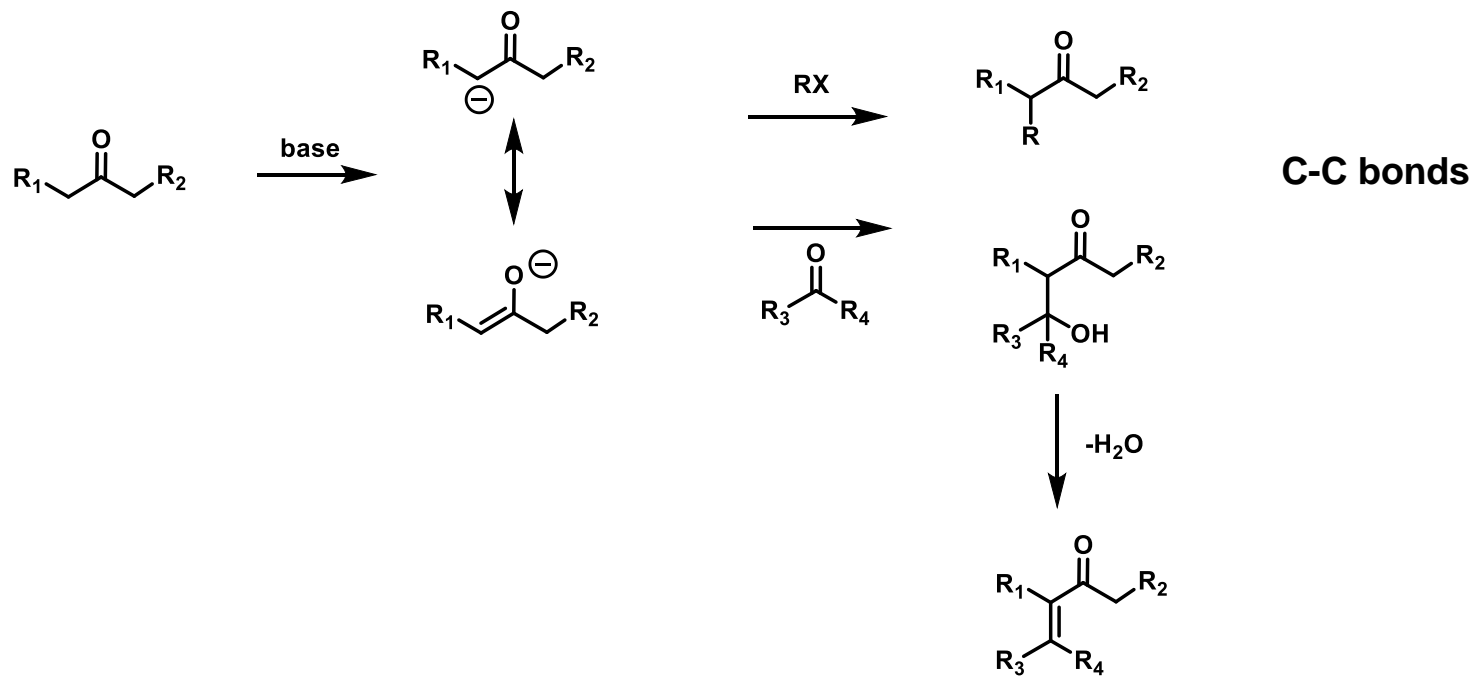
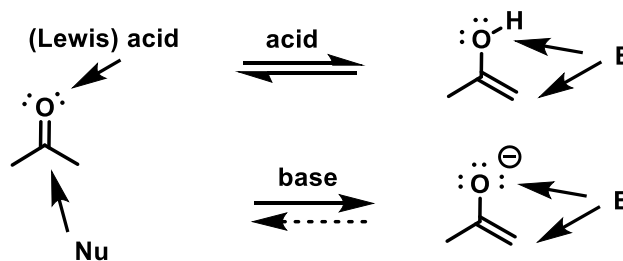


Organic synthesis

Kamil Paruch

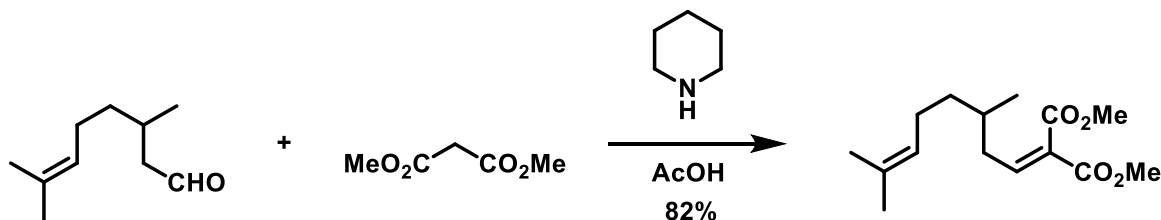
Masaryk University, Brno

Enols & enolates: formation, structure, reactivity

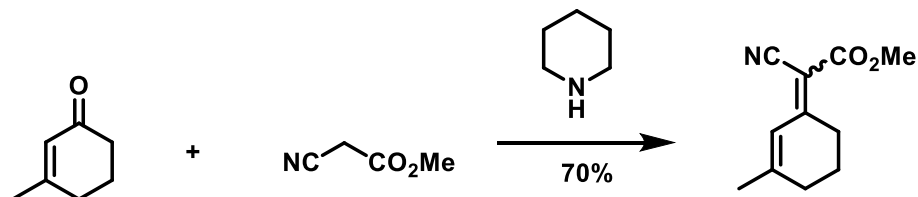


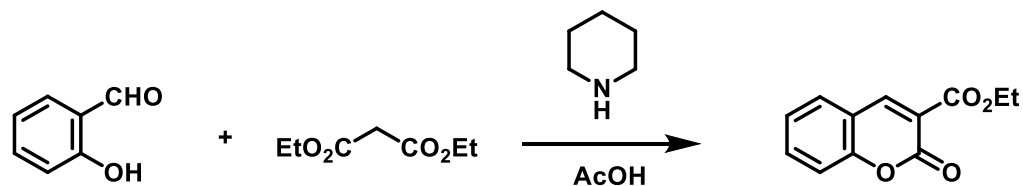
Knoevenagel condensations

- enolate attacks carbonyl C, subsequent elimination of H₂O



Tetrahedron Lett. **1986**, 27, 1767.

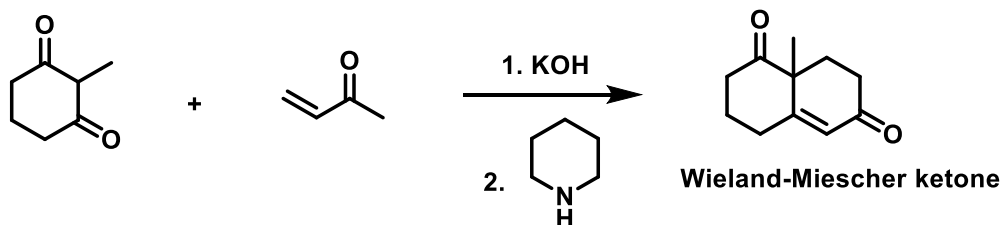




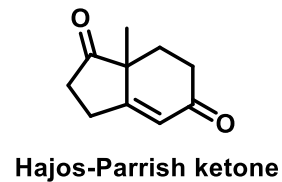
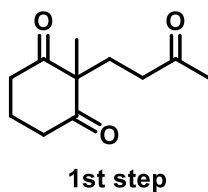
Org. Synth. Coll. Vol. 3, 1955, 165.

Robinson annulation

- Michael addition + aldol condensation

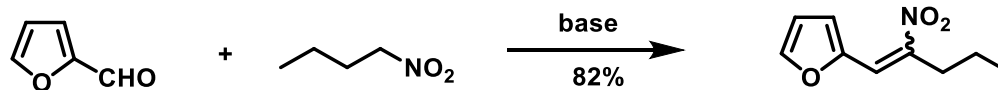
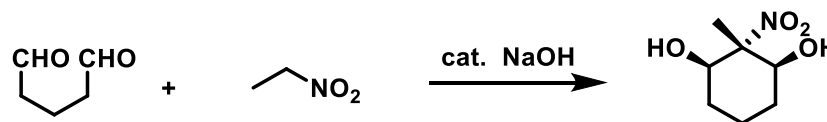


Helv. Chim. Acta 1950, 33, 2215.

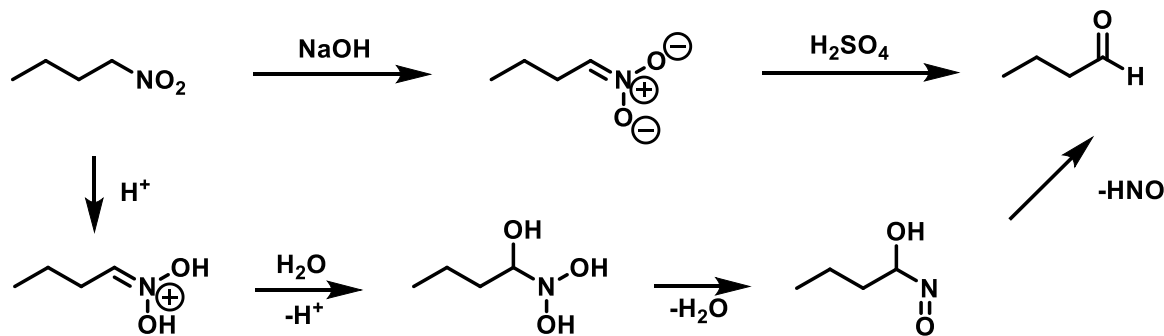


- both ketones can be prepared non-racemic by proline-catalyzed Robinson annulation

Henry reaction

*J. Org. Chem.* **1950**, 15, 8.*Helv. Chim. Acta* **1988**, 71, 1.

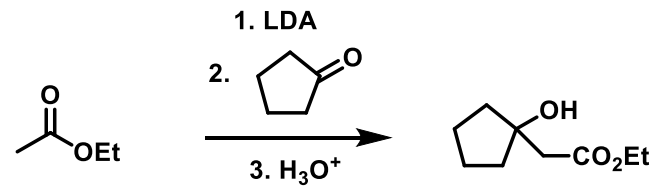
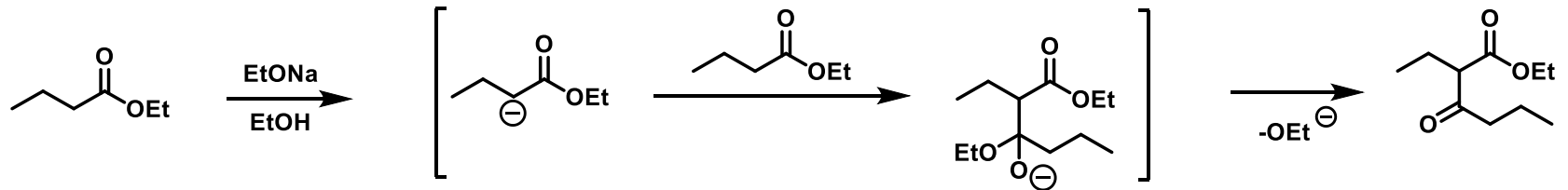
Nef reaction



modern version:

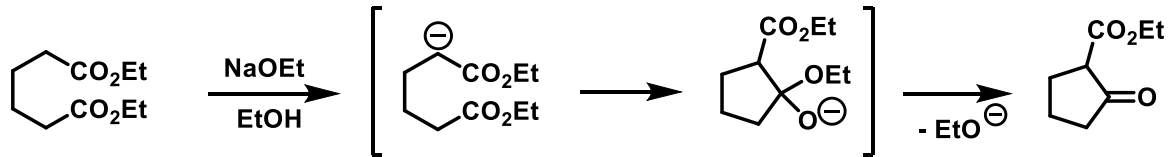
1. LDA 2. MoOPh
or TiCl₃
or 1. KOH 2. KMnO₄

Claisen condensation



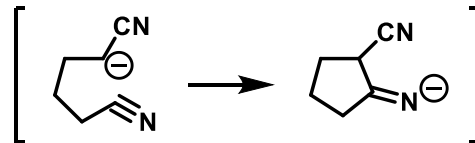
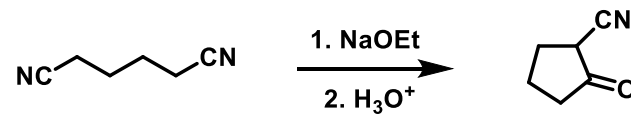
Dieckmann condensation

- intramolecular version of Claisen condensation



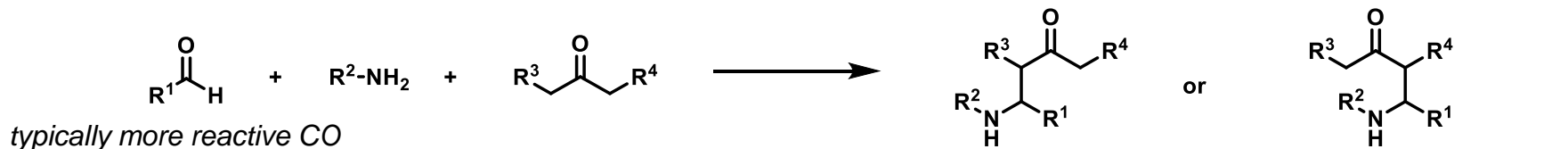
Thorpe reaction

- „enolates“ of nitriles

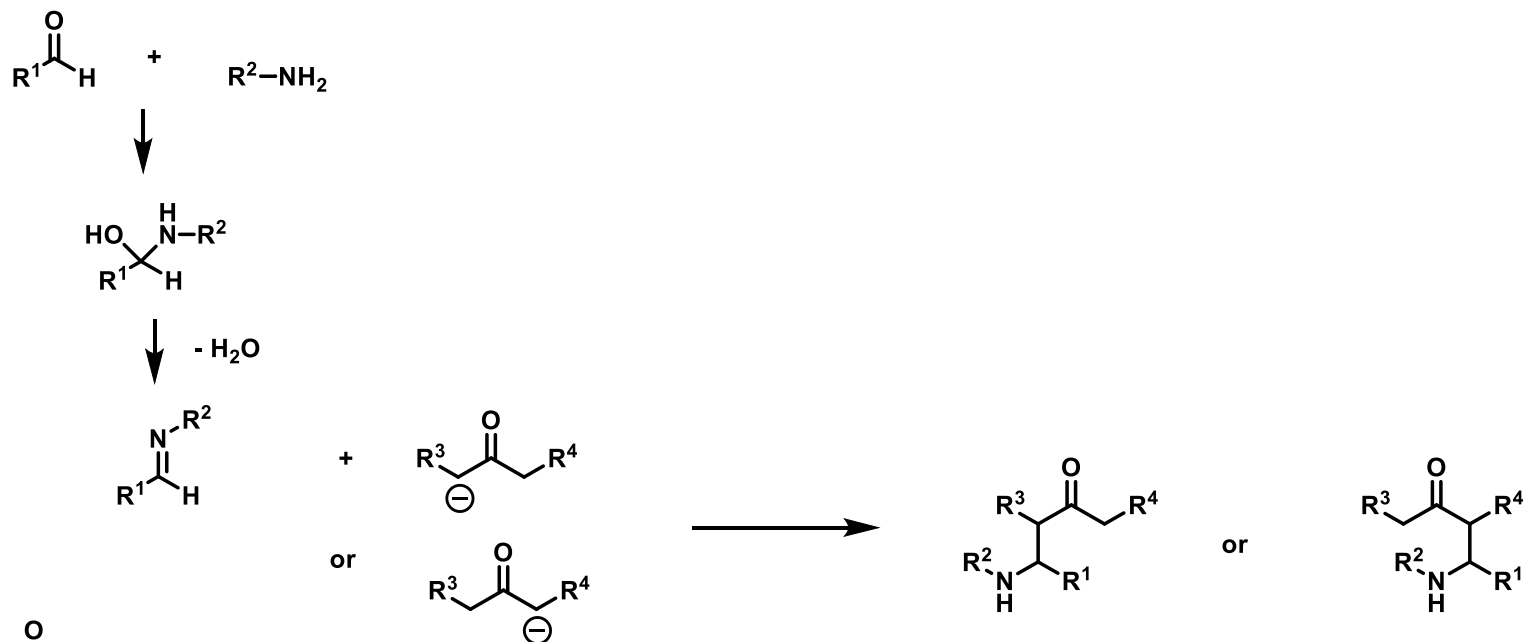


Mannich reaction

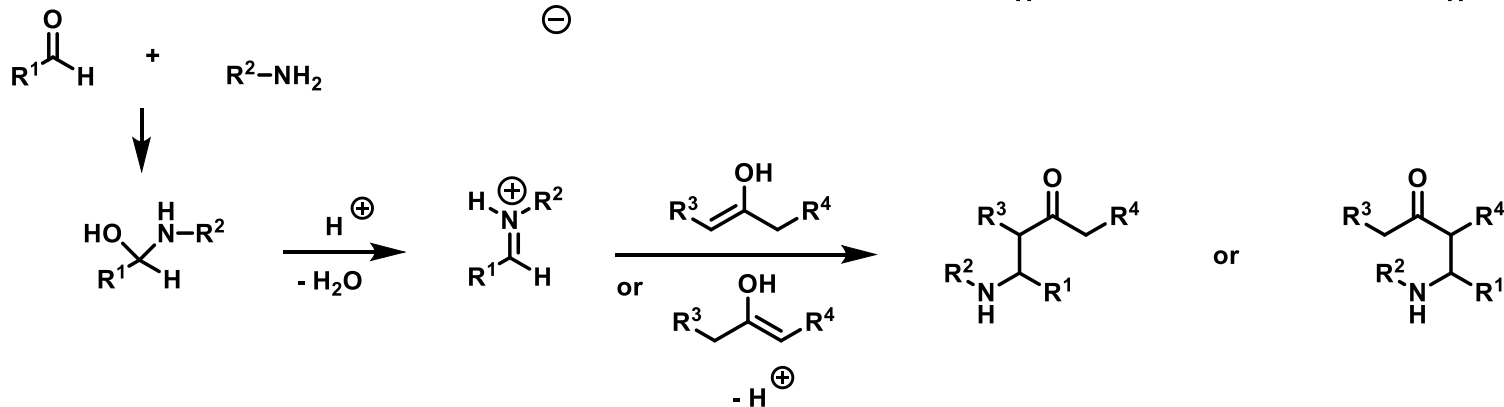
- frequently used in assembly of cyclic N-containing systems

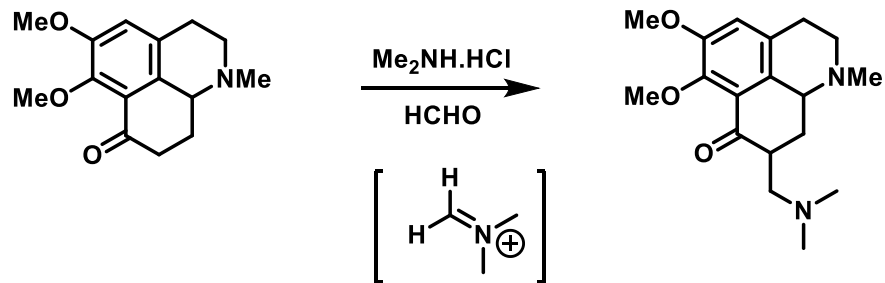


base-catalyzed



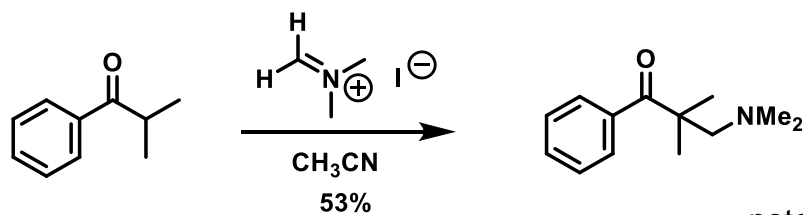
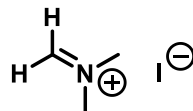
acid-catalyzed



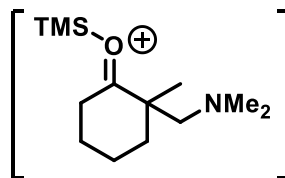
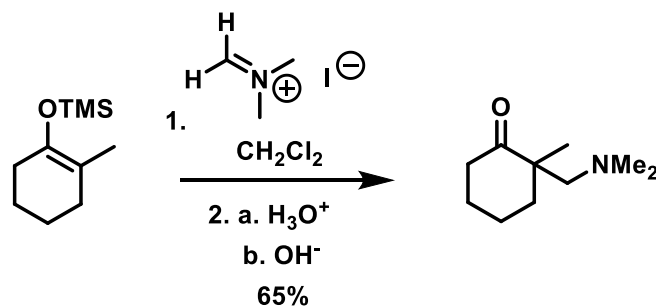


Chem. Pharm. Bull. **1991**, 39, 1349.

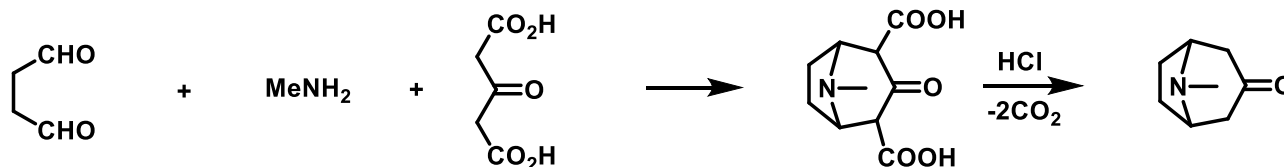
Eschenmoser's salt



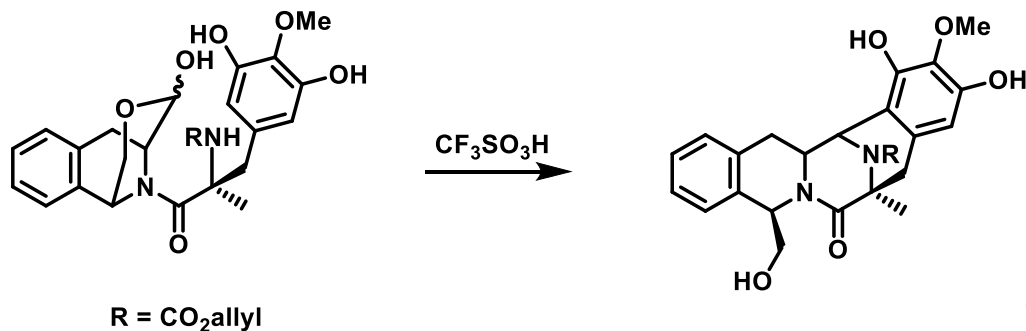
note: only 6% yield with $\text{HCHO} + \text{Me}_2\text{NH}$
(sterically hindered substrate)



Mannich reaction is frequently used in assembly of cyclic N-containing systems “*biomimetic approach*”

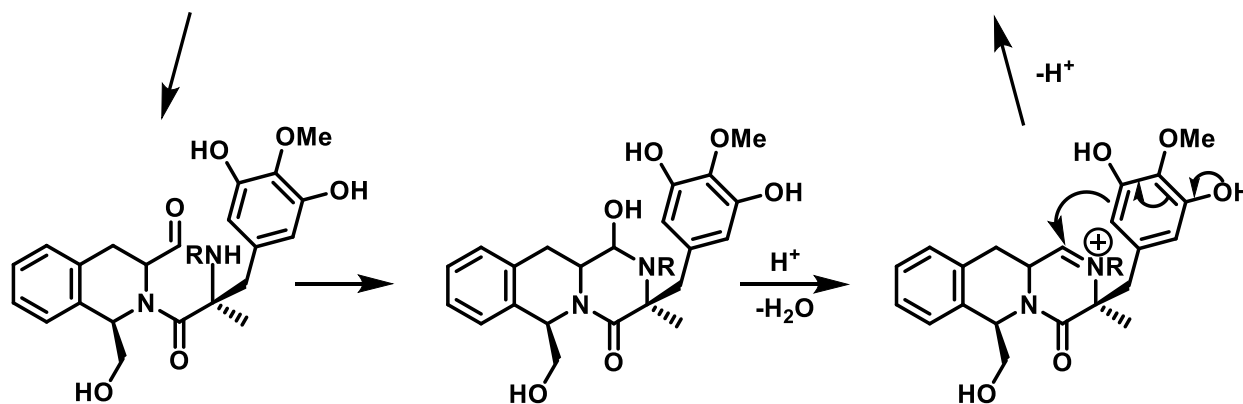


J. Chem. Soc. **1917**, 762.



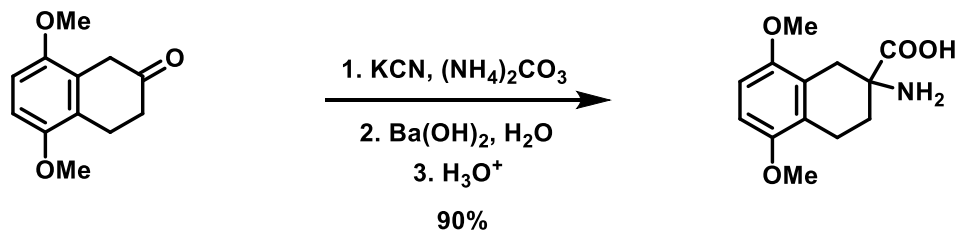
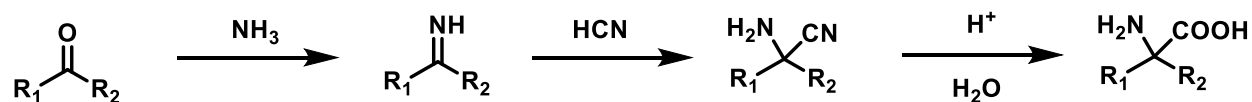
J. Am. Chem. Soc. **1996**, *118*, 9202.

Org. Lett. **2000**, *2*, 993.



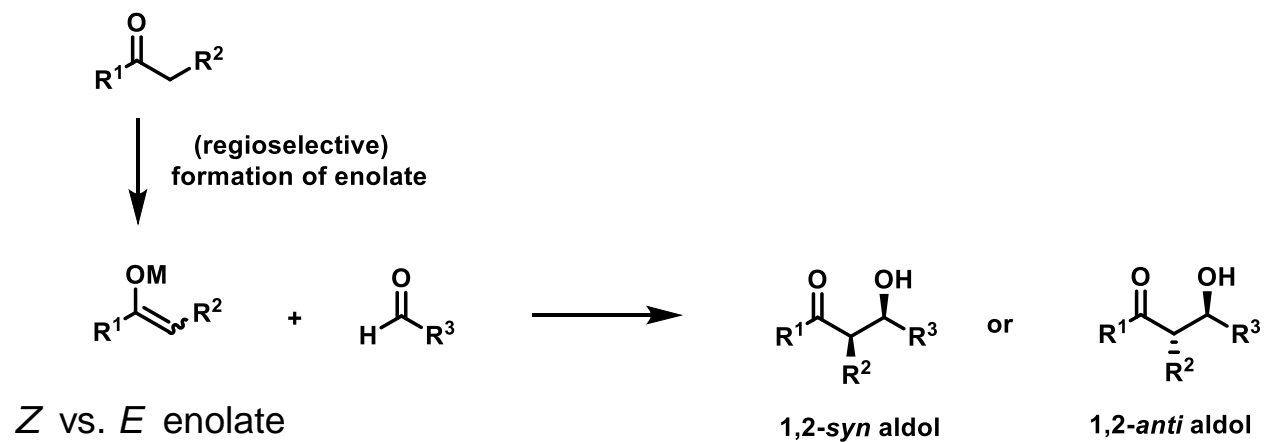
Strecker reaction

- synthesis of amino acids



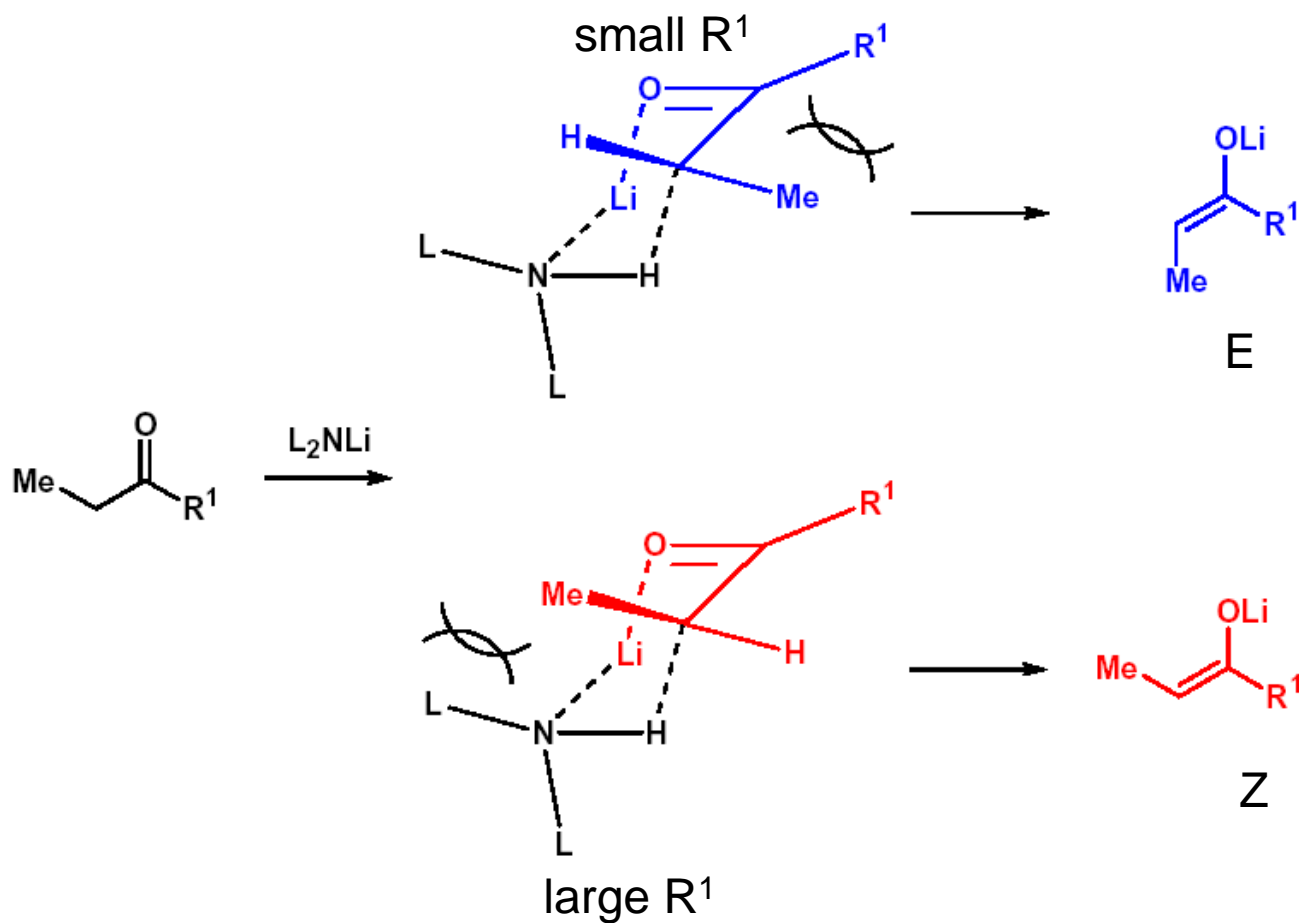
J. Org. Chem. **1987**, *52*, 4477.

Aldol reaction: 2 new stereogenic centers can be created

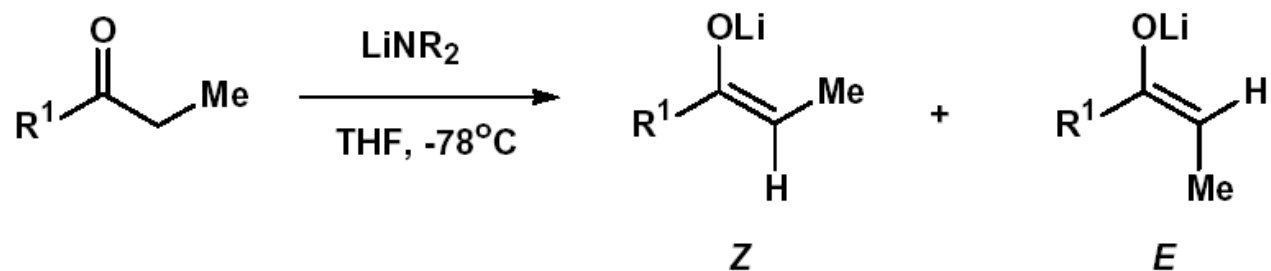


- stereochemistry of products depends on the configuration of the starting enolates

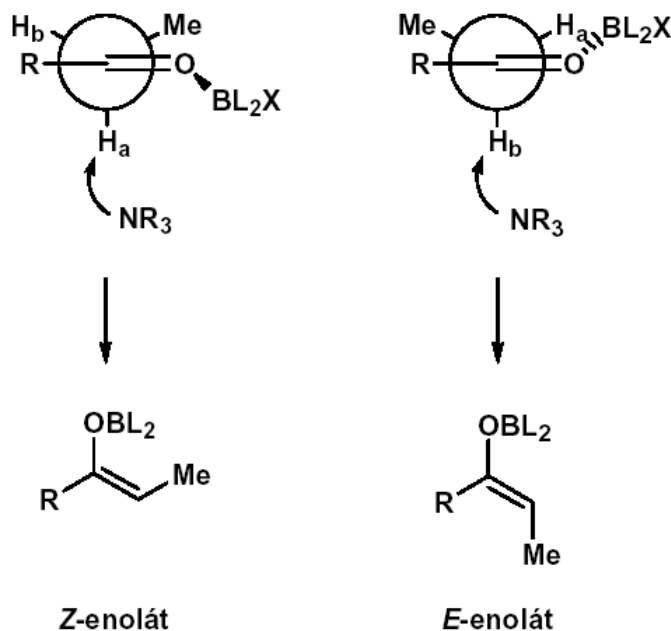
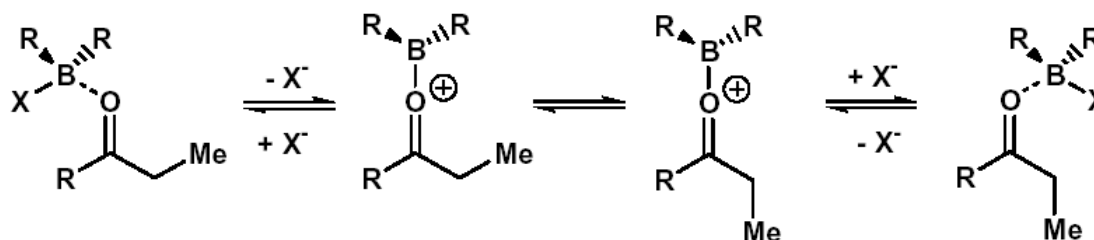
GEOMETRY OF ENOLATES - IRELAND MODEL



GEOMETRY OF ENOLATES - EFFECT OF BASE



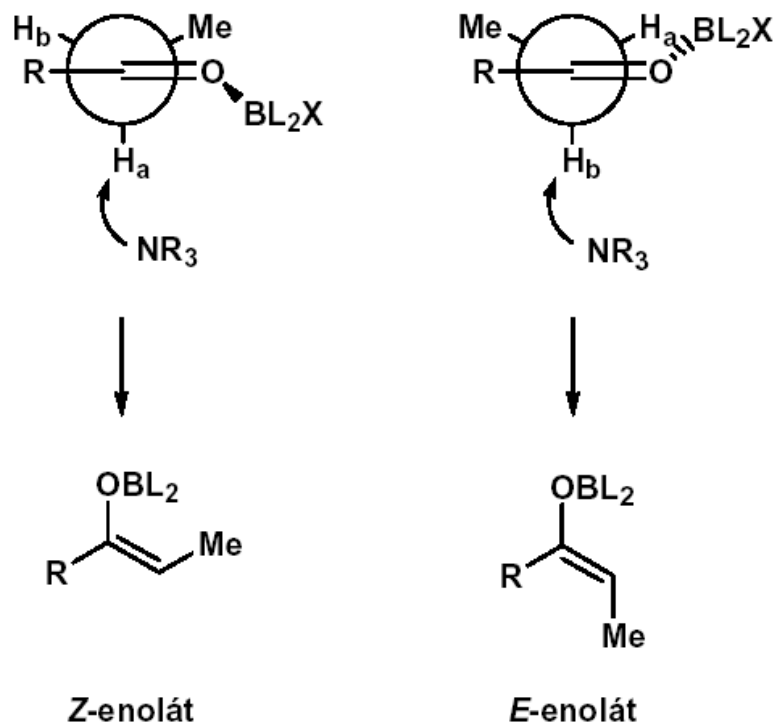
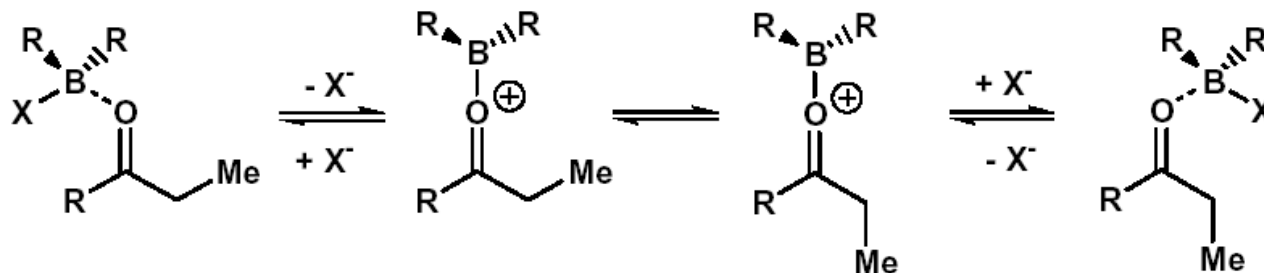
BÁZE	$R_1=Et$ (Z : E)	$R_1=cyklohexyl$ (Z : E)
$LiN(i-Pr)_2$	30 : 70	61 : 39
$LiN(SiMe_3)_2$	70 : 30	85 : 15
$LiN(SiEt_3)_2$	99 : 1	96 : 4
$LiN(SiMe_2Ph)_2$	100 : 0	100 : 0

SELECTIVE FORMATION OF *E* OR *Z* ENOL BORINATES

R_2BCl with large alkyls (e.g. cyclohexyl) + small base (Et_3N) \rightarrow *E* enolates

R_2BOTf with small alkyls (e.g. *n*-butyl) + large base (DIPEA) \rightarrow *Z* enolates

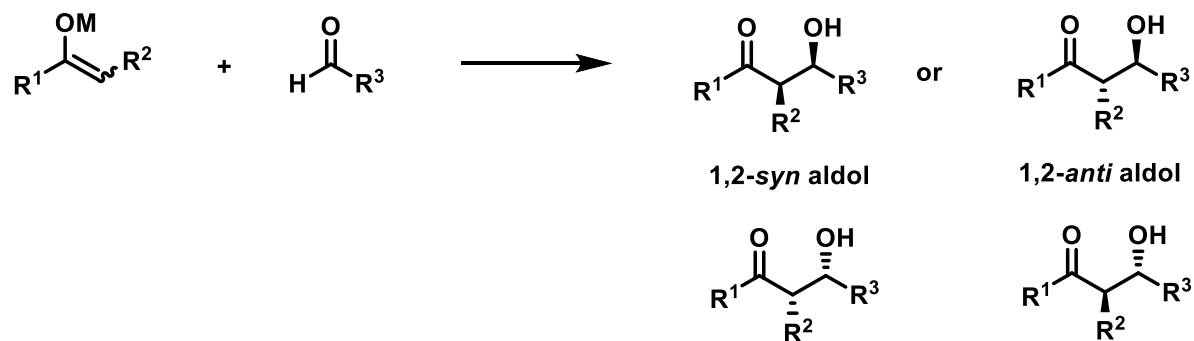
SELECTIVE FORMATION OF *E* OR *Z* ENOL BORINATES



R_2BCl with large alkyls (e.g. cyclohexyl) + small base (Et_3N) \rightarrow *E* enolates

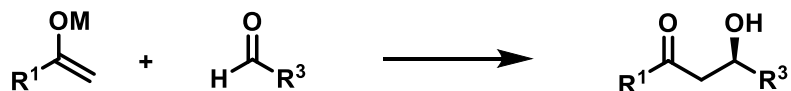
R_2BOTf with small alkyls (e.g. n-butyl) + large base (DIPEA) \rightarrow *Z* enolates

Aldol reaction: 2 new stereogenic centers can be created

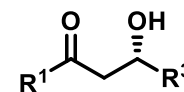


- stereochemistry of products depends on the configuration of the starting enolates
- stereochemistry can also depend on R³

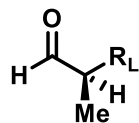
$R^2 = H$,
 R^1, R^3 achiral



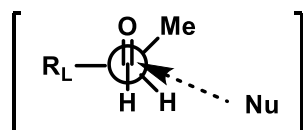
racemic mixture



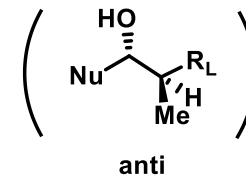
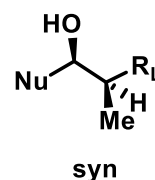
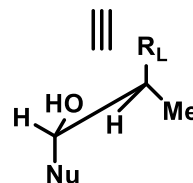
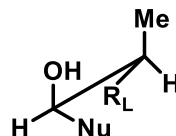
$R^2 = H$,
 R^1 achiral
 R^3 chiral



Felkin-Anh

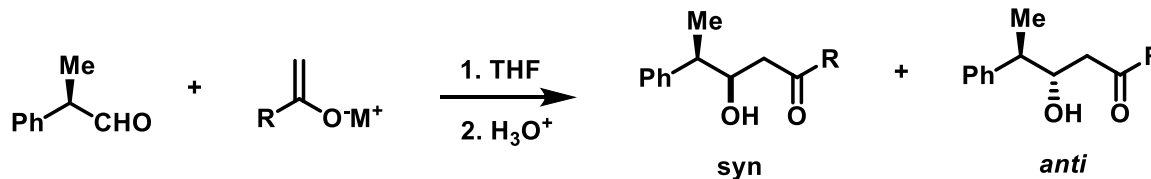


Nu attacks C=O: 107° angle



• stereoselective reactions with large Nu

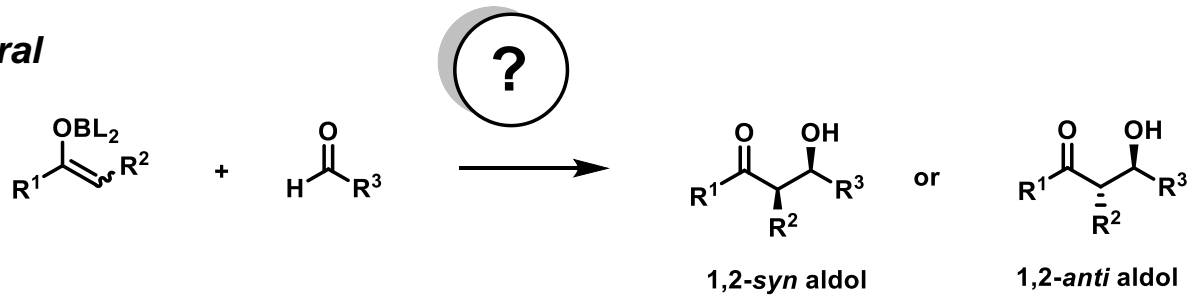
mixture of diastereomers



R :	OMe	75 : 25
	Me	76 : 24
	t-Bu	80 : 20

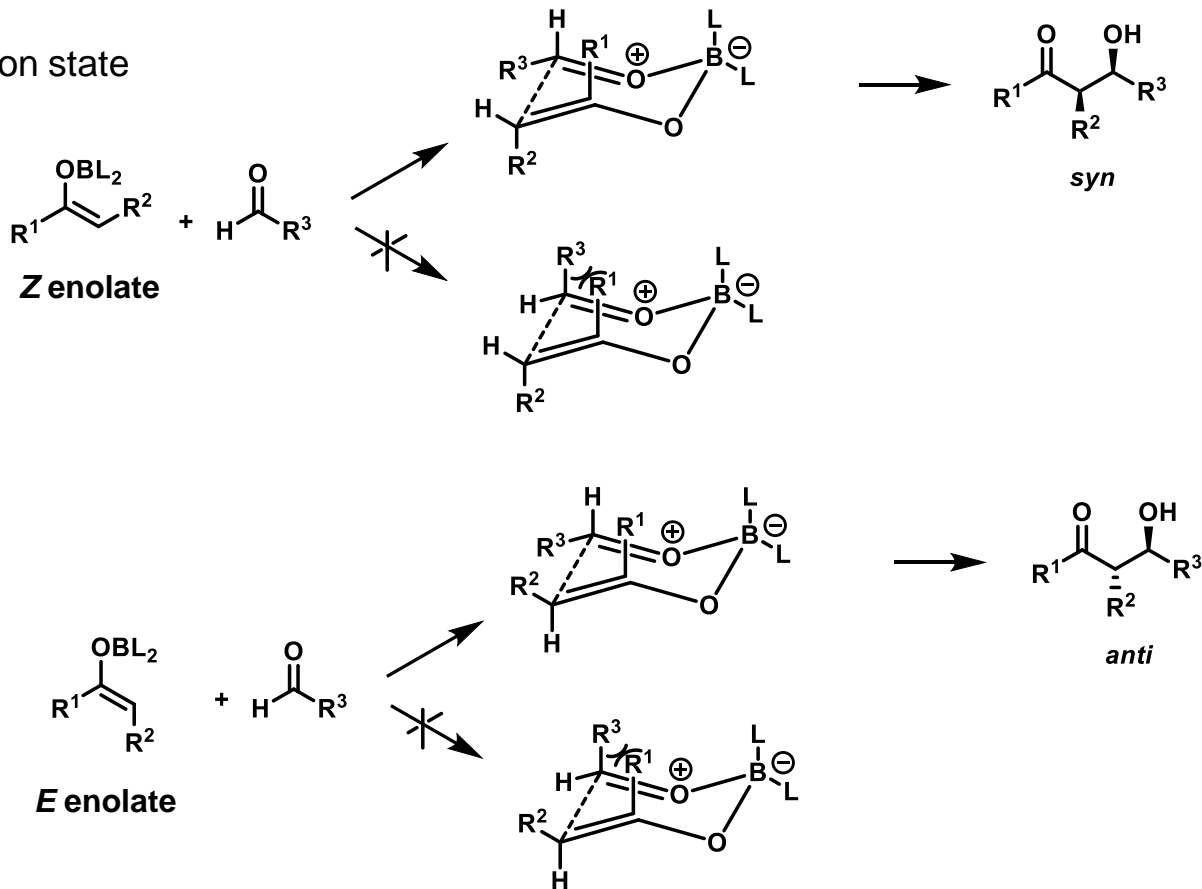
Aldol reaction: 2 new stereogenic centers can be created

R^2 is not H, R^3 achiral

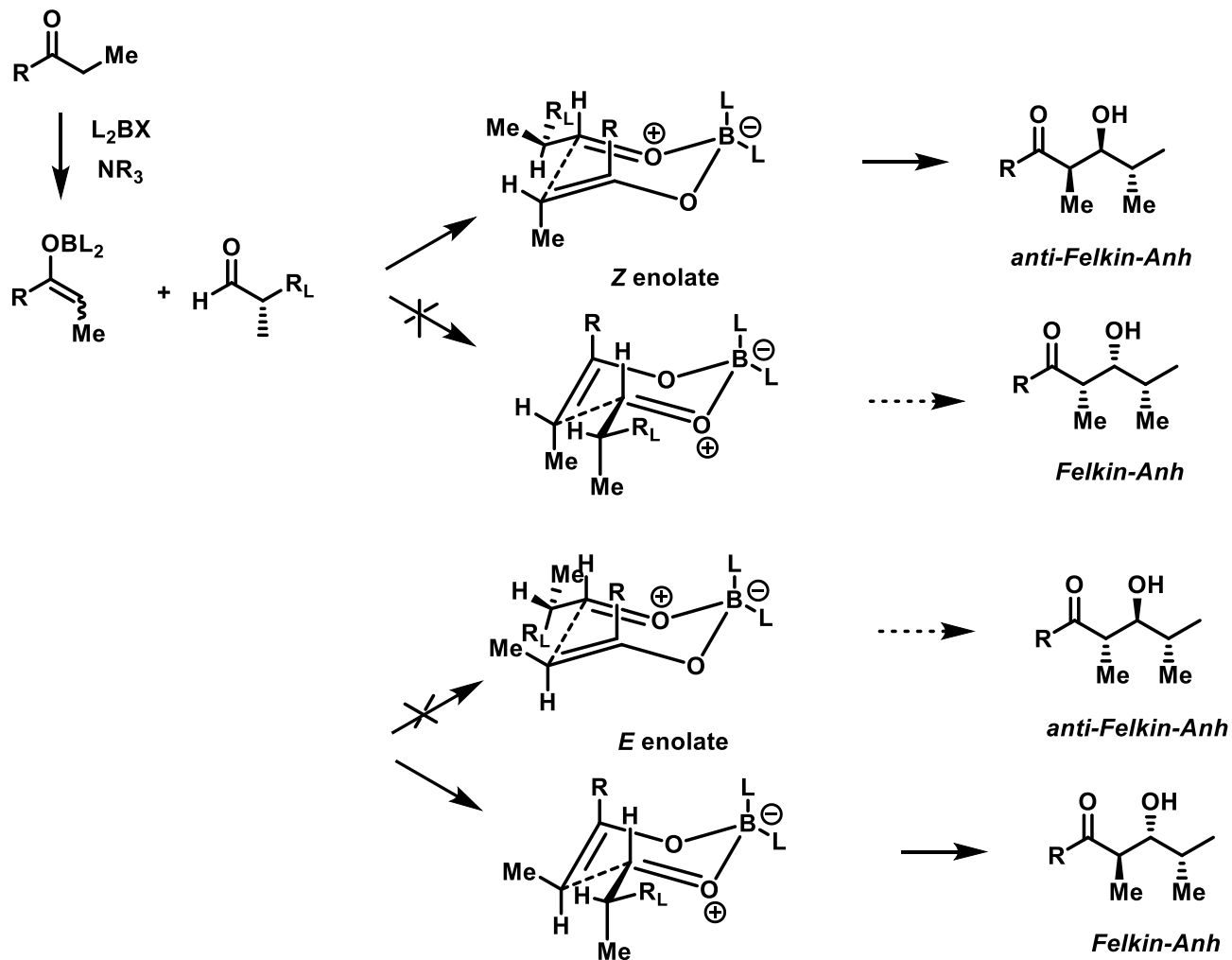


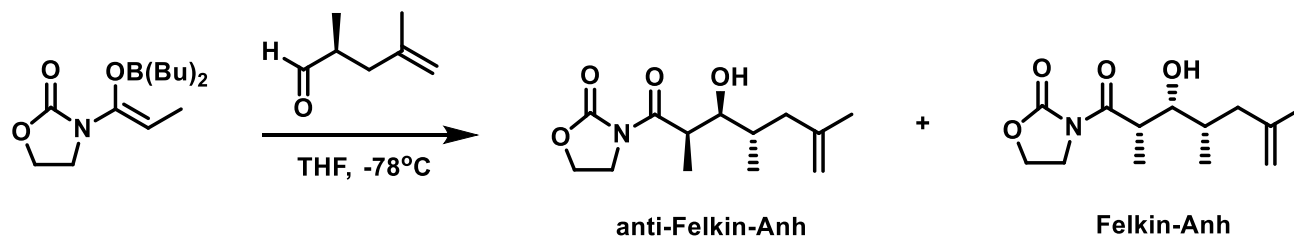
Zimmerman-Traxler

• cyclic transition state

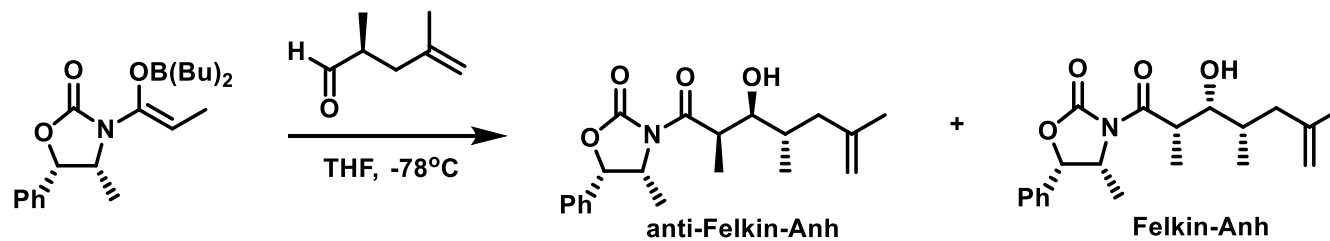


R^2 is not H, R^3 chiral



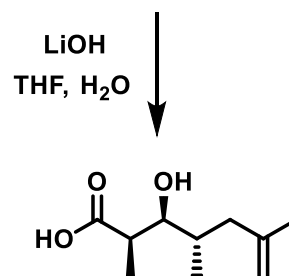


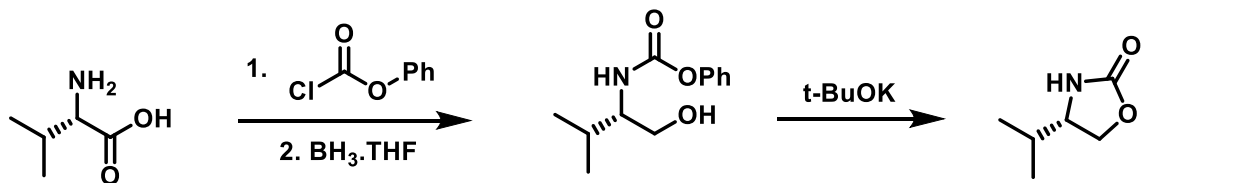
1.75 : 1



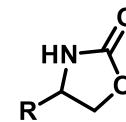
Evans' oxazolidinone

660 : 1

*Tetrahedron Lett.* **1982**, 23, 807.



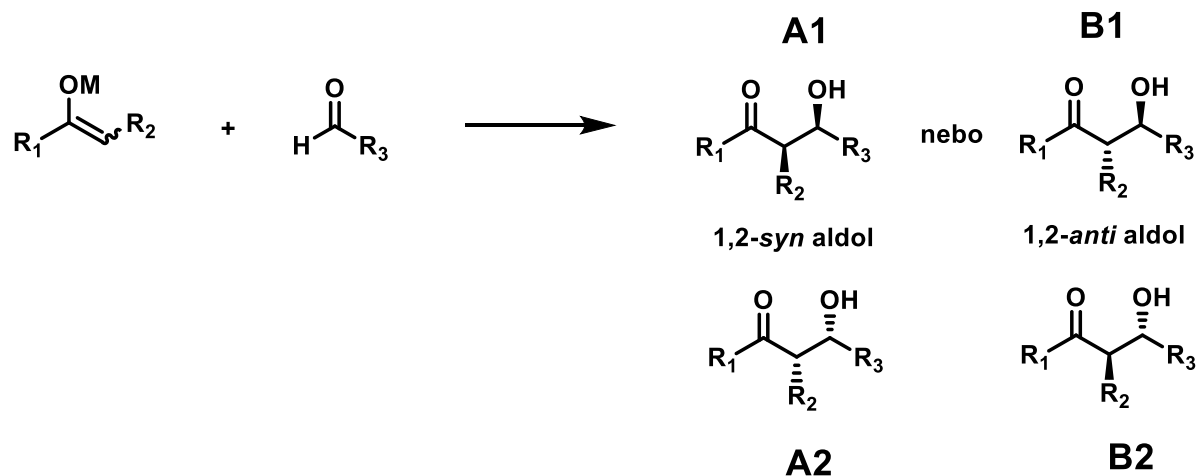
Evans' oxazolidinone



R : Bn, i-Pr, t-Bu ...

com. available

Aldol reaction: asymmetric induction



R₃ contains stereogenic center: typically, conditions can be adjusted so that the *syn*- or *anti*- product is predominant