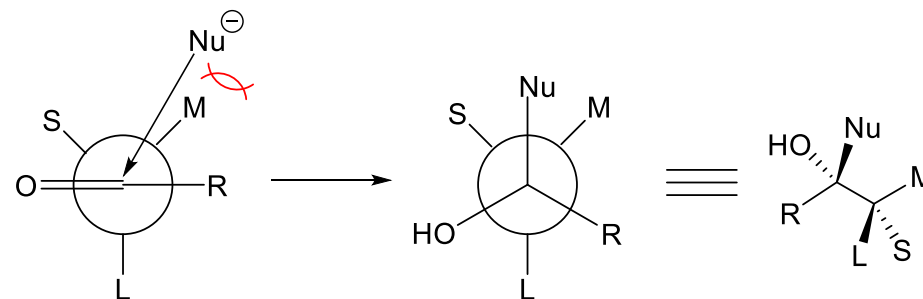
Only the bond in anti-arrangement to the leaving group undergoes the migration

Nucleophilic addition to ketones and aldehydes

Cram-rule

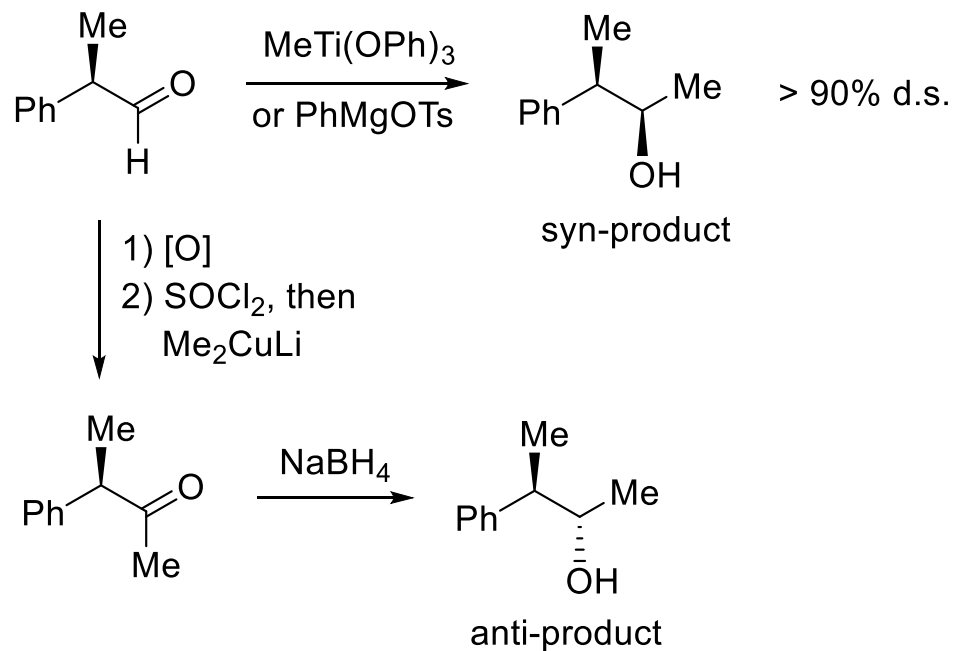


preferred direction
of the addition

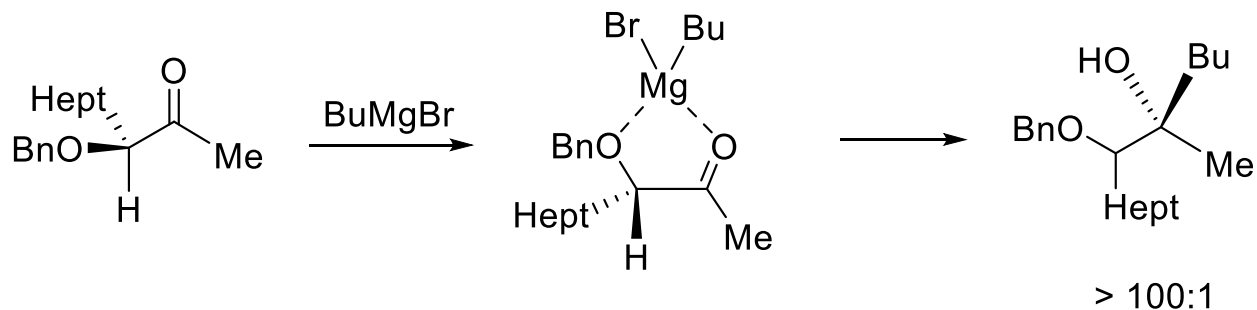


preferred direction
of the addition

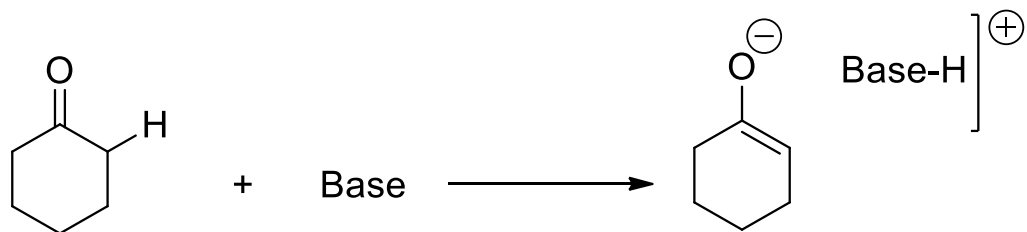
Diastereoselective reactions



Chelate model



The aldol reaction: the acidity of various C-H bonds

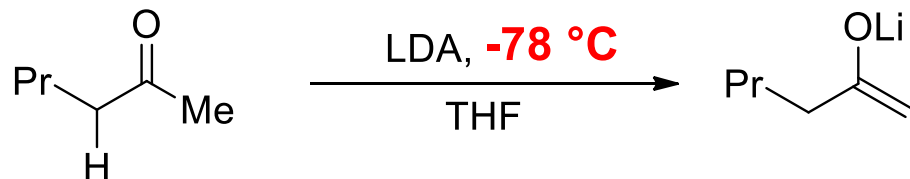


	pK _{DMSO}
MeCH ₂ -NO ₂	16.7
PhCOCH ₃	24.7
EtCOCH ₂ Me	27.1
PhSO ₂ CH ₃	29.0
(Me ₃ Si) ₂ NH	30.0
CH ₃ CN	31.0
<i>i</i> -Pr ₂ NH	35.0
PhCH ₃	43.0
CH ₄	56.0

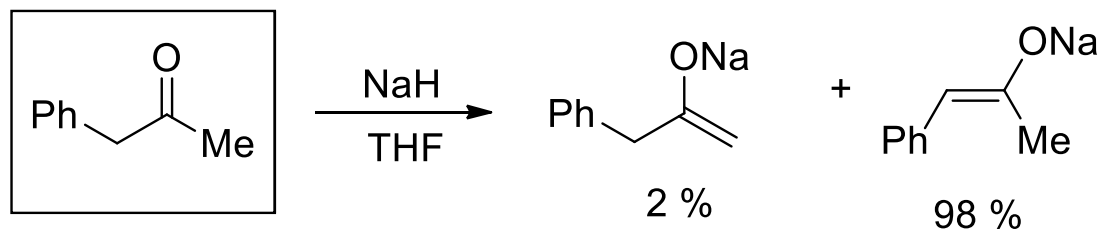
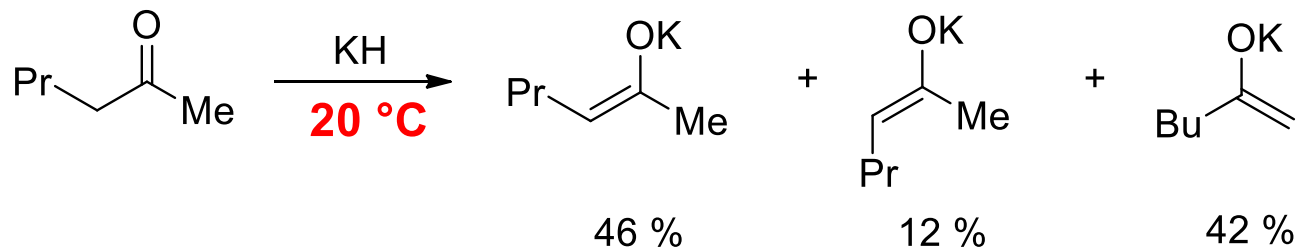
Bordwell acidity scale in DMSO: *Acc. Chem. Res.* **1988**, 21, 456.

The aldol reaction

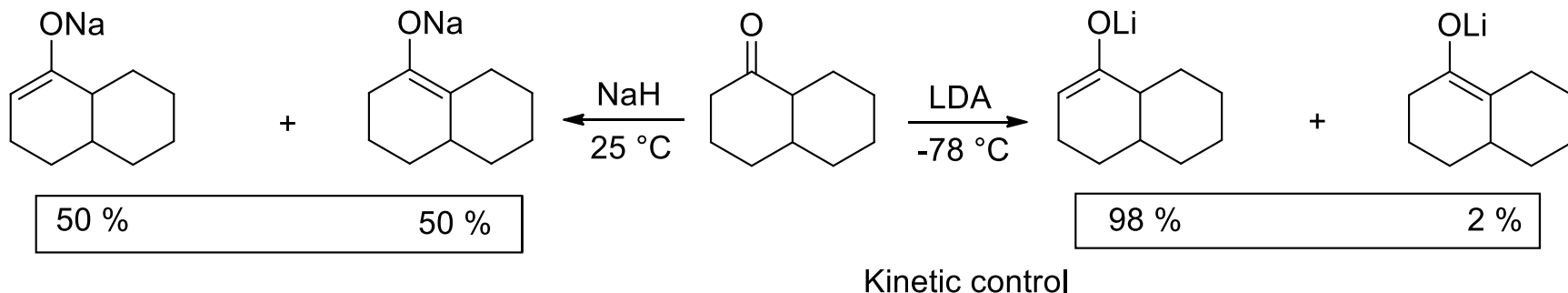
Kinetic control:



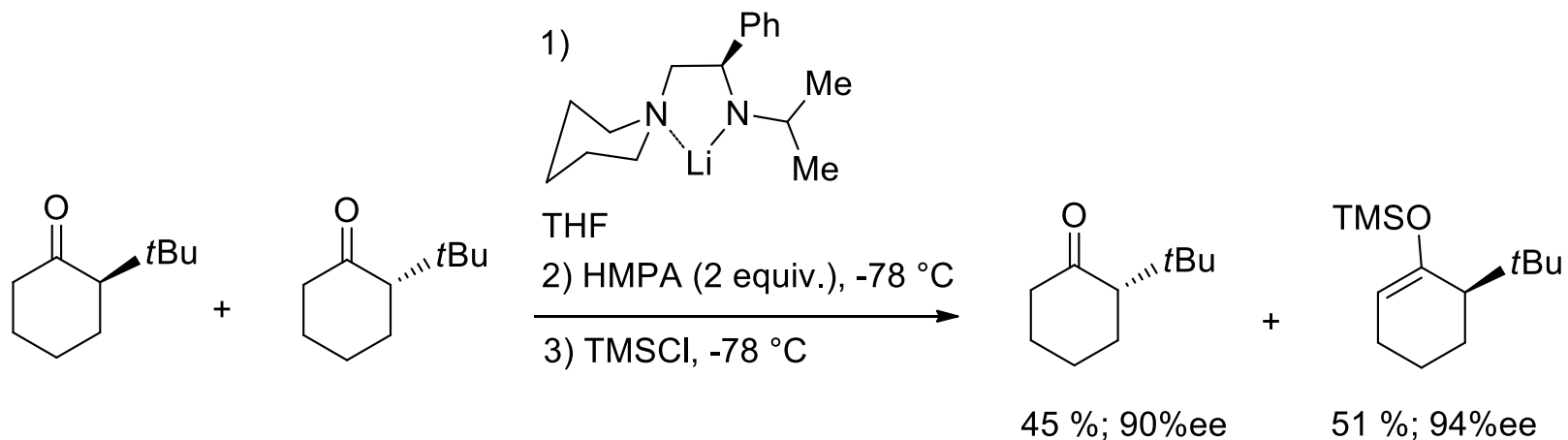
Thermodynamic control:



The aldol reaction

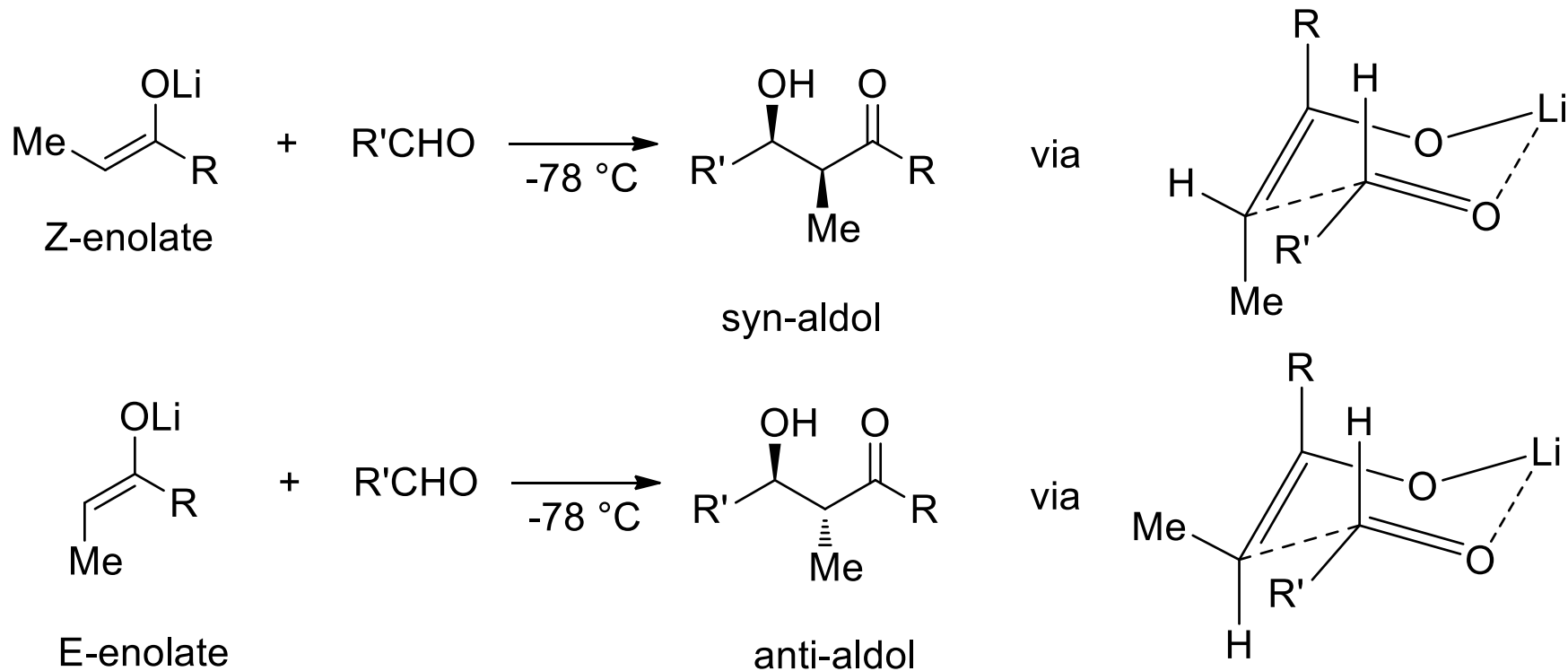


Enantioselective deprotonation: kinetic resolution

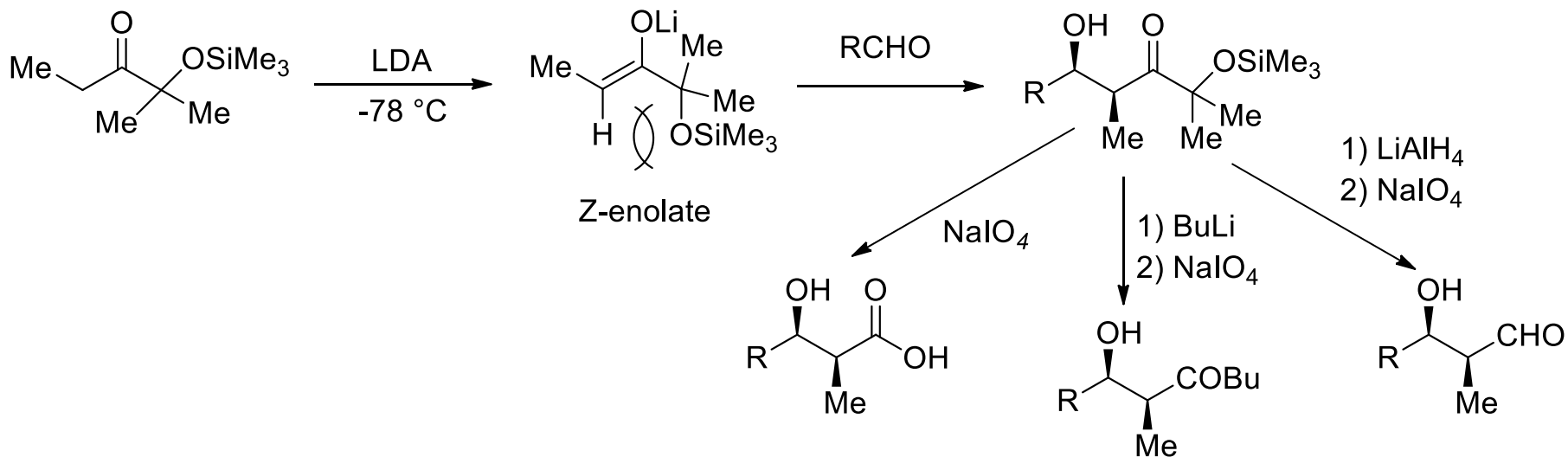


R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc.* **1986**, 108, 543.

Stereoselectivity in the aldol reaction

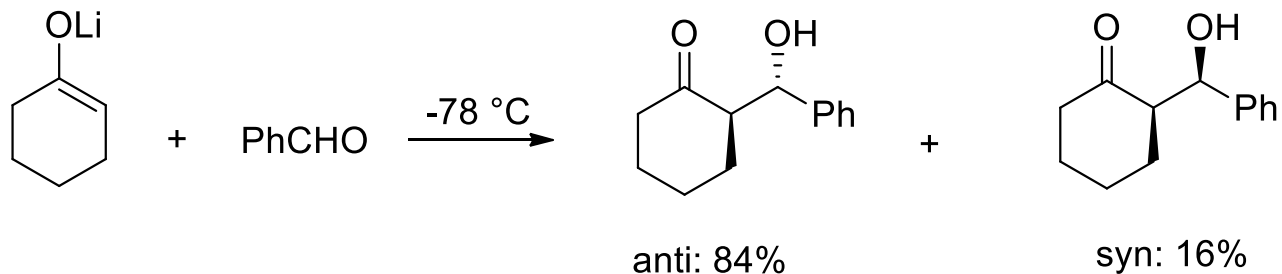


Enantioselective aldol synthesis

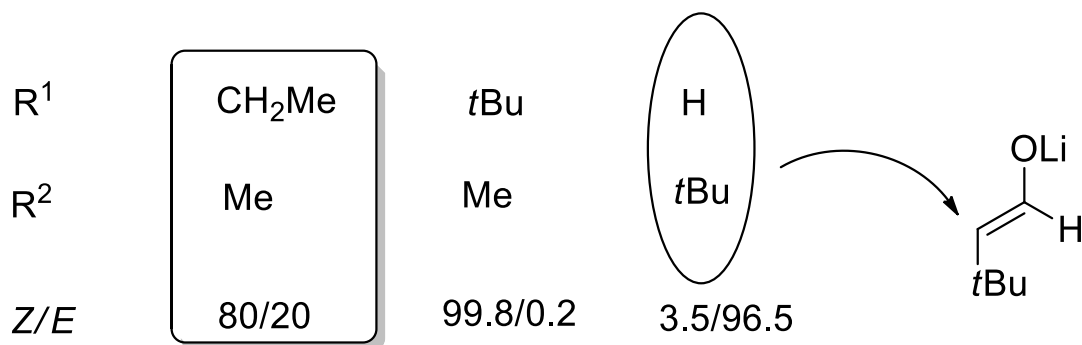
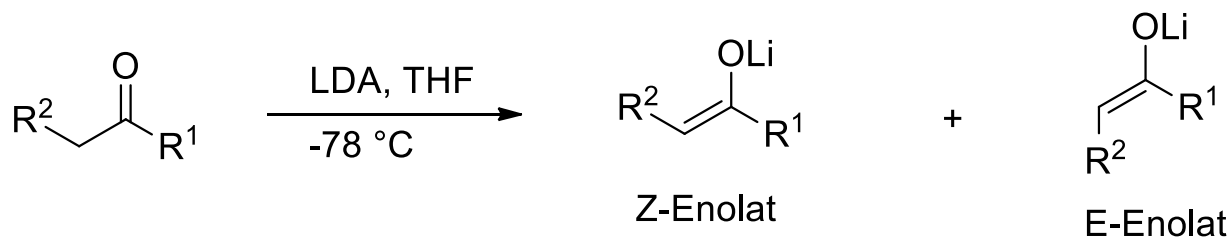


C. Heathcock, *J. Am. Chem. Soc.* **1977**, 99, 2337;
J. Org. Chem. **1981**, 46, 191;
J. Org. Chem. **1985**, 50, 2095.

The aldol reaction

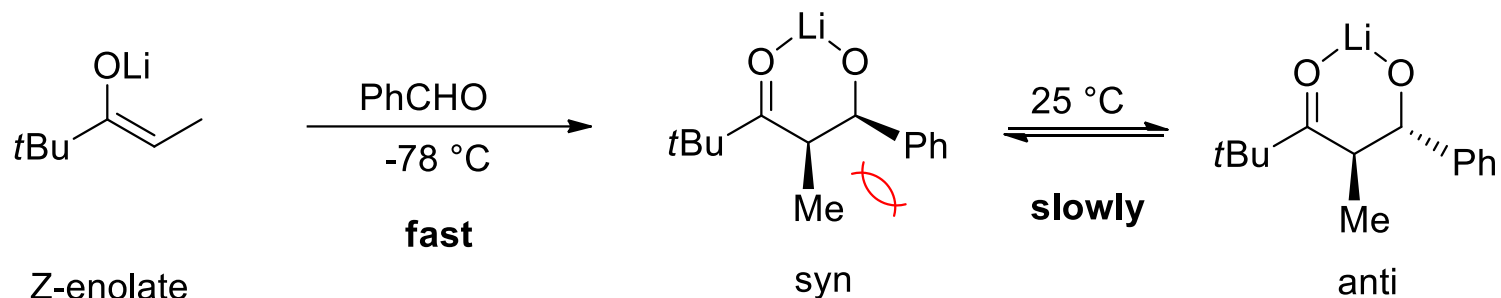


M. Majewski, D. M. Gleave, *Tetrahedron Lett.* **1989**, 30, 5681.

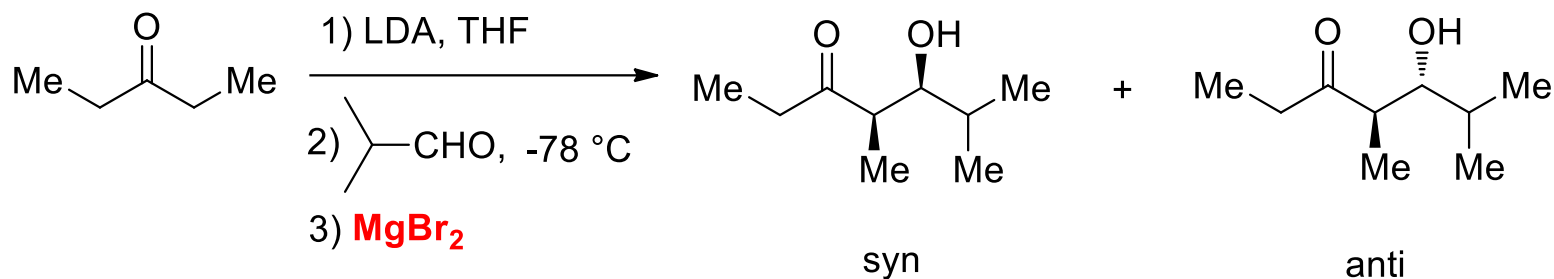


*unselective stereoselective enolization
with Li-bases*

The aldol reaction



C. H. Heathcock, J. Lampe, *J. Org. Chem.* **1983**, 48, 4330.



Kinetic control at $-78\text{ }^{\circ}\text{C}$: syn : anti = 31 : 69

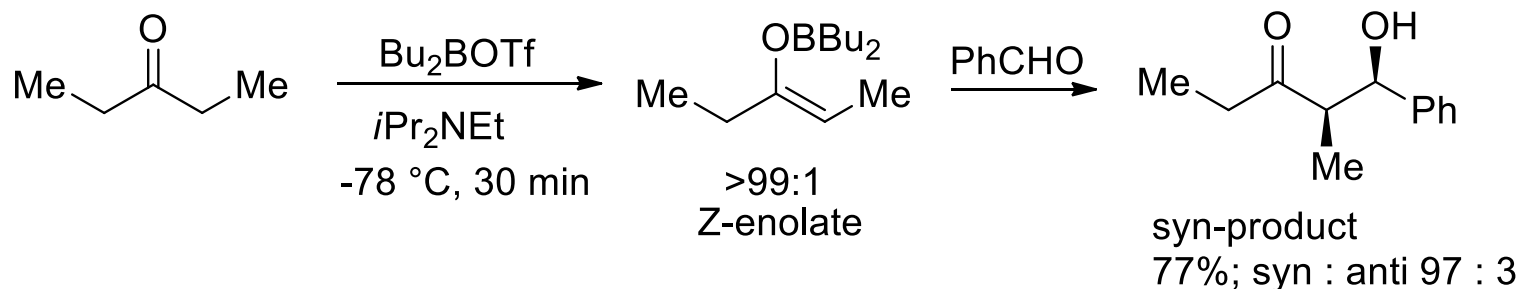
Thermodynamic control at $25\text{ }^{\circ}\text{C}$: syn : anti = 9 : 91

K. A. Swiss, W. B. Choi, D. C. Liotta, A. F. Abdel-Magid, C. A. Maryanoff, *J. Org. Chem.* **1991**, 56, 5978.

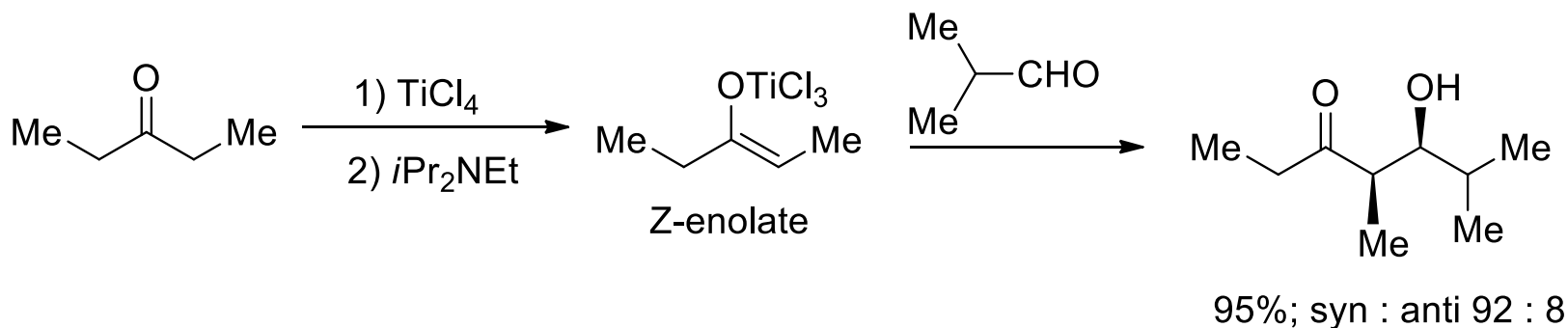
The aldol reaction

General synthesis of Z-enolates

Boron enolates are usually more selective than Li-enolates



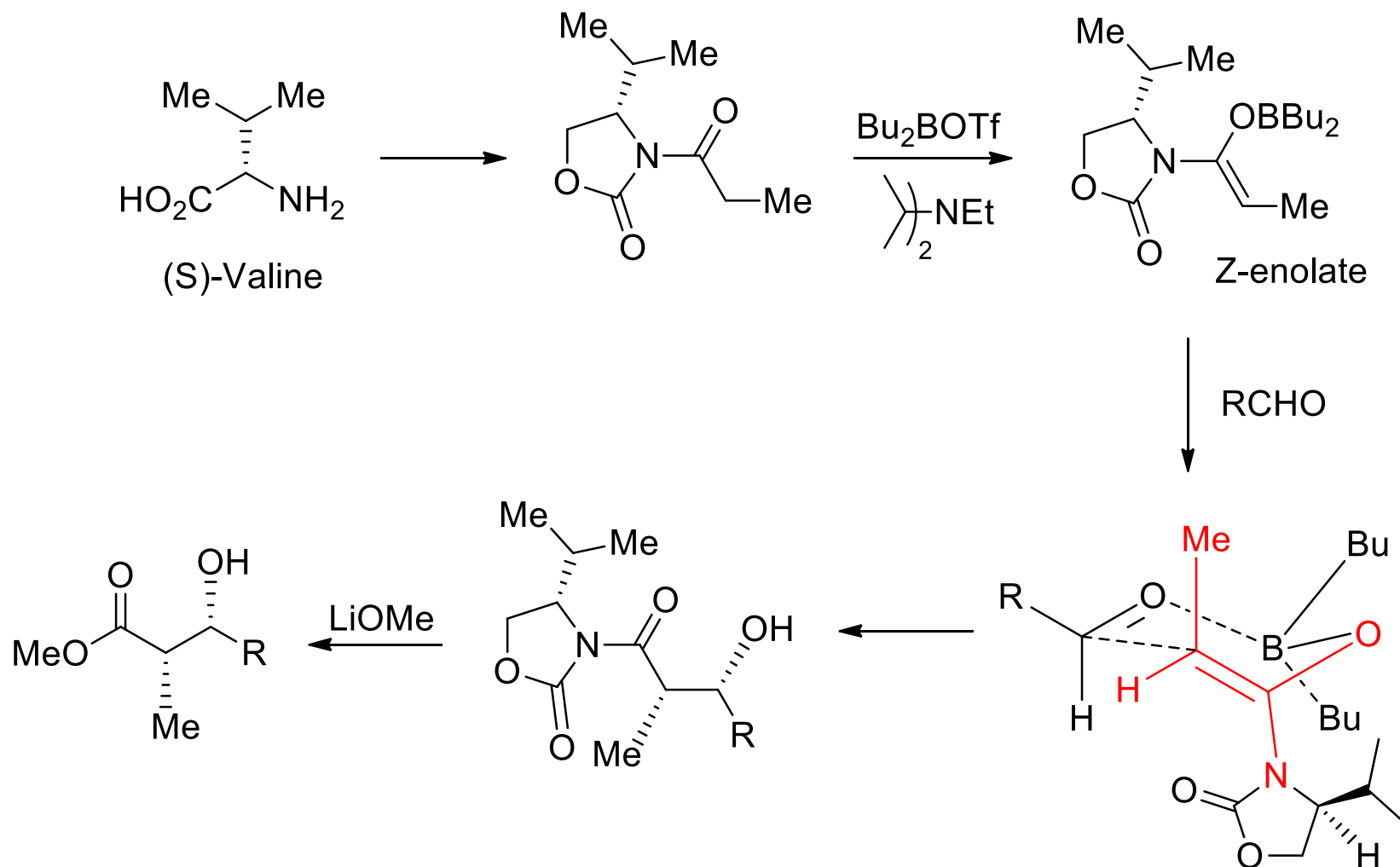
D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, 101, 6120.



C. Siegel, E. R. Thornton, *J. Am. Chem. Soc.* **1989**, 111, 5722.

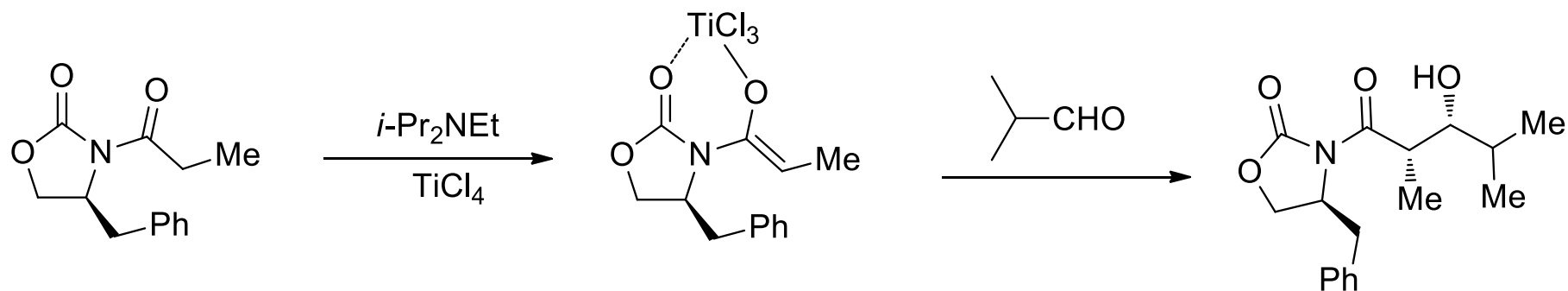
D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, 113, 1047.

Enantioselective aldol reaction

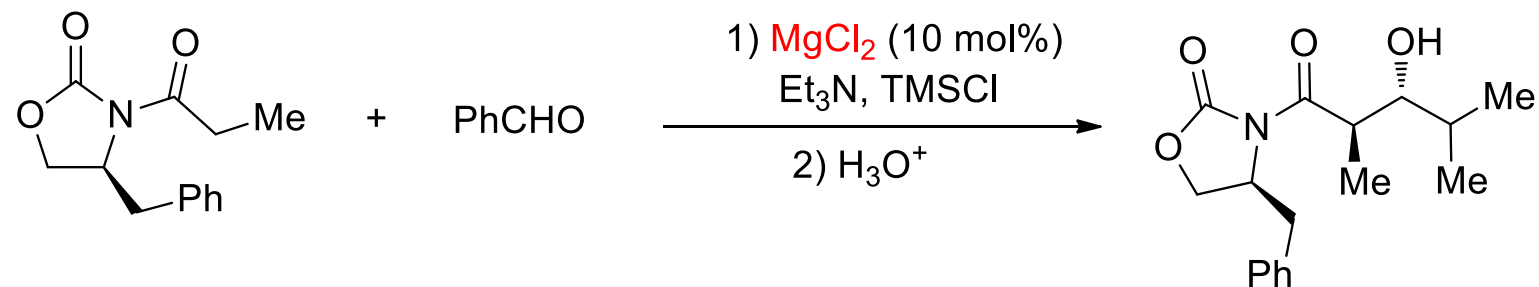


D. A. Evans, *J. Am. Chem. Soc.* **1981**, 103, 2876.

Enantioselective aldol reaction via Ti-enolates



D. A. Evans, *J. Am. Chem. Soc.* **1991**, 113, 1047.

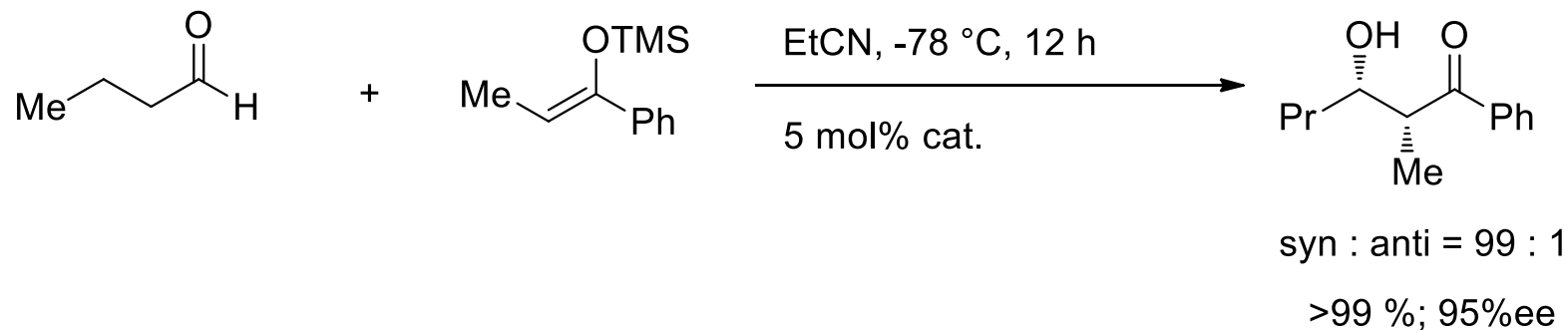


D. A. Evans, *J. Am. Chem. Soc.* **2002**, 124, 392.

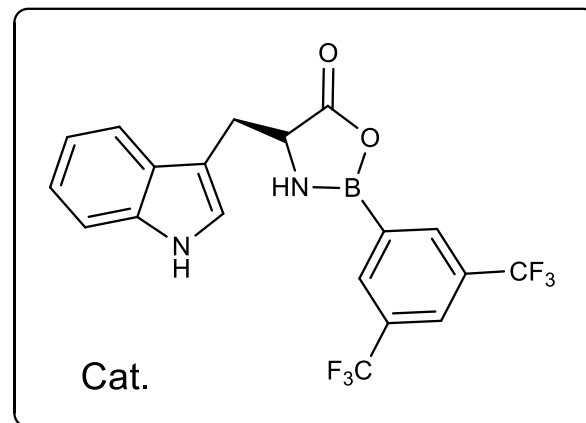
91 %; syn : anti = 1 : 32

Enantioselective enolate synthesis

Asymmetric Mukaiyama reaction

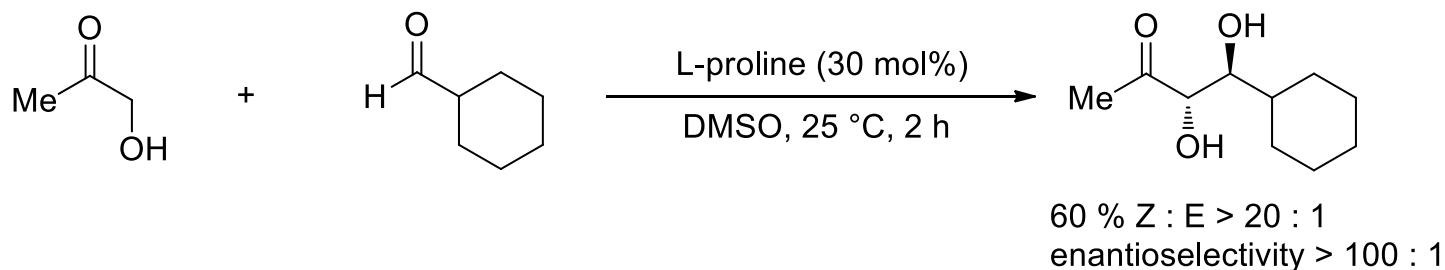


H. Yamamoto, *J. Org. Chem.* **2000**, 65, 9125



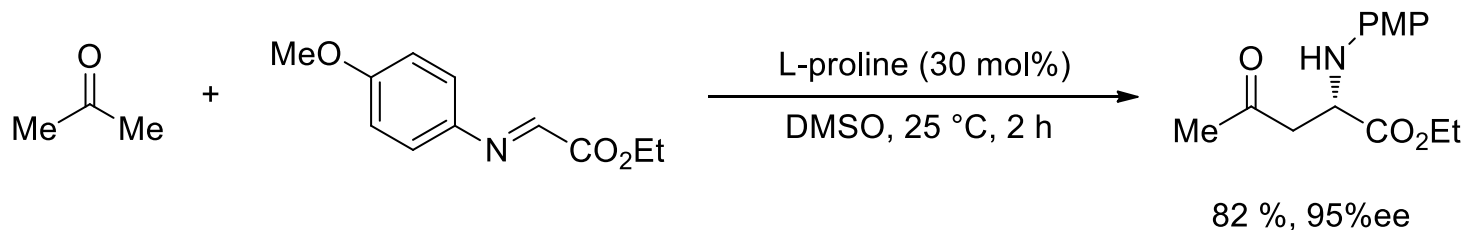
Enantioselective enolate synthesis

Organocatalysis



B. List, *J. Am. Chem. Soc.* **2000**, 122, 7386; *Org. Lett.* **2001**, 3, 573.

Review: B. List, *Synlett*, **2001**, 1663.



W. J. Liu, N. Li, L. Z. Gong, *Asymmetric Organocatalysis*, Topics in Organometallic Chemistry, **2011**, Vol. 36/2011, 153-205.

U. Scheffler, R. Mahrwald, *Synlett* **2011**, 1660.

H. Pellissier, *Adv. Synth. Catal.* **2011**, 353, 659.

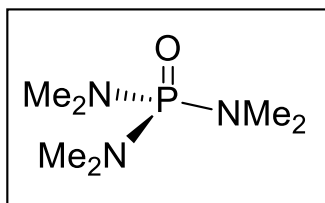
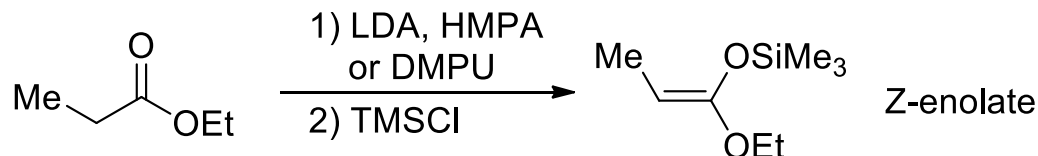
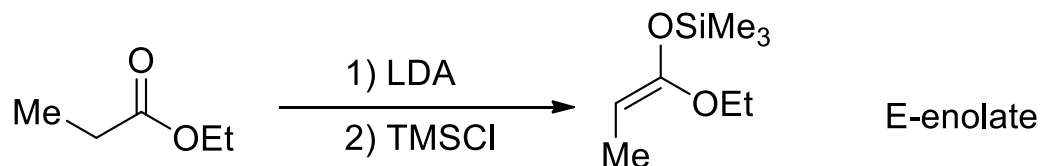
S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russian Chem. Rev.* **2009**, 7, 737.

D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, 15, 11058.

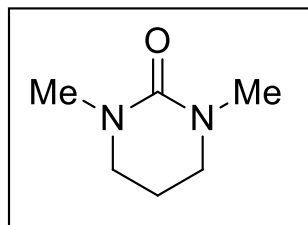
H. Pellissier, *Tetrahedron* **2007**, 63, 9267.

A. Cordova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, 124, 1842.

The aldol reaction via ester enolates – the Ireland-Claisen reaction



HMPA

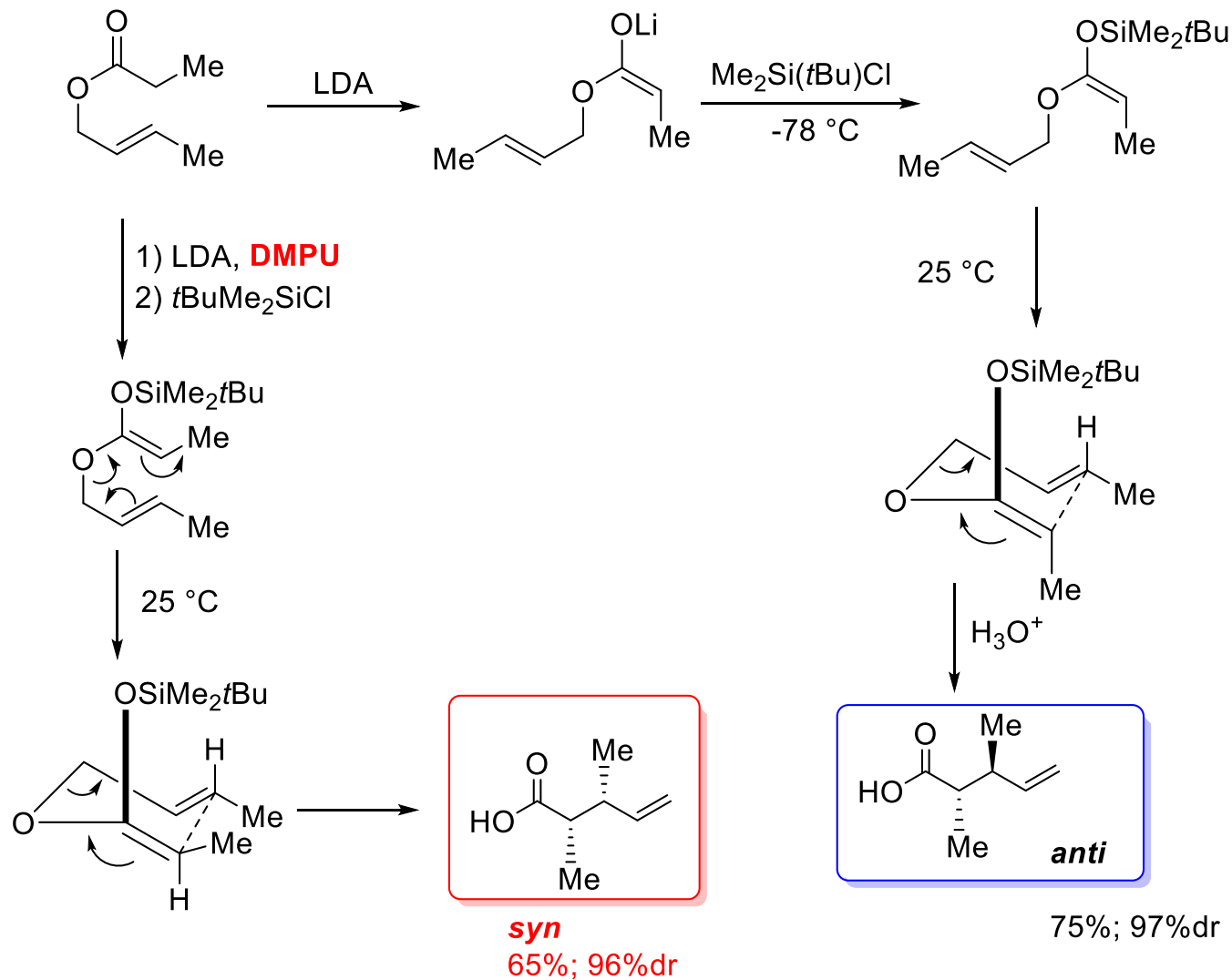


DMPU

Review: D. Enders, M. Knopp, R. Schiffers, *Tetrahedron: Asymmetry* **1996**, 7, 1847-1882.

Y. Chai, S.-P. Hong, H. A. Lindsay, C. McFarland, M. C. McIntosh, *Tetrahedron* **2002**, 58, 2905-2928.

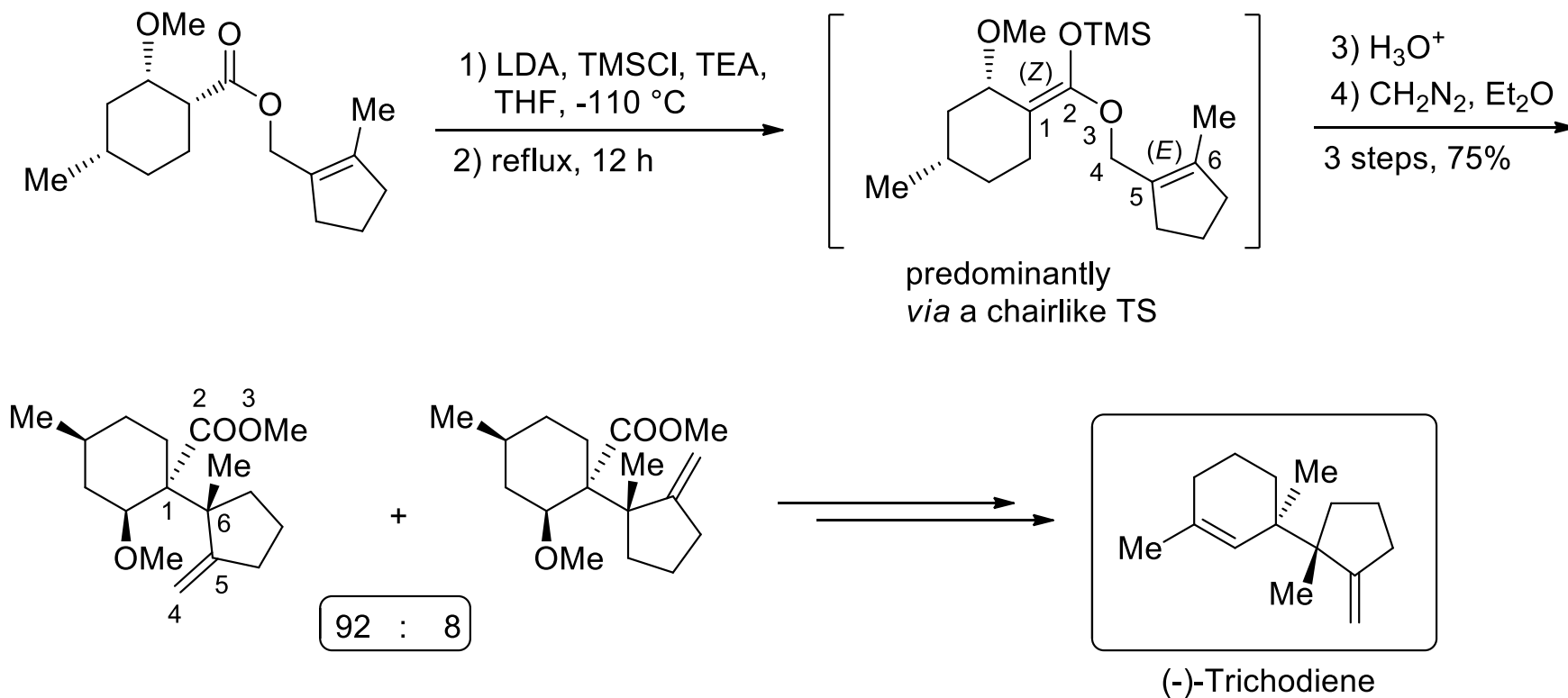
The aldol reaction via ester enolates – the Ireland-Claisen reaction



Review: D. Enders, *Tetrahedron: Asymmetry* **1996**, 7, 1847-1882.

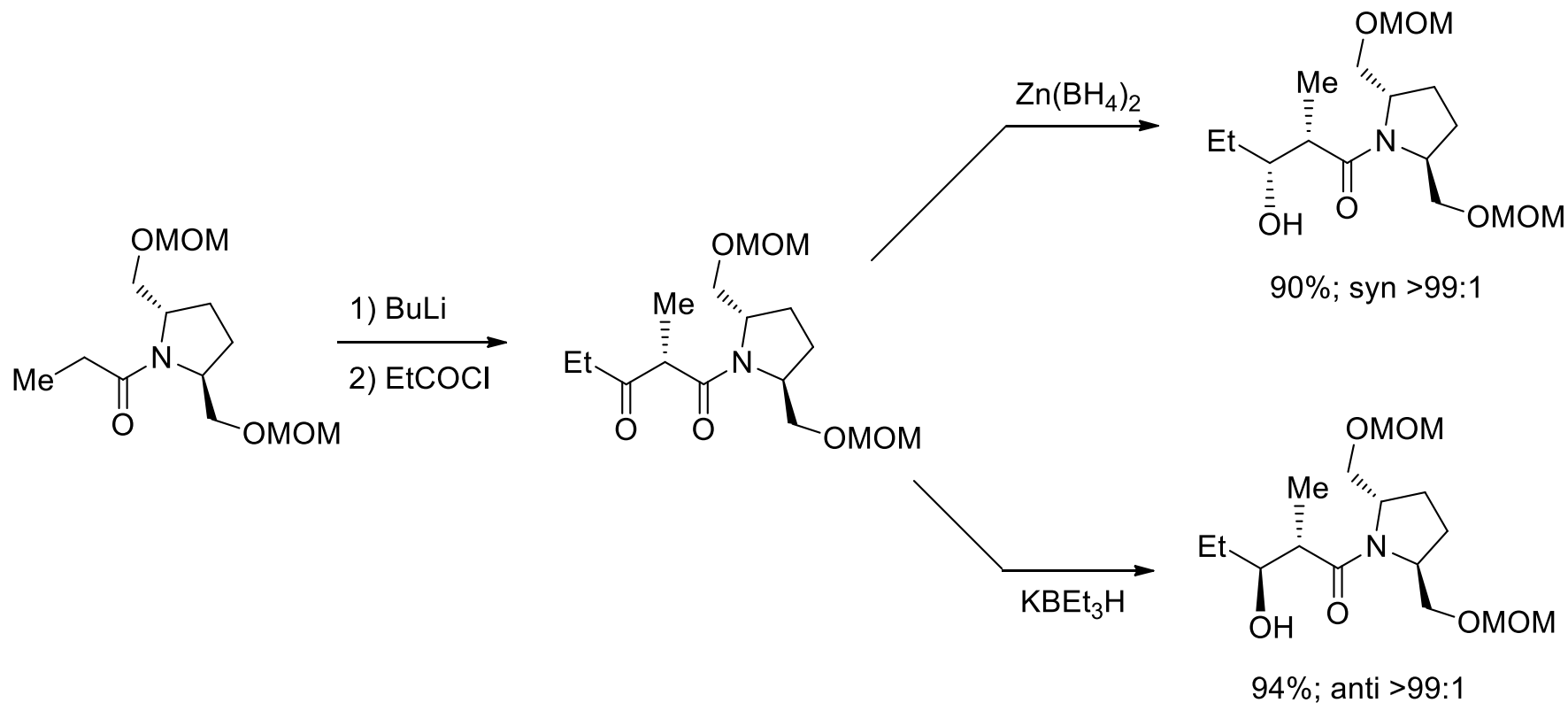
Y. Chai, *Tetrahedron* **2002**, 58, 2905-2928.

The aldol reaction via ester enolates – the Ireland-Claisen reaction



J. C. Gilbert, R. D. Selliah, *J. Org. Chem.* **1993**, 58, 6255-6265.

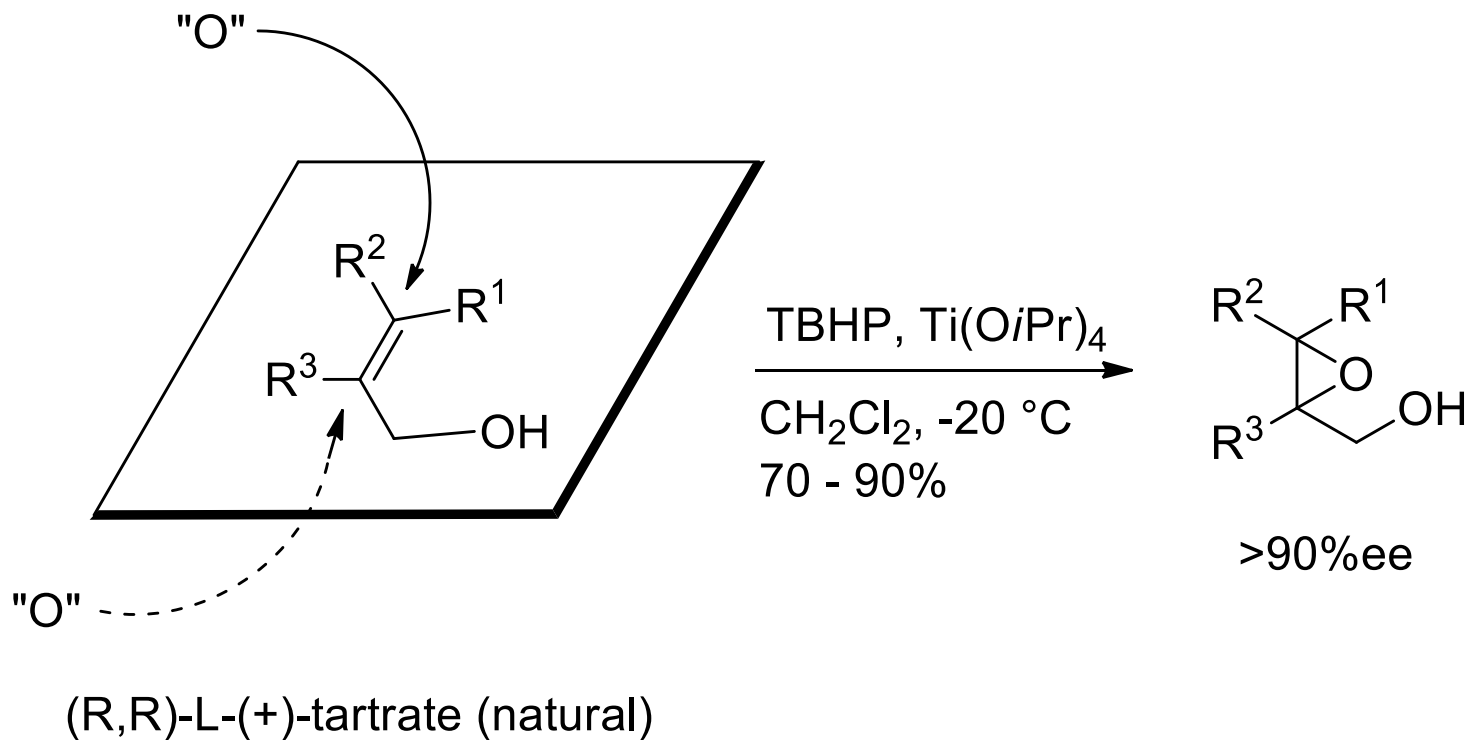
Alternative synthesis of aldol products



Y. Ito, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **1985**, 26, 4643.

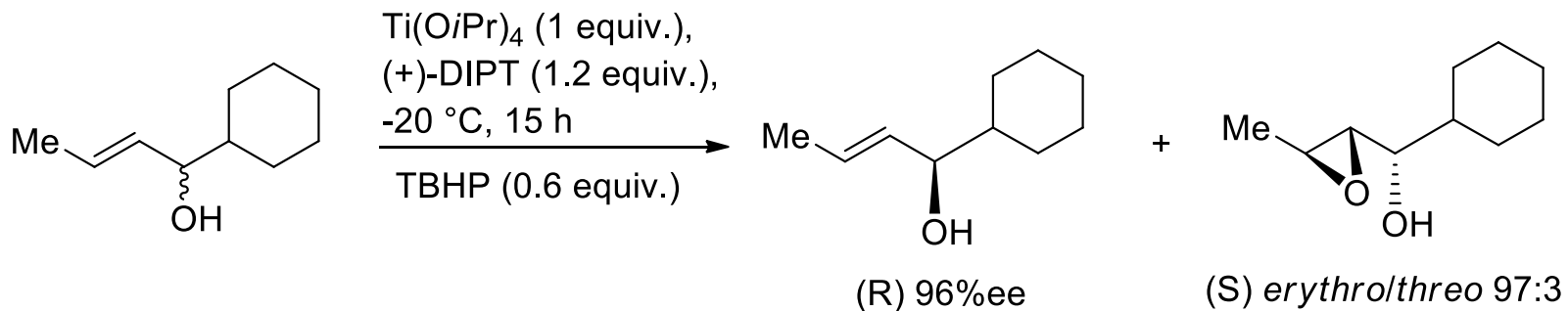
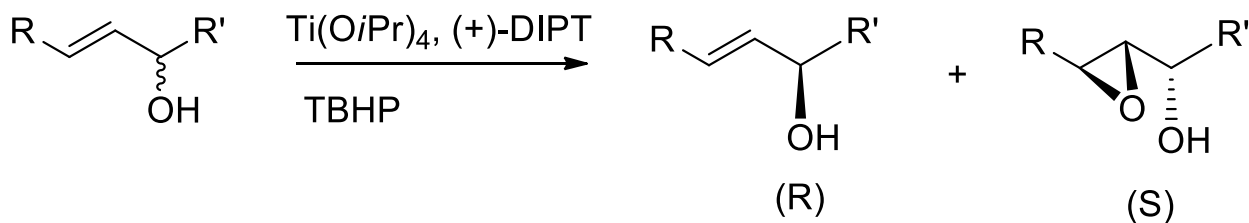
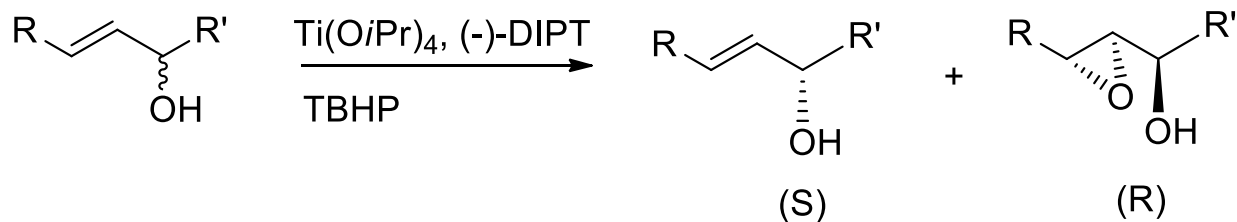
Asymmetric catalysis – Asymmetric oxidations

The Sharpless oxidation



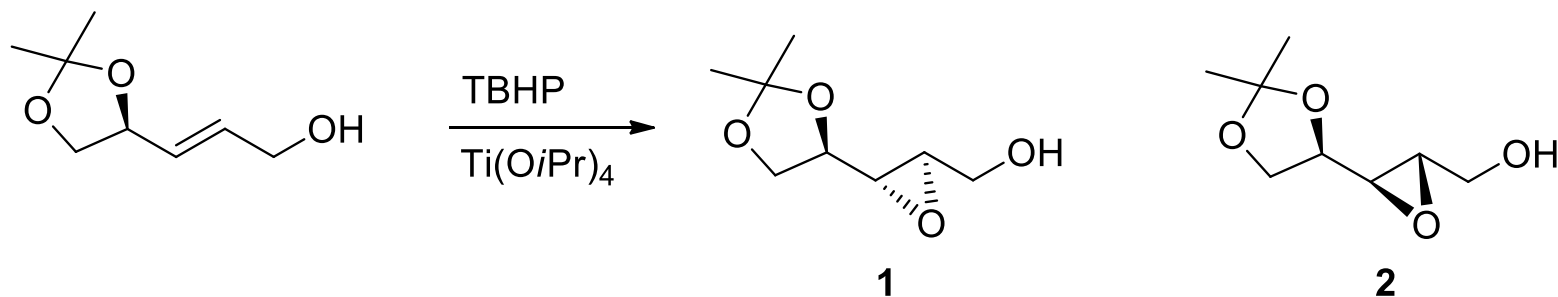
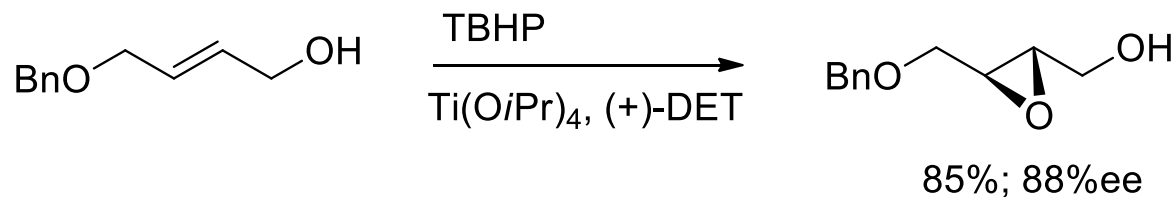
T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, 102, 5974.

Kinetic resolution of secondary alcohols



V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless,
J. Am. Chem. Soc. **1981**, *103*, 6237.

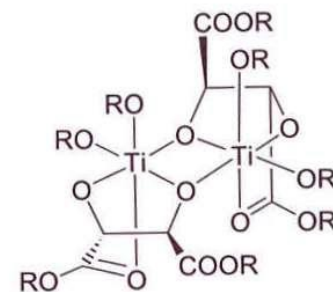
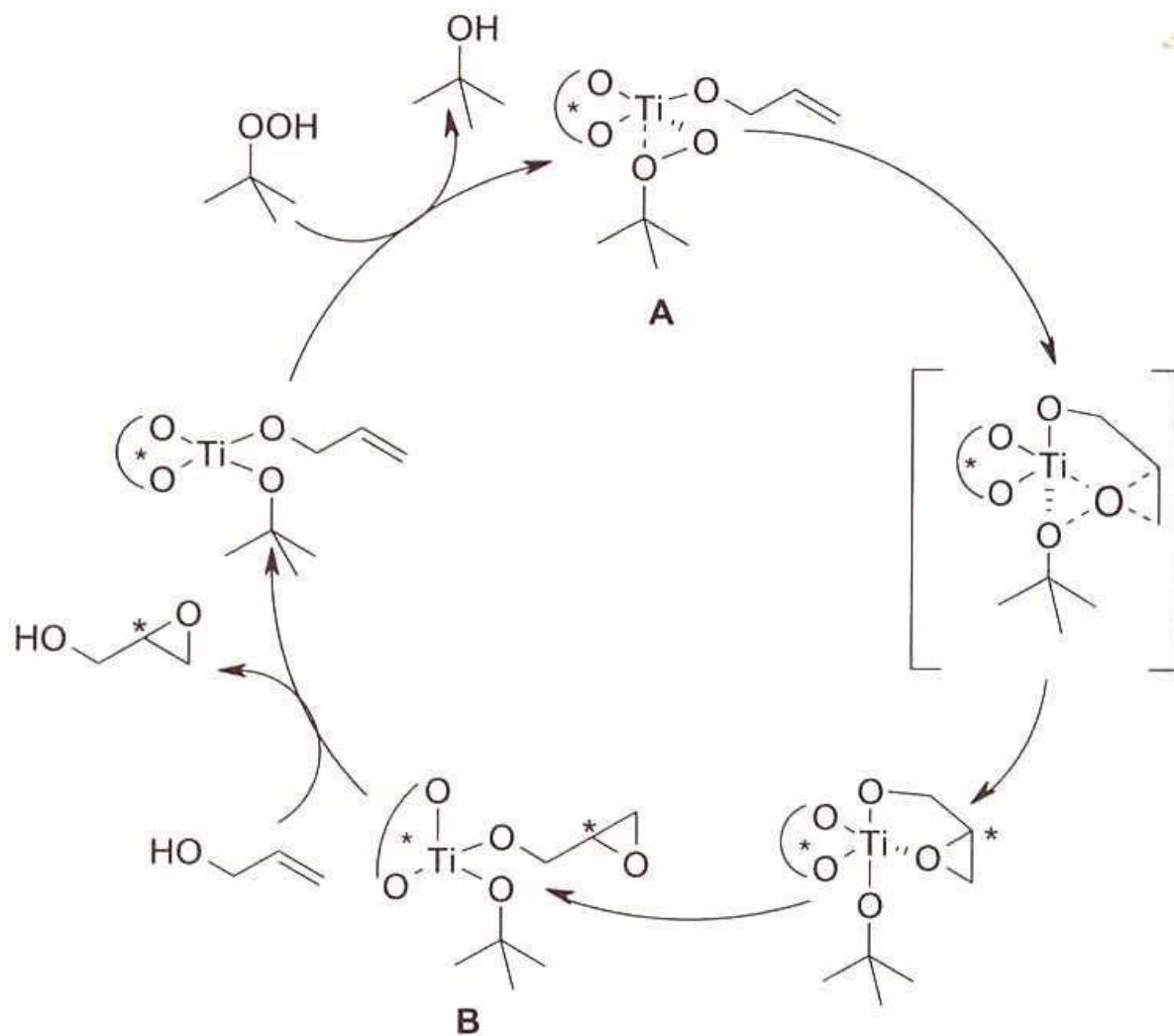
Matched and mismatched cases



in the absence of tartrate:	1 : 2 = 2.3 : 1
in the presence of (+)-DET, mismatched	1 : 2 = 1 : 22
in the presence of (-)-DET, matched	1 : 2 = 90 : 1

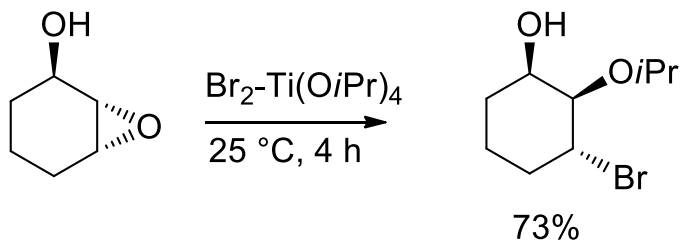
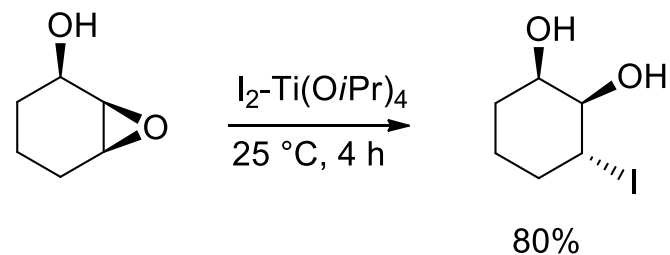
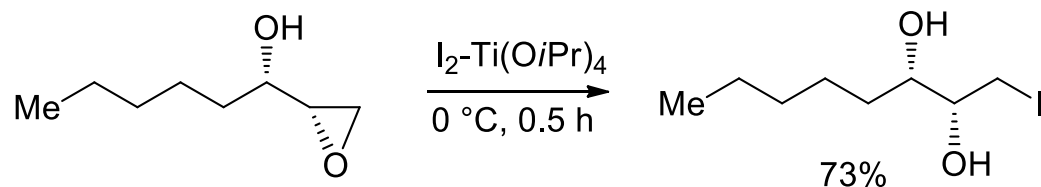
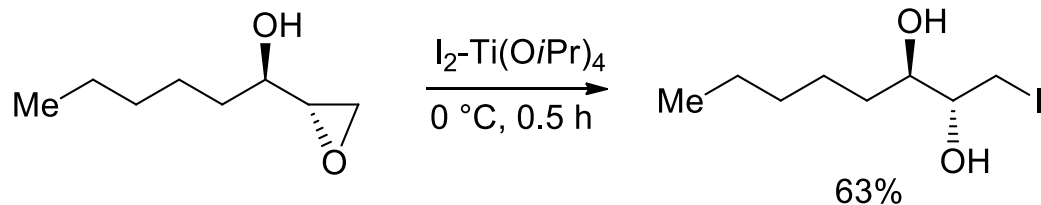
S. Takano, K. Samizu, T. Sugihara, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1989**, 1344.

Mechanism of Ti-catalyzed Sharpless epoxidation



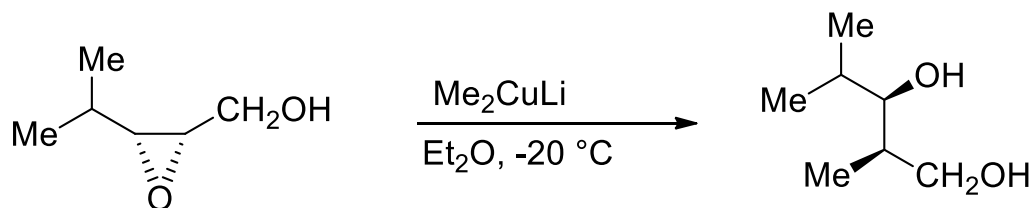
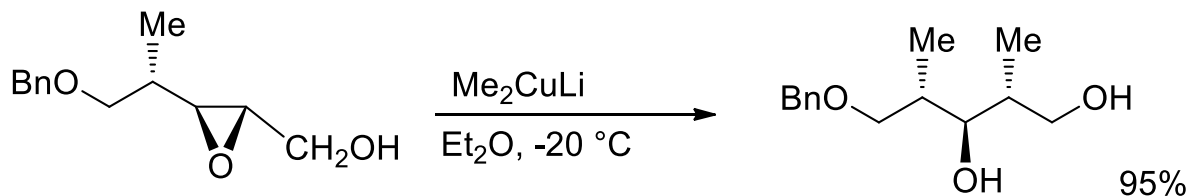
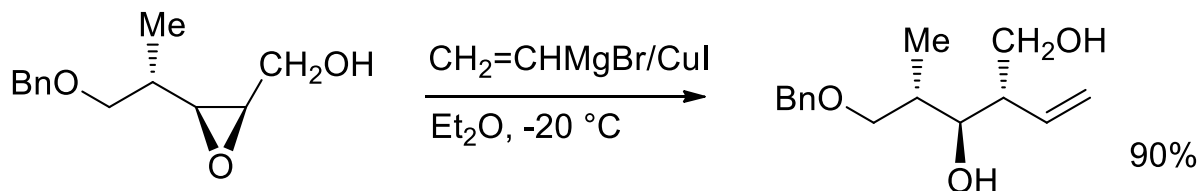
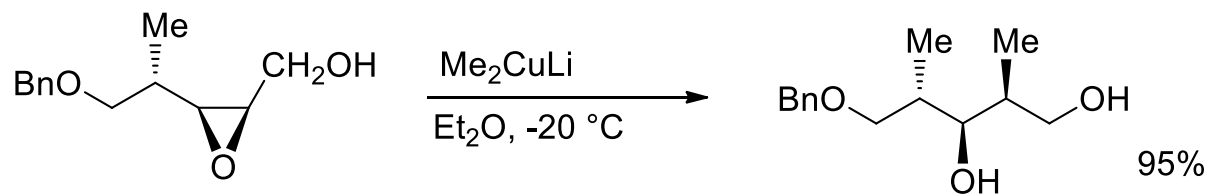
Structure of dinuclear Ti-tartrate complexes.

Synthetic applications of the Sharpless epoxidation



E. Alvarez, M. T. Nunez, V. S. Martin, *J. Org. Chem.* **1990**, 55, 3429.

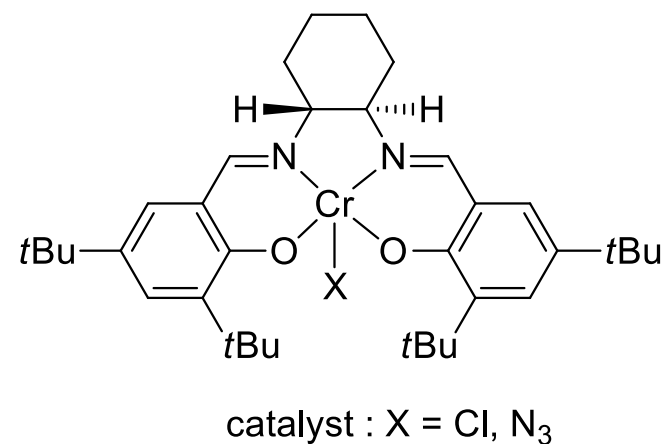
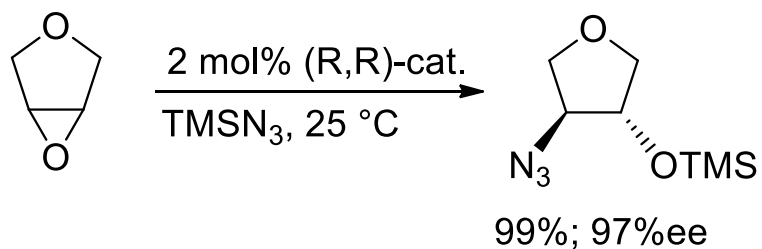
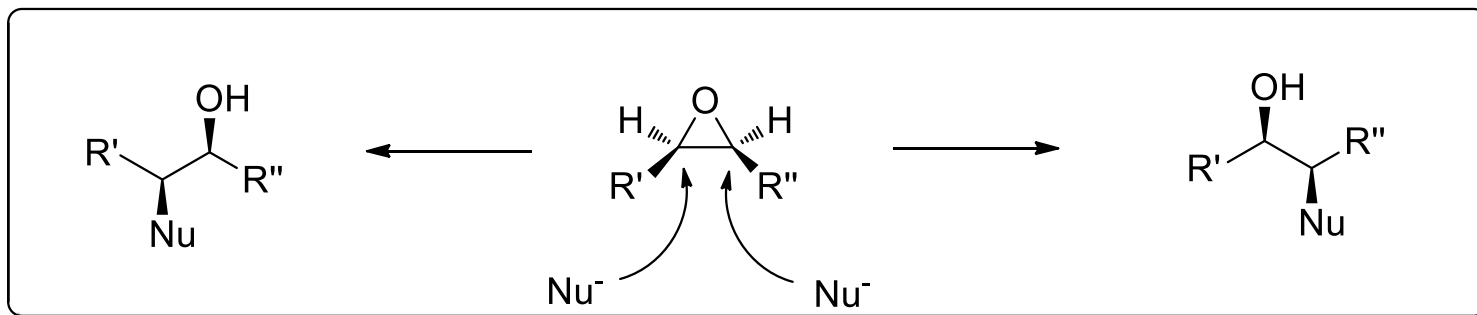
Ring opening with cuprates



M. R. Johnson, T. Nakata, Y. Kishi, *Tetrahedron Lett.* **1979**, 20, 4343.

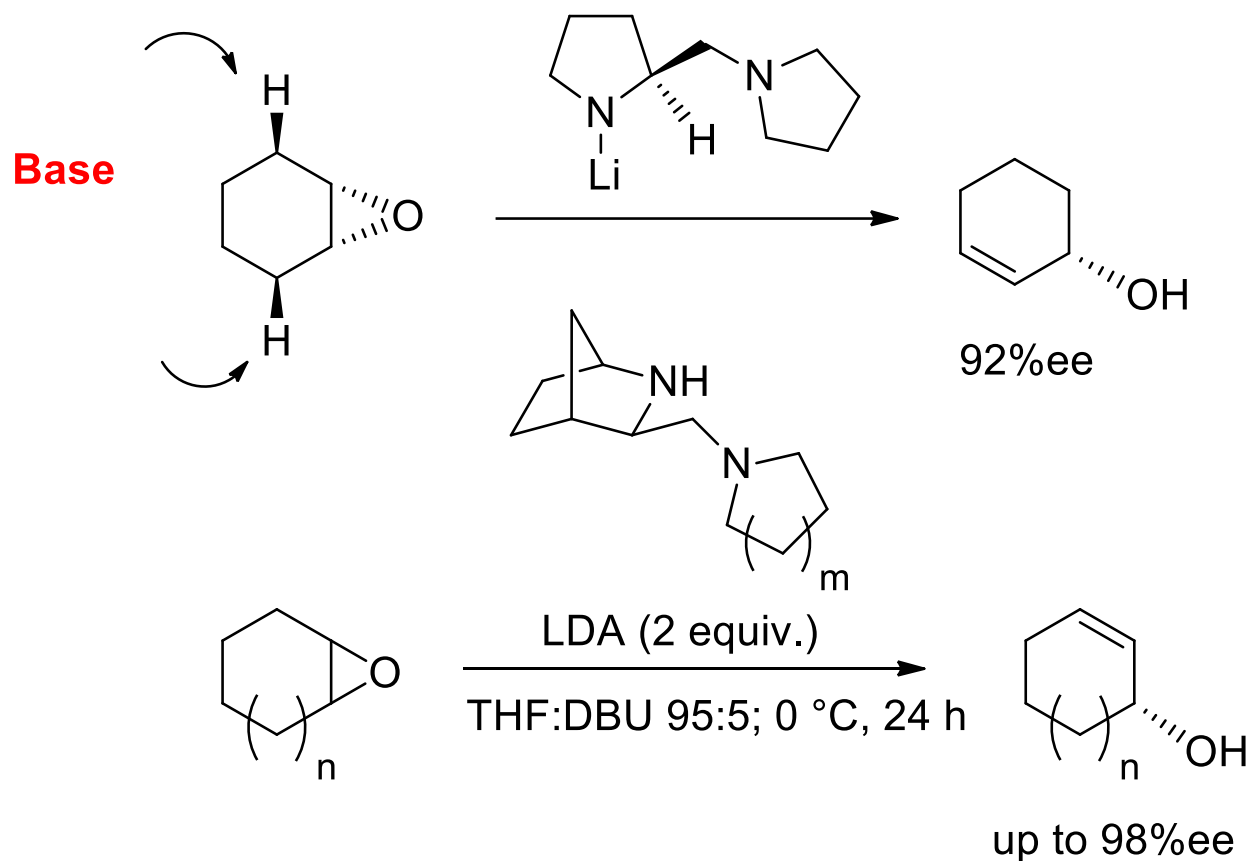
R. D. Wood, B. Ganem, *Tetrahedron Lett.* **1982**, 23, 707.

Desymmetrization of meso-epoxides



S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *J. Org. Chem.* **1997**, 62, 4197.

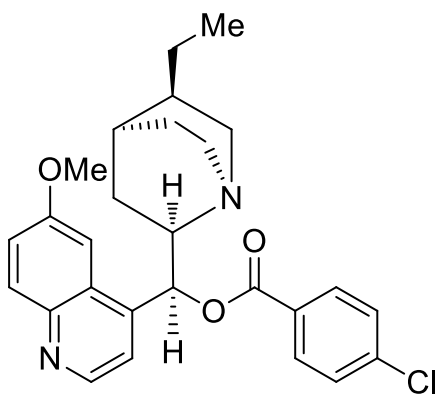
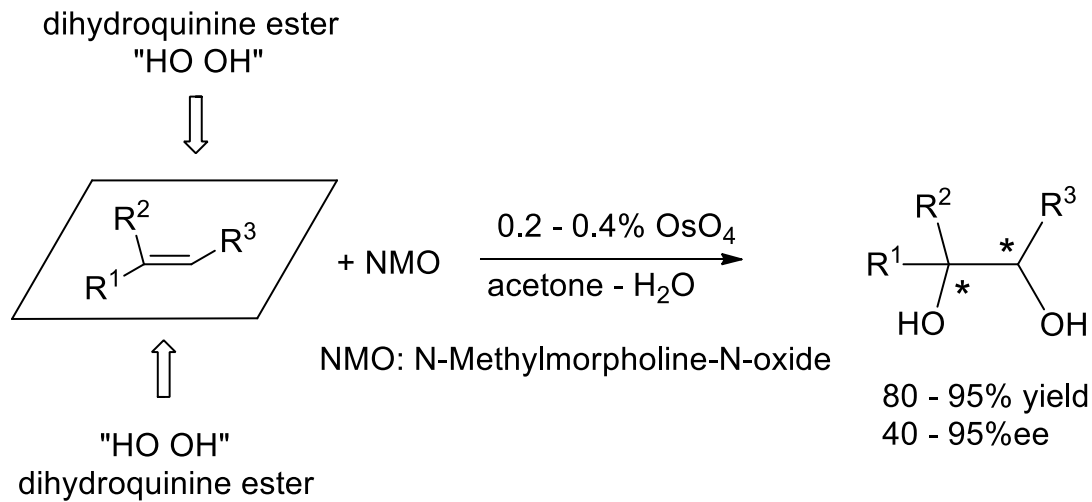
Desymmetrization of meso-epoxides



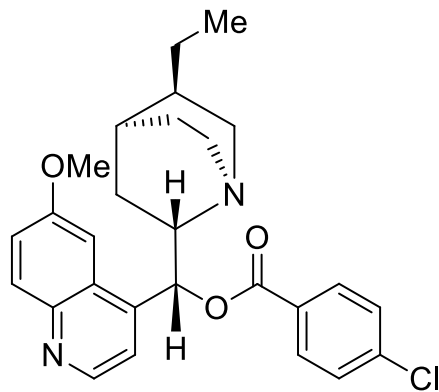
I. Paterson, D. J. Berrisford, *Angew. Chem. Int. Ed.* **1992**, 31, 1179.

M. J. Södergren, P. G. Andersson, *J. Am. Chem. Soc.* **1998**, 120, 10760.

Asymmetric dihydroxylation



dihydroquinine ester



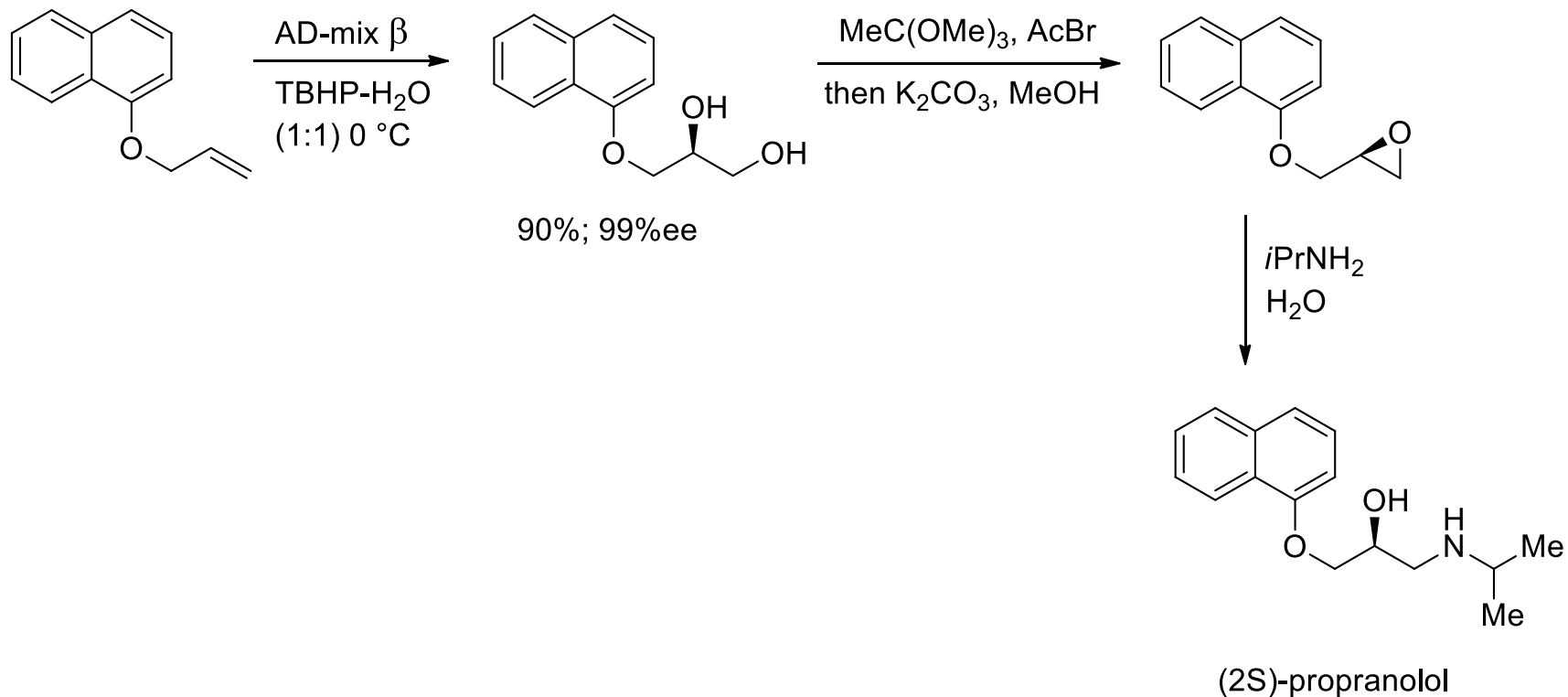
dihydroquinine ester

A. E. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, 110, 1968.

A. E. Jacobsen, I. Markó, M. B. France, J. S. Svendsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, 111, 737.

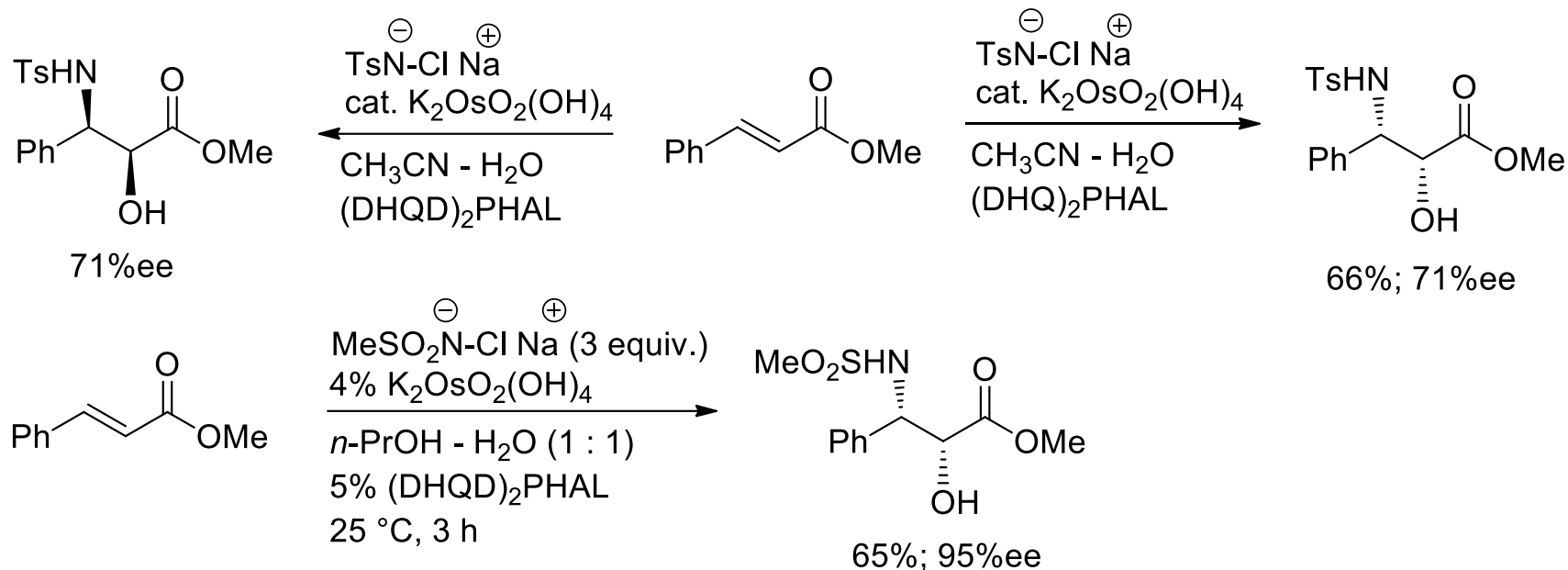
J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, A. E. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, 111, 1123.

Asymmetric dihydroxylation leading to (2S)-propranolol



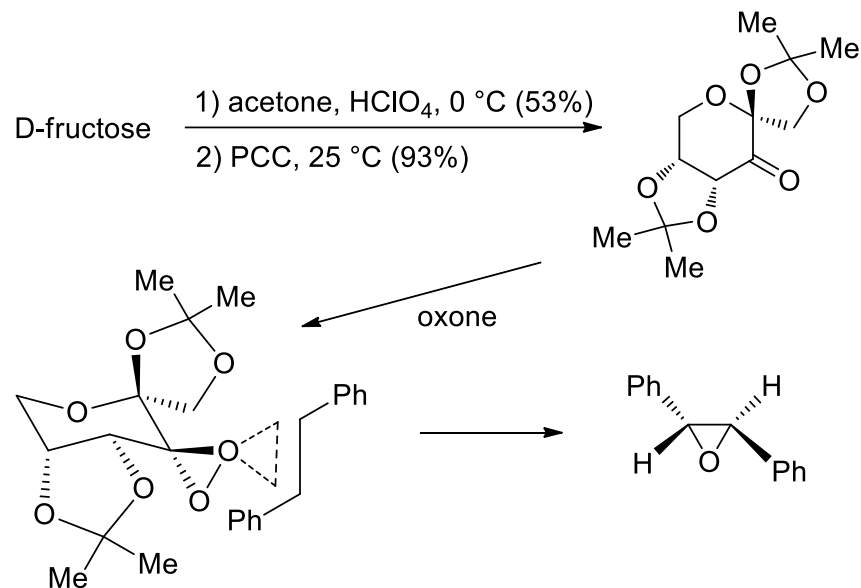
Z. Wang, X. Zhang, K. B. Sharpless, *Tetrahedron Lett.* **1993**, 34, 2267.

Asymmetric aminohydroxylation



G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1996**, 35, 451.
 O. Reiser, *Angew. Chem. Int. Ed.* **1996**, 35, 1308.

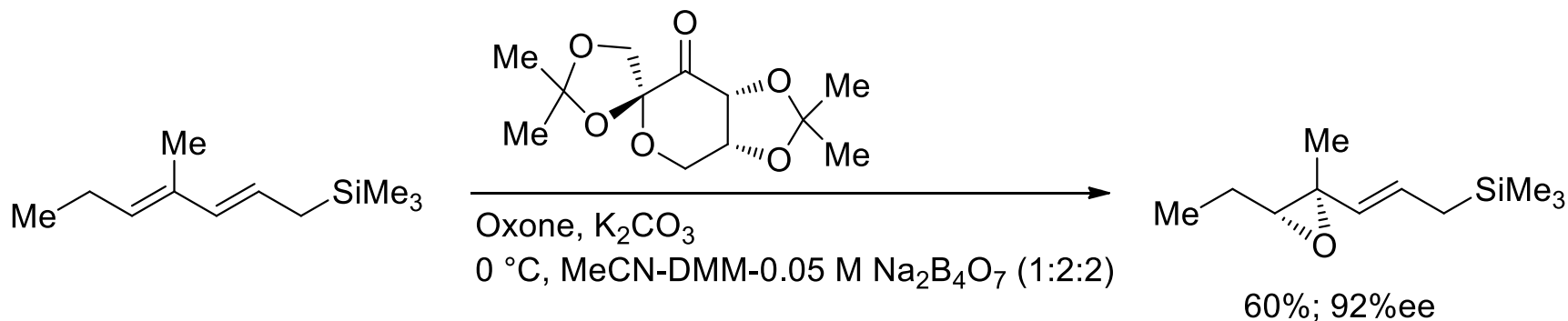
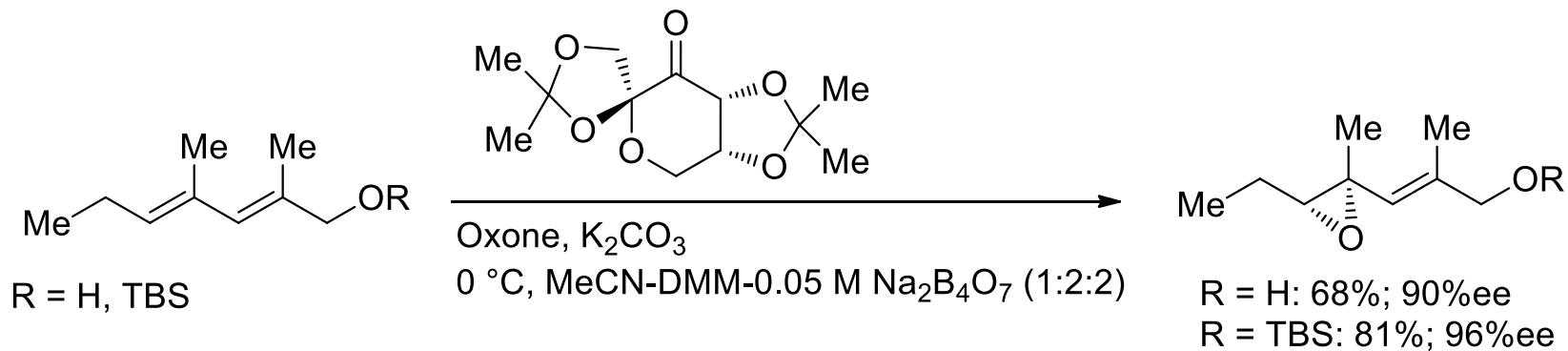
Epoxidation of non-functionalized epoxides



Y. Tu, Z. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, 118, 9806.

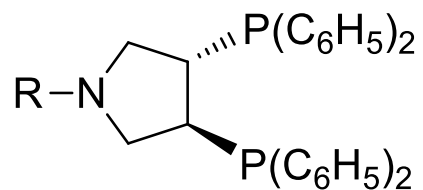
Substrate	Yield (%)	ee(%)	config.
	73	>95	<i>R, R</i>
	81	88	<i>R, R</i>
	61	93	<i>2S, 3R</i>
	73	92	<i>R, R</i>
	69	91	<i>R, R</i>

Epoxidation of non-functionalized epoxides

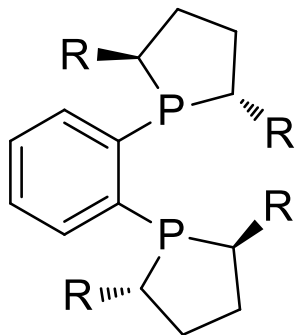


M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, 63, 2948.

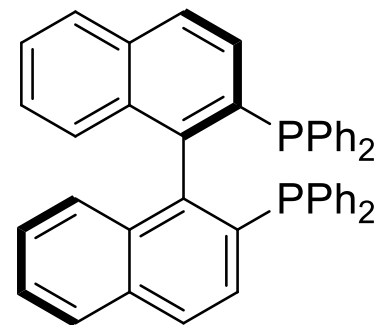
Ligands for asymmetric hydrogenation



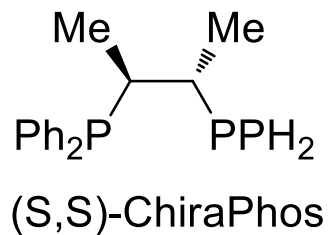
DeguPhos



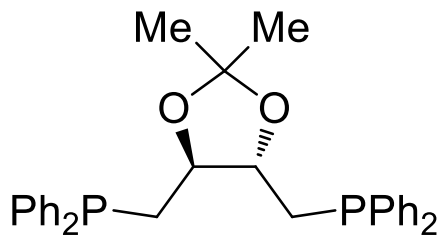
DuPhos



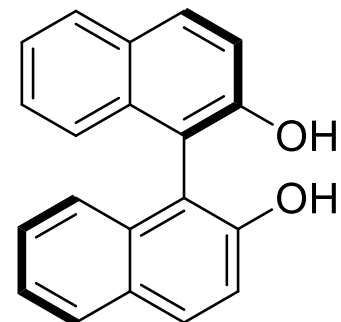
(R)-BINAP



(S,S)-ChiraPhos

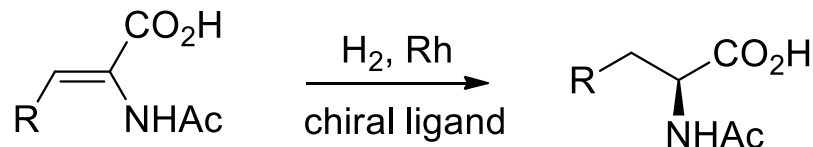


DIOP



(R)-BINOL

Catalytic hydrogenation of enamides

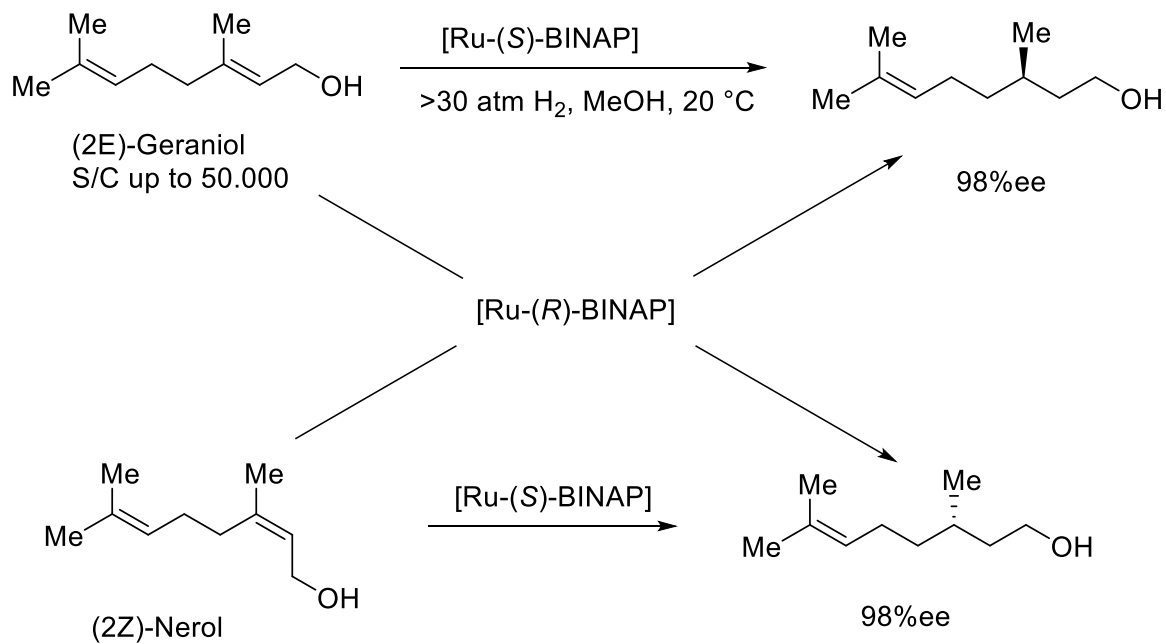
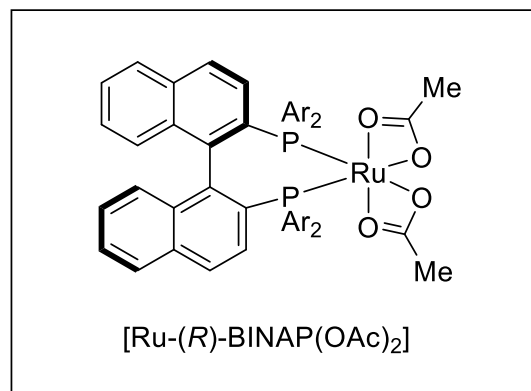


Phosphine ligand	product ee (%)	
	R = C ₆ H ₅	R = H
(R,R)-DIPAMP	96 (S)	94 (S)
(S,S)-ChiraPhos	99 (R)	91 (R)
(S,S)-NorPhos	95 (S)	90 (R)
(R,R)-DIOP	85 (R)	73 (R)
(S,S)-BPPM	91 (R)	98.5 (R) ^a
(S)-BINAP	100 (R) ^a	98 (R)
(S)-(R)-BPPFA	93 (S)	
(S,S)-SkewPhos	92 (R)	
(S,S)-CycPhos	88 (R)	
(S,S)-Et-DuPhos	99 (S)	99.4 (S)

^a hydrogenation of the N-benzoyl derivative

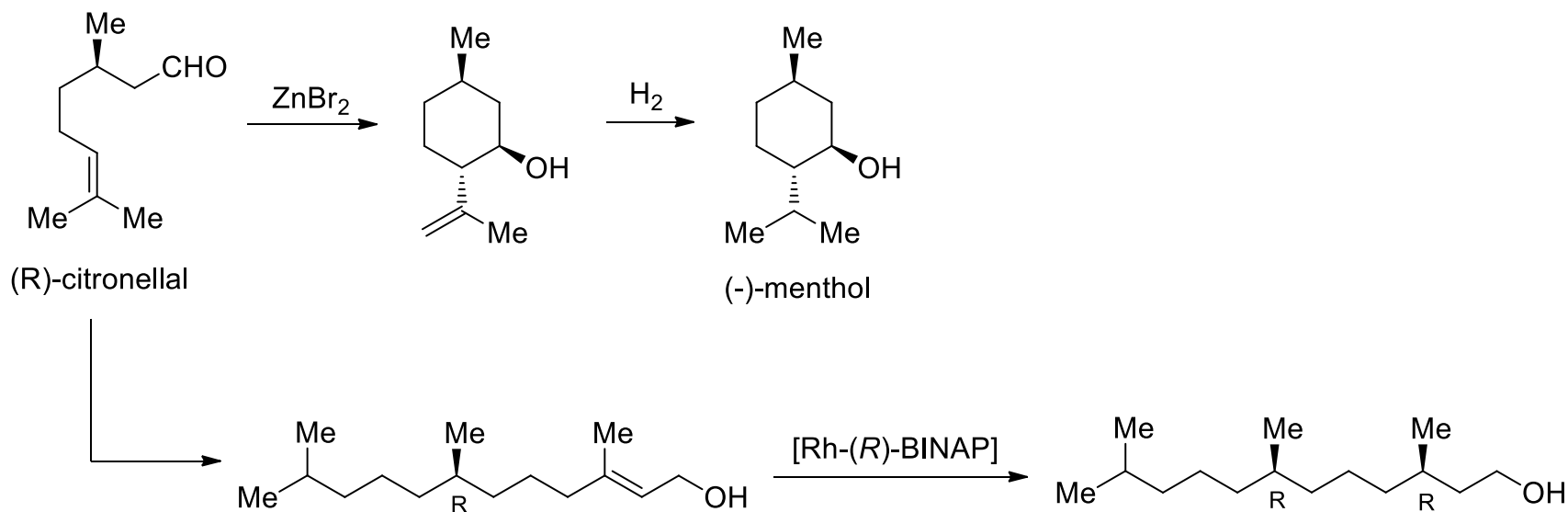
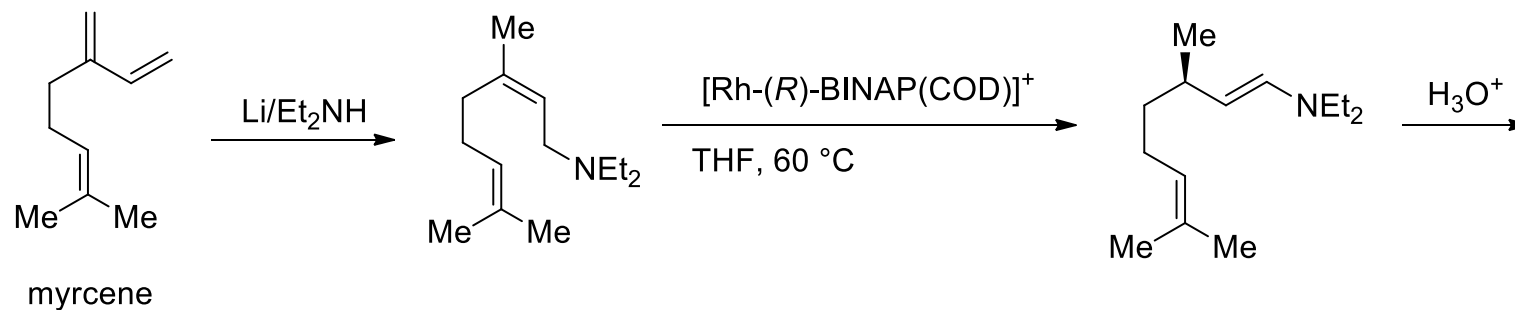
K. E. Koenig "Asymmetric Hydrogenation of Prochiral Olefins" in *Catalysis of Organic Reactions*, Marcel Dekker, New York, **1984**, Chap. 3.

Ru-catalyzed hydrogenations



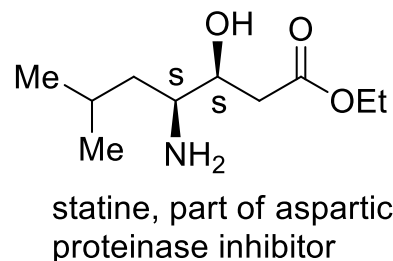
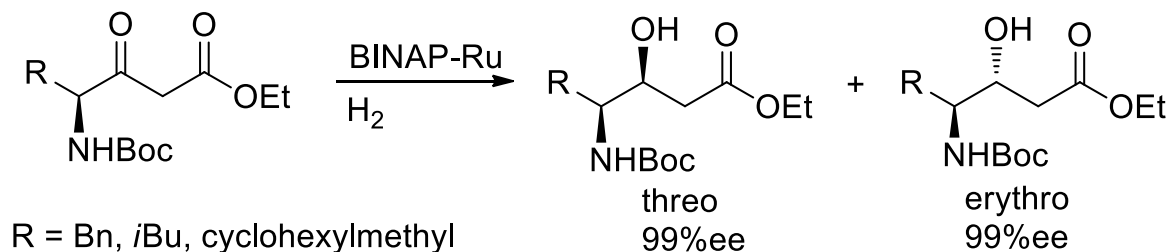
H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, R. Noyori, *J. Am. Chem. Soc.*, **1987**, 109, 1596.

Rh-catalyzed hydrogenations

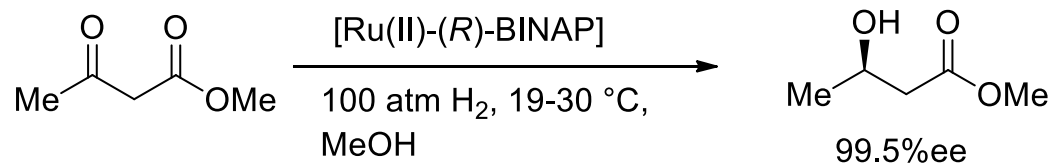
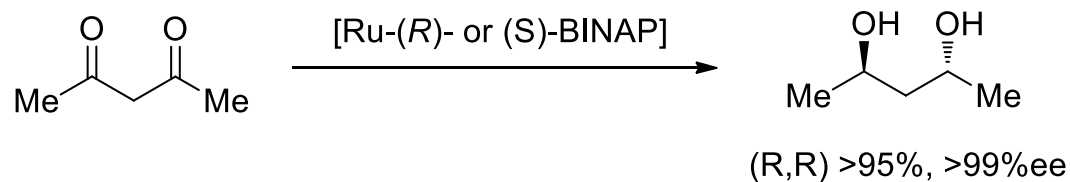


R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, Inc., New York, **1994**, Chap. 3.

Asymmetric hydrogenation of carbonyl compounds

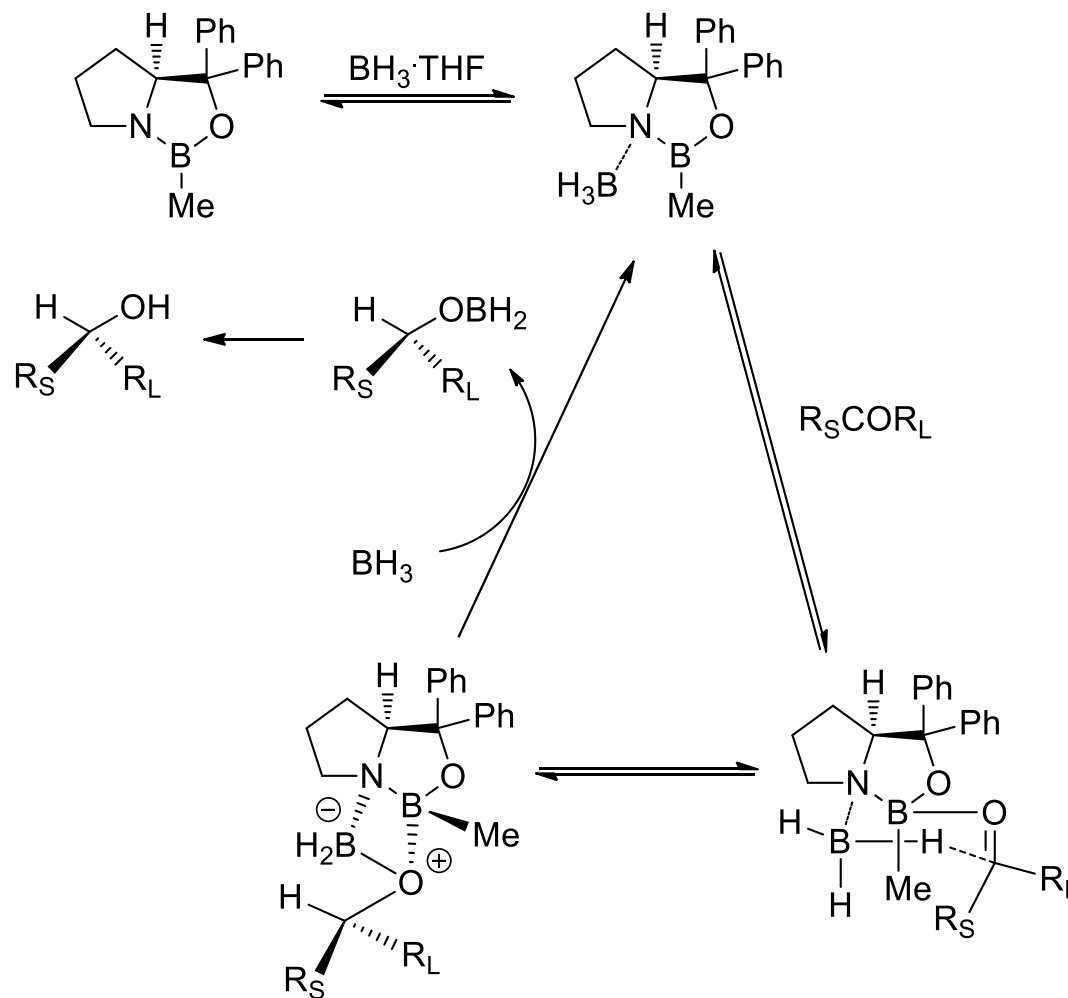


T. Nishi, M. Kitamura, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **1988**, 29, 6327.



Q. Fan, C. H. Yeung, A. S. C. Chan, *Tetrahedron Asymmetry* **1997**, 8, 4041.

The oxazaborolidine catalyst system



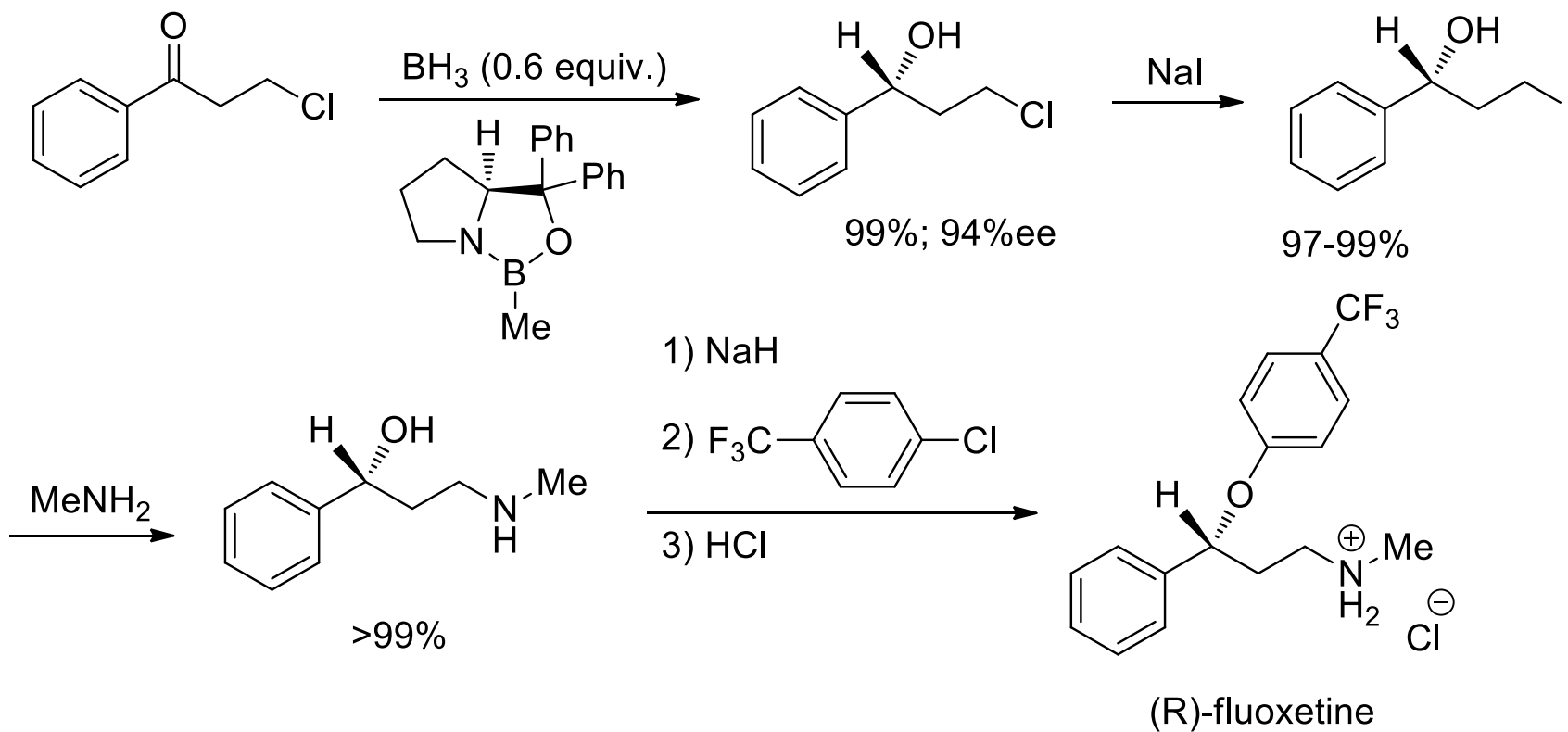
E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, 109, 5551.

E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, 33, 4141.

V. Nevalainen, *Tetrahedron Asymmetry* **1991**, 2, 1133.

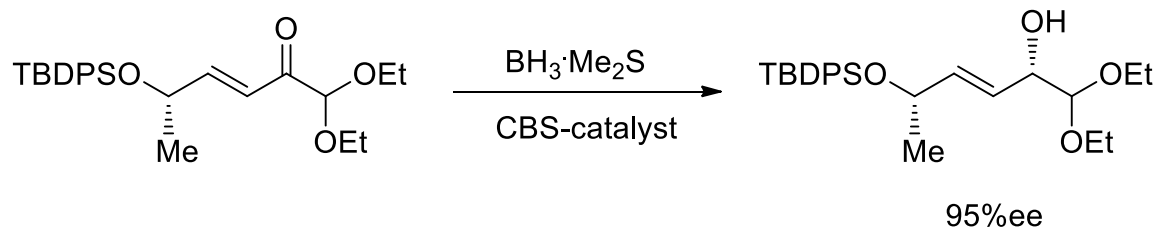
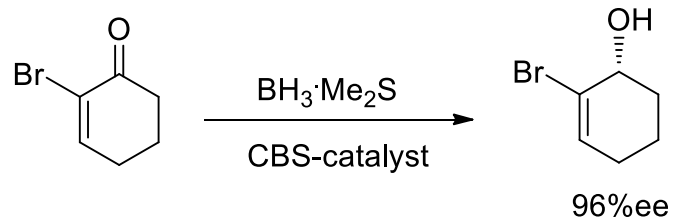
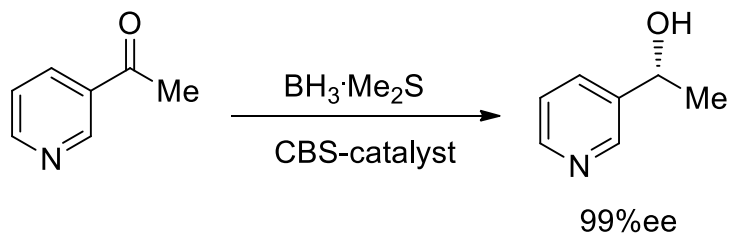
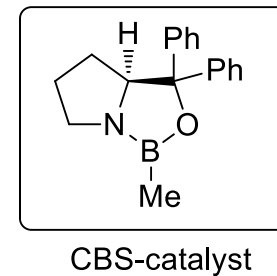
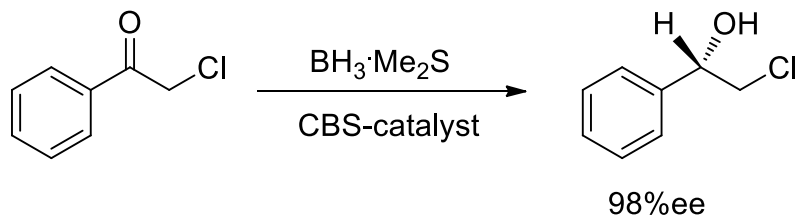
E. J. Corey, J. O. Link, S. Sarshar, Y. Shao, *Tetrahedron Lett.* **1992**, 33, 7103.

The oxazaborolidine catalyst system



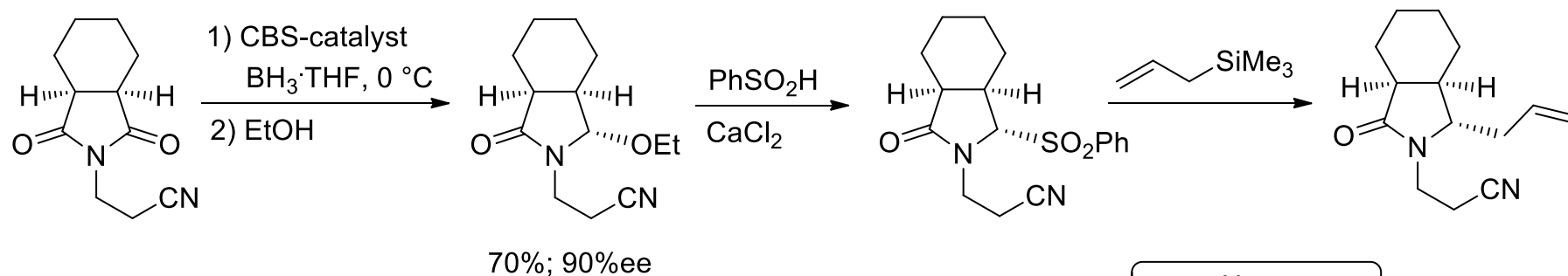
E. J. Corey, G. A. Reichard, *Tetrahedron Lett.* **1989**, 30, 5207.

CBS-Reduction

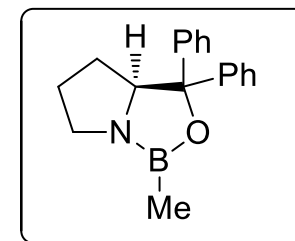


Review: E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, 37, 1986-2012.

CBS-Reduction



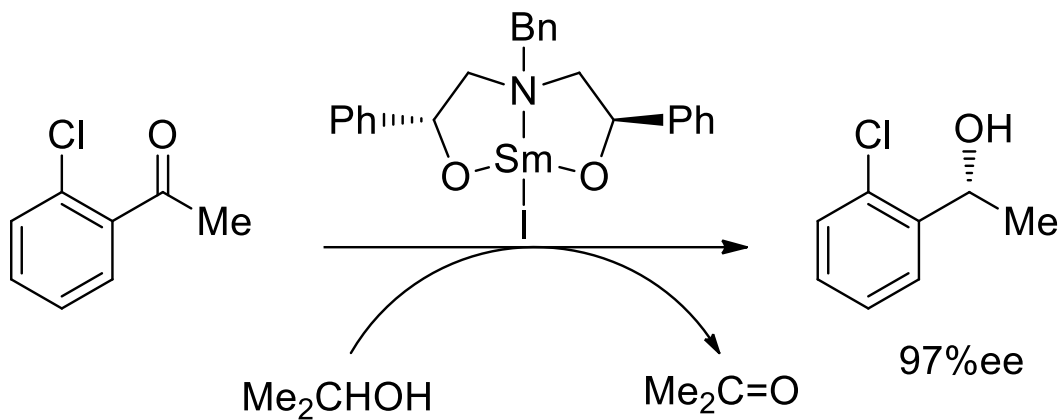
H. Hiemstra, *Tetrahedron: Asymmetry* **1997**, 8, 1773.
Tetrahedron Lett. **1994**, 35, 1087.



CBS-catalyst

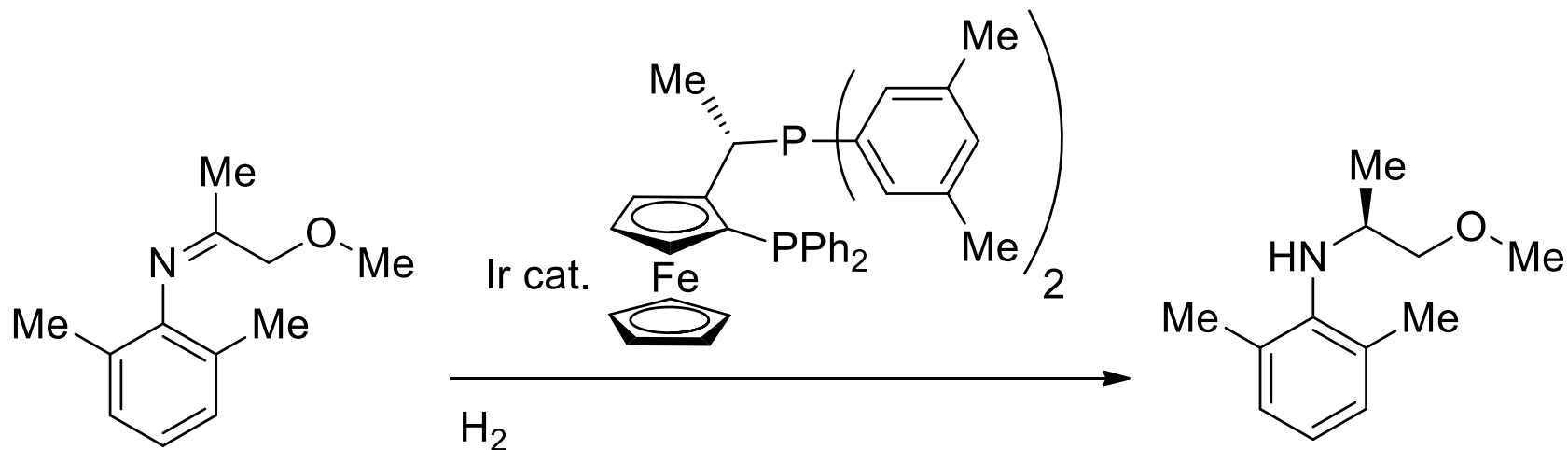
Asymmetric transfer hydrogenation

Meerwein-Ponndorf-Verley reaction



D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J. Am. Chem. Soc.* **1993**, 115, 9800.

Enantioselective imine hydrogenation



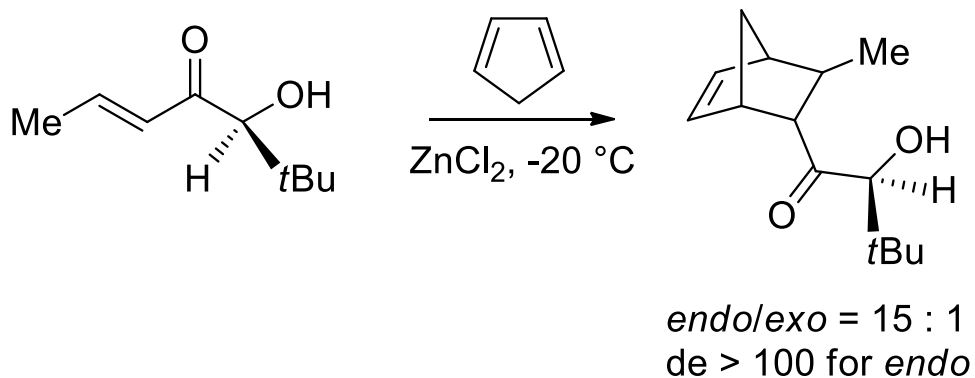
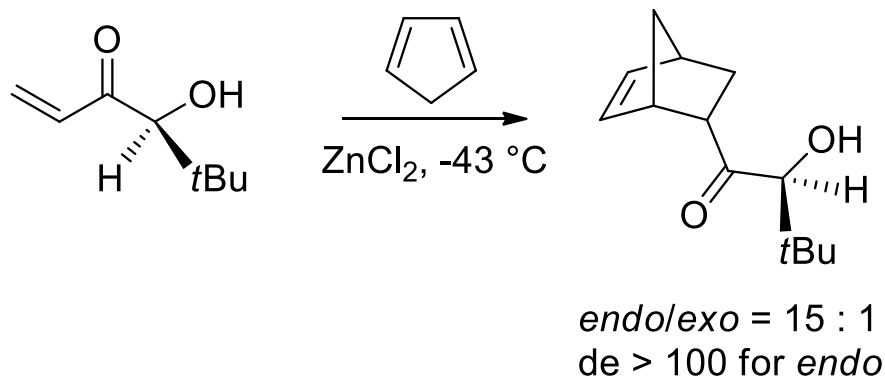
substrat / Ir < 100.000;
TOF > 10.000 h⁻¹

80%ee

A. Togni, *Angew. Chem.* **1996**, 108, 1581.

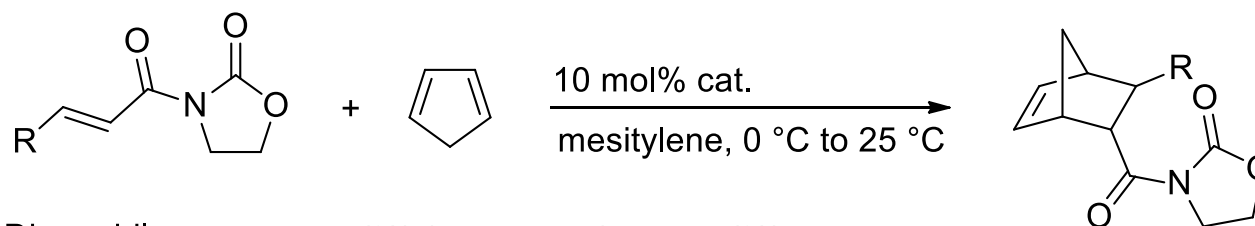
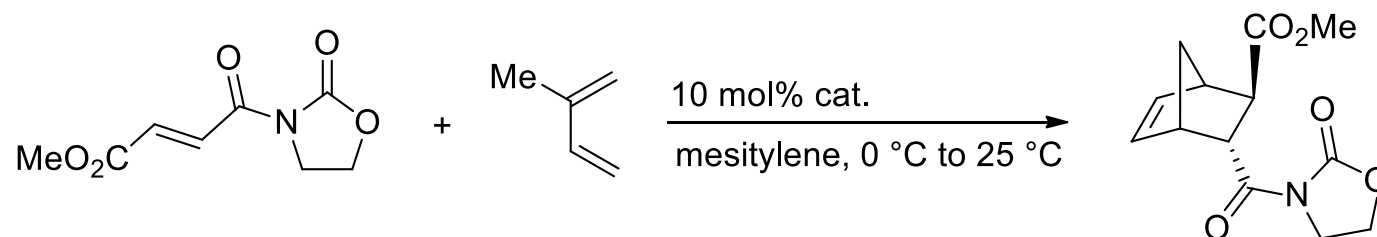
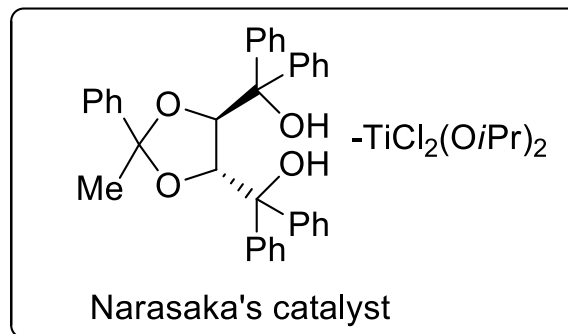
F. Spindler, *Chimia*, **1997**, 6, 297, Patent LONZA AG

Asymmetric Diels-Alder reaction



S. Masamune, L. A. Reed, J. T. Davis, W. J. Choy, *J. Org. Chem.* **1983**, 48, 4441.
W. J. Choy, L. A. Reed, S. Masamune, *J. Org. Chem.* **1983**, 48, 1137.

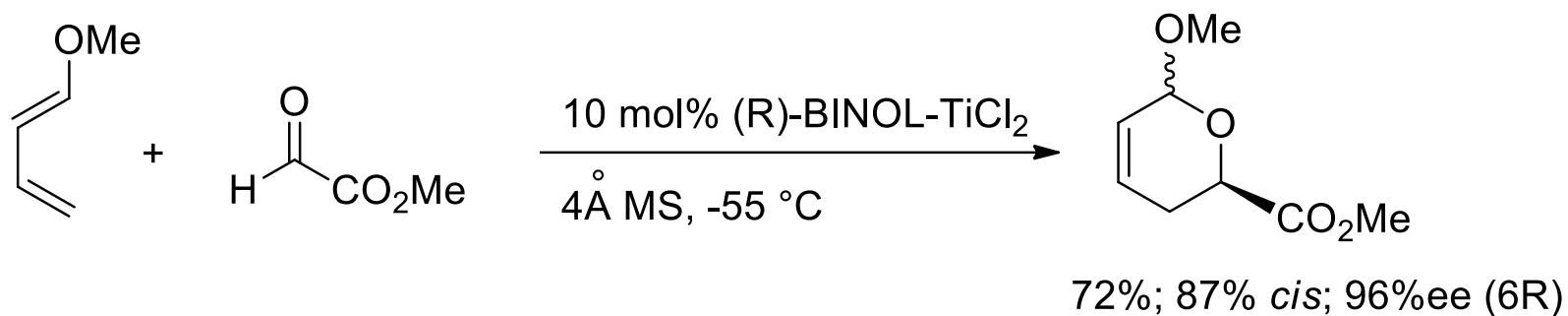
Asymmetric Diels-Alder reaction



Dienophile	Yield (%) (<i>endo</i> : <i>exo</i>)	ee (%)
R = Me	90 (91 : 9)	91
R = Ph	97 (92 : 8)	82
R = <i>n</i> Pr	75 (91 : 9)	75

K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, N. Iwasawa, *Chem. Lett.* **1987**, 2409.

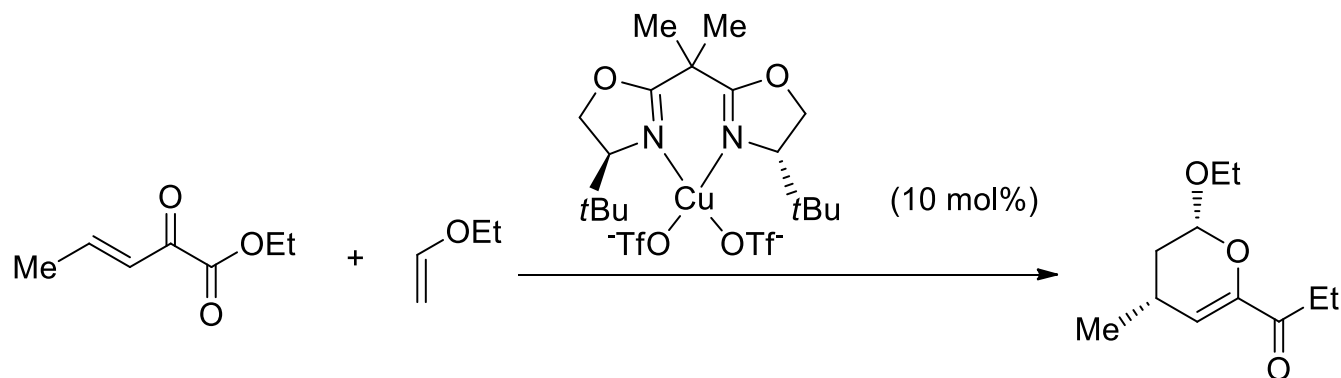
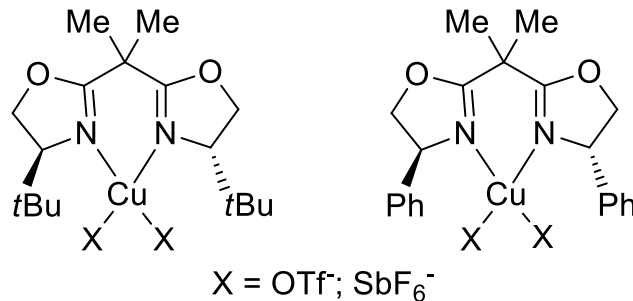
Hetero Diels-Alder reaction



K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, 116, 2812.

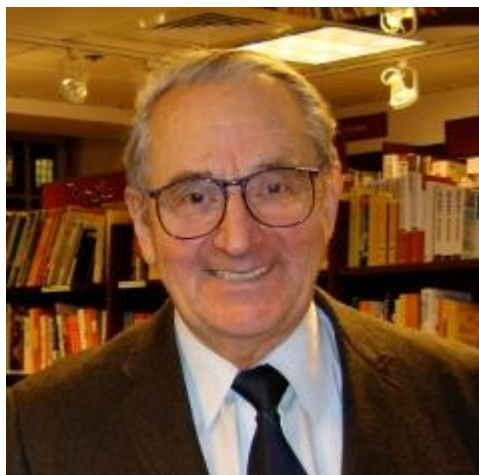
M. Terada, K. Mikami, T. Nakai, *Tetrahedron Lett.* **1991**, 32, 935.

Hetero Diels-Alder reaction



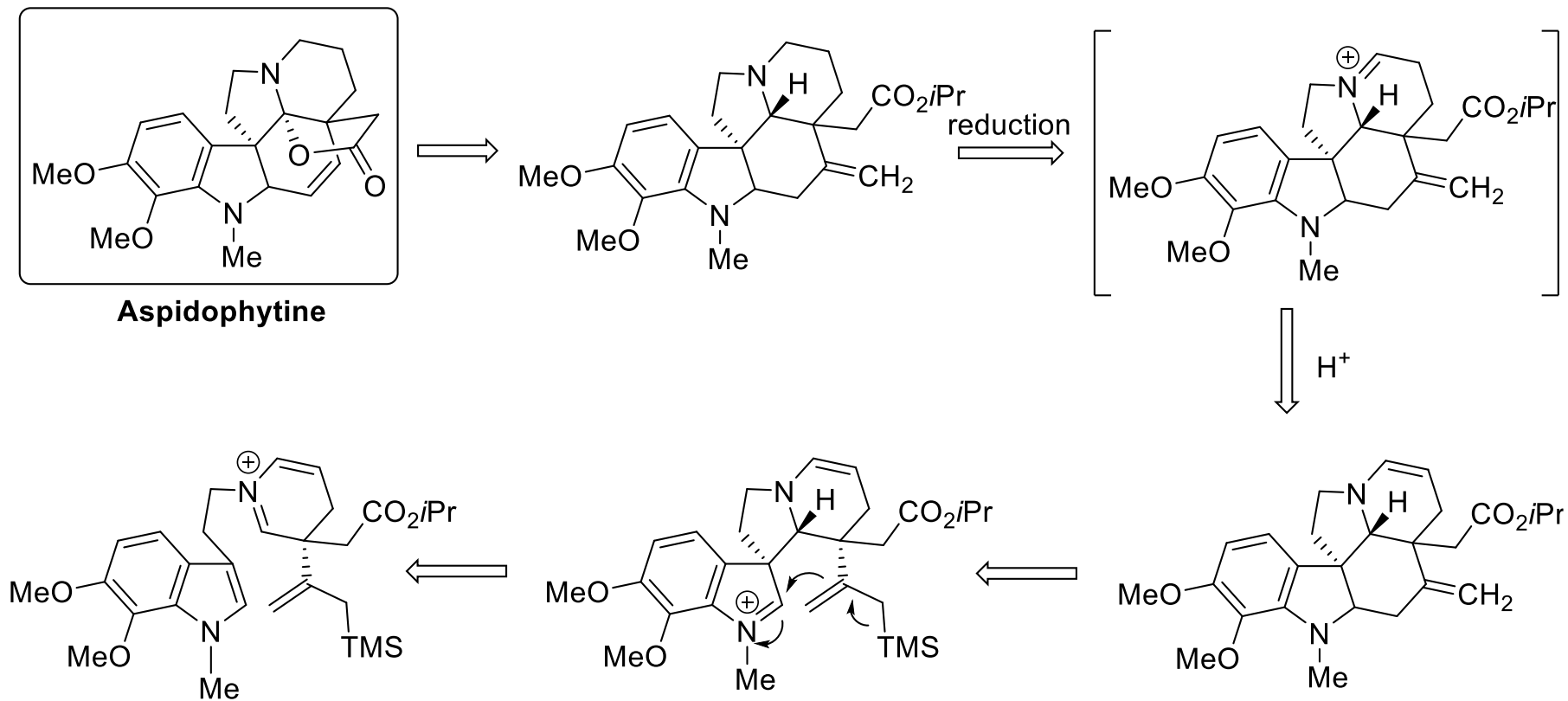
Entry	Solvent	T (°C)	Yield (%)	ee (%)
1	CH ₂ Cl ₂	-45 °C	100	95.6
2	CH ₂ Cl ₂	-78 °C	100	97.5
3	THF	-45 °C	100	99.0
4	THF	-78 °C	100	99.7
			(89 isolated yield)	
5	CH ₃ NO ₂	-20 °C	100	75.8

Asymmetric synthesis in Natural Product Chemistry

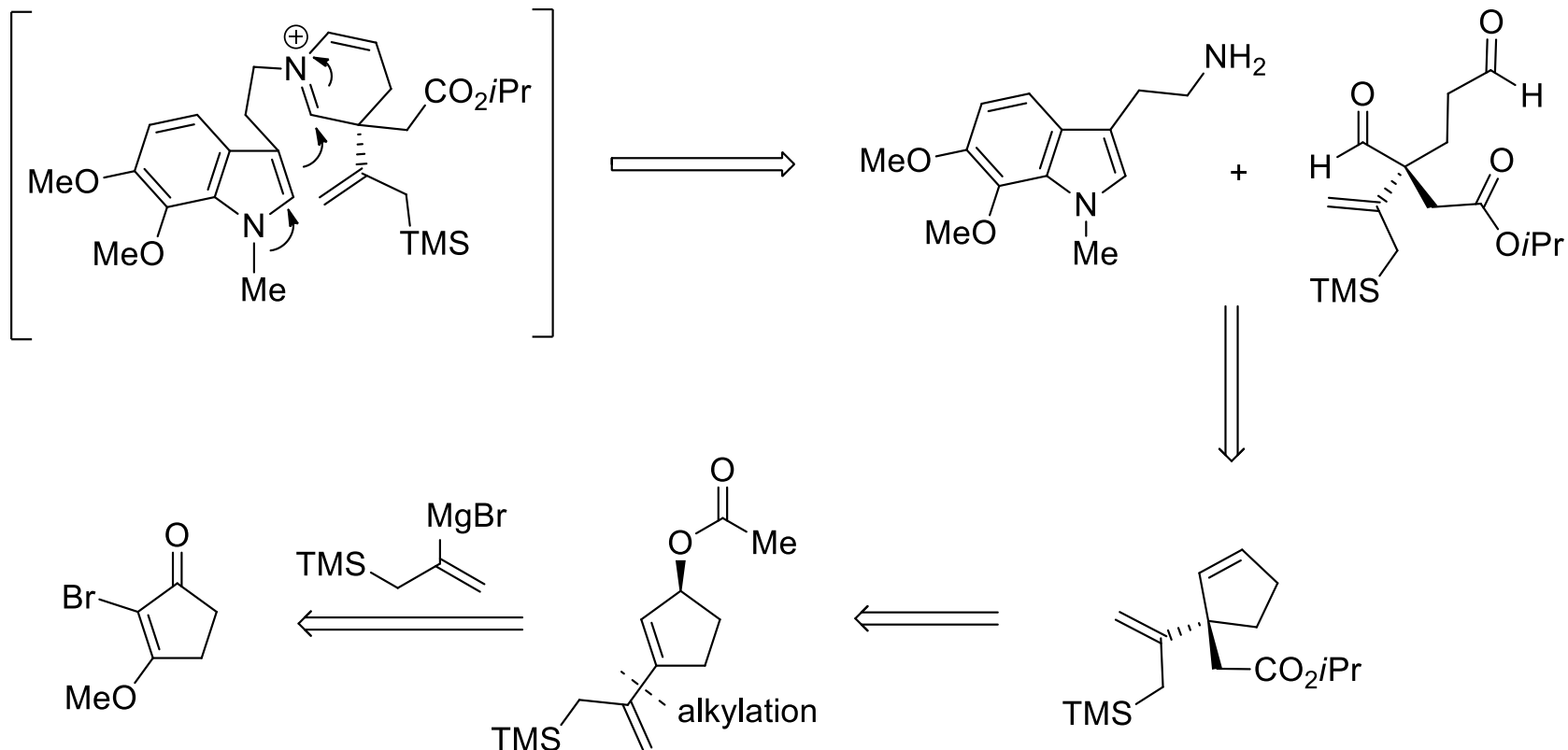


Prof. E. J. Corey

Corey's retrosynthetic analysis of aspidophytine

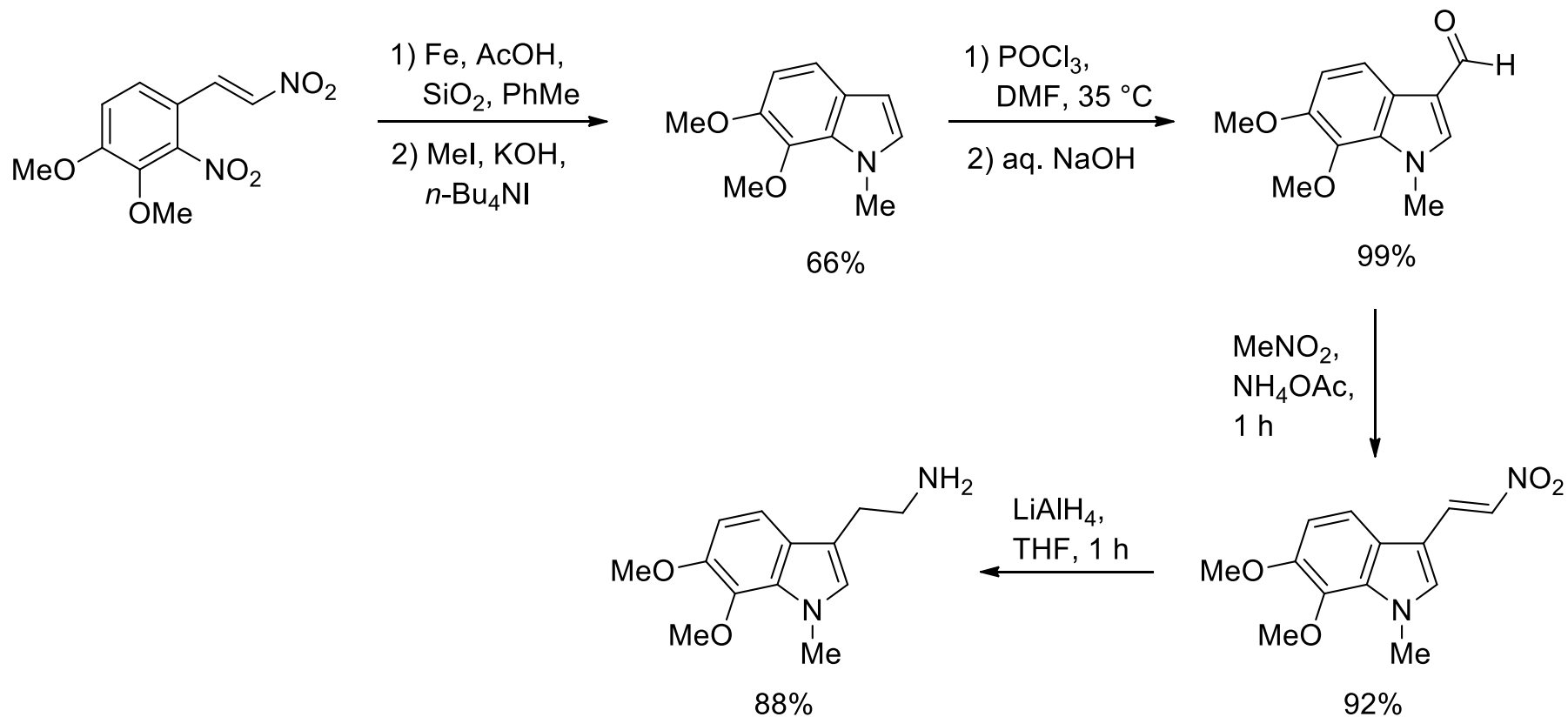


Corey's retrosynthetic analysis of aspidophytine



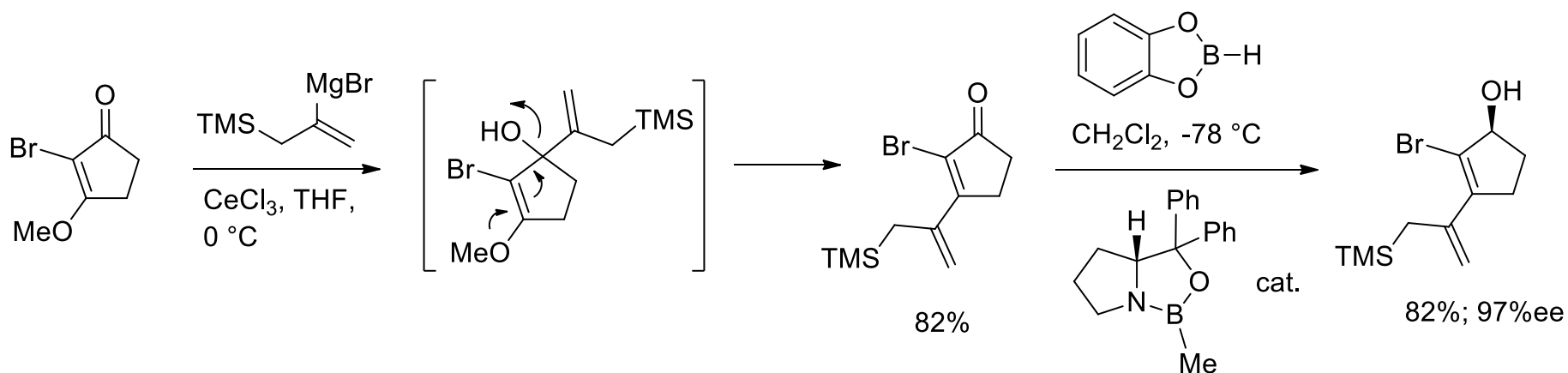
He, F., Bo, Y., Altom, J. D. Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

Corey's total synthesis of aspidophytine



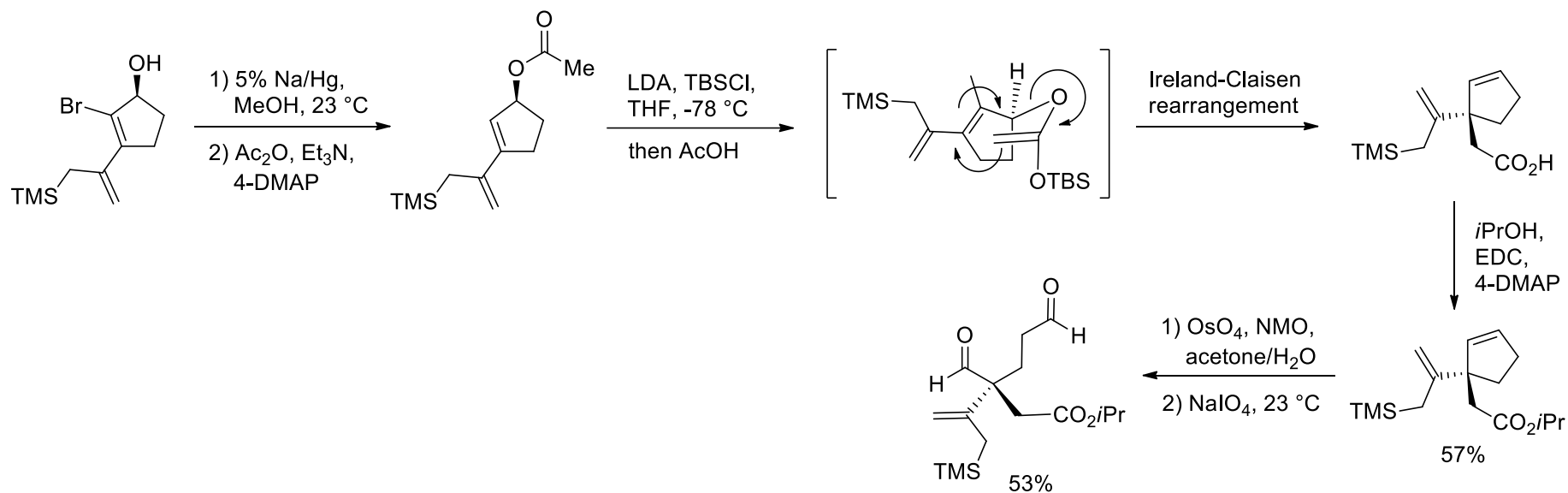
He, F., Bo, Y., Altom, J. D. Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

Corey's total synthesis of aspidophytine



He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

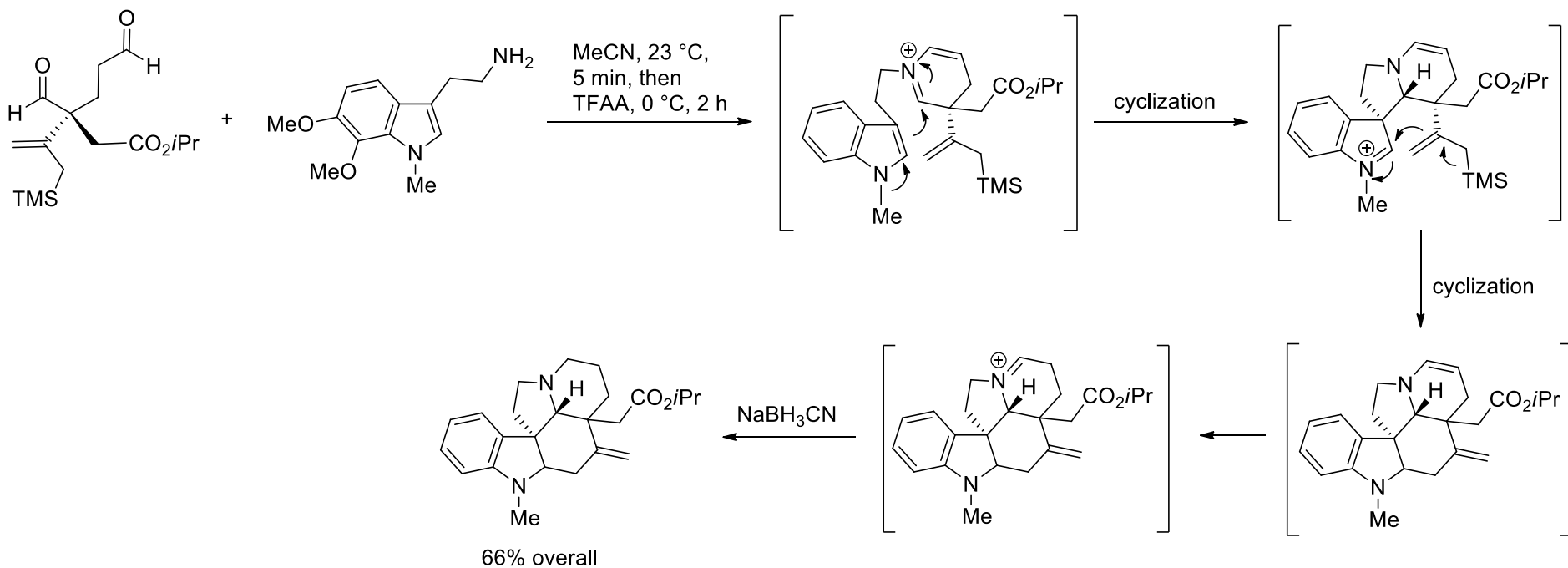
Corey's total synthesis of aspidophytine



He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

Corey's total synthesis of aspidophytine

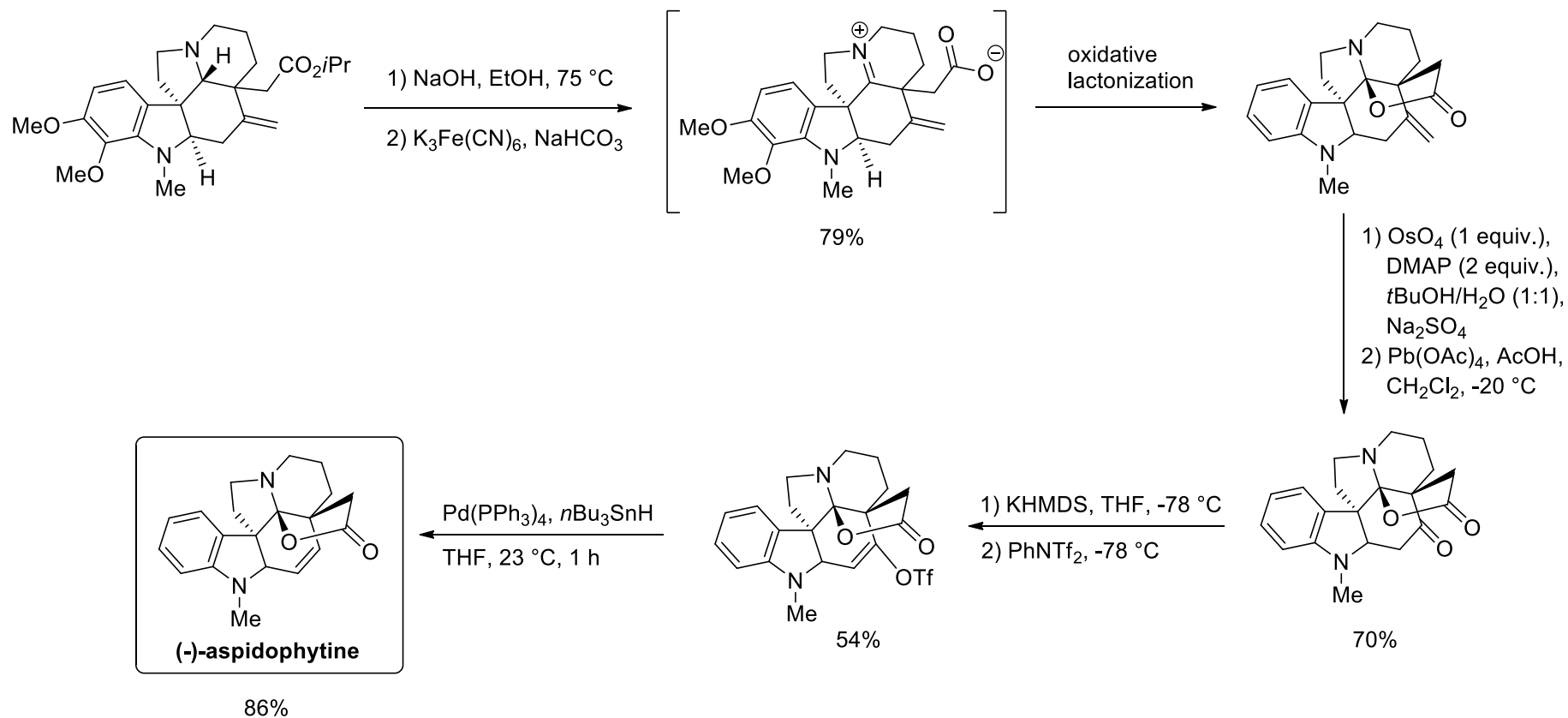
The final cascade sequence



He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

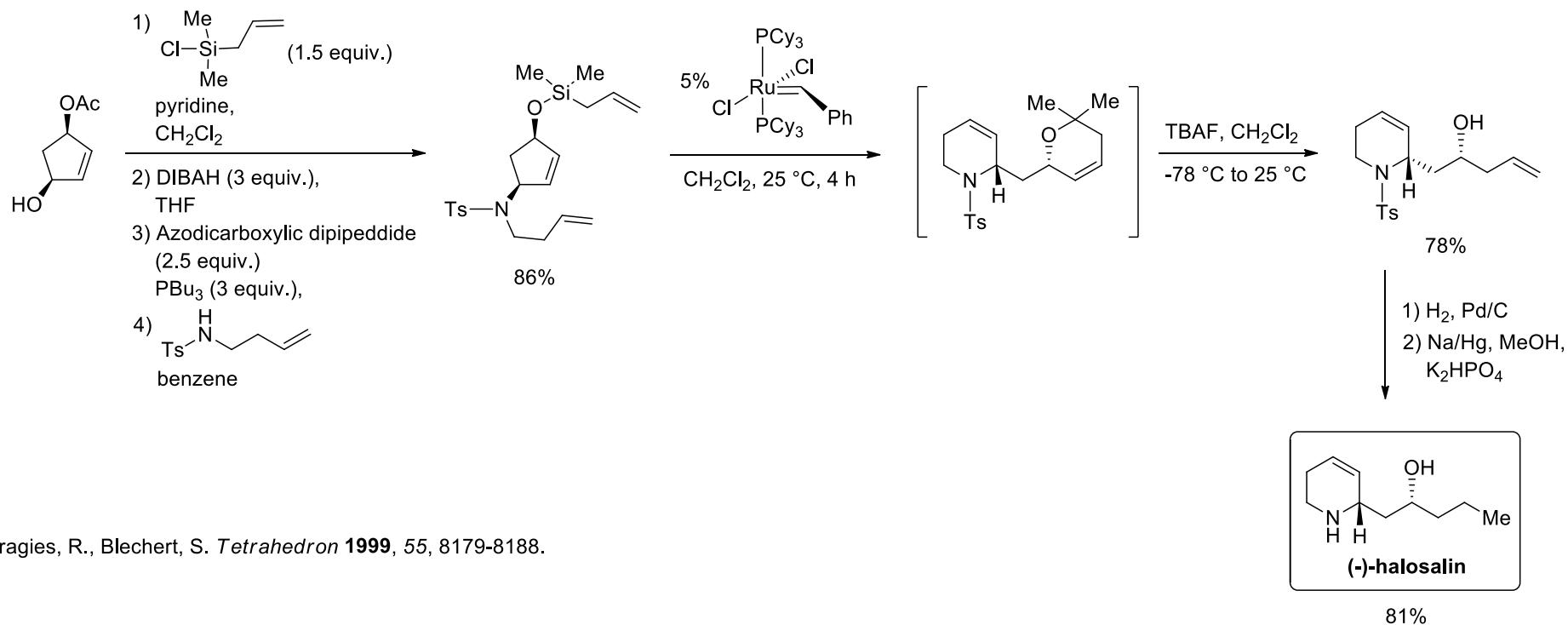
Corey's total synthesis of aspidophytine

Final stages and completion



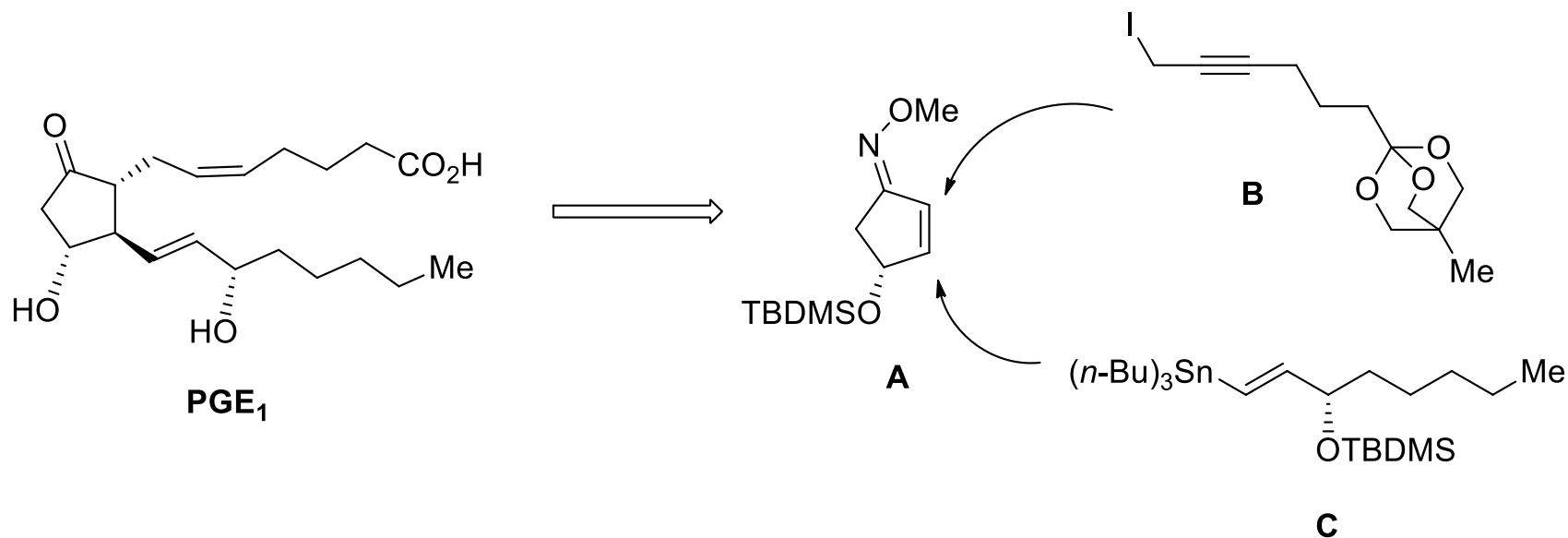
He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 6771-6772.

A domino olefin metathesis strategy for the synthesis of (-)-halosalin



Stragies, R., Blechert, S. *Tetrahedron* **1999**, 55, 8179-8188.

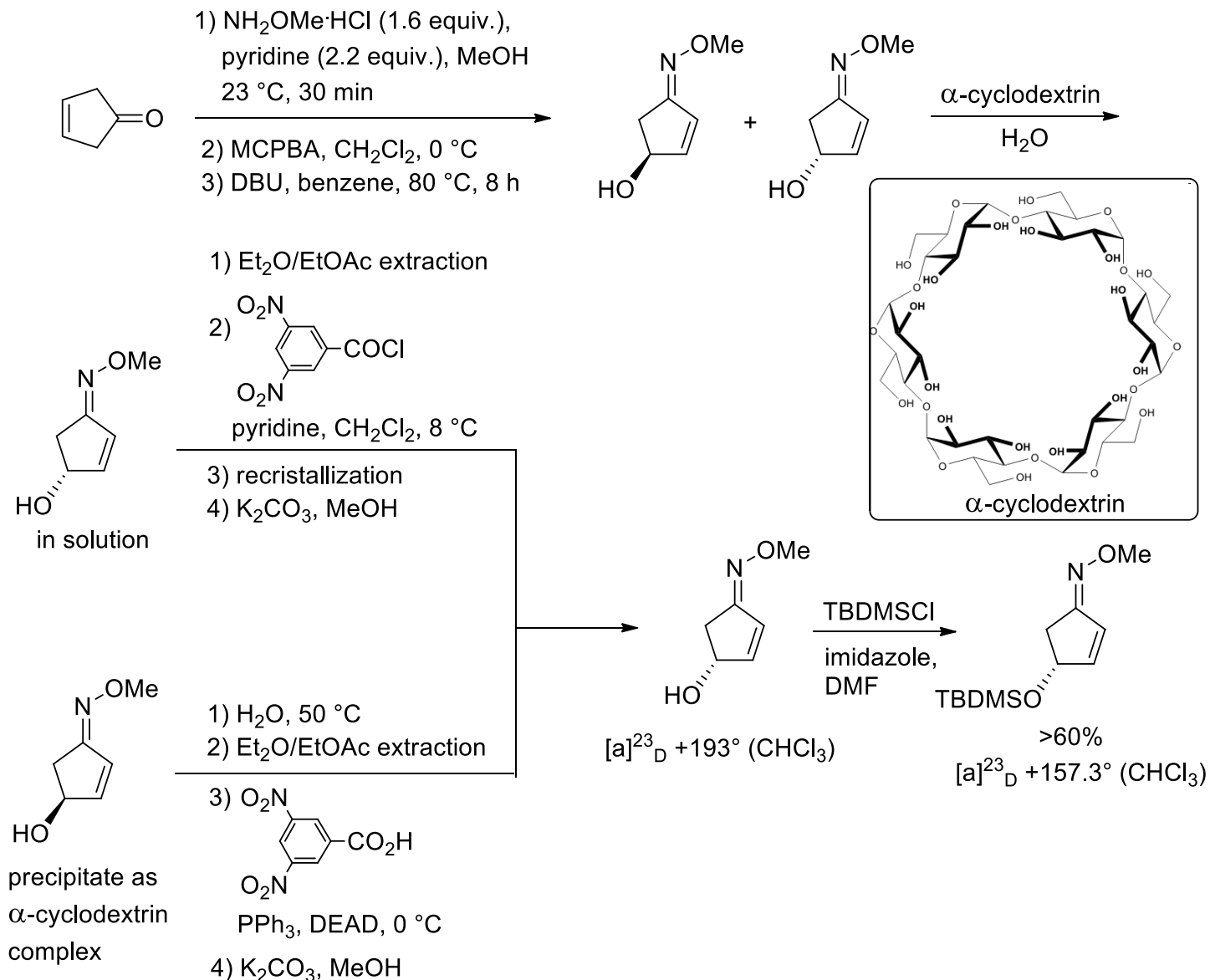
Conjugated addition-alkylation route to prostaglandins



Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, 27, 2199-2202;
Corey, E. J., Raju, N. *Tetrahedron Lett.* **1983**, 24, 5571-5574.

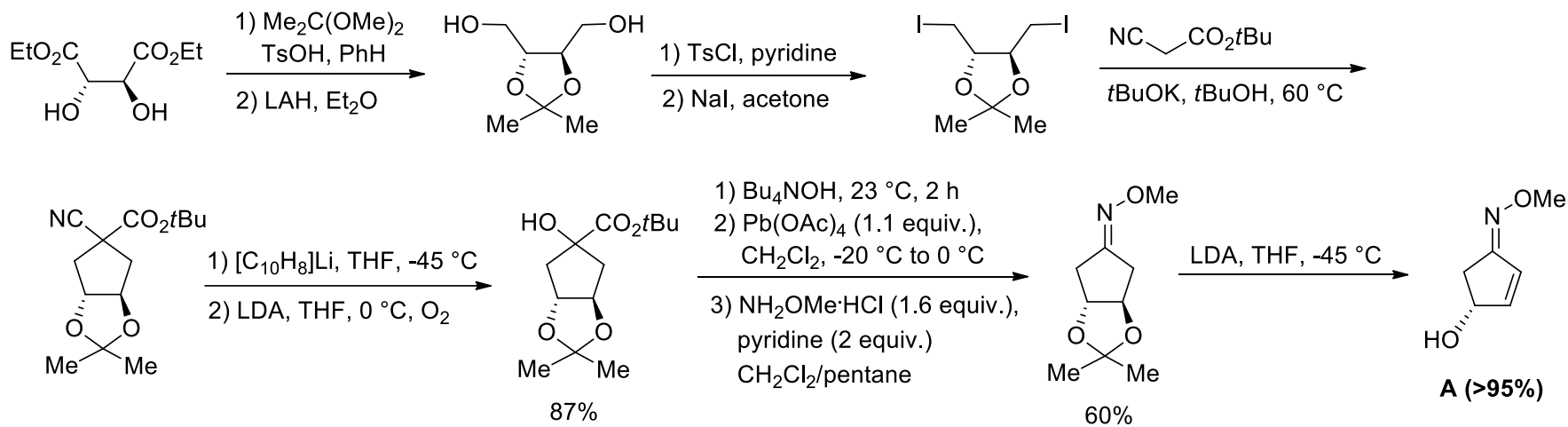
Conjugated addition-alkylation route to prostaglandins

Synthesis of fragment A



Conjugated addition-alkylation route to prostaglandins

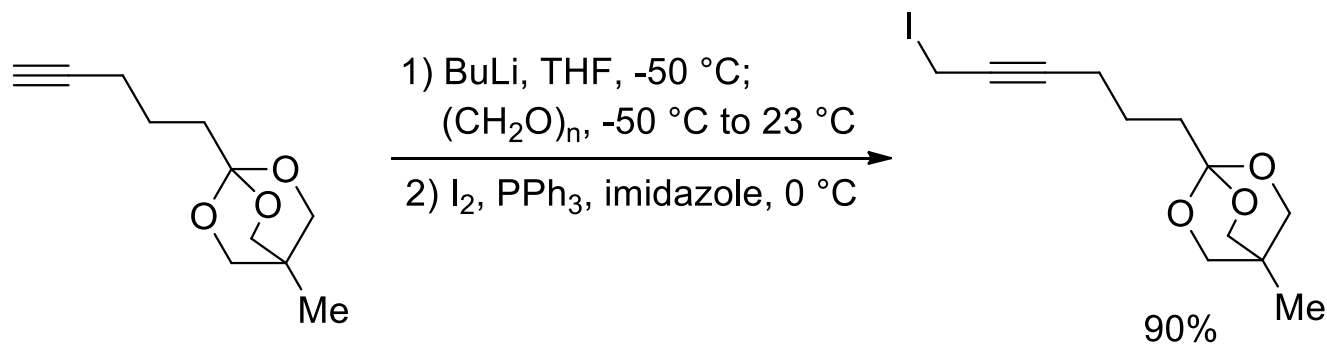
Alternative synthesis of fragment A starting from diethyl (S,S)-tartrate



Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, 27, 2199-2202.

Conjugated addition-alkylation route to prostaglandins

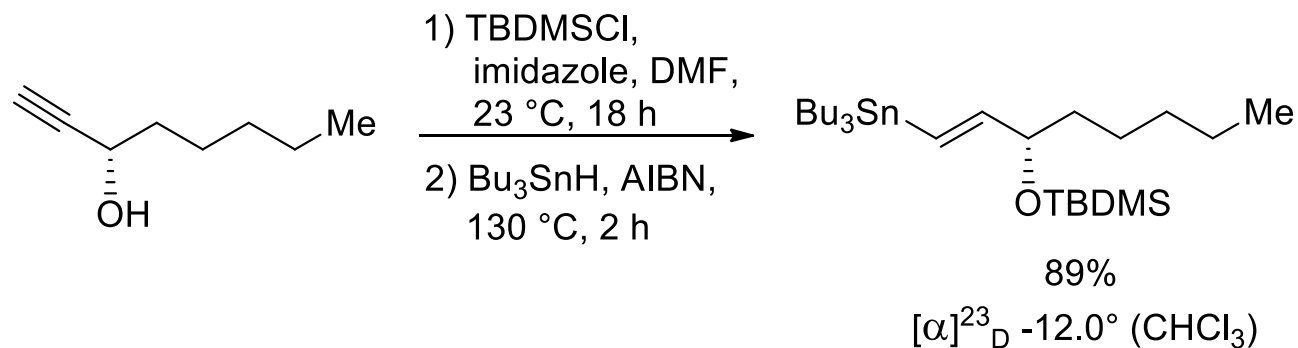
Synthesis of fragment B



Corey, E. J., Raju, N. *Tetrahedron Lett.* **1983**, 24, 5571-5574.

Conjugated addition-alkylation route to prostaglandins

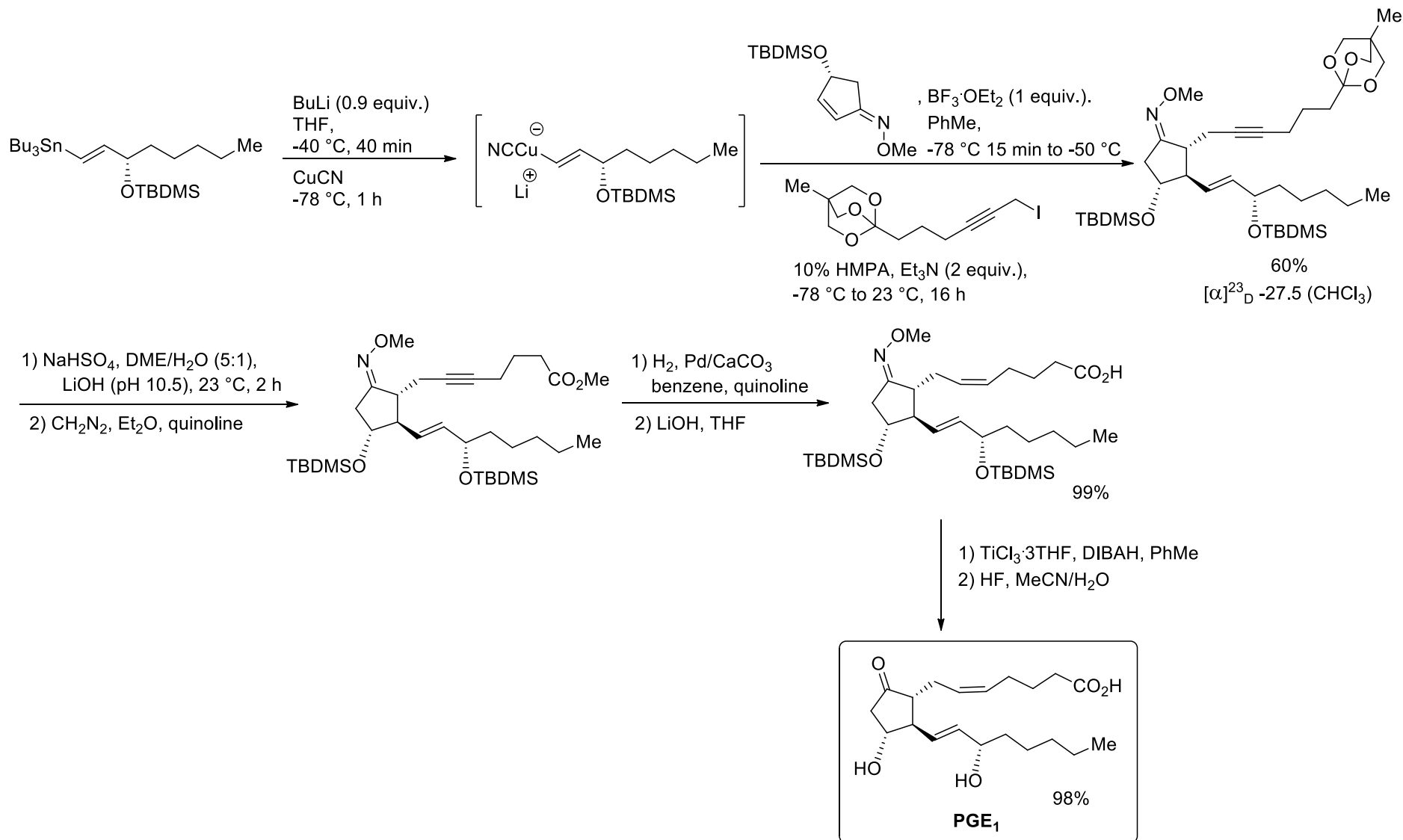
Synthesis of fragment C



Corey, E. J., Raju, N. *Tetrahedron Lett.* **1983**, 24, 5571-5574.

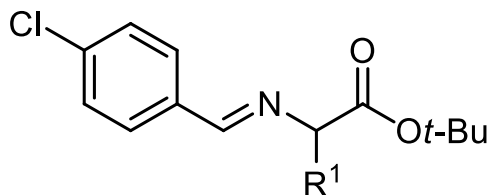
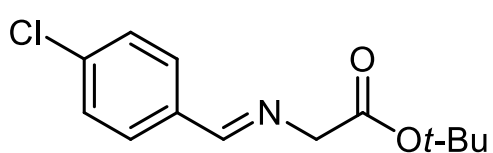
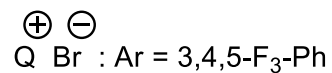
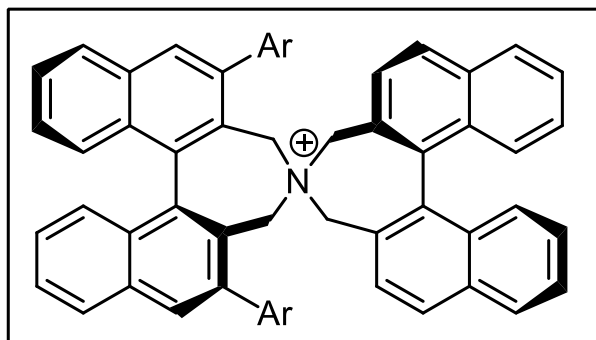
Conjugated addition-alkylation route to prostaglandins

Final assembly of the PGE₁



Additional asymmetric syntheses

Enantioselective alkylation by chiral phase-transfer catalysis



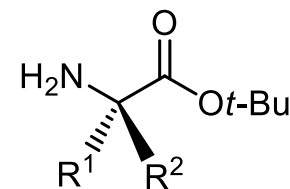
1) R¹-X

2) R²-X
 CsOH, toluene
 -10 °C → 0 °C

QX (1 mol%)

R²-X, CsOH, H₂O
 toluene, -20 °C → 0 °C

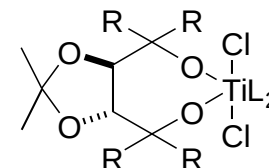
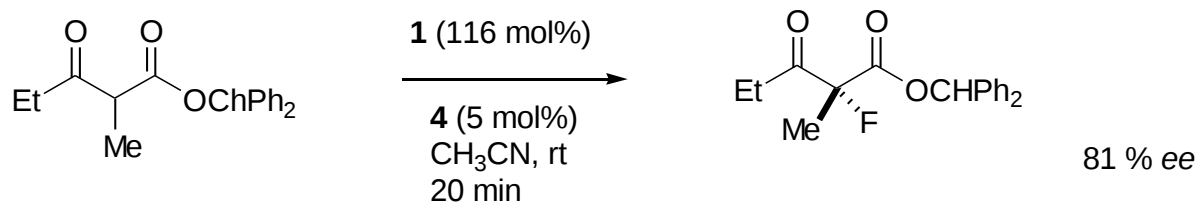
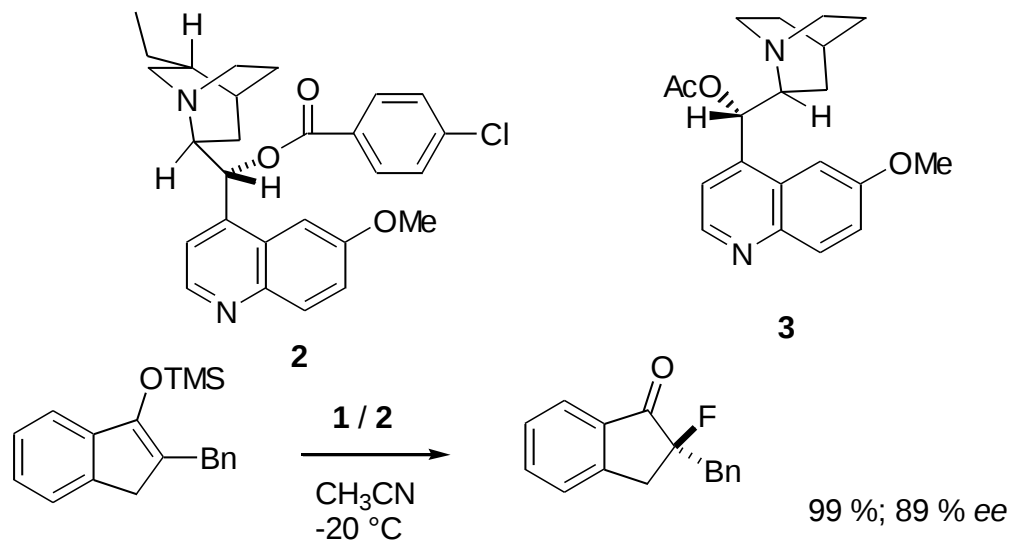
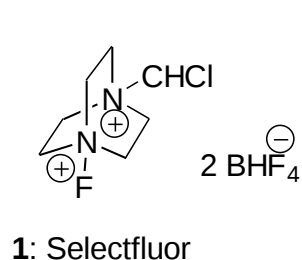
H⁺



51-85%
 91-99% ee

K. Maruoka, *Synlett* **2001**, 1185.

Enantioselective fluorination reactions

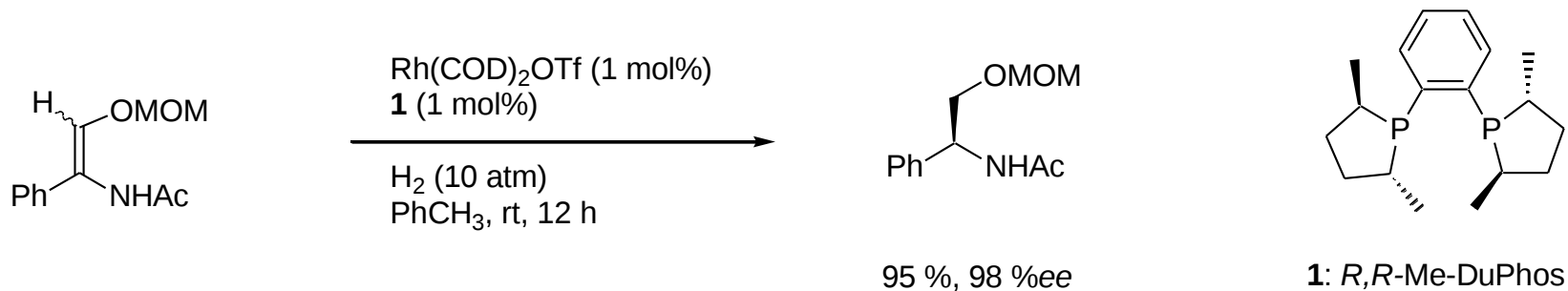


4: R = 1-Naph
 L₂ = (CH₃CN)₂

Munoz, K. *Angew. Chem. Int. Ed.* **2001**, 40, 1653

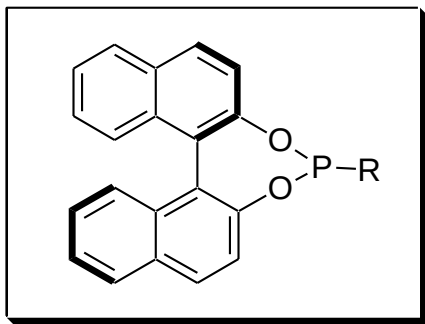
Asymmetric reduction of C=C-bonds

Synthesis of amino-alcohol derivatives



Zhang, X. *J. Org. Chem.* **1998**, 63, 8100.

Chiral monophosphines for the enantioselective hydrogenation of functionalized olefins



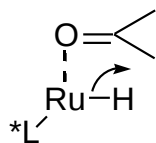
$R = t\text{-Bu, Et, NMe}_2, (R)\text{-O-CH(Me)Ph}$

High enantioselectivities are reached with BINAP-derived phosphines and phosphoramidates for asymmetric hydrogenations.

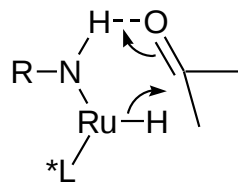
Review: Börner, A. *Angew. Chem. Int. Ed.* **2001**, 40, 1197

Asymmetric reduction of C=O bonds

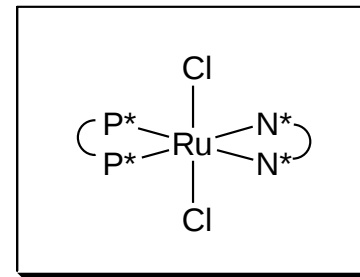
Rapid, catalytic and stereoselective hydrogenation of ketones
Noyori, R. *Pure Appl. Chem.* **1999**, 71, 1493.



difficult

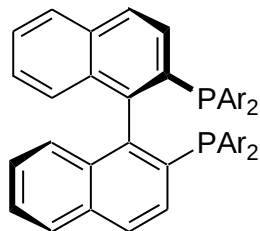


easy

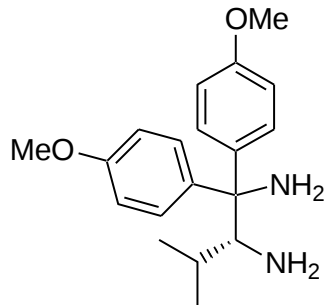


chiral Ru-complex

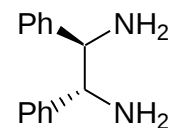
Noyori-catalyst system



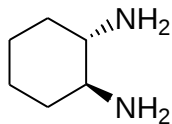
Ar = C₆H₅: (R)-BINAP
 Ar = 4-Me-C₆H₄: (R)-ToIBINAP
 Ar = 3,5-Me₂C₆H₃: (R)-XylBINAP



(R)-DAIPEN

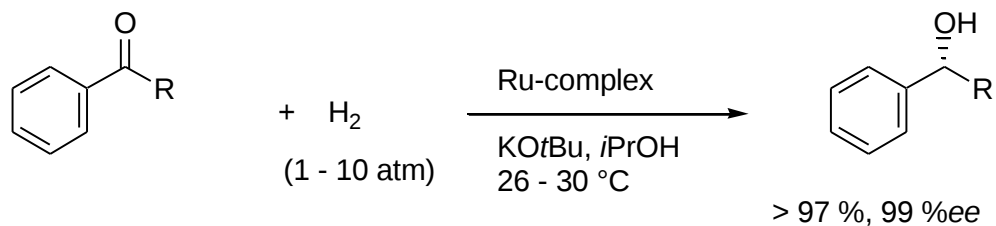


(R,R)-DPEN



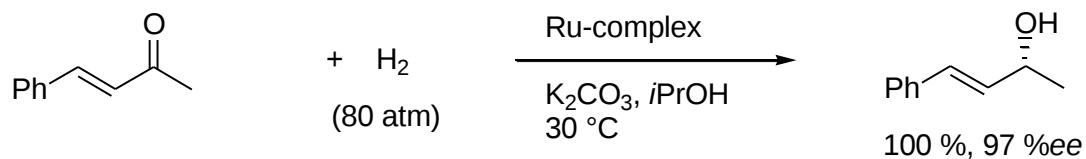
(R,R)-cyclohexanediamine

Asymmetric reduction of ketones

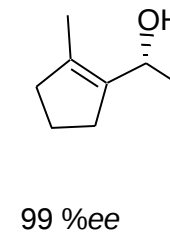
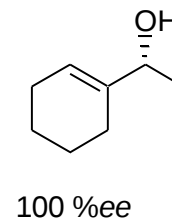
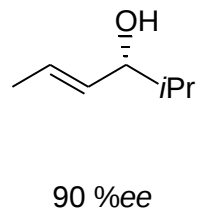
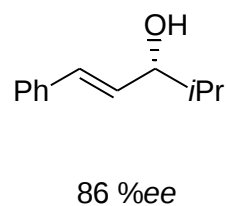
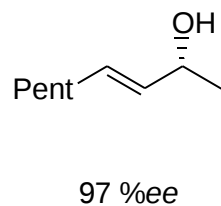


Ru : ketone = 1 : 500 to 1 : 5000

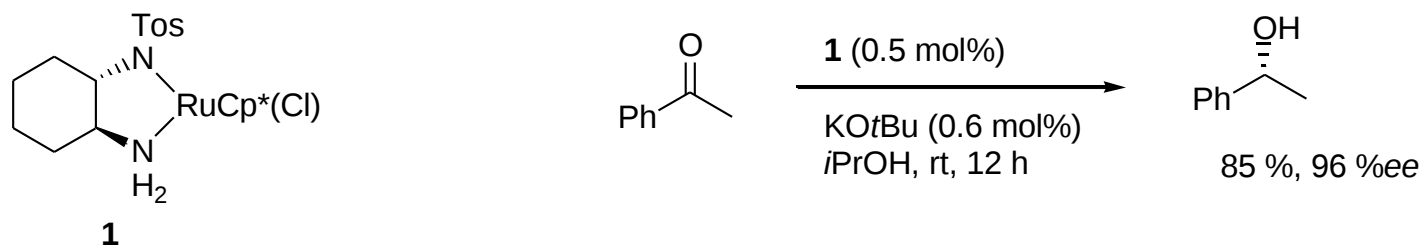
R = Me, Et, *i*Pr
R = cyclopropyl: 96 %ee



ketone : Ru : K_2CO_3 = 100 000 : 1 : 10 000
Ru-complex: RuCl_2 -(*S*)-XylBINAP-(*S*)-DAIPEN

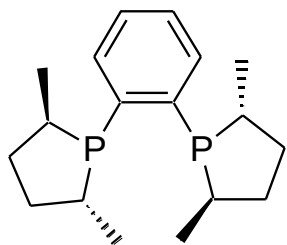


Asymmetric transfer hydrogenation

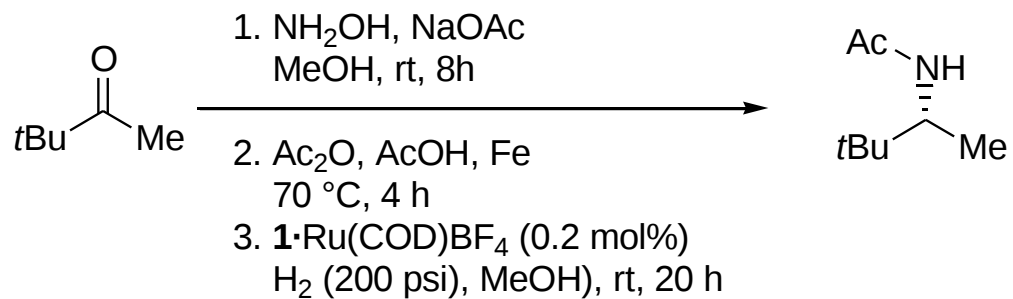


Noyori, R. *J. Org. Chem.* **1999**, 64, 2186.

Asymmetric reduction of C=N-bonds

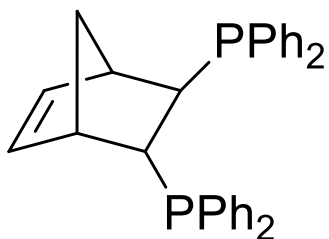
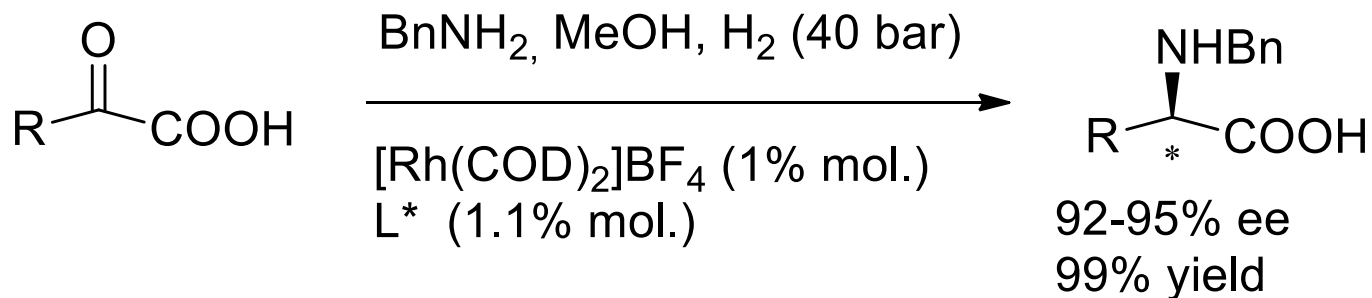


1: *R,R*-Me-DuPhos

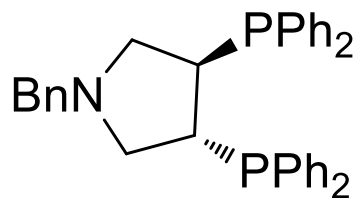


Burk, M.J. *J. Org. Chem.* **1998**, 63, 6084.

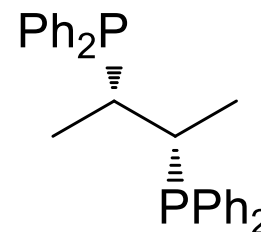
Catalytic asymmetric reductive amination



(*R,R*)-Norphos



(*R,R*)-Deguphos

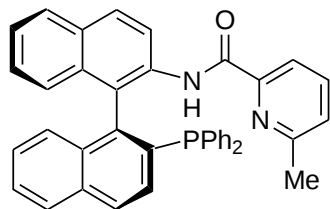
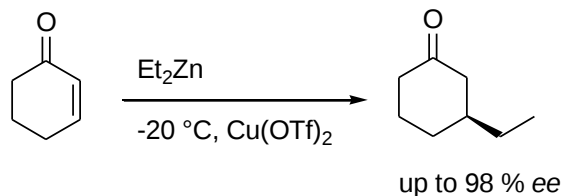


(*S,S*)-Chiraphos

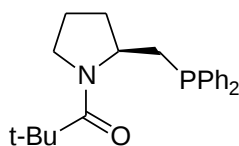
R. Kadyrov, *J. Org. Chem.*, **2003**, 68, 4067

Asymmetric C-C-bond formation

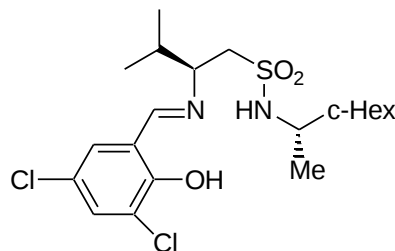
1,4-Addition using Zn-reagents



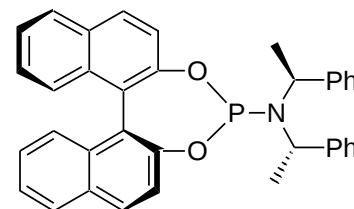
Zhang (3 mol %)



Tomioka (4.5 equiv.)



Gennari (3 mol %)



Feringa

Zhang, X. *Angew. Chem.* **1999**, *111*, 3720.

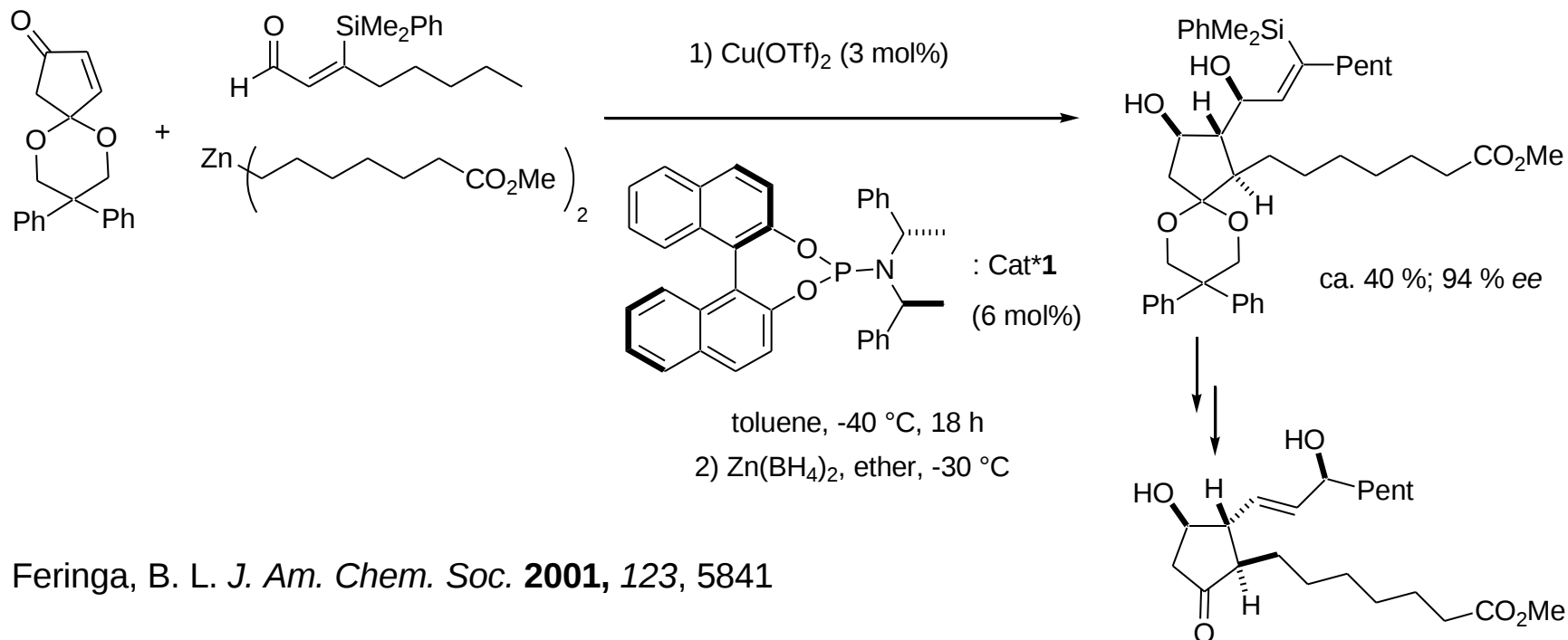
Tomioka, K. *Tetrahedron* **1999**, *55*, 3831.

Gennari, C. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 916.

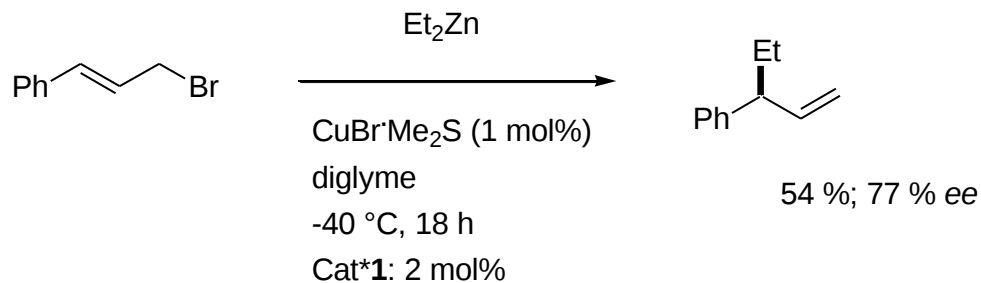
Feringa, B.L. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 916.

Review: Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346 and Krause, N. *Synthesis*, **2001**, 171

Catalytic enantioselective synthesis of prostaglandin E₁ methyl ester

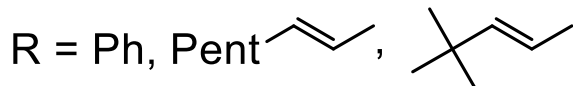
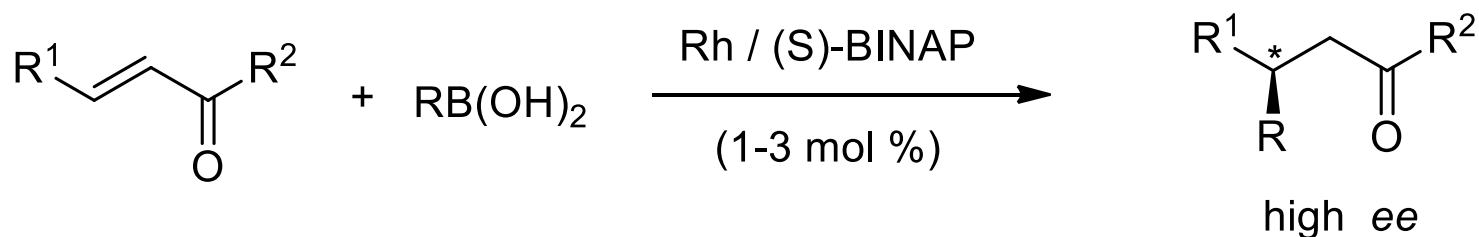
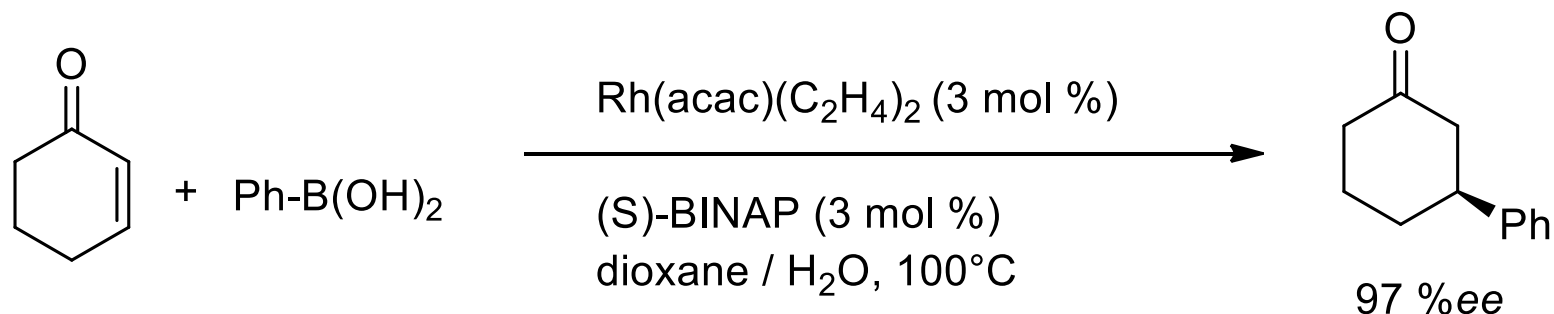


Feringa, B. L. *J. Am. Chem. Soc.* **2001**, 123, 5841



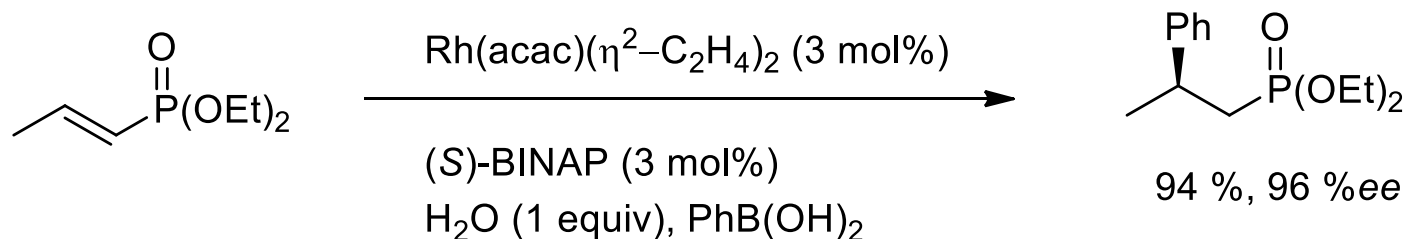
Feringa, B. L. *Org. Lett.* **2001**, 3, 1169

Asymmetric conjugated additions



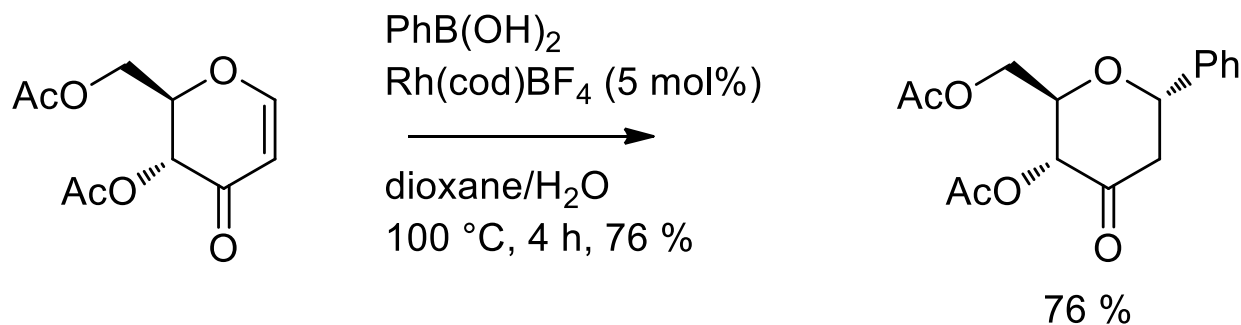
T. Hayashi *J. Am. Chem. Soc.* **1998**, 120, 5597; **2002**, 124, 5052;
 M. T. Reetz, *Org. Lett.* **2002**, 3, 4083

Hayashi-Michael-addition



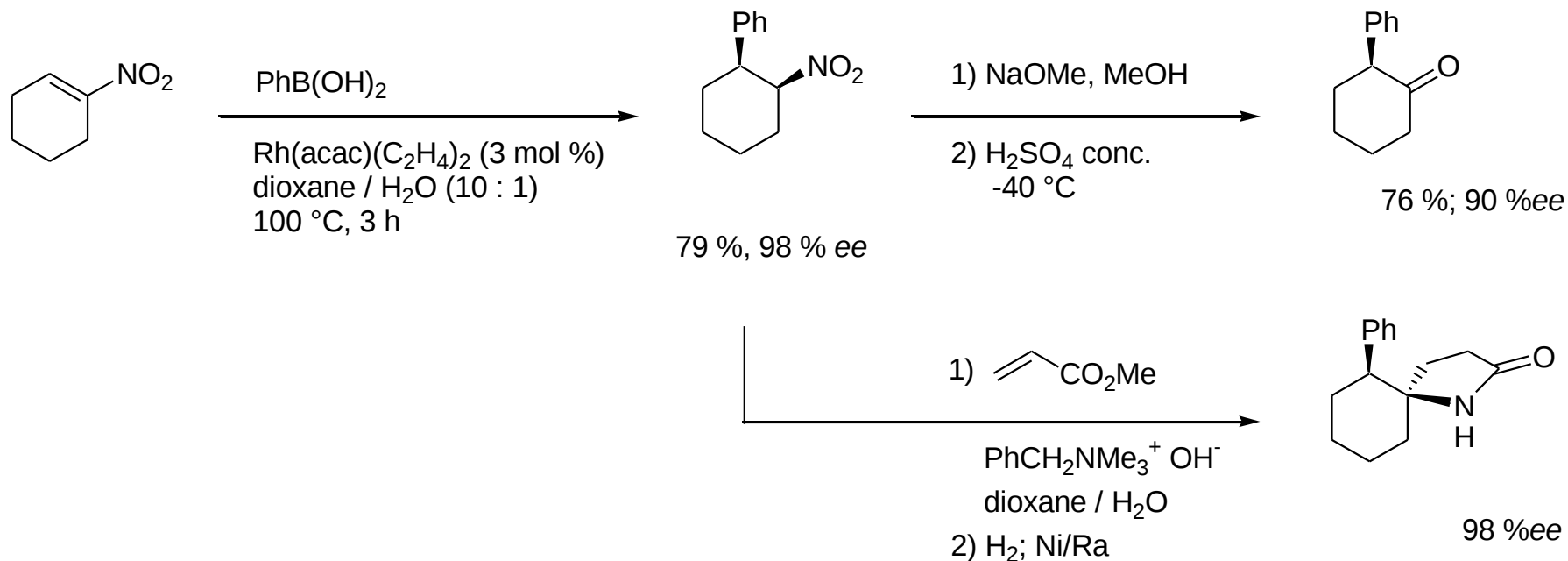
T. Hayashi, *J. Am. Chem. Soc.* **1999**, 121, 11591.

For a review on the Hayashi reaction :T. Hayashi, *Synlett*, 2001, 879



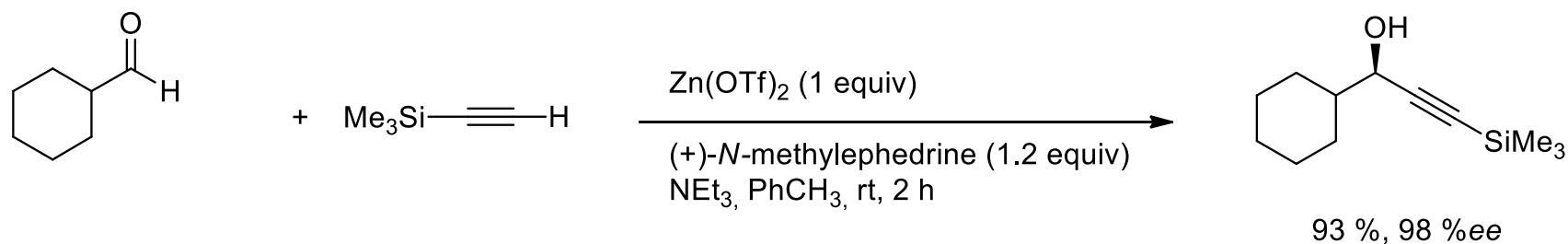
S. P. Maddaford, *Org. Lett.* **2001**, 3, 2571

Rh-catalyzed asymmetric conjugate addition of organoboronic acids to nitroalkenes



Hayashi, T. *J. Am. Chem. Soc.*, **2000**, *122*, 10716

Zinc(II) mediated enantioselective synthesis of propargylic alcohols

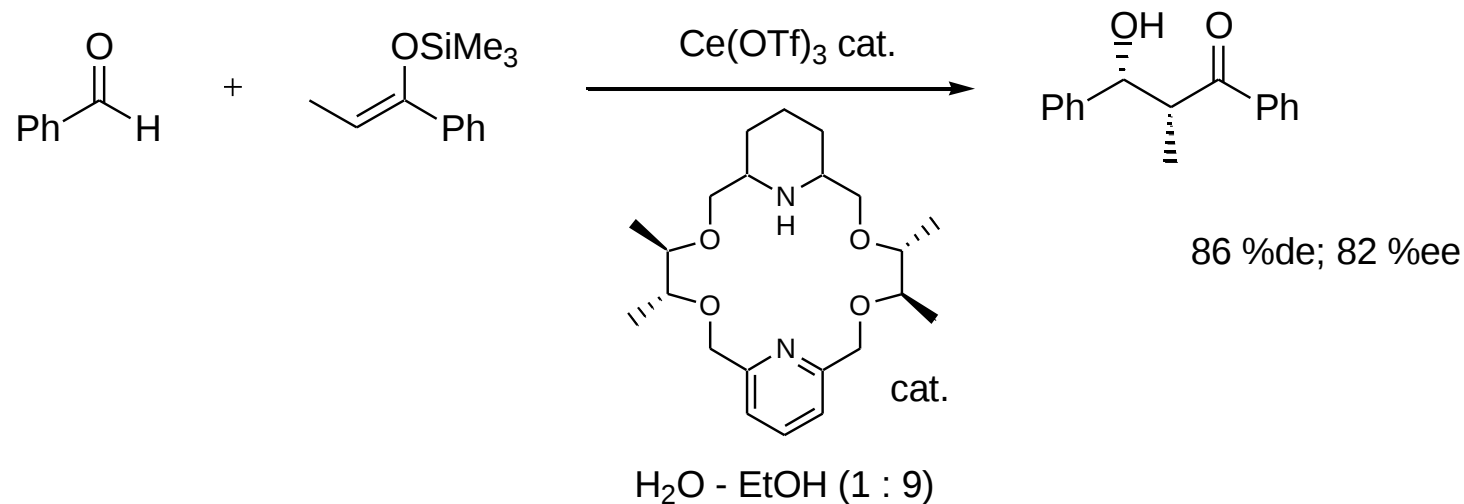


E. M. Carreira, *J. Am. Chem. Soc.* **2000**, 122, 1806.

E. M. Carreira, *Org. Lett.* **2000**, 2, 4233; **2001**, 3, 3017

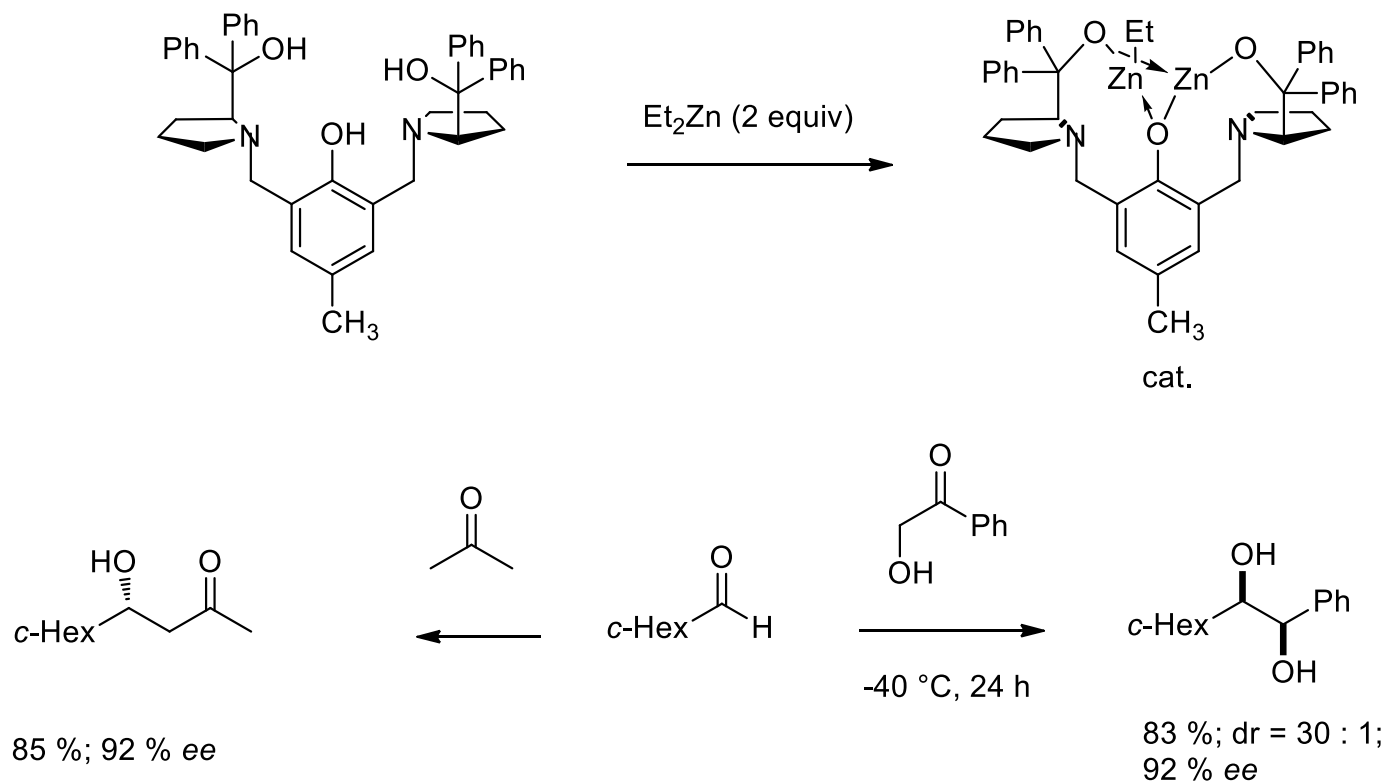
see also *Org. Lett.* **2002**, 4, 1855

Lanthanide trifluoromethanesulfonate - catalyzed asymmetric aldol reaction in water



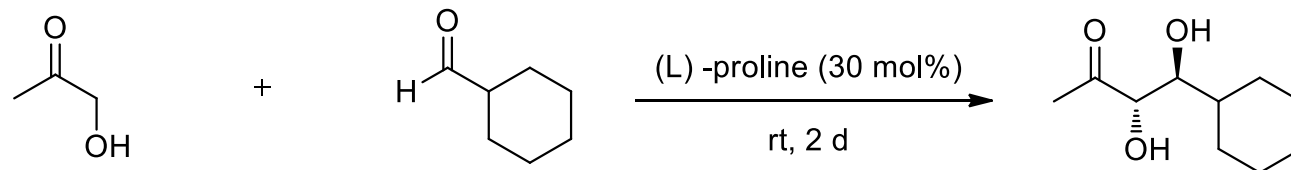
Kobayashi, S. *Org. Lett.* **2001**, 3, 165

Asymmetric aldol reaction via a dinuclear zinc catalyst

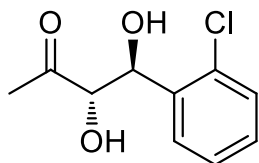


B. M. Trost, *J. Am. Chem. Soc.* **2001**, 123, 3367; *Org. Lett.* **2001**, 3, 2497

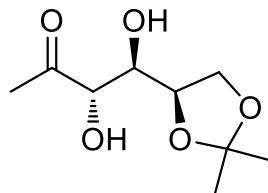
Catalytic synthesis of 1,2-diols mediated by (L)-proline



60 %; diastereoselect. > 20 : 1
enantioselect. > 100 : 1



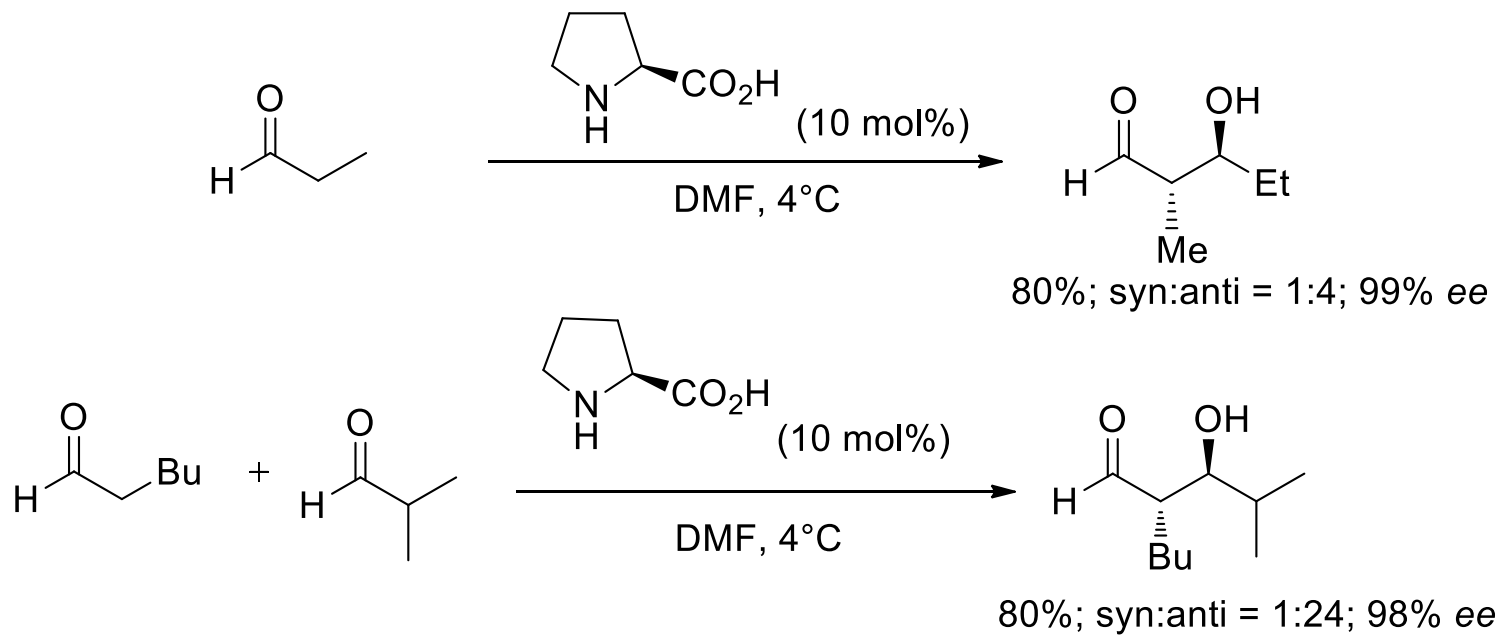
67 %ee
d.r. = 1.5 : 1



97 %ee
d.r. = 2 : 1

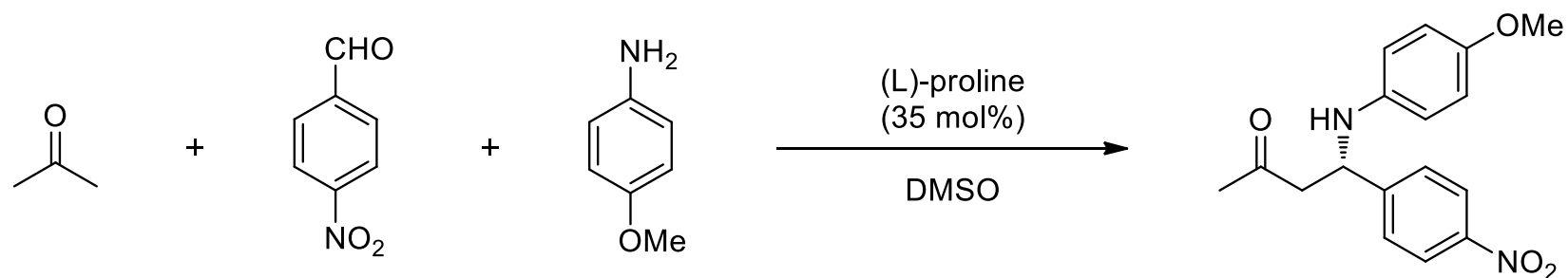
B. List, *J. Am. Chem. Soc.* **2000**, 122, 7386; *Org. Lett.* **2001**, 3, 573
For a review, see: B. List, *Synlett* **2001**, 1663

Enantioselective cross-aldol reaction of aldehydes



D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 6798

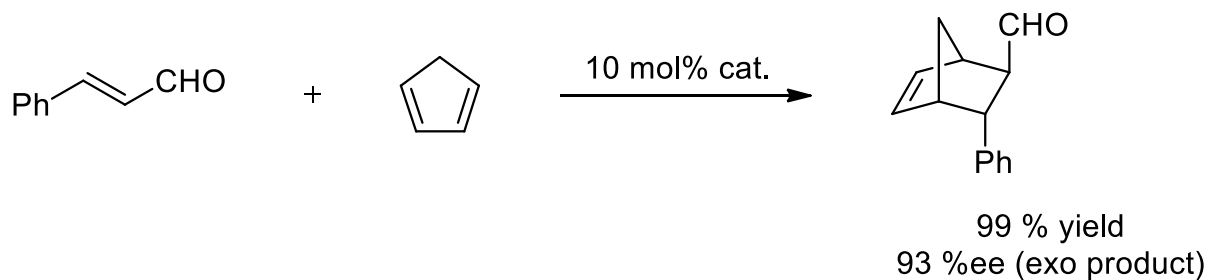
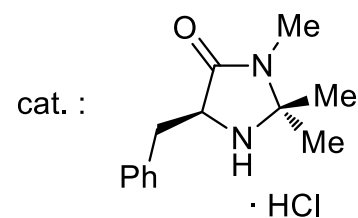
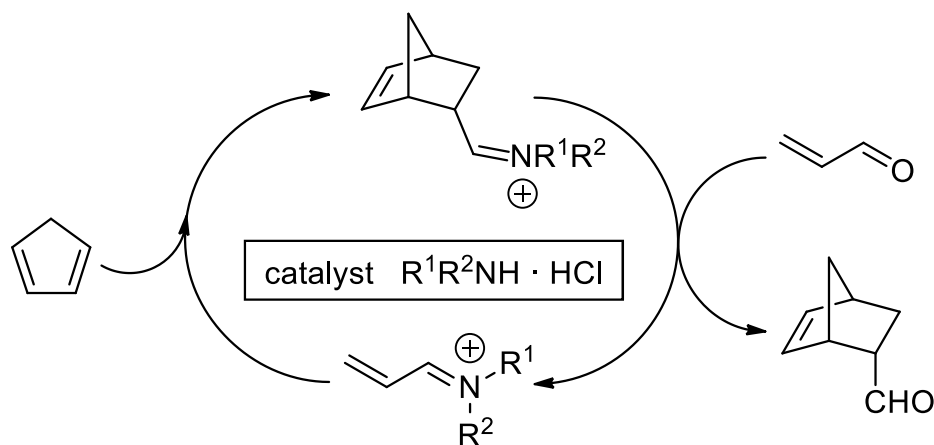
Catalytic asymmetric Mannich reaction mediated by (L)-proline



50 %; 94 %ee

B. List *J. Am. Chem. Soc.* **2000**, 122, 9336; **2002**, 124, 827

Organocatalytic Diels - Alder reaction

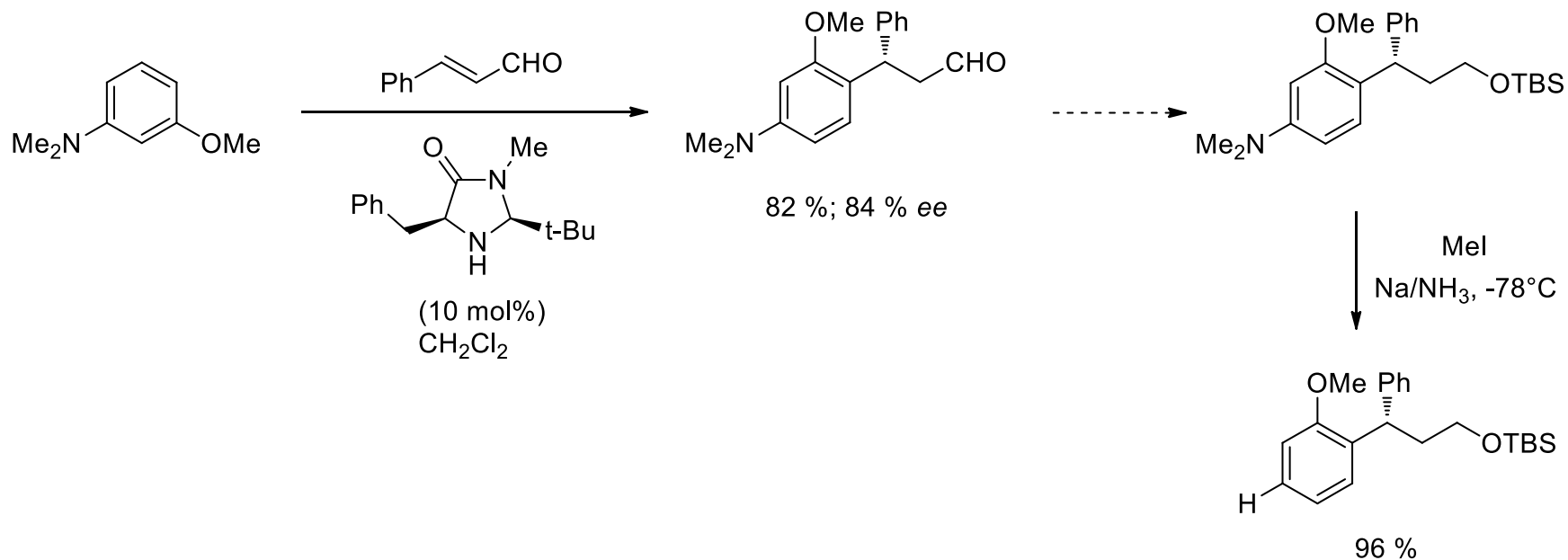
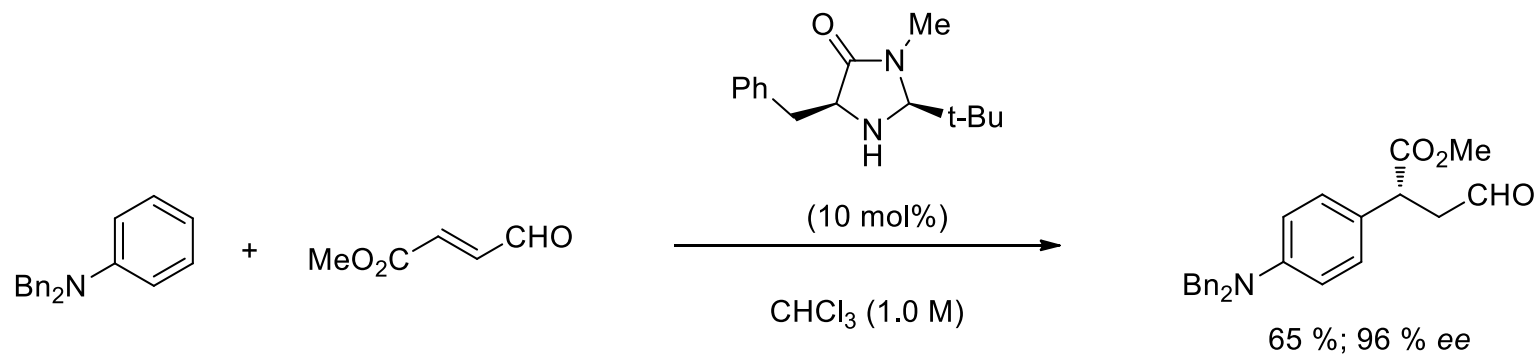


endo : exo = 1.3:1

D.W.C. McMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243.

For a review on organocatalysis : D. I. Dalgo, *Angew. Chem. Int. Ed.* **2001**, 40, 3726

Organocatalytic alkylation of methyl 4-oxobutenoate



D. W. C. McMillan, *J. Am. Chem. Soc.* **2002**, 124, 7894