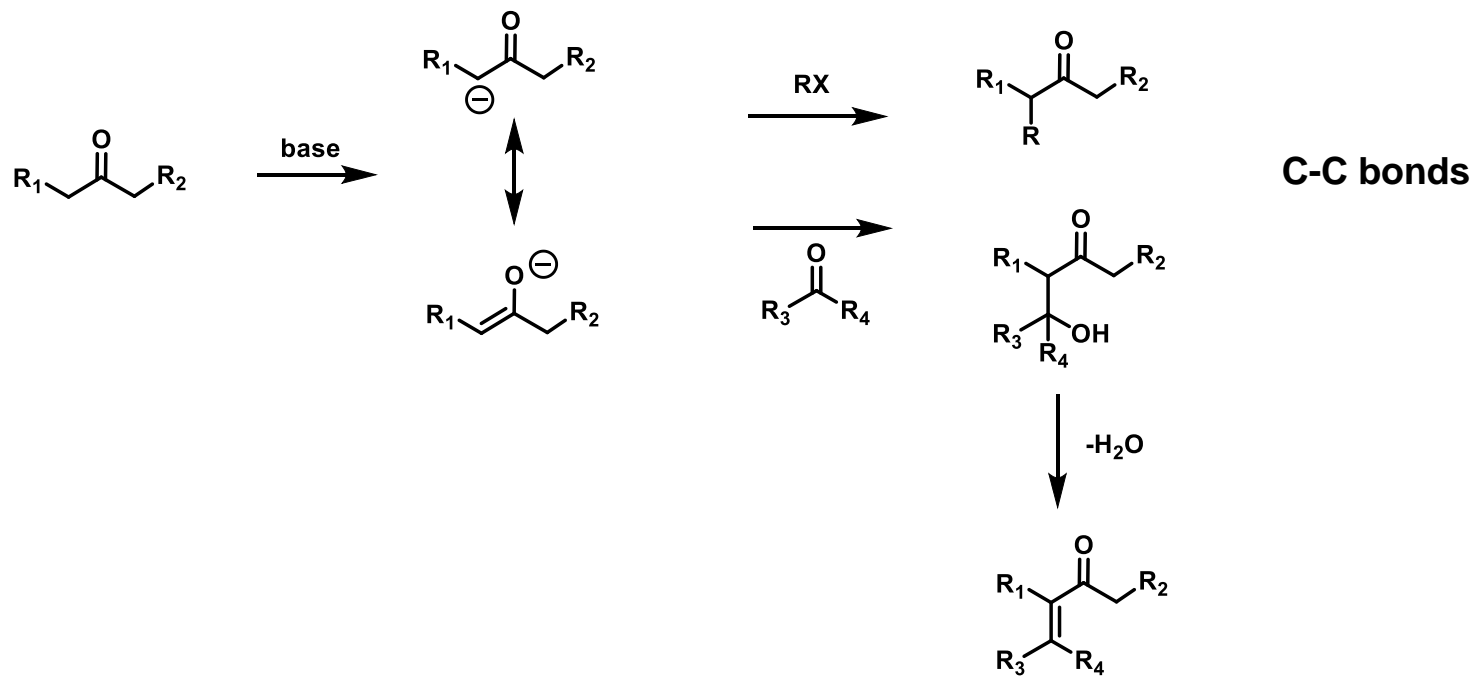
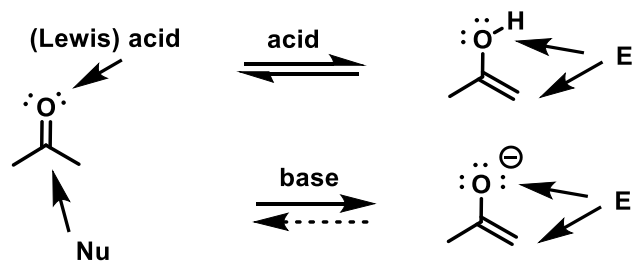


Organic synthesis

Kamil Paruch

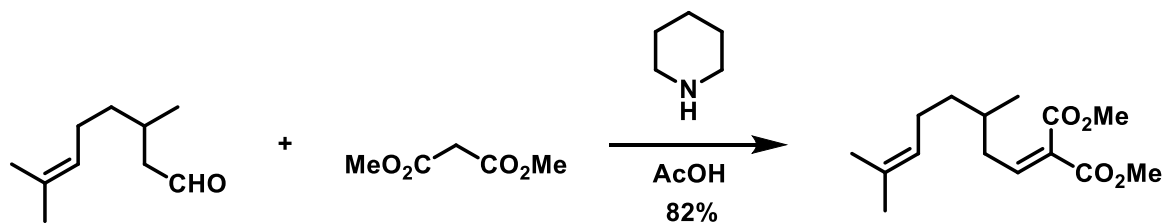
Masaryk University, Brno

Enols & enolates: formation, structure, reactivity

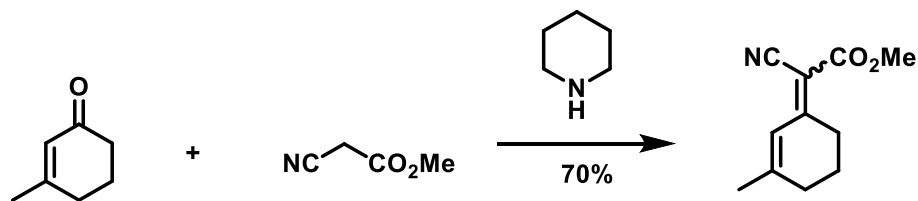


Knoevenagel condensations

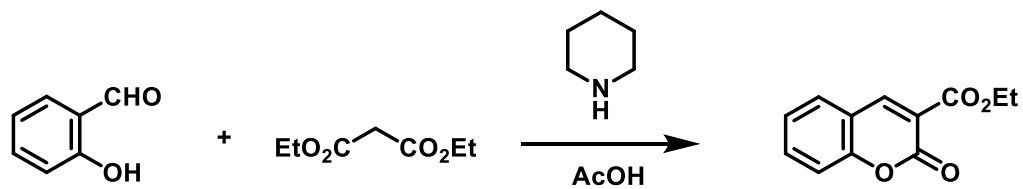
- enolate attacks carbonyl C, subsequent elimination of H₂O



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



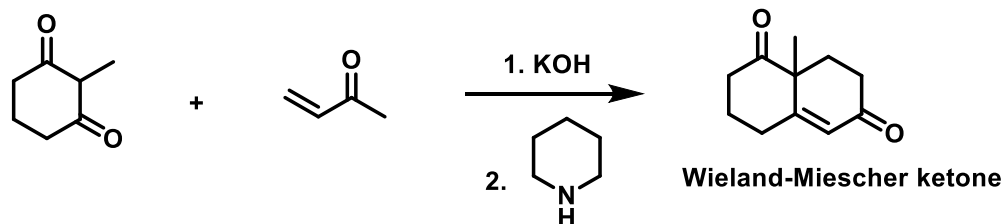
J. Chem. Soc. **1926**, 1570.



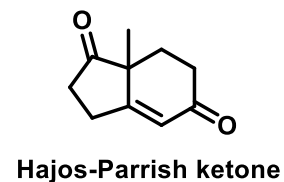
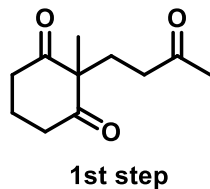
Org. Synth. Coll. Vol. 3, 1955, 165.

Robinson annulation

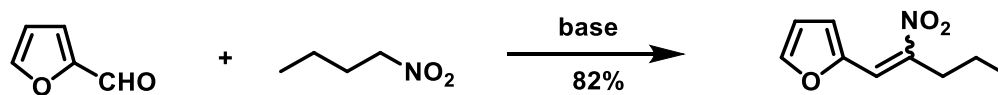
- Michael addition + aldol condensation



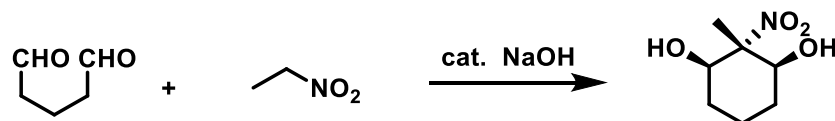
Helv. Chim. Acta 1950, 33, 2215.



Henry reaction

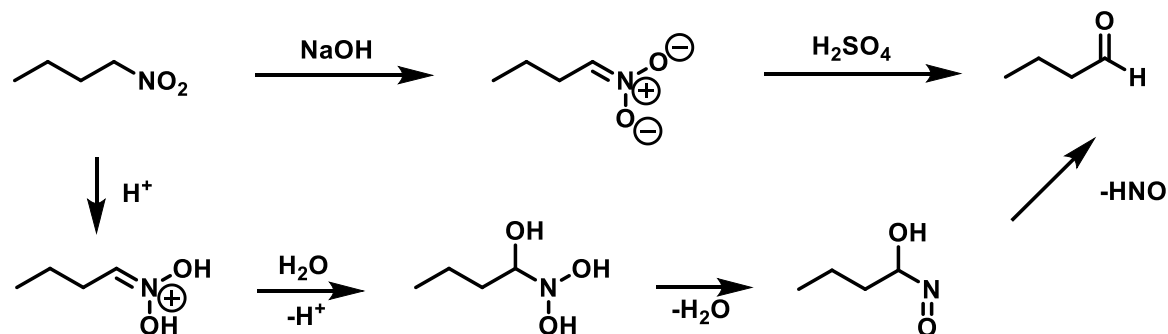


J. Org. Chem. **1950**, 15, 8.



Helv. Chim. Acta **1988**, 71, 1.

Nef reaction

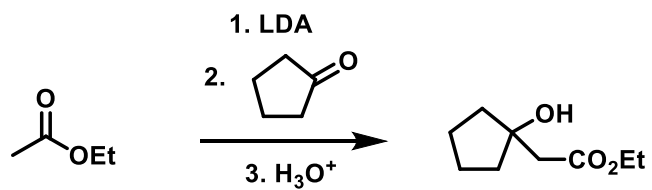
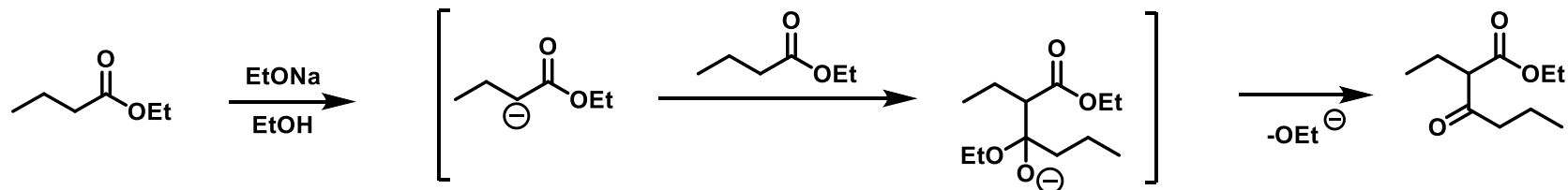


modern version:

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

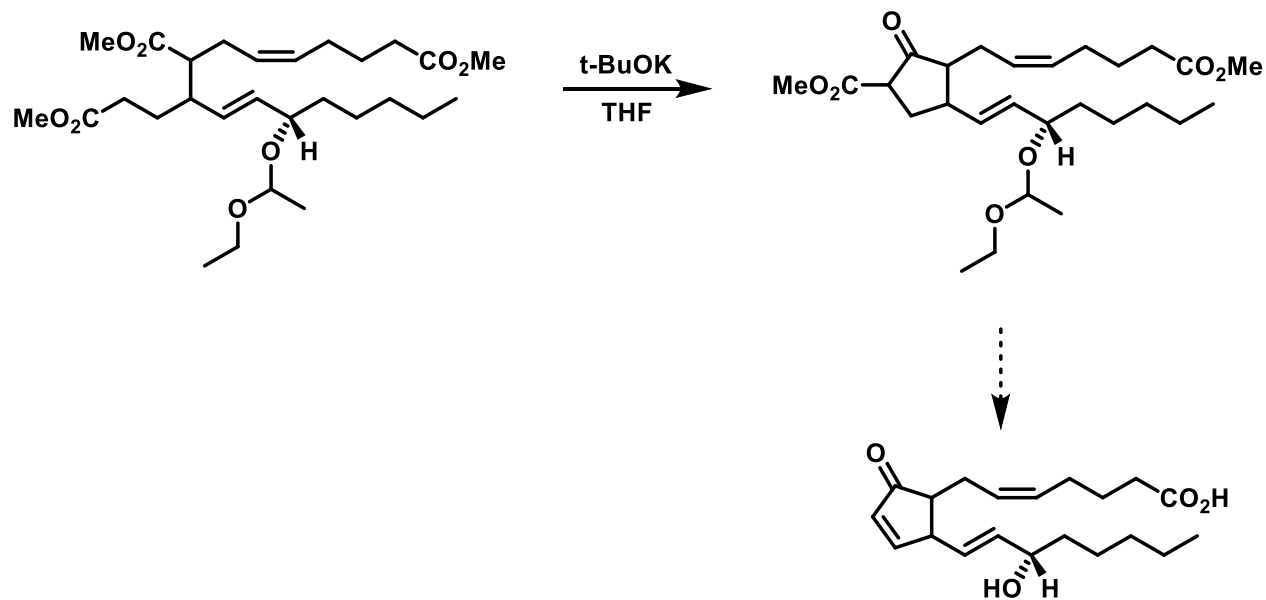
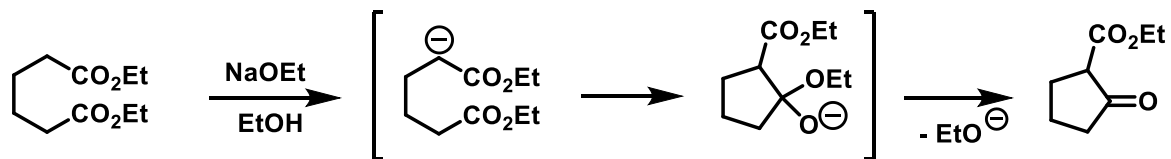
J. Org. Chem. **1985**, 501, 4971.

Claisen condensation



Dieckmann condensation

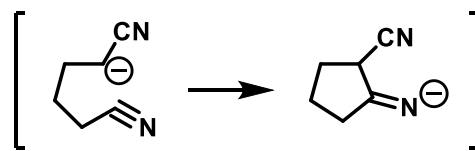
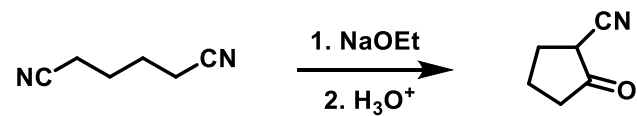
- intramolecular version of Claisen condensation



J. Am. Chem. Soc. **1976**, 98, 1583.

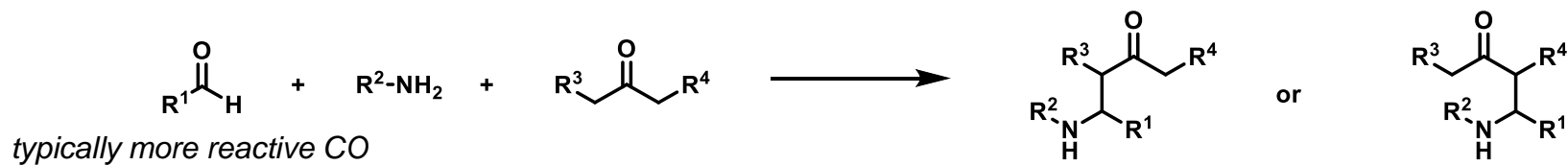
Thorpe reaction

- „enolates“ of nitriles

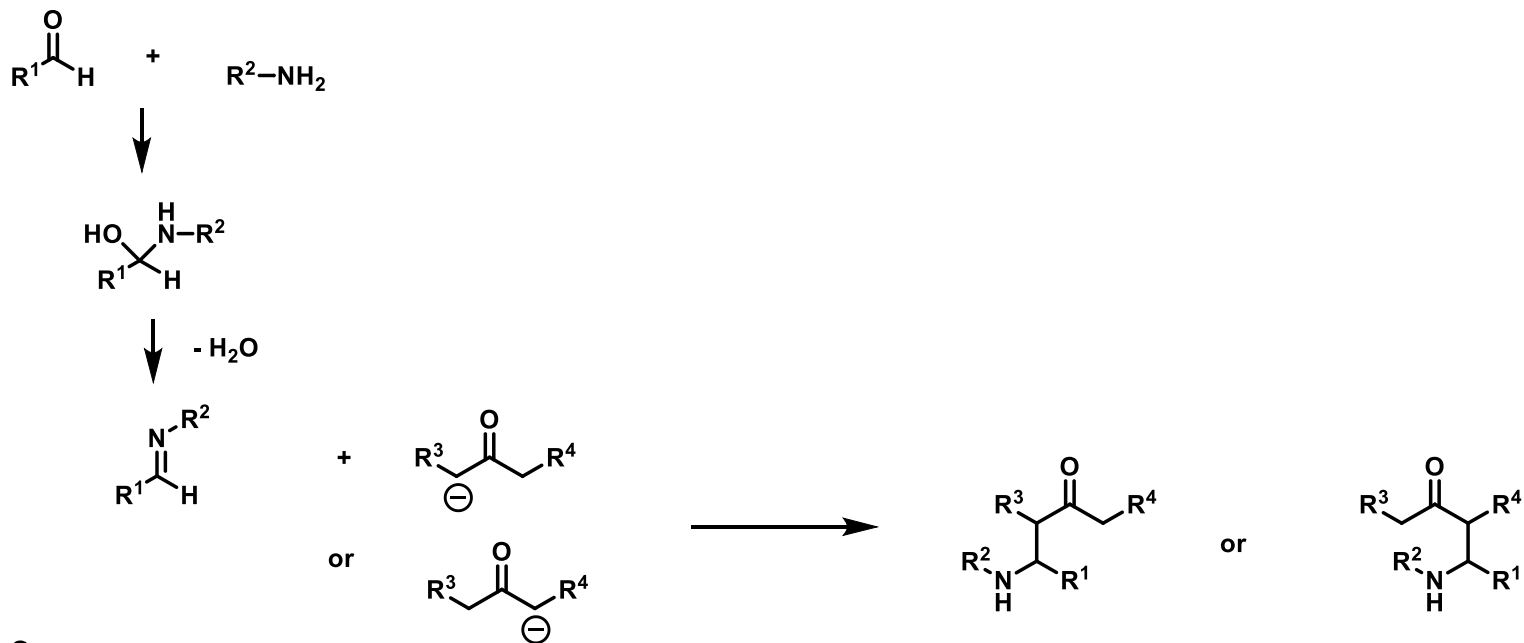


Mannich reaction

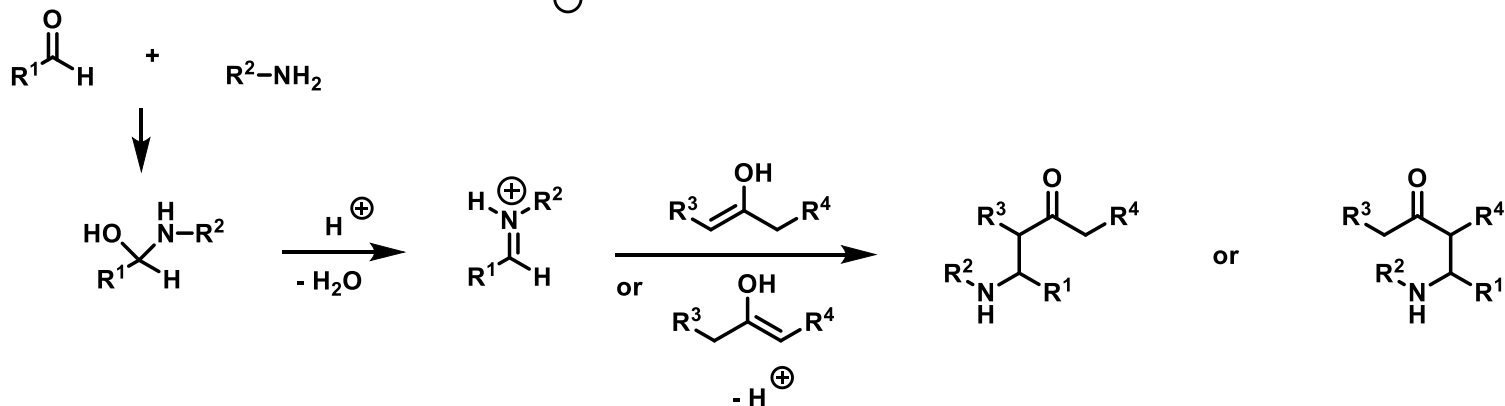
- frequently used in assembly of cyclic N-containing systems

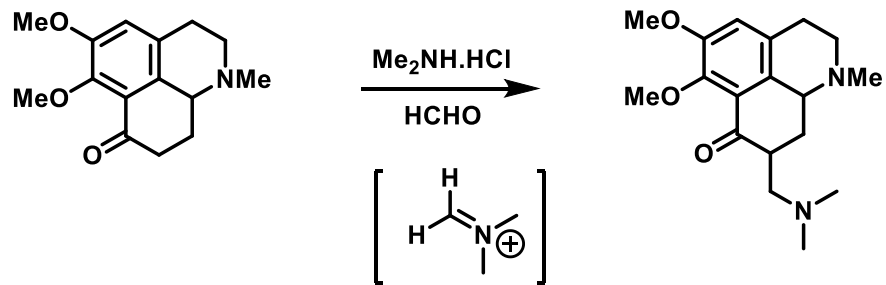


base-catalyzed



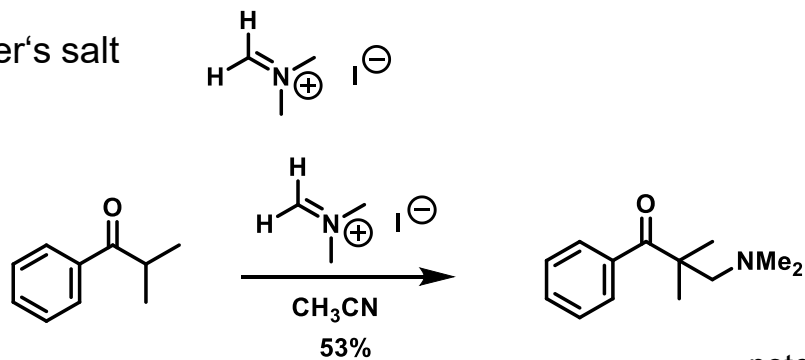
acid-catalyzed



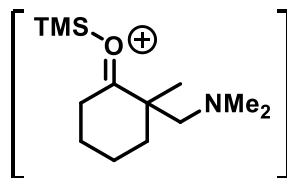
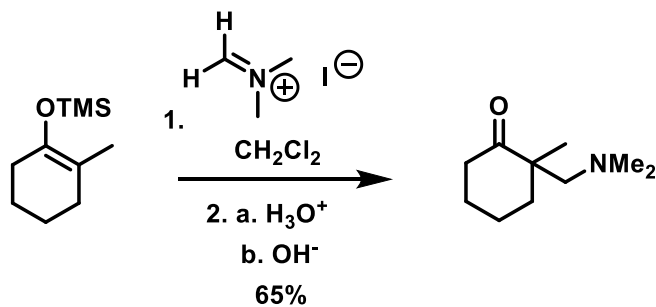


Chem. Pharm. Bull. **1991**, 39, 1349.

Eschenmoser's salt

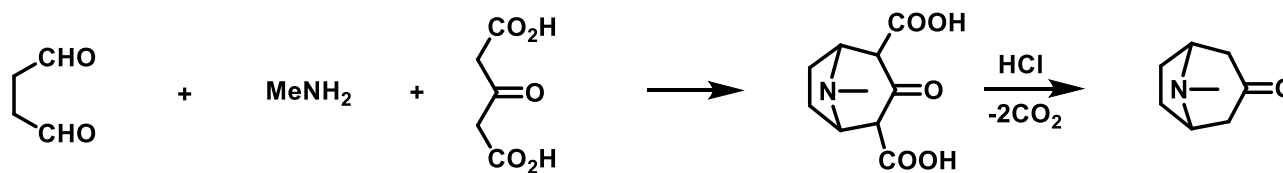


note: only 6% yield with HCHO + Me₂NH
(sterically hindered substrate)

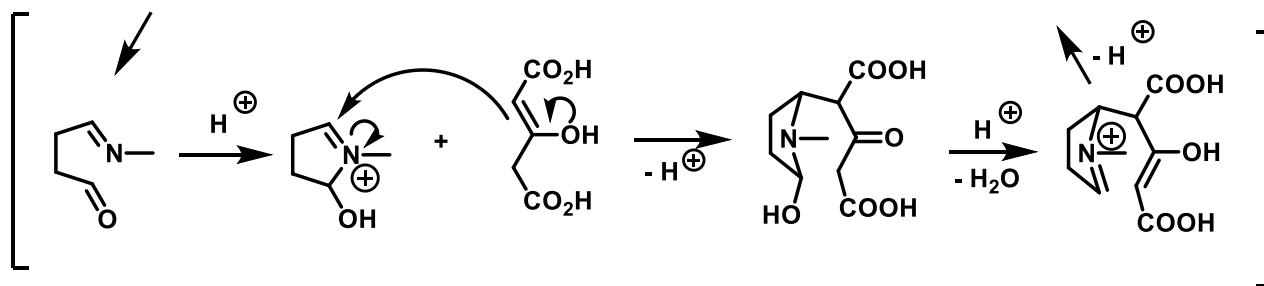


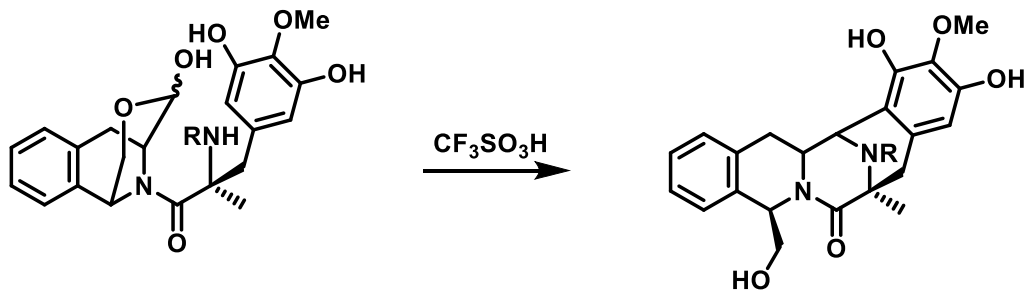
Mannich reaction is frequently used in assembly of cyclic N-containing systems

“biomimetic approach”



J. Chem. Soc. 1917, 762.

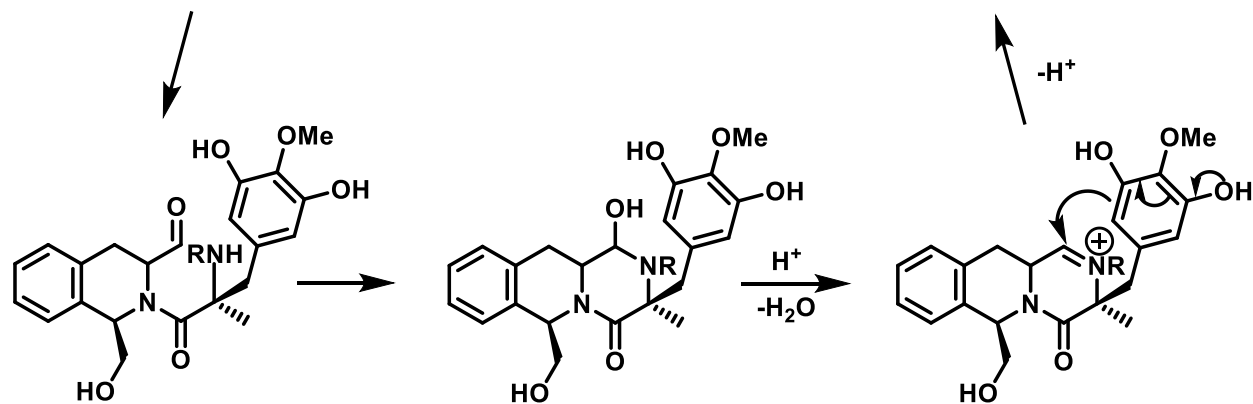




R = CO_2allyl

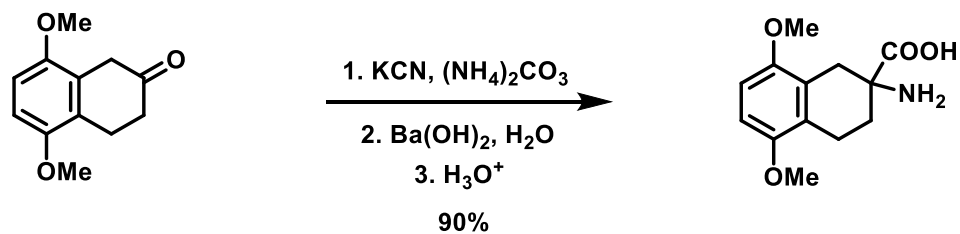
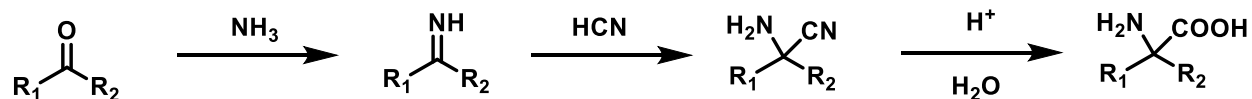
J. Am. Chem. Soc. **1996**, *118*, 9202.

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



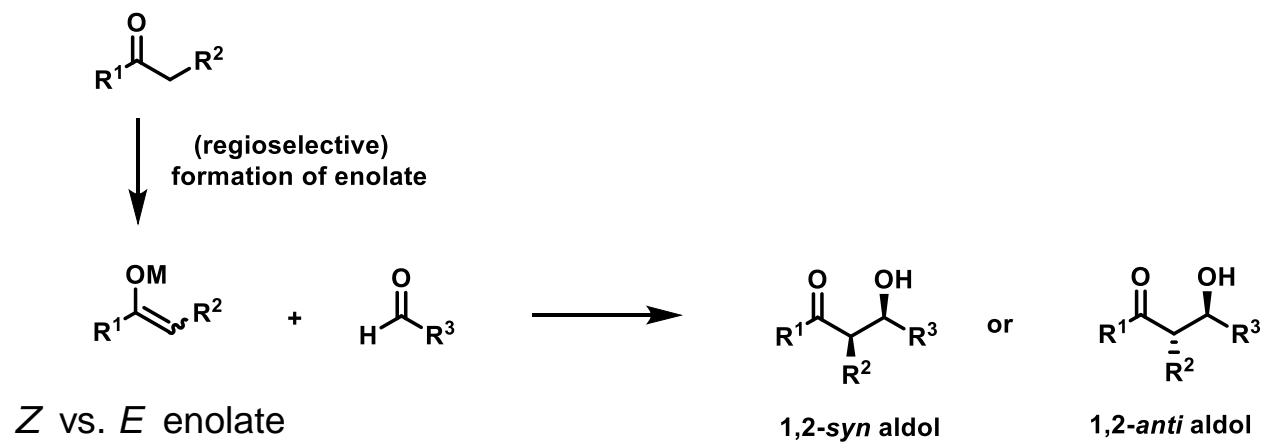
Strecker reaction

- synthesis of amino acids



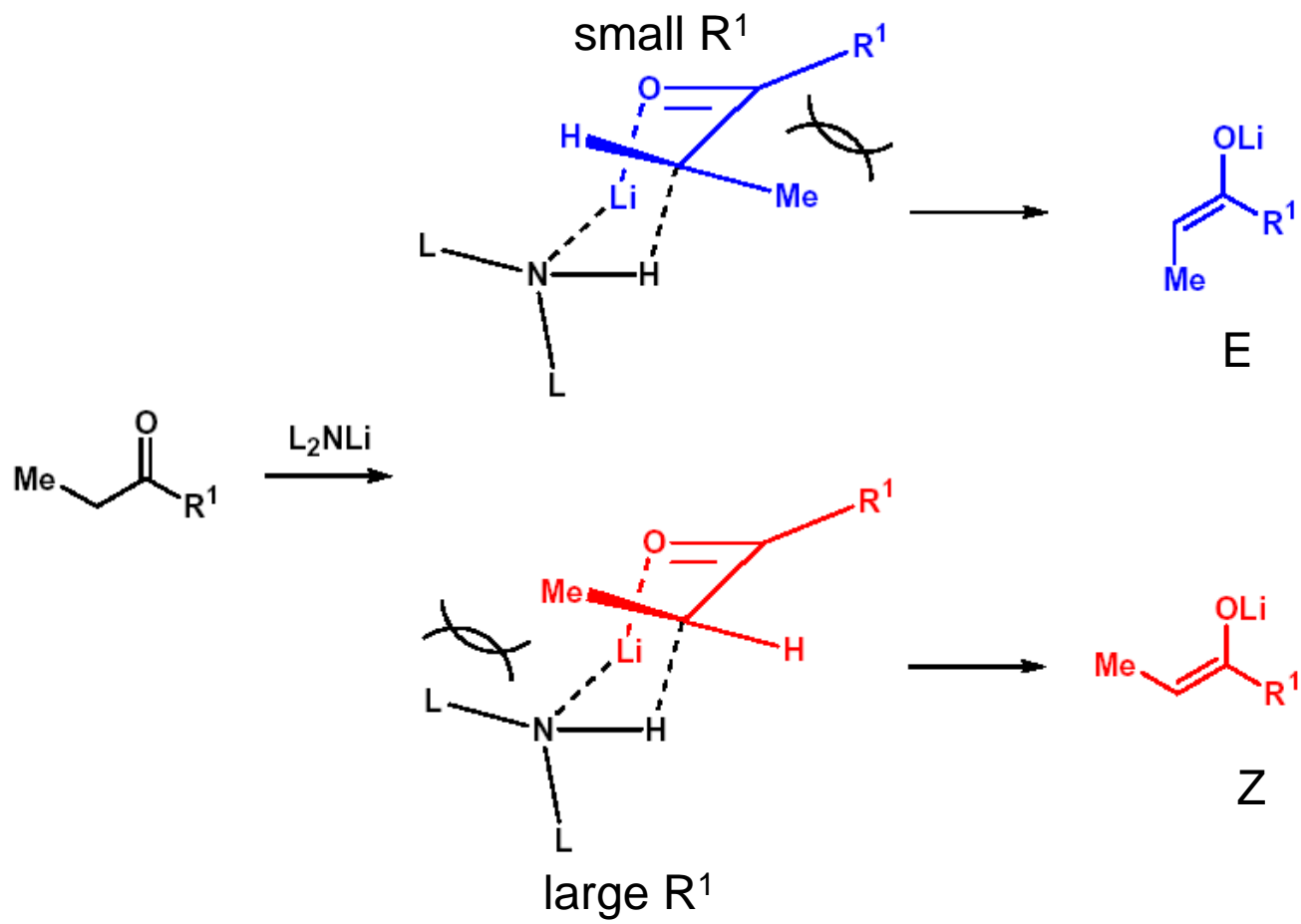
J. Org. Chem. **1987**, *52*, 4477.

Aldol reaction: 2 new stereogenic centers can be created

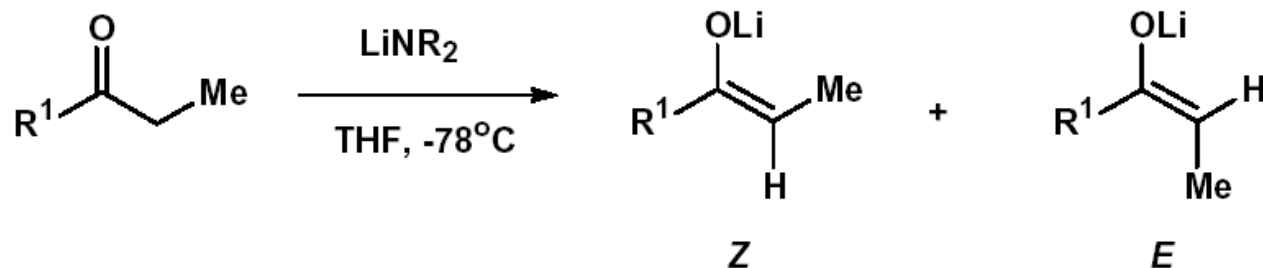


- stereochemistry of products depends on the configuration of the starting enolates

GEOMETRY OF ENOLATES - IRELAND MODEL



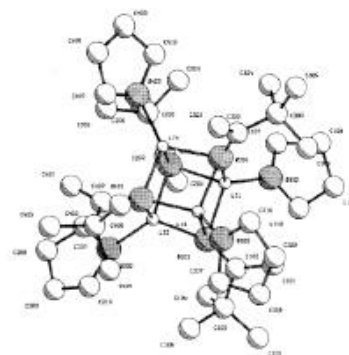
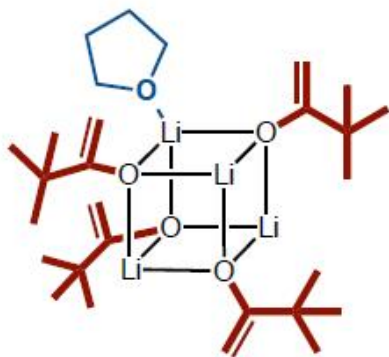
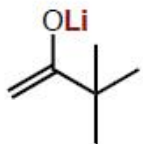
GEOMETRY OF ENOLATES - EFFECT OF BASE



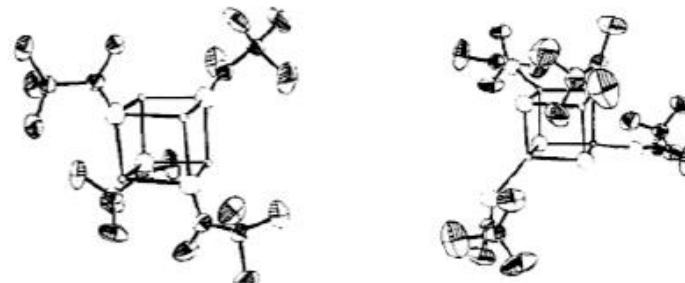
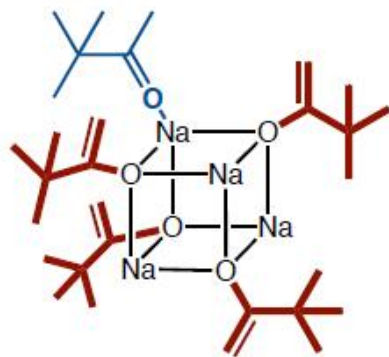
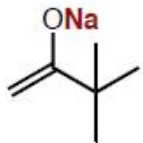
BÁZE	R ₁ =Et (Z : E)	R ₁ =cyklohexyl (Z : E)
LiN(<i>i</i> -Pr) ₂	30 : 70	61 : 39
LiN(SiMe ₃) ₂	70 : 30	85 : 15
LiN(SiEt ₃) ₂	99 : 1	96 : 4
LiN(SiMe ₂ Ph) ₂	100 : 0	100 : 0

- enolates often form clusters

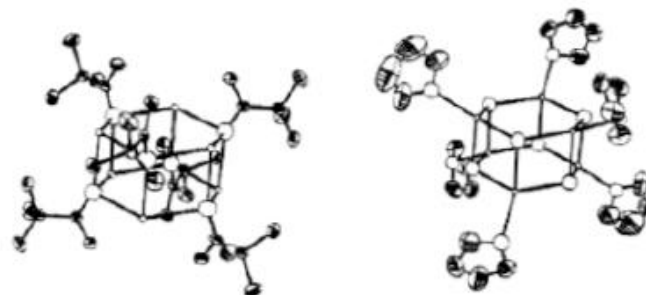
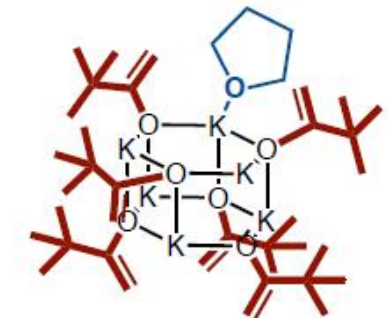
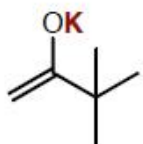
- Lithium enolate



- Sodium enolate



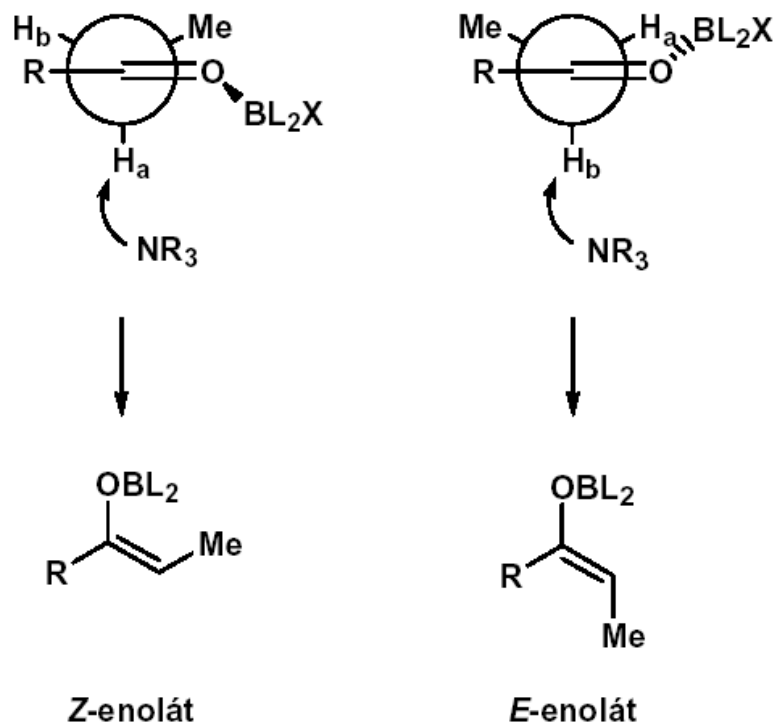
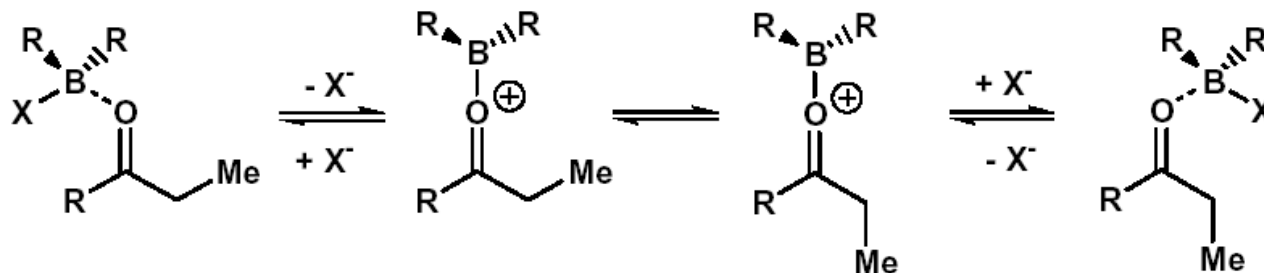
- Potassium enolate



J. Am. Chem. Soc. 1986, 108, 462.

Helv. Chim. Acta 1981, 64, 2617.

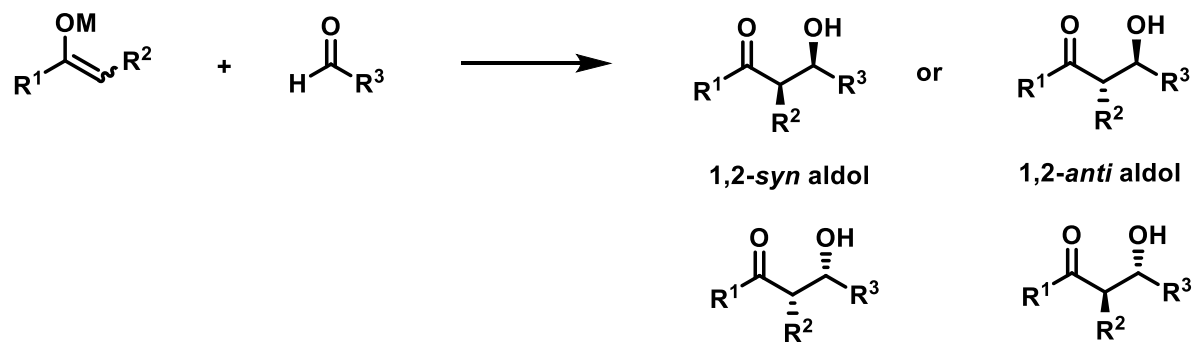
SELECTIVE FORMATION OF *E* OR *Z* ENOL BORINATES



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

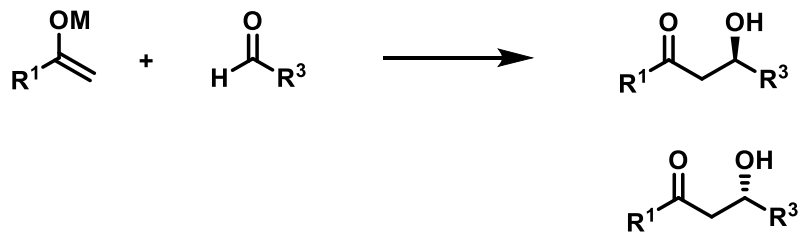
Aldol reaction: 2 new stereogenic centers can be created



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

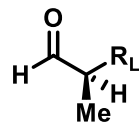
Nucleophilic attack on C=O

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

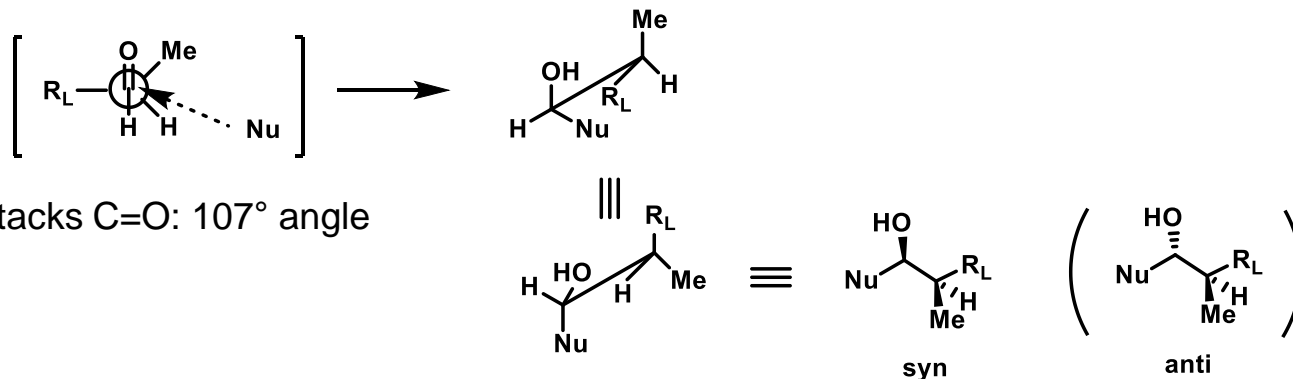


racemic mixture

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



Felkin-Anh



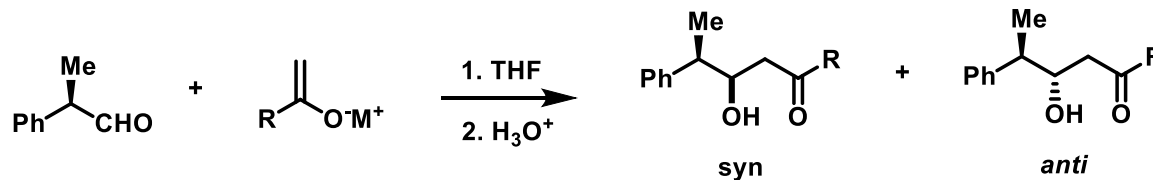
Nu attacks $C=O$: 107° angle

syn

anti

mixture of diastereomers

• stereoselective reactions with large Nu



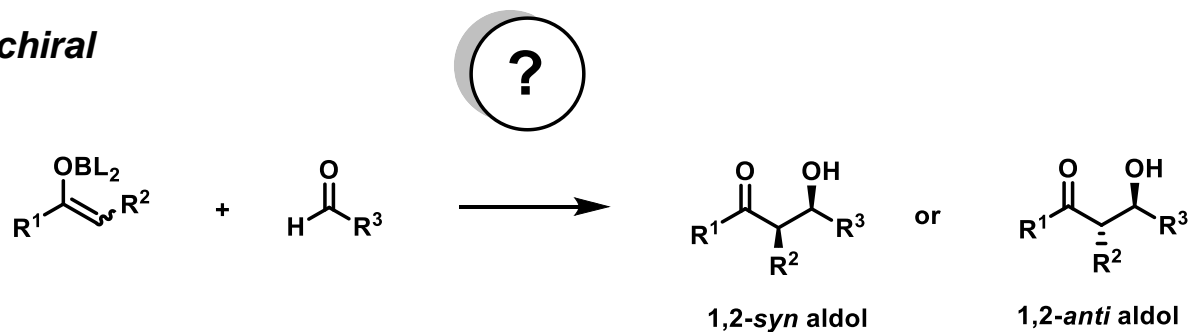
R : OMe 75 : 25

Me 76 : 24

t-Bu 80 : 20

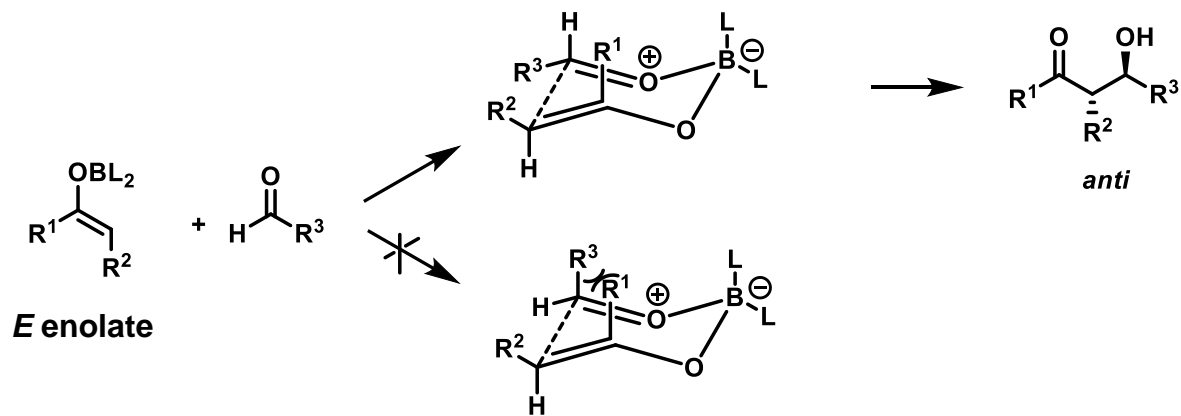
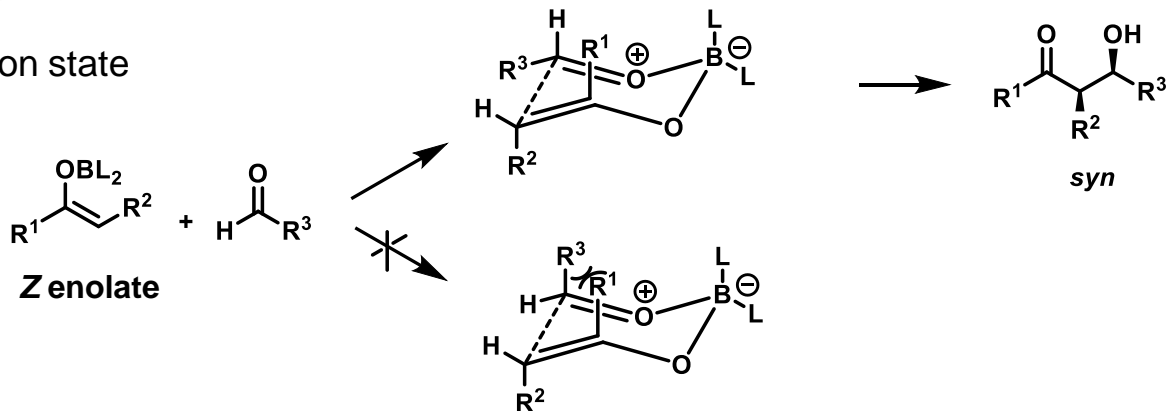
Aldol reaction: 2 new stereogenic centers can be created

R^2 is not H, R^3 achiral



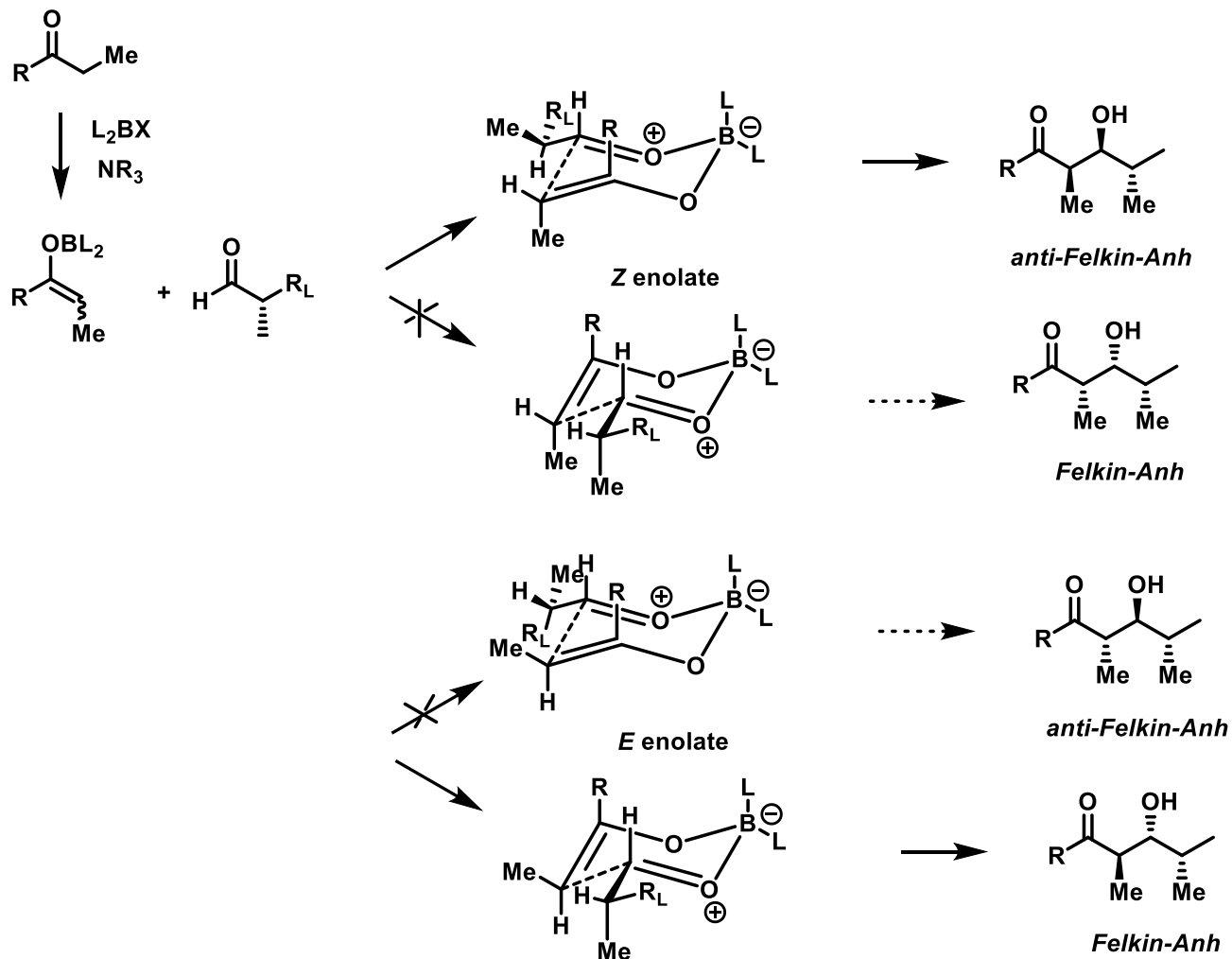
Zimmerman-Traxler

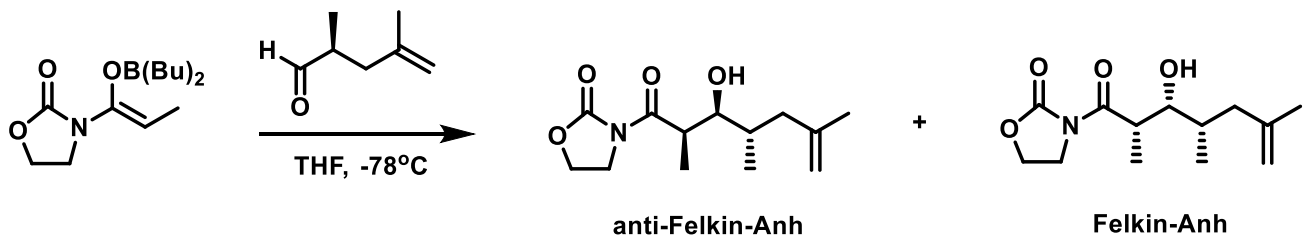
- cyclic transition state



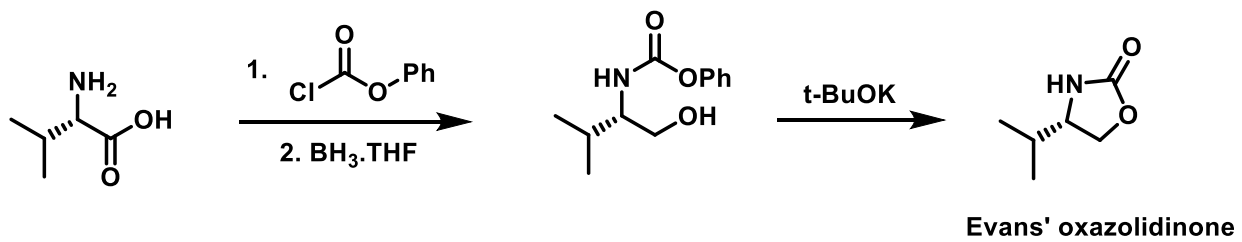
Aldol reaction: 2 new stereogenic centers can be created

R^2 is not H, R^3 chiral

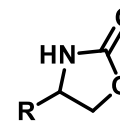




1.75 : 1



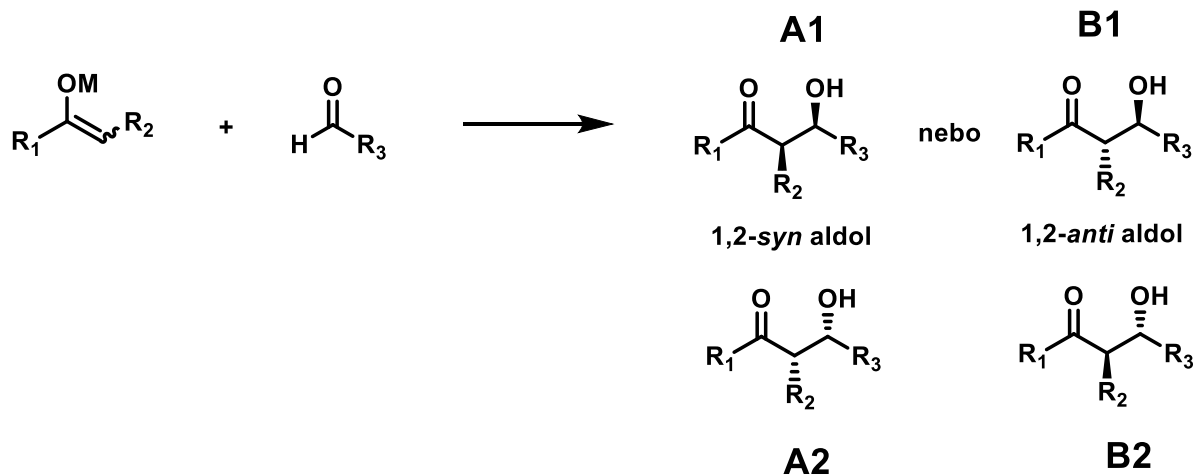
Evans' oxazolidinone



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