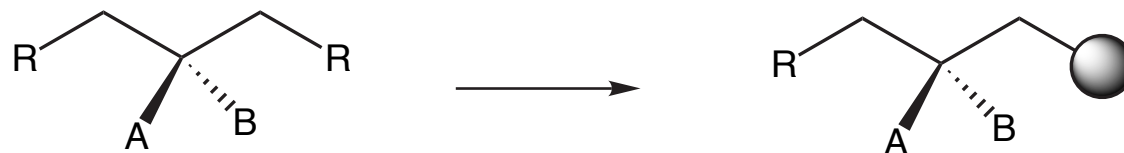


Enantioselective Desymmetrization



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

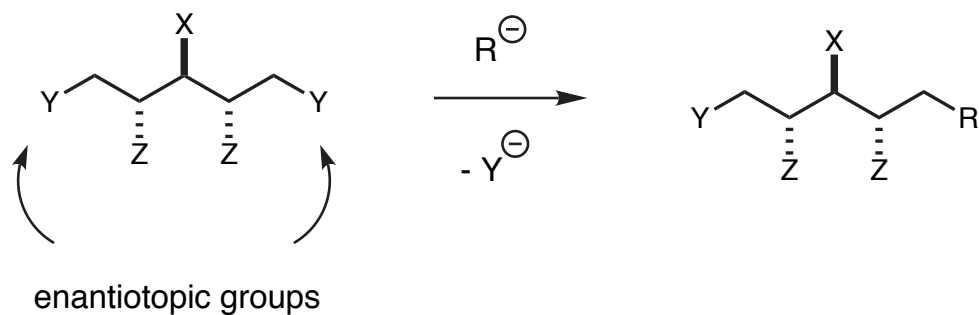
- I. *Meso* anhydrides
- II. Divinyl carbinols and *meso* dienes
- III. Achiral epoxides
- IV. Carbon-carbon bond formation
- V. Alcohol protection strategies
- VI. *Meso* ketones

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

Wes Trotter
April 4, 1997

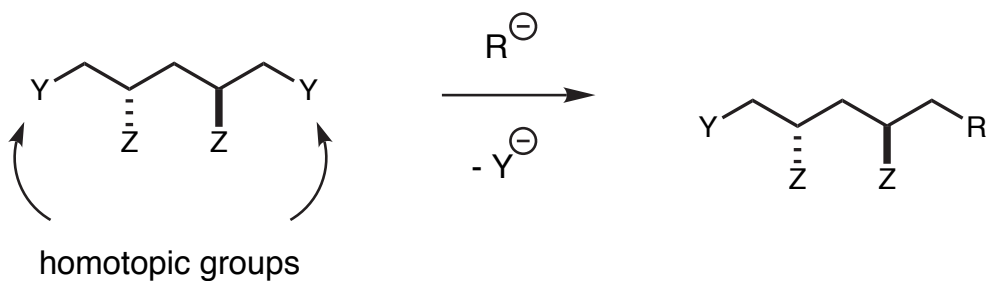
Desymmetrization of Symmetric Compounds

- Achiral and *meso* compounds:



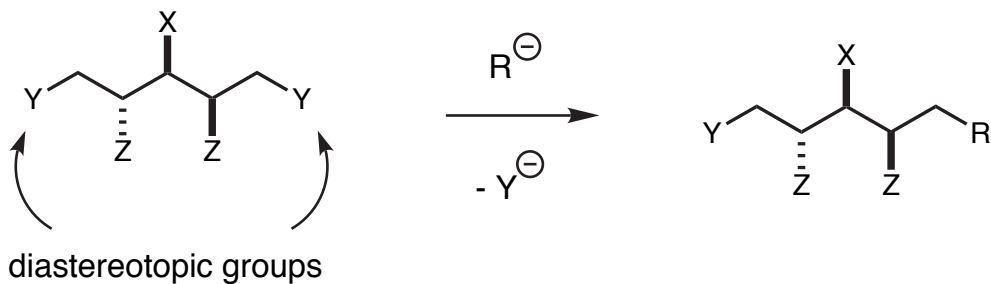
enantiotopic group selection

- C_2 symmetric compounds (chiral):



monofunctionalization

- pseudo C_2 symmetric compounds (chiral):

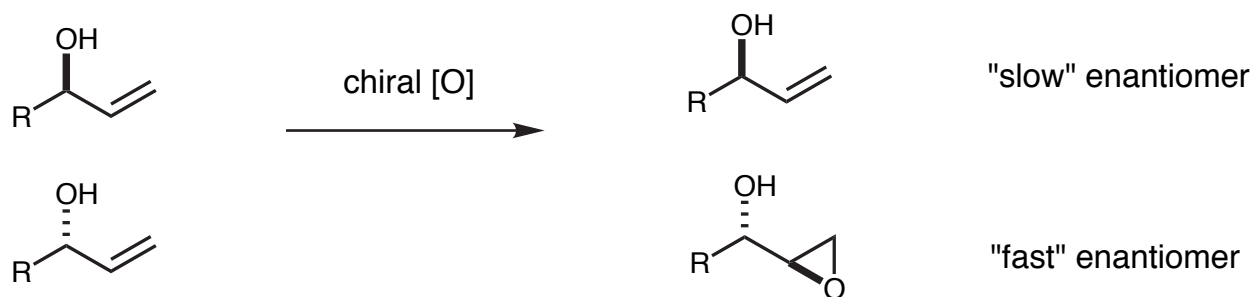


diastereotopic group selection

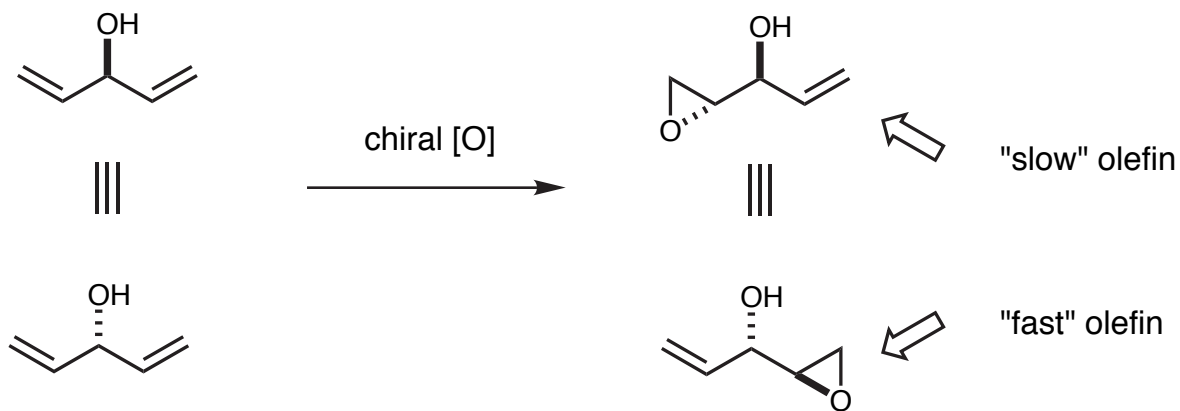
Magnuson, *Tet.*, **1995**, 2167

Enantioselective Desymmetrization and Kinetic Resolution

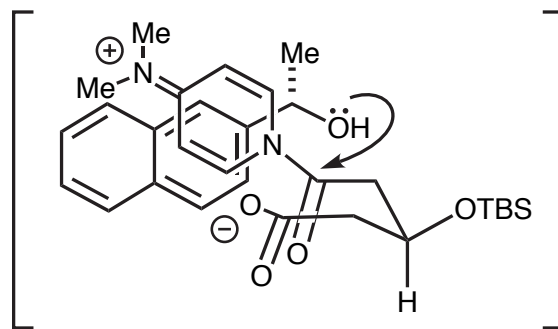
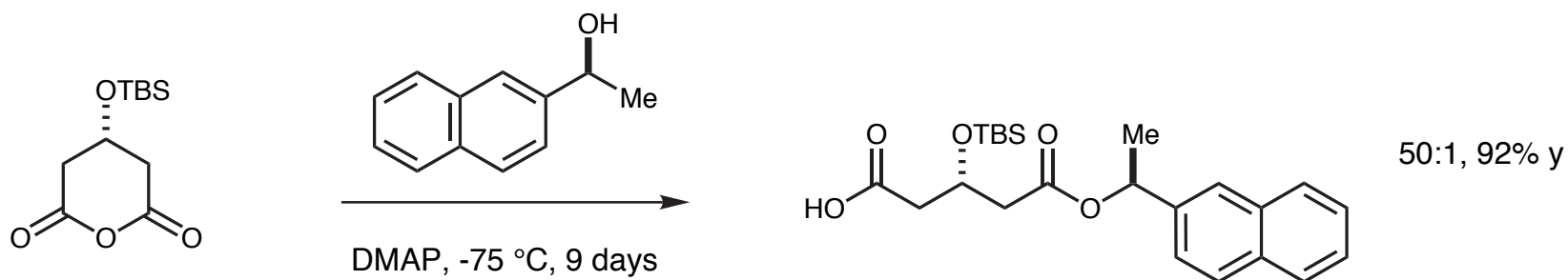
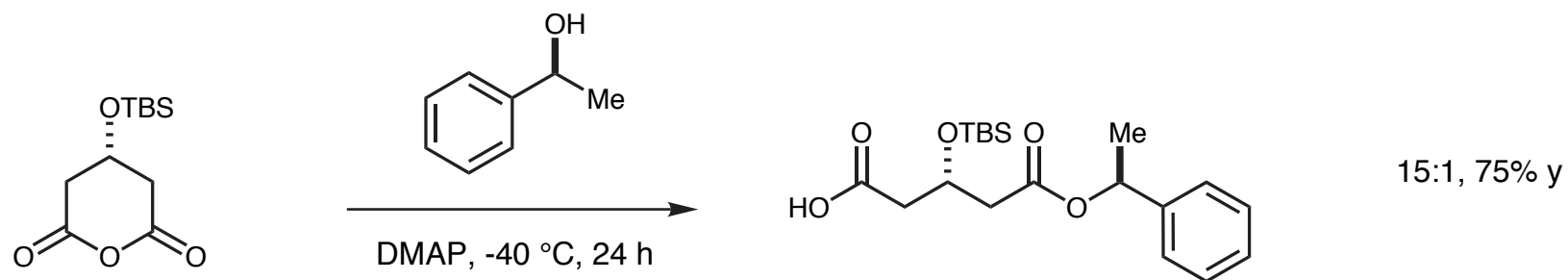
- Kinetic resolution relies on differing rates of reactions between a chiral reagent and each of the two enantiomers composing a racemic substance. A sufficient rate difference allows consumption of one enantiomer and recovery of the other.



- 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.

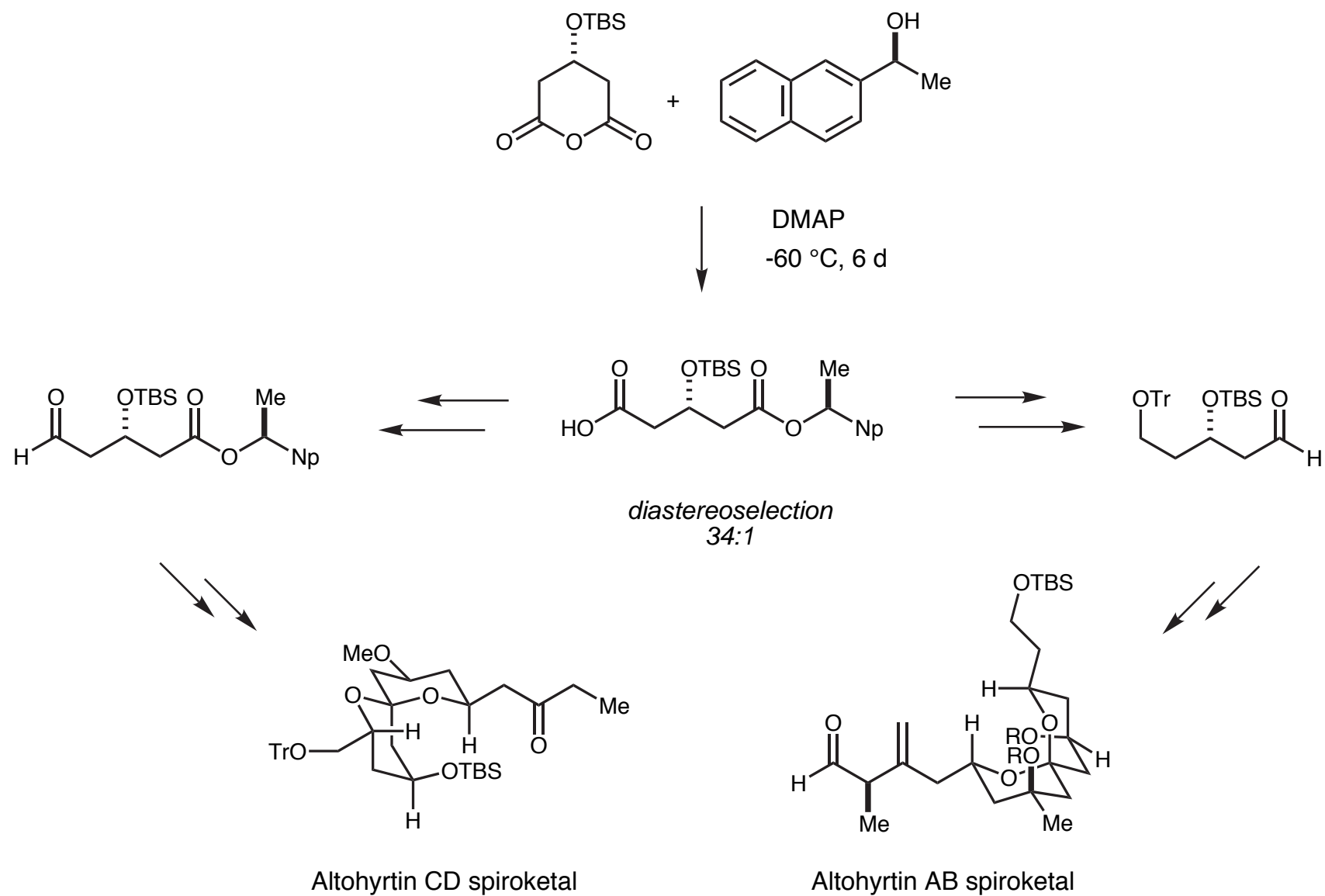


Meso Anhydrides: Arylethanol Transesterification



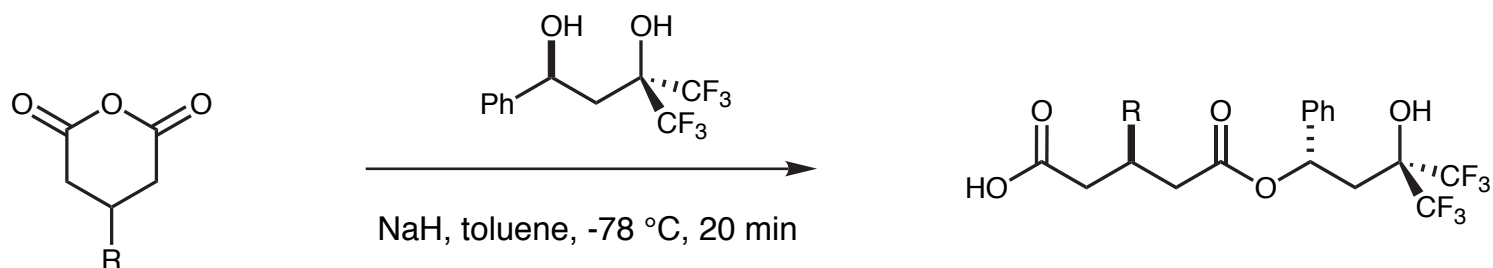
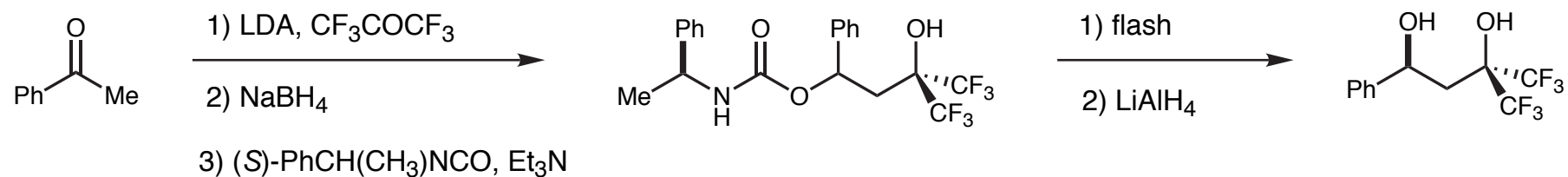
Thiesen, Heathcock, *JOC*, **1988**, 2374
Heathcock et al., *J. Med. Chem.*, **1987**,
1858
Coleman, research report, **1996**

Applications: Altohyrtin Fragments

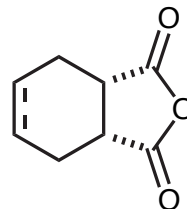


research reports: Coleman, **1996**; Dias, **1995**

Alcoholysis of Substituted Glutaric Anhydrides



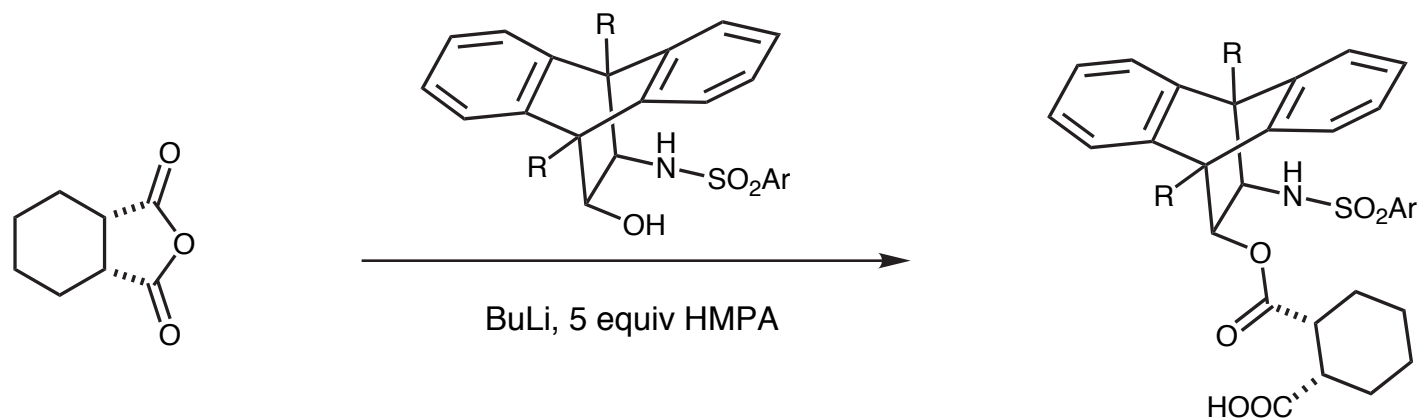
R	d.e. (%)	yield (%)
TBSO	92	90
<i>i</i> Pr	90	94
CF ₃	90	95
PhCH ₂	76	96
Ph	66	95
CH ₃	66	90



Bicyclic anhydrides are also effectively desymmetrized.

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

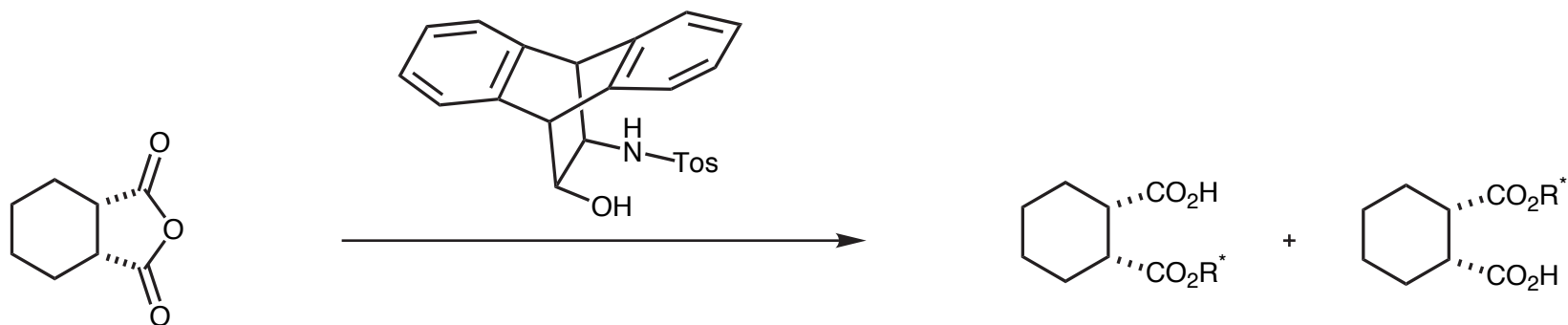
Meso Anhydrides: Aminoalcohol Transesterification



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

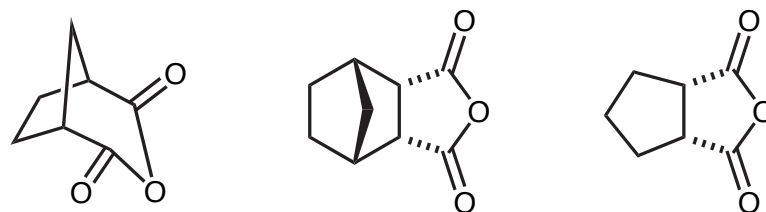


Conditions:

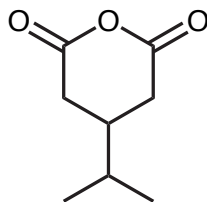
1 equiv BuLi, 5 equiv HMPA, THF, -78 °C, 2 h 500 : 1

1 equiv Et₂Zn, 1 equiv THF, CH₂Cl₂, reflux, 6 h 1 : 26

Effective for a variety of bi- and tricyclic substrates:

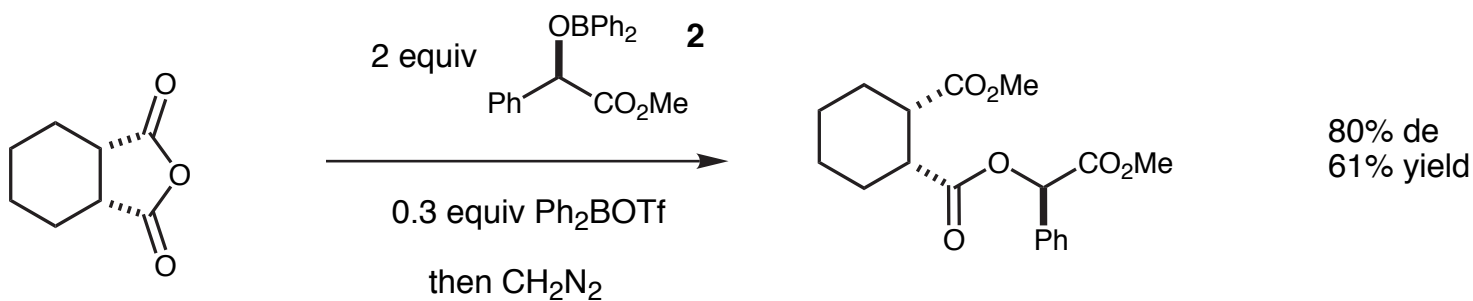
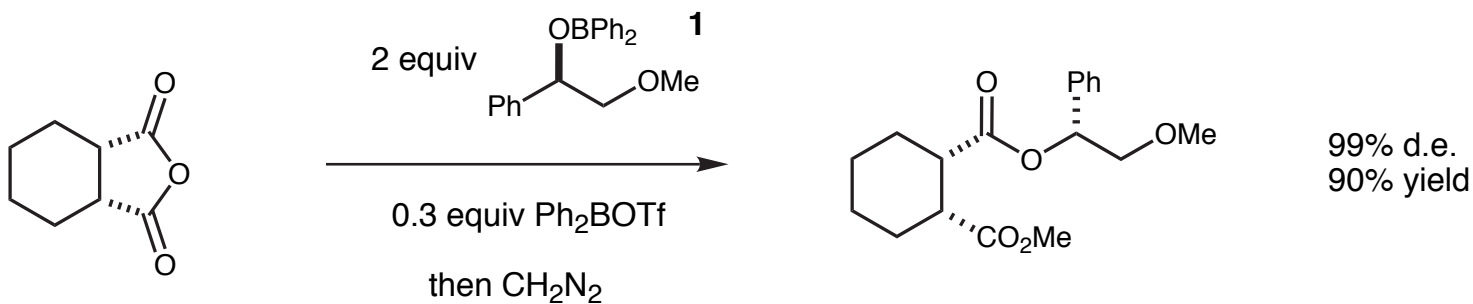


Low selectivity observed for monocyclic substrates:



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

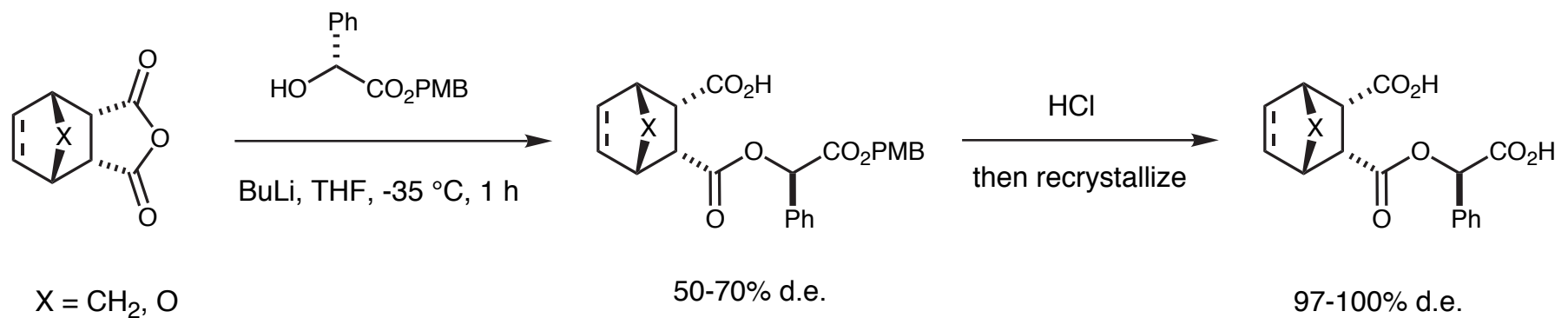
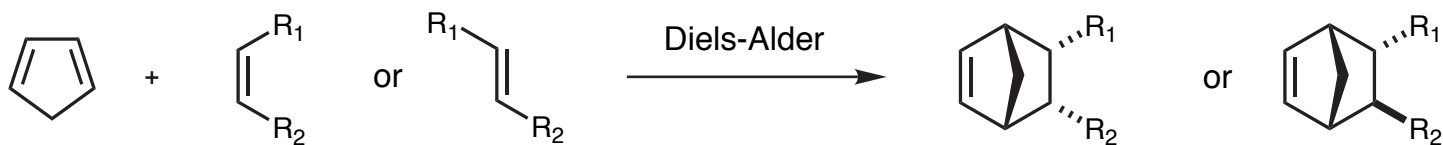
Diphenylboron Triflate-Catalyzed Alcoholysis



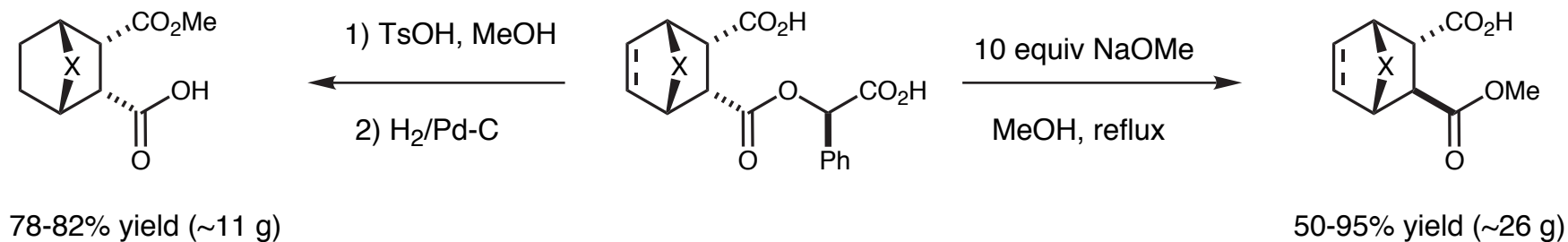
- **1** is prepared from (*R*)-methyl mandelate (**2**) in 4 steps.

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

Functional Equivalents of Asymmetric Diels-Alder Adducts

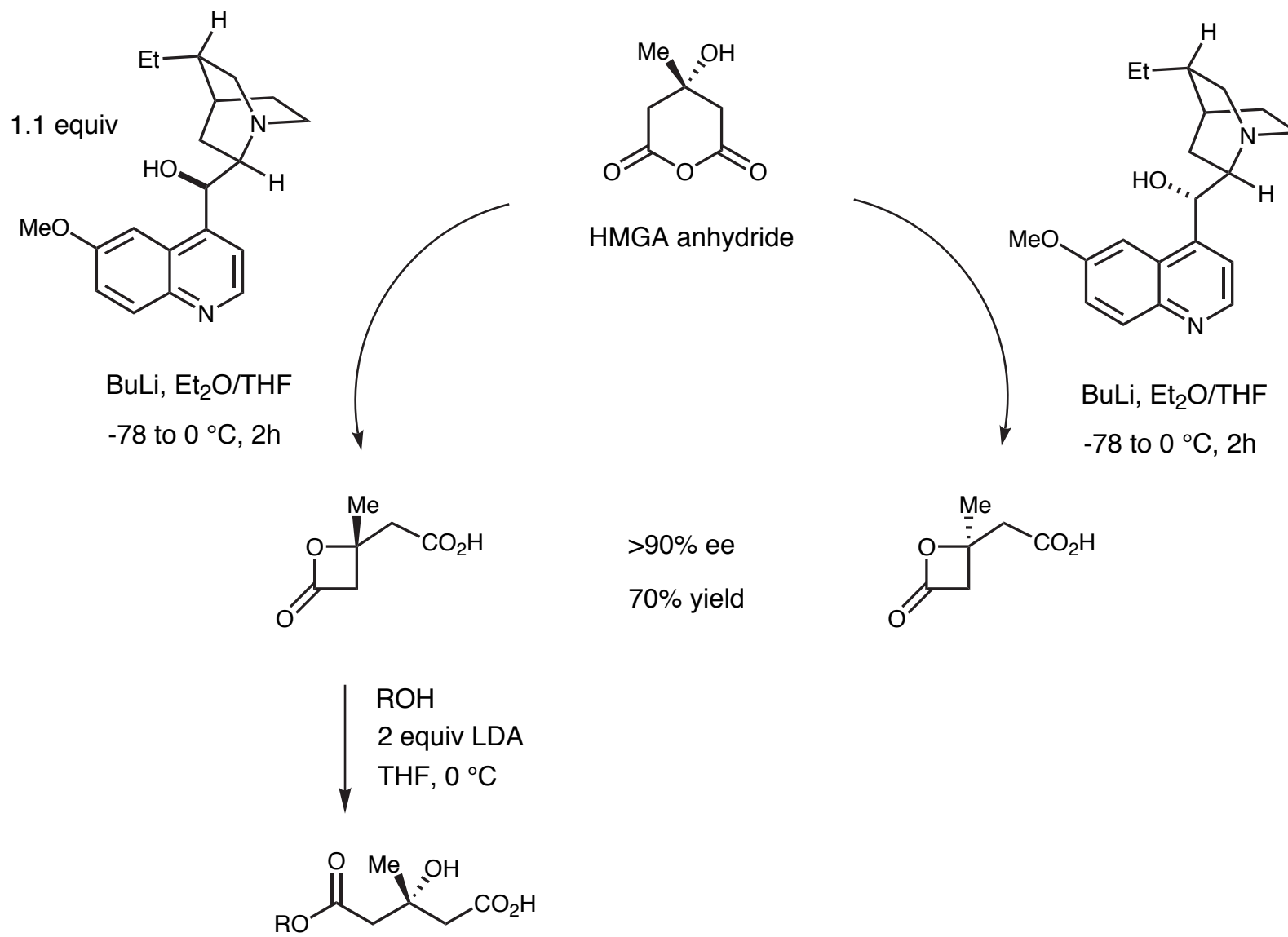


36-66% isolated yield
from anhydride



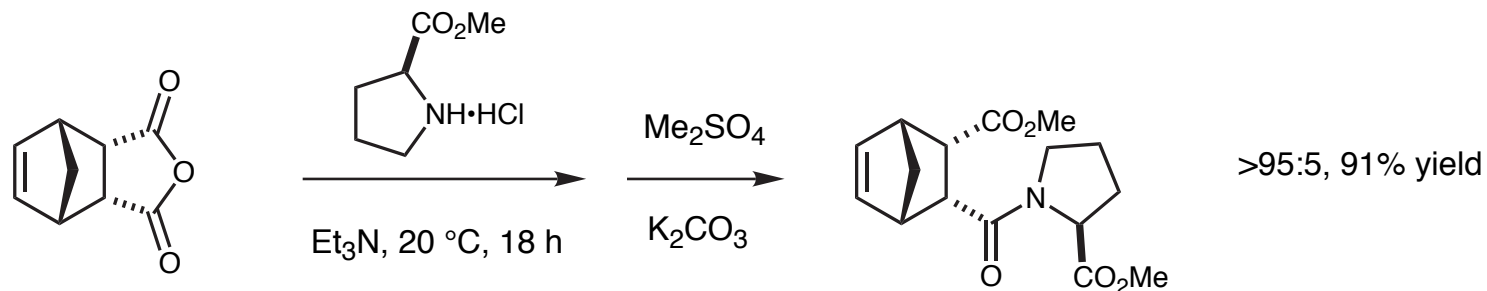
Ohtani, Matsuura, Watanabe, Narisada, *JOC*, **1991**, 4120

β -Lactones from Meso Anhydrides

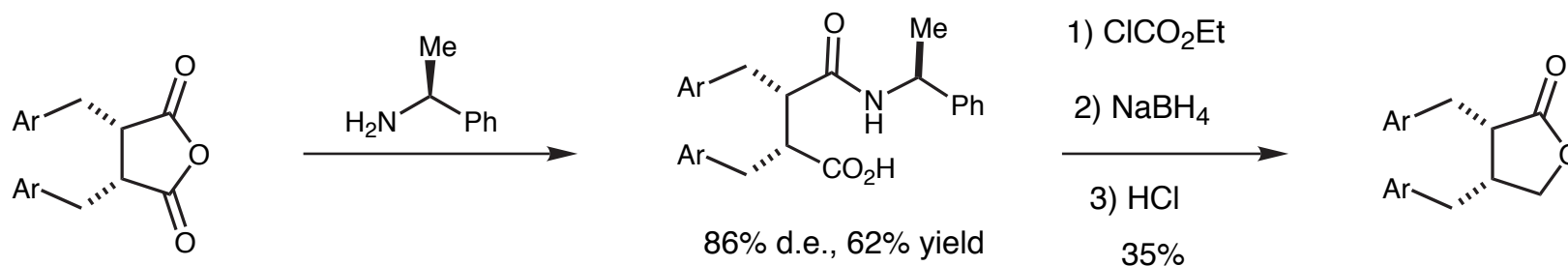


Hashimoto, Kitaguchi, Mizuno, Kobayashi, Shirahama, *TL*, **1996**, 2275

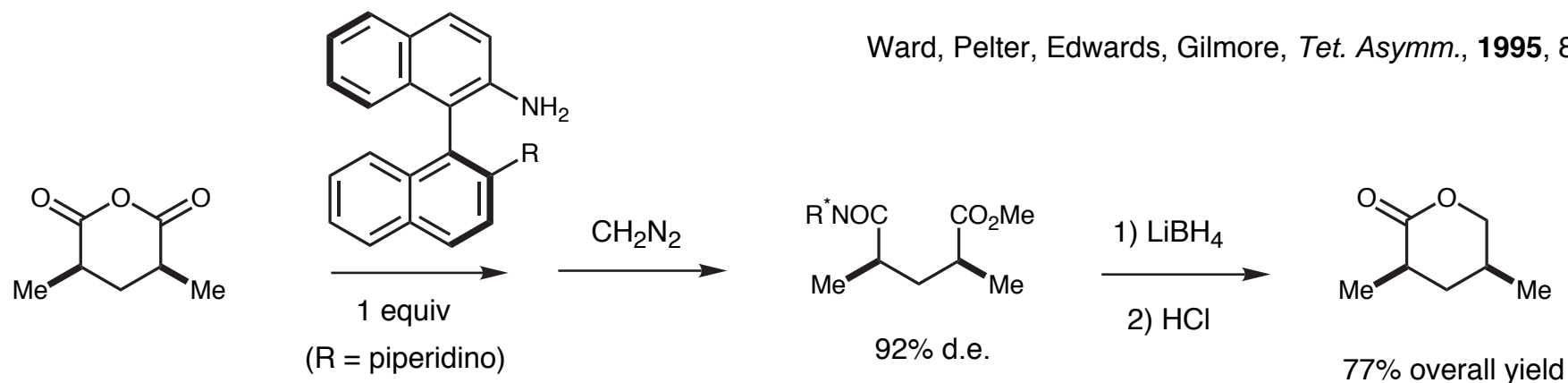
Amine Nucleophiles



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

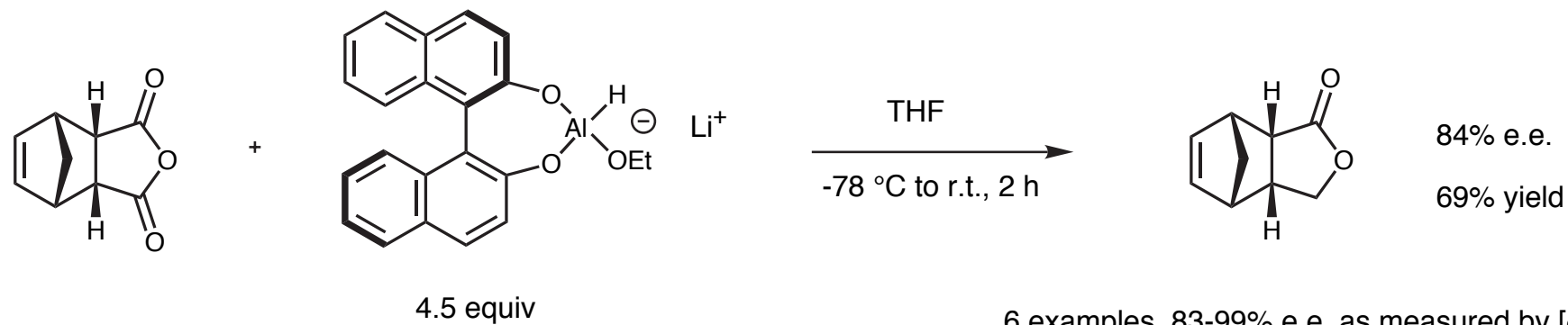


Ward, Pelter, Edwards, Gilmore, *Tet. Asymm.*, **1995**, 843



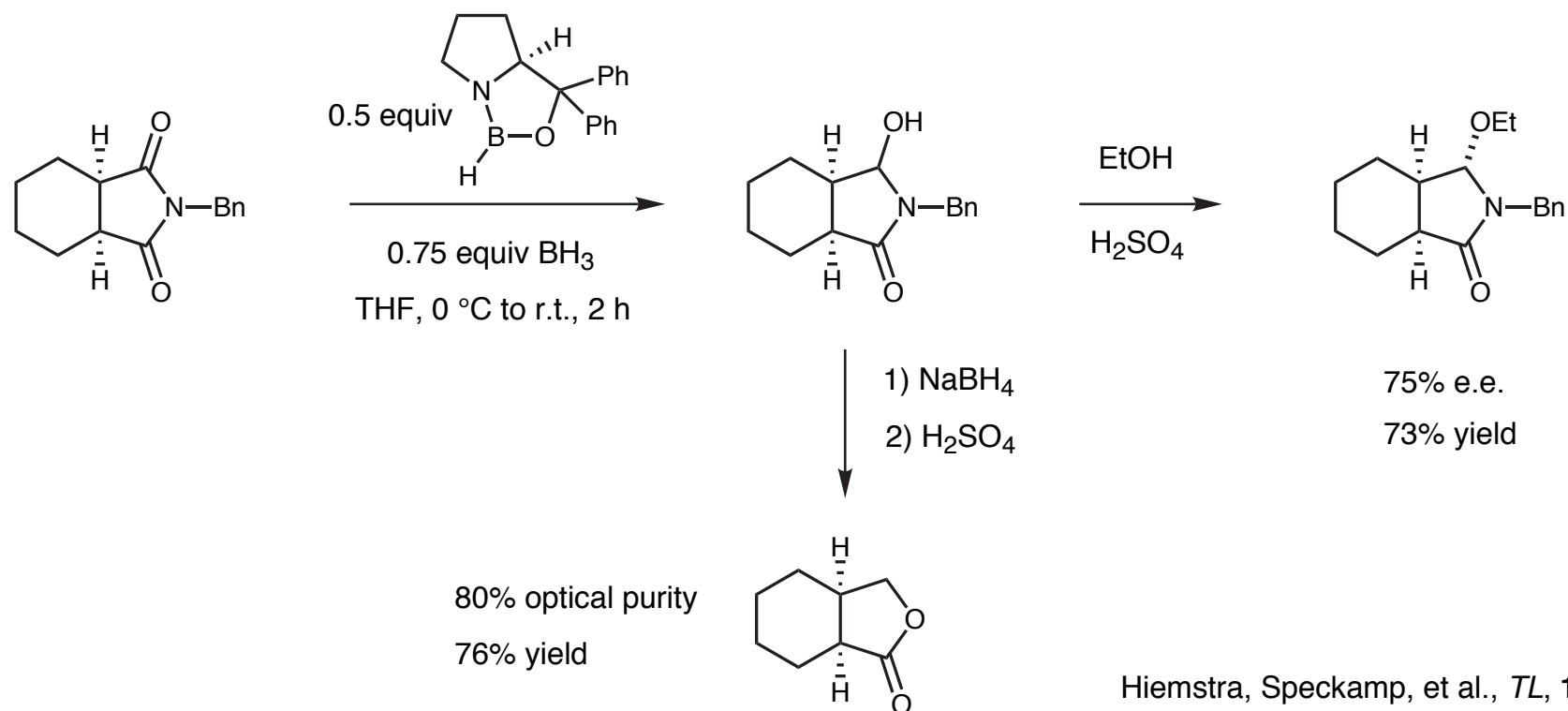
Kawakami, Hiratake, Yamamoto, Oda, *Chem. Comm.*, **1984**, 779

Symmetry-Breaking Reductions



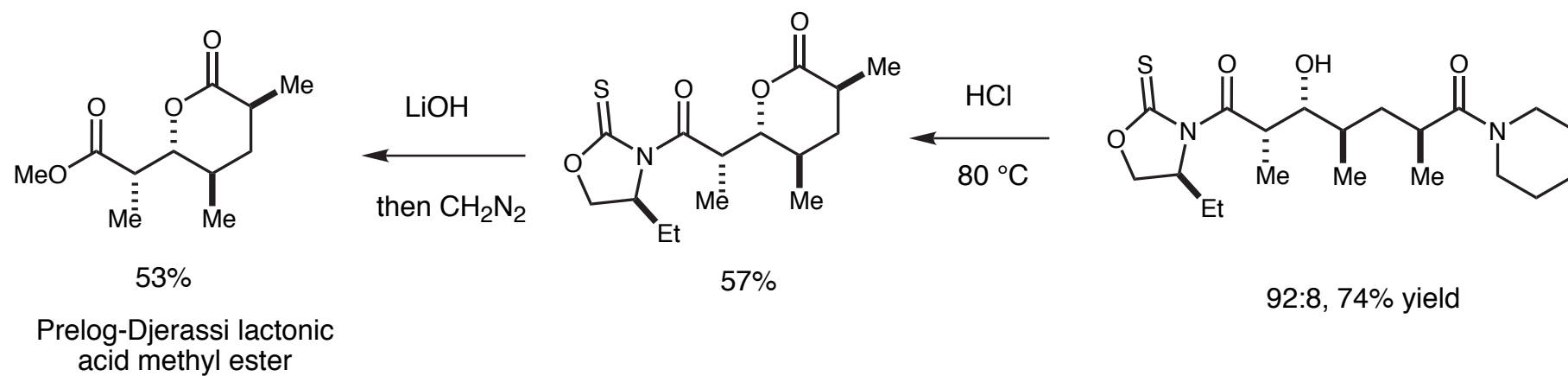
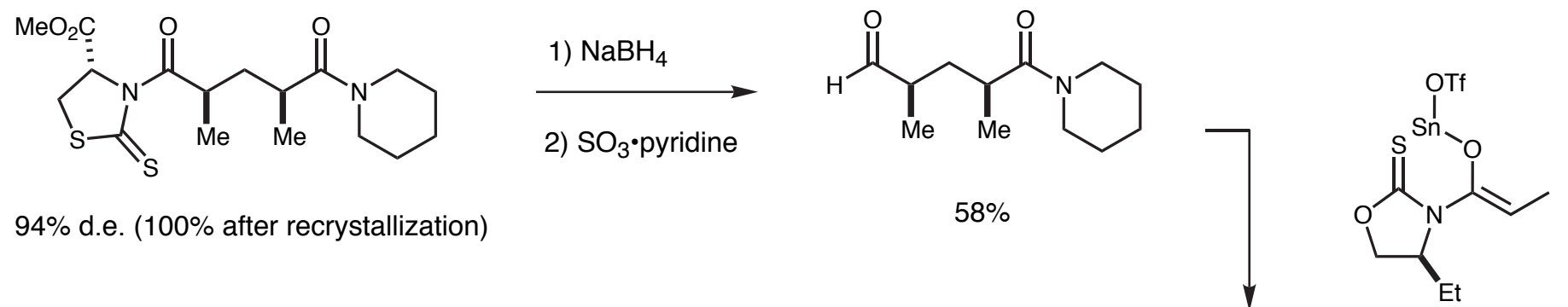
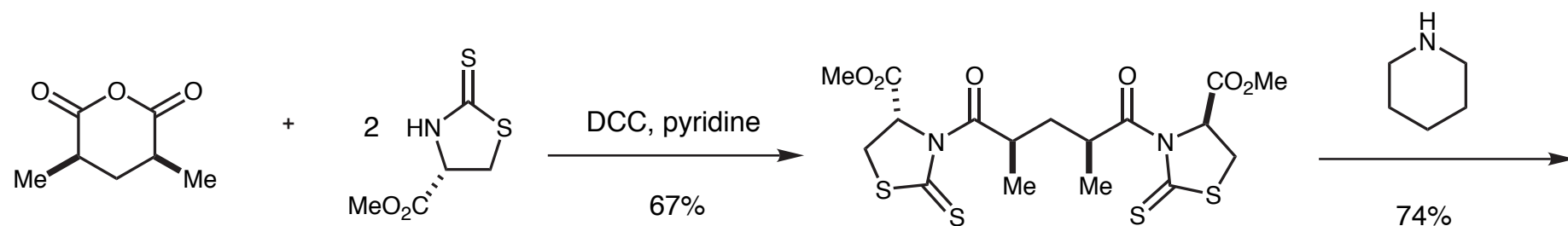
6 examples, 83-99% e.e. as measured by $[\alpha]$

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



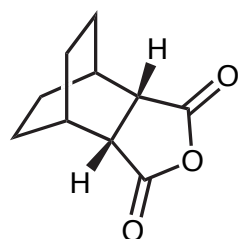
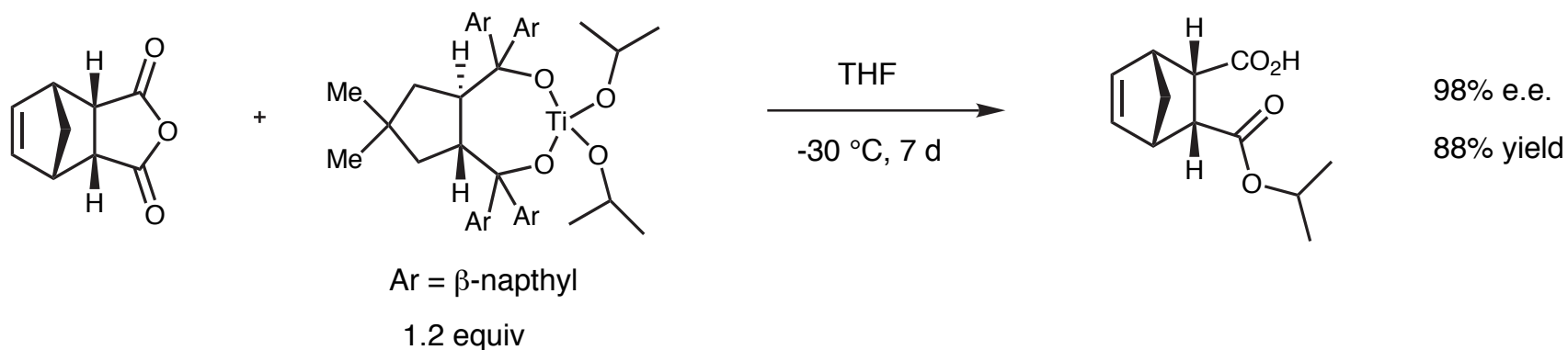
Hiemstra, Speckamp, et al., *TL*, **1994**, 1087

Thioimide Mediated Anhydride Desymmetrization



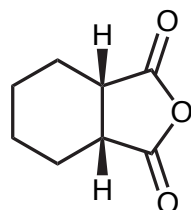
Nagao, Yamada, Kumagai, Ochiai, Fujita, *Chem. Comm.*, **1985**, 1418

Titanium TADDOLate Chemistry



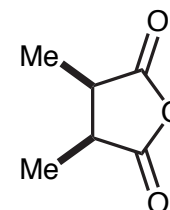
94% e.e.

92% yield



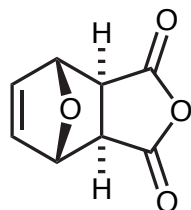
>90% e.e.

87% yield



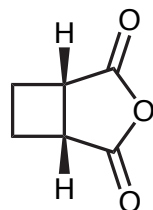
96% e.e.

73% yield



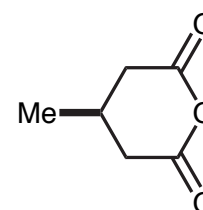
98% e.e.

63% yield



94% e.e.

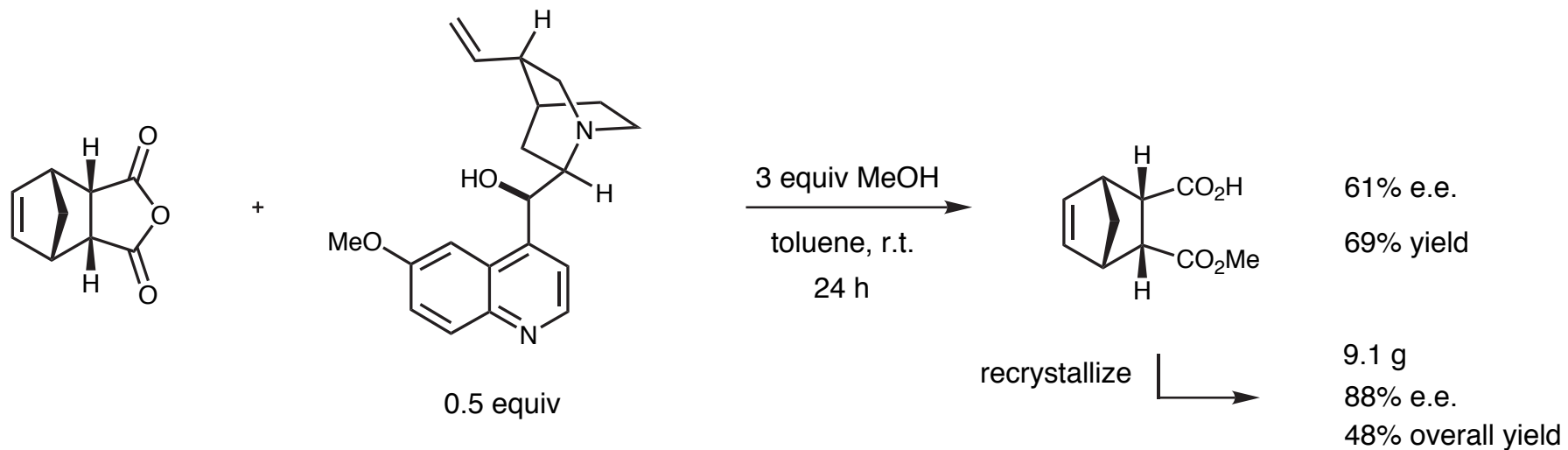
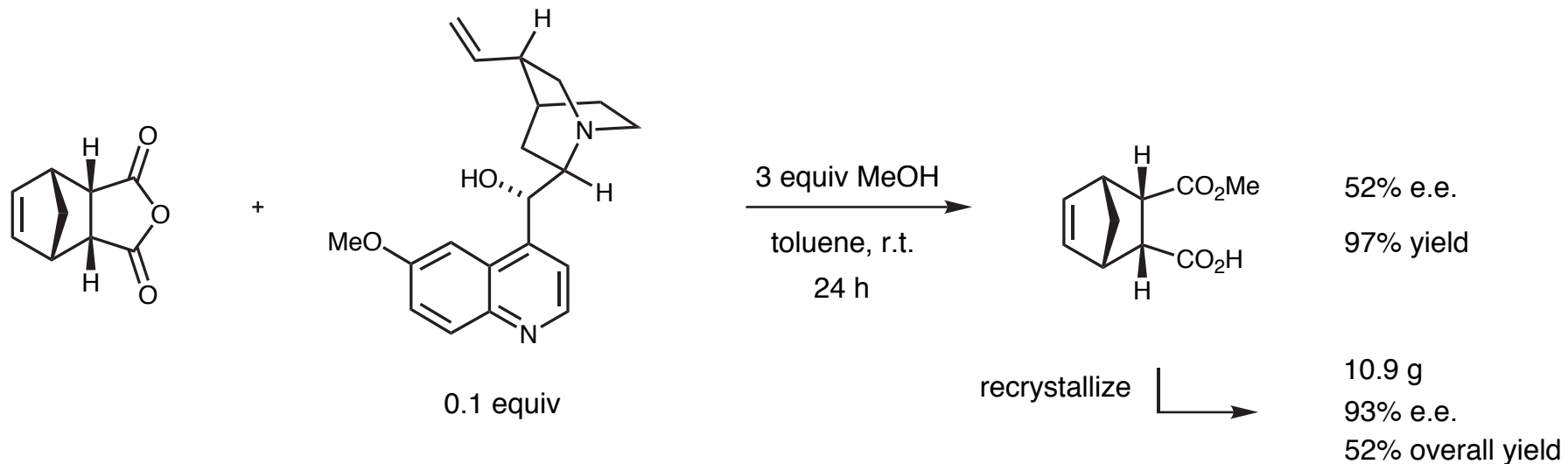
76% yield



50% e.e.

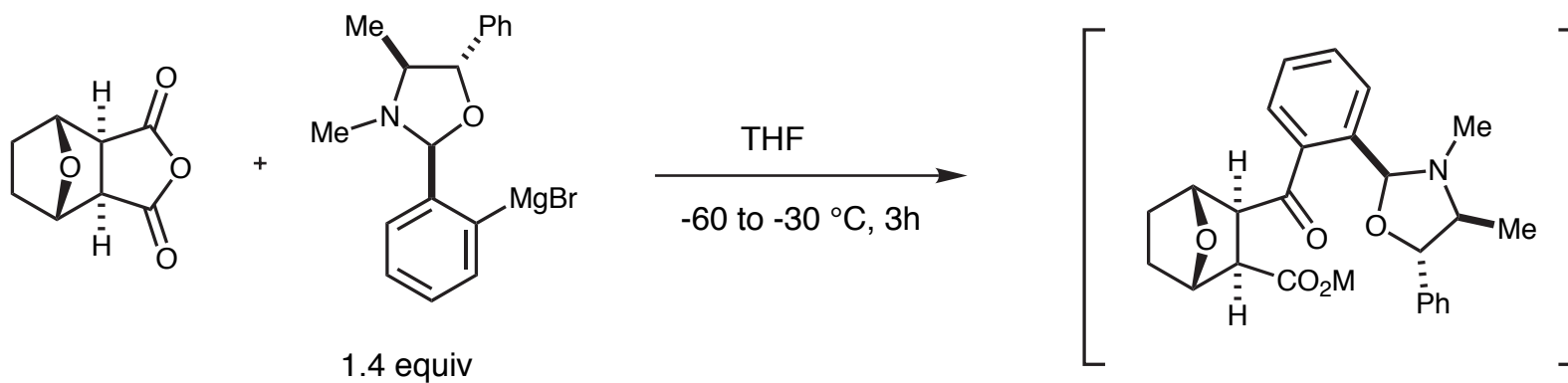
Seebach, Jaeschke, Wang, *ACIEE*, 1995, 2395

Catalytic Desymmetrization of Anhydrides

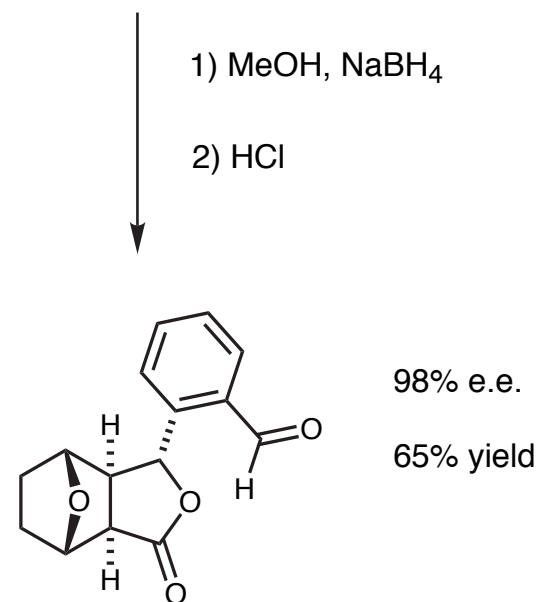


Aitken, Gopal, *Tet. Asymm.*, **1990**, 517

Anhydride Opening by Carbon Nucleophiles

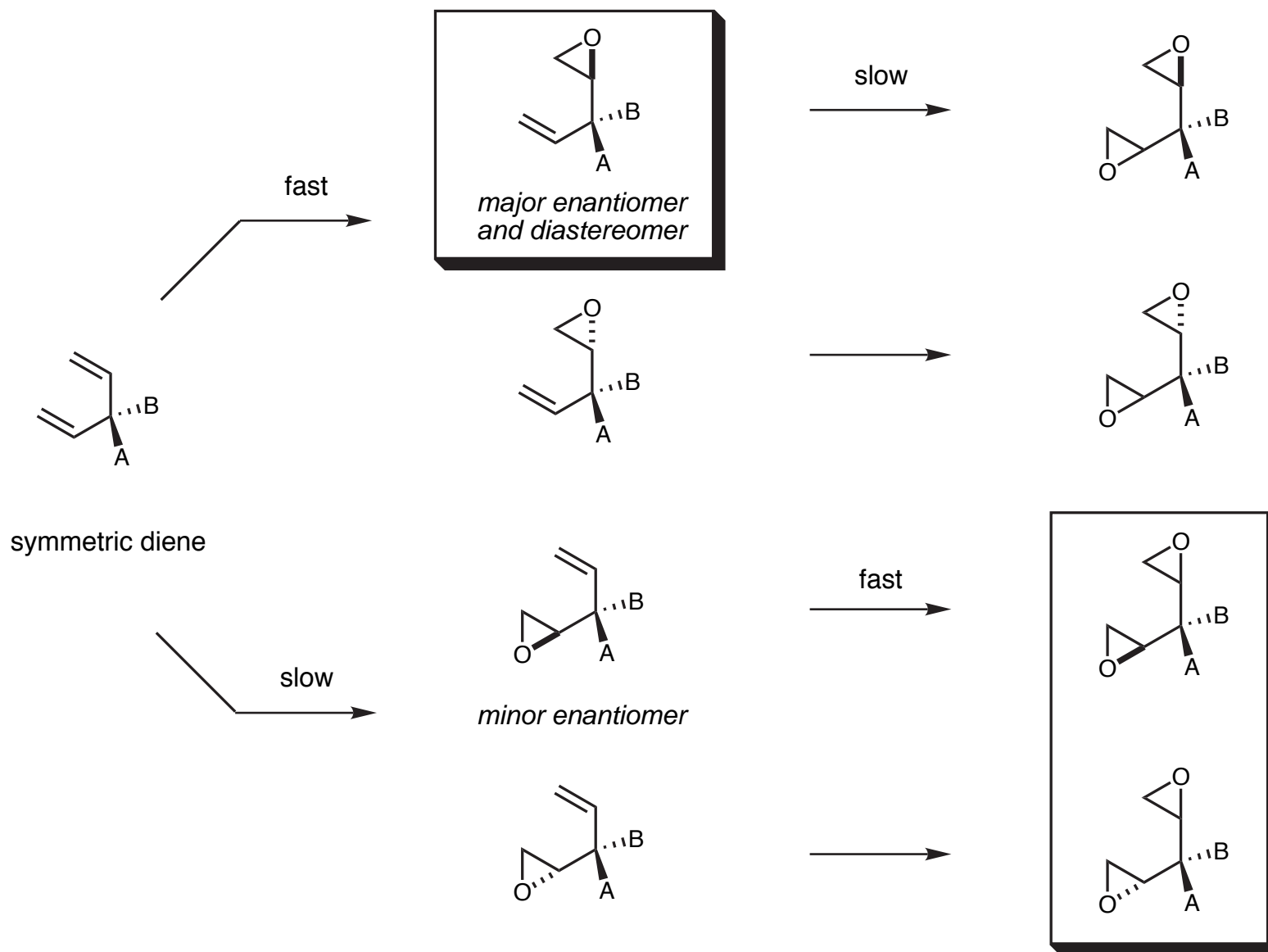


- Sodium borohydride reduction proceeds in 99.4% d.e.
- Pseudoephedrine can be recovered in 75% yield (unoptimized).
- The corresponding aryllithium provides the enantiomeric product in low (25-30%) e.e.



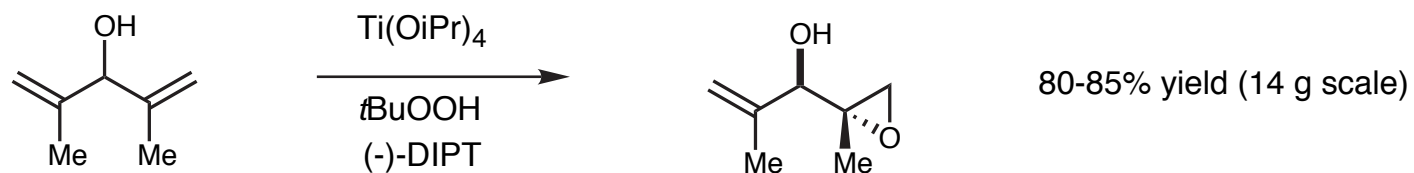
Real, Kronenthal, Wu, *TL*, **1993**, 8063

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

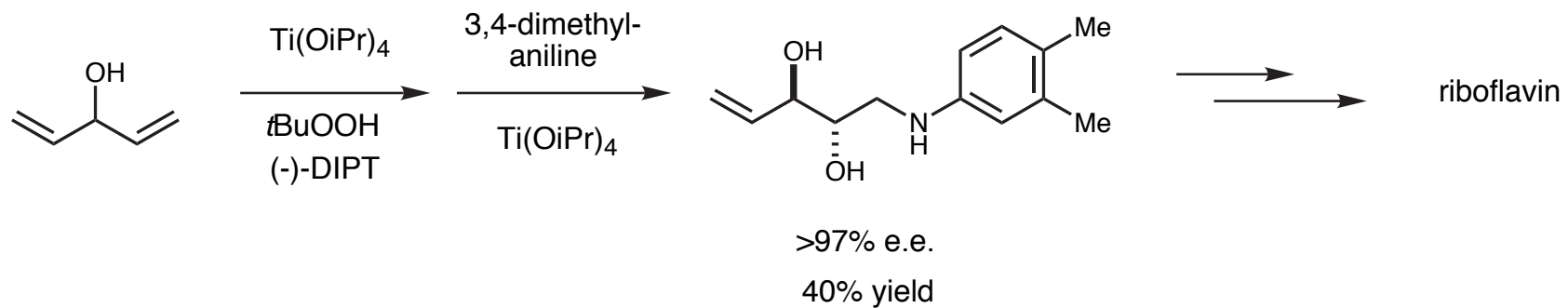
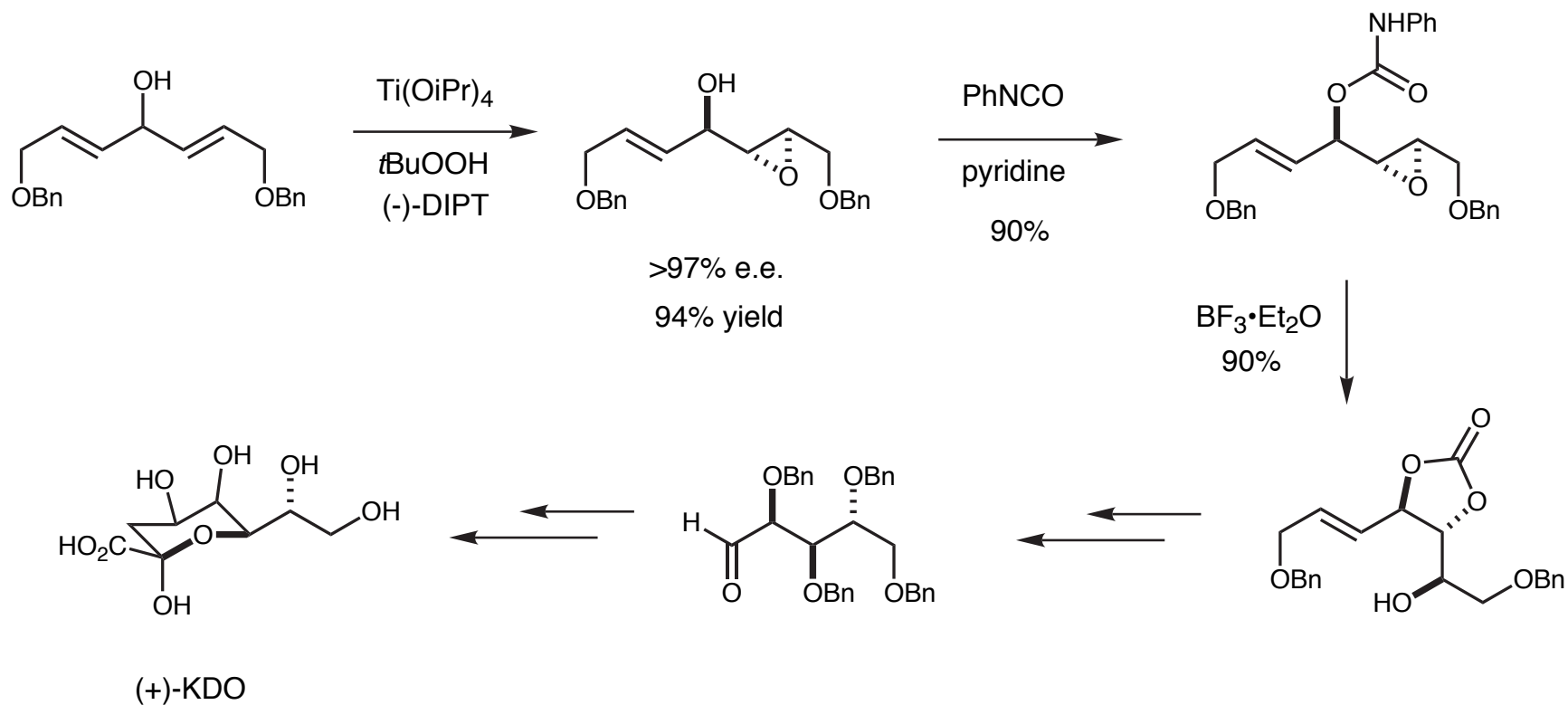
A historical note...



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

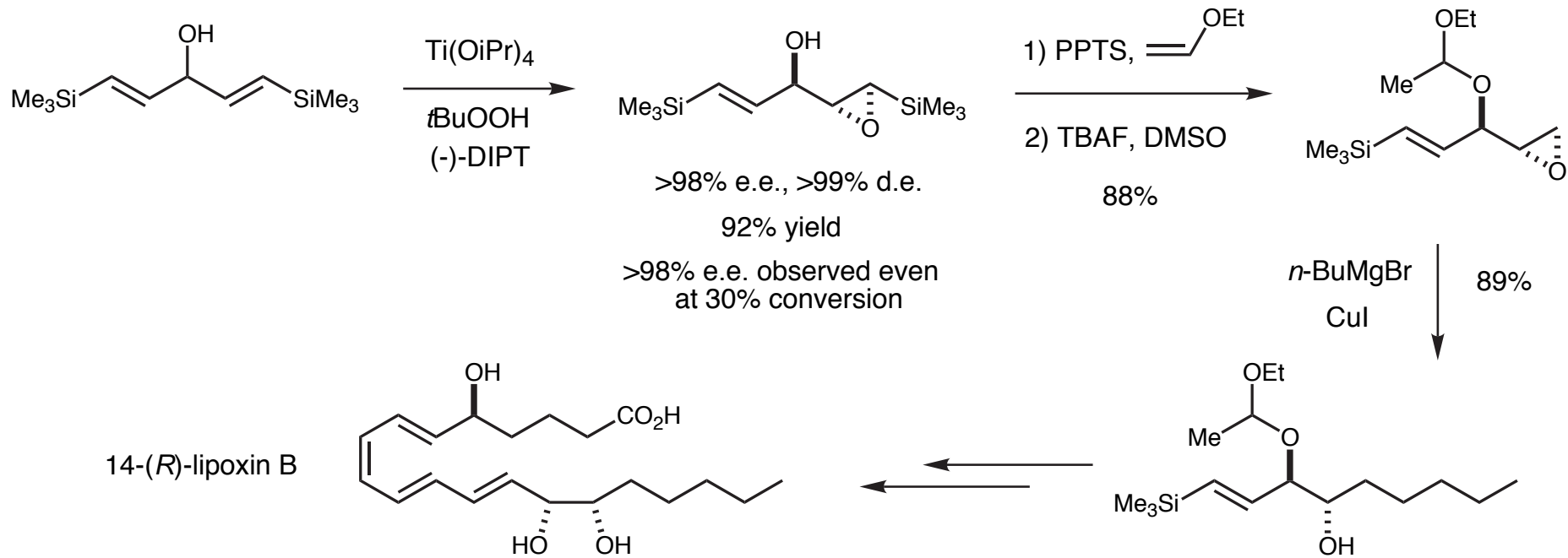
see also Hafele, Schroter, Jager, *ACIEE*, **1986**, 87

Synthetic Applications

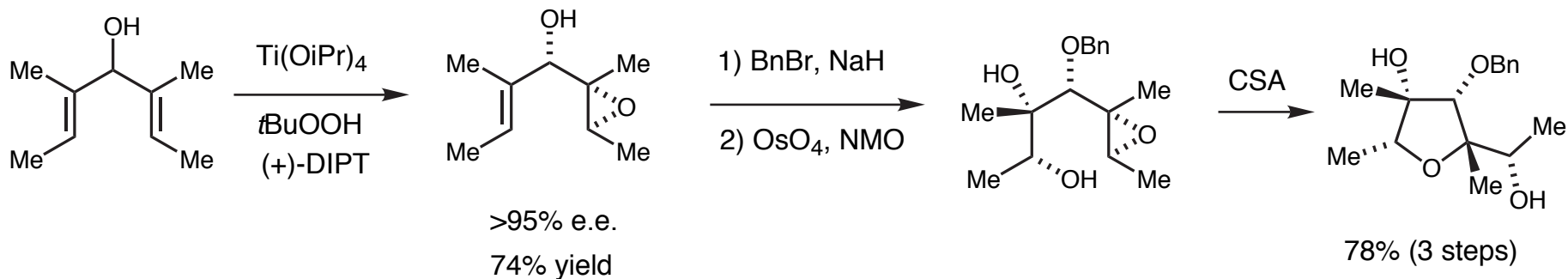


Smith, Wang, Schreiber, *Tet.*, **1990**, 4793

Synthetic Applications

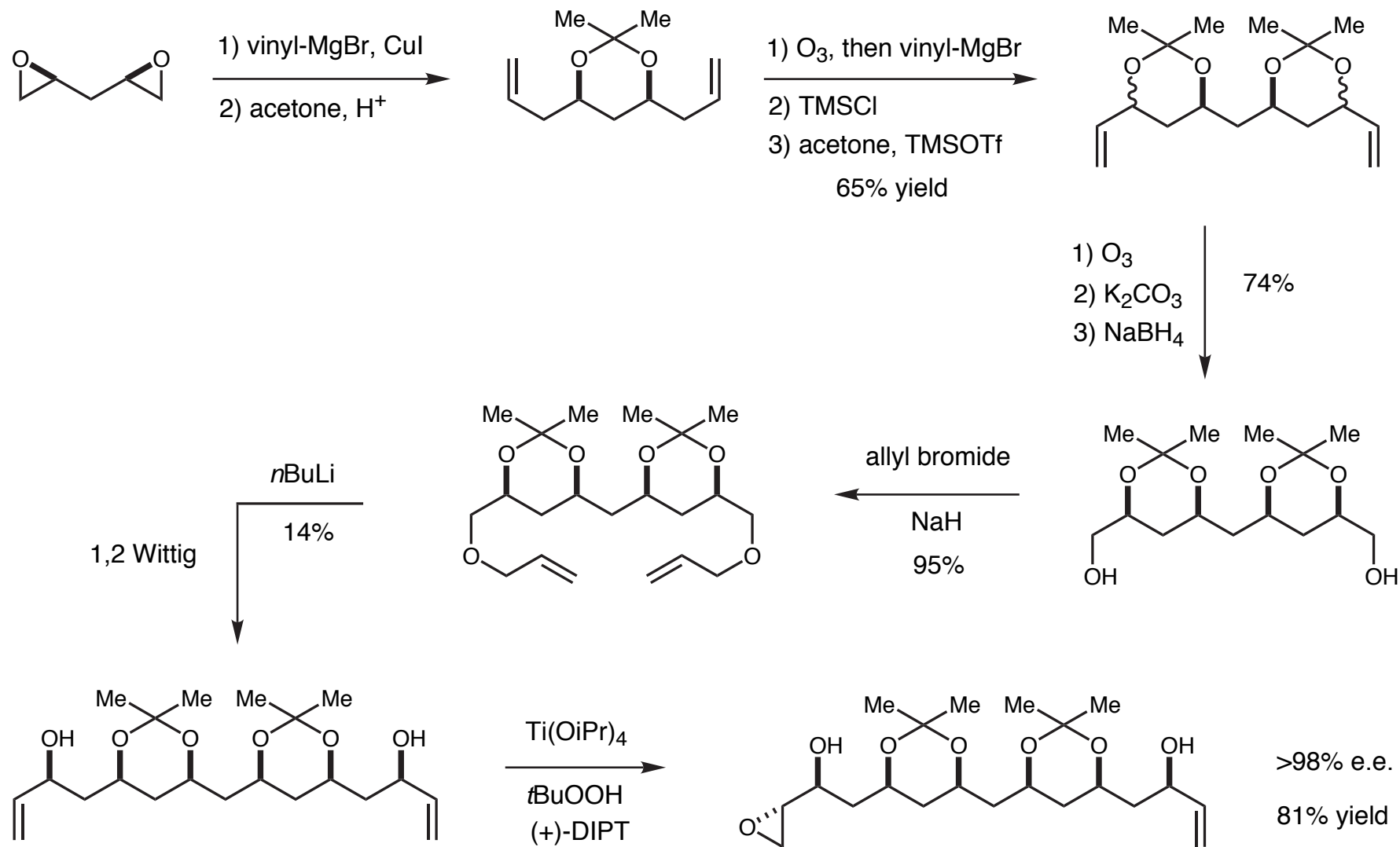


Kobayashi, Kato, Shimazaki, Sato, *TL*, **1988**, 6297



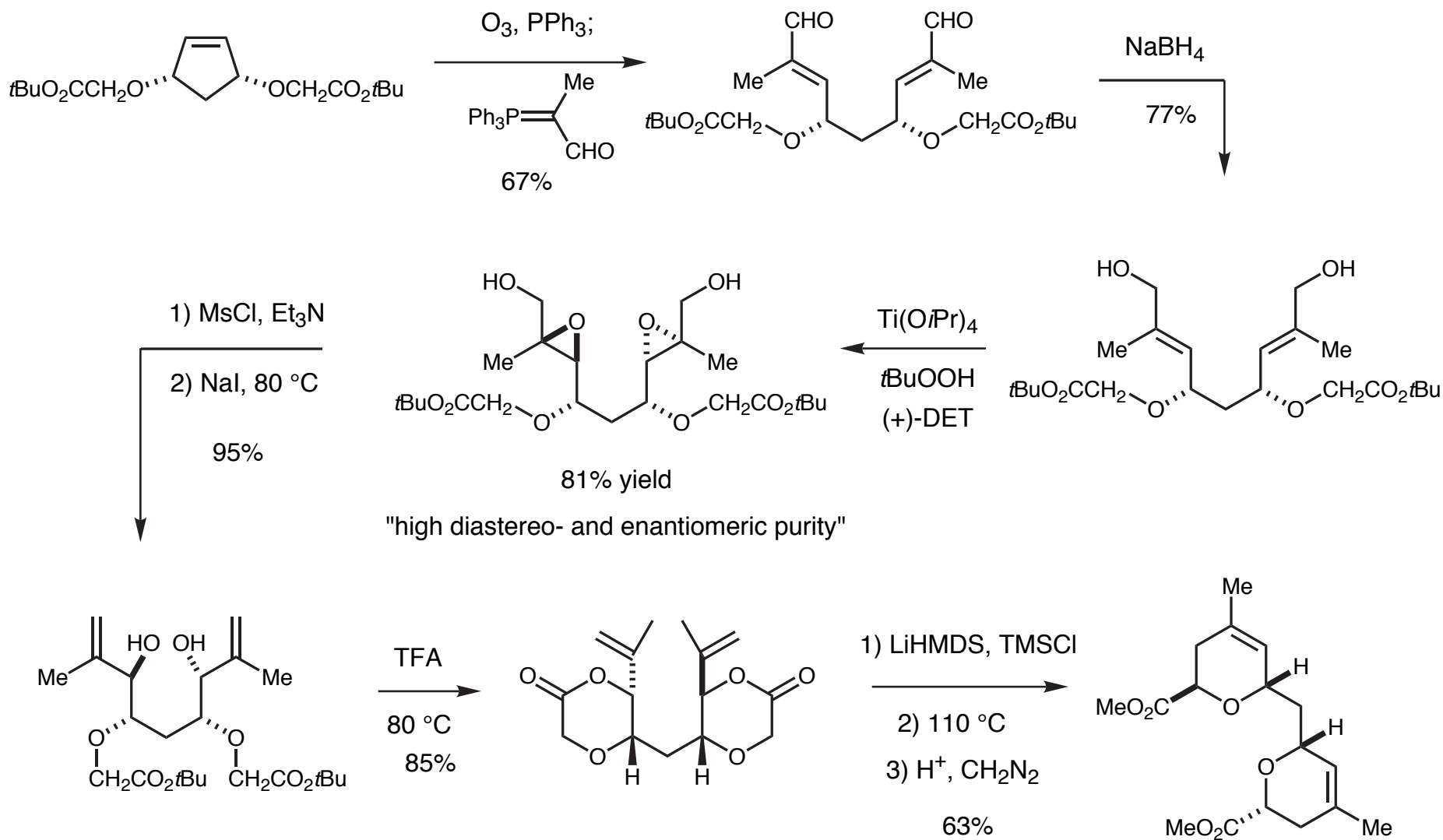
Hatakeyama, Sakurai, Numata, Ochi, Takano, *JACS*, **1988**, 5201

Desymmetrization of Advanced Intermediates



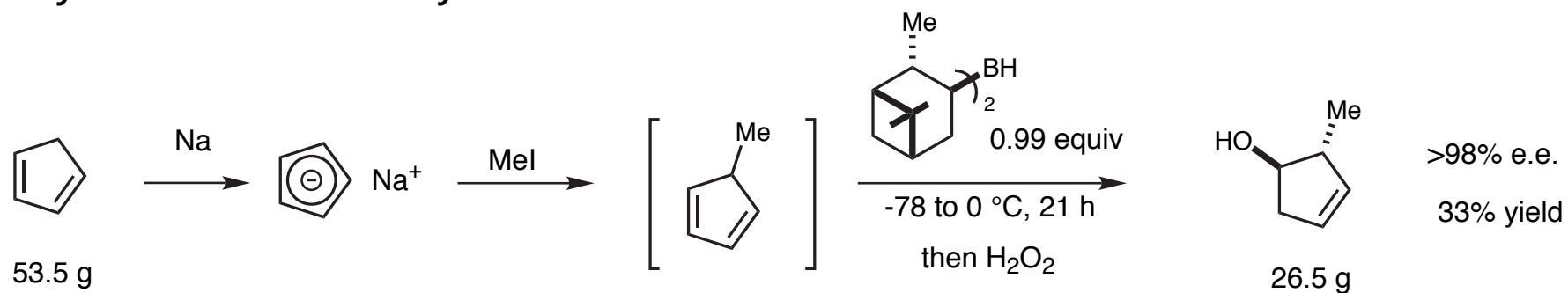
Schreiber, Goulet, Schulte, *JACS*, **1988**, 4718

Desymmetrization via Bis-epoxidation



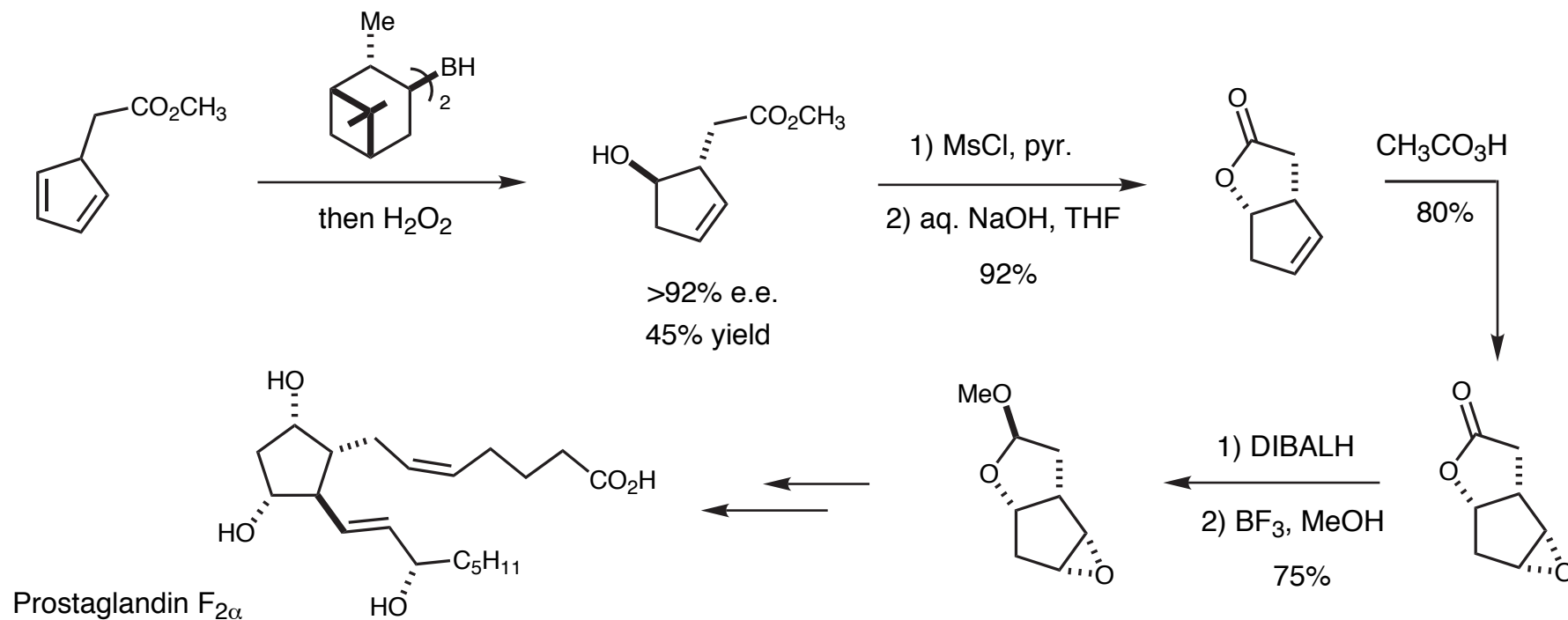
Burke, Buchanan, Rovin, *TL*, **1991**, 3961

Desymmetrization via Hydroboration



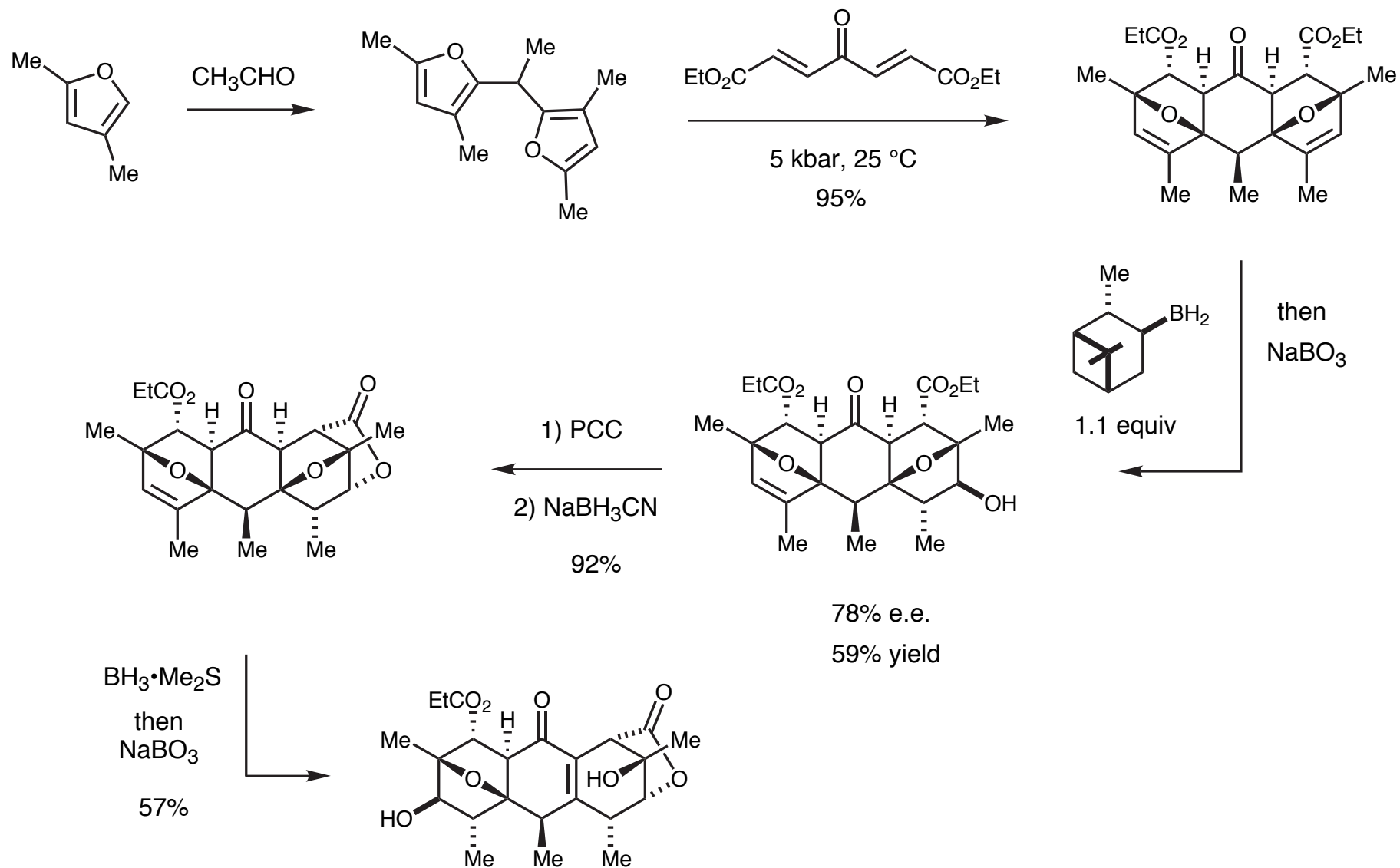
• Low yield is due largely to dimerization of the diene.

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



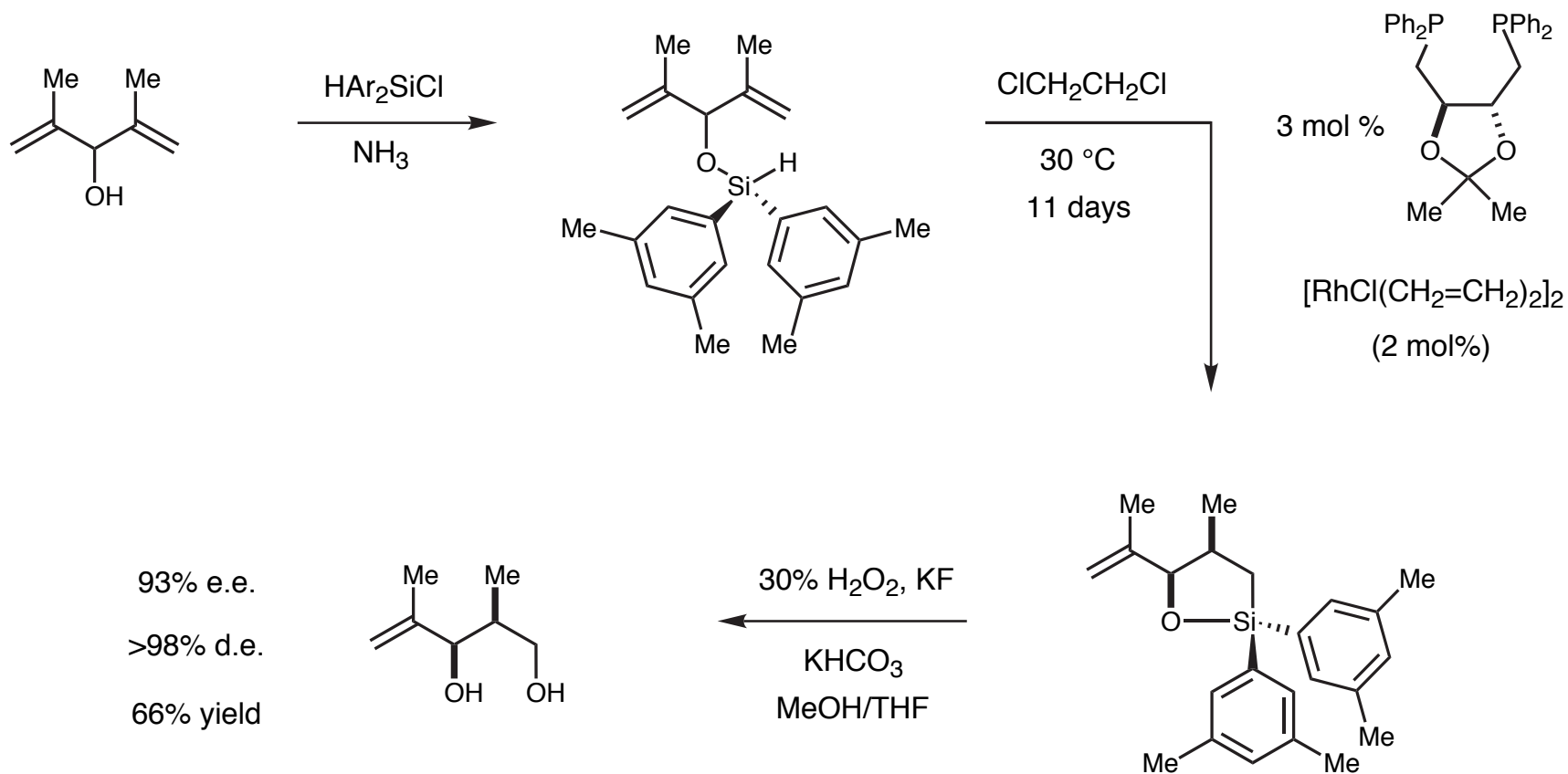
Partridge, Chadha, Uskokovic, *JACS*, **1973**, 7171

Desymmetrization via Hydroboration



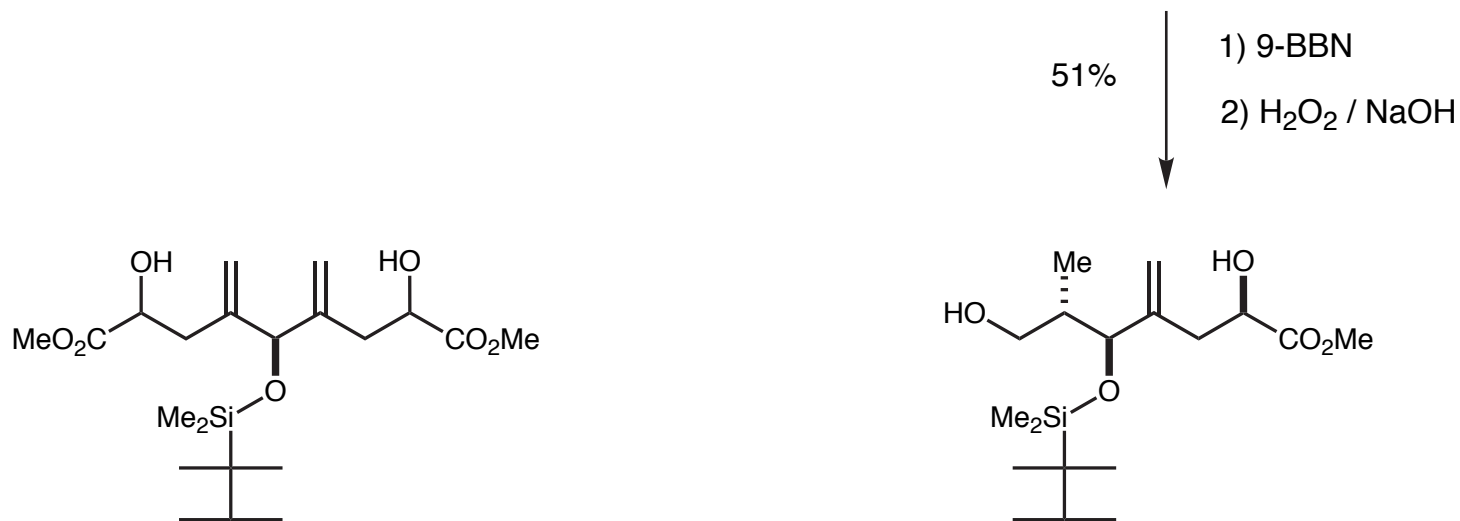
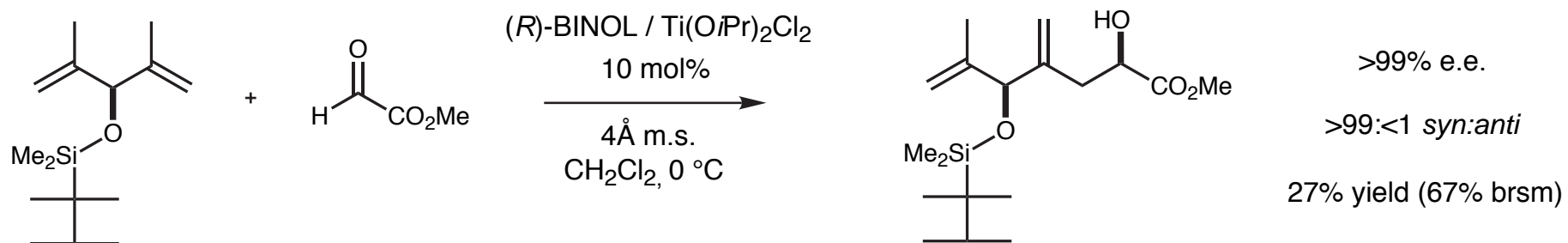
Marchionni, Vogel, Roversi, *TL*, **1996**, 4149

Desymmetrization via Intramolecular Hydrosilylation



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

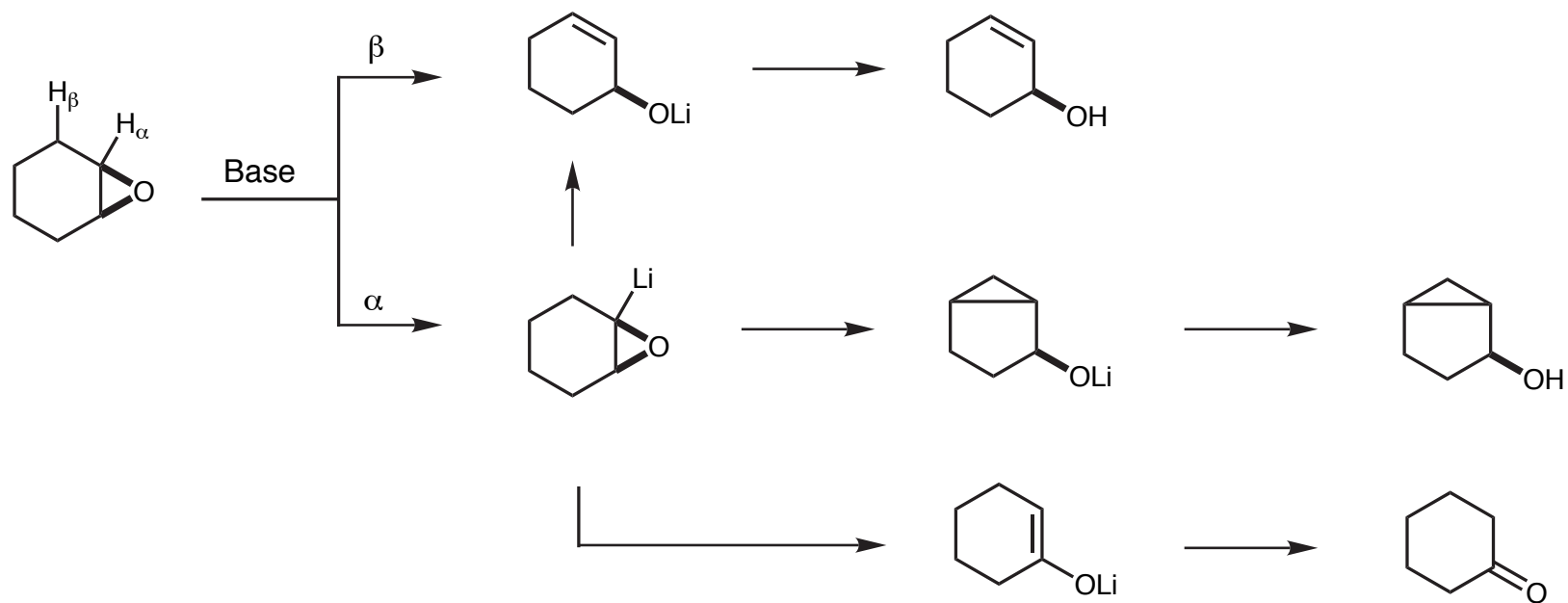
Ene Reaction



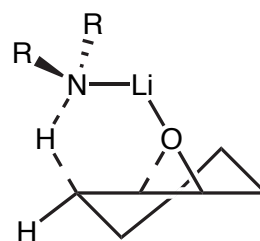
- No "double ene" product obtained, even using 2 equiv glyoxylate.

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

Base-Induced Transformations of Cyclic Epoxides



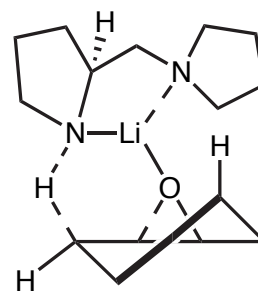
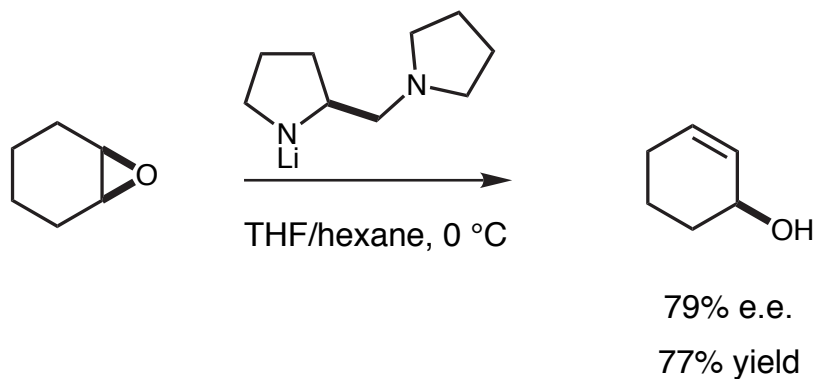
- β -elimination is expected to proceed via a *syn* mechanism:



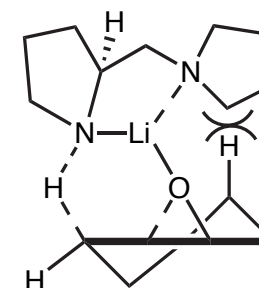
- The β : α ratio depends in part on the ability of the substrate to adopt the above conformation; base, solvent, and temperature are also significant factors.

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

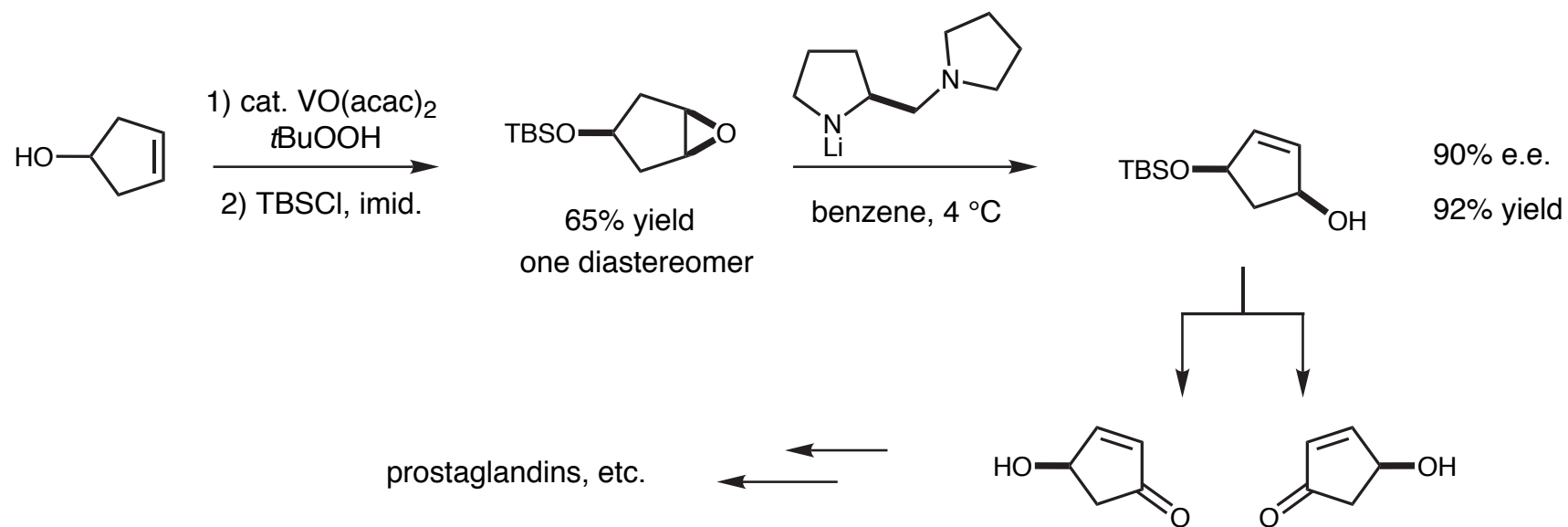
Enantioselective β -Elimination



vs.

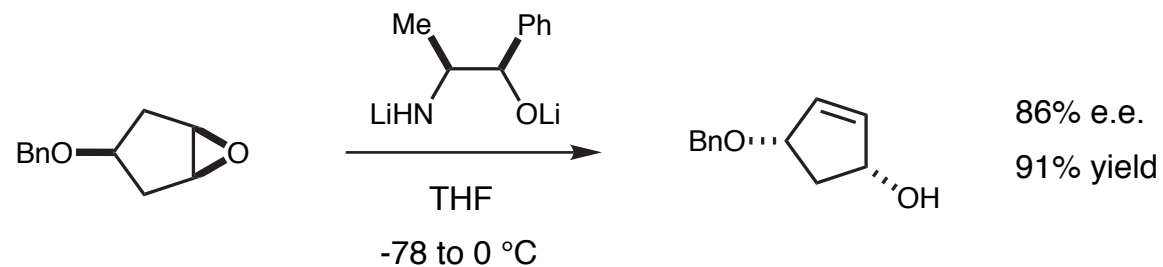


Asami, *Chem. Lett.*, **1984**, 829



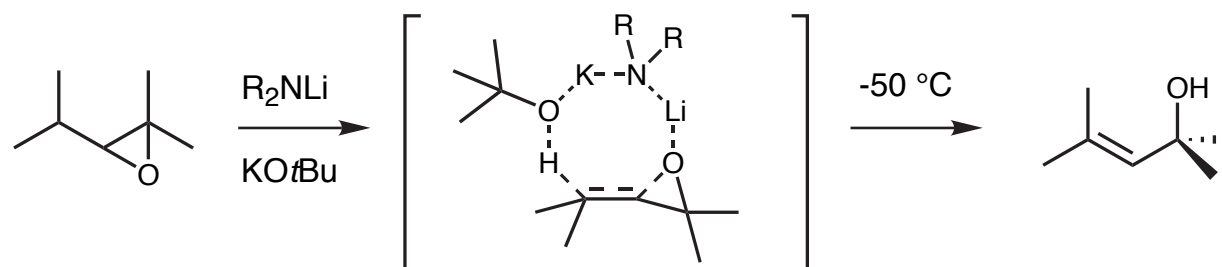
Asami, *TL*, **1985**, 5803

Enantioselective β -Elimination: Dilithiated Aminoalcohols



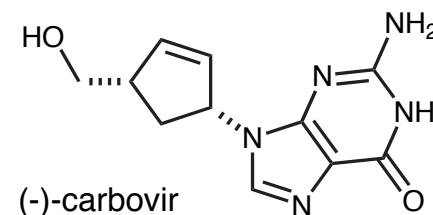
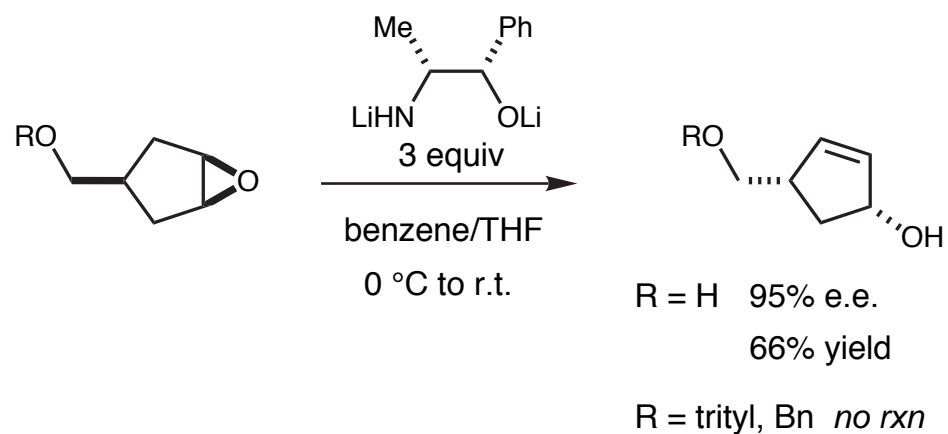
Milne, Murphy, *Chem. Comm.*, **1993**, 884

• Inspired by KO^tBu induced rate accelerations:



• R_2NLi alone requires refluxing THF

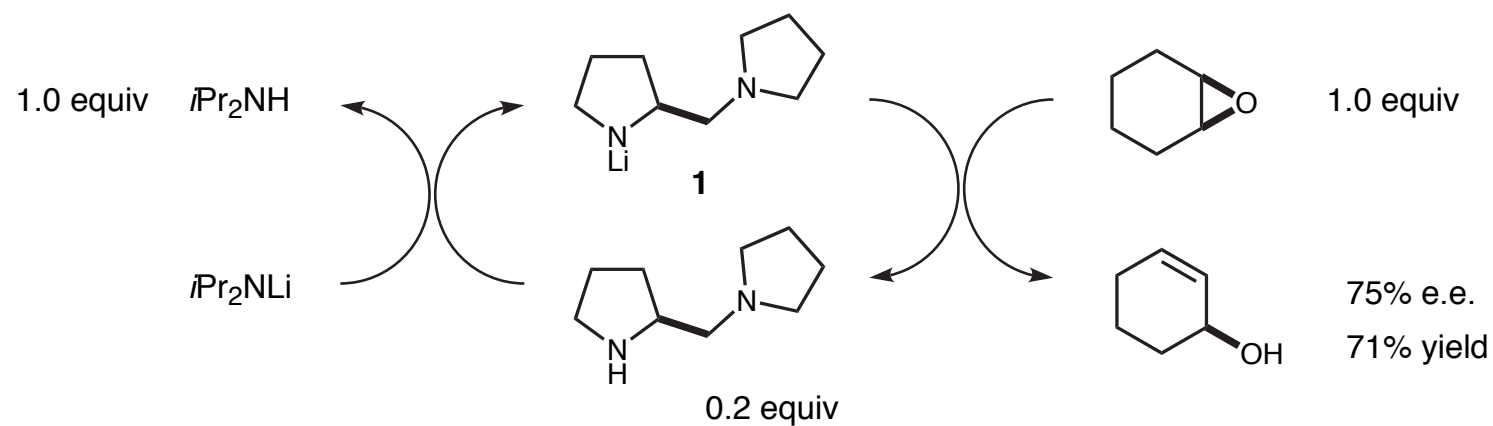
Mordidi, Rayana, Margot, Schlosser, *Tet.*, **1990**, 2401



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

Catalytic Enantioselective β -Elimination

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

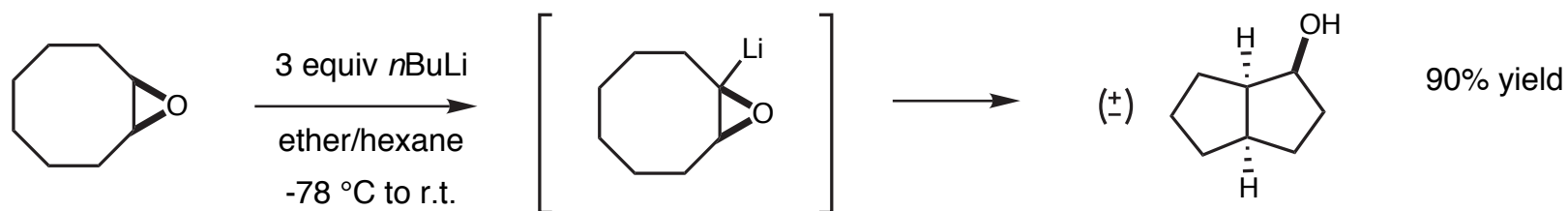


- Addition of 6.0 equiv DBU was necessary for optimal results; the additive may facilitate proton transfer between LDA and the chiral amine.
- 1.2 equiv $n\text{BuLi}$ were employed for metallation.

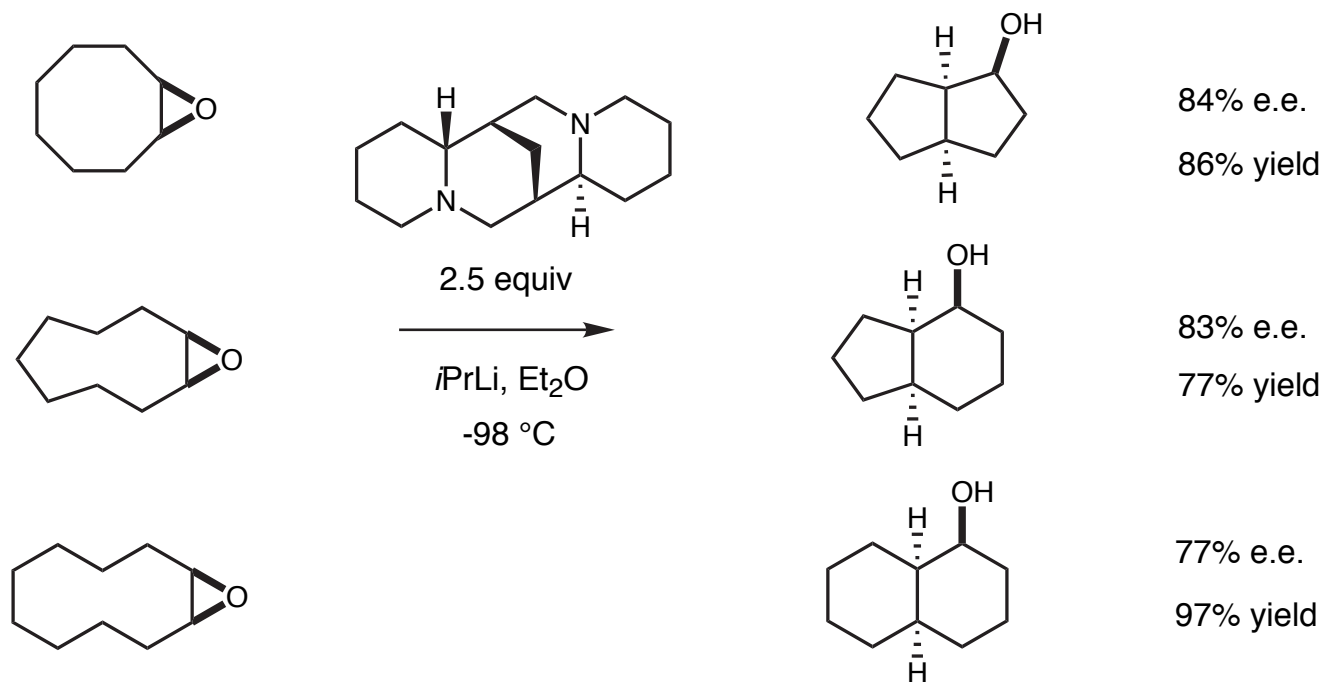
Asami, Ishizaki, Inoue, *Tet. Asymm.*, **1994**, 793

Enantioselective α -Elimination

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

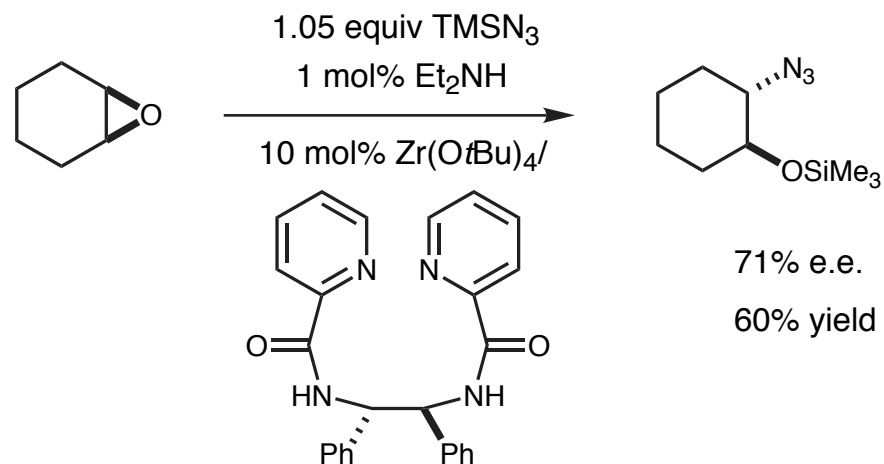


Boeckman, *TL*, **1977**, 4281



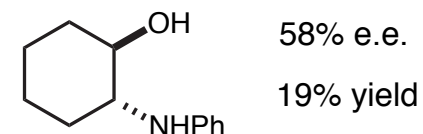
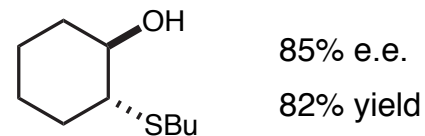
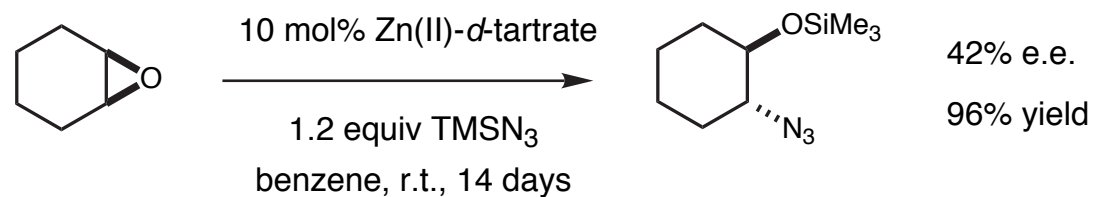
Hodgson, Lee, *Chem. Comm.*, **1996**, 1015

Catalytic Enantioselective TMSN_3 Addition



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

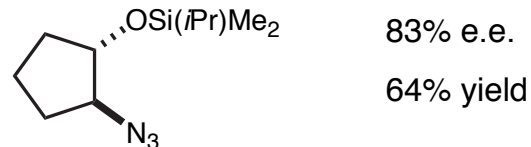
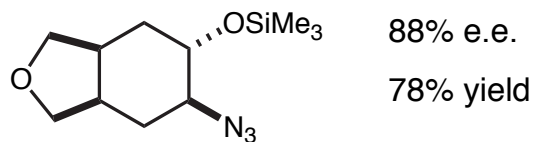
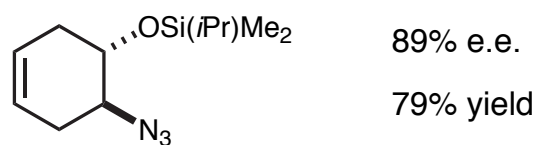
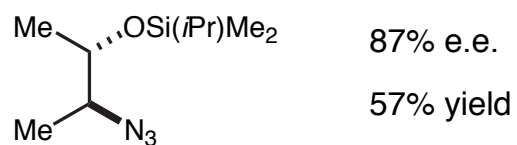
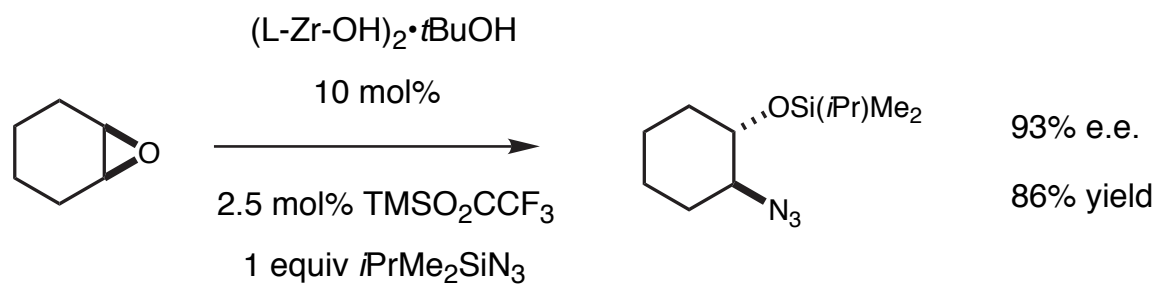
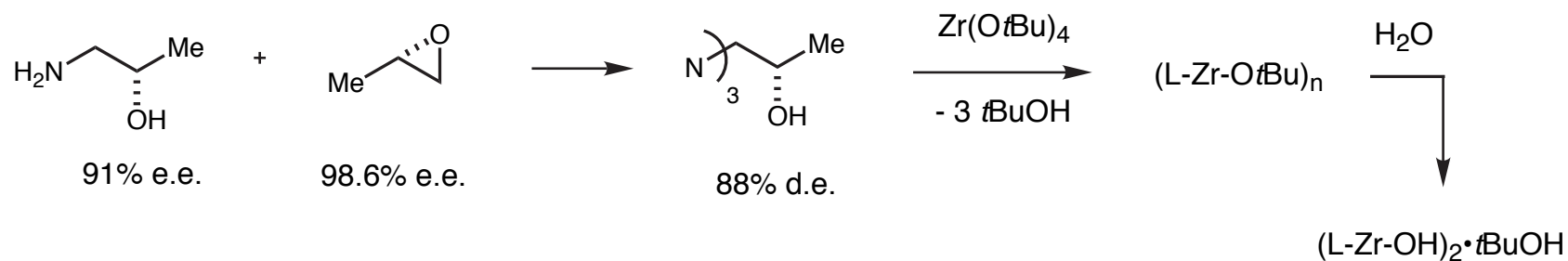
Adolfsson, Moberg, *Tet. Asymm.*, **1995**, 2023



- The reaction is heterogeneous; catalyst can be recovered by filtration.
- 15 metal(II) tartrates were screened.
- The catalyst is prepared by treatment of ZnCl_2 with aqueous Rochelle's salt or tartaric acid.

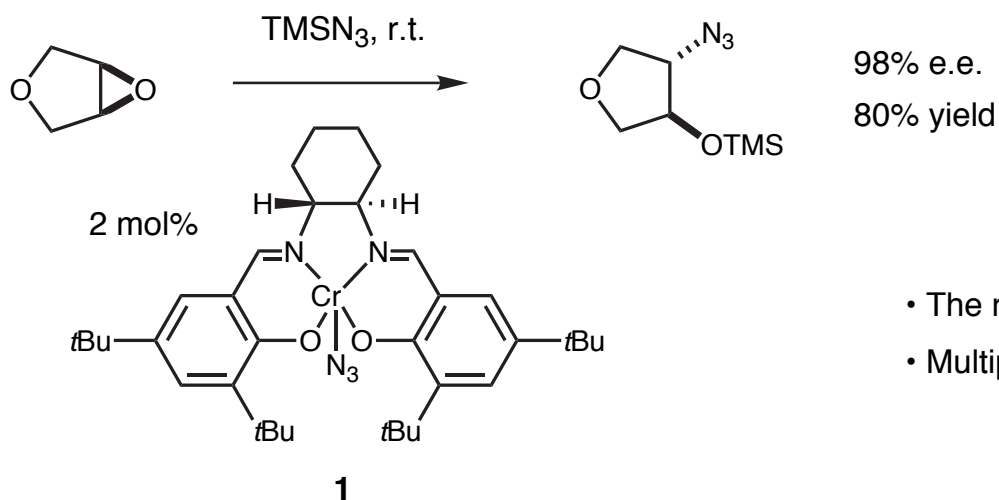
Yamashita, *Bull. Chem. Soc. Japan*, **1988**, 1213

Catalytic Enantioselective TMSN₃ Addition

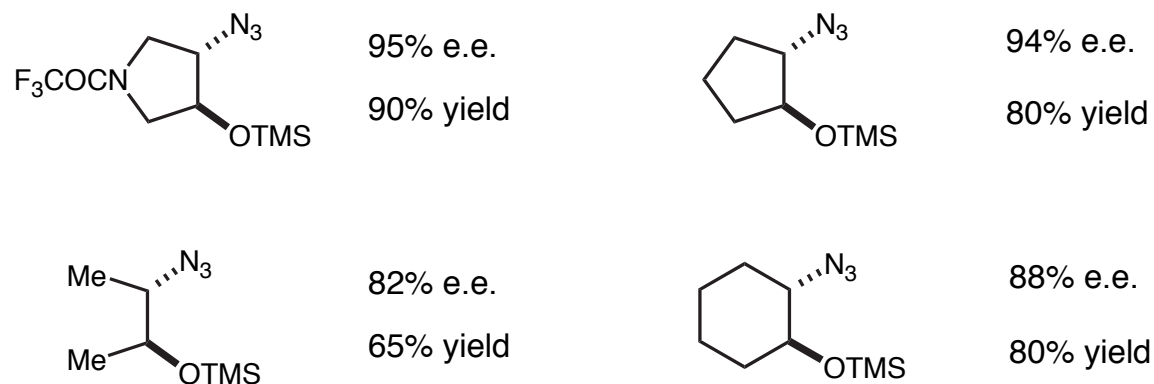


Nugent, *JACS*, **1992**, 2768

Catalytic Enantioselective TMSN_3 Addition

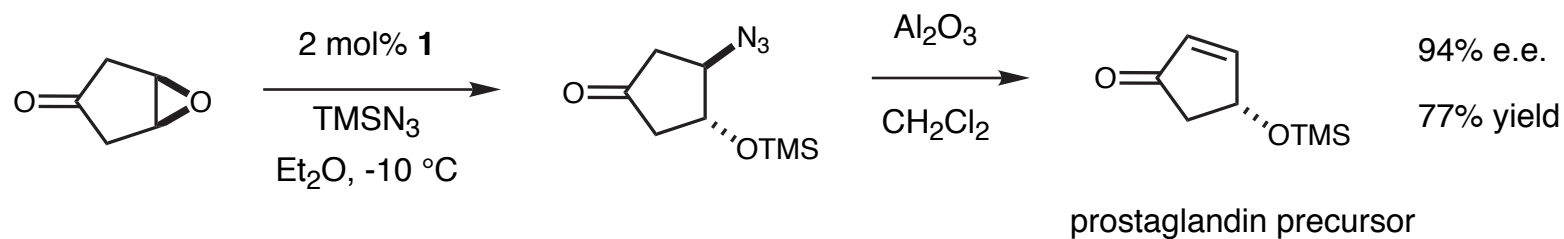
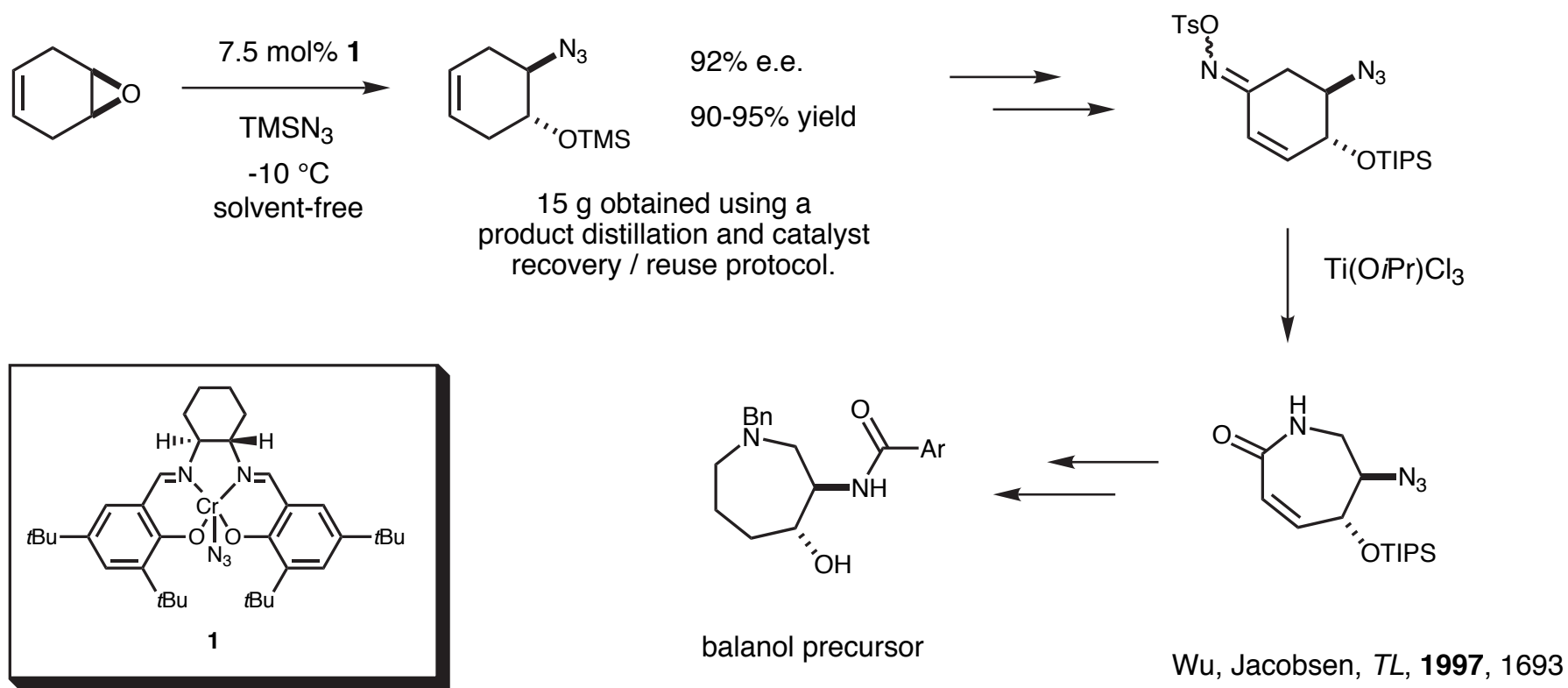


- The reaction proceeds equally well without solvent.
- Multiple recycles of the catalyst provide identical results.

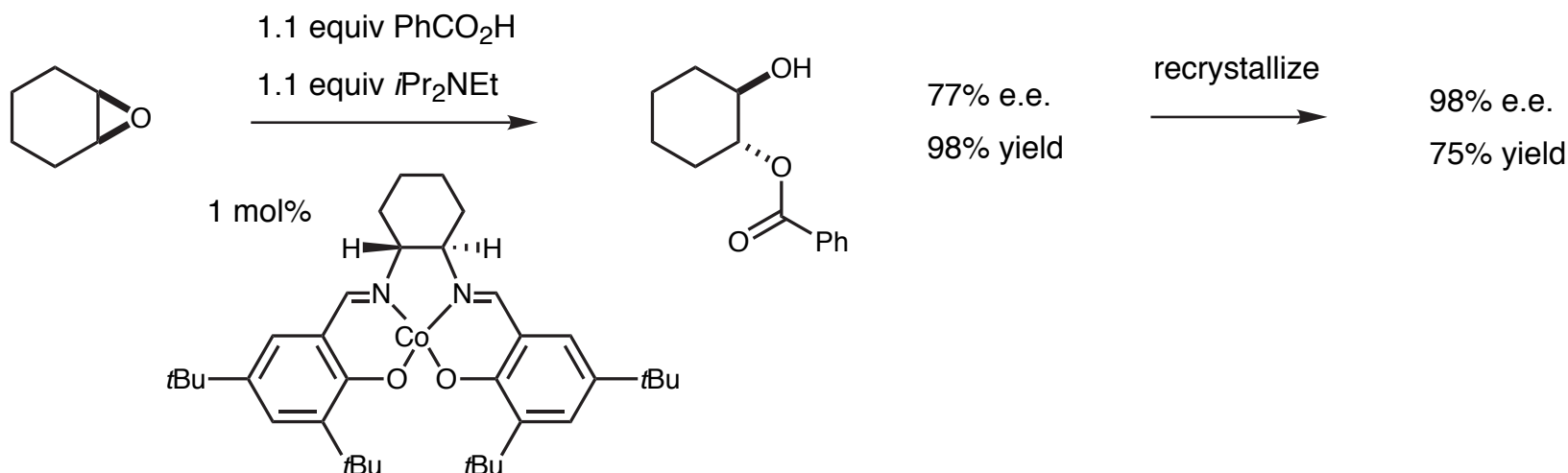


Martinez, Leighton, Carsten, Jacobsen, *JACS*, **1995**, 5897

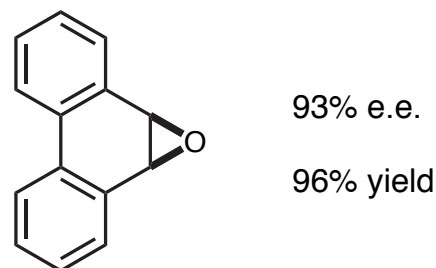
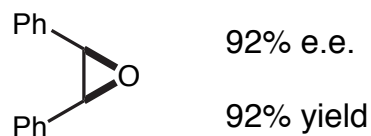
Catalytic Enantioselective TMSN_3 Addition: Applications



Catalytic Enantioselective Benzoic Acid Addition

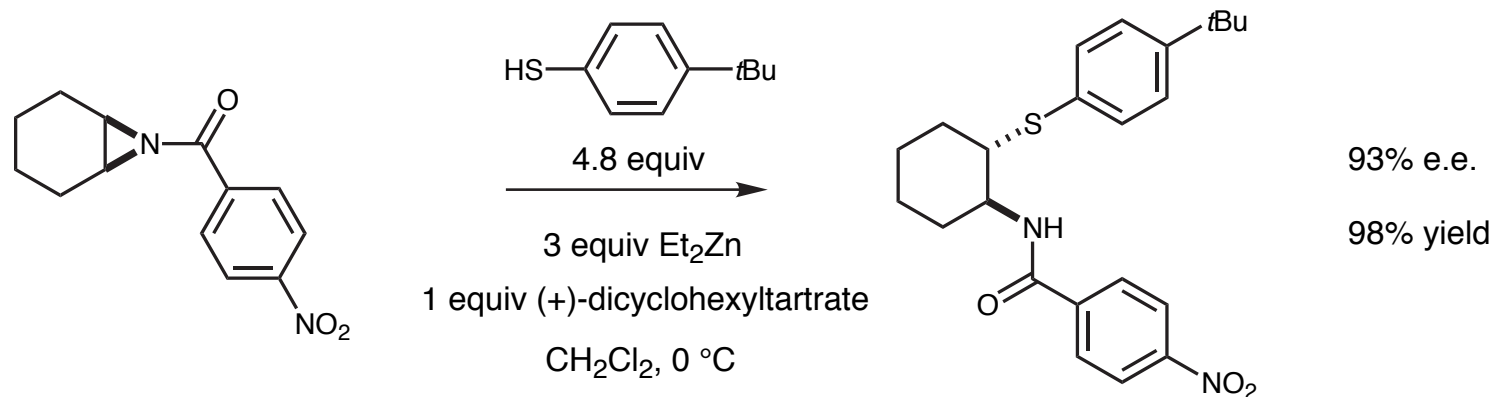


- The Co(II) complex depicted is a precatalyst; formation of the active Co(III) complex is best accomplished by stirring the precatalyst and benzoic acid under an oxygen atmosphere.
- The benzoate ester adducts are generally crystalline and can thus be recrystallized to obtain high e.e.
- *i*Pr₂NEt appears to confer solubility to benzoic acid (TBME solvent).
- Best substrates:



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

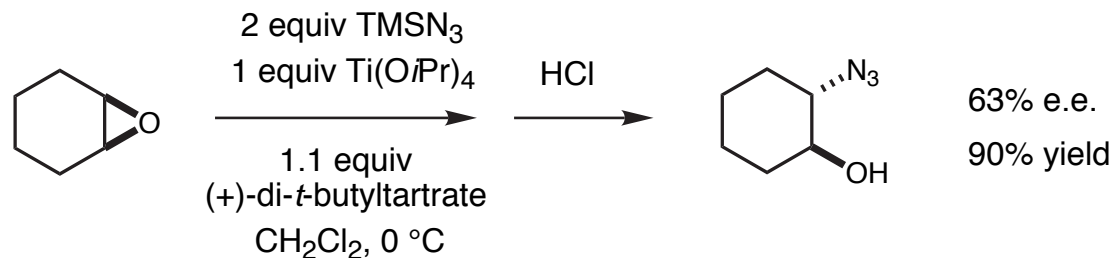
Enantioselective Aziridine Opening



- 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

- TMSN_3 addition can be effected under similar conditions:

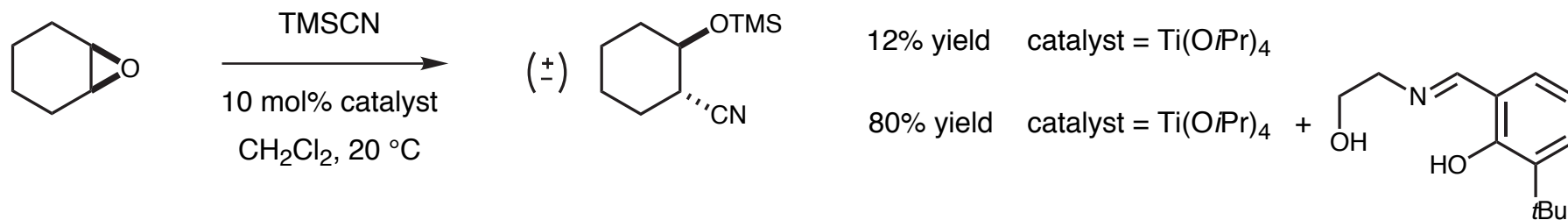


- Use of 10 mol% $\text{Ti}(\text{O}i\text{Pr})_2\text{Cl}_2$ and 10 mol% tartrate gives 62% e.e., 65% yield.

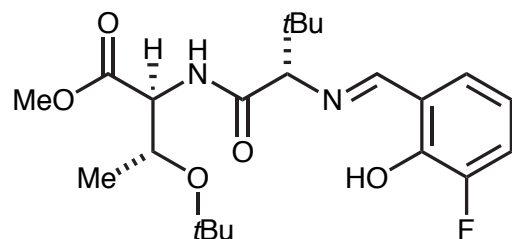
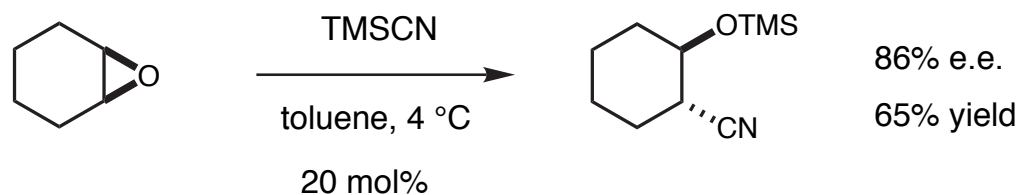
Hayashi, Kohmura, Oguni, *Synlett*, **1991**, 774

Catalytic Enantioselective TMSCN Addition

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



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

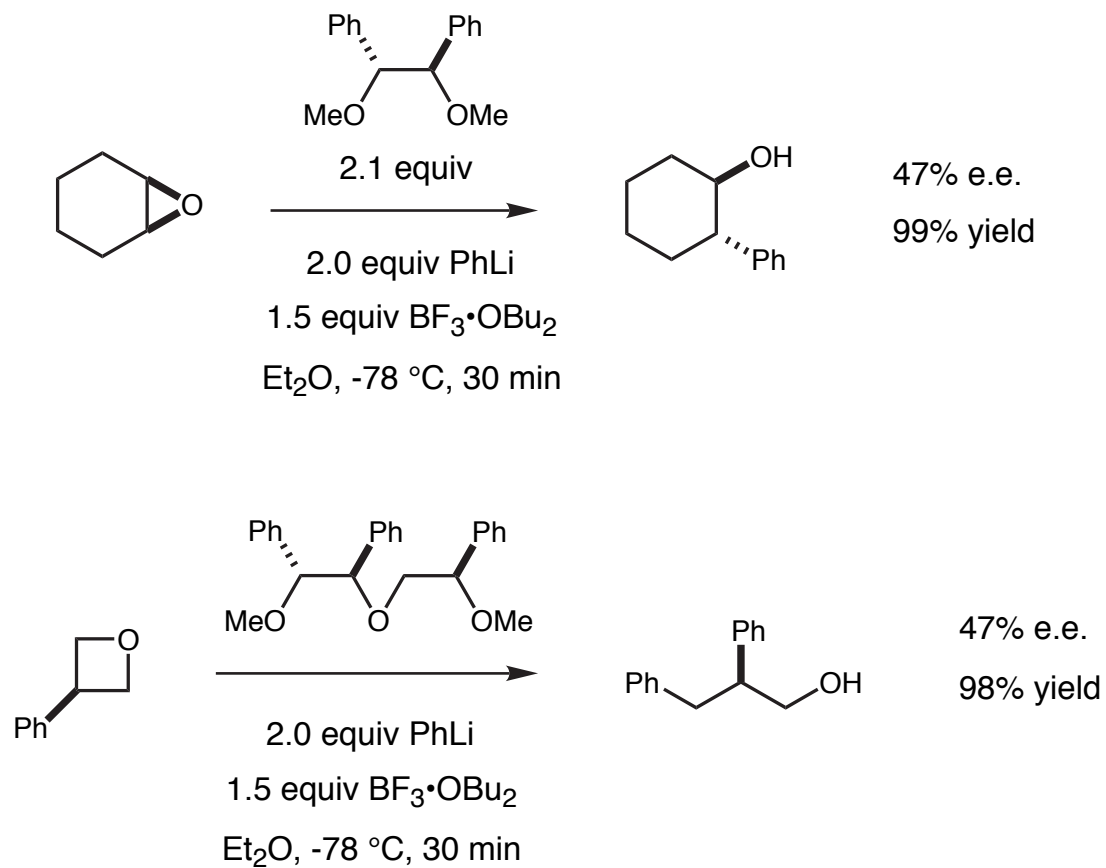


+ $\text{Ti}(\text{O}i\text{Pr})_4$

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

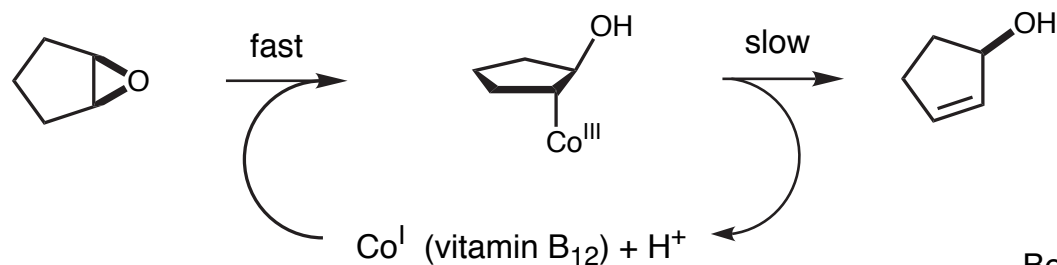
Cole, Shimizu, Krueger, Harrity, Snapper, Hoveyda, *ACIEE*, **1996**, 1668

Phenyllithium Addition to Epoxides and Oxetanes

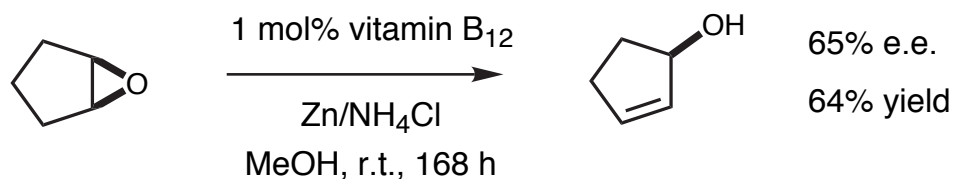


Mizuno, Kanai, Iida, Tomioka, *Tet. Asymm.*, **1996**, 2483

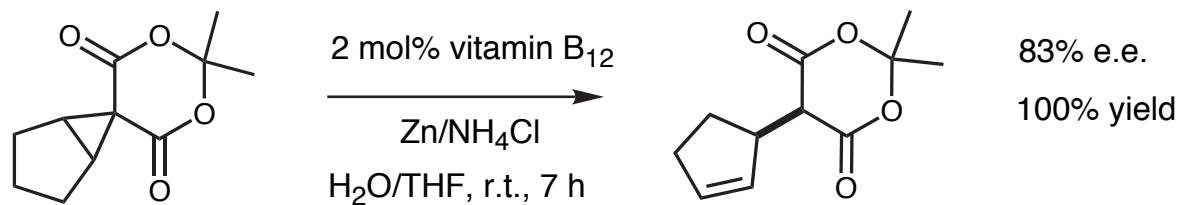
Vitamin B₁₂ Catalyzed Isomerizations



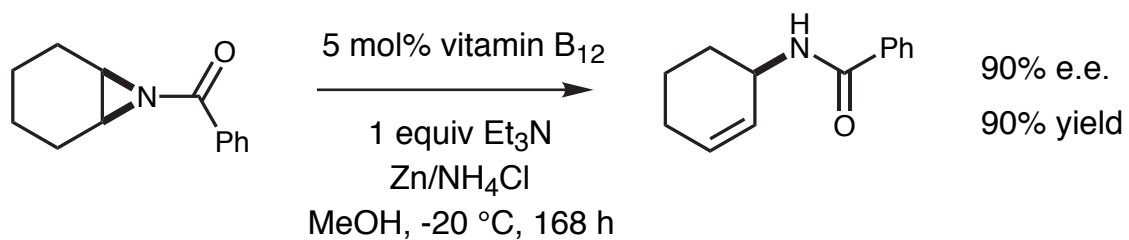
Bonhote, Scheffold, *Helv. Chim. Acta*, **1991**, 1425



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

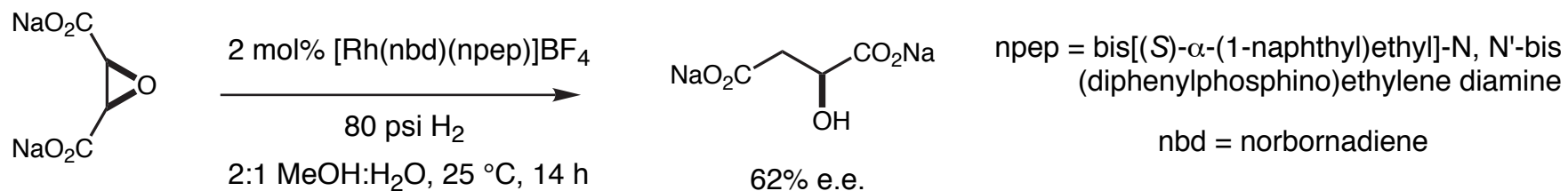


Troxler, Scheffold, *Helv. Chim. Acta*, **1994**, 1193

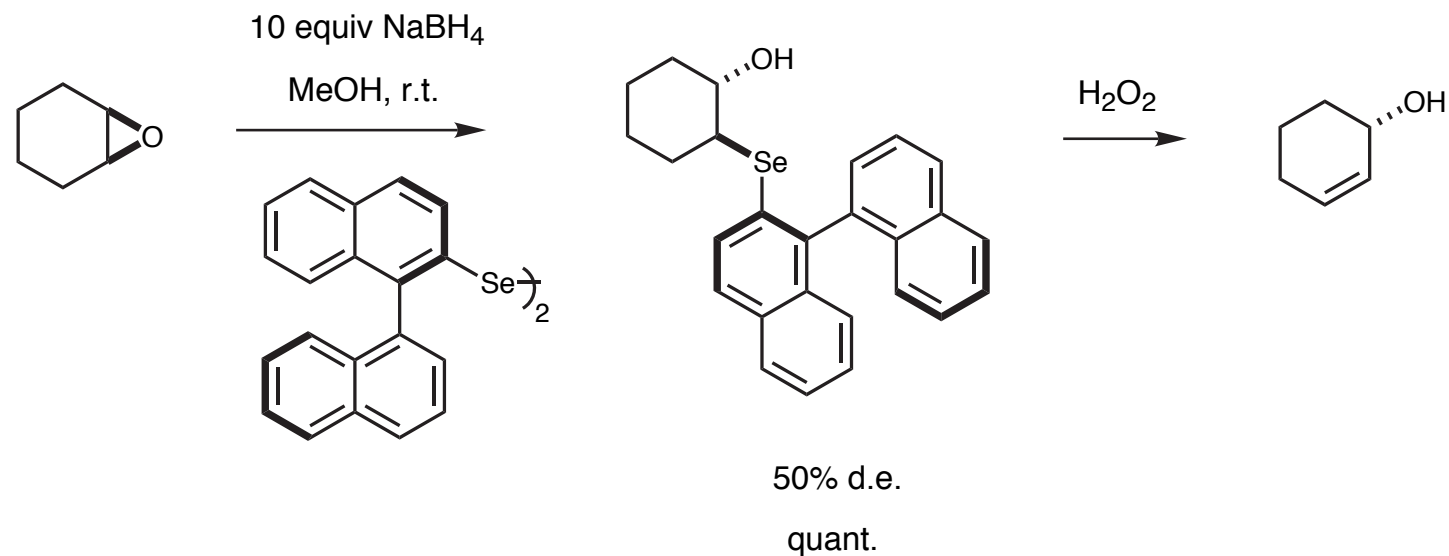


Zhang, Scheffold, *Helv. Chim. Acta*, **1993**, 2602

Additional Transformations of Epoxides



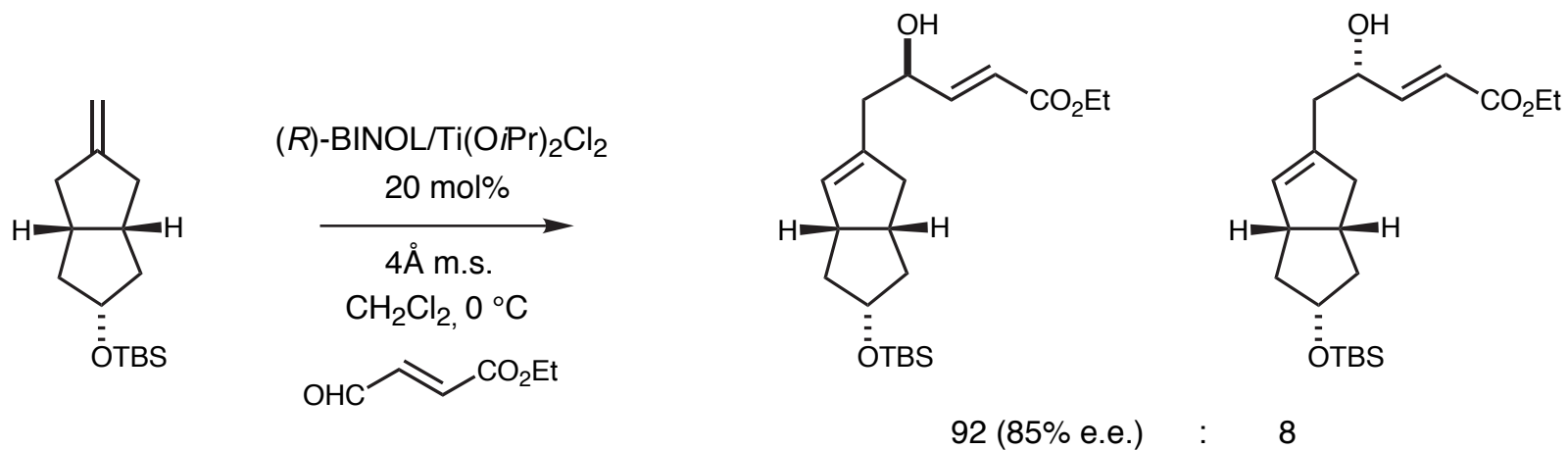
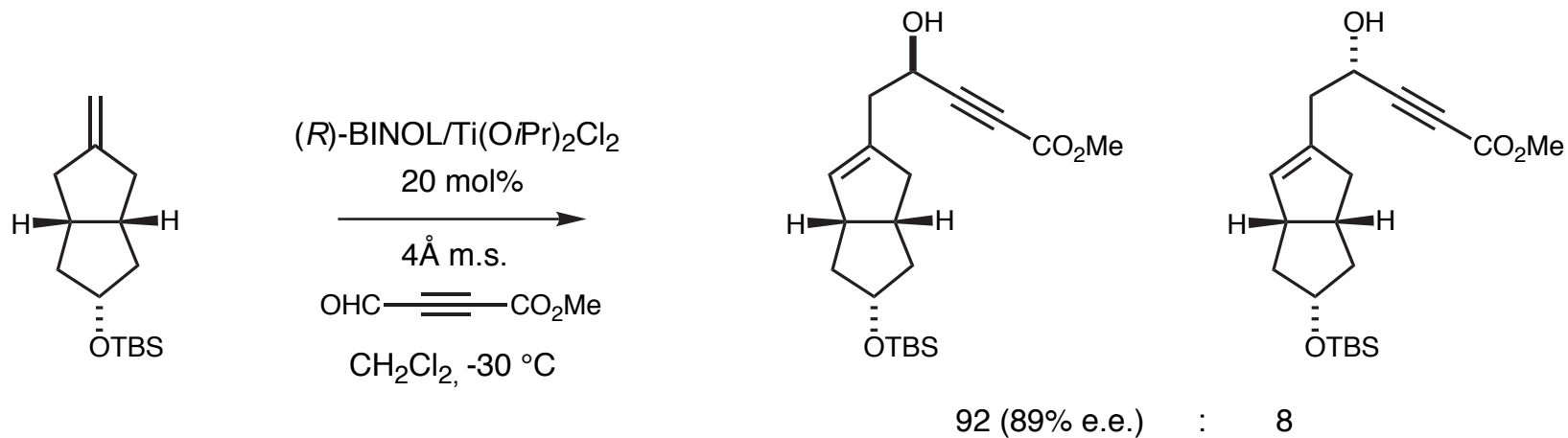
- Carboxylate functionality is necessary for the reaction to proceed.
- Deuterium labelling indicates that direct C-O bond cleavage is operative.



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

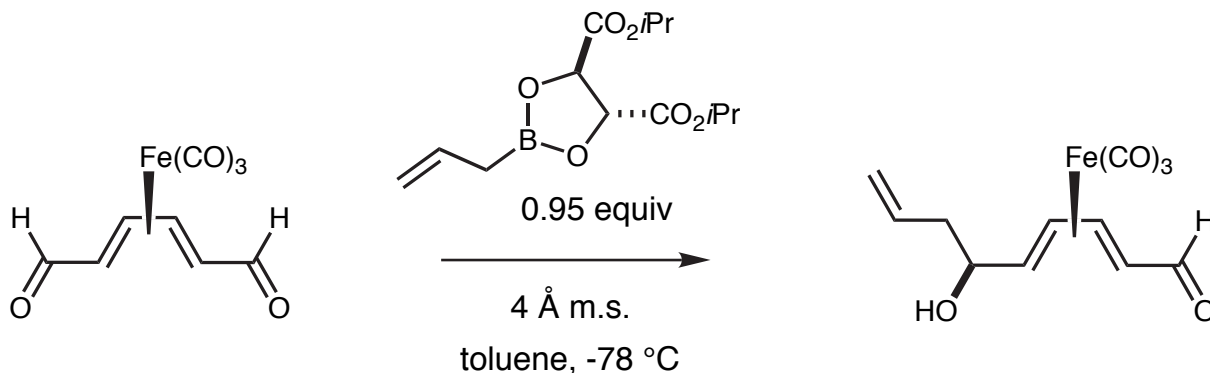
Tomoda, Iwaoka, *Chem. Comm.*, **1988**, 1283

Ene Reaction



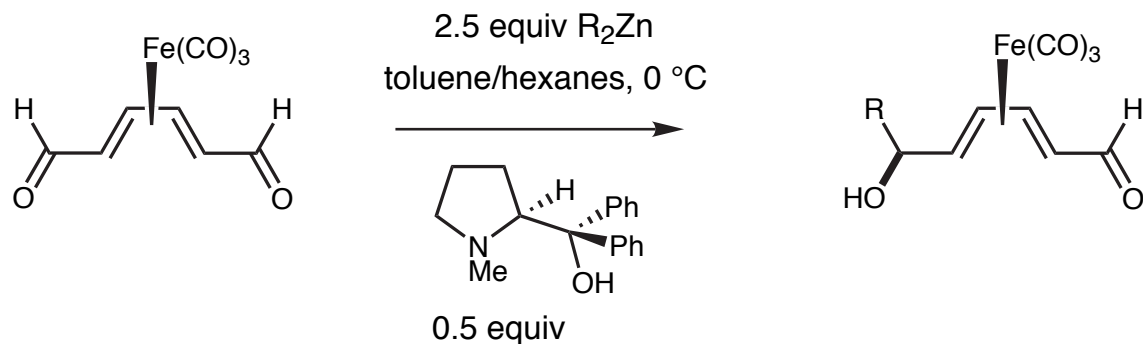
Mikami, Yoshida, Matsumoto, *TL*, **1996**, 8515

Meso Dialdehydes: $Fe(CO)_3$ Complexes

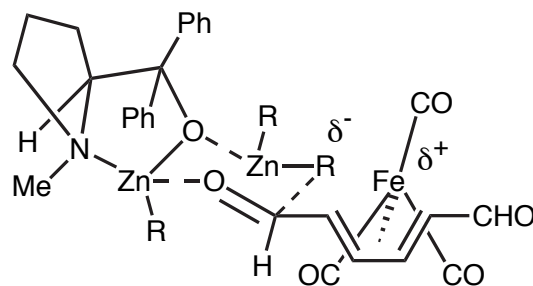


$>98\%$ e.e.
 $45:1$ d.s.
 82% yield

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

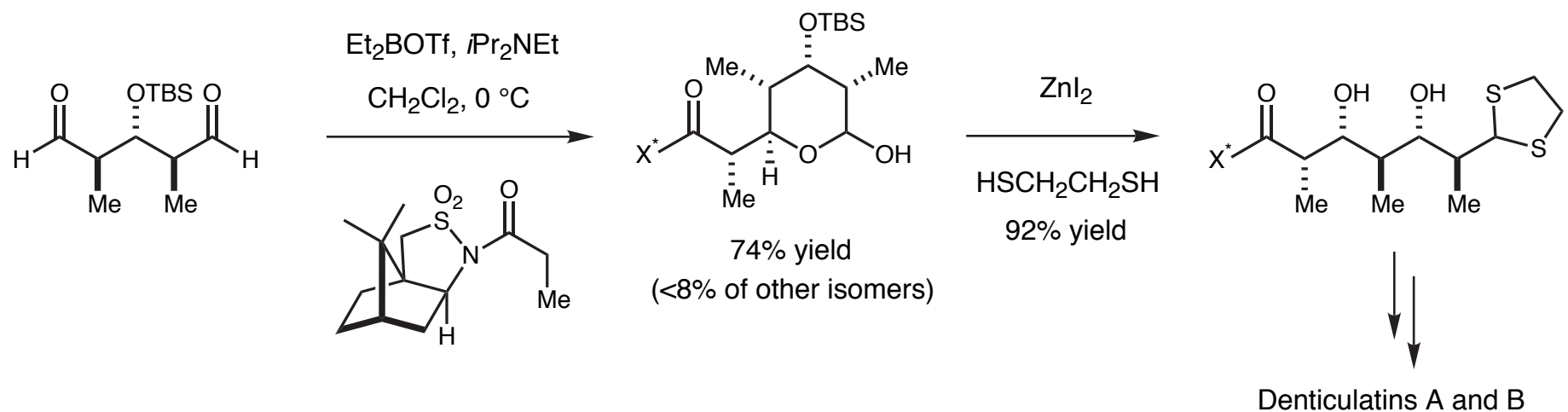


$R = Et$ $>98\%$ e.e., 78% yield
 $R = nPent$ $>98\%$ e.e., 76% yield
 $R = Me$ 86% e.e., 12% yield
 $>90\%$ d.e. observed in all cases.

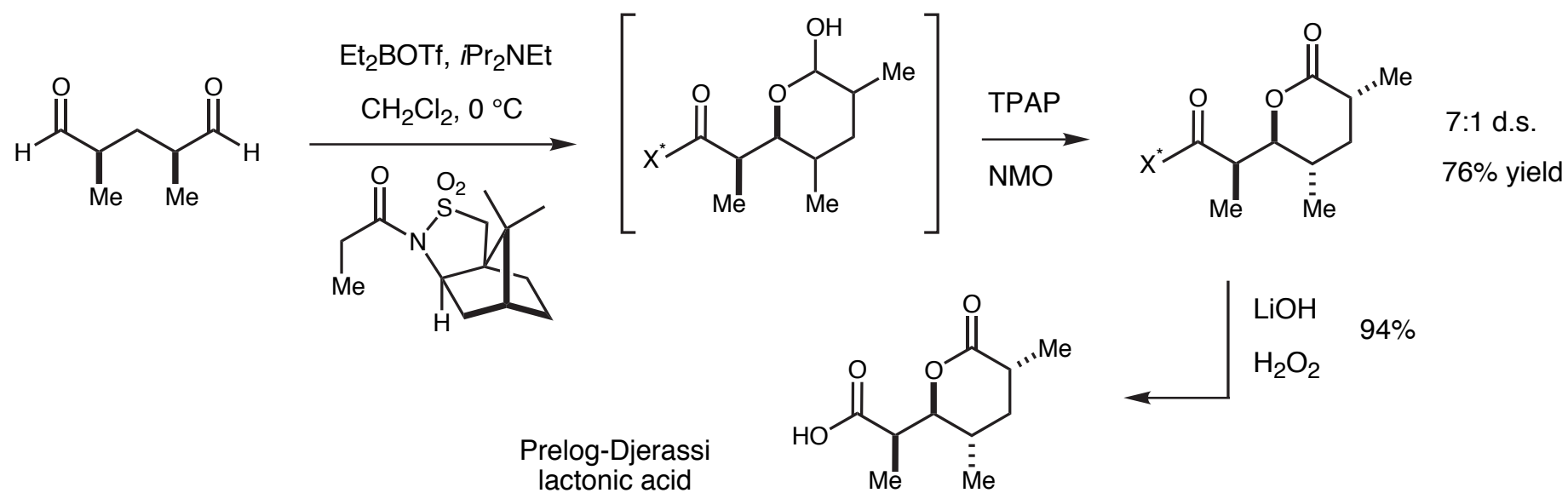


Takemoto, Baba, Noguchi, Iwata, *TL*, **1996**, 3345

Aldol Reactions of Meso Dialdehydes

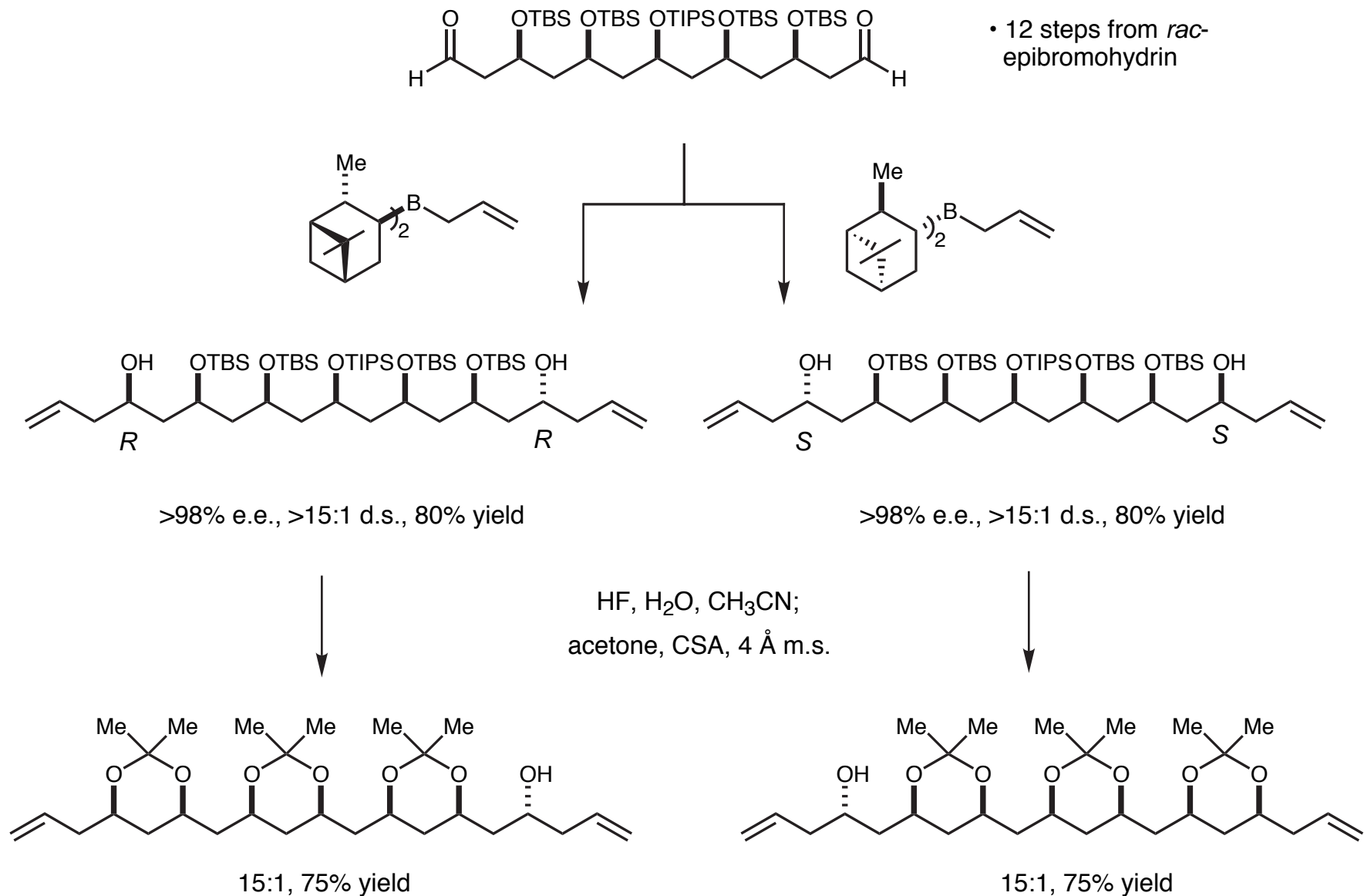


Oppolzer, Brabander, Walther, Bernardinelli, *TL*, **1995**, 4413



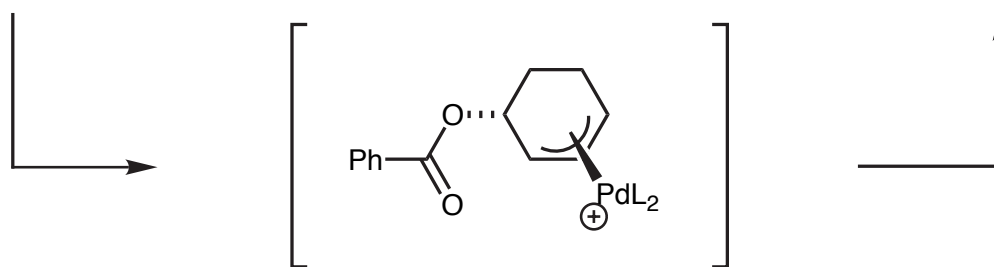
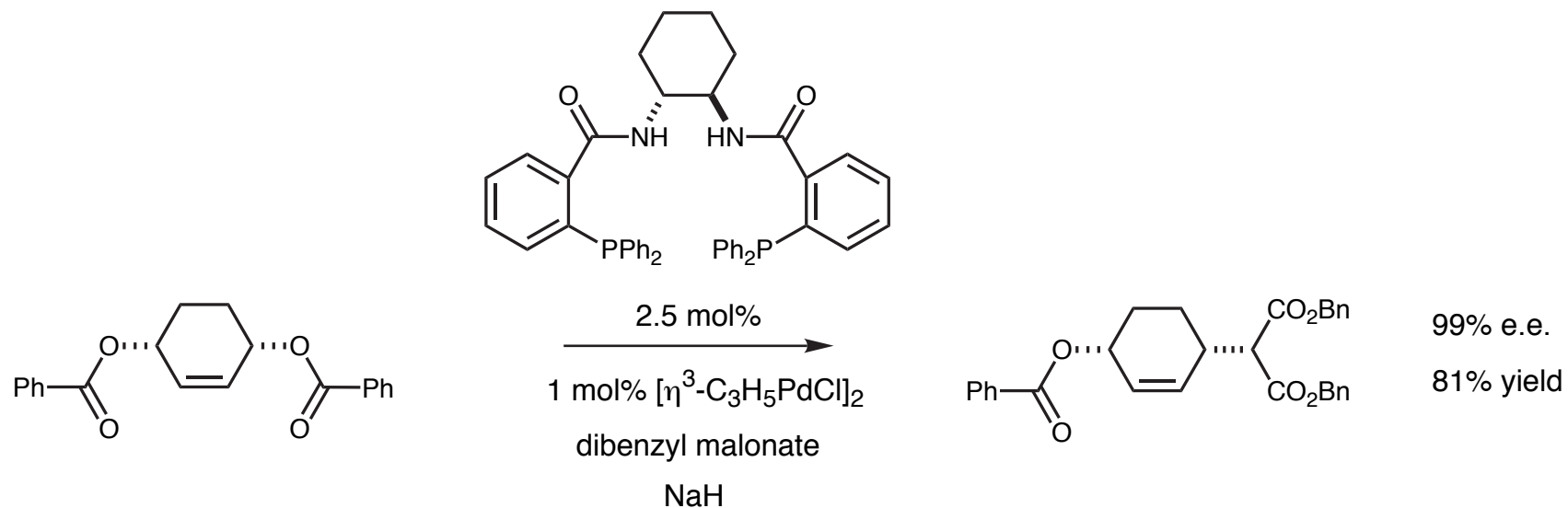
Oppolzer, Walther, Balado, Brabander, *TL*, **1997**, 809

Two Step Symmetry-Breaking via Allylboration



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

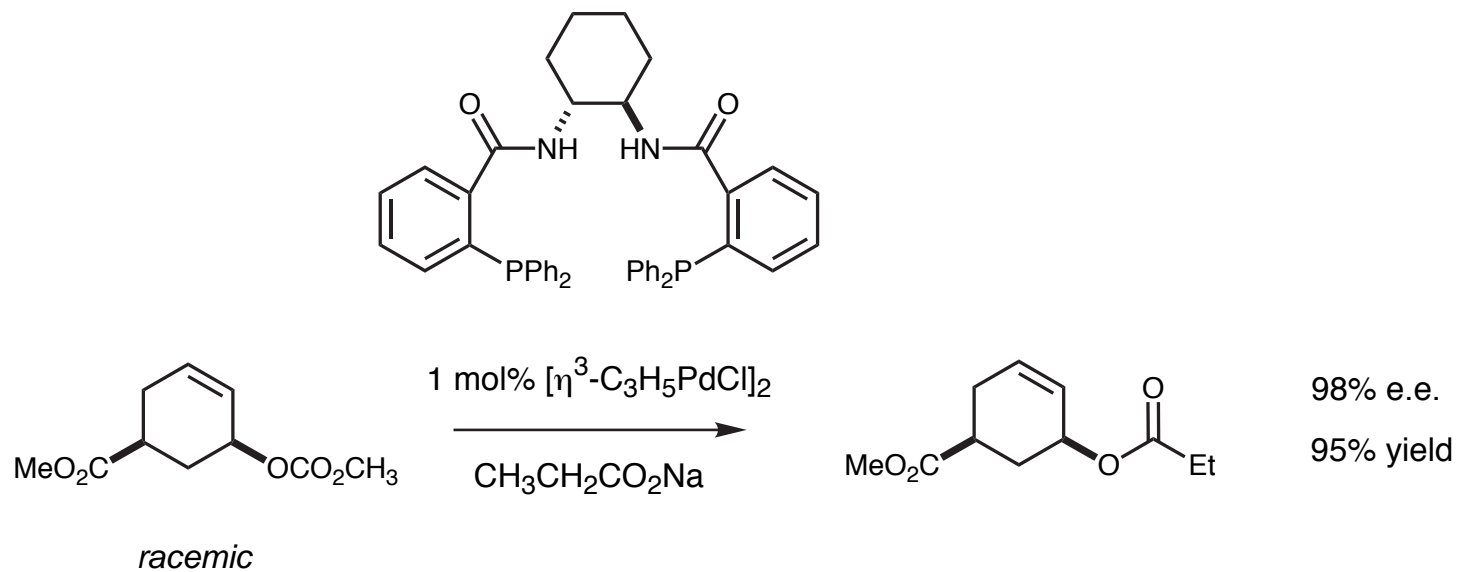
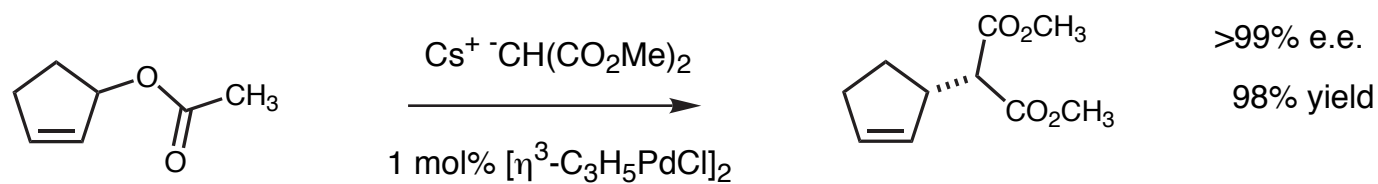
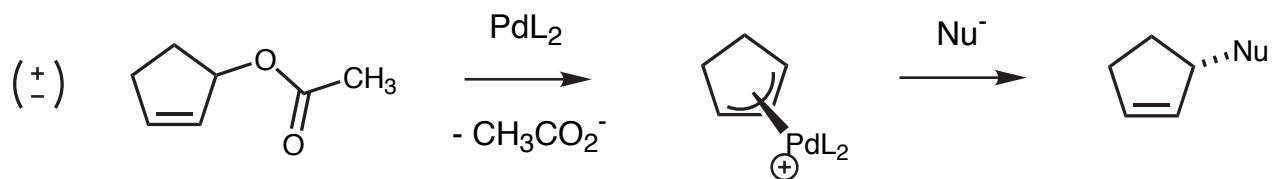
Palladium-Catalyzed Allylic Alkylation



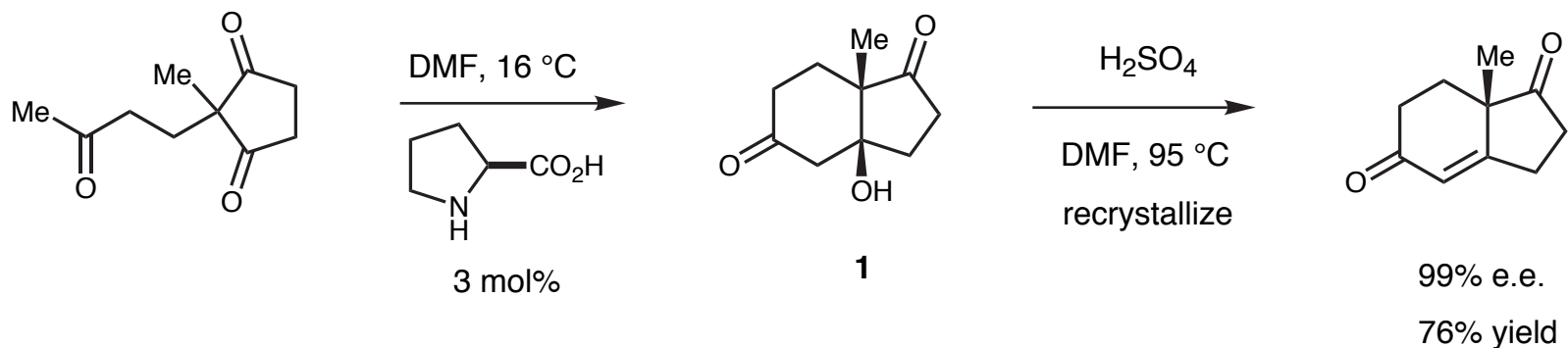
- A variety of nucleophiles can be substituted for malonate (e.g. amines, azides, sulfones).
- 5- and 7-membered rings are also good substrates for this transformation.

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

Deracemization via Meso Intermediates

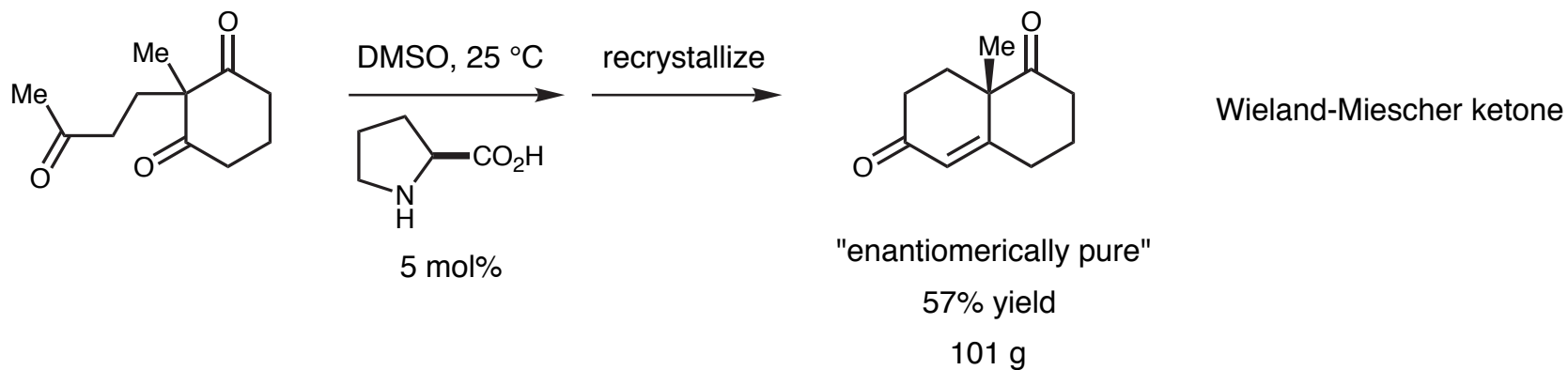


Asymmetric Alkene Formation via Intramolecular Aldol Condensation



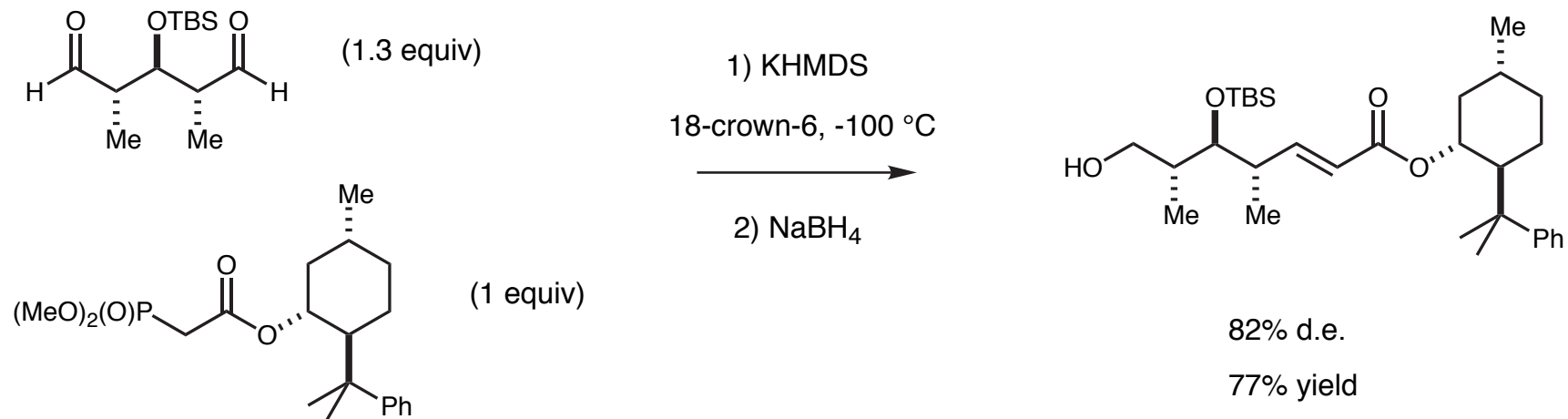
- The optical purity of the unpurified intermediate ketol (**1**) is estimated at 92%.

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



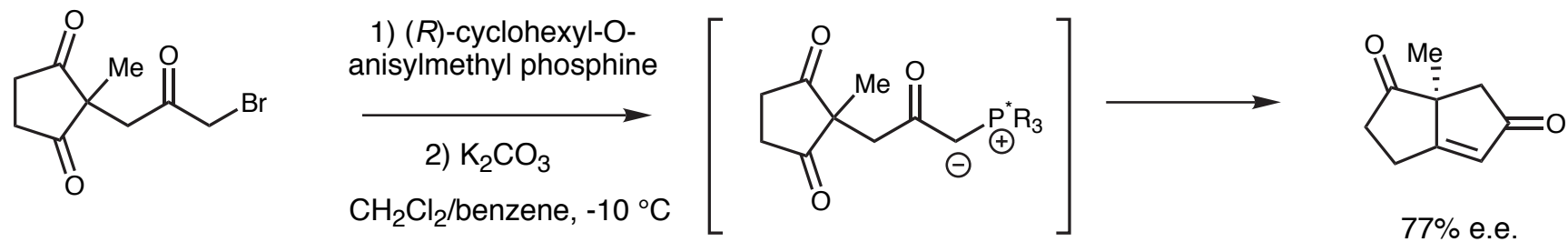
Buchsacher, Furst, Gutzwiller, *Org. Synth.*, **VII**, 368
see also Hagiwara, Uda, *JOC*, **1988**, 2308
Corey, Virgil, *JACS*, **1990**, 6429

Asymmetric Alkene Formation



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

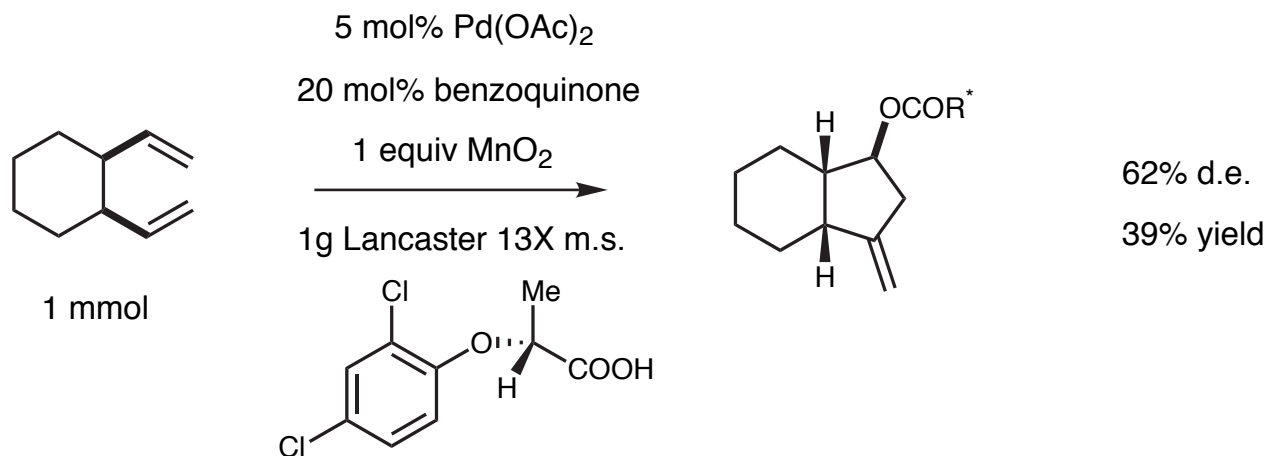
Kann, Rein, *JOC*, **1993**, 3802



"corrected for 88% optical purity of phosphine"

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

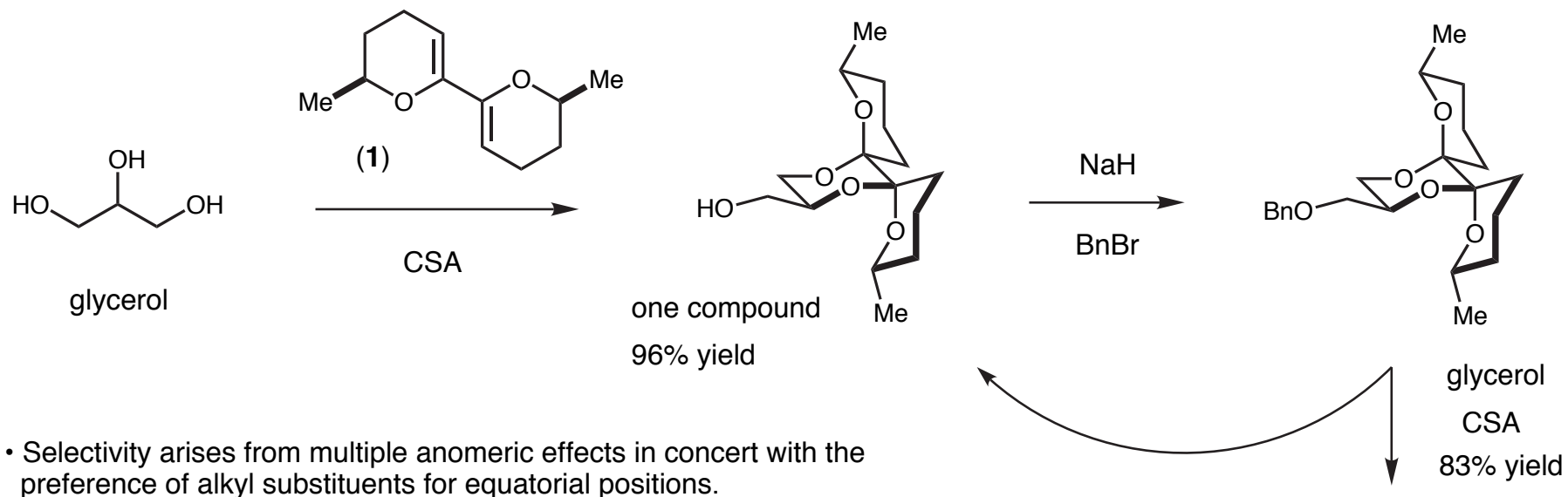
Palladium-Mediated Cyclization



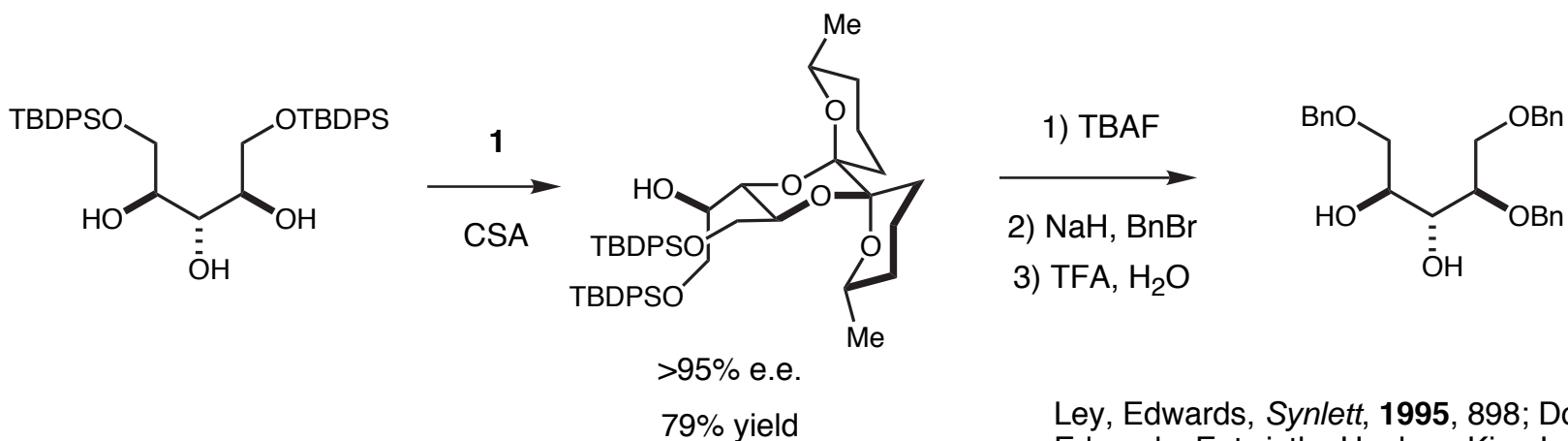
- Only *nondried* molecular sieves were found to increase the observed d.e.
- A wide variety of chiral acids and molecular sieves were screened.
- Evidence suggests that a chiral catalyst is formed and that molecular sieves increase the rate of its formation.
- Sieves with higher sodium content provide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

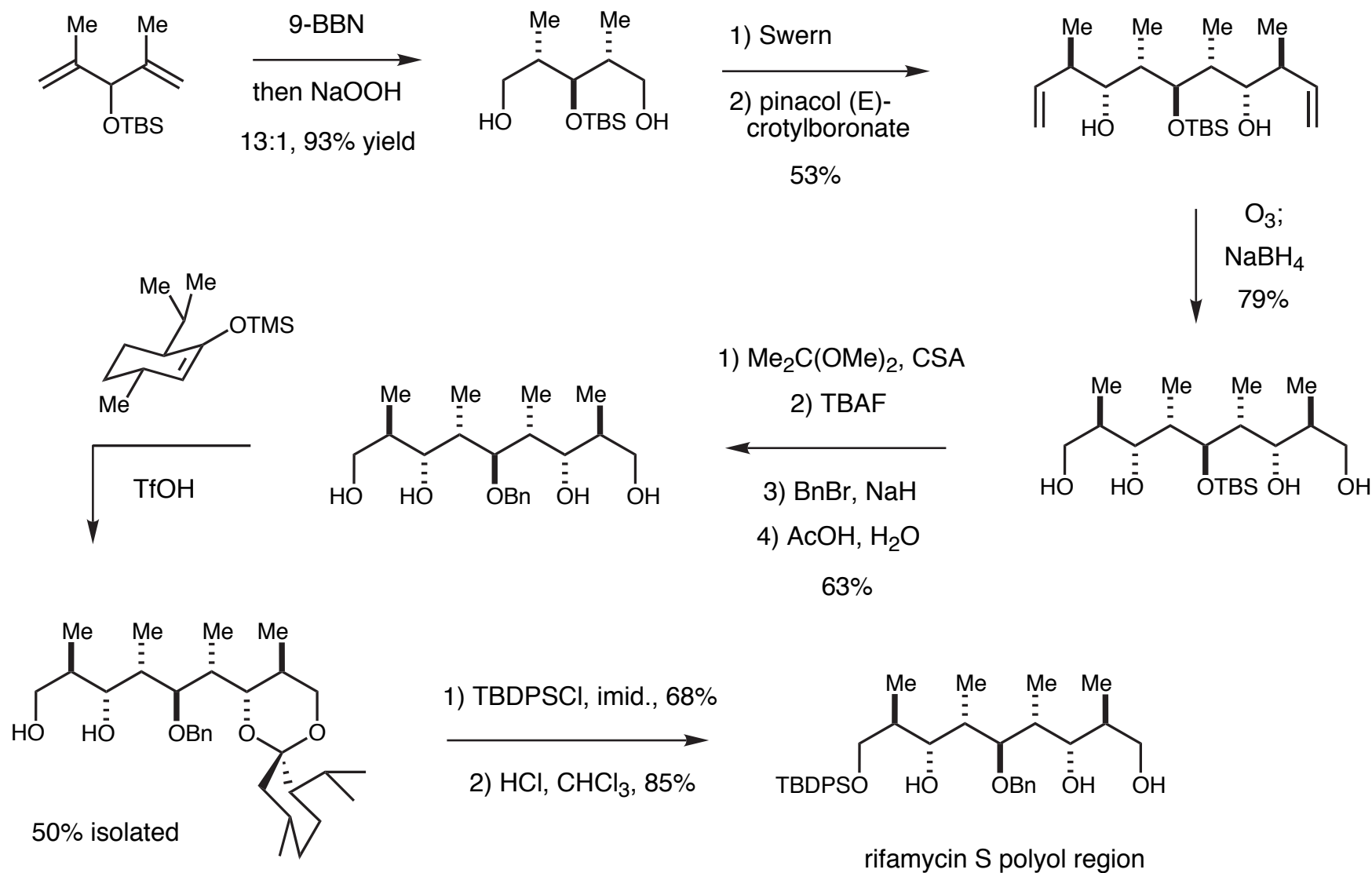


Boons, Entwistle, Ley, Woods, *TL*, **1993**, 5649



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

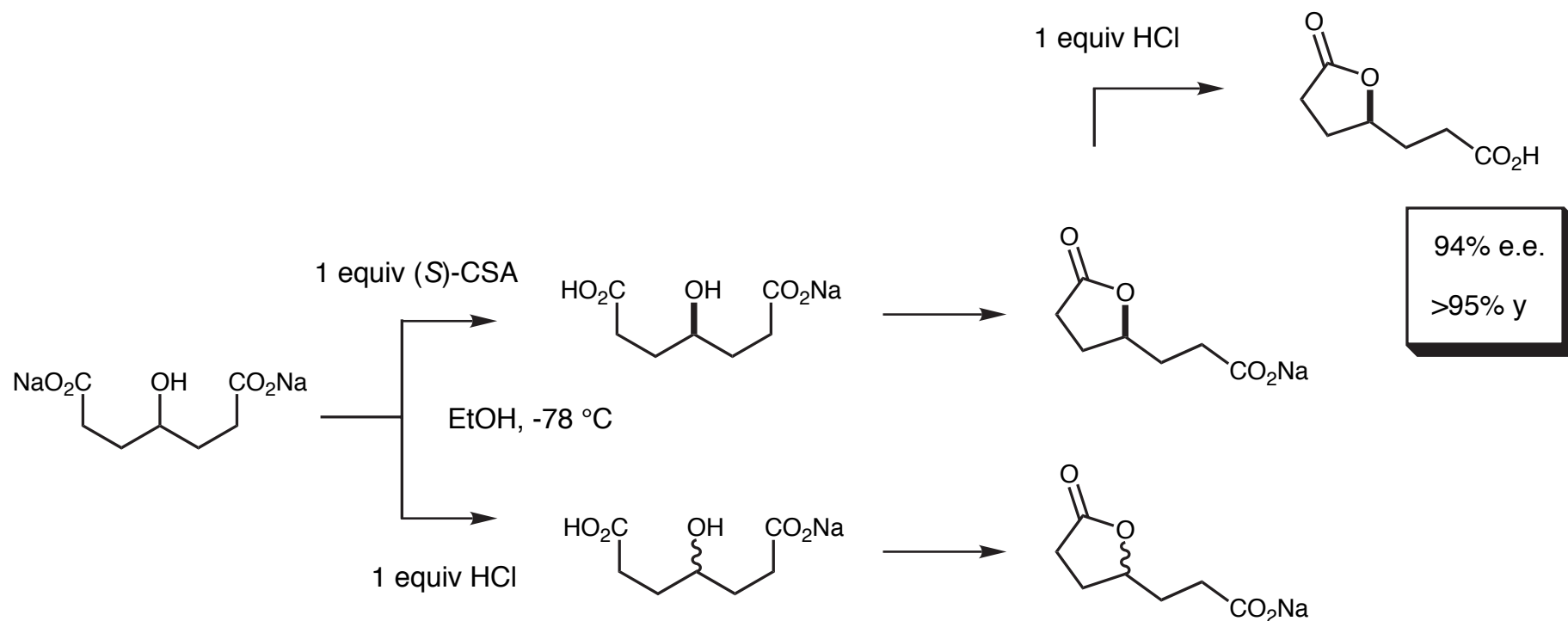
Polyol Desymmetrization via Menthone Ketalization: Applications



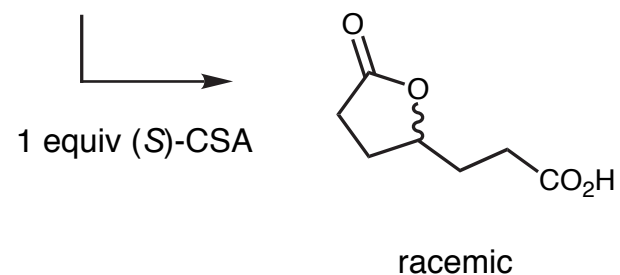
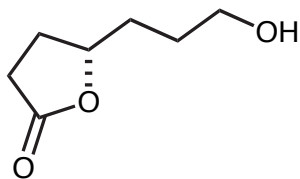
(11% undesired, 12% bis(ketal), 10% s.m.)

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

Enantioselective Lactonization

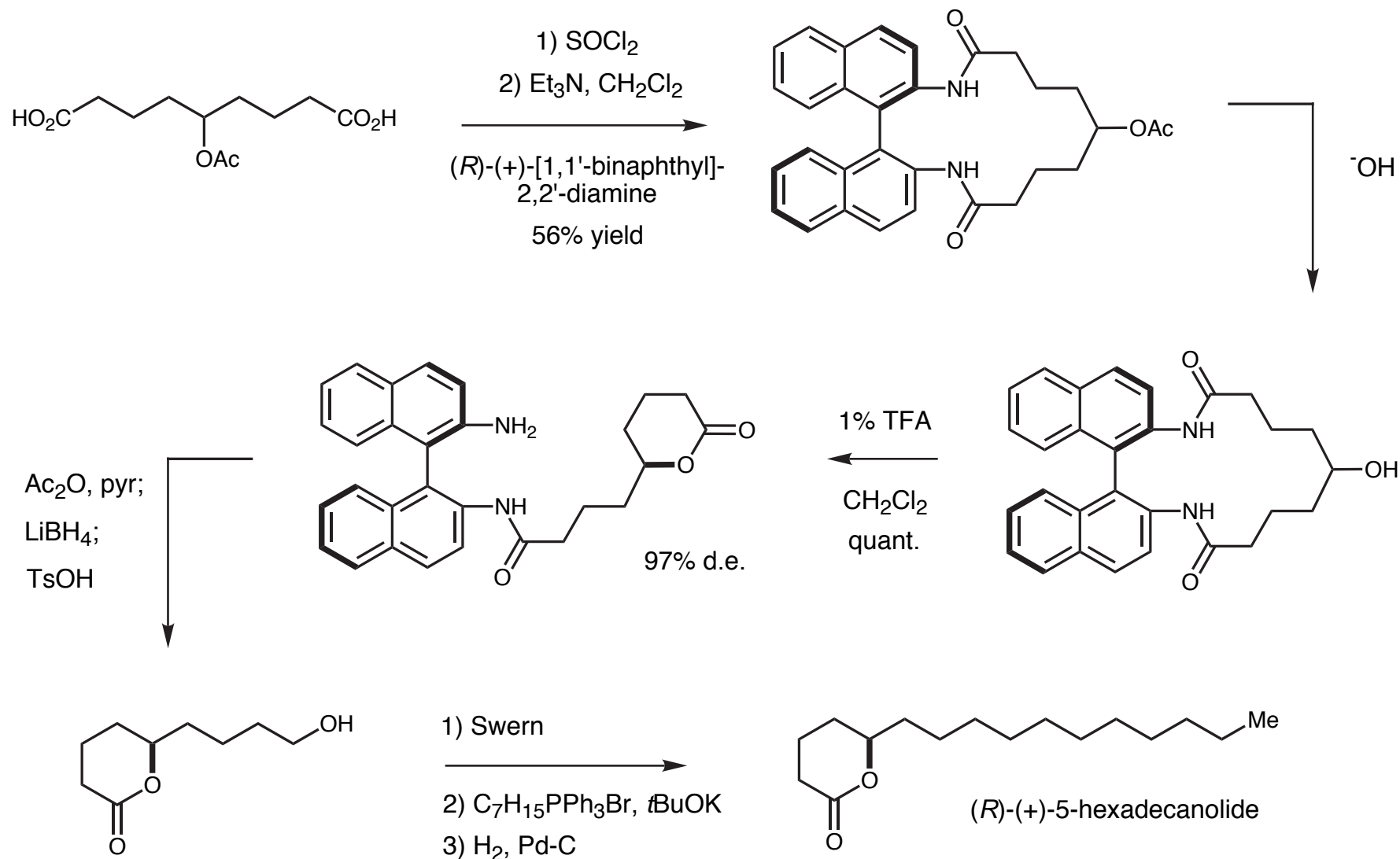


- A concentration of .002-.005 M is optimal (78 mg in 100 ml).
- CSA was used as its monohydrate.
- One recrystallization of the product gives enantiopure material.
- Reduction of the product with BH_3 or LAH gives either antipode of:



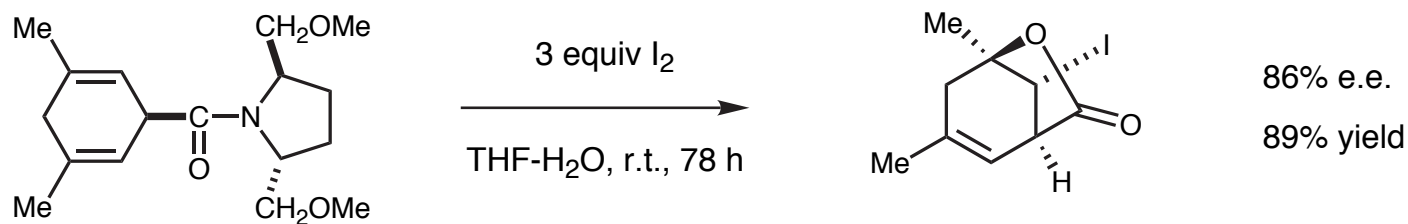
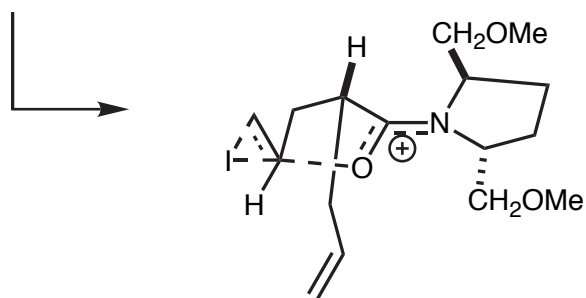
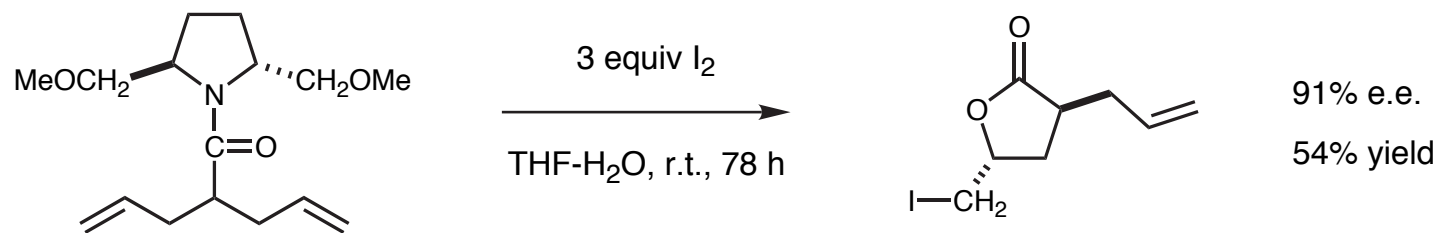
Fuji, Node, Terada, Murata, Nagasawa, *JACS*, **1985**, 6404

Enantioselective Lactonization via Binaphthyl Amides



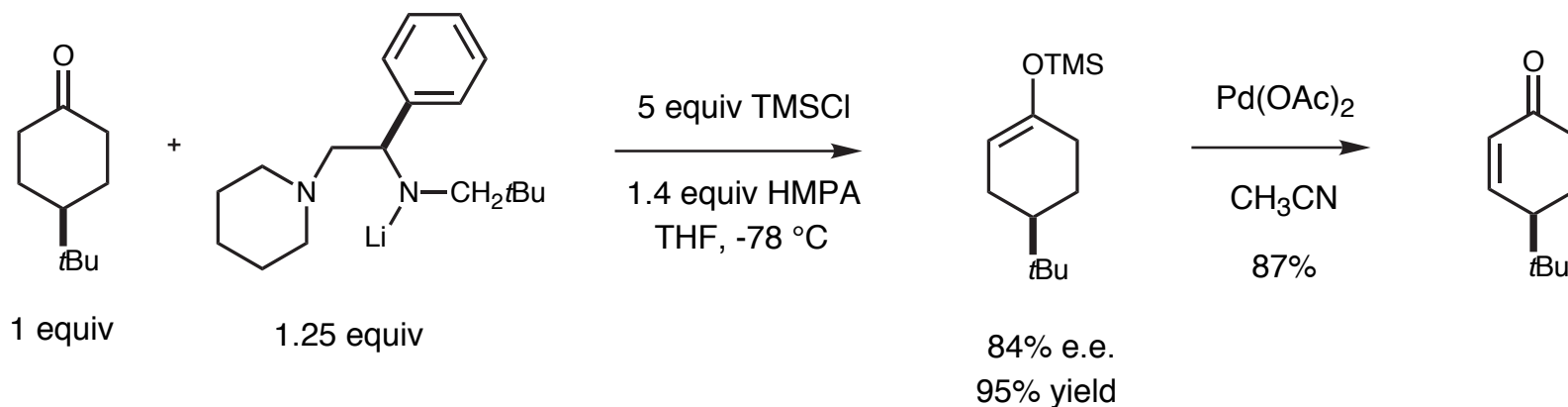
Sakamoto, Yamamoto, Oda, *JACS*, **1987**, 7188

Enantioselective Iodolactonization



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

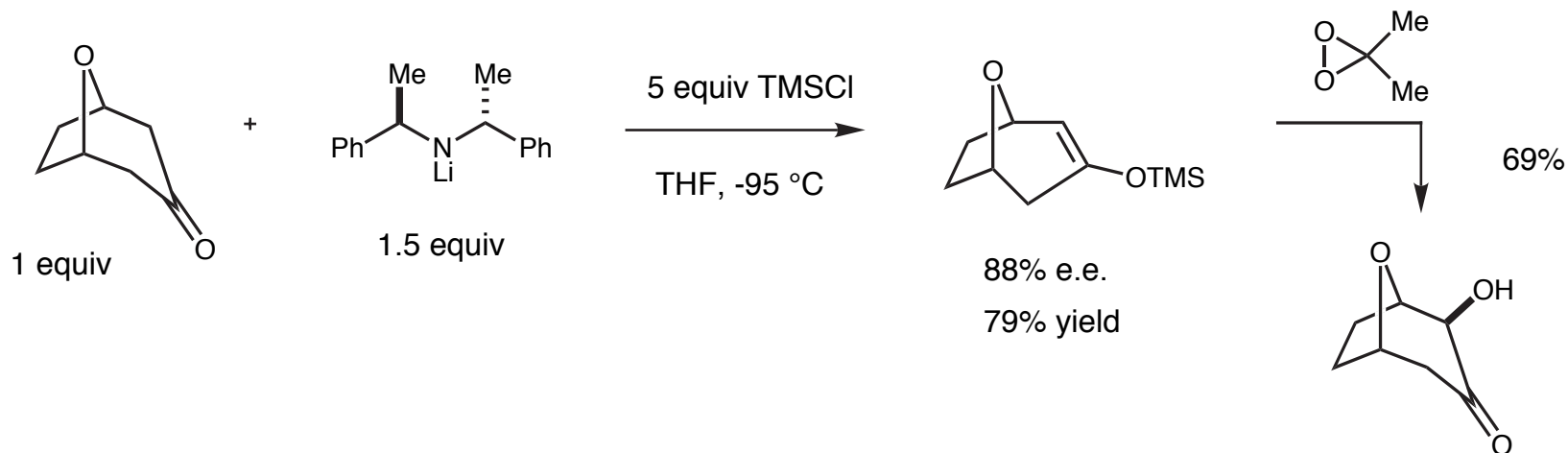
Enantioselective Ketone Deprotonation



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

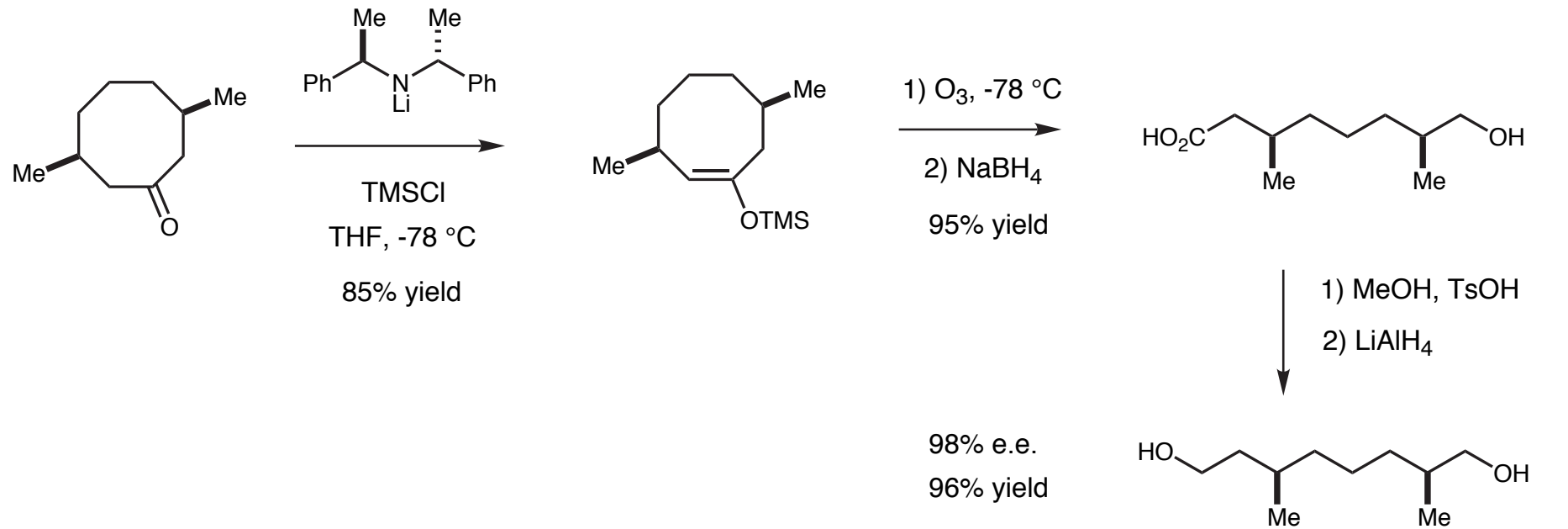
Toriyama, Sugasawa, Shindo, Tokutake, Koga, *TL*, **1997**, 567

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

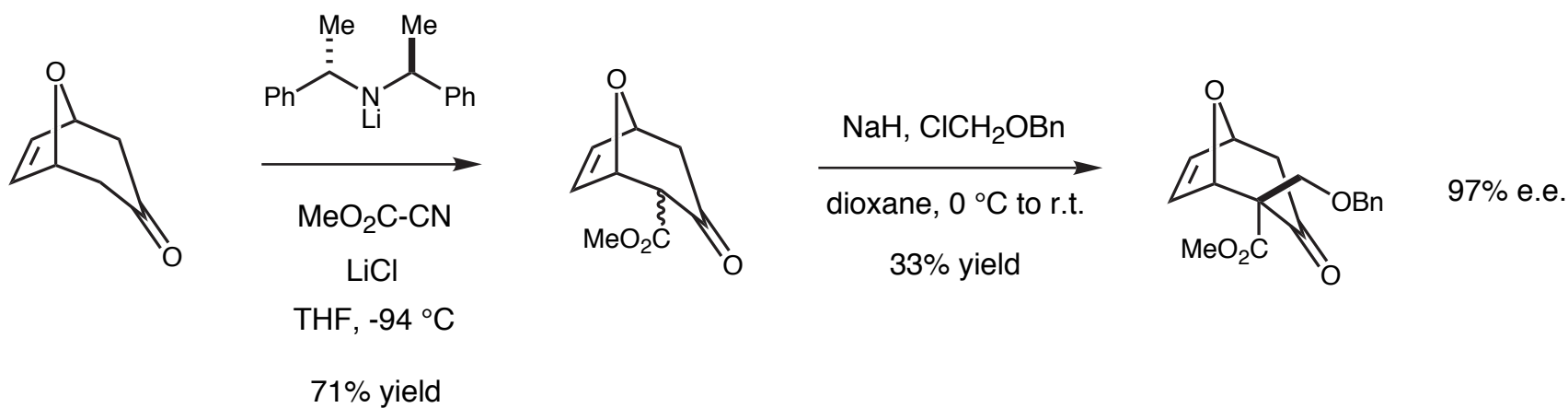


Bunn, Cox, Simpkins, *Tet.*, **1993**, 207

Enantioselective Ketone Deprotonation: Applications

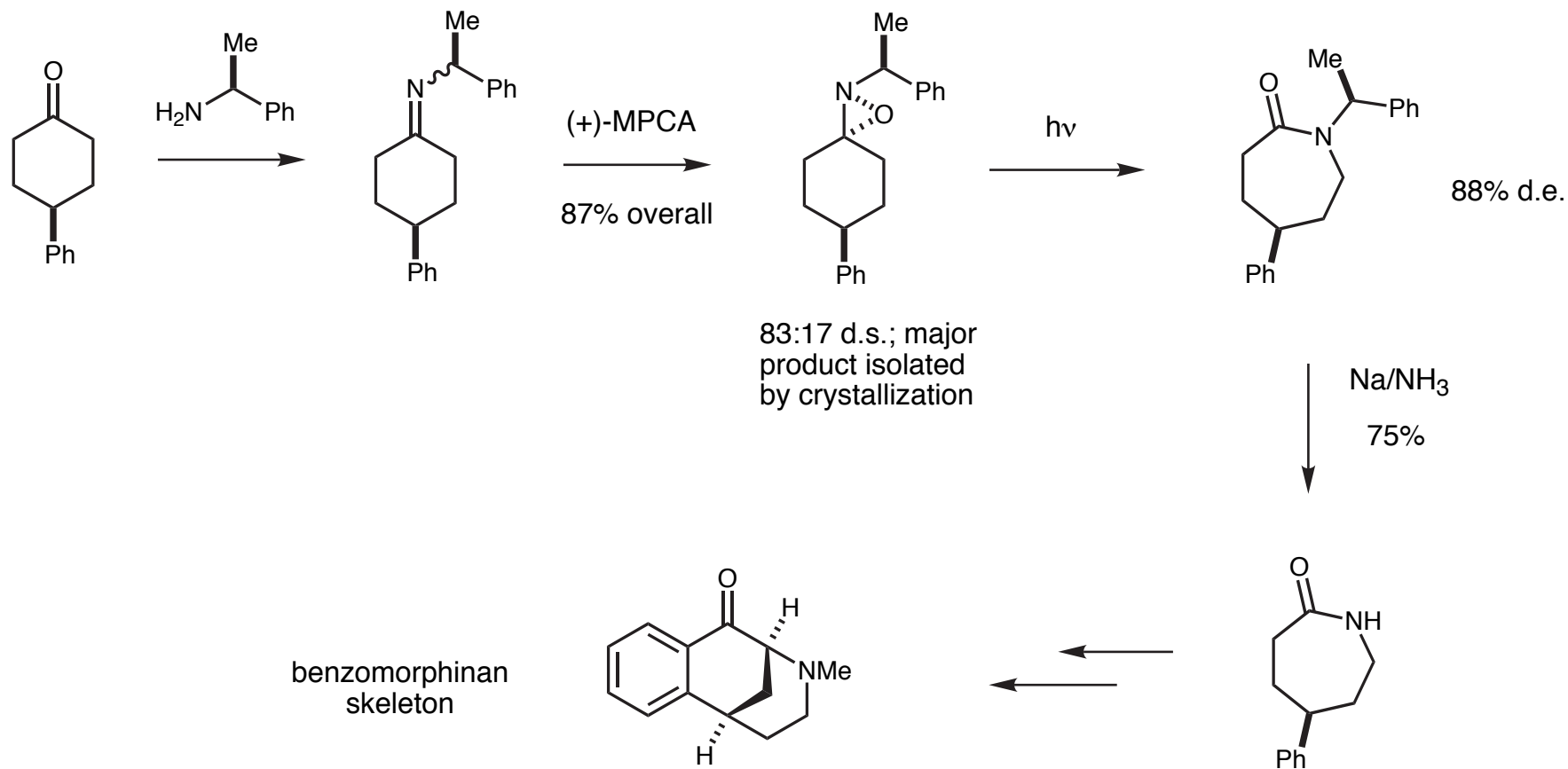


Berkowitz, Wu, *JOC*, **1997**, 1536



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

Asymmetric Nitrogen Insertion



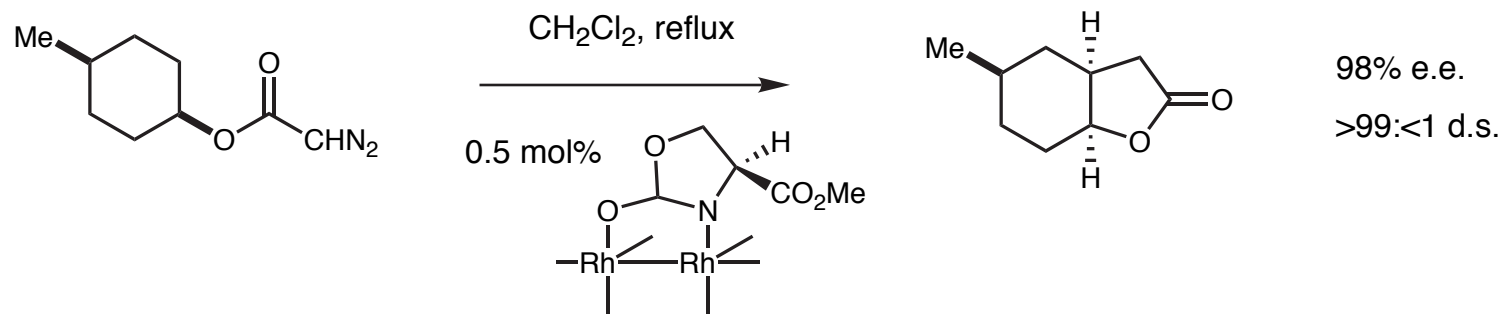
• (+)-MPCA = monoperoxycamphoric acid

• 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

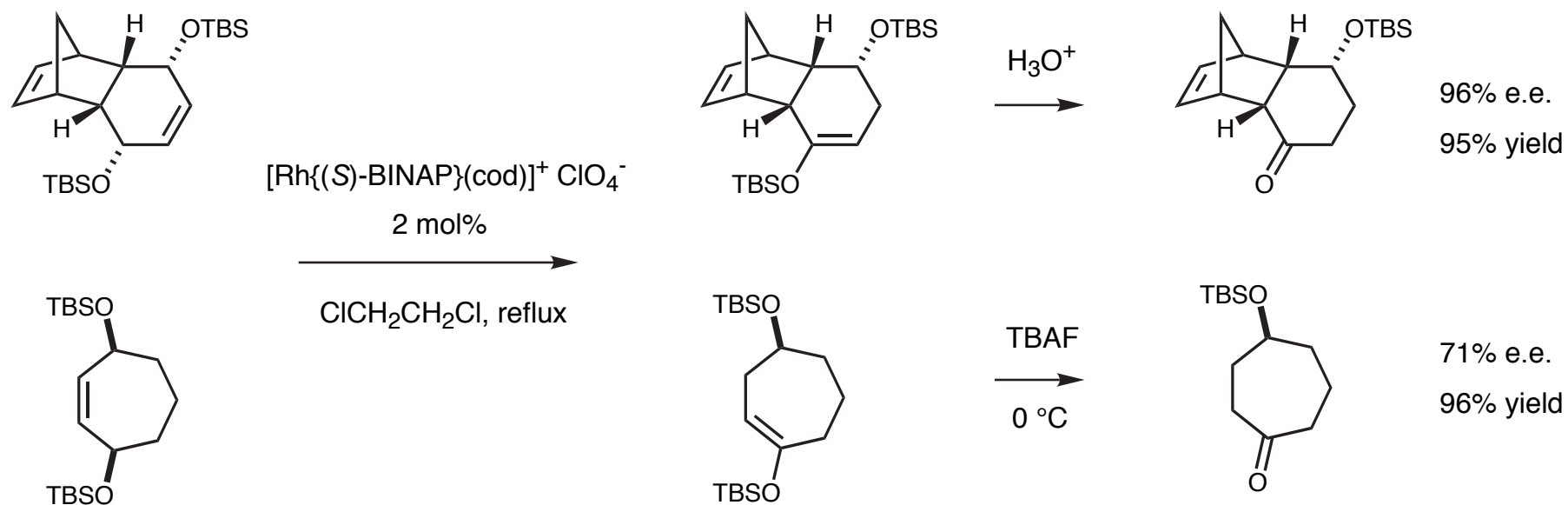
Rhodium Catalyzed Processes

- Enantioselective C-H Insertion



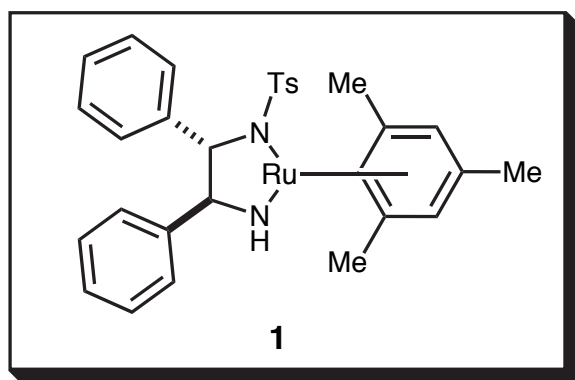
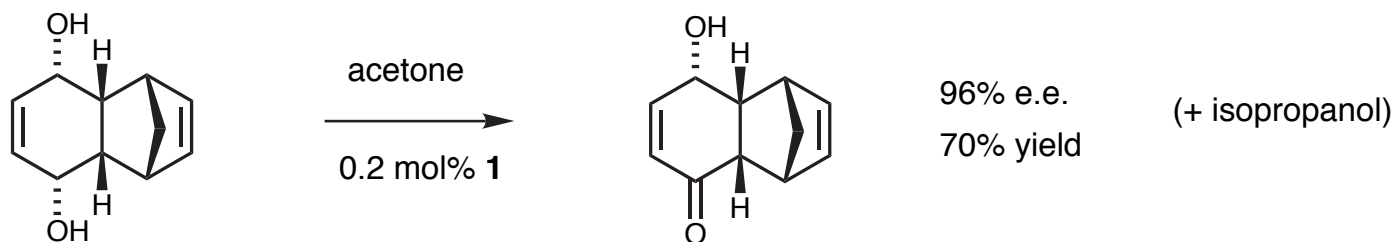
Doyle, Dyatkin, Roos, Canas, Pierson, Basten, *JACS*, **1994**, 4507

- 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.

