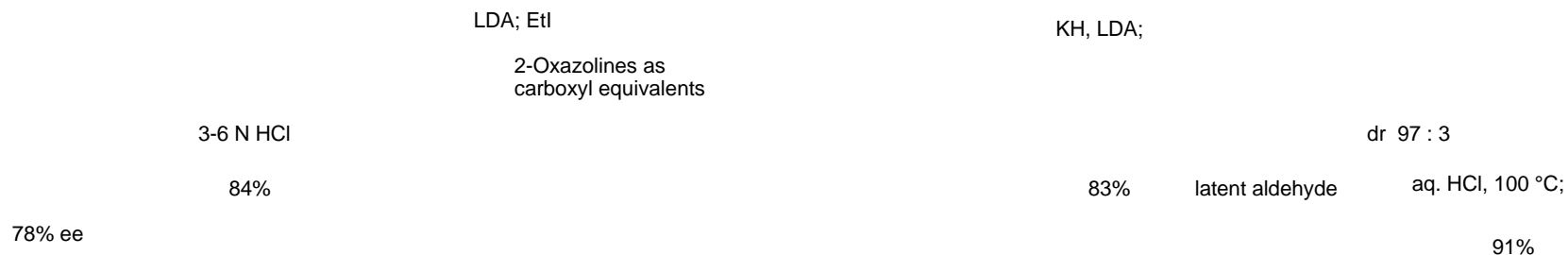


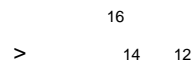
- An early milestone in the use of a chiral auxiliary for asymmetric alkylation:

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



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:



(S)-2-Pyrrolidinemethanol  
Aldrich: \$7.5/g (25 g)

(R)-2-Pyrrolidinemethanol  
Aldrich: \$35.0/g (5 g)

2 LDA  
• 3° amides  
form Z-enolates  
selectively



1 N HCl, 6

75% yield, 76% de

Ionomycin Calcium Complex

92% yield,  $[\alpha]_D: -18.89^\circ$ , Lit.  $-25.4^\circ$

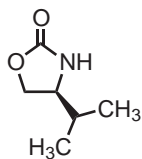
Evans, D.A.; Takacs, J.M.; Tetrahedron Lett. 1980, 21, 4233.

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

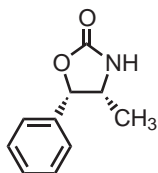
Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. J. Am. Chem. Soc. 1990, 112, 5290-5313.

## Evans Oxazolidinone Auxiliaries in Asymmetric Synthesis: Alkylations

As Originally Introduced, Two Enantio-complimentary Reagents:



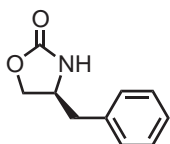
(S)-(-)-4-Isopropyl-2-oxazolidinone 5 g \$135



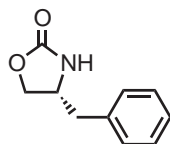
(4R, 5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone 5 g \$167

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

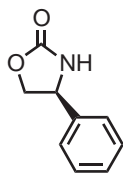
Now, several oxazolidinones are commercially available, in both enantiomeric forms:



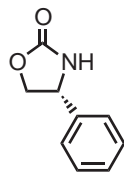
(S)-(-)-4-Benzyl-2-oxazolidinone 25 g \$185



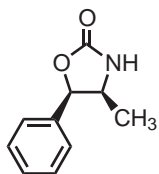
(R)-(+)-4-Benzyl-2-oxazolidinone 25 g \$240



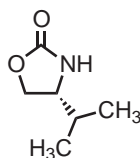
(S)-(-)-4-Phenyl-2-oxazolidinone 5 g \$134



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



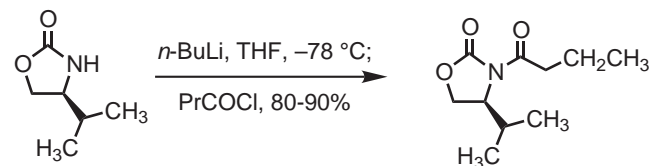
(4S, 5R)-(-)-4-Methyl-5-phenyl-2-oxazolidinone 5 g \$156



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

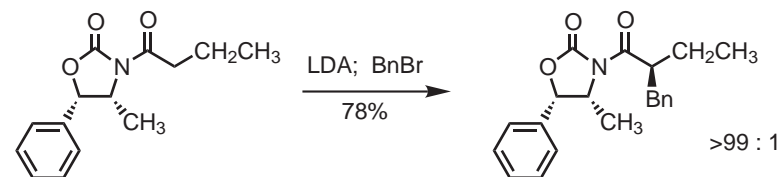
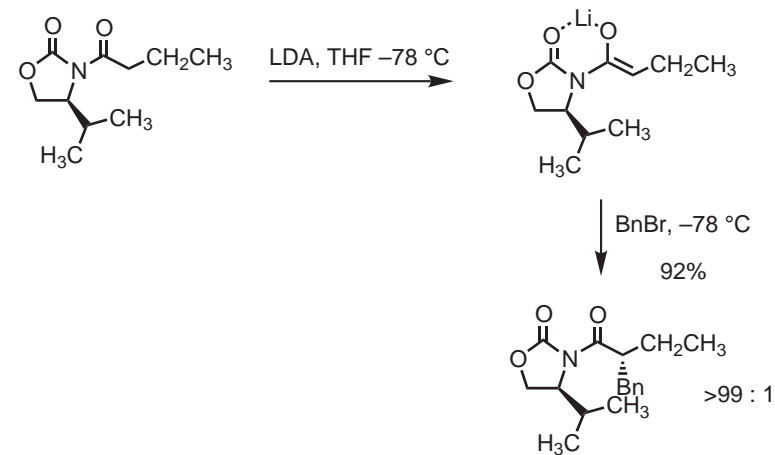
\*1999 Aldrich Prices, can be dramatically lower from bulk suppliers.

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



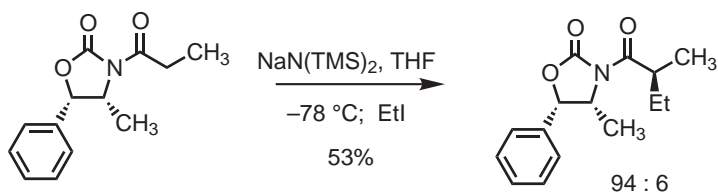
Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

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

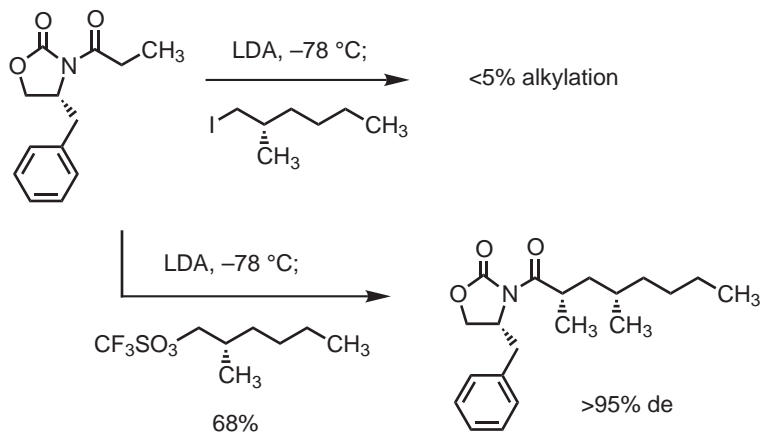


Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739

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



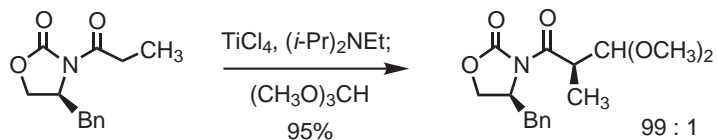
Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.



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.

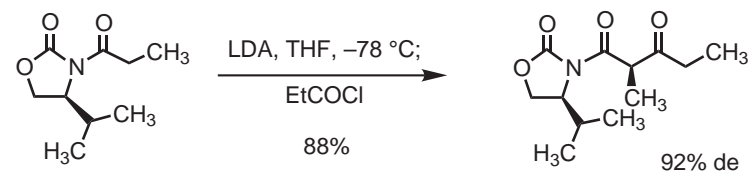
- Titanium enolates provide a route for diastereoselective  $\text{S}_{\text{N}}1$ -like coupling reactions:



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

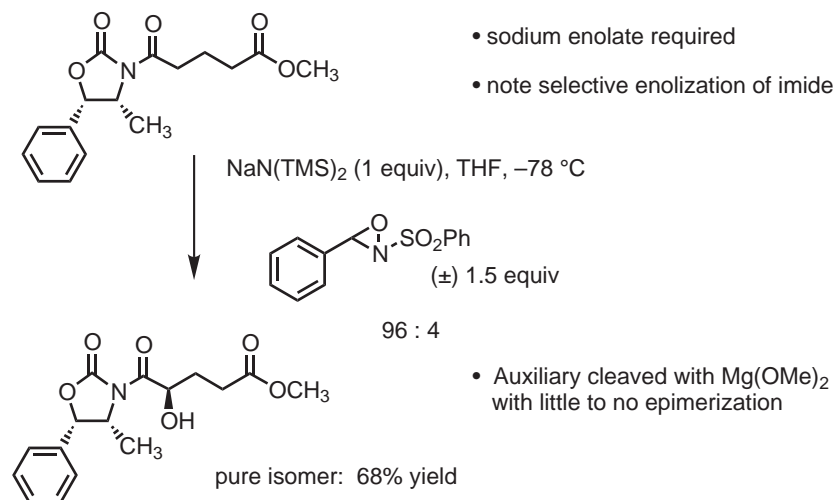
- Highly diastereoselective acylation of imide enolates is possible:

**Exercise:** Why are the products configurationally stable?



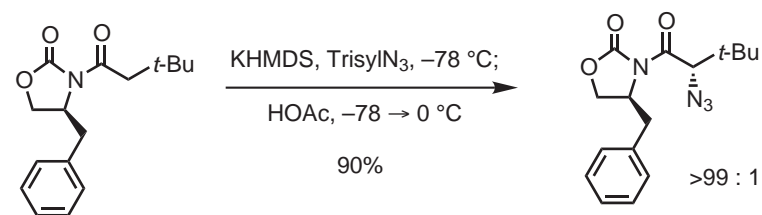
Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156.

- Diastereoselective hydroxylation has been demonstrated:



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

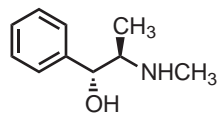
- Asymmetric azidation provides an important route to amino acid derivatives:



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.

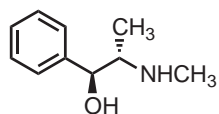
## Pseudoephedrine as a Chiral Auxiliary in Asymmetric Alkylations



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

cost ~ \$150 / kilo

mp 118-120 °C



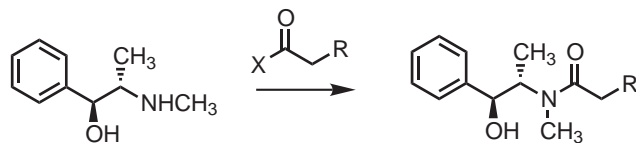
(*S,S*)-(+)-Pseudoephedrine

cost ~ \$65 / kilo

mp 118-120 °C

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

## Preparation of Pseudoephedrine Amides:



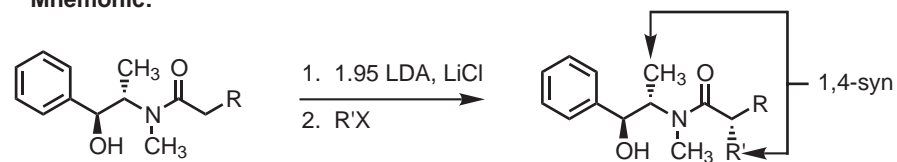
R	X	Yield (%)	mp
CH <sub>3</sub>	O <sub>2</sub> CCH <sub>2</sub> R	95	114-115
CH <sub>3</sub>	* OCH <sub>3</sub>	89	114-115
<i>n</i> -Bu	O <sub>2</sub> CCH <sub>2</sub> R	91	62-63
Bn	Cl	83	102-104
Ph	Cl	88	145-146
Cl	Cl	90	79-81
<i>i</i> -Pr	Cl	92	73-74
<i>t</i> -Bu	Cl	88	68-69
CH <sub>2</sub> Bn	Cl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

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

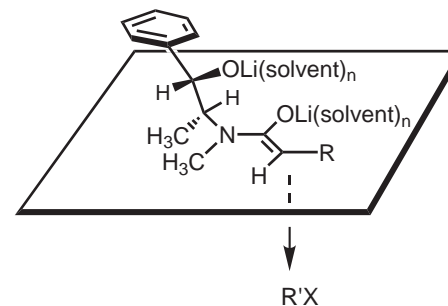
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

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

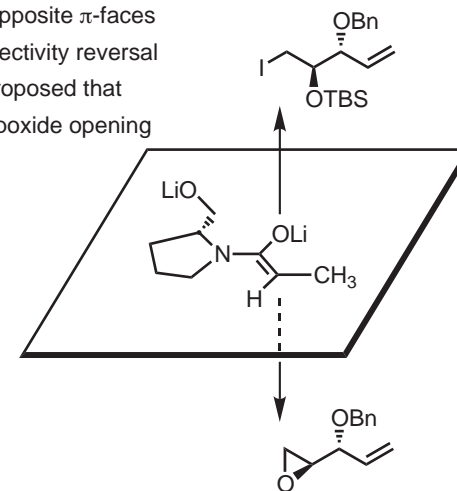
## Mnemonic:



- 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  $\pi$ -face by solvent:



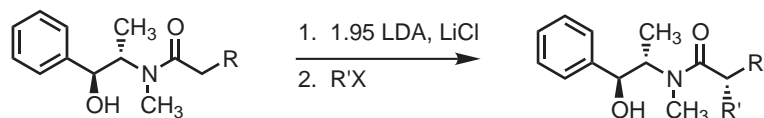
- Epoxydes and alkyl halides attack opposite  $\pi$ -faces
- Askin et al. reported this type of selectivity reversal with prolinol amide enolates and proposed that Li cation coordinates, directs the epoxide opening



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.

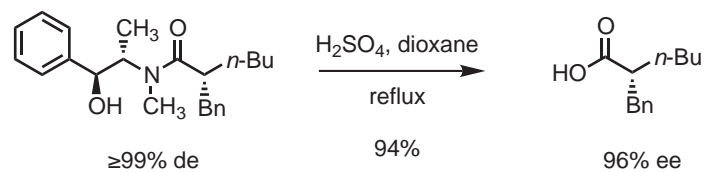
## Diastereoselective Alkylation Reactions



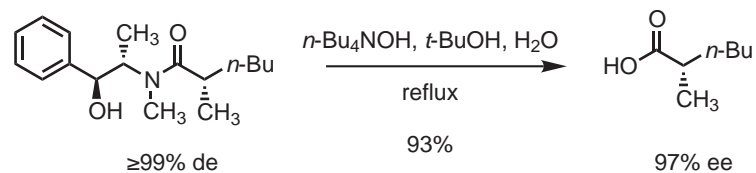
R	R'X	temp (°C)	crude (isol de (%)	isol yield (%)
CH <sub>3</sub>	BnBr	0	94 (≥99)	90
CH <sub>3</sub>	<i>n</i> -BuI	0	98 (≥99)	80
CH <sub>3</sub>	BrCH <sub>2</sub> CO <sub>2</sub> <i>t</i> -Bu	-78	94 (96)	78
Bn	CH <sub>3</sub> I	0	94 (94)	99
<i>n</i> -Bu	CH <sub>3</sub> I	0	94 (94)	94
<i>n</i> -Bu	BnBr	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.

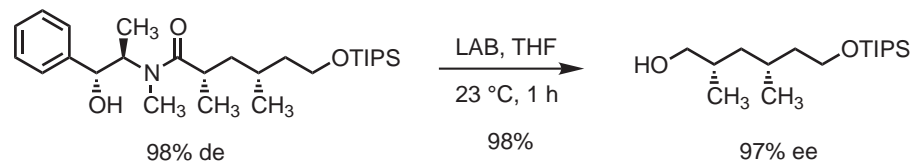


- Alkaline conditions work well with many substrates, but not those susceptible to facile epimerization ( $\alpha$ -aryl).



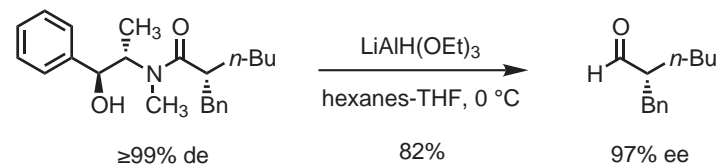
## Reduction of Pseudoephedrine Amides

- Lithium Amidotrihydroborate (LiH<sub>2</sub>NBH<sub>3</sub>, LAB), prepared by deprotonation (LDA) of commercial, crystalline ammonia-borane complex, provides primary alcohols.



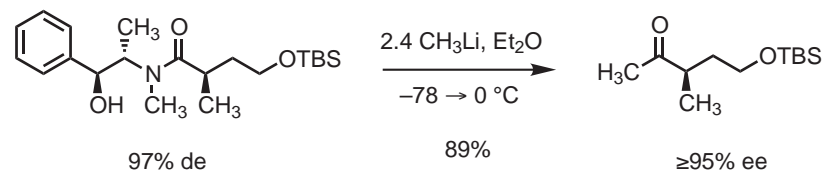
- Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, 37, 3623.  
Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 5, 457.

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



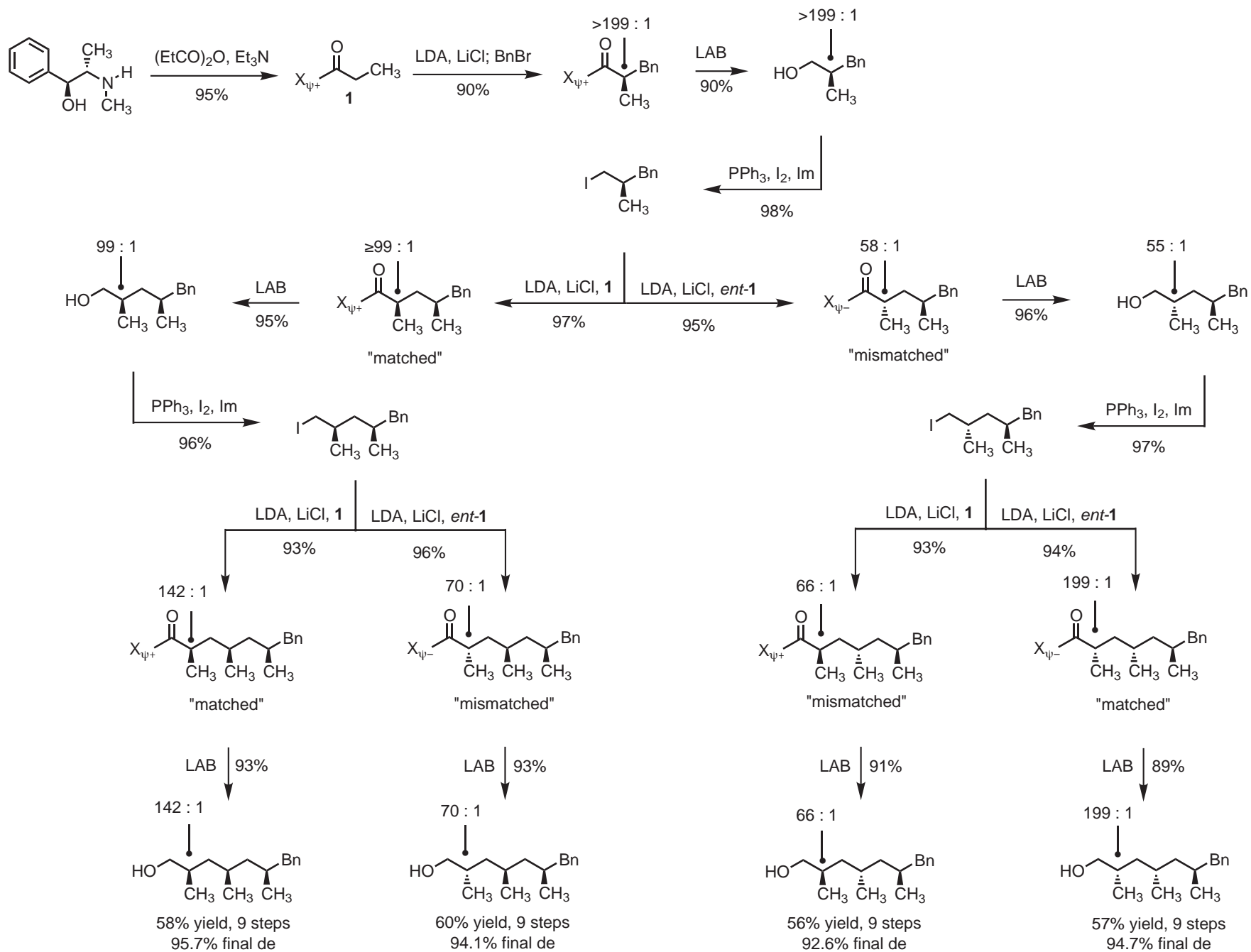
- Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, 86, 1089.

## Addition of Alkylolithium Reagents to form Ketones

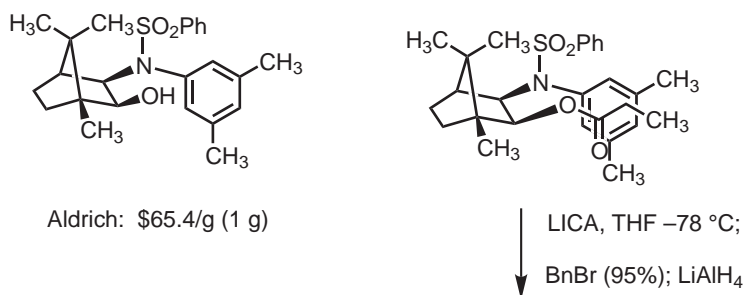


- Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496-6511.

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



• Helmchen camphor-derived auxiliaries

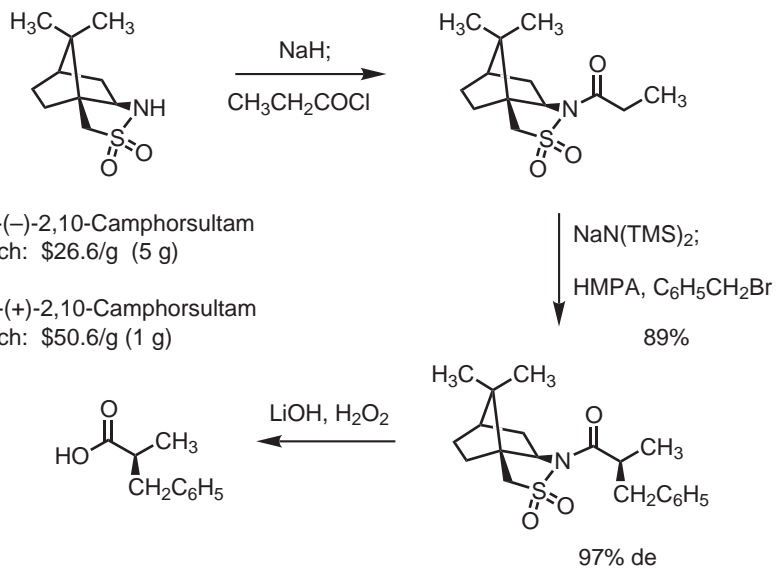


Aldrich: \$65.4/g (1 g)

**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

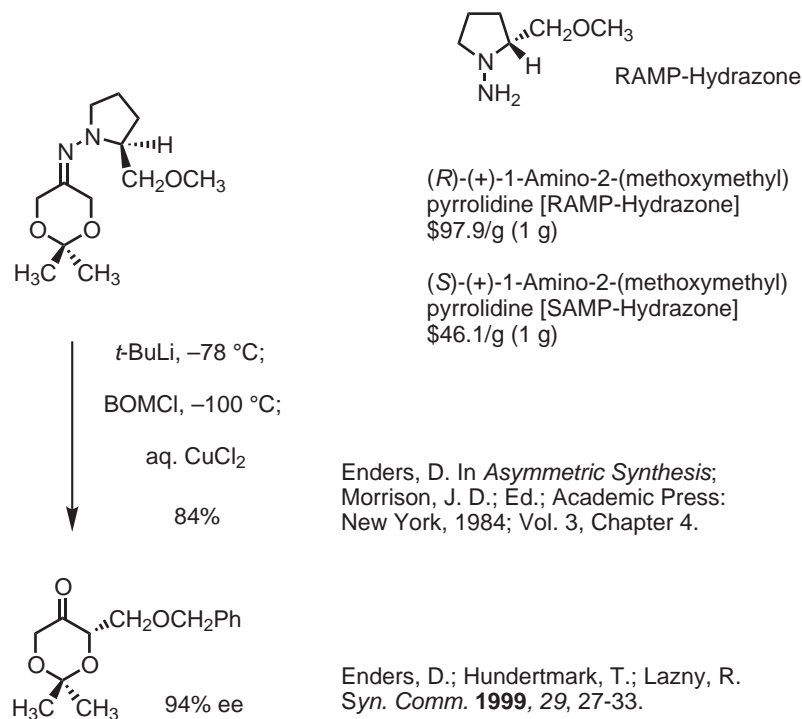


(1S)-(-)-2,10-Camphorsultam  
Aldrich: \$26.6/g (5 g)

(1R)-(+)-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



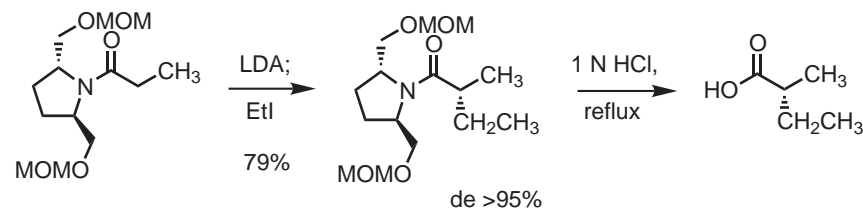
(R)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine [RAMP-Hydrazone]  
\$97.9/g (1 g)

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

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 C<sub>2</sub>-symmetric amine - auxiliary for asymmetric alkylation

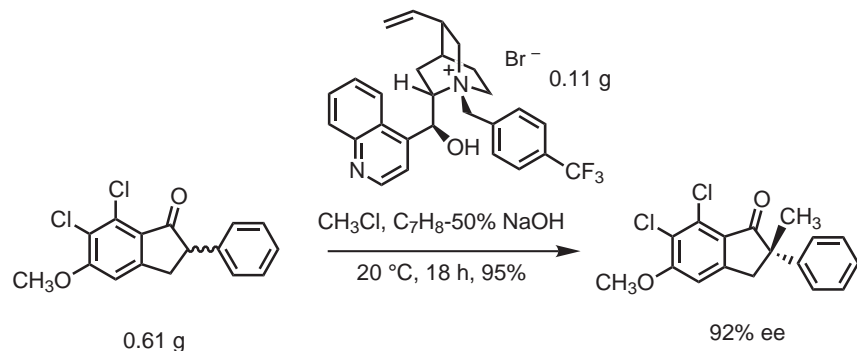


• Highly diastereoselective.

• 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.

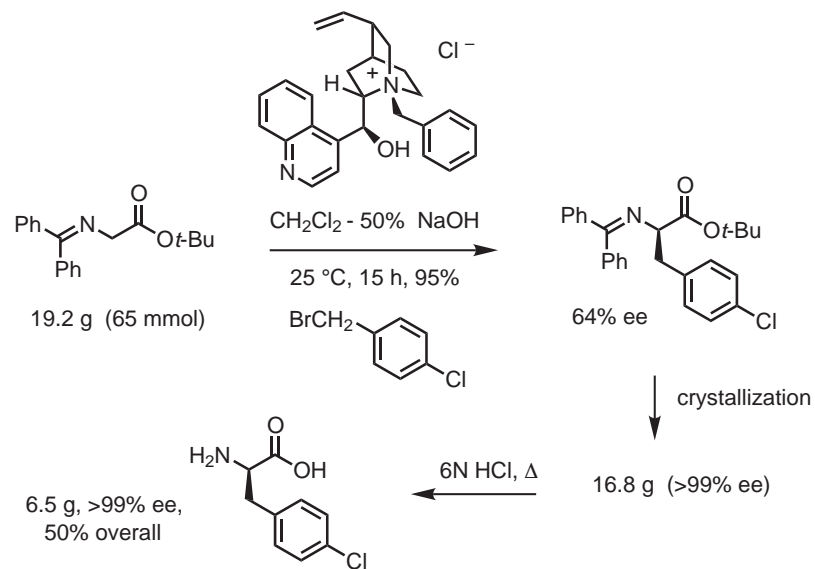
- An early, remarkable result from the Merck Process group:



- although narrow in scope, this provided a dramatic illustration of the potential of chiral phase-transfer catalysis for C-C bond formation.

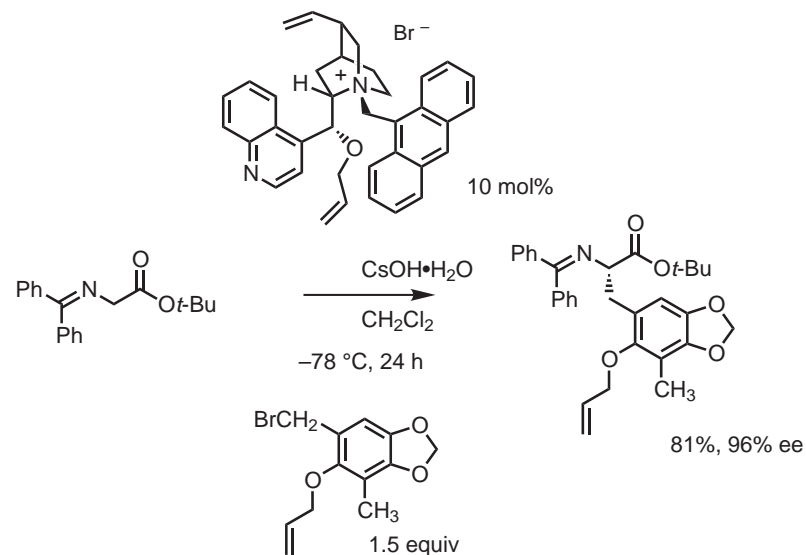
Dolling, U.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

- The method was adapted by O'Donnell, who had earlier developed a PT method for the synthesis of racemic  $\alpha$ -amino acids:



O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355.

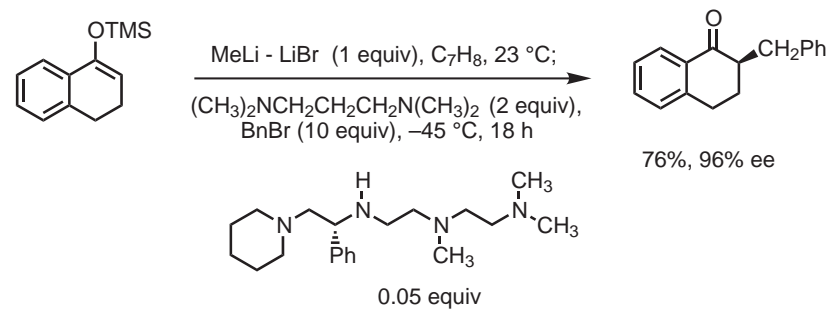
- Corey and co-workers have developed catalysts that are highly enantioselective:



Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

Phosphazene bases can be used with the above catalyst, see: O'Donnell, M. F.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775-8778.

- Koga has developed chiral additives for the asymmetric alkylation of lithium enolates. The work has recently been extended to include examples of catalysis:



Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829-8830.