Stereochemistry and stereocontrolled synthesis (OC 8)

A lecture from Prof. Paul Knochel,

Ludwig-Maximilians-Universität München

WS 2017-18

Wichtig!

- Klausur Stereochemistry

06. Februar 2018

8:00 – 10:00

Willstätter-HS

- Nachholklausur Stereochemistry

12. April 2018

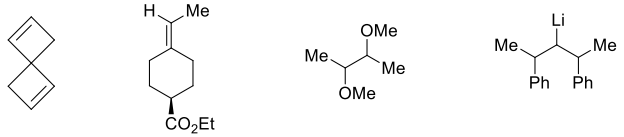
08:00 – 10:00

Wieland-HS

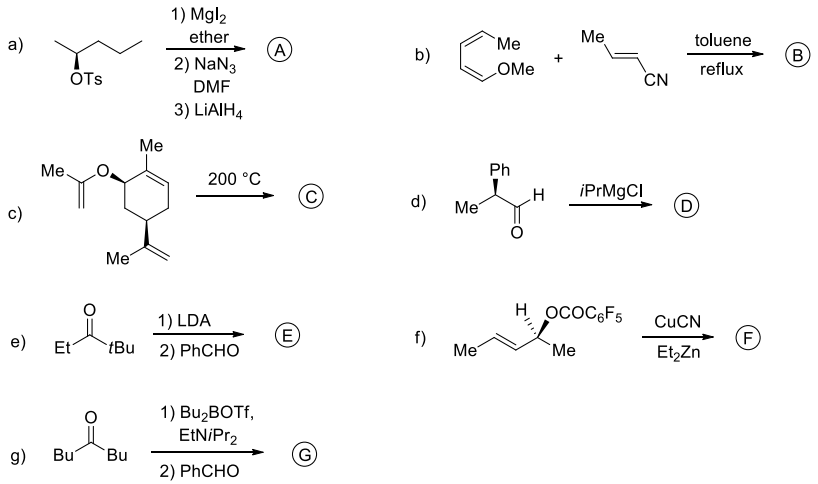
Problem set part I

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

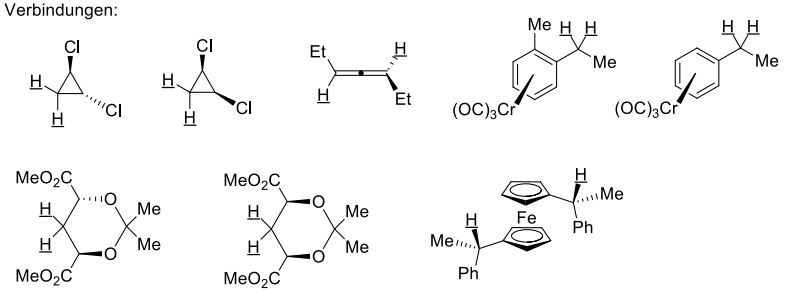
1) Geben Sie die Anzahl von Stereoisomeren sowie ihre stereochemische Bezeichnung (Enantiomer, Diasteroisomer) der folgenden Verbindungen:



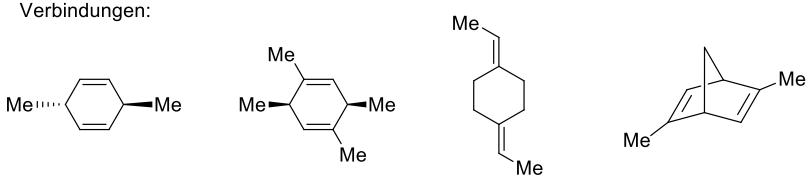
2) Geben Sie das Produkt der folgenden Umsetzungen:



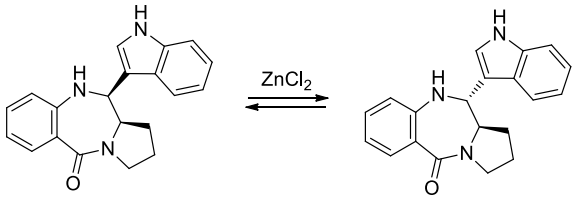
3) Klassifizieren Sie die markierten prochiralen Protonen (homotop, enantiotop, diastereotop) der folgenden Verbindungen:



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



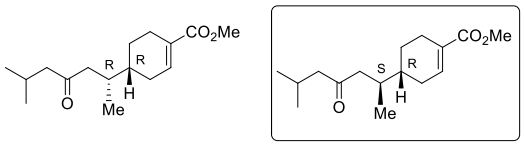
5) Durch Zugabe von $ZnCl_2$ wird das hier vorliegende Molekül epimerisiert, d. h. es entstehen zwei Diastereoisomere. Geben Sie einen möglichen Mechanismus für die Epimerisierung an:



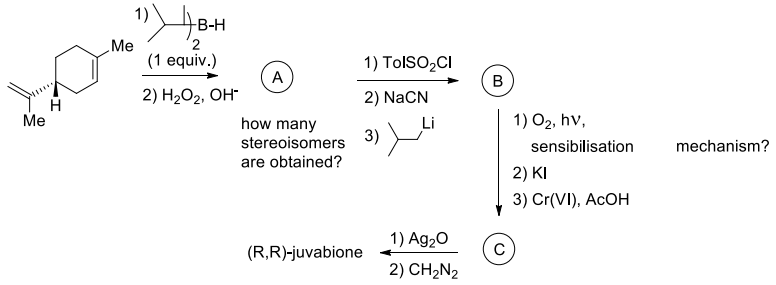
Problem set part II

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

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

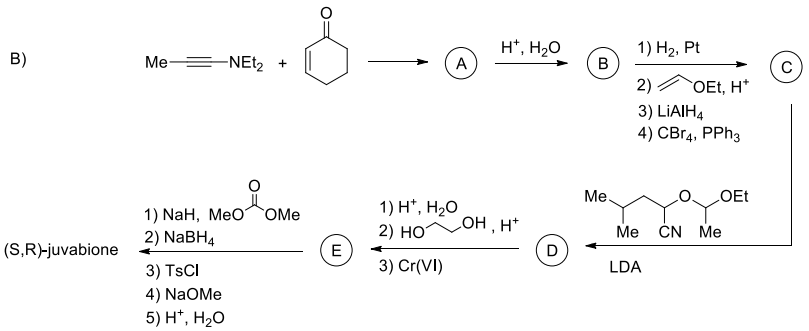


A)



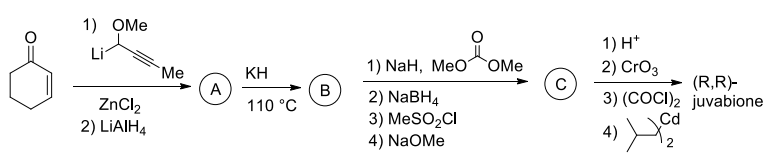
G. Saucy, *J. Am. Chem. Soc*. **1970**, *92*, 336

B)



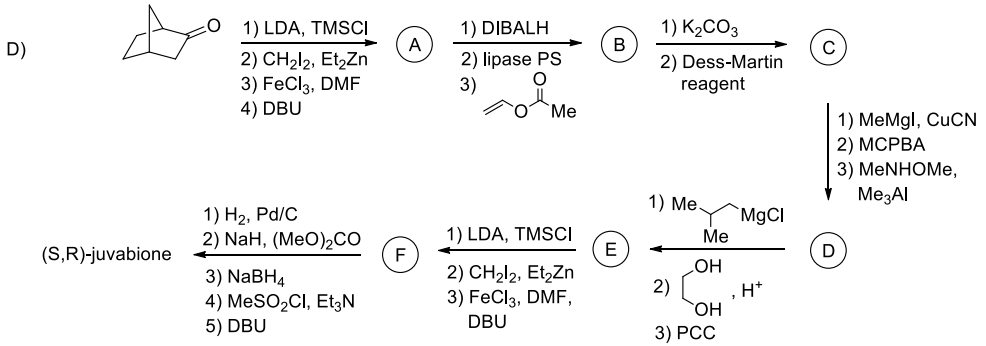
J. Ficini, *J. Am. Chem. Soc*. **1974**, *96*, 1213

C)



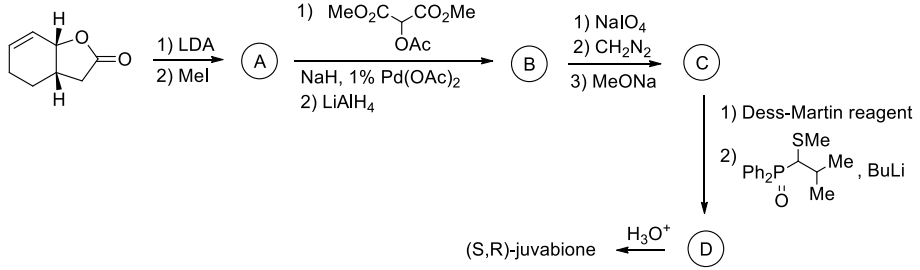
D. A. Evans, *J. Am. Chem. Soc*. **1980**, *102*, 774

D)



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

E)

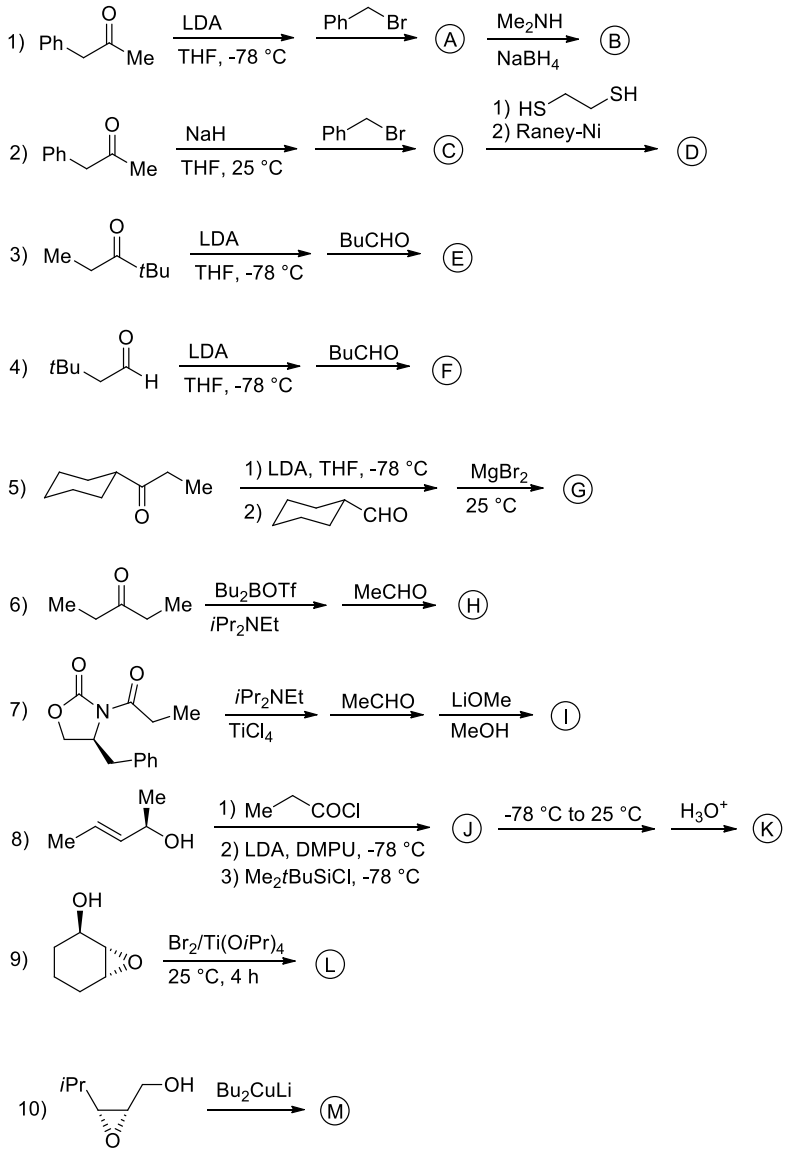


G. Helmchen, *J. Org. Chem.* **2000**, *65*, 5072

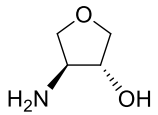
Problem set part III

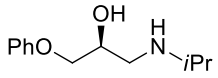
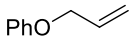
First Problem Set for OC I part III
Prof. Paul Knochel

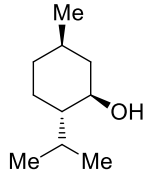
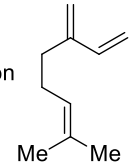
1) Geben Sie das Produkt der folgenden Reaktionen:

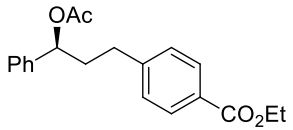
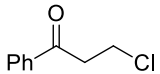
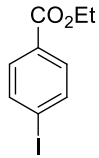


2) Wie können Sie folgende chirale Verbindungen herstellen?

a)  ausgehend von 

b)  ausgehend von  und $iPrNH_2$

c)  ausgehend von 
Myrcen

d)  ausgehend von  und 

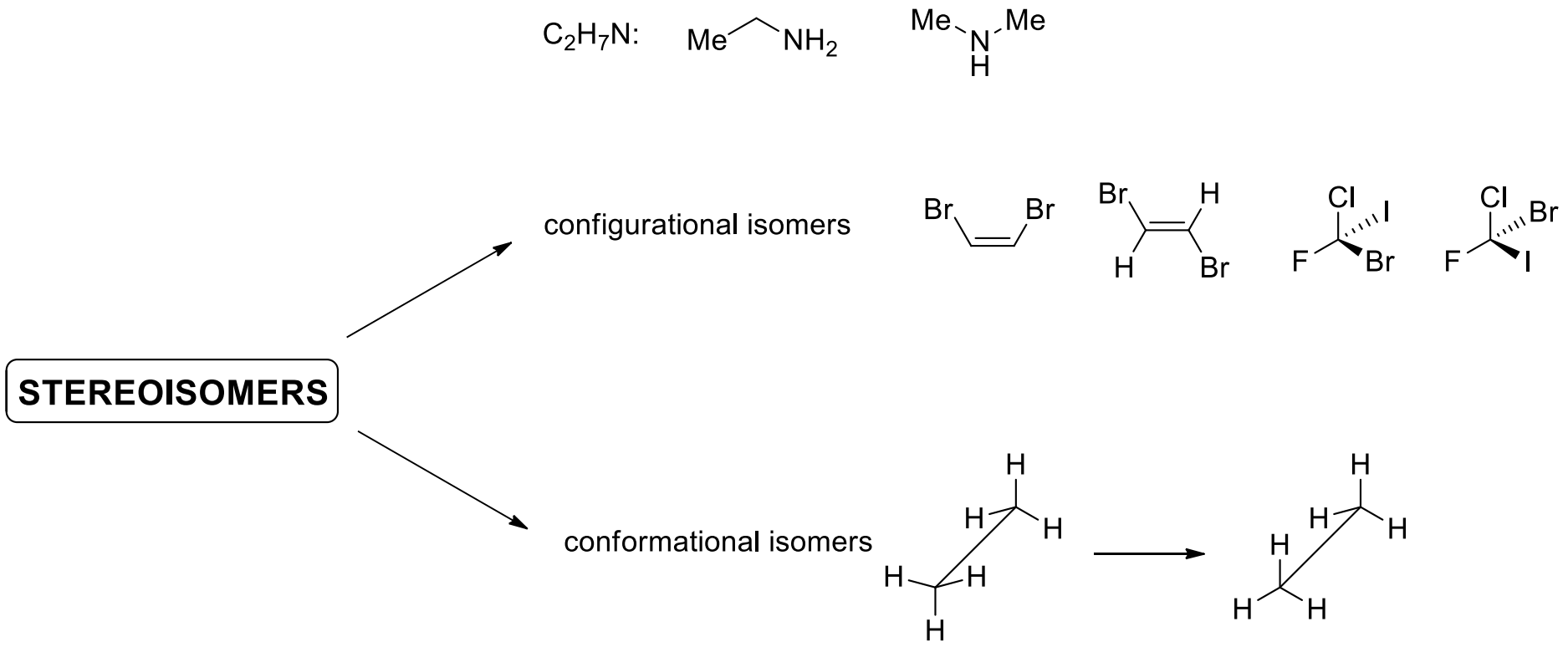
Recommended Literature

- 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.

Stereochemical principles - introduction and definitions

- Isomers are molecules having the same composition

- Structural isomers have different connectivities:

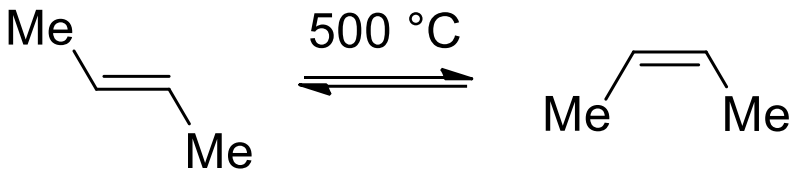


Classification of stereoisomers

Enantiomers are two stereoisomers which are mirror images

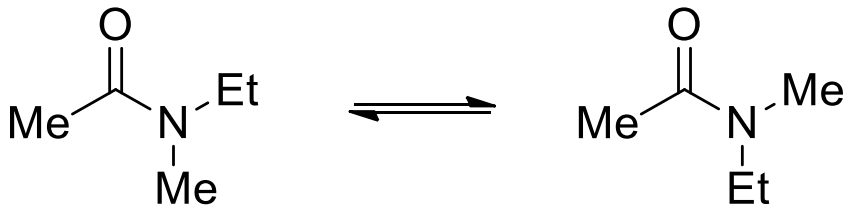
Diastereomers are stereoisomers which are not enantiomers

Configuration isomers:



ΔG = 1 kcal/mol ΔG^* = 40 kcal/mol

Conformation isomers:

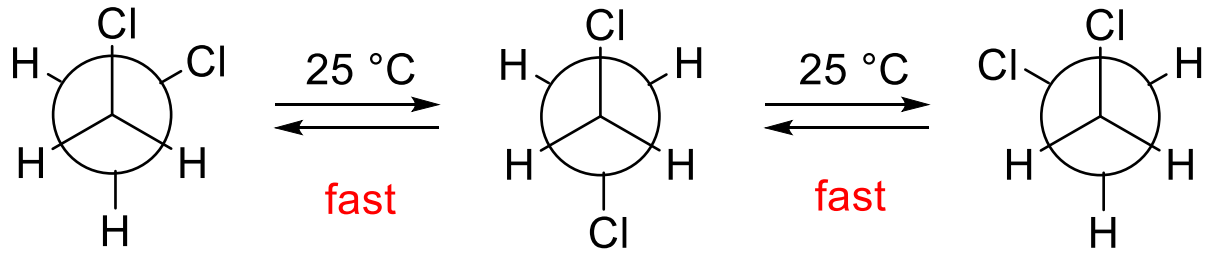


ΔG^* = 18 kcal/mol
therefore these 2 amides are conformers

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

Introduction: classification of stereoisomers

- Conformation isomers:

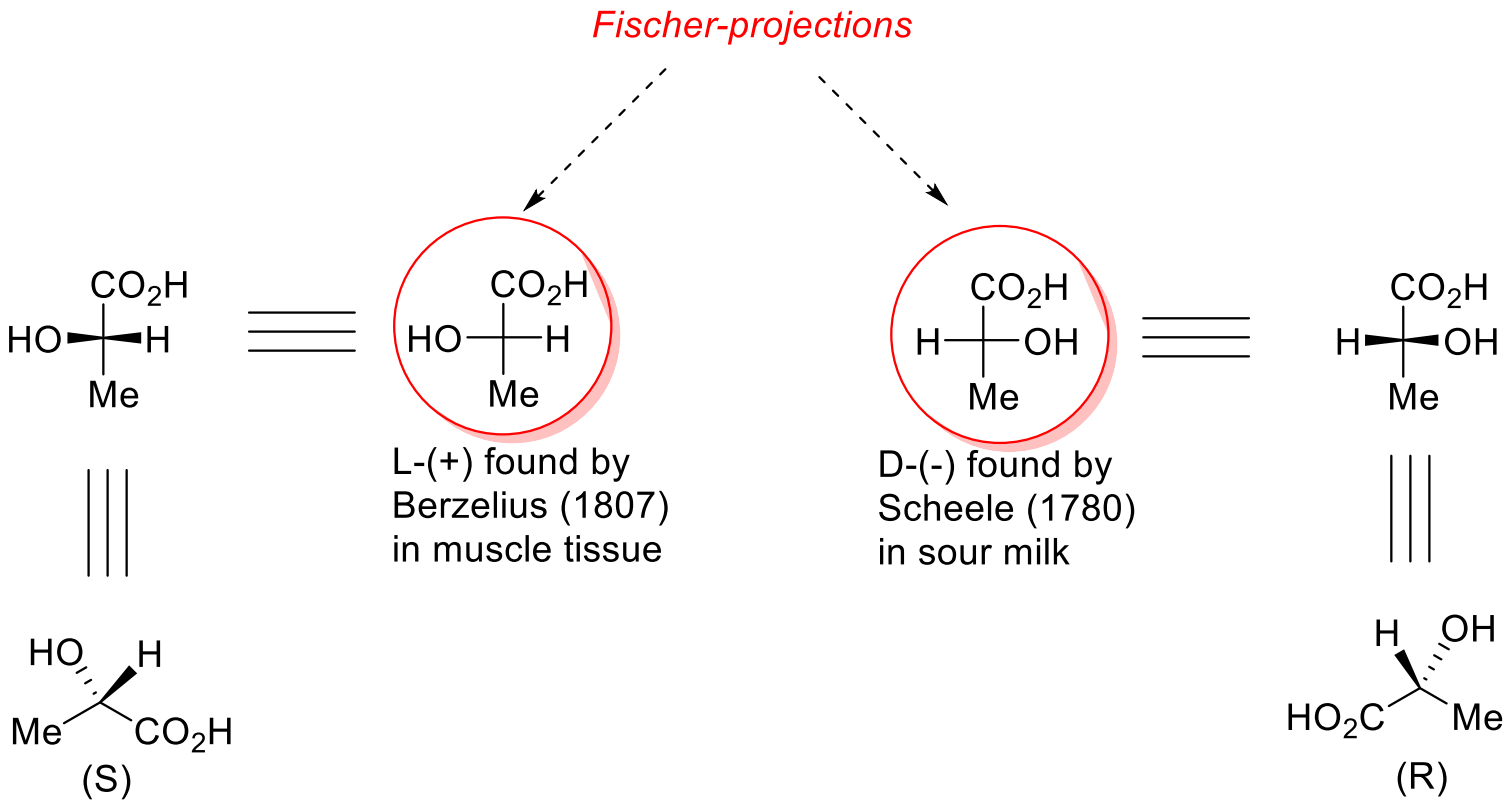


Δ E* = 3-5 Kcal/mol

All processes having an energetic barrier (activation energy Δ E*) 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 Csp^3 carbon centers.

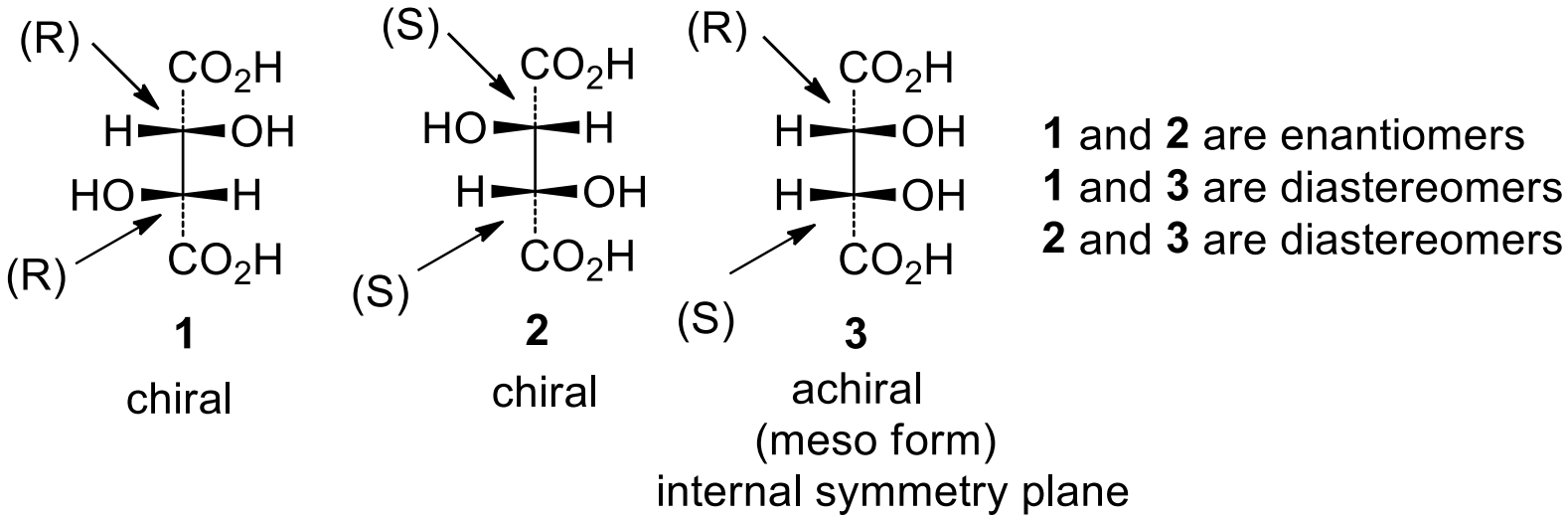
Definitions

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)

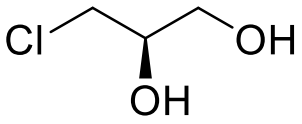
Tartaric acid exists only as 3 different stereoisomers:



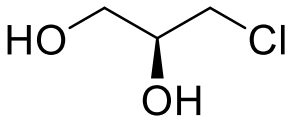
Properties of enantiomers

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

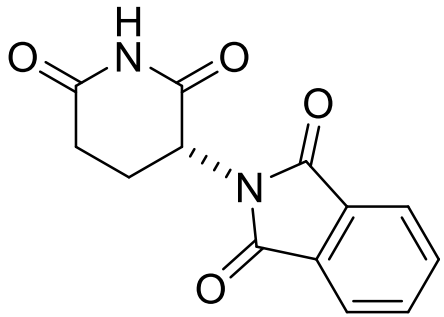
Importantly, the biological properties of enantiomers are different!



poison



useful pharmaceutic

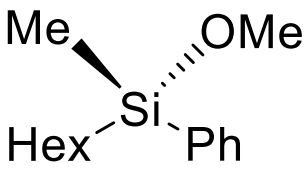


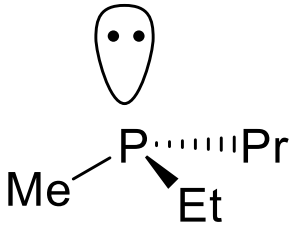
potent hypnotic

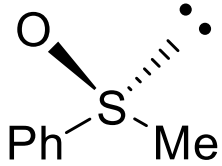
the enantiomer is teratogenic!

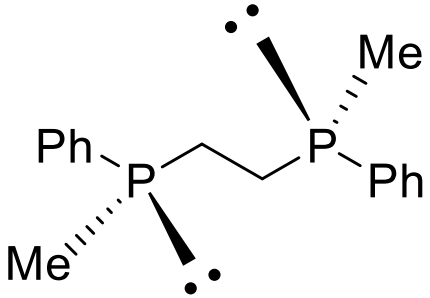
95% of all drugs are chiral, therefore the enantioselective synthesis of organic molecules is of key importance.

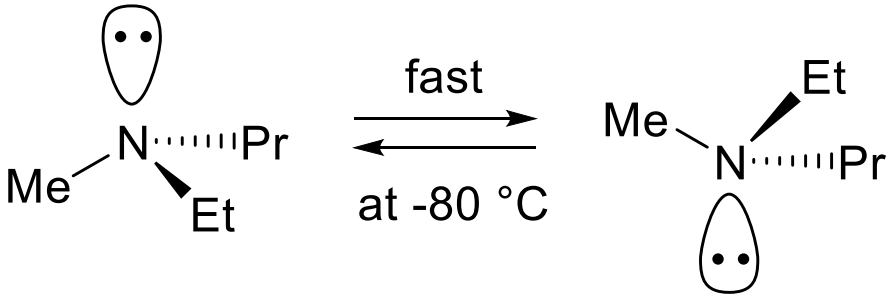
Chiral molecules not centered at carbon





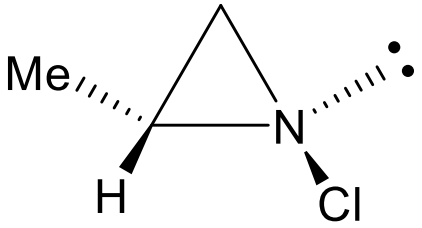






Δ E* = 5 Kcal/mol

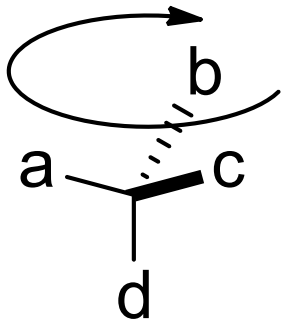
2 x 10^{11} inversions every second!



configurationally stereoisomer

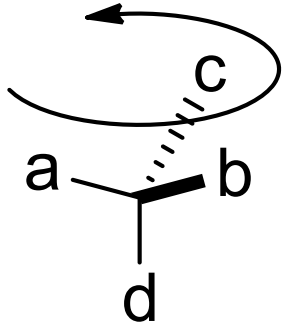
Nomenclature of stereoisomers

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



(R)

clockwise



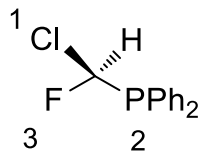
(S)

anti-clockwise

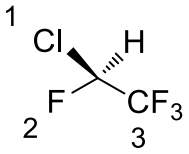
Nomenclature of stereoisomers

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

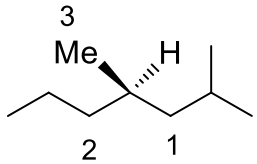
2. $CH_2Br > CH_2Cl > CH_2OH > CH_2CH_3 > CH_3$ $CH_2Br > CCl_3$!



(R)

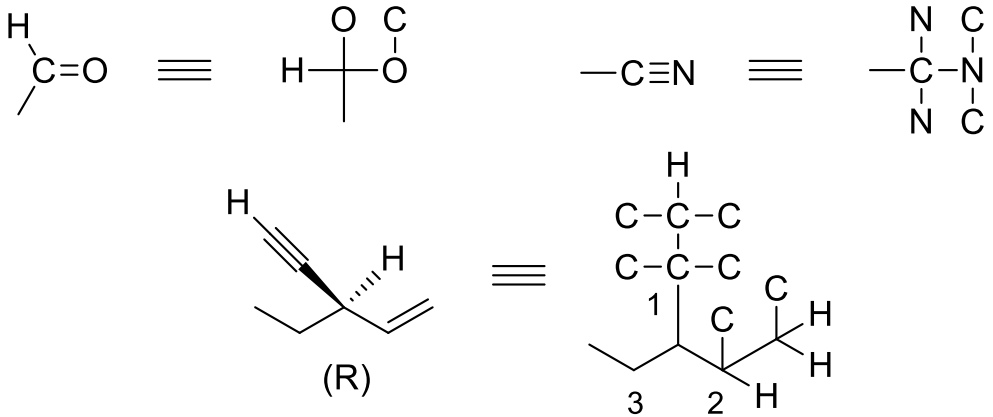


(S)



(R)

3. The case of multiple bonds



—Ph > —C(H)=CH2 —CHO > CH(CH3)OH

Nomenclature of stereoisomers

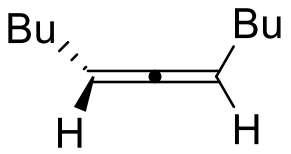
Ascending Order of Priority of Some Common Groups, According to the Sequency Rules

1. Electronic pair	21. -C≡CH	41. –$NHCH_3$
2. –H	22. –C_6H_5	42. –$NHCH_2CH_3$
3. –D	23. –$C_6H_4CH_3$-*p*	43. –$NHCOCH_3$
4. –T	24. –$C_6H_4NO_2$-*p*	44. –$NHCOC_6H_5$
5. –CH_3	25. –$C_6H_4CH_3$-*m*	45. –$N(CH_3)_3$
6. –CD_3	26. –$C_6H_4NO_2$-*m*	46. –$N^+(CH_3)_3$
7. –$CH_2CH_2CH_3$	27. -C≡C-CH_3	47. –N=O
8. –$CH_2CH_2CH_2CH_3$	28. –$C_6H_4CH_3$-*o*	48. –NO_2
9. –$CH_2CH_2CH(CH_3)_2$	29. –$C_6H_4NO_2$-*o*	49. -OH
10. –$CH_2CH(CH_3)_2$	30. –$C_6H_3(NO_2)_2$	50. -OMe
11. –$CH_2CH=CH_2$	31. -CHO	51. –$OCOCH_3$
12. –$CH_2C(CH_3)_3$	32. –$COCH_3$	52. –OSO_2CH_3
13. –$CH_2C\equiv CH$	33. –COC_6H_5	53. -F
14. –$CH_2C_6H_5$	34. –CO_2H	54. -SH
15. –$CH(CH_3)_2$	35. –CO_2CH_3	55. –SCH_3
16. –$CH=CH_2$	36. –$CO_2CH_2CH_3$	56. –$S(O)CH_3$
17. –$CH(CH_3)CH_2CH_3$	37. –$CO_2C_6H_5$	57. –SO_2CH_3
18. –C_6H_{11}-*c*	38. –$CO_2C(CH_3)_3$	58. -Cl
19. –CH=CH-CH_3	39. –NH_2	59. -Br
20. –$C(CH_3)_3$	40. –NH_3^+	60. -I

Nomenclature of stereoisomers

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

allenes:



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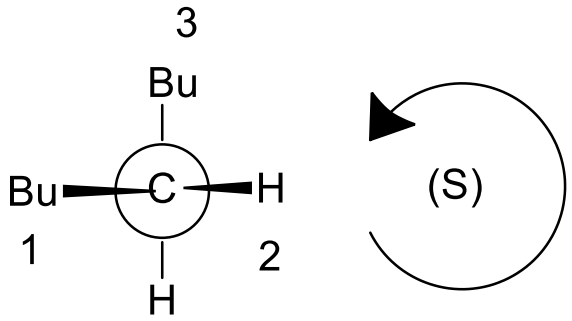

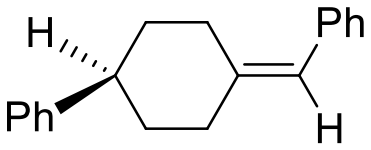

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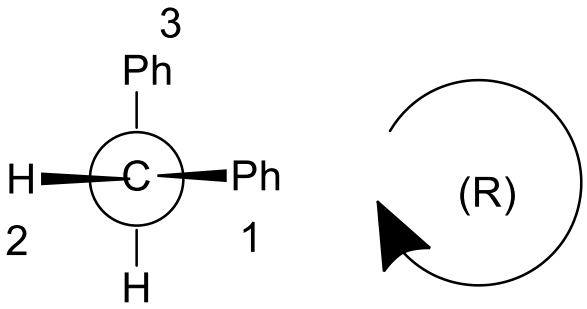

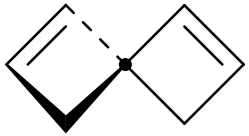

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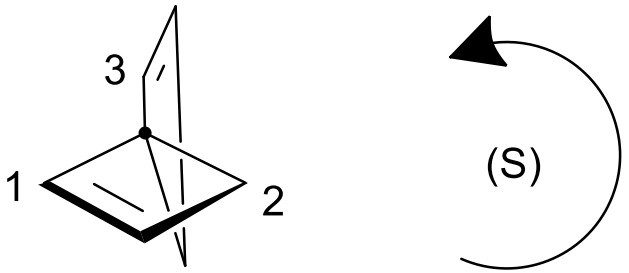
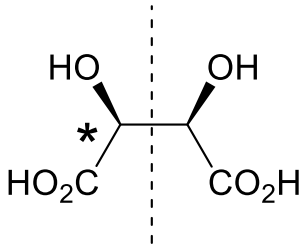


Prochirality: homotopicity, enantiotopicity, diastereotopicity

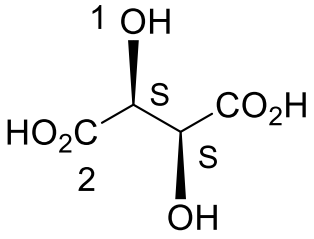
Relevance of symmetry:

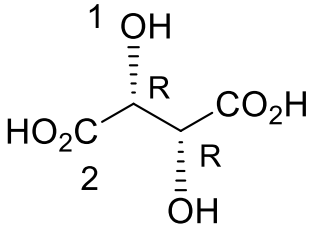


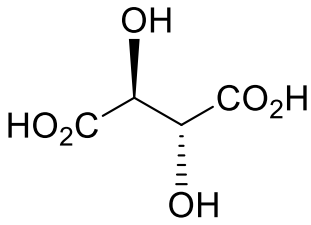
σ_h

2 stereocenters but only 3 stereoisomers

meso



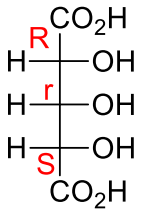




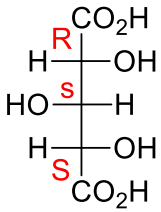
meso

Pseudo-asymmetric and chirotopic centers

Fischer-Projection

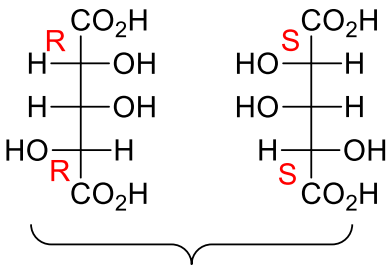


meso-1



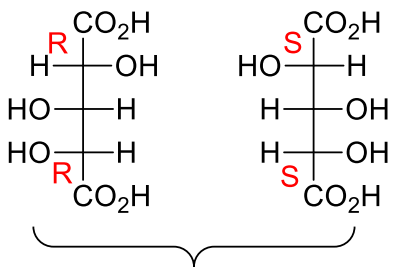
meso-2

2 diastereomeric achiral molecules with a pseudo-asymmetric center

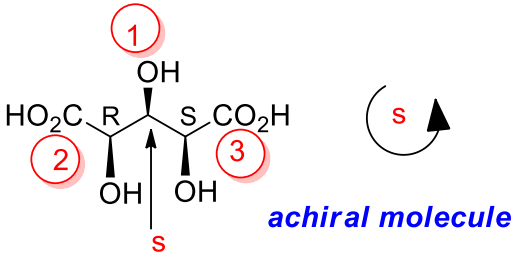


2 enantiomeric chiral molecules with a chirotopic center

identical to



chiral molecules with a chirotopic center

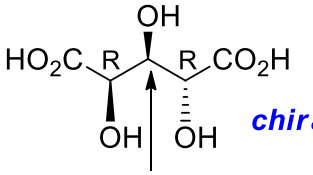


achiral molecule

a pseudo-asymmetric center

is a stereogenic center

in an achiral environment

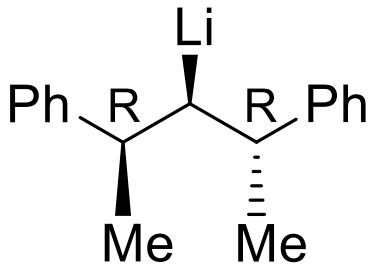


chiral molecule

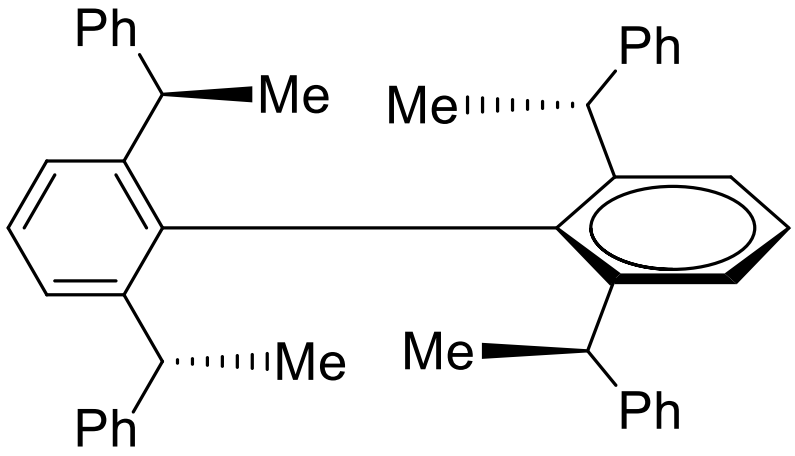
a chirotopic center is a non-stereogenic center in a chiral environment

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

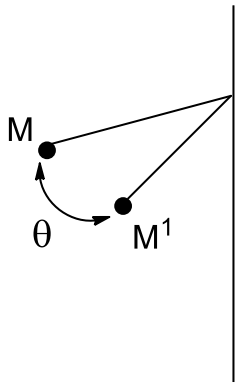


chirotopic chirality axis

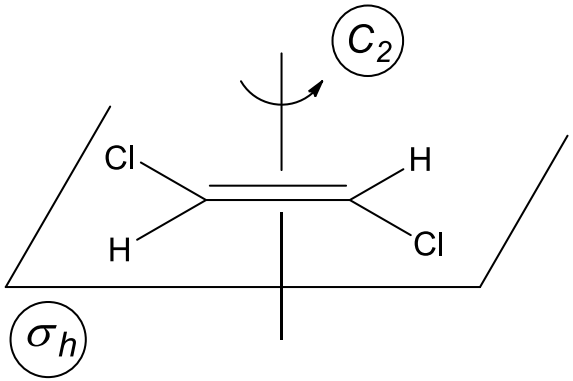
Symmetry and stereochemistry

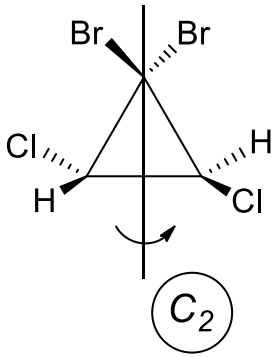
Symmetric operations:

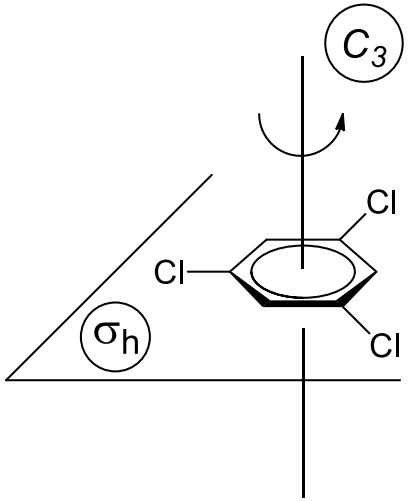
1. C_n: n-fold rotation axes: rotation by an angle 360°/n

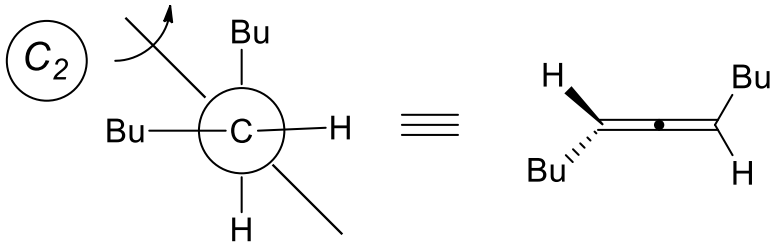


$\theta = 360/n$



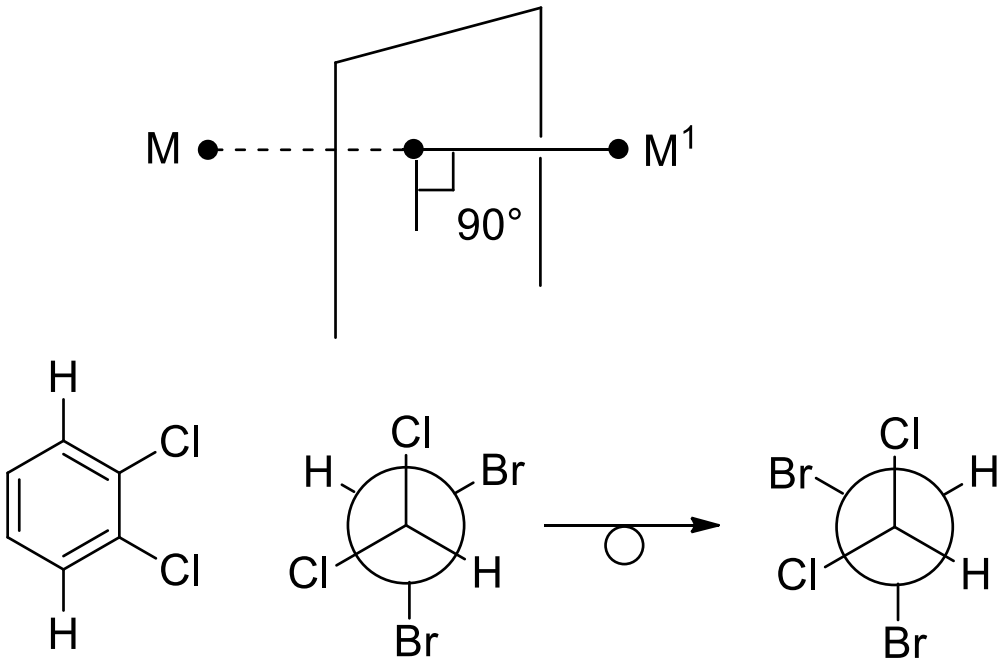






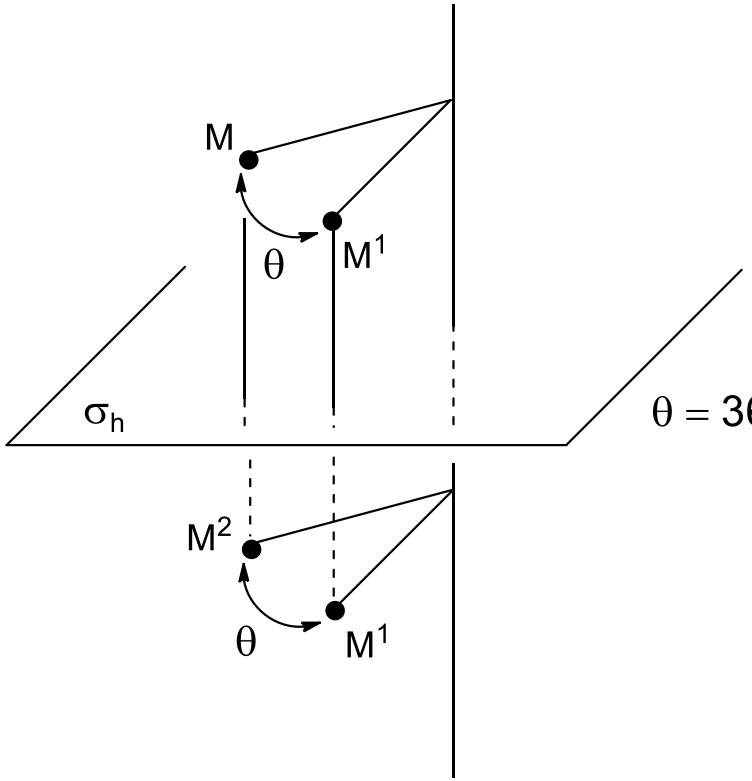
Symmetry and stereochemistry

2. σ_h: mirror plane



Symmetry and stereochemistry

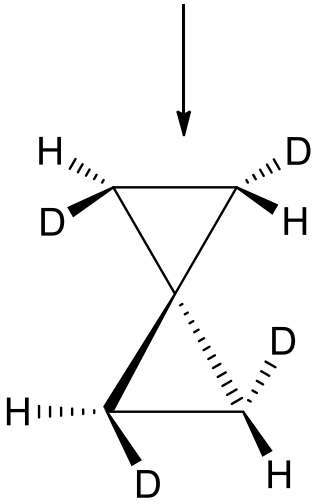
3. Rotating mirror axis

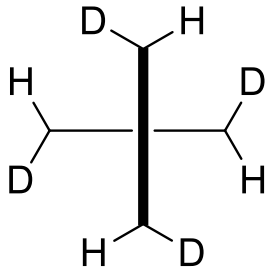


$\theta = 360/n$ $S_n = \sigma_h \times C_n$

Symmetry and stereochemistry

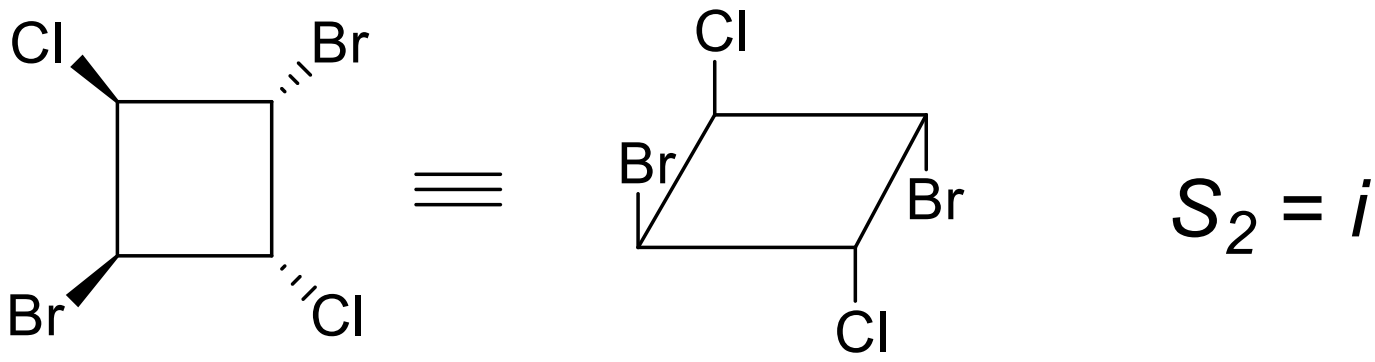
Rotating mirror axis





$S_4 = C_4 \times \sigma_h$

Symmetry and stereochemistry



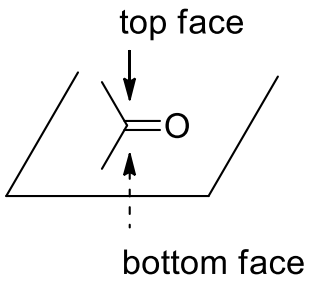
$S_2 = i$

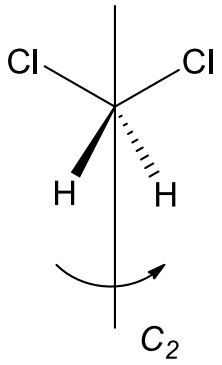
- molecules possessing C_n symmetry operations are chiral
- molecules possessing σ_h or S_n symmetry operations are achiral

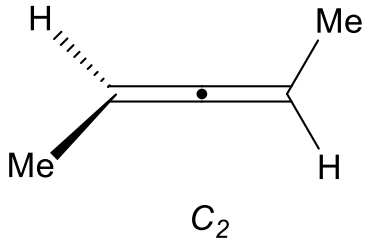
Heterotopic groups and faces (Prochirality)

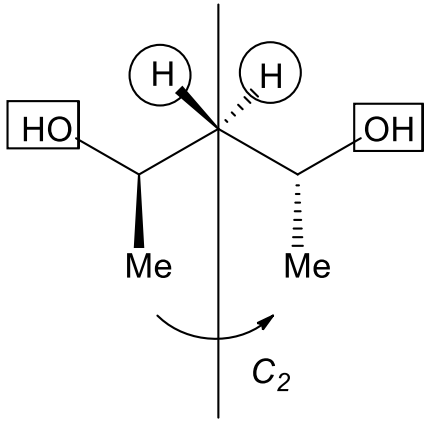
Two identical groups in one molecule can be either
homotopic, **enantiotopic** or **diastereotopic** and show the corresponding properties.

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





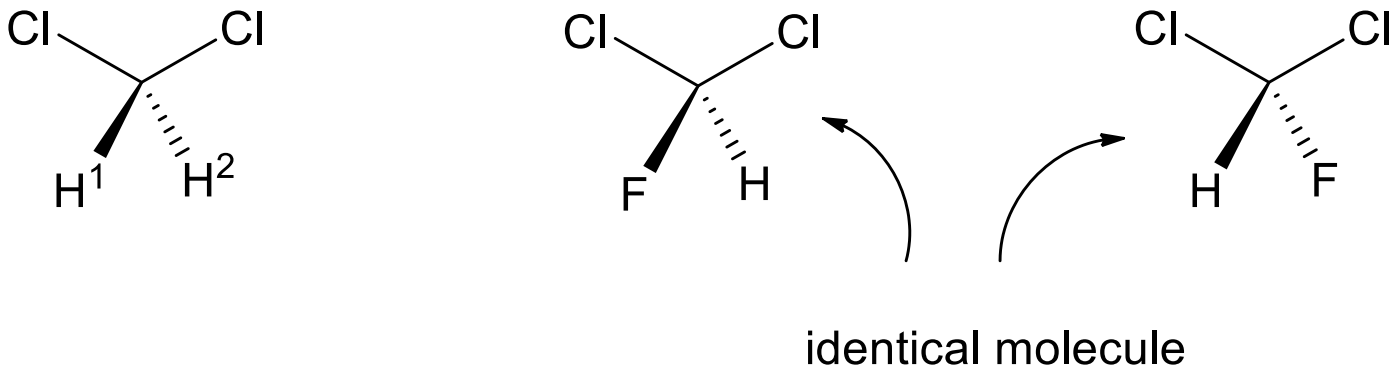




The reactivity of homotopic groups is the same towards all reagents. It is not possible to make a chemical distinction between homotopic groups.

Homotopic groups and faces

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

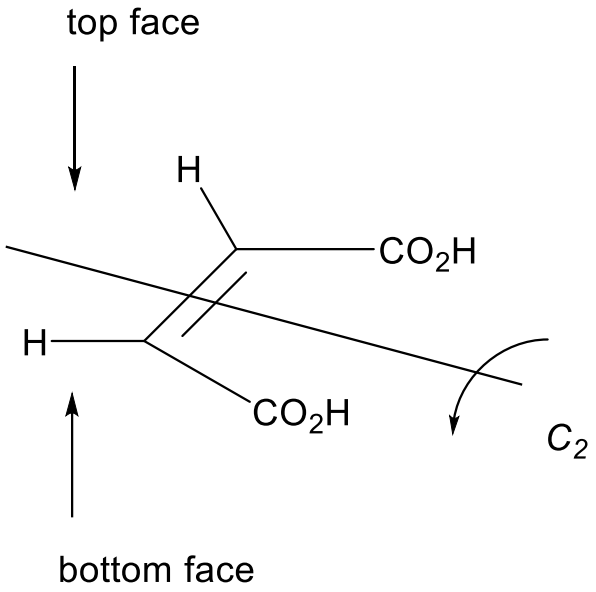


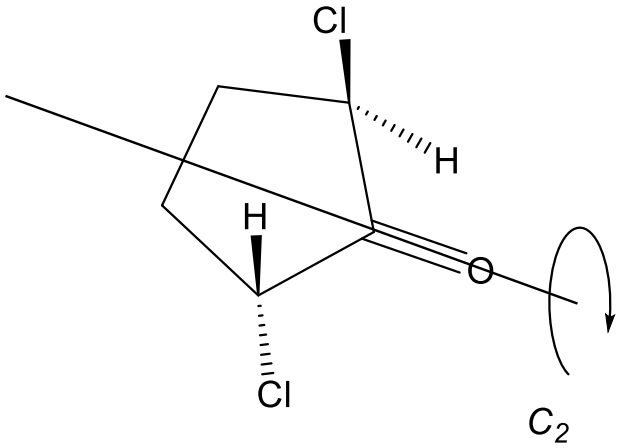
Feature: Homotopic groups and faces cannot be distinguished by any reagent.

The same chemical behaviour towards all reagents is observed.

Homotopic faces of a molecule

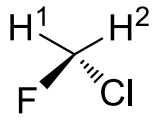
Homotopic faces: two faces are homotopic, if the plane defined by the two faces contains a C_2 axis.

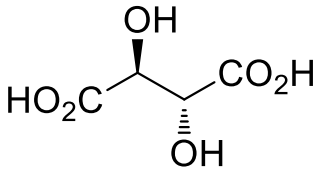


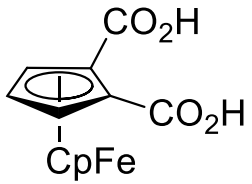


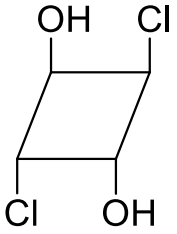
Enantiotopic groups and faces

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.

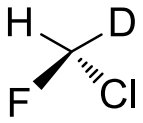




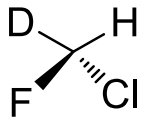




Enantiotopic groups are always found in achiral molecules.



1



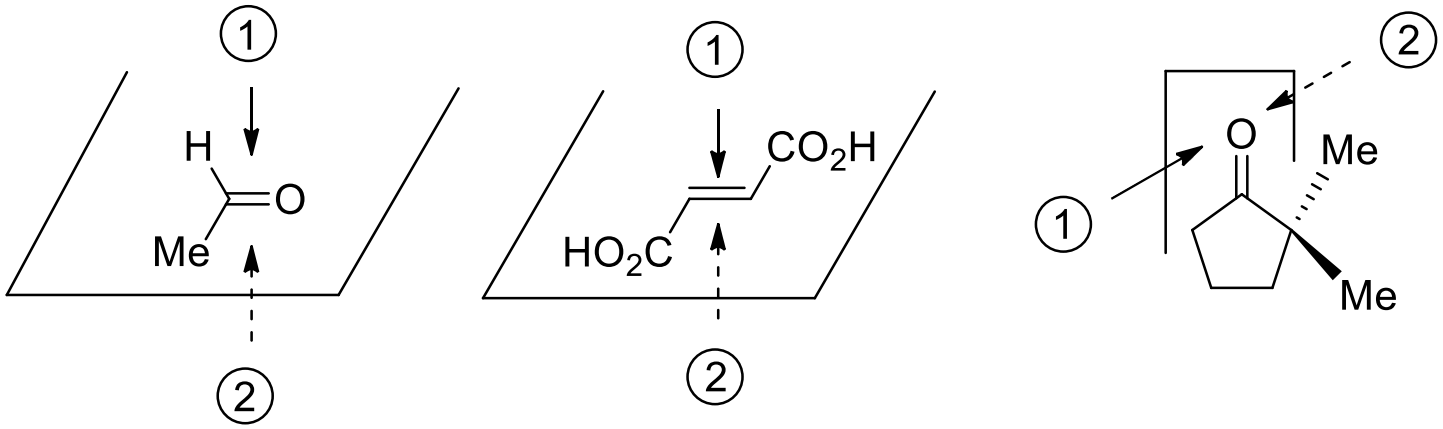
2

molecules **1** and **2** are enantiomer

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

Enantiotopic groups and faces

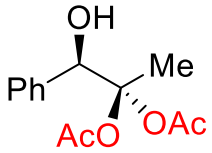
Enantiotopic faces are 2 faces that are defined by a plane of symmetry.

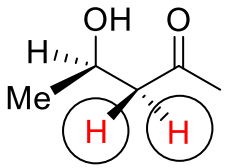


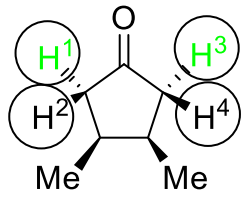
Features: Only chiral reagents can distinguish between enantiotopic groups.
Achiral reagents can not differentiate between enantiotopic groups and faces.

Diastereotopic groups and faces

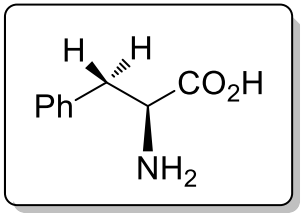
Diastereomeric groups can be transformed into one another only by the identity symmetry operation.

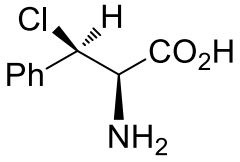


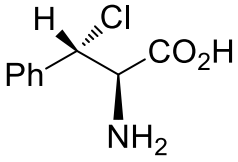




H^1 and H^3 (or H^2 and H^4) are enantiotopic groups
H^1 and H^2 (or H^3 and H^4) are diastereotopic groups







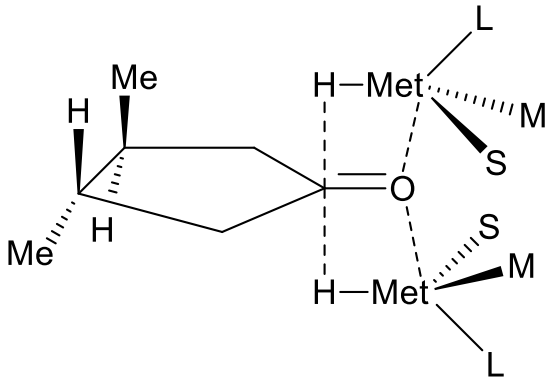
Substitution test:
provides two diastereoisomers.

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

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

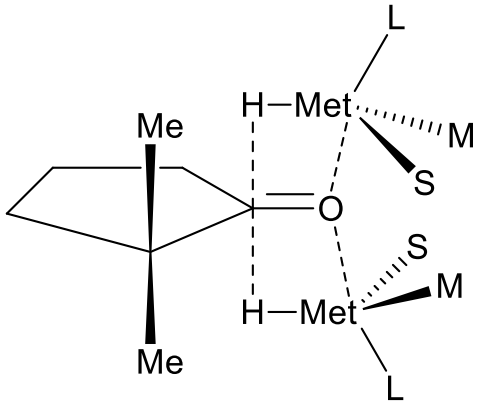
Additions to homotopic and enantiotopic faces

molecule with homotopic faces



identical transition states
the same activation energy

molecule with enantiotopic faces



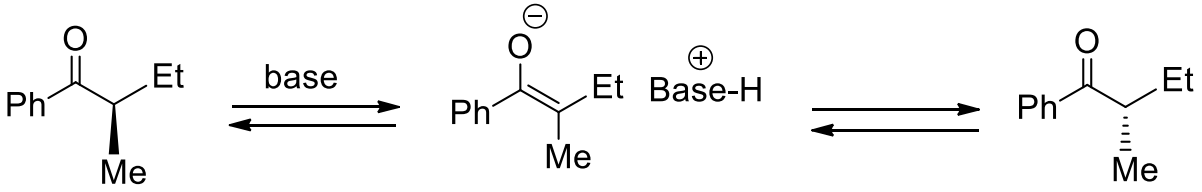
diastereomeric transition states
leads to activation energy

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

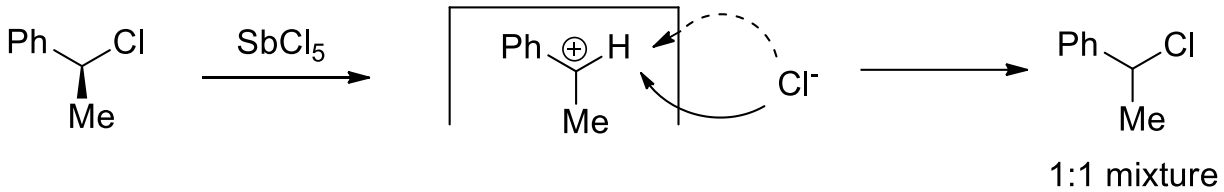
Enantiomers and racemates

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

racemization under basic conditions

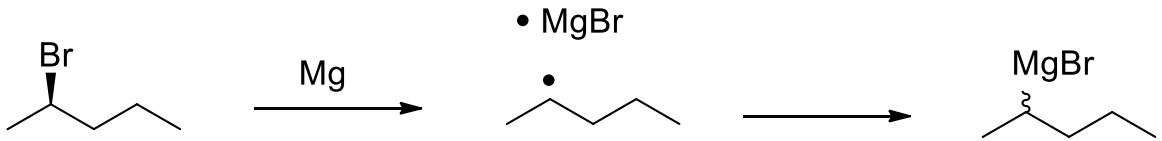


racemization under acidic conditions:



1:1 mixture

racemization under radical conditions:

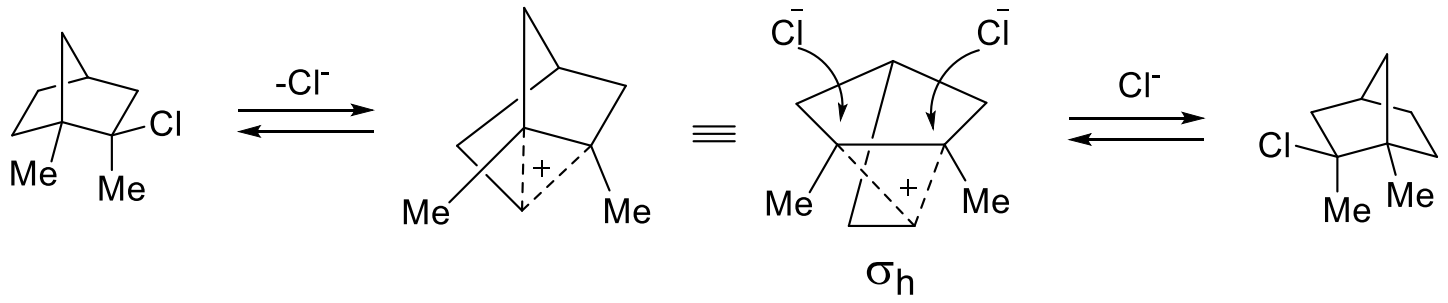


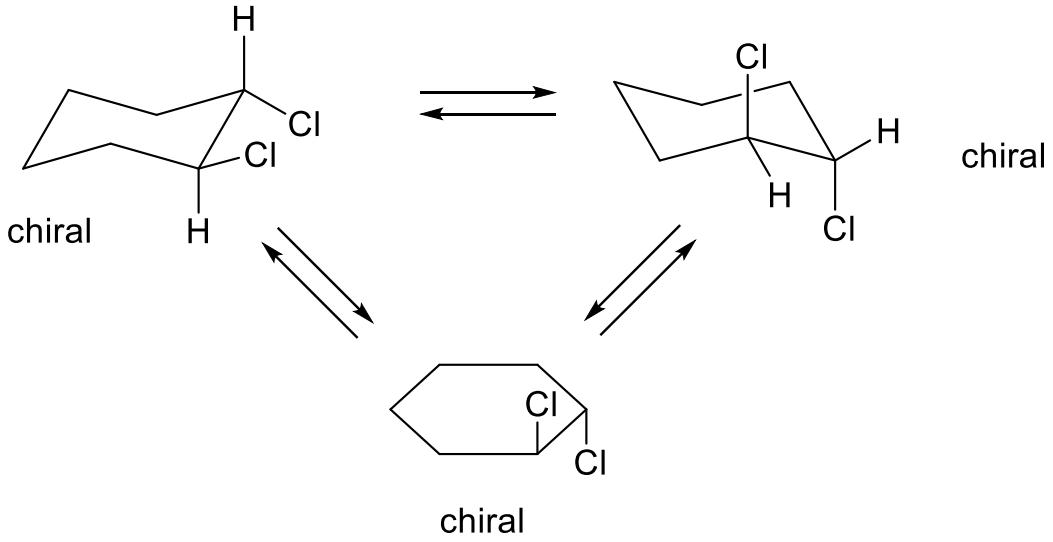
1:1 mixture

Racemization

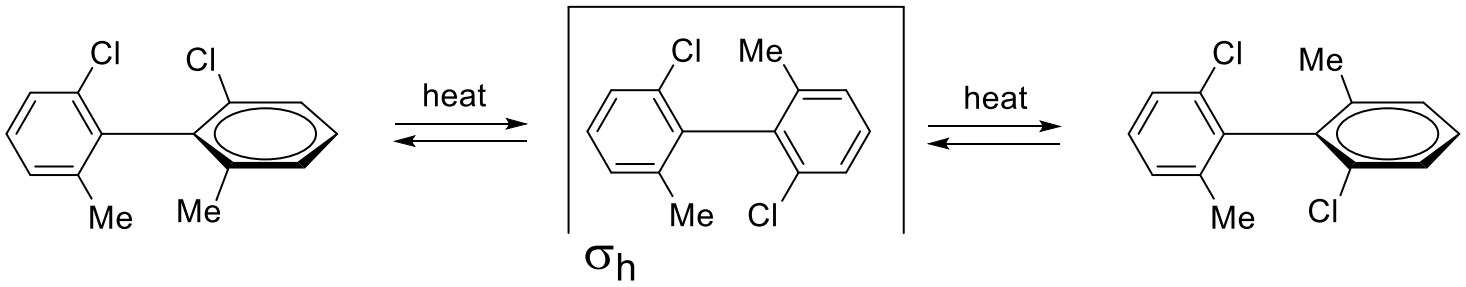
Process which convert a pure enantiomer into the racemate

A racemization – process implies an achiral intermediate

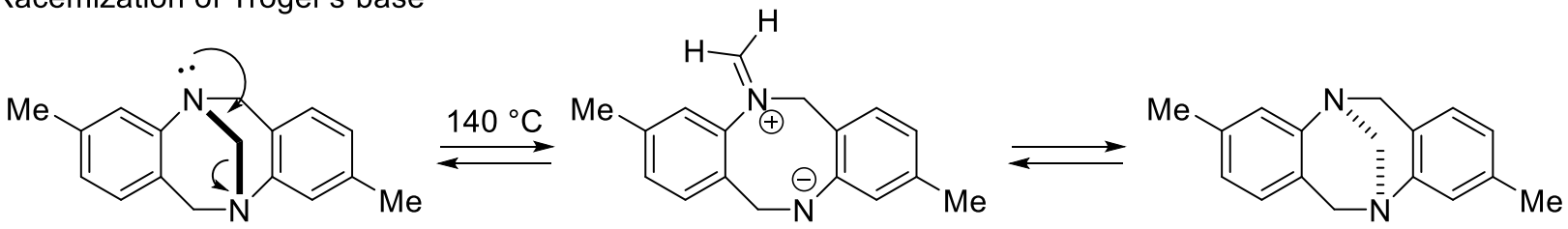




Racemization

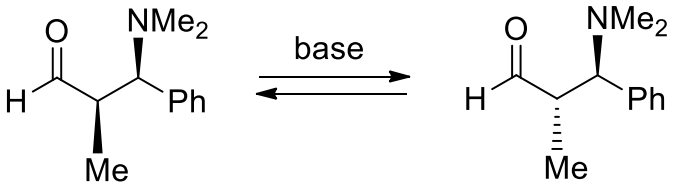


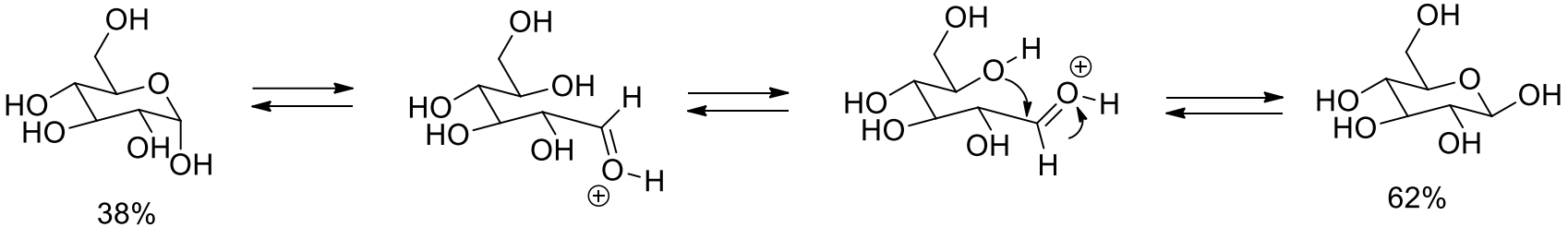
Racemization of Tröger's base



Epimerization of diastereoisomers

Epimerization: racemization of only one from several chiral centers.





38%

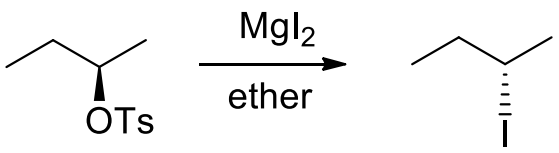
α-form of D-Glucose

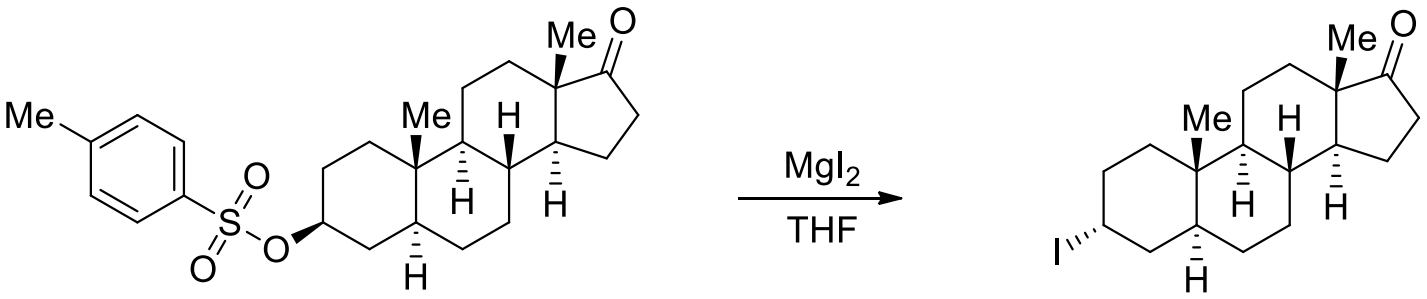
62%

β-form of D-Glucose

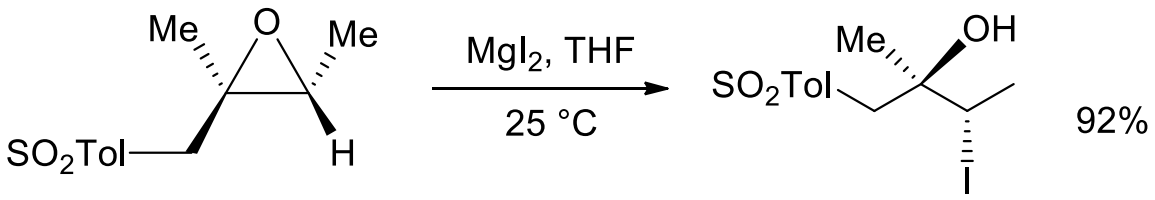
Selective inversion of the configuration at Csp^3-centers

S_N2-substitutions :



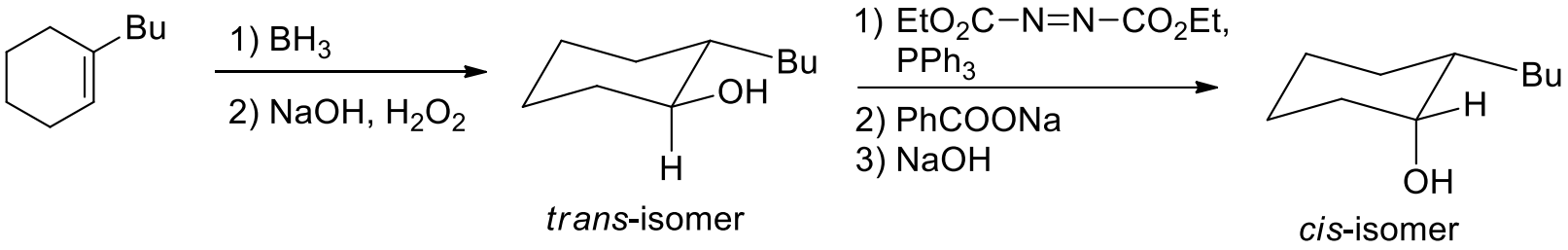


H.-J. Schneider, U. Buchheit, N. Becker, G. Schmidt, U. Siehlt, *J. Am. Chem. Soc.* **1985**, *107*, 1021-1039.



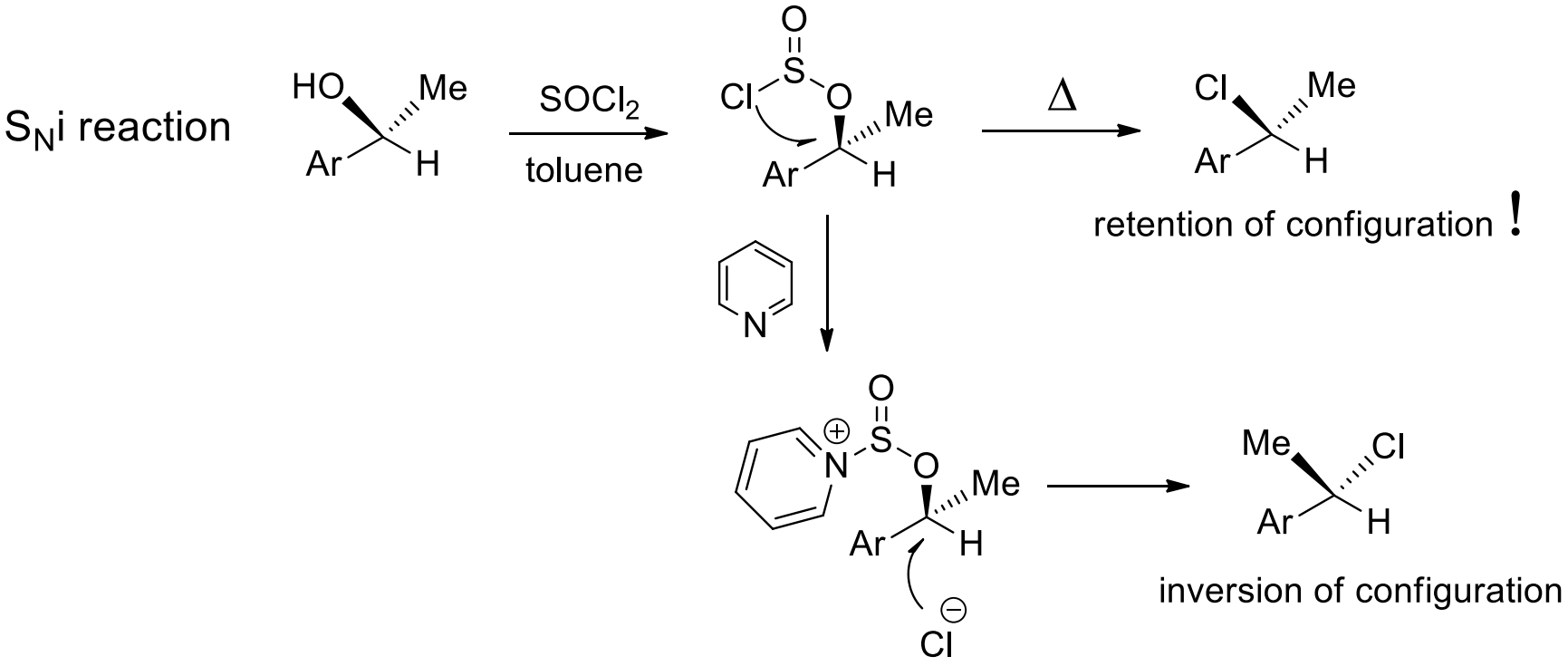
C. Banini, G. Righi, G. Sothiu, *J. Org. Chem*. **1991**, *56*, 6206.

Inversion of alcohols: Mitsunobu reaction

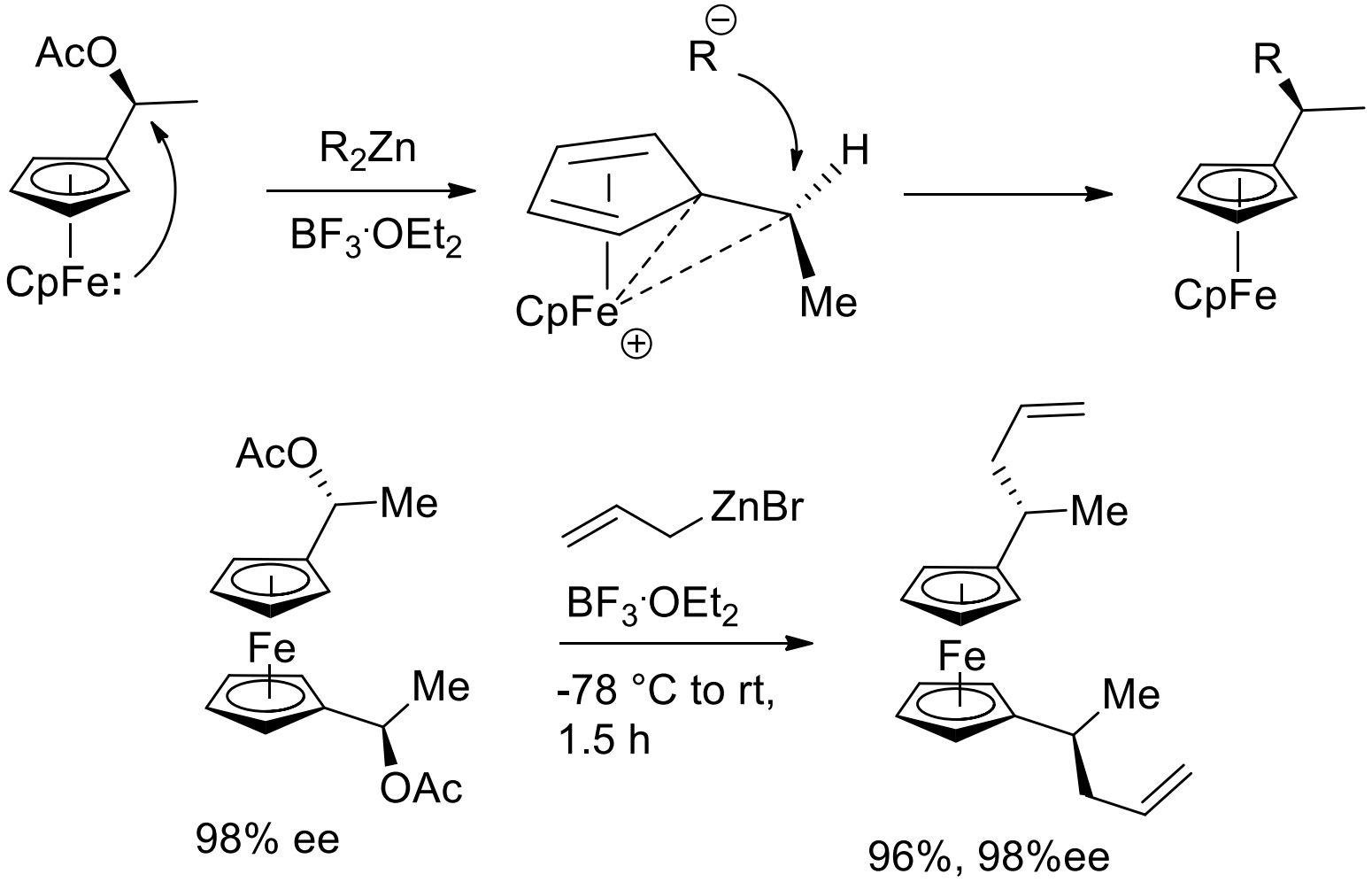


Mitsunobu reaction: D. L. Hughes, *Org. React*. **1992**, *42*, 335-656.

S_Ni-reaction

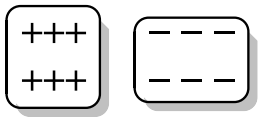


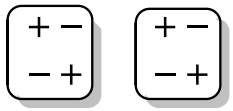
Substitution with retention of configuration

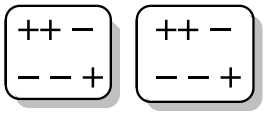


J. J. Almena Perea, T. Ireland, P. Knochel, *Tetrahedron Lett*. **1997**, *38*, 5961-5964.

Methods for Racemate Resolution
Separation of enantiomers

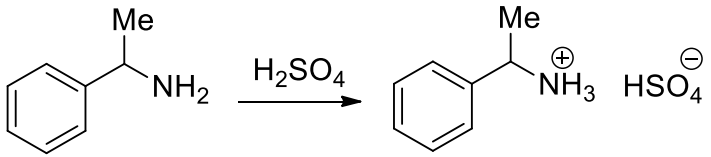
Conglomerates:  20% of all racemates

Racemates: 

Pseudoracemates:  unordered crystals

1) Separation based on the crystal shape. Pasteur (1845): crystal picking. Triage

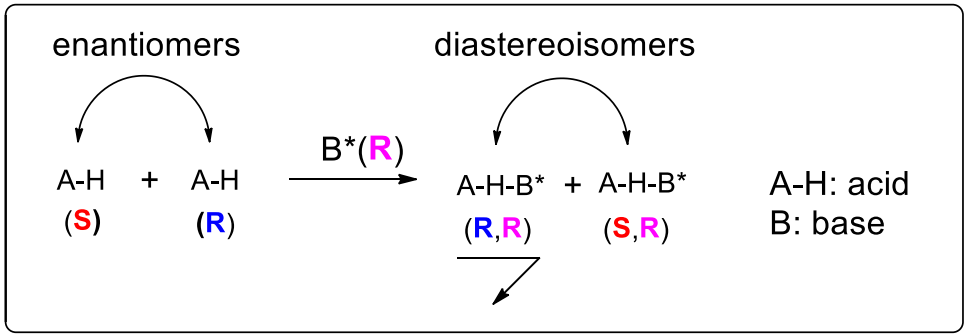
2) Selective crystallization using a seed crystal
Example: (+)-tartaric acid is easily crystallized by the addition of (-)-asparagine

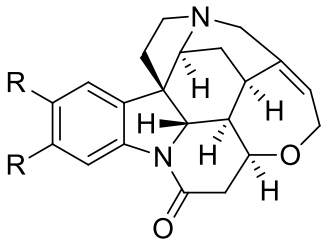


Mp of (-) or (+): 272 °C
Mp of (±): 245 °C

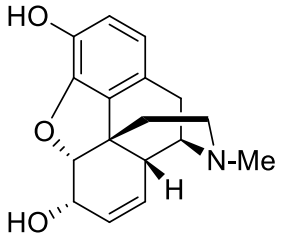
Resolution *via* separation of diastereomers

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

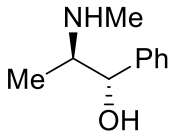




R = H : strychnine
R = OMe : brucine

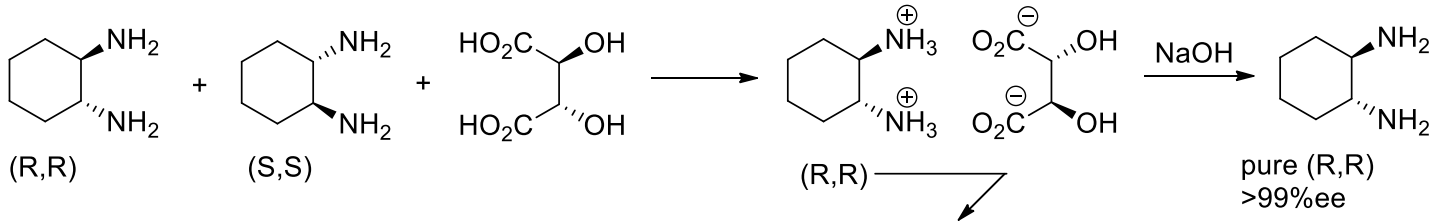


morphine



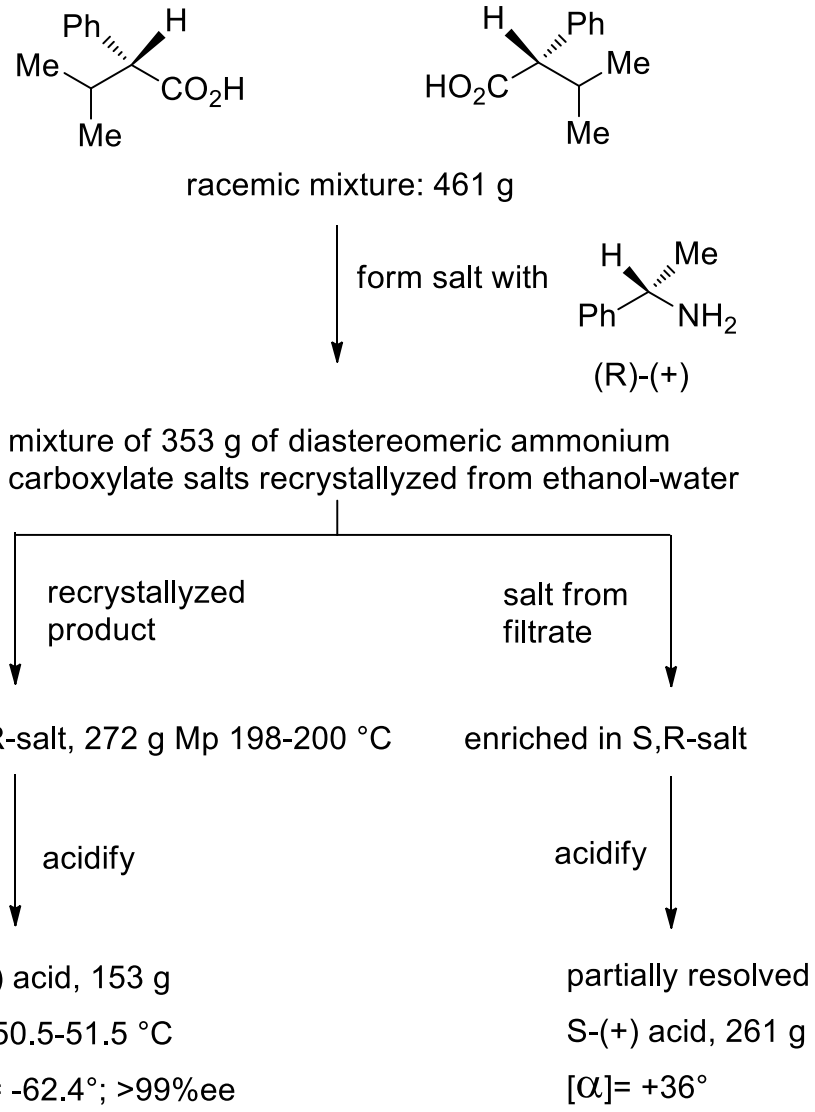
ephedrine

further example:



J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C. M. Zepp, *J. Org. Chem*. **1994**, *59*, 1939.

Resolution of 3-methyl-2-phenylbutanoic acid



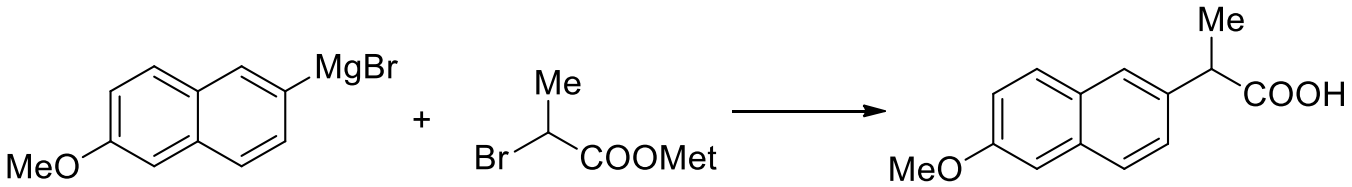
C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohahi, H. S. Mosher, *J. Org. Chem*. **1967**, *32*, 2797.

Resolution *via* separation of diastereomers

Commonly used resolving agents

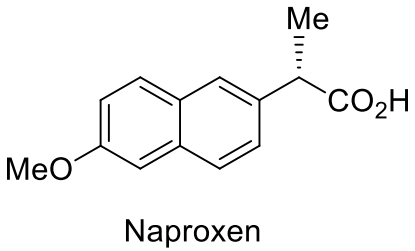
For acids	For bases
α-Methylbenzylamine	1-Camphor-10-sulphonic acid
α-Methyl-*p*-nitrobenzylamine	Malic acid
α-Methyl-*p*-bromobenzylamine	Mandelic acid
2-Aminobutane	α-Methoxyphenylacetic acid
N-Methylglucamine	α-Methoxy-α-trifluoromethylphenylacetic acid
Dehydroabietylamine	2-Pyrrolidone-5-carboxylic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

Separation of enantiomers

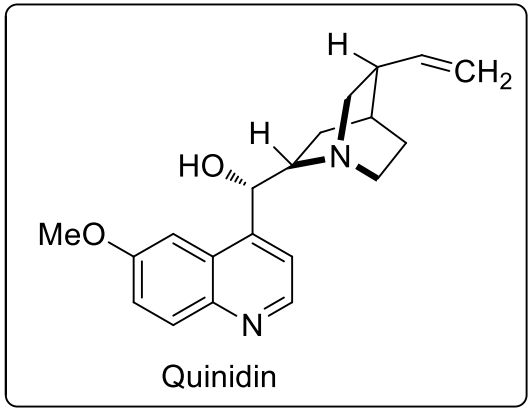


Met = Na, MgBr

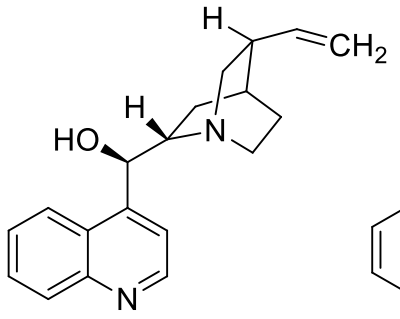
The resolution of enantiomers by preferential crystallization is the most common method used in industry:



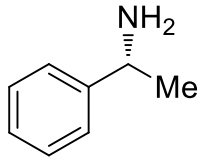
Naproxen



Quinidin



Cinchonidin

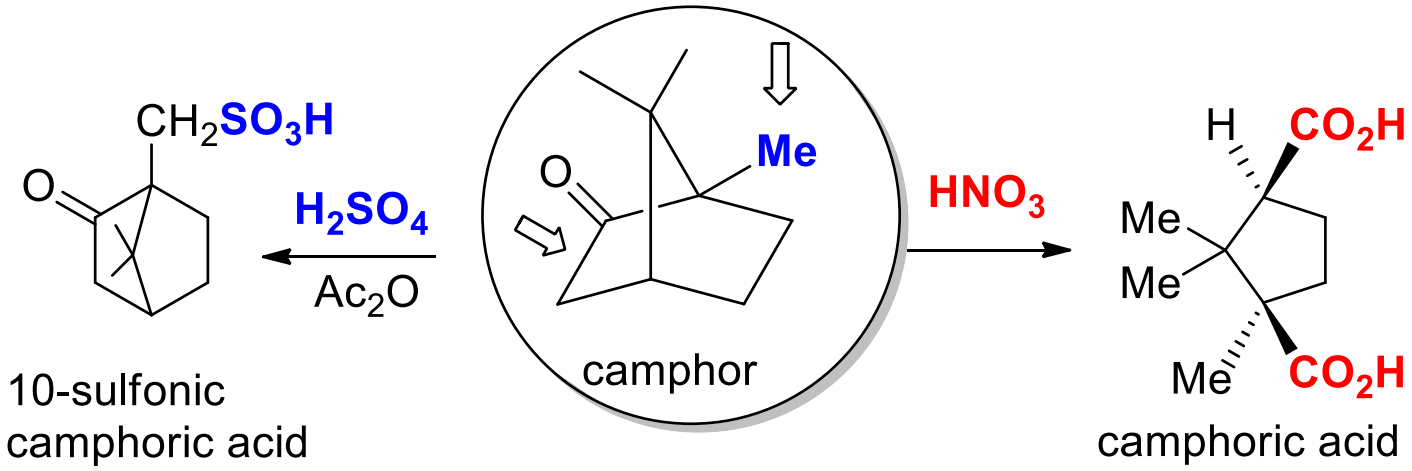


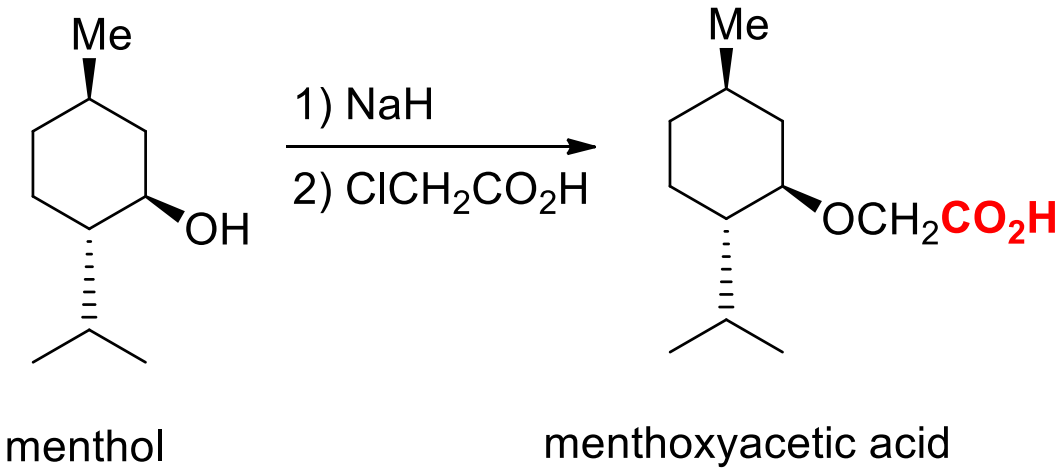
α-(-)-Phenylethylamine

Resolution of Naproxen using Quinidine

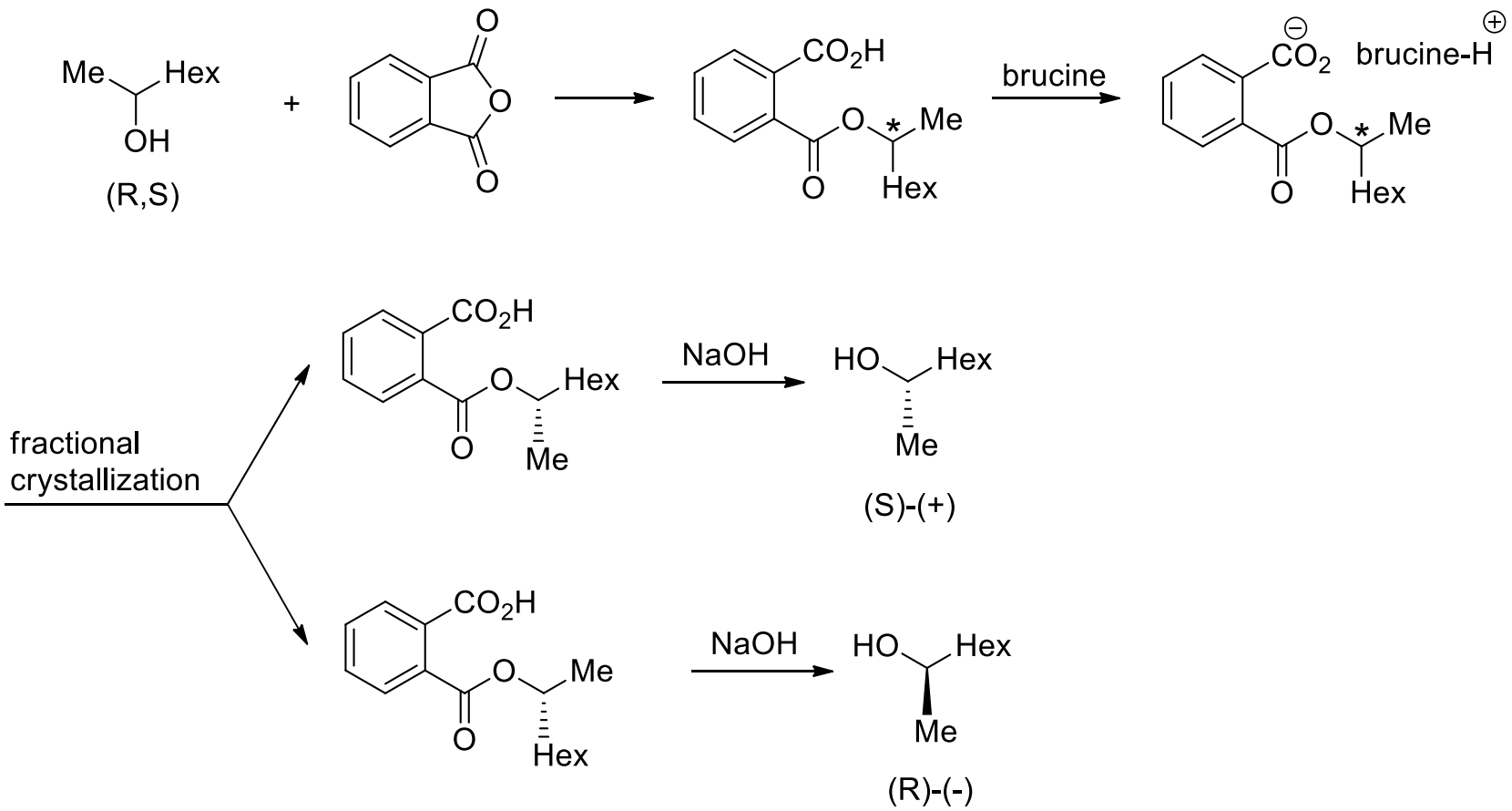
C. G. M. Villa and S. Panossian, Chirality in industry, **1992**, Vol. 1, 303.

Preparation of acidic resolution agents

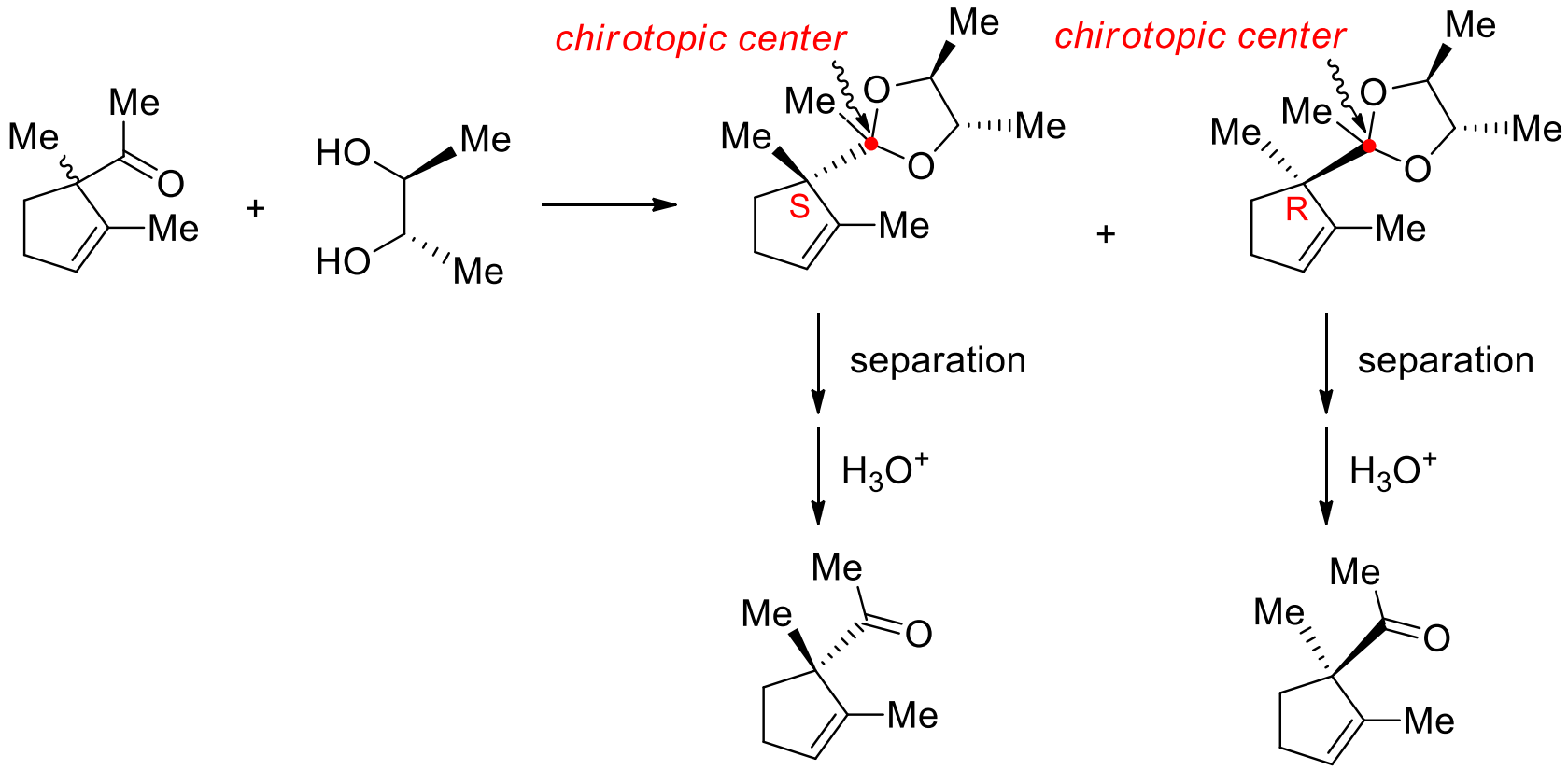




Extension to the resolution of alcohols



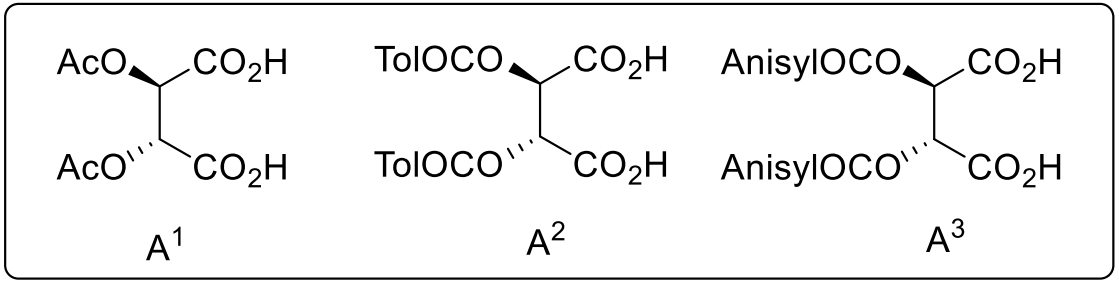
Resolution of ketones by the formation of diastereoisomers

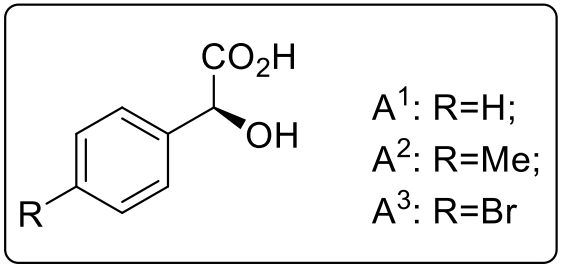


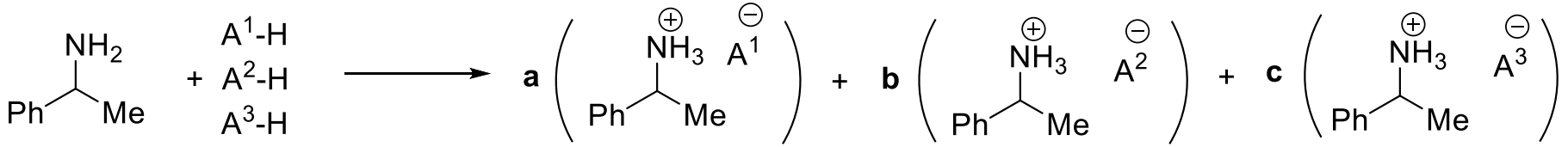
The diastereomeric ketals are separated by chromatography and hydrolyzed leading to the pure enantiomers

Improved resolution procedure: the method of Wynberg

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

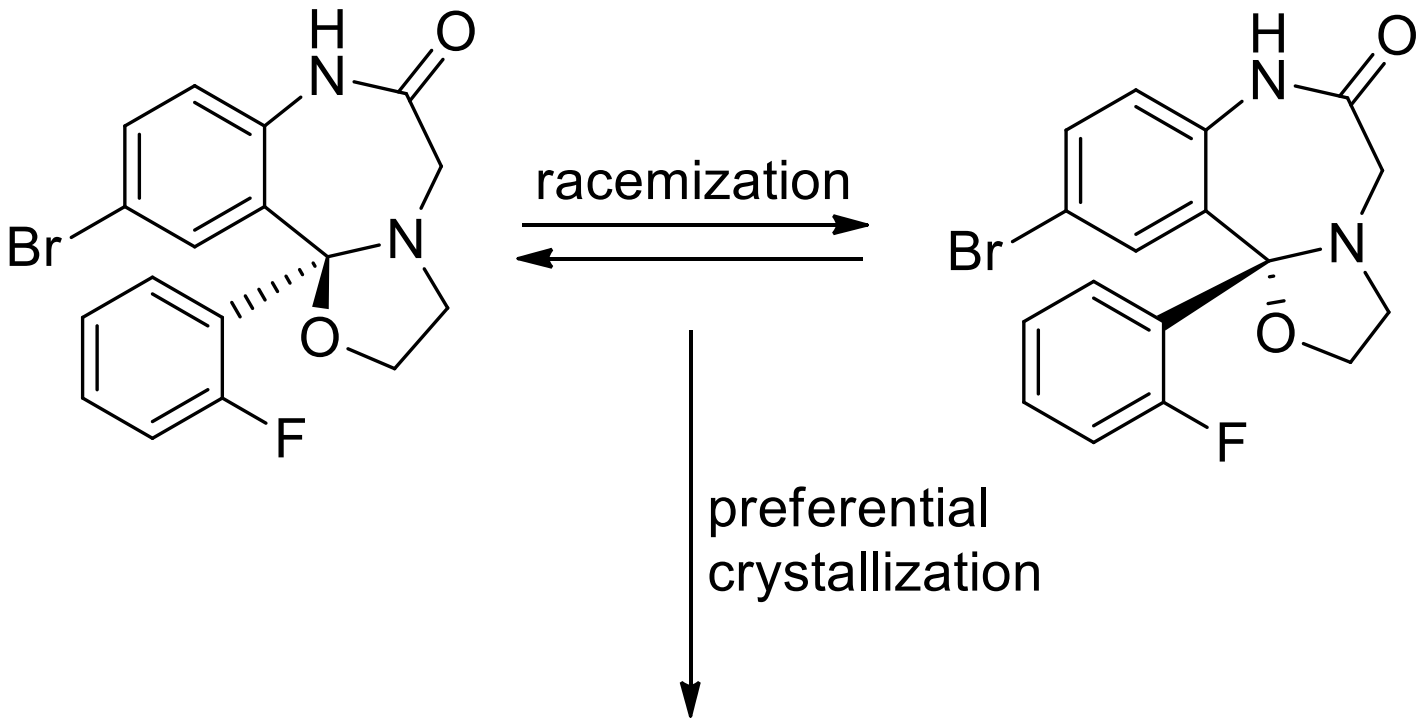






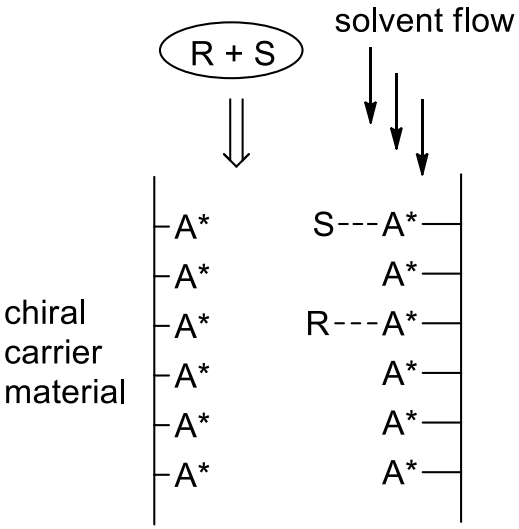
T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra *Angew. Chem*. **1998**, *110*, 2491; *Angew. Chem*. *Int. Ed*. **1998**, *37*, 2349.

Resolution with *in situ* racemization

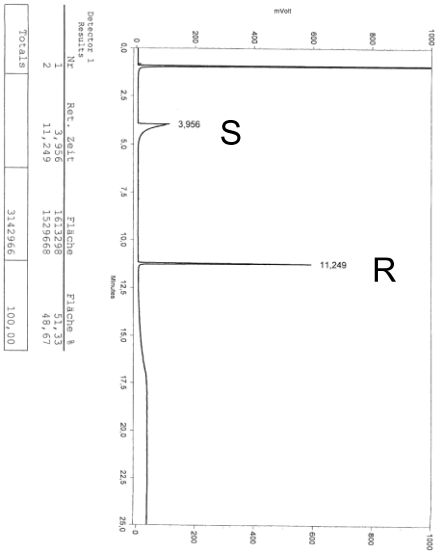


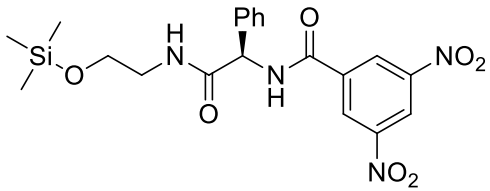
Y. Okada, T. Takebayashi, *Chem. Pharm. Bull.* **1988**, **36**, 3787.

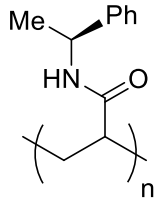
Separation using a chiral chromatographic columns



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

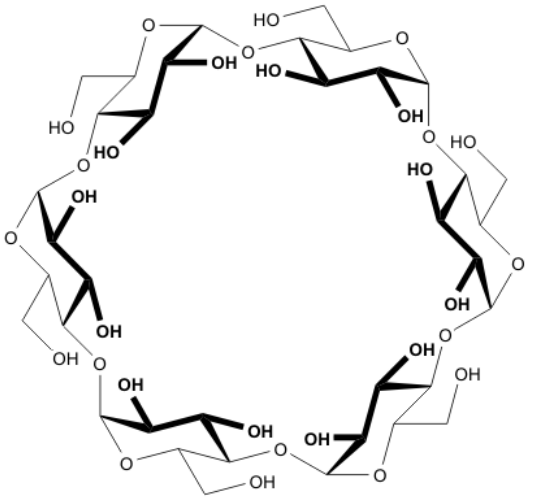






Chiral phases

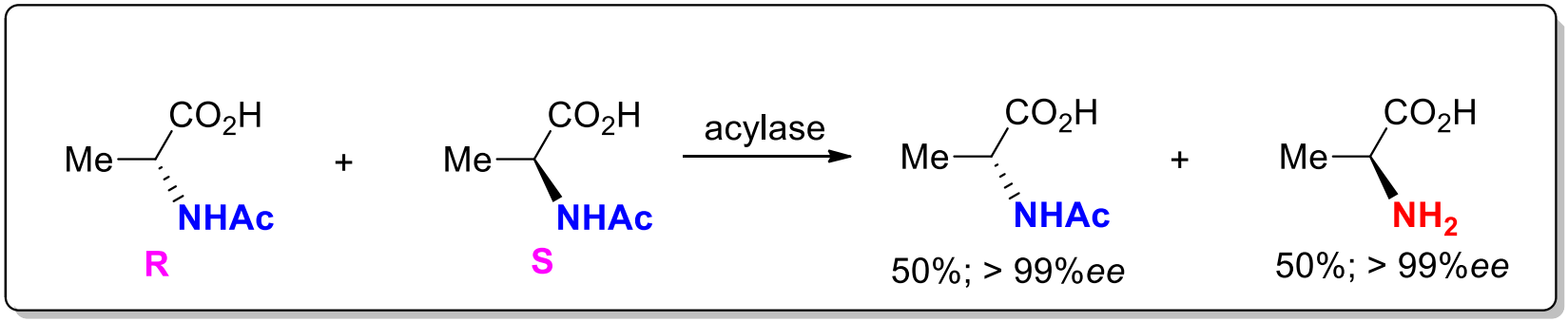
polysaccharides (α-Cyclodextrin)



Enzymatic resolution: an example of kinetic resolution

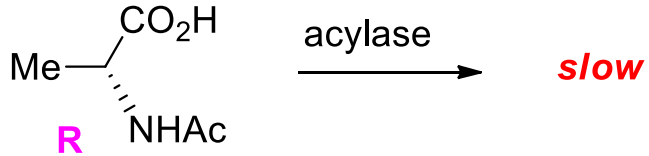
Pasteur:

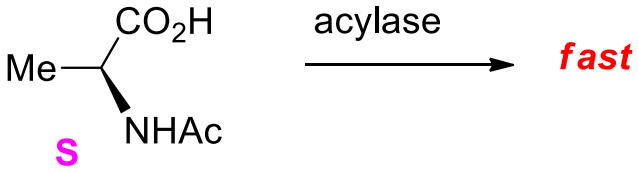
(±)-tartaric acid $\xrightarrow{\text{yeast}}$ (-)-tartaric acid + metabolites of (+)-tartaric acid



The two enantiomers react with different rates.

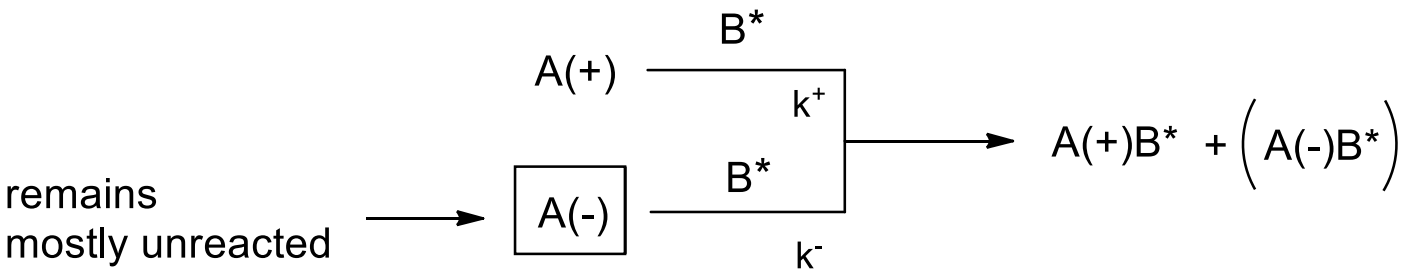
This differentiation is possible because a chiral reagent is used (an enzyme)





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

Kinetic resolution



$k^+ > k^-$ S = selectivity factor = k^+/k^-

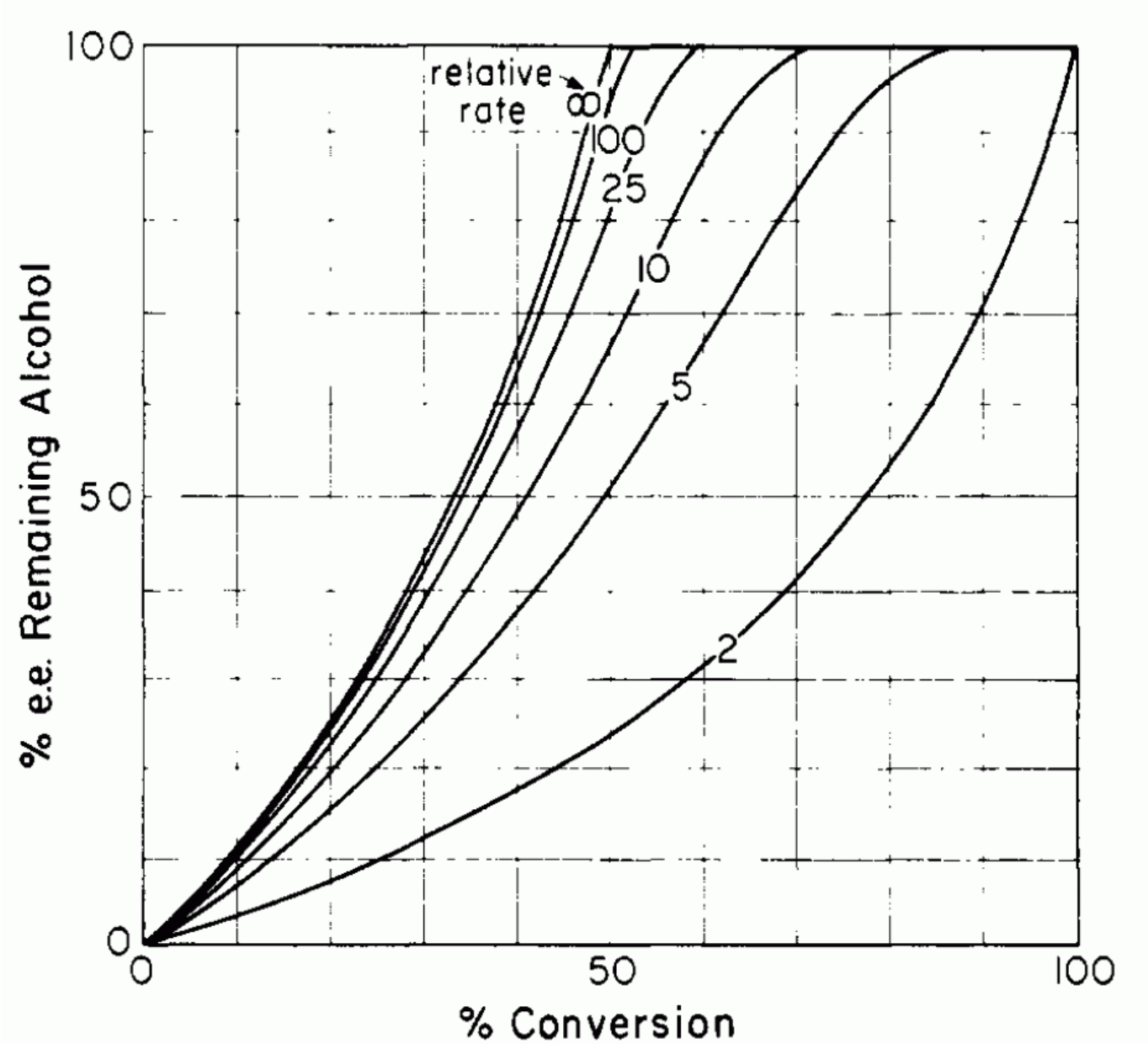
The kinetic resolution is only useful if the reaction rates of the two reactions are very different.

For example for a given conversion:

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

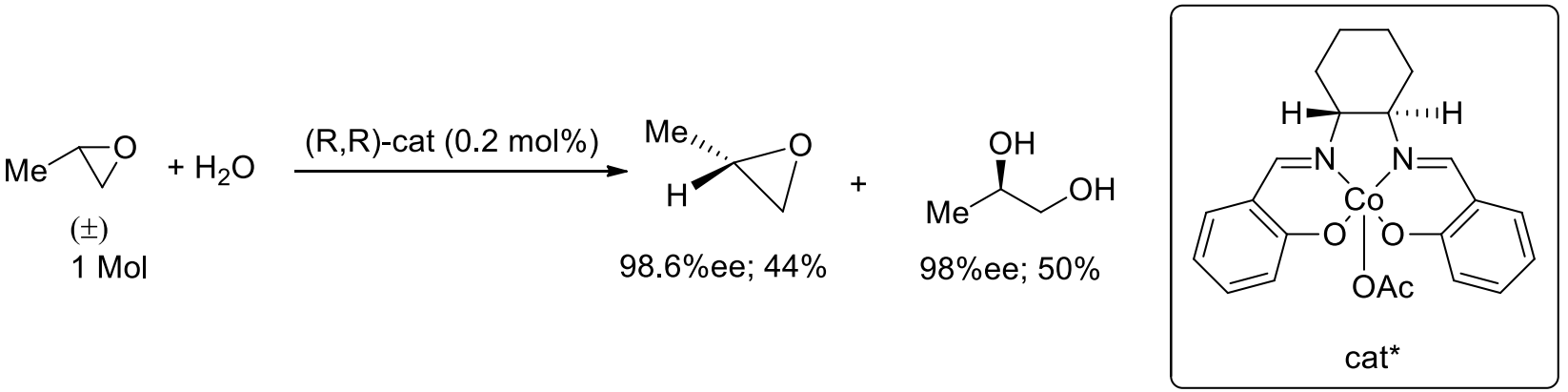
93%ee of the unreacted starting material is obtained if k+/k- = S = 100

Dependence of enantiomeric excess on relative rate of reaction

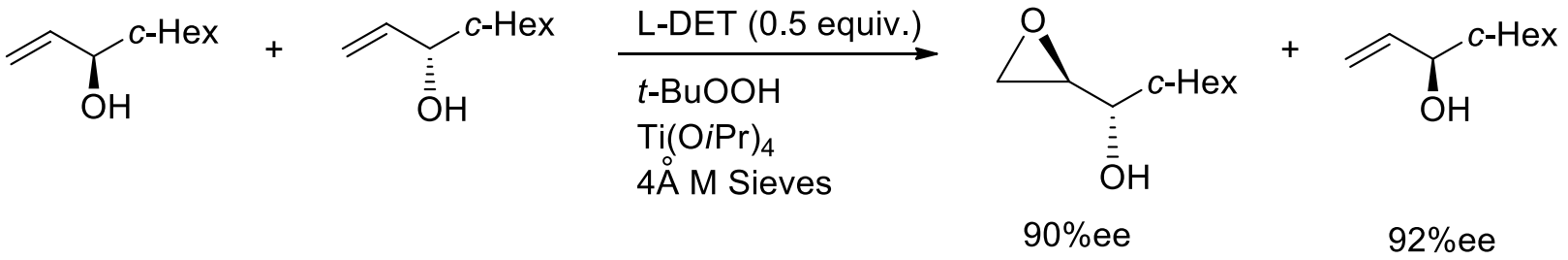


V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc*. **1981**, *103*, 6237.

Kinetic resolution

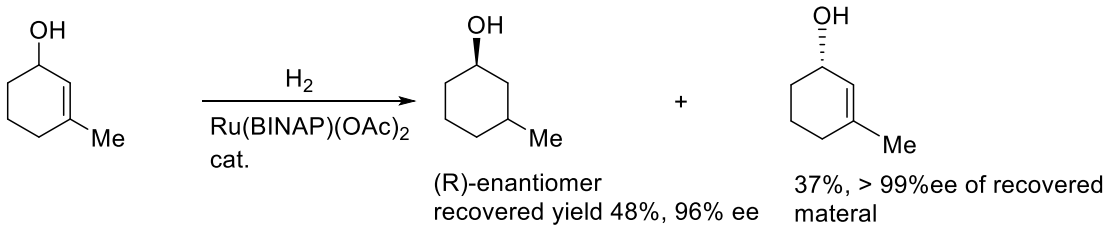


M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936.

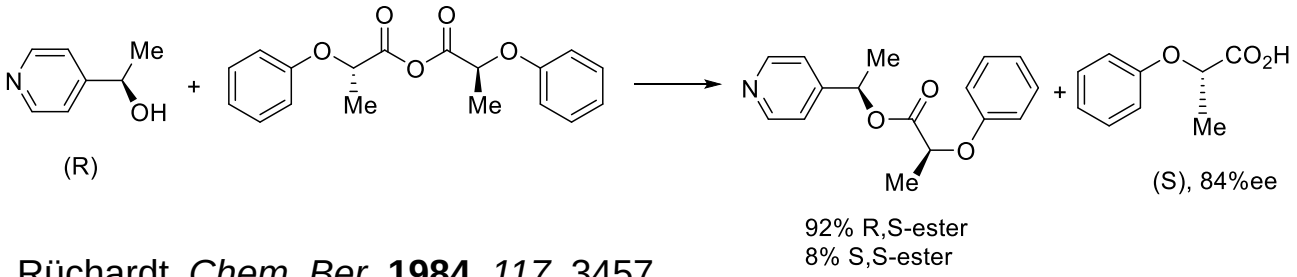


B. E. Rossiter, T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1981**, *103*, 464.
P. R. Carlier, W. S. Mungall, G. Schroder, K. B. Sharpless, *J. Am. Chem. Soc*. **1988**, *110*, 2978.

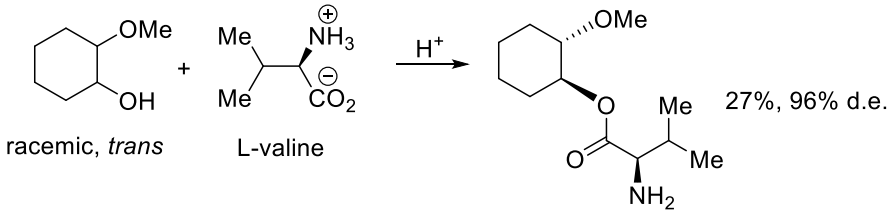
Examples of kinetic resolution



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.

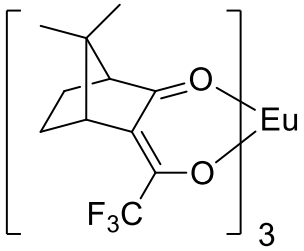


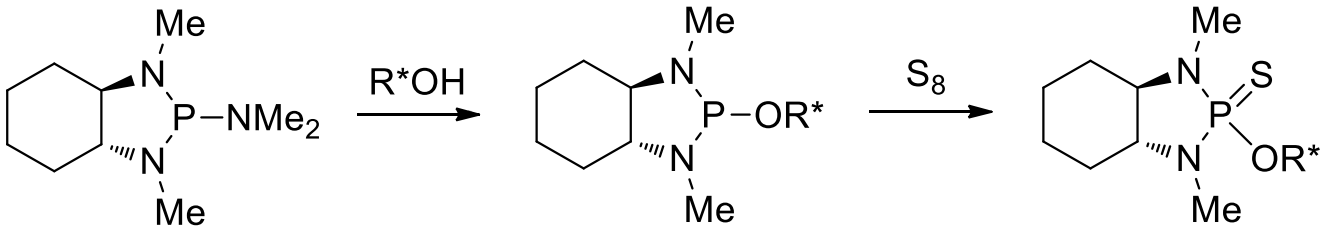
P. Stead, H. Marley, M. Mahmoudoan, G. Webb, D. Noble, Y. T. Ip, E. Piga, S. Roberts, M. J. Dawson, *Tetrahedron: Asymmetry* **1996**, *7*, 2247.

Determination of the enantiomeric purity by NMR methods

Use of chiral shifts reagents:

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





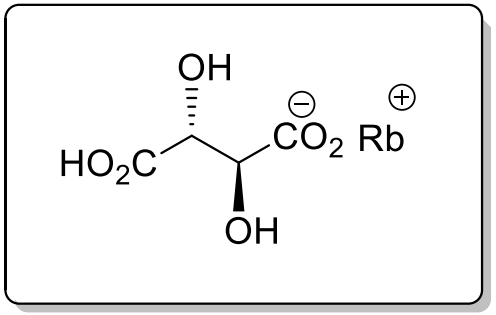
A. Alexakis, J. C. Frutos, S. Mutti, P. Mangeney, *J. Org. Chem*. **1994**, *59*, 3326.

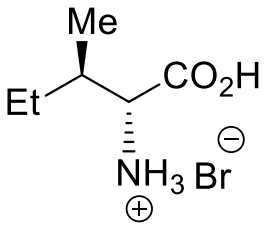
Determination of ee% by NMR Methods: review article D. Parker *Chem. Rev*. **1991**, *91*, 1441

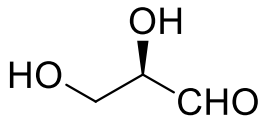
Determination of the absolute configuration

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.





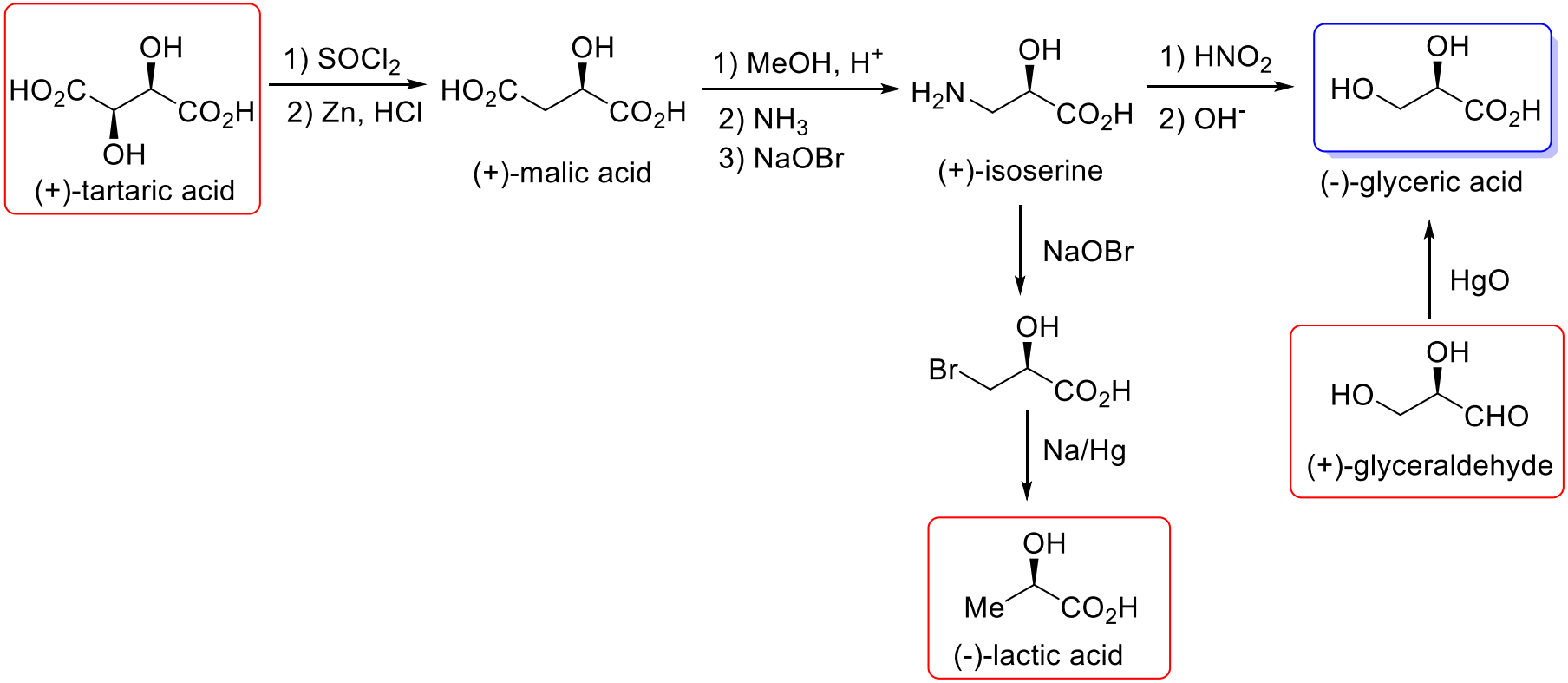


(+)-glyceraldehyde

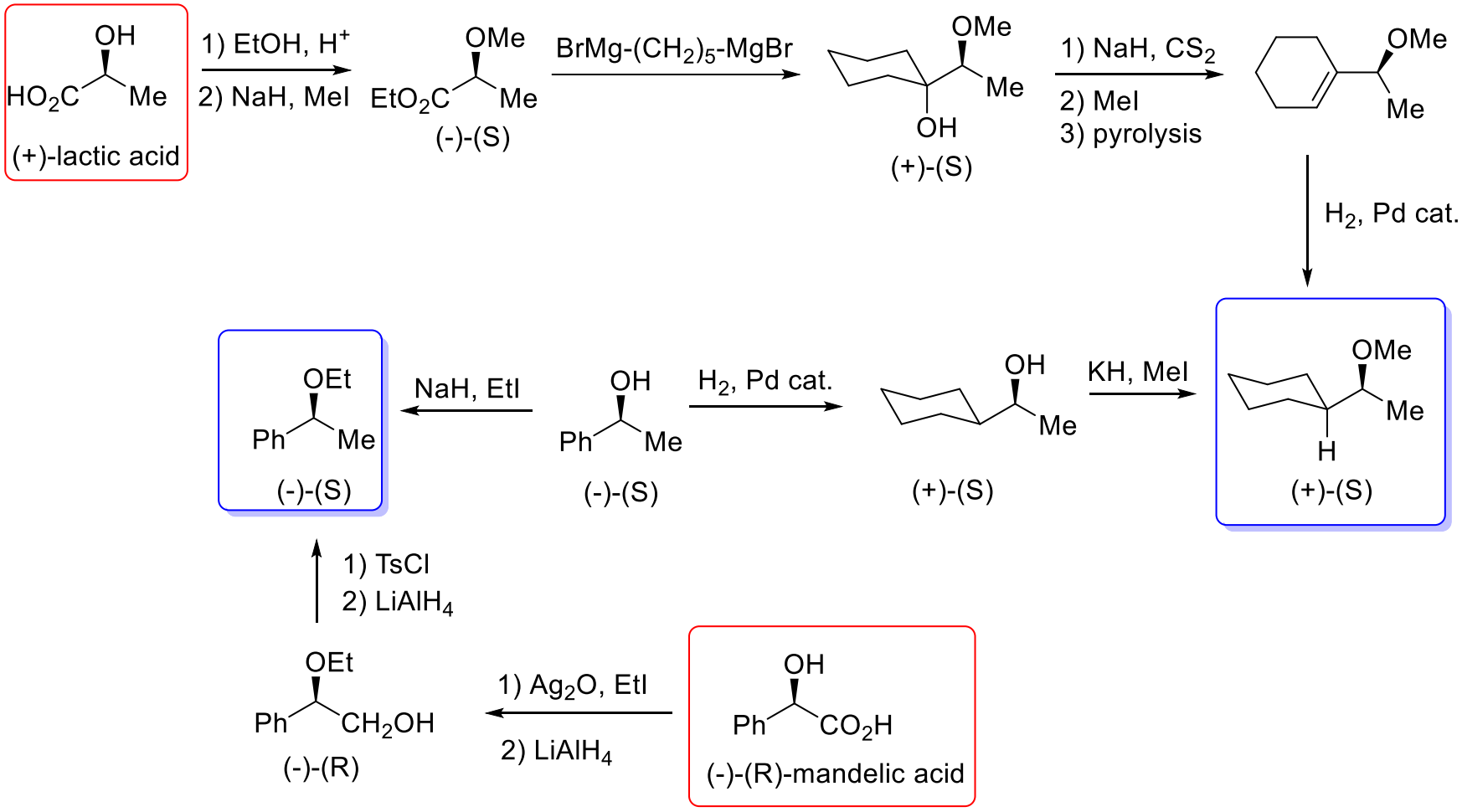
* The absolute configuration of (+)-glyceraldehyde was correct

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

Chemical correlation (1)

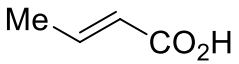


Chemical correlation (2)

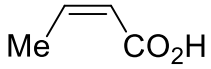


Determination of the relative stereochemistry by NMR methods

Diastereisomers have different properties: compare with



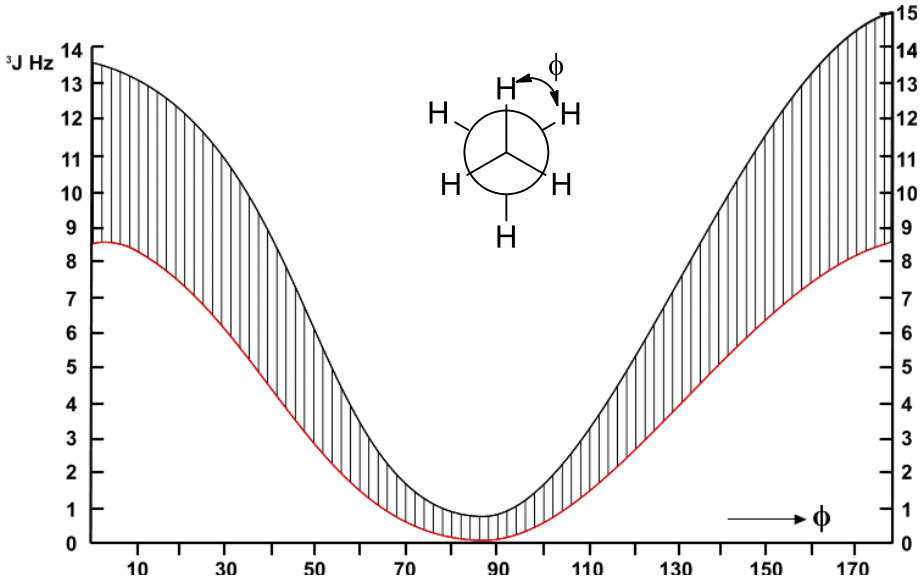
melting point: 72 °C

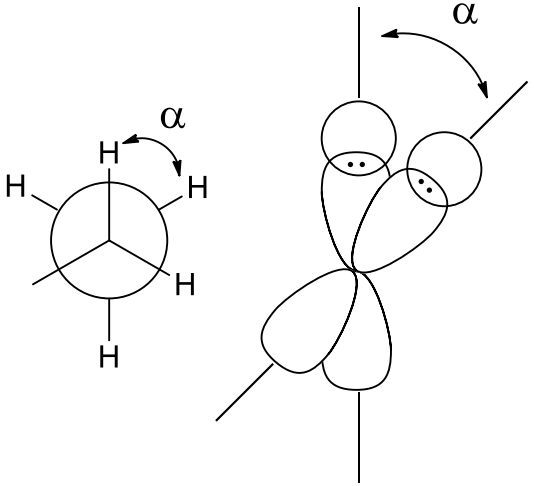


melting point: 15 °C

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

Karplus rules

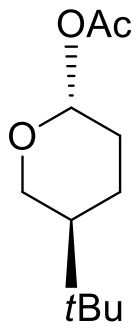




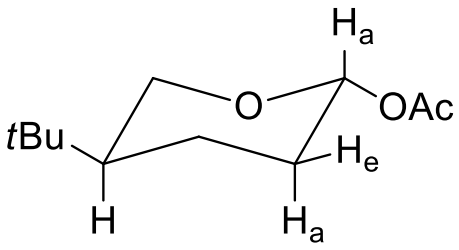
α small>> large overlapping>>

large coupling constant

Determination of the relative stereochemistry by NMR methods

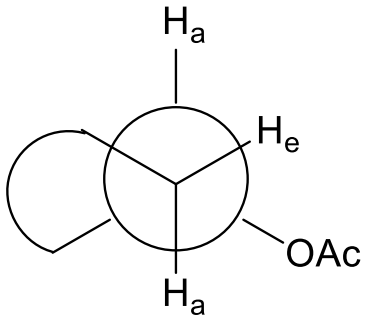


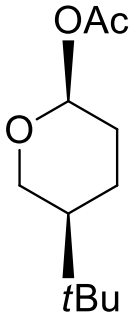
trans



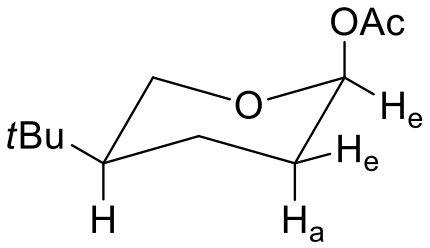
J_{aa} = 11 Hz

J_{ae} = 4 Hz



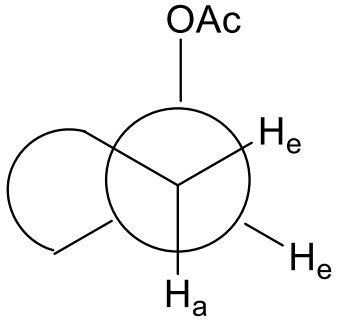


cis

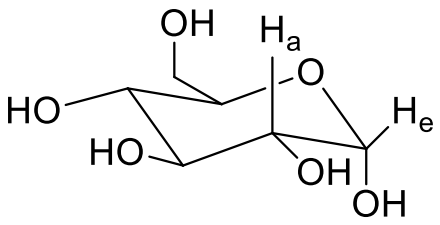


J_{ee} = 3 Hz

J_{ea} = 3 Hz

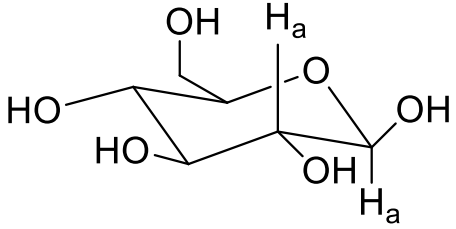


Determination of the configuration of the anomeric center of sugar



α-form of D-glucose

J_{ae} = 3 Hz



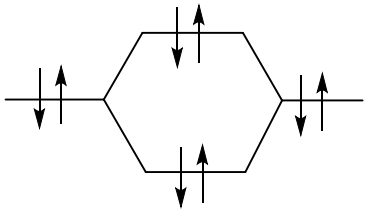
β-form of D-glucose

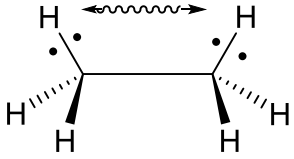
J_{aa} = 7.5 Hz

Conformational analysis

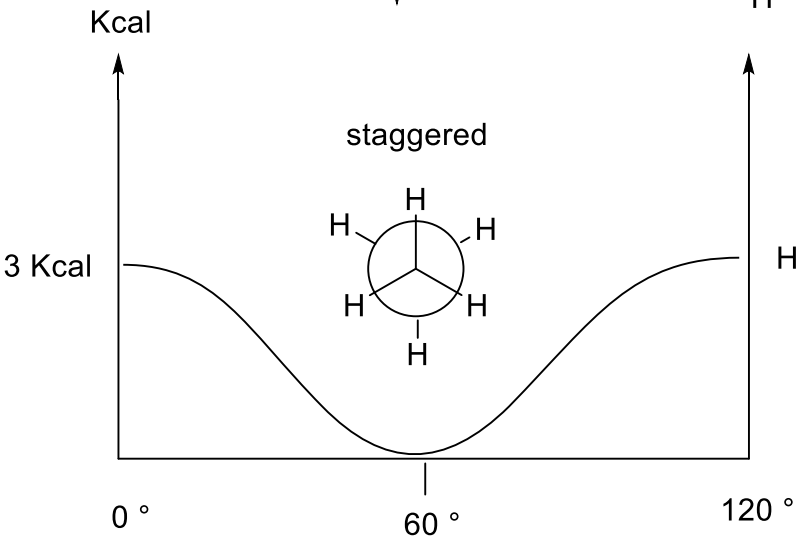
1943: X-Ray analysis shows a chair conformation for cyclohexane derivatives

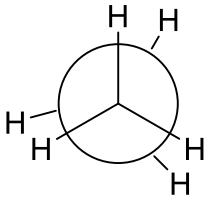
1950: Barton shows the difference between axial and equatorial positions in cyclohexane derivatives



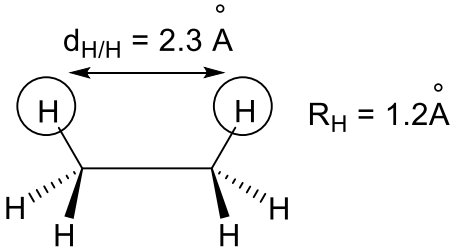


Pitzer strain: destabilization of 3 kcal/mol
(eclipsed conformation)
σ/σ-interactions





CH_3-CH_3	CH_3-NH_2	CH_3-OH
3 kcal/mol	2 kcal/mol	1 kcal/mol



Conformational analysis

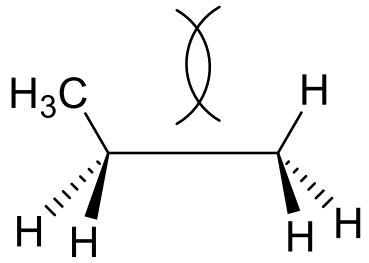
$$\Delta G^\circ = -3.0 \text{ Kcal} \Longrightarrow K = e^{\frac{-\Delta G^\circ}{RT}} = \text{ca. } 100$$

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

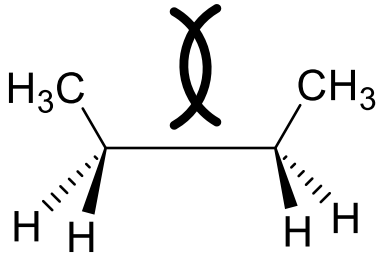
Isomeric ratios at equilibrium (T = 25 °C)

percent of more stable isomer	K	$\Delta G^\circ_{25^\circ C}$ (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

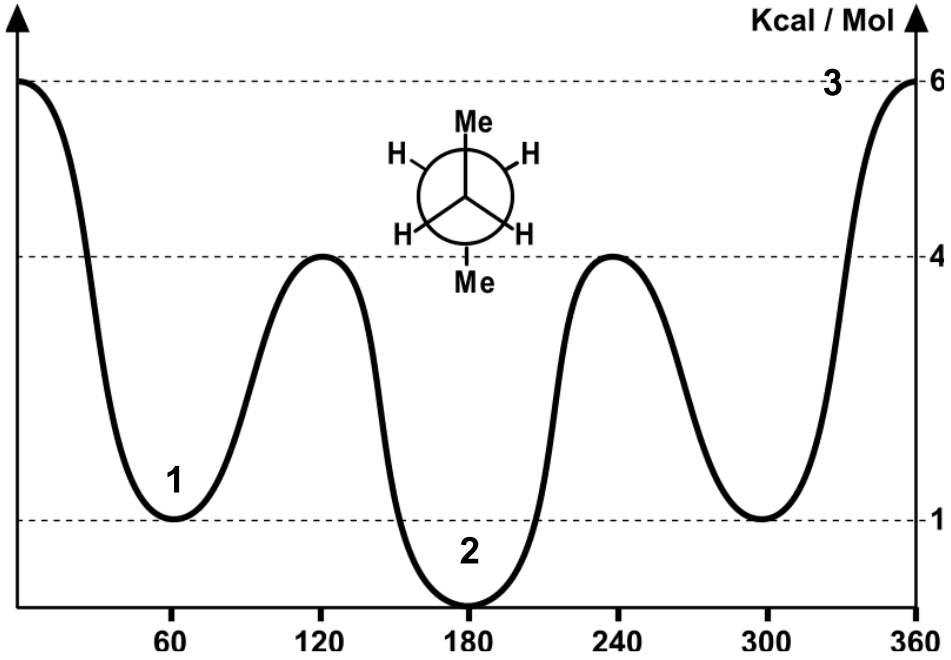


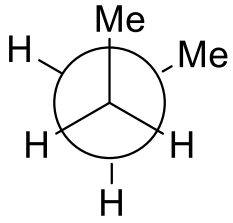
Pitzer strain

van der Waals interactions

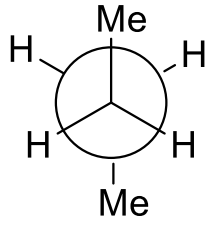
6 kcal/mol = ca. 3 kcal/mol + 3 kcal/mol

Conformational analysis of butane

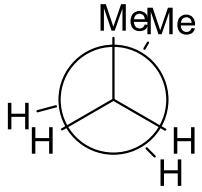




1: gauche



2: antiperiplanar

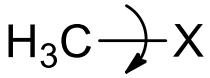


3: synperiplanar

70:30 mixture of antiperiplanar and gauche conformations

Conformational analysis

Rotational barriers of compounds of type CH_3-X

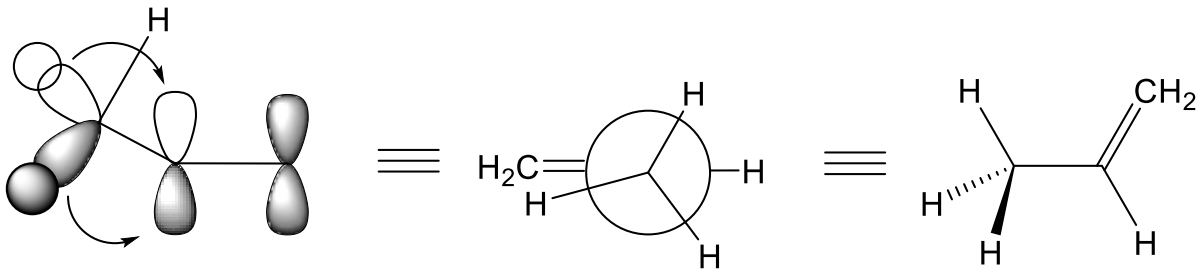


Alkanes	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
CH_3-CH_3	2.9	CH_3-NH_2	2.0
CH_3-CH_2CH_3	3.4	CH_3-$NHCH_3$	3.0
CH_3-$CH(CH_3)_2$	3.9	CH_3-$N(CH_3)_2$	4.4
CH_3-$C(CH_3)_3$	4.7	CH_3-OH	1.1
$(CH_3)_3C$-$C(CH_3)_3$	8.4	CH_3-OCH_3	4.6

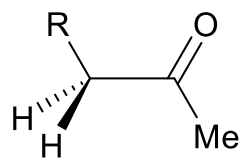
J. P. Lowe, *Prog. Phys. Org. Chem.* **1968**, *6*, 1.

Conformational analysis of bonding between Csp^2 and Csp^3

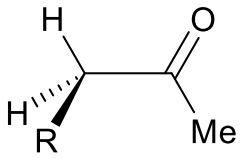
Propene: 2.7 kcal/mol stabilization effects of the Me-group (n ⟶ π*)



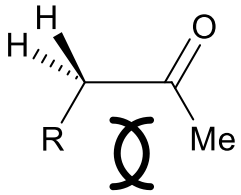
eclipsed conformation

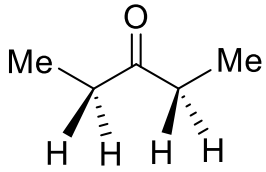


preferred conformation

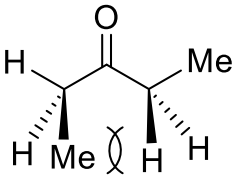


less preferred

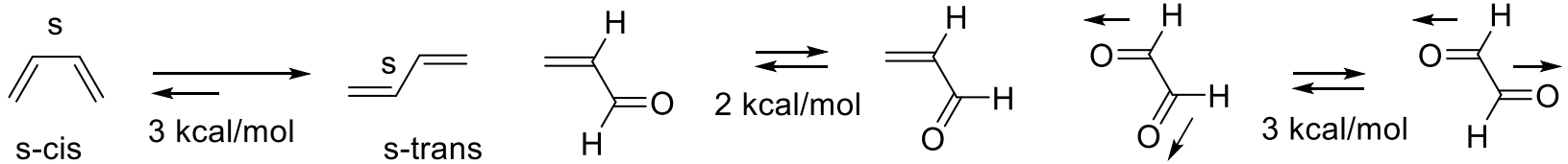




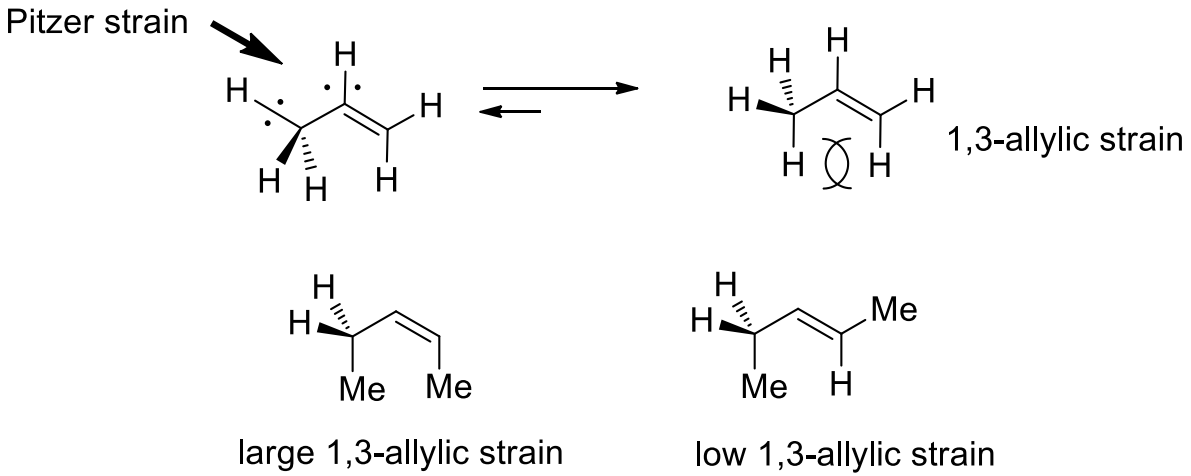
preferred

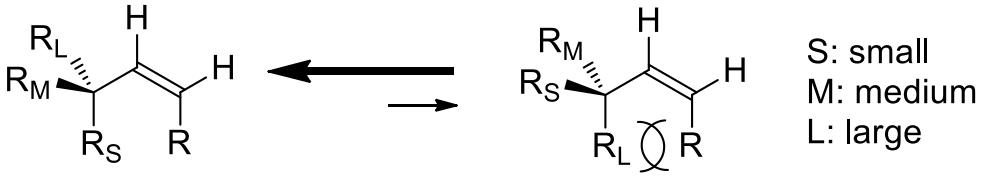


less stable

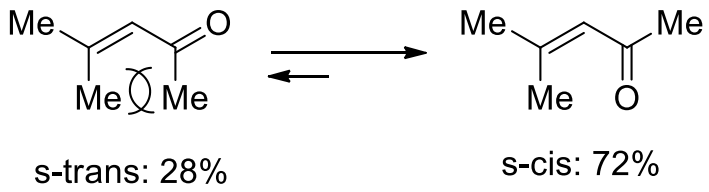


1,3-Diaxial strain



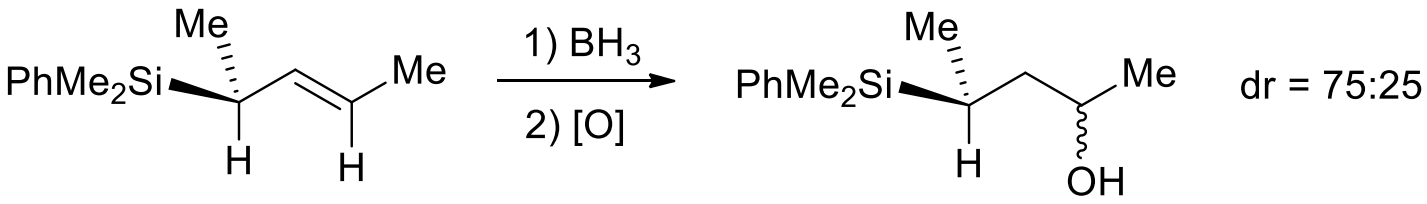


R. W. Hoffmann, *Chem. Rev*. **1989**, *89*, 1841



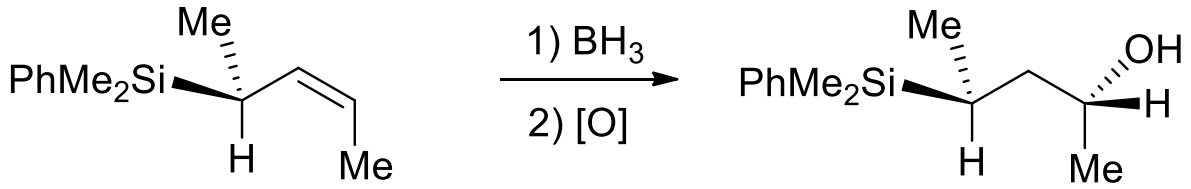
A. Bienvenue, *J. Am. Chem. Soc*. **1973**, *95*, 7345

1,3-Diaxial strain

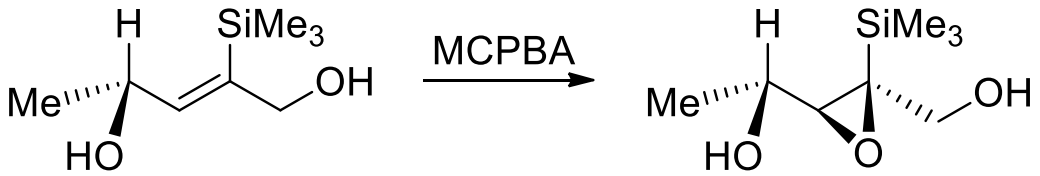


dr = 75:25

but

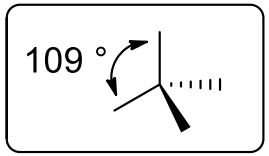


ca. 100% of
one diastereoisomer

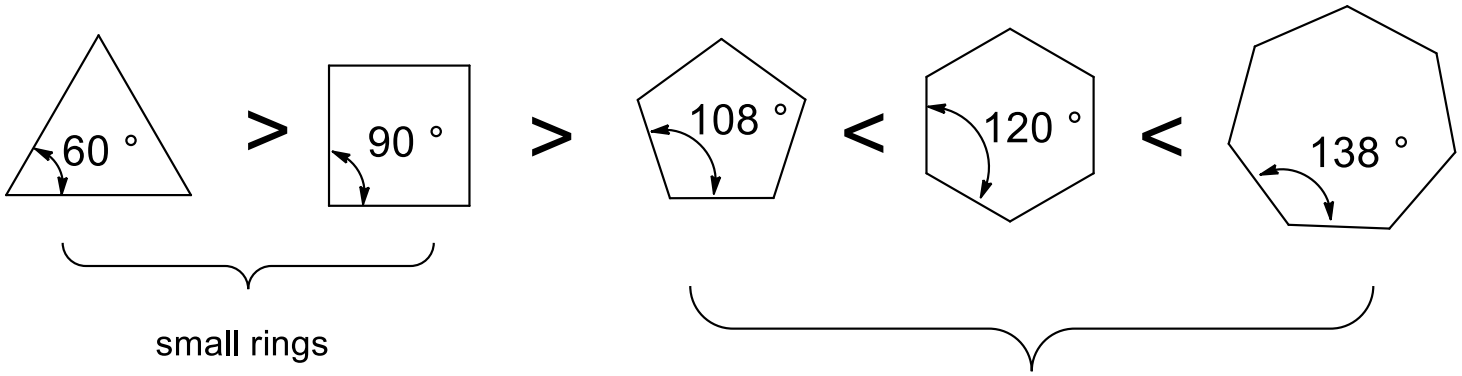


only product

Conformational analysis of cyclic systems: Bayer strain



ideal tetrahedric angle



small rings

normal rings 5 - 7

Classification of cyclic organic molecules

Cyclic molecules can be classified in 4 categories:

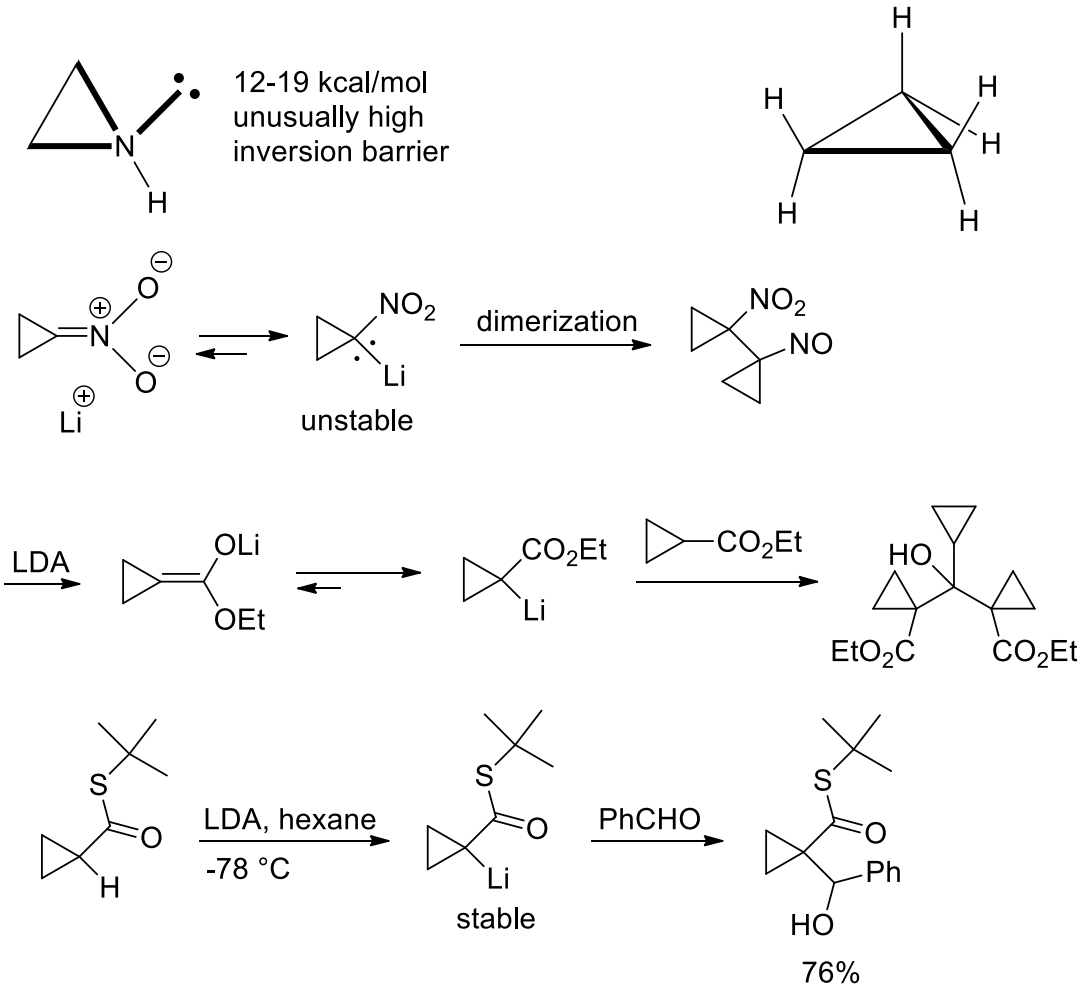
small rings: 3-4;
normal rings: 5-7;
medium-sized rings: 8 -12;
large rings: 13-membered rings and larger

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

large rings behave like a per-chain systems

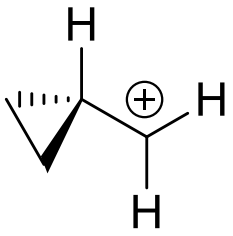
The cyclopropane ring

planar ring system: Pitzer strain 6 Kcal/mol



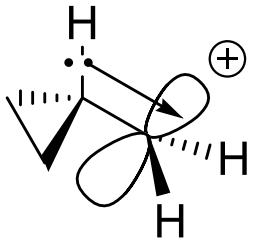
J. Wemple, *Tetrahedron Lett.*, **1975**, *38*, 3255.

Conformation of the cyclopropylmethyl cation

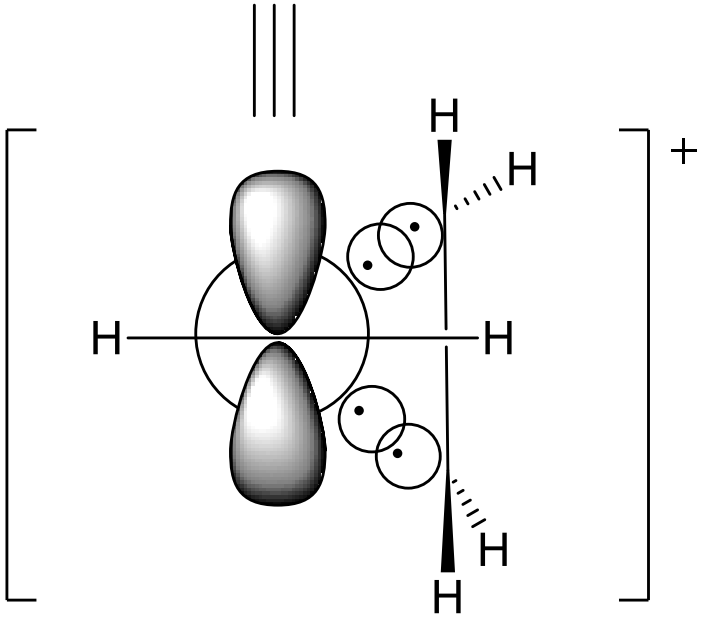


eclipsed conformation

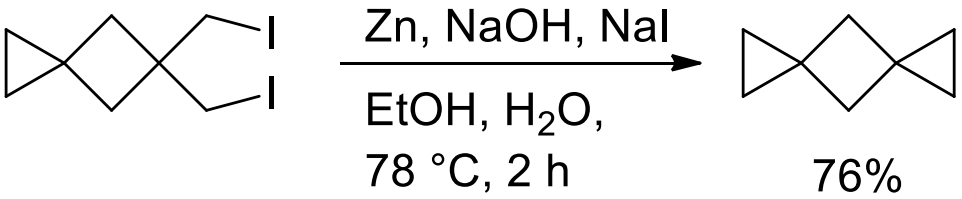
more stable than



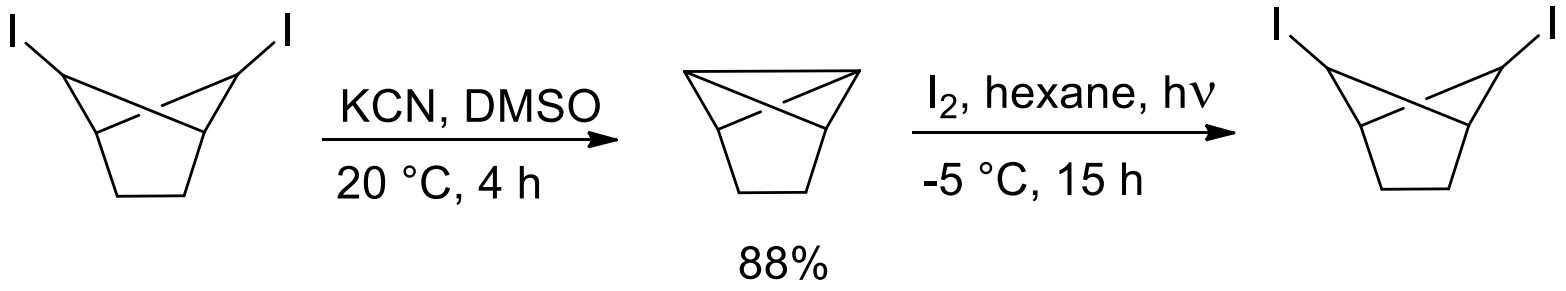
staggered conformation



Synthesis of cyclopropanes

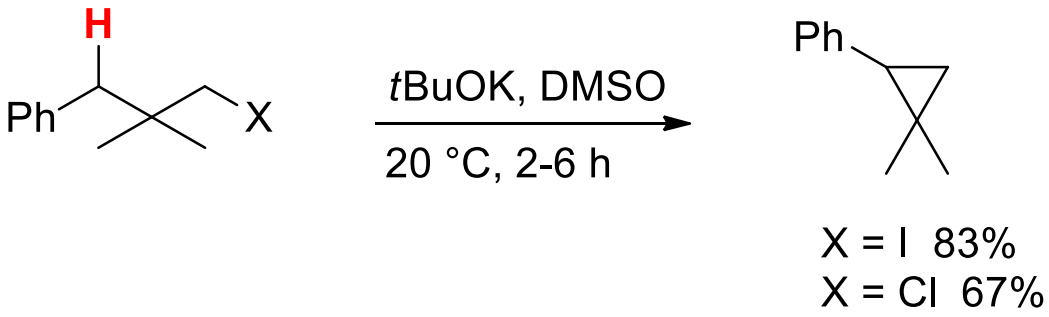


H.-D. Beckhaus, C. Rüchardt, S. I. Kozhushkov, V. N. Belov, S. P. Verevkin, A. de Meijere, *J. Am. Chem. Soc*. **1995**, *117*, 11854.

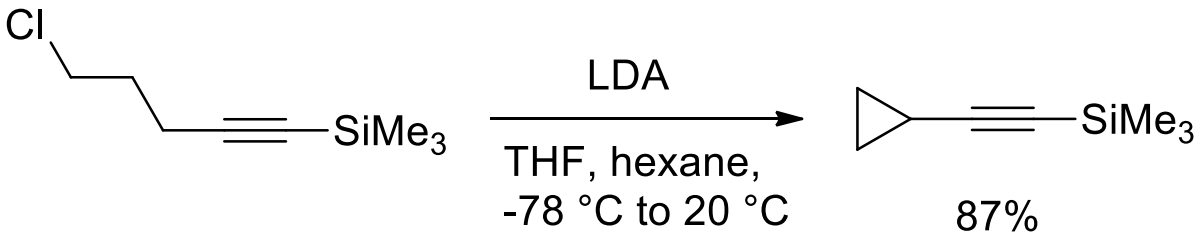


C. Mazal, O. Skarka, J. Kaleta, J. Michl, *Org. Lett*. **2006**, *8*, 749.

Synthesis of cyclopropanes

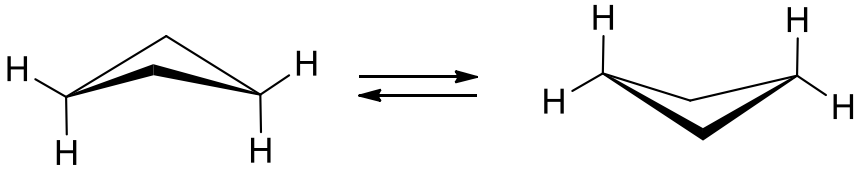


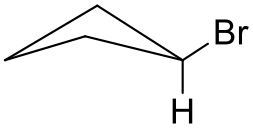
J. E. Argüello, A. B. Peñéñory, R. A. Rossi, *J. Org. Chem.* **1999**, *64*, 6115.



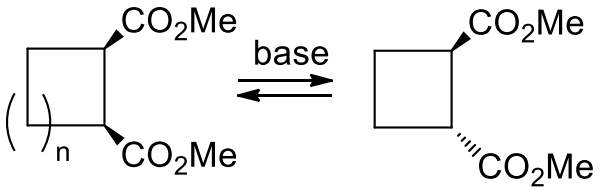
H.-C. Militzer, S. Schömenauer, C. Otte, C. Puls, J. Hain, S. Bräse, A. de Meijere, *Synthesis* **1993**, 998.

The cyclobutane and cyclopentane systems

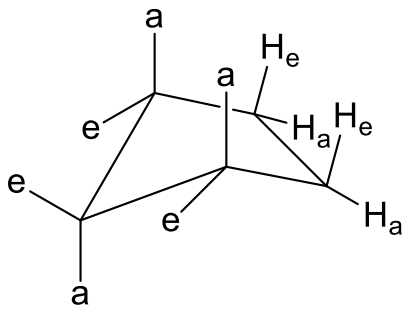




1.5 kcal/mol inversion barrier

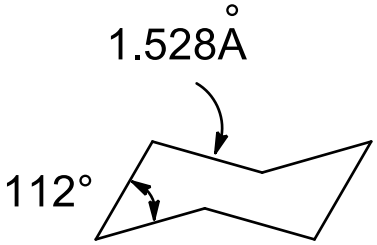


n = 1 90:10
n = 3 97(trans):3(cis)

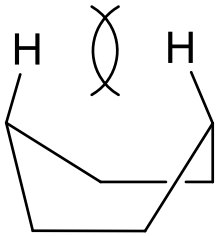


pseudo-axial

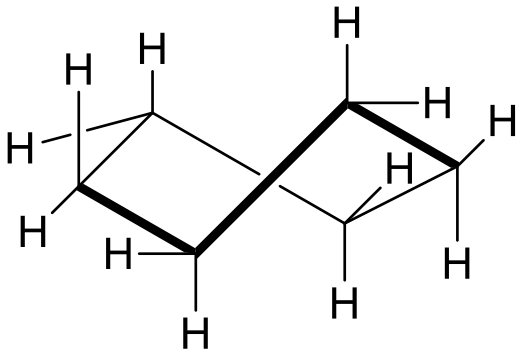
The conformations of cyclohexane



Chair form
0 kcal/mol



Boat form
7.1 kcal/mol



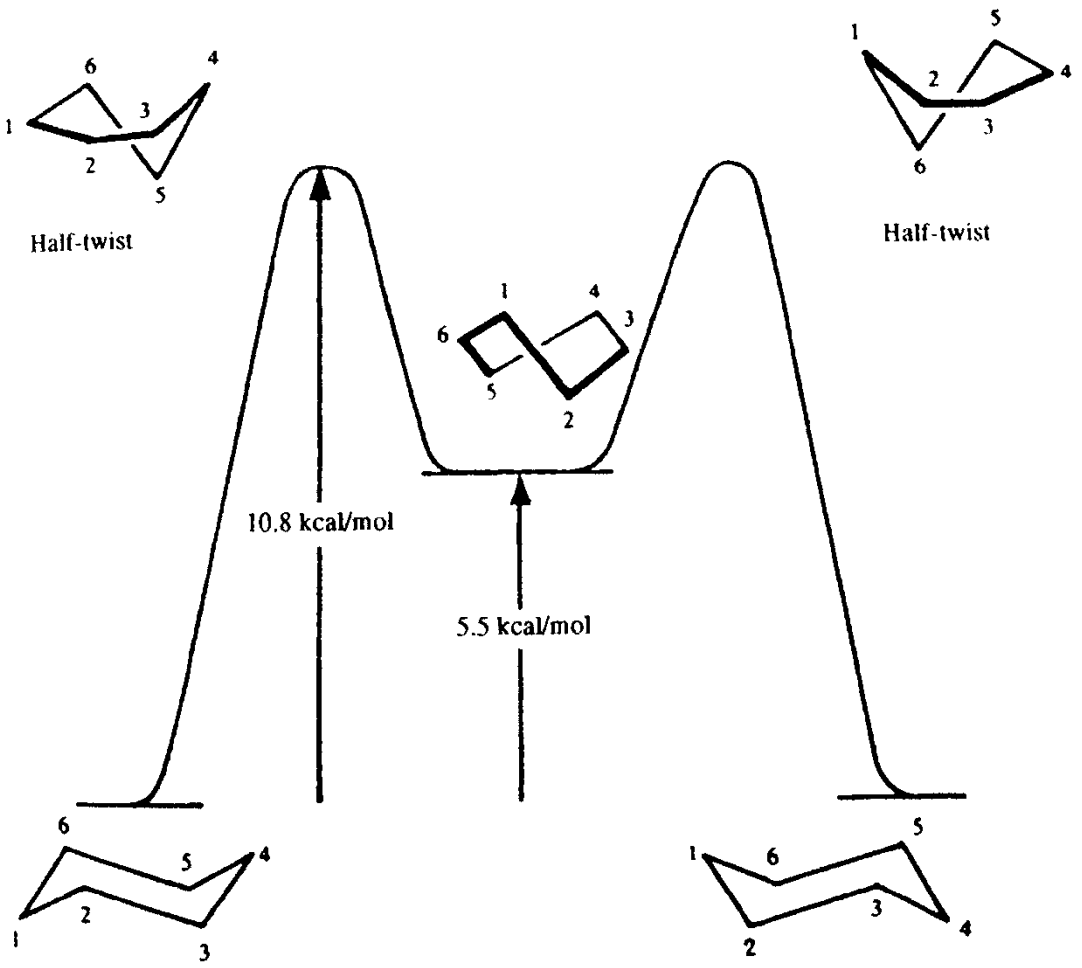
5.5 kcal/mol

inversion barrier of cyclohexane
ca. 10 kcal/mol

$\Longrightarrow$

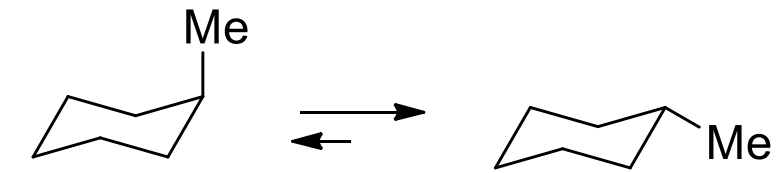
100 000 inversions/s
at 25 °C

Energy diagram for ring inversion of cyclohexane

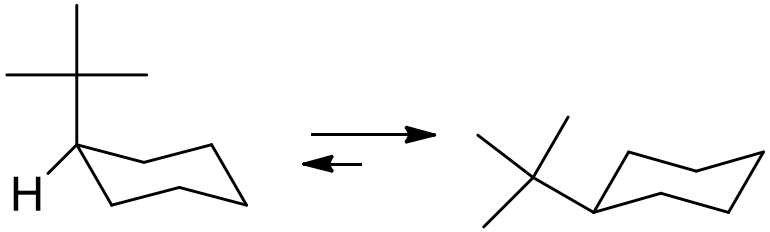


N. Leventis, S. B. Hanna, C. Sotiriou-Leventis, *J. Chem. Educ*. **1997**, *74*, 813.

The conformation of substituted cyclohexane

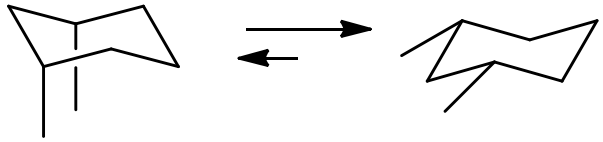


-1.8 kcal/mol



- 4.9 kcal/mol

> 99.9% equatorial

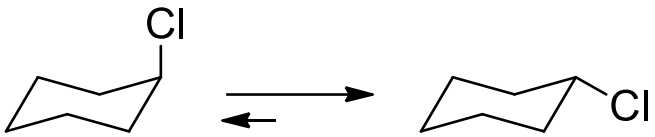


-4 kcal/mol

> 99.5% equatorial

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

Inversion of cyclohexane

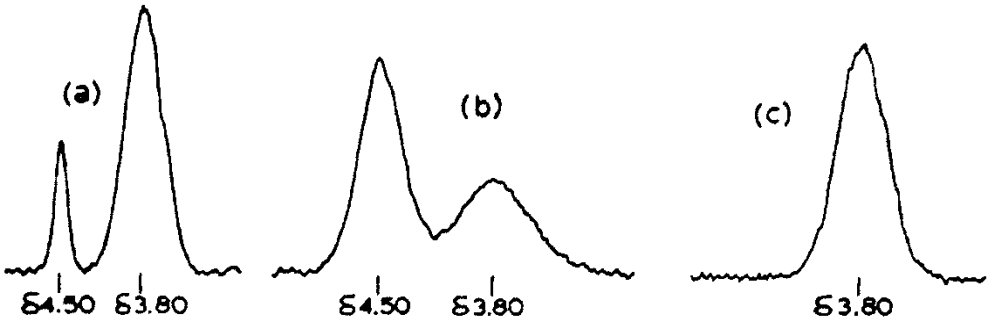


Half-life for conformation inversion of cyclohexane at various temperatures

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

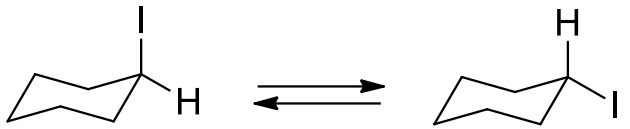
A crystallization of the equatorial isomer at -150 °C is possible

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



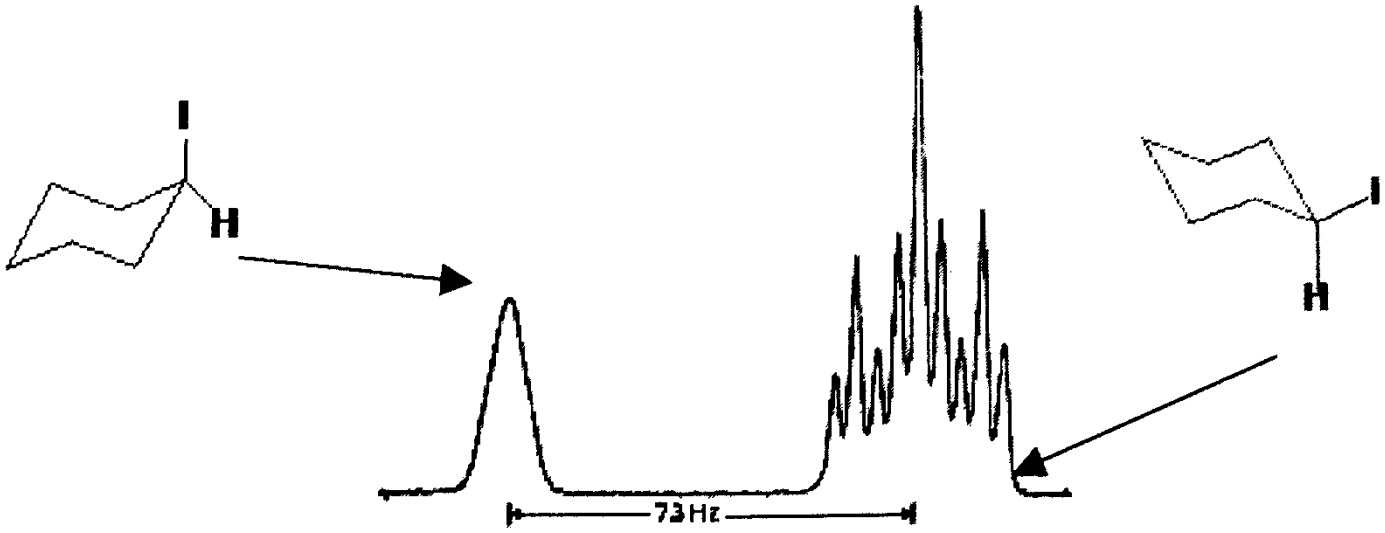
60-MHz ^{1}H-NMR spectrum for the C(1)H in chlorocyclohexane. a) axial-equatorial equilibrium at -115 °C, b) axial enriched mixture at -150 °C, c) pure equatorial conformer at -150 °C

Cyclohexyl iodide



ΔG = -0.47 kcal/mol

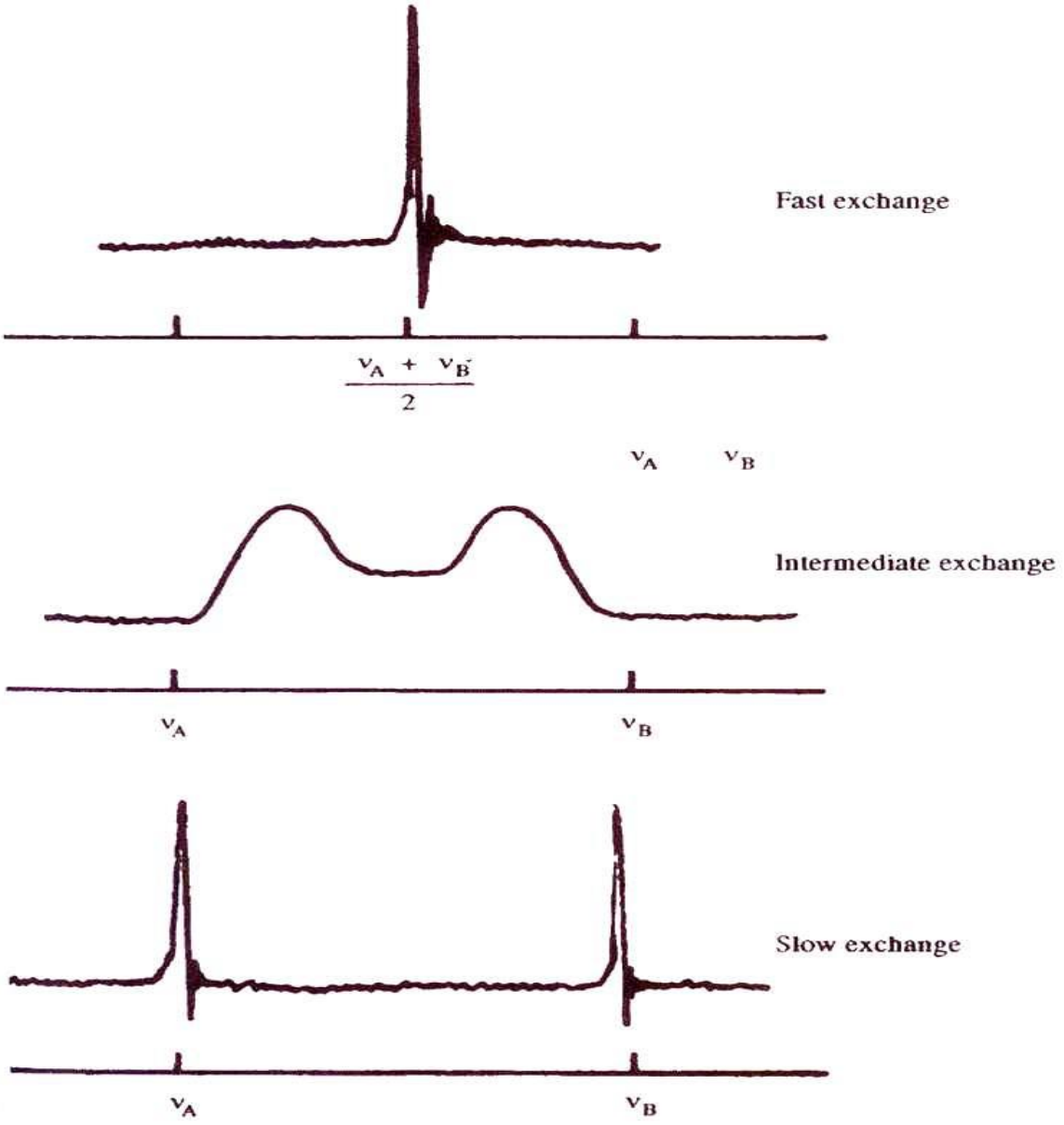
1 : 3.4



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

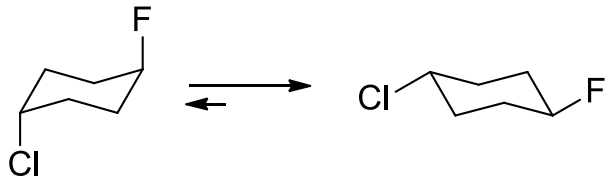
F. R. Jensen, *J. Am. Chem. Soc*. **1969**, *91*, 344.

Temperature depending NMR-spectra / exchange rate of protons

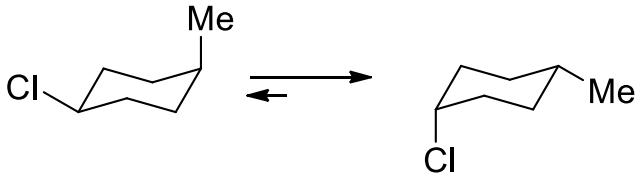


Conformational free energies (-ΔG) for some substituents

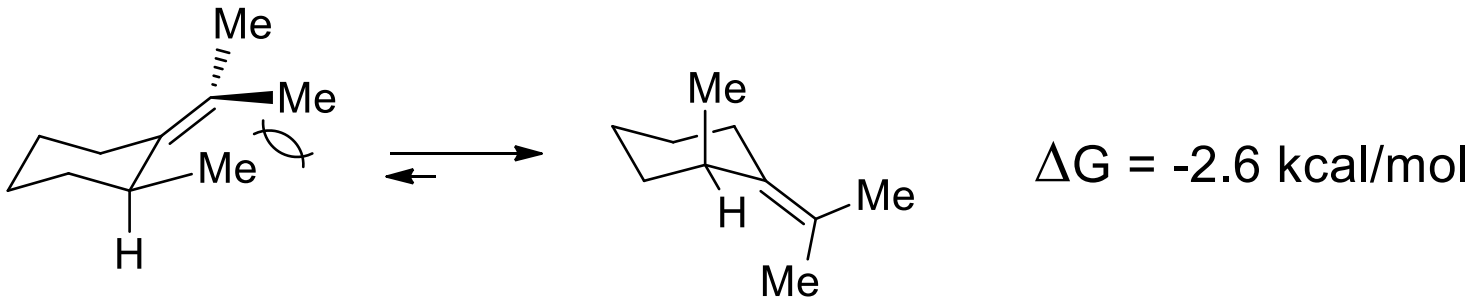
Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26	C_6H_5	2.9
Cl	0.53	CN	0.2
I	0.47	CH_3CO_2	0.71
CH_3	1.8	HO_2C	1.35
CH_3CH_2	1.8	$C_2H_5O_2C$	1.1-1.2
$(CH_3)_2CH$	2.1	HO (aprotic solvent)	0.52
$(CH_3)_3C$	>4.7	HO (protic solvent)	0.87
CH_2=CH	1.7	CH_3O	0.60
HC≡C	0.5	O_2N	1.16



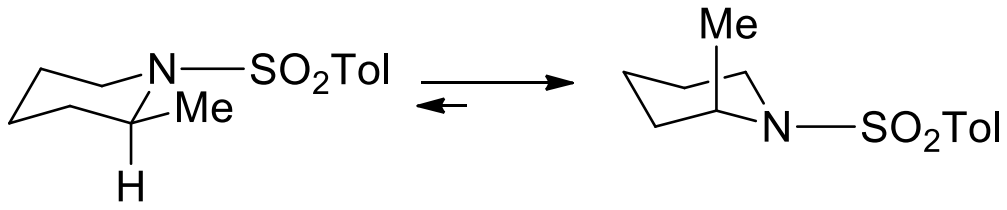
$\Delta G = -(0.26 + 0.53) = -0.79$ kcal/mol



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

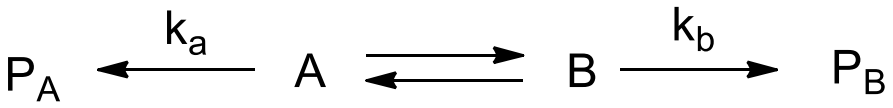


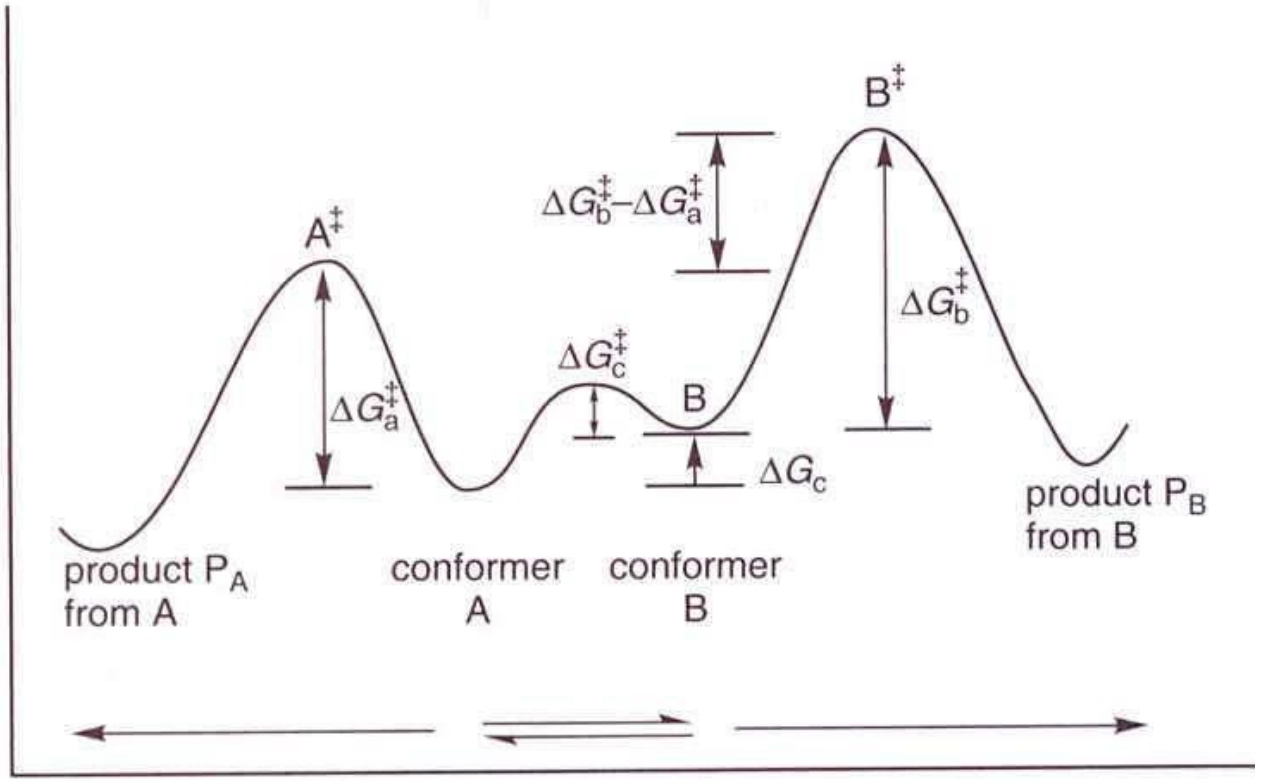
F. Johnson, *Chem. Rev*. **1968**, *68*, 375



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

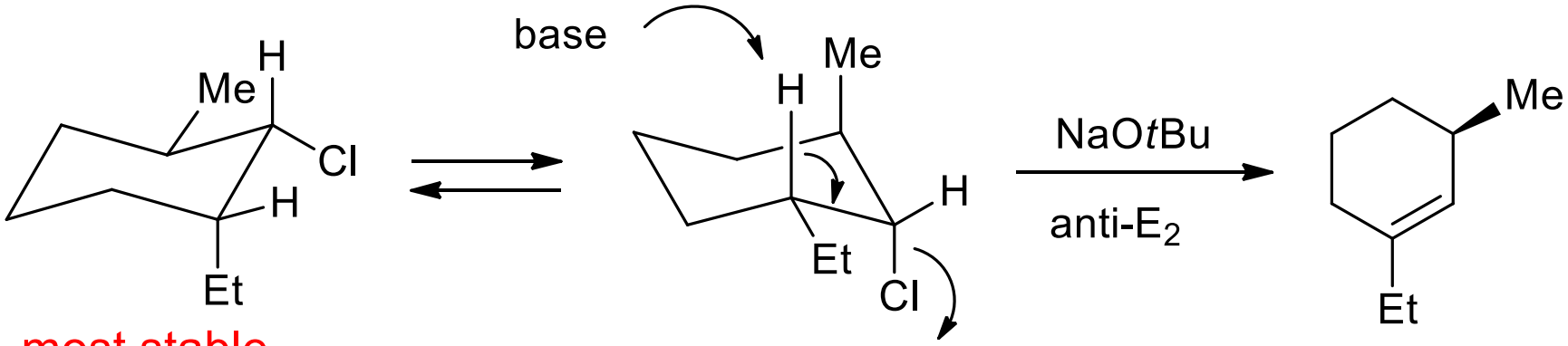




According to the Curtin-Hammett principle, the position of the equilibrium between two molecules **A** and **B** cannot be used to predict the ratio between the products $\mathbf{P_A}$ and $\mathbf{P_B}$, only the difference between the activation energies $\Delta G_B^* - \Delta G_A^*$ is relevant

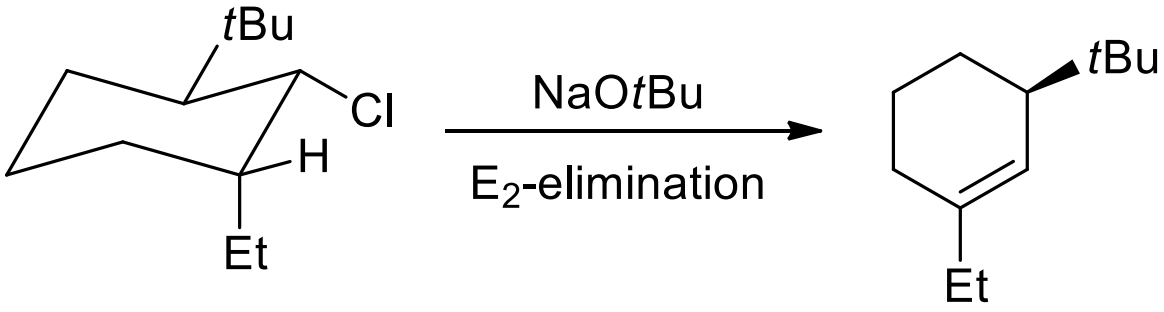
The Curtin-Hammett principle

Stereoselective E_2-elimination

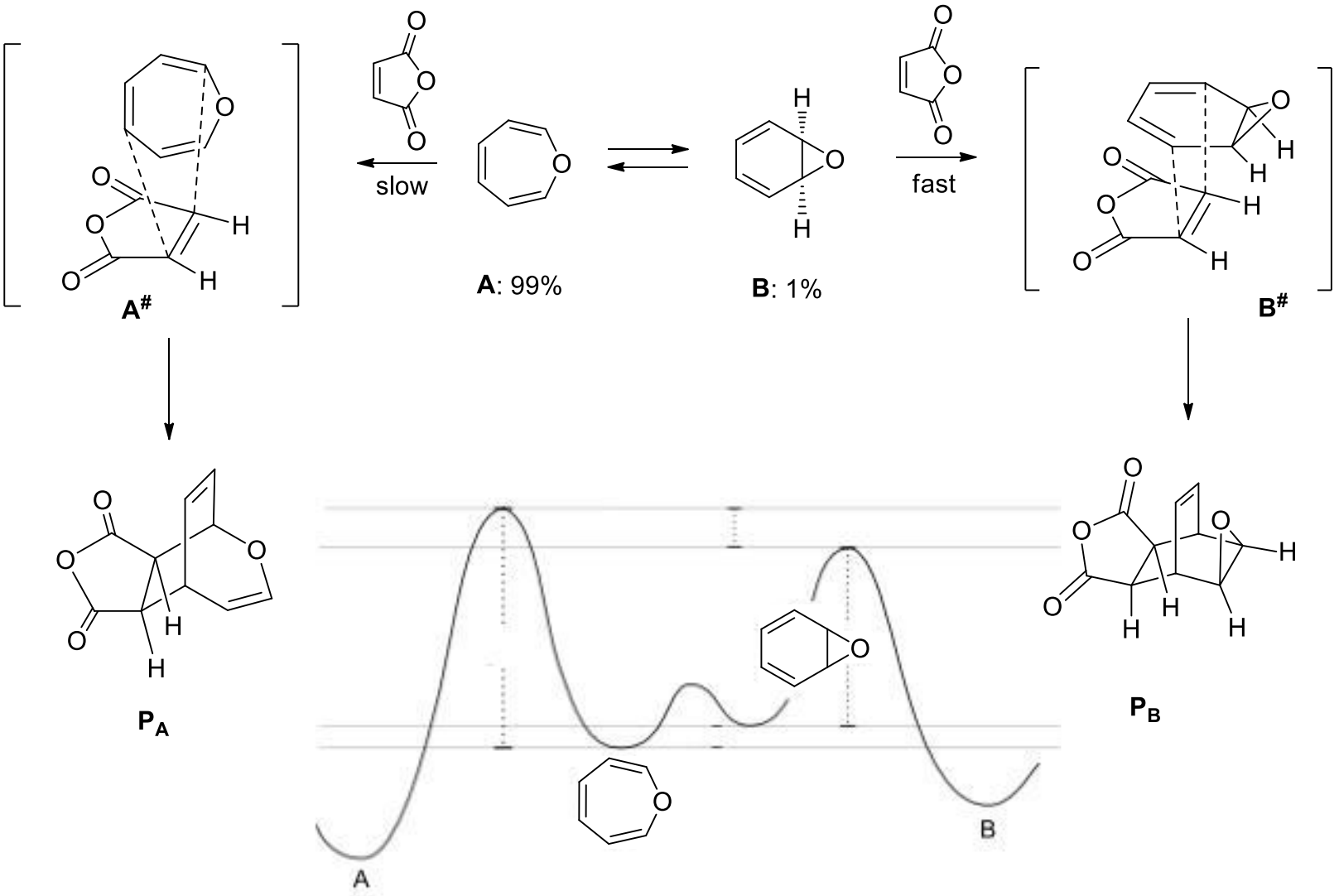


most stable conformer but unreactive for an E_2-elimination

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



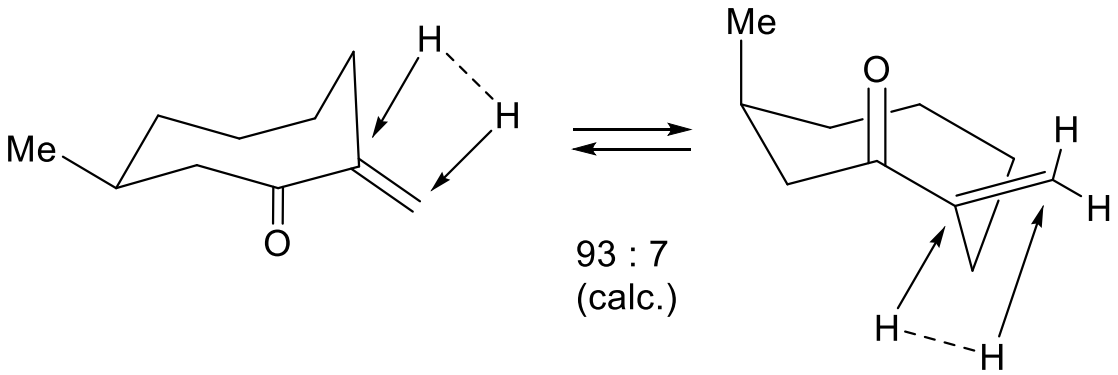
Example of the Curtin-Hammett principle

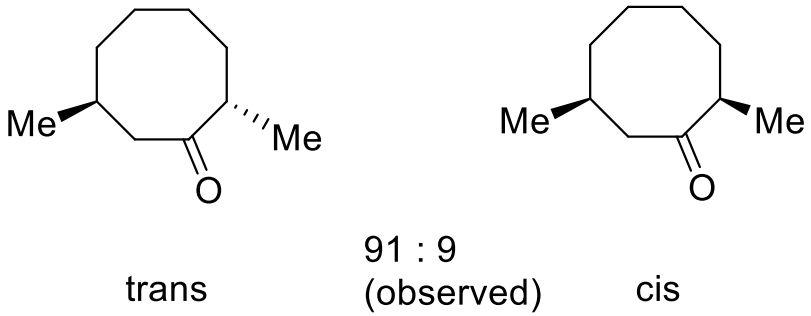


The Curtin-Hammett principle

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.

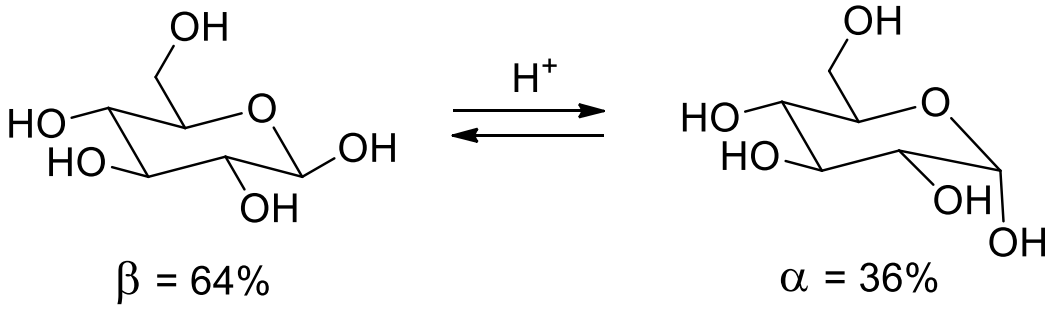
Exception: when the activation energy are very similar





W. C. Still, *Tetrahedron* **1981**, *23*, 3981

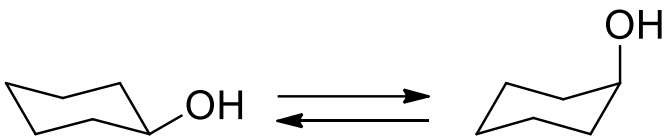
The anomeric effect



β = 64%

α = 36%

ΔG = +0.34 kcal/mol



89%

11%

ΔG = +1.24 kcal/mol

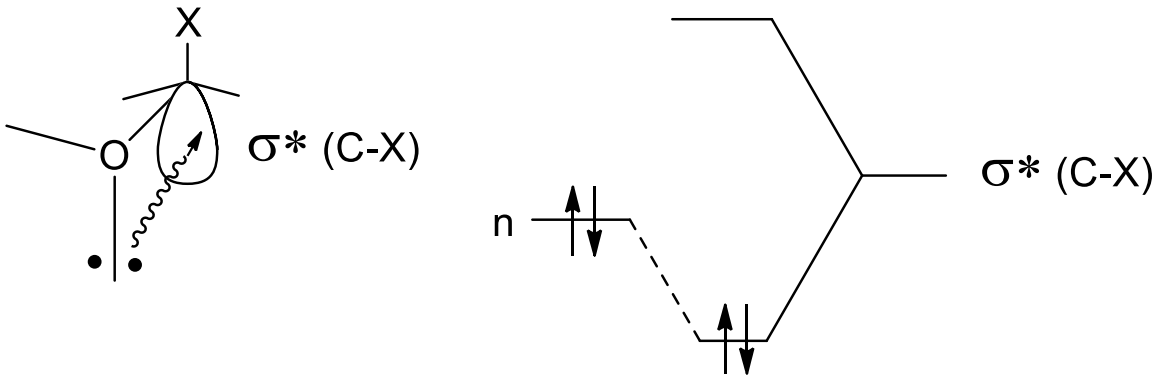
Anomeric effect: 0.9 kcal/mol

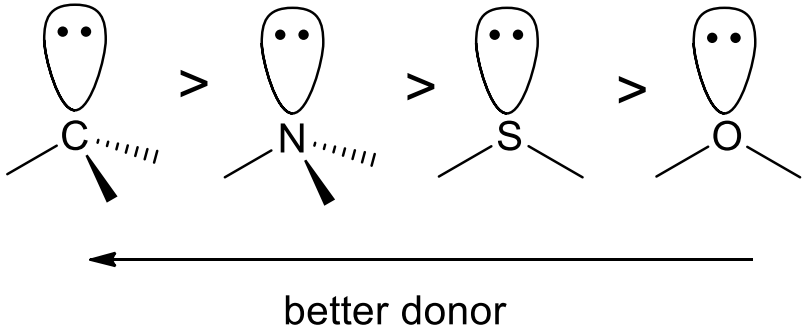
The tendency to prefer a substituent in an axial position increases with the electronegativity of the substituents. X = OAc, Cl, F,…

E. Juaristi, *Tetrahedron*, **1992**, *48*, 5019

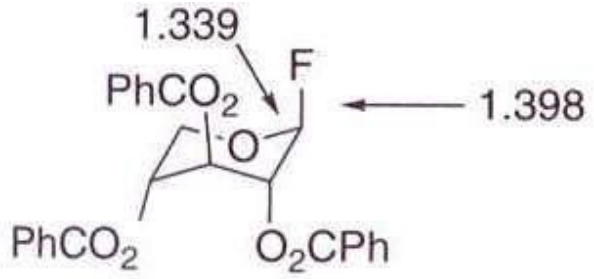
Origin of the anomeric effect

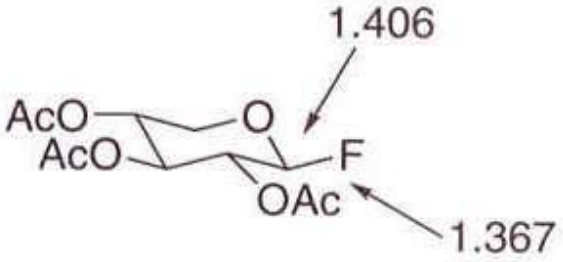
Most probable origin: hyperconjugation effect between electron lone pair of oxygen and the σ* (C-X) bond

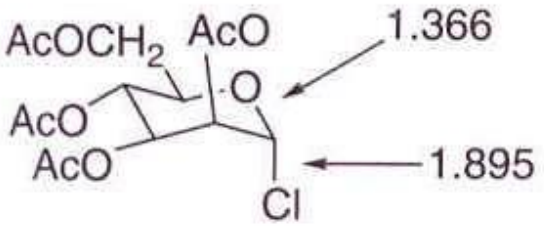


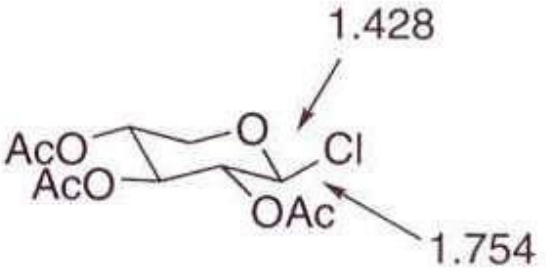


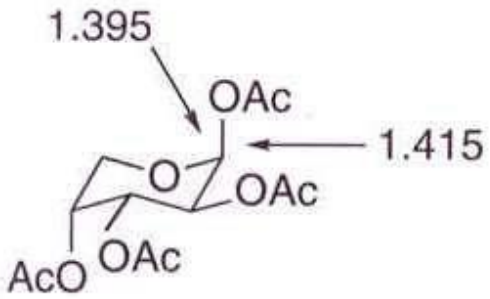
The anomeric effect

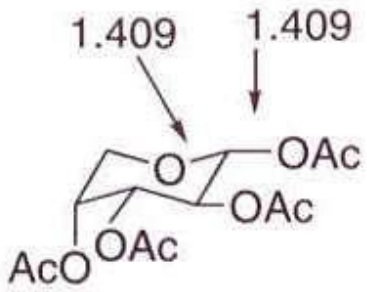








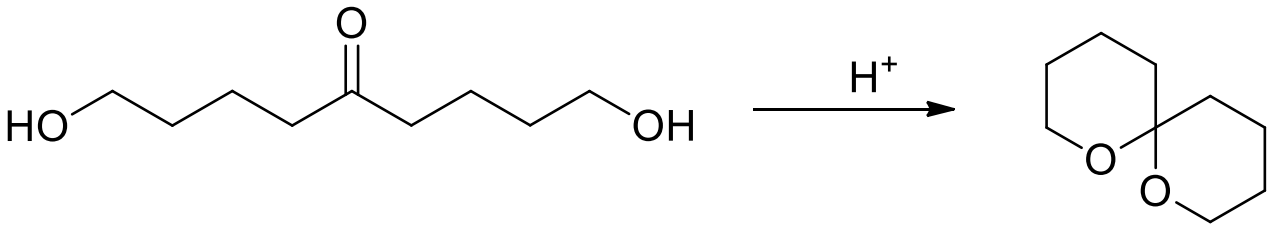


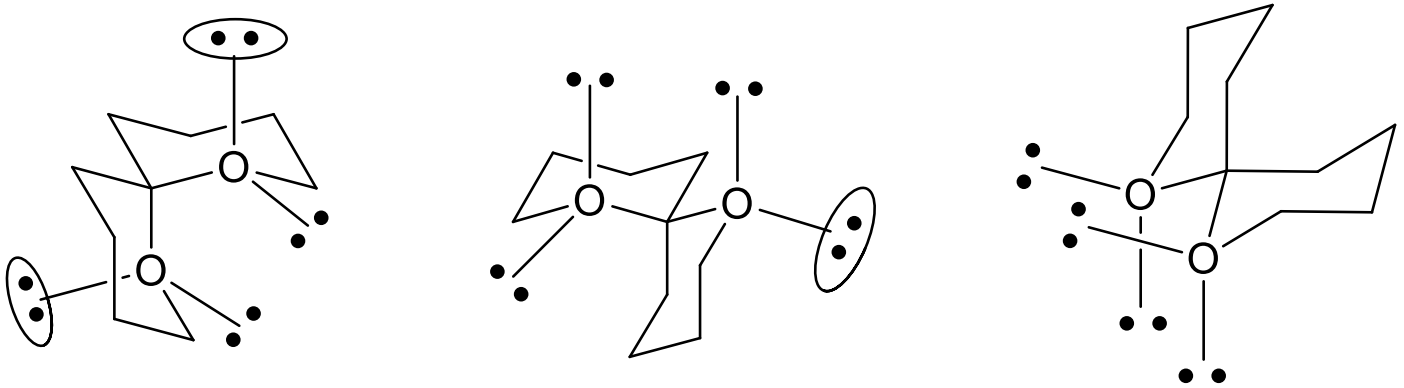


H. Paulsen, P. Luger, F. P. Heiker, *Anomeric Effect: Origin and Consequences*, ACS Symposium Series No. 87, ACS, **1975**, Chap. 5

The anomeric effect

Application: Determination of the conformation of a ketal





2 anomeric effects

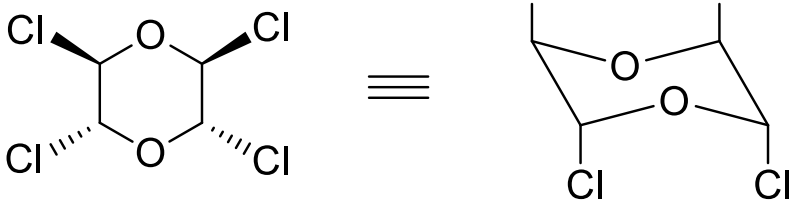
1 anomeric effect

0 anomeric effect

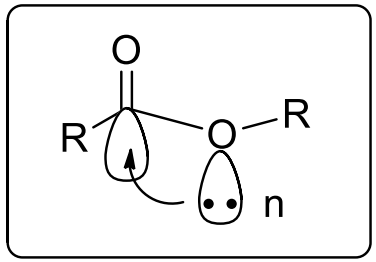
The anomeric effect

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

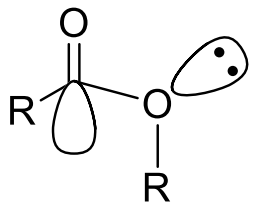
Preferred conformation for



Preferred conformation of esters :



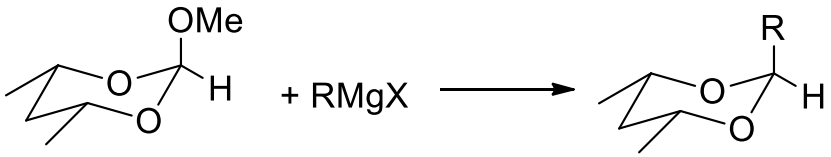
σ*(C-O)

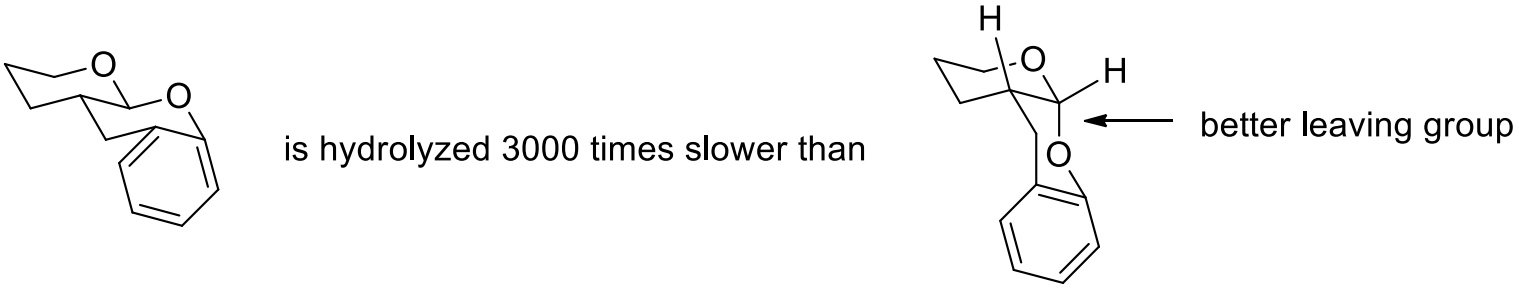


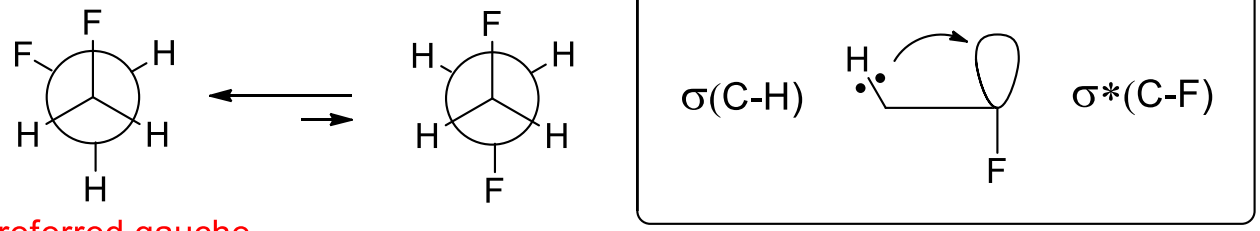
no overlap

The kinetic anomeric effect

Kinetic effects:

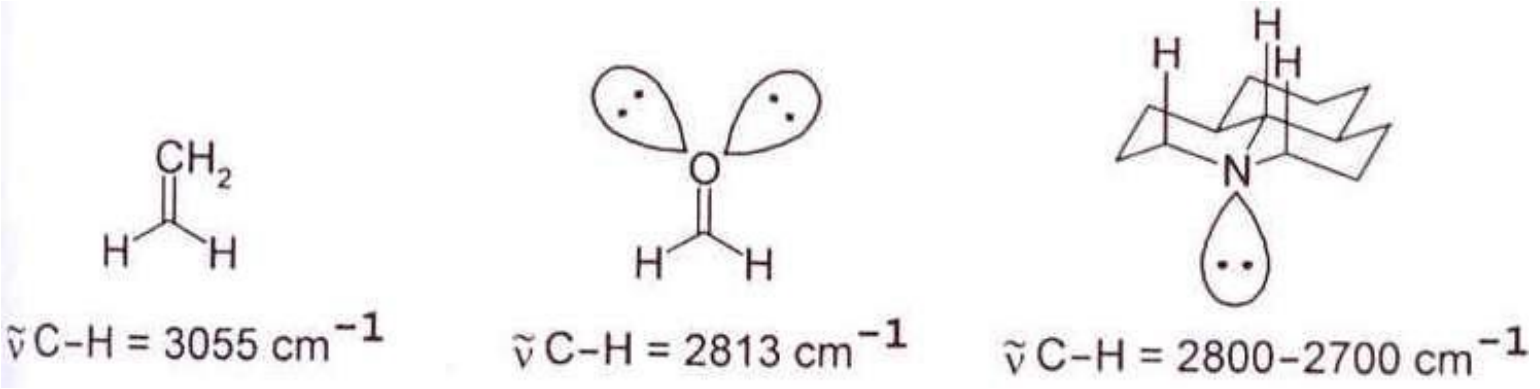






preferred gauche conformation

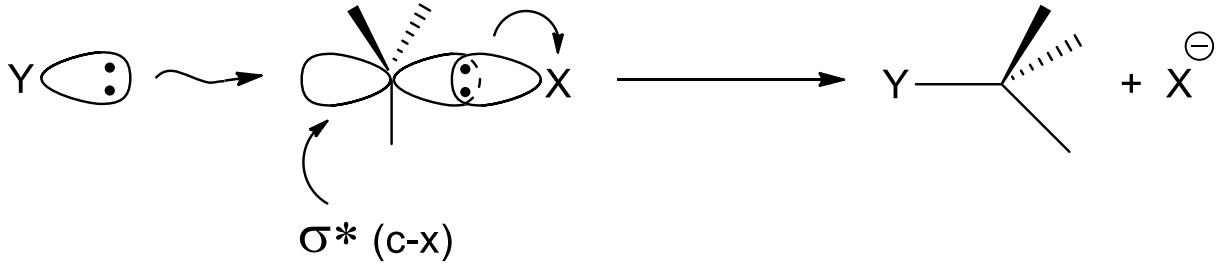
Effects on spectra and structure

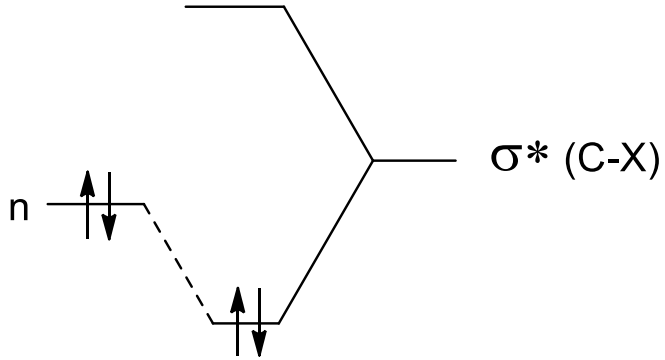


Antiperiplanar lone pairs weaken C-H bonds and reduce their IR wavenumber

Stereoelectronic effects and the Baldwin rules

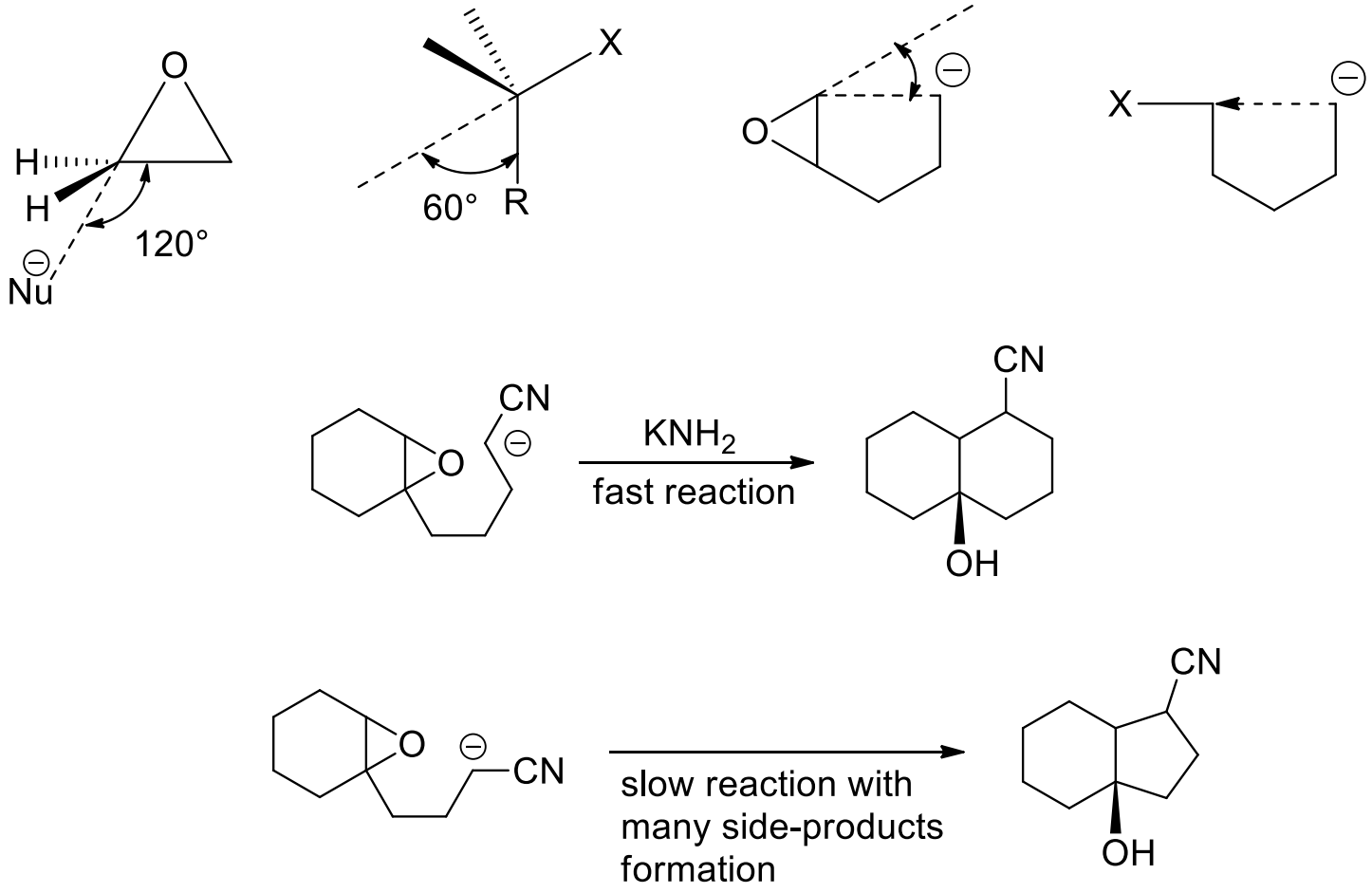
Stereochemical requirements for the S_N2-substitution: linear arrangement between the leading group and the entering nucleophile





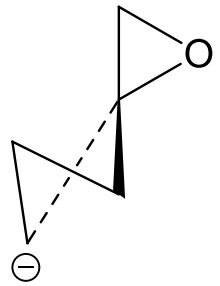
J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734-736.

Epoxide-opening

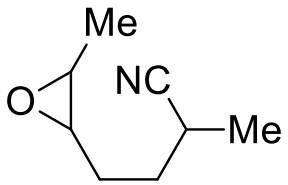


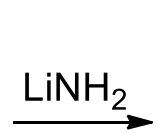
G. Stork, L. D. Cama, D. R. Coulson, *J. Am. Chem. Soc*. **1974**, *96*, 5268.

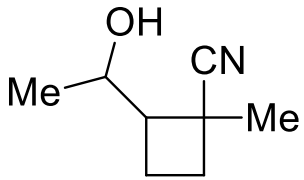
Epoxide-opening

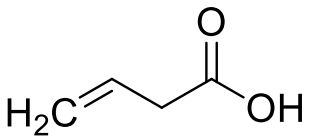


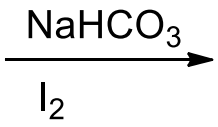
preferred conformation

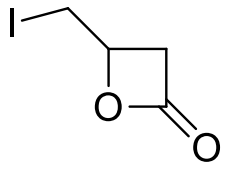


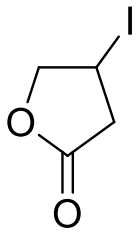




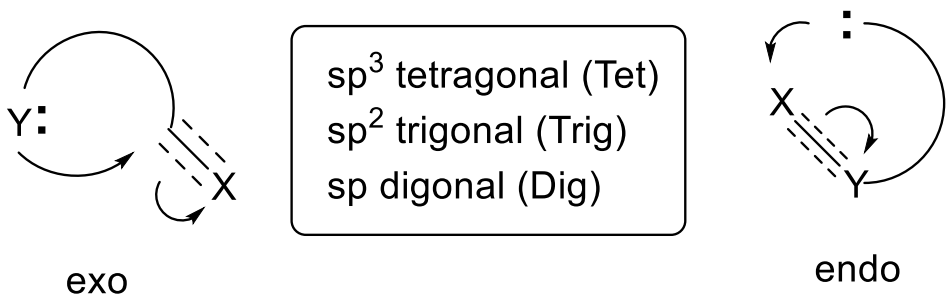








Baldwin rules



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

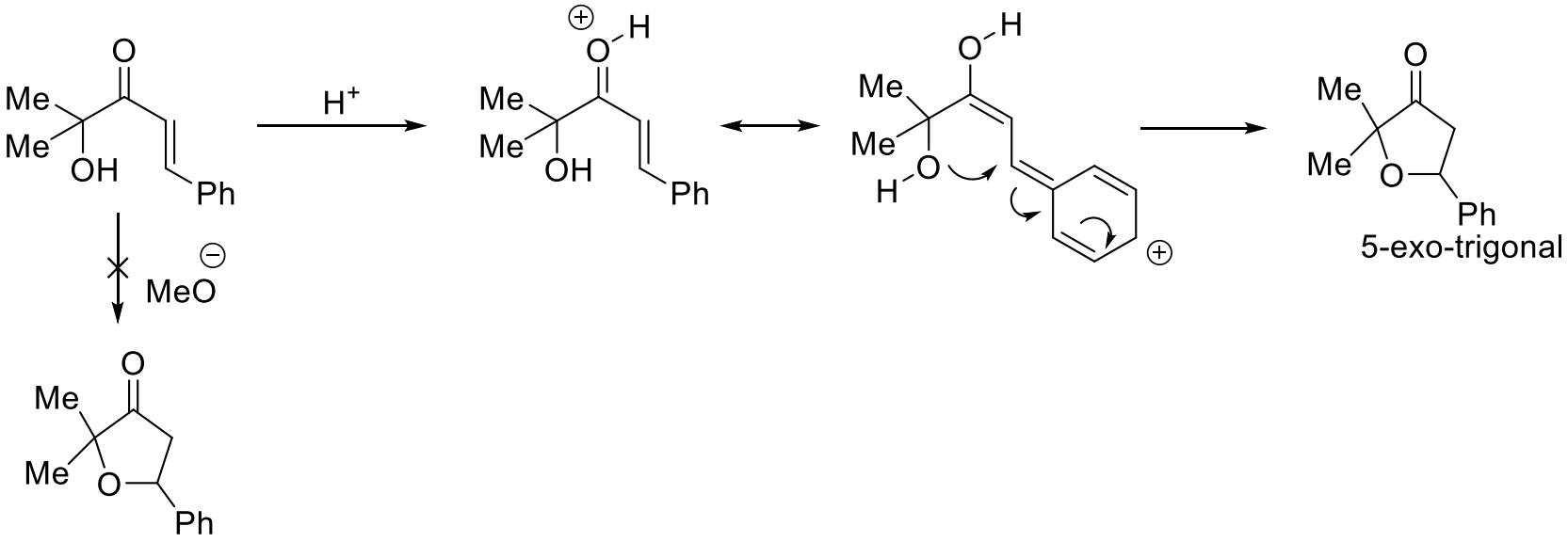
5 to 7-*Exo-Dig* are favoured

3 to 7-*Endo-Dig* are favoured

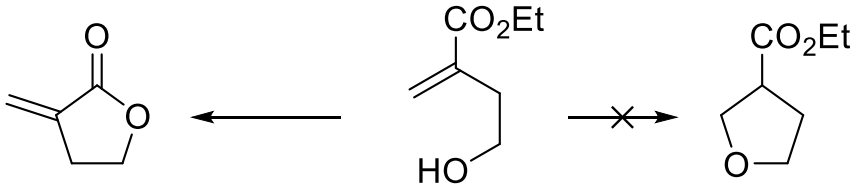
J. E. Baldwin, J. Chem. Soc., Chem. Commun., **1976**, 734-736

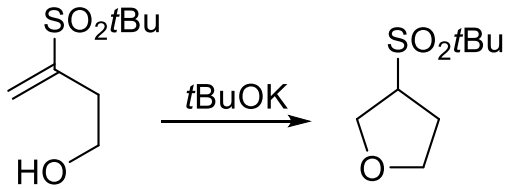
Stereoselective reactions

Examples:



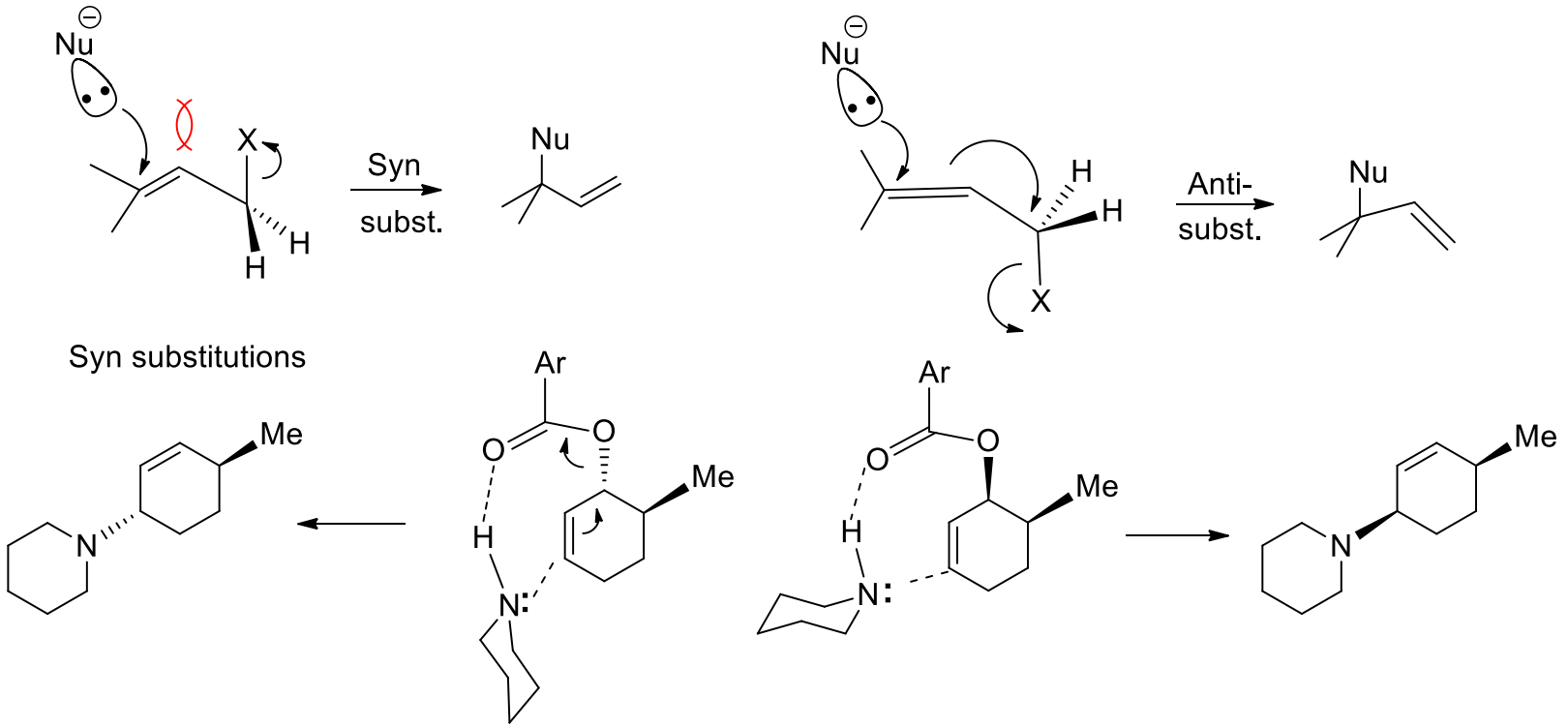
J. E. Baldwin, R. C. Thomas, L. I. Kruse, L. Silberman *J. Org. Chem*. **1977**, *42*, 3846.





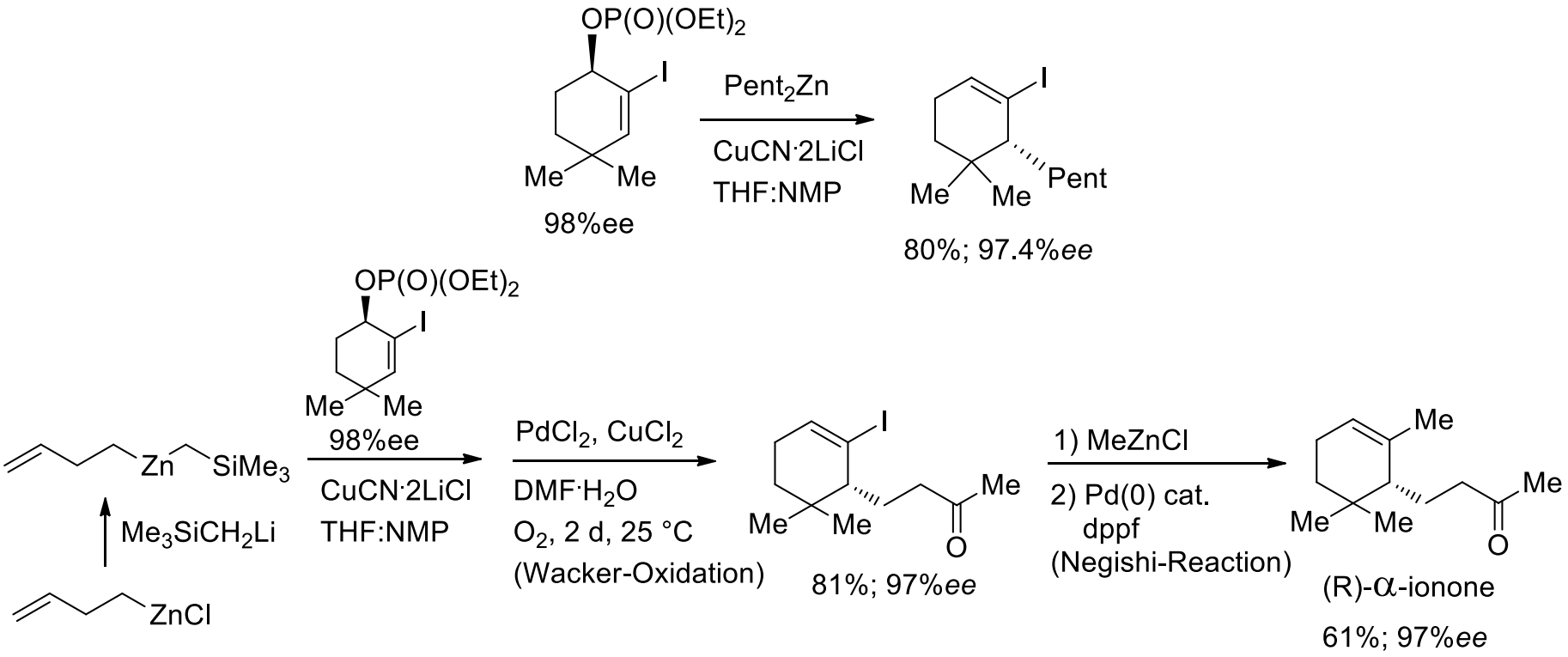
P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron Lett*. **1985**, *26*, 4455.

S_N2'-substitutions



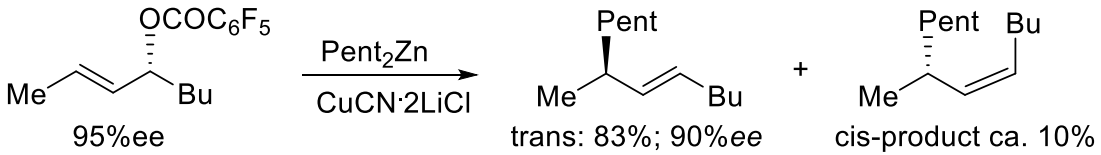
G. Stork, W. N. White, *J. Am. Chem. Soc*. **1956**, *78*, 4609. For a review see: R. M. Magid, *Tetrahedron* **1980**, *36*, 1901.

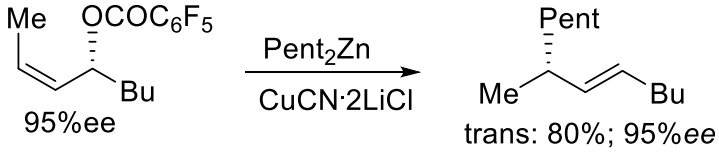
S_N2‘-substitutions with organocopper



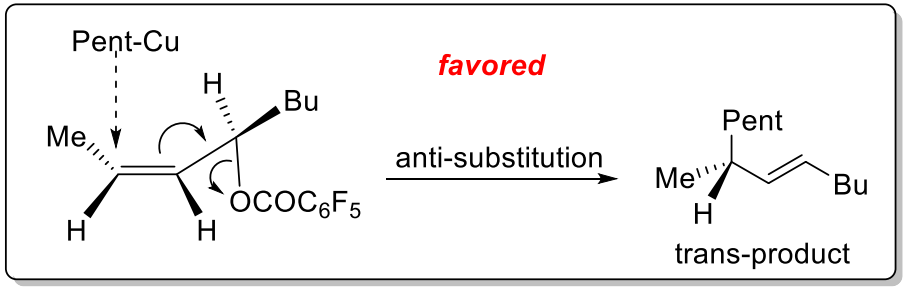
D. Soorukram, P. Knochel *Org. Lett.* **2004**, *6* , 2409

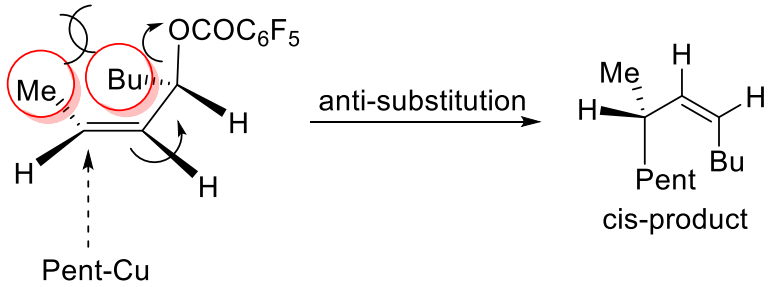
Anti-S_N2'-substitutions with organocopper





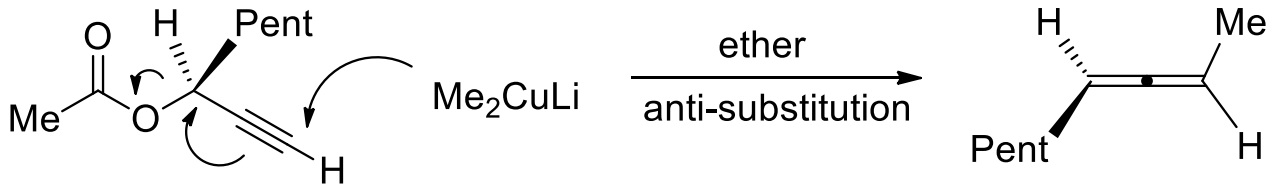
two anti-substitution TS-structures are possible:





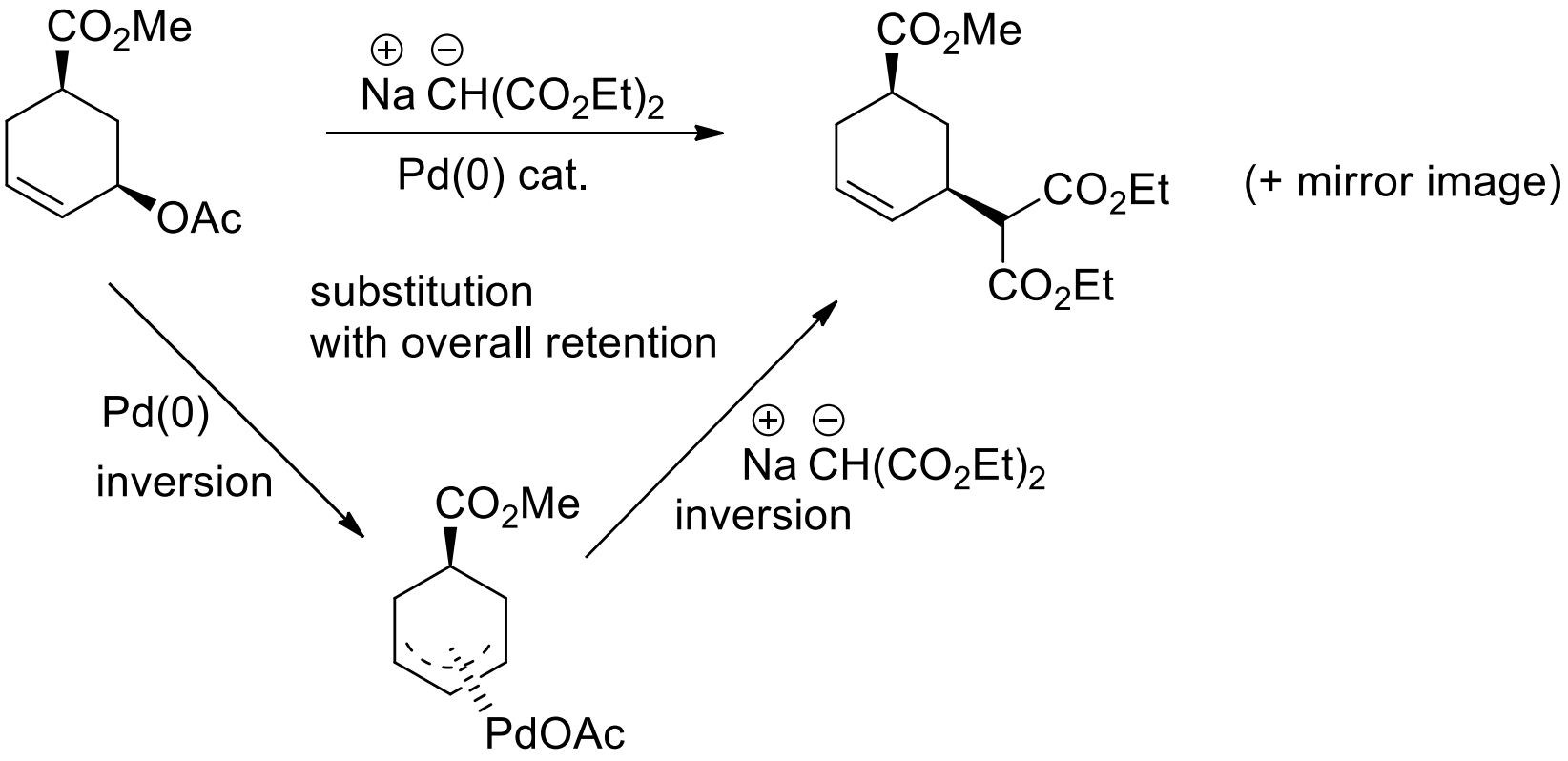
N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel, *Org. Lett.*, **2003**, *5*, 2111

Anti-substitutions at propargylic systems



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

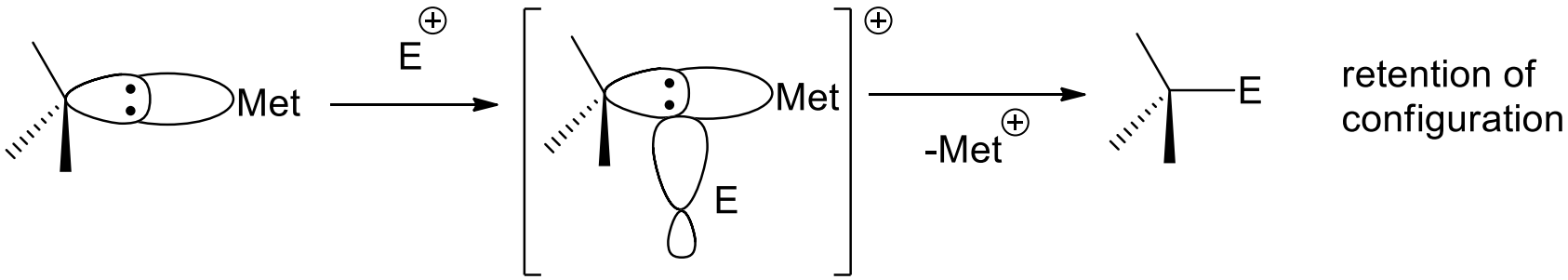
Stereoselective palladium-catalyzed allylic substitutions

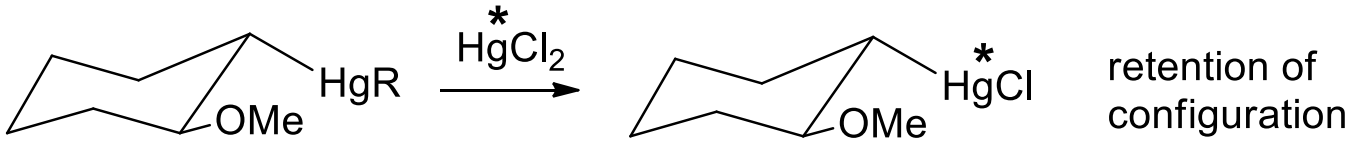


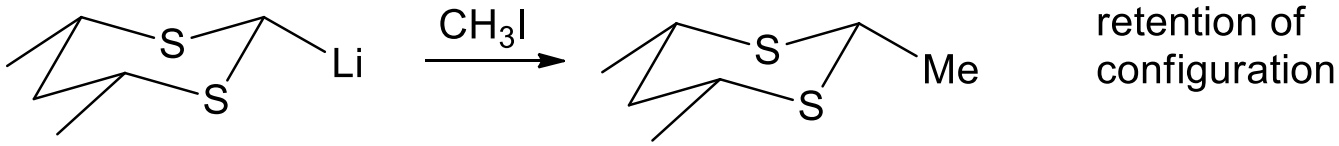
B. M. Trost, *Acc. Chem. Res*. **1980**, *13*, 385.

Electrophilic substitutions

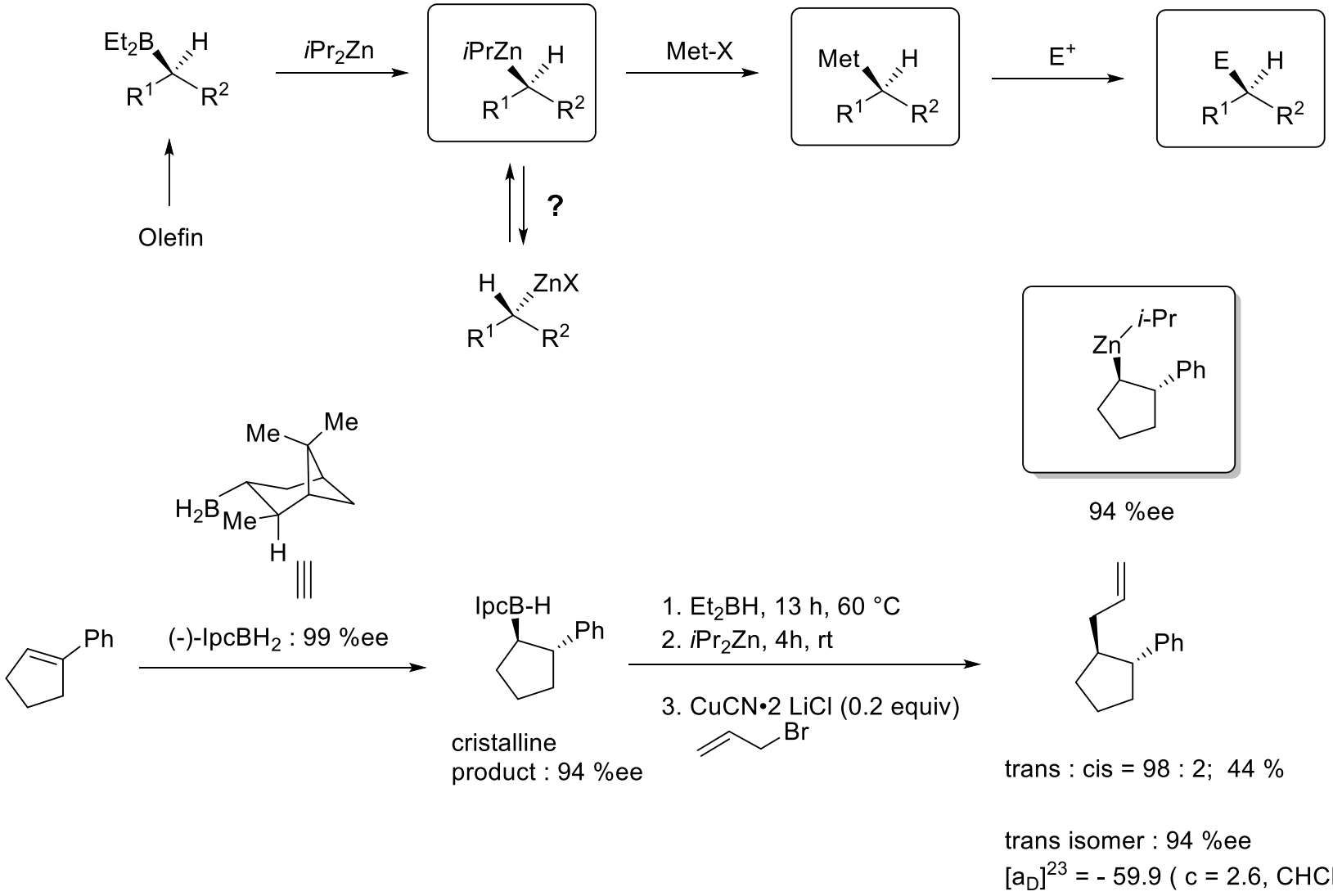
S_E2





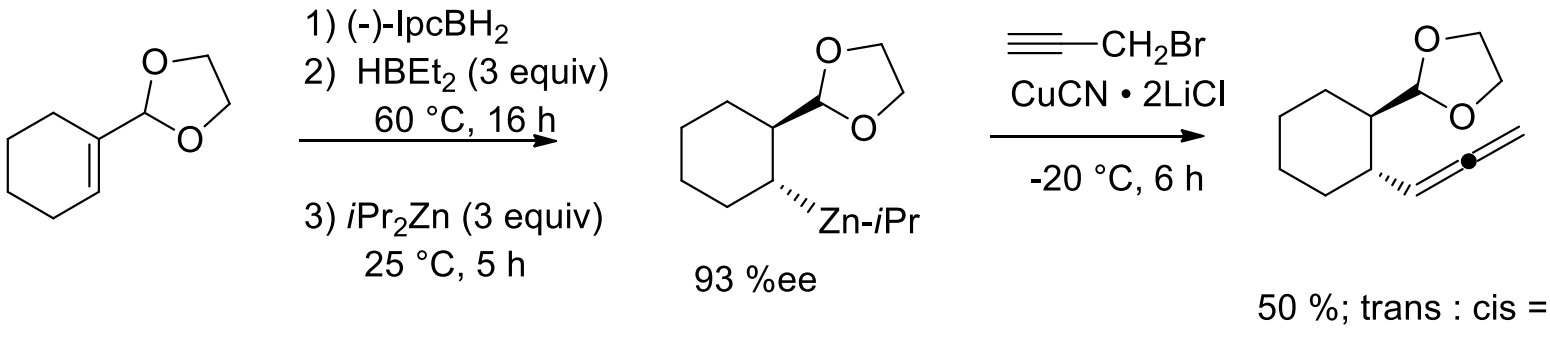


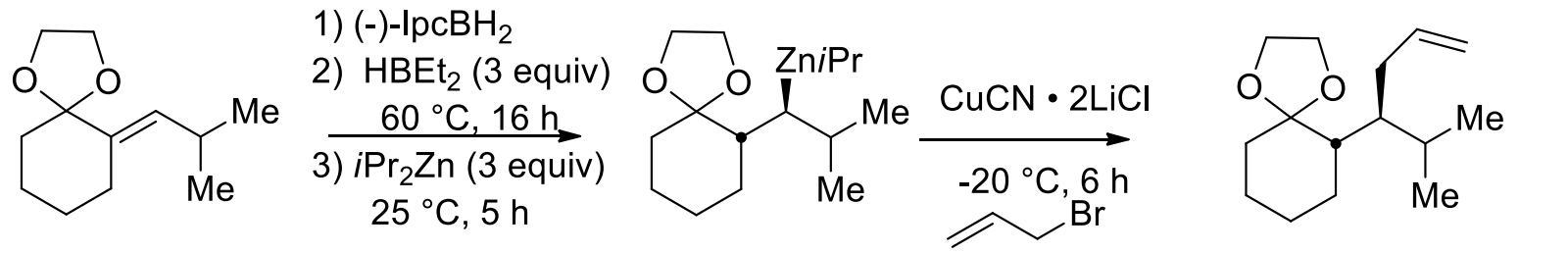
First synthesis of an optically active zinc reagent



A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel, *Chem. Eur. J*. **2000**, *6*, 2748;
C. Darcel, F. Flachsmann, P. Knochel, *J. Chem. Soc., Chem. Commun*. **1998**, 205-209.

Preparation of chiral zinc reagents

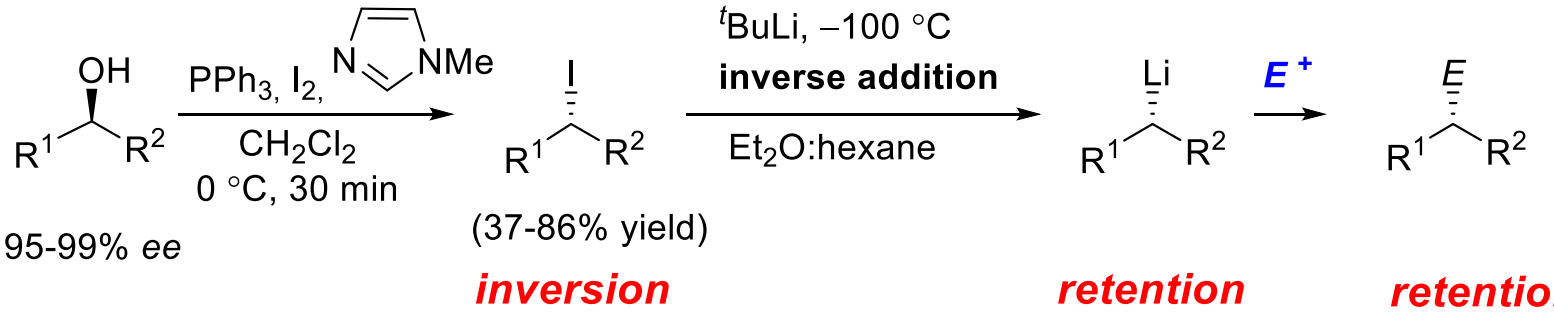


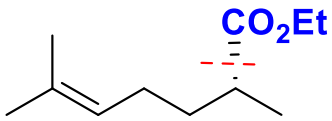


68 %; trans : cis = 94 : 6

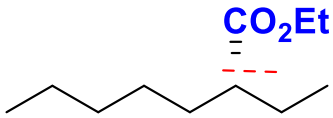
E. Hupe, Knochel, P. *Angew. Chem. Int. Ed*. **2001**, *40*, 3022

Enantiomerically enriched secondary alkyllithium reagents

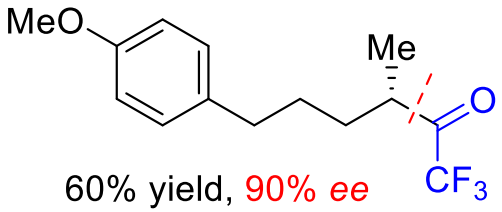




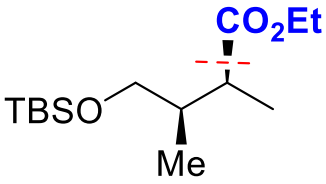
56% yield, 96% *ee*
(from 98% *ee*)



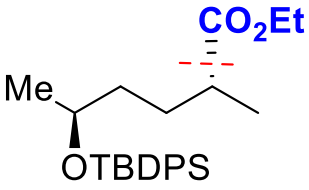
54% yield, 92% *ee*
(from 95% *ee*)



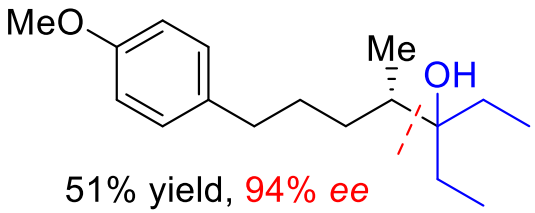
60% yield, 90% *ee*
(from 98% *ee*)



70% yield, 99% *ee*,
d.r.=95:5
(from 99% *ee* and d.r.=98:2)



62% yield, 99% *ee*,
d.r.=99:1
(from 99% *ee* and d.r.=99:1)



51% yield, 94% *ee*
(from 98% *ee*)

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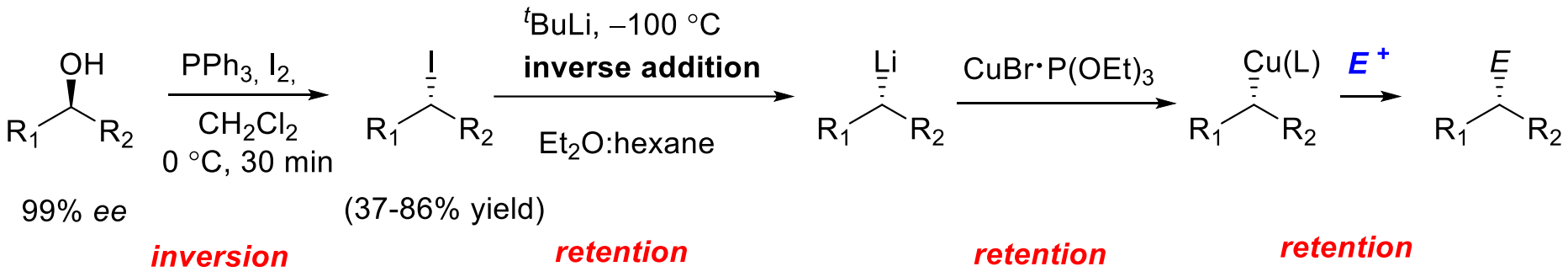
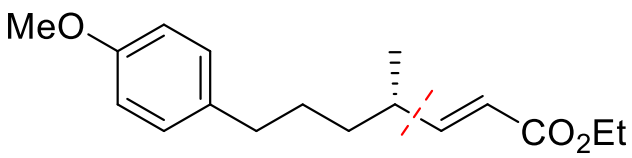
Enantiomerically enriched secondary alkylcopper reagents



99% *ee*

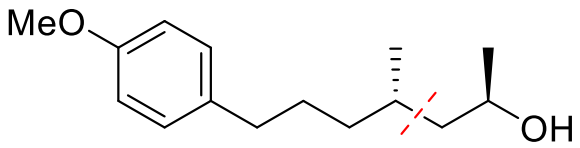
(37-86% yield)

inversion ***retention*** ***retention*** ***retention***



47% yield, **92% *ee***

E $^{+}$ = CO_2Et



56% yield, **99% *ee***, d.r. = 90:10

E $^{+}$ = O Me

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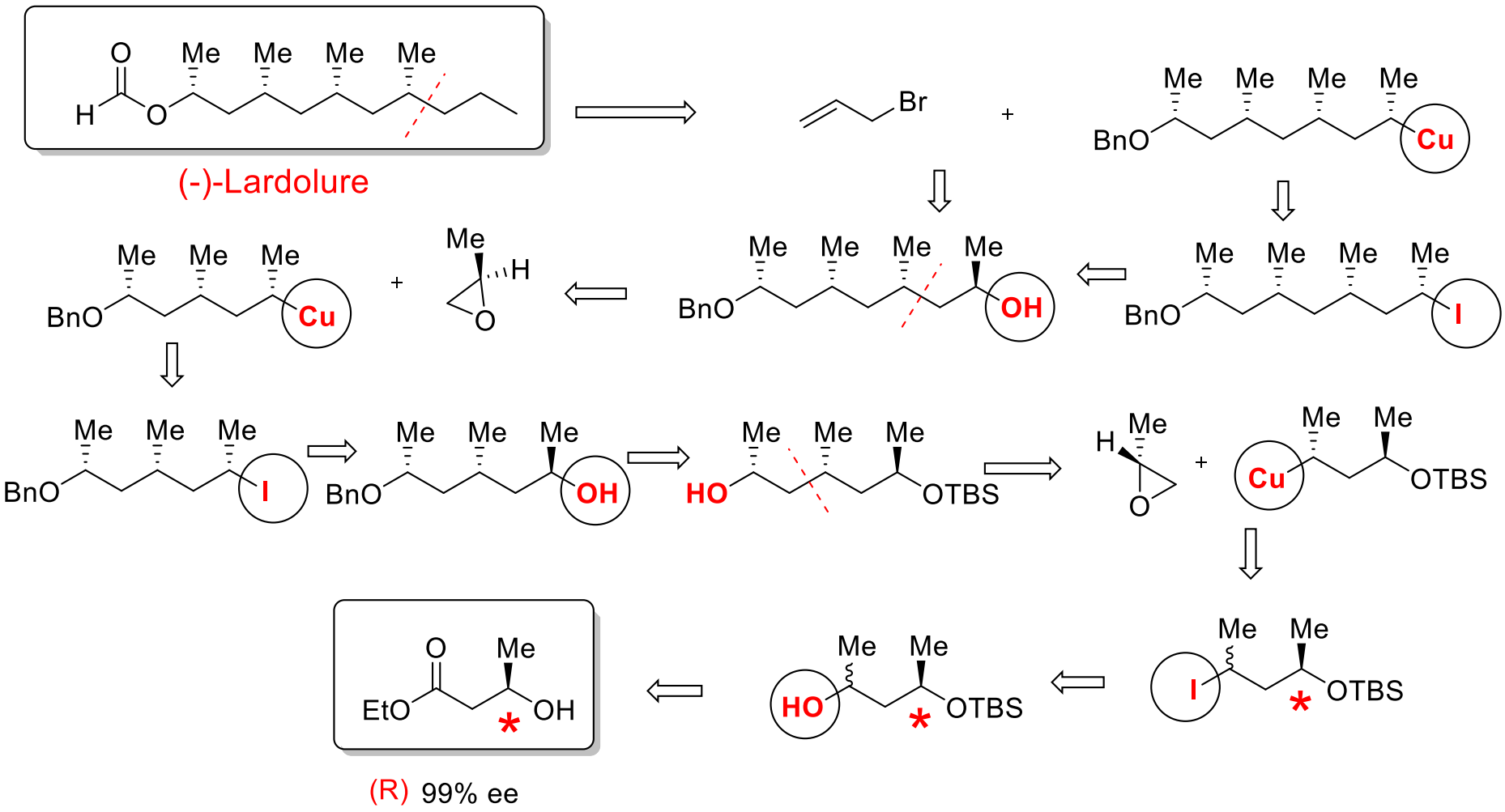
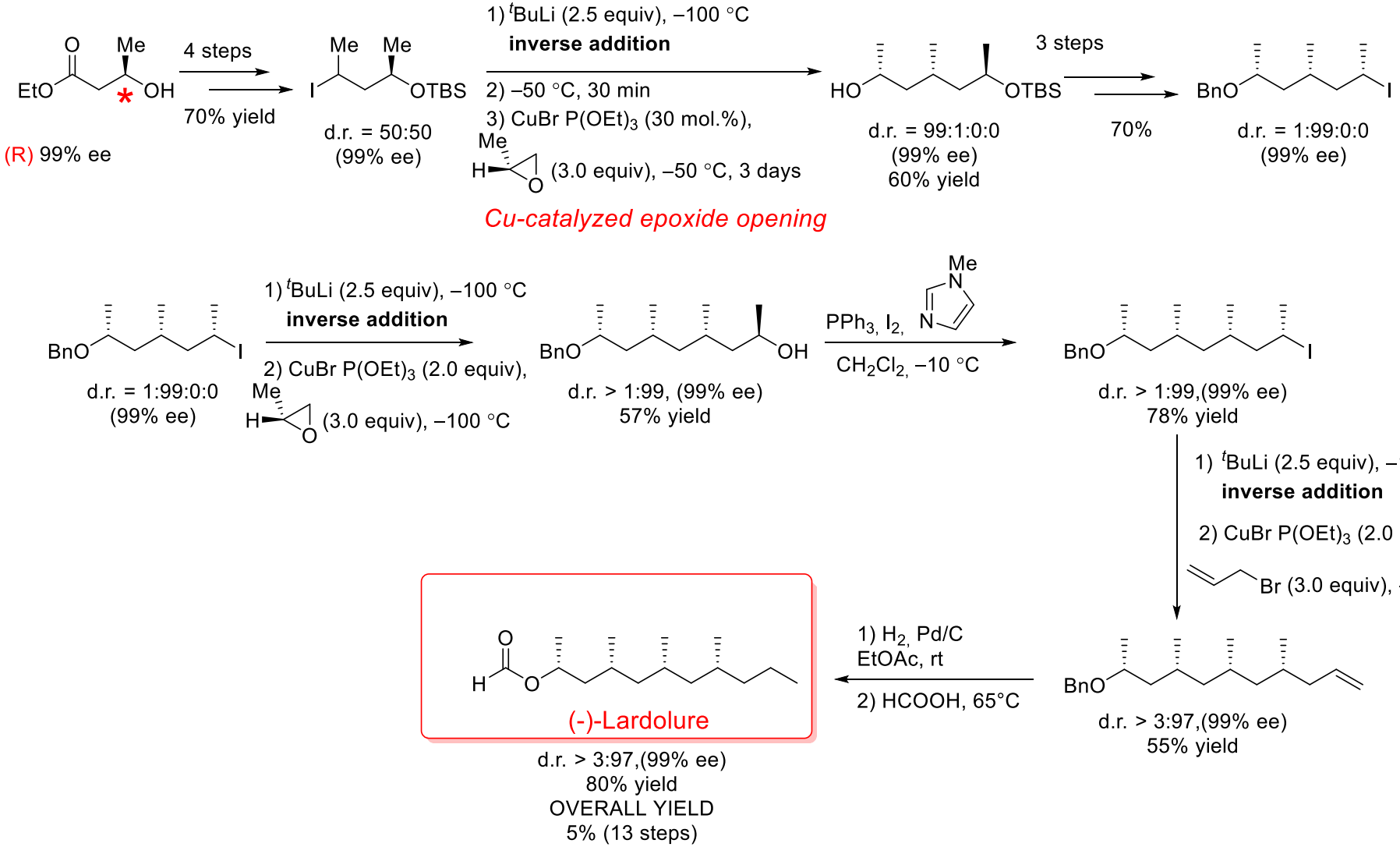
Synthesis of (-)-lardolure using chiral lithium and chiral copper reagents



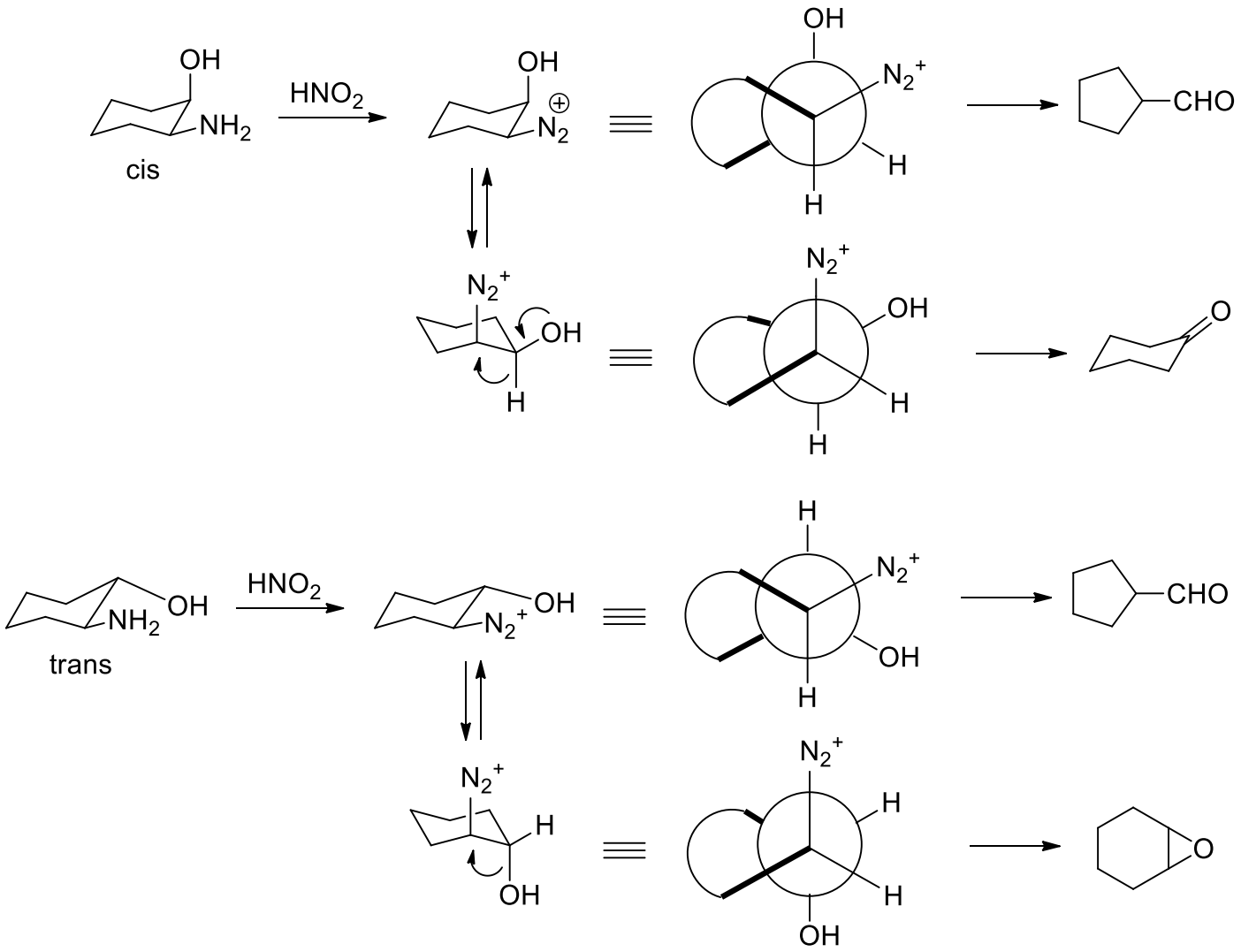
Varvara Morozova, Kohei Moriya, Karl Nehlsen, Paul Knochel, **2016**

Synthesis of (-)-lardolure using enantiomerically enriched Li- and Cu-reagents



Varvara Morozova, Kohei Moriya, Paul Knochel, **2017**

Stereoselective rearrangements

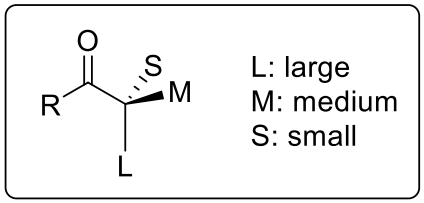


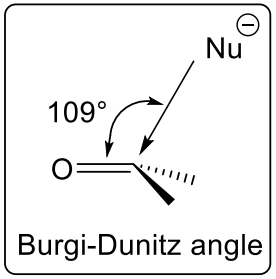
Only the bond in anti-arrangement to the leading group undregoes the migration

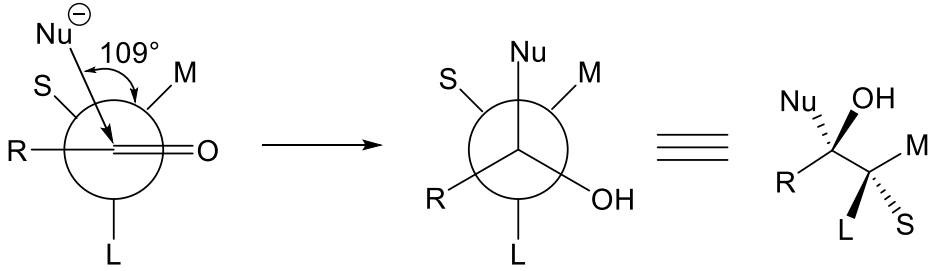
M. Chérest, H. Felkin, *J. Chem. Soc*. **1965**, 2513.

Nucleophilic addition to ketones and aldehydes

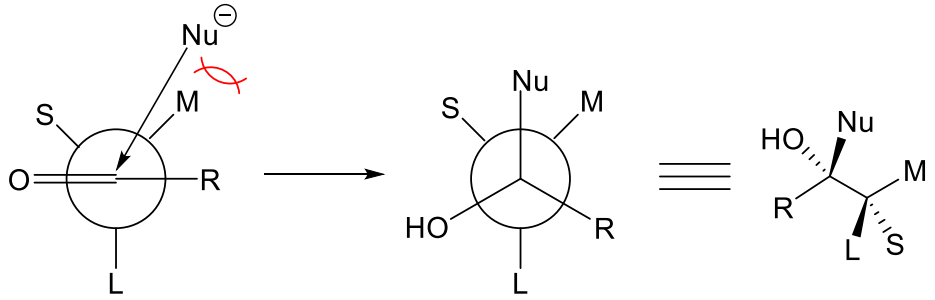
Cram-rule





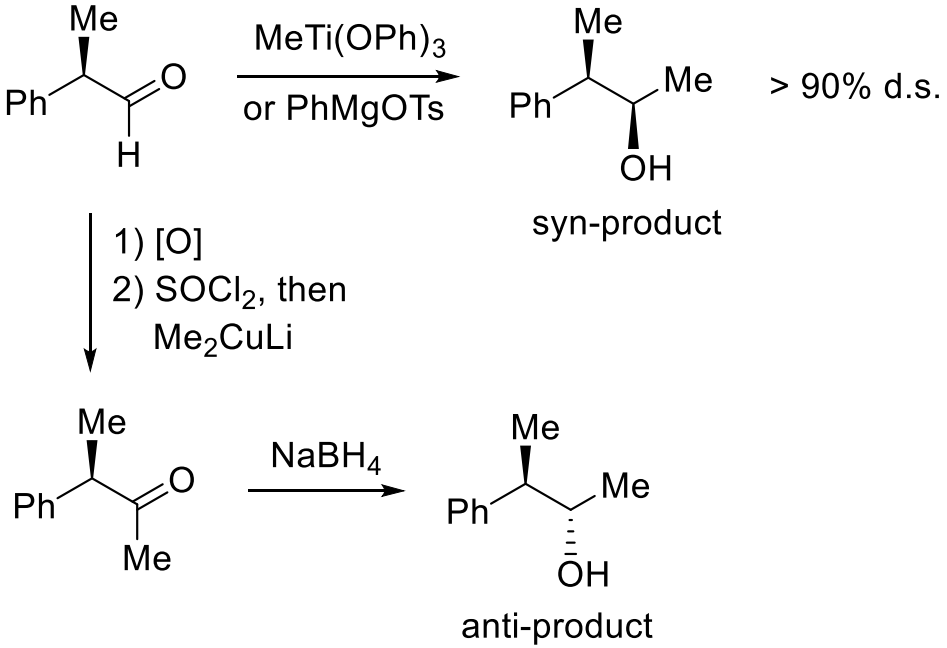


preferred direction
of the addition

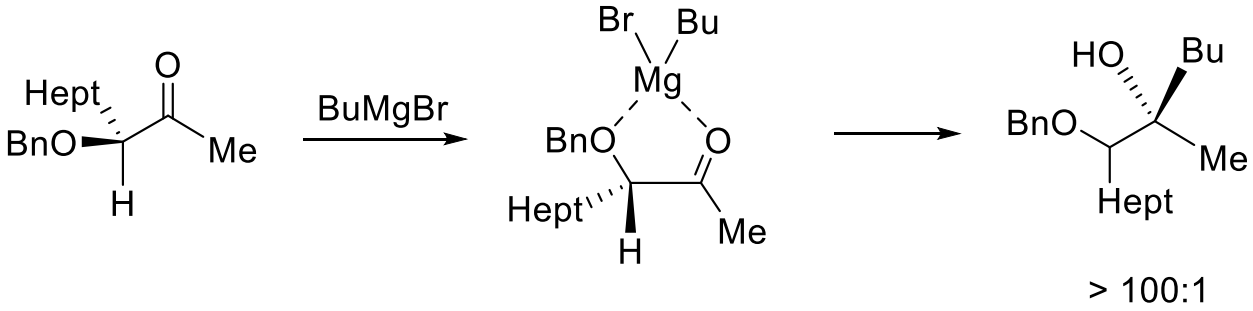


preferred direction
of the addition

Diastereoselective reactions

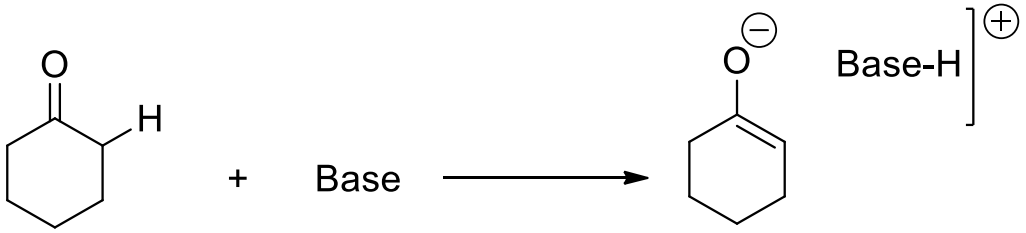


Chelate model



M. Reetz, Angew. Chem. 1992, 104, 333

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

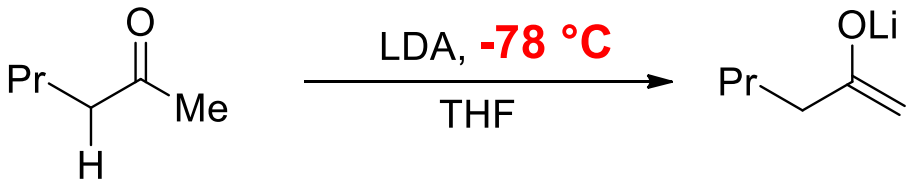


	pK_{DMSO}
$MeCH_2$-NO_2	16.7
$PhCOCH_3$	24.7
$EtCOCH_2Me$	27.1
$PhSO_2CH_3$	29.0
$(Me_3Si)_2NH$	30.0
CH_3CN	31.0
i-Pr_2NH	35.0
$PhCH_3$	43.0
CH_4	56.0

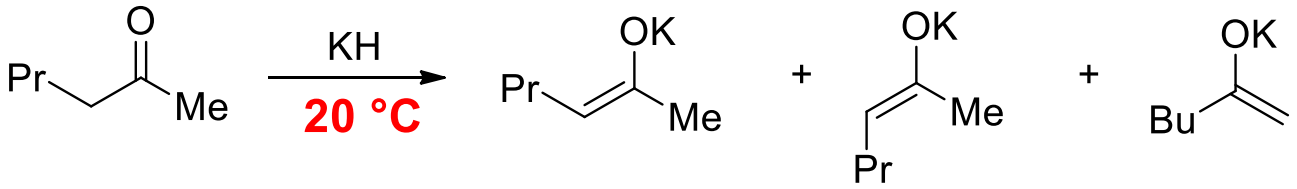
Bordwell acidity scala in DMSO: *Acc. Chem. Res*. **1988**, *21*, 456.

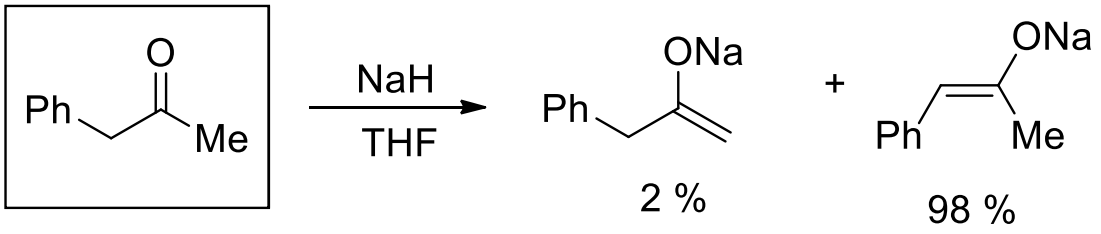
The aldol reaction

Kinetic control:

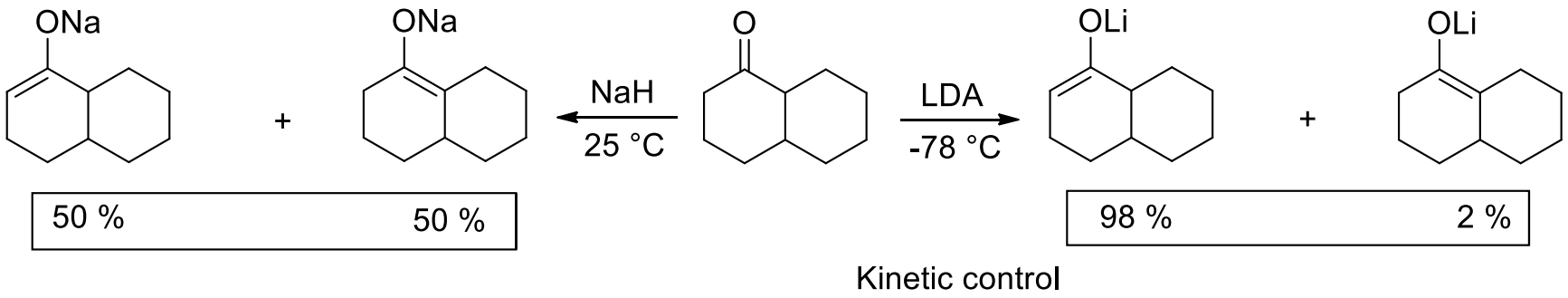


Thermodynamic control:

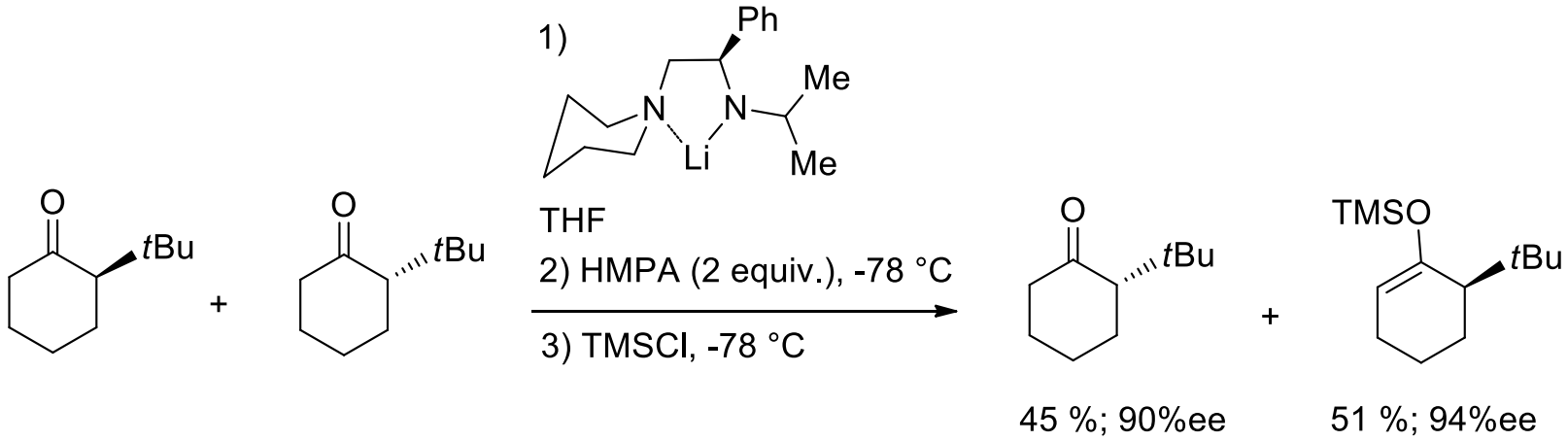




The aldol reaction

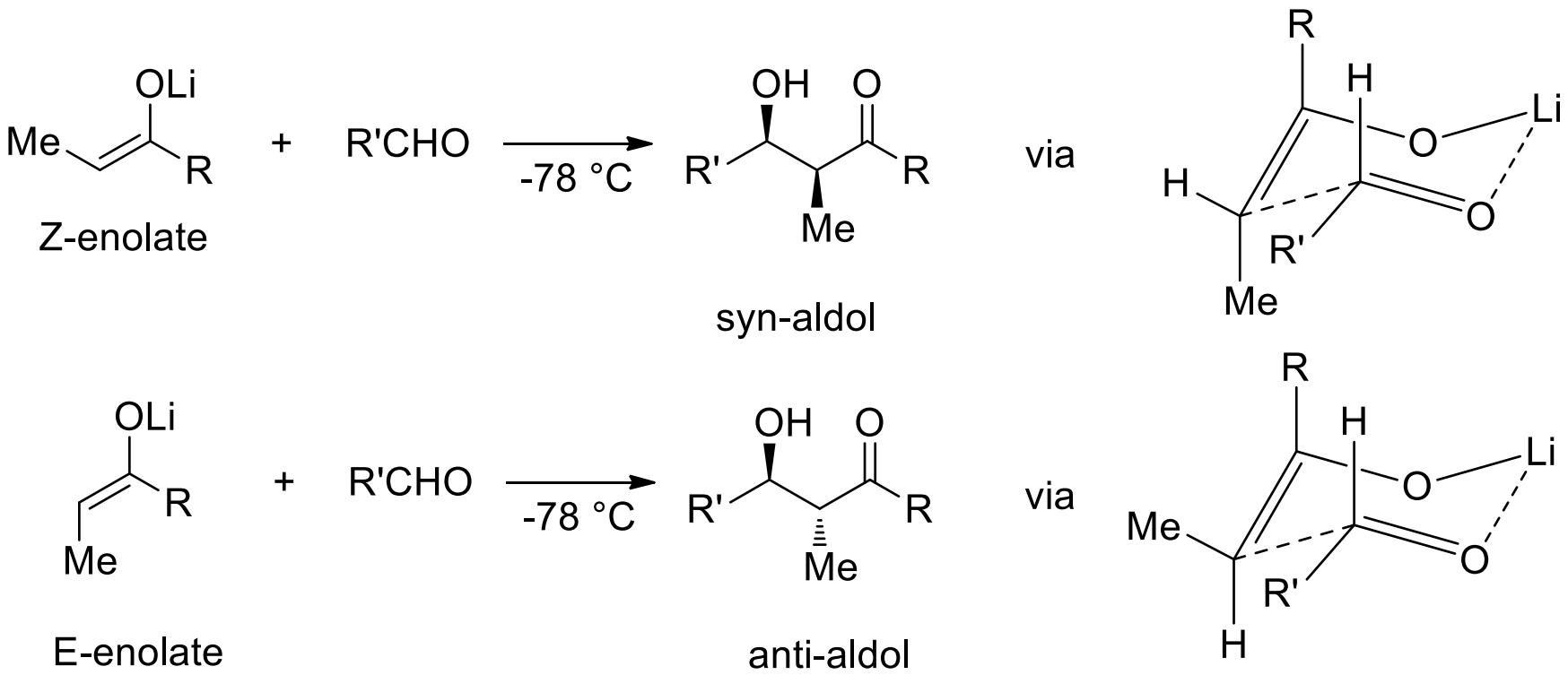


Enantioselective deprotonation: kinetic resolution

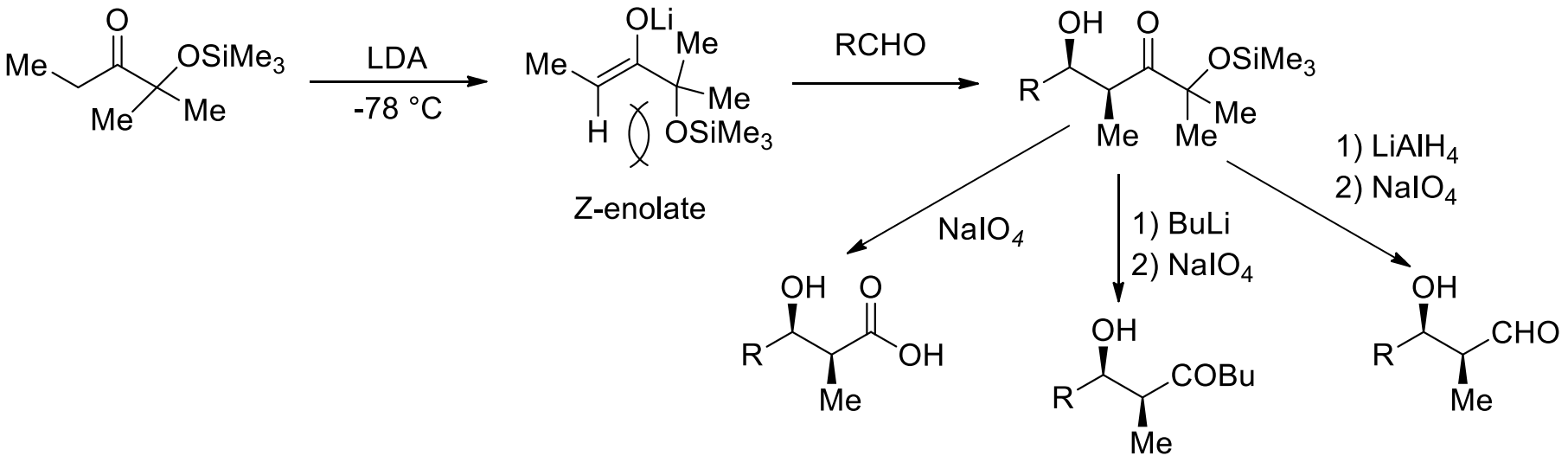


R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc*. **1986**, *108*, 543.

Stereoselectivity in the aldol reaction

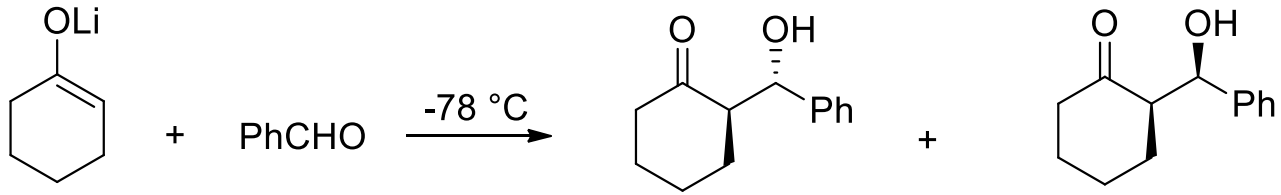


Enantioselective aldol synthesis



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

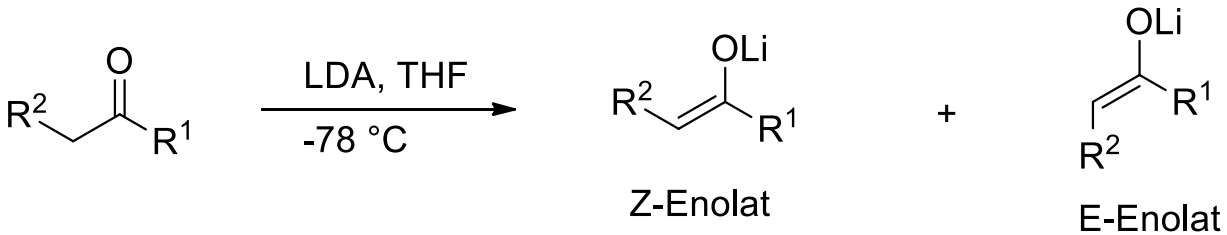
The aldol reaction



anti: 84%

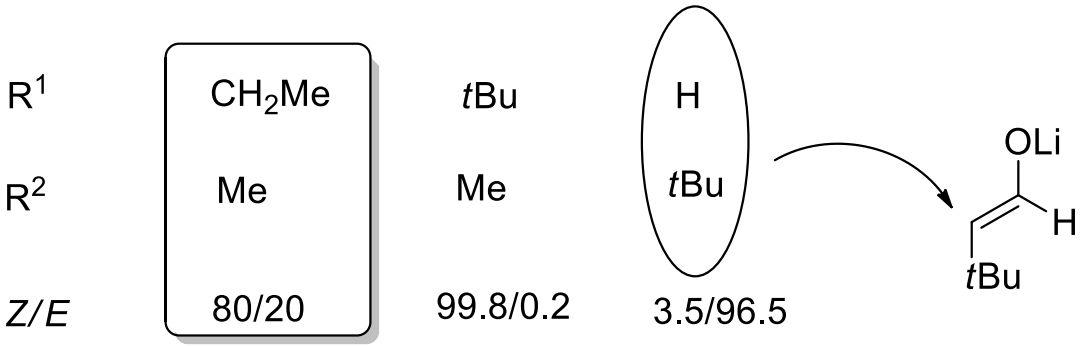
syn: 16%

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



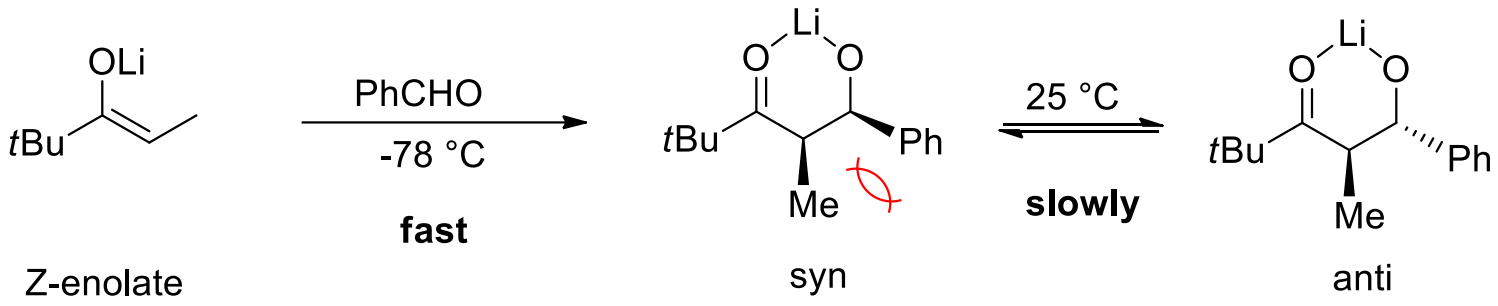
Z-Enolat

E-Enolat



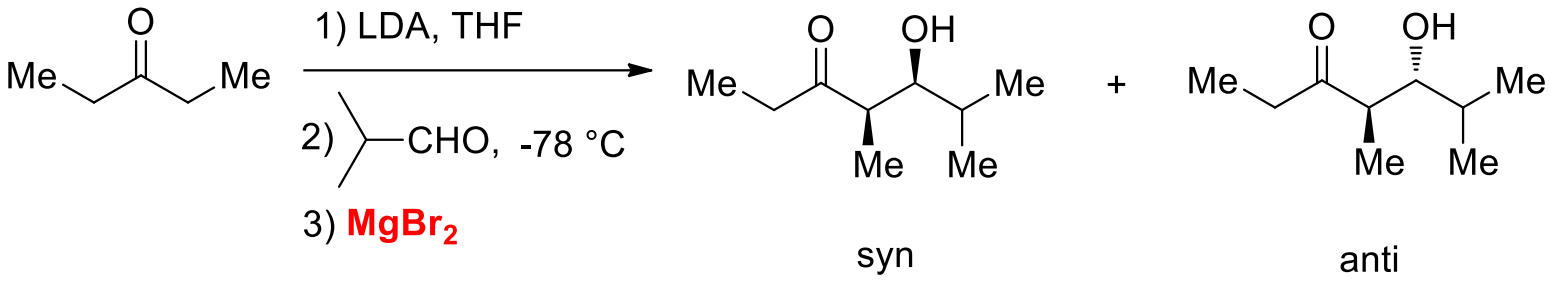
unselective stereoselective enolization with Li-bases

The aldol reaction



Z-enolate

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



Kinetic control at -78 °C: syn : anti = 31 : 69

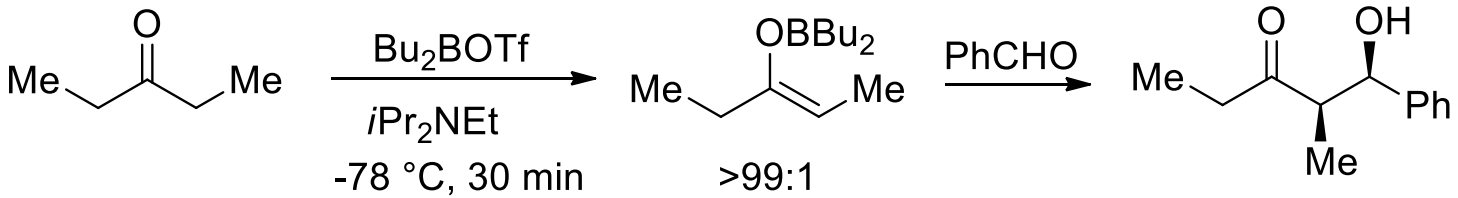
Thermodynamic control at 25 °C: syn : anti = 9 : 91

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

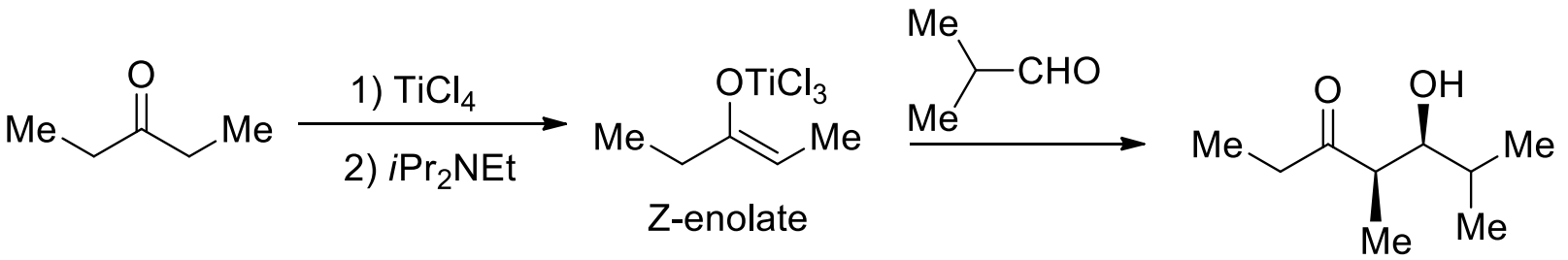
The aldol reaction

General synthesis of Z-enolates

Boron enolates are usually more selective than Li-enolates

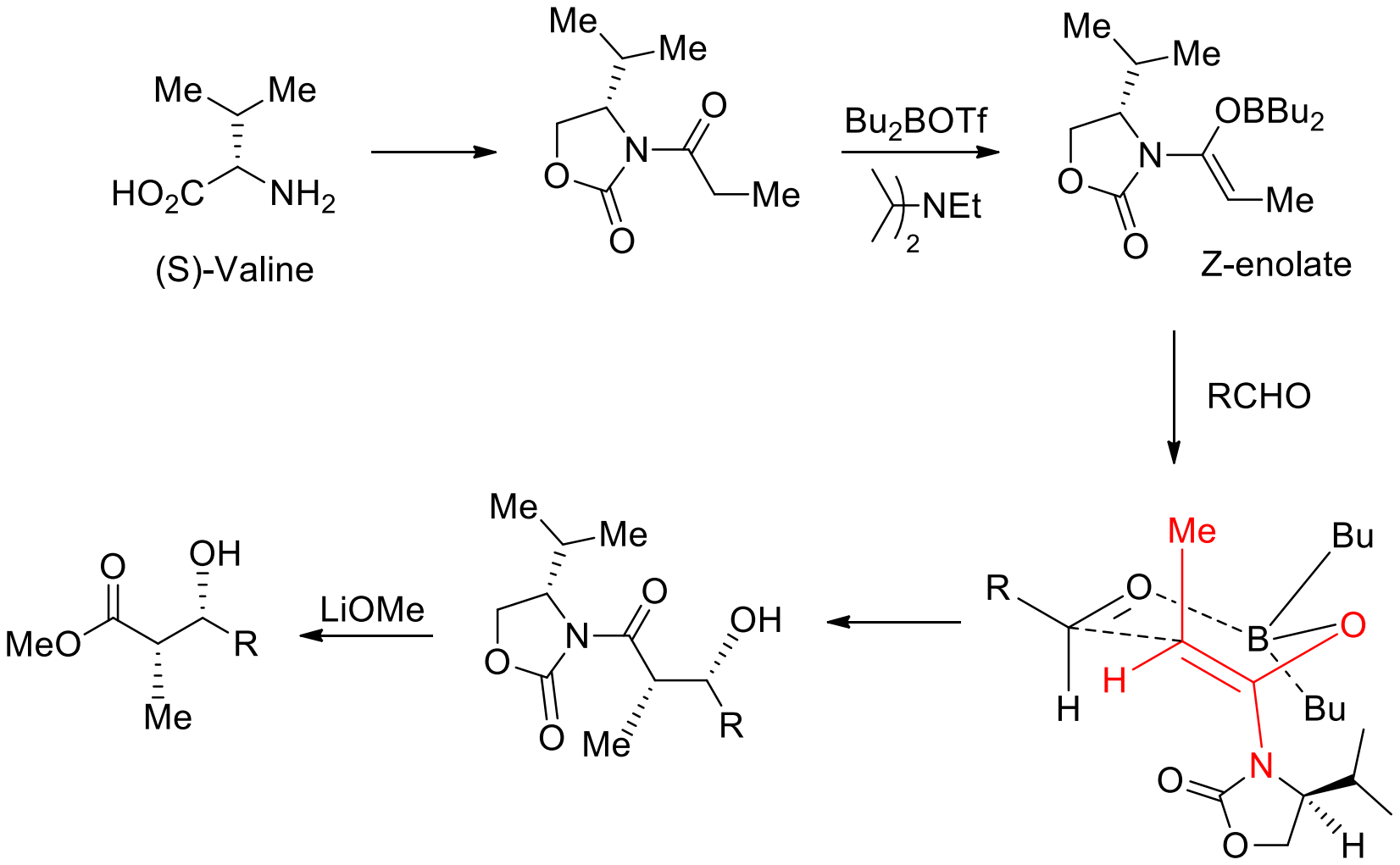


D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc*. **1979**, *101*, 6120.



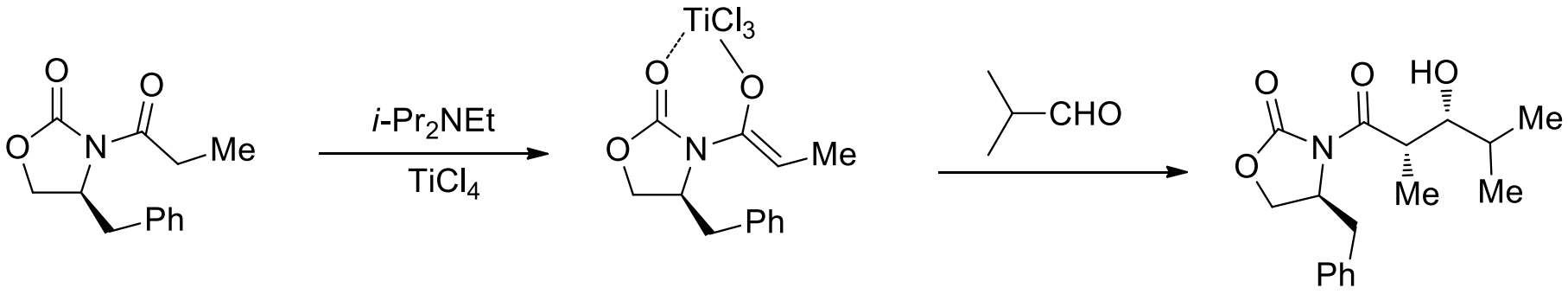
C. Siegel, E. R. Thornton, *J. Am. Chem. Soc*. **1989**, *111*, 5722.
D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc*. **1991**, *113*, 1047.

Enantioselective aldol reaction



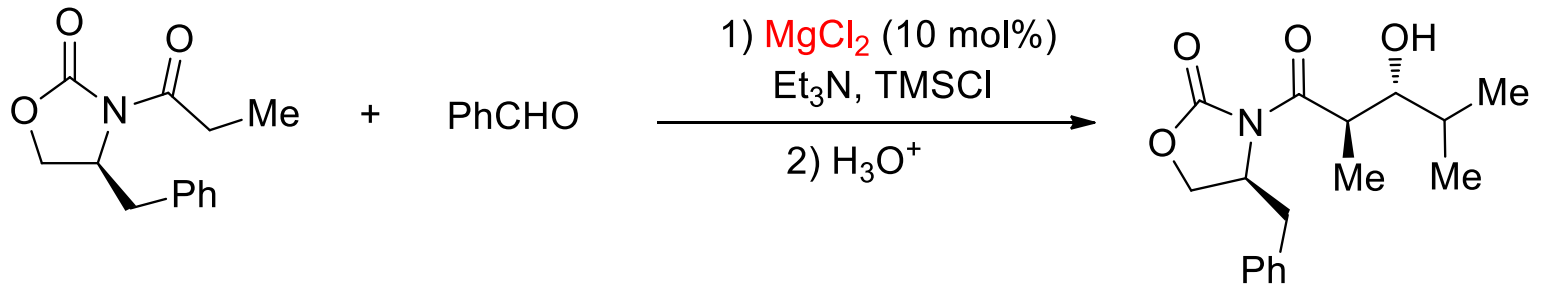
D. A. Evans, *J. Am. Chem. Soc*. **1981**, *103*, 2876.

Enantioselective aldol reaction via Ti-enolates



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

87 %; syn : anti = 94 : 6

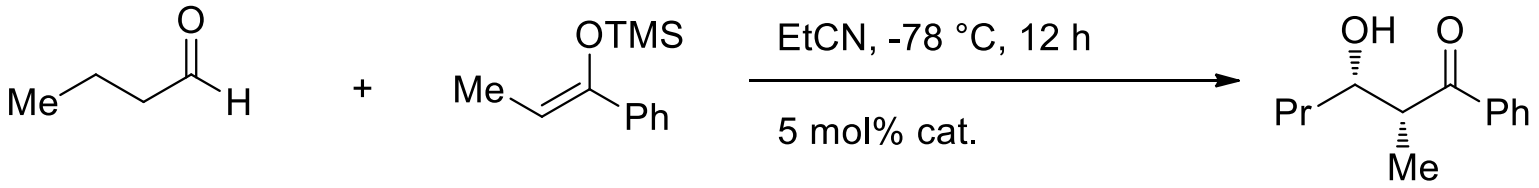


D. A. Evans, *J. Am. Chem. Soc*. **2002**, *124*, 392.

91 %; syn : anti = 1 : 32

Enantioselective enolate synthesis

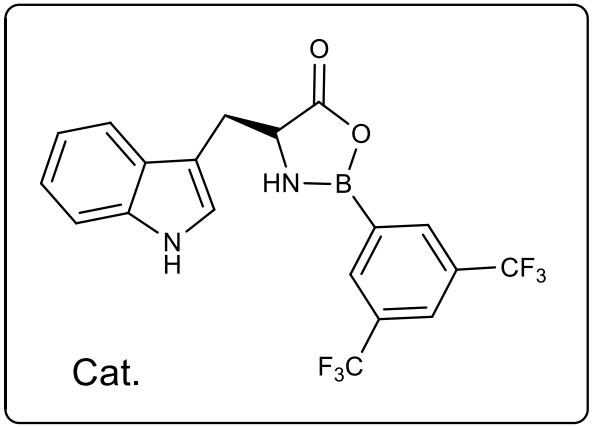
Asymmetric Mukaiyama reaction



syn : anti = 99 : 1

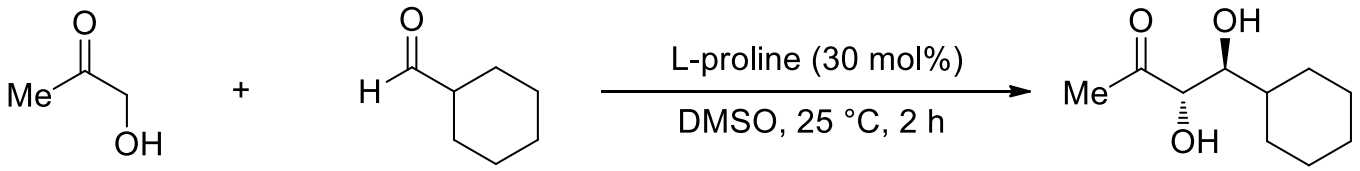
>99 %; 95%ee

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



Enantioselective enolate synthesis

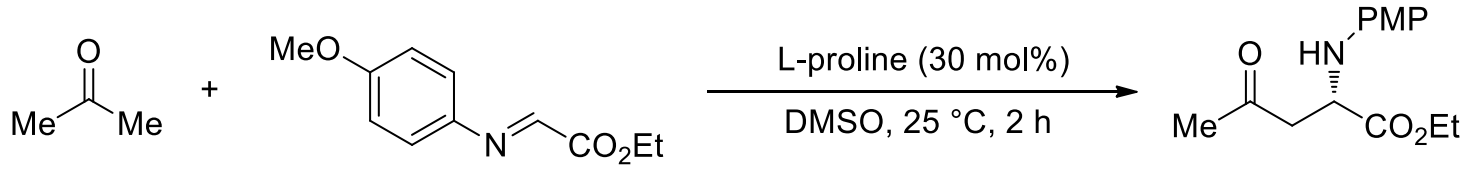
Organocatalysis



60 % Z : E > 20 : 1
enantioselectivity > 100 : 1

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

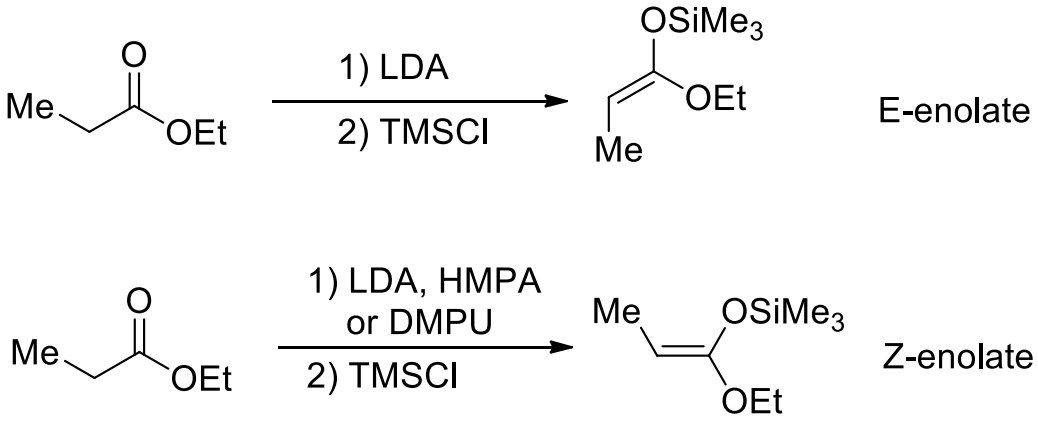
Review: B. List, *Synlett*, **2001**, 1663.

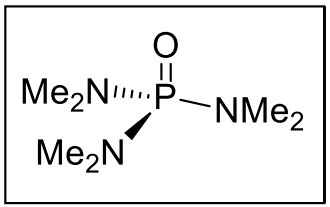


82 %, 95%ee

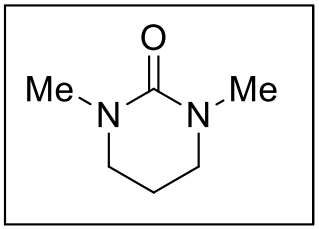
W. J. Liu, N. Li, L. Z. Gong, *Asymmetric Organocatalysis,* Topics in Organometallic Chemistry, **2011**, Vol. 36/2011, 153-205.
U. Scheffler, R. Mahrwald, *Synlett* **2011**, 1660.
H. Pellissier, Adv. Synth. .Catal. **2011**, *353*, 659.
S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russian Chem. 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

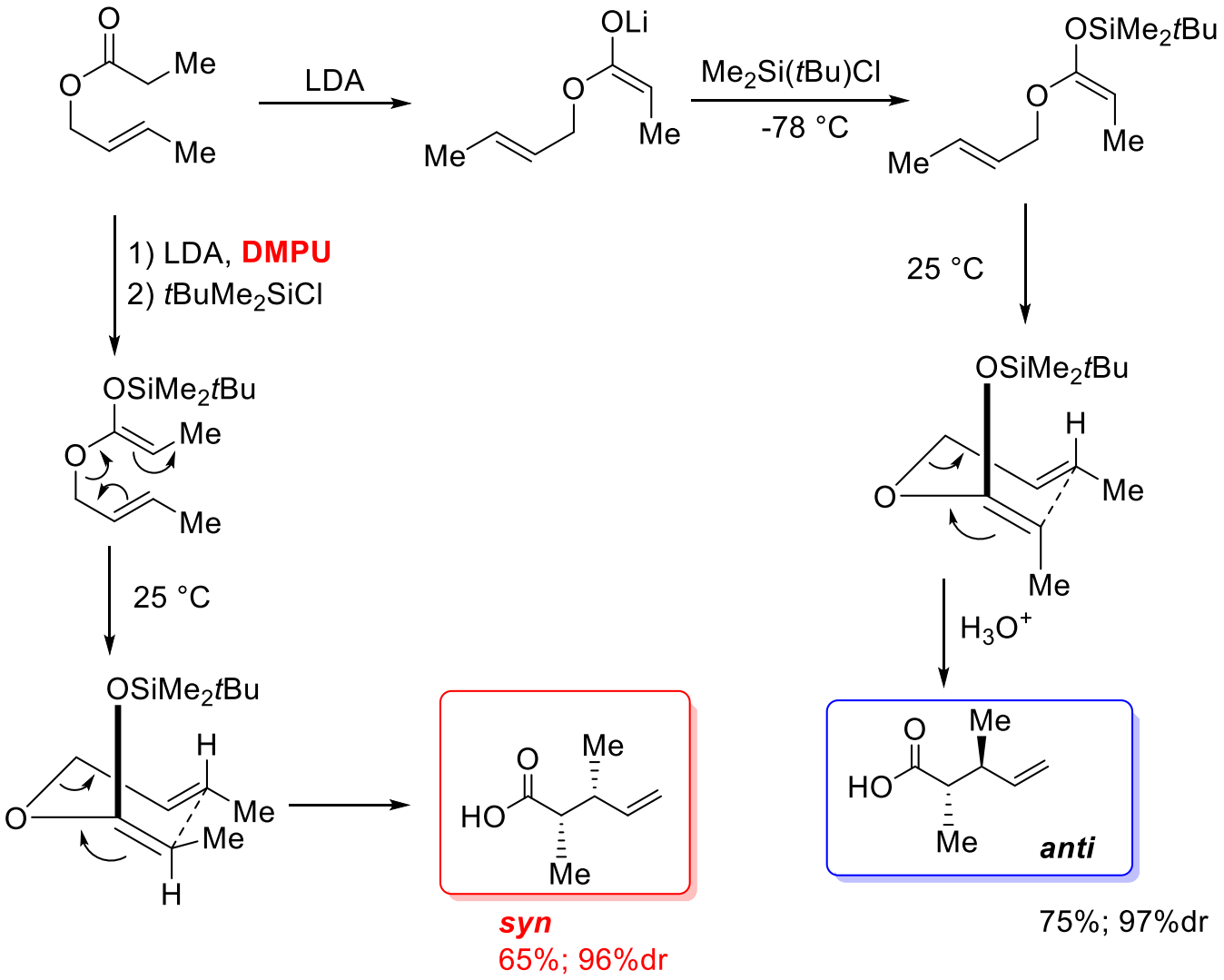


DMPU

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

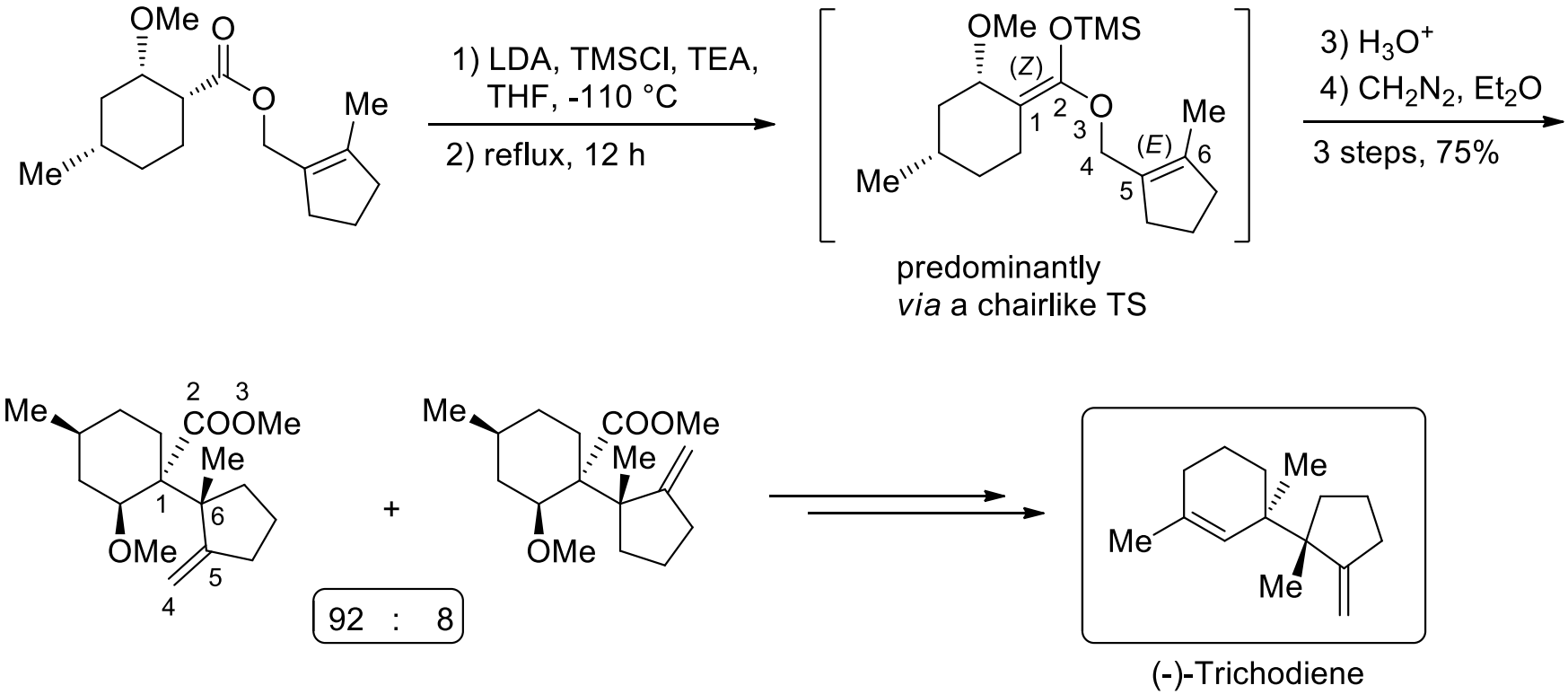
Y. Chai, S.-P. Hong, H. A. Lindsay, C. McFarland, M. C. McIntosh, *Tetrahedron* **2002**, *58*, 2905-2928.

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



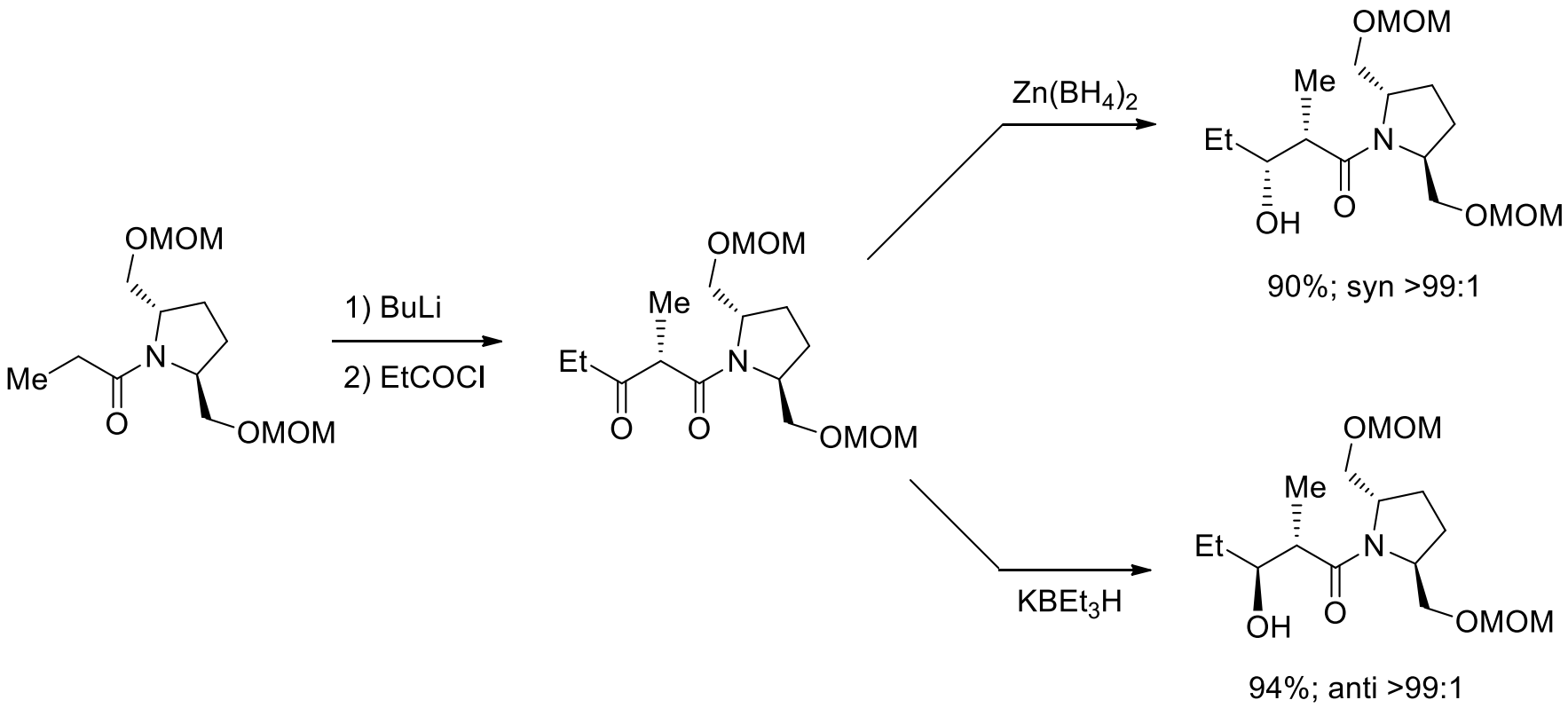
Review: D. Enders, *Tetrahedron: Asymmetry* **1996**, *7*, 1847-1882.
Y. Chai, *Tetrahedron* **2002**, *58*, 2905-2928.

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



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

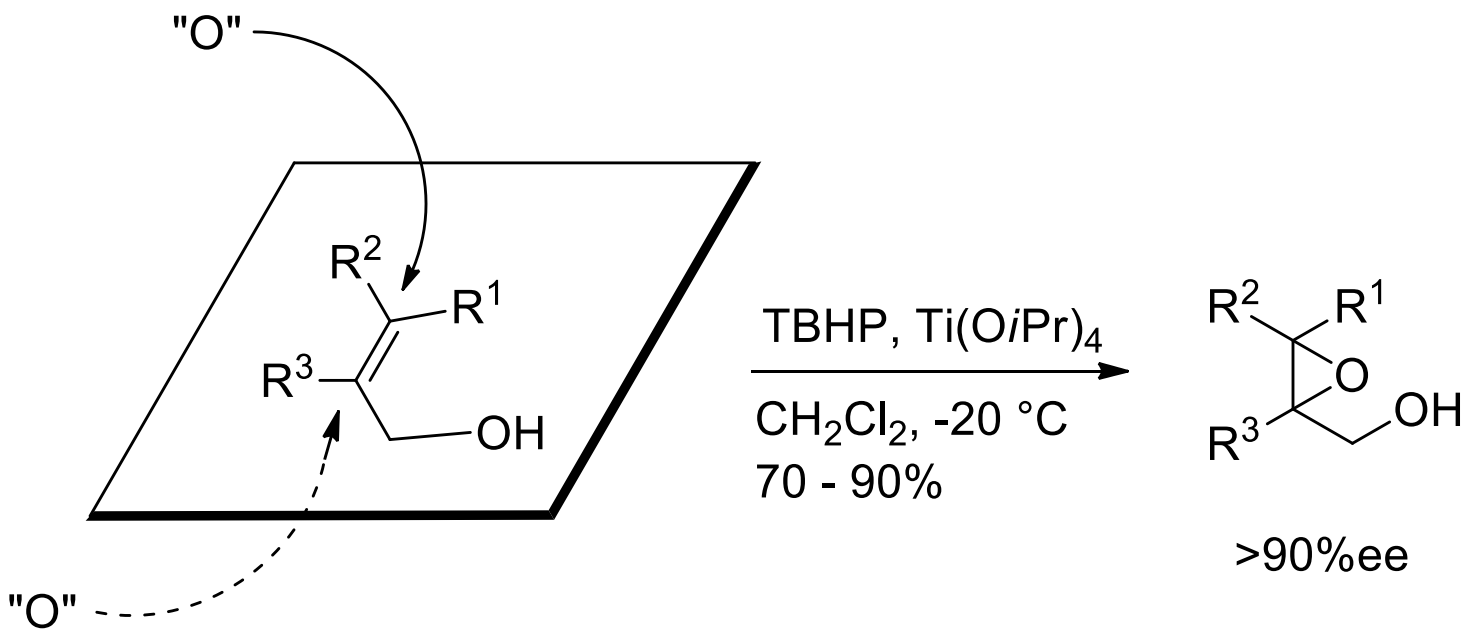
Alternative synthesis of aldol products



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

Asymmetric catalysis – Asymmetric oxidations

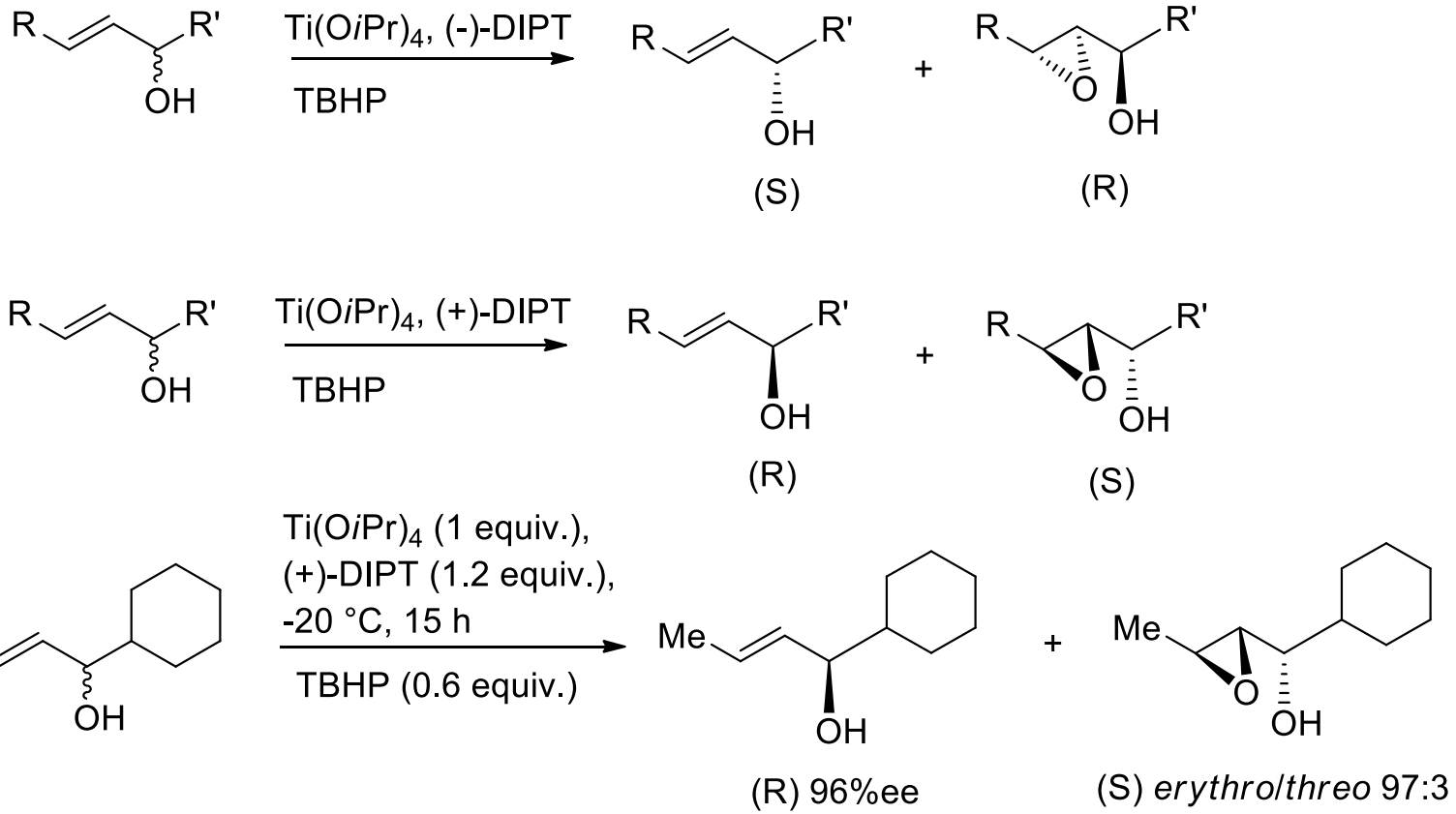
The Sharpless oxidation



(R,R)-L-(+)-tartrate (natural)

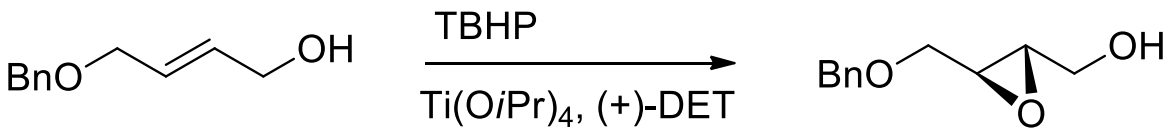
T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5974.

Kinetic resolution of secondary alcohols

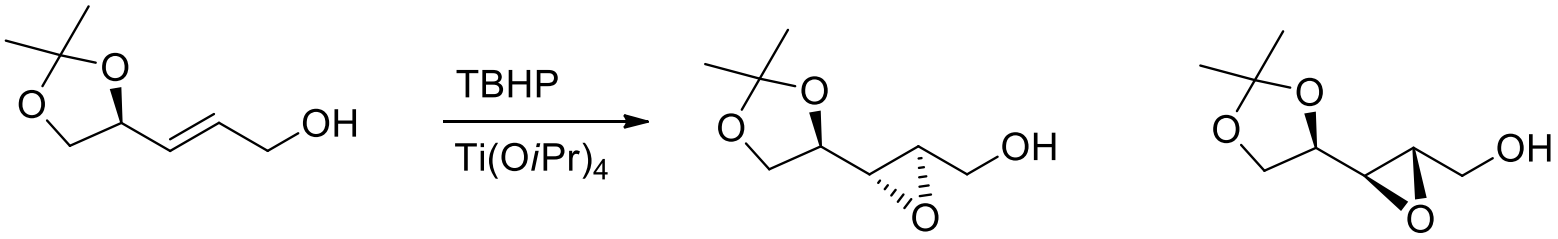


V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless,
J. Am. Chem. Soc. **1981**, *103*, 6237.

Matched and mismatched cases



85%; 88%ee

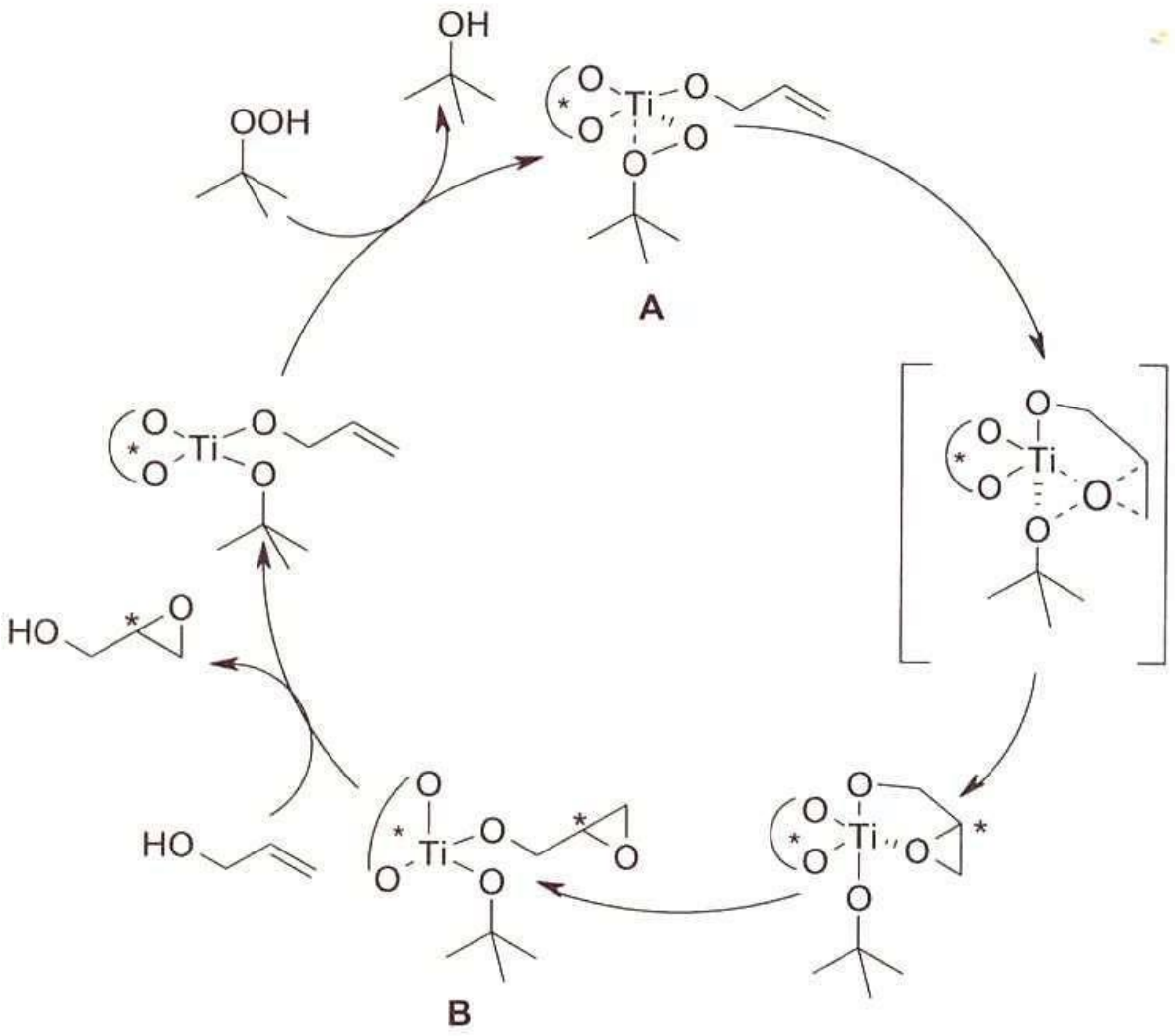


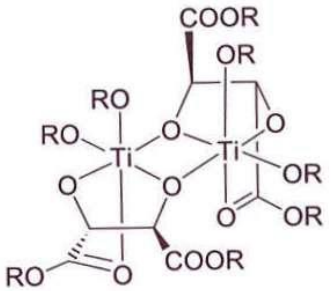
1 **2**

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

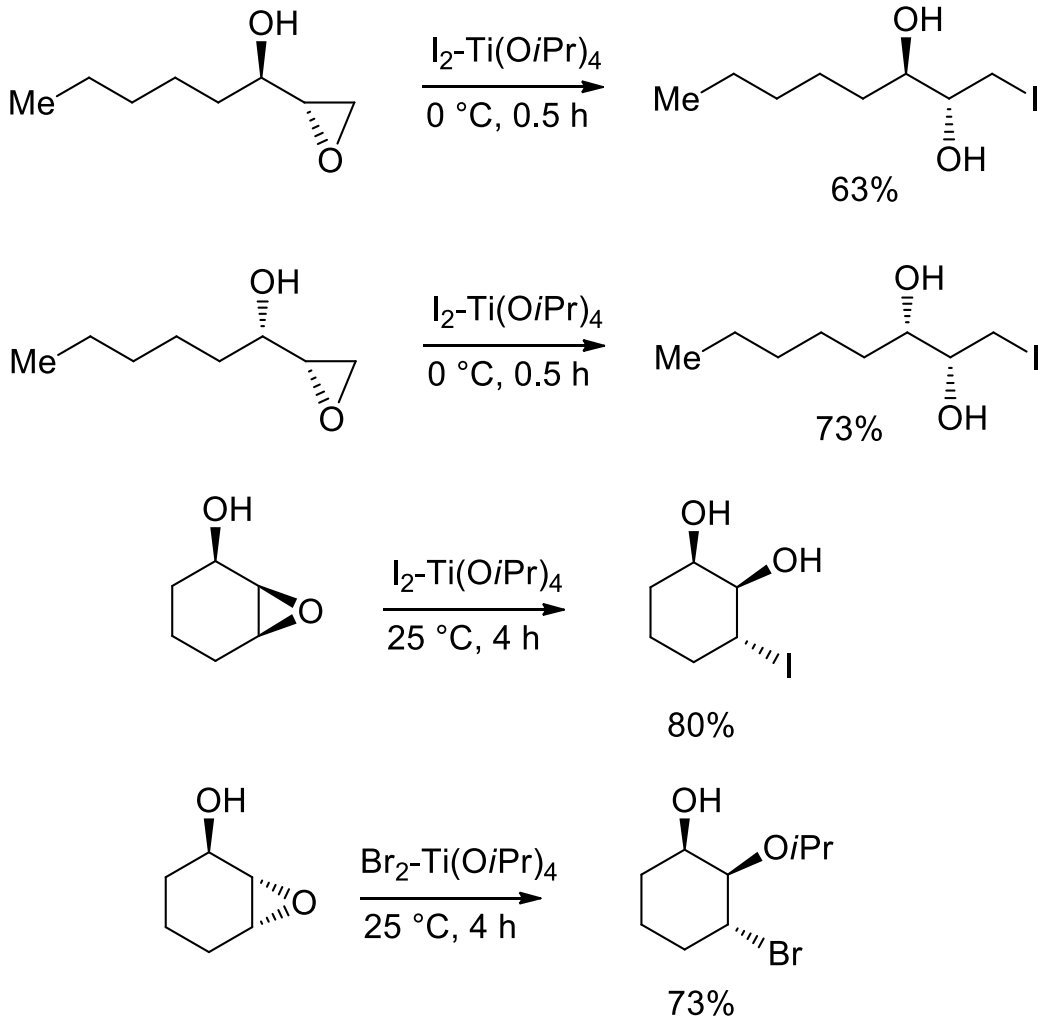




Structure of dinuclear Ti–tartrate complexes.

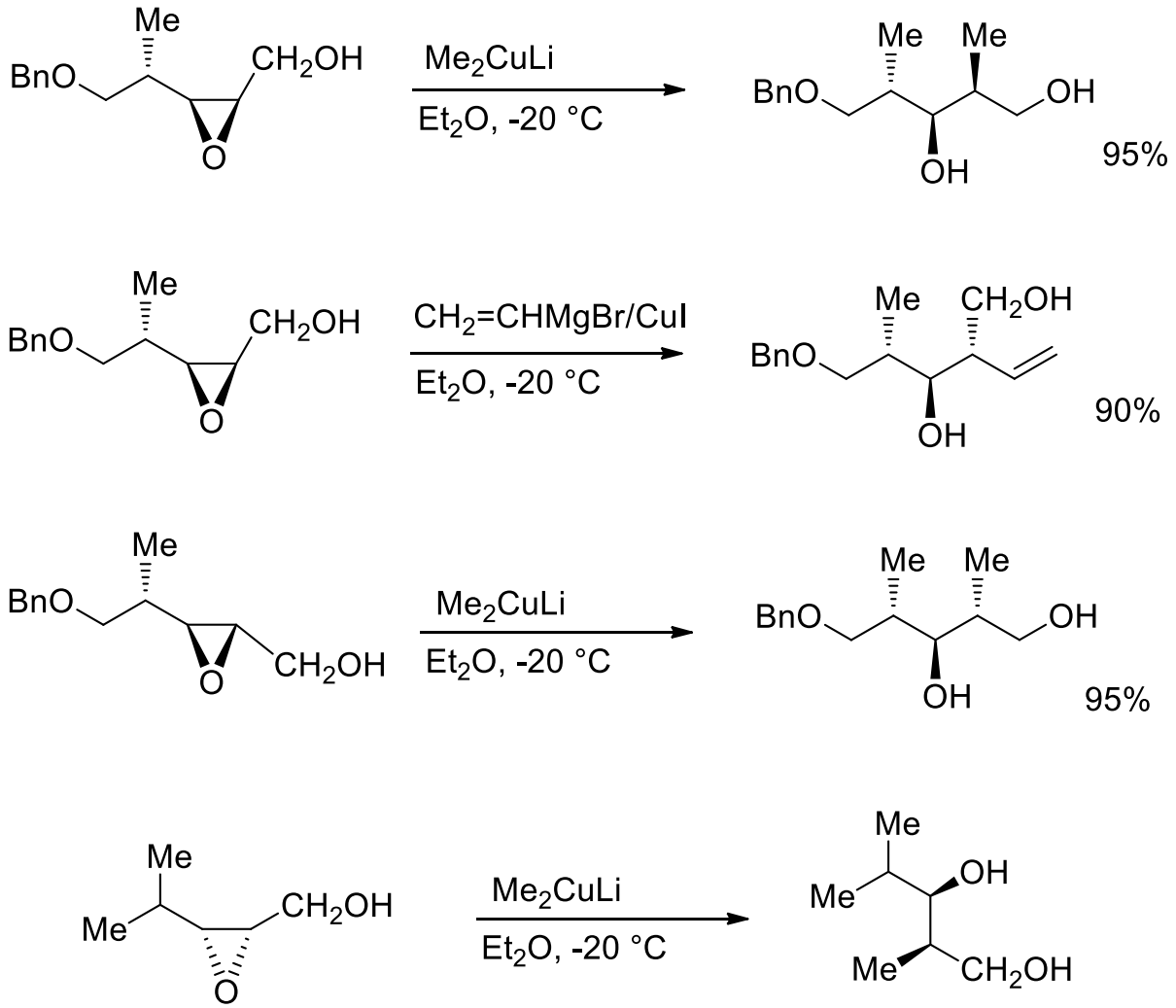
M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc*. **1991**, *113*, 113.

Synthetic applications of the Sharpless epoxidation



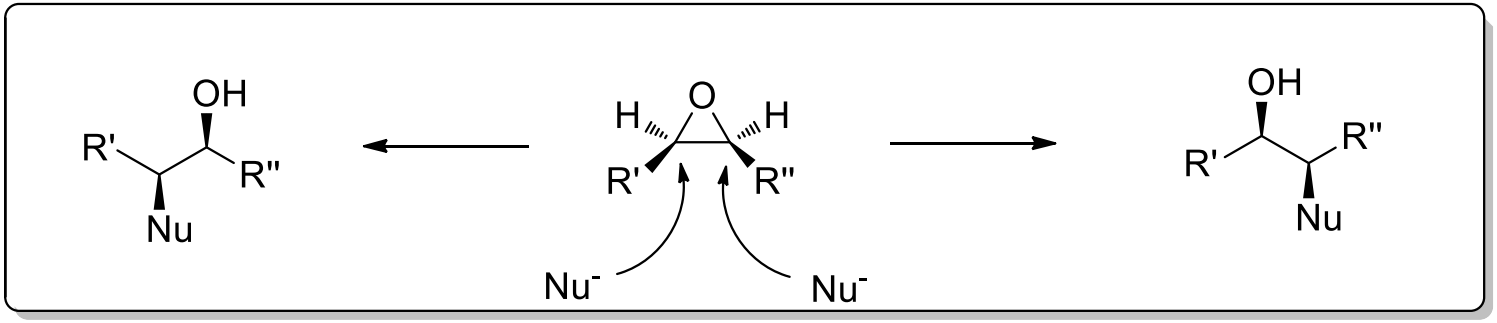
E. Alvarez, M. T. Nunez, V. S. Martin, *J. Org. Chem*. **1990**, *55*, 3429.

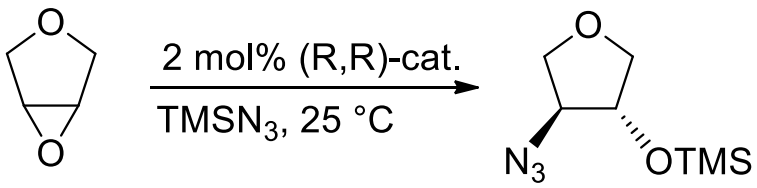
Ring opening with cuprates



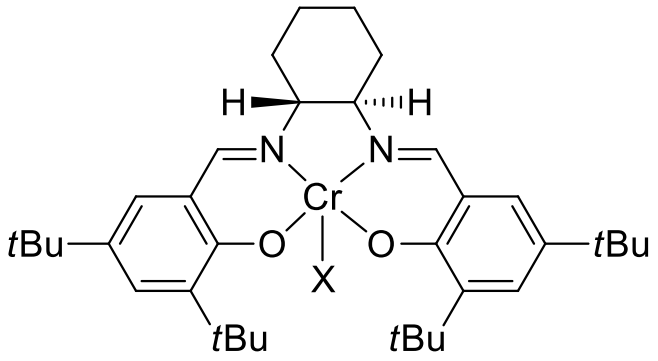
M. R. Johnson, T. Nakata, Y. Kishi, *Tetrahedron Lett*. **1979**, *20*, 4343.
R. D.Wood, B. Ganem, *Tetrahedron Lett*. **1982**, *23*, 707.

Desymmetrization of meso-epoxides





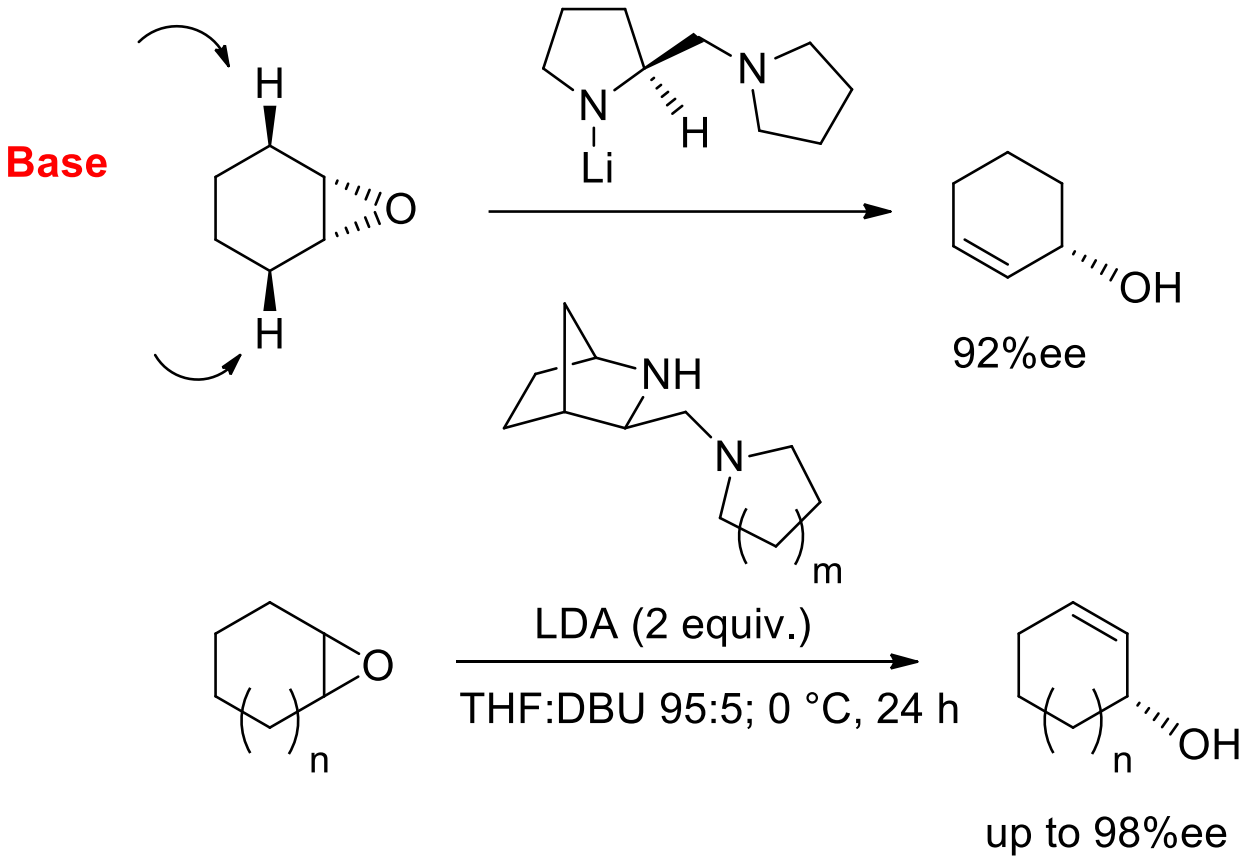
99%; 97%ee



catalyst : X = Cl, N_3

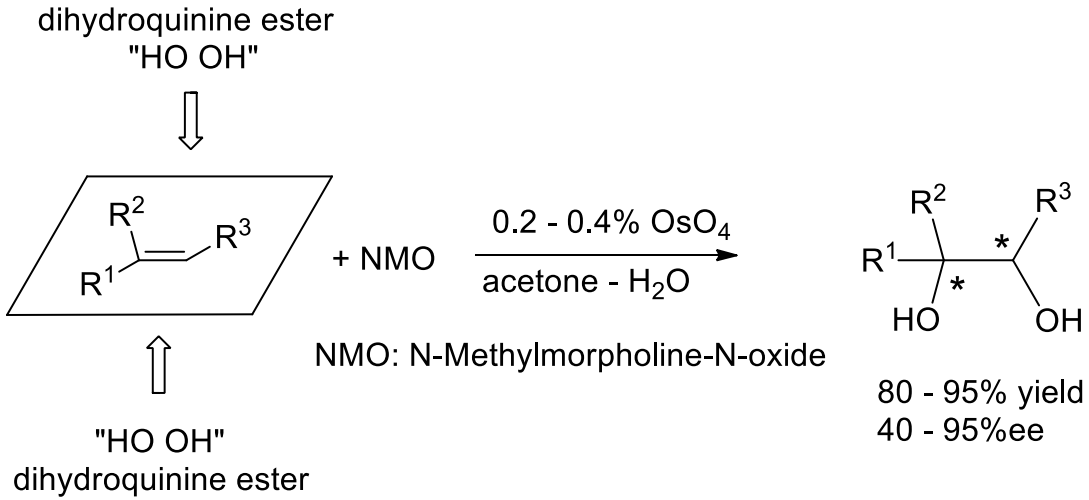
S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *J. Org. Chem.* **1997**, *62*, 4197.

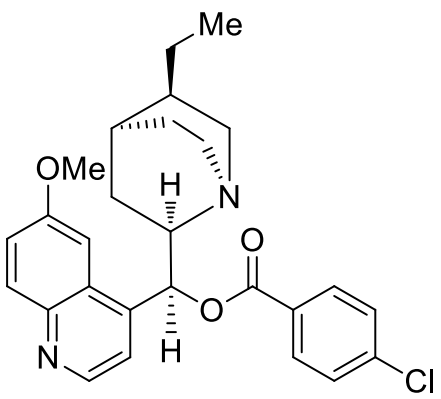
Desymmetrization of meso-epoxides



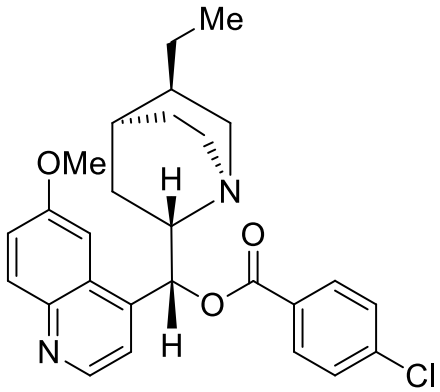
I. Paterson, D. J. Berrisford, *Angew. Chem. Int. Ed*. **1992**, *31*, 1179.
M. J. Södergren, P. G. Andersson, *J. Am. Chem. Soc*. **1998**, *120*, 10760.

Asymmetric dihydroxylation





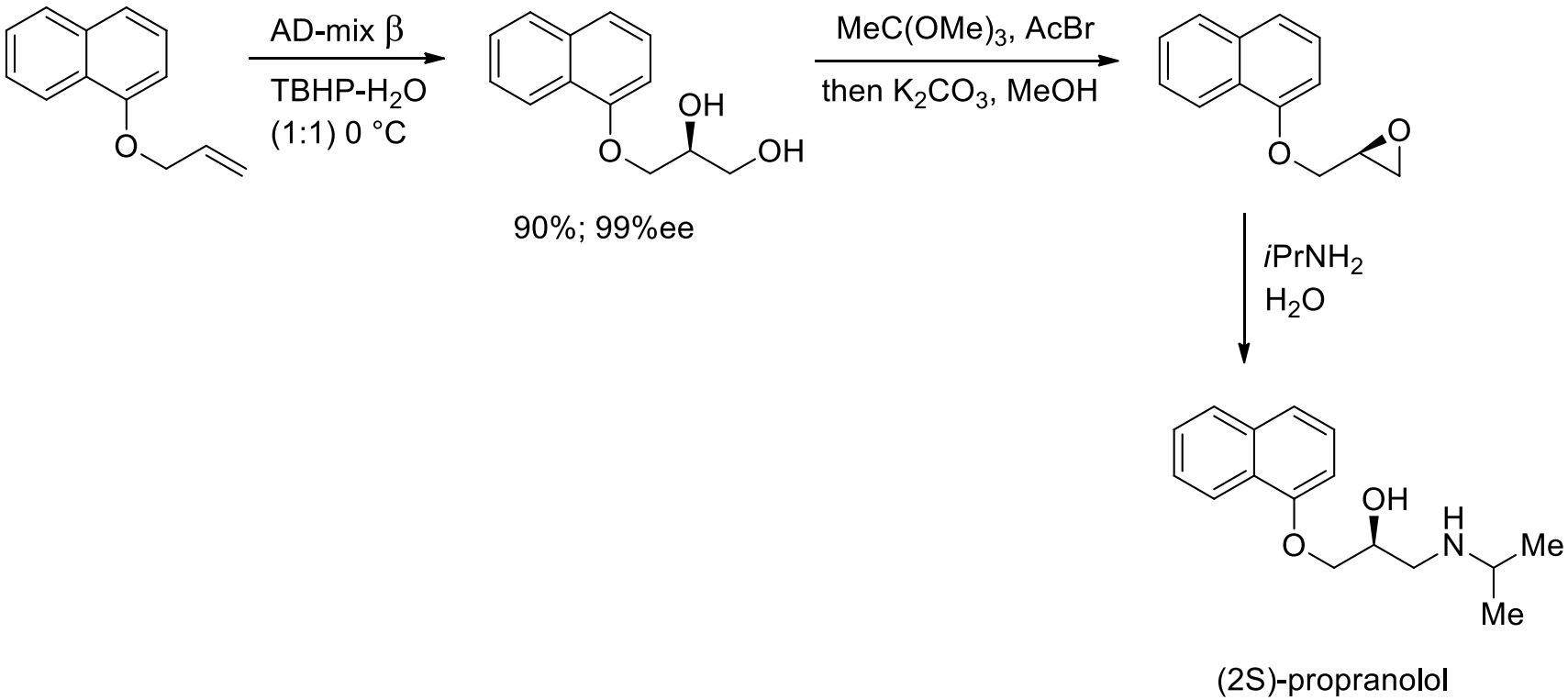
dihydroquinine ester



dihydroquinine ester

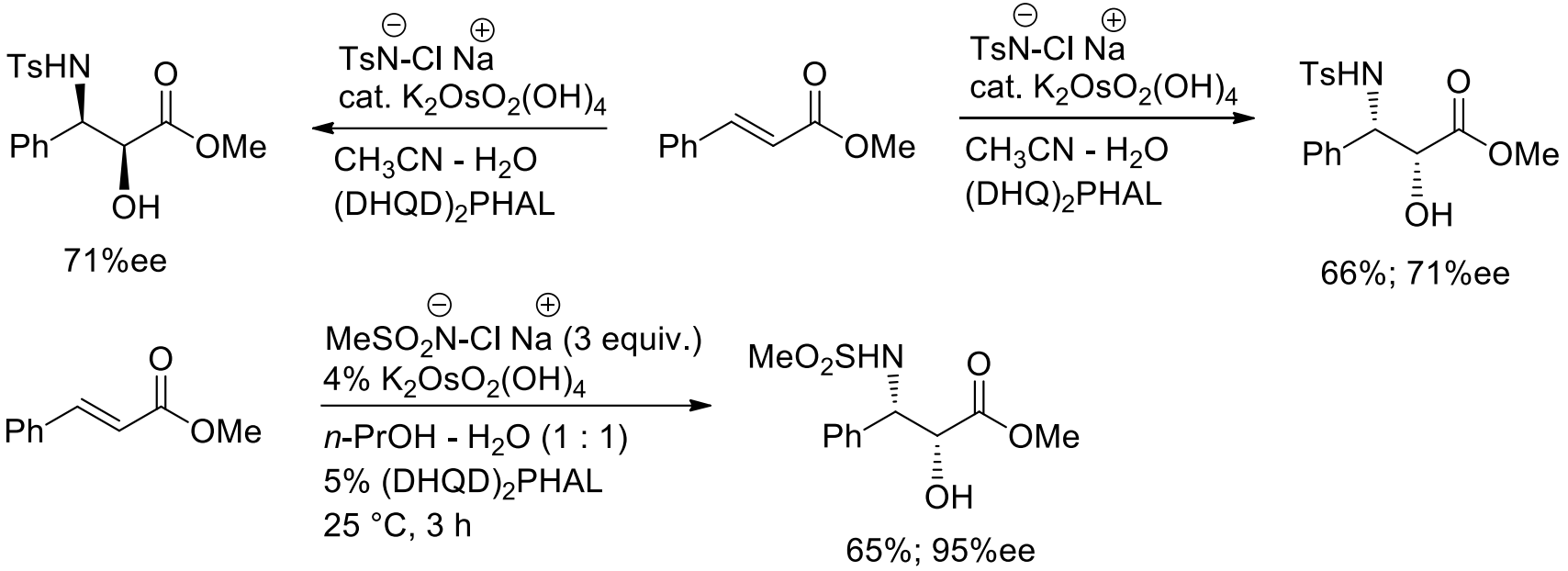
A. E. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968.
A. E. Jacobsen, I. Markó, M. B. France, J. S. Svendsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 737.
J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, A. E. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123.

Asymmetric dihydroxylation leading to (2S)-propanolol



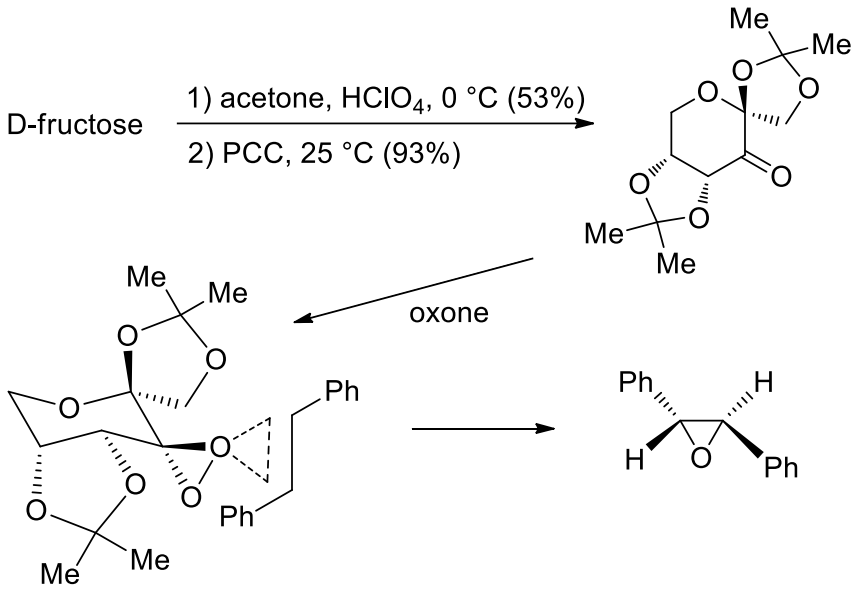
Z. Wang, X. Zhang, K. B. Sharpless, *Tetrahedron Lett*. **1993**, *34*, 2267.

Asymmetric aminohydroxylation

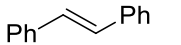
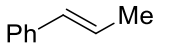
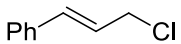
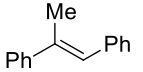
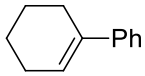


G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed*. **1996**, *35*, 451.
O. Reiser, *Angew. Chem. Int. Ed*. **1996**, *35*, 1308.

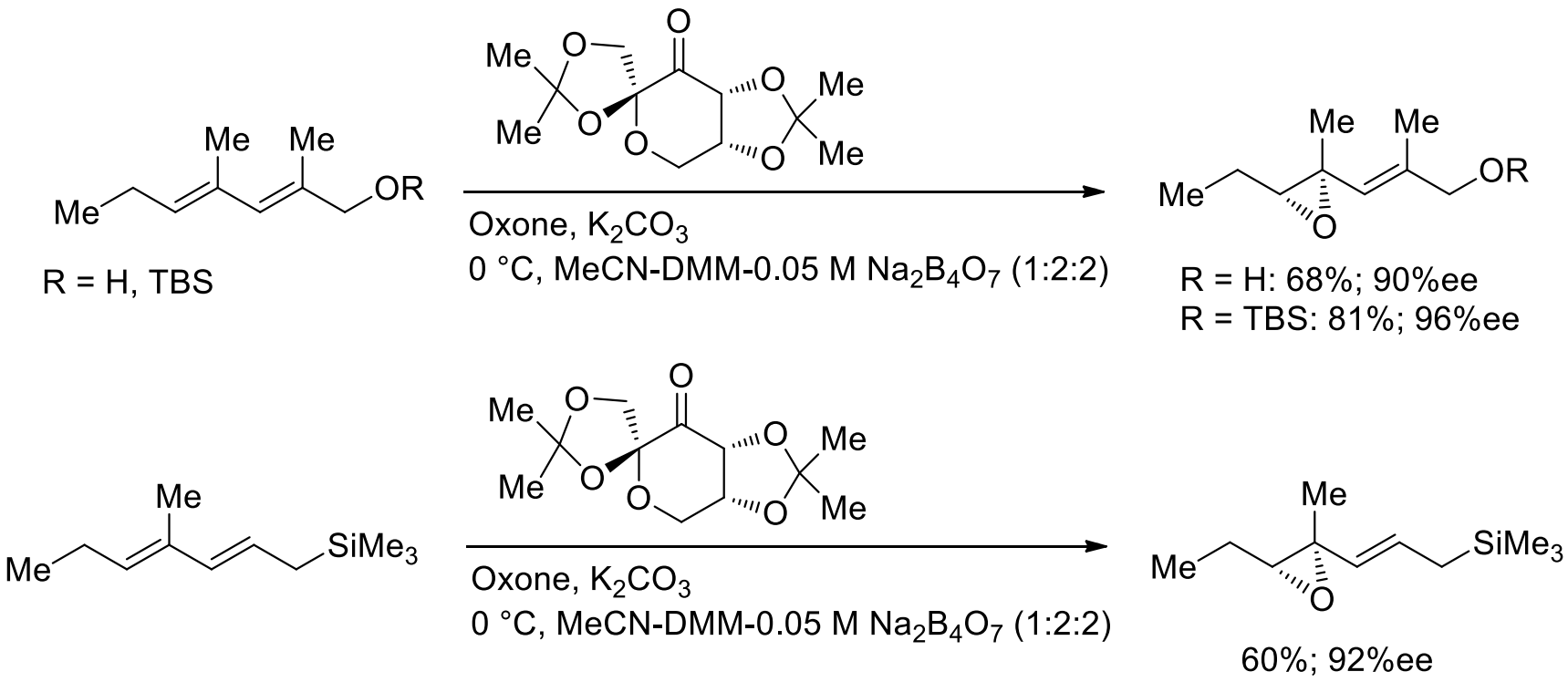
Epoxidation of non-functionalized epoxides



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

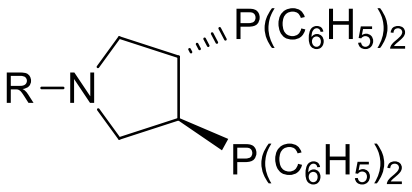
Substrate	Yield (%)	ee(%)	config.
	73	>95	*R*, *R*
	81	88	*R*, *R*
	61	93	2*S*, 3*R*
	73	92	*R*, *R*
	69	91	*R*, *R*

Epoxidation of non-functionalized epoxides

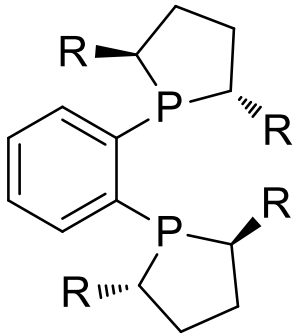


M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem*. **1998**, *63*, 2948.

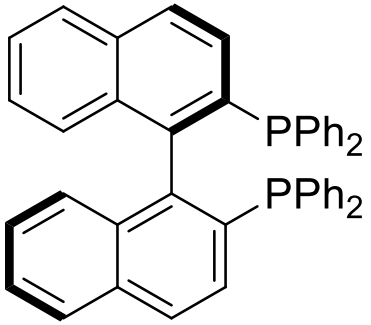
Ligands for asymmetric hydrogenation



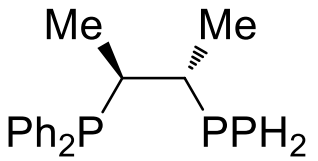
DeguPhos



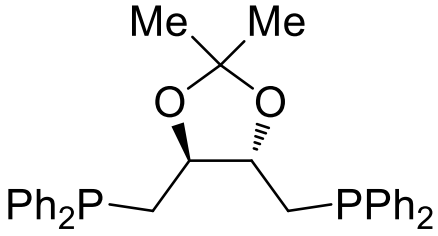
DuPhos



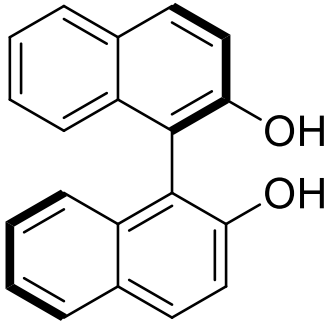
(R)-BINAP



(S,S)-ChiraPhos

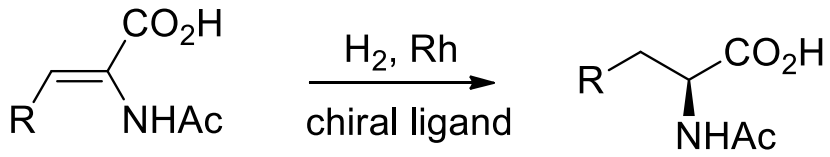


DIOP



(R)-BINOL

Catalytic hydrogenation of enamides

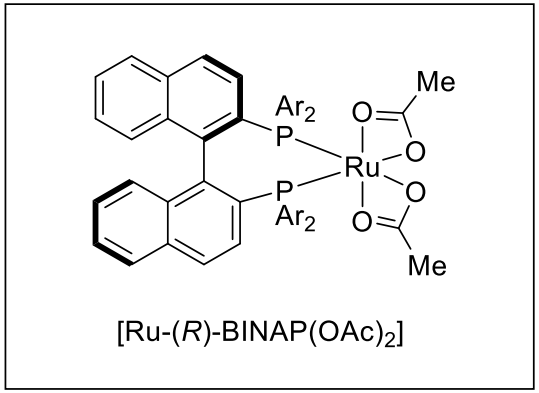


Phosphine ligand	product ee (%) R = C_6H_5	R = H
(*R*,*R*)-DIPAMP	96 (*S*)	94 (*S*)
(*S*,*S*)-ChiraPhos	99 (*R*)	91 (*R*)
(*S*,*S*)-NorPhos	95 (*S*)	90 (*R*)
(*R*,*R*)-DIOP	85 (*R*)	73 (*R*)
(*S*,*S*)-BPPM	91 (*R*)	98.5 (*R*)[a]
(*S*)-BINAP	100 (*R*)[a]	98 (*R*)
(*S*)-(*R*)-BPPFA	93 (*S*)	
(*S*,*S*)-SkewPhos	92 (*R*)	
(*S*,*S*)-CycPhos	88 (*R*)	
(*S*,*S*)-Et-DuPhos	99 (*S*)	99.4 (*S*)

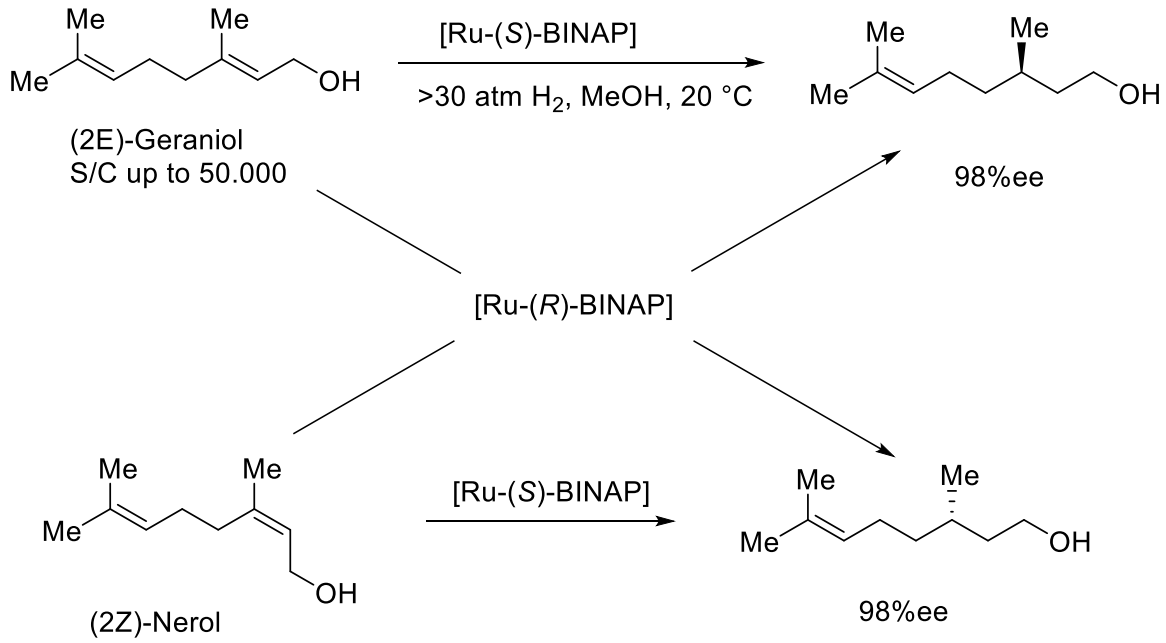
[a] hydrogenation of the N-benzoyl derivative

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

Ru-catalyzed hydrogenations

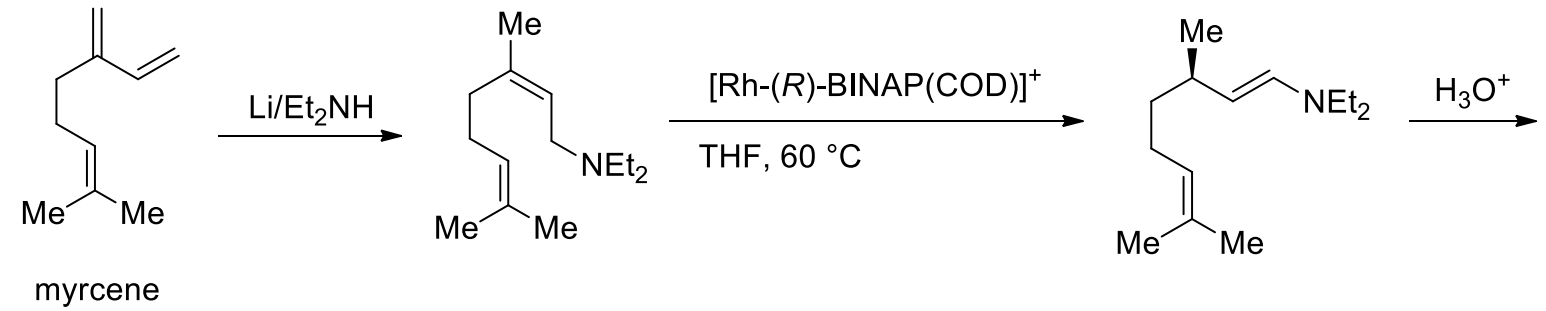


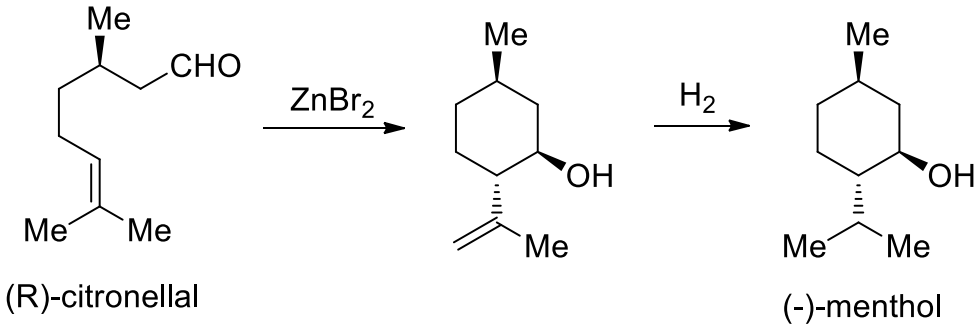
[Ru-(*R*)-BINAP(OAc)$_2$]

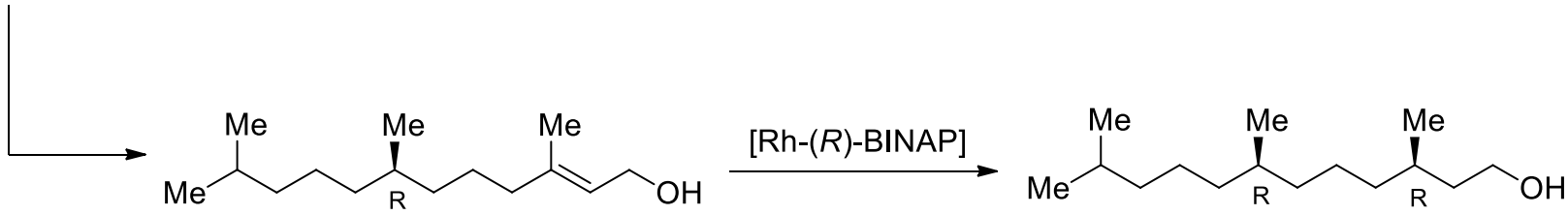


H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, R. Noyori, *J. Am. Chem. Soc*, **1987**, *109*, 1596.

Rh-catalyzed hydrogenations

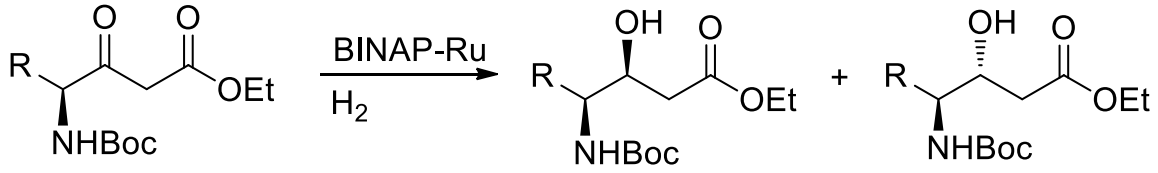




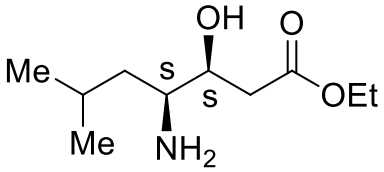


R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Whiley & Sons, Inc., New York, **1994**, Chap. 3.

Asymmetric hydrogenation of carbonyl compounds

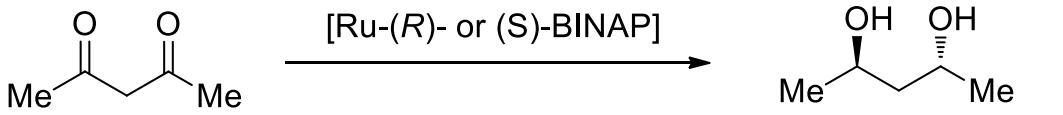


R = Bn, *i*Bu, cyclohexylmethyl

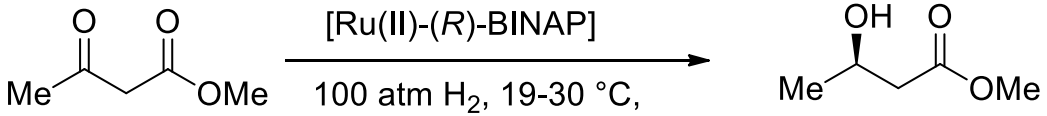


statine, part of aspartic proteinase inhibitor

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



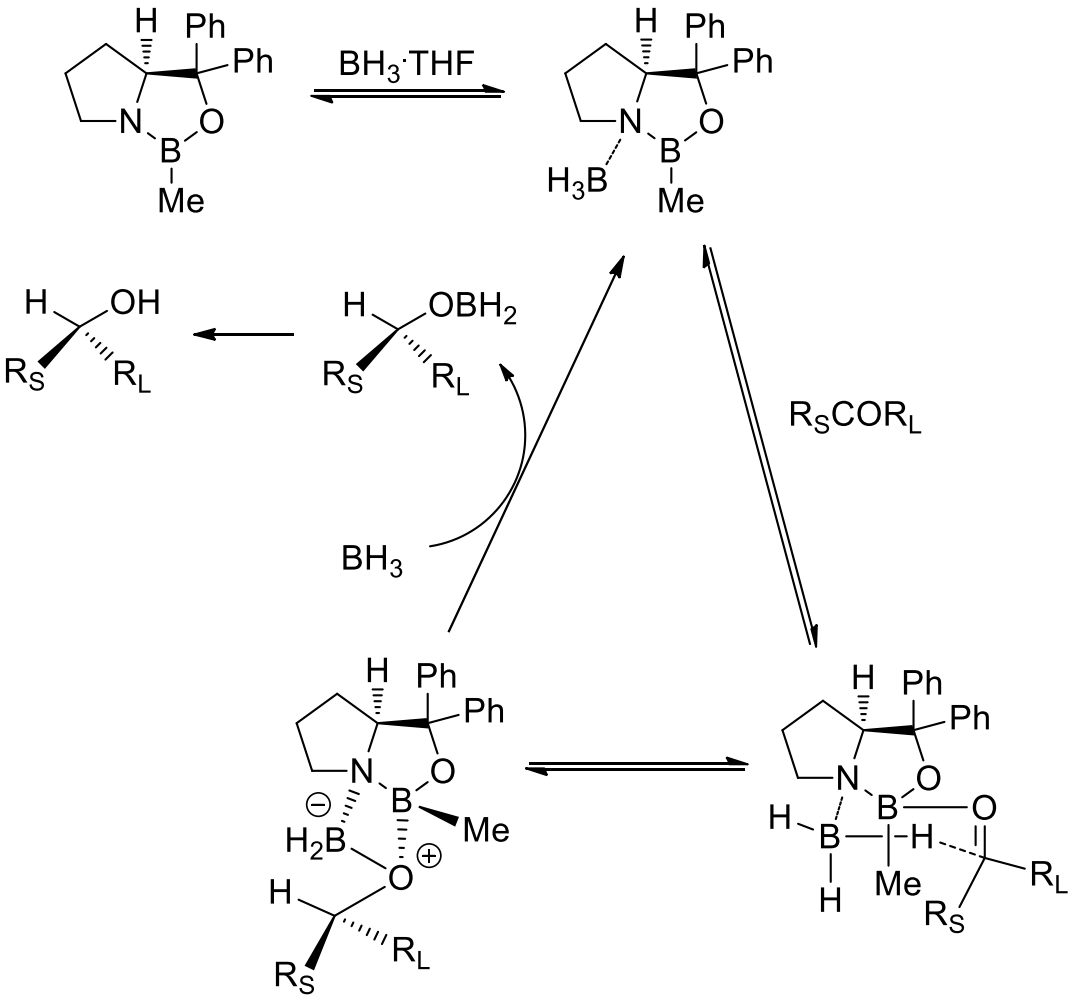
(R,R) >95%, >99%ee



99.5%ee

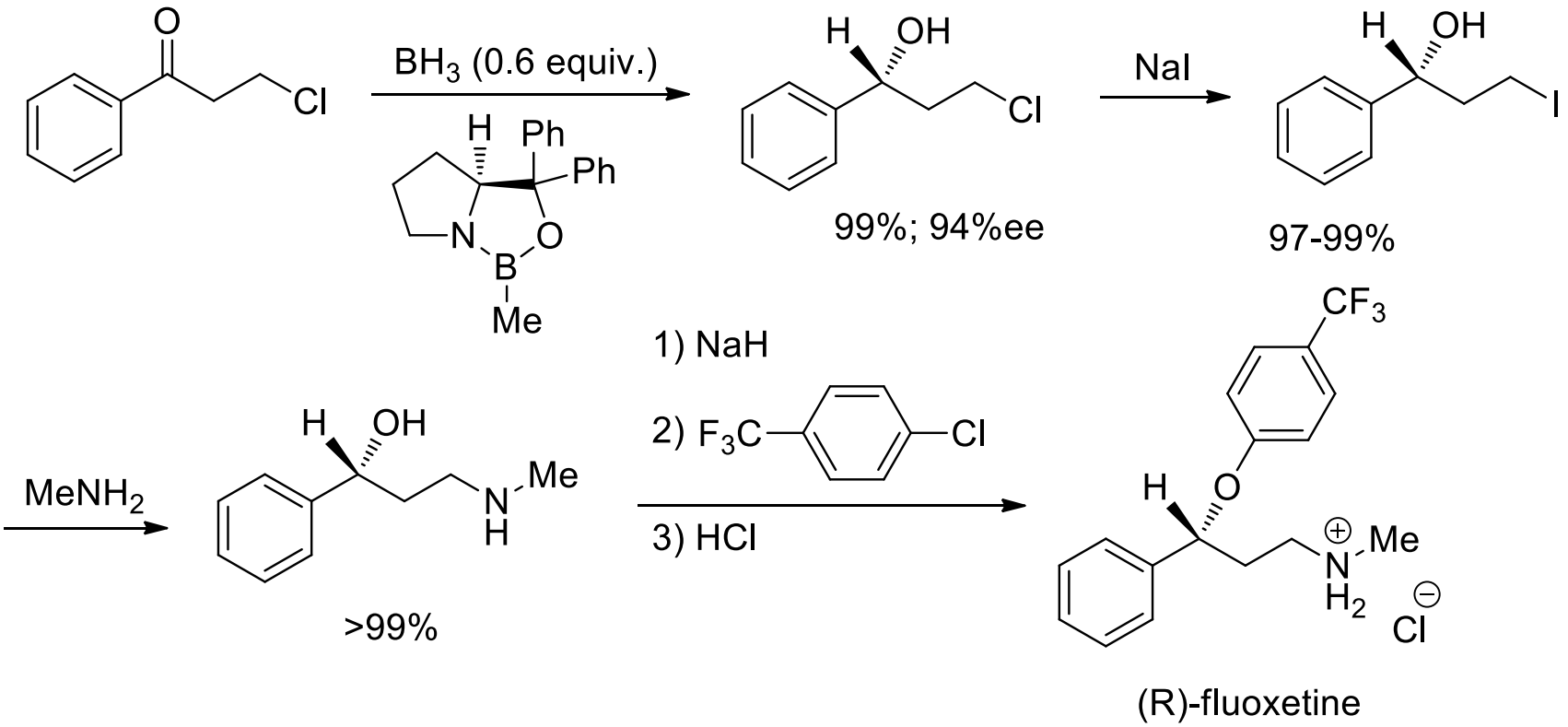
Q. Fan, C. H. Yeung, A. S. C. Chan, *Tetrahedron Asymmetry* **1997**, *8*, 4041.

The oxazaborolidine catalyst system



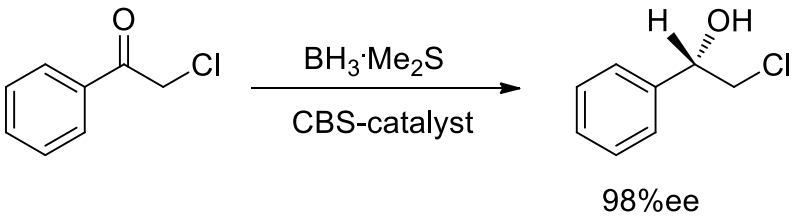
E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551.
E. J. Corey, J. O. Link, *Tetrahedron Lett*. **1992**, *33*, 4141.
V. Nevalainen, *Tetrahedron Asymmetry* **1991**, *2*, 1133.
E. J. Corey, J. O. Link, S. Sarshar, Y. Shao, *Tetrahedron Lett*. **1992**, *33*, 7103.

The oxazaborolidine catalyst system

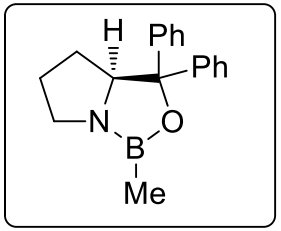


E. J. Corey, G. A. Reichard, *Tetrahedron Lett*. **1989**, *30*, 5207.

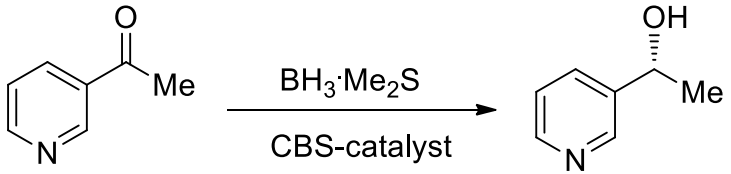
CBS-Reduction



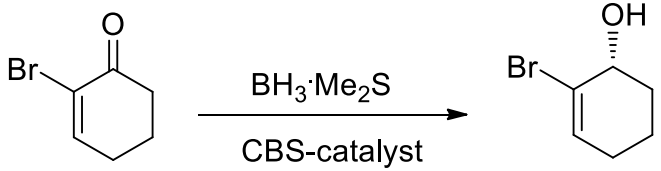
98%ee



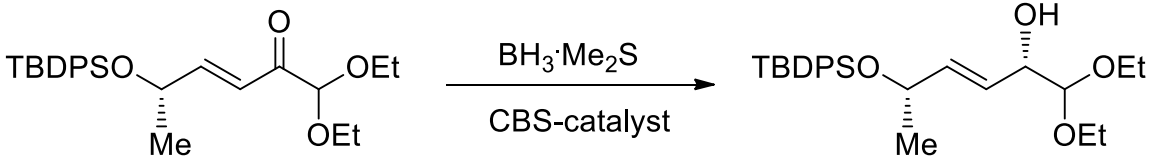
CBS-catalyst



99%ee



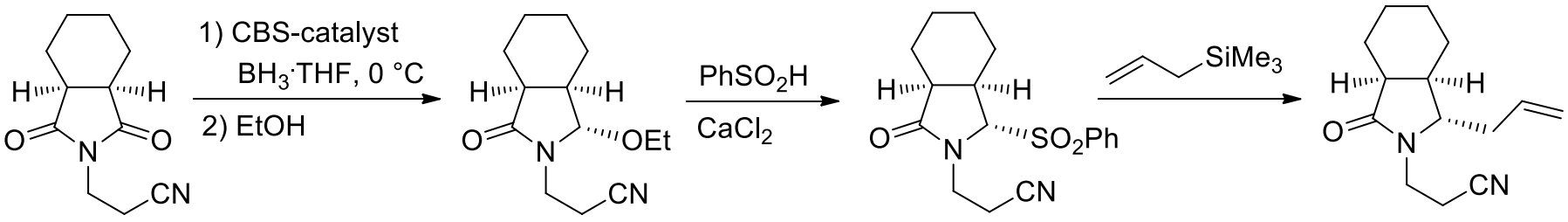
96%ee



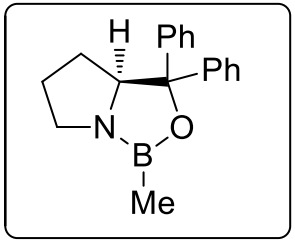
95%ee

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

CBS-Reduction



70%; 90%ee

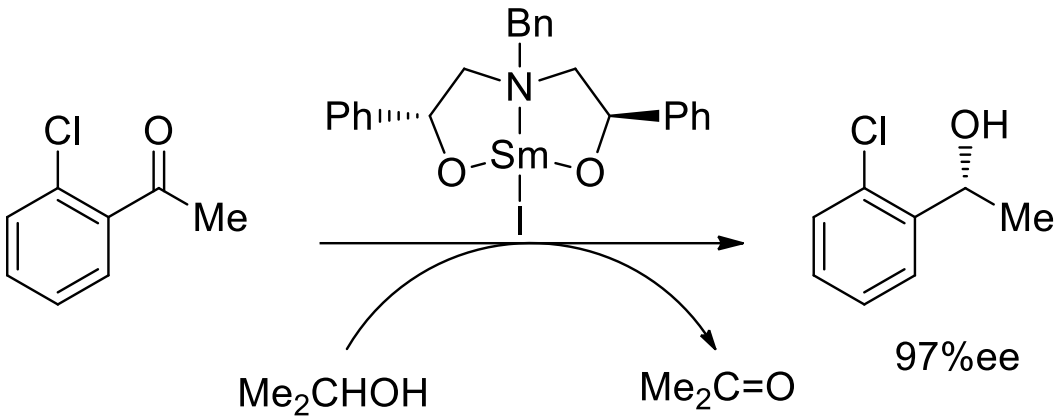


CBS-catalyst

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

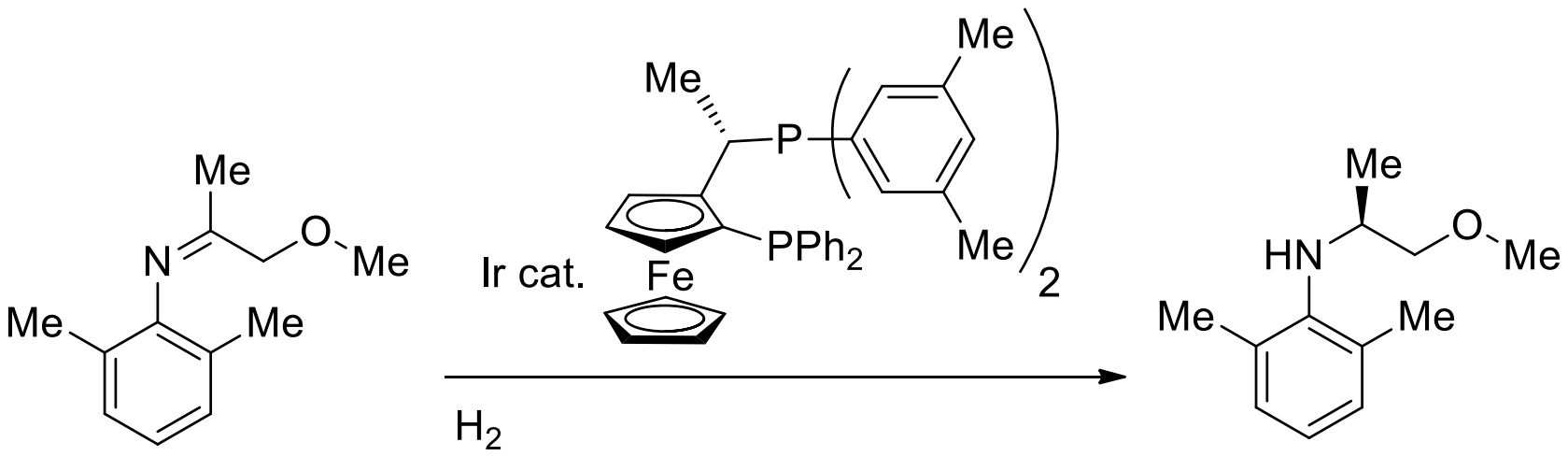
Asymmetric transfer hydrogenation

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;

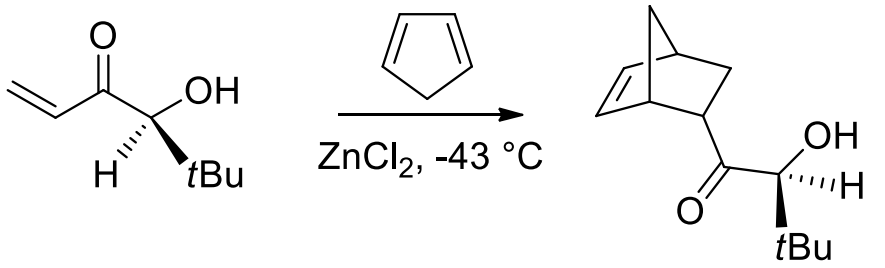
TOF > 10.000 h^{-1}

80%ee

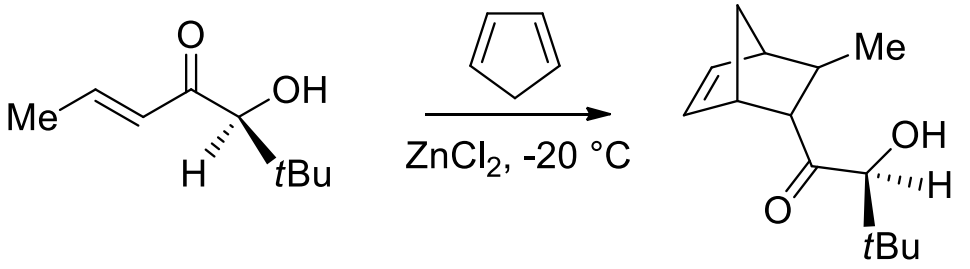
A. Togni, *Angew. Chem.* **1996**, *108*, 1581.

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

Asymmetric Diels-Alder reaction



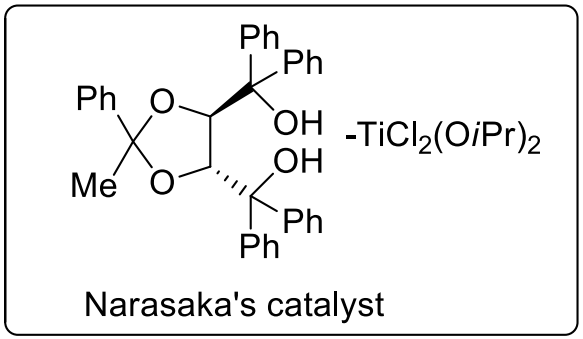
endo/*exo* = 15 : 1
de > 100 for *endo*

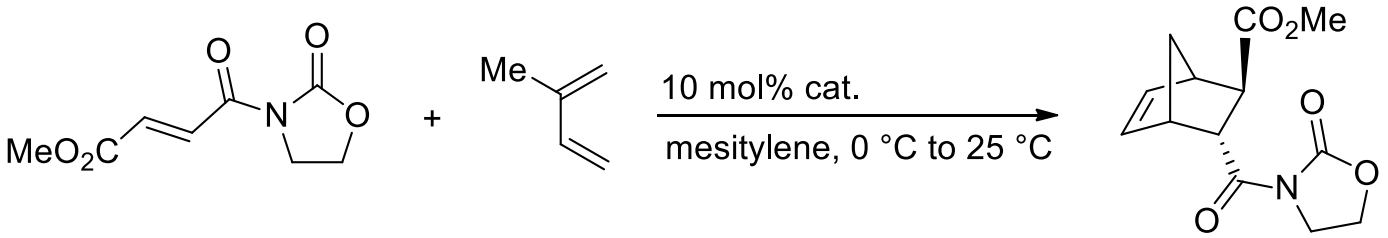


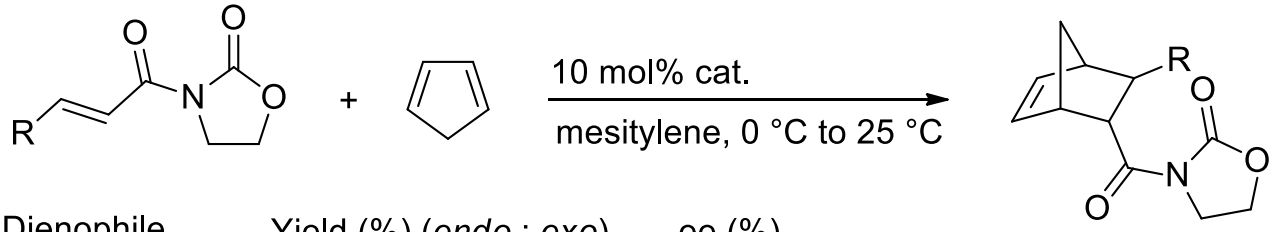
endo/*exo* = 15 : 1
de > 100 for *endo*

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



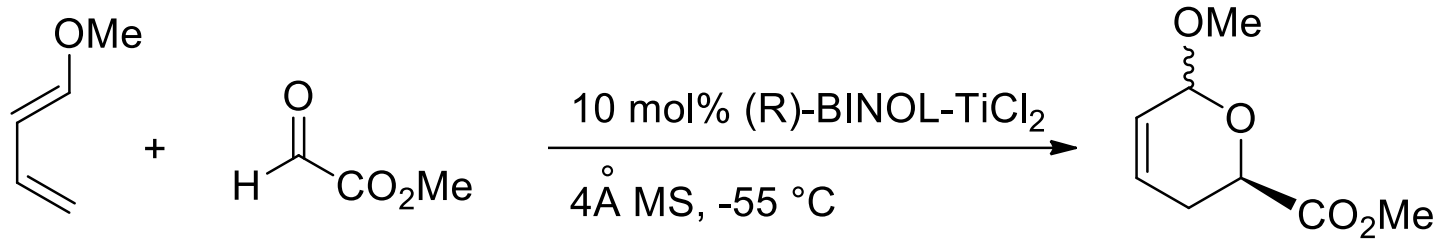




Dienophile	Yield (%) (*endo* : *exo*)	ee (%)
R = Me	90 (91 : 9)	91
R = Ph	97 (92 : 8)	82
R = *n*Pr	75 (91 : 9)	75

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

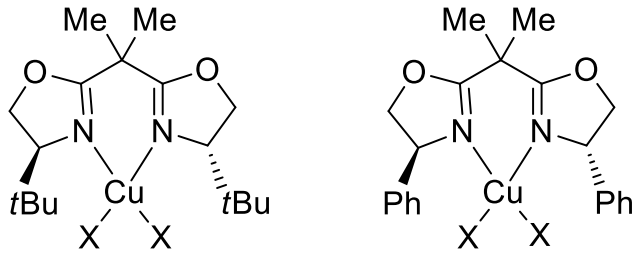
Hetero Diels-Alder reaction



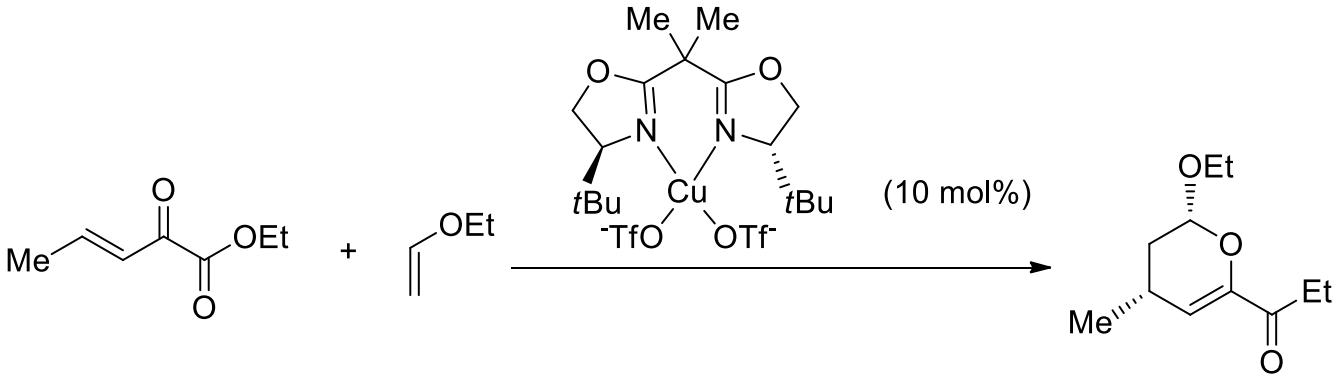
72%; 87% *cis*; 96%ee (6R)

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



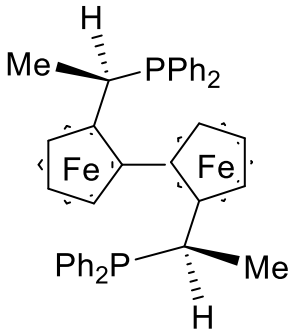
X = OTf^-; SbF_6^-



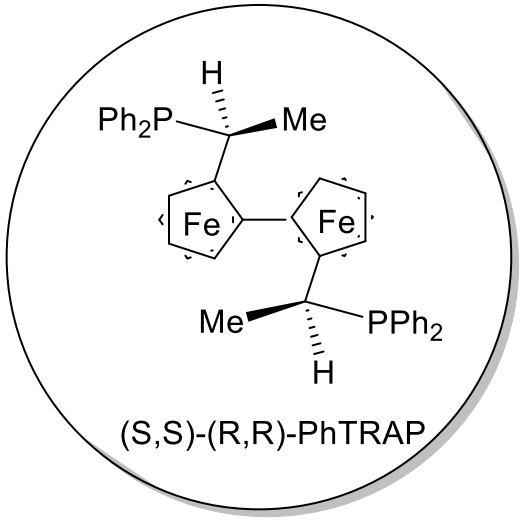
Entry	Solvent	T (°C)	Yield (%)	ee (%)
1	CH_2Cl_2	-45 °C	100	95.6
2	CH_2Cl_2	-78 °C	100	97.5
3	THF	-45 °C	100	99.0
4	THF	-78 °C	100 (89 isolated yield)	99.7
5	CH_3NO_2	-20 °C	100	75.8

J. Thorauge, M. Johannsen, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 2404.

Asymmetric Hydrogenation of Heterocyclic Compounds

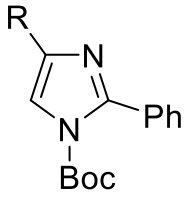


(R,R)-(S,S)-PhTRAP



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

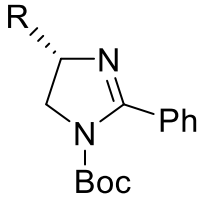
chiral ligand



R = Alk

$Ru(\eta^3\text{-methallyl})_2(cod)$ (2.5 mol%)
(R,R)-(S,S)-PhTRAP (2.8 mol%)

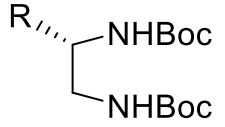
50 atm H_2, Et_3N (25 mol%)
EtOAc, 80 °C, 24 h



6 examples
35 - 99% yield

1) Pd/C (10 mol%
H_2, MeOH

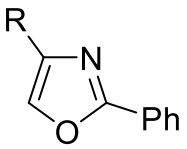
2) Boc_2O, THF



R = Me, 92% yield

enantioselectivity

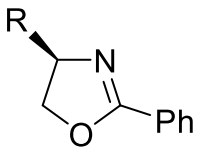
86 - 97%ee



R = Alk, Ar

$Ru(\eta^3\text{-methallyl})_2(cod)$ (2.5 mol%)
(S,S)-(R,R)-PhTRAP (2.8 mol%)

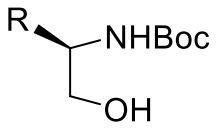
50 atm H_2, TMG (25 mol%)
iBuOH, 80 °C, 4 h



8 examples
78% to >99% yield
50 - 98%ee

aq HCl (1 M)

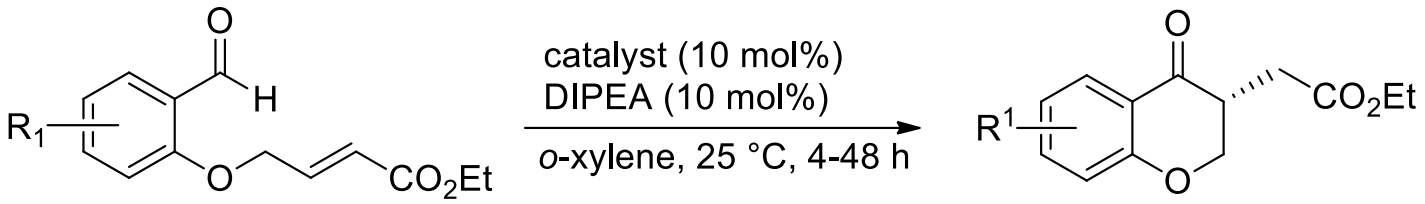
1,4-dioxane
50 °C, 1 h



4 examples
28% to >99% yield

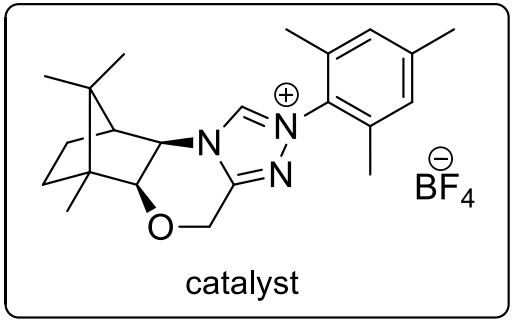
R. Kuwano, N. Kameyama, R. Ikeda, *J. Am. Chem. Soc*. **2011**, *133*, 7312-7315.

Camphor-Derived Organocatalytic Synthesis of Chromanones

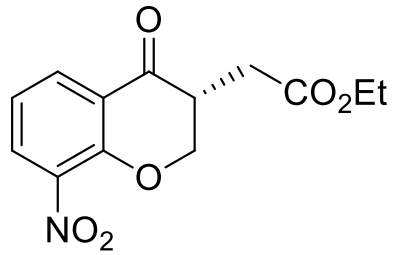


R^1 = H, 3-Me, 5-Me, 3-OMe, 4-OMe, 5-OMe, 5-Cl, 5-Br, 4-NEt_2

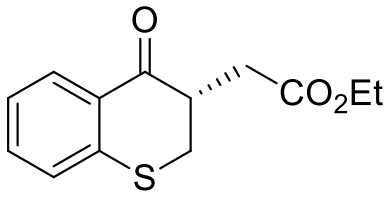
9 examples
89 - 97% yield
93 - 97%ee



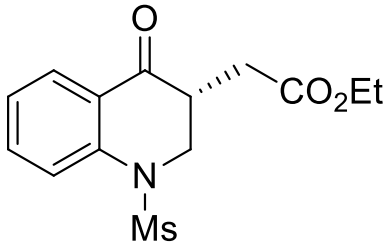
catalyst



85% yield
68%ee



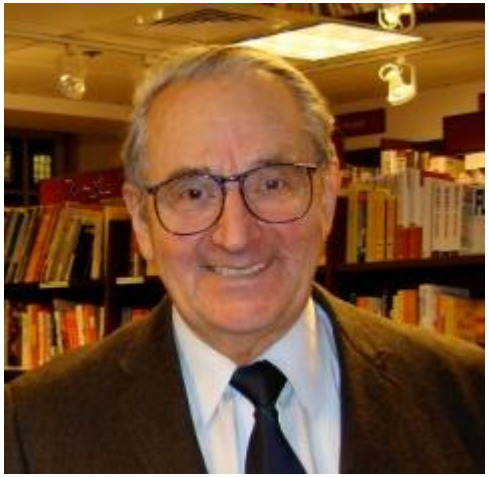
26% yield
88%ee



77% yield
56%ee

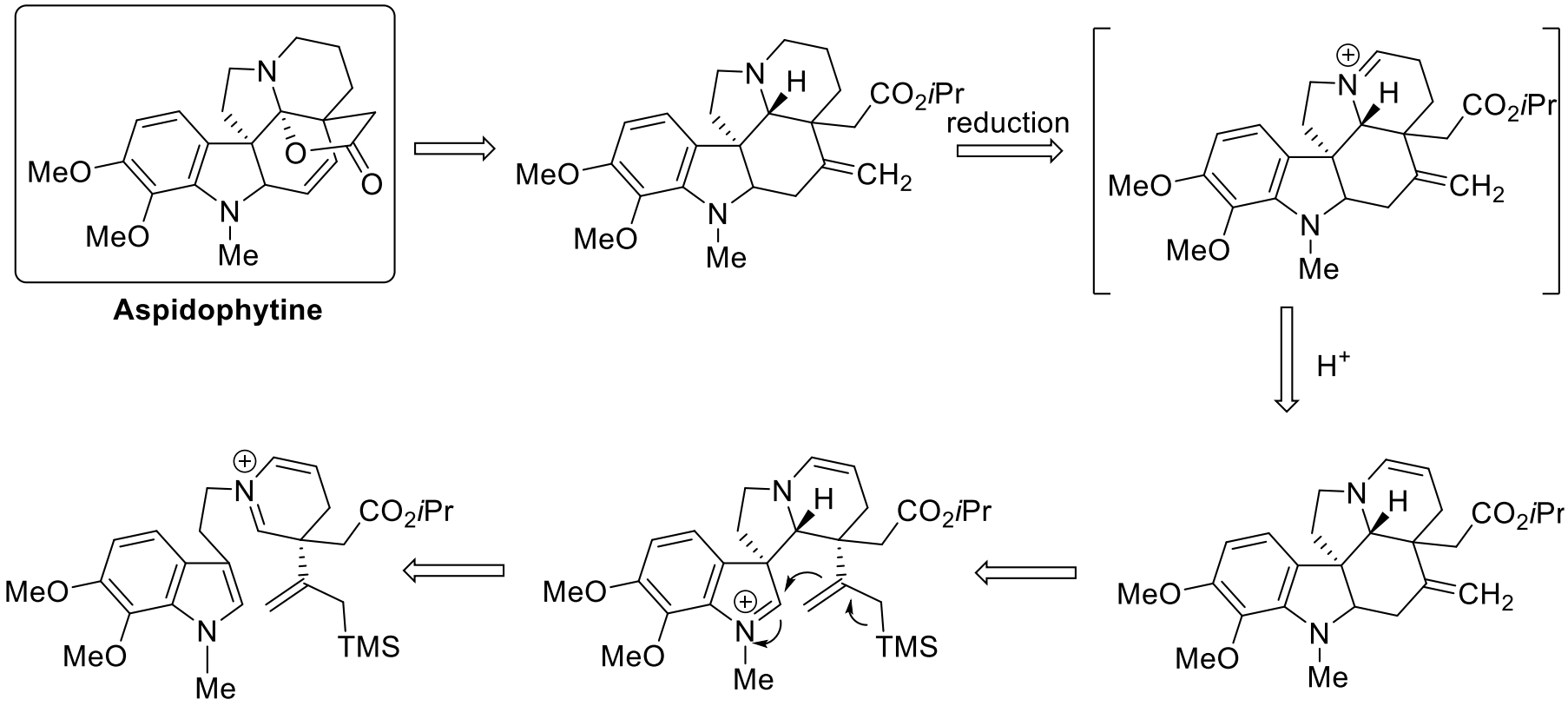
Z.-Q. Rong, Y. Li, G.-Q. Yang, S.-L. You, *Synlett* **2011**, 1033-1037.

Asymmetric synthesis in Natural Product Chemistry

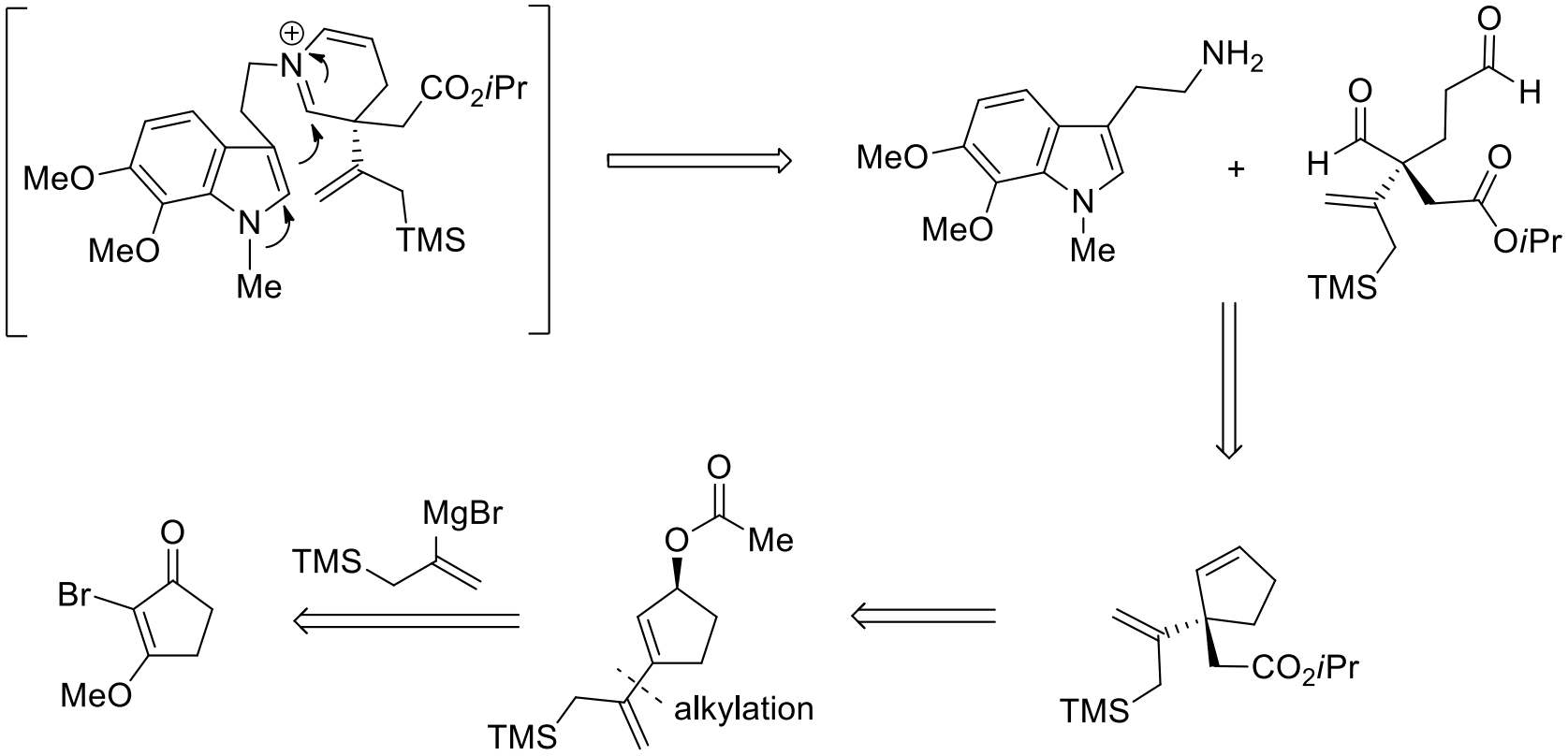


Prof. E. J. Corey

Corey‘s rethrosynthetic analysis of aspidophytine

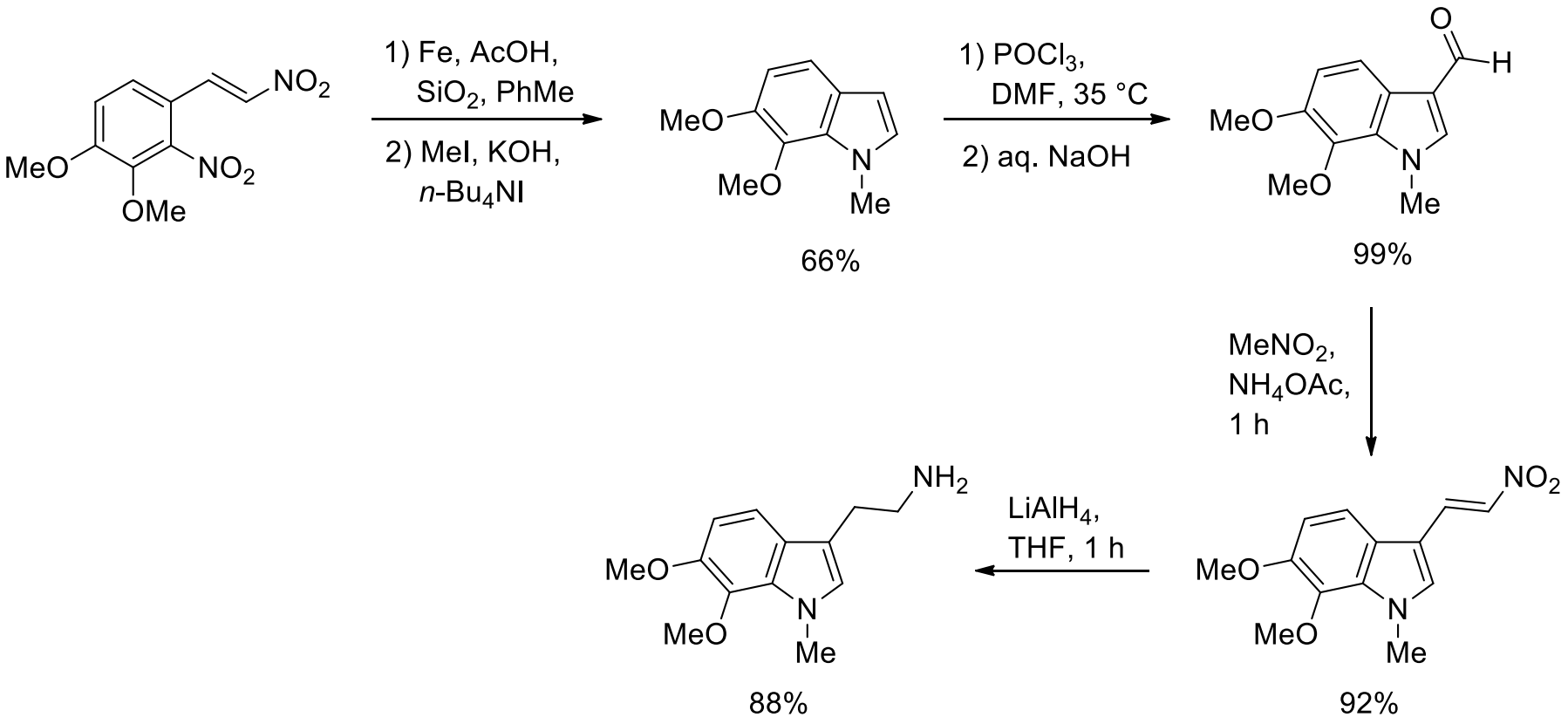


Corey‘s rethrosynthetic analysis of aspidophytine



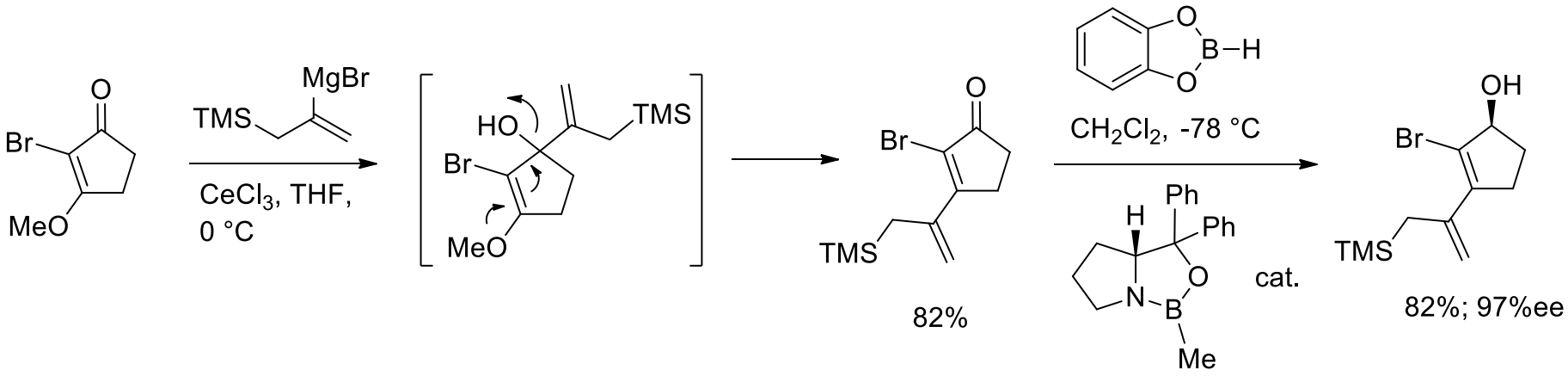
He, F., Bo, Y., Altom, J. D. Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

Corey‘s total synthesis of aspidophytine



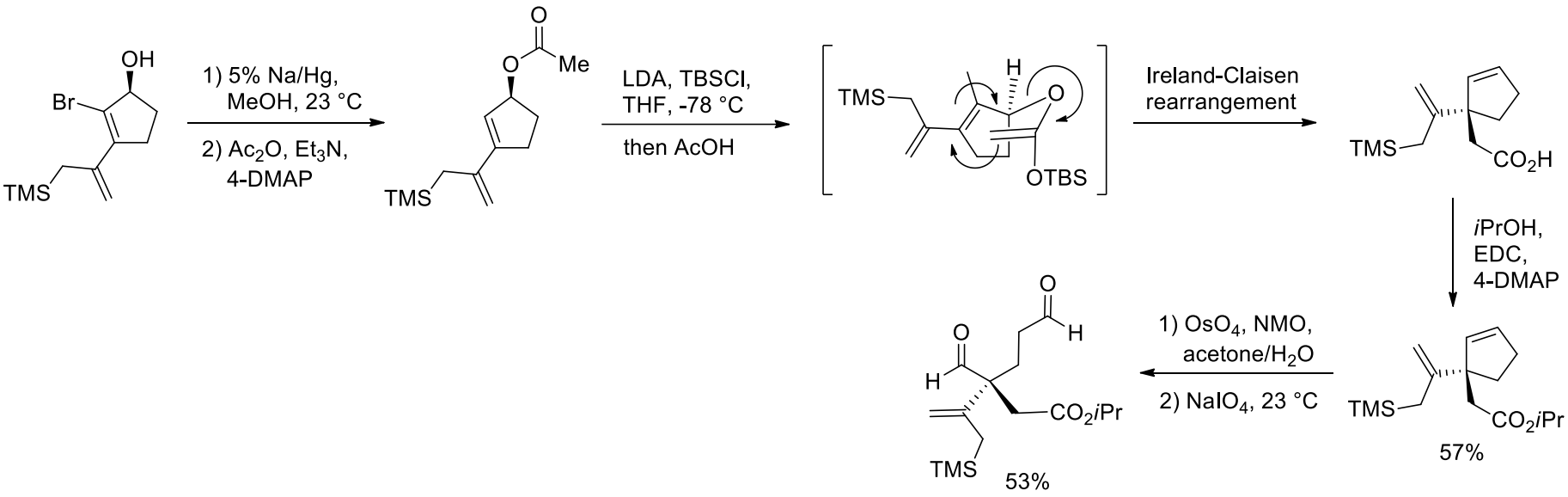
He, F., Bo, Y., Altom, J. D. Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

Corey‘s total synthesis of aspidophytine



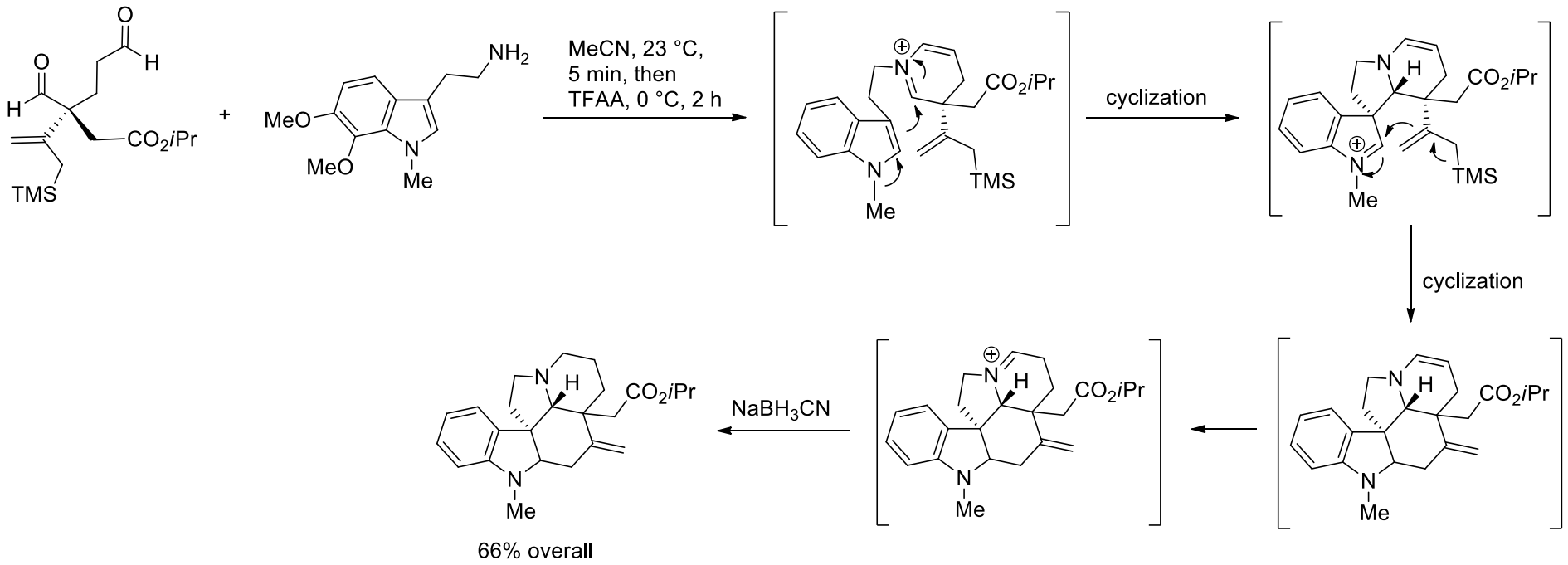
He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

Corey‘s total synthesis of aspidophytine



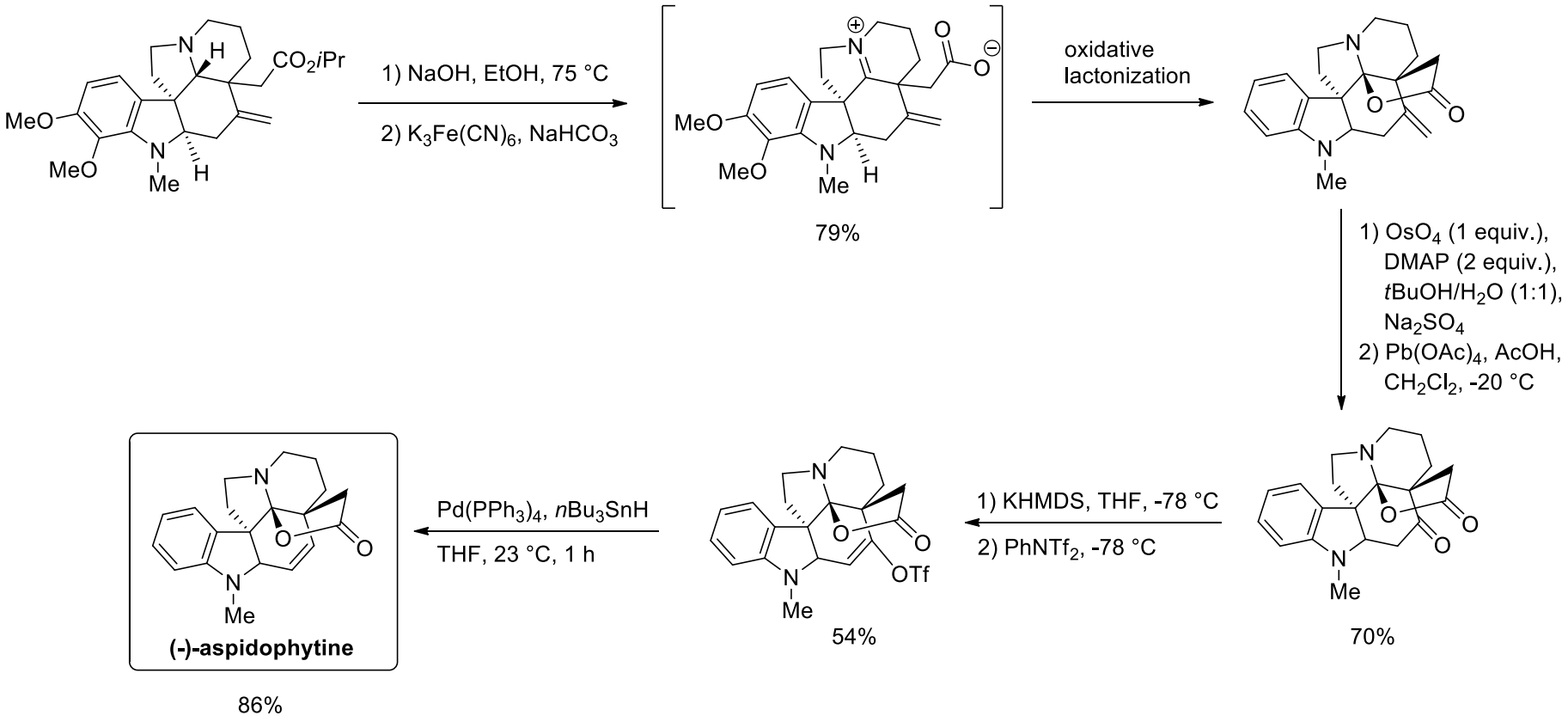
He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

Corey‘s total synthesis of aspidophytine
The final cascade sequence



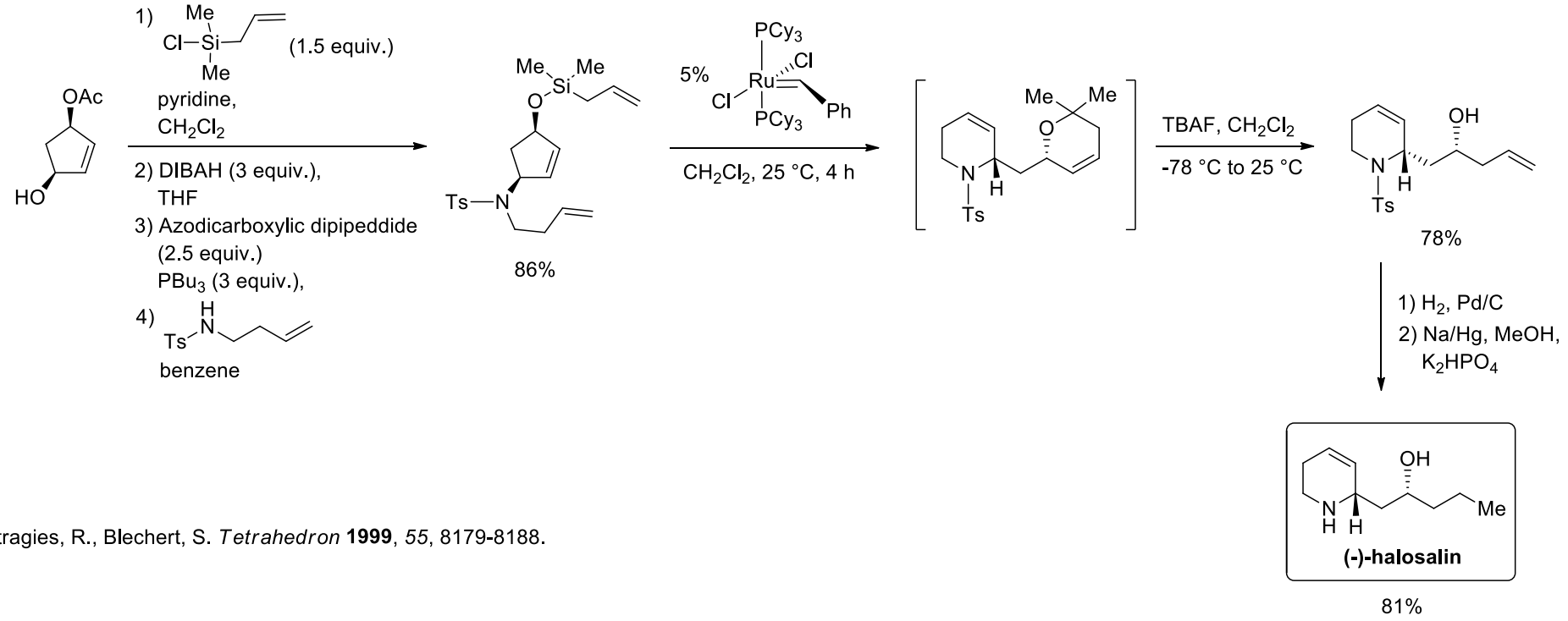
He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

Corey‘s total synthesis of aspidophytine
Final stages and completion



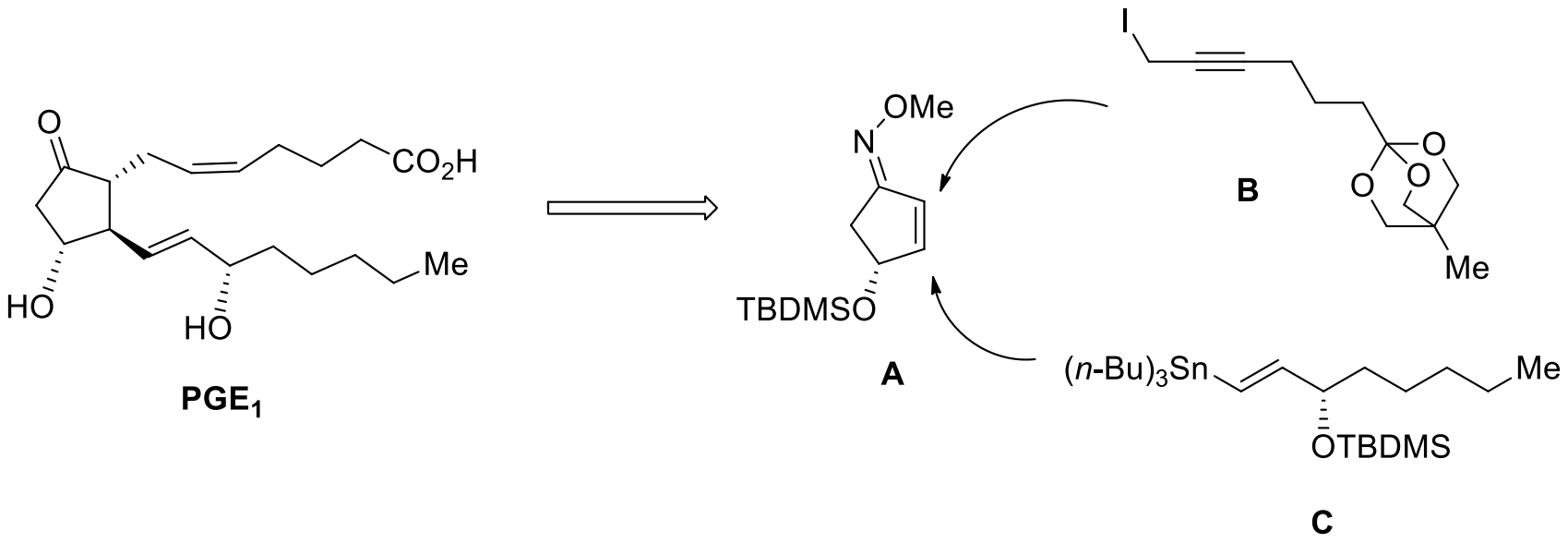
He, F., Bo, Y., Altom, J. D., Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

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



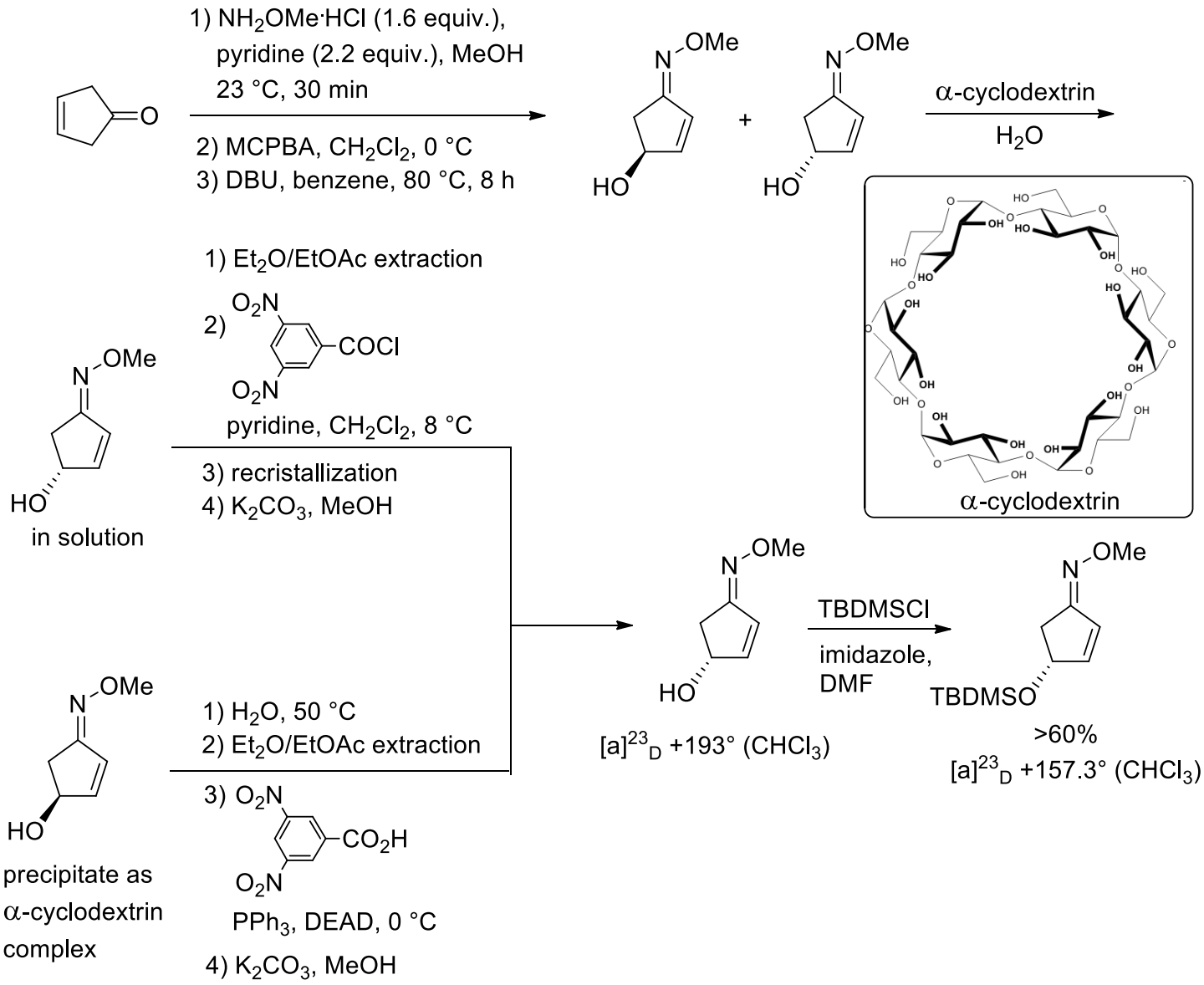
Stragies, R., Blechert, S. *Tetrahedron* **1999**, *55*, 8179-8188.

Conjugated addition-alkylation route to prostaglandins



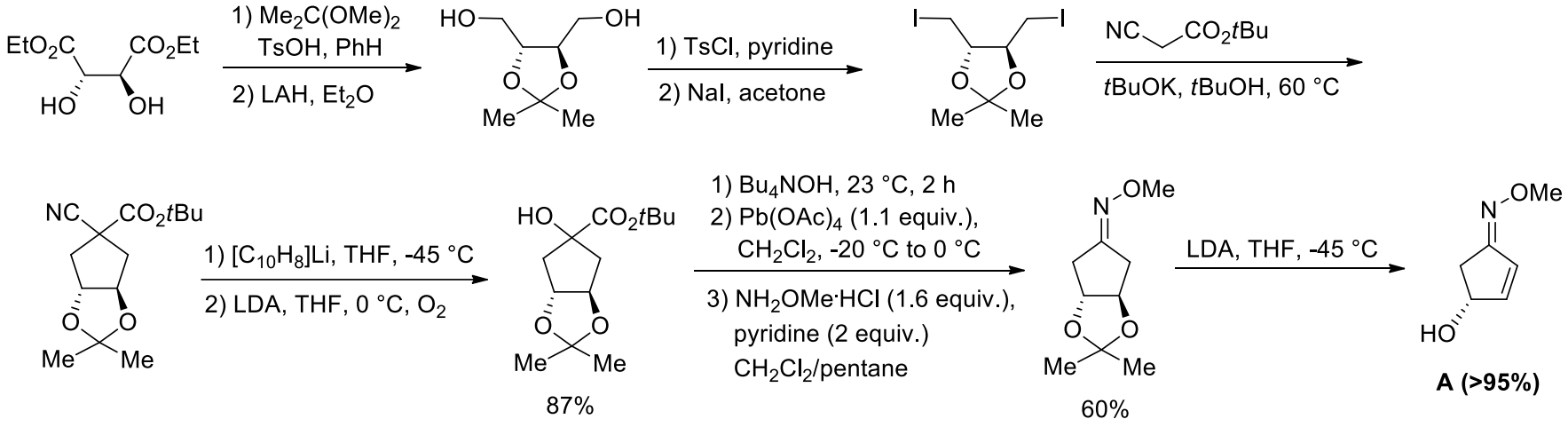
Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199-2202;
Corey, E. J., Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571-5574.

Conjugated addition-alkylation route to prostaglandins
Synthesis of fragment A



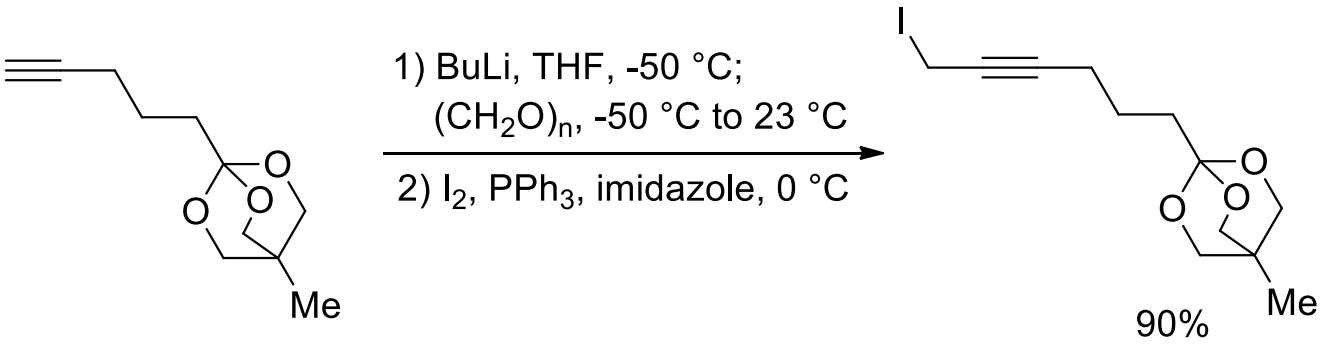
Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199-2202.

Conjugated addition-alkylation route to prostaglandins
Alternative synthesis of fragment A starting from diethyl (*S*,*S*)-tartrate



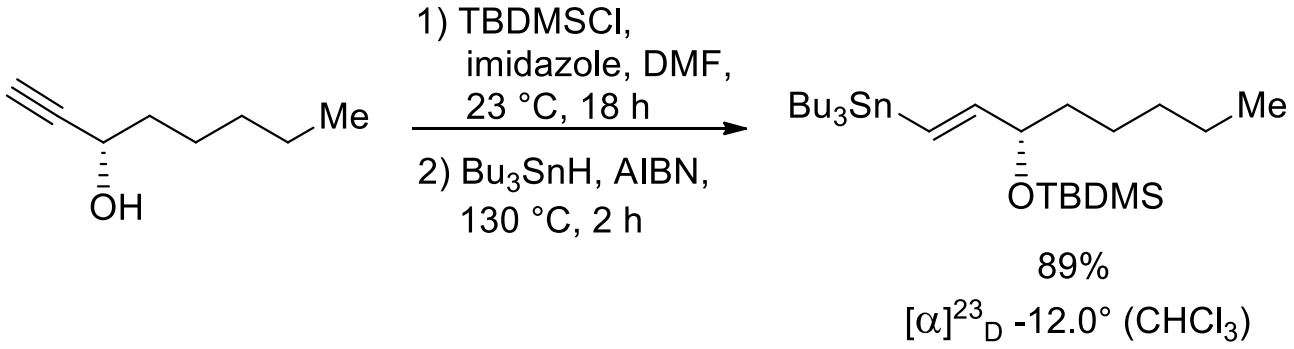
Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199-2202.

Conjugated addition-alkylation route to prostaglandins
Synthesis of fragment B



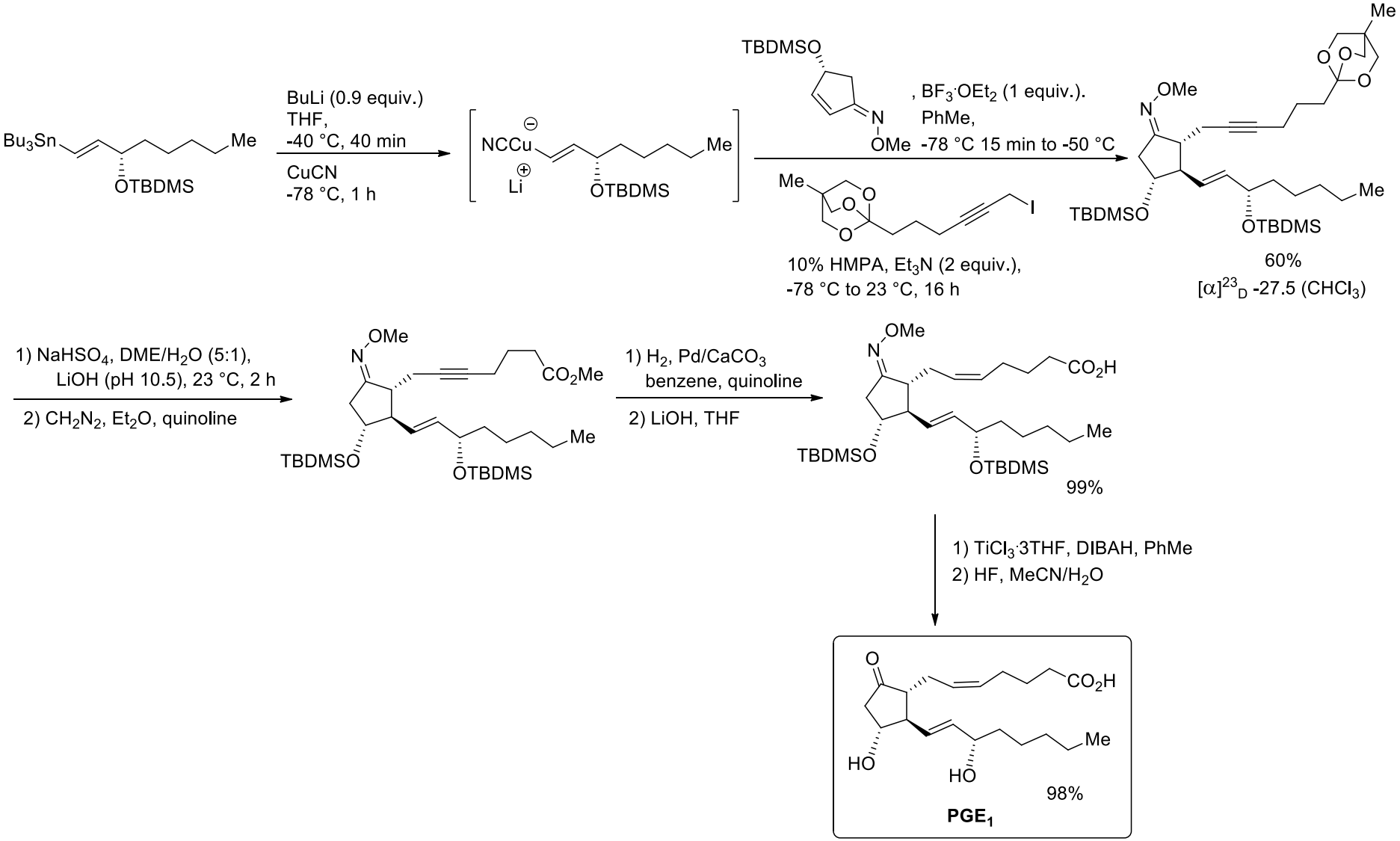
Corey, E. J., Raju, N. *Tetrahedron Lett*. **1983**, *24*, 5571-5574.

Conjugated addition-alkylation route to prostaglandins
Synthesis of fragment C



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

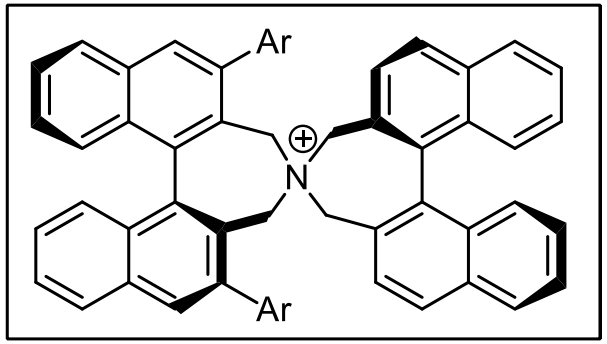
Conjugated addition-alkylation route to prostaglandins
Final assembly of the PGE1



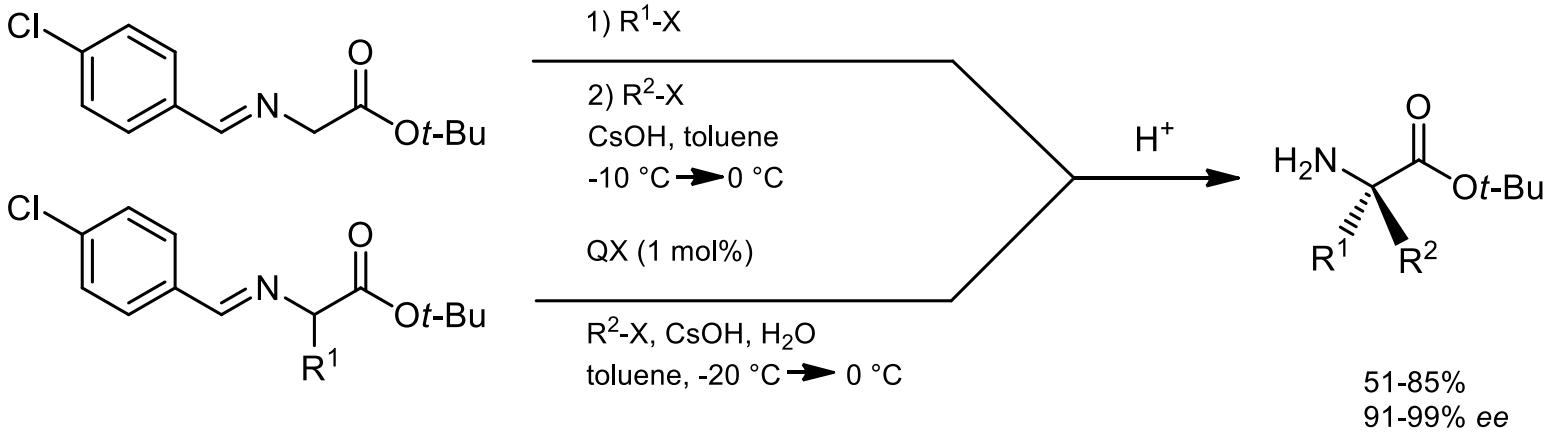
Corey, E. J., Nimura, K., Konishi, Y., Hashimoto, S., Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199-2202;
Corey, E. J., Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571-5574.

Additional asymmetric syntheses

Enantioselective alkylation by chiral phase-transfer catalysis

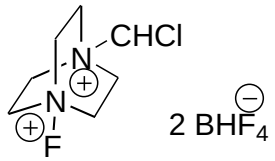


$\oplus\ \ominus$
Q Br : Ar = 3,4,5-F_3-Ph

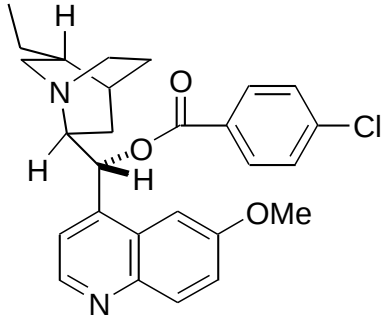


K. Maruoka, *Synlett* **2001**, 1185.

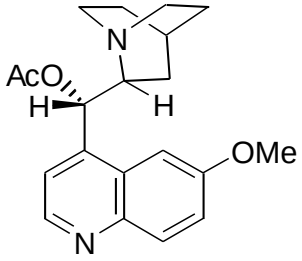
Enantioselective fluorination reactions



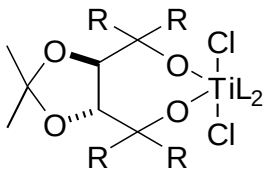
1: Selectfluor



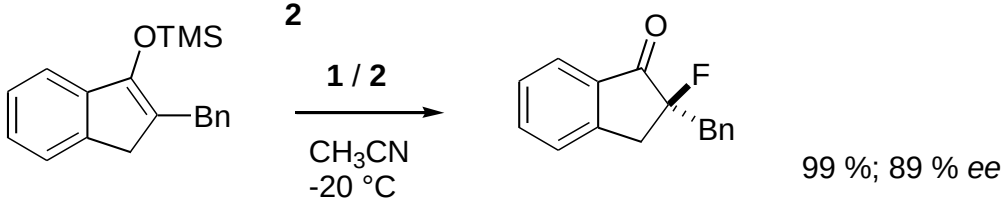
2



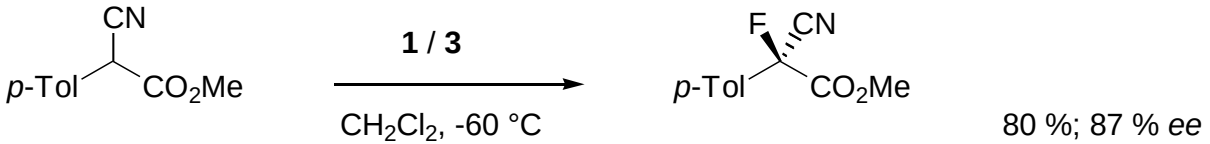
3



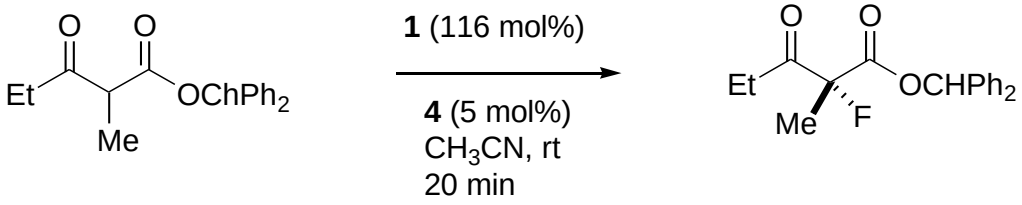
4: R = 1-Naph
$L_2 = (CH_3CN)_2$



99 %; 89 % *ee*



80 %; 87 % *ee*

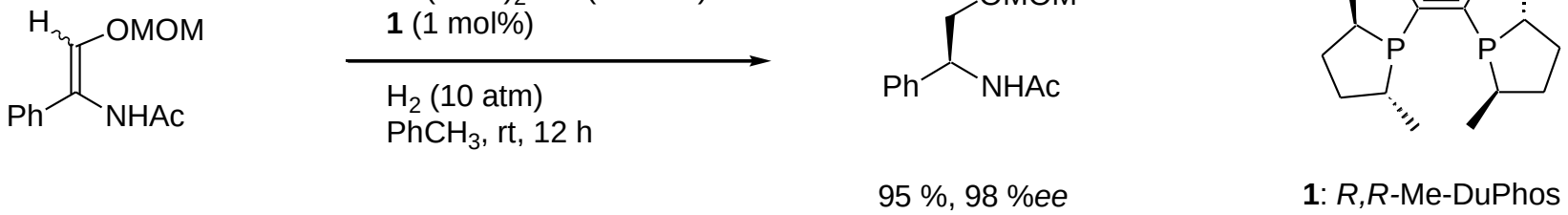


81 % *ee*

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

Asymmetric reduction of C=C-bonds

Synthesis of amino-alcohol derivatives

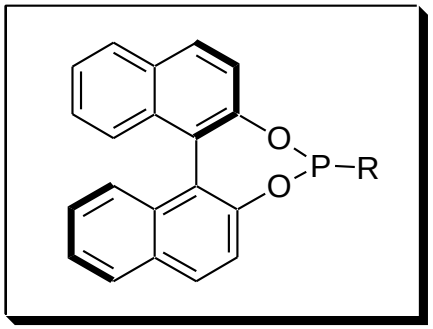


95 %, 98 %*ee*

1: *R,R*-Me-DuPhos

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

Chiral monophosphines for the enantioselective hydrogenation of functionalized olefins



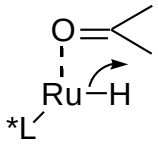
R = *t*-Bu, Et, NMe_2, (R)-O-CH(Me)Ph

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

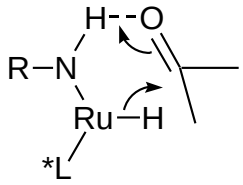
Review: Börner, A. *Angew. Chem. Int. Ed.* **2001**, *40,* 1197

Asymmetric reduction of C=O bonds

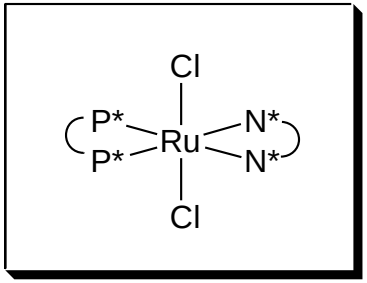
Rapid, catalytic and stereoselective hydrogenation of ketones
Noyori, R. *Pure Appl. Chem.* **1999**, *71,* 1493.



difficult



easy

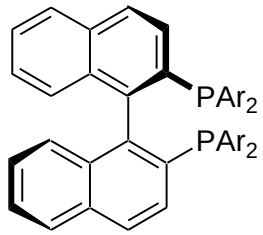


chiral Ru-complex

Noyori-catalyst system

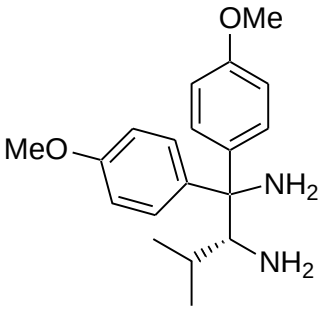
$RuCl_2$ + $(P_2)_{ligand}$ + $(N_2)_{ligand}$

$(P_2)_{ligand}$

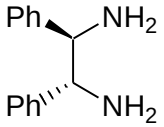


Ar = C_6H_5: (*R*)-BINAP
Ar = 4-Me-C_6H_4: (*R*)-TolBINAP
Ar = 3,5-$Me_2C_6H_3$: (*R*)-XylBINAP

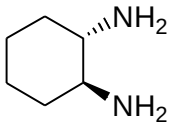
$(N_2)_{ligand}$



(*R*)-DAIPEN

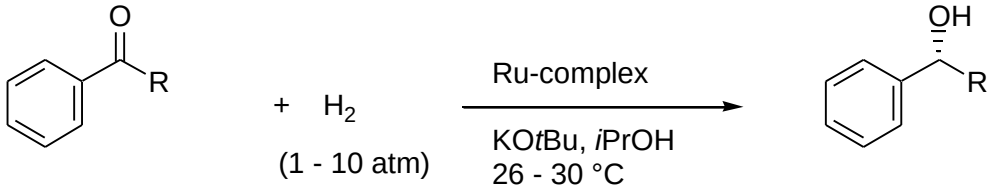


(*R,R*)-DPEN



(*R,R*)-cyclohexanediamine

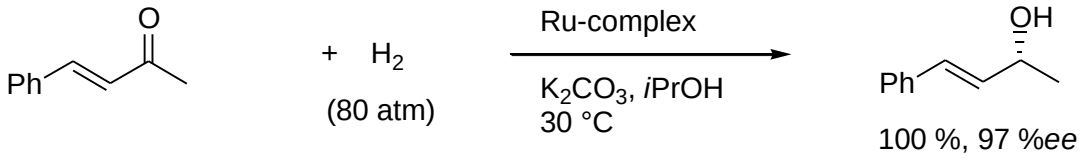
Asymmetric reduction of ketones



> 97 %, 99 %*ee*

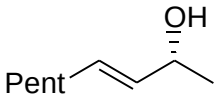
R = Me, Et, iPr
R = cyclopropyl: 96 %*ee*

Ru : ketone = 1 : 500 to 1 : 5000

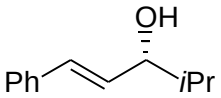


100 %, 97 %*ee*

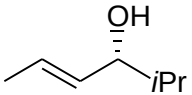
ketone : Ru : K_2CO_3 = 100 000 : 1 : 10 000
Ru-complex: $RuCl_2$-(*S*)-XylBINAP-(*S*)-DAIPEN



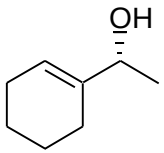
97 %*ee*



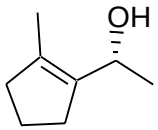
86 %*ee*



90 %*ee*

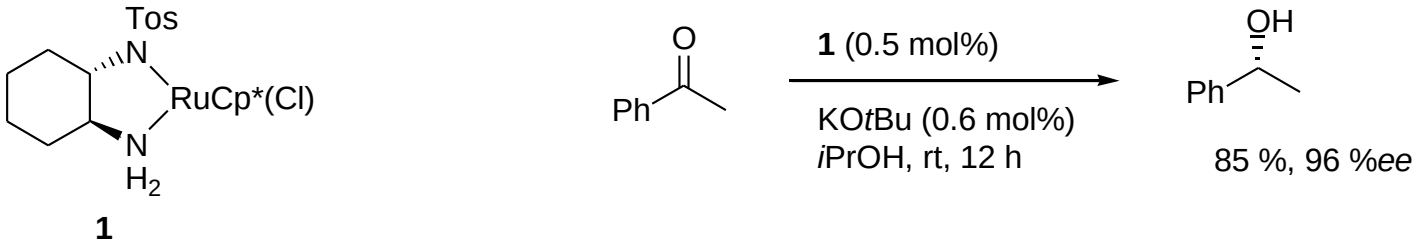


100 %*ee*



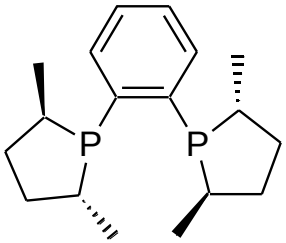
99 %*ee*

Asymmetric transfer hydrogenation

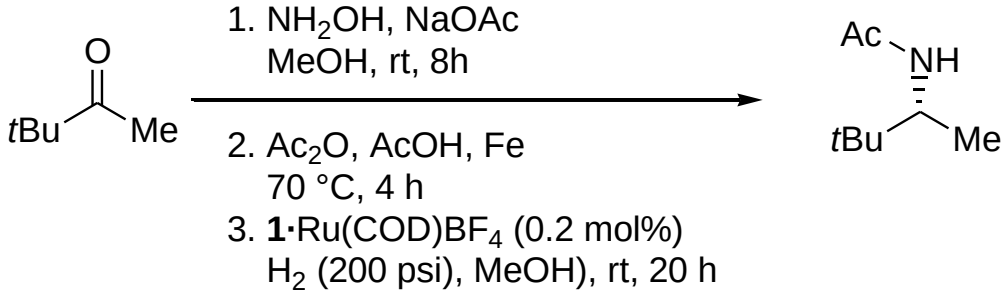


Noyori, R. *J. Org. Chem.* **1999,** *64,* 2186.

Asymmetric reduction of C=N-bonds

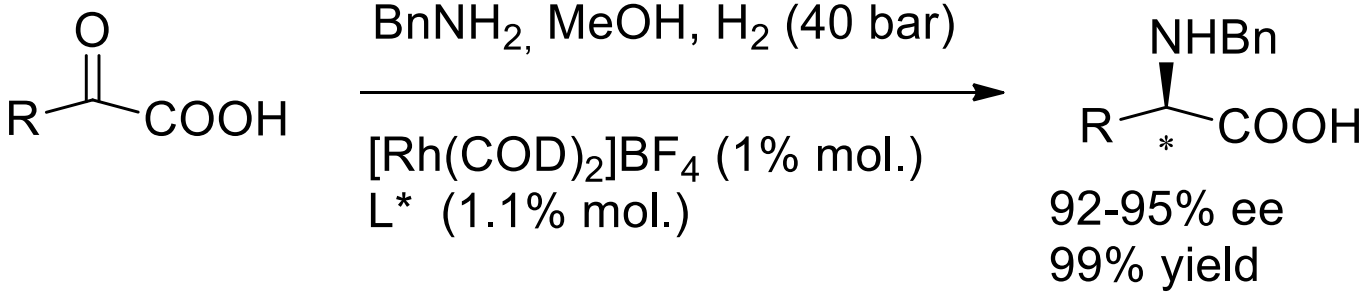


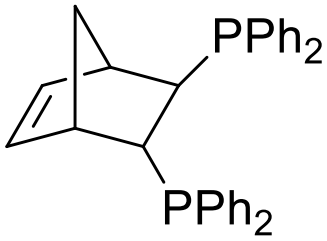
1: *R,R*-Me-DuPhos



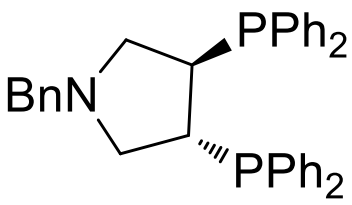
Burk, M.J. *J. Org. Chem.* **1998,** *63,* 6084.

Catalytic asymmetric reductive amination

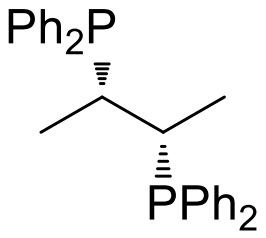




(*R,R*)-Norphos



(*R,R*)-Deguphos

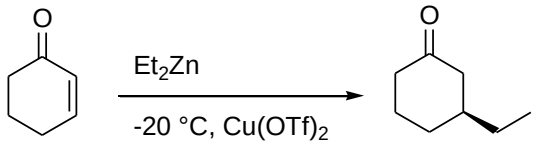


(*S,S*)-Chiraphos

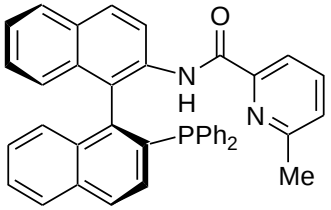
R. Kadyrov, *J. Org. Chem*., **2003**, *68,* 4067

Asymmetric C-C-bond formation

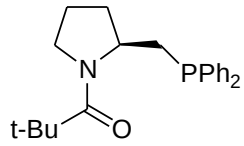
1,4-Addition using Zn-reagents



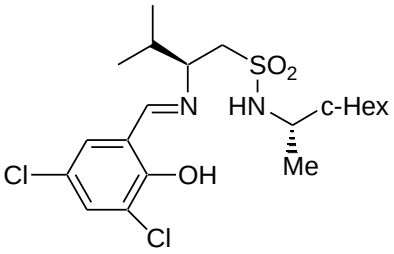
up to 98 % *ee*



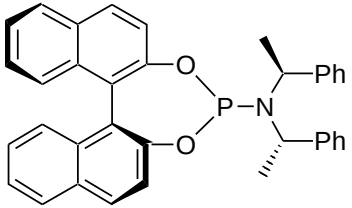
Zhang (3 mol %)



Tomioka (4.5 equiv.)



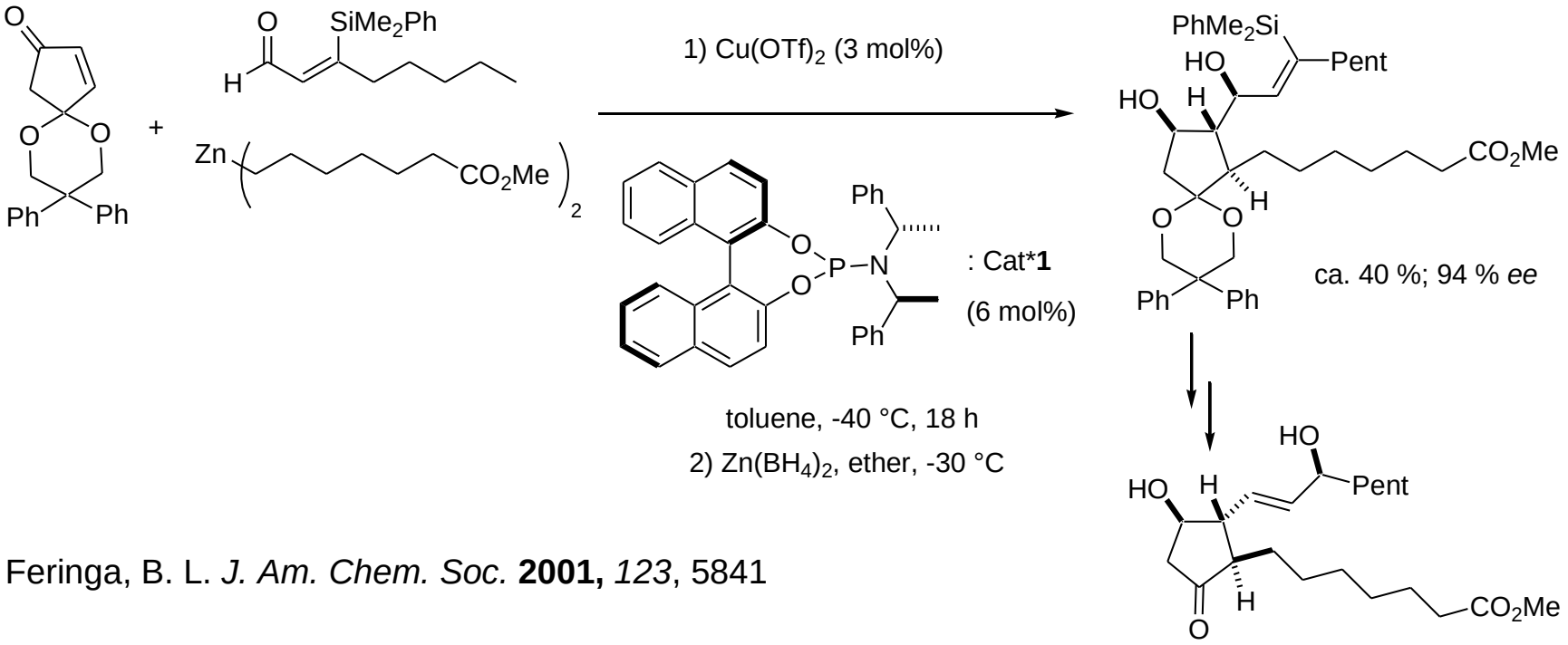
Gennari (3 mol %)



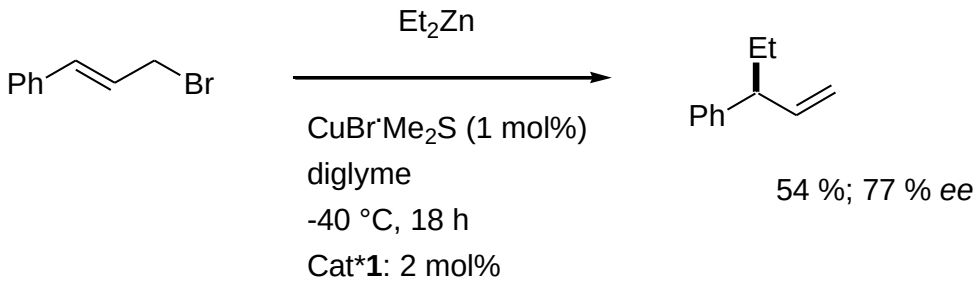
Feringa

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 E_1 methyl ester

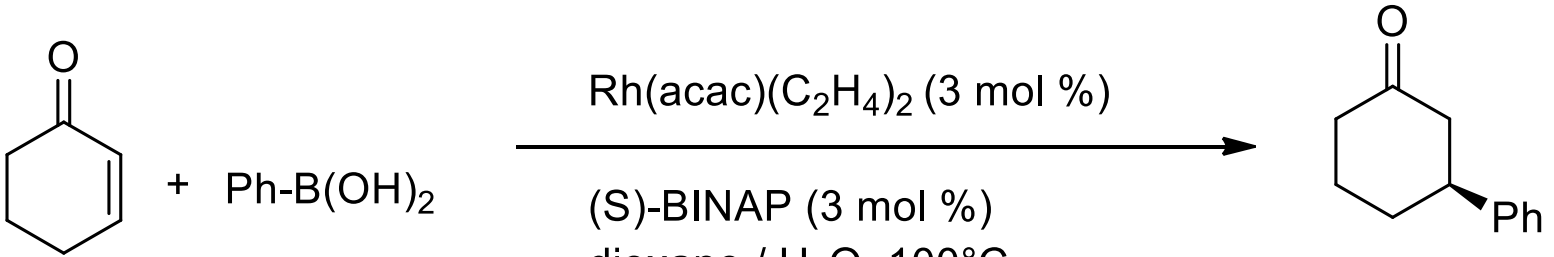


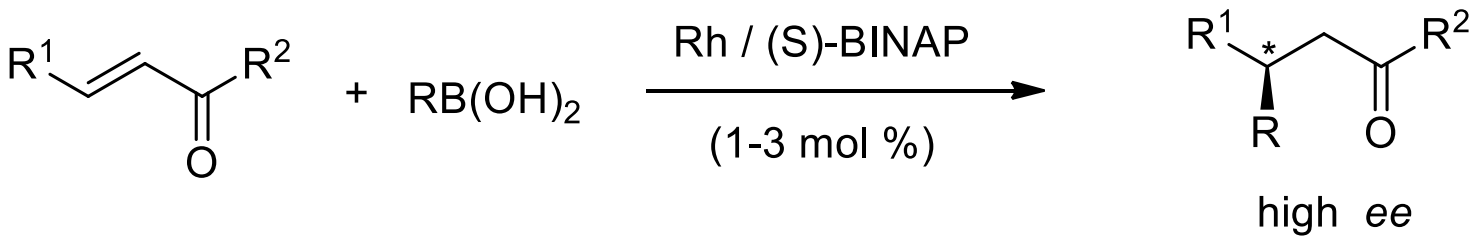
Feringa, B. L. *J. Am. Chem. Soc.* **2001,** *123*, 5841

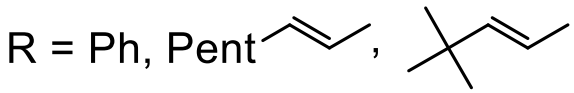


Feringa, B. L. *Org. Lett.* **2001,** *3*, 1169

Asymmetric conjugated additions

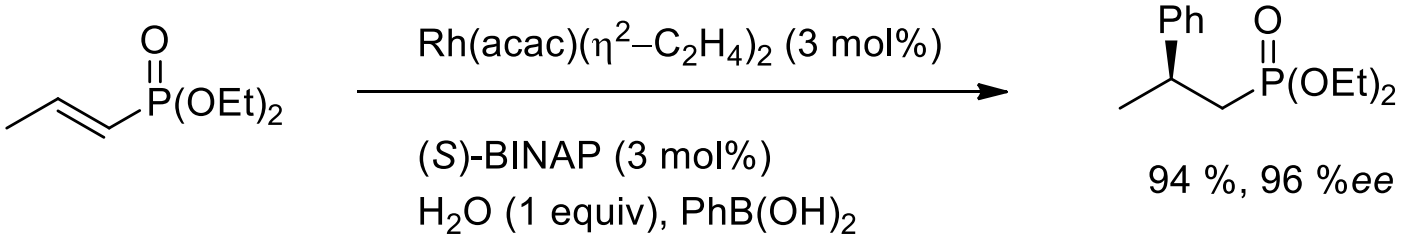






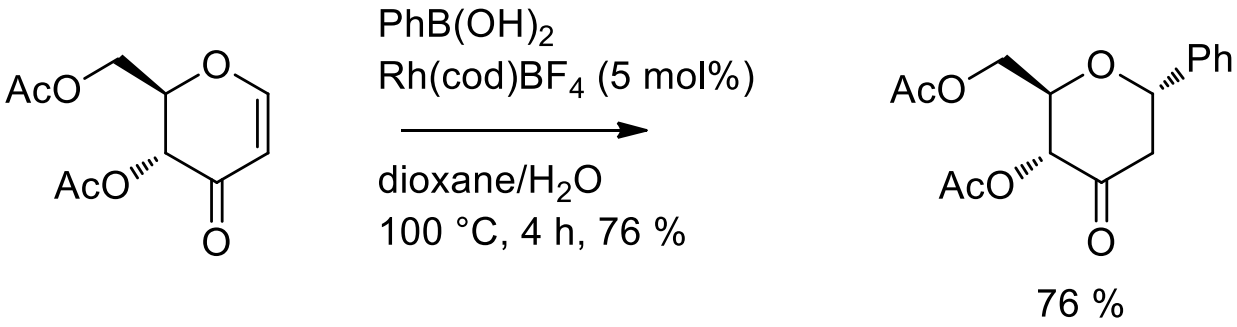
T. Hayashi *J. Am. Chem. Soc*. **1998**, *120*, 5597; **2002**, *124*, 5052;
M. T. Reetz, *Org. Lett.* **2002**, *3*, 4083

Hayashi-Michael-addition



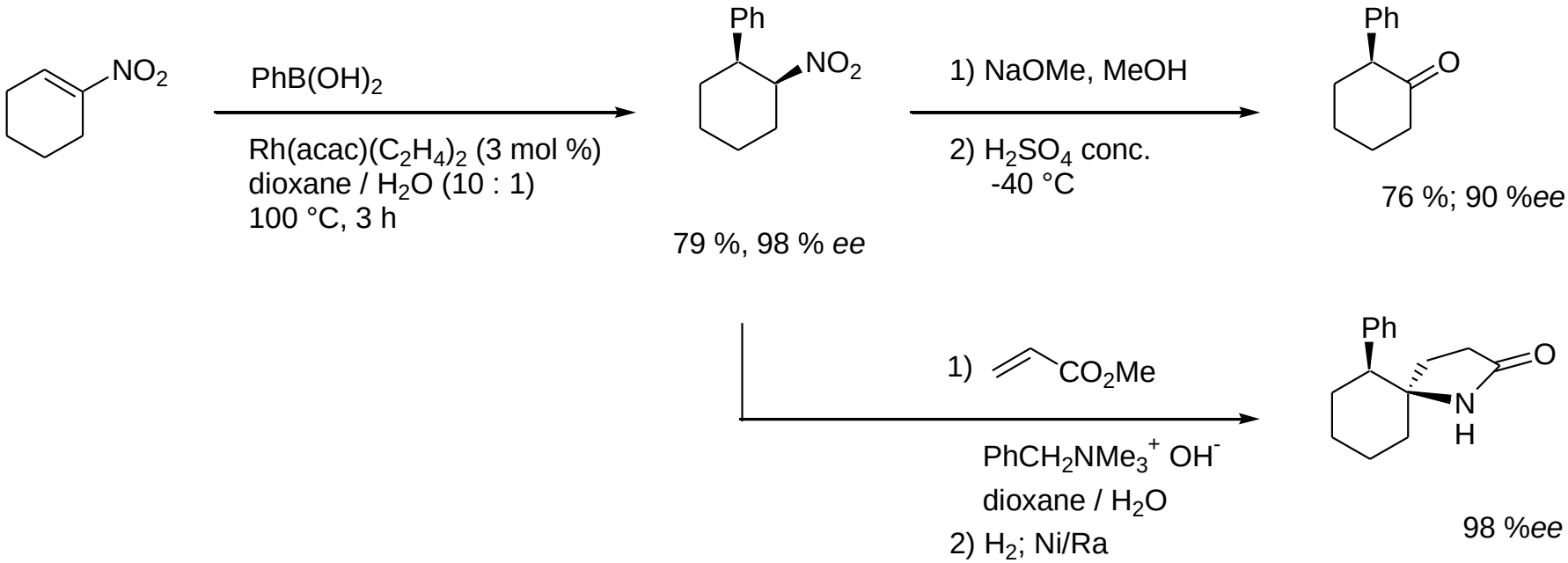
T. Hayashi, *J. Am. Chem. Soc*. **1999**, *121*, 11591.

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



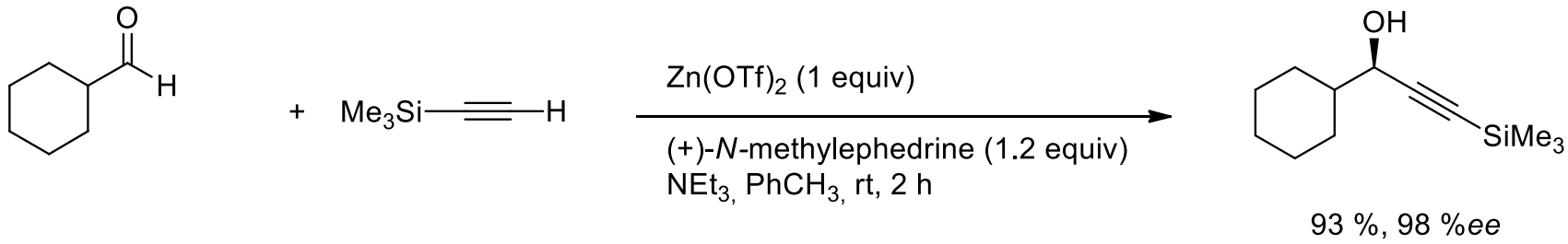
S. P. Maddaford, *Org. Lett*. **2001**, *3*, 2571

Rh-catalyzed asymmetric conjugate addition of organoboronic acids to nitroalkenes



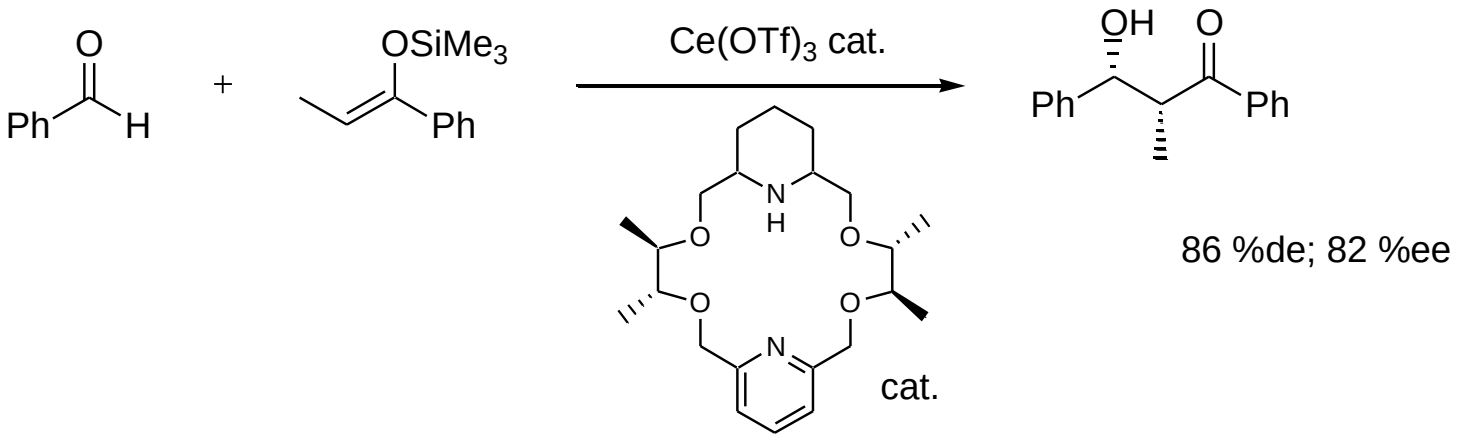
Hayashi, T. *J. Am. Chem. Soc.*, **2000,** *122,* 10716

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

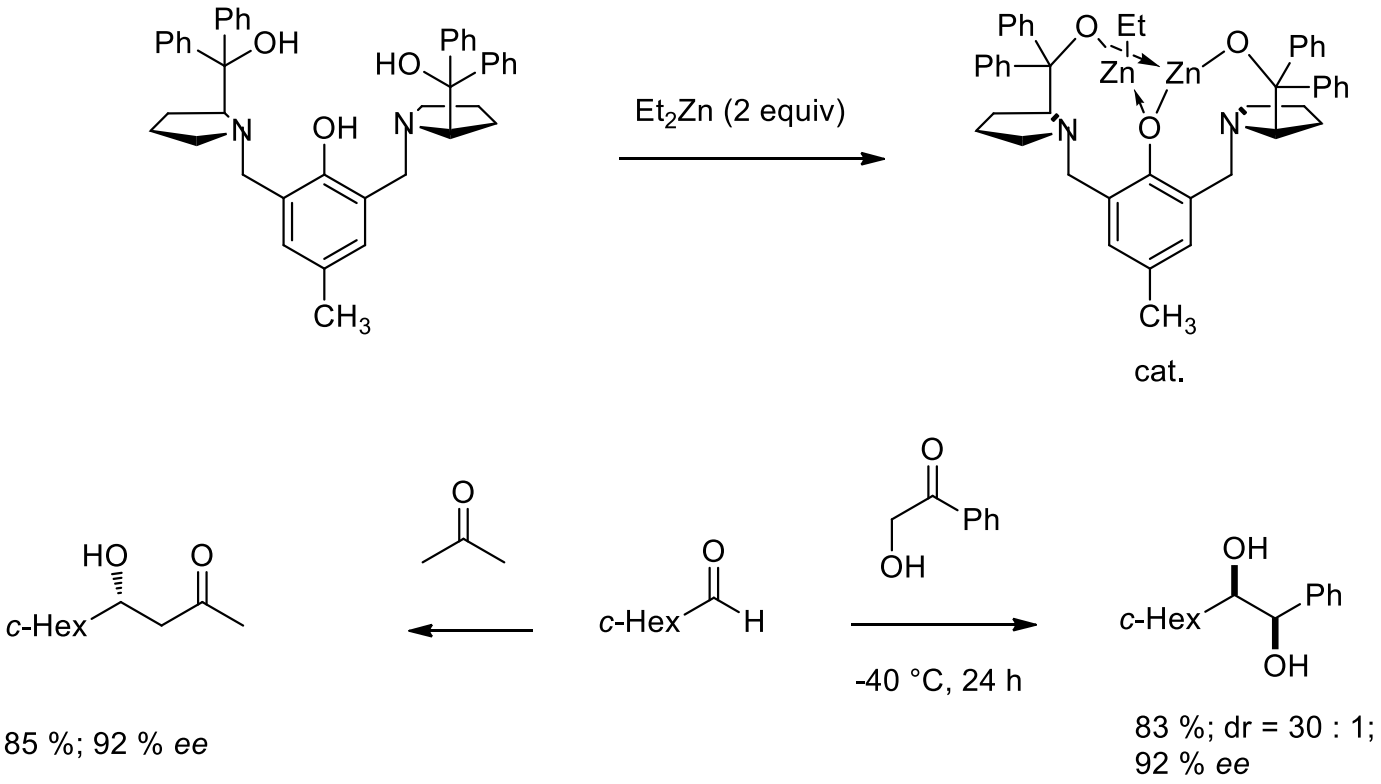
Lanthanide trifluoromethanesulfonate - catalyzed asymmetric aldol reaction in water



86 %de; 82 %ee

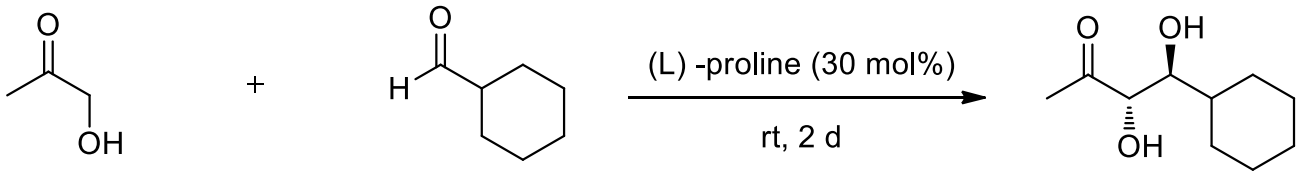
Kobayashi, S. *Org. Lett.* **2001,** *3,* 165

Asymmetric aldol reaction via a dinuclear zinc catalyst

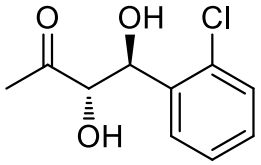


B. M. Trost, *J. Am. Chem. Soc*. **2001**, *123,* 3367; *Org. Lett.* **2001**, *3*, 2497

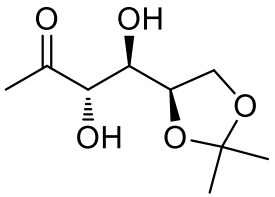
Catalytic synthesis of 1,2-diols mediated by (L)–proline



60 %; diastereosel > 20 : 1
enantiosel. > 100 : 1



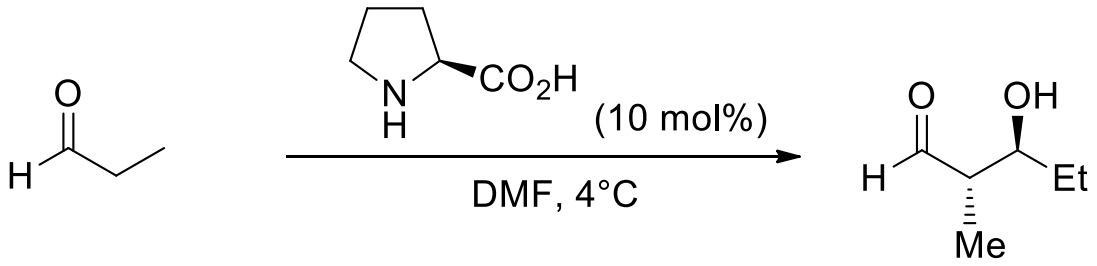
67 %ee
d.r. = 1.5 : 1



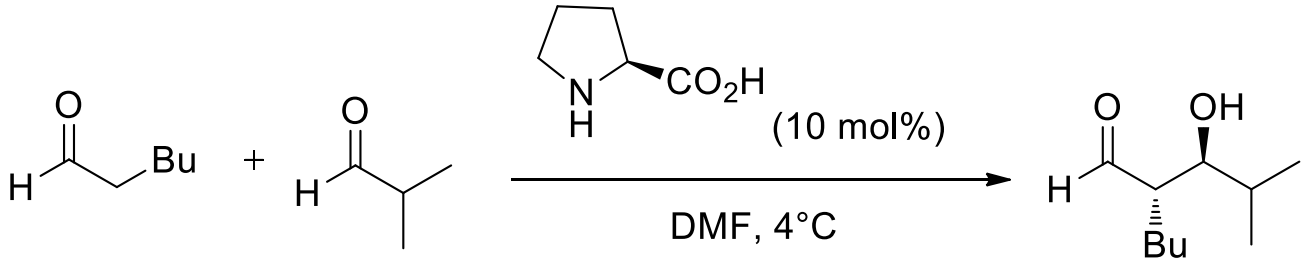
97 %ee
d.r. = 2 :1

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



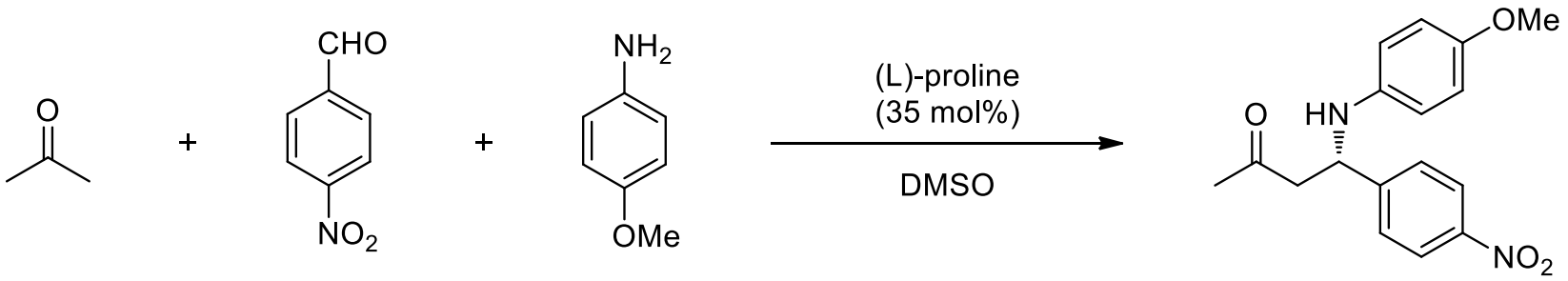
80%; syn:anti = 1:4; 99% *ee*



80%; syn:anti = 1:24; 98% *ee*

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

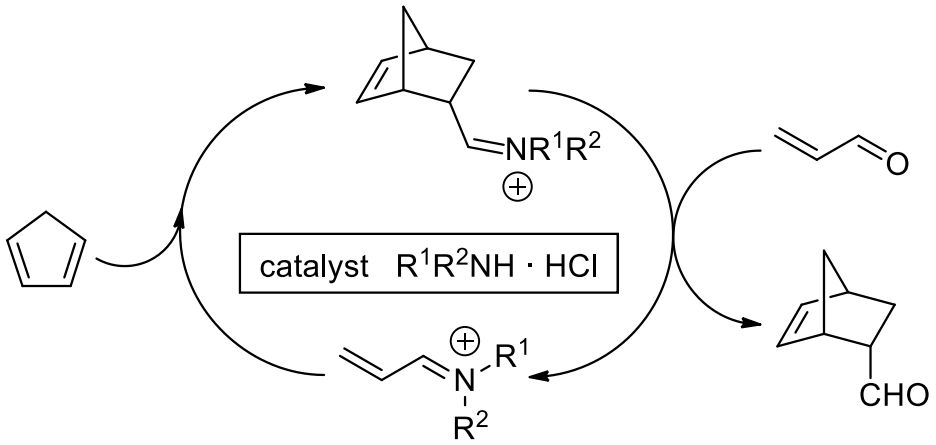
Catalytic asymmetric Mannich reaction mediated by (L)-proline



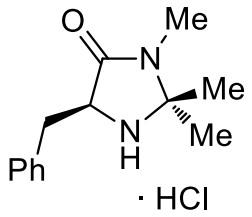
50 %; 94 %*ee*

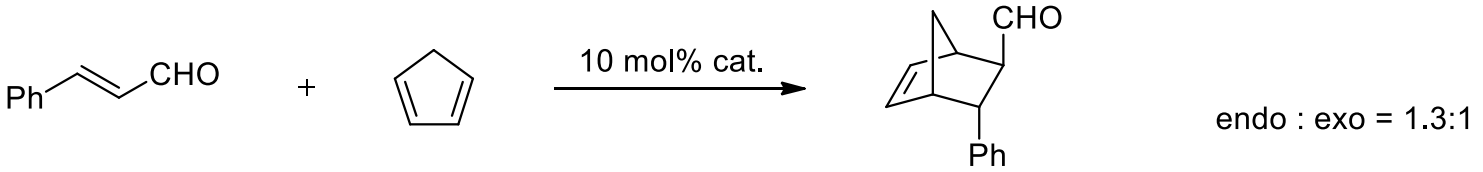
B. List *J. Am. Chem. Soc.* **2000,** *122,* 9336; **2002**, *124*, 827

Organocatalytic Diels - Alder reaction



cat. :





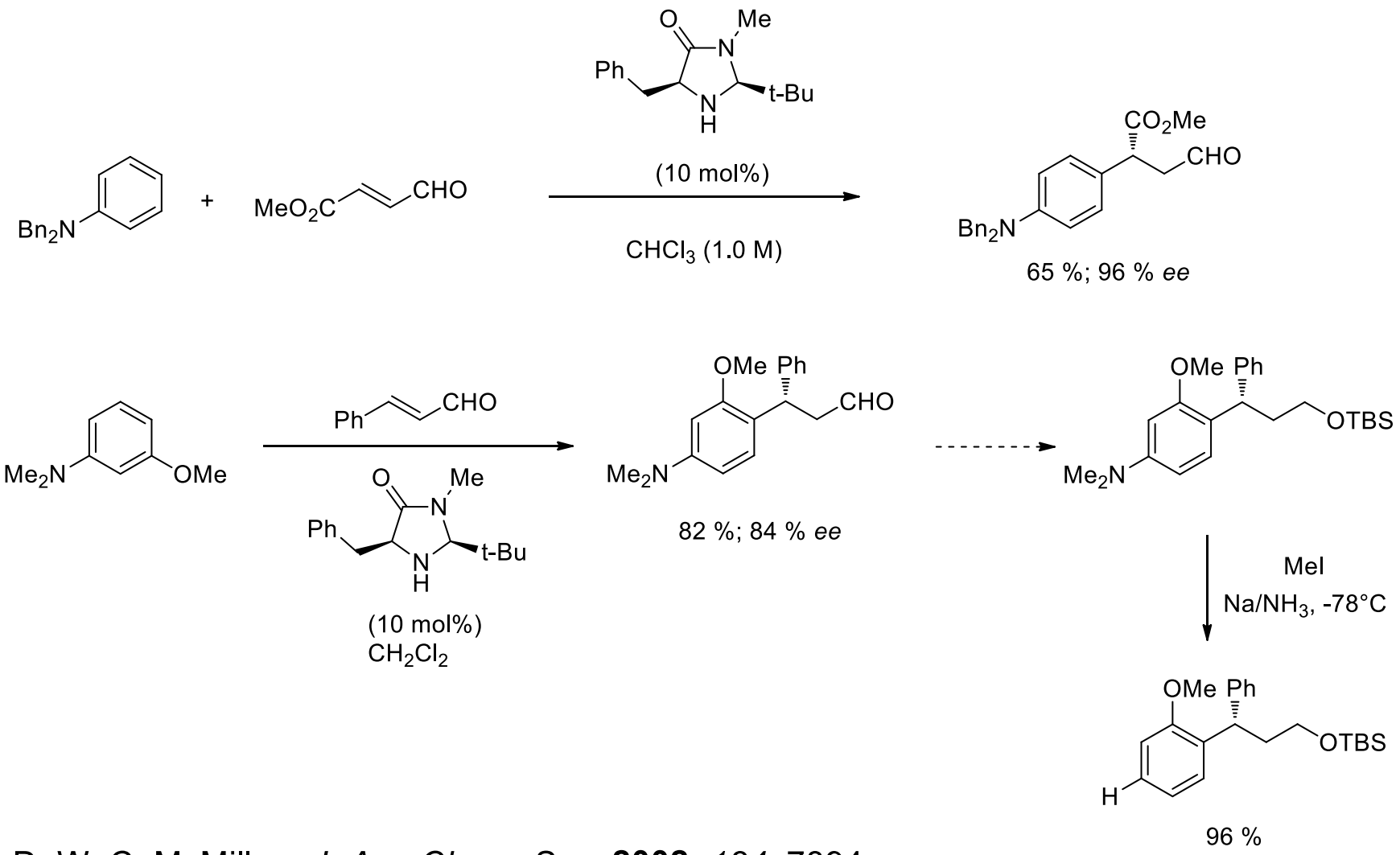
endo : exo = 1.3:1

99 % yield
93 %ee (exo product)

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

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

Organocatalytic alkylation of methyl 4-oxobutenoate



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