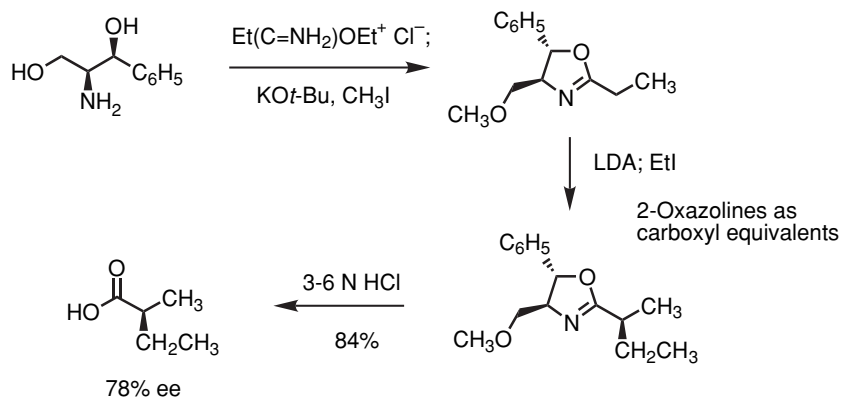
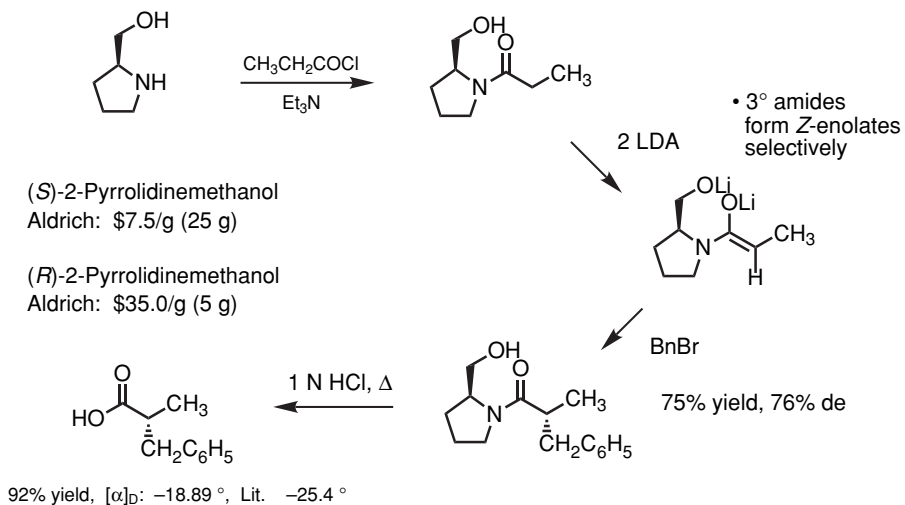


- An early milestone in the use of a chiral auxiliary for asymmetric alkylation:



Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567-576.

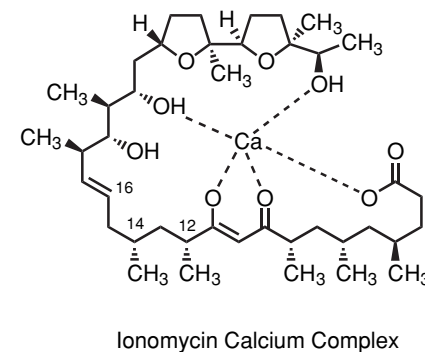
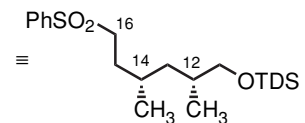
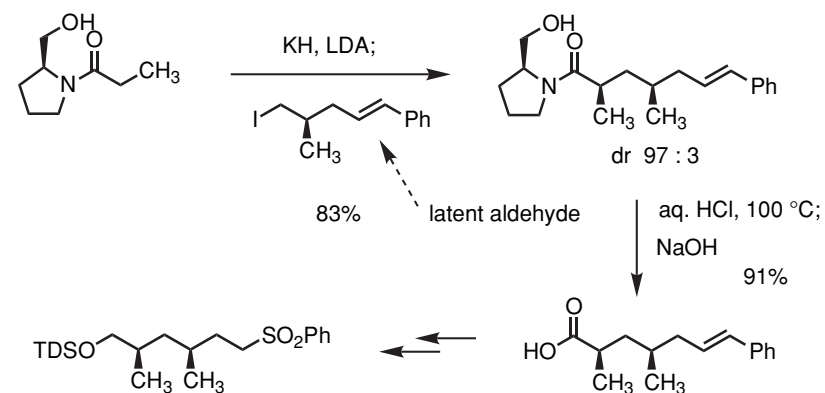
- Prolinol amide enolates provided an important advance:



Evans, D.A.; Takacs, J.M.; *Tetrahedron Lett.* **1980**, *21*, 4233.

Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

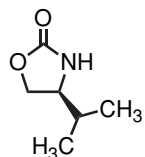
- Strongly nucleophilic prolinol amide enolates react with β -branched alkyl halides.
- proposal and application to iterative assembly of 1,3,*n*-substituted carbon chains by Evans et al. in synthesis of ionomycin:



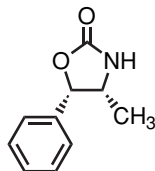
Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

Evans Oxazolidinone Auxiliaries in Asymmetric Synthesis: Alkylations

As Originally Introduced, Two Enantio-complimentary Reagents:



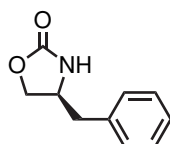
(*S*)-(-)-4-Isopropyl-2-oxazolidinone 5 g \$135



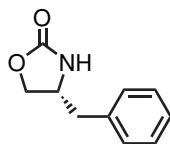
(4*R*, 5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone 5 g \$167

Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

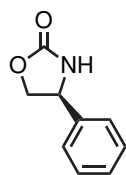
Now, several oxazolidinones are commercially available, in both enantiomeric forms:



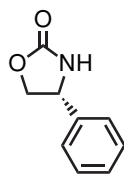
(*S*)-(-)-4-Benzyl-2-oxazolidinone 25 g \$185



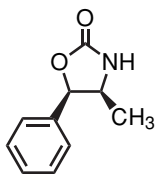
(*R*)-(+)-4-Benzyl-2-oxazolidinone 25 g \$240



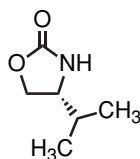
(*S*)-(-)-4-Phenyl-2-oxazolidinone 5 g \$134



(*R*)-(+)-4-Phenyl-2-oxazolidinone 5 g \$133



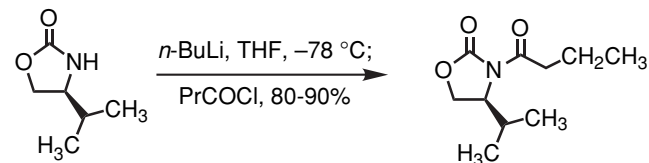
(4*S*, 5*R*)-(-)-4-Methyl-5-phenyl-2-oxazolidinone 5 g \$156



(*R*)-(+)-4-Isopropyl-2-oxazolidinone 2.5 g \$102

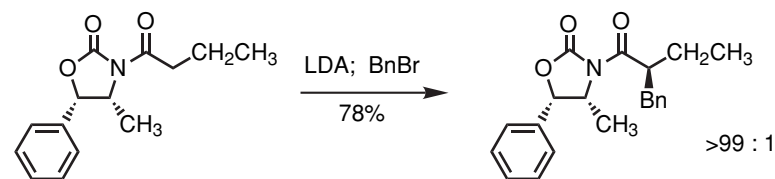
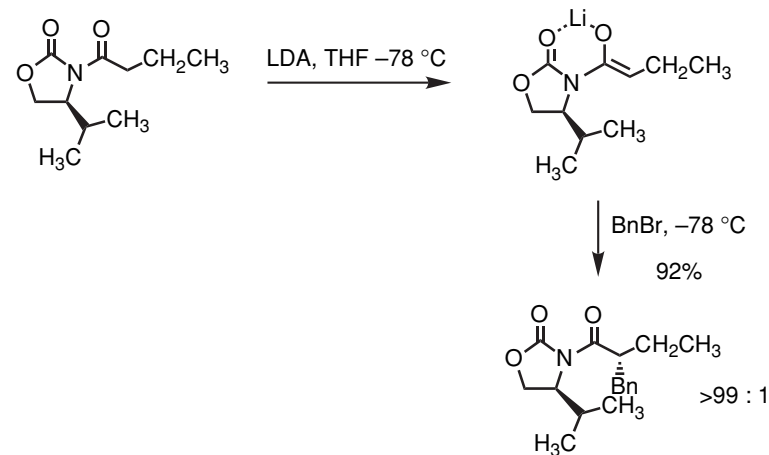
*1999 Aldrich Prices, can be dramatically lower from bulk suppliers.

Acylation provides **Imides**, closer to esters than amides in terms of acidity, enolate nucleophilicity and cleavage chemistry.



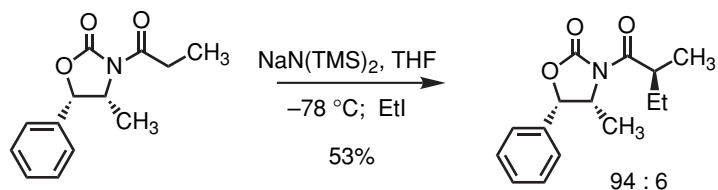
Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

Z-Enolates are formed with very high selectivity. Chelated geometry presumed in ground and transition states.

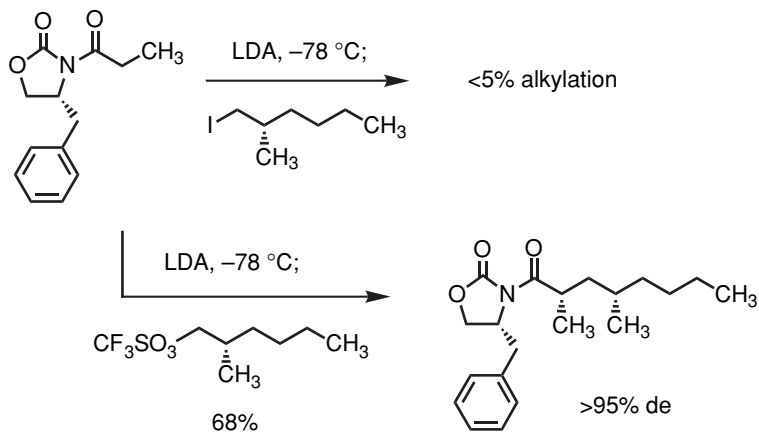


Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

- Less reactive (non-allylic/benzylic) electrophiles require the use of sodium enolates or triflate as leaving group:



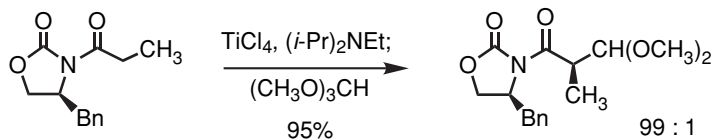
Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.



Decicco, C. P.; Grover, P. *J. Am. Chem. Soc.* **1996**, *61*, 3534-3541.

see also: Williams, D. R.; McGill, J. M. *J. Org. Chem.* **1990**, *55*, 3457-3459.

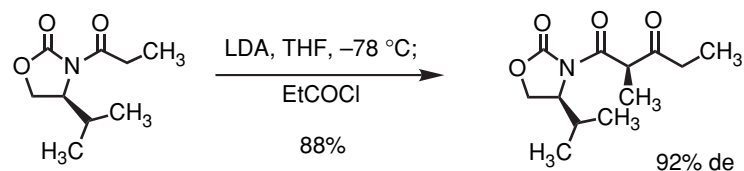
- Titanium enolates provide a route for diastereoselective $\text{S}_{\text{N}}1$ -like coupling reactions:



Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215-8216.

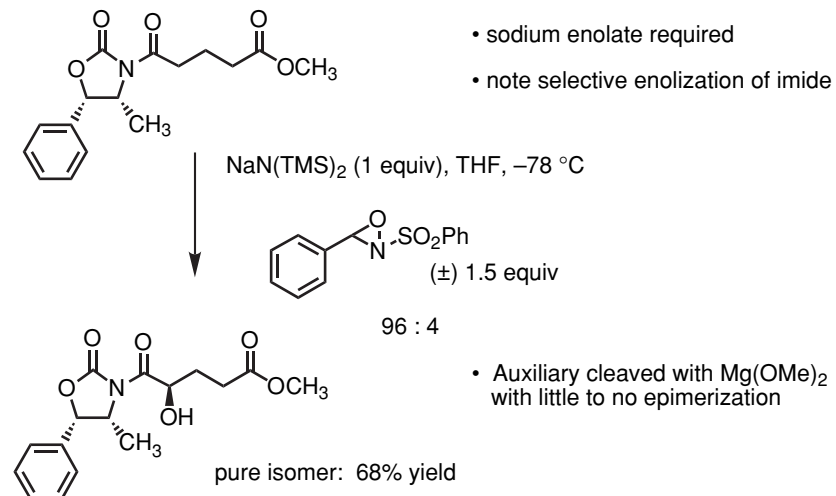
- Highly diastereoselective acylation of imide enolates is possible:

Exercise: Why are the products configurationally stable?



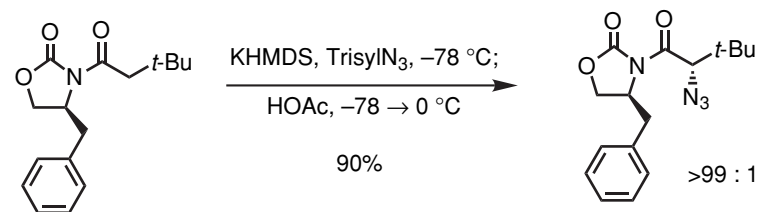
Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156.

- Diastereoselective hydroxylation has been demonstrated:



Evans, D. A.; Morissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346-4348.

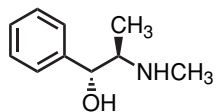
- Asymmetric azidation provides an important route to amino acid derivatives:



Trisyl = 2,4,6-triisopropylbenzenesulfonyl

Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

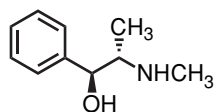
Pseudoephedrine as a Chiral Auxiliary in Asymmetric Alkylations



(*R,R*)-(-)-Pseudoephedrine

cost ~ \$150 / kilo

mp 118-120 °C



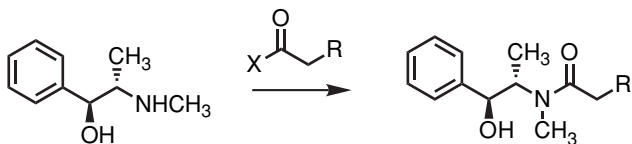
(*S,S*)-(+)-Pseudoephedrine

cost ~ \$65 / kilo

mp 118-120 °C

- Pseudoephedrine is a commodity chemical, manufactured on multi-ton scale/annum

Preparation of Pseudoephedrine Amides:



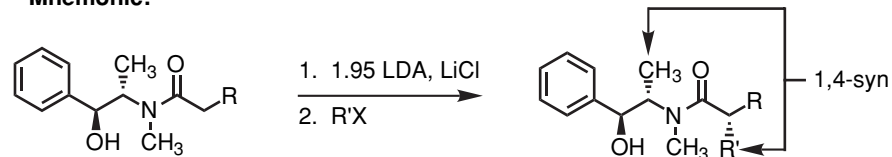
R	X	Yield (%)	mp
CH ₃	O ₂ CCH ₂ R	95	114-115
CH ₃	*OCH ₃	89	114-115
<i>n</i> -Bu	O ₂ CCH ₂ R	91	62-63
Bn	Cl	83	102-104
Ph	Cl	88	145-146
Cl	Cl	90	79-81
<i>i</i> -Pr	Cl	92	73-74
<i>t</i> -Bu	Cl	88	68-69
CH ₂ Bn	Cl	81	100-102
2-thiophene	Cl	87	110-111
3-pyridyl	O ₂ CC(CH ₃) ₃	97	117.5-118.5

*Even unactivated esters react, under basic catalysis, presumably by transesterification followed by intramolecular *N*→*O* Acyl Transfer

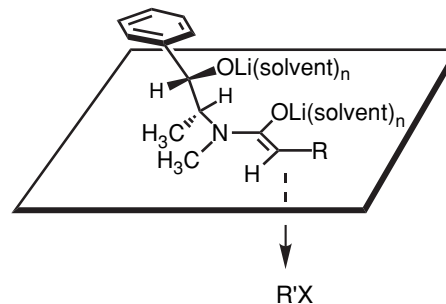
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

- Enolates are formed using 1.95 equiv LDA
- Alkylations are highly diastereoselective
- LiCl (~6 equiv) promotes rapid, clean reaction

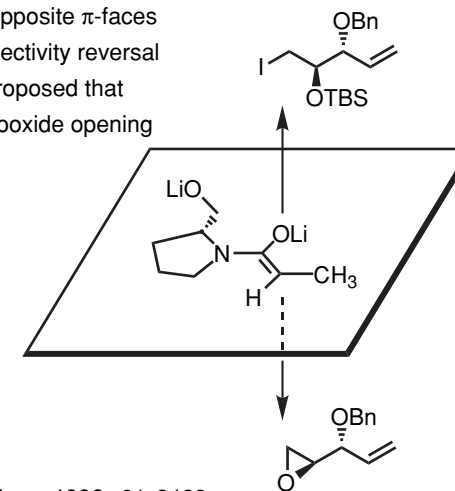
Mnemonic:



- Electrophile enters from same face as methyl group, when drawn in extended (zig-zag or all-anti) conformation
- A model is proposed to explain diastereoselectivity that invokes blocking of one enolate π -face by solvent:



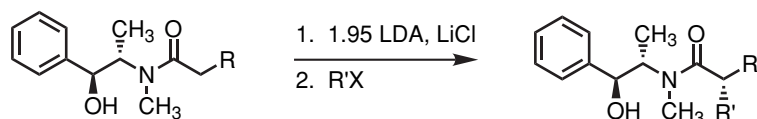
- Epoxides and alkyl halides attack opposite π -faces
- Askin et al. reported this type of selectivity reversal with prolinol amide enolates and proposed that Li cation coordinates, directs the epoxide opening



Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245.

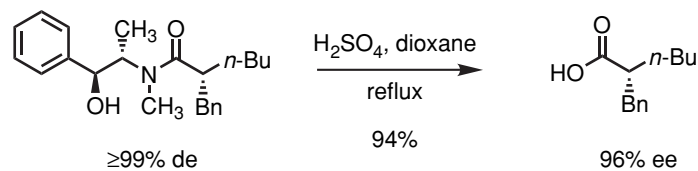
Diastereoselective Alkylation Reactions



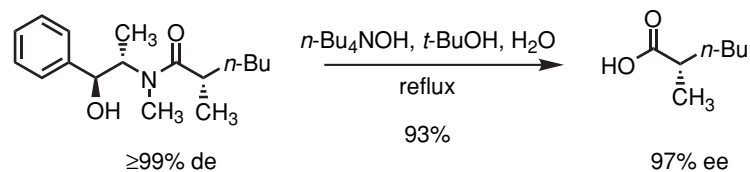
R	R'X	temp (°C)	crude (isol de (%)	isol yield (%)
CH ₃	BnBr	0	94 (≥99)	90
CH ₃	<i>n</i> -BuI	0	98 (≥99)	80
CH ₃	BrCH ₂ CO ₂ <i>t</i> -Bu	-78	94 (96)	78
Bn	CH ₃ I	0	94 (94)	99
<i>n</i> -Bu	CH ₃ I	0	94 (94)	94
<i>n</i> -Bu	BnBr	0	98 (≥99)	87
Ph	EtI	0	96 (≥99)	92
<i>i</i> -Pr	BnBr	0	98 (≥99)	83
<i>t</i> -Bu	BnBr	0	98 (≥99)	84
Cl	BnBr	-45	90 (≥99)	88

Hydrolysis of Alkylation Products

- Occurs under acidic or basic conditions. Both methods likely involve initial N→O acyl transfer.
- Strongly acidic conditions are required, but are well tolerated by many simple substrates.

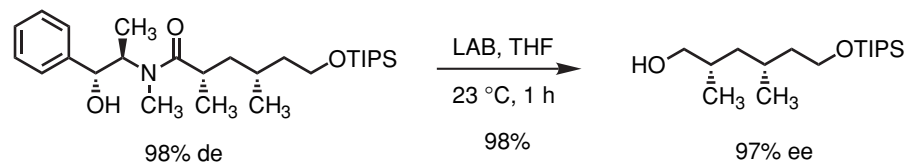


- Alkaline conditions work well with many substrates, but not those susceptible to facile epimerization (α -aryl).



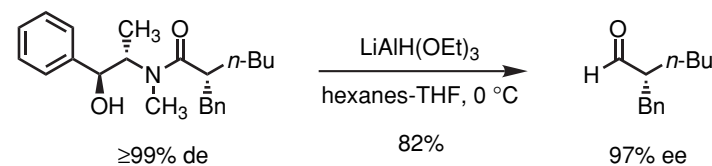
Reduction of Pseudoephedrine Amides

- Lithium Amidotrihydroborate (LiH₂NBH₃, LAB), prepared by deprotonation (LDA) of commercial, crystalline ammonia-borane complex, provides primary alcohols.



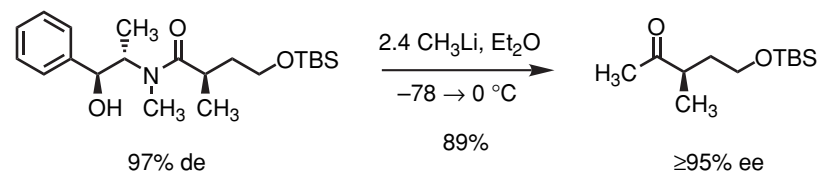
Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.
Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457.

- Semi-reduction with Brown's lithium triethoxyborohydride provides aldehydes directly.



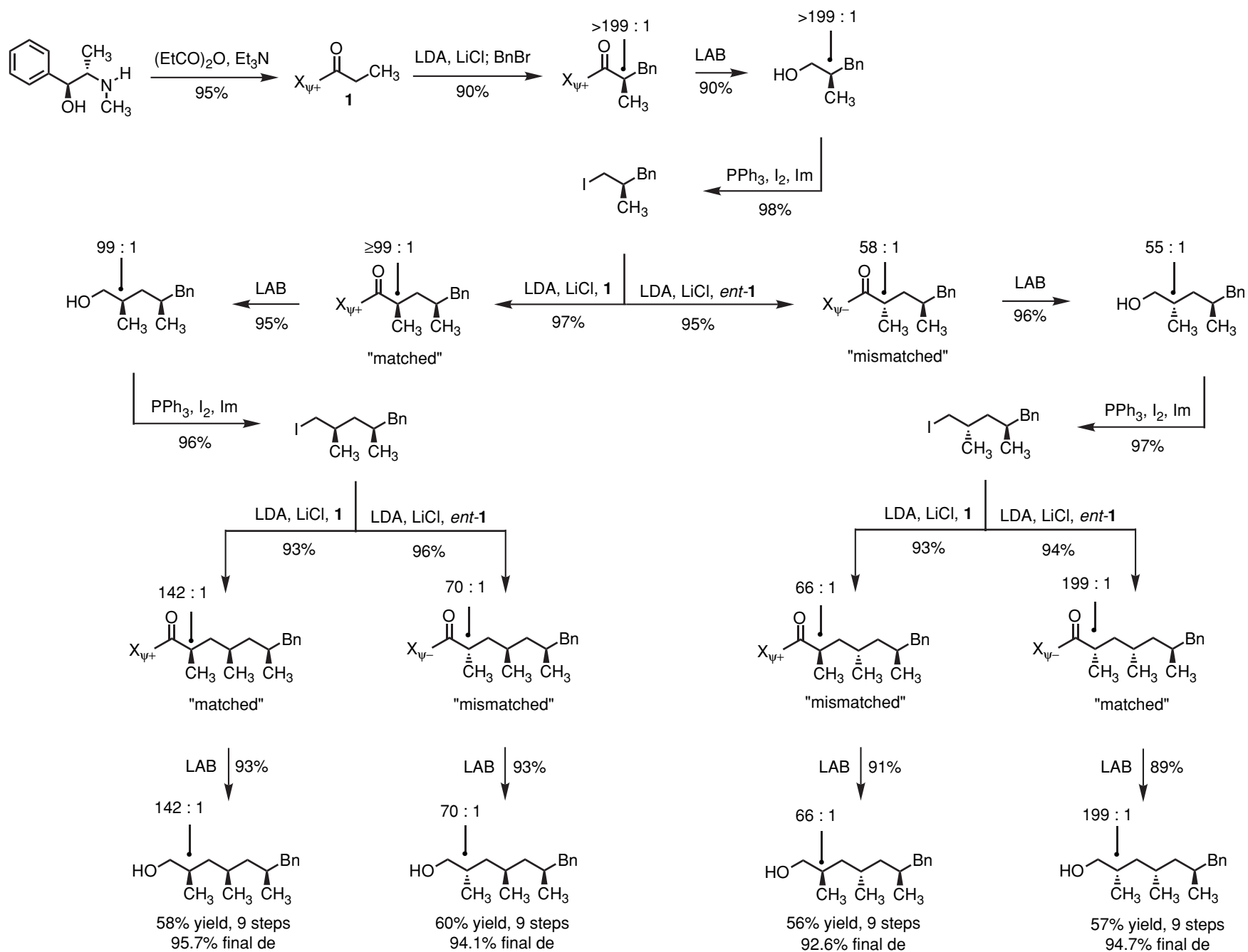
Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

Addition of Alkylolithium Reagents to form Ketones

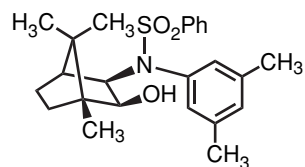


Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

Application to the Synthesis of 1,3,n-Substituted Carbon Chains by Iteration:



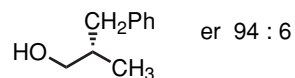
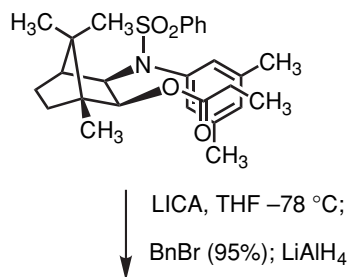
• Helmchen camphor-derived auxiliaries



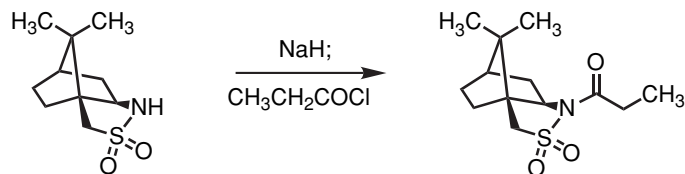
Aldrich: \$65.4/g (1 g)

Exercise: use of HMPA in the enolization gives alkylated product of inverted configuration (dr 30 : 70). Rationalize these findings.

Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207-208.

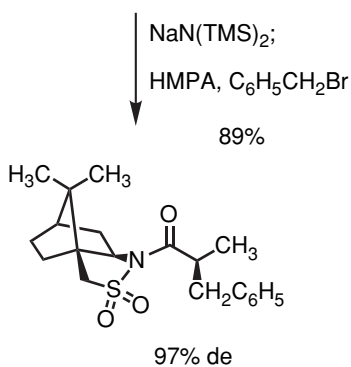
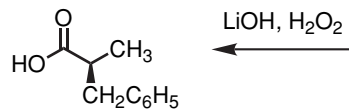


• Oppolzer camphorsultam auxiliaries in asymmetric alkylation



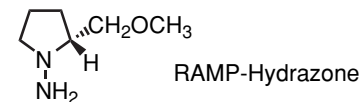
(1*S*)-(-)-2,10-Camphorsultam
Aldrich: \$26.6/g (5 g)

(1*R*)-(+)-2,10-Camphorsultam
Aldrich: \$50.6/g (1 g)



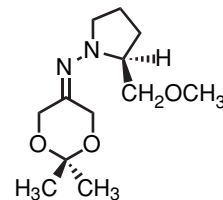
Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *41*, 5603-5606

• Enders chiral hydrazone methodology

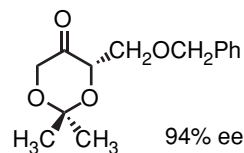


(*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine [RAMP-Hydrazone]
\$97.9/g (1 g)

(*S*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine [SAMP-Hydrazone]
\$46.1/g (1 g)



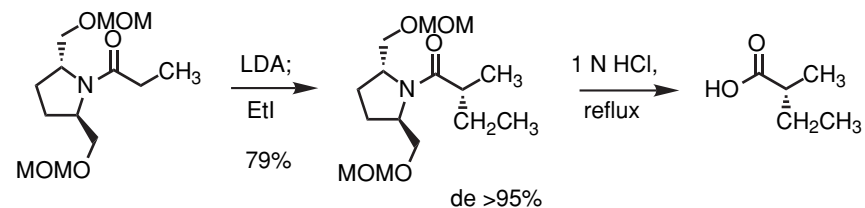
t-BuLi, -78 °C;
BOMCl, -100 °C;
aq. CuCl₂
84%



Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 4.

Enders, D.; Hundertmark, T.; Lazny, R. *Syn. Comm.* **1999**, *29*, 27-33.

• Yamaguchi C₂-symmetric amine - auxiliary for asymmetric alkylation



• Highly diastereoselective.

• Auxiliary is not yet available for practical use; its removal is difficult.

Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857-860.