CHEM-E4109
MODERN METHODS IN BIOCATALYSIS

chapter #5: decarboxylations & C-C-couplings

15.3.2022

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Chemistry

HOUSEKEEPING NOTES

Change in Sessions Next Week

- no live session on Tuesday, 22.3.
- instead: video podcast on Directed Evolution & Protein Engineering, feat. Silvan Scheller BIO^2

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Seminar Topics

- list of publications available in the evening
- instructions on the seminar presentations added to MyCourses tomorrow
- also on Wednesday, registrations opens for those that are available on only one day
- on Thursday, everyone else registers

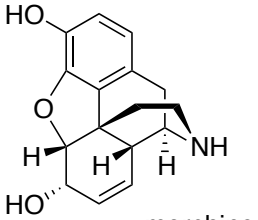
- during week 14, individual online discussion meetings available

TODAY'S MENU

C-C coupling reactions

- most important transformation in organic synthesis
- lyases offer interesting applications
- two mechanistic lyase pathways are discussed
- in-depth view on carbene catalysis

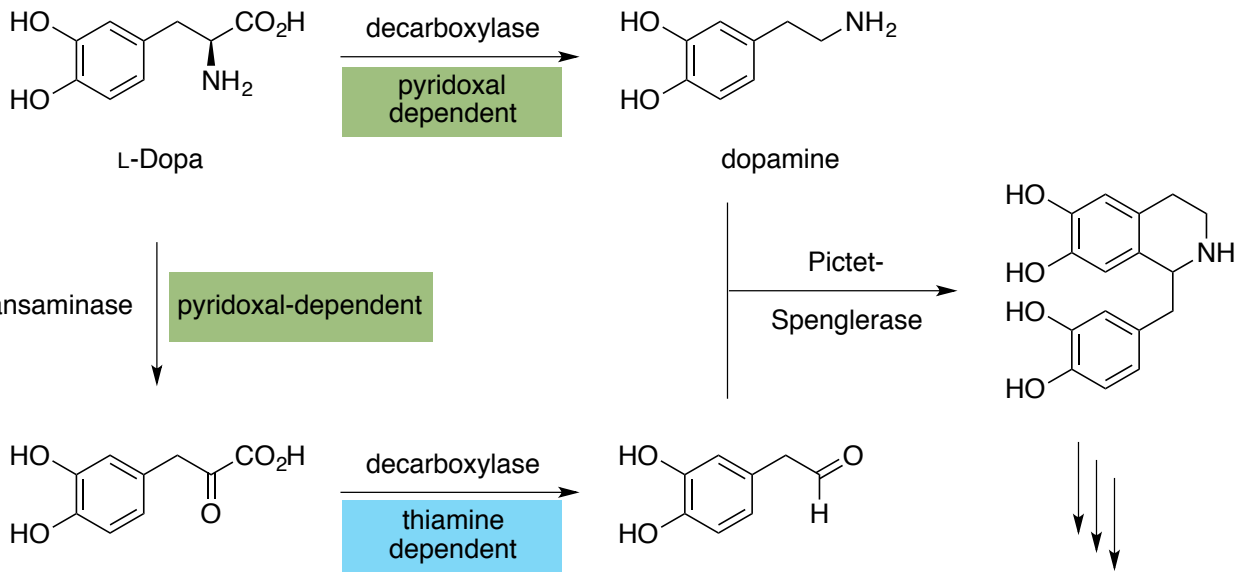
Amino acid metabolism



morphine

e.g. metabolic fate of Dopa

- L-Dopa used in Parkinson treatment
- source of dopamine (and other neurotransmitters)



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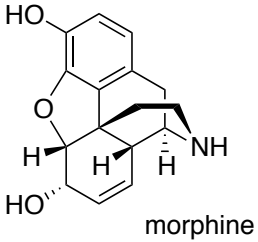

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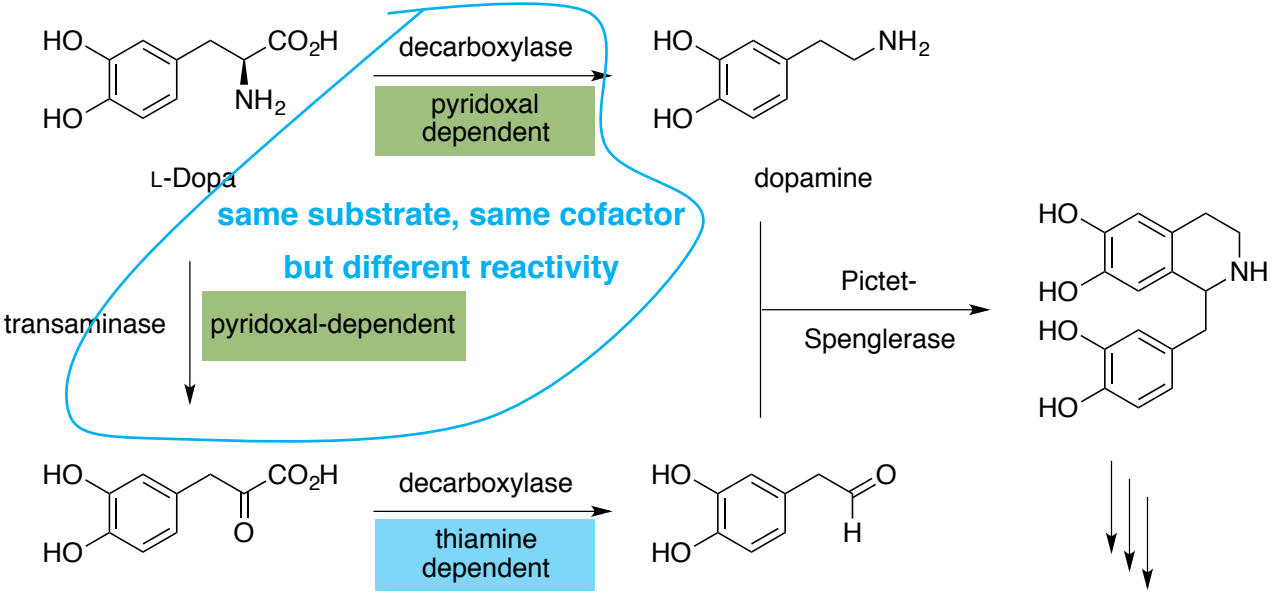

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E.C. 4 - LYASES

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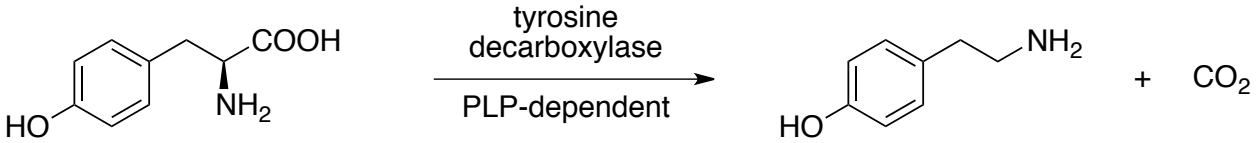
Lyases - features

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

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

amino acid decarboxylase



only bond cleavage

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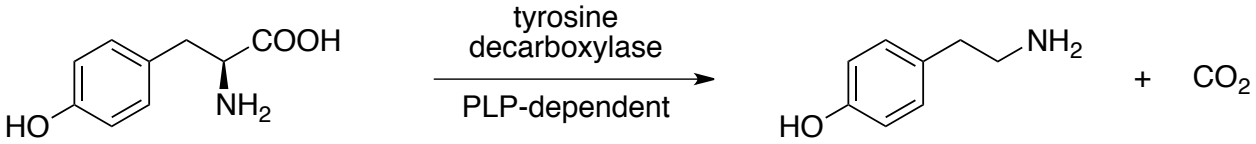
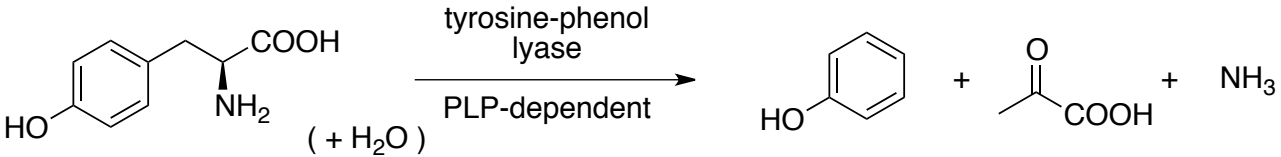


only bond cleavage

tyrosine-phenol lyase



both directions possible

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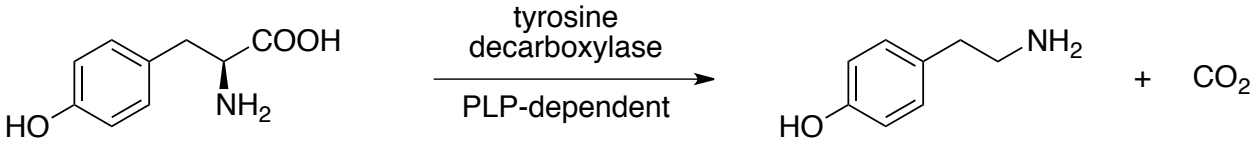

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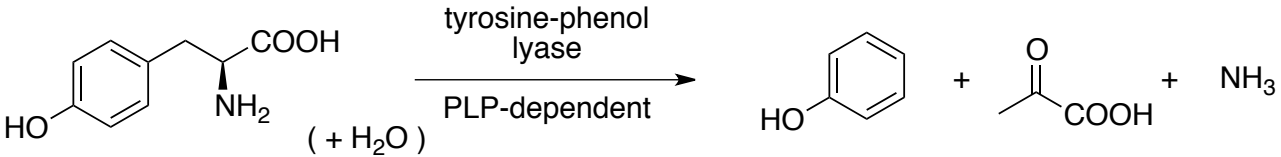
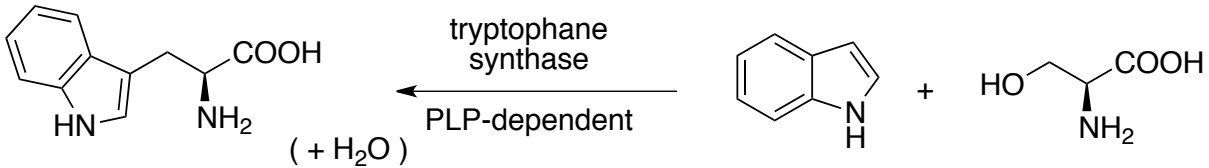


both directions possible

tryptophane synthase



mainly bond formation

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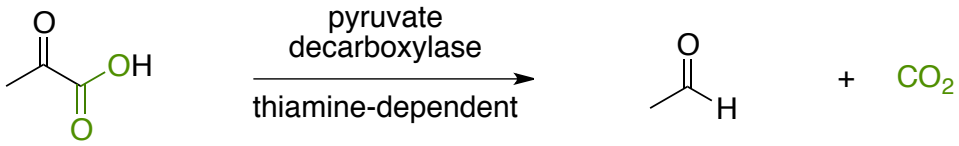
pyruvate decarboxylase



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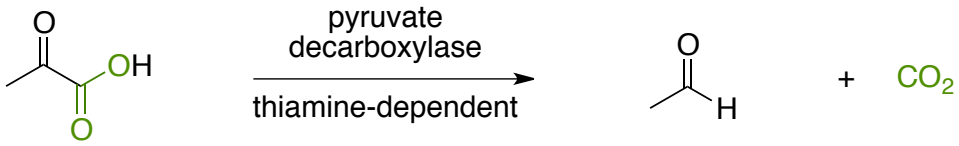
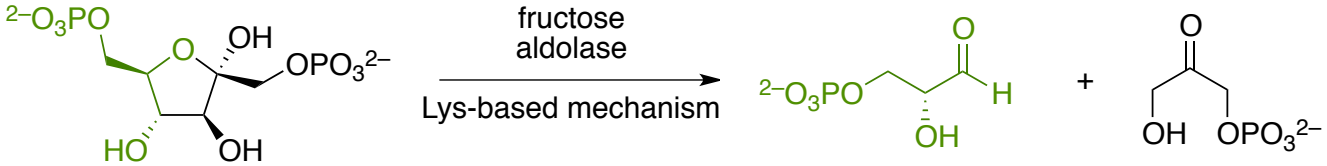


aldolase



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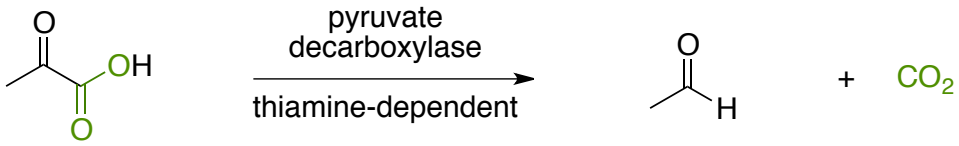

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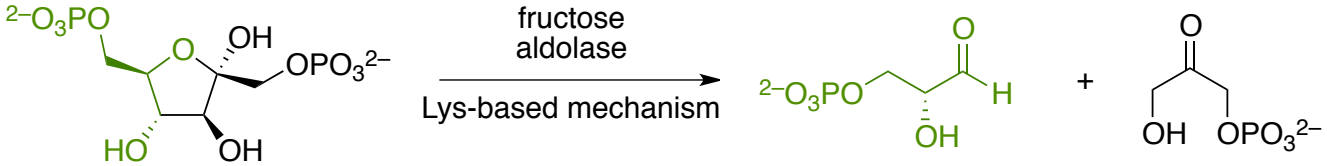
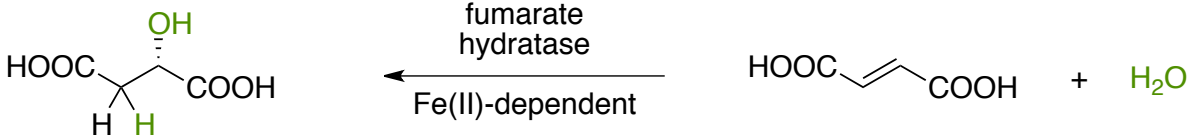


fumarate hydratase



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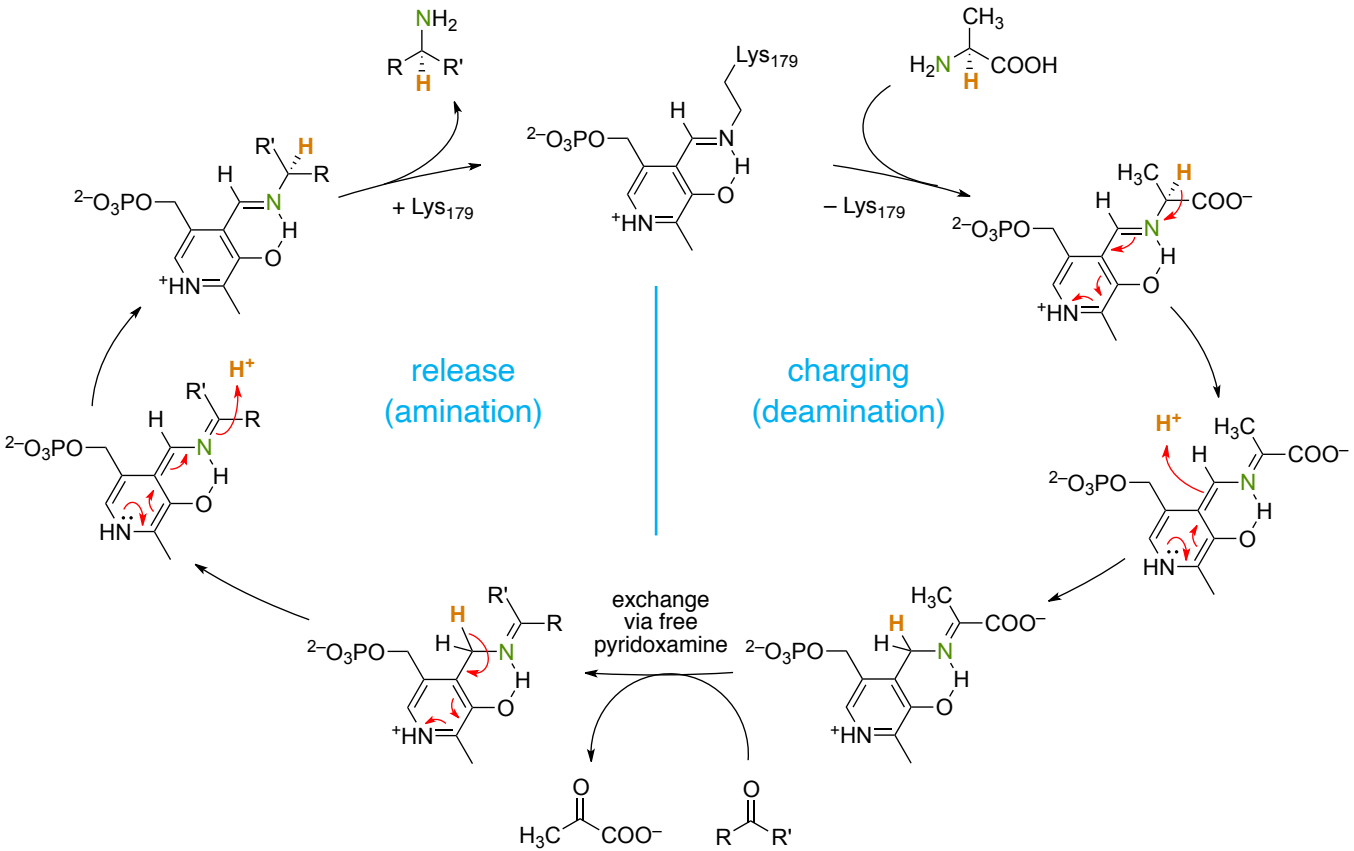
Recap: omega-transaminases

mechanism: combination of deamination & amination closes catalytic cycle



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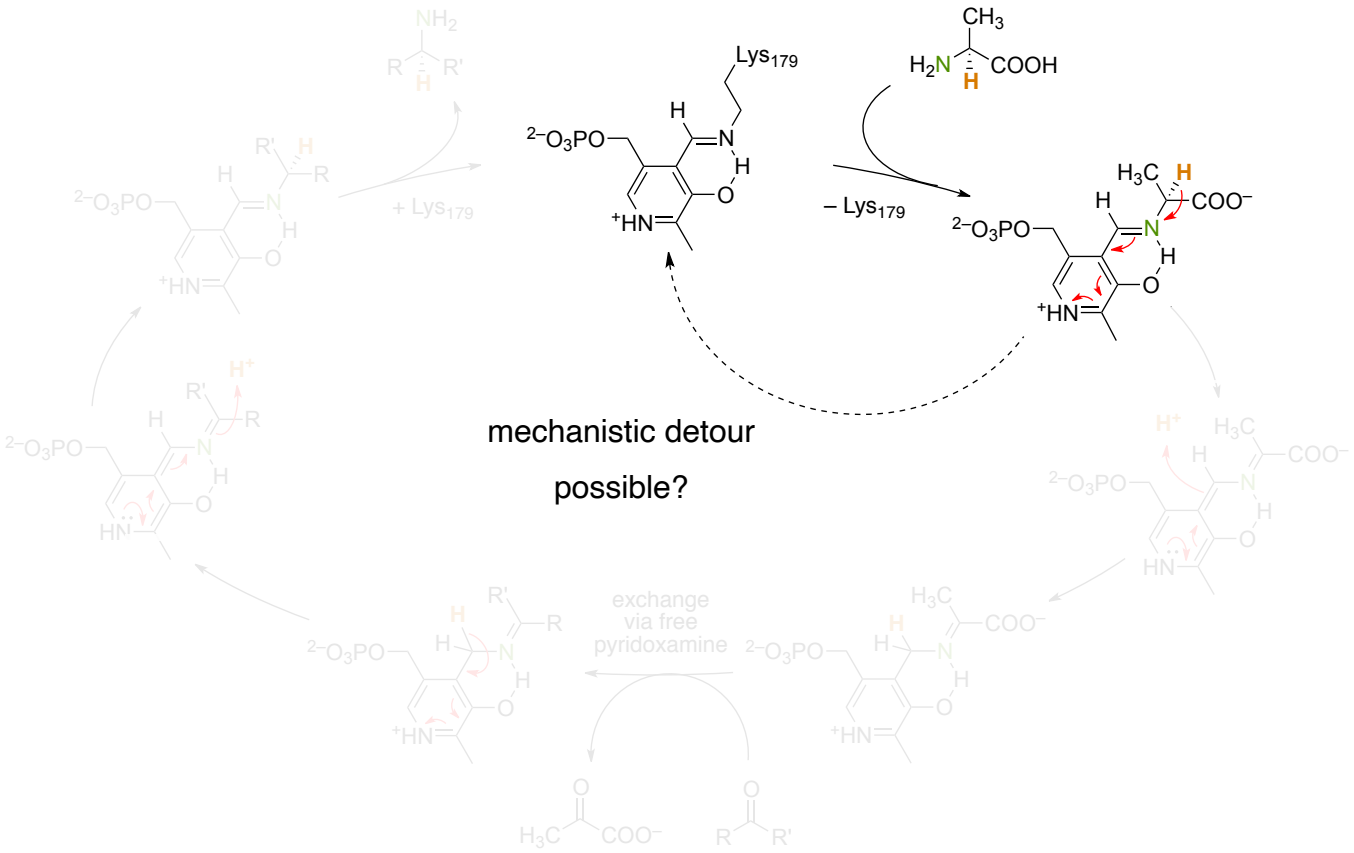

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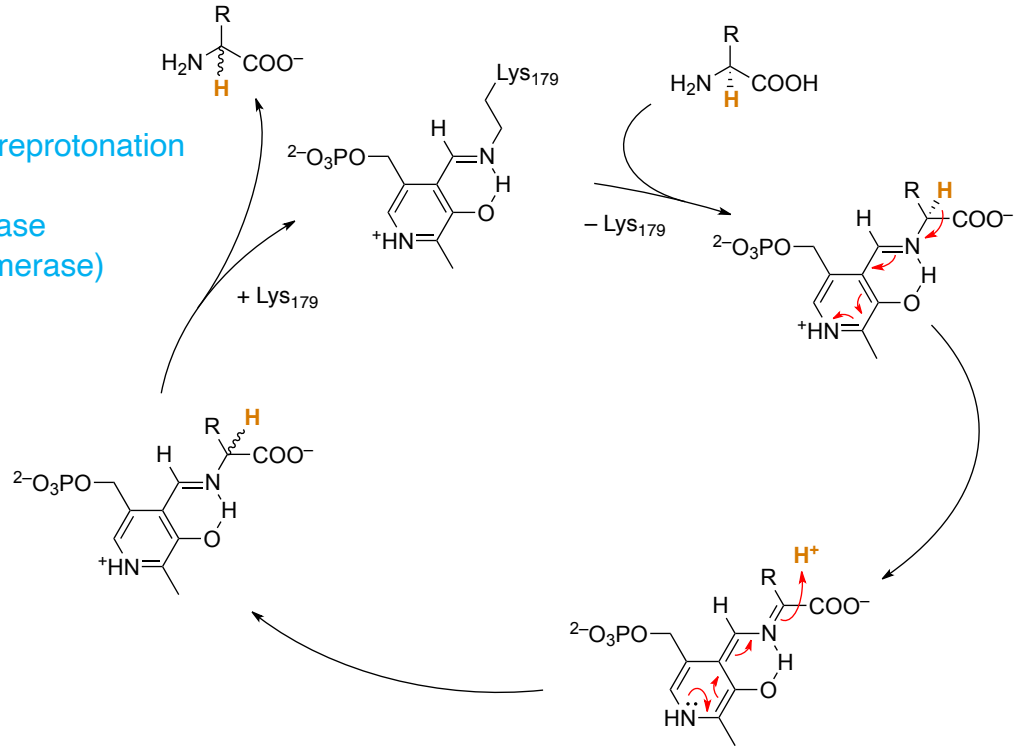
Alternative PLP-dependent pathways

deprotonation – reprotonation
=
racemase
(EC 5, isomerase)



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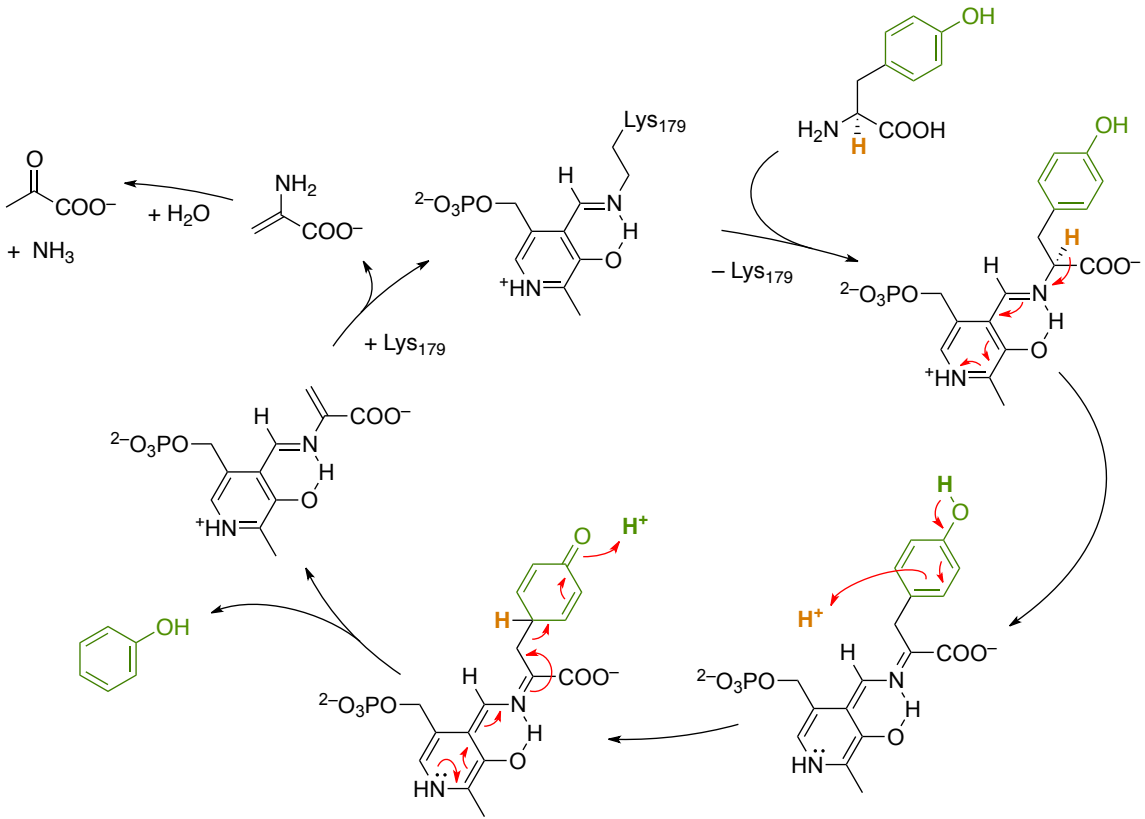

loss of aromatic side chain function
=
tyrosine-phenol lyase

if aromatic group = indol: tryptophane-indol lyase

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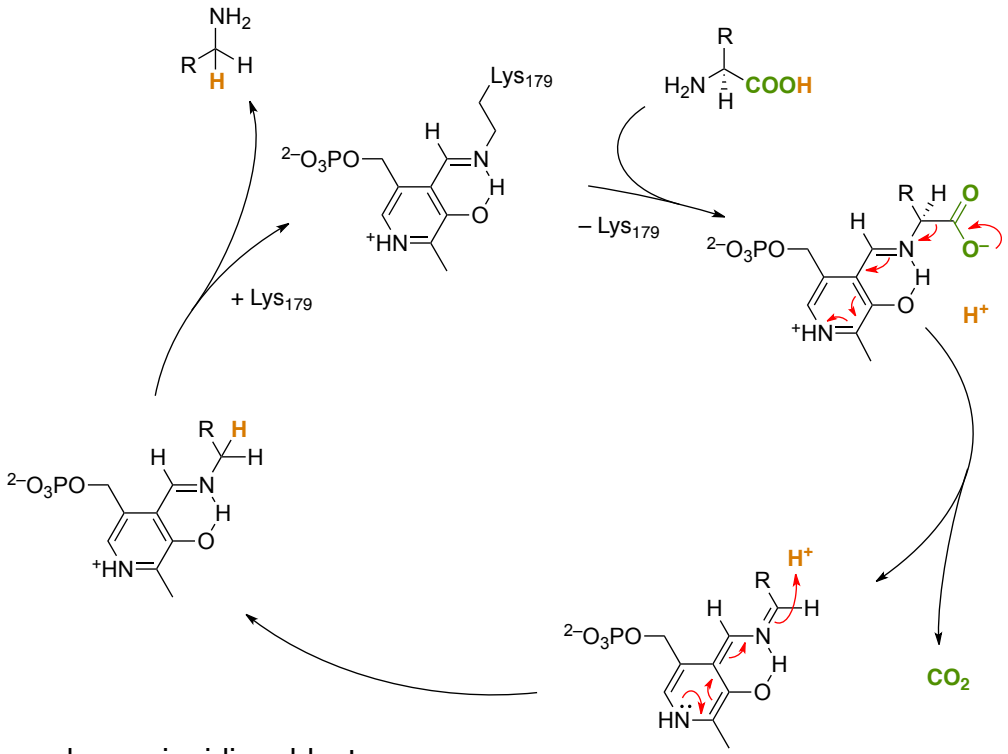
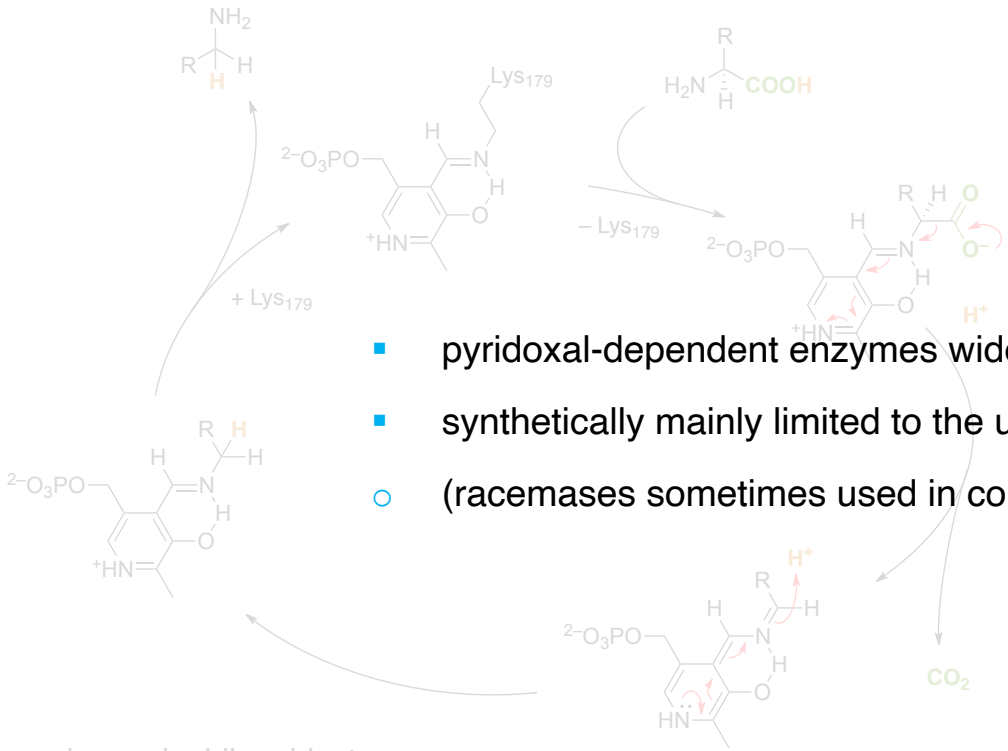
Amino acid decarboxylases



- CO_2 release renders quinoidic adduct
- reprotonation yields unbranched amine

Amino acid decarboxylases



- pyridoxal-dependent enzymes widespread in metabolic pathways
- synthetically mainly limited to the use of transaminases
  - (racemases sometimes used in combination with other enzymes)

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- reprotonation yields unbranched amine

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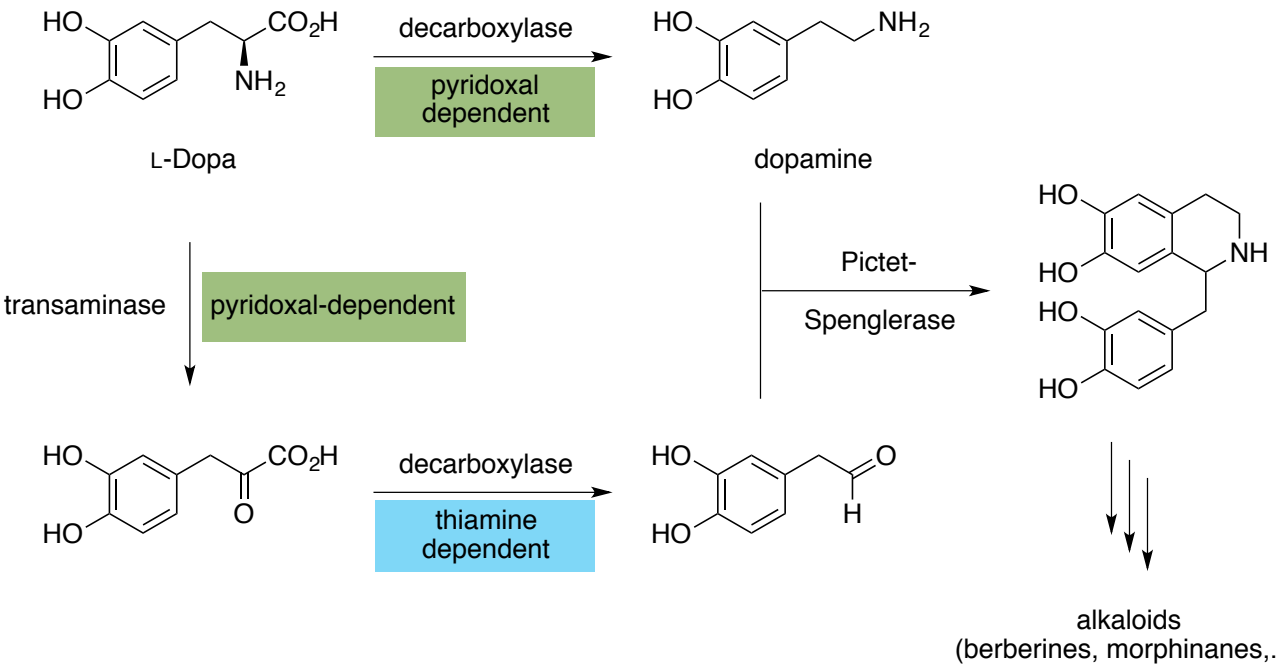

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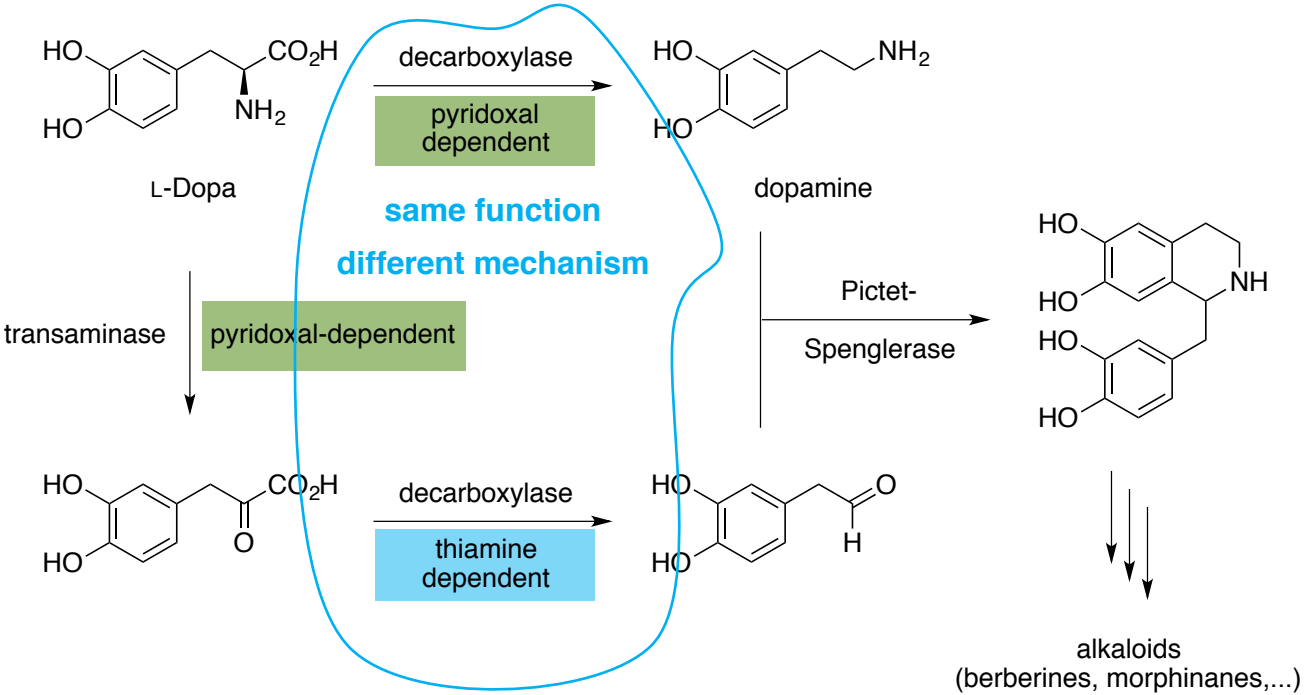

Ketocarboxylate decarboxylase

Pyruvate decarboxylase (*Saccharomyces cerevisiae*)

- homo tetramer, 556 amino acids per subunit
- Mg^{2+} and thiamine pyrophosphate (TPP) dependent
- catalyzes loss of CO_2 from pyruvate and related α-ketoacids under liberation of aldehydes
- **but**: reactive decarboxylated intermediates can also be transfered to aldehyde electrophiles under C-C-coupling

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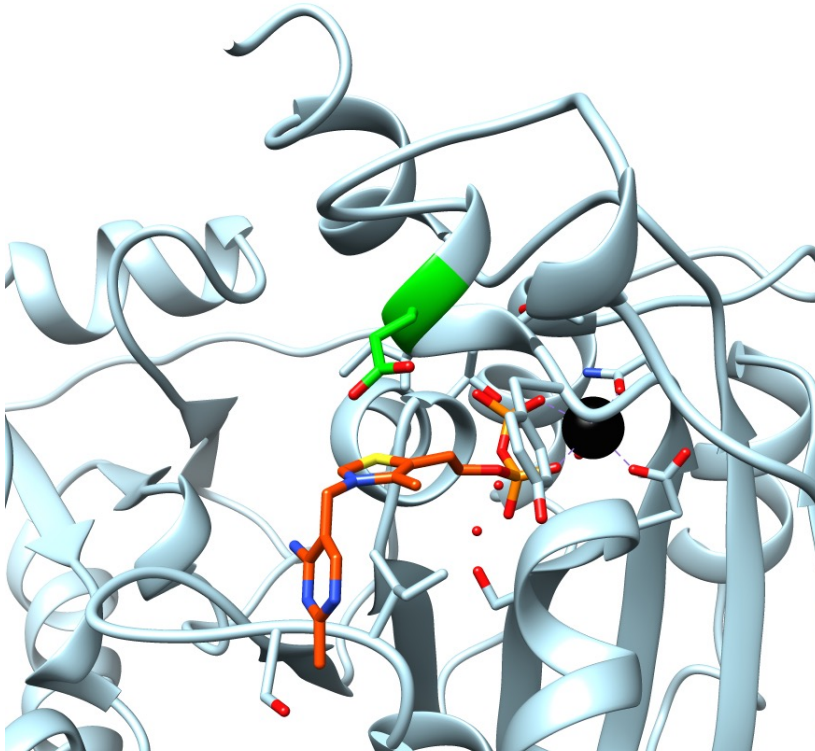
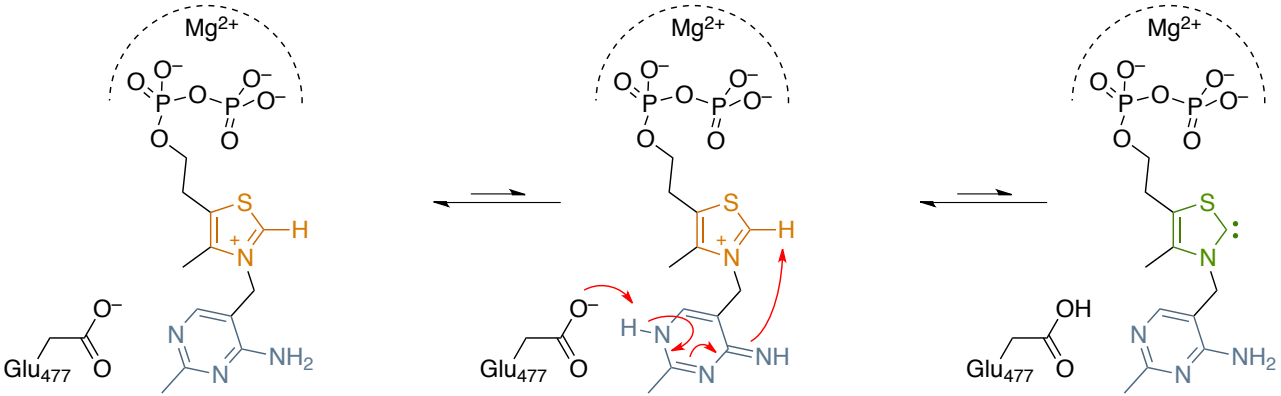
- **but**: reactive decarboxylated intermediates can also be transfered to aldehyde electrophiles under C-C-coupling
- magnesium (black) fixes TPP via its pyrophosphate
- pyrimidine acts as proton shuttle for the deprotonation of the thiazole by Glu_{477} (green)

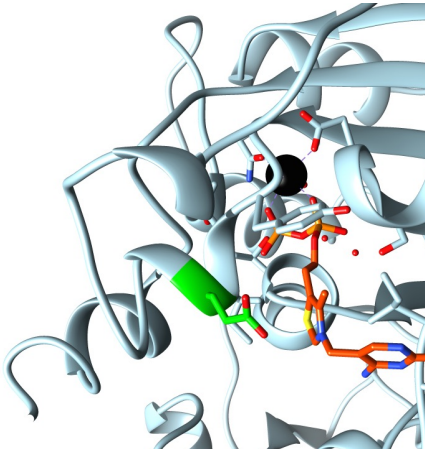


Pyruvate decarboxylase

Mechanism of carbene formation



nucleophilic
N-heterocyclic
carbene



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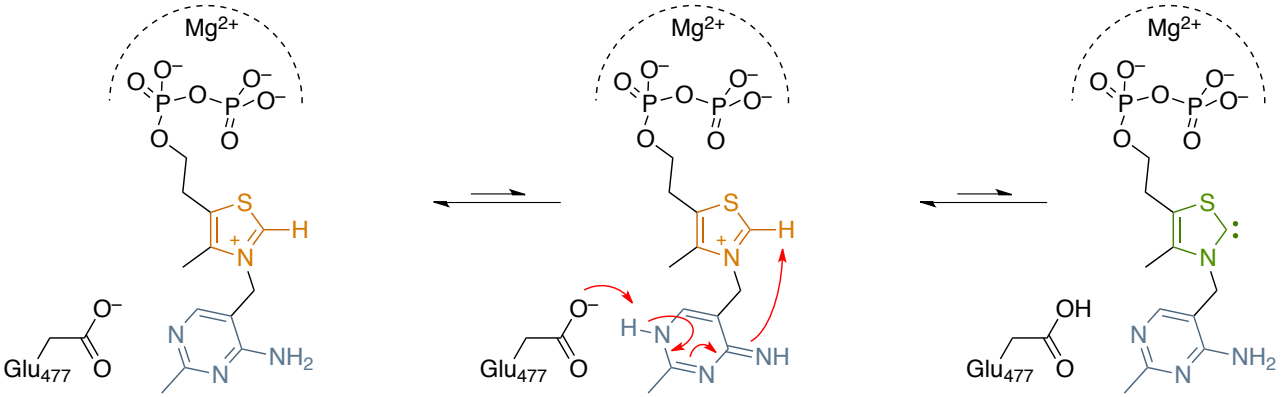

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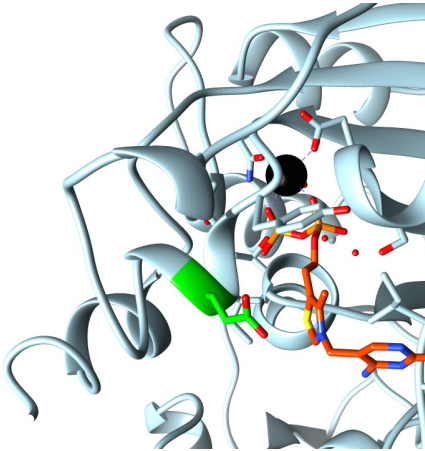
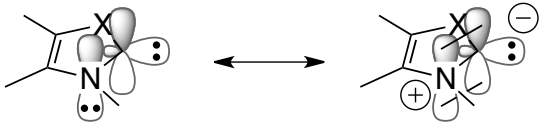


singlet carbene
due to n-p_z
interaction



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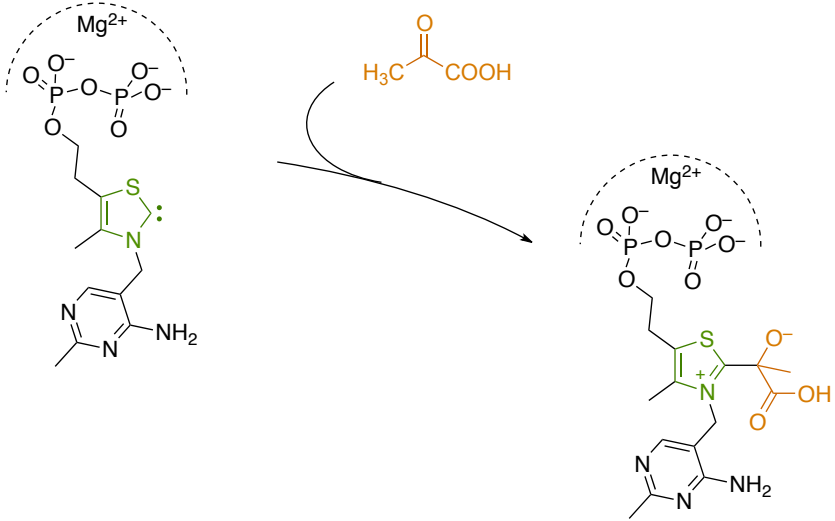

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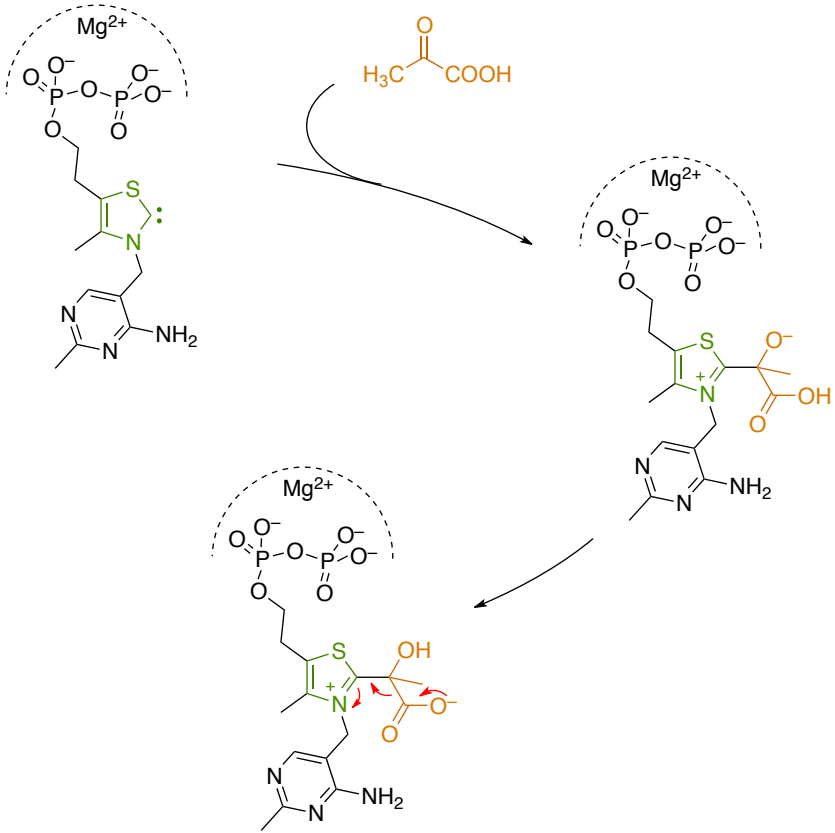

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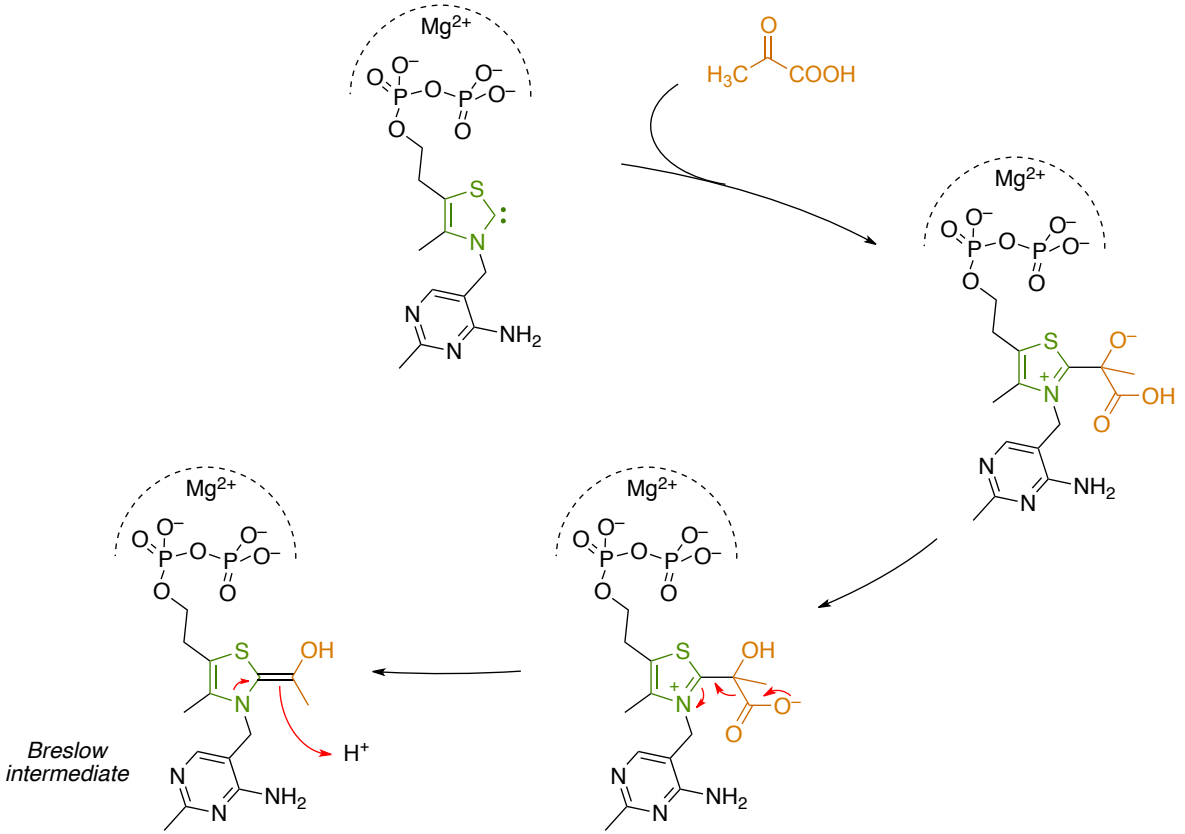

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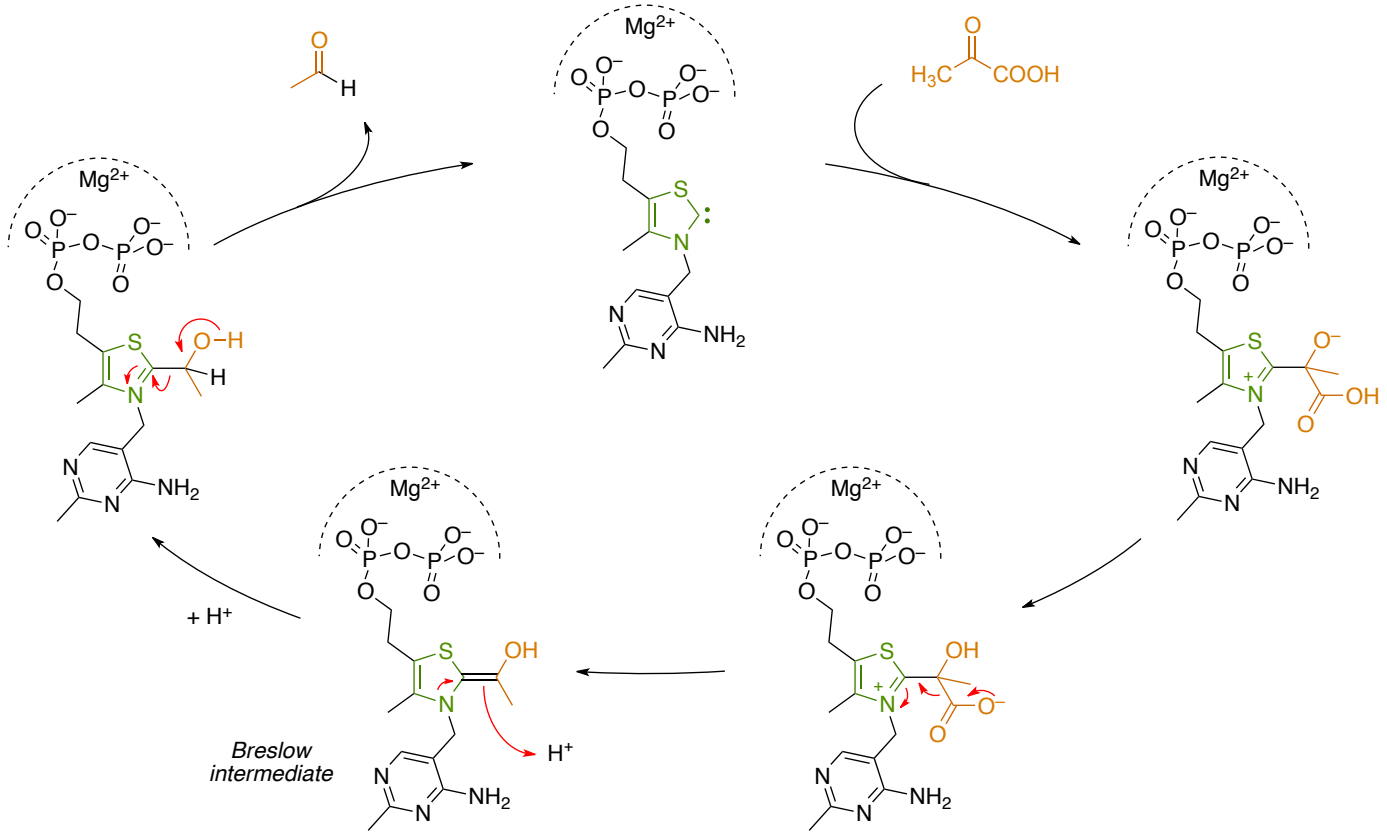

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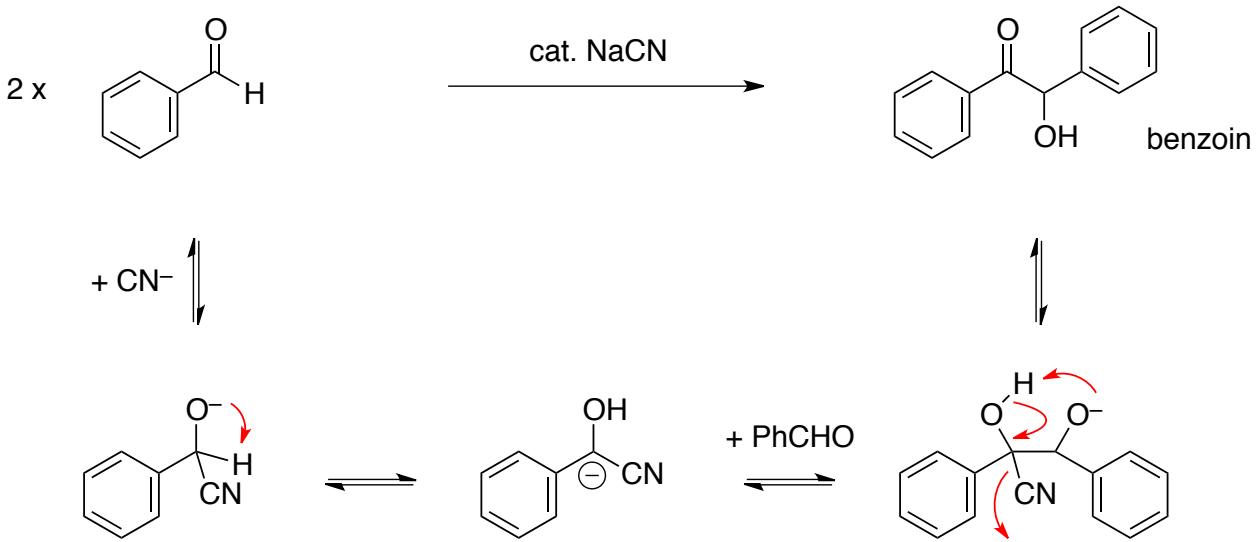
Mechanistic deviations

Acyloin reaction

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



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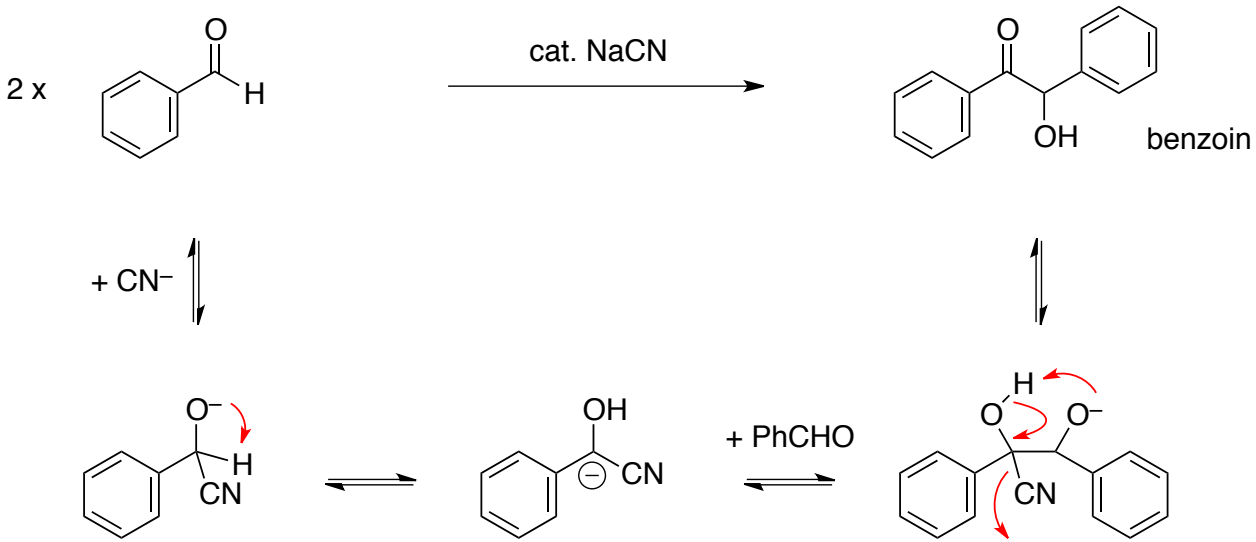

- cyanide-mediated benzoin reaction only homocoupling
- mostly limited to aromatic aldehydes

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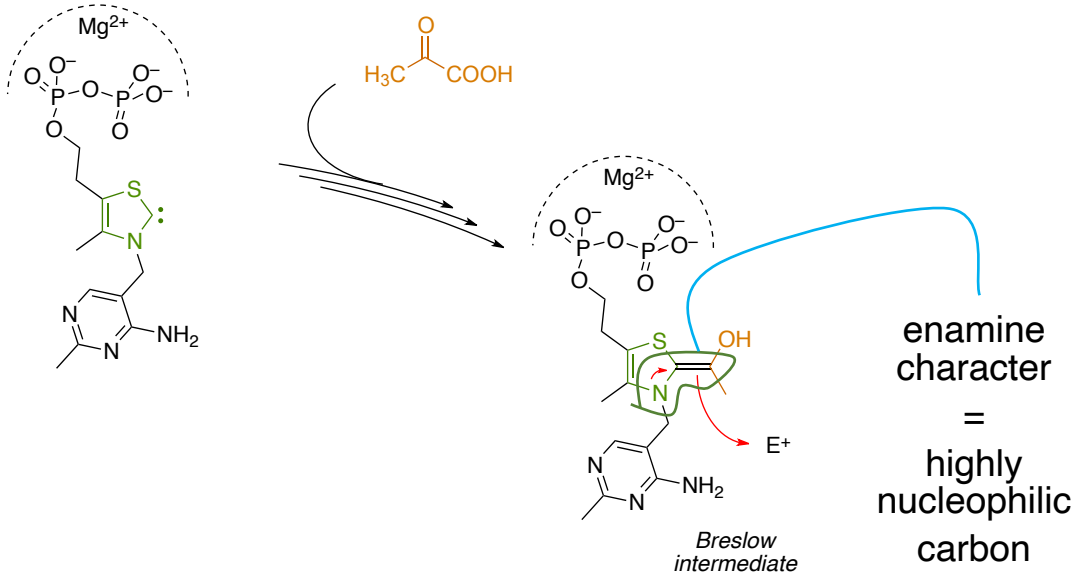
Mechanistic deviations

Benzoin-like reactions of the Breslow intermediates



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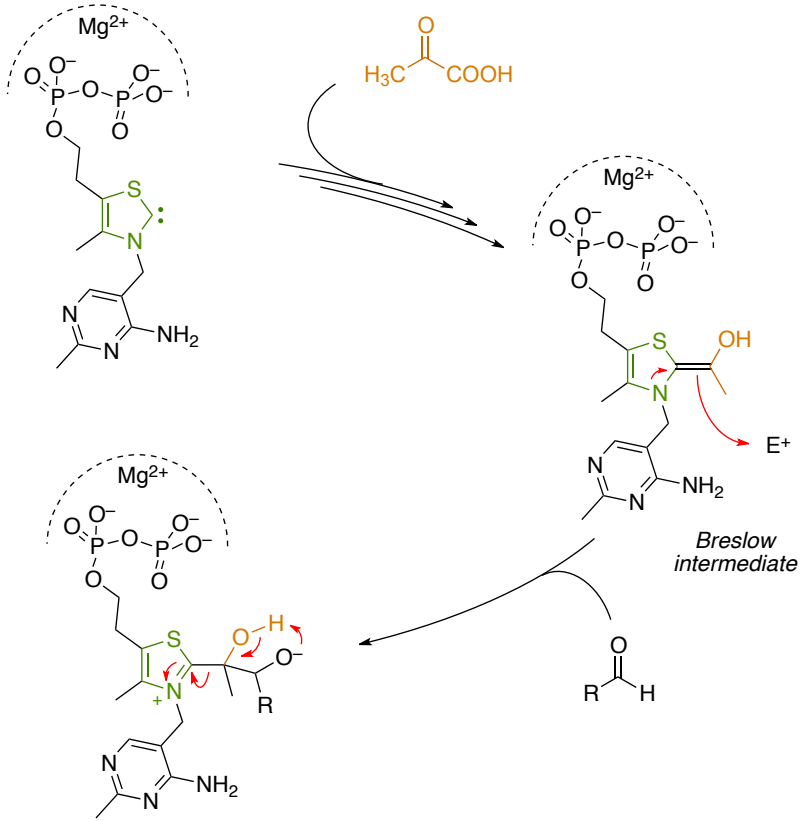

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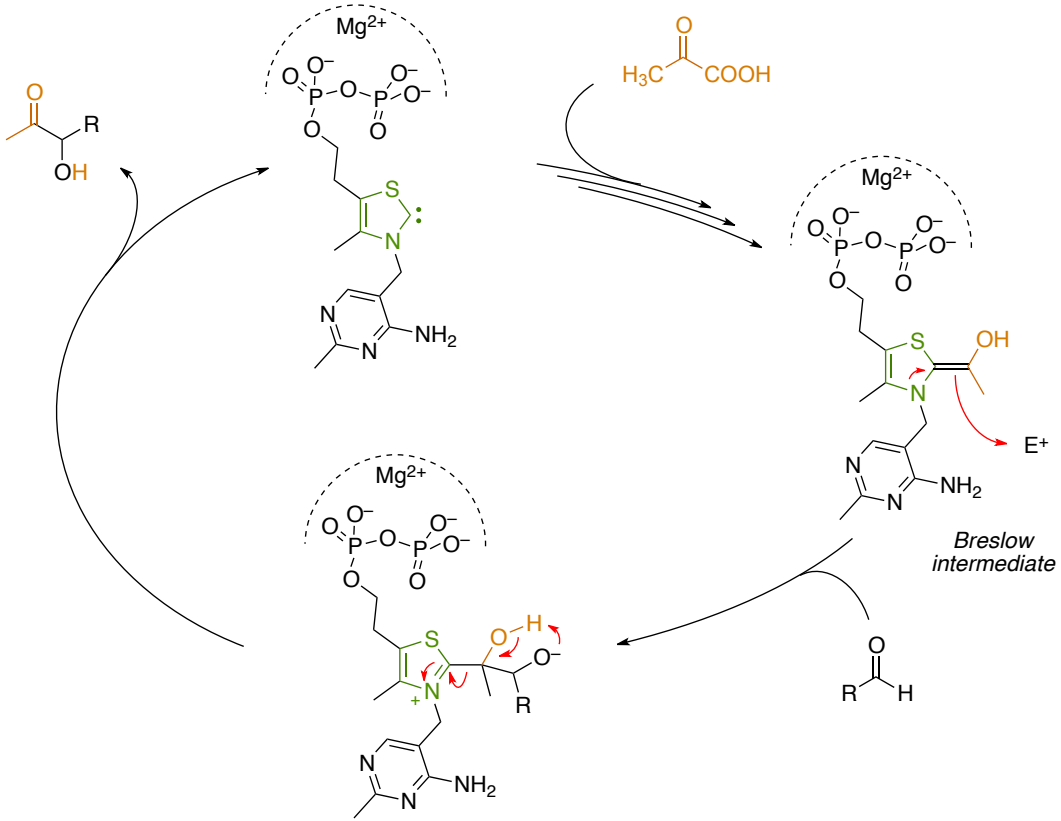

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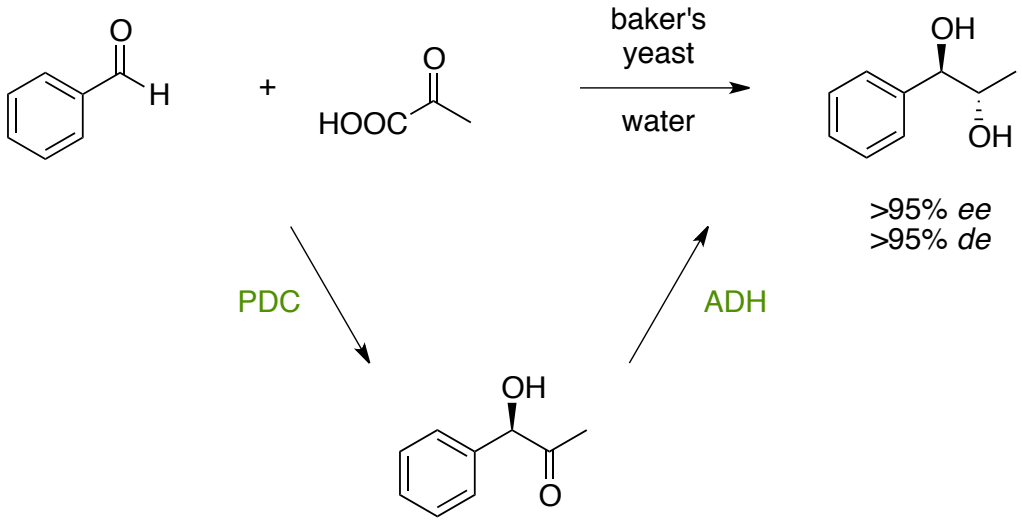
Synthetic applications

pyruvate as masked acetaldehyde



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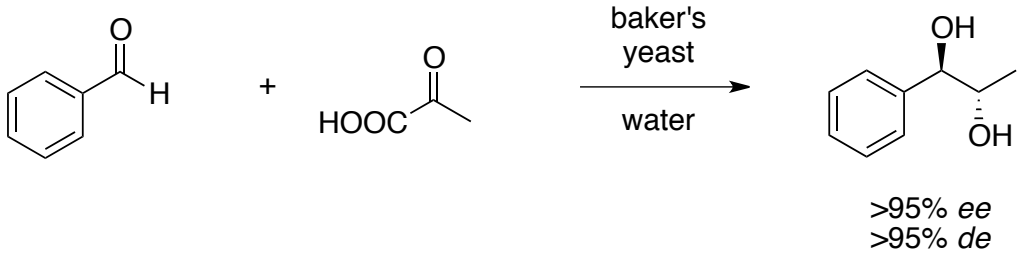
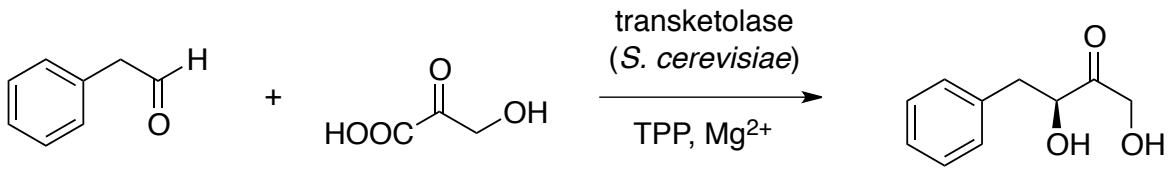


>95% *ee*
>95% *de*

but also: pyruvate derivatives are decarboxylated and transferred (here by transketolase)



97% *ee*

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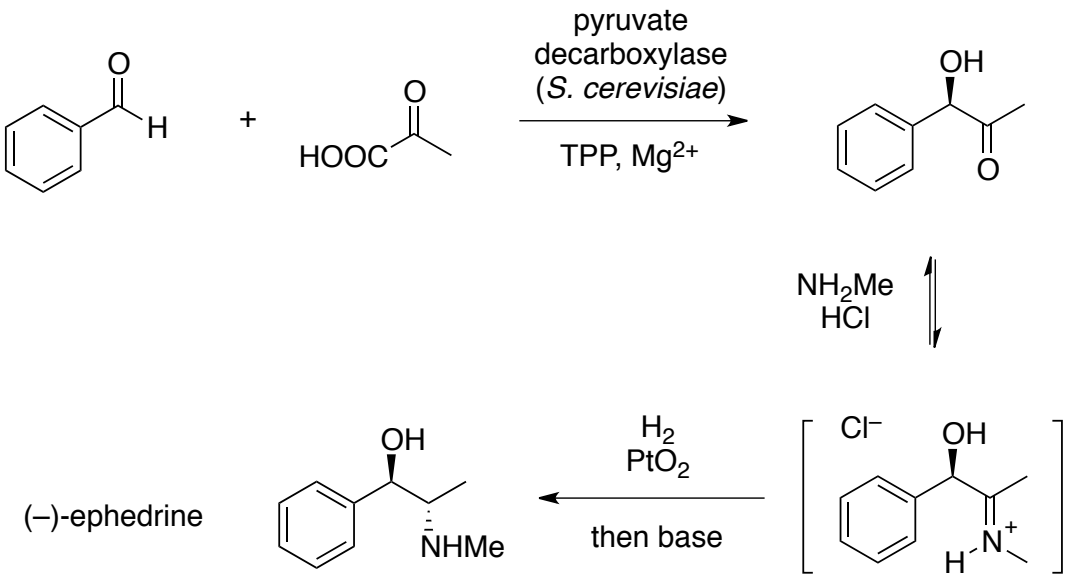
Synthetic applications

trapping of acyloin products



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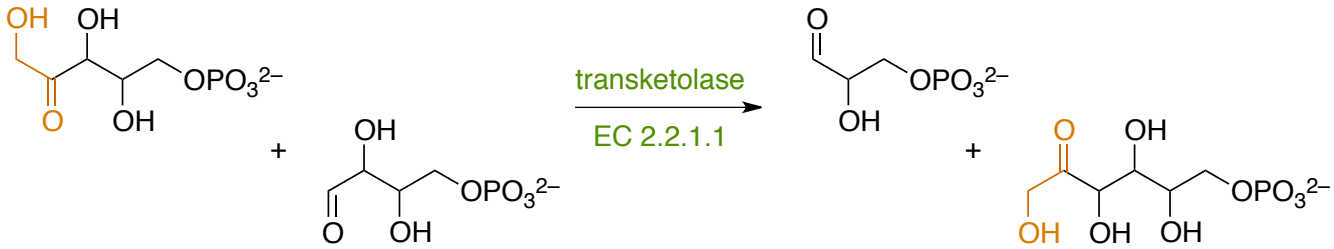
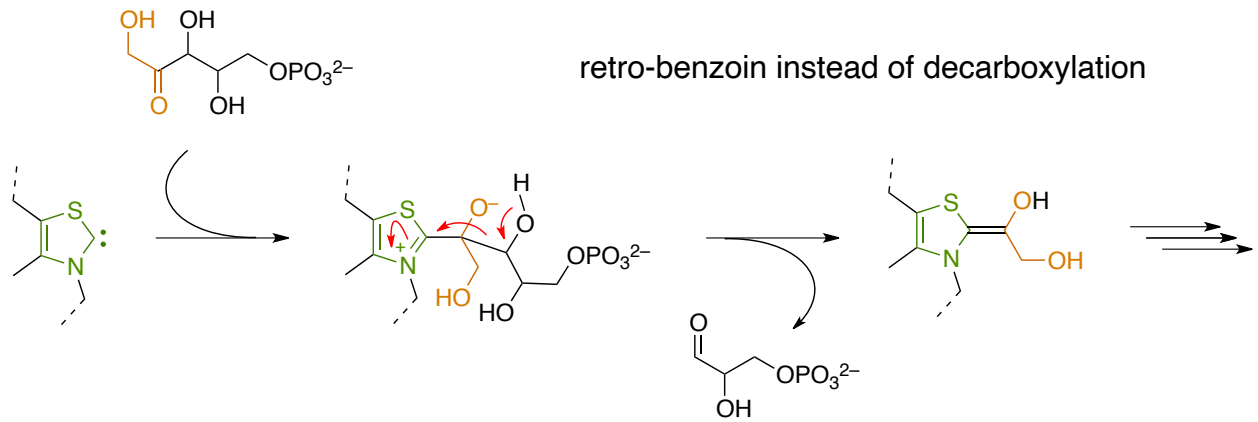
Analogies from transketolases



Breslow intermediate from α-hydroxyketones



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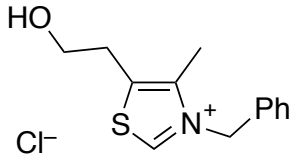
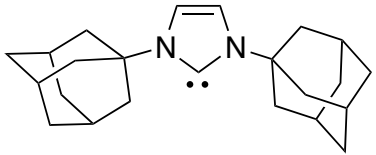
Biomimetic developments

Vitamin B_1 as prototype for stable organic catalysts



Stetter, 1977
sold as imidazolium salt



Arduengo, 1991
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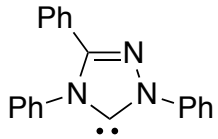
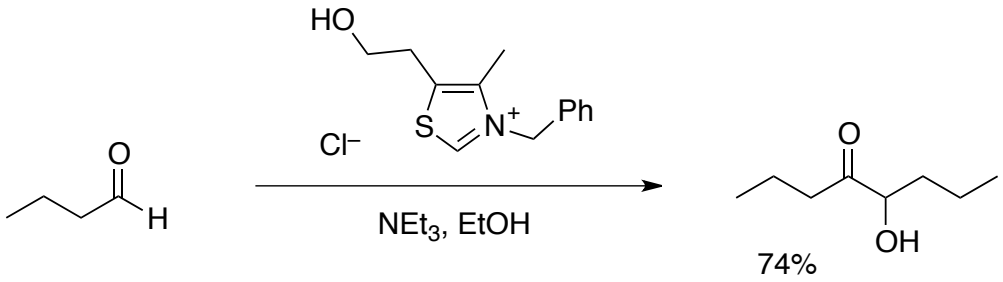


Enders/Teles, 1995
stable, sold as free carbene!

simple analogues catalyze aldehyde homo-coupling



Enders, Niemeier, Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655.

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Biomimetic developments

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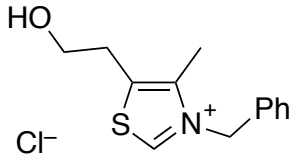

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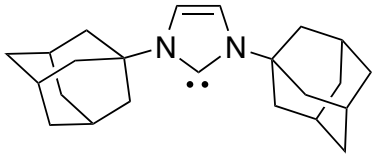

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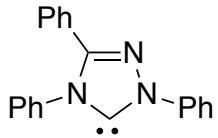

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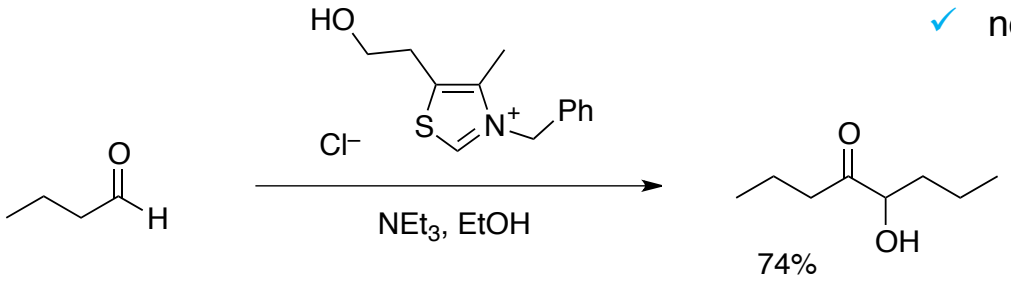

- ✓ no cyanide
- ✓ no limitation to aromatic aldehydes

Enders, Niemeier, Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655.

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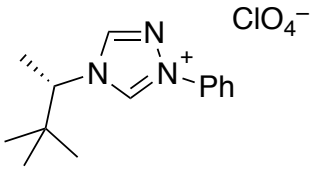
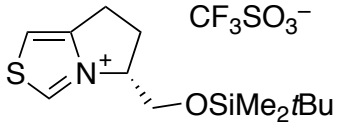
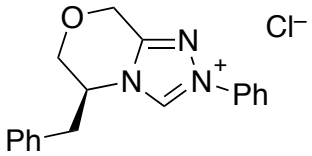
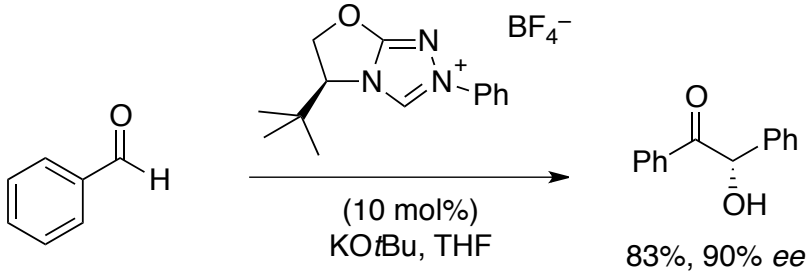
Biomimetic developments

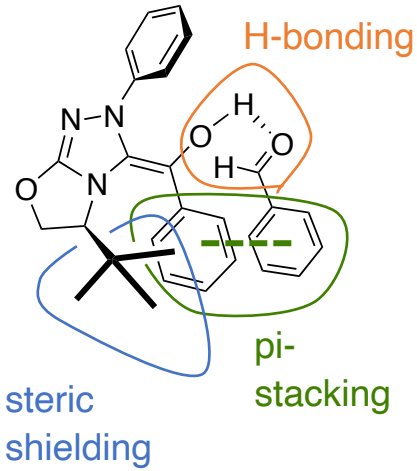
chiral azolium salts as potential asymmetric organocatalysts









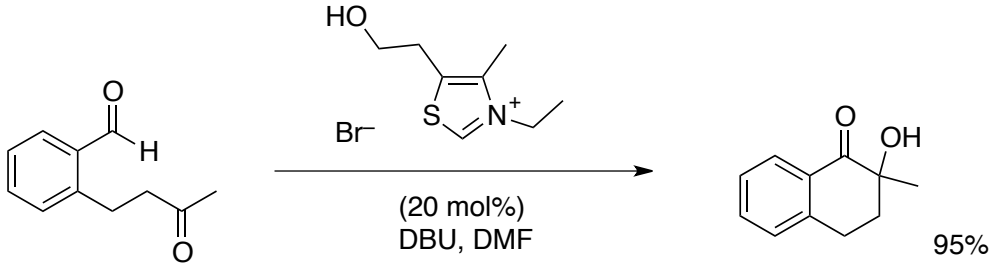


Enders, Niemeier, Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655.

Biomimetic developments

genuine cross coupling still challenging, but...

- intramolecular crossed benzoin reaction



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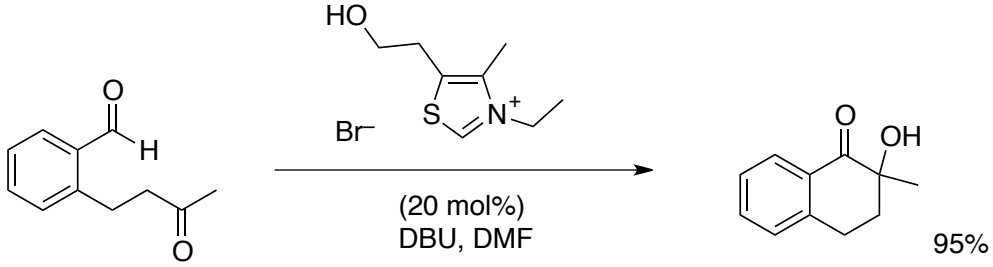
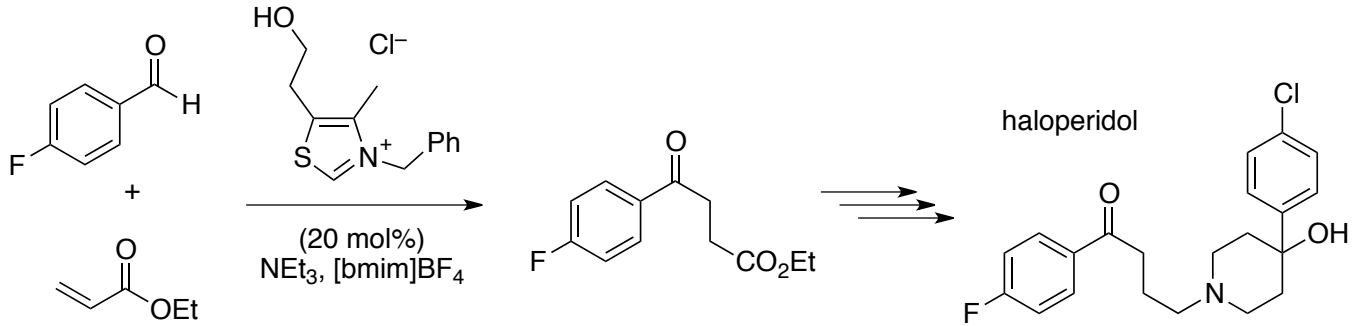


- addition to non-aldehyde electrophiles (e.g. Stetter reaction)



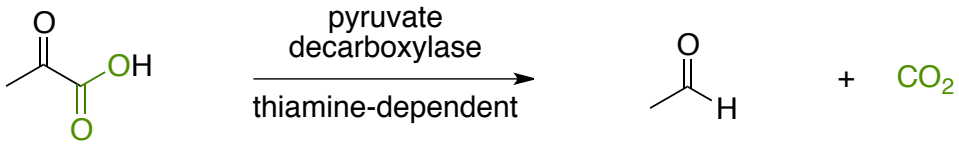
Enders, Niemeier, Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655.

Lyases - features

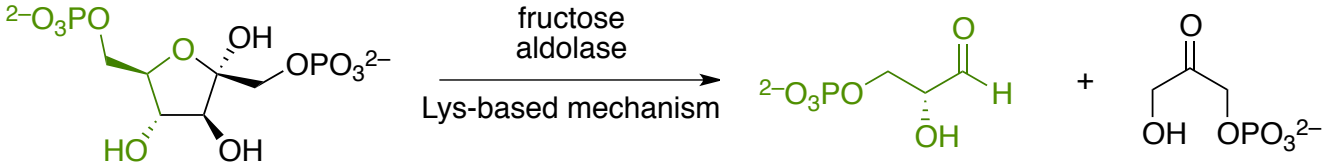
enzymes of class EC 4 catalyze the cleavage of chemical bonds (non-hydrolytic!)

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

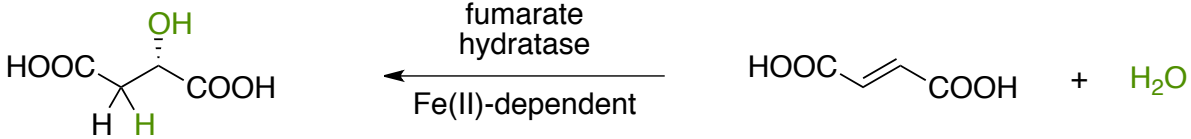
pyruvate decarboxylase



aldolase



fumarate hydratase



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Lyases - features

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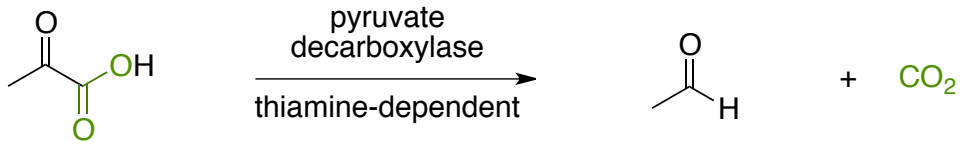
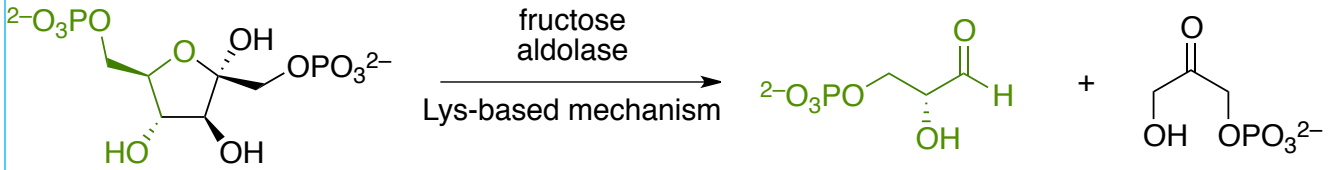
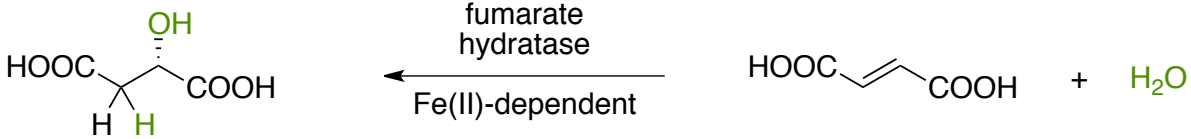


aldolase



more on that in the next session

fumarate hydratase



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SUMMARY

PLP catalysis

- reversible imine formation goes way beyond only transaminases
- multiple routes in amino acid metabolism and catabolism are based on reversible imine formation

TPP: carbene catalysis

- attractive for non-amino acid synthetic chemistry
- one of the first templates in biomimetic chemistry