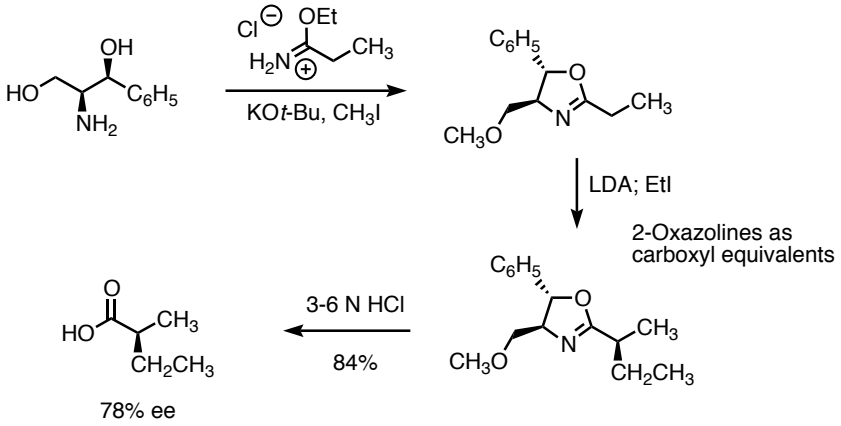
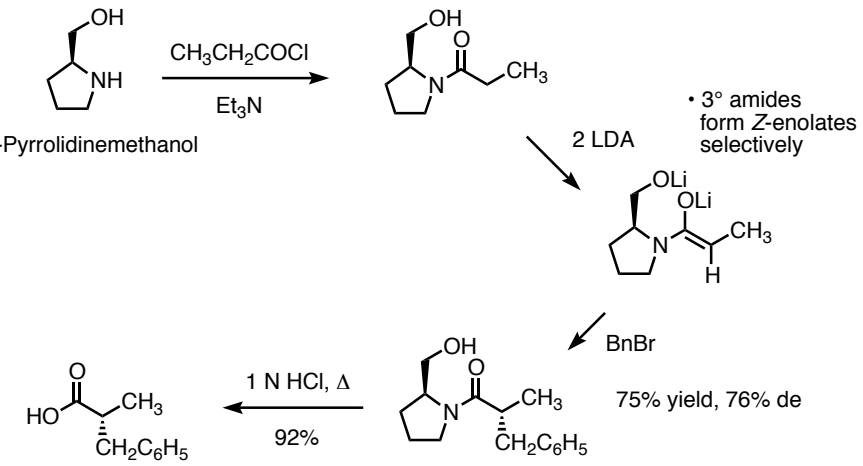
• An early milestone in the use of a chiral auxiliary for asymmetric alkylation:



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:

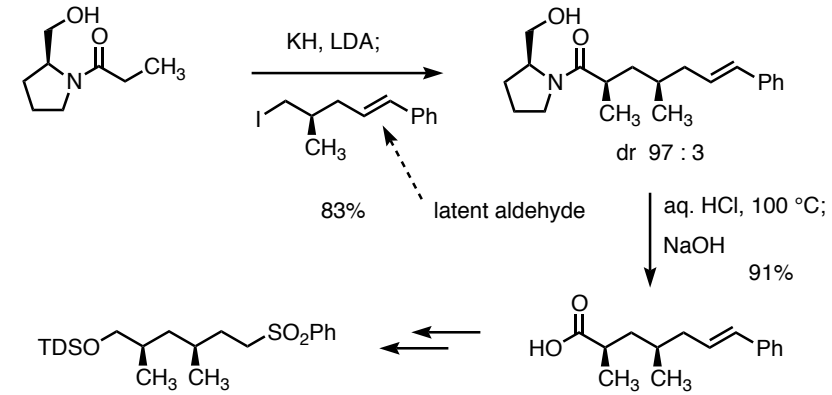


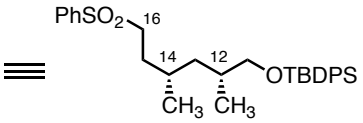
Evans, D. A.; Takacs, J. M.; *Tetrahedron Lett.* **1980**, *21*, 4233.

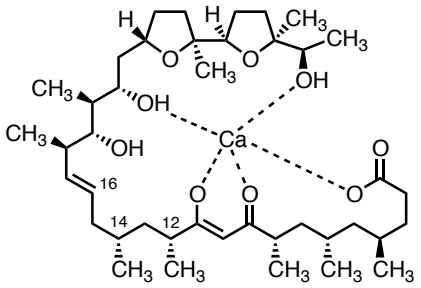
Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

• Strongly nucleophilic prolinol amide enolates react with β-branched alkyl halides.

• Application to iterative assembly of 1,3,n-substituted carbon chains by Evans et al. in synthesis of ionomycin:





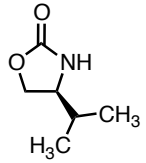


Ionomycin Calcium Complex

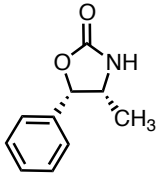
Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

Evans Oxazolidinone Auxiliaries in Asymmetric Synthesis: Alkylations

As originally introduced, two enantio-complimentary reagents:



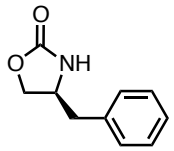
(*S*)-(–)-4-Isopropyl-2-oxazolidinone



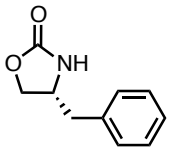
(*4R, 5S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone

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

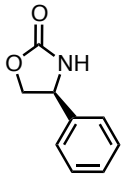
Several oxazolidinones are now commercially available, in both enantiomeric forms:



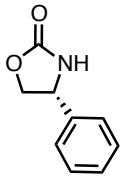
(*S*)-(–)-4-Benzyl-2-oxazolidinone



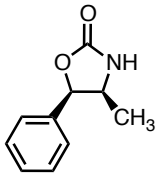
(*S*)-(+)-4-Benzyl-2-oxazolidinone



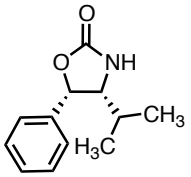
(*S*)-(–)-4-Phenyl-2-oxazolidinone



(*S*)-(+)-4-Phenyl-2-oxazolidinone

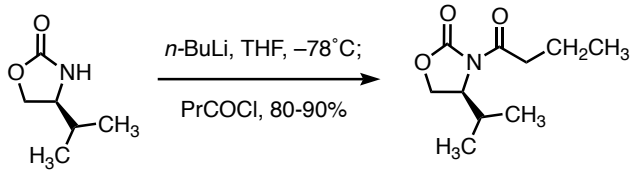


(4*S,5R*)-(–)-4-Methyl-5-phenyl-2-oxazolidinone



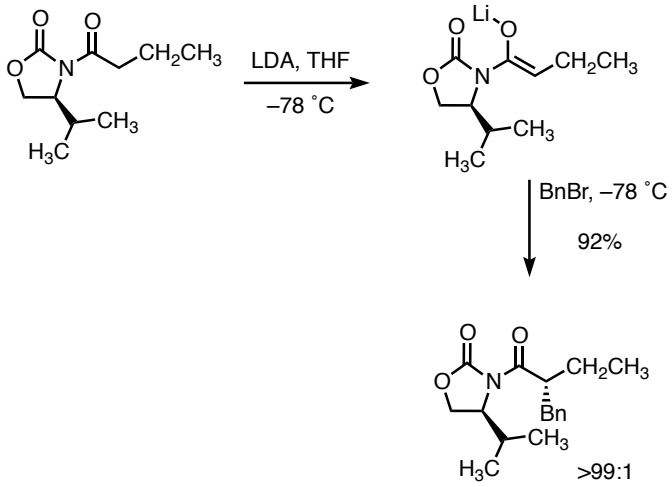
(*R*)-(+)-4-Phenyl-2-oxazolidinone

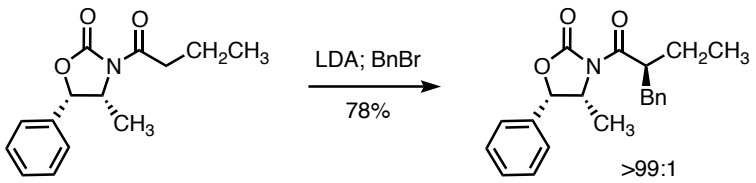
Acylation provides **imides**, closer to esters than amides in terms of acidity, enolate nucleophilicity and cleavage chemistry:



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

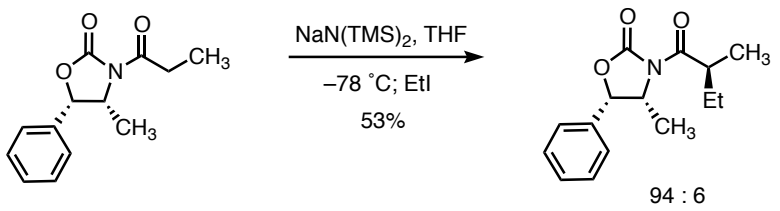
Z-Enolates are formed with very high selectivity. Chelated geometry presumed in ground and transition states:



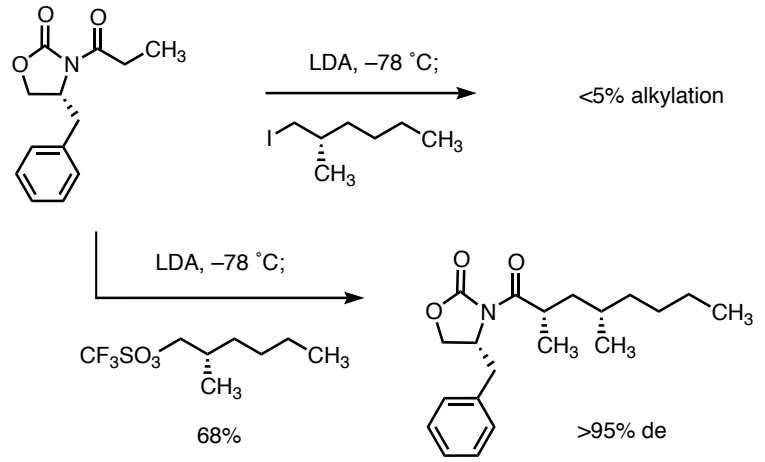


Evans, D. A.; Ennis, M. D.; Mathre, D. J. . *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

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



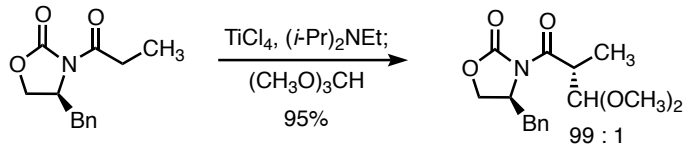
Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.



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*, 3447-3459.

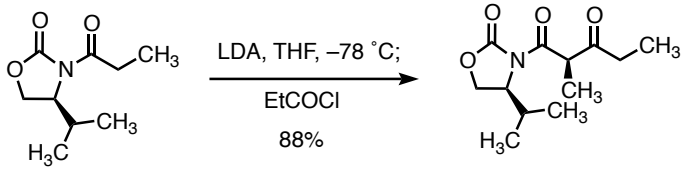
• Titanium enolates provide a route for diastereoselective S_N1-like coupling reactions:



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

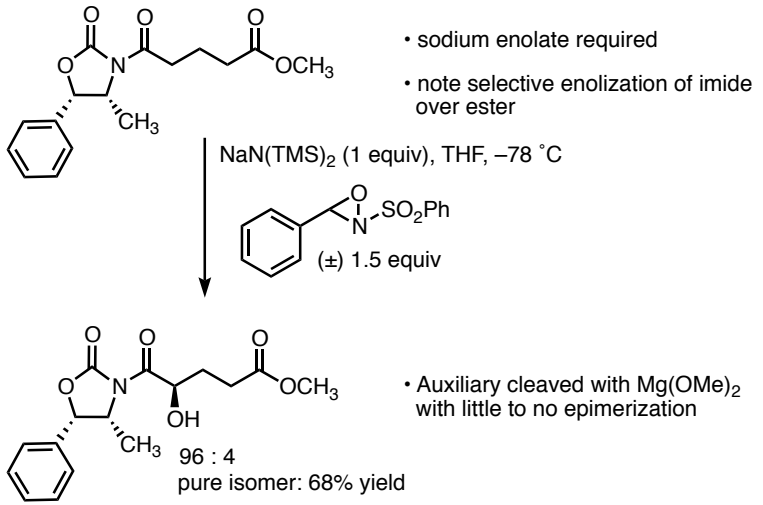
• Highly diastereoselective acylation of imide enolates is possible:

Exercise: Why are the products configurationally stable?



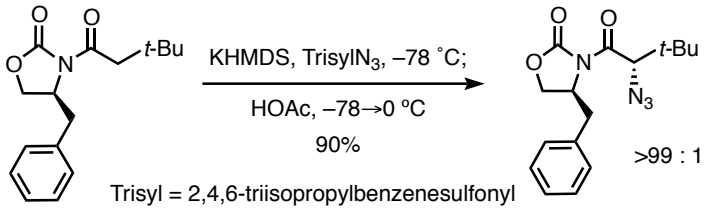
Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

• Diastereoselective hydroxylation has been demonstrated:

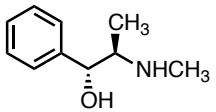


Evans, D. A.; Morissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346-4348.

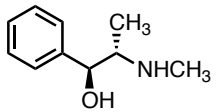
• Asymmetric azidation provides a route to α-amino acid derivatives:



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

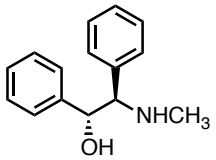


(*R,R*)-(–)-Pseudoephedrine

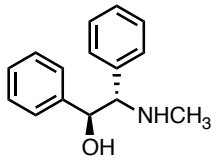


(*S,S*)-(+)-Pseudoephedrine

- Pseudoephedrine is a commodity chemical, manufactured on multi-ton scale/annum. Its use is highly regulated in many countries.



(*R,R*)-(+)-Pseudoephenamine

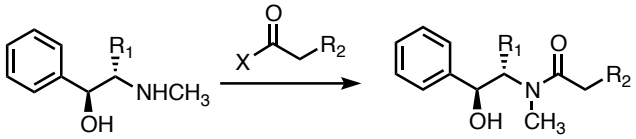


(*S,S*)-(–)-Pseudoephenamine

- Use of pseudoephenamine is not restricted; it appears to be a superior auxiliary in many instances.

Morales, M.R.; Mellem, K.T.; Myers, A.G. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4568–4571.

Preparation of Pseudoephedrine and Pseudoephenamine Amides:



R_1	R_2	X	Yield (%)	mp (°C)
Ph	CH_3	$EtCO_2$	88	188–191
Ph	Et	*n*-$PrCO_2$	83	133–135
Ph	Bn	Cl	80	147–149
Ph	*n*-Bu	$R'CH_2CO_2$	70	88–90
CH_3	CH_3	CH_3O*	89	114–115
CH_3	Ph	Cl	88	145–146
CH_3	Cl	Cl	90	79–81
CH_3	*i*-Pr	Cl	92	73–74
CH_3	3-pyridyl	$(H_3C)_3CCO_2$	97	117.5–118.5

*Even unactivated esters react (under basic conditions), presumbly by transesterification followed by intramolecular *O*→*N* Acyl Transfer

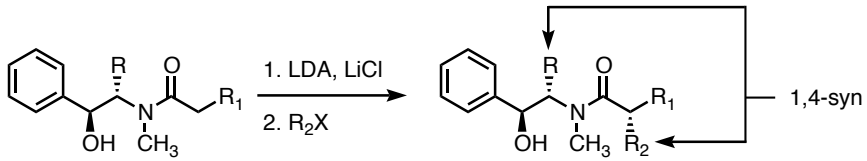
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.: Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

Morales, M.R.; Mellem, K.T.; Myers, A.G. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4568–4571.

Alkylation of Pseudoephenamine and Pseudoephedrine Amides:

- Enolates are formed using 1.95–2.2 equiv LDA.
- Alkylations are highly diastereoselective.
- LiCl (~6 equiv) promotes a rapid, clean reaction.

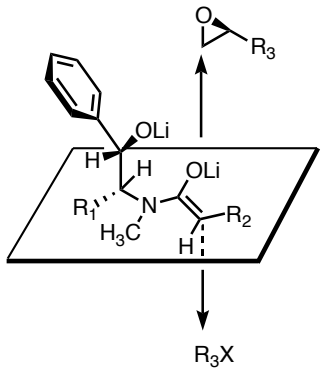
Mnemonic:



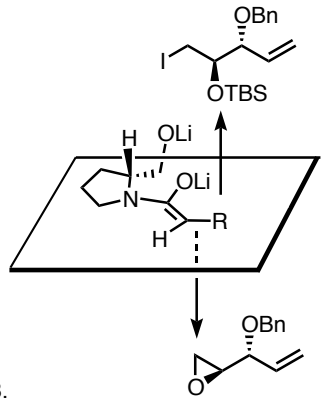
R = CH_3 or Ph

R = CH_3 or Ph

- Epoxides approach from the opposite enolate π-face.



- Askin et al. reported this type of selectivity reversal for epoxide electrophiles with prolinol amide enolates and proposed that the Li cation coordinates and directs the epoxide opening:

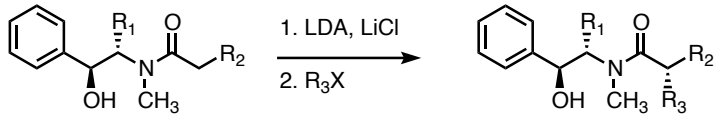


Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

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

Kevin Mellem

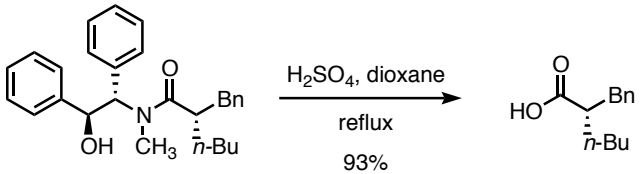
Diastereoselective Alkylation Reactions:



R_1	R_2	R_3X	temp (˚C)	crude (isol) de (%)	isol yield (%)
Ph	CH_3	BnBr	0	90 (≥99)	85
Ph	CH_3	EtI	0	88 (96)	96
Ph	*n*-Bu	CH_3I	0	90 (96)	84
Ph	Bn	*n*-BuI	–78	≥99 (≥99)	99
CH_3	CH_3	$BrCH_2CO_2t$-Bu	–78	94 (96)	78
CH_3	Ph	EtI	0	96 (≥99)	92
CH_3	*i*-Pr	BnBr	0	98 (≥99)	83
CH_3	*t*-Bu	BnBr	0	98 (≥99)	84
CH_3	Cl	BnBr	–45	90 (≥99)	88

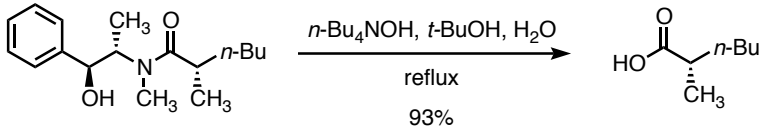
Hydrolysis of Alkylation Products:

- 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.



≥99% de 97% ee

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



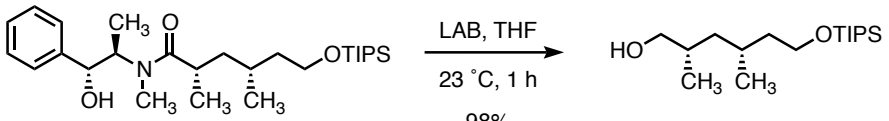
≥99% de 97% ee

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

Morales, M.R.; Mellem, K.T.; Myers, A.G. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4568–4571.

Reduction of Alkylation Products:

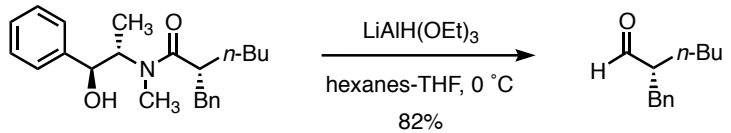
- Lithium amidotrihydroborate (LiH_2NBH_3 (LAB)), prepared by deprotonation (LDA) of commercial, crystalline ammonia-borane complex, provides primary alcohols:



98% de 97% ee

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 triethoxyaluminium hydride provides aldehydes directly but it can be complicated by low yields, epimerization of the α-stereocenter, and formation of a stable aminal intermediate:

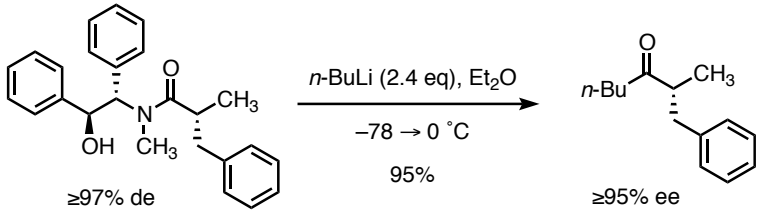


≥99% de 97% ee

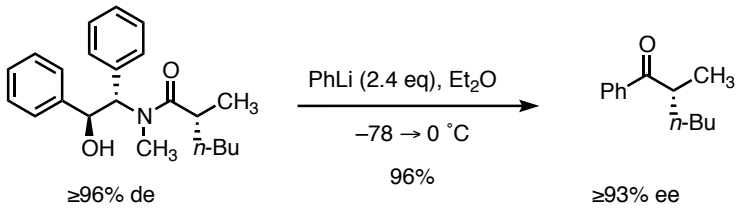
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

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

Addition of Alkyllithium Reagents to form Ketones:



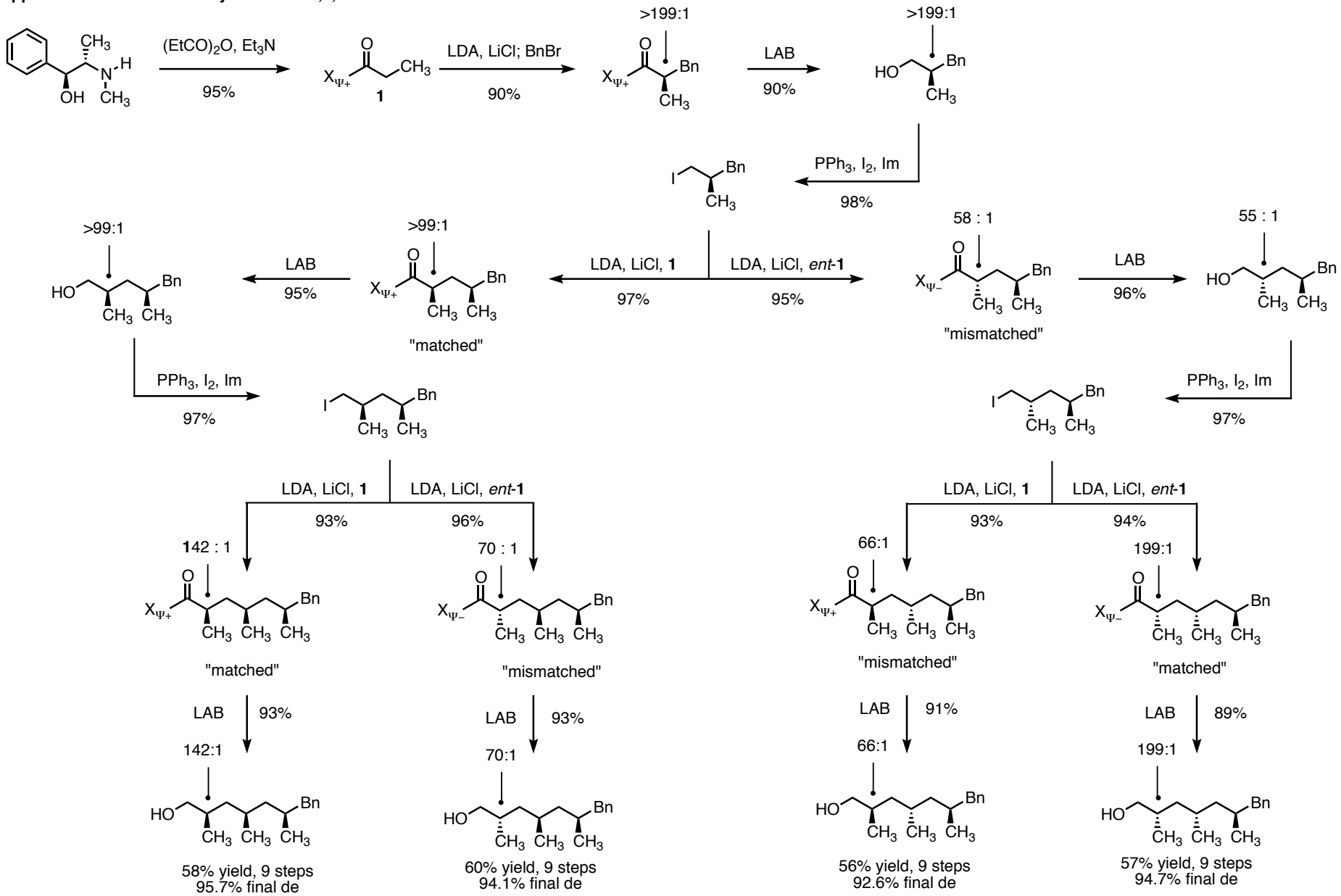
≥97% de ≥95% ee



≥96% de ≥93% ee

Kevin Mellem

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

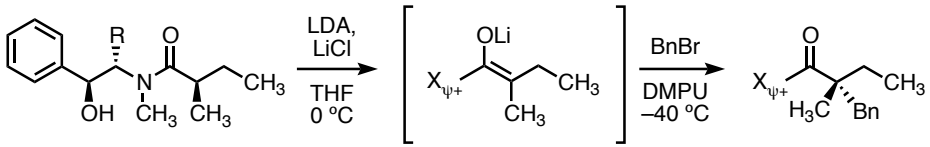


Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457-459.

Construction of Quaternary Centers

• Pseudoephenamine and pseudoephedrine can be used to direct the formation of quaternary centers by two methods: enolization–alkylation or conjugate addition–alkylation.

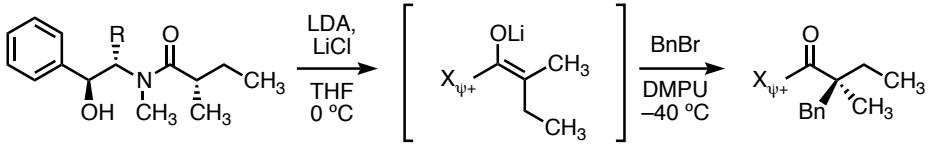
Enolization–Alkylation:



Matched
R = CH_3 or Ph

***Z*-enolate**

95%, 9.9:1 dr



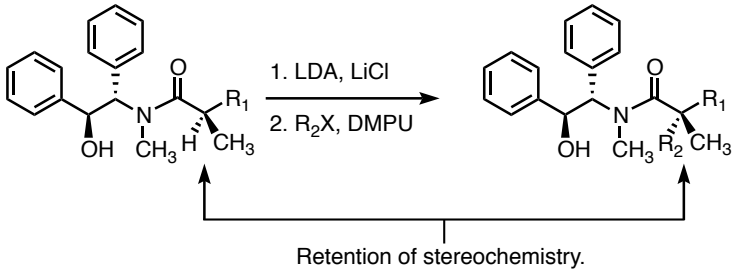
Mismatched
R = CH_3 or Ph

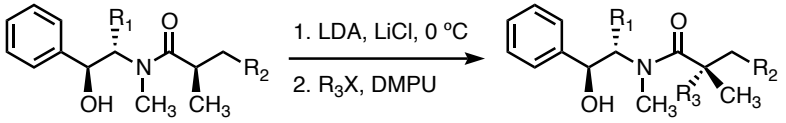
***E*-enolate**

89%, 5.2:1 dr

Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.

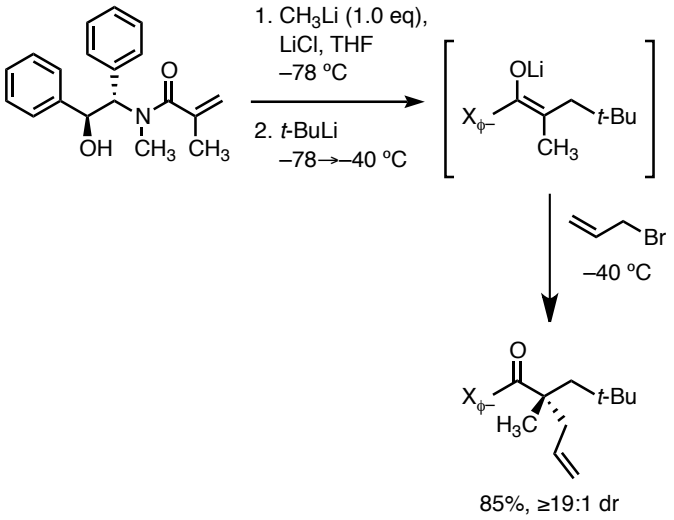
Mnemonic:





R_1	R_2	R_3X	temp (˚C)	crude dr	isol yield (%)
Ph	CH_3	BnBr	–40→0	≥19:1	85
Ph	CH_3	allylBr	–40→0	≥19:1	99
Ph	*n*-Pr	BnBr	–40→0	≥19:1	87
Ph	Ph	allylBr	–40→0	≥19:1	82
CH_3	Ph	EtI	–40	6.2:1	87
CH_3	vinyl	BnBr	–40	19:1	90

Conjugate Addition–Alkylation:

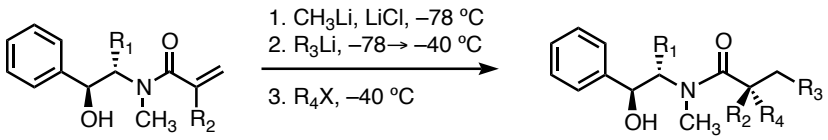


85%, ≥19:1 dr

• Even bulky organolithium reagents such as *tert*-buyllithium are suitable reagents for this transformation.

Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4568–4571.
E. Reyes, J. L. Vicario, L. Carrillo, D. Badia, A. Iza, U. Uria, *Org. Lett.* **2006**, *8*, 2535–2538.

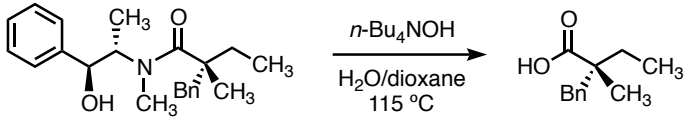
Kevin Mellem



R_1	R_2	R_3	R_4X	crude dr	isol yield (%)
Ph	CH_3	*n*-Bu	BnBr	≥19:1	75
Ph	CH_3	Ph	AllylBr	≥19:1	80
Ph	Et	*t*-Bu	CH_3I	≥19:1	79
Ph	*n*-pentyl	*t*-Bu	CH_3I	≥19:1	76
CH_3	CH_3	*n*-Bu	allylBr	11.1:1	72
CH_3	CH_3	*t*-Bu	allylBr	12.5:1	98
CH_3	Et	*t*-Bu	CH_3I	9.1:1	99
CH_3	Et	Ph	CH_3I	19:1	89

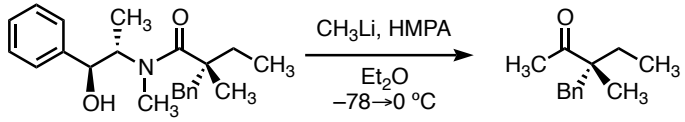
Transformations of α-quaternary pseudoephenamine and pseudoephedrine amides

Hydrolysis of α-quaternary alkylation products:

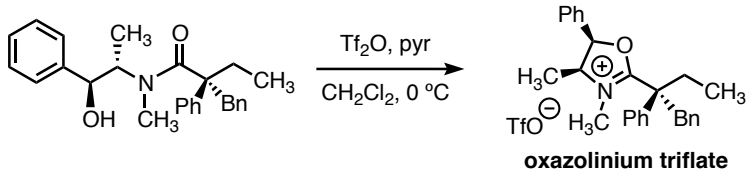


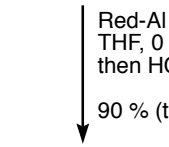
Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.

Addition of alkyllithium reagents to form ketones:

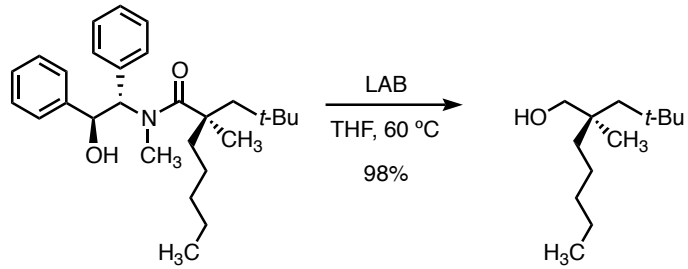


Reduction to form aldehydes:



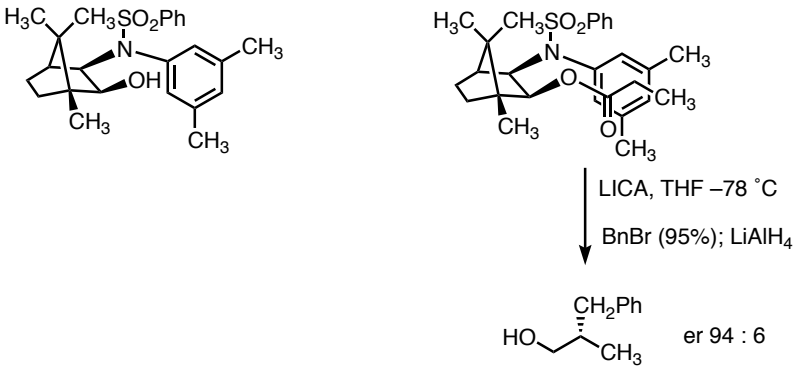


LAB reduction to form primary alcohols:



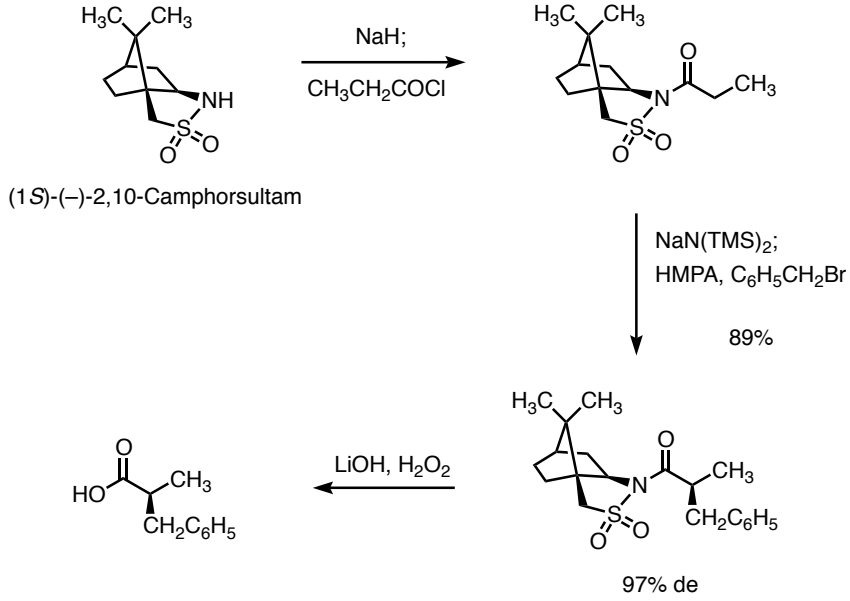
Kevin Mellem

• Helmchen camphor-derived auxiliaries:



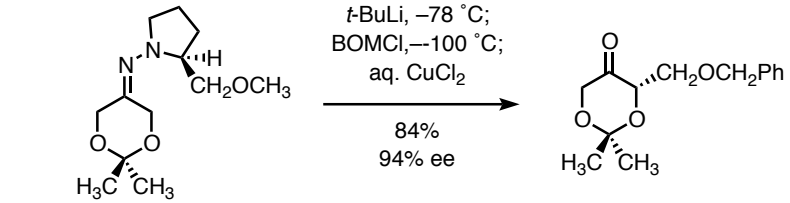
Schmierier, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207-208.

• Oppolzer camphorsultam auxiliaries in asymmetric alkylation:



Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603-5606.

• Enders chiral hydrazone methodology:

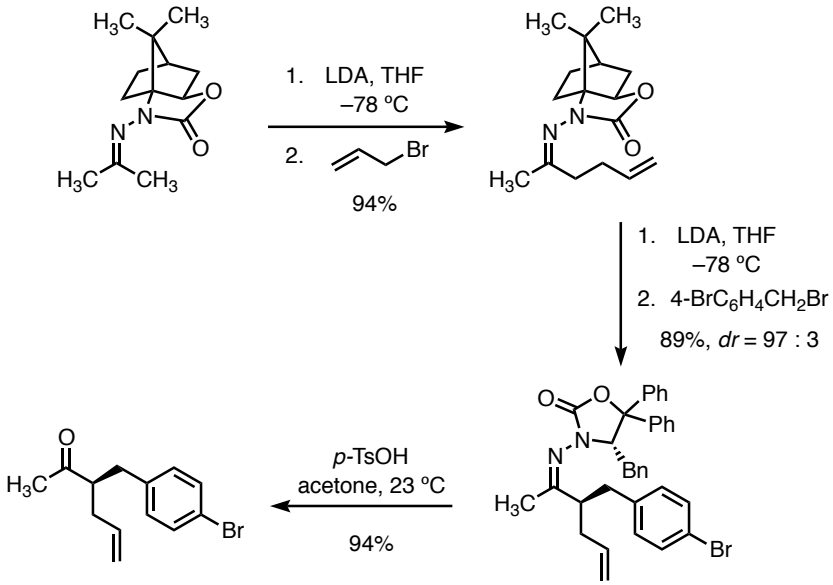


(S)-(+)-1-Amino-2-(methoxymethyl) pyrrolidine [SAMP-Hydrazone]

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

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

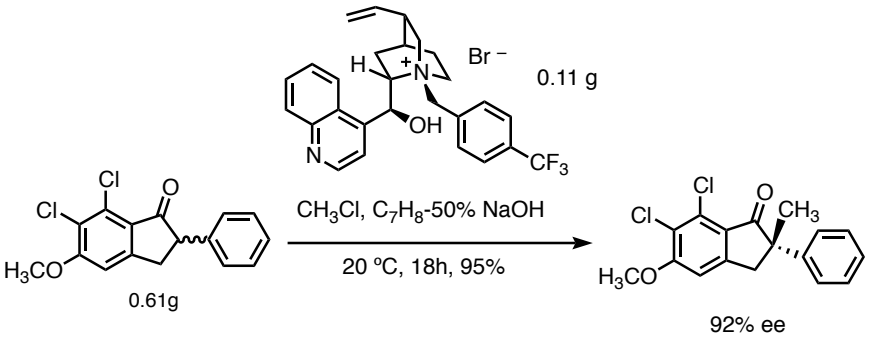
• An alternative oxazolidinone-based auxiliary allows α-alkylation of ketones with excellent stereoselectivities. The ease of synthesis and removal of the auxiliary makes it a practical alternative to the traditional RAMP/SAMP methodology:



Lim, D.; Coltart, D. M. *Angew. Chem., Int. Ed. Engl.* **2008**, *47*, 5207–5210.

Fan Liu

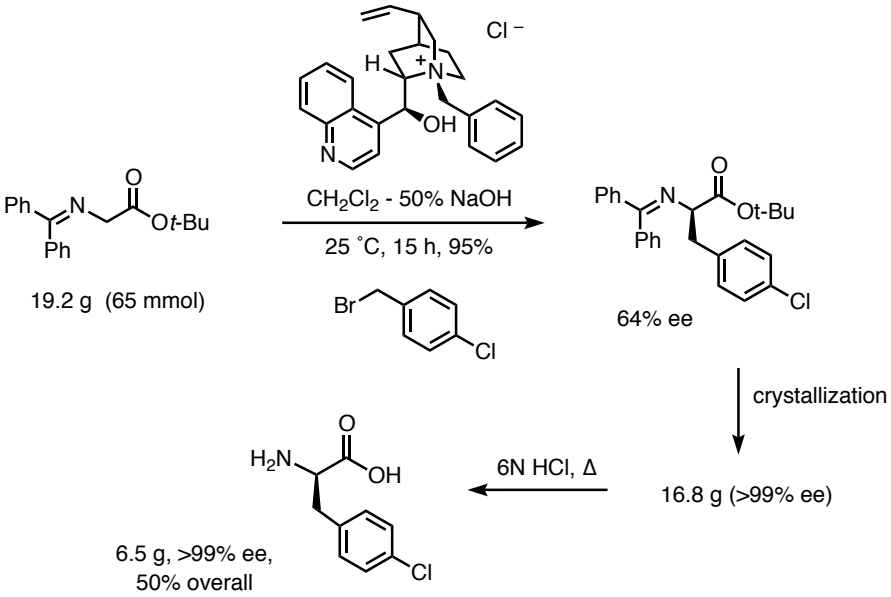
• An early, remarkable result from the Merck Process group:



• Although limited to a single example, this provided a dramatic illustration of the potential of chiral phase-transfer catalysis for C-C bond formation.

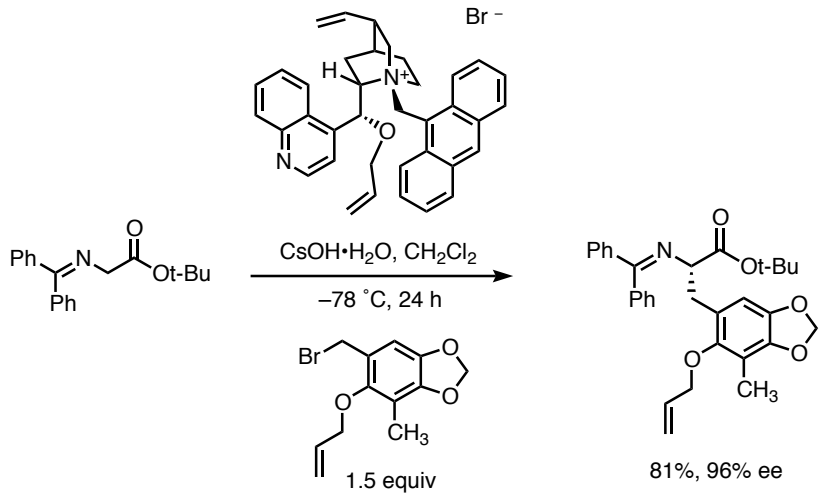
Dolling, U.; David, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

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



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

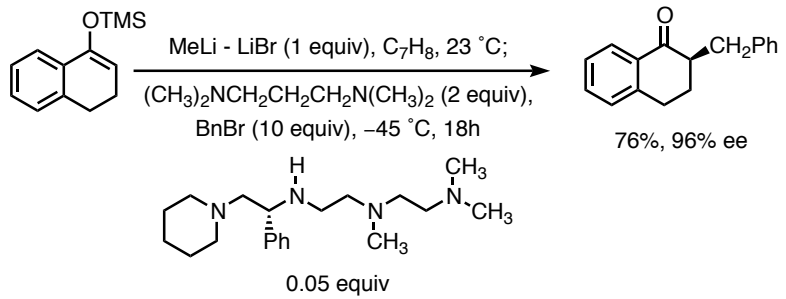
• Corey and co-workers have developed catalysts that are highly enantioselective:



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

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

• Koga and co-workers have developed chiral additives for the asymmetric alkylation of lithium enolates. The work has been extended to include examples that employ additives in catalytic amounts:



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