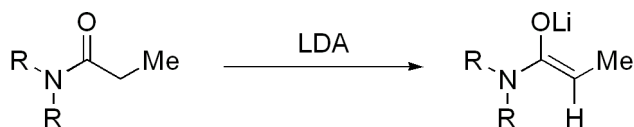


Enolate Stereocontrol

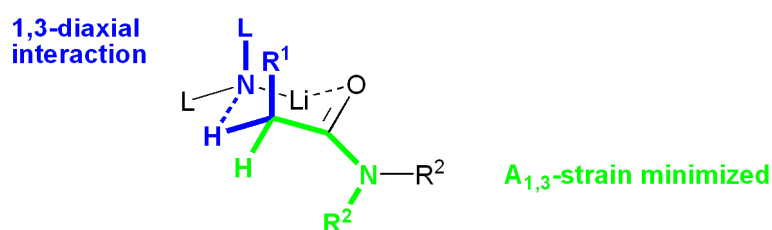
1. Generation of Enolates: (E) vs (Z)

monosubstituted amides: high (Z) selectivity

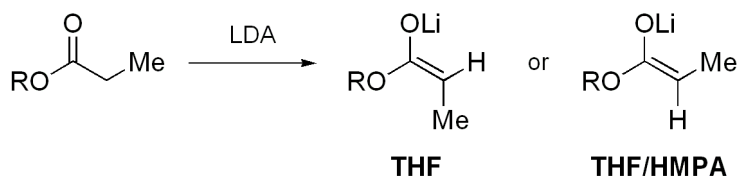


Evans *Tetrahedron Lett.* **1980**, 21, 4233.

model: six-membered cyclic transition state

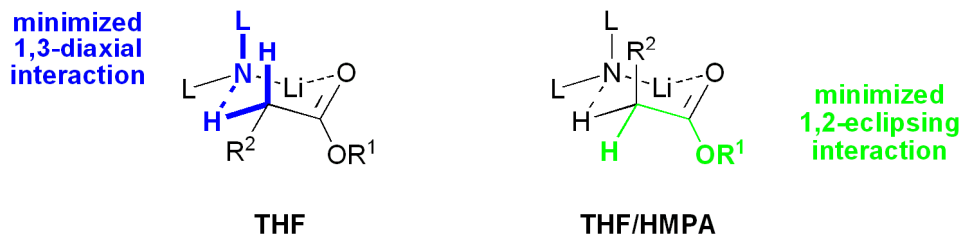


monosubstituted esters: (E) or (Z) selectivity dependent on solvent



Ireland *J. Am. Chem. Soc.* **1976**, 98, 2868.
J. Org. Chem. **1991**, 56, 650.

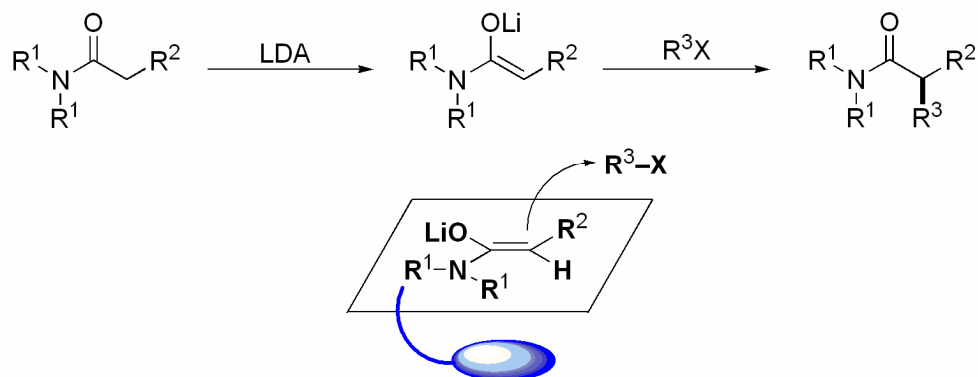
model: six-membered cyclic transition state



may not react via cyclic six-membered transition state

2. Diastereoselective Alkylation of Enolates Using Chiral Auxiliaries

2.1. Alkylation of Carboxamides



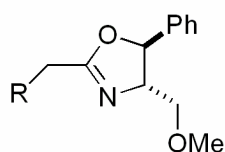
desirable characteristics:

- readily synthesized chiral auxiliary
- inexpensive materials
- broad substrate scope
- facile auxiliary cleavage
- recyclable auxiliary

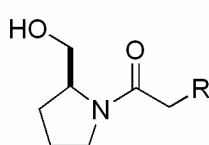
access to both stereochemical configurations of new stereocenter:

- reverse alkylating agent and enolate substituent
- invert enolate geometry
- use stereochemical antipode of the auxiliary

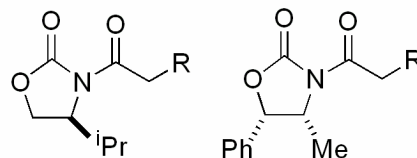
chiral auxiliaries for monosubstituted enolate alkylation



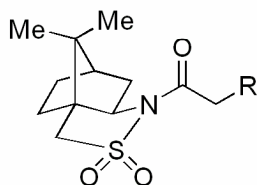
Meyers
J. Am. Chem. Soc.
1976, 98, 567.



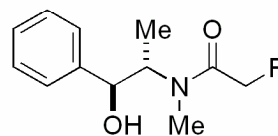
Evans
Tetrahedron Lett. **1980**, 21,
4233; *J. Org. Chem.* **1980**,
45, 3137.



Evans
J. Am. Chem. Soc. **1982**, 104, 1737.

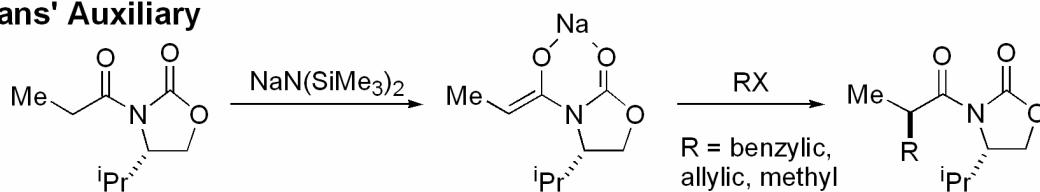


Oppolzer
Tetrahedron Lett. **1989**, 30,
5603.



Myers
J. Am. Chem. Soc.
1997, 118, 6496.

2.1.1. Evans' Auxiliary

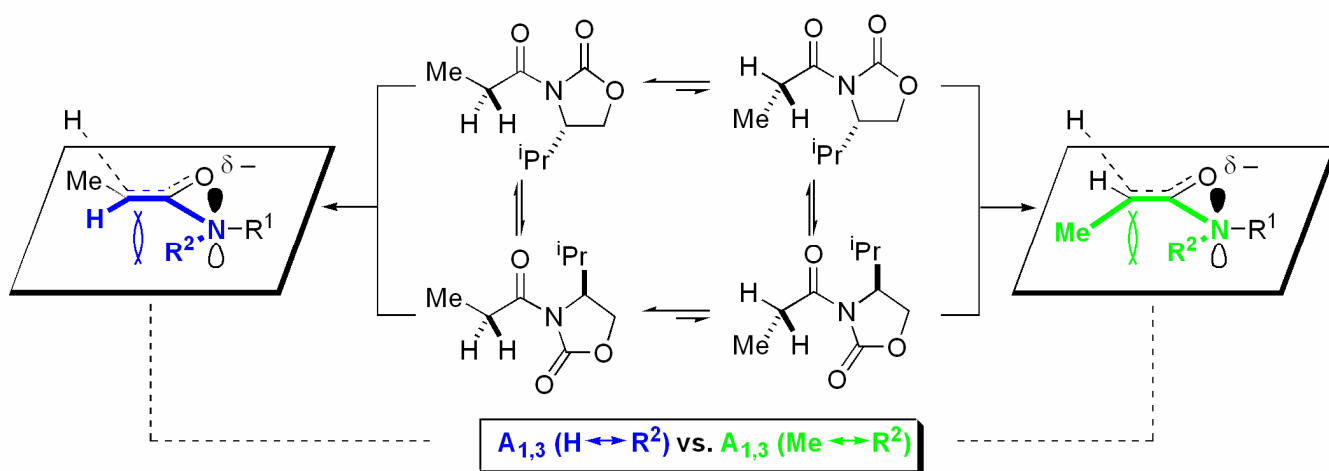
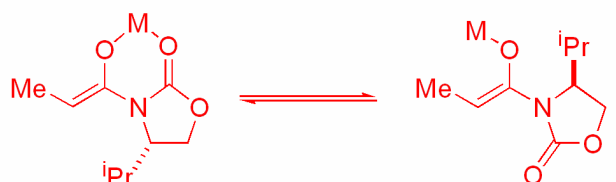


92-98% yield
dr = 20:1

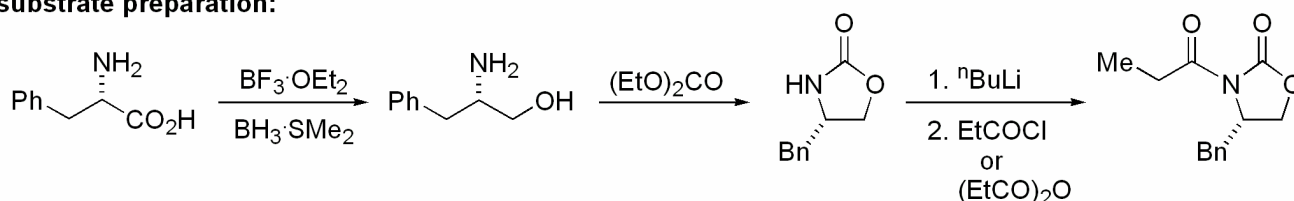
reactive Na-enolate, alkylation with reactive reagents

Evans *J. Am. Chem. Soc.* **1982**, *104*, 1737.

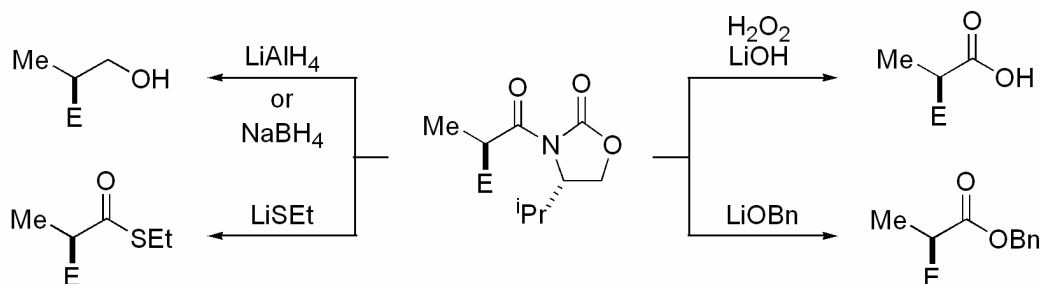
working model:



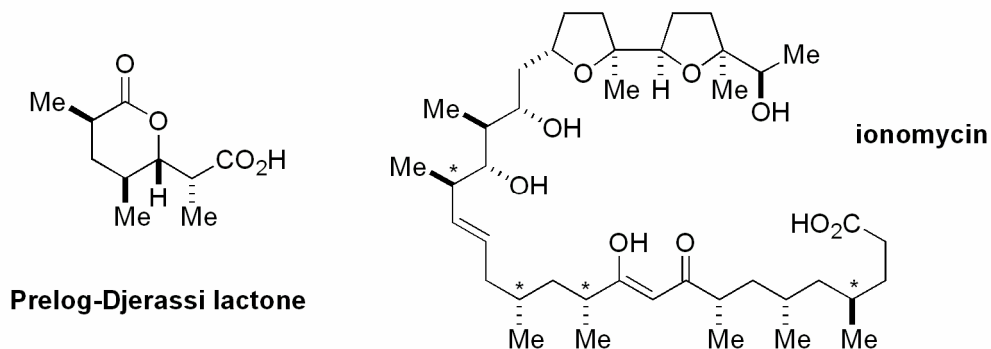
substrate preparation:



auxiliary cleavage:

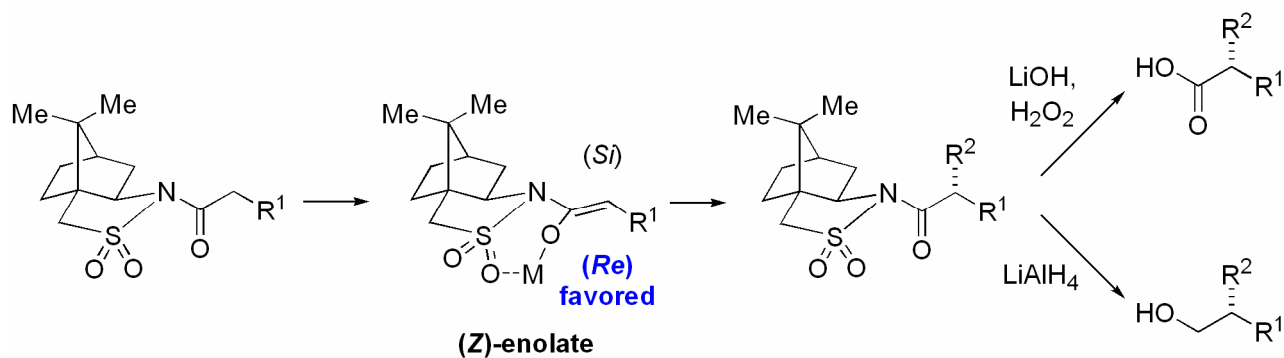


example for application: Syntheses using (in part) asymmetric alkylation of oxazolidinone enolates, e. g. Prelog-Djerassi lactone and ionomycin. The stereocenters created by alkylation are indicated with an asterix.



Evans *J. Am. Chem. Soc.* **1990**, *112*, 5290.
Tetrahedron Lett. **1989**, *30*, 5603.

2.1.2. Oppolzer's Camphor Sultam Auxiliary

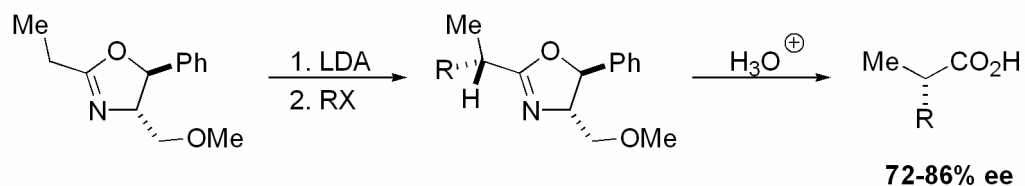


R ¹	R ²	ds [%]	dr	yield [%]
Me	Bn	98.5	> 99:1	89
Bn	Me	97.4	> 99:1	88
Me	allyl	98.3	> 98:2	74
allyl	Me	97.7	> 99:1	nd
Me	methallyl	89.6	> 99:1	70
Me	ⁿ C ₅ H ₁₁	98.9	98:2	81
ⁿ C ₅ H ₁₁	Me	98.1	98:2	nd

Oppolzer *Tetrahedron Lett.* **1989**, *30*, 5603.

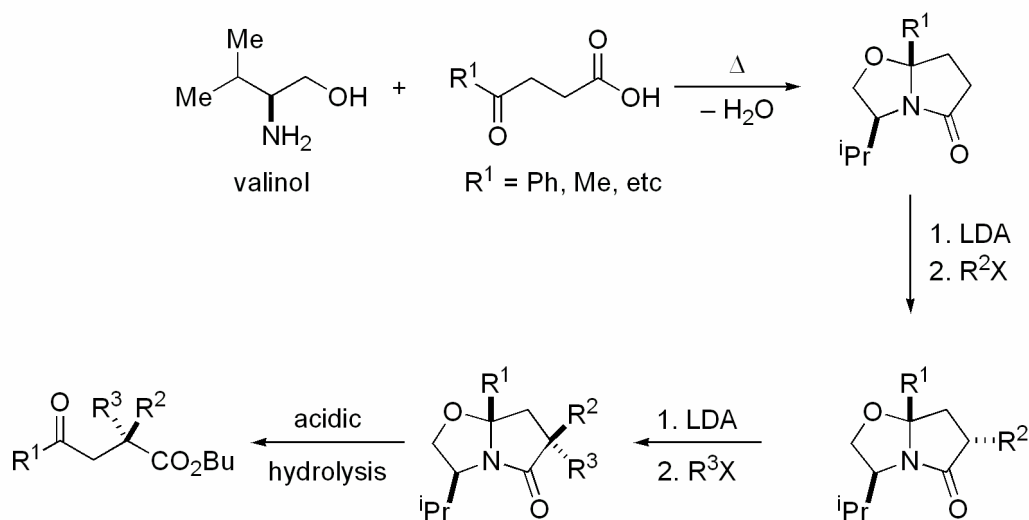
2.1.3. Meyers' Chiral Oxazolines

pioneering studies:



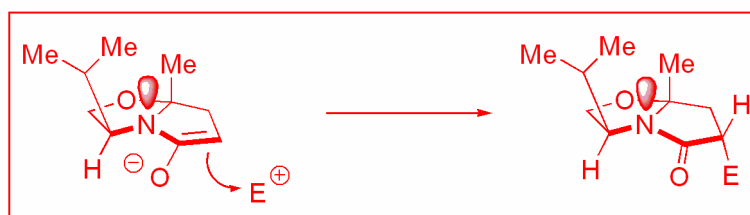
Meyers *Tetrahedron Lett.* **1984**, 25, 3667.
J. Am. Chem. Soc. **1984**, 106, 1865.
J. Am. Chem. Soc. **1992**, 114, 1010.

modern variant: bicyclic lactams - useful for the synthesis of quaternary stereogenic centers

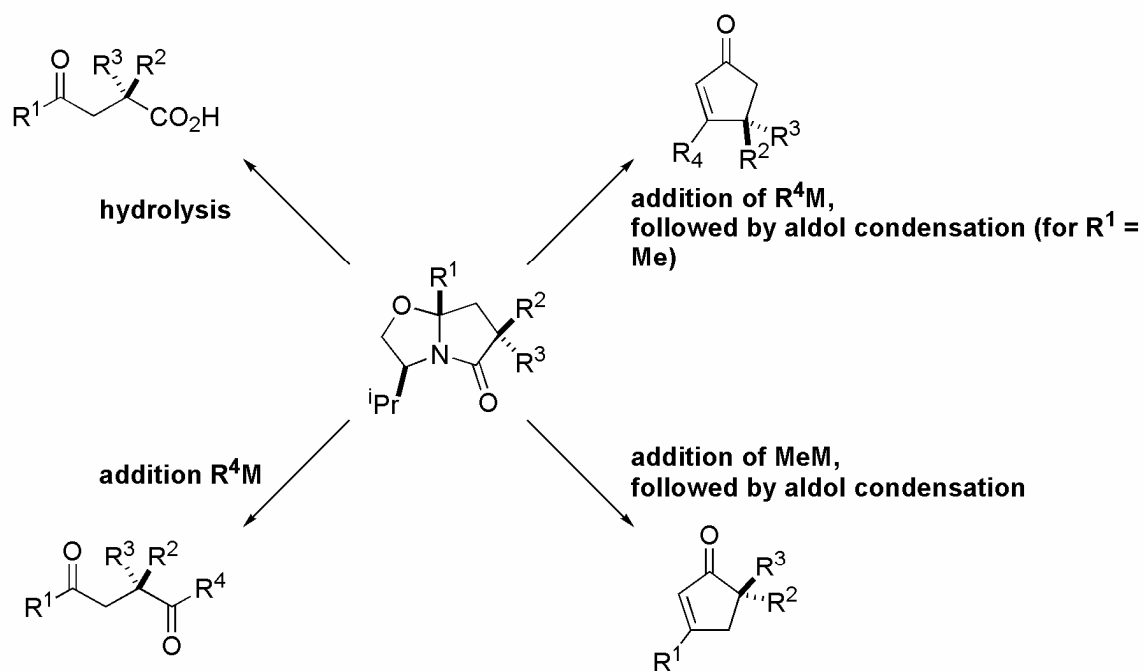


Meyers *J. Am. Chem. Soc.* **1998**, 120, 7429.

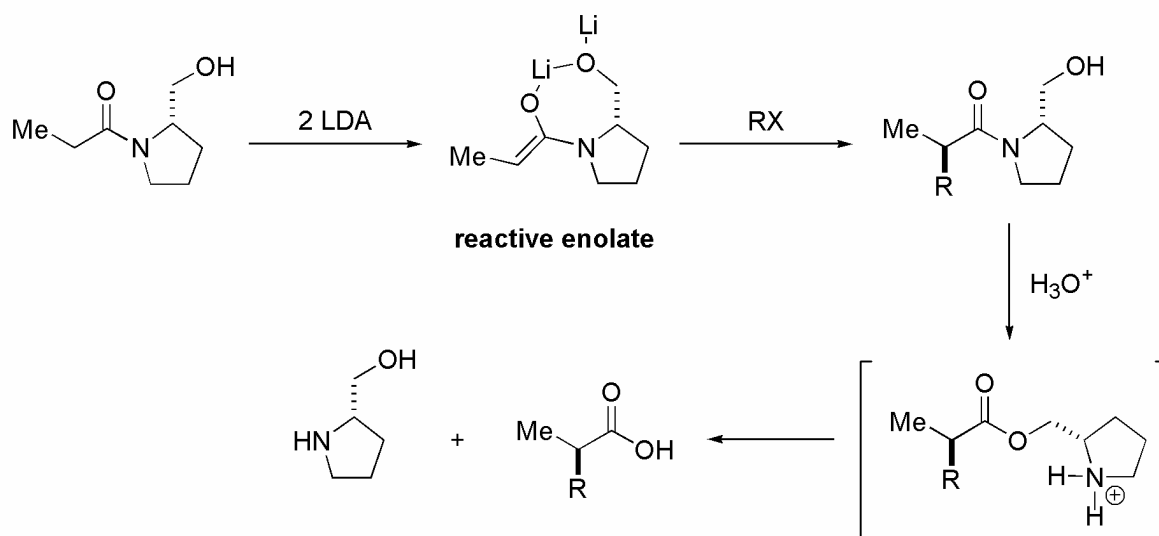
model:



Range of different products accessible from bicyclic lactams:

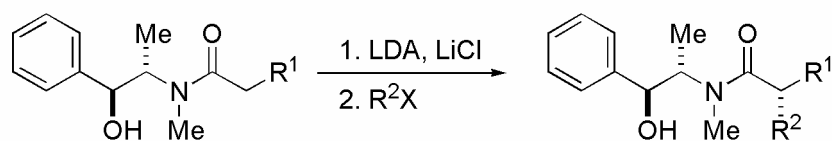


2.1.4. Evans' Prolinol-Based Auxiliary



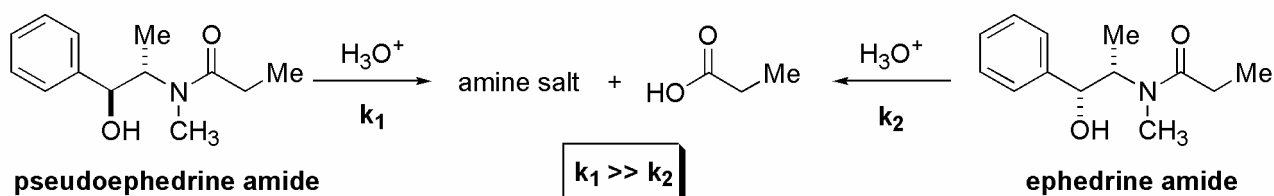
Evans *Tetrahedron Lett.* **1980**, *21*, 4233.

2.1.5. Myers' Pseudoephedrine Auxiliary



85-95%
dr > 40:1

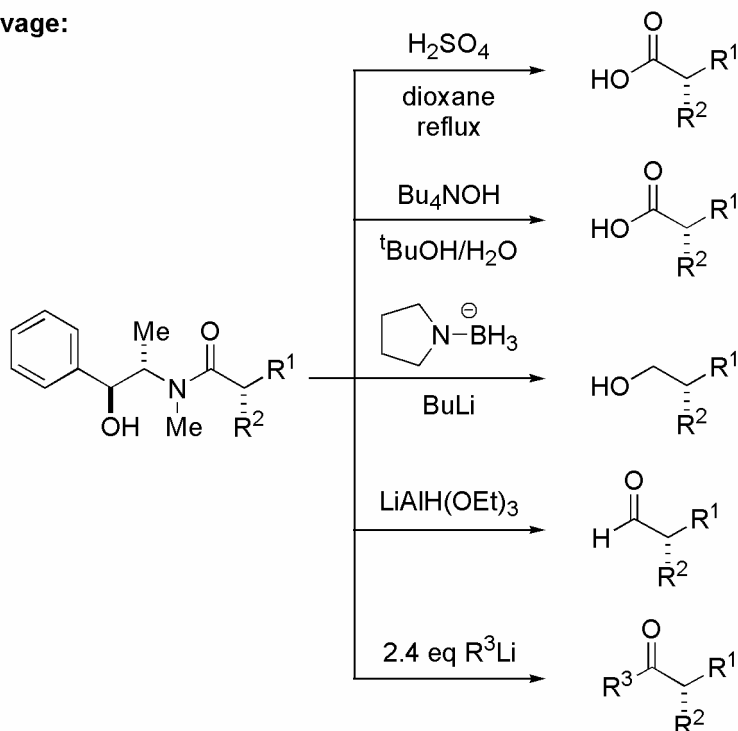
Myers *J. Am. Chem. Soc.* **1994**, *116*, 9361.
J. Am. Chem. Soc. **1995**, *117*, 8488.
J. Am. Chem. Soc. **1997**, *119*, 656.
J. Am. Chem. Soc. **1997**, *119*, 6496.



no LiCl, 0 °C: dr = 4:1
LiCl, -75 °C: dr = 99:1

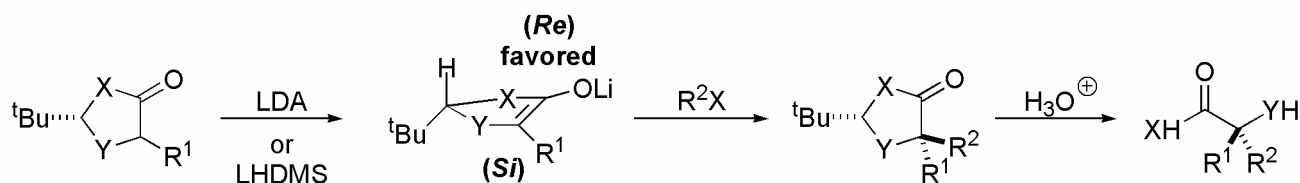
Seebach *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624.

auxiliary cleavage:



2.2. Amino Acid Synthesis

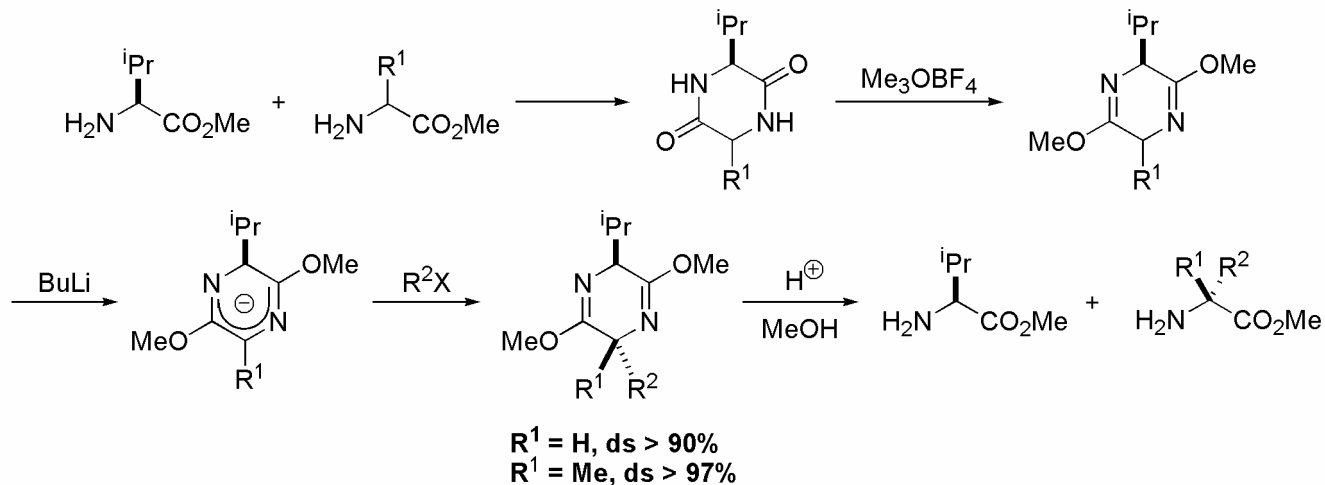
2.2.1. Seebach's Self-Regeneration of Stereocenters



X/Y	R ¹ /R ²	dr [%]	yield [%]
O/O	Me/Et	94:6	82
O/O	Ph/n-Pr	90:10	84
O/S	Me/allyl	> 96:4	92
O/NCOPh	Me/Bn	> 96:4	93
O/NCOPh	Bn/Me	> 96:4	88
O/NCOPh	i-Pr/Me	100:0	53
MeN/NCOPh	Me/Et	> 90:10	90
MeN/NCOPh	Me/Bn	> 90:10	73
MeN/NBoc	H/Bn	100:0	64
MeN/NBoc	H/allyl	100:0	85
MeN/Cbz	H/i-Pr	100:0	59

Seebach *Tetrahedron* **1984**, *40*, 1313.
Tetrahedron **1988**, *44*, 5277.
Helv. Chim. Acta **1985**, *68*, 1243.
Helv. Chim. Acta **1985**, *68*, 144.
Helv. Chim. Acta **1992**, *75*, 913.

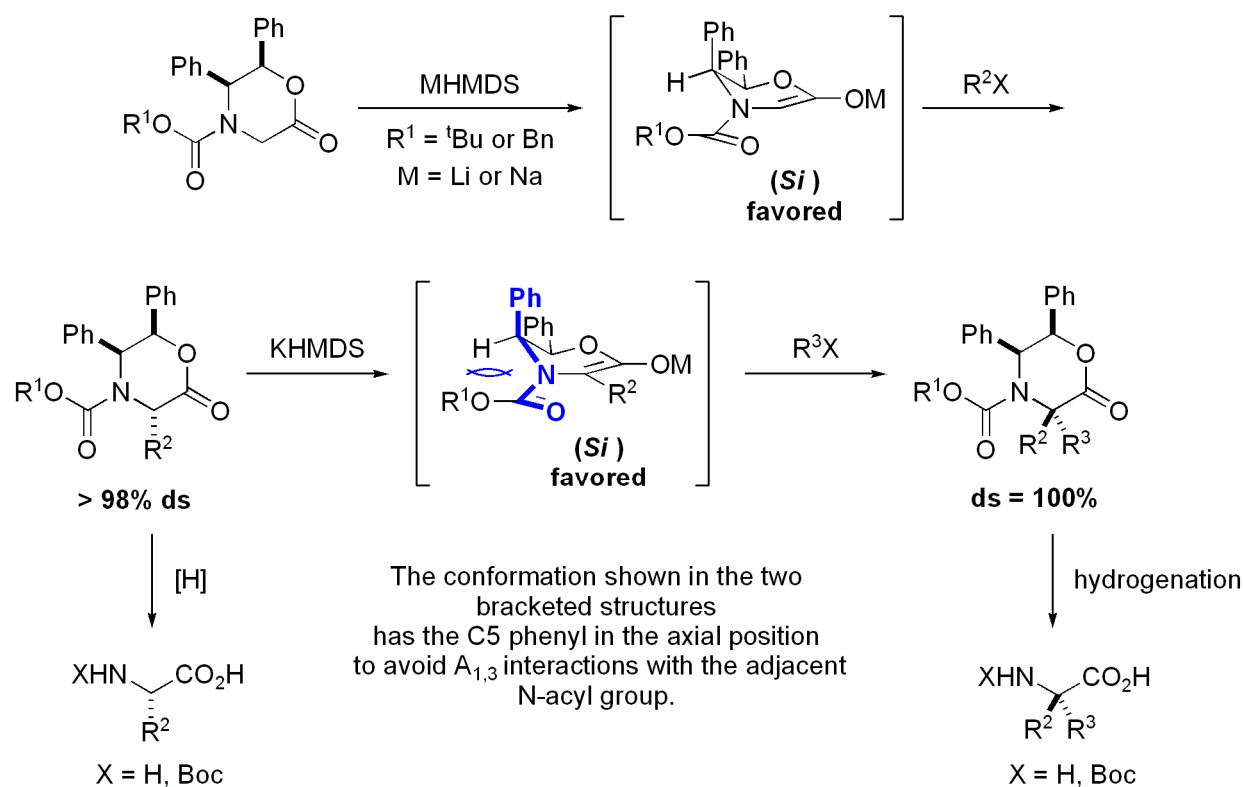
2.2.2. Schöllkopf's Bis-Lactim Ether Amino Acid Synthesis



R ¹ /R ²	ds [%]	yield [%]
H/Bn	96	81
H/PhCH=CHCH ₂	97	90
H/n-C ₇ H ₁₅	87	62
Me/Bn	98	68
Me/PhCH=CHCH ₂	98	89
Me/n-C ₇ H ₁₅	98	43

Schöllkopf *Tetrahedron* **1983**, *39*, 2085.

2.2.3. Williams' Oxazinone Enolate Amino Acid Synthesis

Williams *J. Am. Chem. Soc.* **1991**, *113*, 9276.

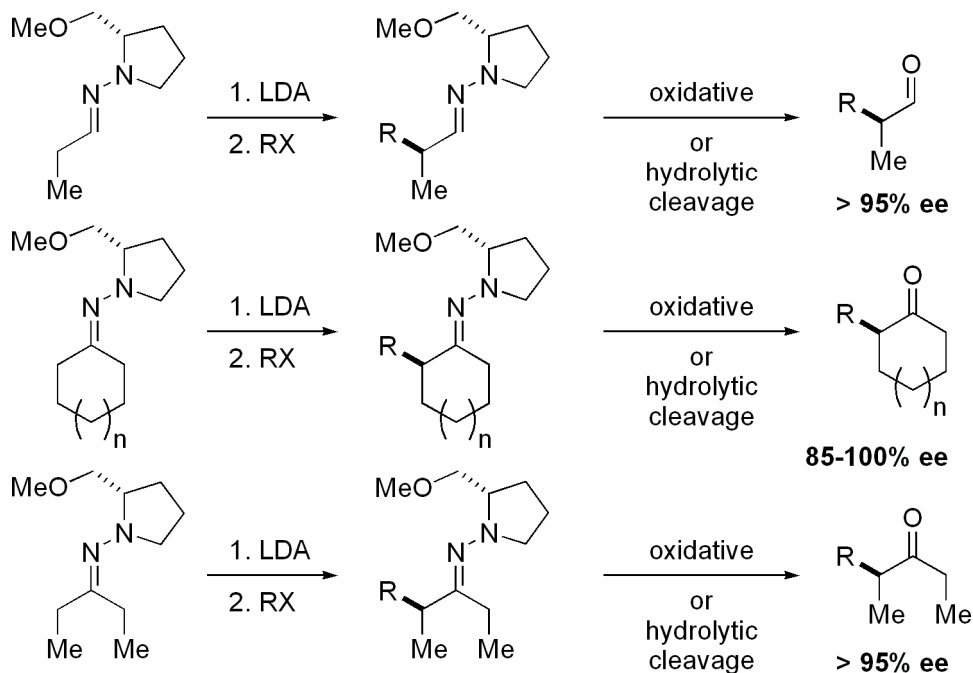
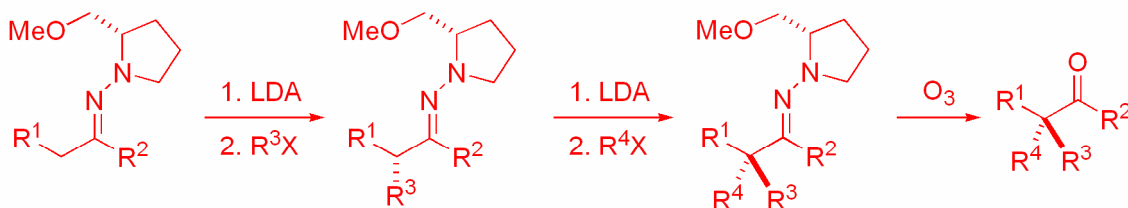
R ¹	R ²	R ³	base	yield [%] (alkylation)	yield [%] (amino acid)	% ee
^t Bu	allyl	-	LiHMDS	86	50-70	98
^t Bu	Me	-	NaHMDS	91	54	97
^t Bu	Bn	-	NaHMDS	70	76	98
Bn	Bn	-	NaHMDS	77	93	> 99
^t Bu	Me	allyl	KHMDS	87	70	100
^t Bu	Me	Bn	KHMDS	84	93	100
^t Bu	<i>n</i> -Pr	allyl	KHMDS	90	60	100
Bn	Me	Bn	KHMDS	84	93	100

In all cases, the diastereoselectivity was > 98%.

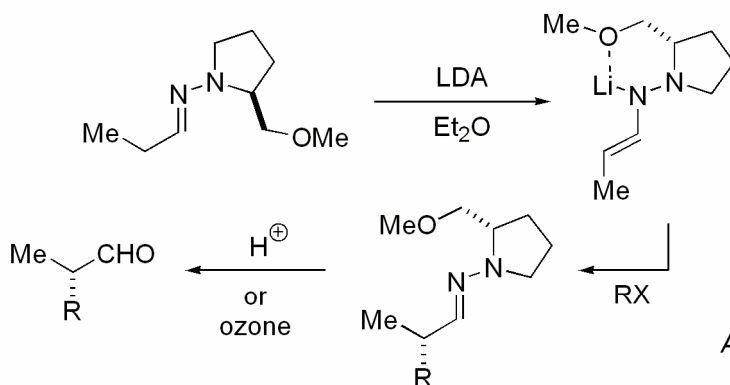
2.3. Ketone Enolate Alkylation

2.3.1. Enders' SAMP/RAMP Hydrazones

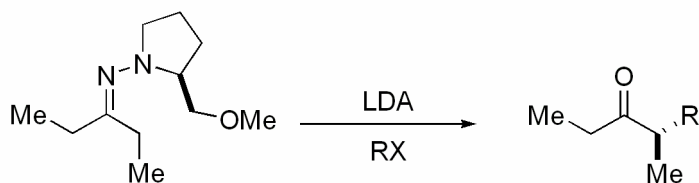
concept:



Enders *Chem. Ber.* **1979**, *111*, 1337.
Tetrahedron **1984**, *40*, 1345.

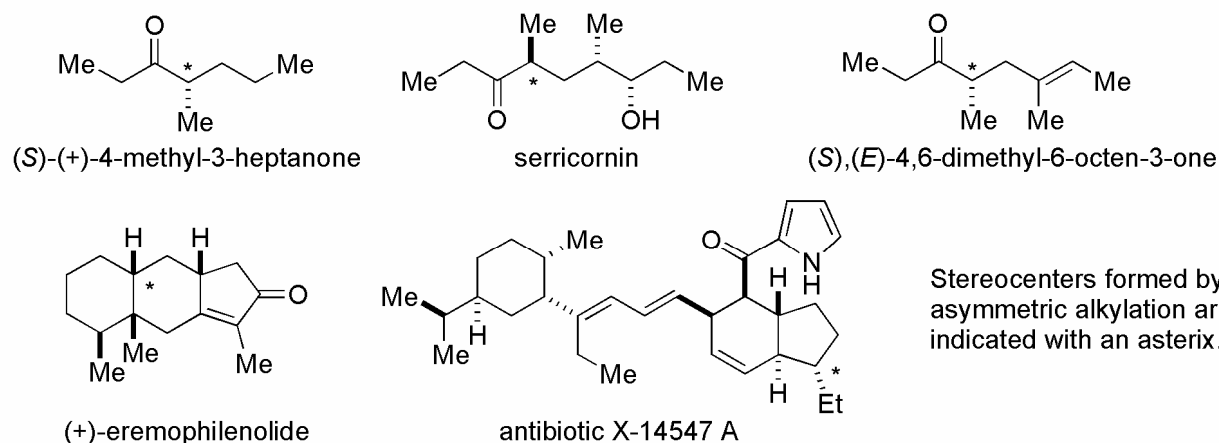


Asymmetric Synthesis Vol. 3, p. 275.
Synlett **1998**, 721.



Tetrahedron **1982**, *38*, 3705.

2.3.2. Applications



Natural product synthesis employing SAMP-RAMP hydrazones:

1. (S)-(+)-4-methyl-3-heptanone, the leaf cutting ant alarm pheromone
2. serricornin, the sex pheromone of the cigarette beetle
3. (S),(E)-4,6-dimethyl-6-octen-3-one, the defense substance of "daddy longlegs"
4. (+)-eremophilinolide
5. antibiotic X-14547 A

2.4. Alkylation of β -Hetero-Enolates