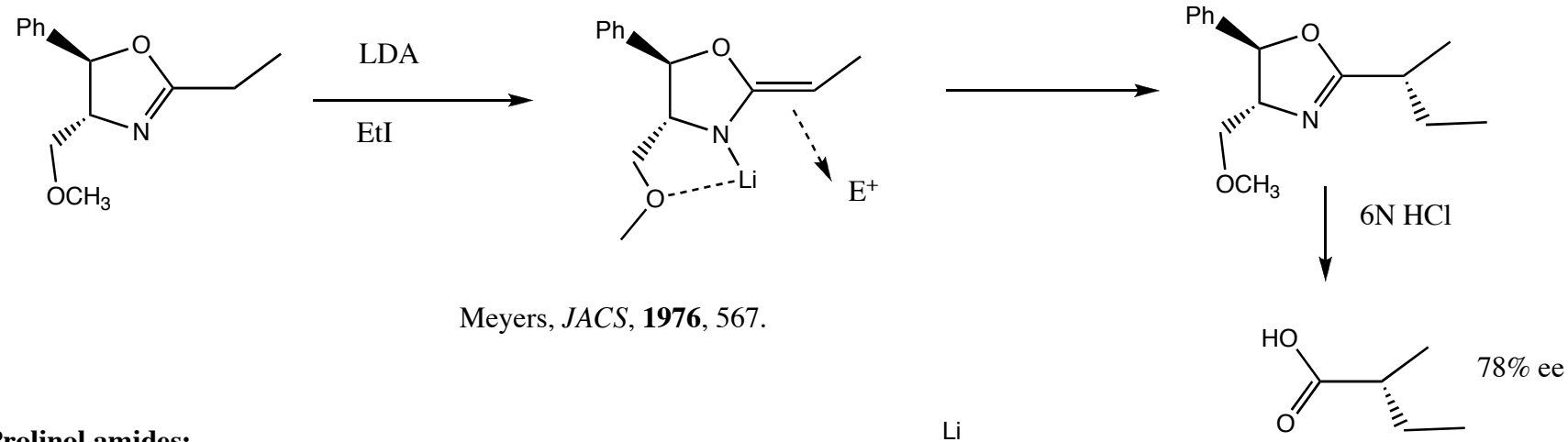
Requirements for an Effective Chiral Auxiliary Enolate Alkylation

1. Xc must be low cost, and available in both enentiomeric forms
2. The cleavage of Xc from the substrate must occur under mild enough conditions so that racemization is avoided.
3. The pi-facial selectivity of electrophile attack on the enolate will be dictated by sterics.
4. Either *E* or *Z* enolate should be formed exclusively
5. Metal ion chelation provides a rigid template and a single conformation, so that the sterics of the auxiliary can enforce facial bias in electrophile attack on the enolate

Early examples of Chiral auxiliaries for enolate alkylation

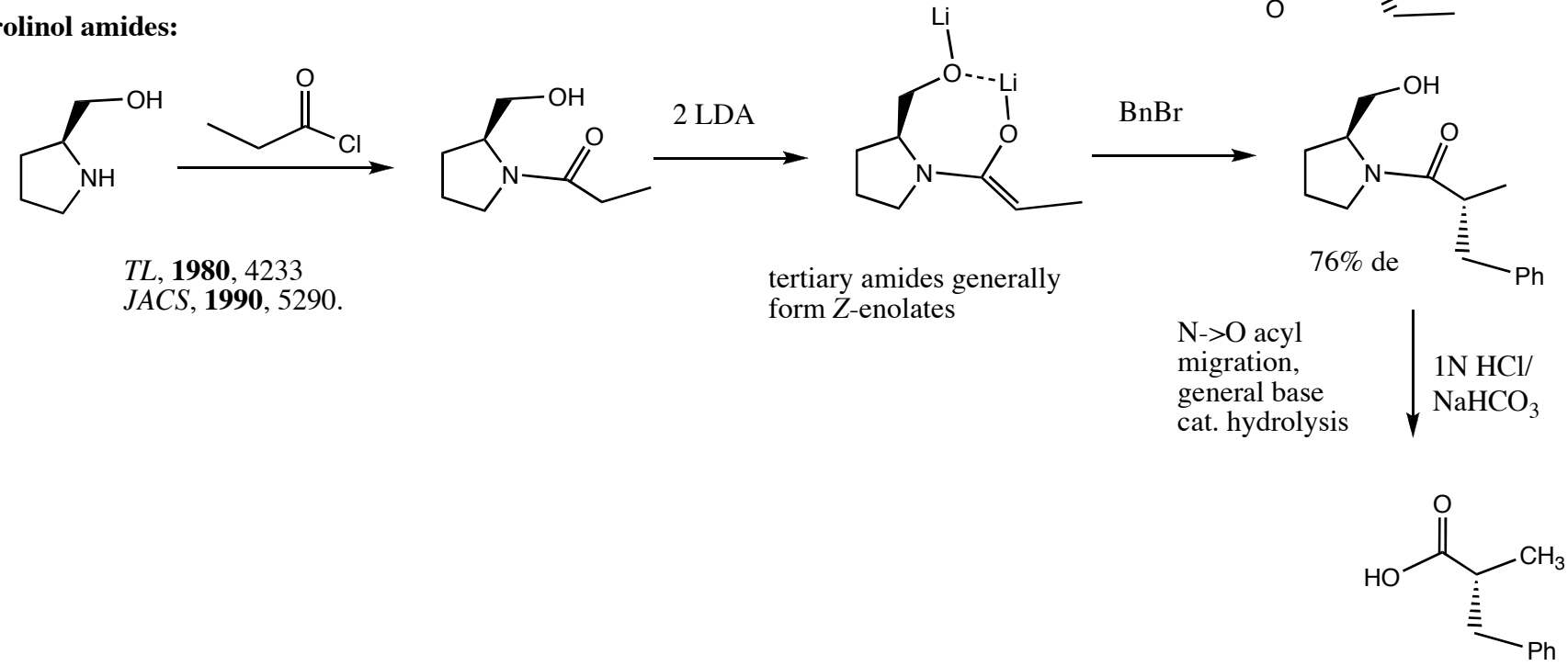
2-Oxazolines as Carbonyl Equivalents

phenyl shields top face



Meyers, *JACS*, **1976**, 567.

Prolinol amides:

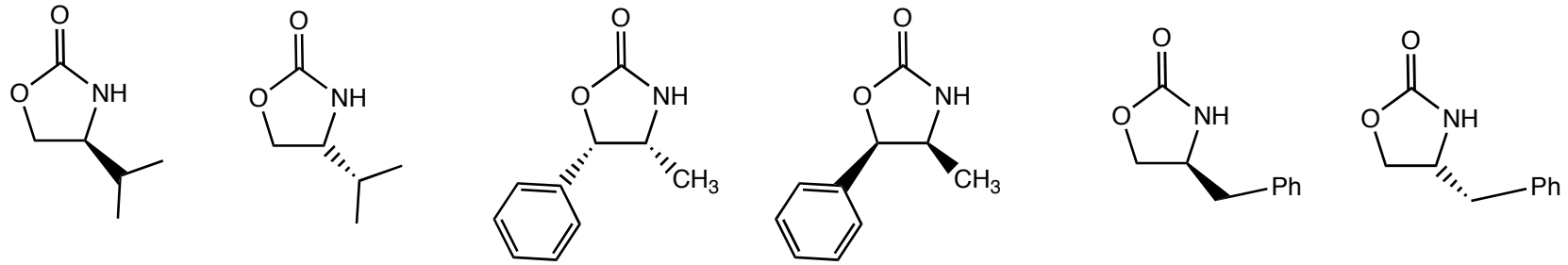


TL, **1980**, 4233
JACS, **1990**, 5290.

tertiary amides generally
form *Z*-enolates

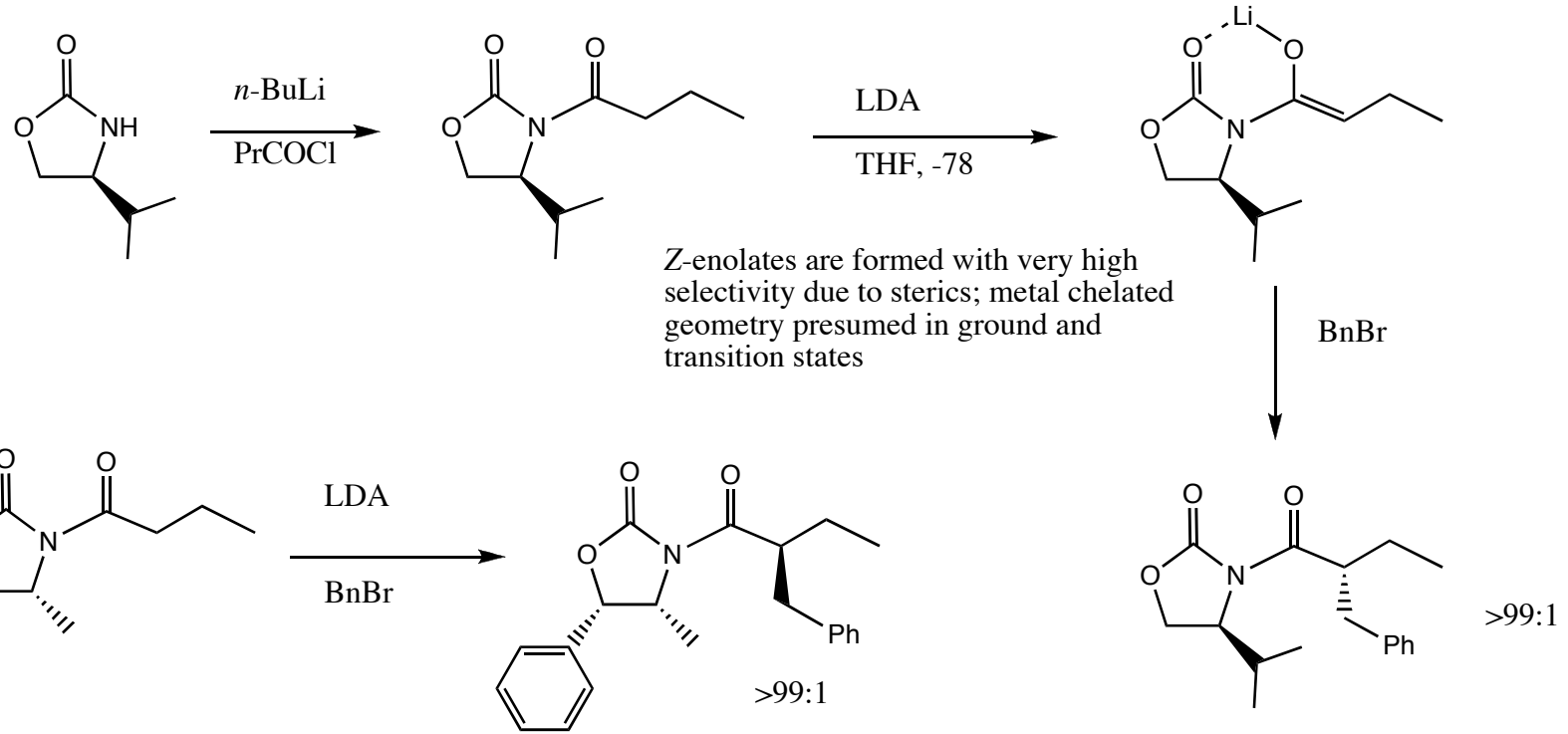
Evans Chiral Auxiliary

Enantiocomplementary Reagents:

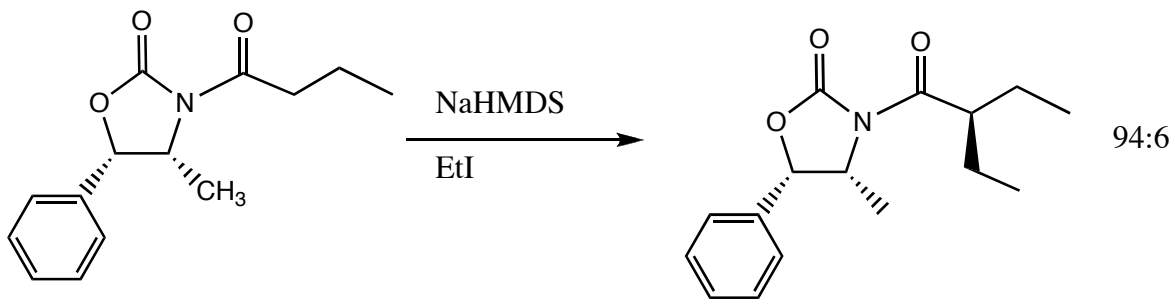


JACS, **1982**, *104*, 1737.

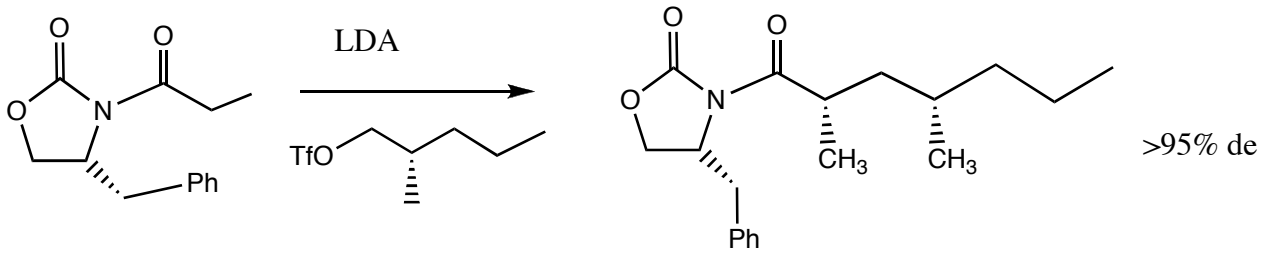
Acylaton provides imides, closer to esters in terms of acidity, enolate nucleophilicity, and cleavage chemistry:



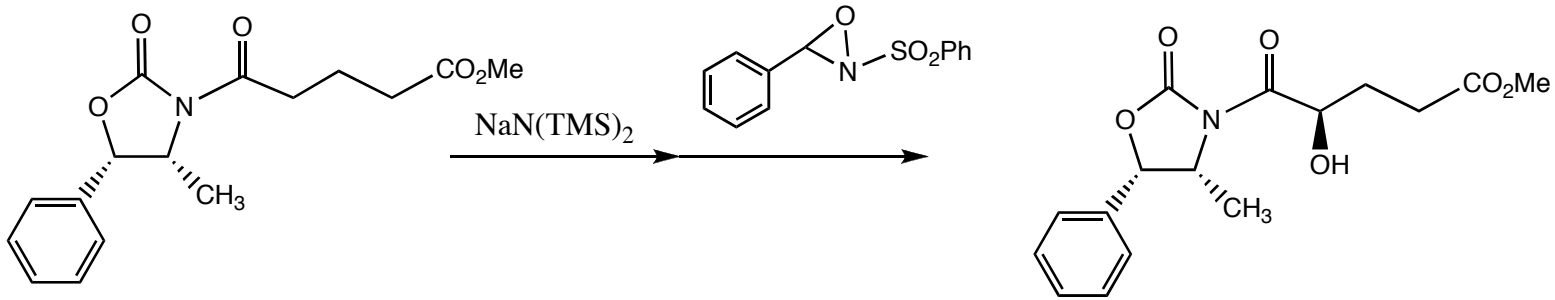
Less Reactive Electrophiles: Use sodium enolate



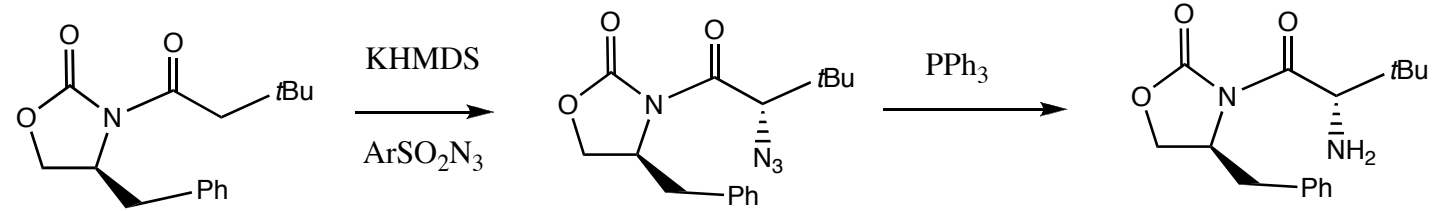
Alternatively, use triflate:



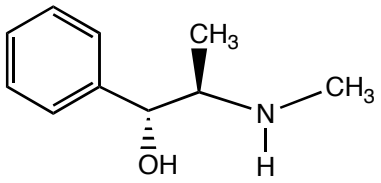
Enolate Oxidation- use Davis Oxaziridine: *JACS*, 1985, 4346



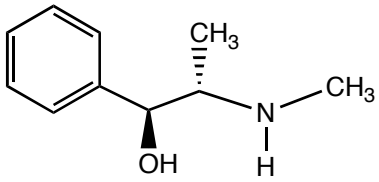
Aziridination: Amino acid synthesis: *JACS*, 1990, 4011.



Pseudoephedrine as a Chiral Auxiliary



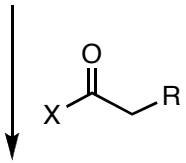
R,R-(-)-pseudoephedrine

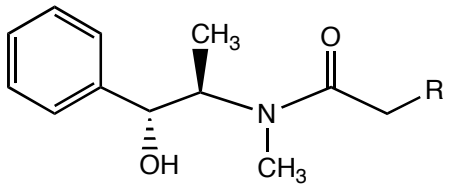


S,S-(+)-pseudoephedrine

cheap, commercially available chiral amino alcohols

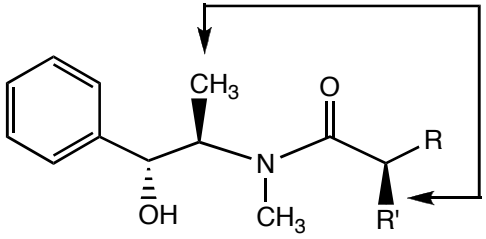
Myers, *JACS*, **1997**, *119*, 6496.





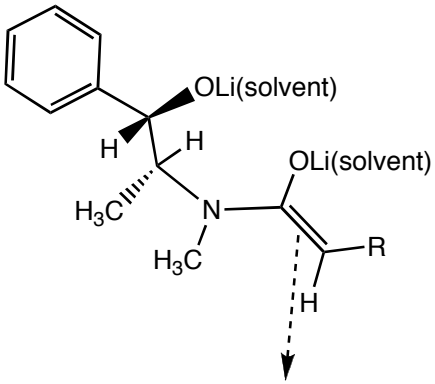
1. 1.95 LDA
LiCl

2. R'X



1,4- syn relationship

>99% de

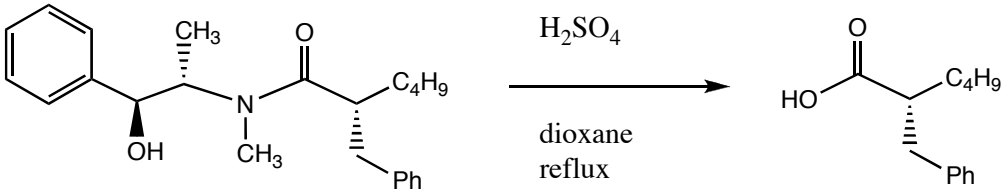


electrophile enters from the same face
as methyl group

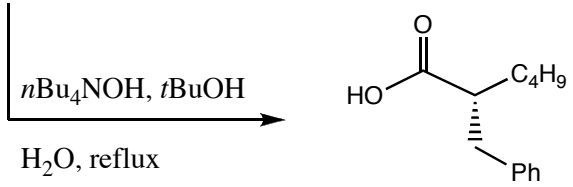
epoxides and alkyl halides attack opposite
faces of the enolate due to lithium coordination of the epoxide O

Myers, *JOC*, **1996**, *61*, 2428

Challenge:Remove Chiral Auxiliary w/o Racemization

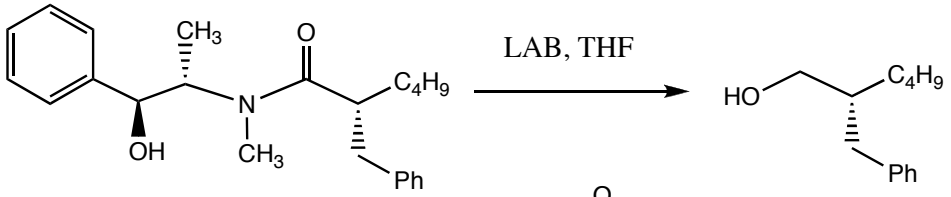


>99%de

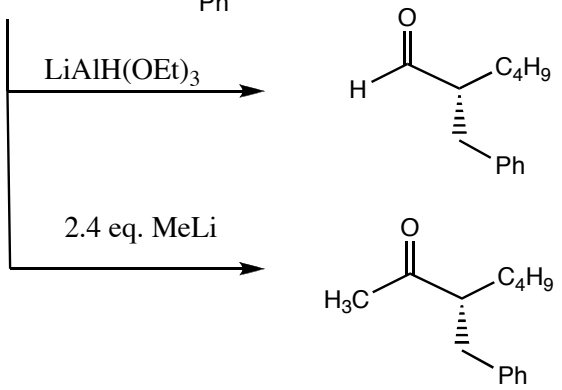


basic conditions lead to facile epimerization
of α-aryl substituted carbonyls

Reduction: $LiNH_2BH_3$

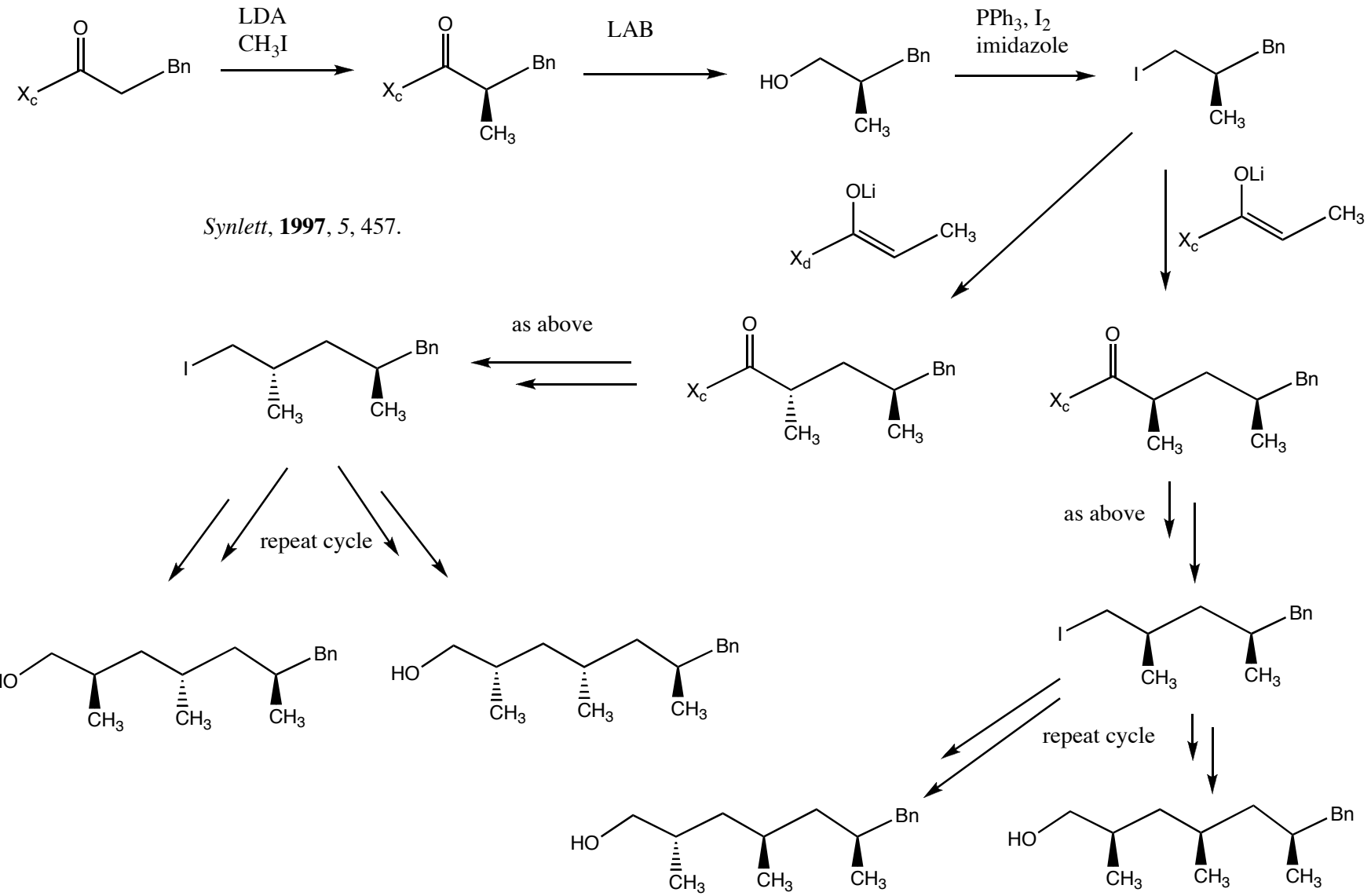


TL, **1996**, 3623



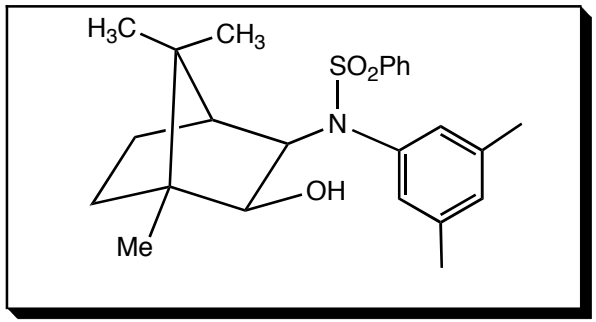
JACS, **1997**, 6496.

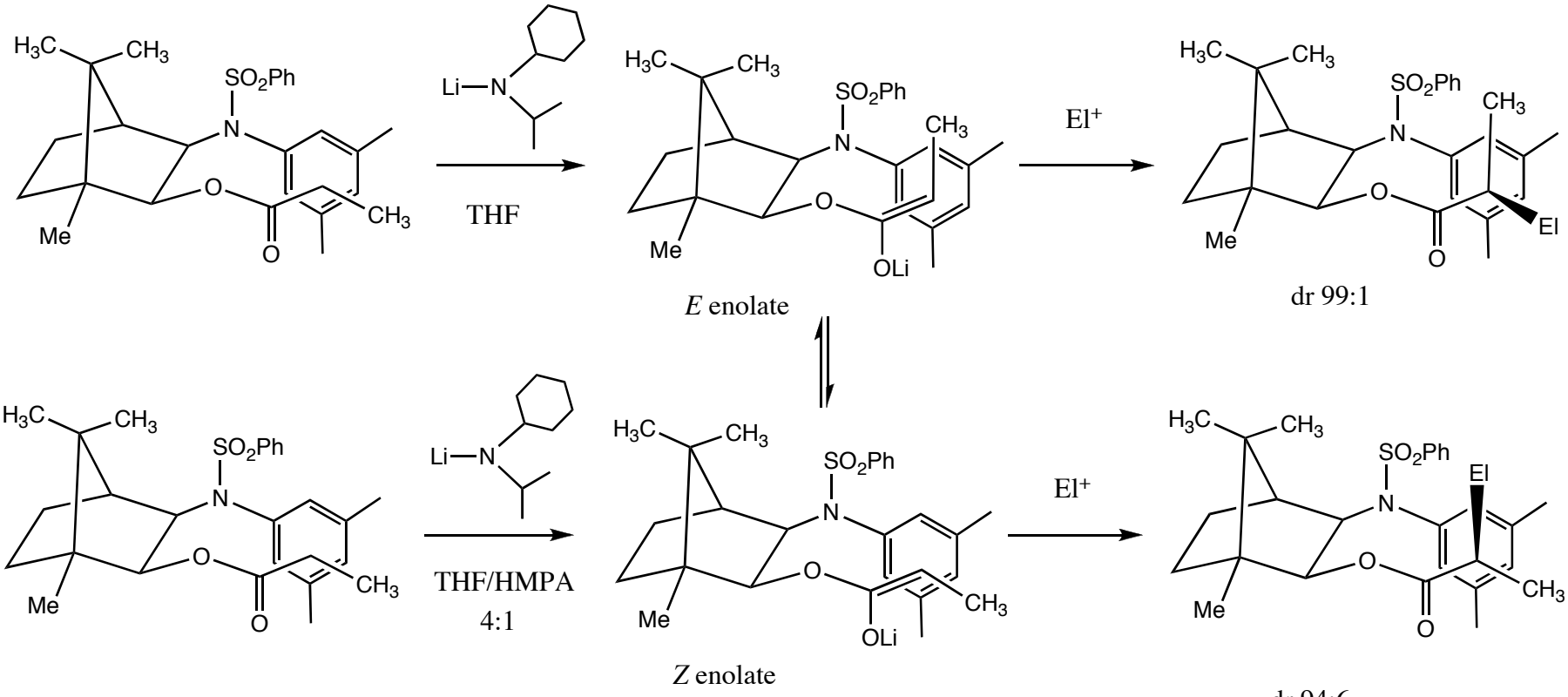
Iterative Synthesis of 1,3 n-Substituted Carbon Chains



Camphor-Based Auxiliaries

Helmchen Chiral Ester Enolate





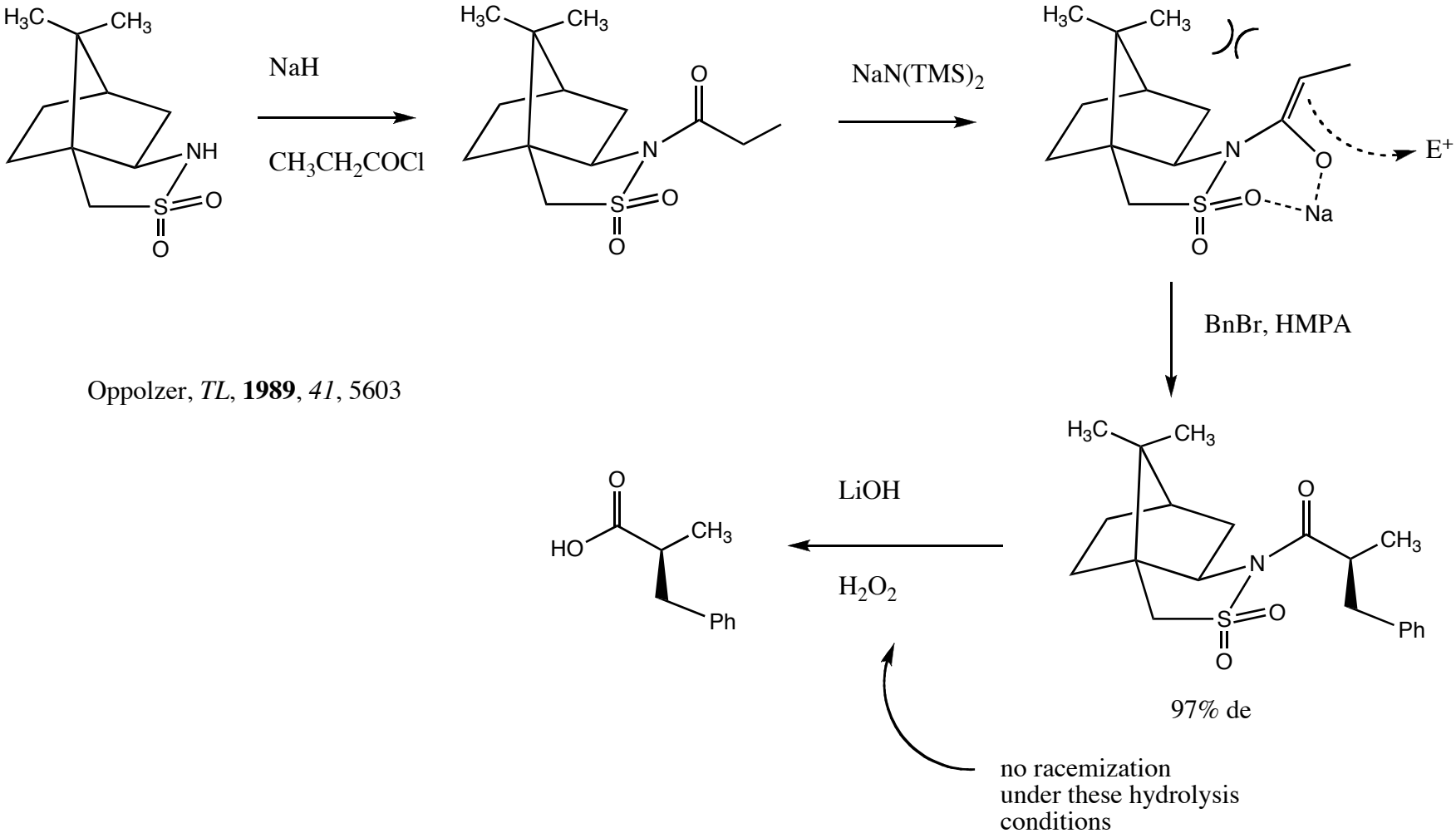
HMPA breaks up higher order lithium enolate aggregates!

Enolization leakage in the presence of HMPA

ACIEE, **1981**, *20*, 207
ACIEE, **1984,** *23*, 60
TL, **1983**, *24*, 1235
TL, **1983**, *24*, 3213

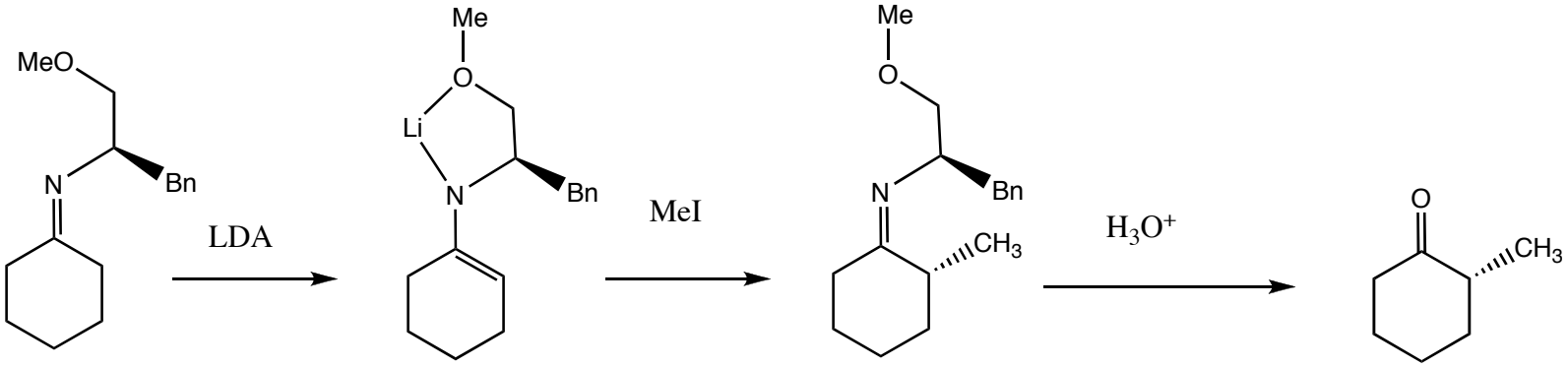
Camphor-Based Auxiliaries

Oppolzer Camphorsultam

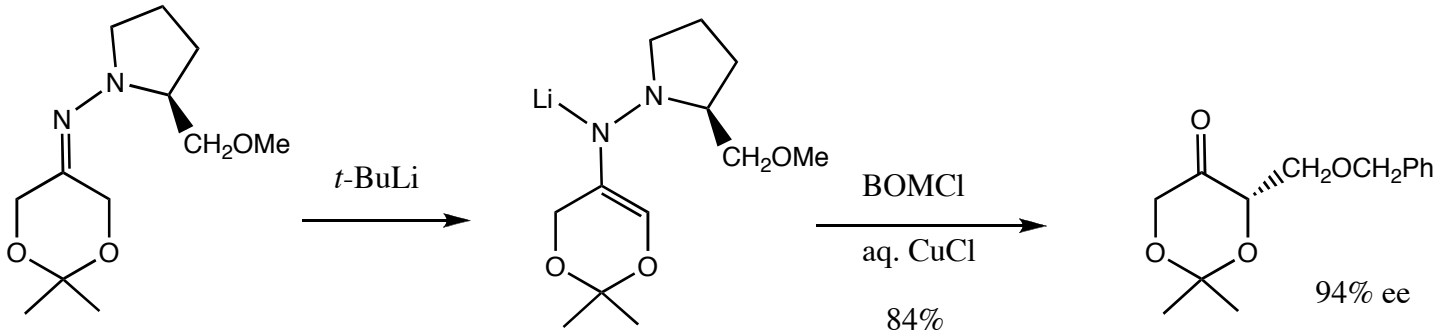


Oppolzer, *TL*, **1989**, *41*, 5603

Chiral Metalloenamines and Metallated Hydrazones

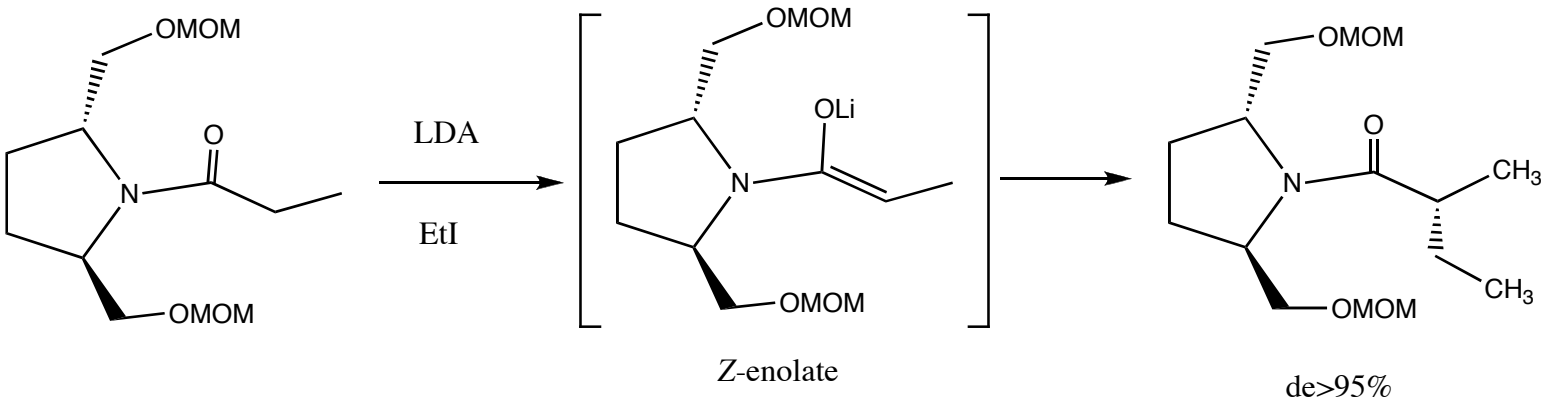


Meyers, *JACS*, **1981**, *103*, 3081.



Enders, *Syn Comm.* **1999**, *29*, 27.

C-2 Symmetric Amine Auxiliaries

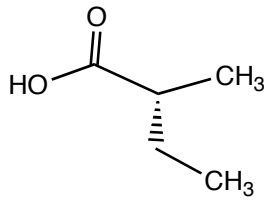


Z-enolate

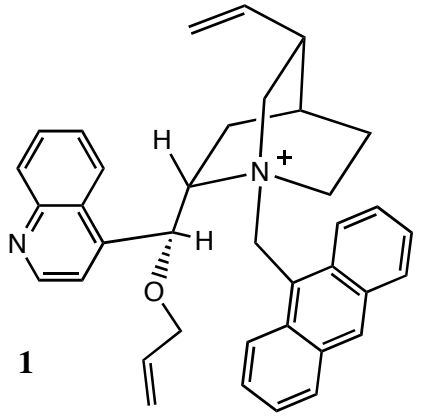
de>95%

Yamaguchi, *TL*, **1984**, *25*, 857.

1N HCl
reflux



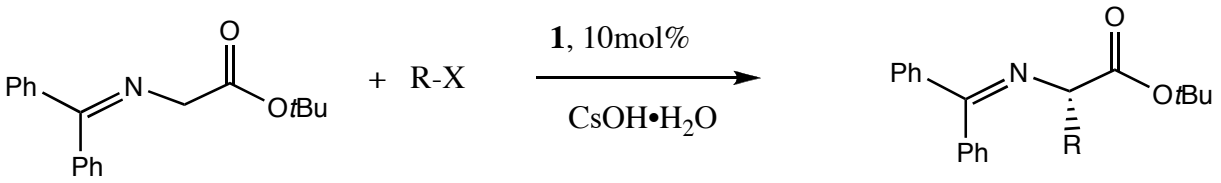
Catalytic Methods for Asymmteric Alkylation

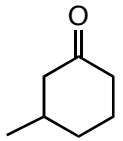


1

chiral phase-transfer catalyst

Corey, *TL*, **1998**, *39*, 5347.



R=	-$(CH_2)_4Cl$	-$(CH_2)_2CO_2CH_3$	-$(CH_2)_2COEt$	
%ee	99	95	91	99