Strategies for Stereocontrolled Synthesis

Chemistry 5.512
Synthetic Organic Chemistry II

Lecture 1

February 28, 2007

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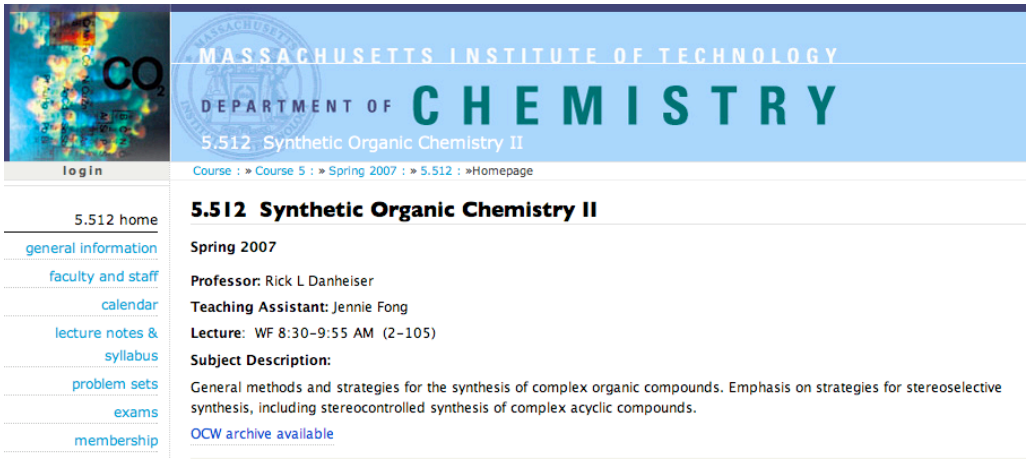
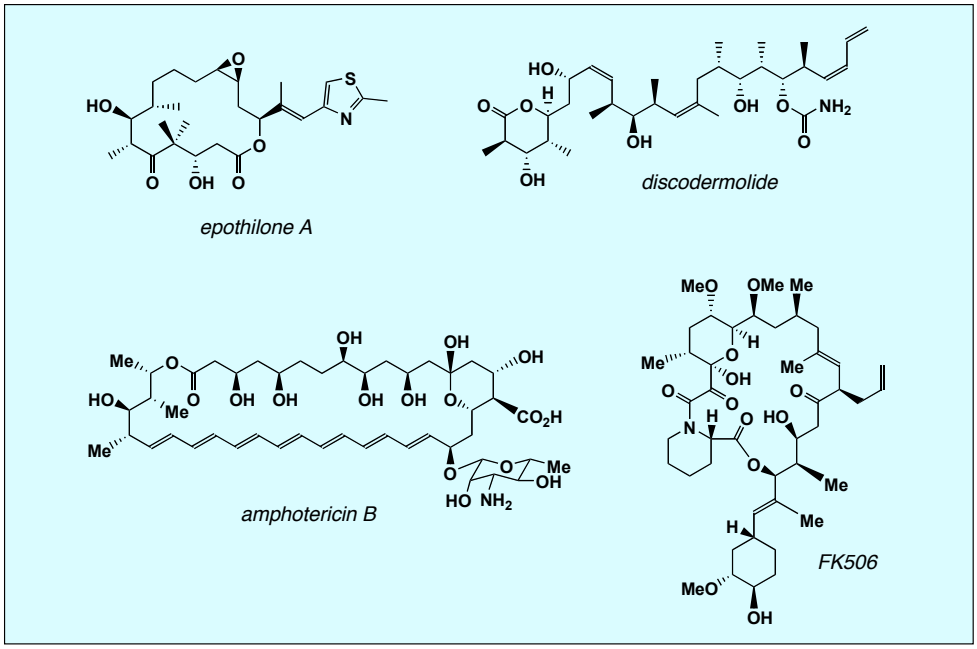
Massachusetts Institute of Technology



Strategies for Stereocontrolled Synthesis



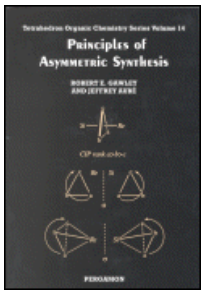
5.512 Course Syllabus

Unit 1	Strategies for Stereocontrolled Synthesis
Unit 2	Stereocontrolled Alkylation
Unit 3	Stereocontrolled Conjugate Addition
Unit 4	Stereocontrolled 1,2 Addition to C=X Bonds
Unit 5	Addition of Allylmetals to Carbonyl Groups
Unit 6	Stereocontrolled Aldol Reactions
Unit 7	Stereocontrolled Carbonyl Reduction
Unit 8	Stereocontrolled Alkene Reduction
Unit 9	Stereocontrolled Hydroboration and Dihydroxylation
Unit 10	Stereocontrolled Epoxidation

Strategies for Stereocontrolled Synthesis

Asymmetric Synthesis

Reaction or sequence that selectively creates one or more stereogenic elements by reaction at heterotopic faces, atoms, or groups in the substrate(s)



5.512 Text
Gawley and Aube

Reading on Stereochemical Principles

Carey and Sundberg "Advanced Organic Chemistry" Part A (2000) Chapters 2 and 3

E. L. Eliel and S. H. Wilen
"Stereochemistry of Organic Compounds" (1994)

Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic Control Strategies
- ★ Kinetic Control Strategies
- ★ Strategies for the Synthesis of Acyclic Target Molecules: Case Studies
  - ✻ Glycinoeclepin A Intermediate (Danheiser)
  - ✻ Prostaglandins from Sugars (Stork)

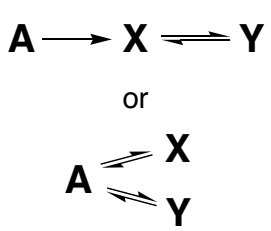
Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
  - ✻ What determines the relative E of stereoisomers
  - ✻ Tactics for establishing thermodynamic control
- ★ Kinetic control strategies
  - ✻ Substrate control strategies
  - ✻ Reagent control strategies
  - ✻ Dynamic kinetic resolution

Strategies for Stereocontrolled Synthesis

Thermodynamic Control

Relative energy of diastereomers determines outcome of reaction



ΔGxy	
0.5 kcal/mol	70:30
1.0 kcal/mol	84:16
1.5 kcal/mol	92:8
2.0 kcal/mol	97:3

9 : 1 = 90 : 10

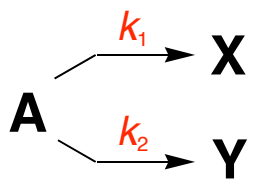
25 : 1 = 96 : 4

49 : 1 = 98 : 2

Strategies for Stereocontrolled Synthesis

Kinetic Control

Ratio of products determined by relative energy of diastereomeric transition states



Strategies for Stereocontrolled Synthesis

Thermodynamic Control

Relative energy of diastereomers determines outcome of reaction

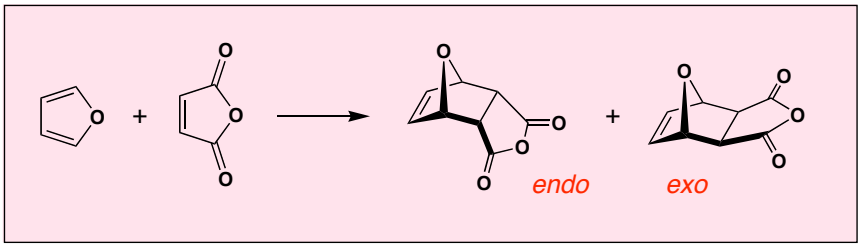
I. What determines the relative energy of stereoisomers?

- ☆ **De-stabilizing Non-bonded Repulsion**
- ☆ **Stabilizing Non-covalent Interactions**
- ☆ **Stereoelectronic Effects**
  - ✳ Deviation from optimal geometry for orbital overlap (angle strain)
  - ✳ Destabilizing torsional interactions
  - ✳ Stabilizing secondary orbital interactions
  - ✳ Dipole-dipole interactions

Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #1 Cycloreversion



$\Delta\Delta G^{\ddagger}$ = 3.8 kcal/mol

activation barrier lower for endo

ΔG = 1.9 kcal/mol

exo more stable

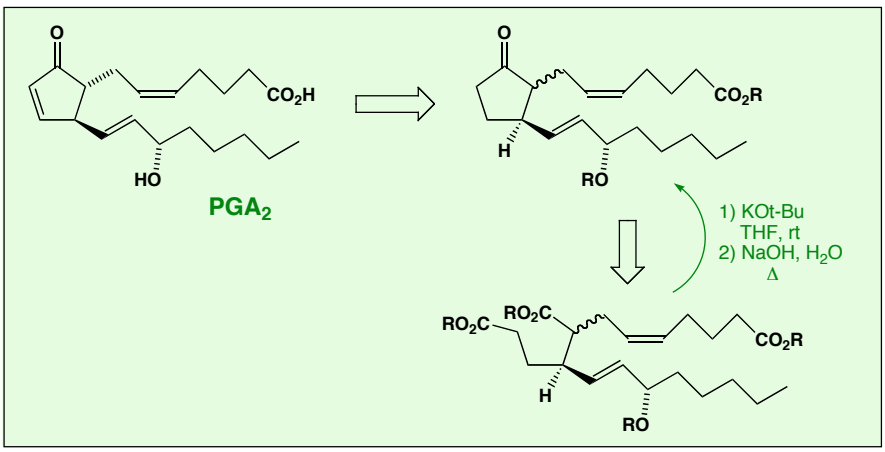
Room temperature	100 : 0
40 °C, 24-48 h	0 : 100

Herndon et al. *J. Org. Chem.* **1978**, *43*, 518

Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #2 Equilibration via Enolates I

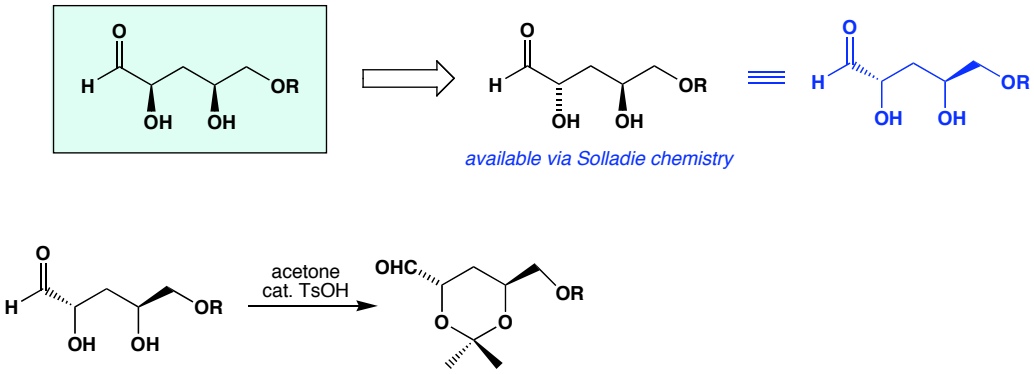


G. Stork et al. *J. Am. Chem. Soc.* **1976**, *98*, 1583

Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #3 Equilibration via Enolates II

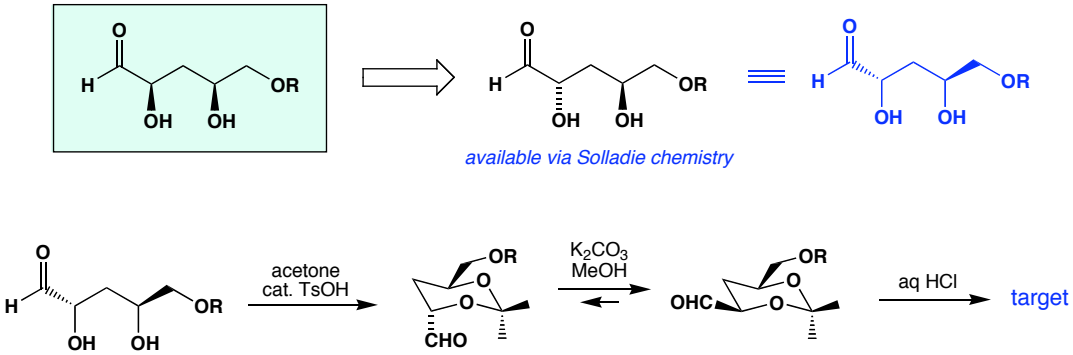


G. Solladie et al. *Tetrahedron Lett.* **1987**, *28*, 797

Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #3 Equilibration via Enolates II

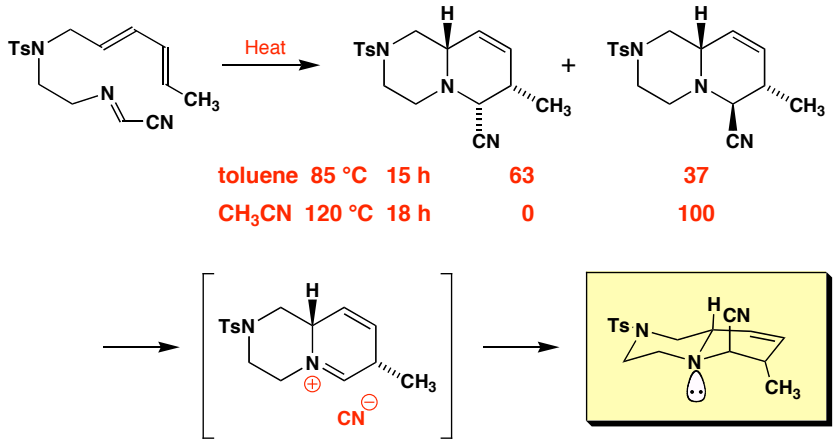


G. Solladie et al. *Tetrahedron Lett.* **1987**, *28*, 797

Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #4 Equilibration via Ionization

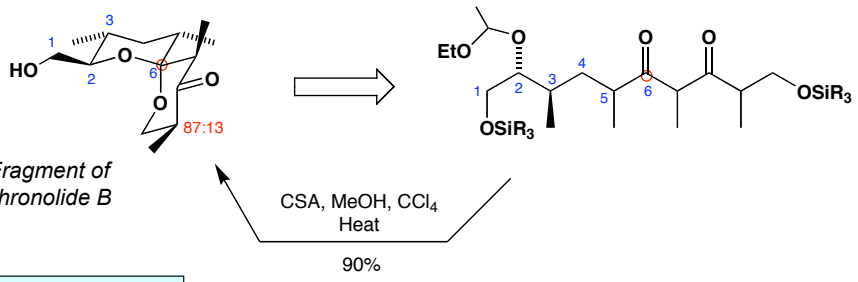


R. L. Danheiser et al. *J. Am. Chem. Soc.* **2003**, *125*, 4970

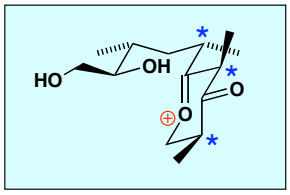
Strategies for Stereocontrolled Synthesis

Tactics for Establishing Thermodynamic Control

Case Study #5 Spiroketals - "Spontaneous Assembly"



C-1 to C-9 Fragment of 6-Deoxyerythronolide B



Review on chemistry of spiroketals:

K. F. Albizati et al. *Chem. Rev.* **1989**, *89*, 1617

D. A. Evans et al. *J. Am. Chem. Soc.* **1979**, *101*, 6789

S. L. Schreiber et al. *J. Org. Chem.* **1991**, *56*, 6255

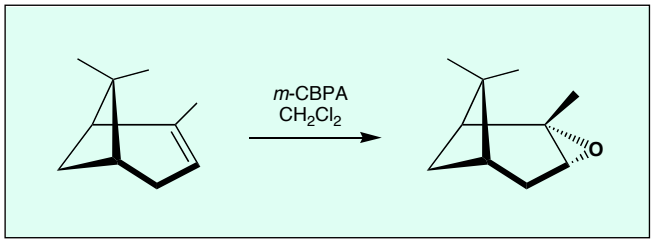
Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
- ★ Kinetic control strategies
  - **Substrate control strategies**
    - Steric approach control
    - Stereoelectronic control
    - Internal stereodirection and chirality transfer
  - **Reagent control strategies**
    - Achiral substrate: enantiotopic face selectivity
    - Achiral substrate: enantiotopic group selectivity
    - Chiral substrate: double asymmetric synthesis
  - **Dynamic kinetic resolution**

Strategies for Stereocontrolled Synthesis

Substrate Kinetic Control Strategies

Steric Approach Control



Strategies for Stereocontrolled Synthesis

Substrate Kinetic Control Strategies

Cyclohexane A Values (kcal/mol)

		CH_3	1.74
		Et	1.70
F	0.25-0.42	*i*-Pr	2.21
Cl	0.53-0.64	*t*-Bu	4.7-4.9
Br	0.48-0.67	Vinyl	1.5-1.7
I	0.47-0.61	Ethynyl	0.41-0.52
		Ph	2.8
OMe	0.55-0.75		
OAc	0.68-0.87	CN	0.2
$OSiMe_3$	0.74	CHO	0.56-0.8
		CH_2OH	1.76
NH_2	1.23-1.7	COMe	1.0-1.5
NMe_2	1.5-2.1	CO_2Me	1.2-1.3
		$SiMe_3$	2.5

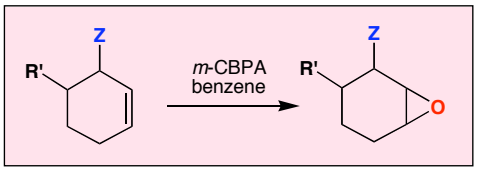
Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
- ★ Kinetic control strategies
  - ✻ **Substrate control strategies**
    - ❋ Steric approach control
    - ❋ Stereoelectronic control
    - ❋ Internal stereodirection and chirality transfer
  - ✻ **Reagent control strategies**
    - ❋ Achiral substrate: enantiotopic face selectivity
    - ❋ Achiral substrate: enantiotopic group selectivity
    - ❋ Chiral substrate: double asymmetric synthesis
  - ✻ **Dynamic kinetic resolution**

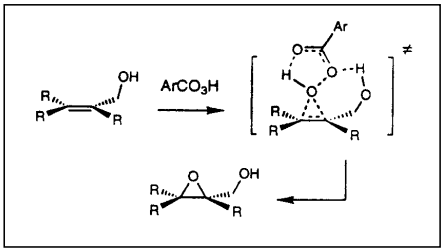
Strategies for Stereocontrolled Synthesis

Substrate Kinetic Control Strategies

Non-covalent internal stereodirection



R'	Z	Rel. Rate	Major Product
H	H	1.0	-
H	OH	0.55	syn (10:1)
H	OMe	0.067	anti
H	OAc	0.046	anti (20:80)
OH	H	0.42	ca. 1 : 1



H. B. Henbest and R. A. Wilson
J. Chem. Soc. **1959**, 1958

Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
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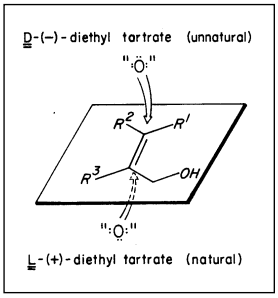
Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Face Selectivity

Katsuki-Sharpless Asymmetric Epoxidation



Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Katsuki-Sharpless Asymmetric Epoxidation

The First Practical Method for Asymmetric Epoxidation

Sir:

As revealed in Scheme I, we have discovered a new metal-catalyzed asymmetric epoxidation process which is far more selective than any of the previously described methods[1] for this type of asymmetric transformation. The simplicity of this new method is one of its more attractive aspects; the necessary components [(+) or (−)-diethyl tartrate,[2] titanium tetraisopropoxide, and

alcohol remains to be tried.

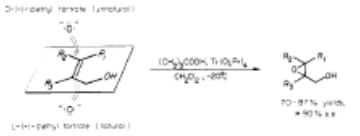
(18) Address correspondence to this author at the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

Tsutomu Katsuki, K. Barry Sharpless[18]

Department of Chemistry, Stanford University
Stanford, California 94305

Received May 5, 1980

Scheme I



tert-butyl hydroperoxide] are all[3] commercially available at low to moderate cost.[4]

This new chiral epoxidation system possesses two especially striking features. First, it gives uniformly high asymmetric inductions throughout a range of substitution patterns[5,17] in the allylic alcohol substrate (Table I). Second, upon use of a given tartrate enantiomer, the system seems obliged to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. This latter characteristic is highlighted in Scheme I: when the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right as shown, the use of (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom. Of course, when (−)-diethyl tartrate is employed, the epoxide oxygen is added from the top.

A 500-mL, 1-neck round-bottom flask equipped with a Teflon-coated magnetic stir bar was oven dried and then fitted with a serum cap and flushed with nitrogen. The flask was charged with 200 mL of dry (distilled from CaH_2) reagent-grade dichloromethane and cooled by stirring in a −23 °C bath (dry

Table I. Asymmetric Epoxidation of Allylic Alcohols[a]

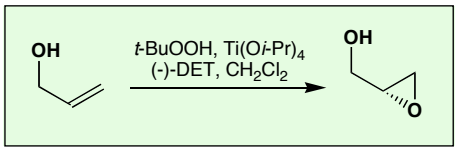
	Allylic Alcohol	Epoxyalcohol	% yield[7]	% e.e.[7]	Configuration[2]
(1)	1a	1b	77	90 (Ex, M)	2(S), 3(S)[7]
(2)	2a	2b	79	94 (Ex, M)	2(S), 3(R)[7]
(3)	3a	3b	70[6]	>95 (Ex)	6(S), 7(S)[7]
(4)[b]	4a	4b	67	>95 (Ex)	2(S), 3(S)[7]
(5)	5a	5b	79	>95 (M)	2(S), 3(S)[7]
(6)[c]	6a	6b	62	90 (M)	2(S), 3(R)[7]
(7)[b,c]	6a	6c	60	90 (M)	2(R), 3(S)[7]
(8)[c]	7a		61	>95 (M)	2(S)[7]

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Face Selectivity

Katsuki-Sharpless Asymmetric Epoxidation



92% ee
(96 : 4)

Reviews on Asymmetric Epoxidation

"Catalytic Asymmetric Epoxidation of Allylic Alcohols" Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH, 2000, pp 231-285

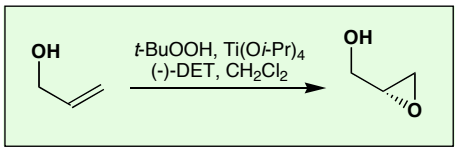
"Asymmetric Epoxidation of Unfunctionalized Olefins and Related Reactions" Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH, 2000, pp 287-326.

"Asymmetric Epoxidation of Allylic Alcohols: The Katsuki-Sharpless Epoxidation Reaction", Katsuki, T.; Martin, V. S. *Org. Reactions* **1996**, *48*, 1.

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Katsuki-Sharpless Asymmetric Epoxidation

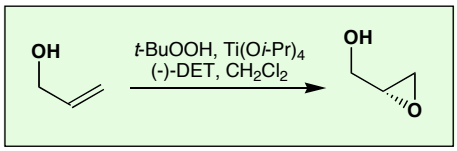


- ★ Reaction can be run as a stoichiometric (100 mol%) or catalytic (5-10 mol%) process
- ★ For high enantioselectivities use excess of tartrate ligand (5% Ti and 6% tartrate)
- ★ Catalytic reactions can be run up to 1.0 M in concentration; stoichiometric at 0.1 M
- ★ TBHP should be as concentrated as possible (commercial 5.5 M preferred to 3.0 M)
- ★ Use of activated molecular sieves greatly expanded the catalytic version

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Katsuki-Sharpless Asymmetric Epoxidation



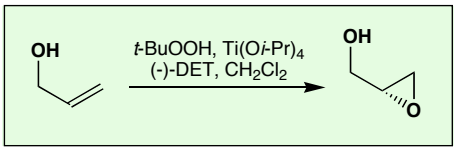
Compatible Functional Groups		Incompatible Groups
Acetals, ketals	Nitriles	Amines (most)
Acetylenes	Nitro	Carboxylic acids
Alcohols (remote)	Olefins	Mercaptans
Aldehydes	Pyridines	Phenols (most)
Amides	Silyl ethers	Phosphines
Azides	Sulfones	
Carboxylic Esters	Sulfoxides	
Epoxides	Tetrazoles	
Ethers	Ureas	
Hydrazides	Urethanes	
Ketones		

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

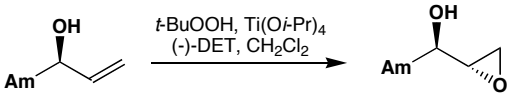
Katsuki-Sharpless Asymmetric Epoxidation

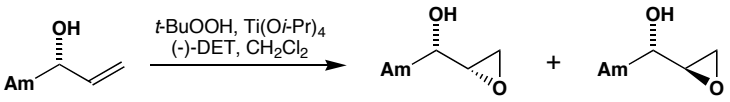
Chiral Substrates



92% ee

(96 : 4)





67 : 33

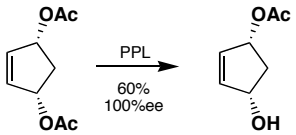
Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Group Selectivity

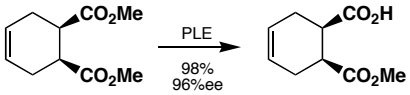
Lipase-Based Desymmetrization Reactions

Review on enzymatic enantioselective group desymmetrization:
V. Gotor *Chem. Rev.* **2005**, *105*, 313

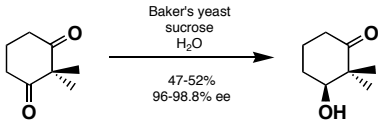


J. Nokami
Tetrahedron Lett. 32, 2409, **1991**

M. Ohno
J. Am. Chem. Soc. **1981**, *103*, 2405



M. Ohno
Tetrahedron Lett. **1984**, *25*, 2557



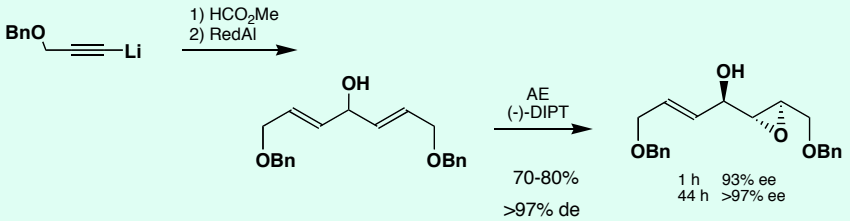
K. Mori and H. Mori
Org. Synth. Coll. Vol. 8, 312, **1993**

Another example of biotransformations in asymmetric synthesis

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Group Selectivity Coupled to Kinetic Resolution



S. L. Schreiber
J. Am. Chem. Soc. **1987**, *109*, 1525