Dynamic Chirality: A Novel Approach to Enantioselective Synthesis

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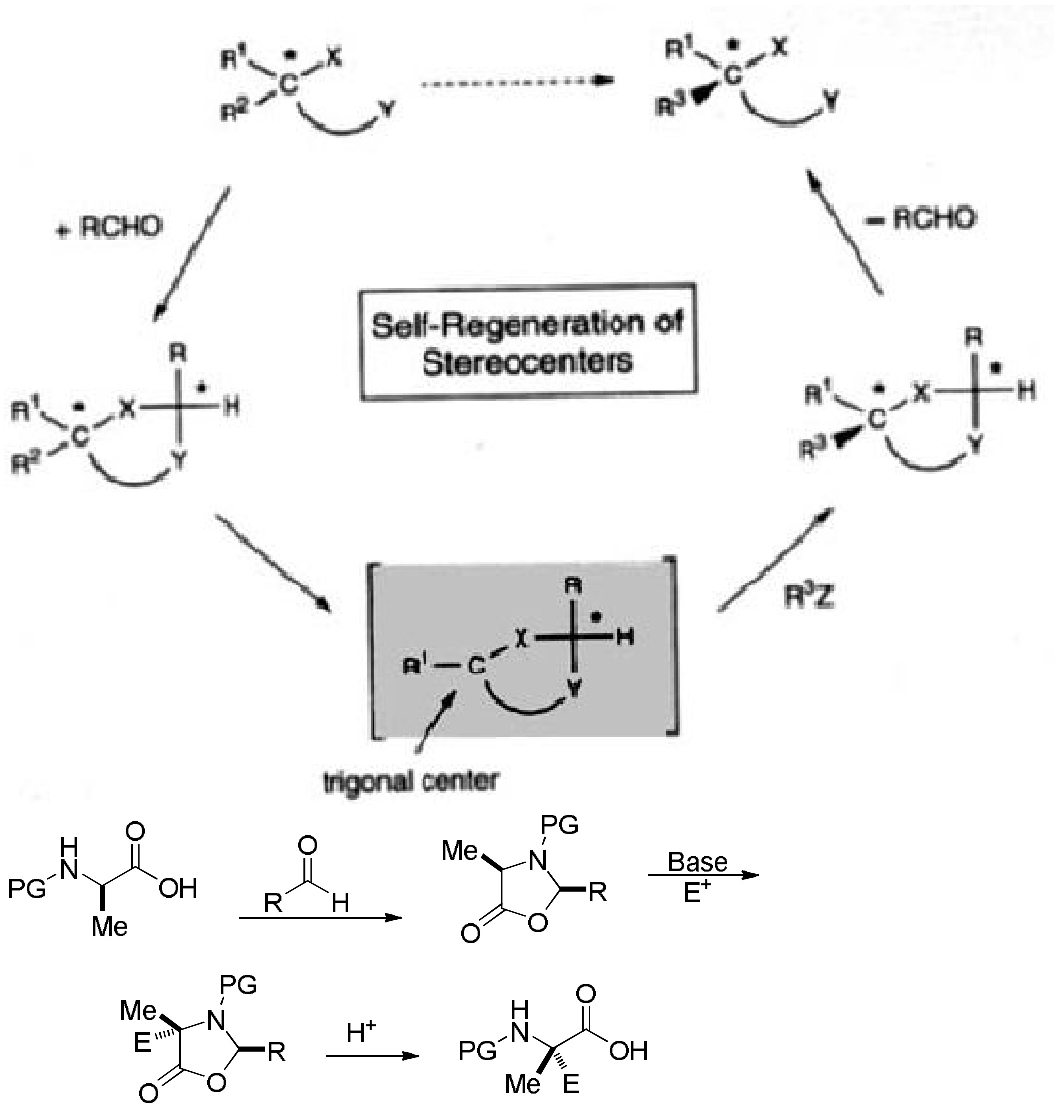
Denmark Group Meeting

Feb 16 2010

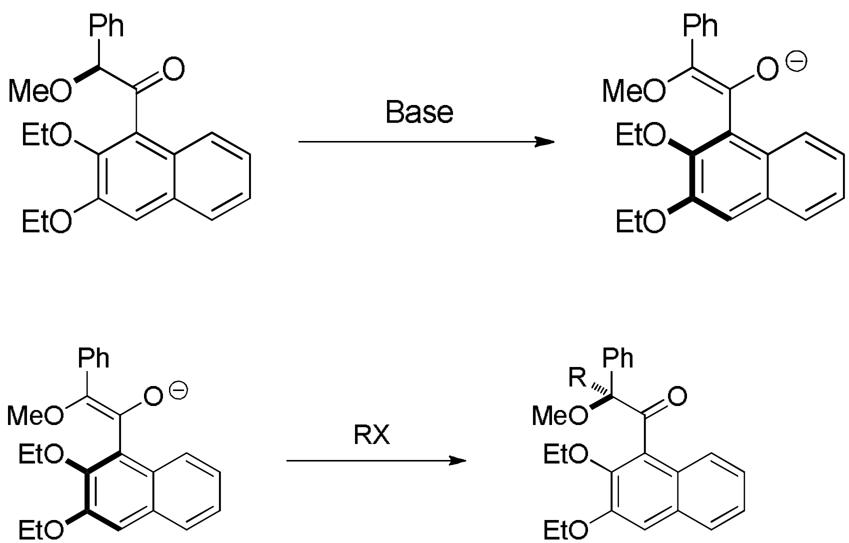
Self-Regeneration of Stereocenters



Seebach; D.; et. al. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708-2748.

The chiral starting material possessing two functional groups but one (and only one) stereogenic center is allowed to react with an aldehyde to form an acetal, with preference for one isomer. Annihilation of the original stereogenic center and concomitant formation of a trigonal center yields an intermediate, which, due to the stereogenic center proceeds diastereoselectively under the influence of this temporary stereogenic center, and finally, cleavage of the acetal unit leads to a product in which one of the substituents at the stereogenic center of the starting material has been replaced by a new one.

“Memory of Chirality”



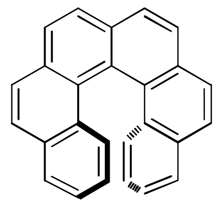
A ‘memory of chirality’ reaction can be defined as a formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.

Zhao, H.; Hsu, D. C.; Carlier, P. R. **Synthesis**, 2005, 1, 1-16.
Kawabata, T.; Fuji, K. In *Topics in Stereochemistry*, Vol. 23; Denmark, S.E. ed. **2003**, John Wiley & Sons Inc.; 175-205

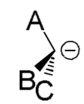
What is Dynamic Chirality

- Stereogenic units that can racemize

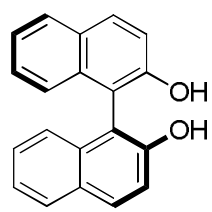
- Helicenes



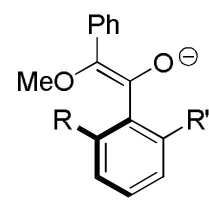
- Carbanions



- Biaryls

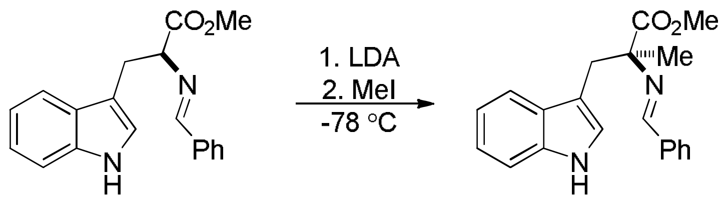


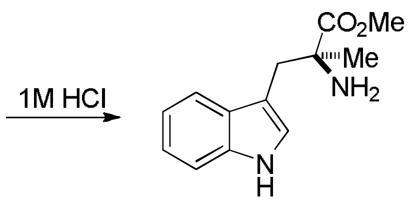
- α-Aryl Enolates



- The formation of a dynamically chiral intermediate can be used to generate chiral non-racemic compounds

Initial Discovery

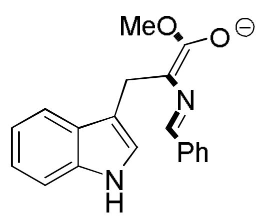




66% over 2 steps

Fully characterized

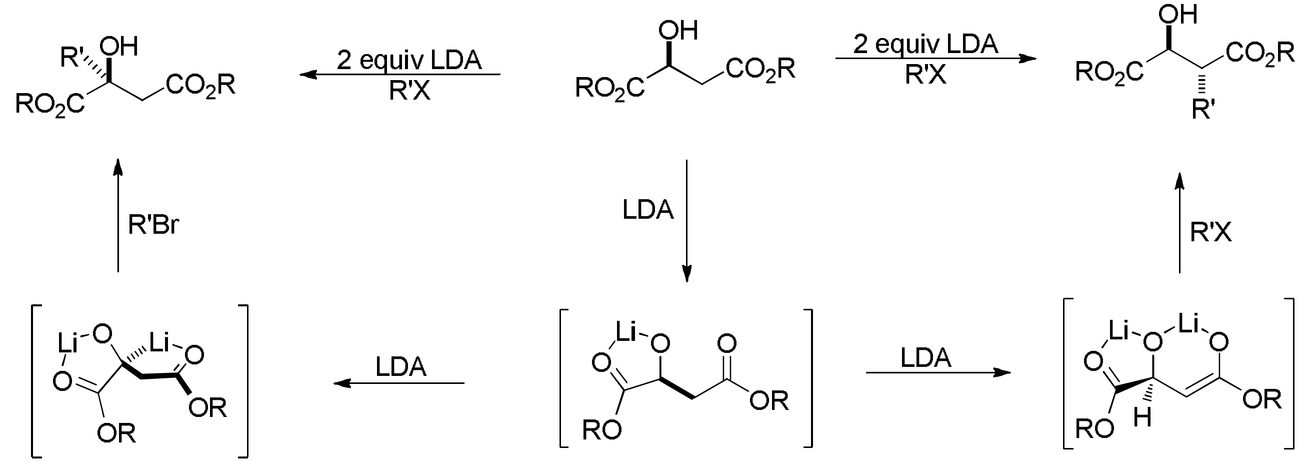
$\alpha^{30}_{[D]}$ = -3.8° (chloroform)



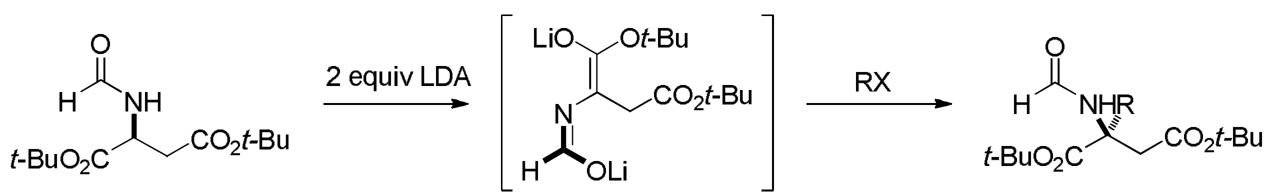
Brana, M. F.; et. al. *J. Hetereocyclic Chem.* **1980**, *17*, 829.

Another Early Example

ca. 15%
80:20 er

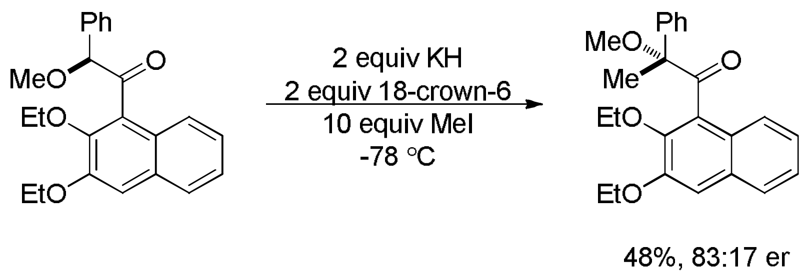


ca. 55%
>99:1 er



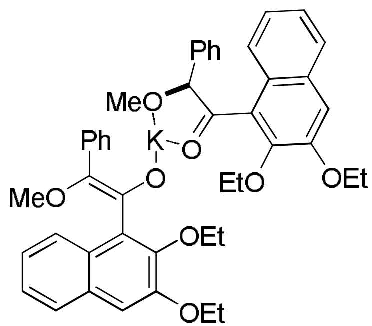
Seebach, D.; Wasmuth, D. *Angew. Chem. Int. Ed.* **1981**, *20*, 971.

Directed Studies - Rational Design

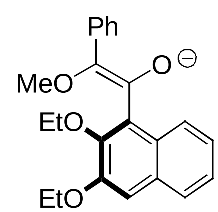


Two possible mechanisms:

Chiral ketone acts as a ligand:



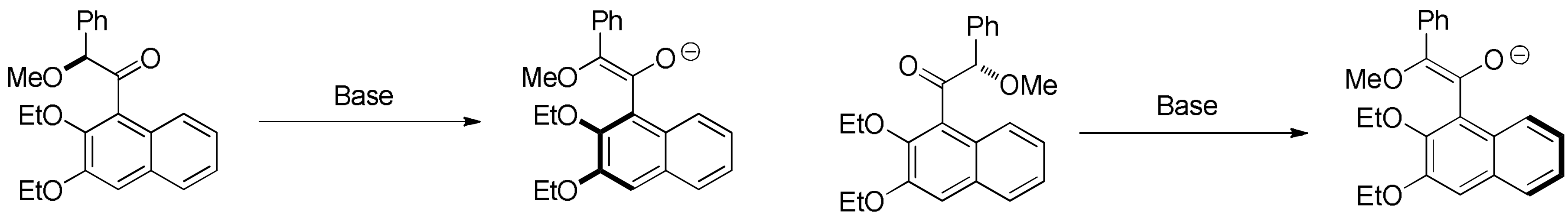
The enolate formed is
chiral and nonracemic:



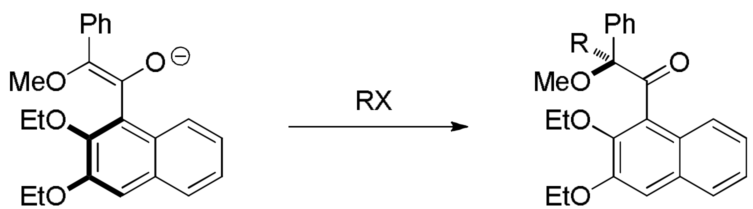
Kawabata, T.; et. al. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

Requirements for an Enatioselective Reaction

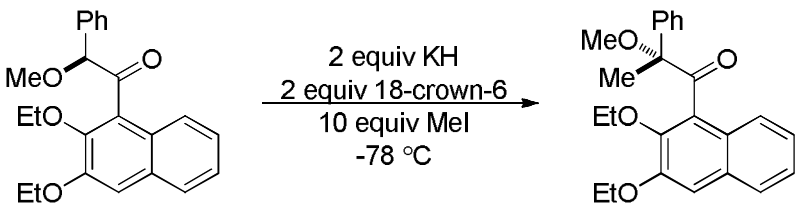
- Enantioselective deprotonation



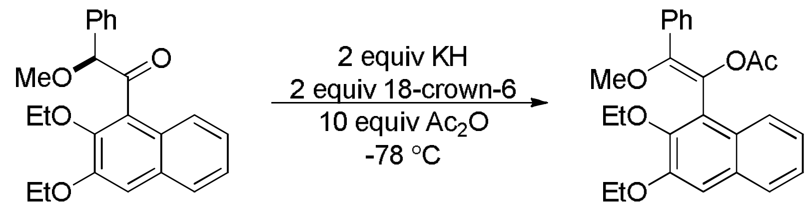
- Reaction rate > Racemization rate
- Enantioselective reaction



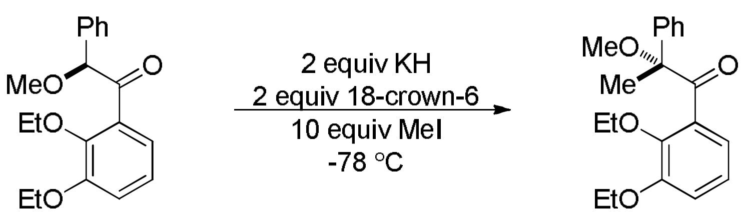
Mechanistic Probes



48%, 83:17 er

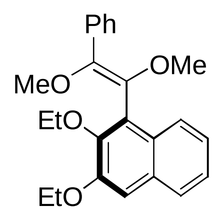


The enol acetate is racemic but recovered ketone is still enantiopure.



51%, 50:50 er

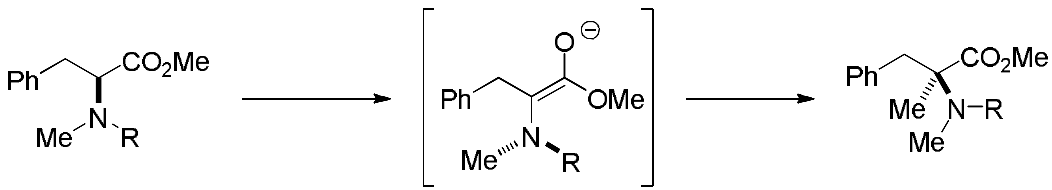
Strongly disfavors the chiral ketone acting as a ligand.



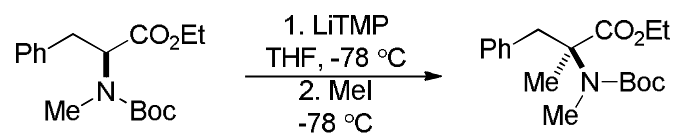
Isolated as a reaction byproduct with 83:17 er

Kawabata, T.; et. al. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

Enantioselective Amino Acid Alkylation

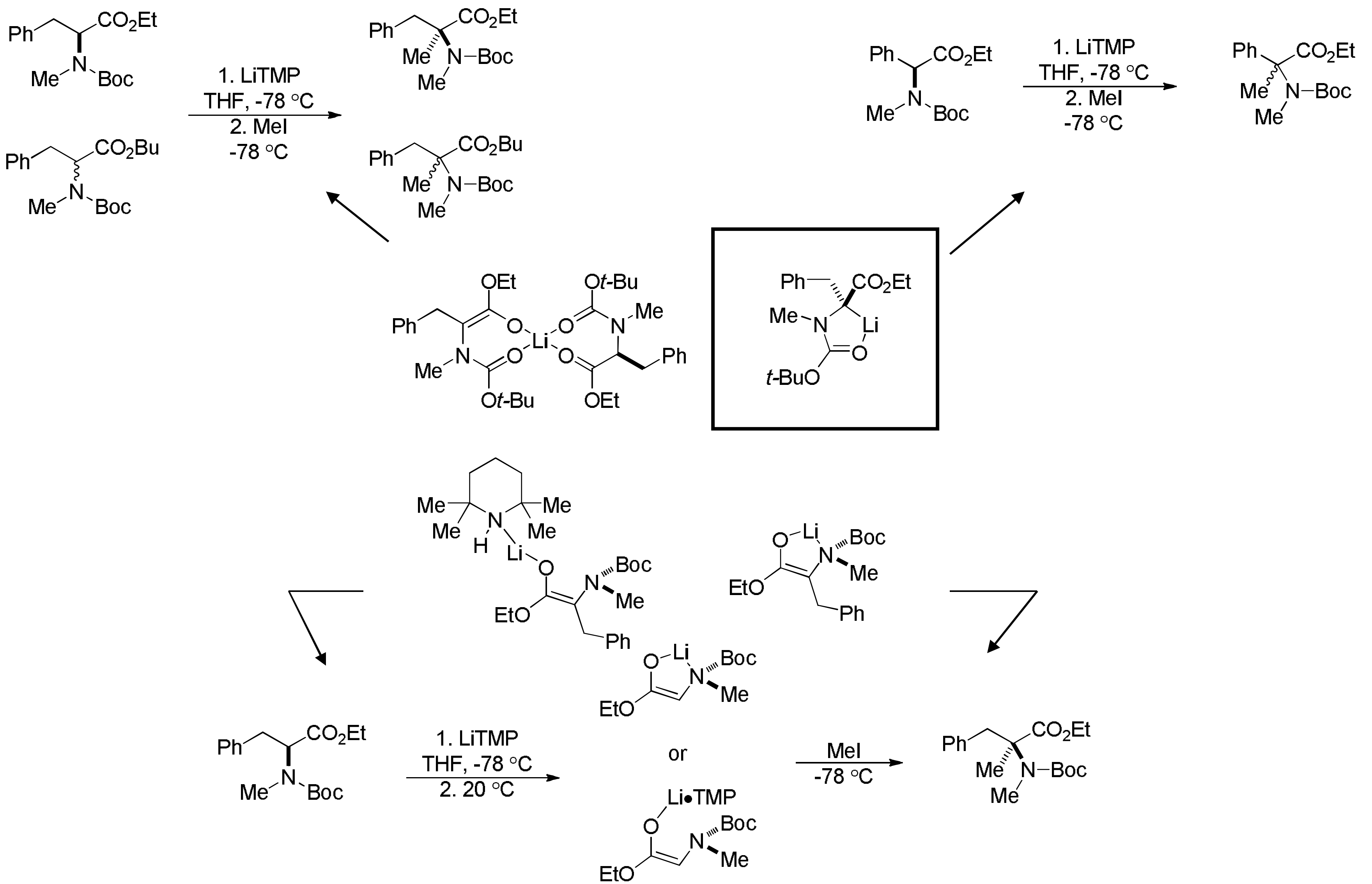


R	% yield	er
CHO	66	0
CO_2Bn	40	26
CO_2Ad	38	35
Boc	30	36



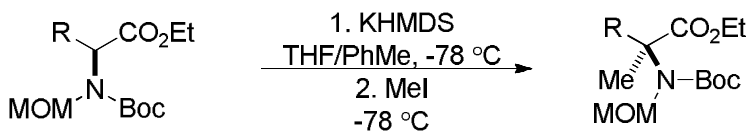
Kawabata, T.; et. al. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10810.

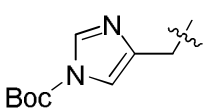
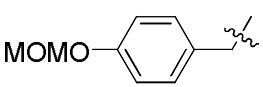
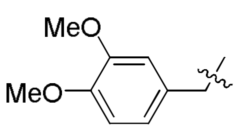
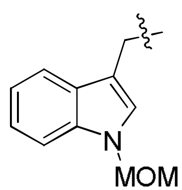
Possible Intermediates

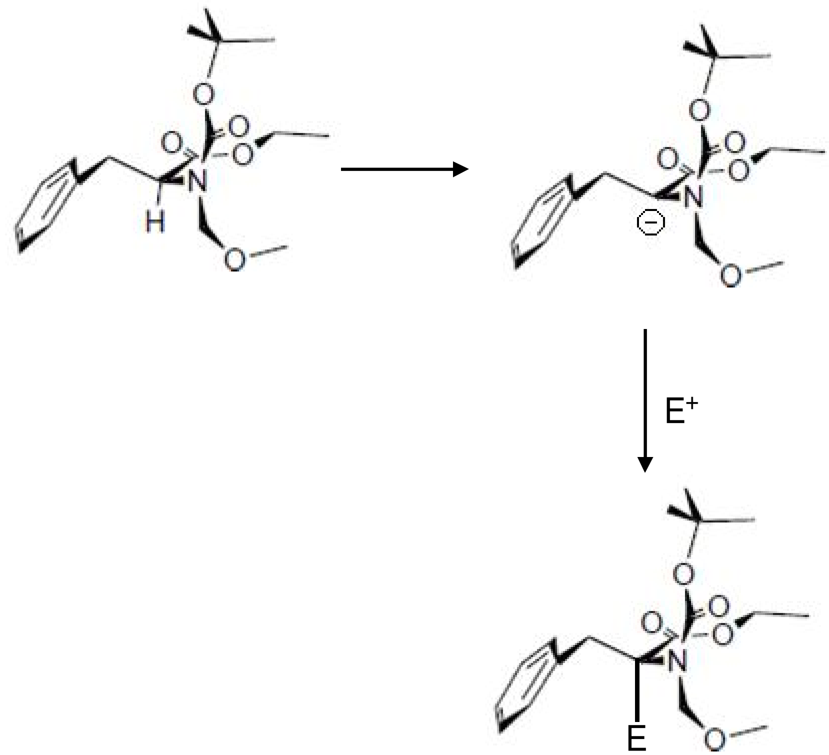


Kawabata, T.; et. al. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10810.

Practical Applications

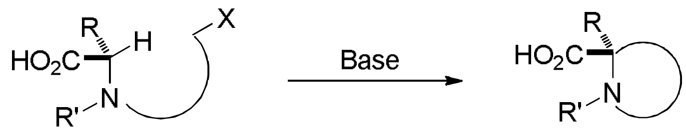


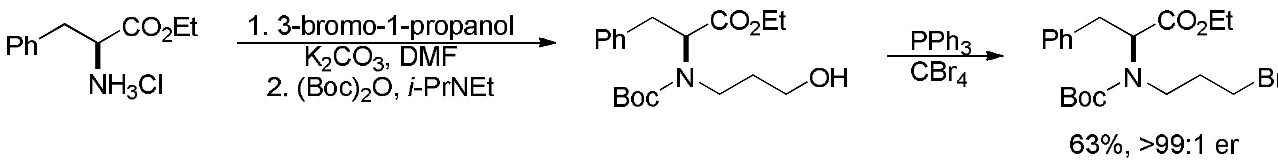
R	% yield	er
Bn	96	91:9
i-Pr	81	94:6
i-Bu	78	89:11
	83	97:3
	94	90:10
	95	90:10
	88	88:12

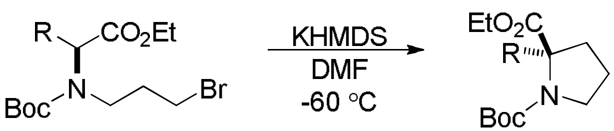


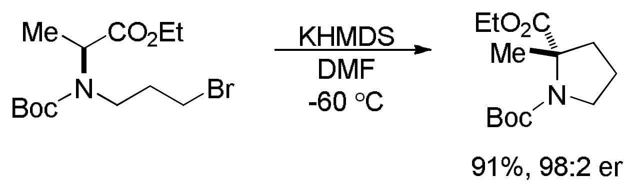
Kawabata, T.; et. al. *Angew. Chemie. Int. Ed.* **2000**, *39 (12)*, 2155-2157

Cyclic Amino Acids

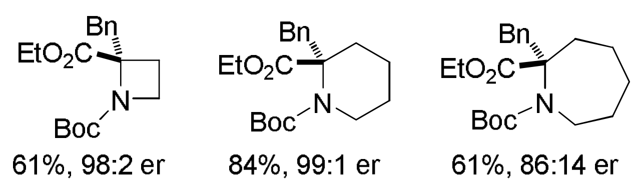






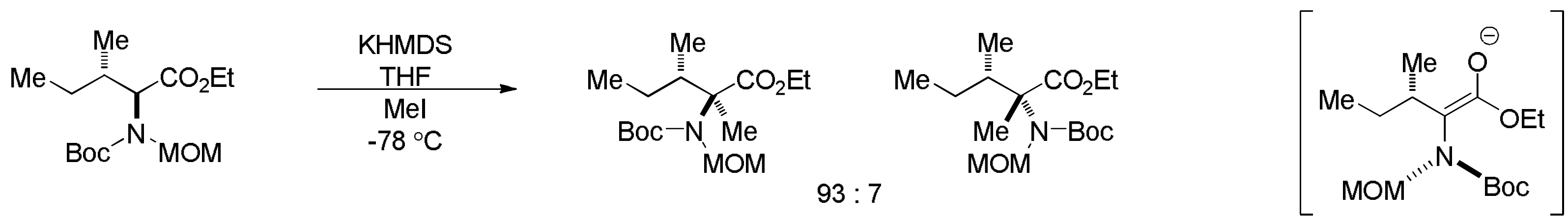


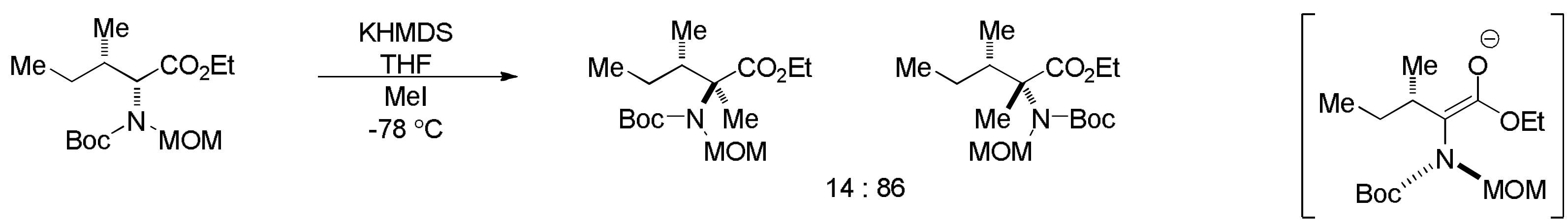
R	% yield	er
Bn	94	99:1
4-EtO-Bn	95	99:1
$MeSCH_2CH_2$	92	99:1
i-Pr	78	97:3

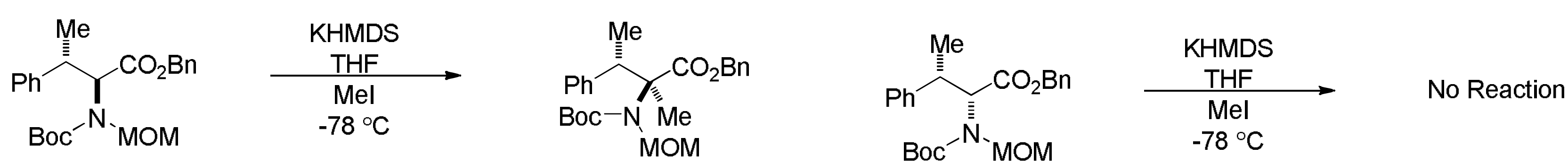


Kawabata, T.; et. al. *J. Am. Chem. Soc.* **2003**, *125*, 13012-13013.

Overriding Diastereoselectivity

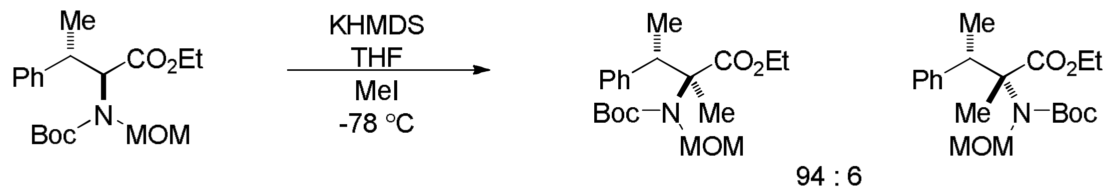


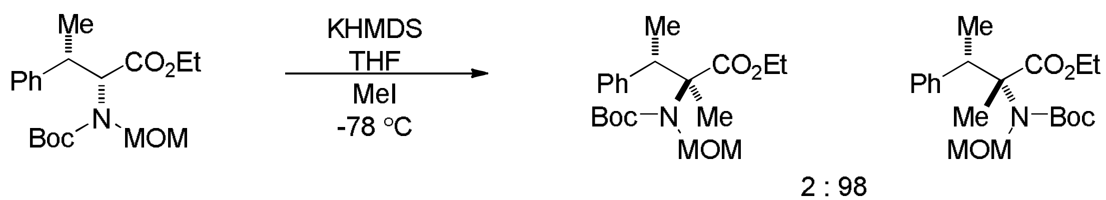


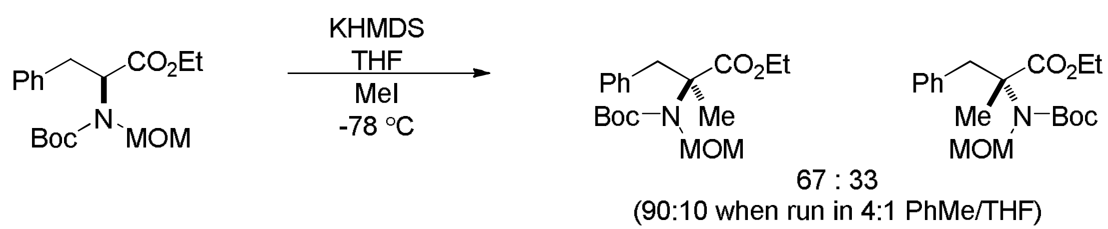


Kawabata, T.; et. al. *Synthesis*, **2005**, *8*, 1368-1377.

Stereocontrolling Factors

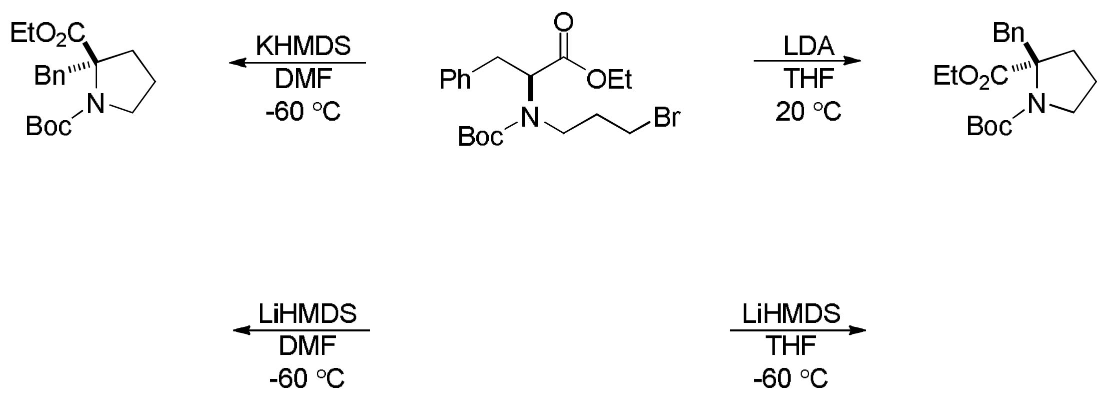






Kawabata, T.; et. al. *Synthesis*, **2005**, *8*, 1368-1377.

Group Problem

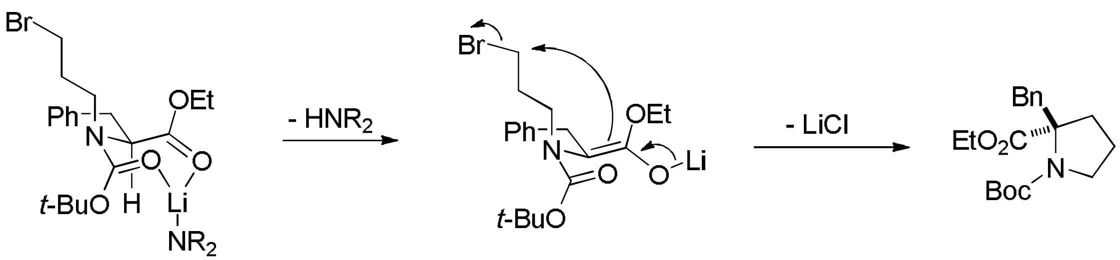


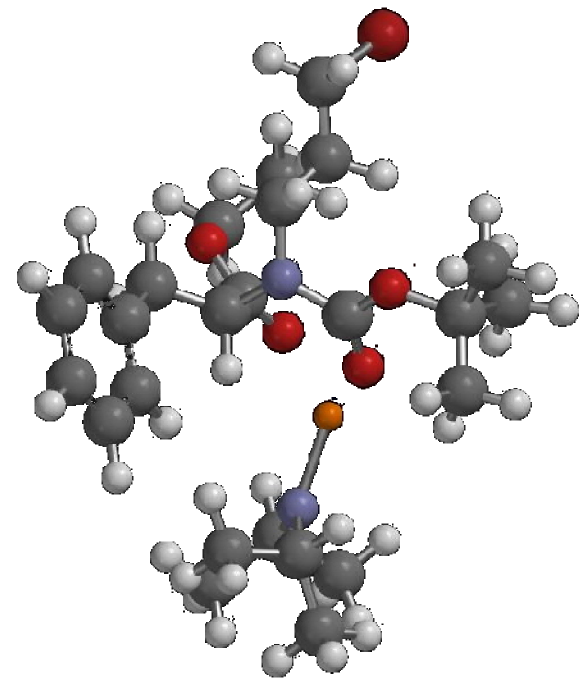
Rationalize the observed enantioselectivity

Kawabata, T.; et. al. *J. Am. Chem. Soc*, **2006**, *128*, 15394-15395.

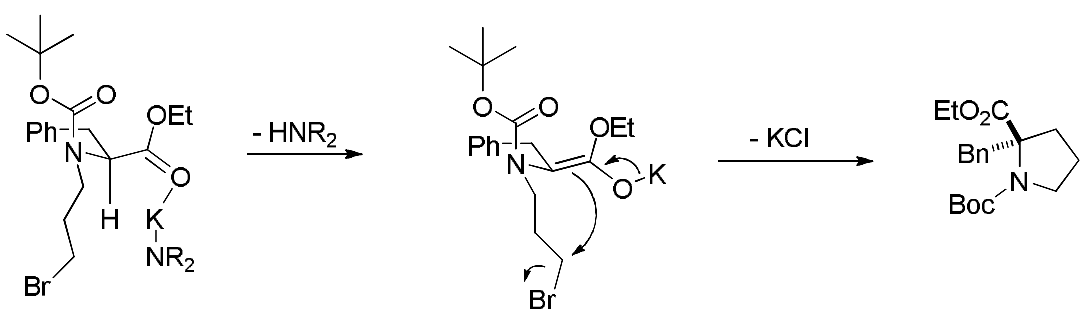
Group Problem - Solution

Li: Chelation Controlled



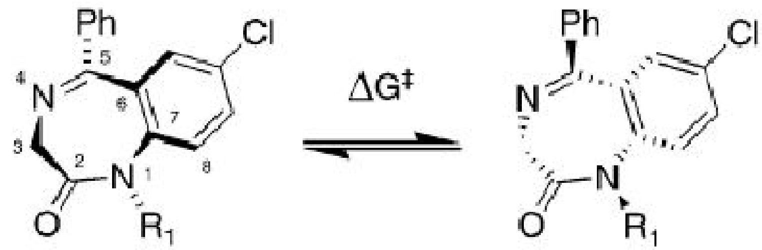


K: Steric Approach Control

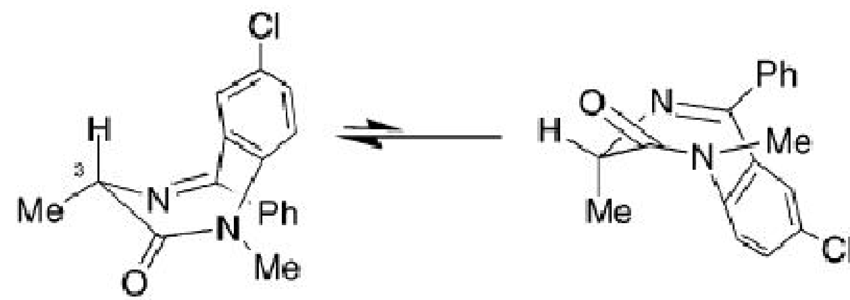


Kawabata, T.; et. al. *J. Am. Chem. Soc*, **2006**, *128*, 15394-15395.

1,4-Benzodiazepine-2-ones



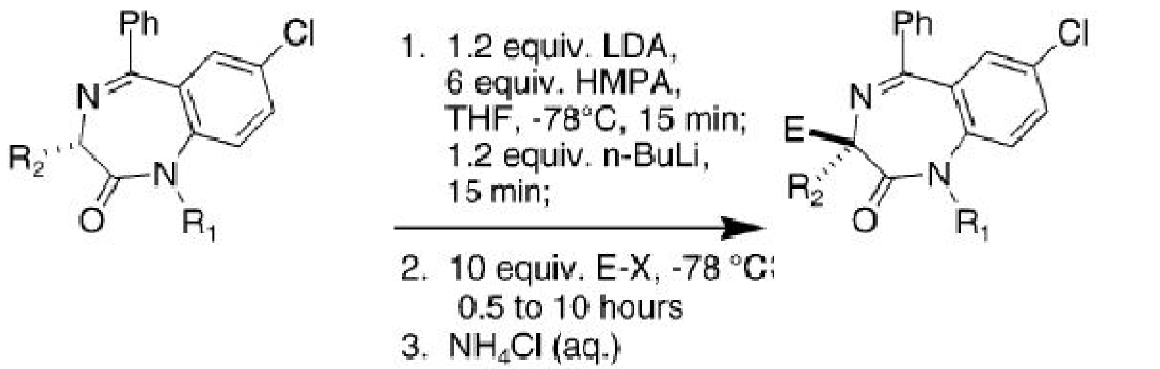
R_1	$\Delta G^{\ddagger}$
H	12.3
Me	18.0
i-Pr	21.1
t-Bu	>24



As measured by NMR

Carlier, P. R..; et. al. *J. Am. Chem. Soc*, **2003**, *125*, 11482-11483.

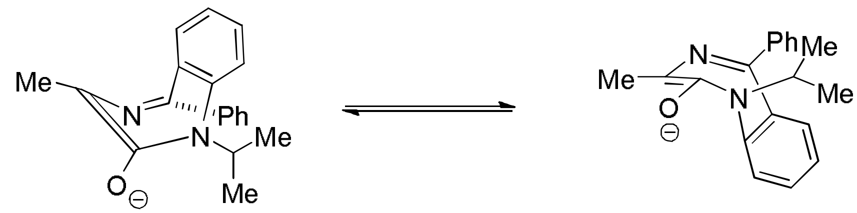
1,4-Benzodiazepine-2-ones

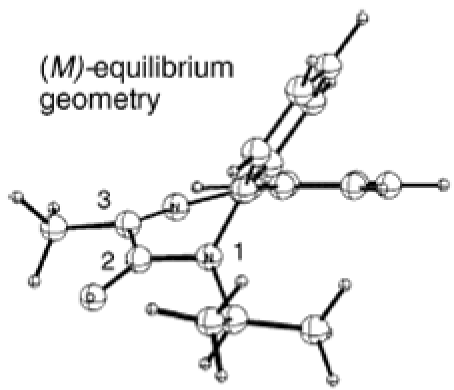


entry	R_1	R_2	E[a]	product	% yield	% ee[b]
1	Me	Me	Bn	(±)-**4**	72	0[c]
2	*i*-Pr	Me	Bn	(+)-**5**	74	97 (3*R*)
3	*i*-Pr	Me	$4\text{-MeC}_6\text{H}_4\text{CH}_2$	(+)-**6**	68	95 (3*R*)
4	*i*-Pr	Me	$2\text{-PhC}_6\text{H}_4\text{CH}_2$	(+)-**7**	70	99
5	*i*-Pr	Me	allyl	(+)-**8**	76	94
6	*i*-Pr	Me	D	(+)-**9**	85[d]	99 (3*S*)
7	*i*-Pr	Bn	Me	(−)-**5**	64	95 (3*S*)
8	*i*-Pr	Bn	allyl	(+)-**10**	57	86

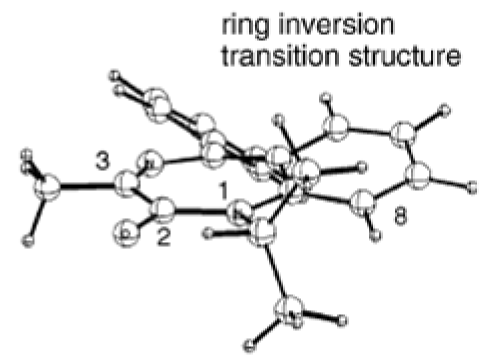
Carlier, P. R..; et. al. *J. Am. Chem. Soc*, **2003**, *125*, 11482-11483.

Interconversion Studies





0.0 kcal/mol

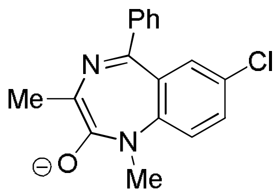


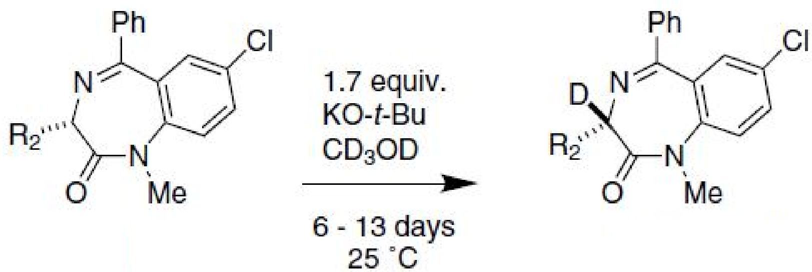
+17.5 kcal/mol

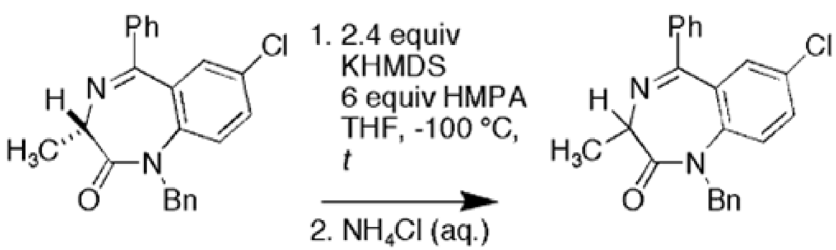
B3LYP/6-31G* geometries and energies

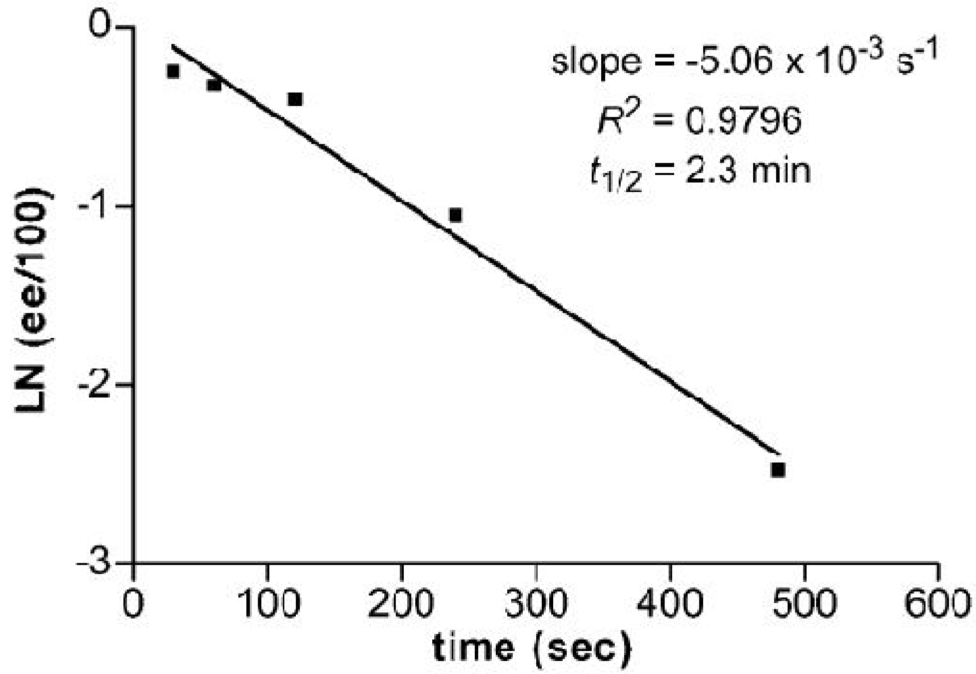
Carlier, P. R..; et. al. *J. Am. Chem. Soc*, **2003**, *125*, 11482-11483.

Achiral or Rapidly Epimerizing Intermediate?



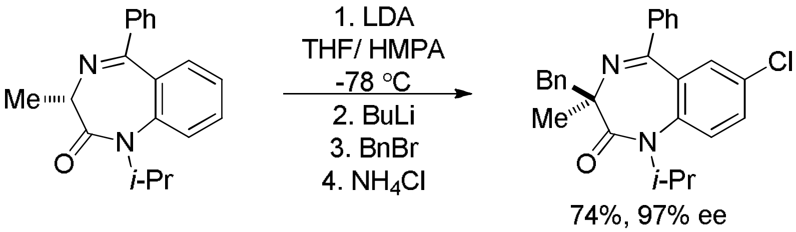


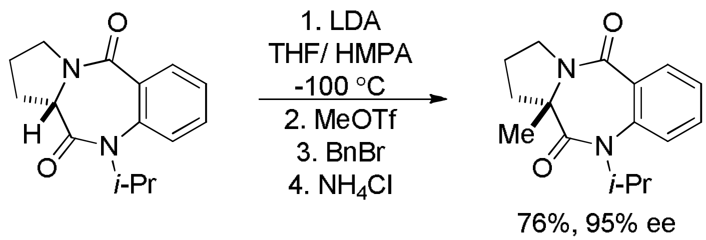


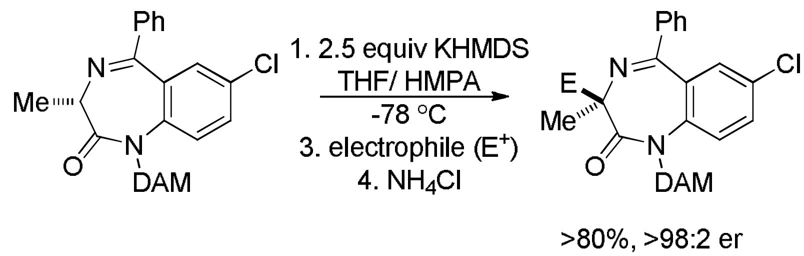


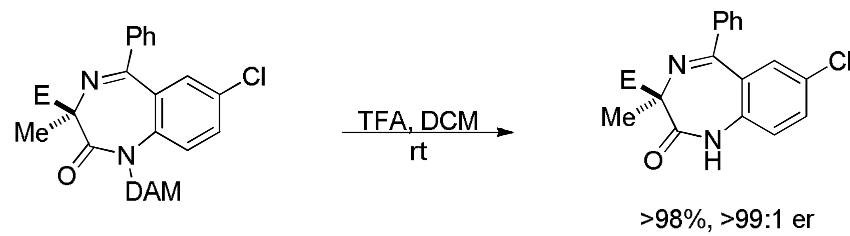
Carlier, P. R..; et. al. *Tetrahedron: Asymmetry*, **2005**, *16*, 2998-3002.

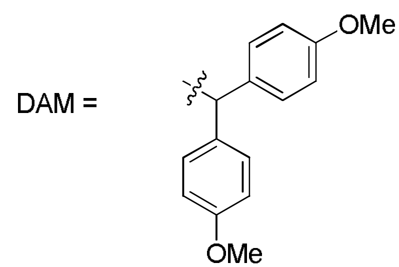
Recent Advances with Enolates





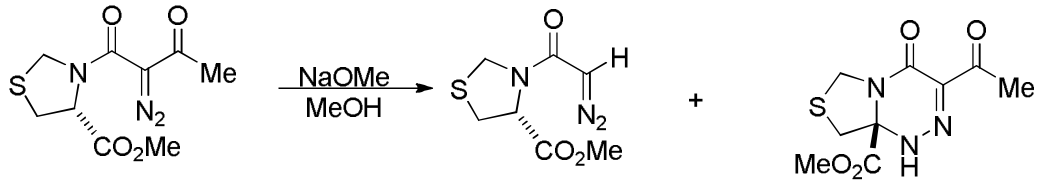






Carlier, P. R.; et. al. *J. Am. Chem. Soc.* **2006**, *128*, 15215-15220.

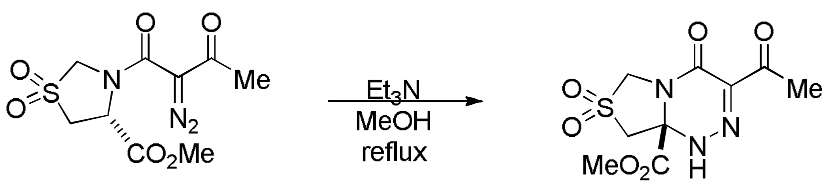
Other Cyclization Reactions



37%

35%, enantiopure

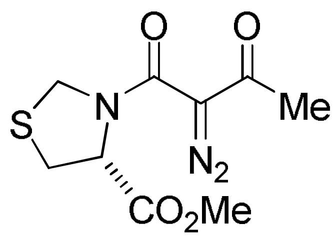
Chiral intermediate:



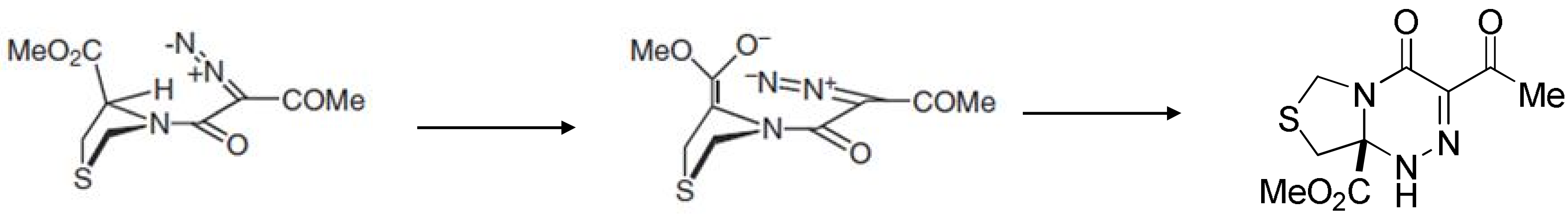
86%, enantiopure

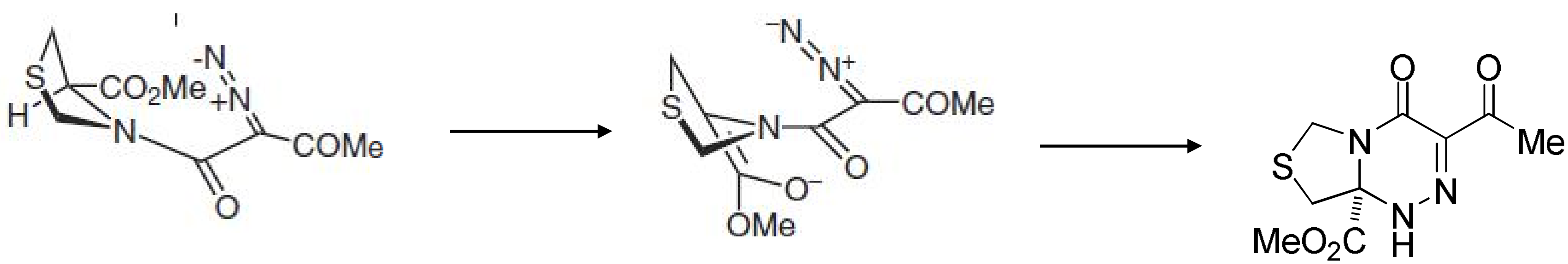
Beagley, B.; et. al. *Chem. Comm.* **1991**, 924-925.
Brewster, A. G.; et. al. *Chem. Comm.* **1998**, 299-.

Stereochemical Rational



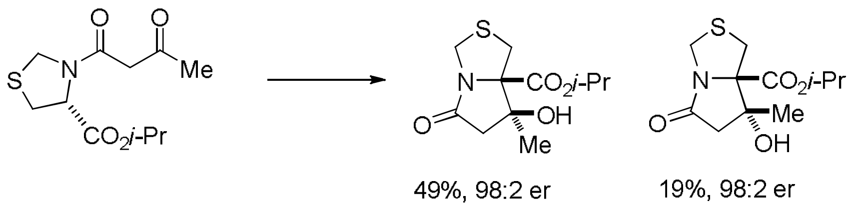
Exists as two rotamers
•Observable by NMR at -60 °C



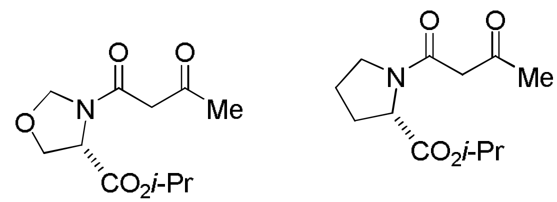


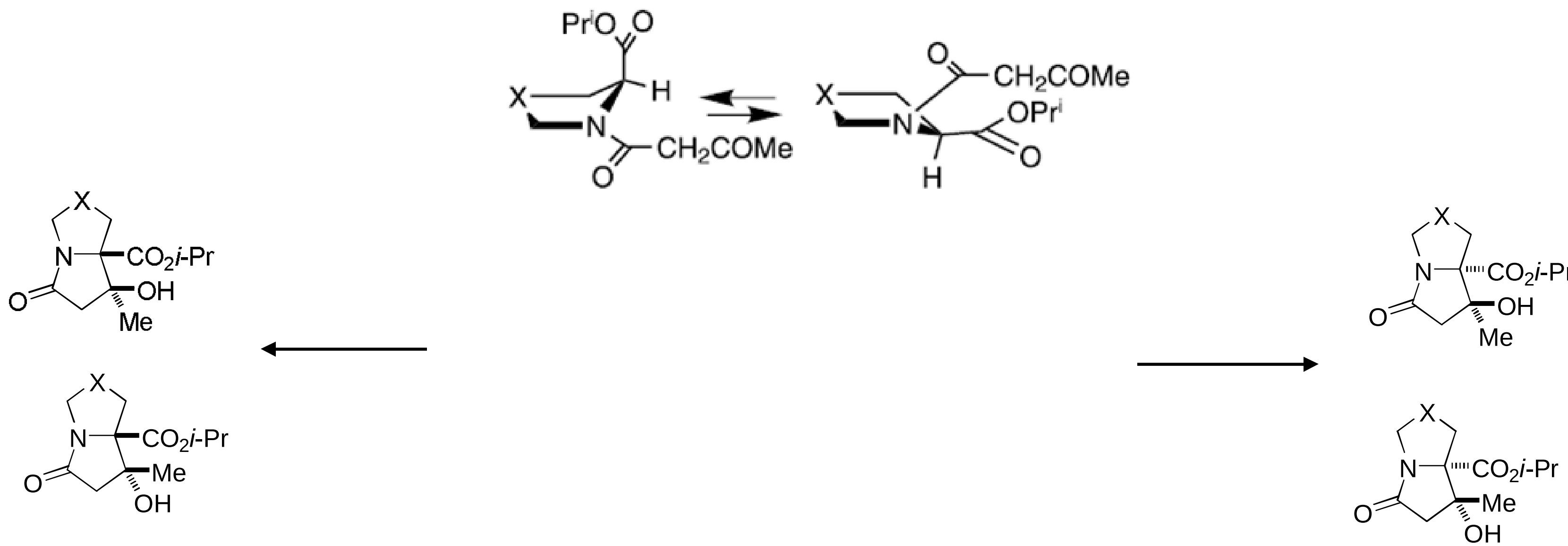
Beagley, B.; et. al. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1761-1770.

Intramolecular Aldol



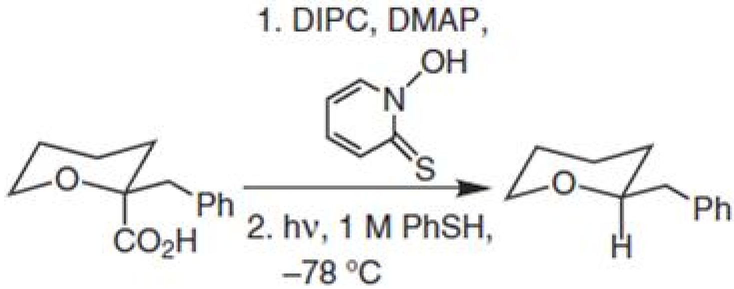
Extentions:



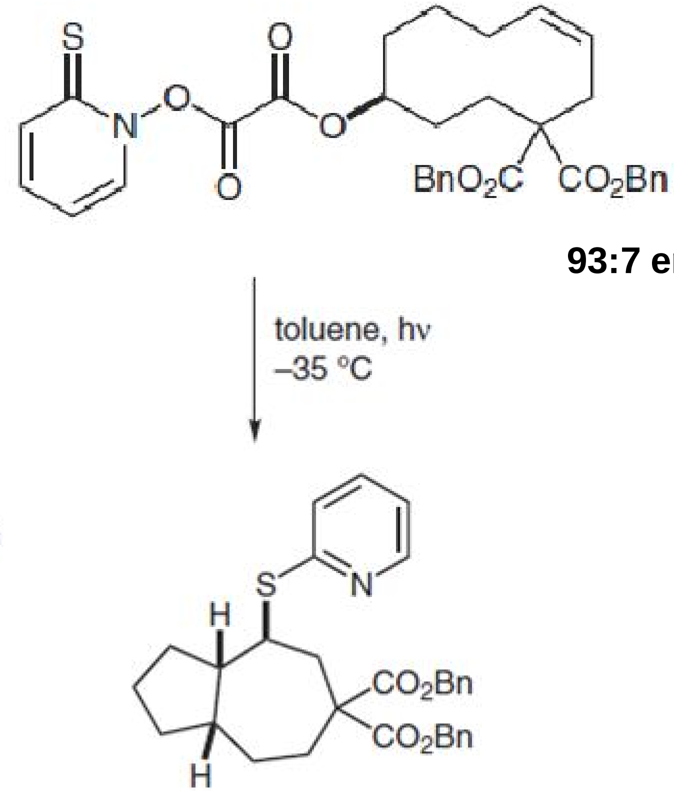


Brewster, A. G.; et. al. *Chem. Comm.* **1998**, 299.
Brewster, A. G.; et. al. *Tet. Lett.* **2002**, *43*, 3919-3922.

Radical Chemistry

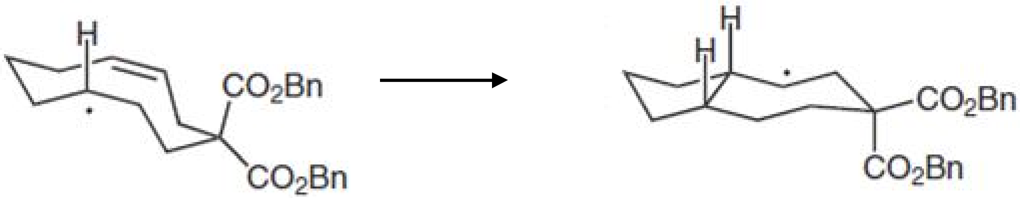


92%, 93:7 er



93:7 er

43%, 84:16 er



Schmalz, V.; et. al. *Angew Chem. Int. Ed.* **1999**, *38*, 1620-1623.
Dalgard, J. E.; et. al. *Org. Lett.* **2004**, *6*, 2713

Conclusions

- Stereospecific reactions can destroy and recreate the sole stereocenter in a molecule provided that the stereochemical information is preserved in a different form

- By definition, these reactions require enantiopure reactants.
  - Amino acids are currently the most useful substrates