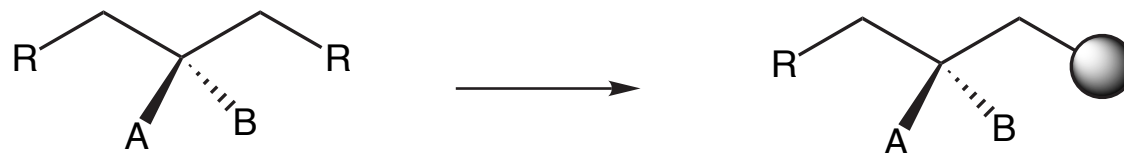


## Enantioselective Desymmetrization



Leading references: Magnuson, *Tetrahedron* , **1995**, 2167  
Hodgson, *Tetrahedron* , **1996**, 14361

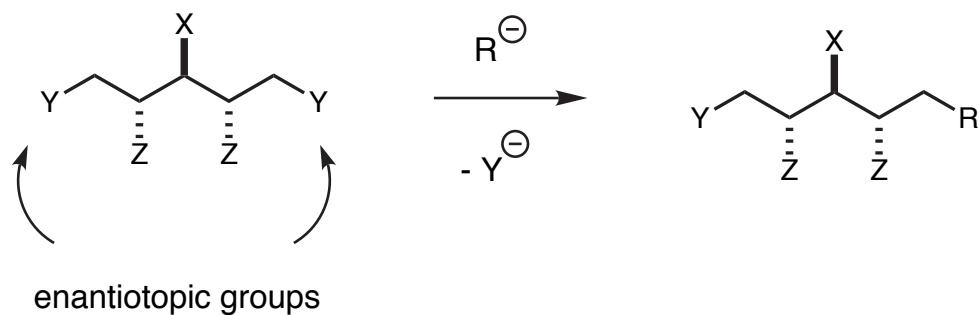
- I. *Meso* anhydrides
- II. Divinyl carbinols and *meso* dienes
- III. Achiral epoxides
- IV. Carbon-carbon bond formation
- V. Alcohol protection strategies
- VI. *Meso* ketones

Not covered here: Enzymatic desymmetrization  
(Johnson, *Tetrahedron* , **1996**, 3769)

Wes Trotter  
April 4, 1997

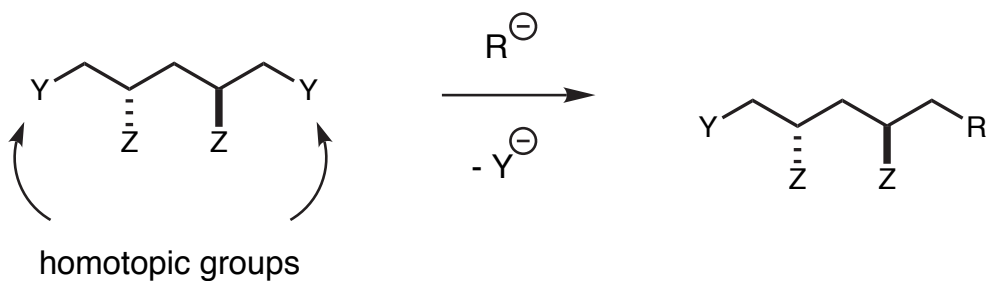
# Desymmetrization of Symmetric Compounds

- Achiral and *meso* compounds:



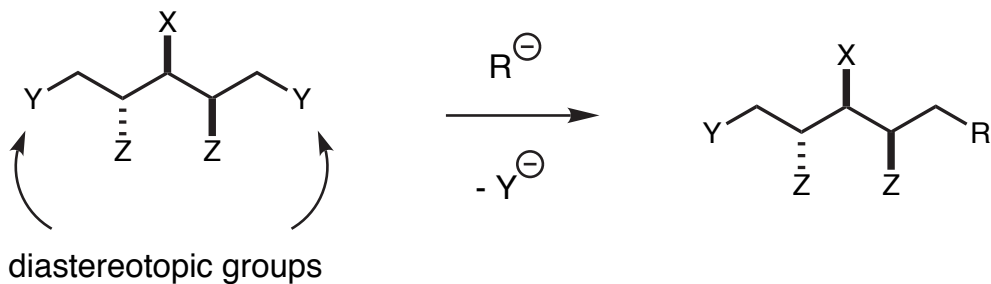
enantiotopic group selection

- $C_2$  symmetric compounds (chiral):



monofunctionalization

- pseudo  $C_2$  symmetric compounds (chiral):

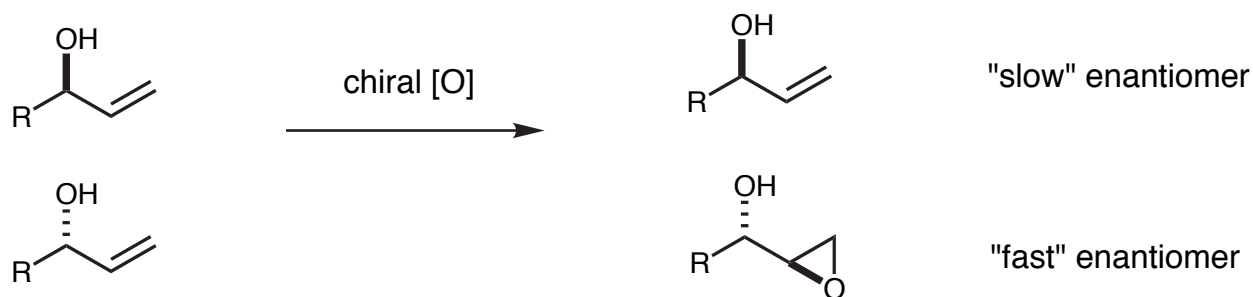


diastereotopic group selection

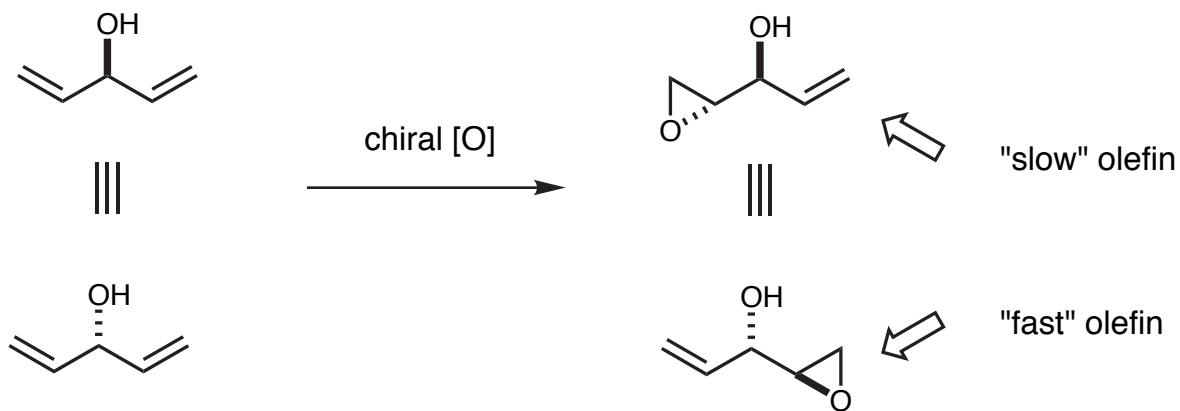
Magnuson, *Tet.*, **1995**, 2167

## Enantioselective Desymmetrization and Kinetic Resolution

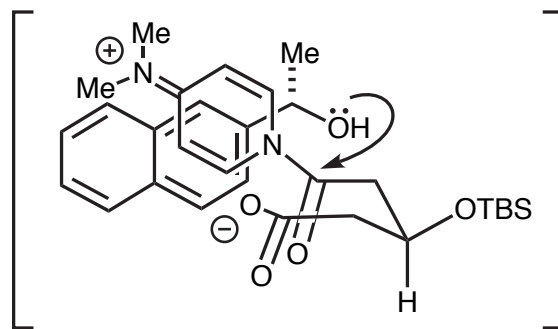
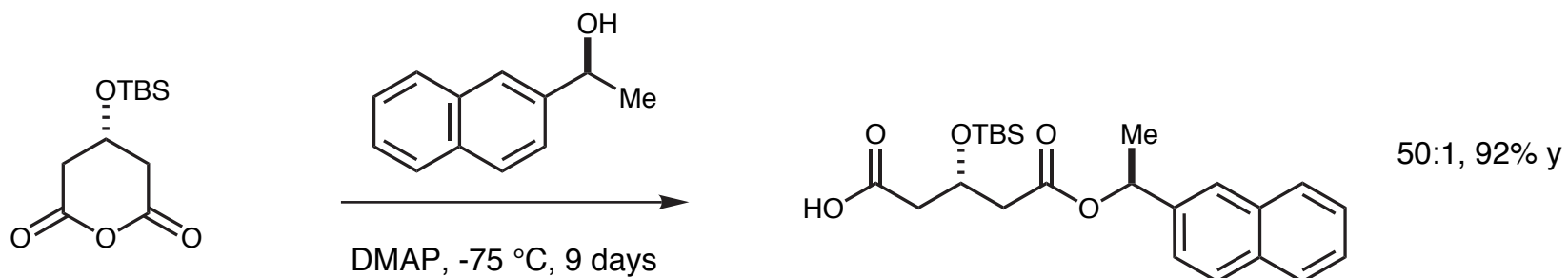
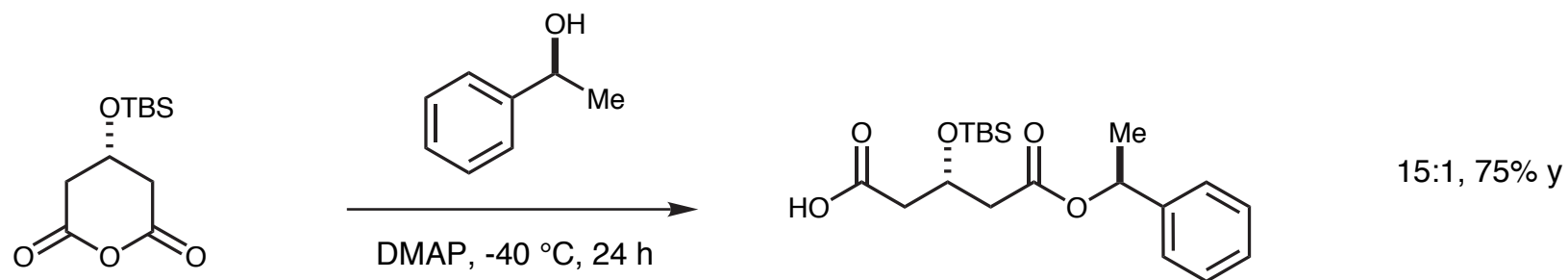
- Kinetic resolution relies on differing rates of reactions between a chiral reagent and each of the two enantiomers composing a racemic substance. A sufficient rate difference allows consumption of one enantiomer and recovery of the other.



- In the case of an appropriate prochiral symmetric molecule containing 2 enantiotopic reactive groups, a chiral reagent will react at different rates with each of the enantiotopic groups. A sufficient rate difference allows reaction at a single group (group selection) to give an asymmetric product.

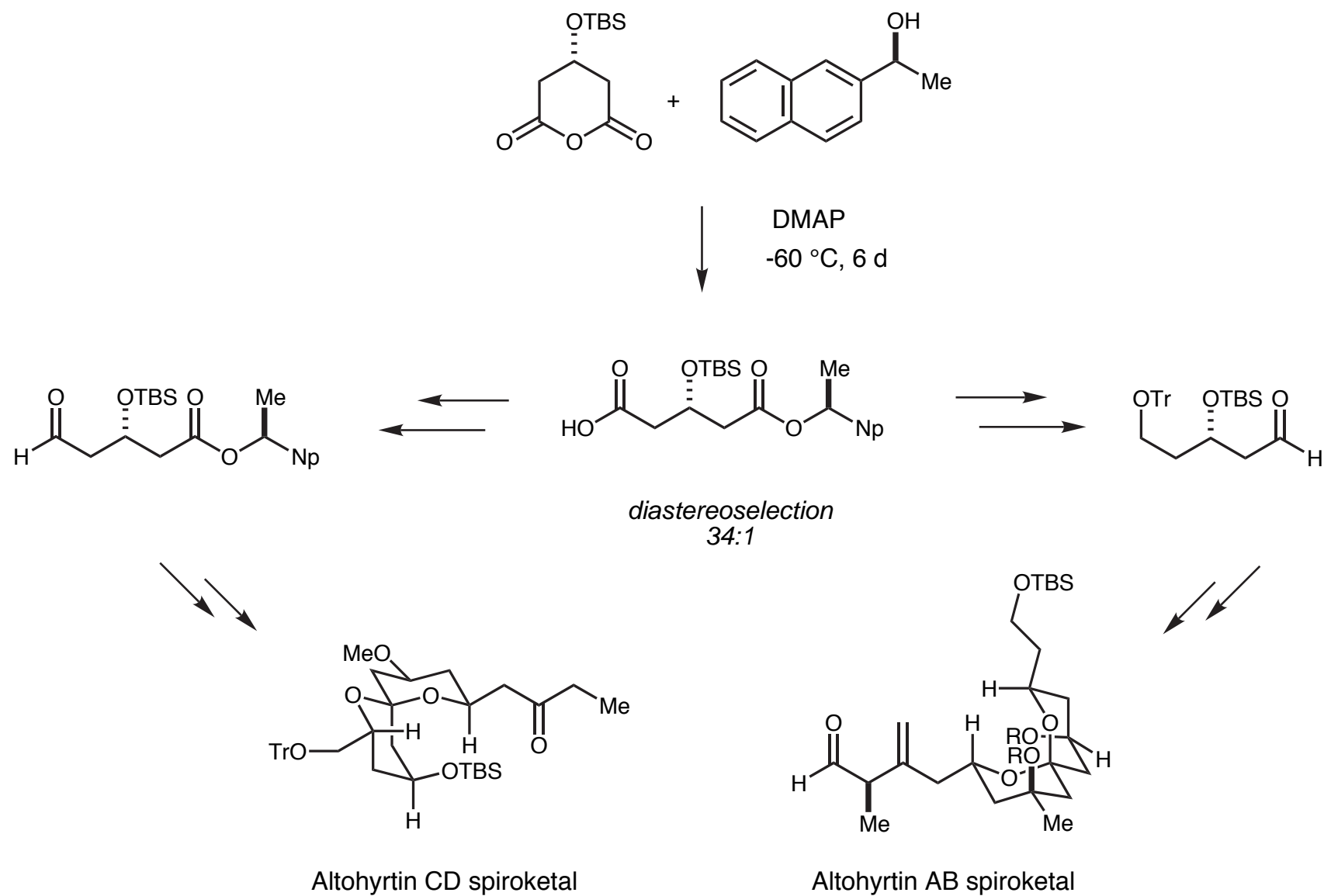


## Meso Anhydrides: Arylethanol Transesterification



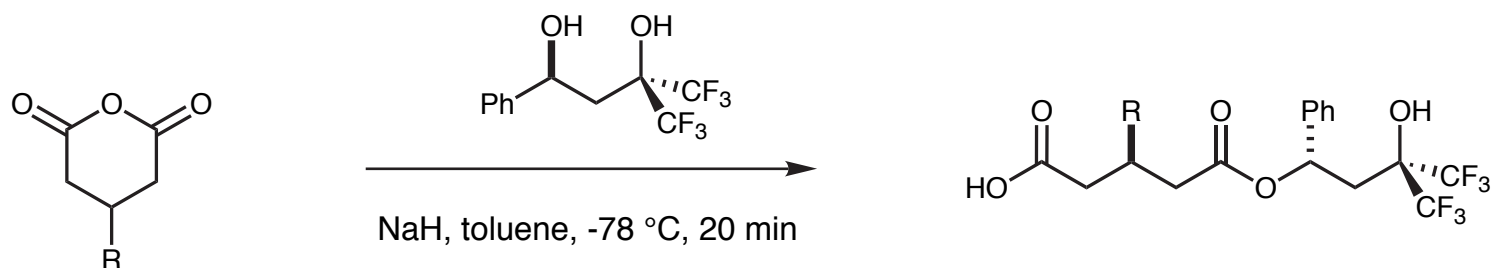
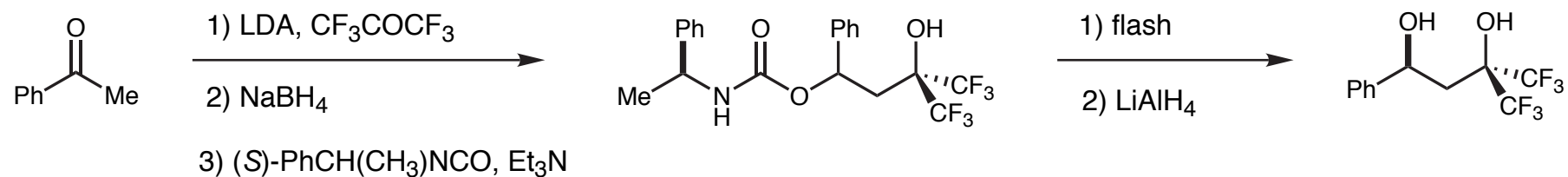
Thiesen, Heathcock, *JOC*, **1988**, 2374  
Heathcock et al., *J. Med. Chem.*, **1987**,  
1858  
Coleman, research report, **1996**

## Applications: Altohyrtin Fragments

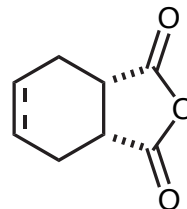


research reports: Coleman, **1996**; Dias, **1995**

## Alcoholysis of Substituted Glutaric Anhydrides



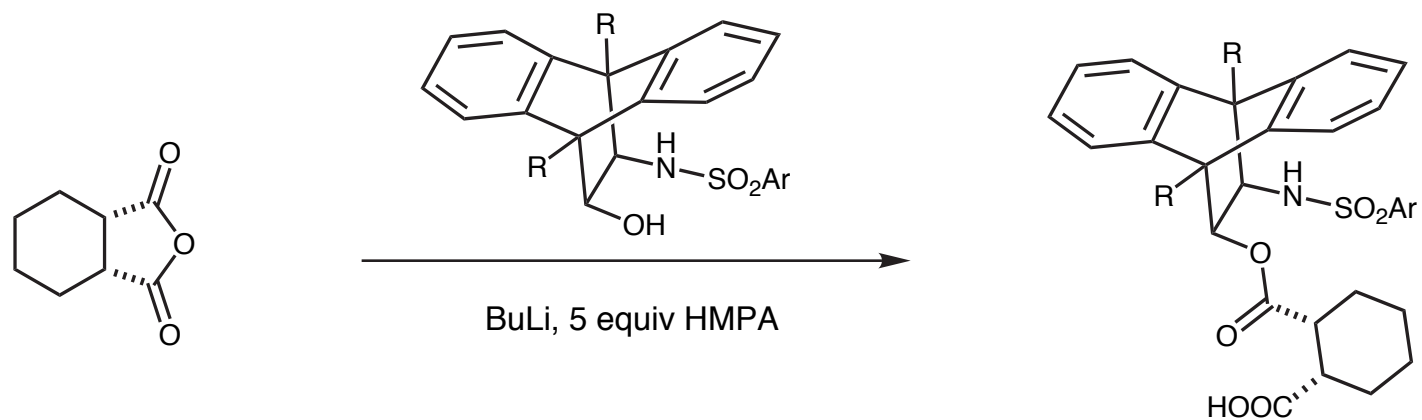
R	d.e. (%)	yield (%)
TBSO	92	90
<i>i</i> Pr	90	94
CF <sub>3</sub>	90	95
PhCH <sub>2</sub>	76	96
Ph	66	95
CH <sub>3</sub>	66	90

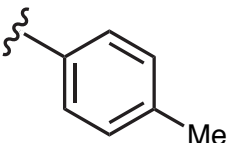
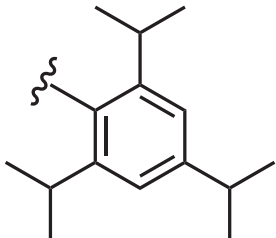


Bicyclic anhydrides are also effectively desymmetrized.

Suda, Yago, Shiro, Taguchi, *Chem. Lett.*, **1992**, 389

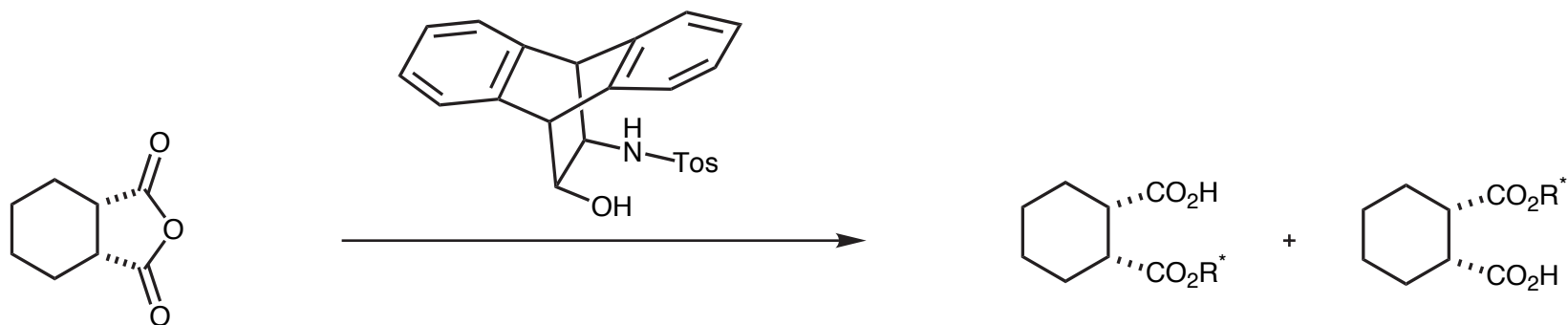
## Meso Anhydrides: Aminoalcohol Transesterification



Ar	R	% d.e.	% yield
	H	82	94
	Me	94	81
	H	92	93
	Me	>99	93

Imado, Ishizuka, Kunieda, *TL*, **1995**, 931

# Aminoalcohol Transesterification: Reversal of Stereoselection

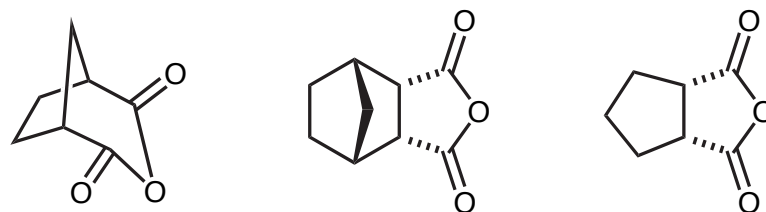


Conditions:

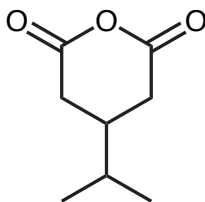
1 equiv BuLi, 5 equiv HMPA, THF, -78 °C, 2 h      500      :      1

1 equiv Et<sub>2</sub>Zn, 1 equiv THF, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 6 h      1      :      26

Effective for a variety of  
bi- and tricyclic substrates:



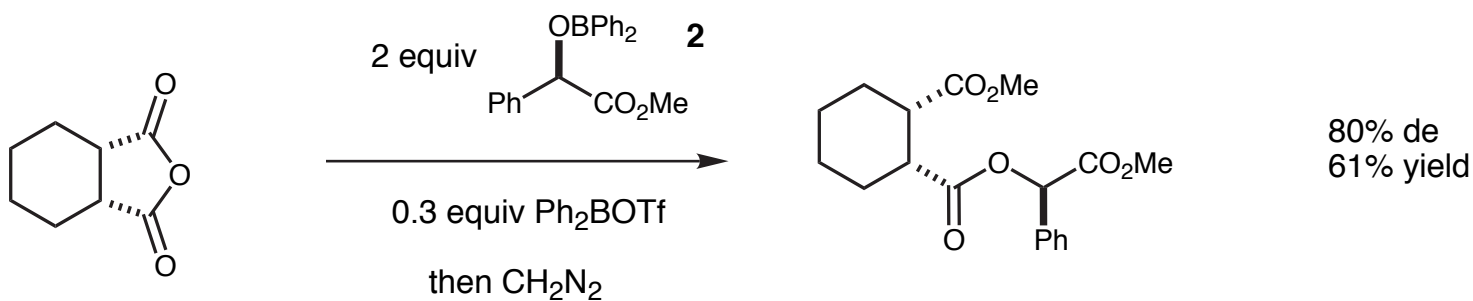
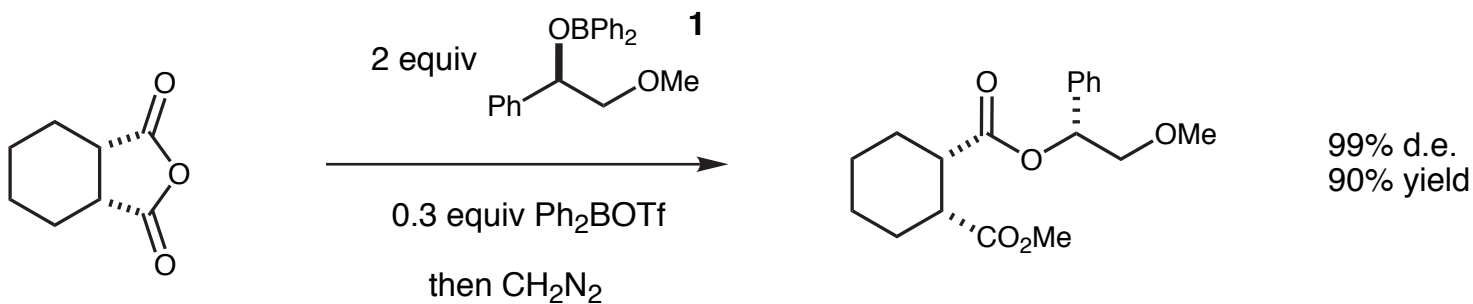
Low selectivity observed for  
monocyclic substrates:



Imado, Ishizuka, Kunieda, *TL*, **1996**,  
9237



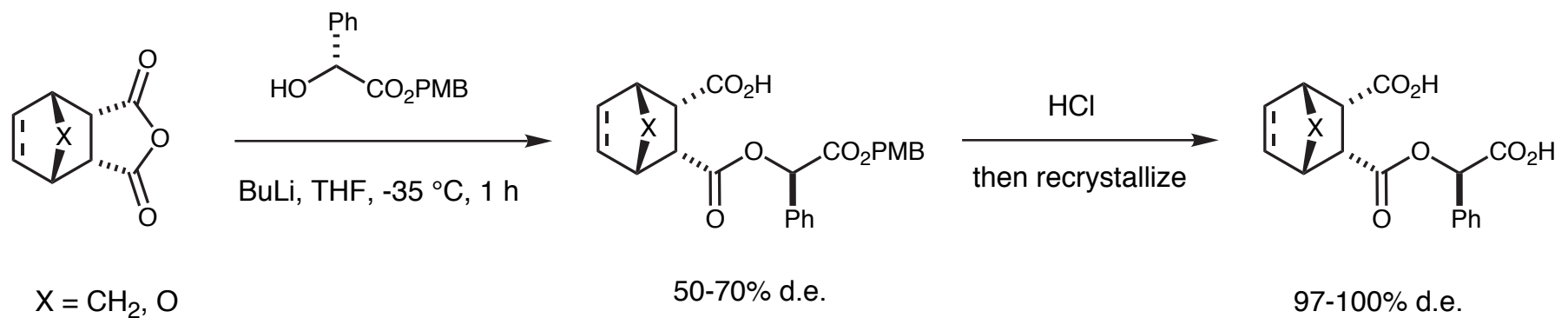
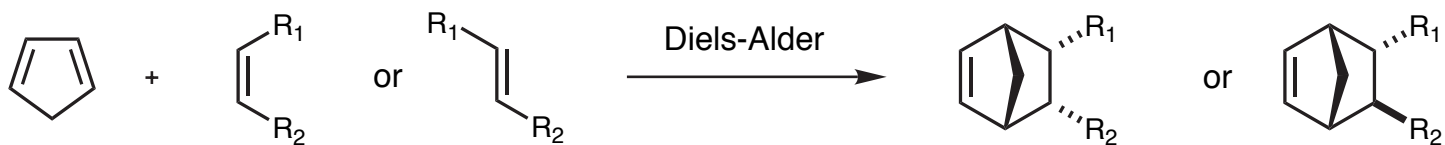
## Diphenylboron Triflate-Catalyzed Alcoholysis



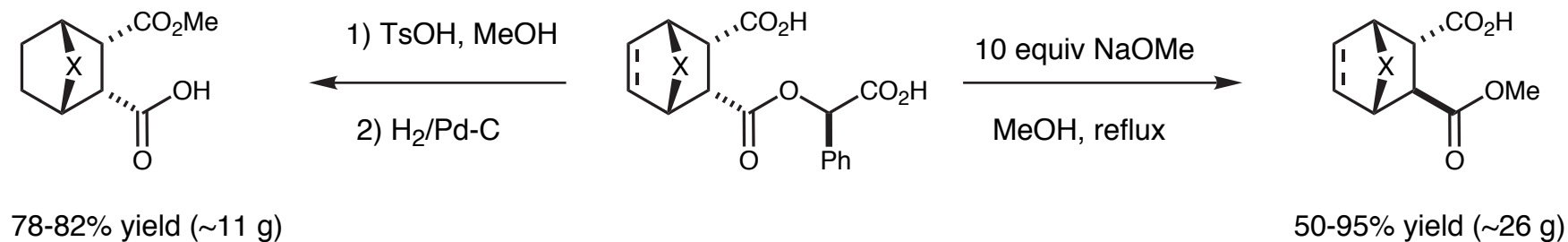
- **1** is prepared from (*R*)-methyl mandelate (**2**) in 4 steps.

Ohshima, Mukaiyama, *Chem. Lett.*, **1987**,  
377

## Functional Equivalents of Asymmetric Diels-Alder Adducts

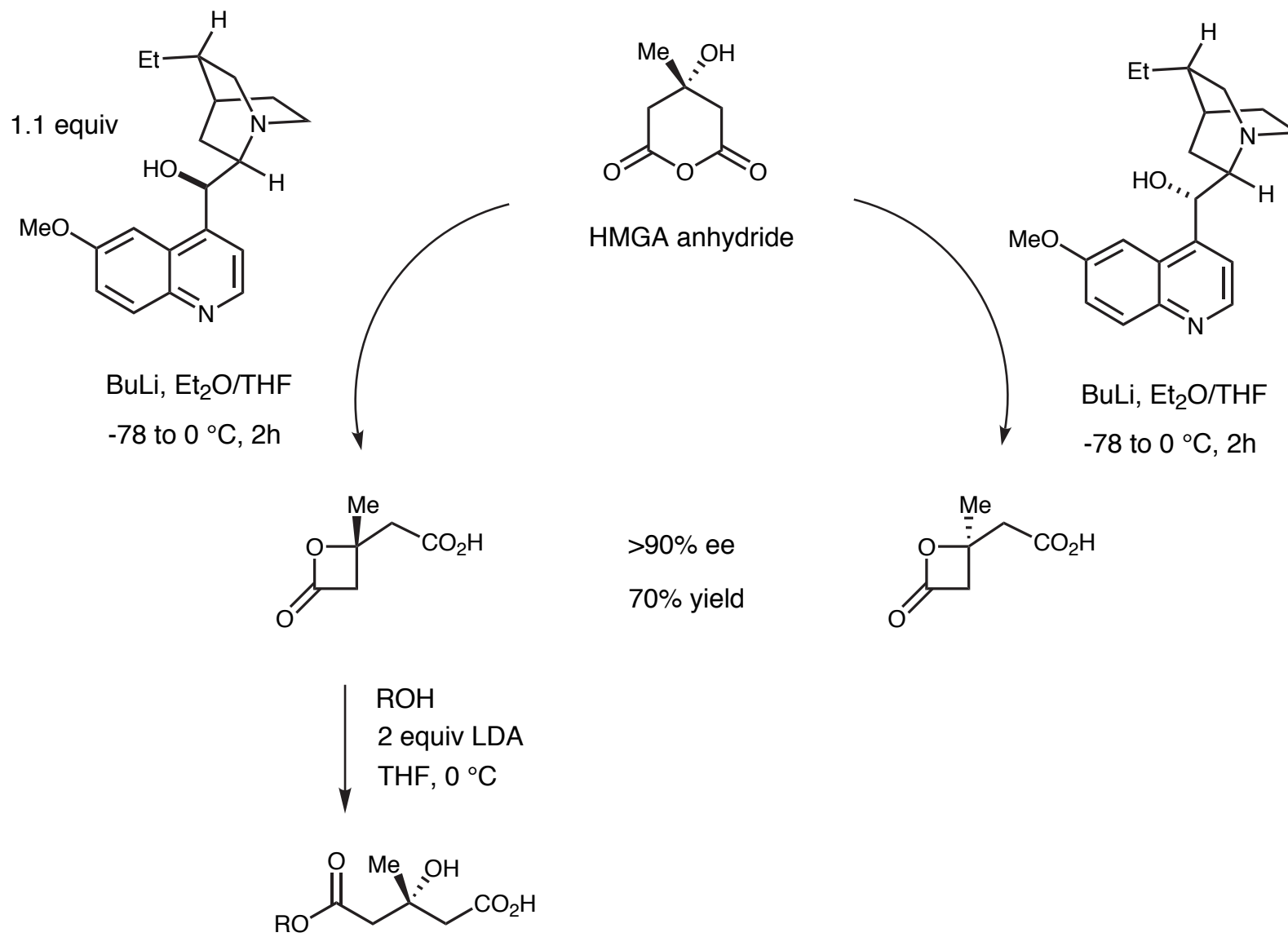


36-66% isolated yield  
from anhydride



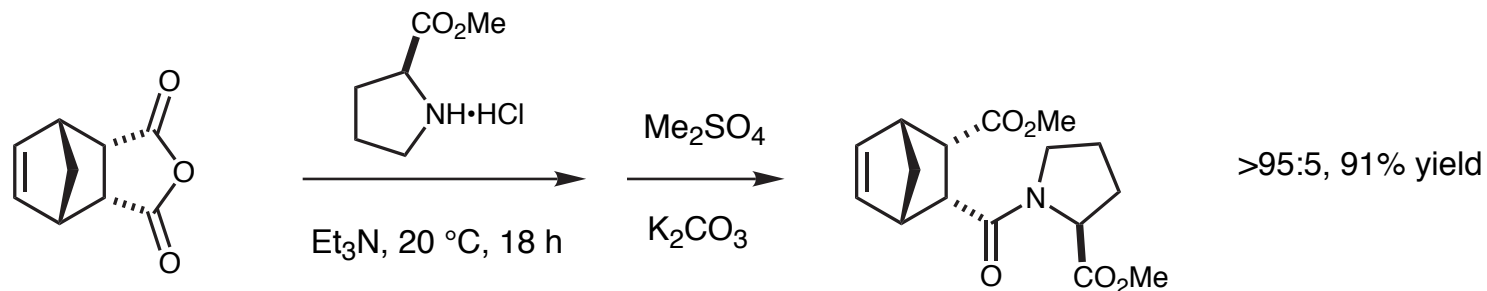
Ohtani, Matsuura, Watanabe, Narisada, *JOC*, **1991**, 4120

## $\beta$ -Lactones from Meso Anhydrides

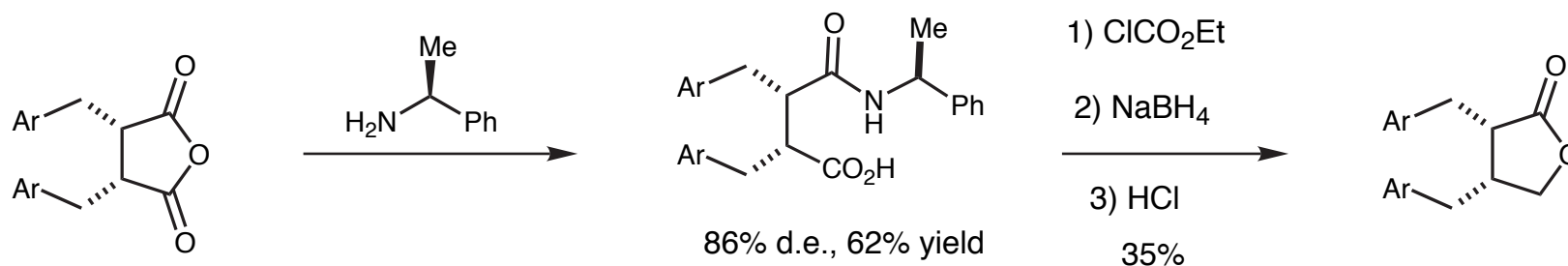


Hashimoto, Kitaguchi, Mizuno, Kobayashi, Shirahama, *TL*, **1996**, 2275

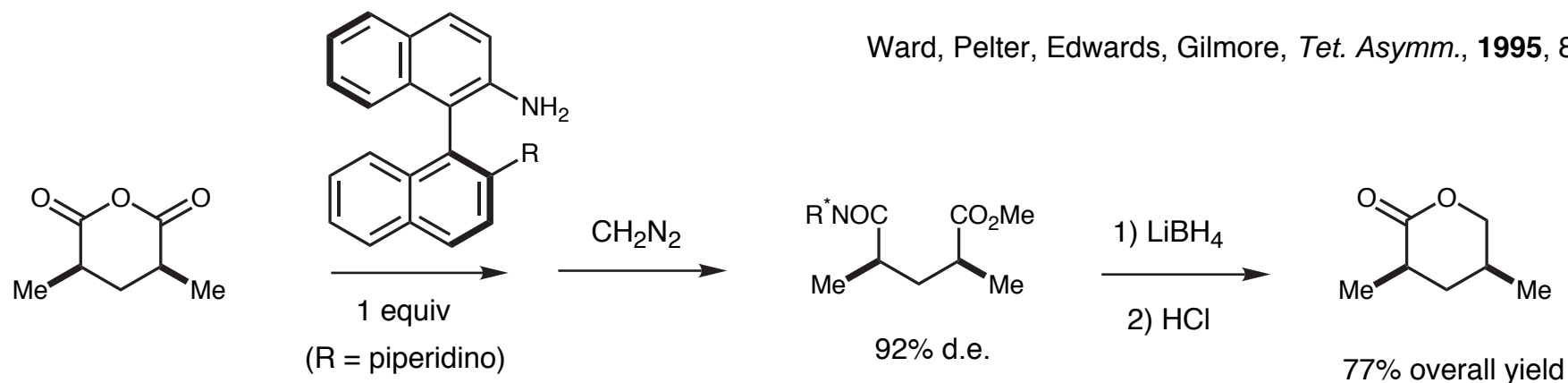
## Amine Nucleophiles



North, Zagotto, et al., *Synthesis*, **1996**, 393

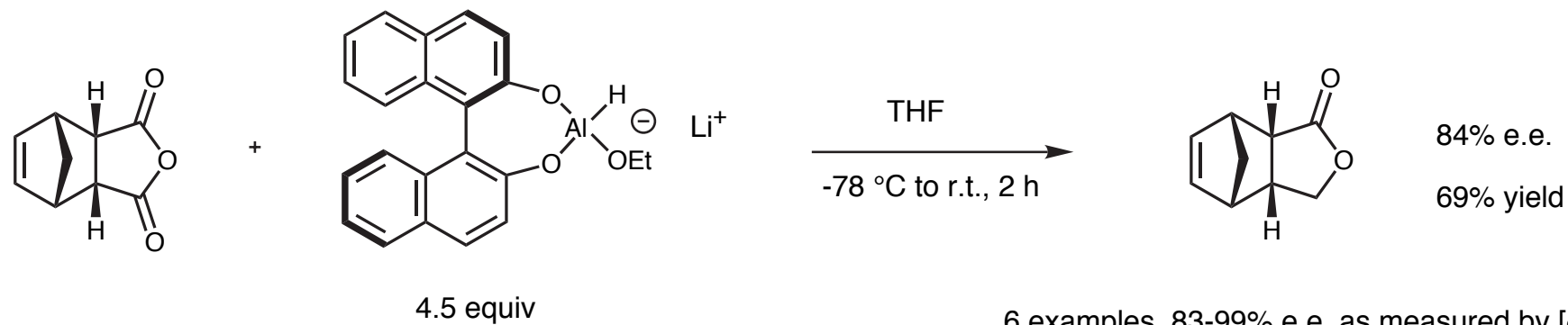


Ward, Pelter, Edwards, Gilmore, *Tet. Asymm.*, **1995**, 843



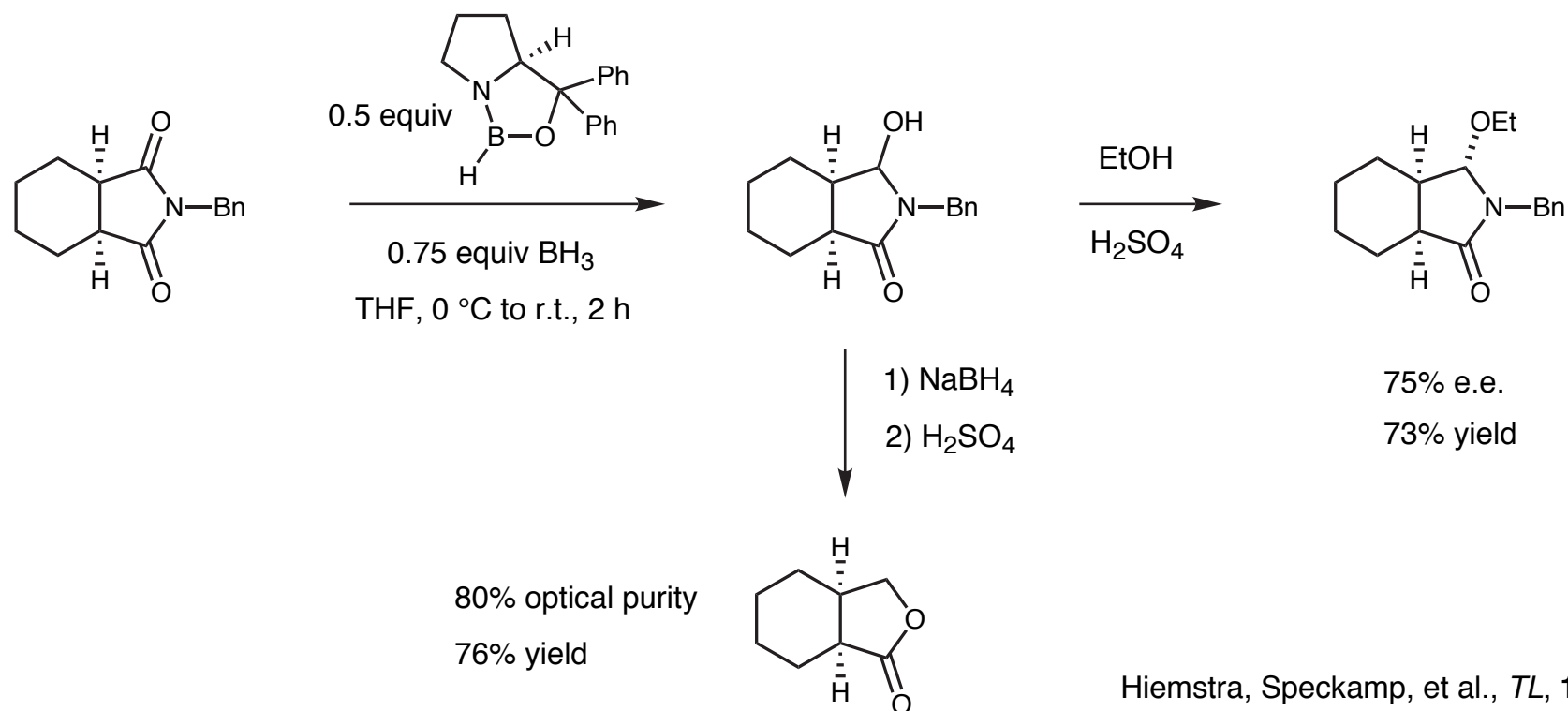
Kawakami, Hiratake, Yamamoto, Oda, *Chem. Comm.*, **1984**, 779

# Symmetry-Breaking Reductions



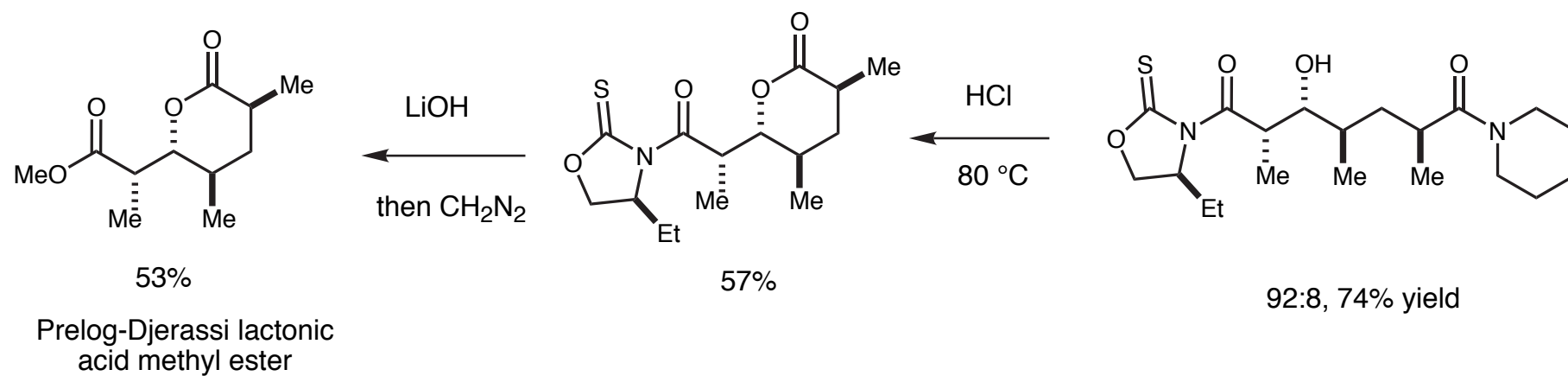
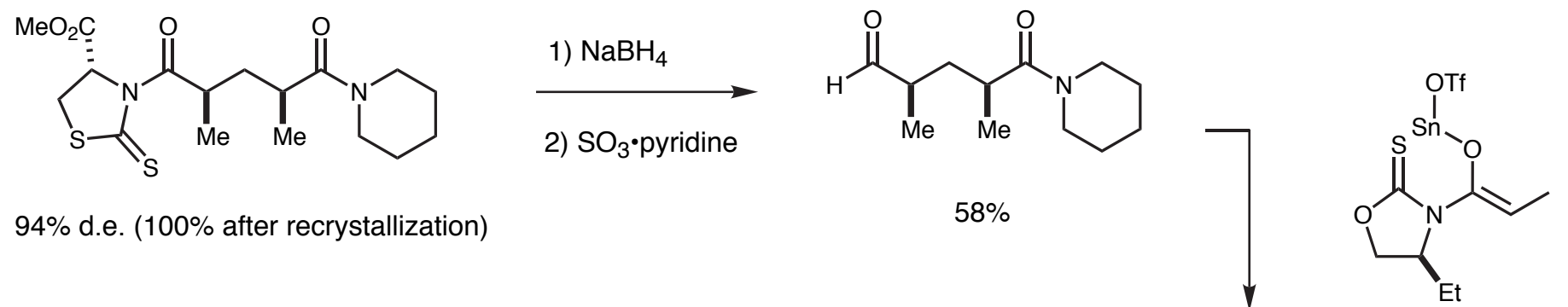
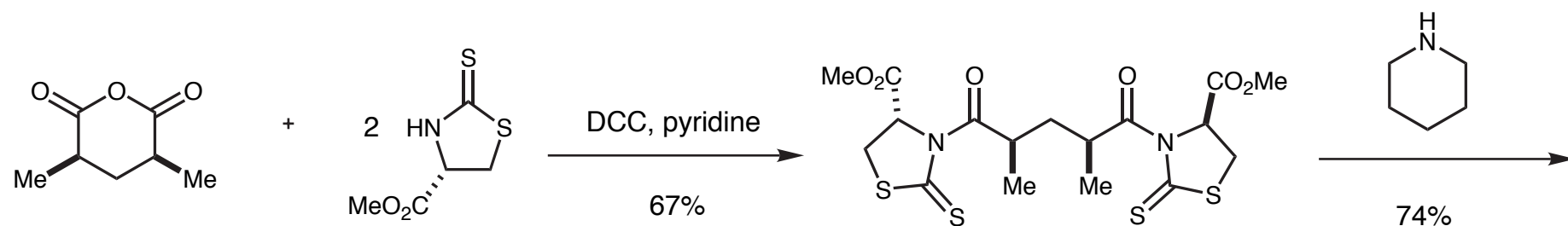
6 examples, 83-99% e.e. as measured by  $[\alpha]$

Matsuki, Inoue, Takeda, *TL*, **1993**, 1167



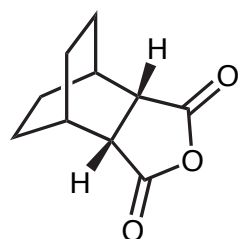
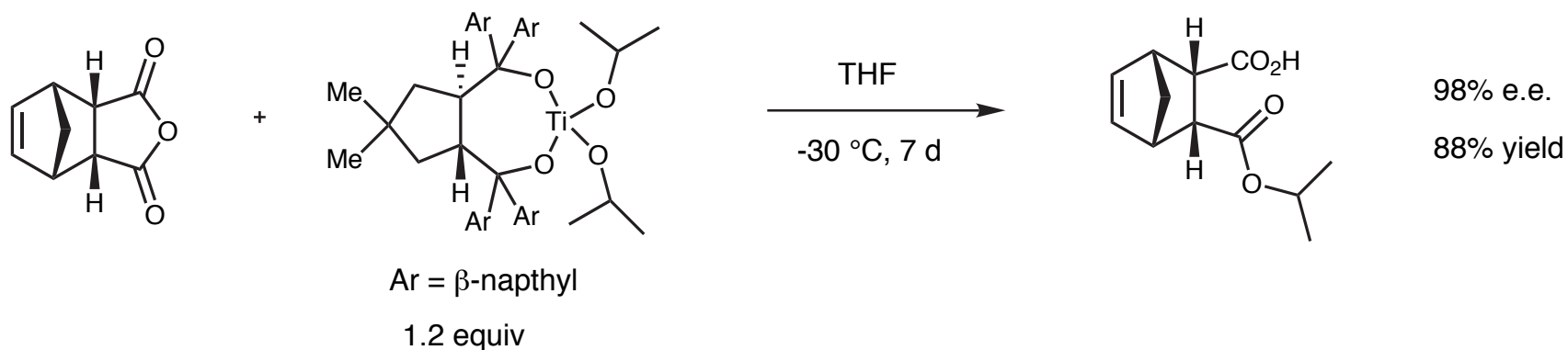
Hiemstra, Speckamp, et al., *TL*, **1994**, 1087

## Thioimide Mediated Anhydride Desymmetrization



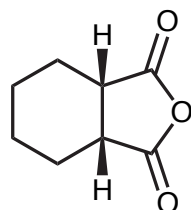
Nagao, Yamada, Kumagai, Ochiai, Fujita, *Chem. Comm.*, **1985**, 1418

# Titanium TADDOLate Chemistry



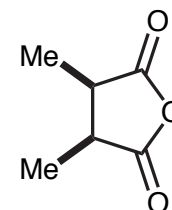
94% e.e.

92% yield



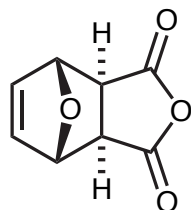
>90% e.e.

87% yield



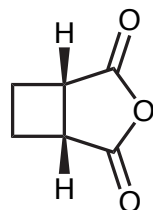
96% e.e.

73% yield



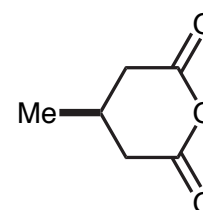
98% e.e.

63% yield



94% e.e.

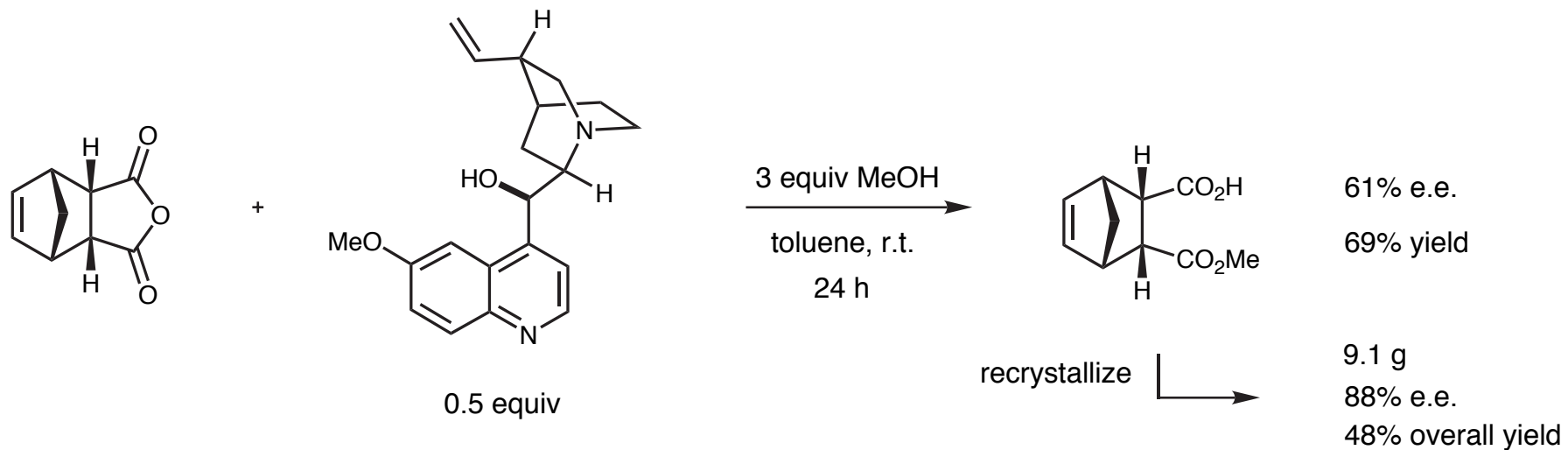
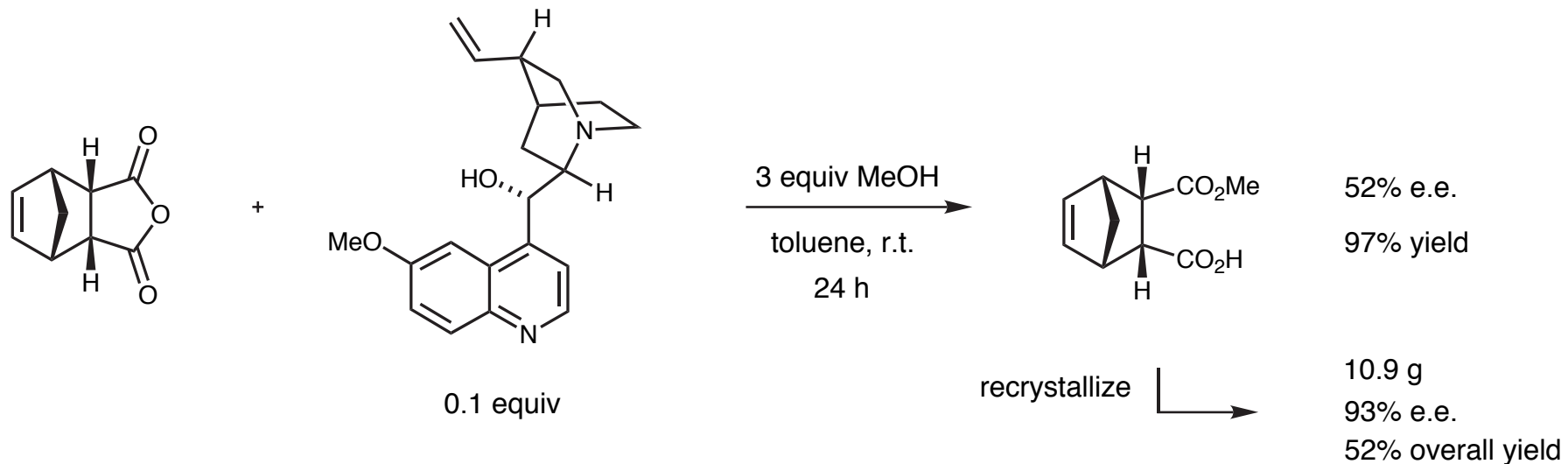
76% yield



50% e.e.

Seebach, Jaeschke, Wang, *ACIEE*, 1995, 2395

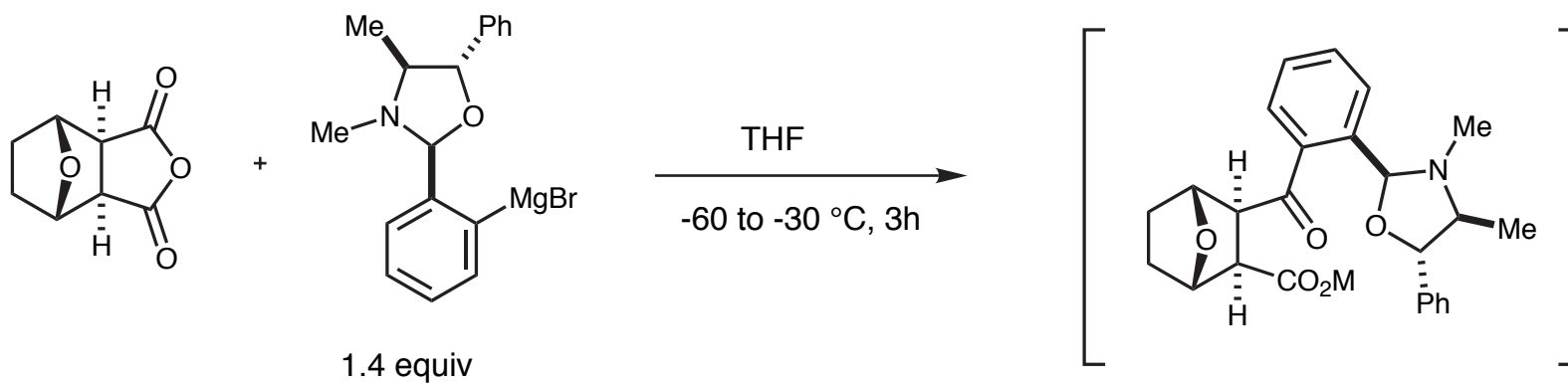
## Catalytic Desymmetrization of Anhydrides



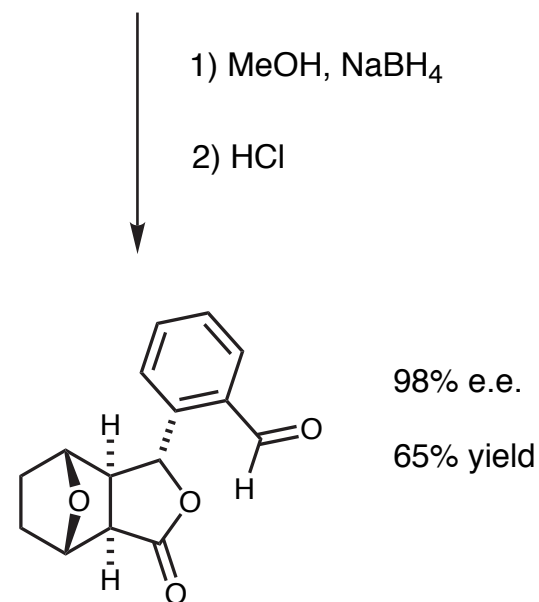
Aitken, Gopal, *Tet. Asymm.*, **1990**, 517



## Anhydride Opening by Carbon Nucleophiles

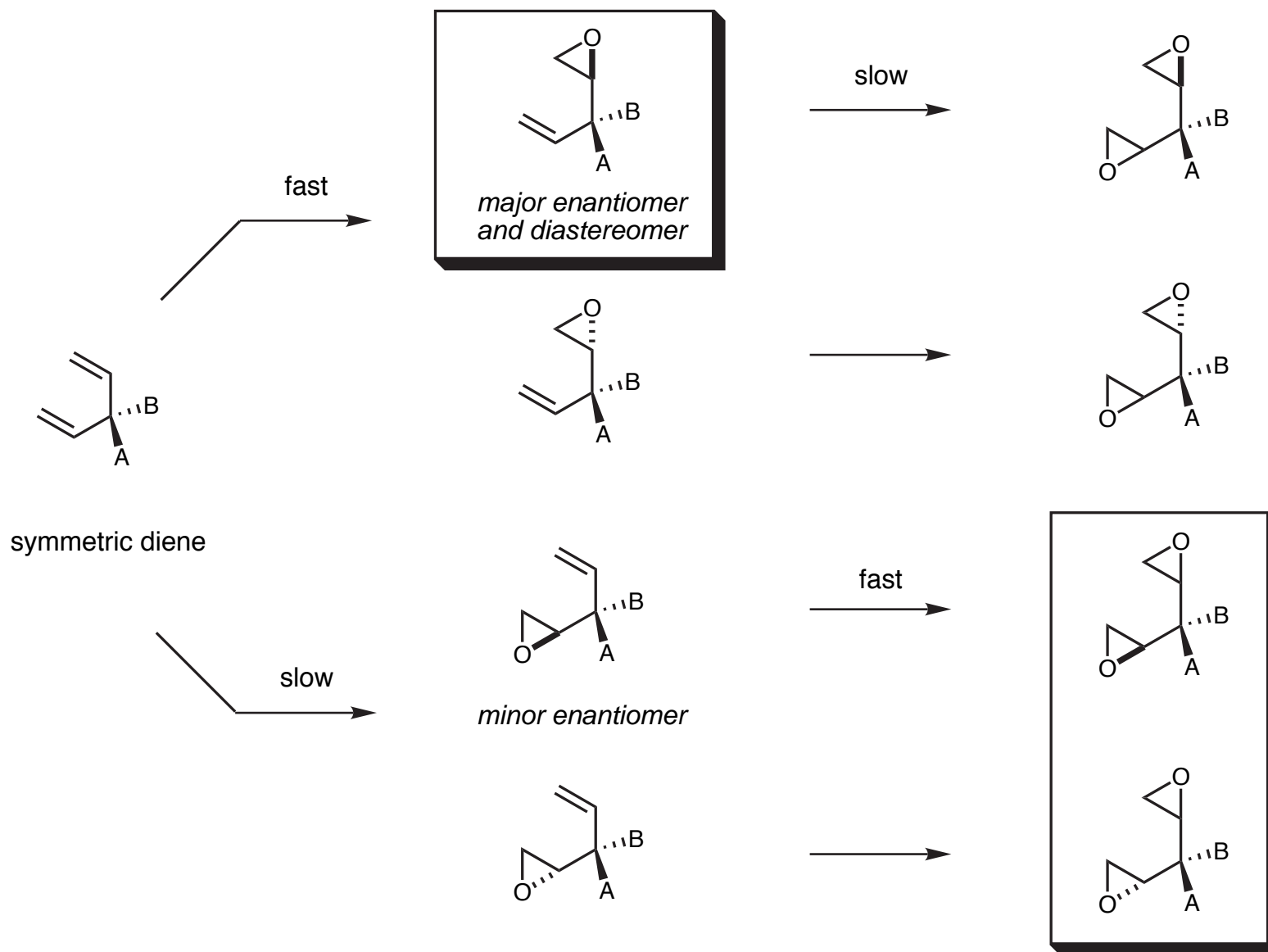


- Sodium borohydride reduction proceeds in 99.4% d.e.
- Pseudoephedrine can be recovered in 75% yield (unoptimized).
- The corresponding aryllithium provides the enantiomeric product in low (25-30%) e.e.



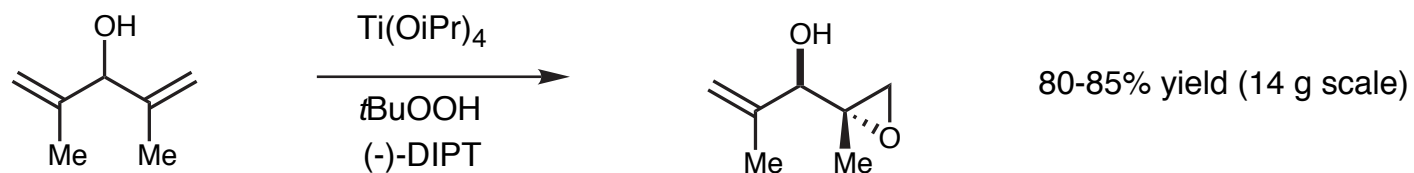
Real, Kronenthal, Wu, *TL*, **1993**, 8063

# Coupled Group Selection and Kinetic Resolution



Schreiber, Schreiber, Smith, *JACS*, **1987**, 1525

## Desymmetrization via Sharpless Epoxidation



Time	% e.e.	% d.e.
0.5 h	88	99
1.0 h	94	99
1.5 h	>99.3	99

- Mathematical model predicts that consumption of the minor enantiomer should increase e.e. over the course of the reaction.

Schreiber, Schreiber, Smith, *JACS*, **1987**, 1525

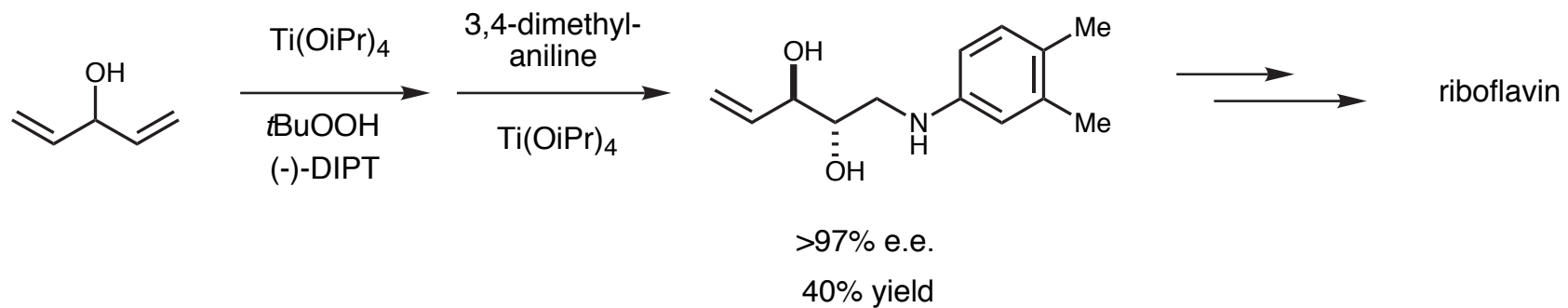
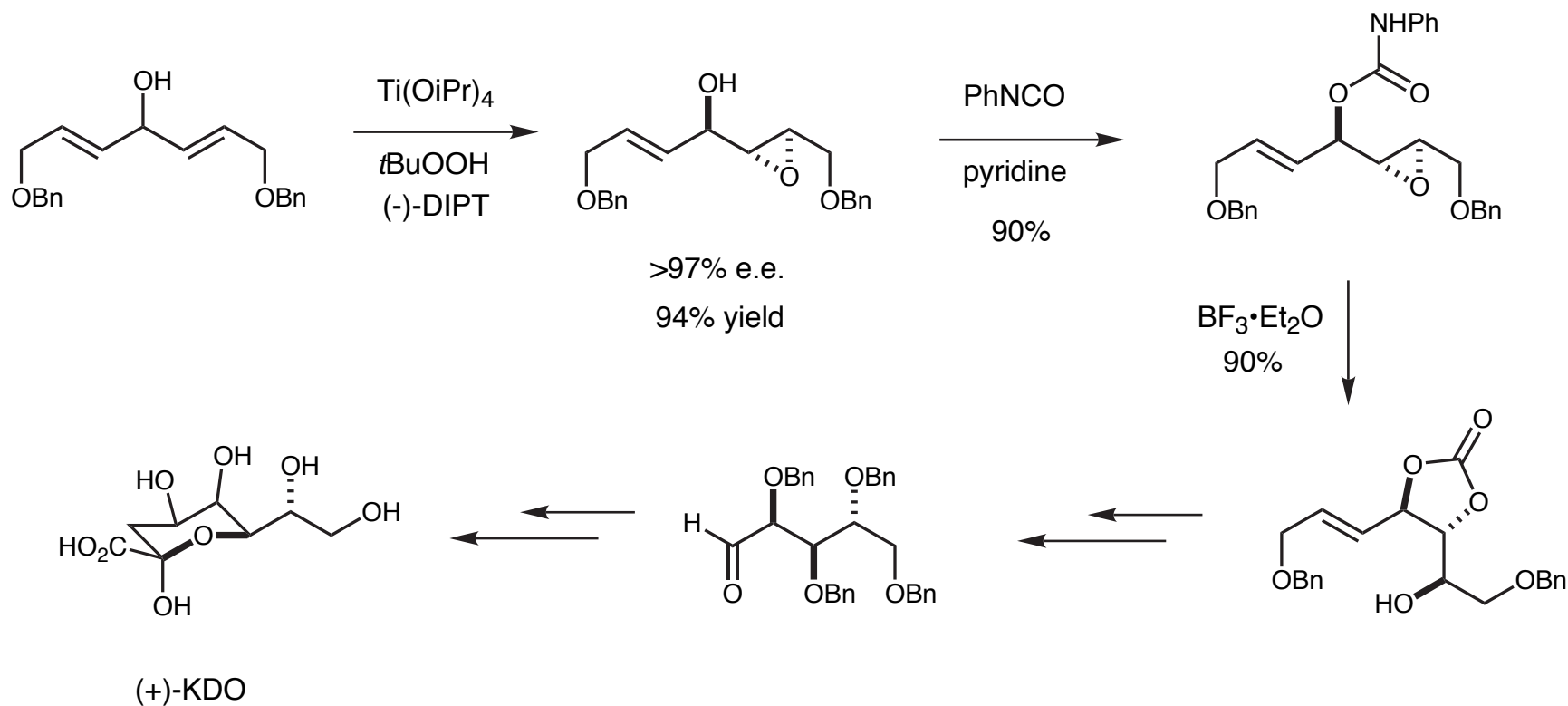
A historical note...



Hatakeyama, Sakurai, Takano, *Chem. Comm.*, **1985**, 1759

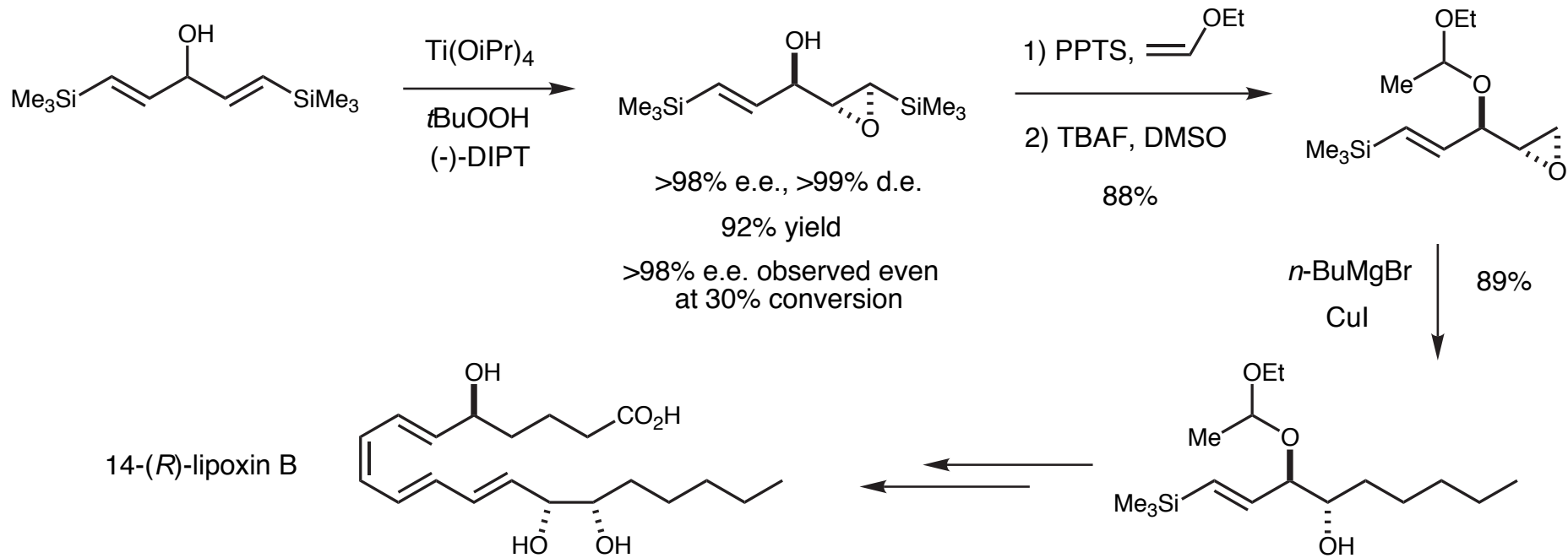
see also Hafele, Schroter, Jager, *ACIEE*, **1986**, 87

## Synthetic Applications

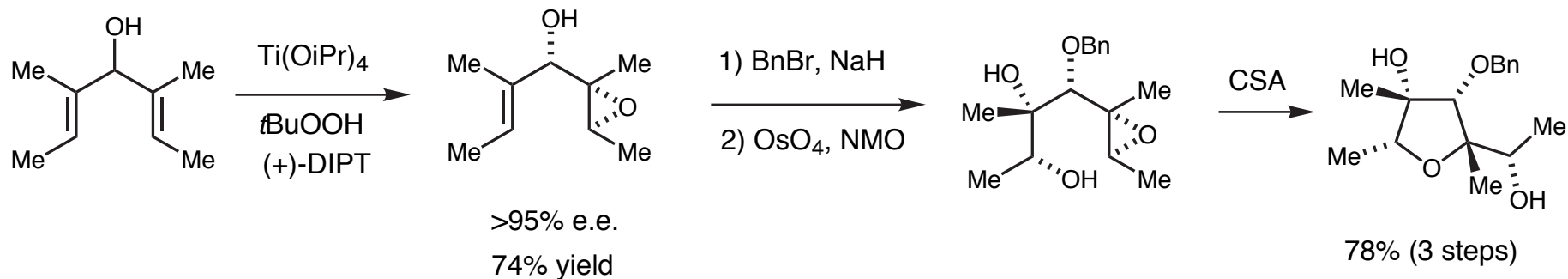


Smith, Wang, Schreiber, *Tet.*, **1990**, 4793

## Synthetic Applications

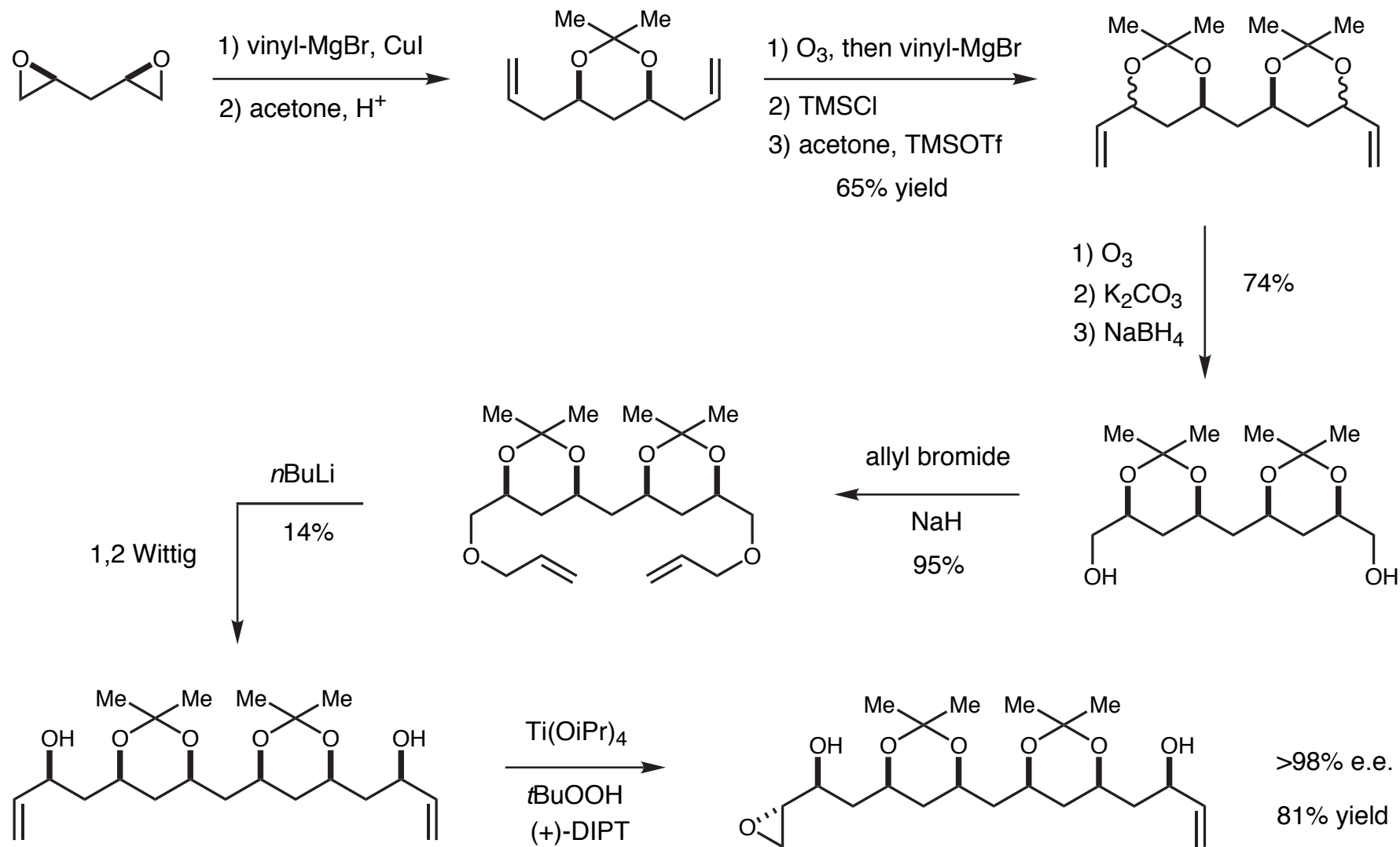


Kobayashi, Kato, Shimazaki, Sato, *TL*, **1988**, 6297



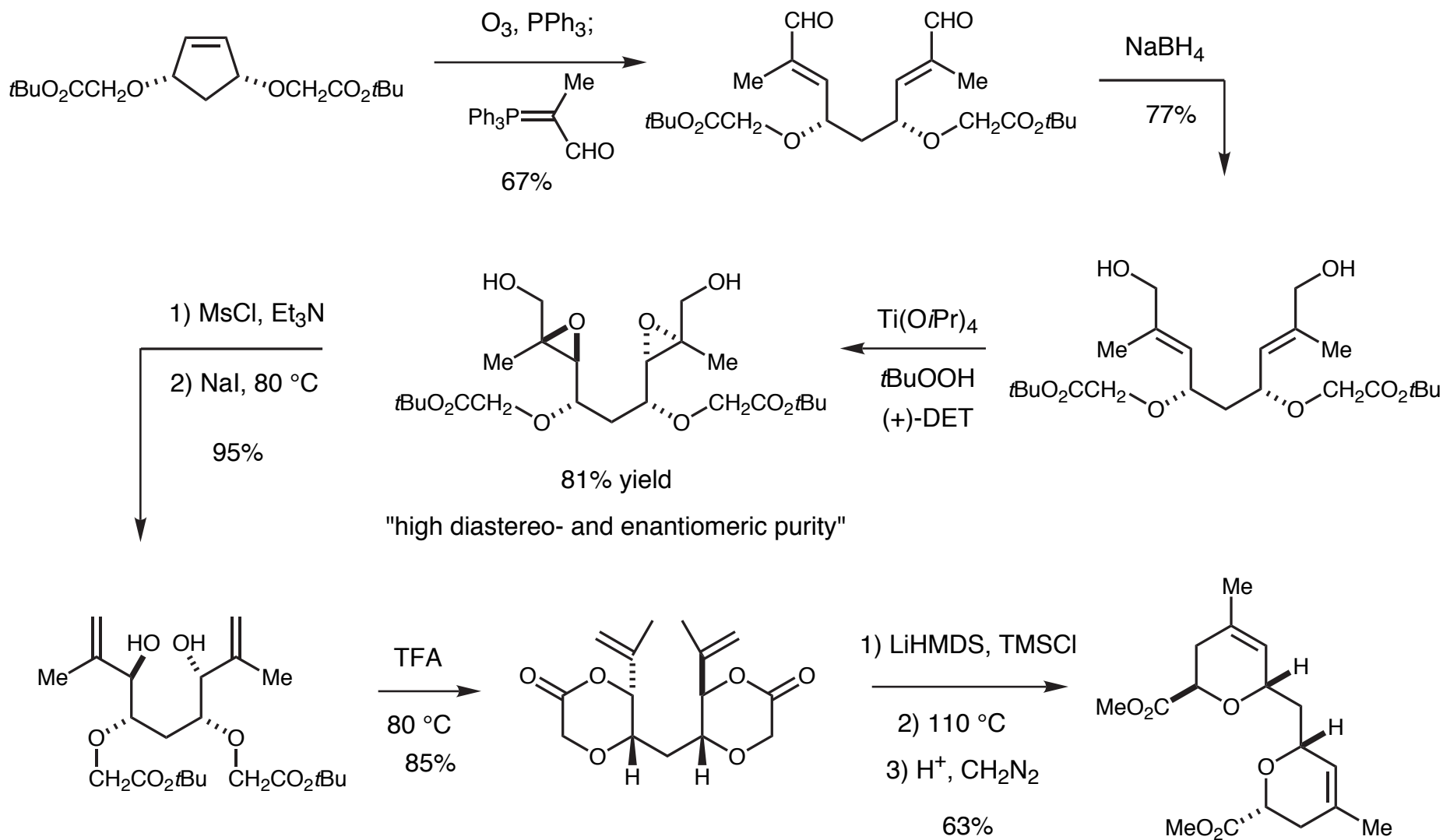
Hatakeyama, Sakurai, Numata, Ochi, Takano, *JACS*, **1988**, 5201

## Desymmetrization of Advanced Intermediates



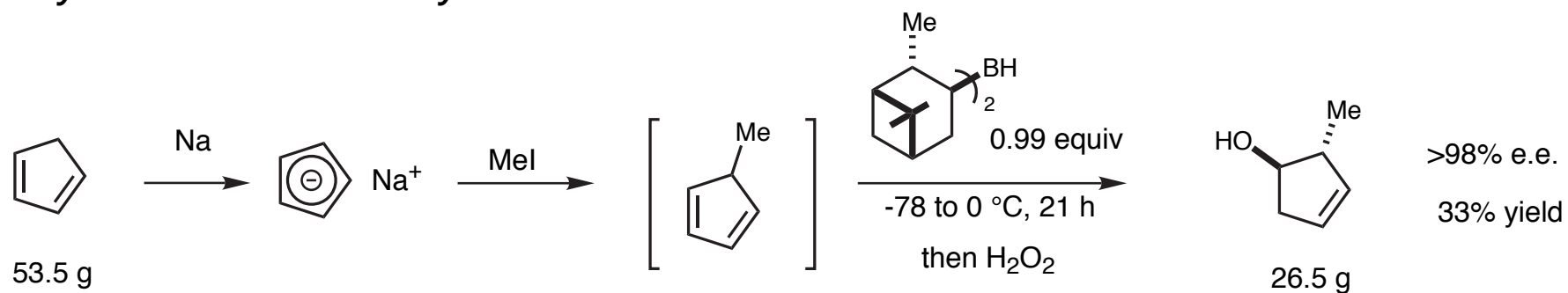
Schreiber, Goulet, Schulte, *JACS*, **1988**, 4718

## Desymmetrization via Bis-epoxidation



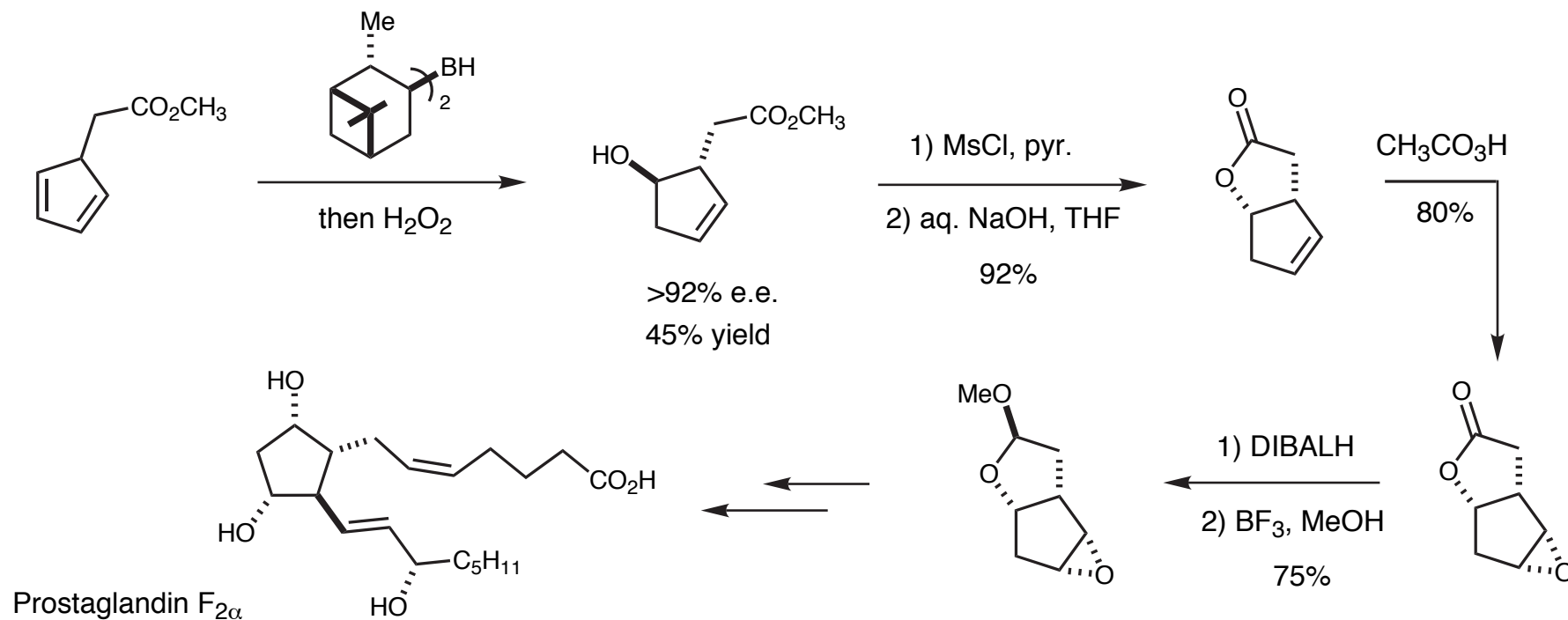
Burke, Buchanan, Rovin, *TL*, **1991**, 3961

## Desymmetrization via Hydroboration



• Low yield is due largely to dimerization of the diene.

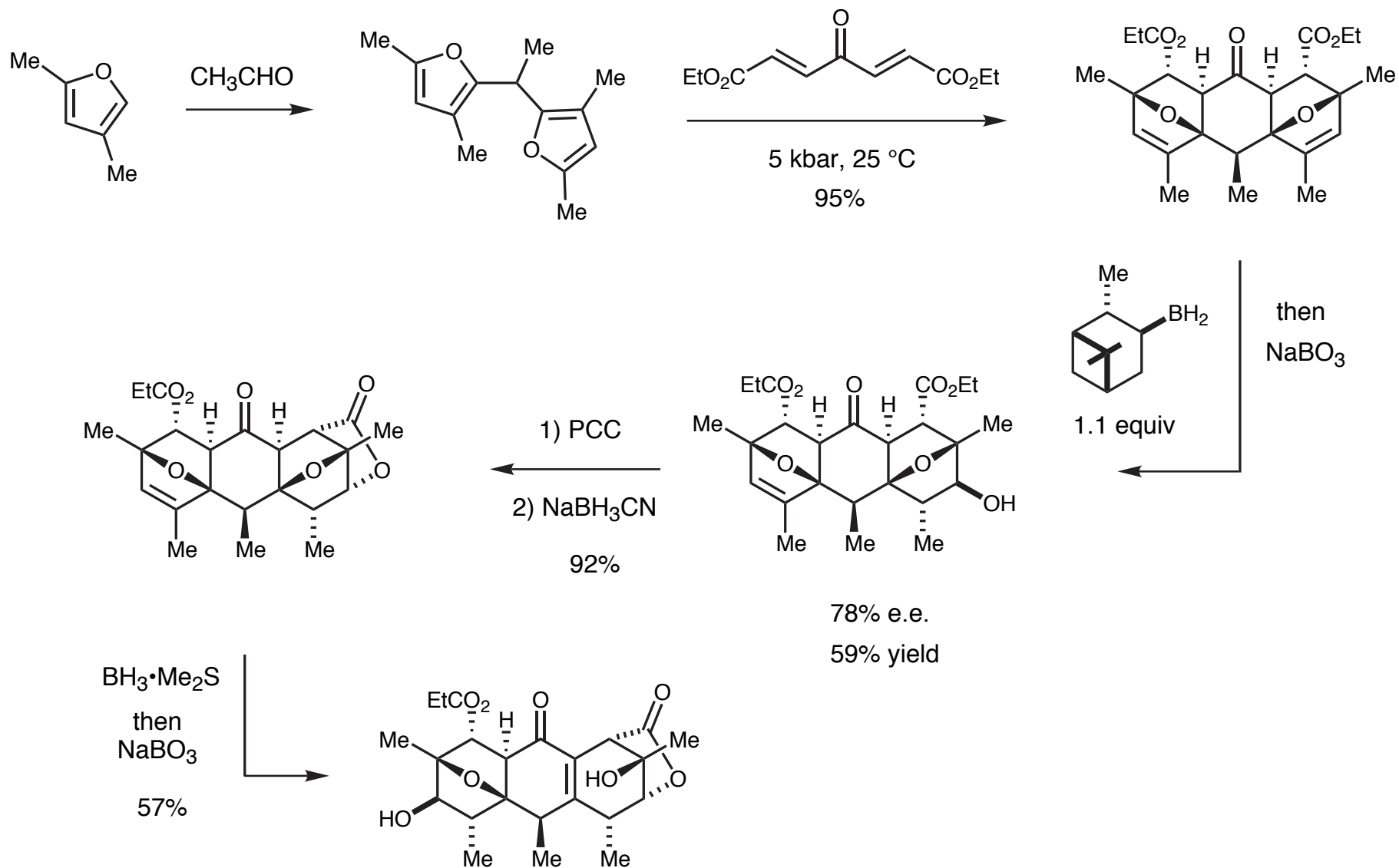
Partridge, Chadha, Uskokovic, *JACS*, **1973**, 532



Partridge, Chadha, Uskokovic, *JACS*, **1973**, 7171

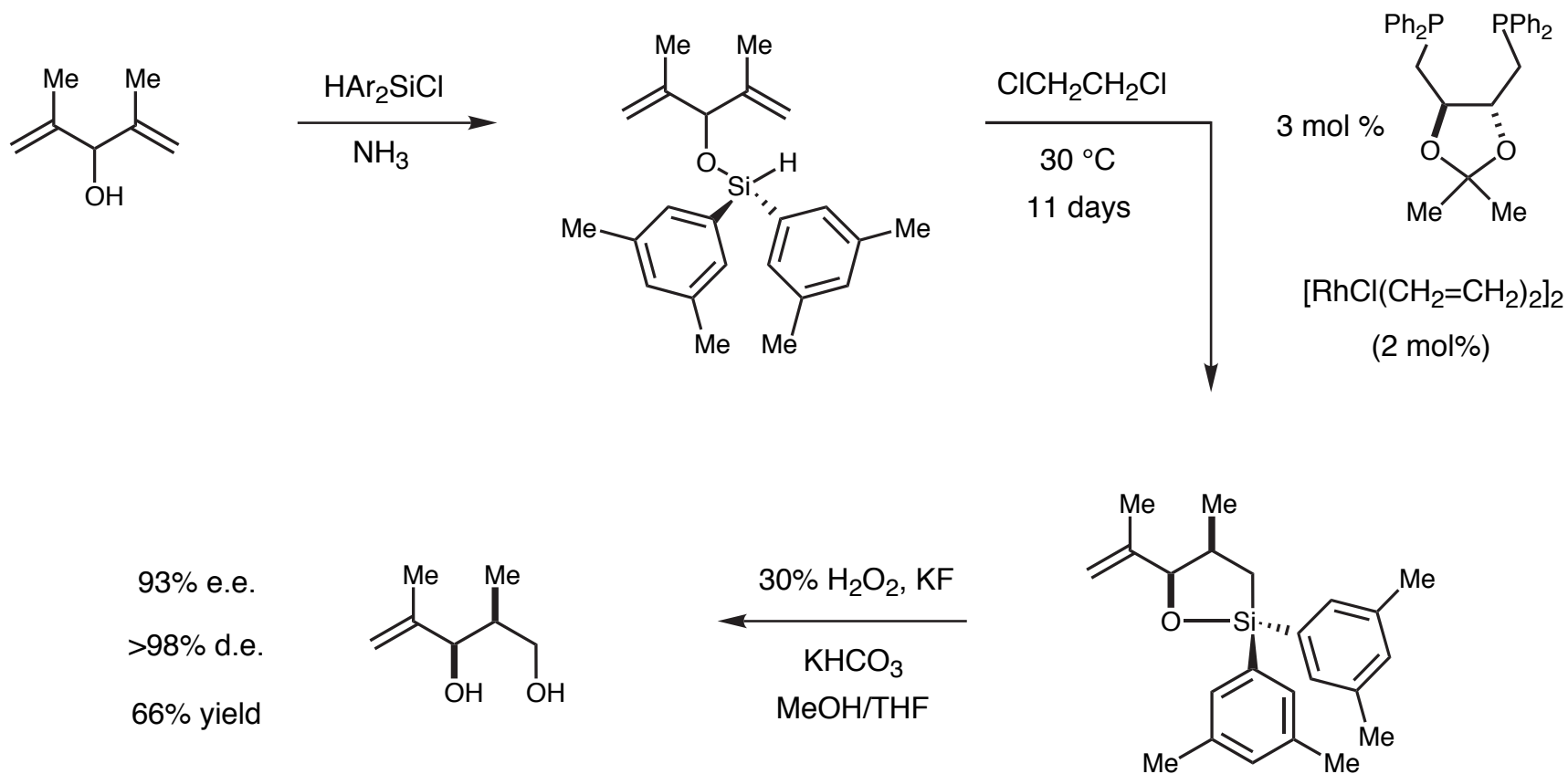


## Desymmetrization via Hydroboration



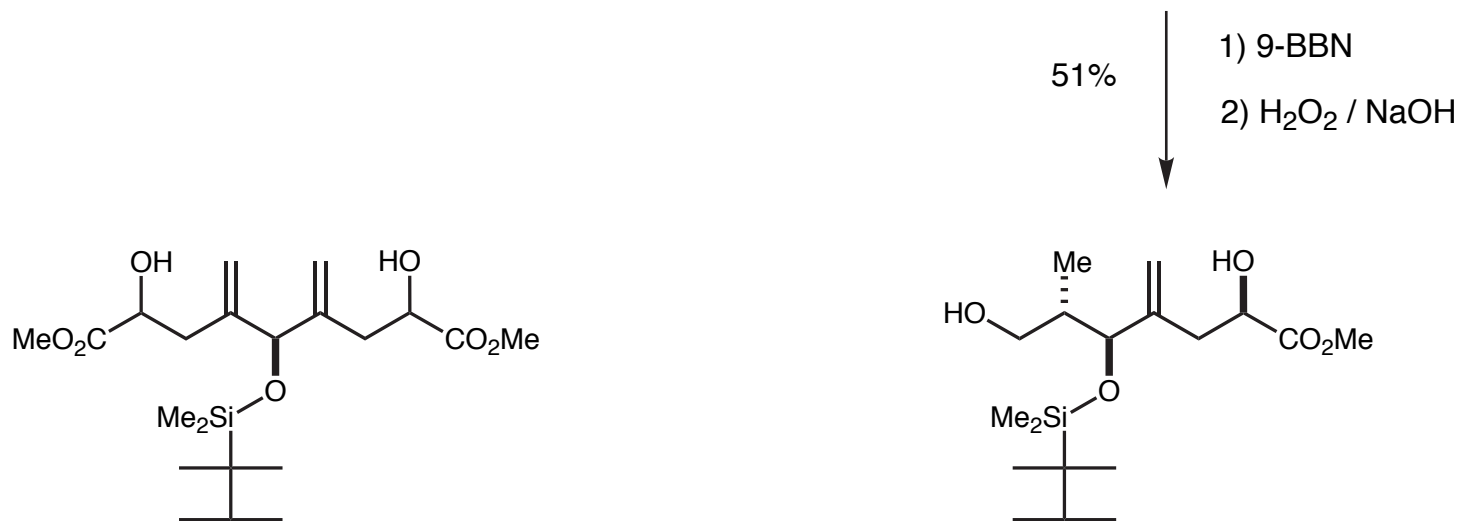
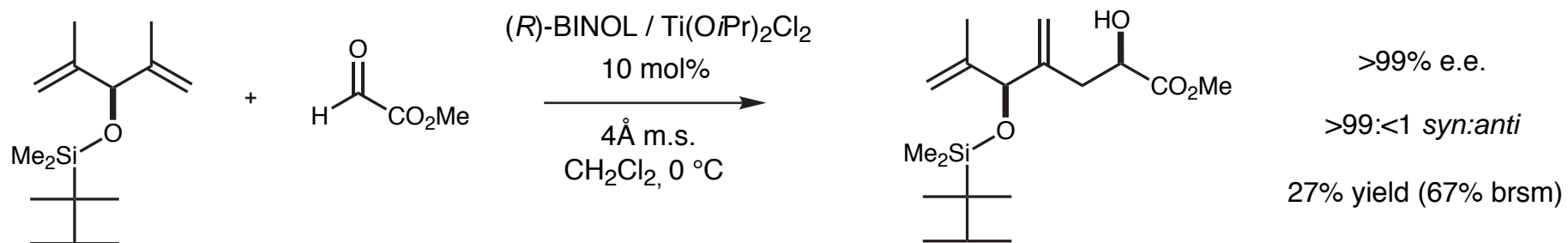
Marchionni, Vogel, Roversi, *TL*, **1996**, 4149

# Desymmetrization via Intramolecular Hydrosilation



Tamao, Tohma, Inui, Nakayama, Ito, *TL*, **1990**, 7333

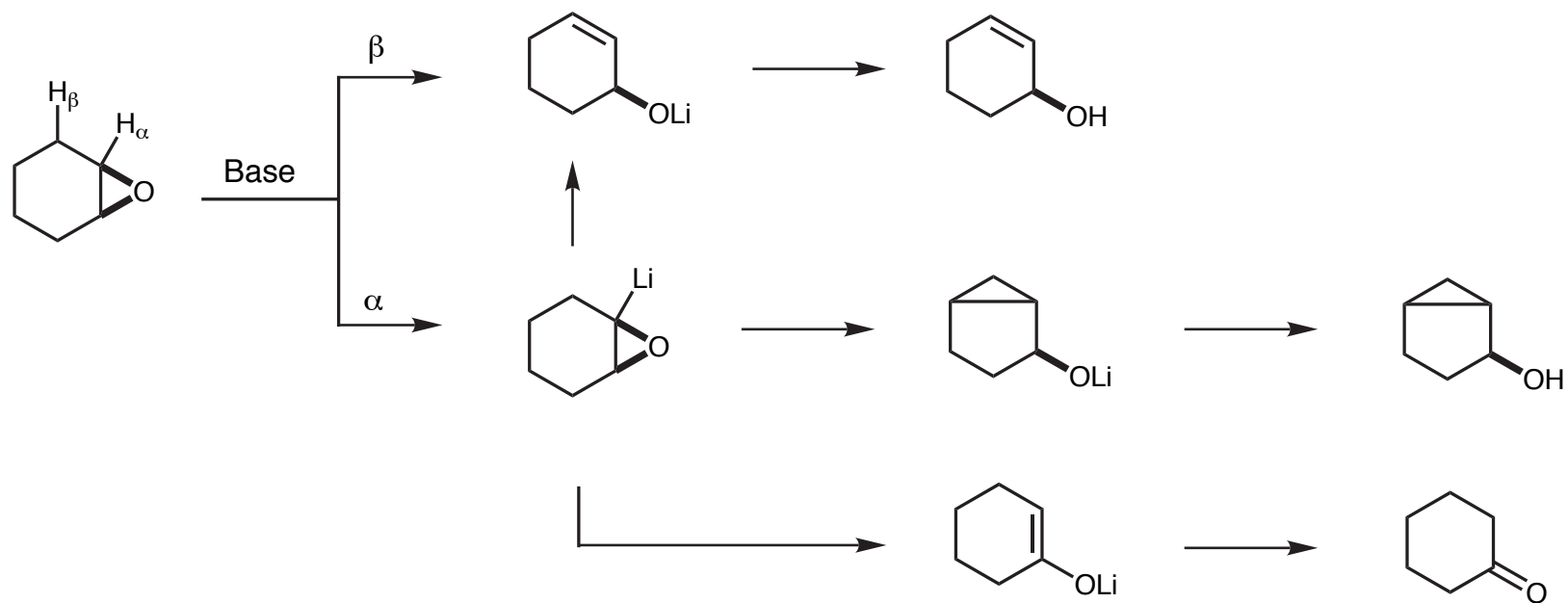
# Ene Reaction



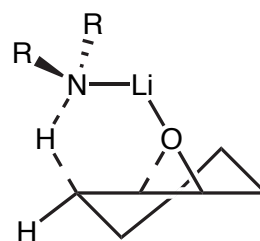
- No "double ene" product obtained, even using 2 equiv glyoxylate.

Mikami, Narisawa, Shimizu, Terada, *JACS*, **1992**, 6566

## Base-Induced Transformations of Cyclic Epoxides



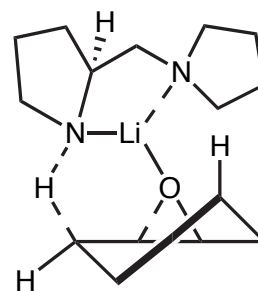
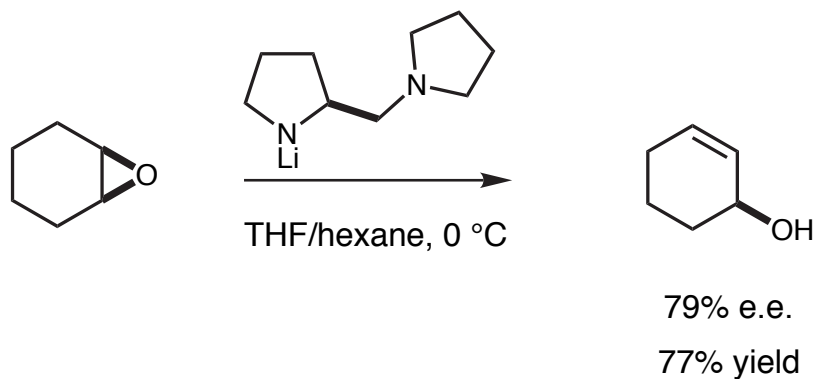
- $\beta$ -elimination is expected to proceed via a *syn* mechanism:



- The  $\beta$ : $\alpha$  ratio depends in part on the ability of the substrate to adopt the above conformation; base, solvent, and temperature are also significant factors.

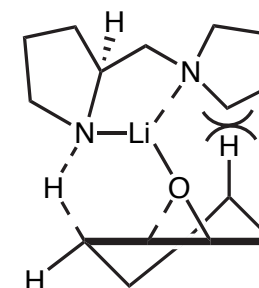
Hodgson, Gibbs, Lee, *Tet.*, **1996**, 14361

## Enantioselective $\beta$ -Elimination



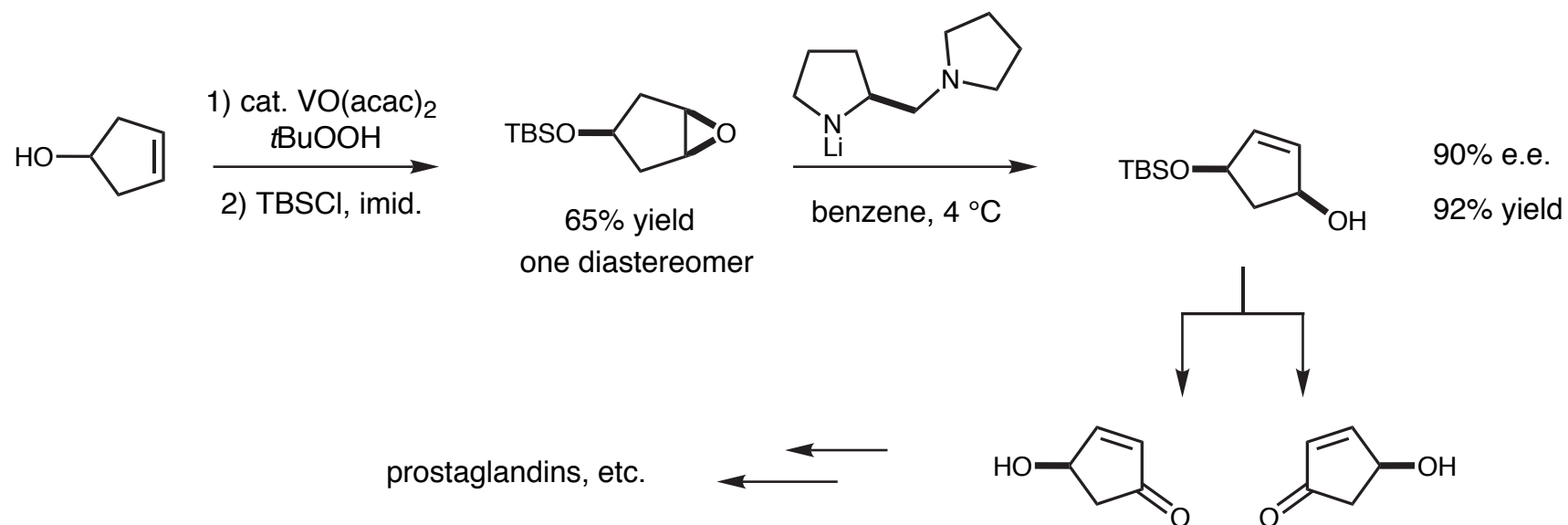
favored

vs.



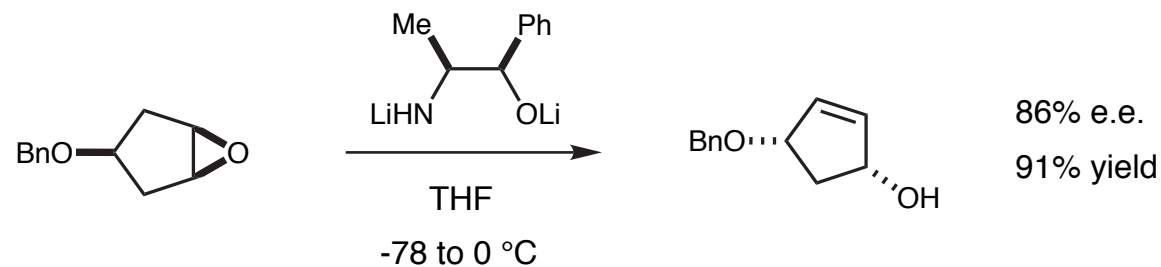
disfavored

Asami, *Chem. Lett.*, **1984**, 829



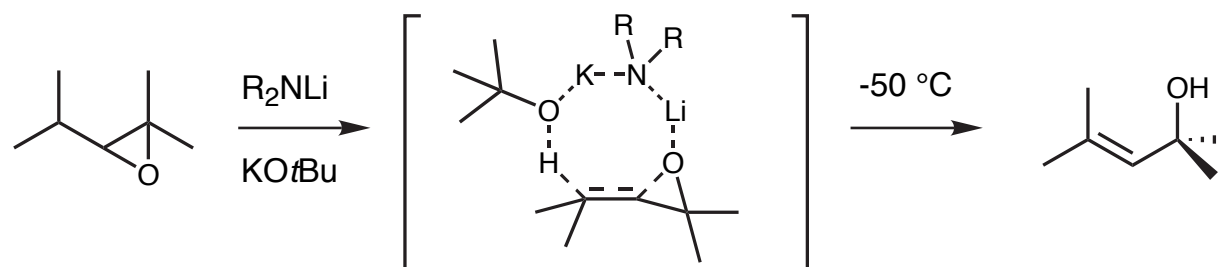
Asami, *TL*, **1985**, 5803

## Enantioselective $\beta$ -Elimination: Dilithiated Aminoalcohols



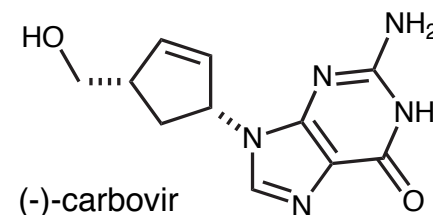
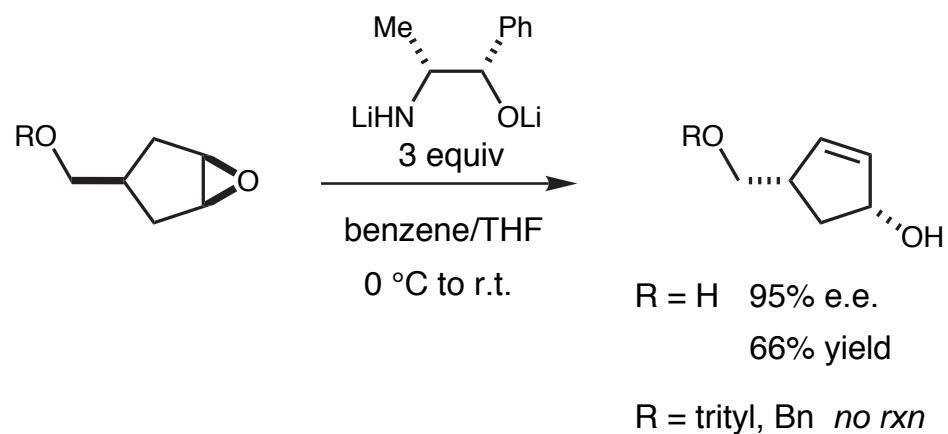
Milne, Murphy, *Chem. Comm.*, **1993**, 884

• Inspired by KO<sup>t</sup>Bu induced rate accelerations:



•  $R_2NLi$  alone requires refluxing THF

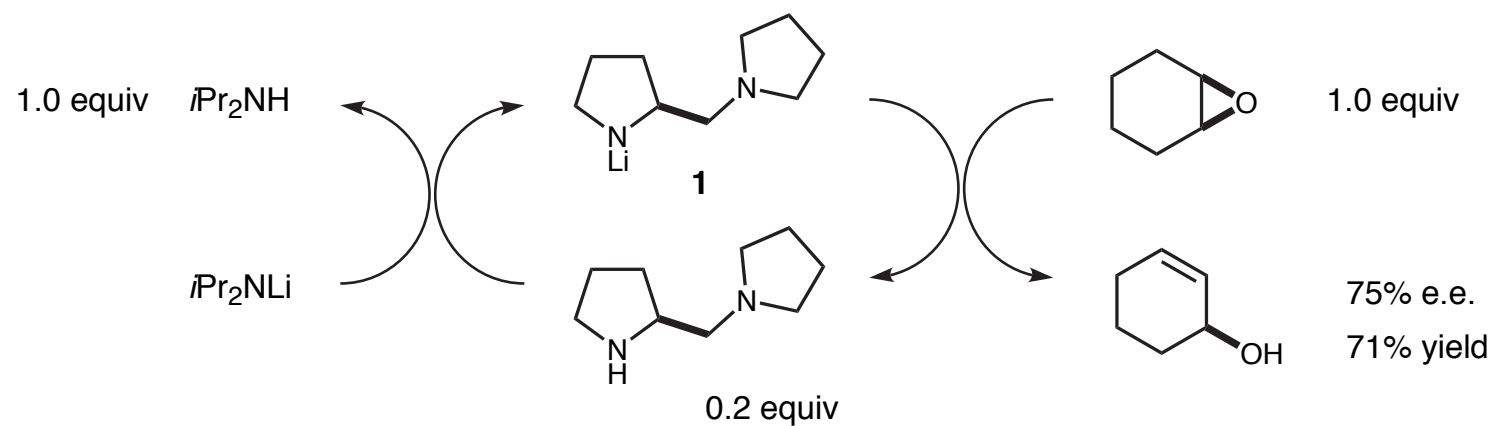
Mordidi, Rayana, Margot, Schlosser, *Tet.*, **1990**, 2401



Hodgson, Witherington, Moloney, *Tet. Asymm.*, **1994**, 337  
*JCS Perkin I*, **1994**, 3373

## Catalytic Enantioselective $\beta$ -Elimination

- Previous observations of Asami indicated that **1** was more reactive toward epoxides than LDA.

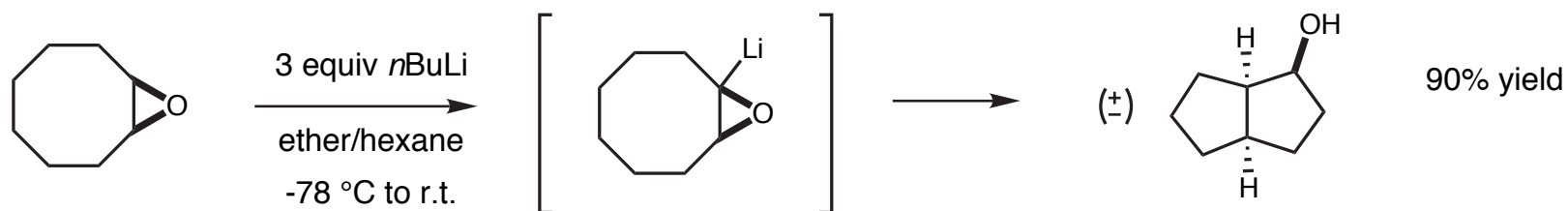


- Addition of 6.0 equiv DBU was necessary for optimal results; the additive may facilitate proton transfer between LDA and the chiral amine.
- 1.2 equiv  $n\text{BuLi}$  were employed for metallation.

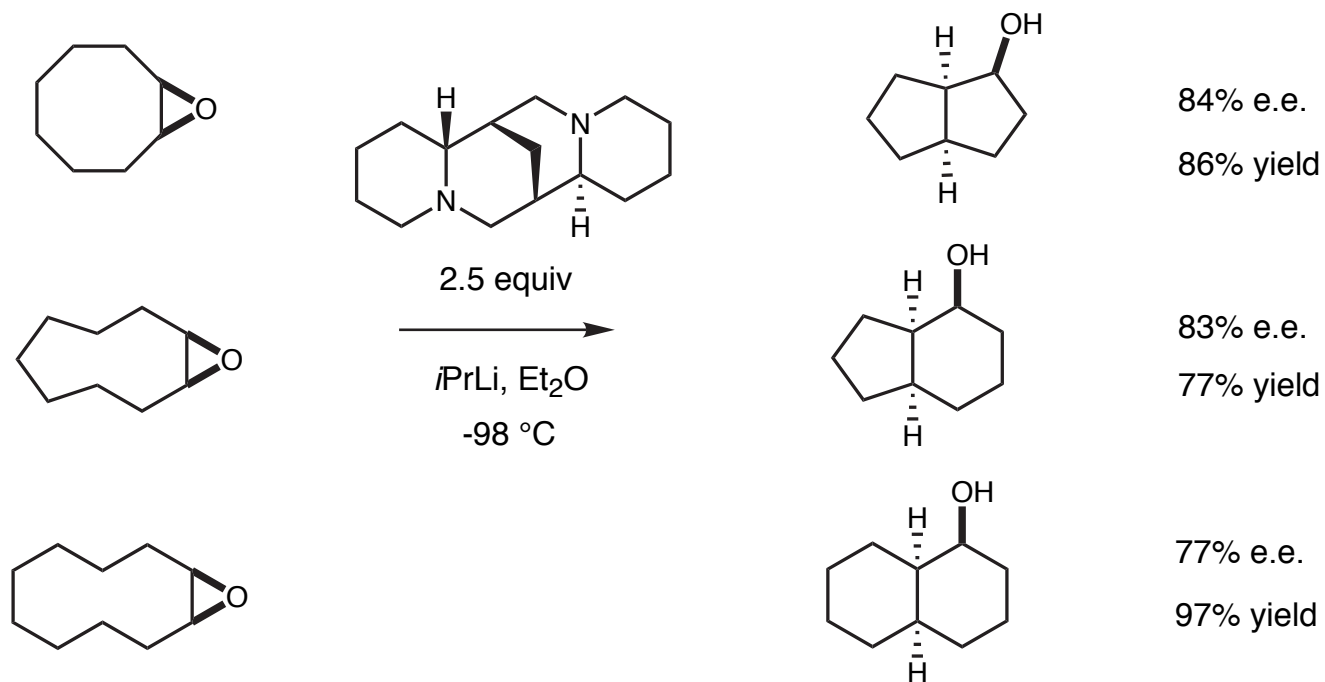
Asami, Ishizaki, Inoue, *Tet. Asymm.*, **1994**, 793

## Enantioselective $\alpha$ -Elimination

- Medium ring epoxides undergo selective  $\alpha$ -elimination followed by carbene formation and C-H insertion.



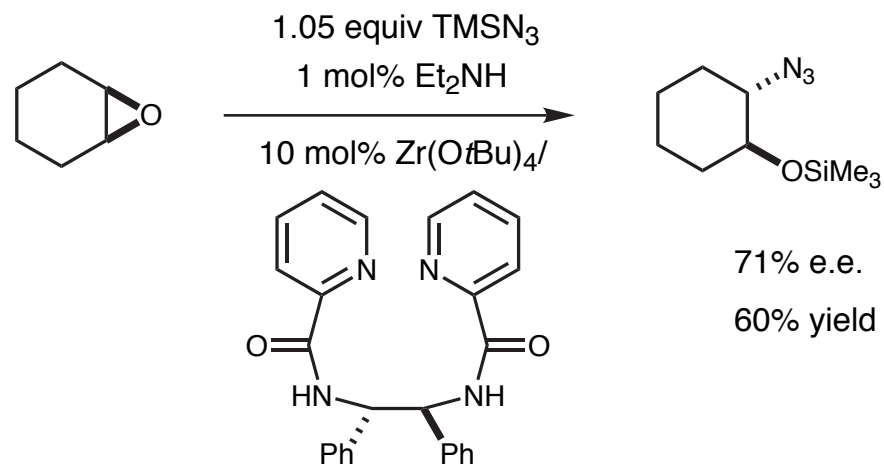
Boeckman, *TL*, **1977**, 4281



Hodgson, Lee, *Chem. Comm.*, **1996**, 1015

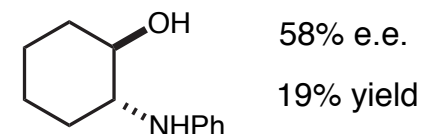
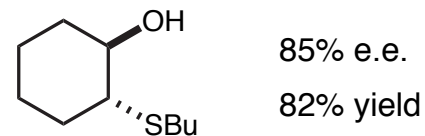
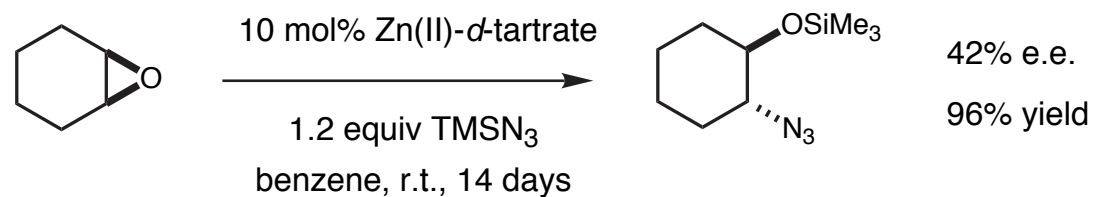


## Catalytic Enantioselective $\text{TMSN}_3$ Addition



- Spectroscopic studies indicate that diethylamine is necessary for quantitative formation of the zirconium/ligand complex.

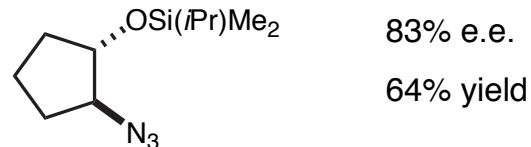
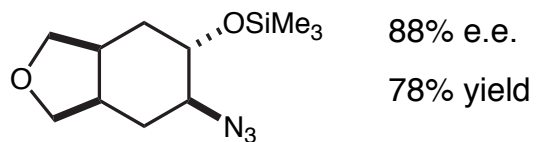
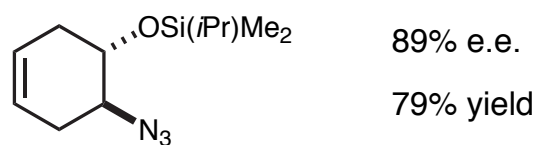
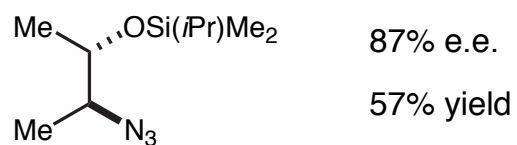
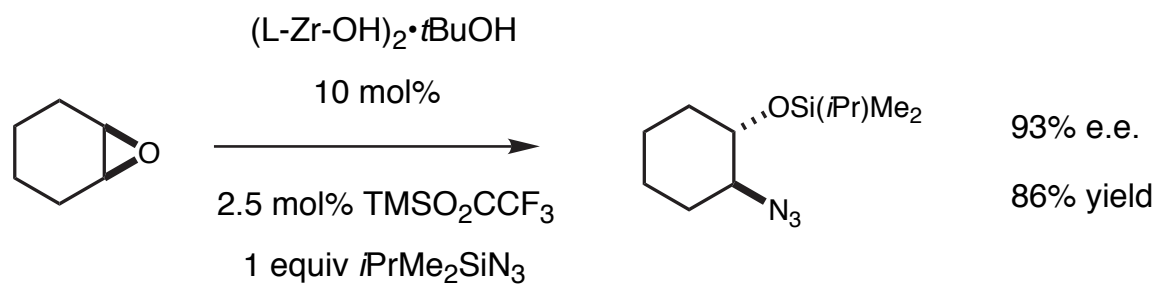
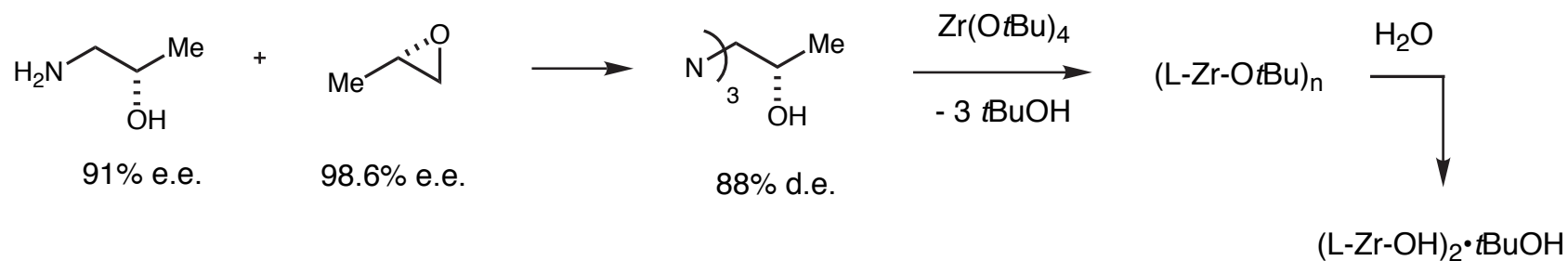
Adolfsson, Moberg, *Tet. Asymm.*, **1995**, 2023



- The reaction is heterogeneous; catalyst can be recovered by filtration.
- 15 metal(II) tartrates were screened.
- The catalyst is prepared by treatment of  $\text{ZnCl}_2$  with aqueous Rochelle's salt or tartaric acid.

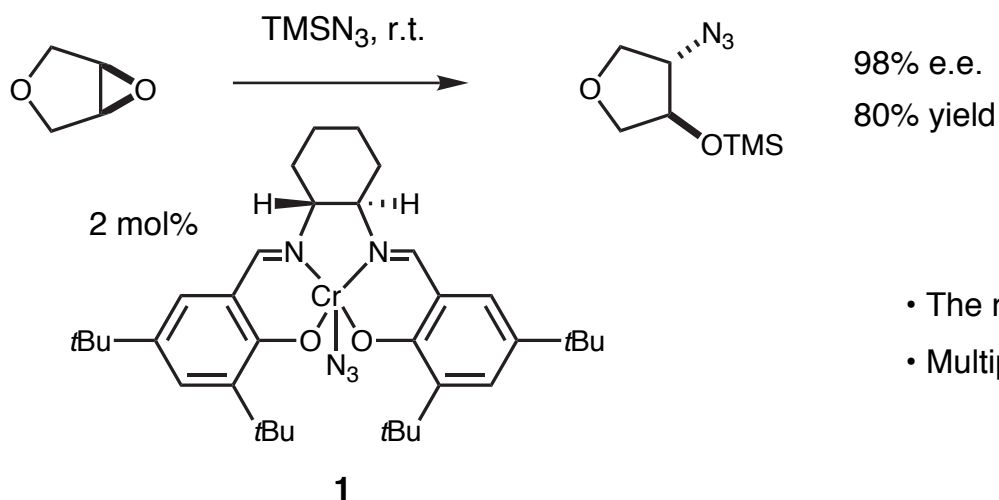
Yamashita, *Bull. Chem. Soc. Japan*, **1988**, 1213

## Catalytic Enantioselective $\text{TMSN}_3$ Addition

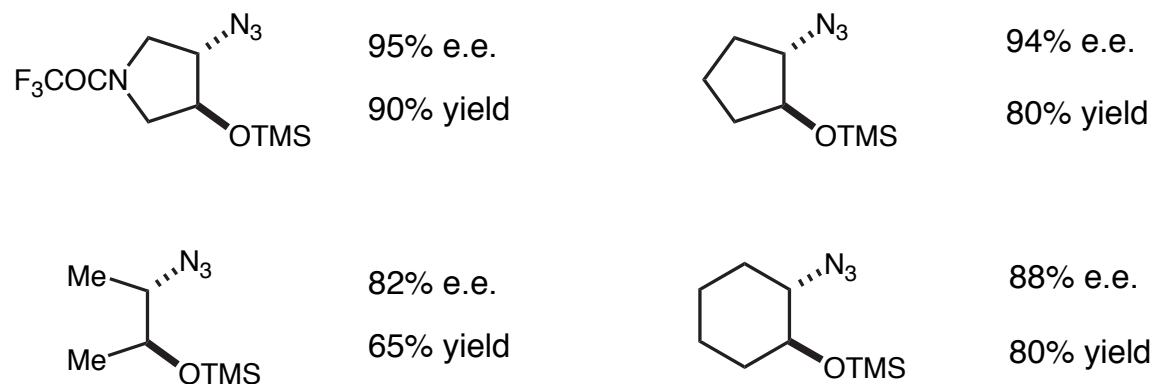


Nugent, *JACS*, **1992**, 2768

## Catalytic Enantioselective $\text{TMSN}_3$ Addition

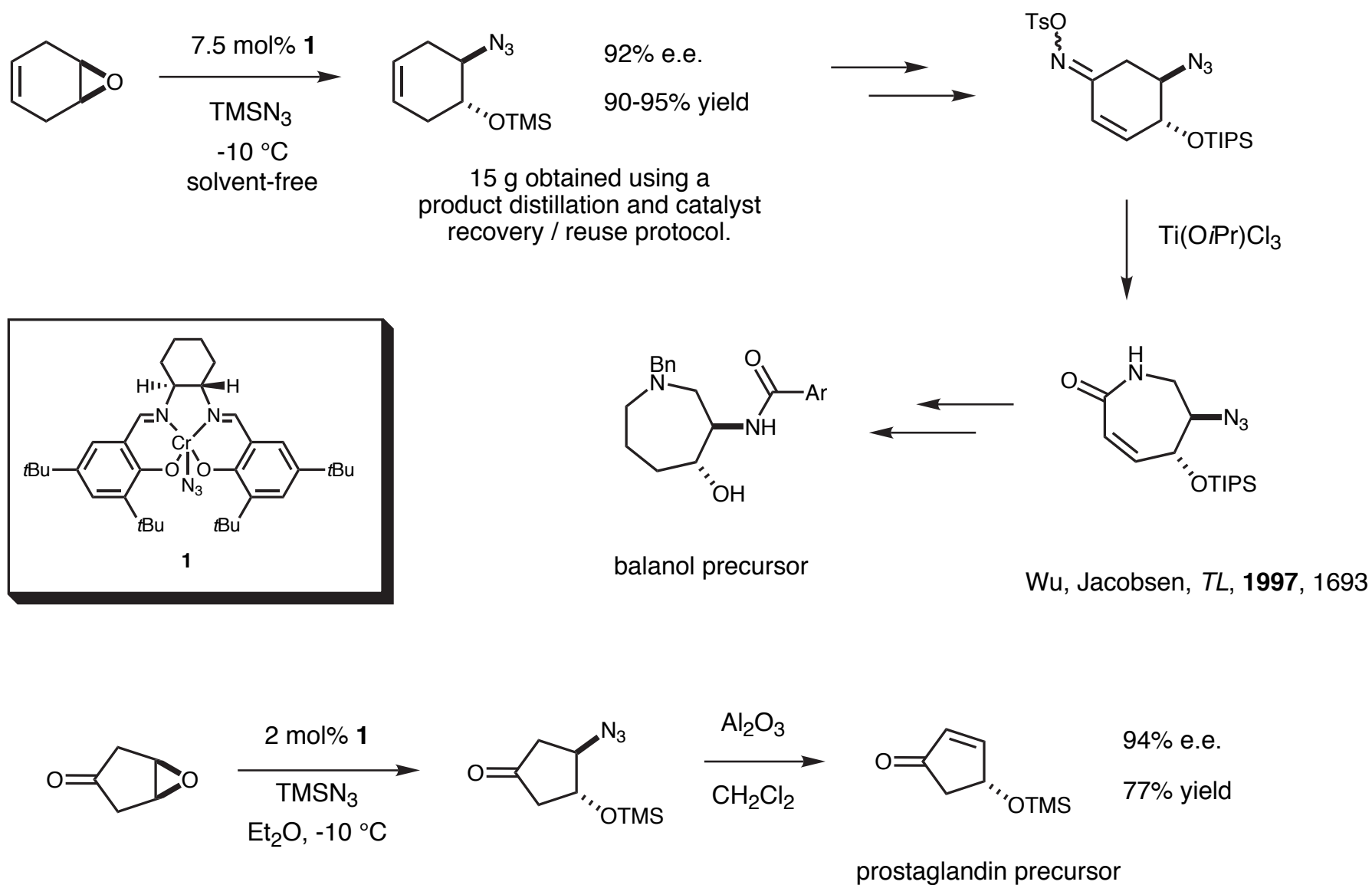


- The reaction proceeds equally well without solvent.
- Multiple recycles of the catalyst provide identical results.

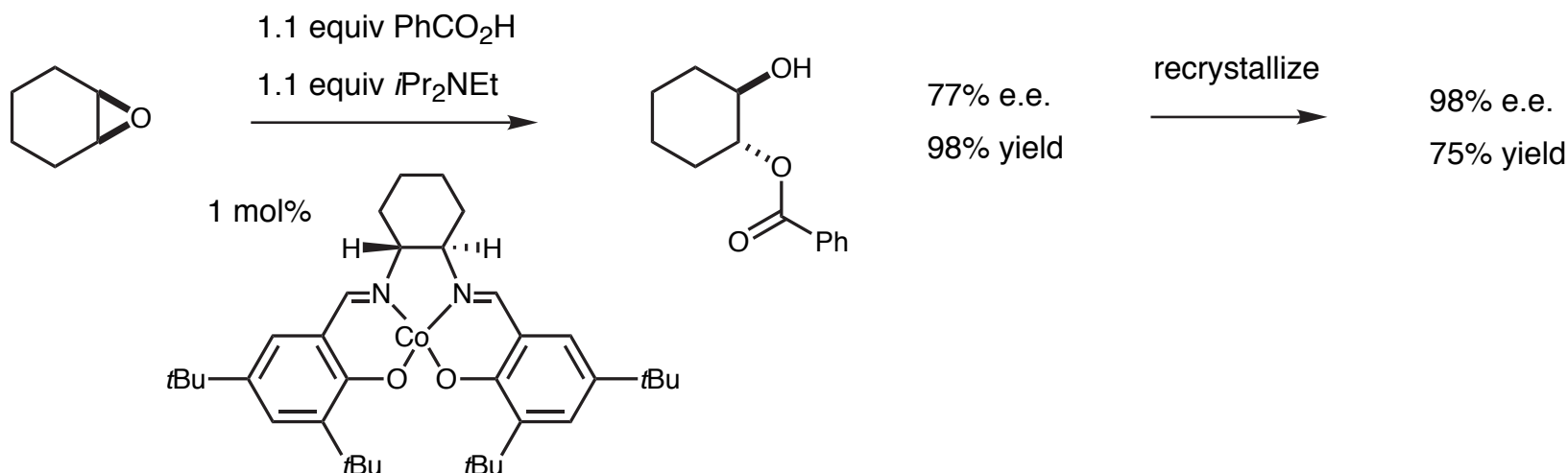


Martinez, Leighton, Carsten, Jacobsen, *JACS*, **1995**, 5897

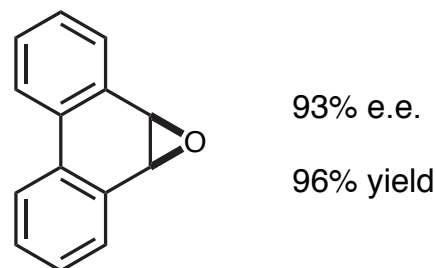
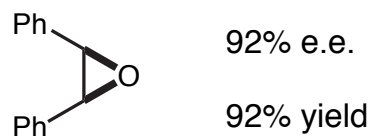
# Catalytic Enantioselective $\text{TMSN}_3$ Addition: Applications



## Catalytic Enantioselective Benzoic Acid Addition

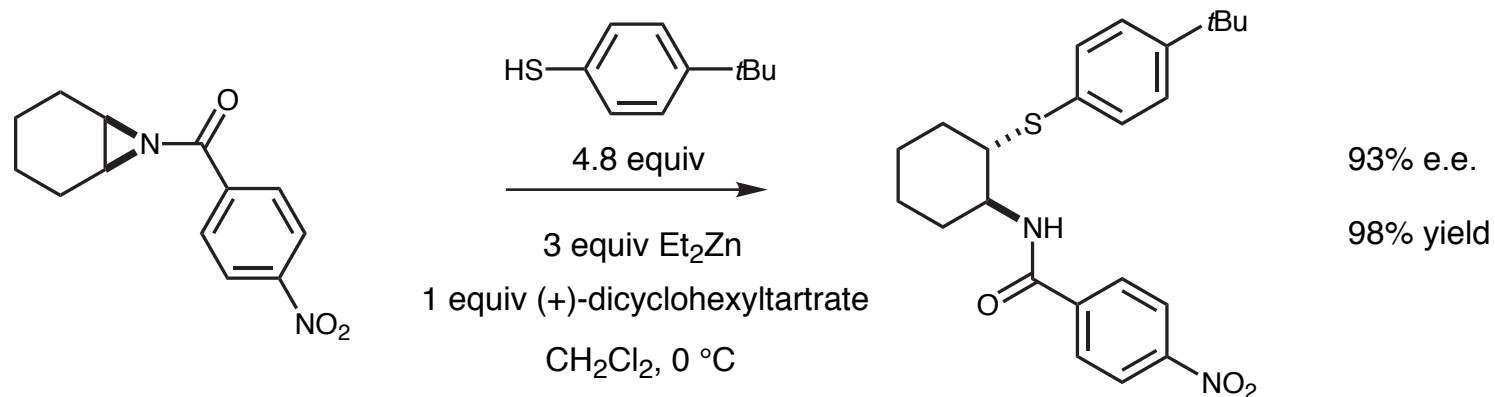


- The Co(II) complex depicted is a precatalyst; formation of the active Co(III) complex is best accomplished by stirring the precatalyst and benzoic acid under an oxygen atmosphere.
- The benzoate ester adducts are generally crystalline and can thus be recrystallized to obtain high e.e.
- *i*Pr<sub>2</sub>NEt appears to confer solubility to benzoic acid (TBME solvent).
- Best substrates:



Jacobsen, Kakiuchi, Konsler, Larrow, Tokunaga, *TL*, **1997**, 773

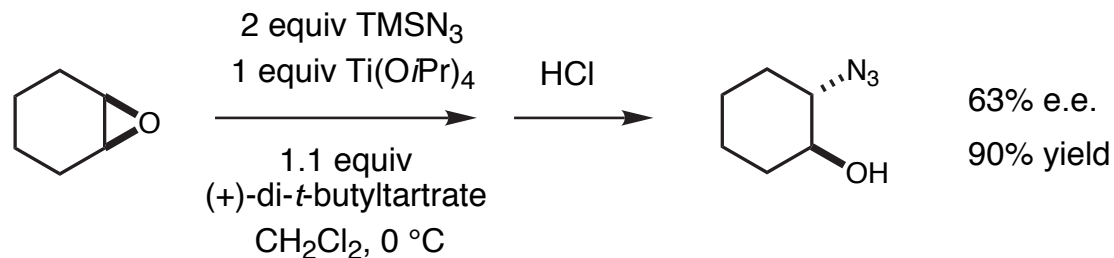
## Enantioselective Aziridine Opening



- Reduced catalyst loading gives lower e.e.: 50 mol%, 78% e.e.; 20 mol%, 17% e.e.
- Use of 4-methylbenzenethiol or benzenethiol gave 89% e.e. and 45% e.e., respectively.
- The *para*-nitro group on the N-acyl moiety was required for optimal e.e.

Hayashi, Ono, Hoshimi, Oguni, *Tet.*, **1996**, 7817  
*Chem. Comm.*, **1994**, 2699

- $\text{TMSN}_3$  addition can be effected under similar conditions:

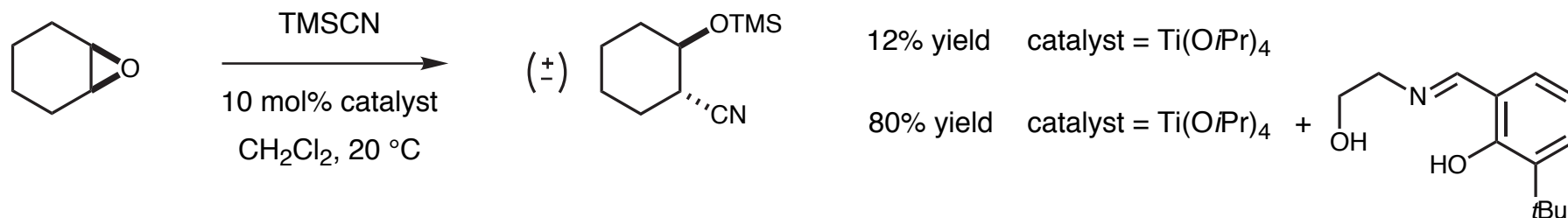


- Use of 10 mol%  $\text{Ti}(\text{O}i\text{Pr})_2\text{Cl}_2$  and 10 mol% tartrate gives 62% e.e., 65% yield.

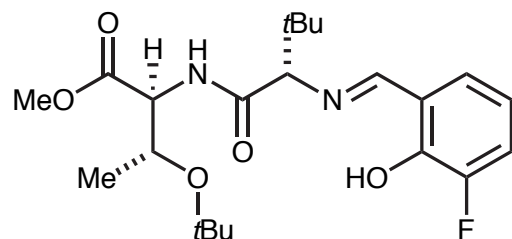
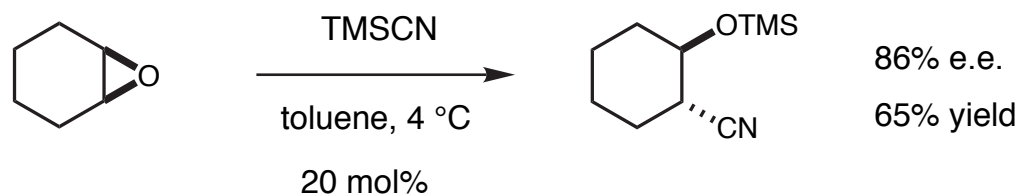
Hayashi, Kohmura, Oguni, *Synlett*, **1991**, 774

## Catalytic Enantioselective TMSCN Addition

- Ligand-accelerated catalysis has been observed for titanium-mediated TMSCN addition to epoxides.



Hayashi, Tomura, Oguni, *Synlett*, **1992**, 663

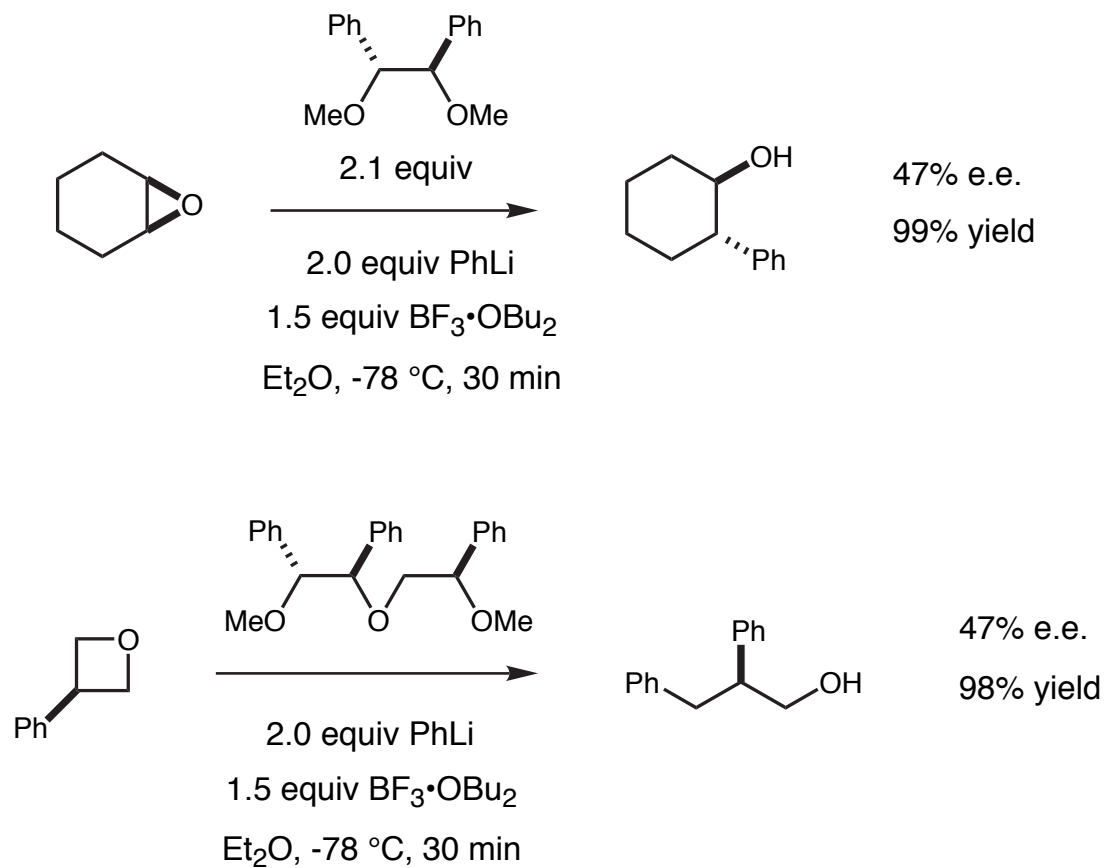


+  $\text{Ti}(\text{O}i\text{Pr})_4$

- The catalyst was identified via a combinatorial synthesis strategy (positional scanning).
- At present, the catalysts developed exhibit high substrate specificity.

Cole, Shimizu, Krueger, Harrity, Snapper, Hoveyda, *ACIEE*, **1996**, 1668

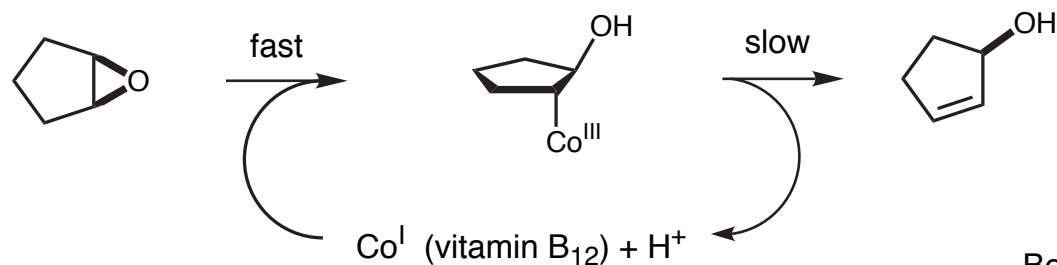
## Phenyllithium Addition to Epoxides and Oxetanes



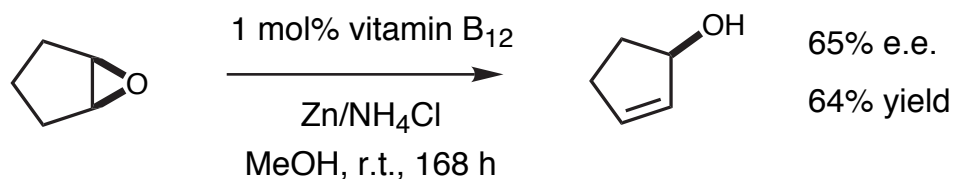
Mizuno, Kanai, Iida, Tomioka, *Tet. Asymm.*, **1996**, 2483



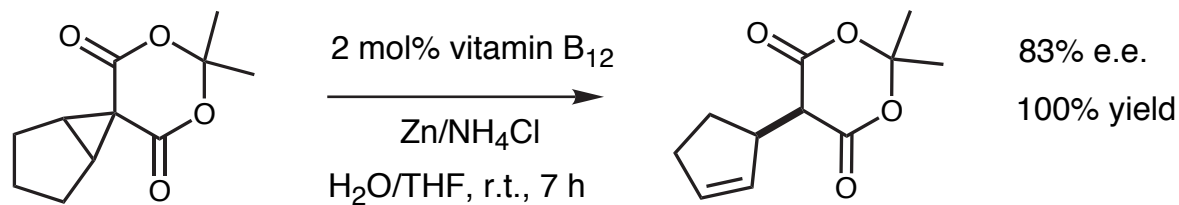
## Vitamin B<sub>12</sub> Catalyzed Isomerizations



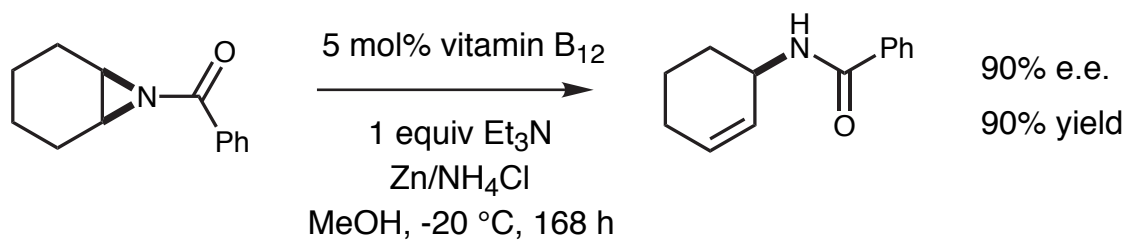
Bonhote, Scheffold, *Helv. Chim. Acta*, **1991**, 1425



Su, Walder, Zhang, Scheffold, *Helv. Chim. Acta*, **1988**, 1073

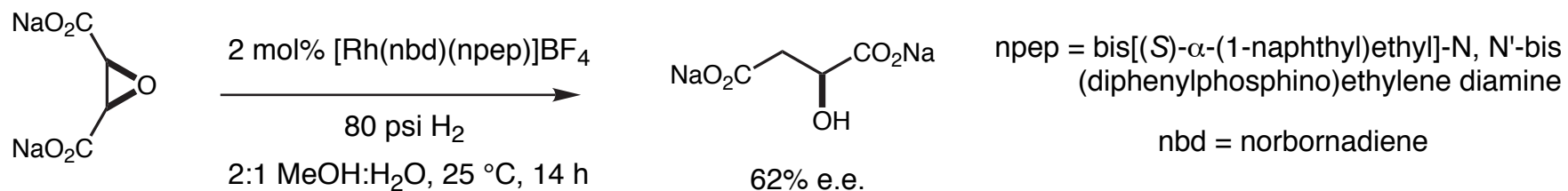


Troxler, Scheffold, *Helv. Chim. Acta*, **1994**, 1193



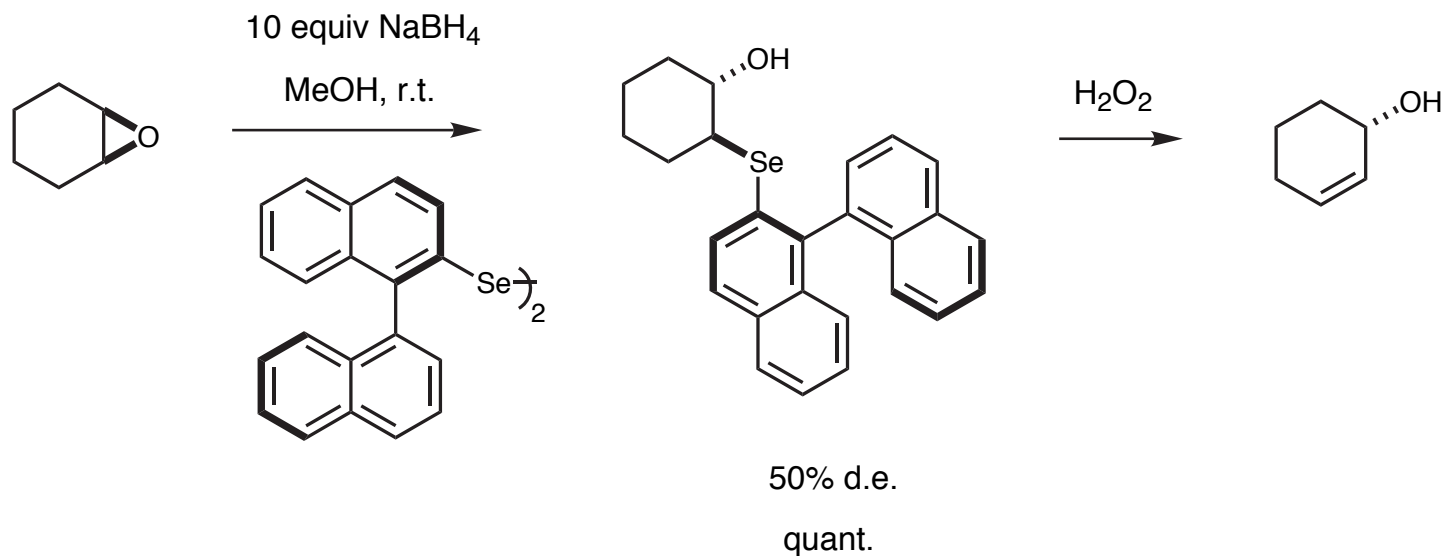
Zhang, Scheffold, *Helv. Chim. Acta*, **1993**, 2602

## Additional Transformations of Epoxides



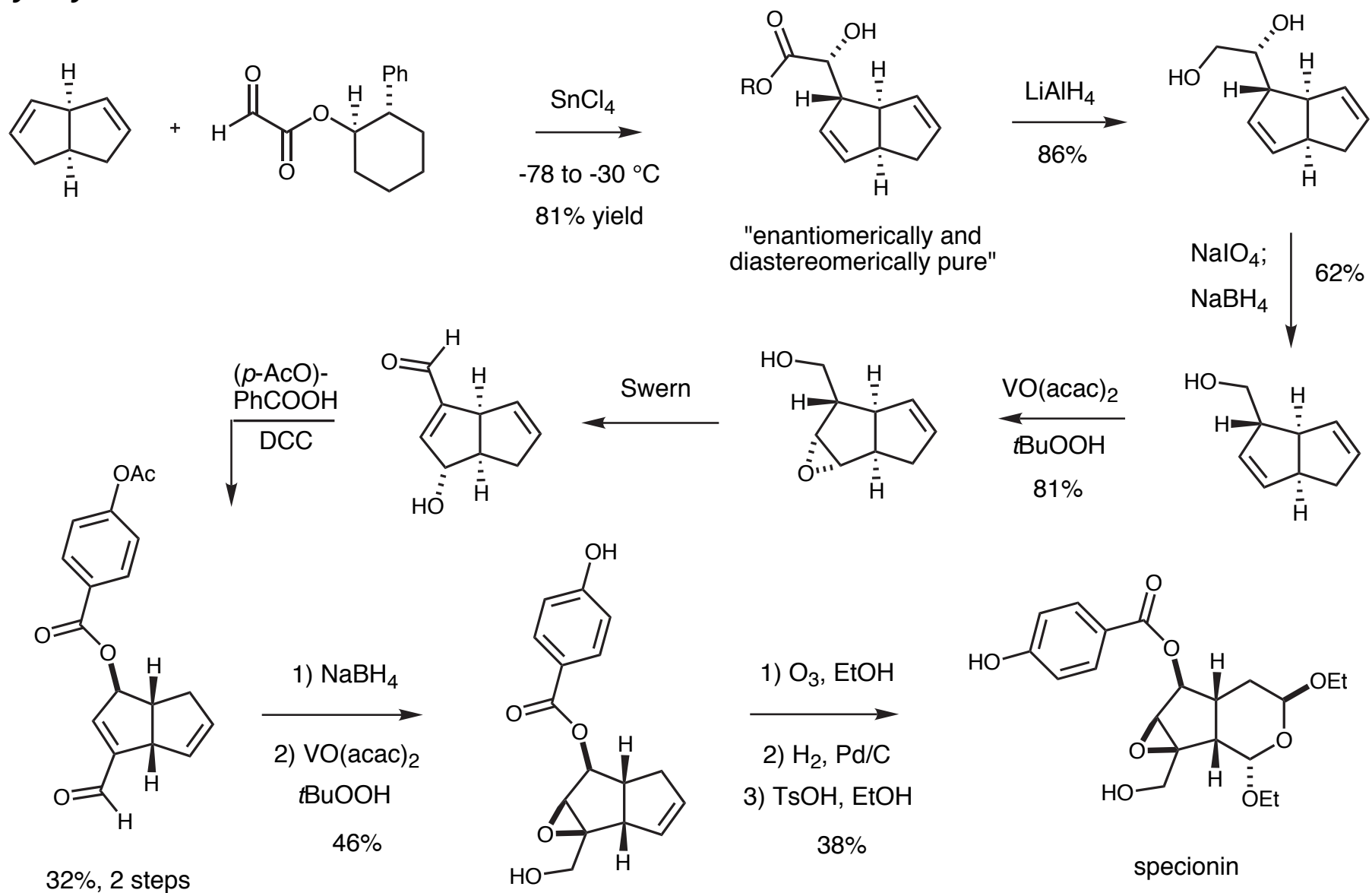
- Carboxylate functionality is necessary for the reaction to proceed.
- Deuterium labelling indicates that direct C-O bond cleavage is operative.

Chan, Coleman, *Chem. Comm.*, **1991**, 535



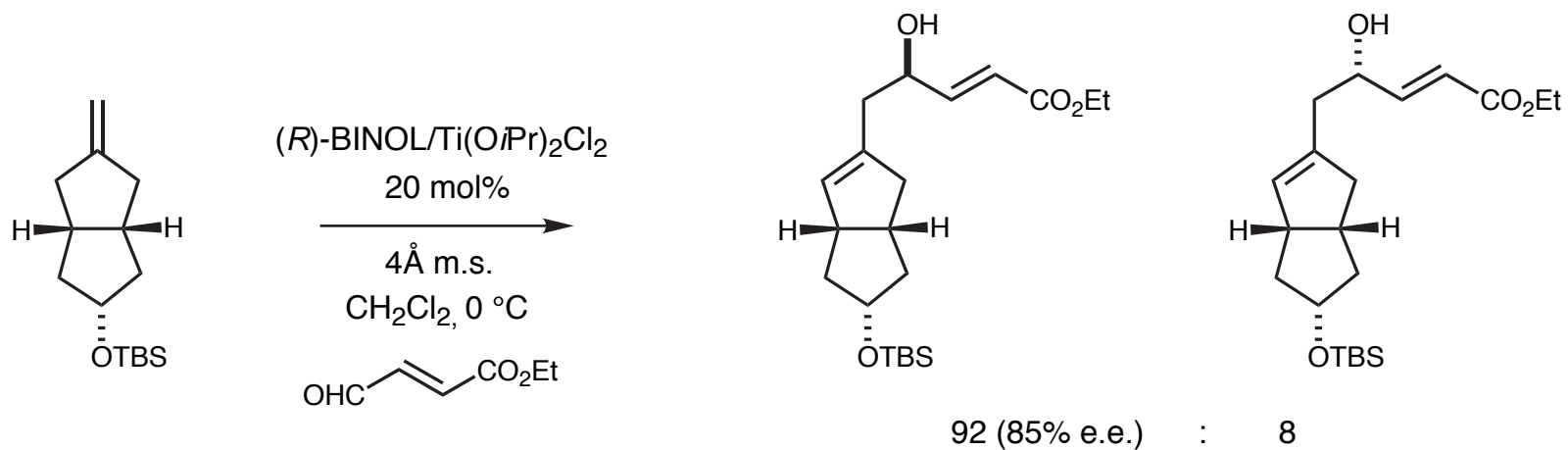
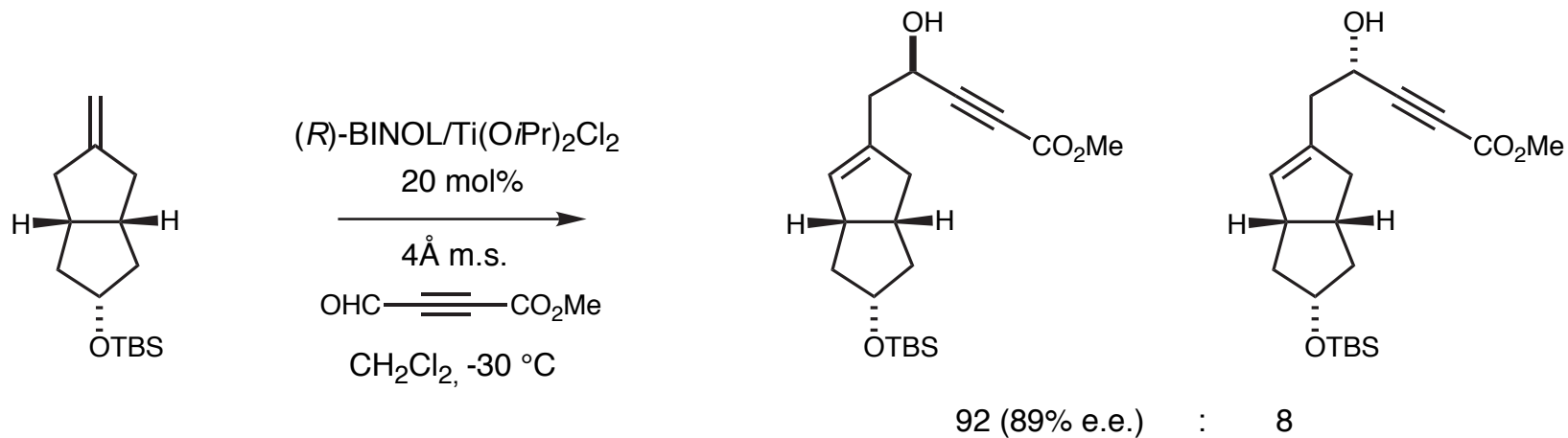
Tomoda, Iwaoka, *Chem. Comm.*, **1988**, 1283

# Glyoxylate Ene Reaction



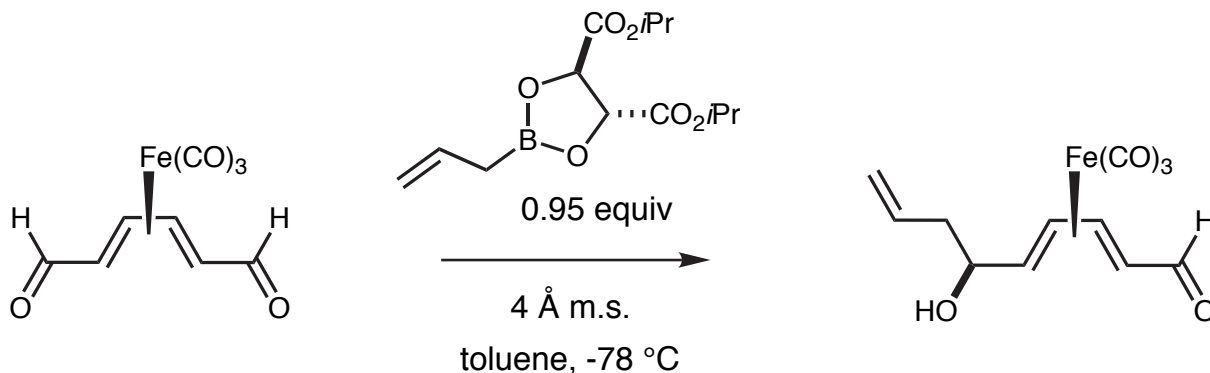
Whitesell, Allen, *JACS*, **1988**, 3585  
*JOC*, **1985**, 3025

# Ene Reaction

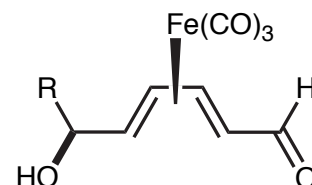
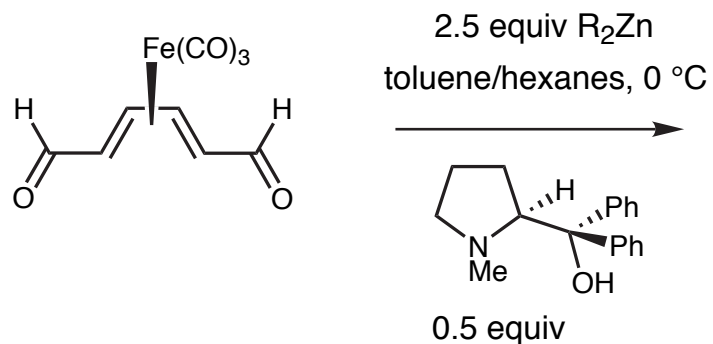


Mikami, Yoshida, Matsumoto, *TL*, **1996**, 8515

## Meso Dialdehydes: $Fe(CO)_3$ Complexes



Roush, Park, *TL*, **1990**, 4707

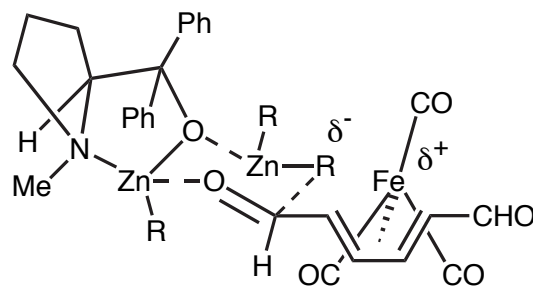


$R = Et$   $>98\%$  e.e.,  $78\%$  yield

$R = nPent$   $>98\%$  e.e.,  $76\%$  yield

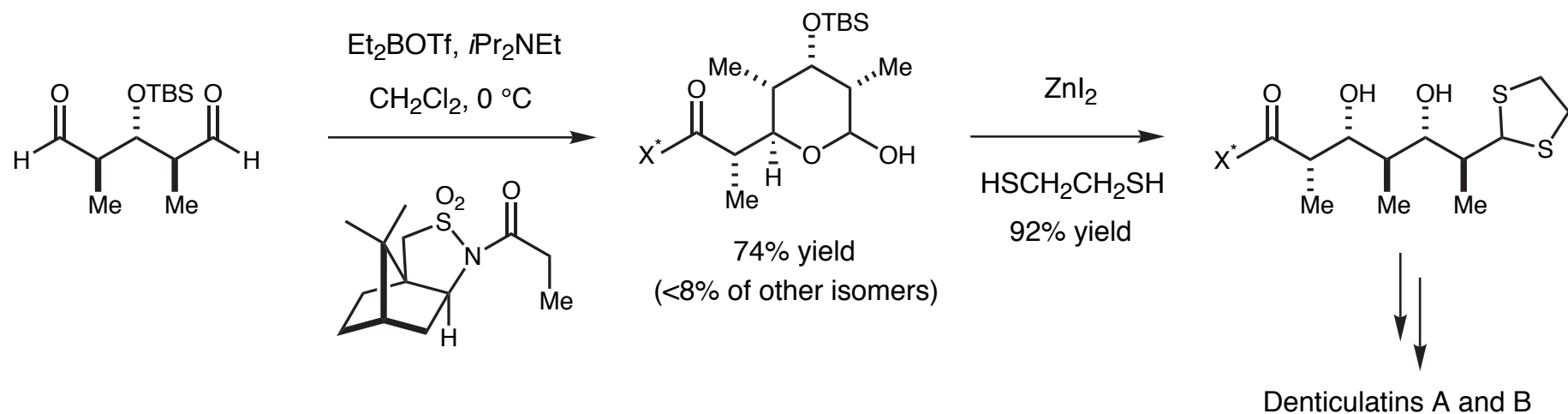
$R = Me$   $86\%$  e.e.,  $12\%$  yield

$>90\%$  d.e. observed in all cases.

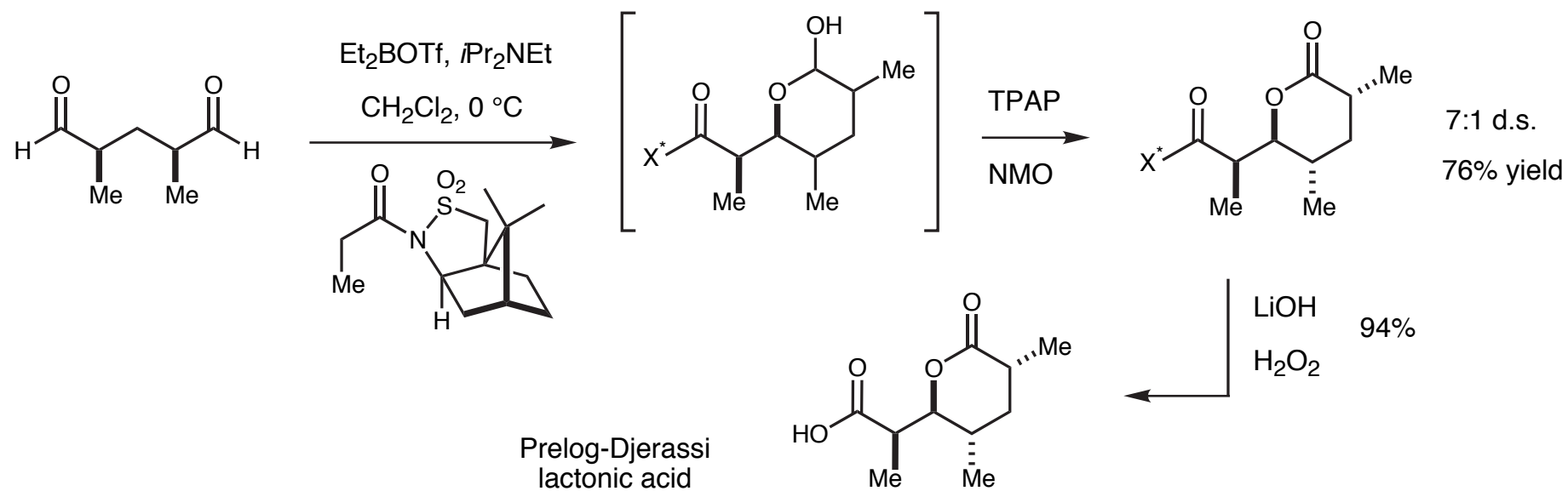


Takemoto, Baba, Noguchi, Iwata, *TL*, **1996**, 3345

## Aldol Reactions of Meso Dialdehydes

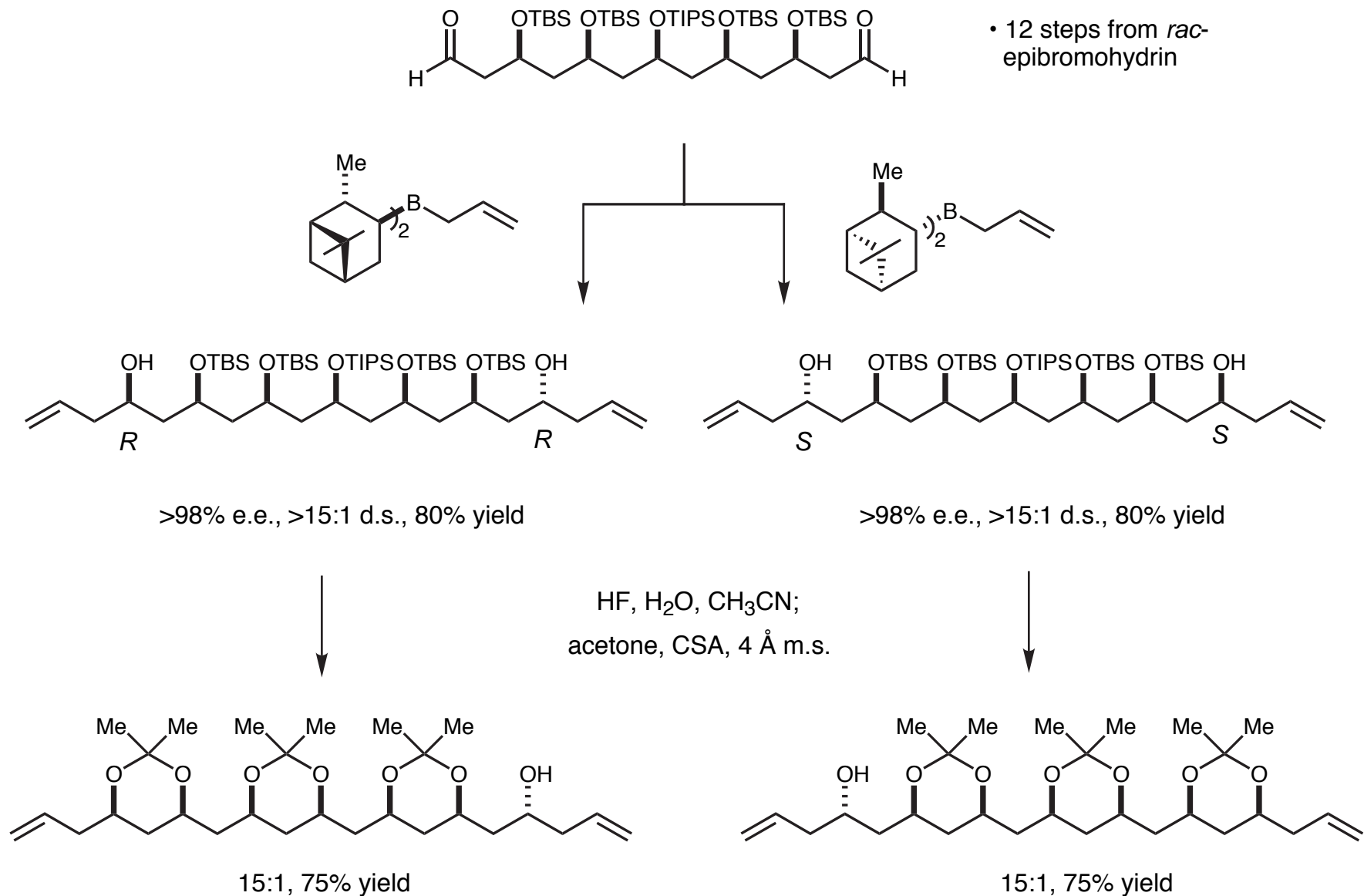


Oppolzer, Brabander, Walther, Bernardinelli, *TL*, **1995**, 4413



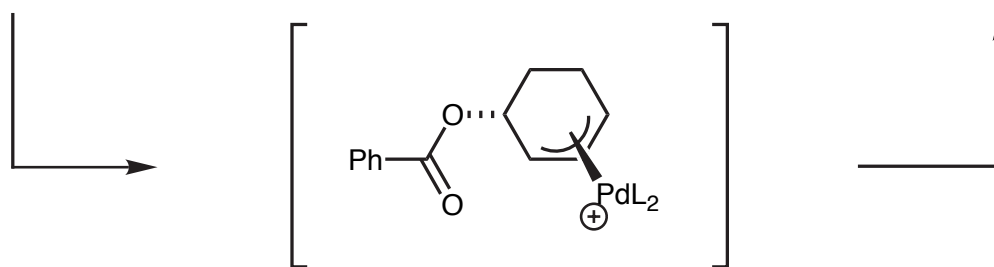
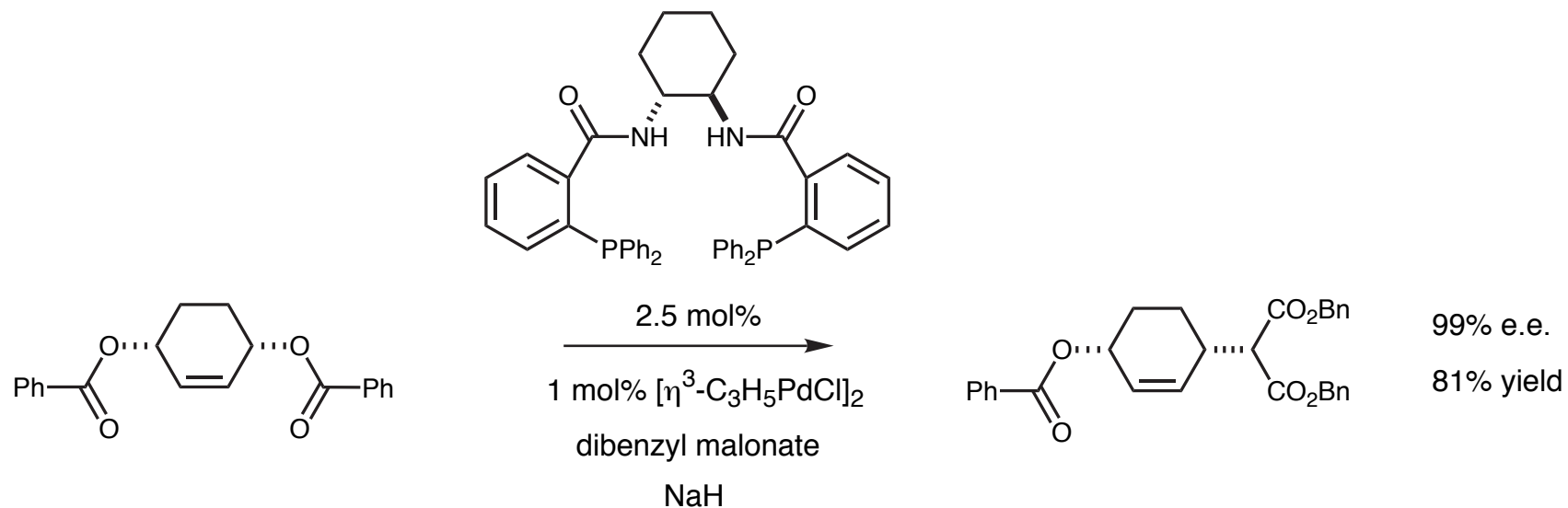
Oppolzer, Walther, Balado, Brabander, *TL*, **1997**, 809

# Two Step Symmetry-Breaking via Allylboration



Wang, Deschenes, *JACS*, **1992**,  
1090

## Palladium-Catalyzed Allylic Alkylation

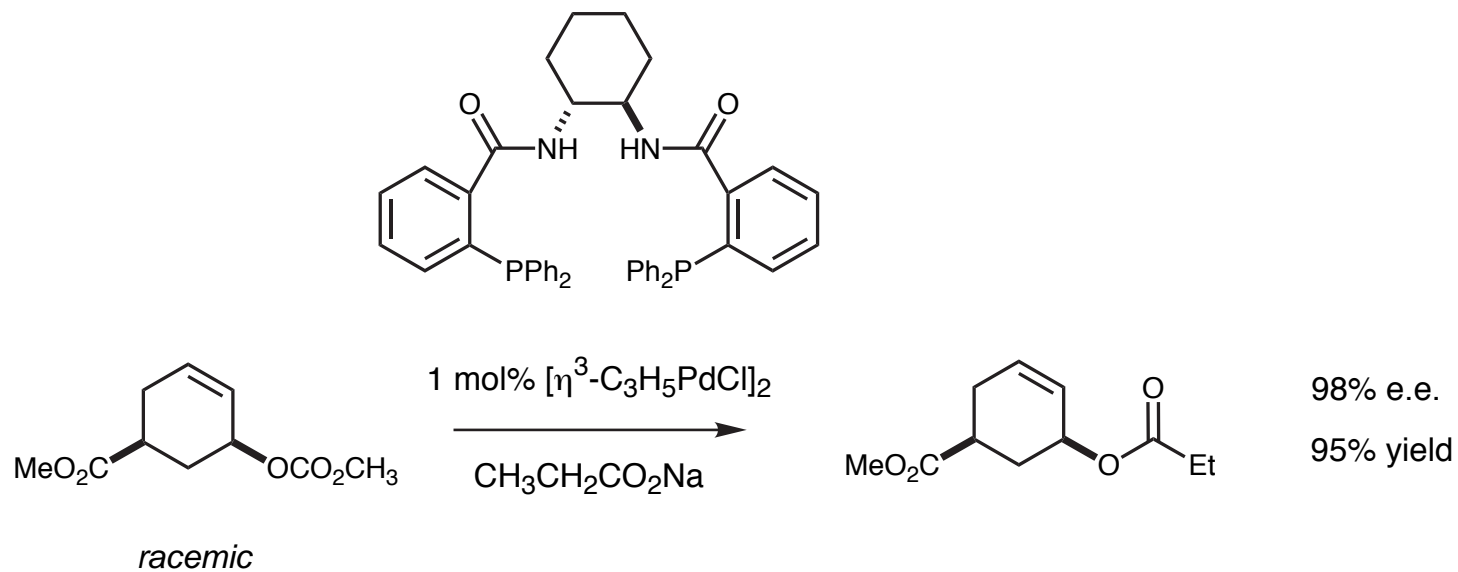
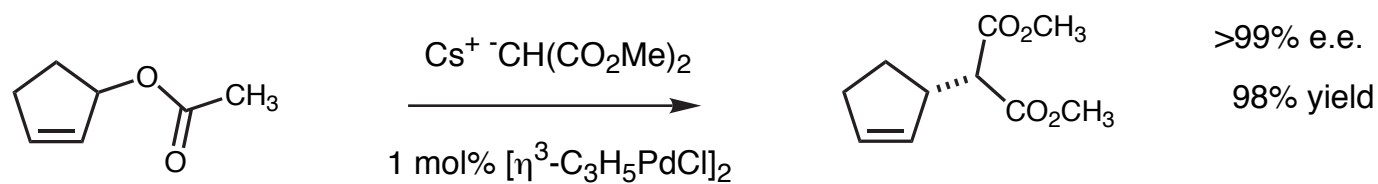
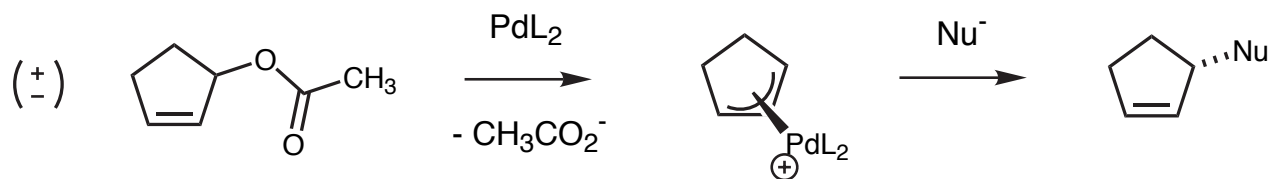


- A variety of nucleophiles can be substituted for malonate (e.g. amines, azides, sulfones).
- 5- and 7-membered rings are also good substrates for this transformation.

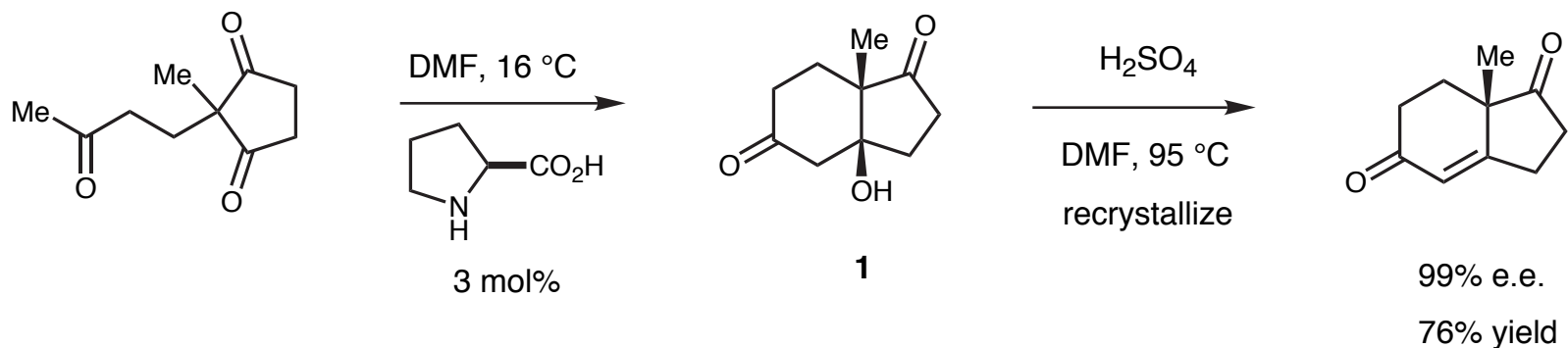
Trost, Tanimori, Dunn, *JACS*, **1997**, 2735  
Trost, *Acc. Chem. Res.*, **1996**, 355



## Deracemization via Meso Intermediates

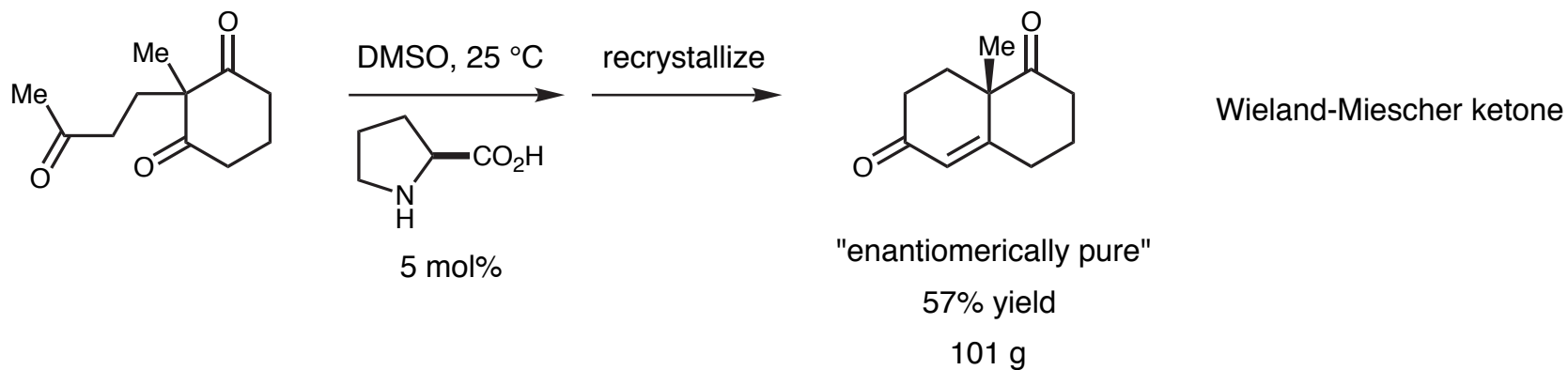


## Asymmetric Alkene Formation via Intramolecular Aldol Condensation



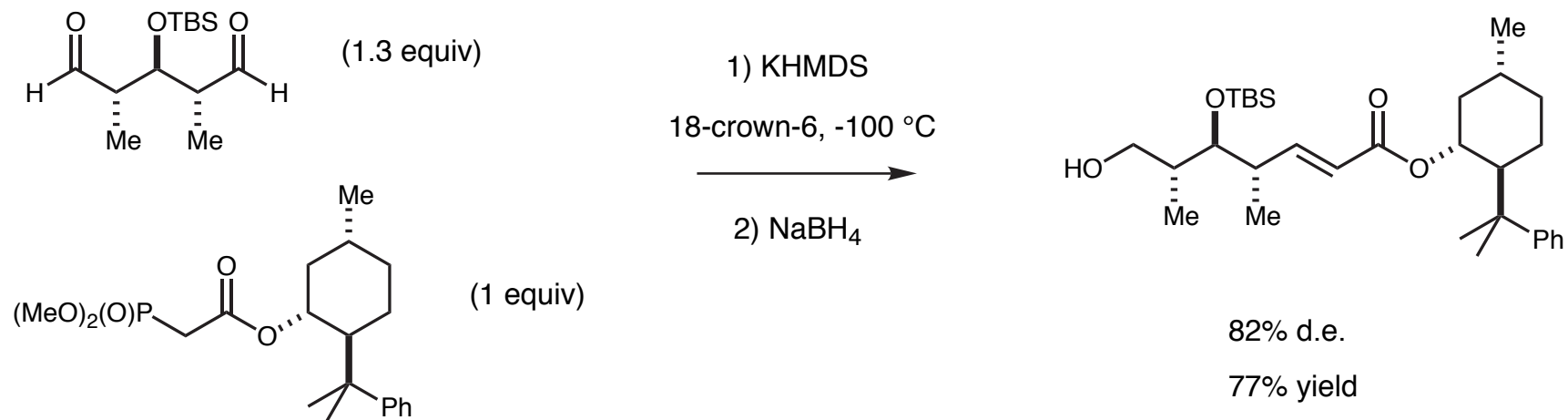
- The optical purity of the unpurified intermediate ketol (**1**) is estimated at 92%.

Hajos, Parrish, *Org. Synth.*, **VII**, 363  
Hajos, Parrish, *JOC*, **1974**, 1615



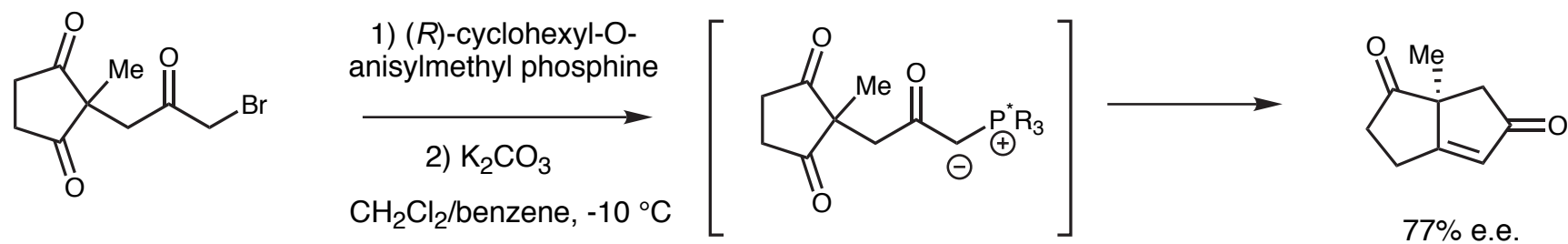
Buchsacher, Furst, Gutzwiller, *Org. Synth.*, **VII**, 368  
see also Hagiwara, Uda, *JOC*, **1988**, 2308  
Corey, Virgil, *JACS*, **1990**, 6429

## Asymmetric Alkene Formation



• At higher conversion, a 36% yield of 94% d.e. material can be obtained.

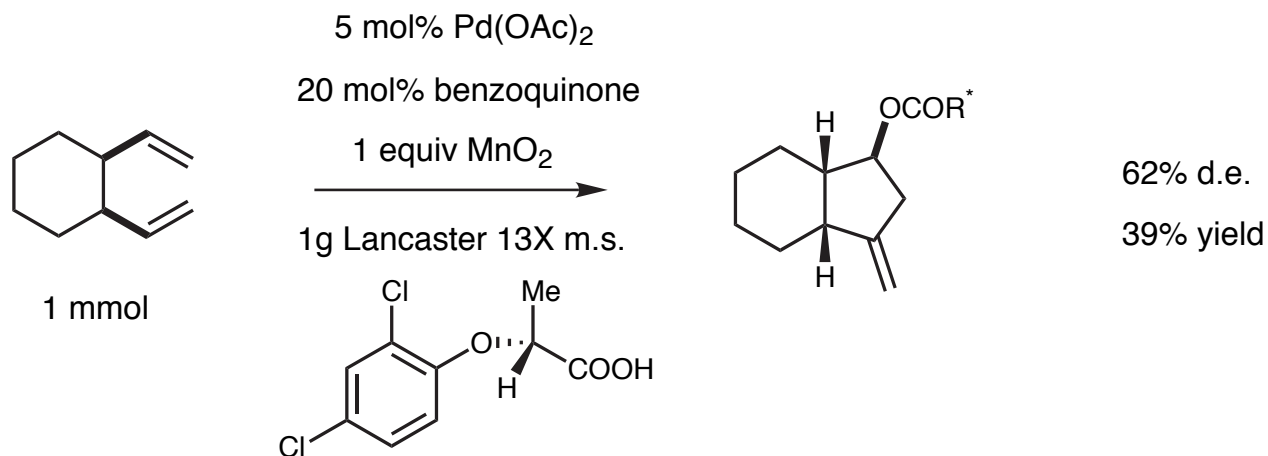
Kann, Rein, *JOC*, **1993**, 3802



"corrected for 88% optical purity of phosphine"

Trost, Curran, *TL*, **1981**, 4929

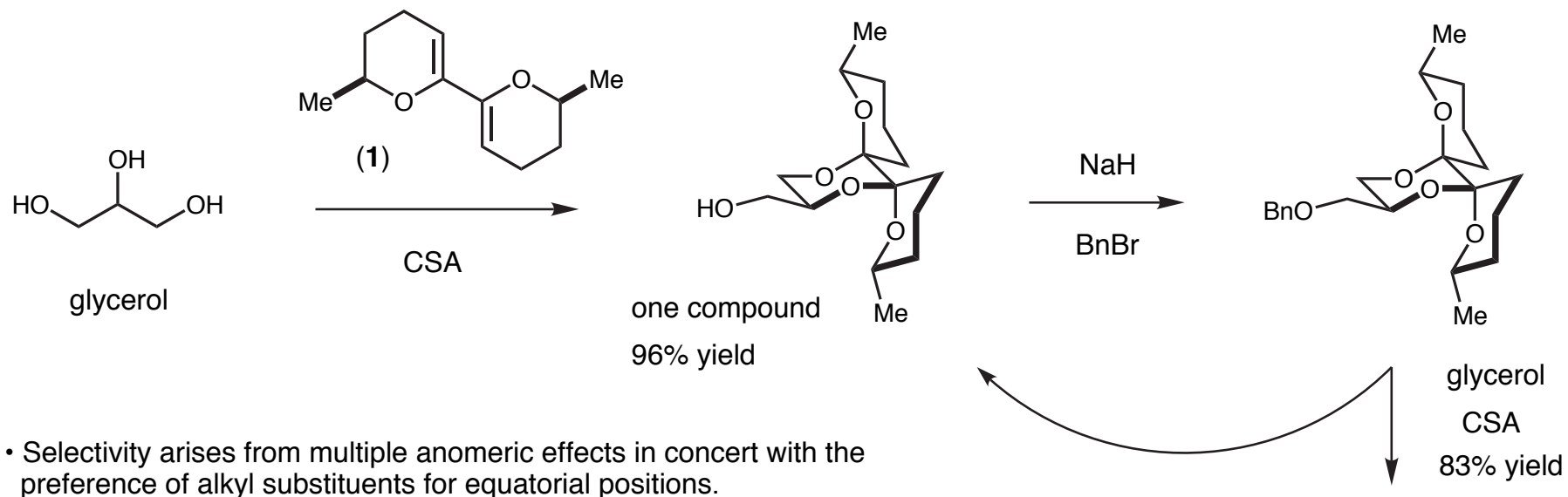
## Palladium-Mediated Cyclization



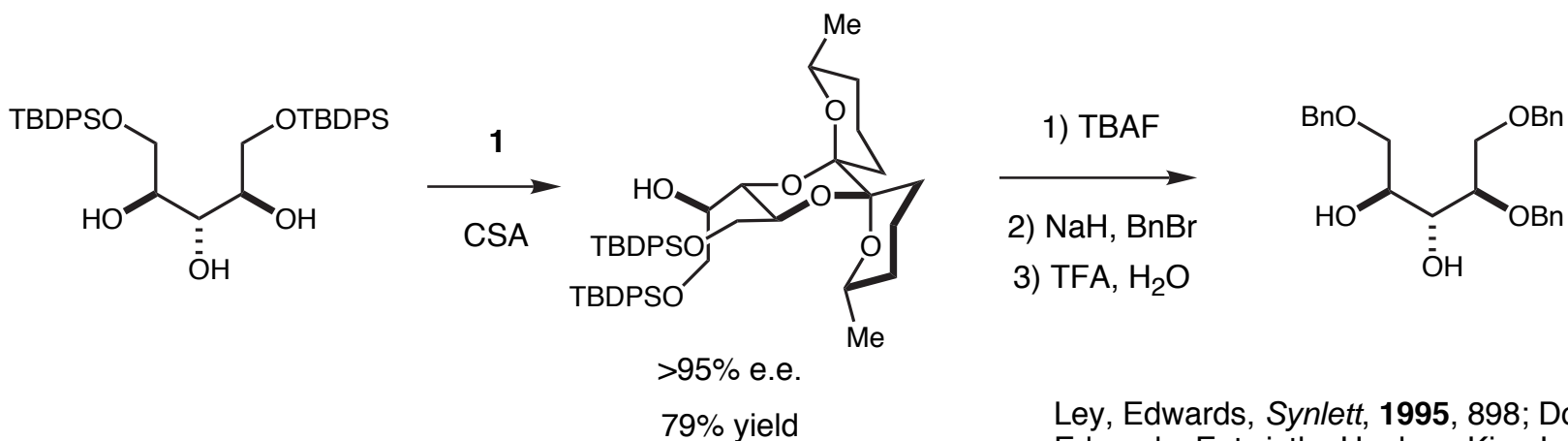
- Only *nondried* molecular sieves were found to increase the observed d.e.
- A wide variety of chiral acids and molecular sieves were screened.
- Evidence suggests that a chiral catalyst is formed and that molecular sieves increase the rate of its formation.
- Sieves with higher sodium content provide better selectivity.

Tottie, Baeckstrom, Moberg, Tegenfeldt, Heumann, *JOC*, **1992**, 6579  
see also Nordstrom, Moberg, Heumann, *J. Organomet. Chem.*, **1996**, 233

# Polyol Desymmetrization via Dispiroketal Formation

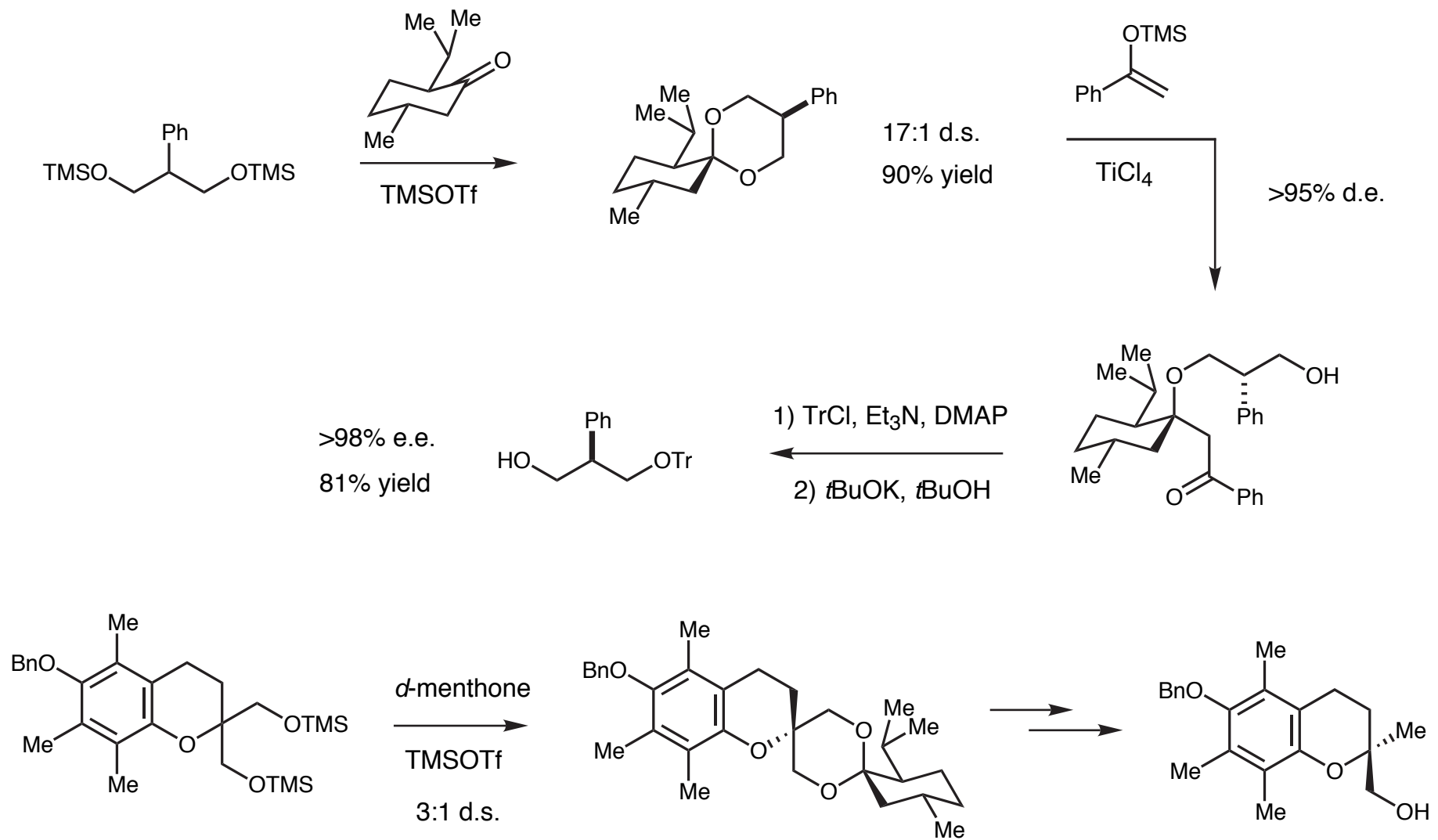


Boons, Entwistle, Ley, Woods, *TL*, **1993**, 5649



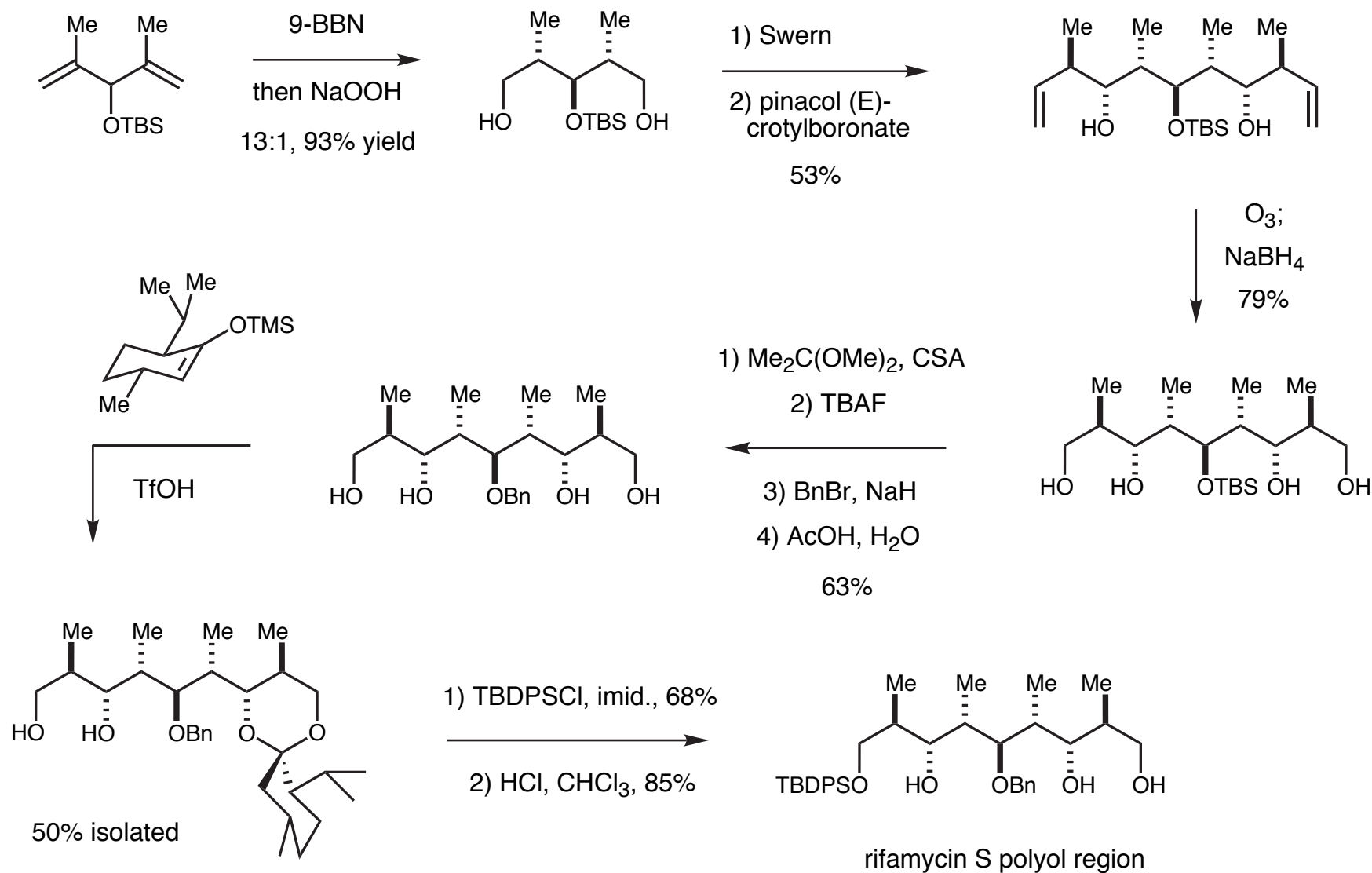
Ley, Edwards, *Synlett*, **1995**, 898; Downham, Edwards, Entwistle, Hughes, Kim, Ley, *Tet. Asymm.*, **1995**, 2403

# Polyol Desymmetrization via Menthone Ketalization



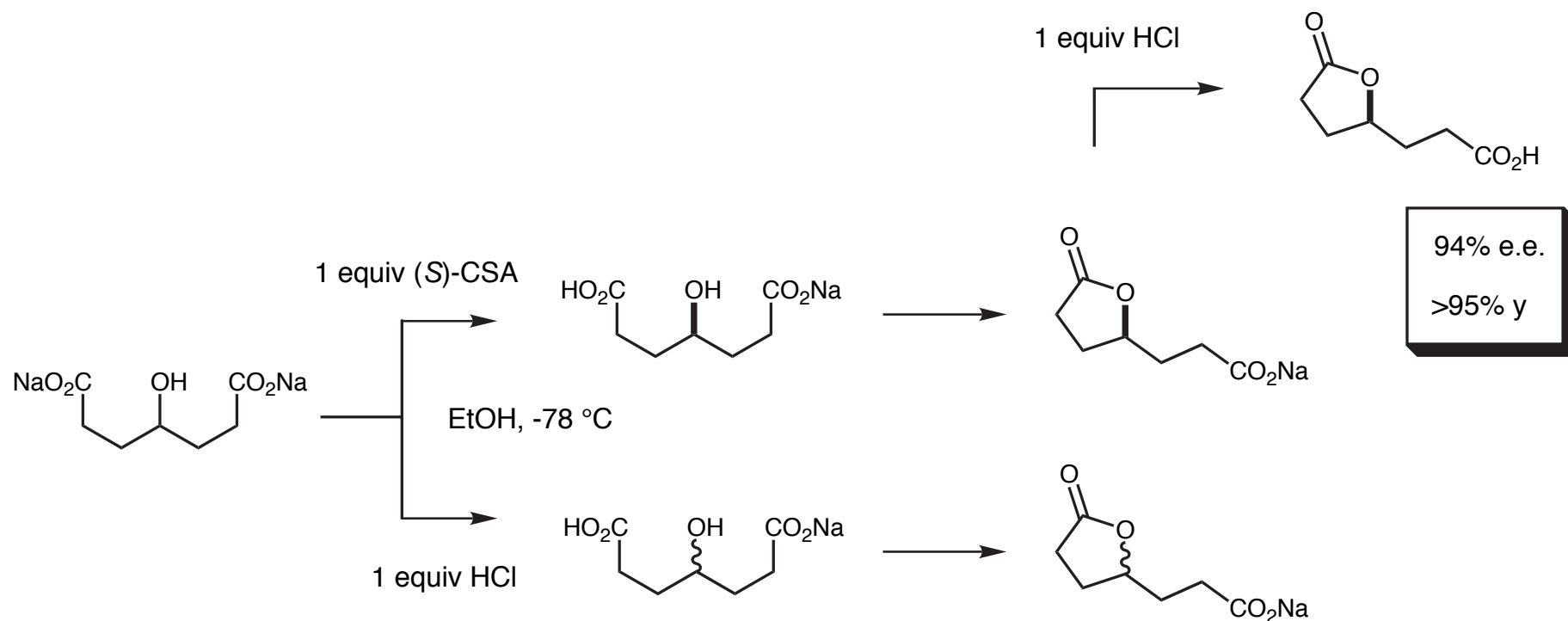
Harada, Oku, *Synlett*, **1994**, 95

# Polyol Desymmetrization via Menthone Ketalization: Applications

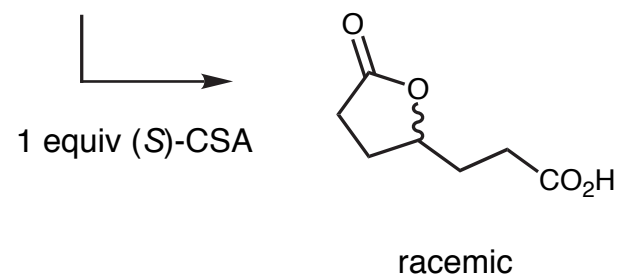
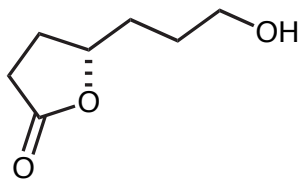


Harada, Oku, *Synlett*, **1994**, 95

## Enantioselective Lactonization



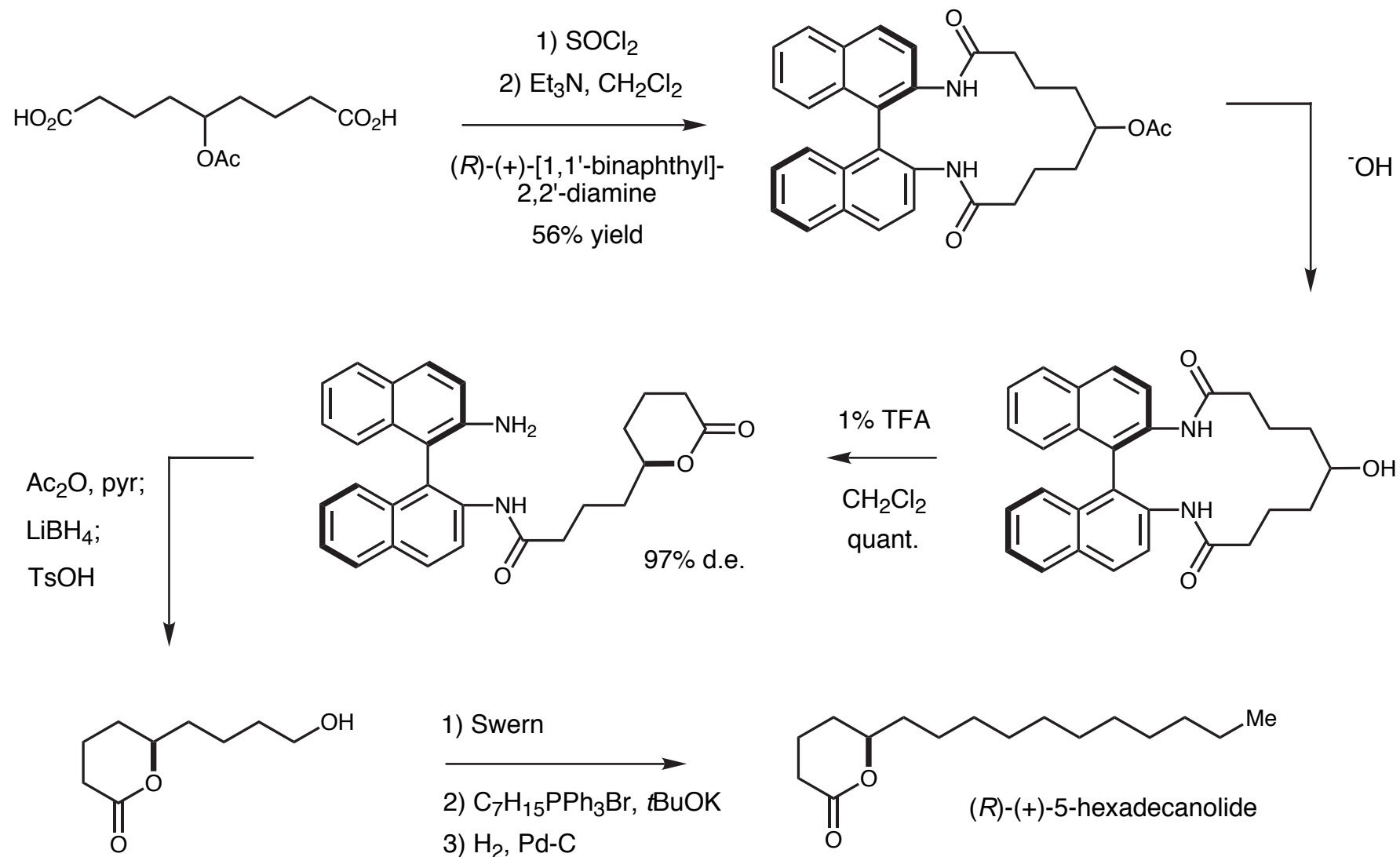
- A concentration of .002-.005 M is optimal (78 mg in 100 ml).
- CSA was used as its monohydrate.
- One recrystallization of the product gives enantiopure material.
- Reduction of the product with  $\text{BH}_3$  or LAH gives either antipode of:



Fuji, Node, Terada, Murata, Nagasawa, *JACS*, **1985**, 6404

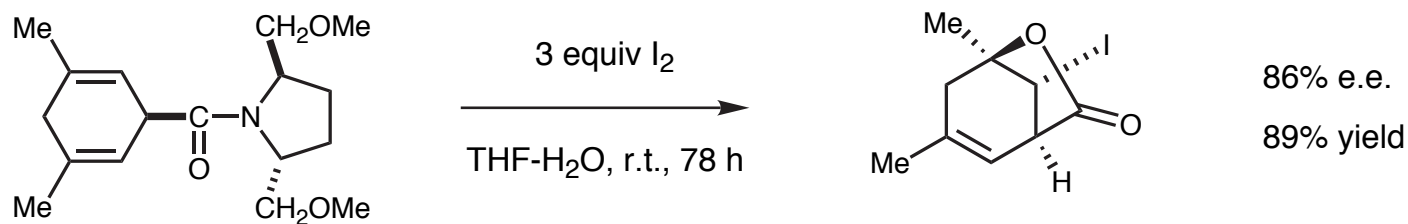
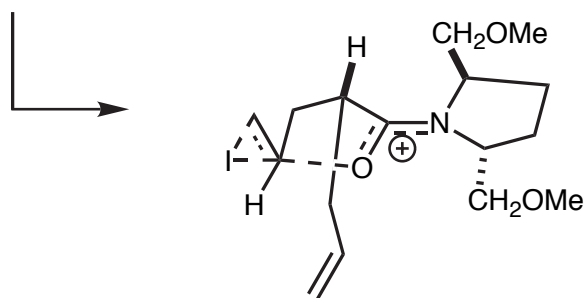
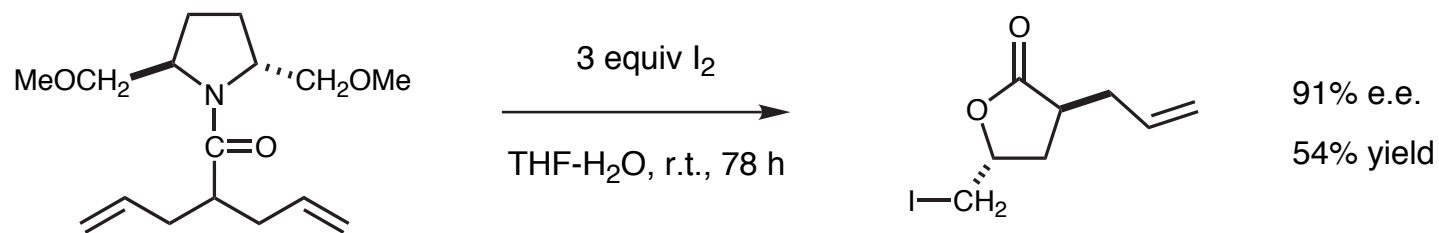


# Enantioselective Lactonization via Binaphthyl Amides



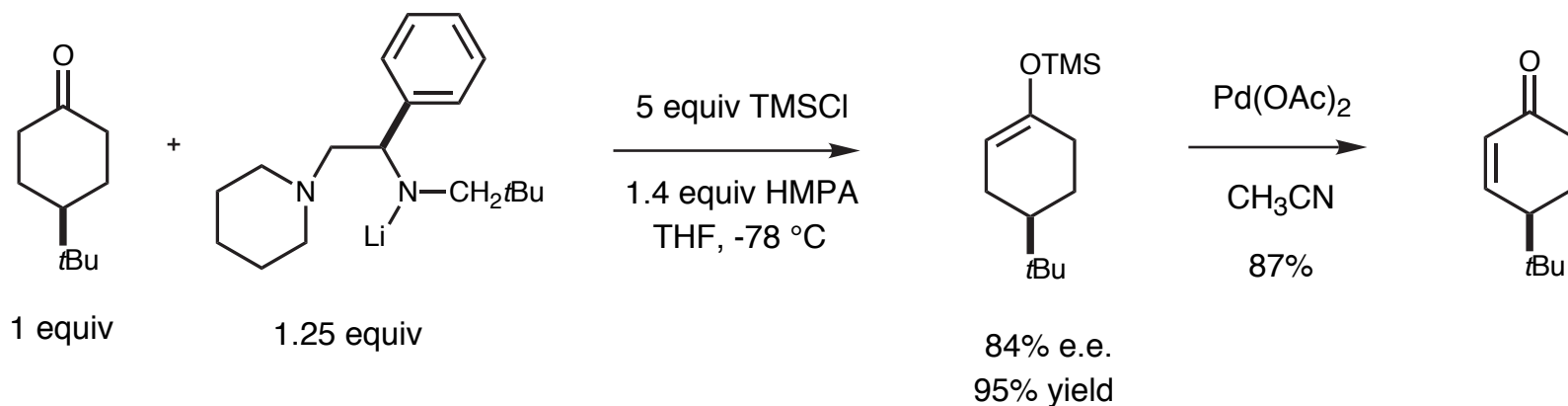
Sakamoto, Yamamoto, Oda, *JACS*, **1987**, 7188

## Enantioselective Iodolactonization



Fuji, Node, Naniwa, Kawabata, *TL*, **1990**, 3175

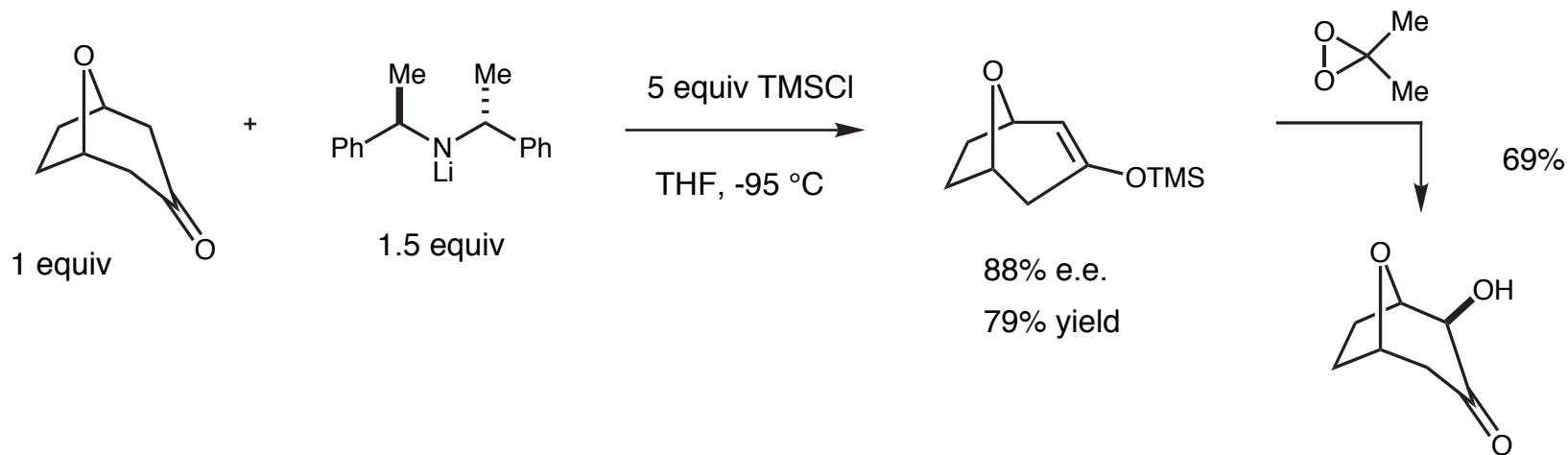
## Enantioselective Ketone Deprotonation



- $^{15}\text{N}$  and  $^6\text{Li}$  NMR suggest that an 8-membered cyclic transition state incorporating LiCl is operative.

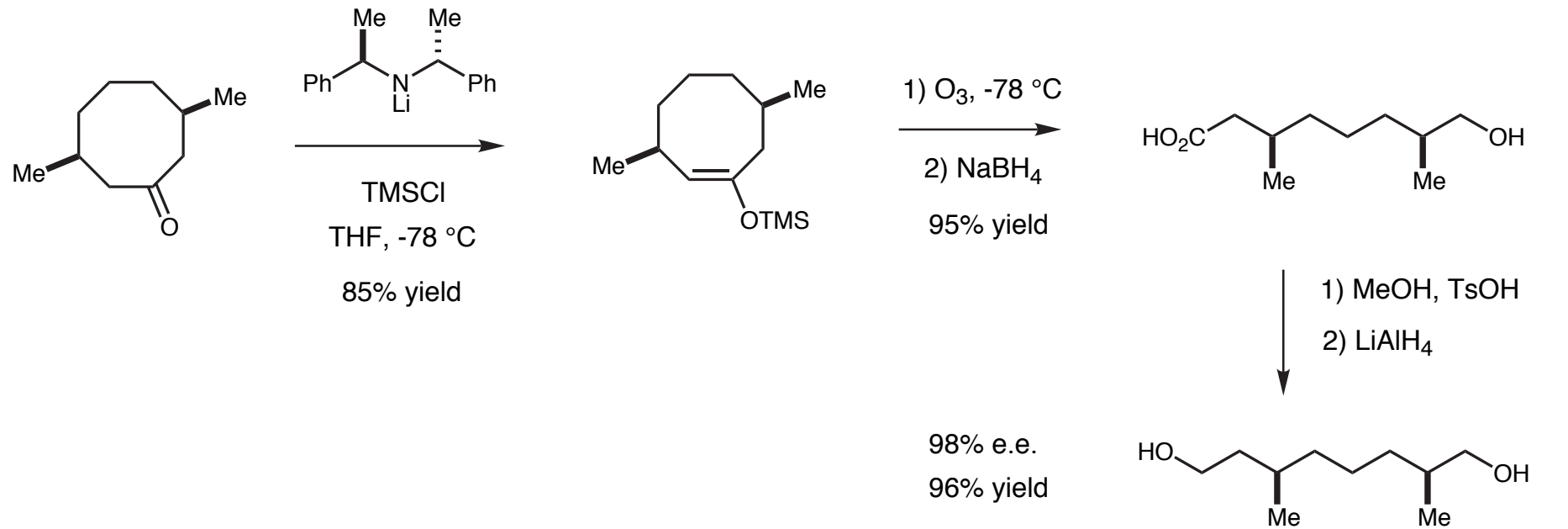
Toriyama, Sugasawa, Shindo, Tokutake, Koga, *TL*, **1997**, 567

Shirai, Tanaka, Koga, *JACS*, **1986**, 543

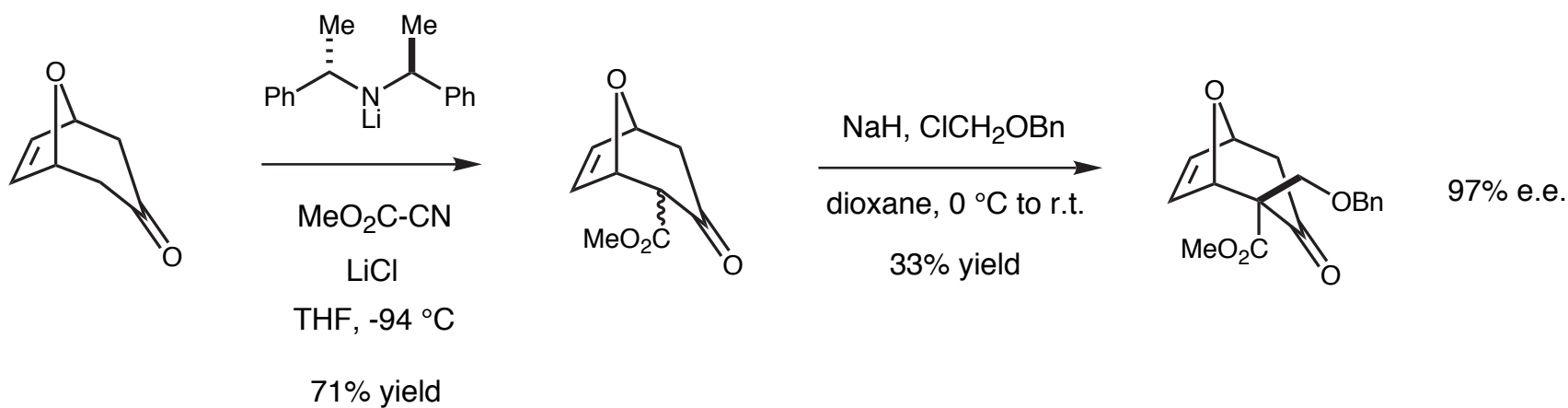


Bunn, Cox, Simpkins, *Tet.*, **1993**, 207

## Enantioselective Ketone Deprotonation: Applications

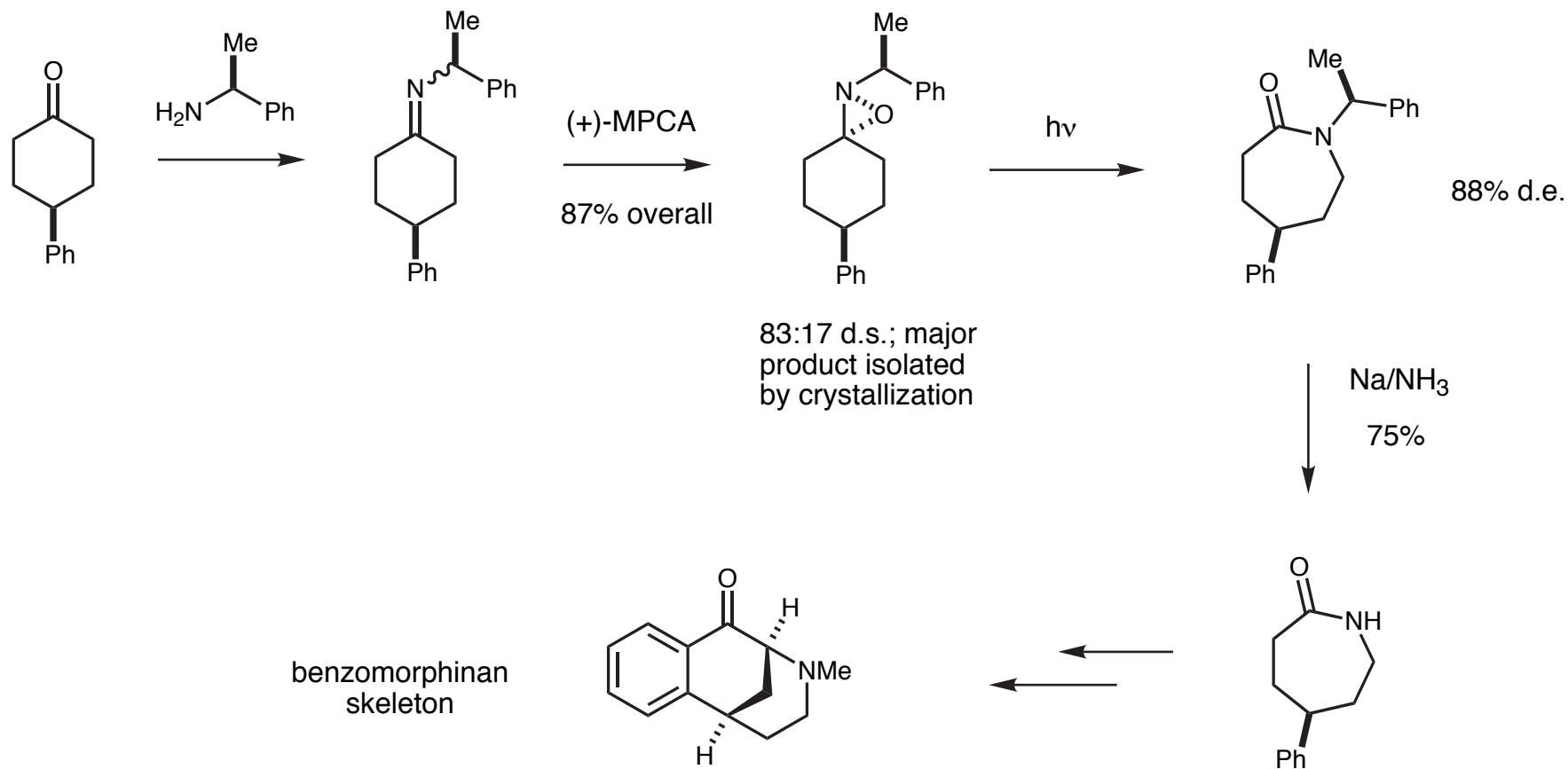


Berkowitz, Wu, *JOC*, **1997**, 1536



Nowakowski, Hoffmann, *TL*, **1997**, 1001

## Asymmetric Nitrogen Insertion



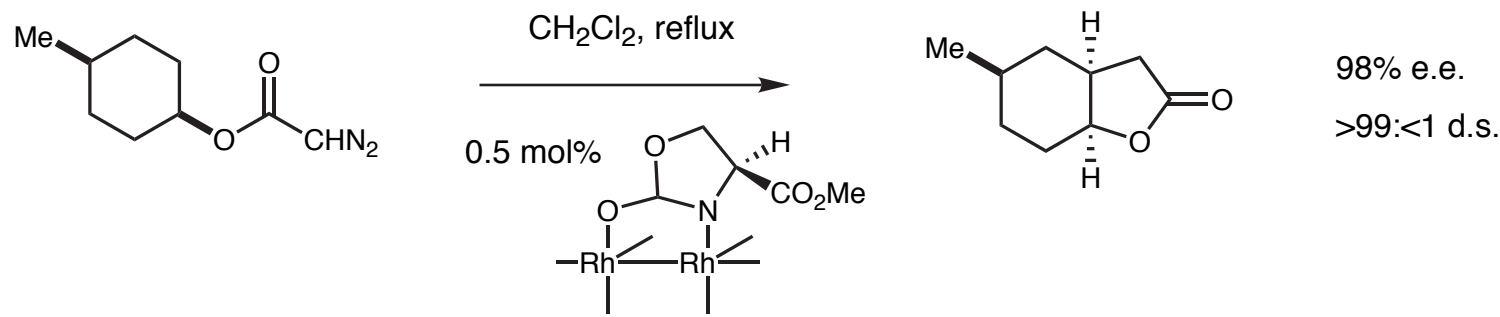
• (+)-MPCA = monoperoxycamphoric acid

• Photoreactions were more conveniently run on mixtures of oxaziridine stereoisomers but gave correspondingly lower d.e.

Aube, Wang, Hammond, Tanol, Takusagawa, Velde, *JACS*, **1990**, 4879  
Aube, Burgett, Wang, *TL*, **1988**, 151

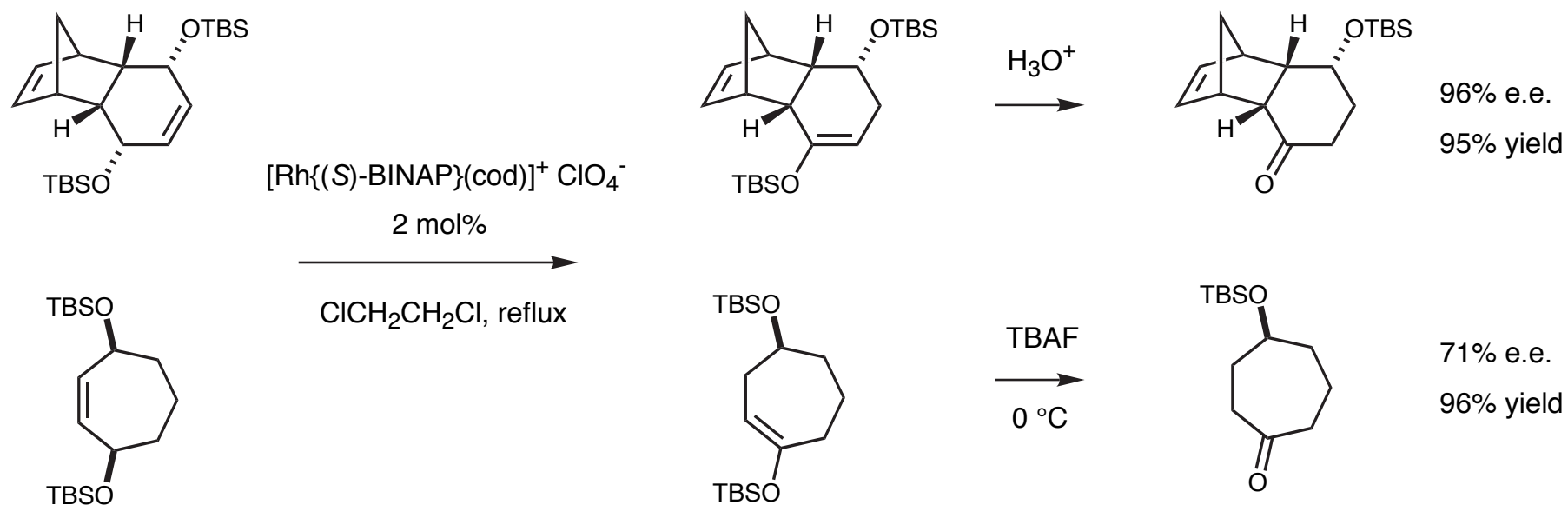
## Rhodium Catalyzed Processes

- Enantioselective C-H Insertion



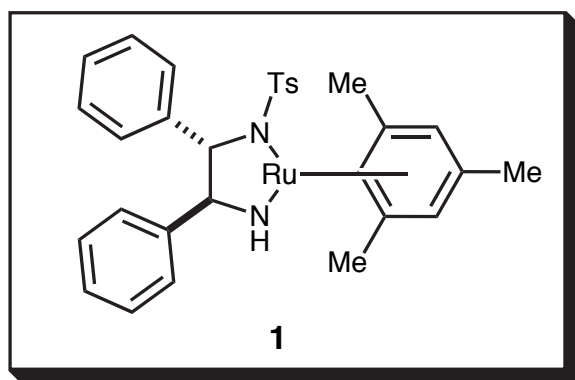
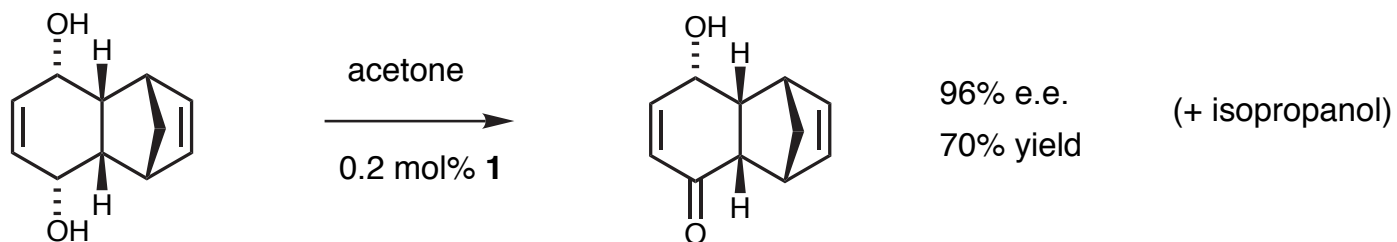
Doyle, Dyatkin, Roos, Canas, Pierson, Basten, *JACS*, **1994**, 4507

- Enantioselective isomerization



Hiroya, Ogasawara, *Chem. Comm.*, **1995**, 2205

## Ruthenium Catalyzed Hydrogen Transfer



- The selectivity observed is especially notable in light of the reversibility of the oxidation/reduction process.

