CHEM-E4109
MODERN METHODS IN BIOCATALYSIS

chapter #6: Aldol chemistry

16.3.2022

Jan Deska
Bioorganic
Chemistry

Updated Schedule

1.3. Introduction & basic principles

4.3. Oxidoreductases I (reduction catalysis)

8.3. Oxidoreductases II (oxygenation catalysis)

11.3. Transferases (transaminases)

15.3. Lyases I (decarboxylases and transketolases)

18.3. Lyases II (aldolases)

22.3. Directed evolution (no live session, video only)

25.3. Hydrolases (lipases, esterases, epoxide hydrolases)

29.3. Muta- and semisynthesis

1.4. Enzymes in non-natural reactions

12./13.4. Seminar presentations

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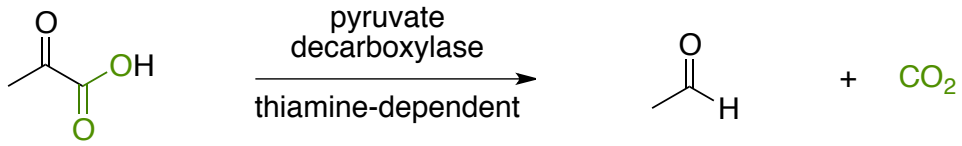
Lyases - features

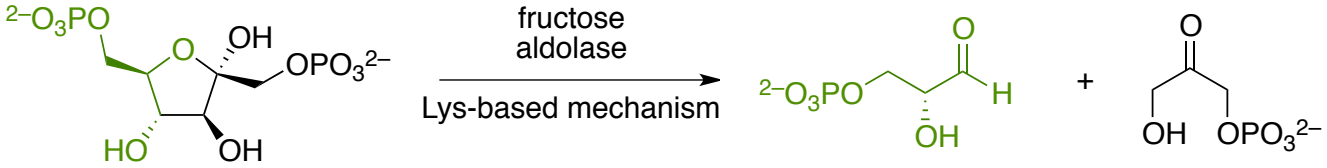
enzymes of class EC 4 catalyze the cleavage of chemical bonds (non-hydrolytic!)

(...and of course, like always, some can do the reverse reaction)

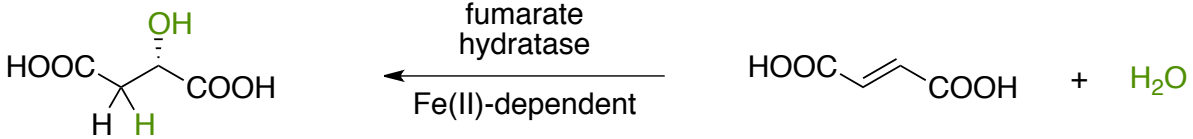
pyruvate decarboxylase



aldolase



fumarate hydratase



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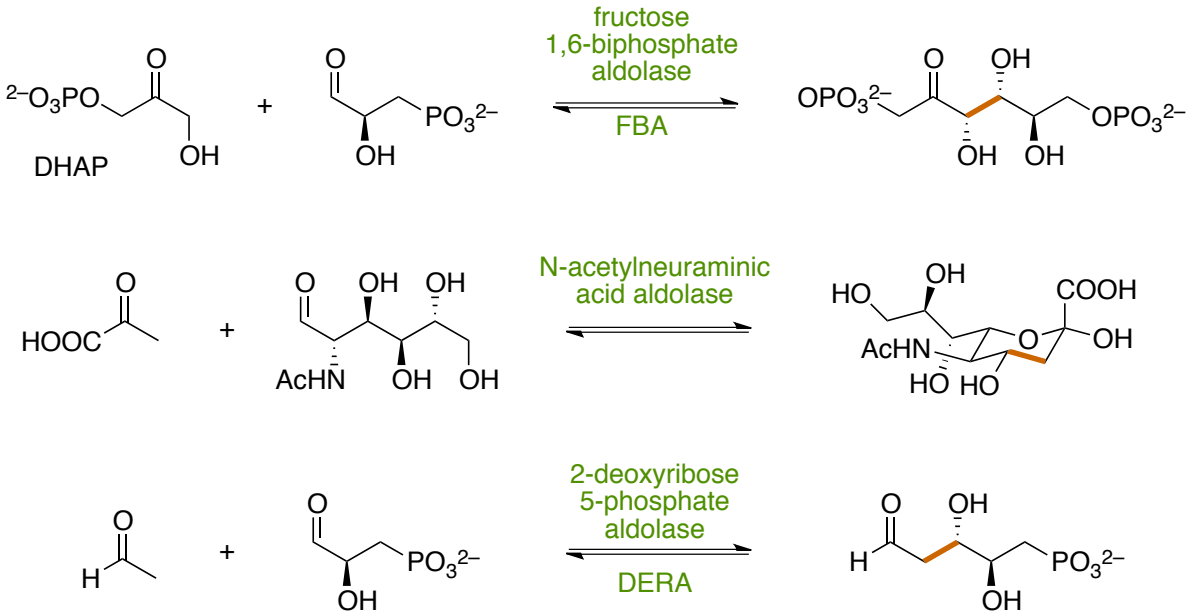
Aldol-catalyzing enzymes

- mainly involved in biosynthesis and degradation of sugars and related biomolecules
- 2 major classes that differ in their basic activation mode
  - ✓ class I mechanism: enamine catalysis or
  - ✓ class II mechanism: enolate catalysis



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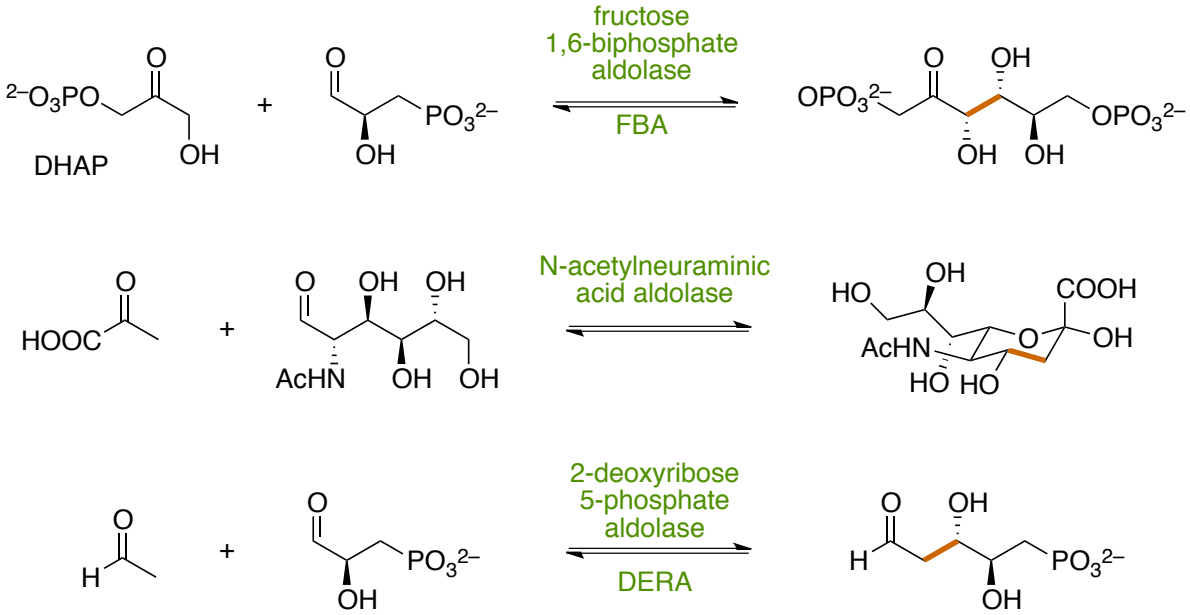

- current main drawback: narrow scope of accepted donors (nucleophiles)

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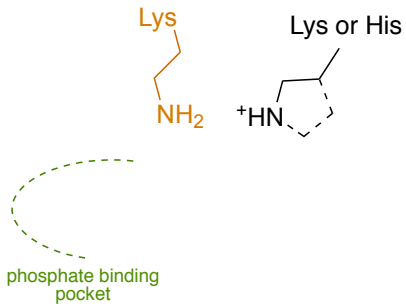
General activation modes

class I aldolase: enamine catalysis



General activation modes

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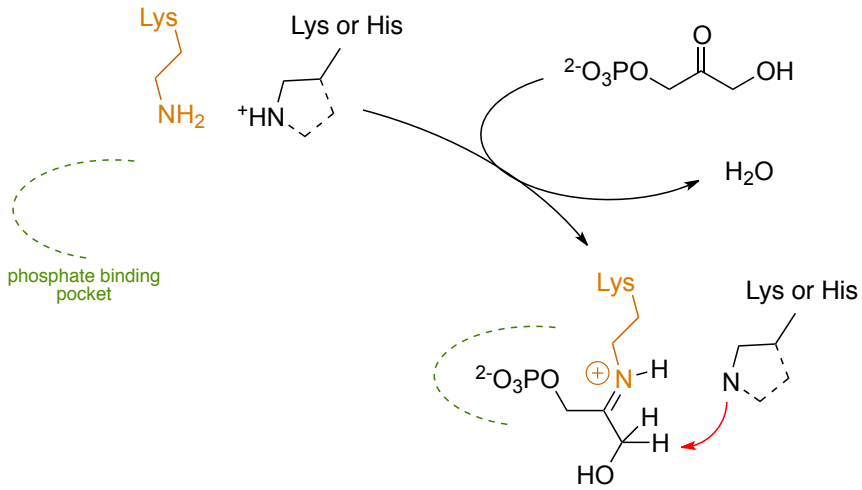

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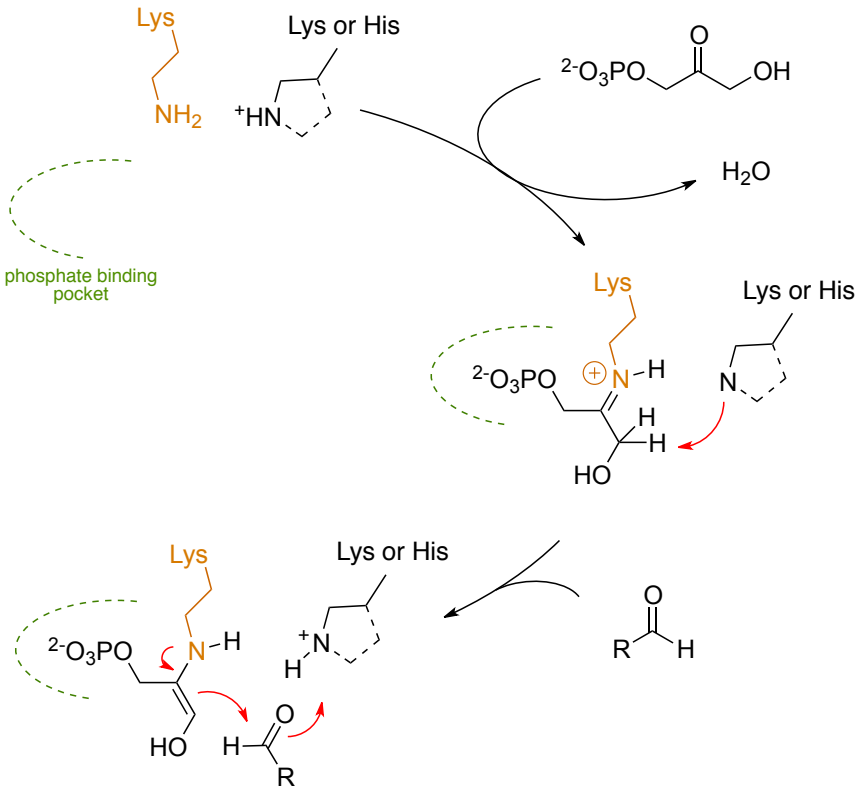
General activation modes

class I aldolase: enamine catalysis



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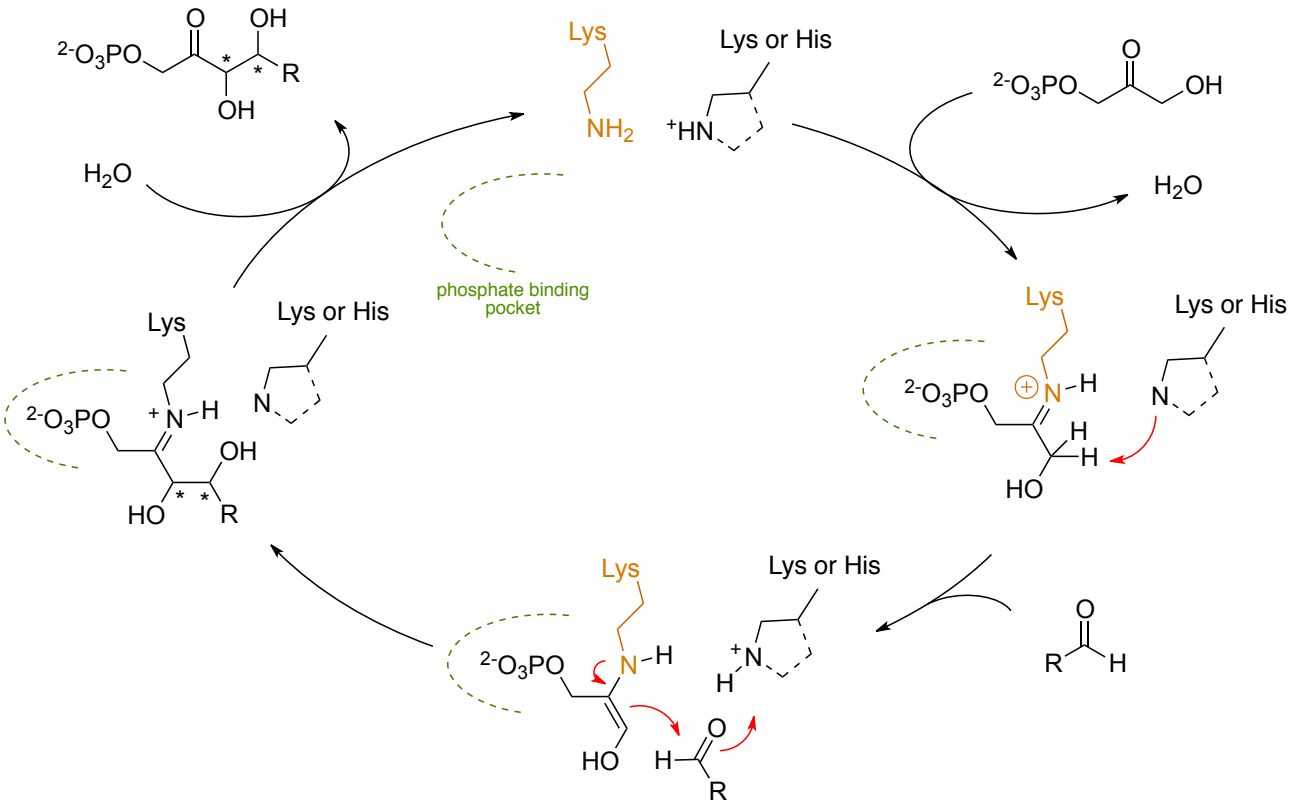
General activation modes

class I aldolase: enamine catalysis



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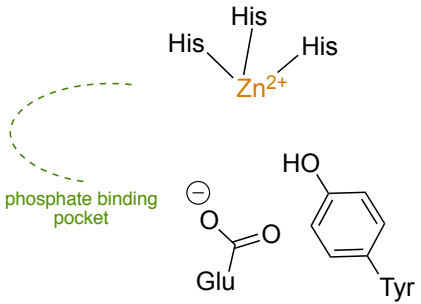
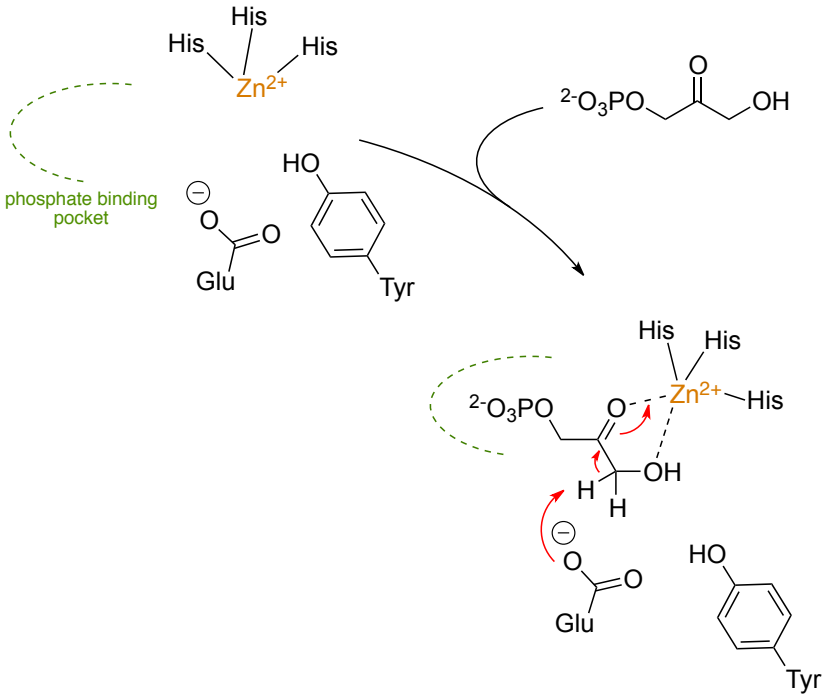
General activation modes

class II aldolase: enolate catalysis



General activation modes

class II aldolase: enolate catalysis



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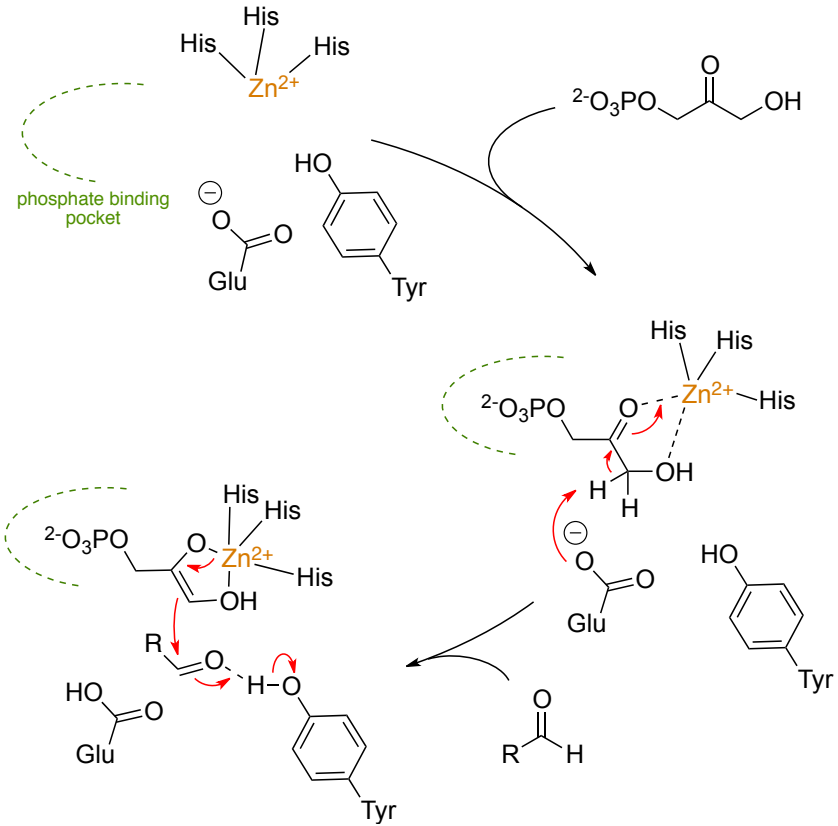
General activation modes

class II aldolase: enolate catalysis



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General activation modes

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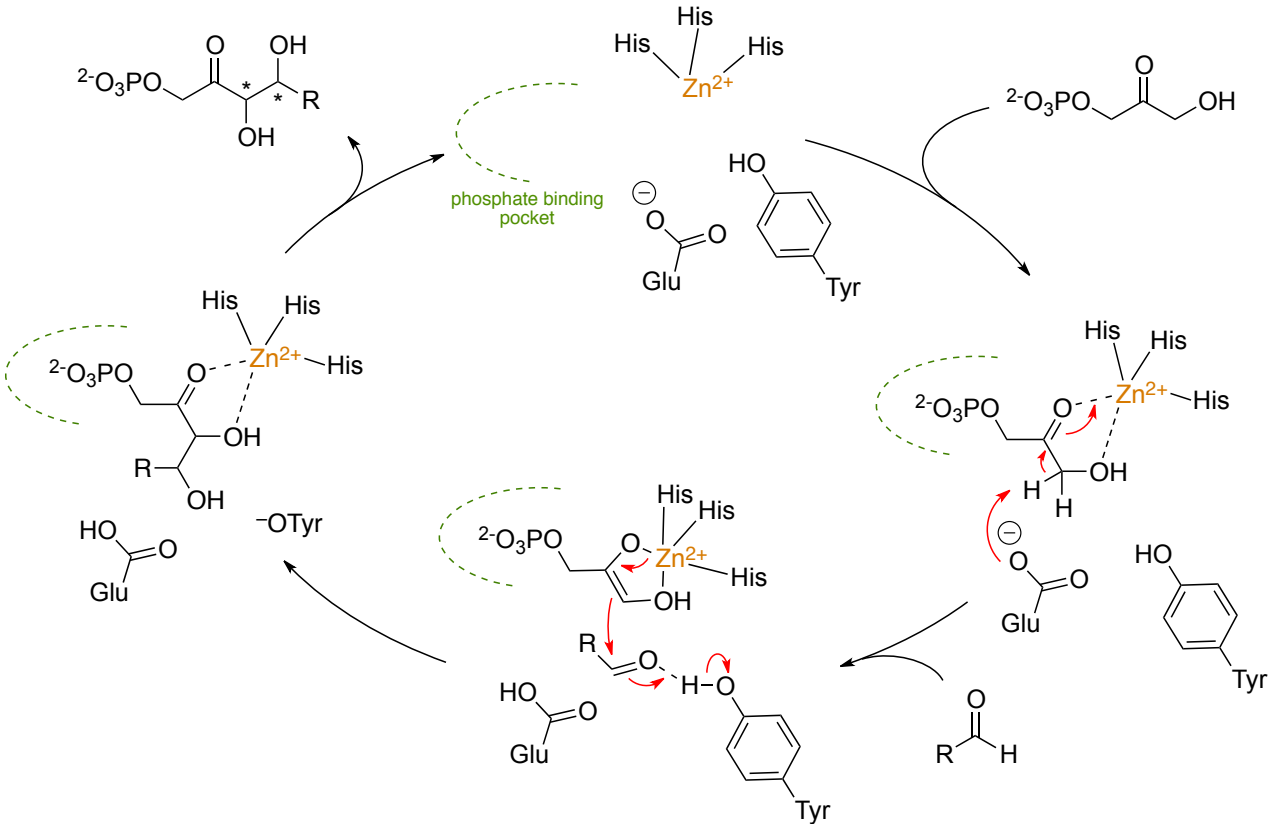

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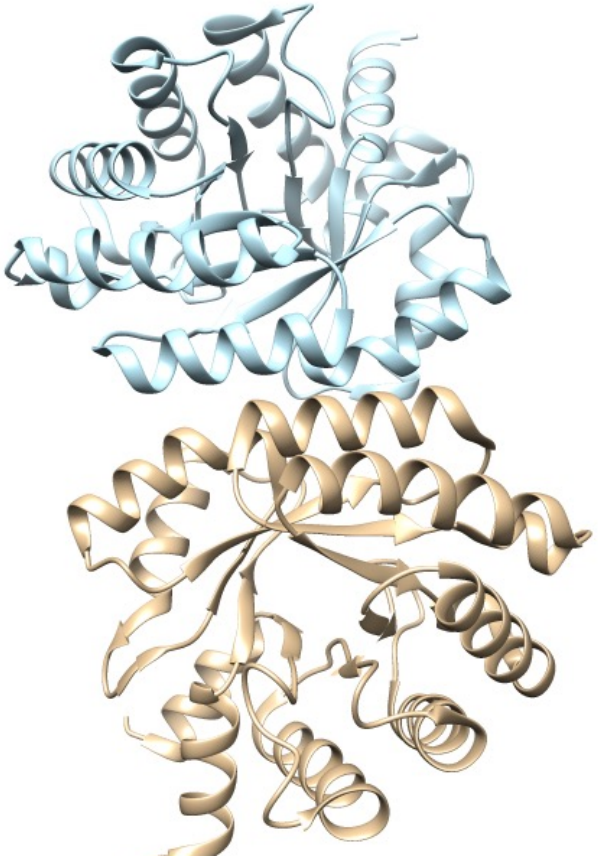
2-Deoxyribose-5-phosphate aldolase

DERA (*Lactobacillus brevis*)

- homo dimer, 259 amino acids per subunit
  (other organisms exploit tetrameric DERAs)
- class I aldolase
- independent on cofactors or metal ions
- physiological role: catabolism of glycosides and deoxyribonucleotides
- catalyzes the reversible cross-aldol reaction between acetaldehyde and other acceptor aldehydes



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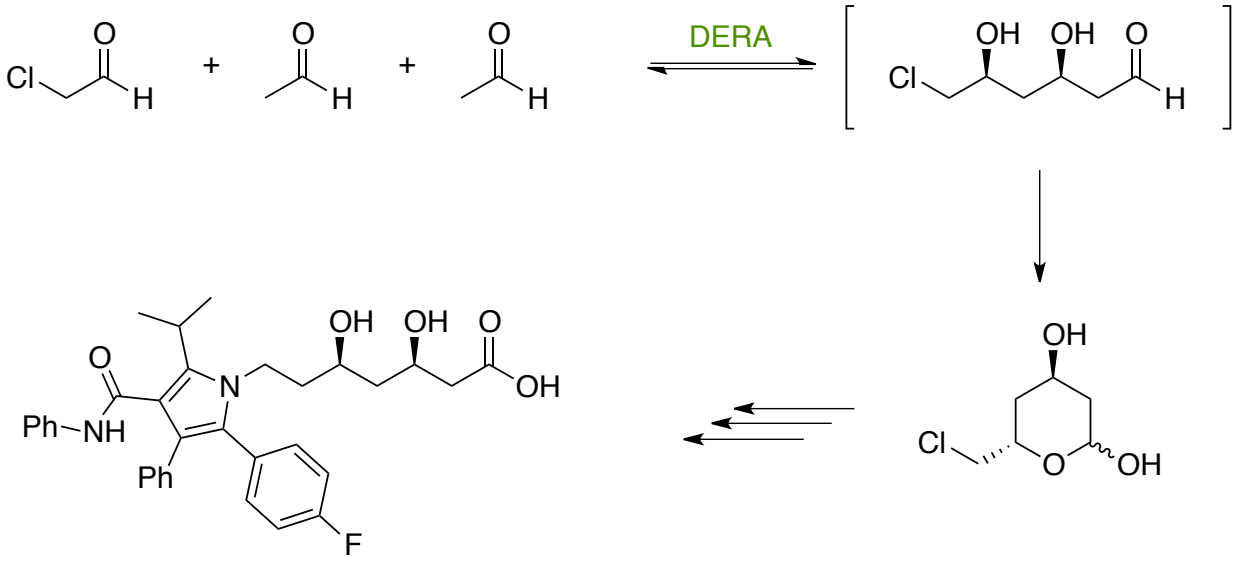
Aldolases: synthetic applications

Synthesis of the statin core structure



Greenberg, Varvak, Hanson, Wong, Huang, Chen, Burk, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5788-5793.

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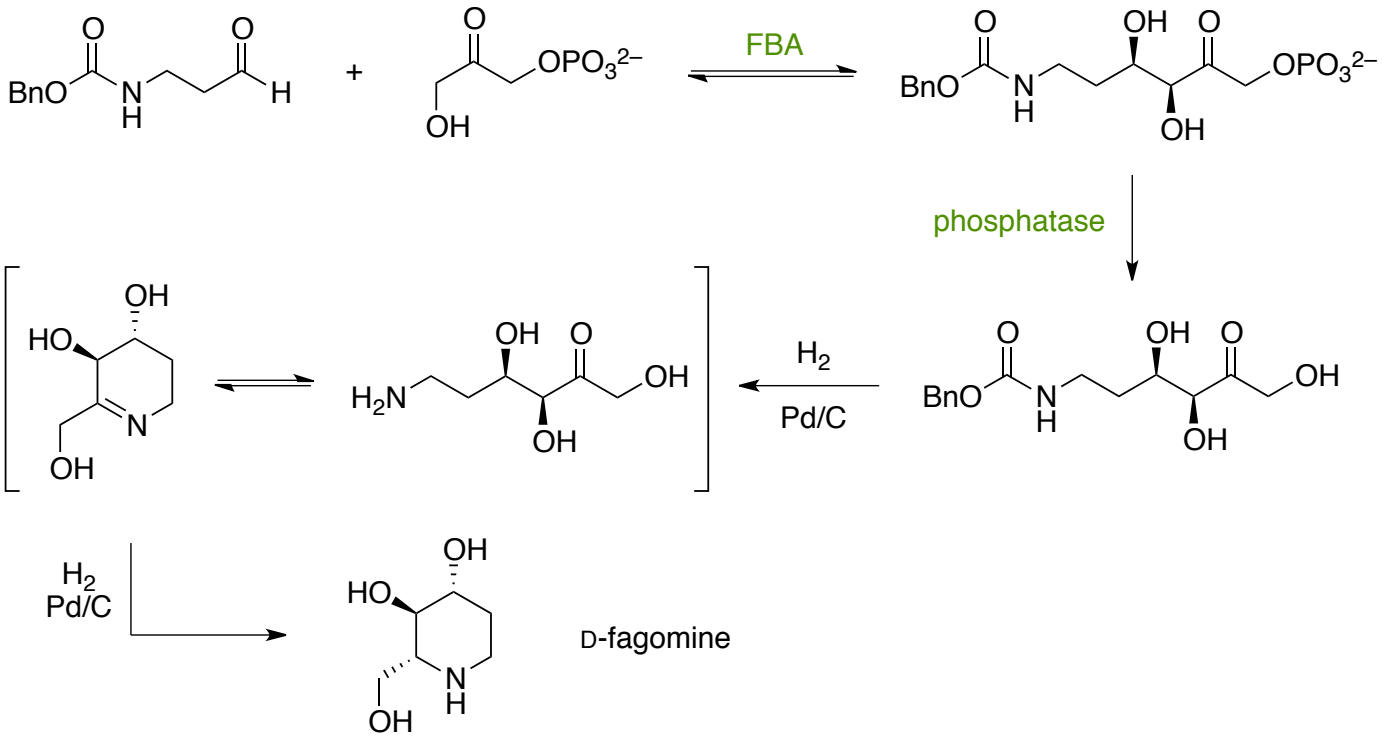
Aldolases: synthetic applications

Synthesis of azasugars



Dean, Greenberg, Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308-1320.

Aldolases: synthetic applications

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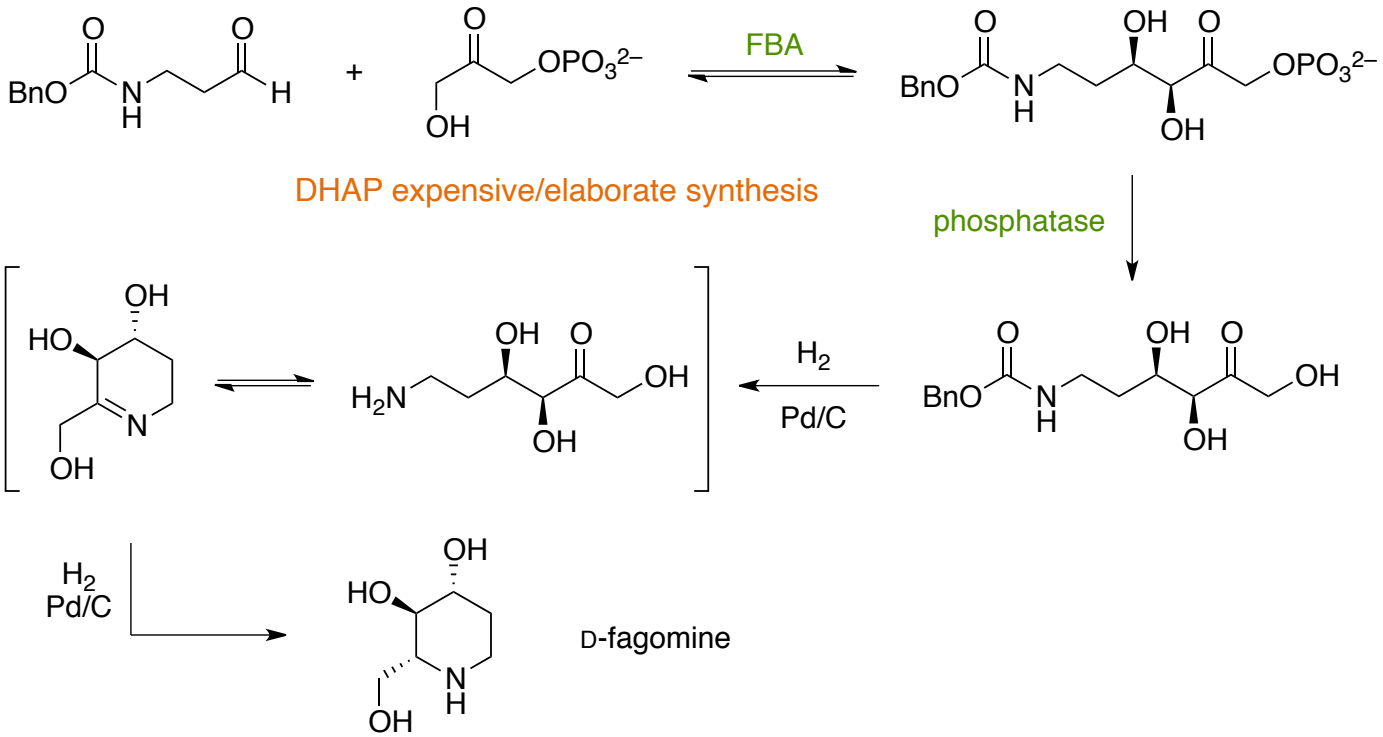

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Aldolases: synthetic applications

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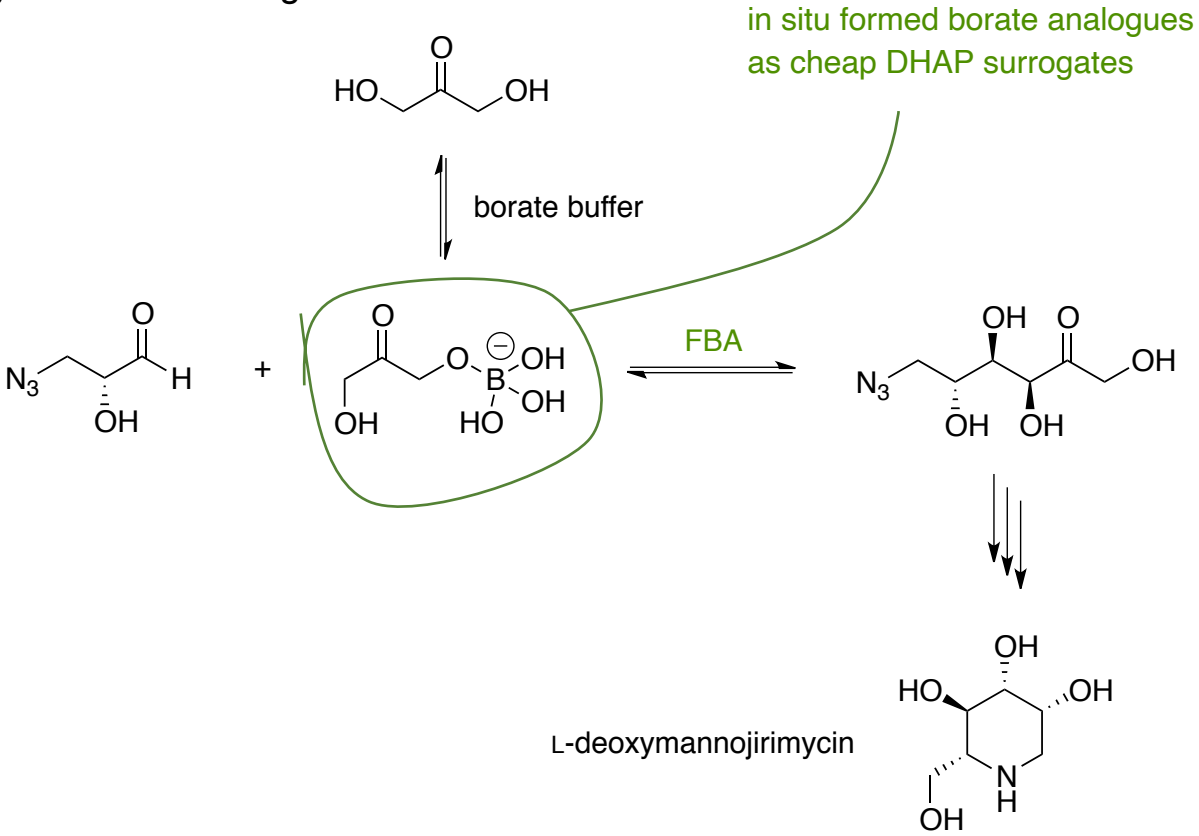

Dean, Greenberg, Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308-1320.

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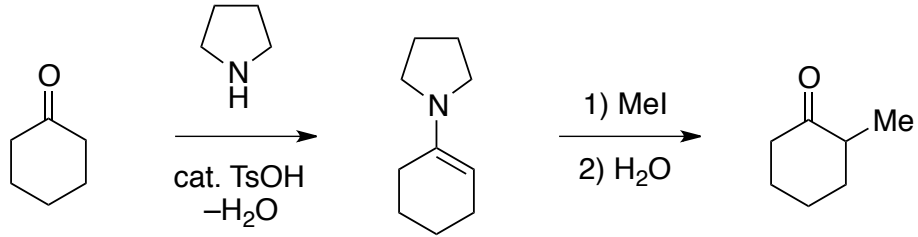
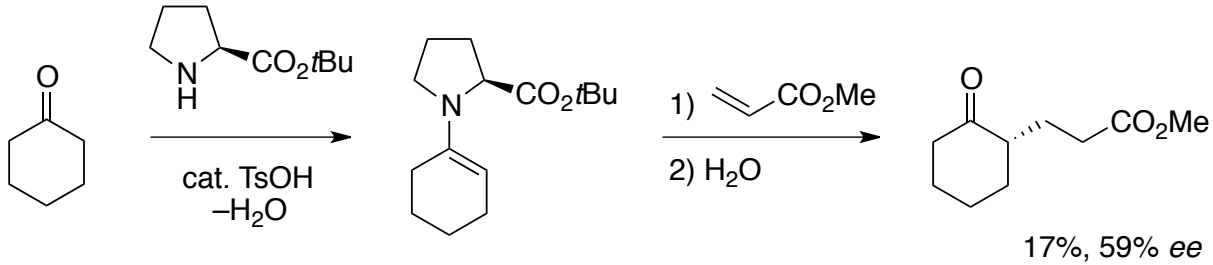
Aldolase biomimetics

Enamine-based biomimetics as the mother of Organocatalysis

based on stoichiometric enamine chemistry



Yamada, 1969: asymmetric enamine reaction (not yet catalysis)

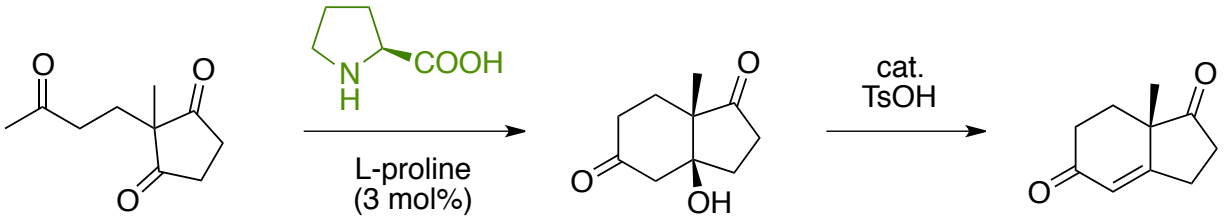


17%, 59% *ee*

Aldolase biomimetics

The Hajos-Parrish-Eder-Sauer-Wiechert reaction

- first highly enantioselective organocatalytic reaction



93% *ee*

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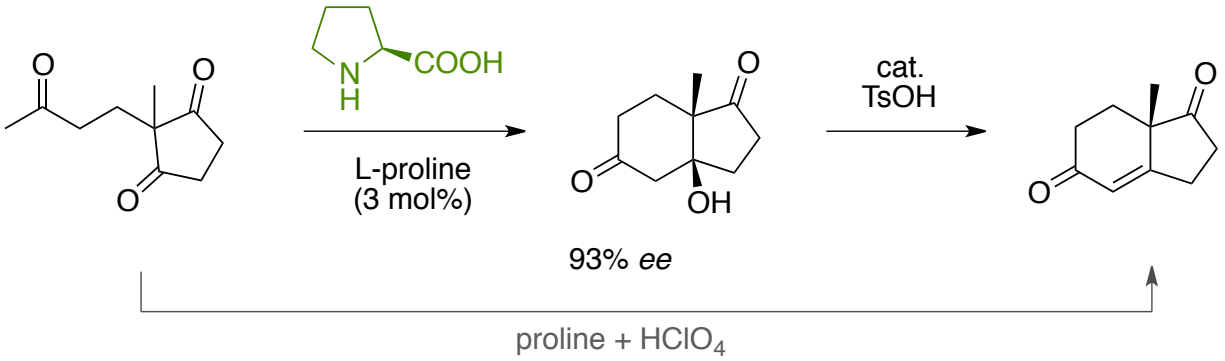

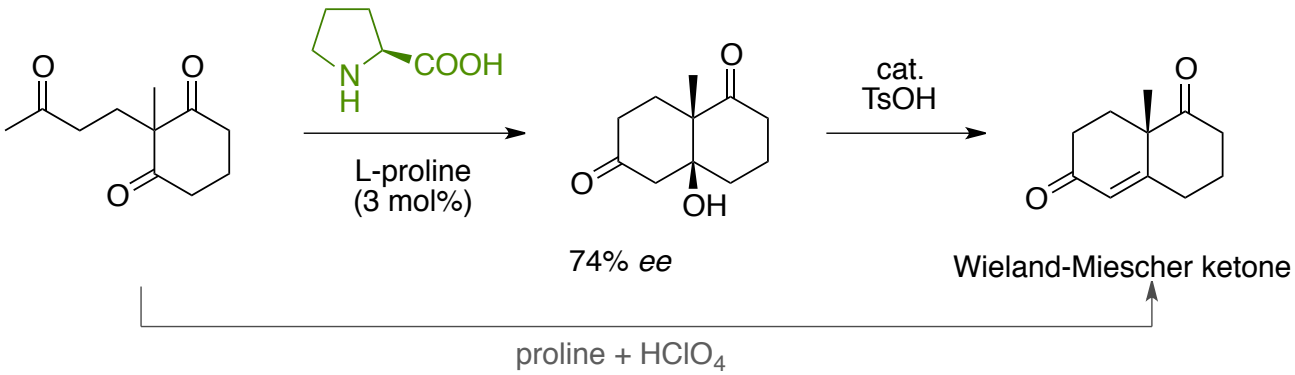

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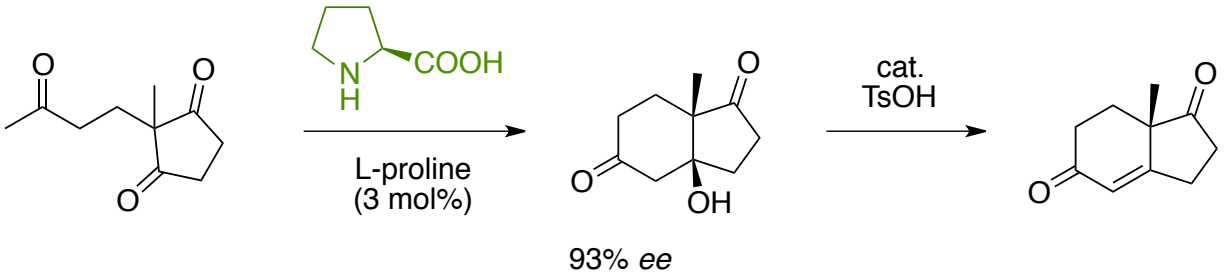
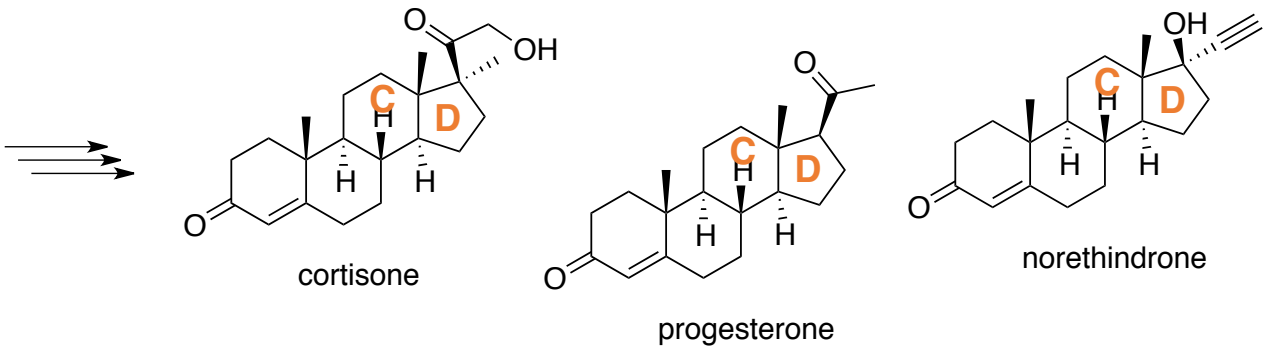
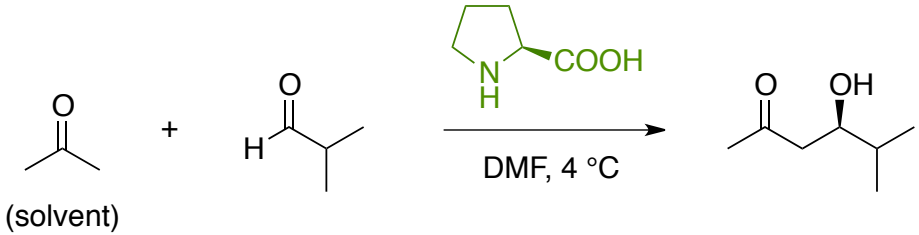




General Aldol catalysis

high enantioselectivity (List 2000)



List, Lerner, Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
Northrup, MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

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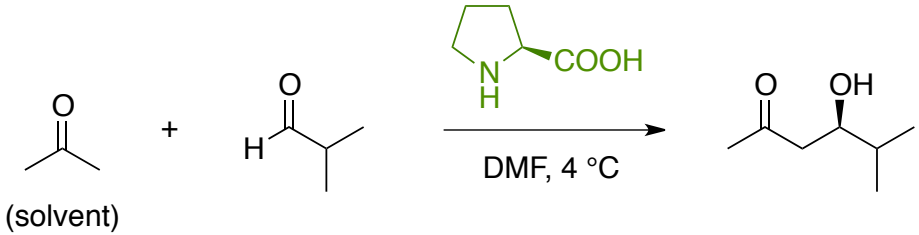
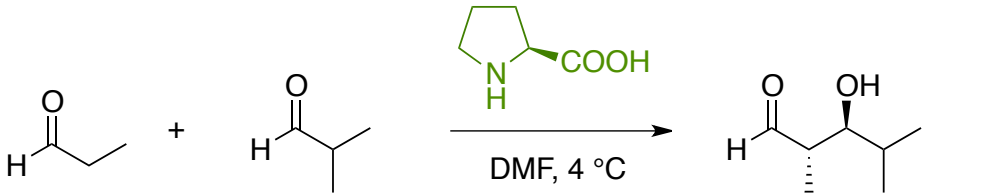


97%, 96% *ee*

with α-substituted donors: high anti-diastereoselectivity (MacMillan 2002)



82%, 99% *ee*, 96% *anti*

List, Lerner, Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

Northrup, MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

Nobel Prize 2021 in Chemistry

"for the development of asymmetric organocatalysis"

Benjamin List

Max-Planck-Institut Mülheim, Germany

David W. C. MacMillan

Princeton, USA

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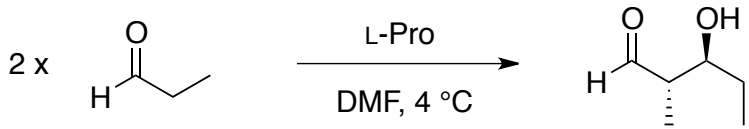
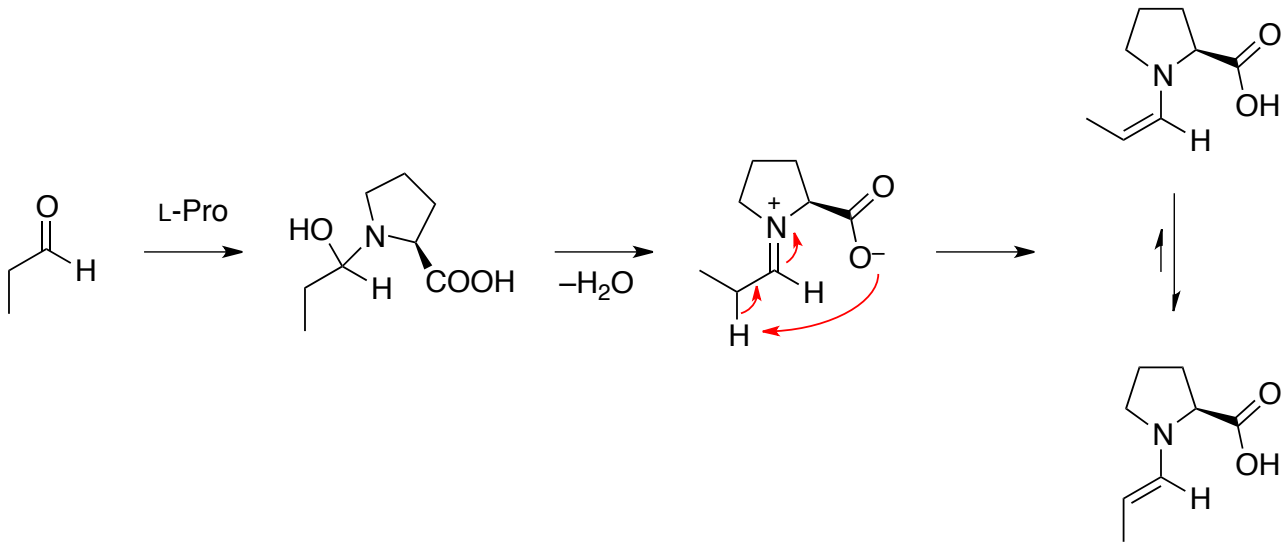
General Aldol catalysis

origin of stereoselectivity (simplified Houk-List model)





Houk, Martin, List, *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

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General Aldol catalysis

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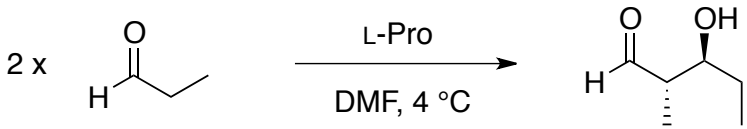

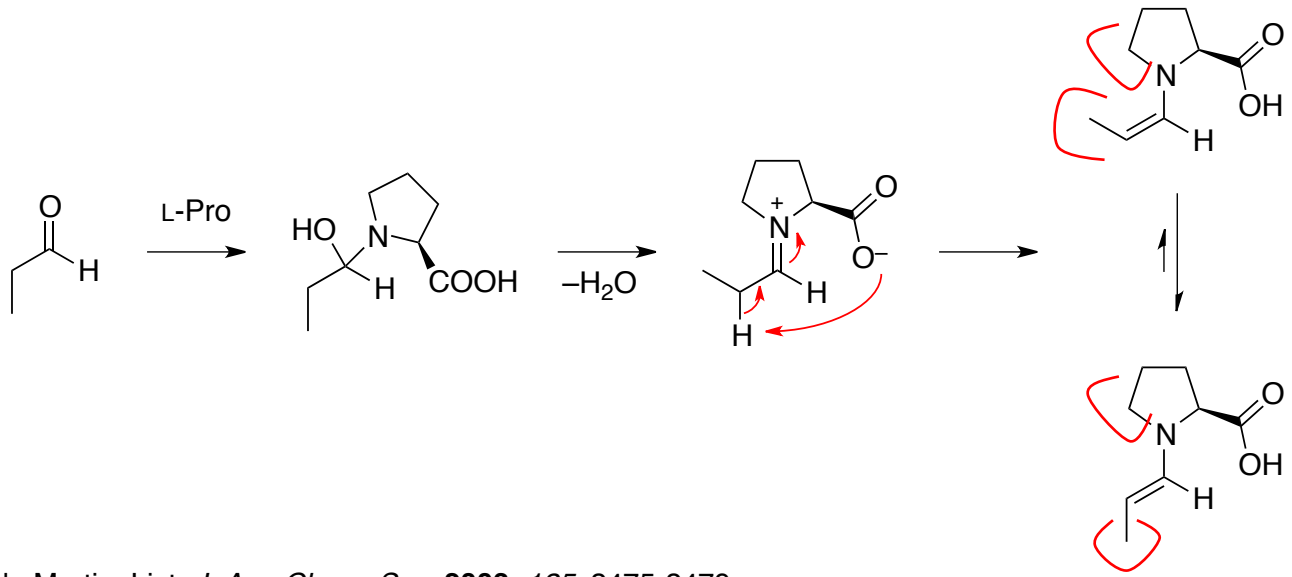

donor activation favours anti-E-enamine

Houk, Martin, List, *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

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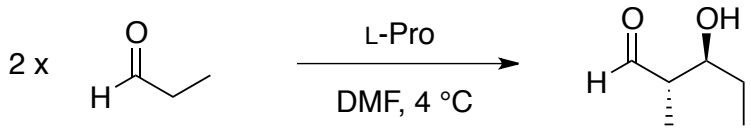
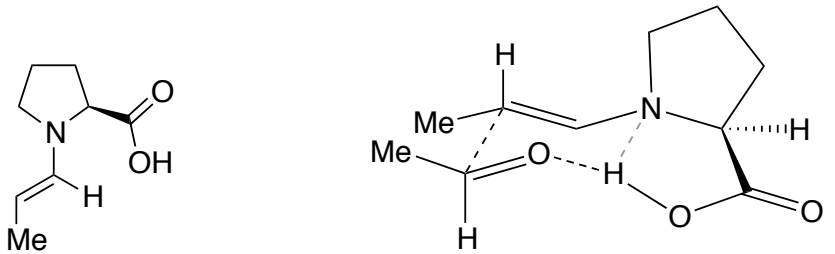
General Aldol catalysis

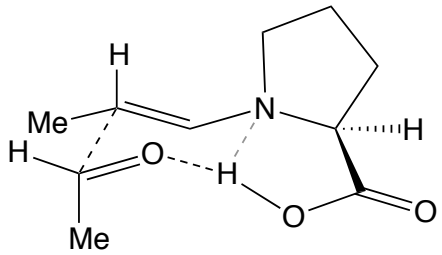
origin of stereoselectivity (simplified Houk-List model)





Zimmerman-Traxler-like
transition state
favours eq-eq-arrangement

vs



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General Aldol catalysis

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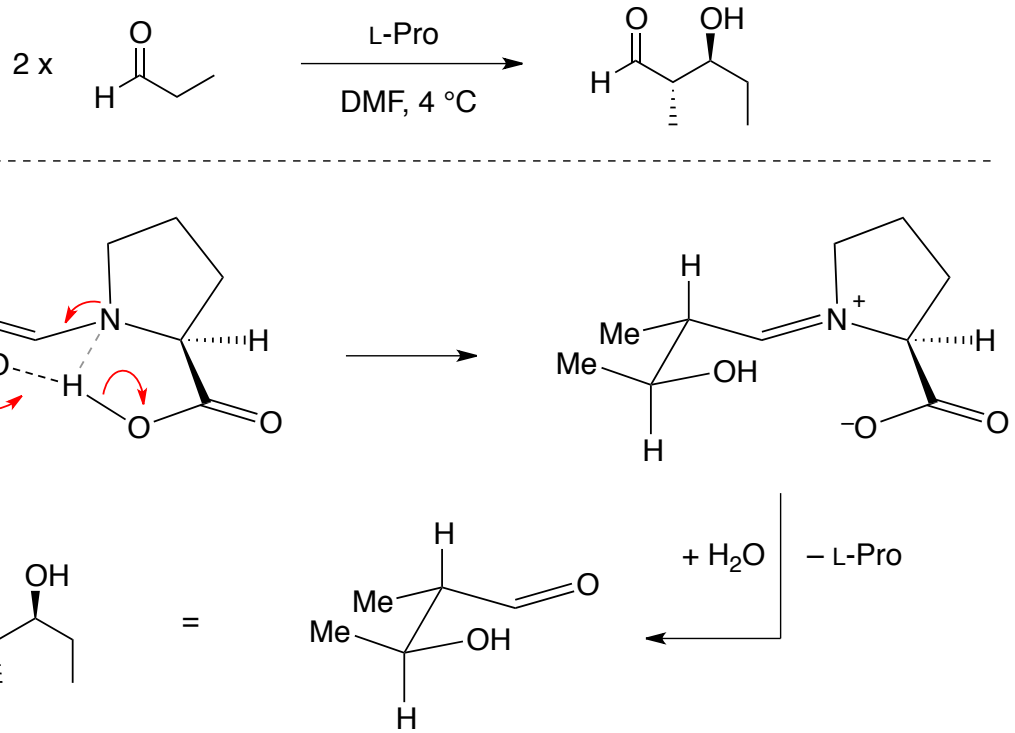

Houk, Martin, List, *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

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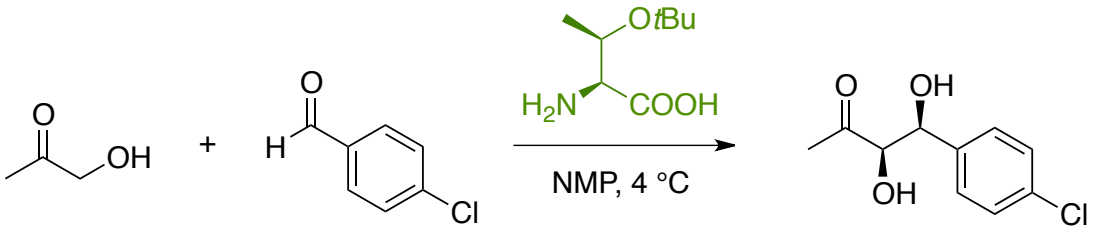
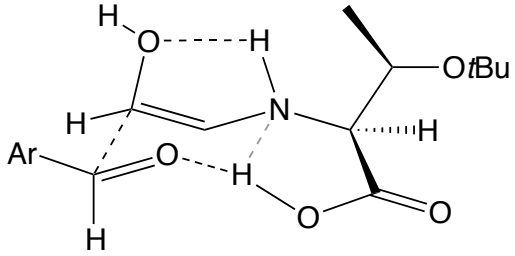
Aldolase biomimetics

syn-selective aldol reactions

by stabilization of anti-Z-enamine



81%, 92% *ee*, 88% *syn*



Ramasatry, Zhang, Tanaka, Barbas *J. Am. Chem. Soc.* **2007**, *129*, 288-289.

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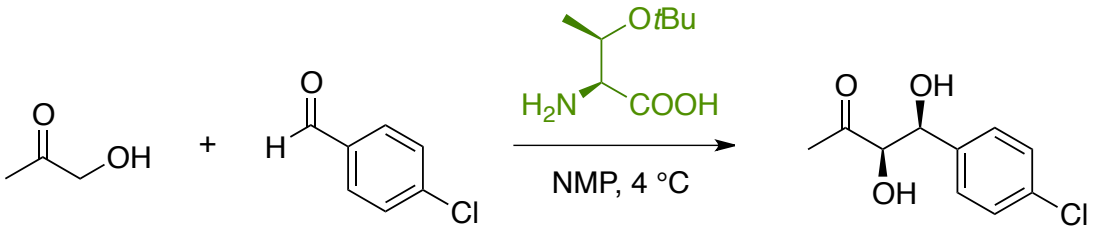
Aldolase biomimetics

syn-selective aldol reactions

by stabilization of anti-Z-enamine



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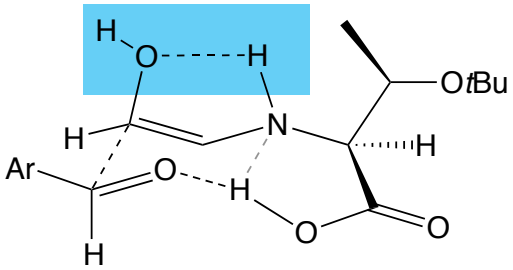

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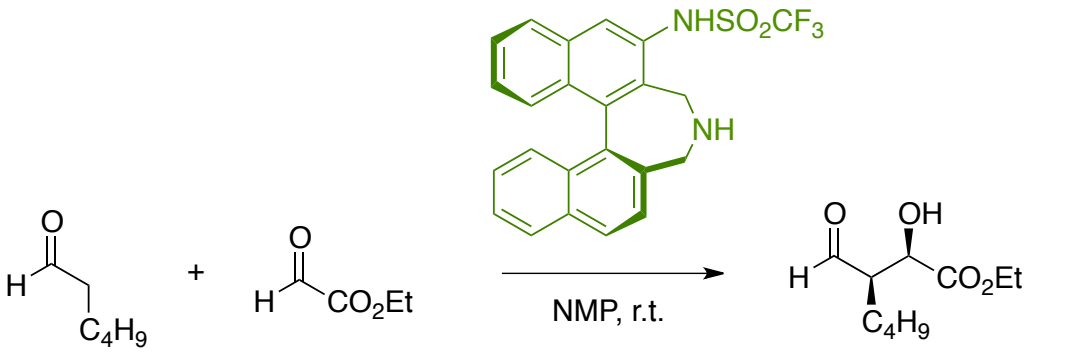
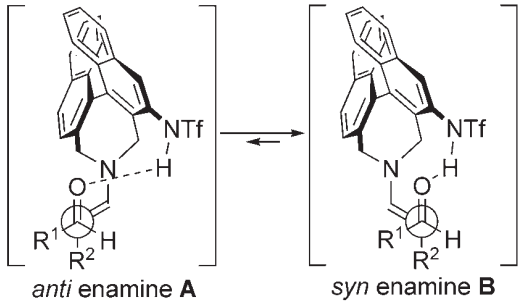
Aldolase biomimetics

syn-selective aldol reactions

by destabilization of Zimmerman-Traxler arrangement



99%, 95% *ee*, 72% *syn*



anti enamine **A** *syn* enamine **B**

Kano, Yamaguchi, Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 1738-1740.

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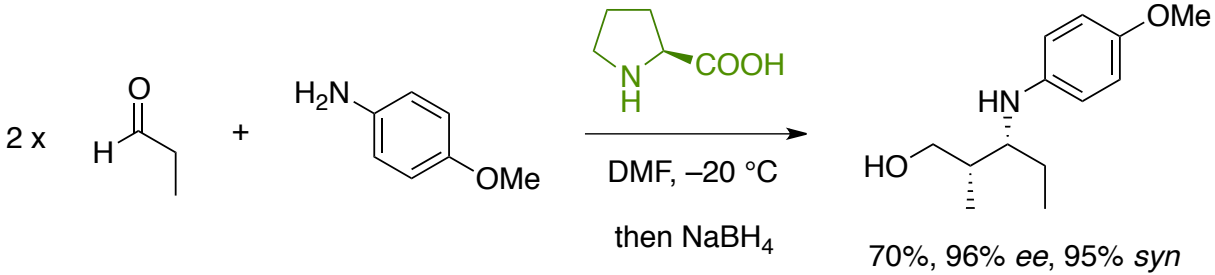
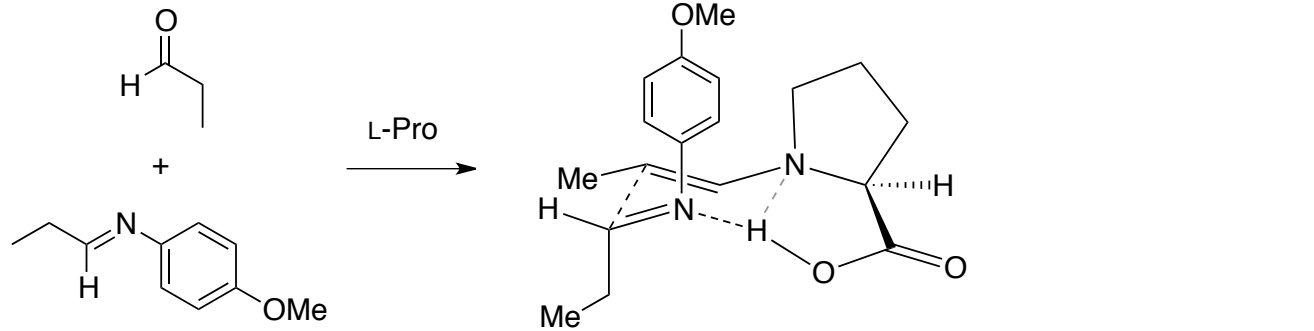
Aldolase biomimetics

replacement of acceptor = other α-functionalizations of aldehydes and ketones

Imine acceptors = Mannich reaction



70%, 96% *ee*, 95% *syn*



formed in situ by condensation

imine forced into ax-ax orientation

Hayashi, Tsuboi, Ashimine, Urushima, Shoji, Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677-3680.

Aldolase biomimetics

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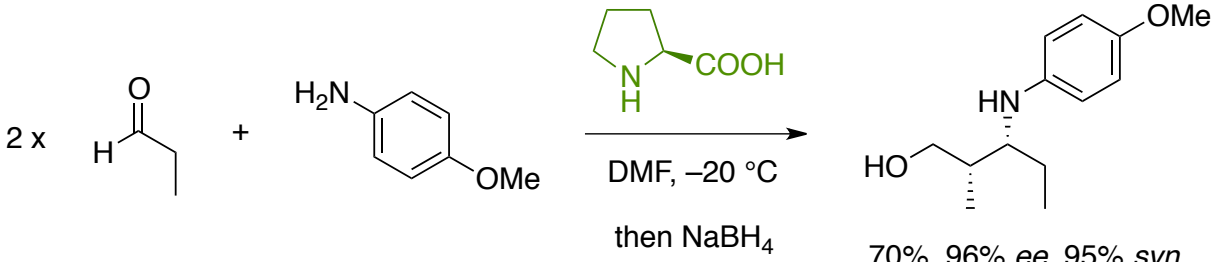
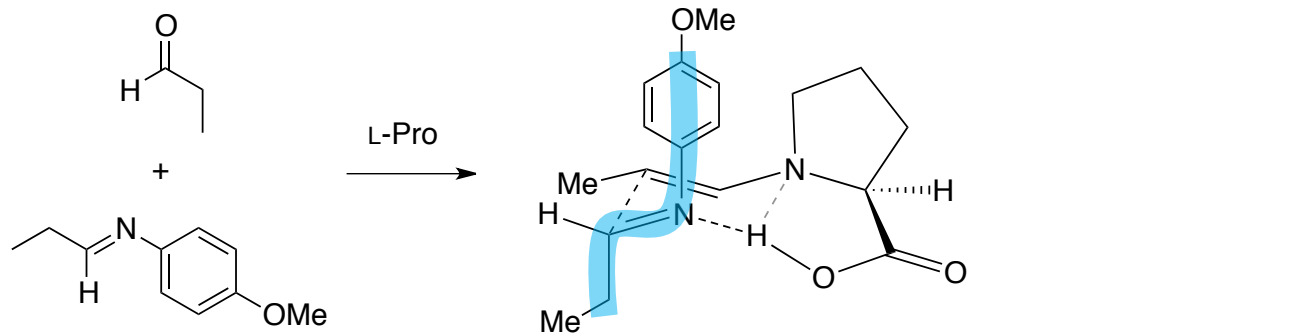


70%, 96% *ee*, 95% *syn*



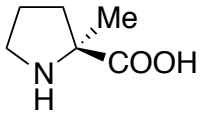
formed in situ by condensation

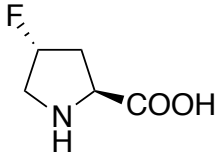
imine forced into ax-ax orientation

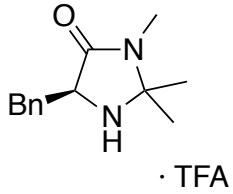
Hayashi, Tsuboi, Ashimine, Urushima, Shoji, Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677-3680.

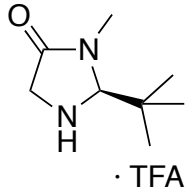
Modern enamine catalysis

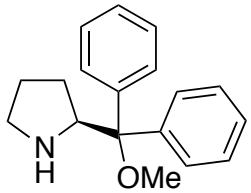
proline as template for the development of next generation organocatalysts

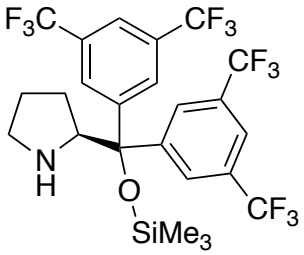


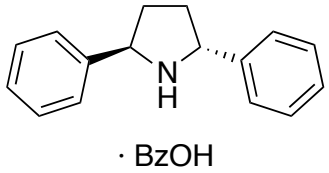


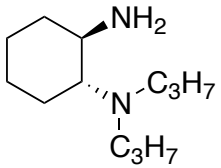


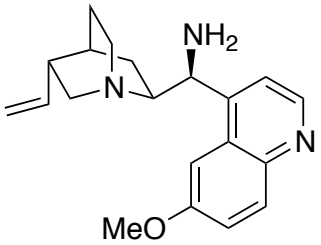












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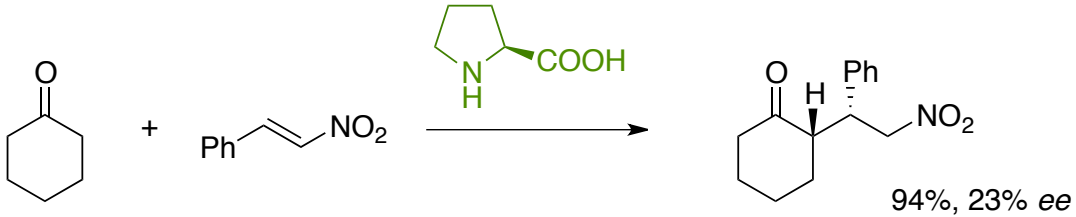
Modern enamine catalysis

alpha-functionalization of aldehydes and ketones



94%, 23% *ee*

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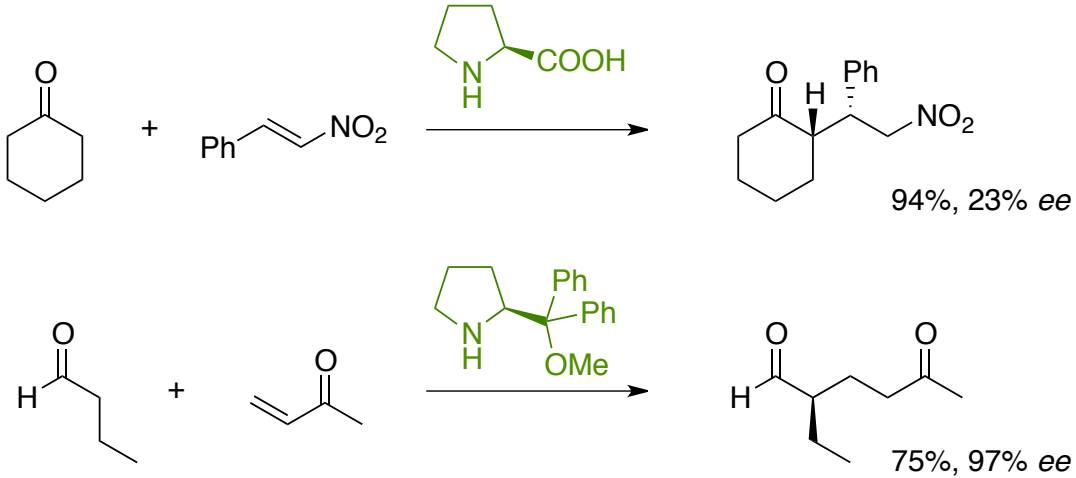

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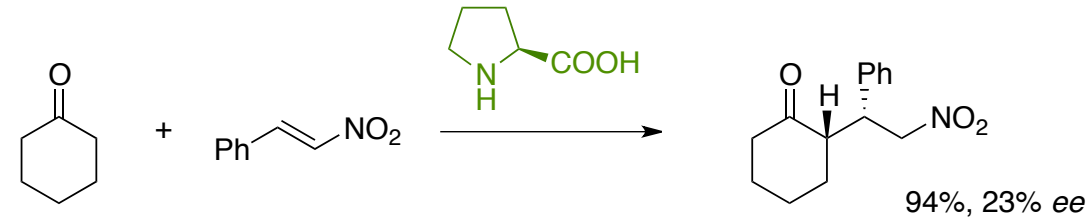

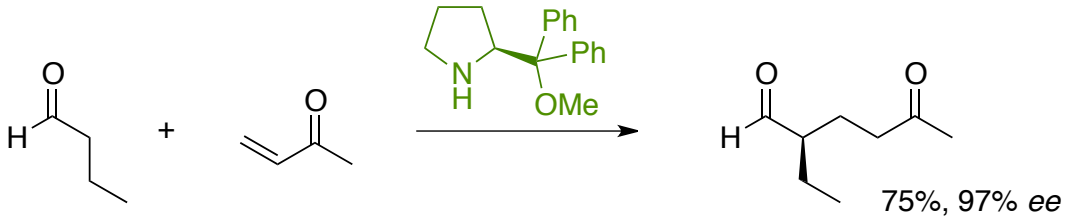

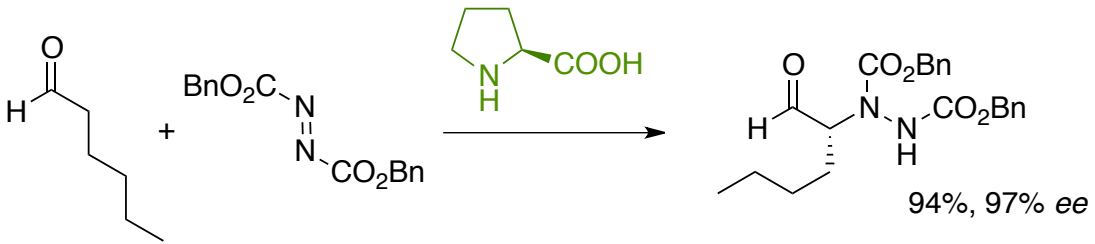

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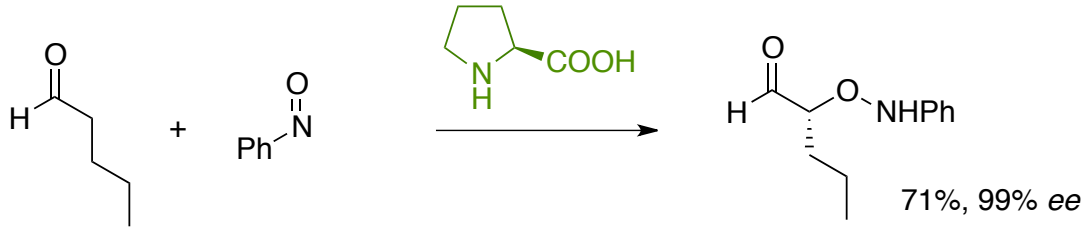
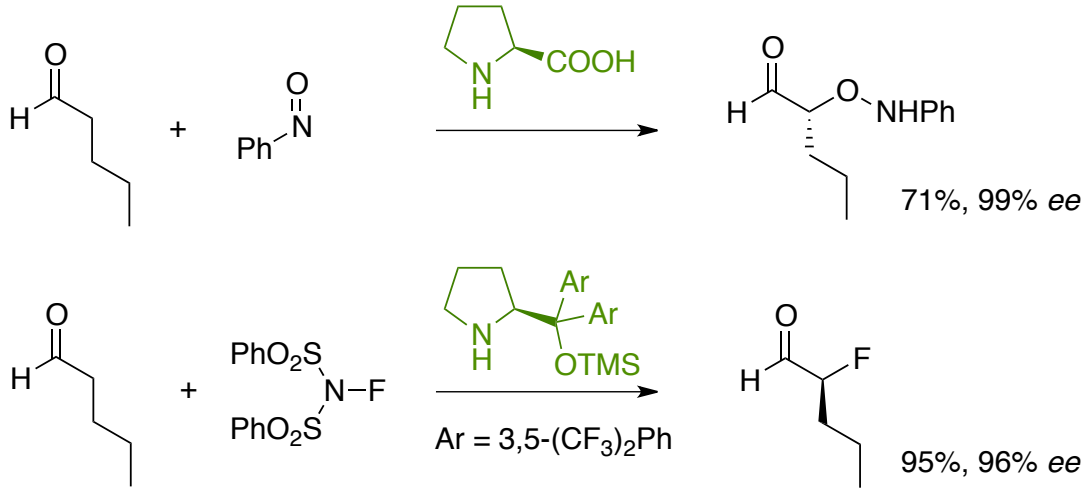


71%, 99% *ee*

Modern enamine catalysis

alpha-functionalization of aldehydes and ketones



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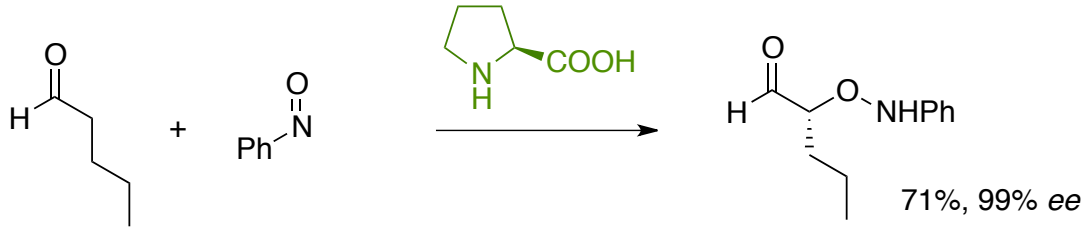
Modern enamine catalysis

alpha-functionalization of aldehydes and ketones



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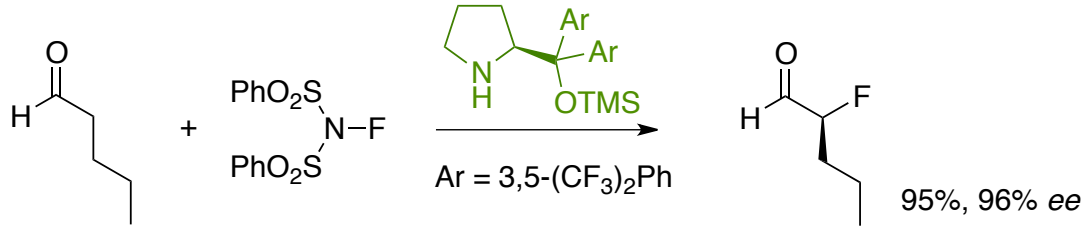

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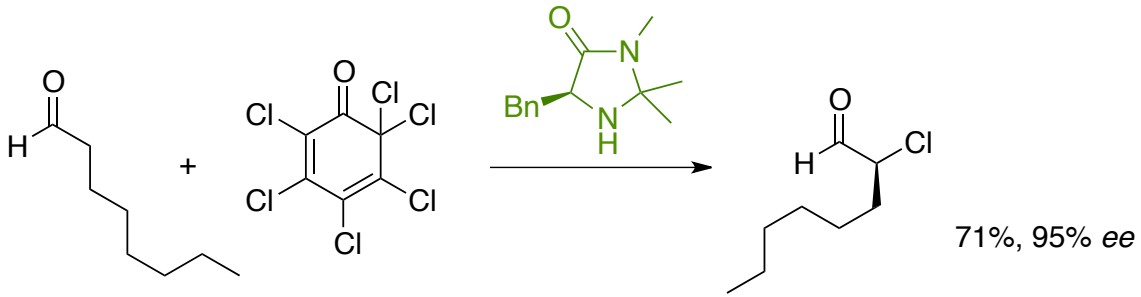

71%, 95% *ee*

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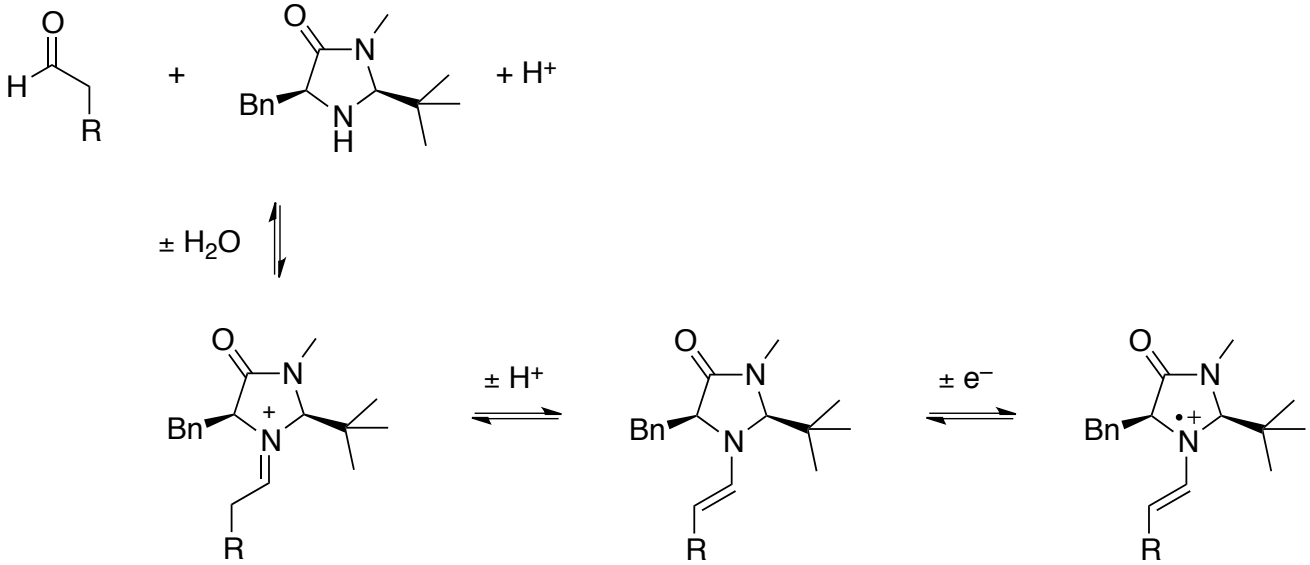
Modern enamine catalysis

enamine activation in radical chemistry



iminium cation

LUMO activation

enamine

HOMO activation

radical cation

SOMO activation

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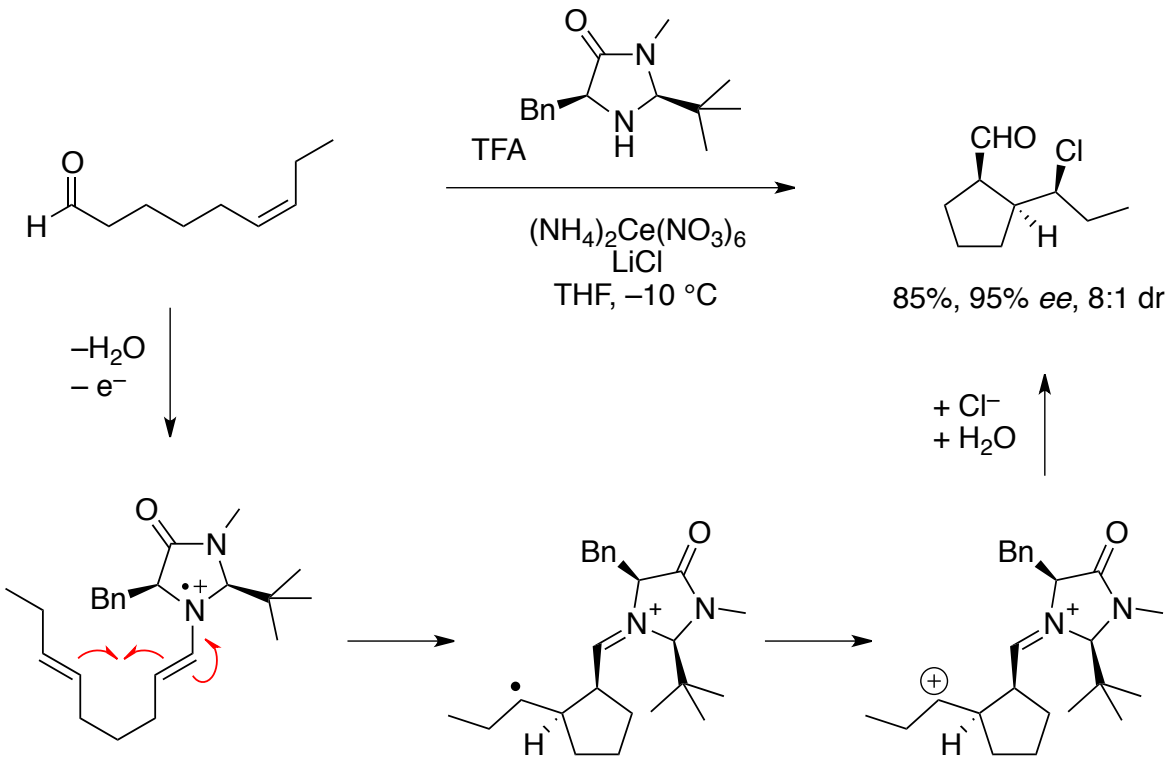
Modern enamine catalysis

enamine activation in radical chemistry



Beeson, Mastracchio, Hong, Ashton, MacMillan, *Science* **2007**, *316*, 582-584.

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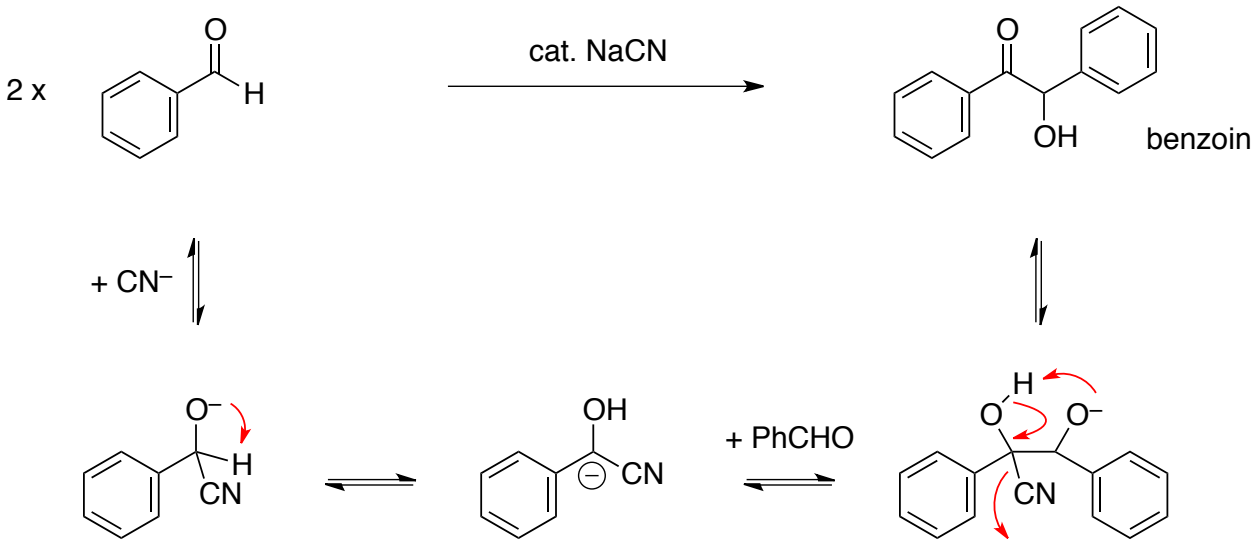
Remember the acyloin reaction?

Acyloin reaction

- PDCs also catalyze C-C-coupling between α-ketoacids and aldehydes
- biochemical equivalent to the Benzoin reaction



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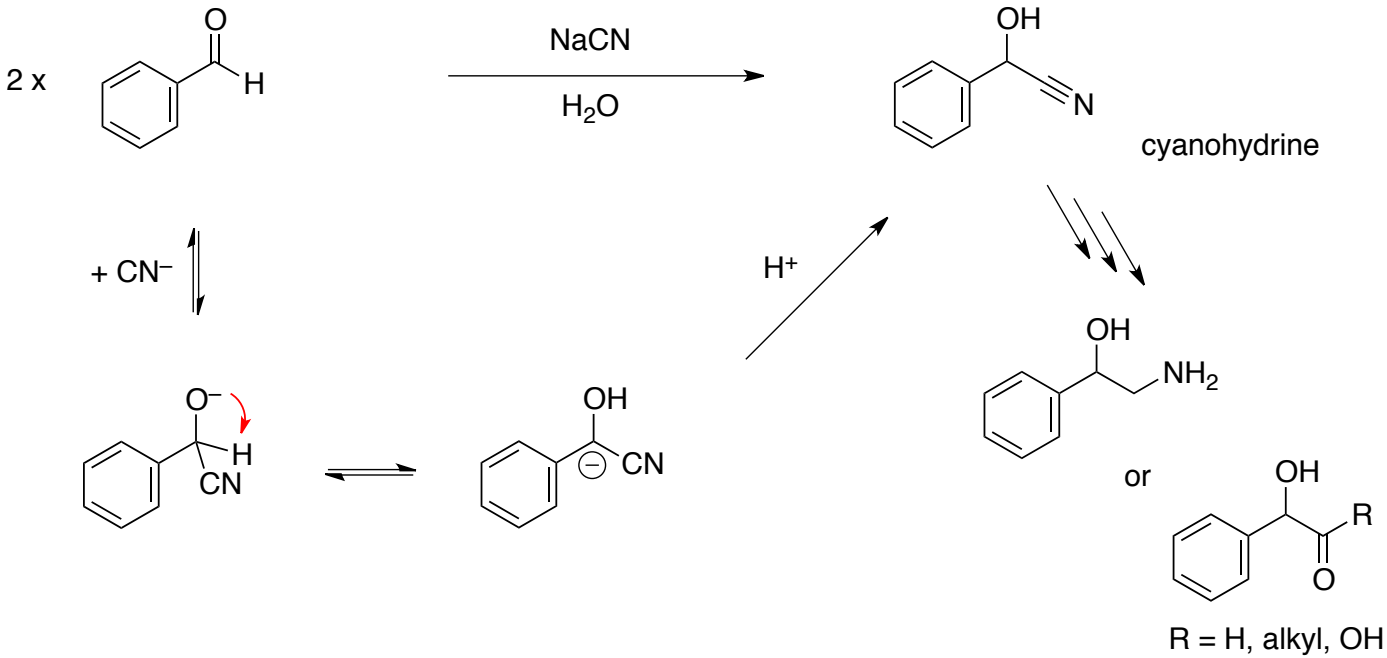
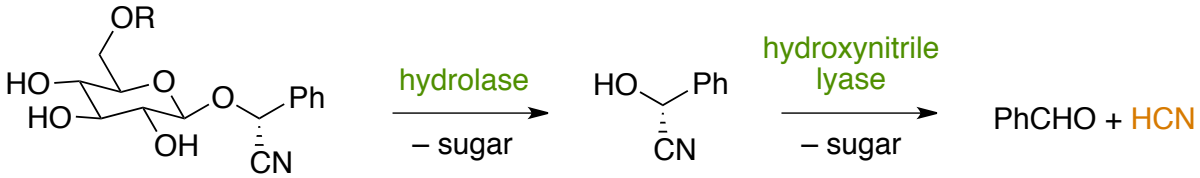


- formal addition of HCN yields cyanohydrines
- analogous to Stetter amino acid synthesis

Cyanohydrine-converting enzymes

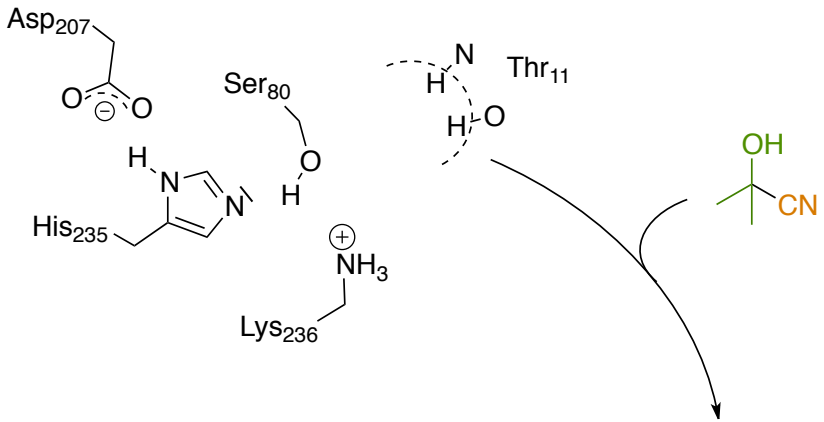
- hydroxynitrile lyases (EC 4.2.1.x) mainly found in higher plants
- main role: defence mechanisms based on cyanogenesis
- 2 major classes that differ in their dependence on FAD
  - ✓ FAD not acting as redox mediator in these enzymes



R = H: prunasin
β-D-Glc: amygdalin

- cheap sources for HNLs: almonds, cherry, manioc, rubber tree

Serine–Histidine–Aspartate: Catalytic triade



mechanism in e.g.
manioc and *Hevea* sp.

Sharma, Nand Sharma, Bhalla, *Enzyme Microb. Technol.* **2005**, *37*, 279-294.

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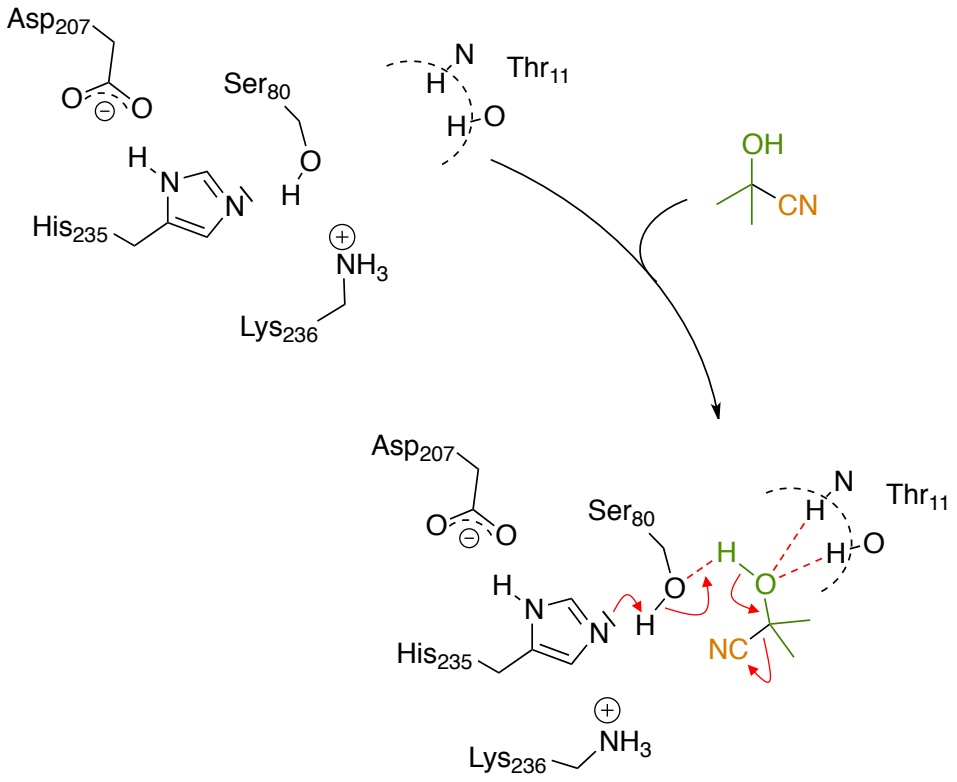
Serine–Histidine–Aspartate: Catalytic triade



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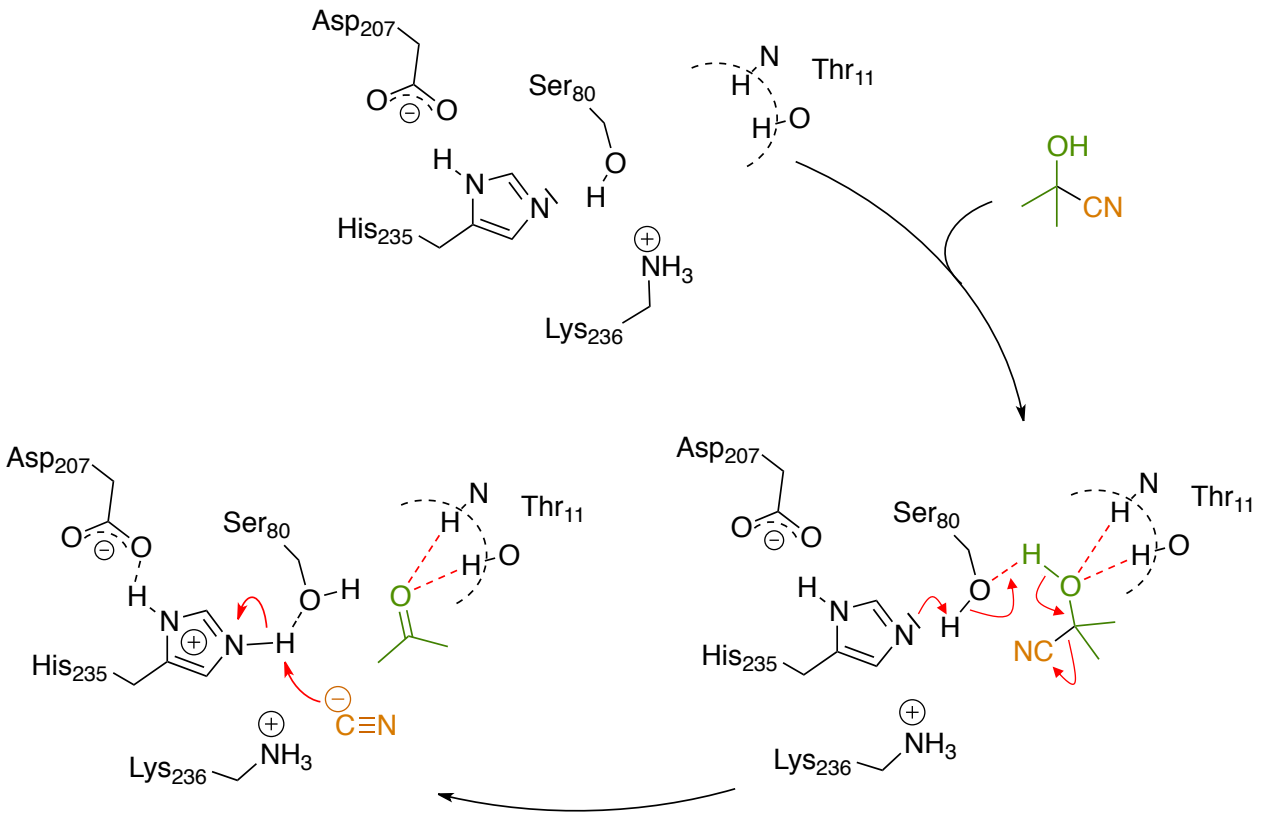

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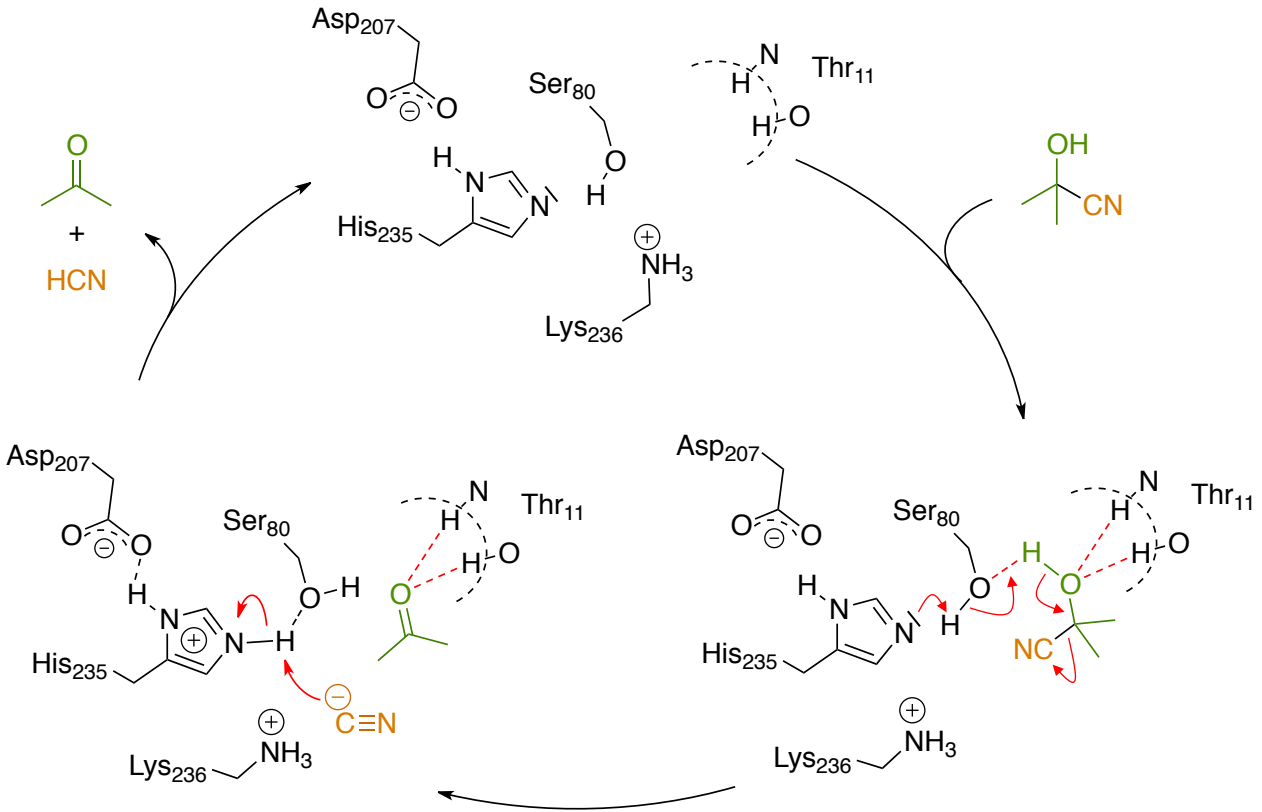

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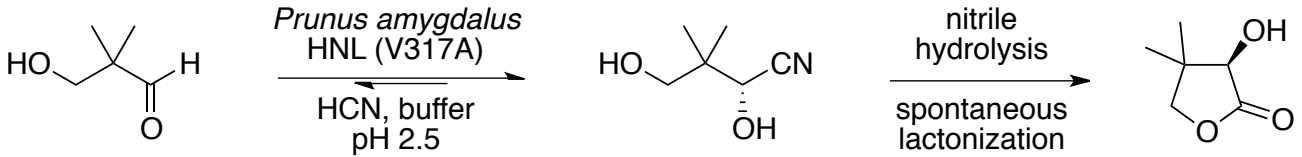
Synthetic applications: addition of HCN to aldehydes



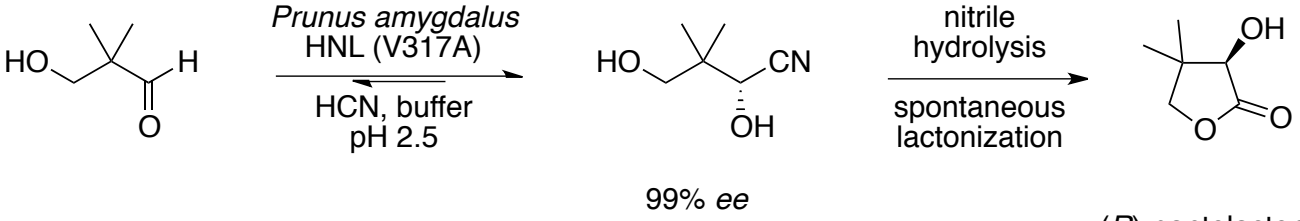
99% *ee*

(*R*)-pantolactone

calcium pantothenate: important animal feed additive

Bracco, Busch, von Langermann, Hanefeld, *Org. Biomol. Chem.* **2016**, *14*, 6375-6389.

Synthetic applications: addition of HCN to aldehydes



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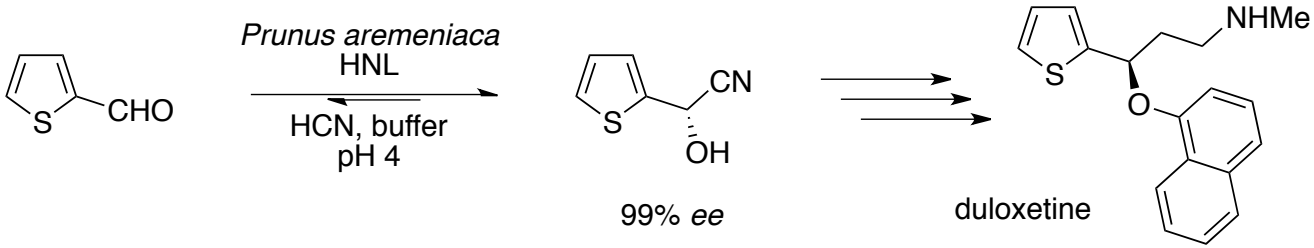


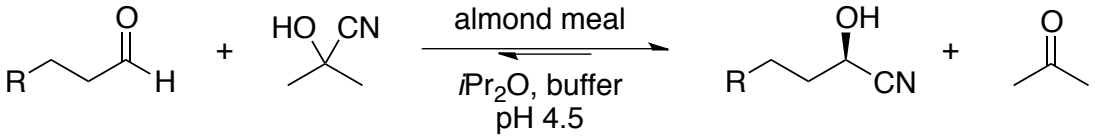
sold as *Cymbalta*

selective serotonine reuptake inhibitor (antidepressant)

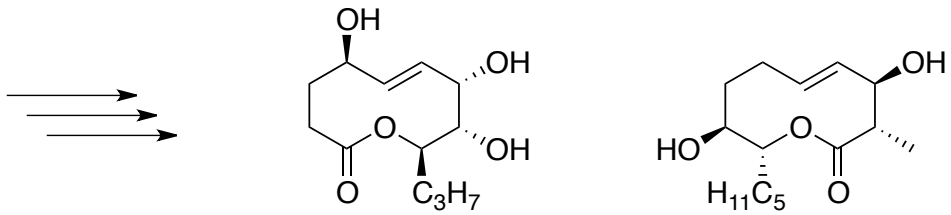
Bracco, Busch, von Langermann, Hanefeld, *Org. Biomol. Chem.* **2016**, *14*, 6375-6389.

Synthetic applications: HCN-free hydrocyanations?

acetone cyanohydrine as masked HCN



also here: reversibility is the key



stagonolide B

cytospolide E

Bracco, Busch, von Langermann, Hanefeld, *Org. Biomol. Chem.* **2016**, *14*, 6375-6389.

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