Lecture 15 and 16

Fundamentals and Applications (CSO201A)

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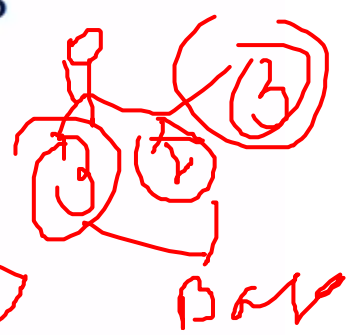
Basic synthetic Methods

Base Catalysed Carbon-carbon Bond Formation reaction

Principles

- The base catalyzed carbon-carbon bond formation is closely related to their formation from organometallic reagents
- In both methods, the negatively polarized carbon reacts with electrophilic carbon of carbonyl groups and related compounds

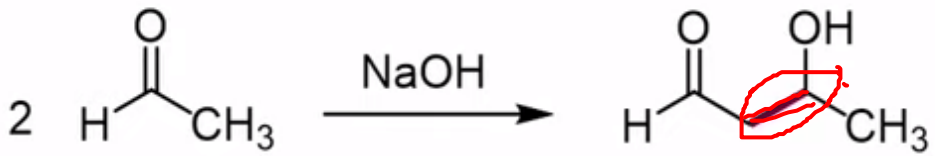


The scope of the base-catalyzed reactions depends on three facts:

- a wide range of organic compounds is able to form carbanions
- these carbanions undergo reaction with electrophilic carbon in a variety of environments
- the basicity of the reagent used to abstract the proton may be widely

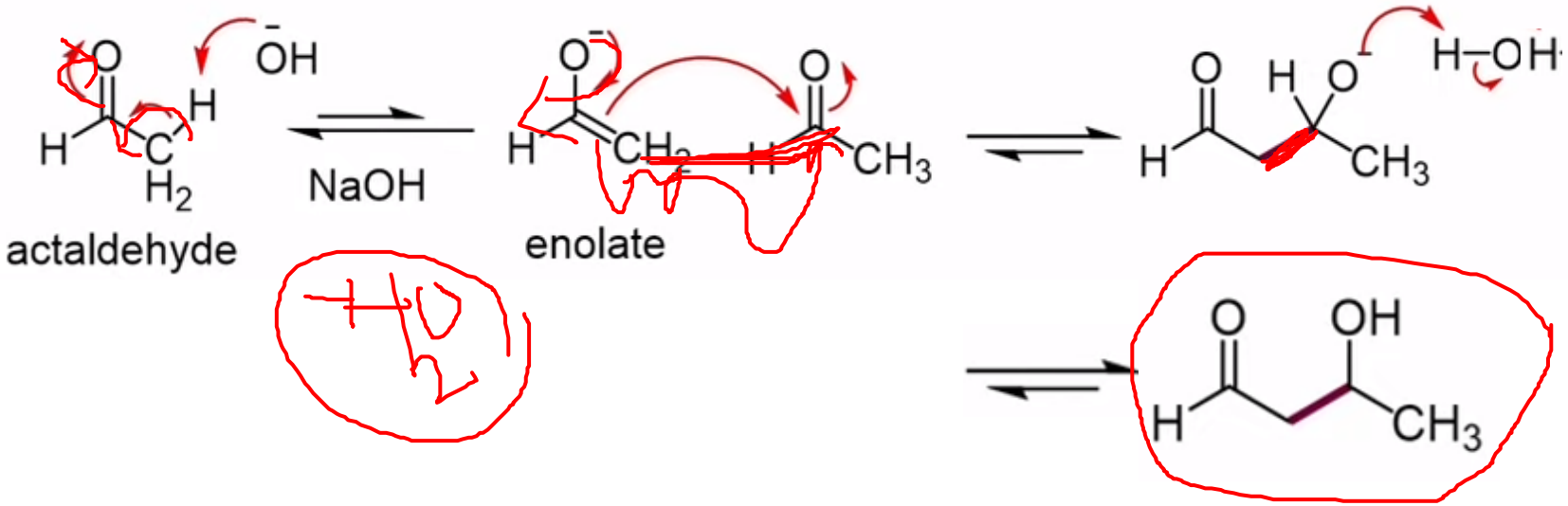
The Aldol Reaction

Base Catalyzed Dimerization of Simple Aldehydes and Ketones

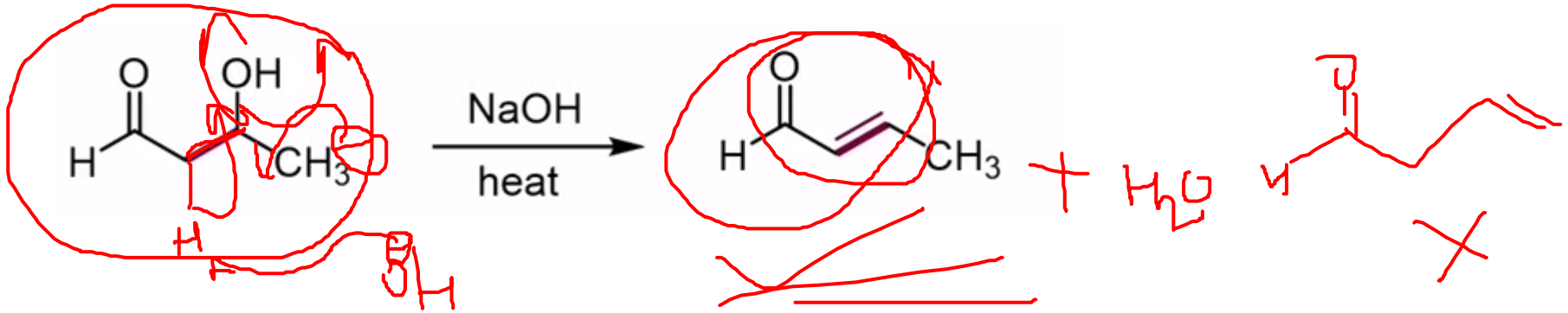


Aldol pdt

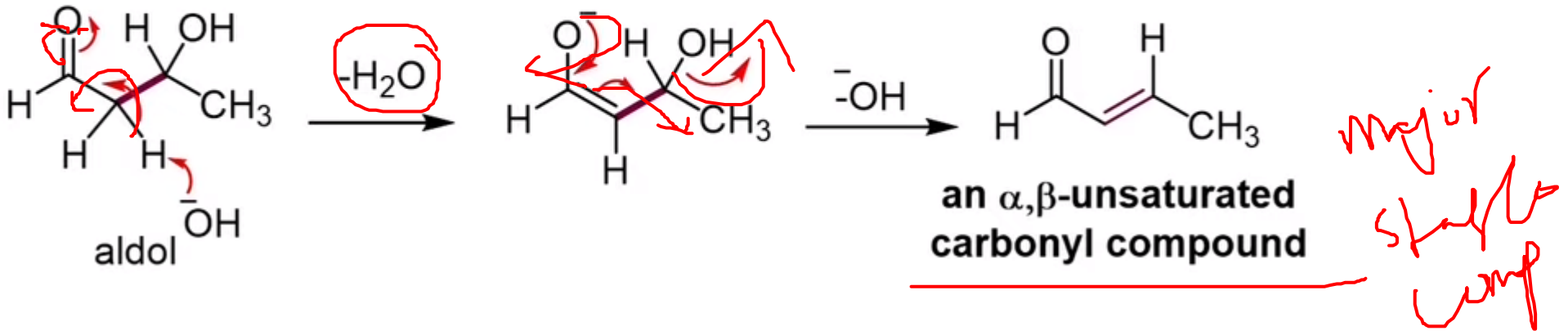
Mechanism



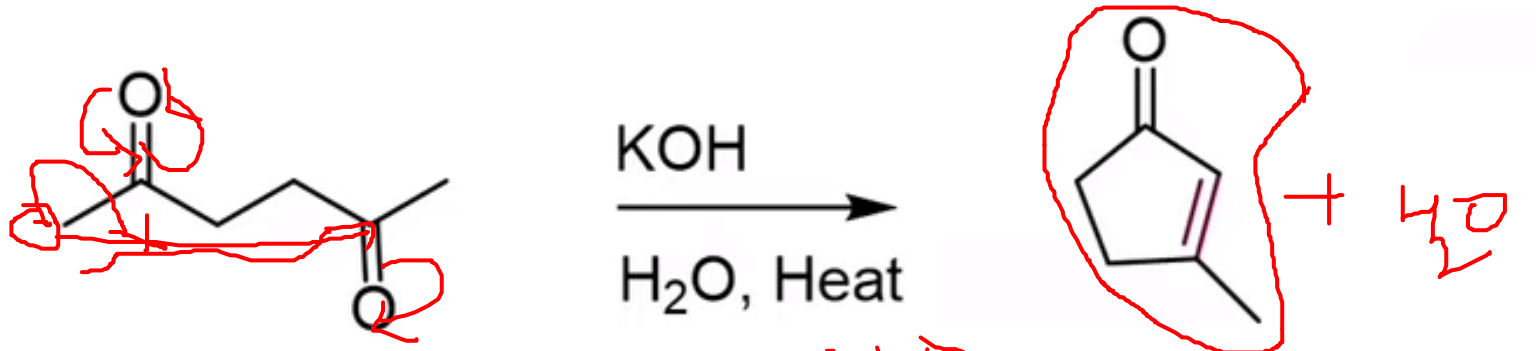
Aldol Condensation

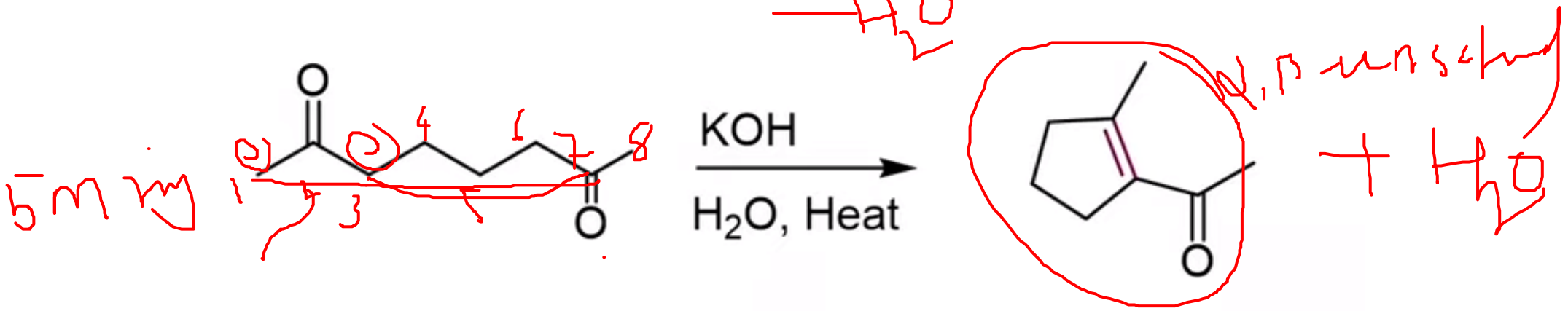


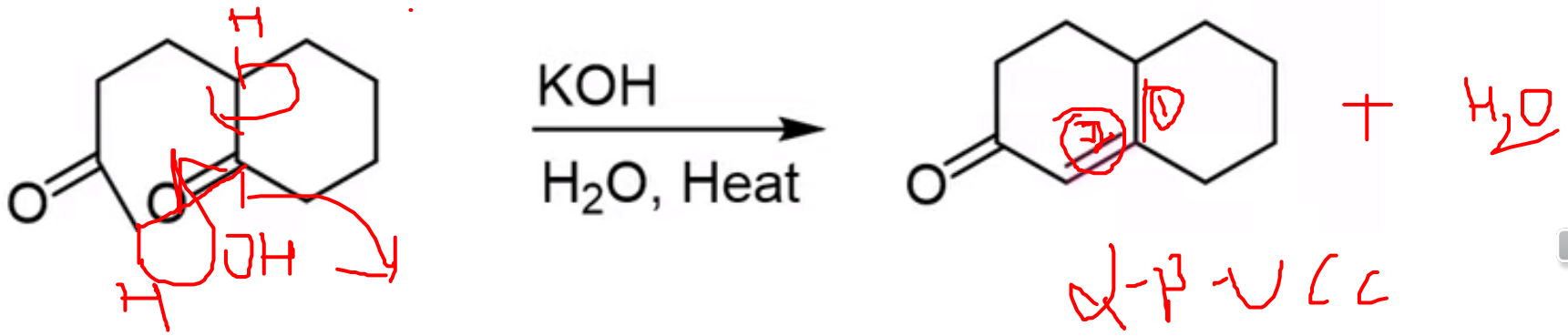
E1cB Mechanism



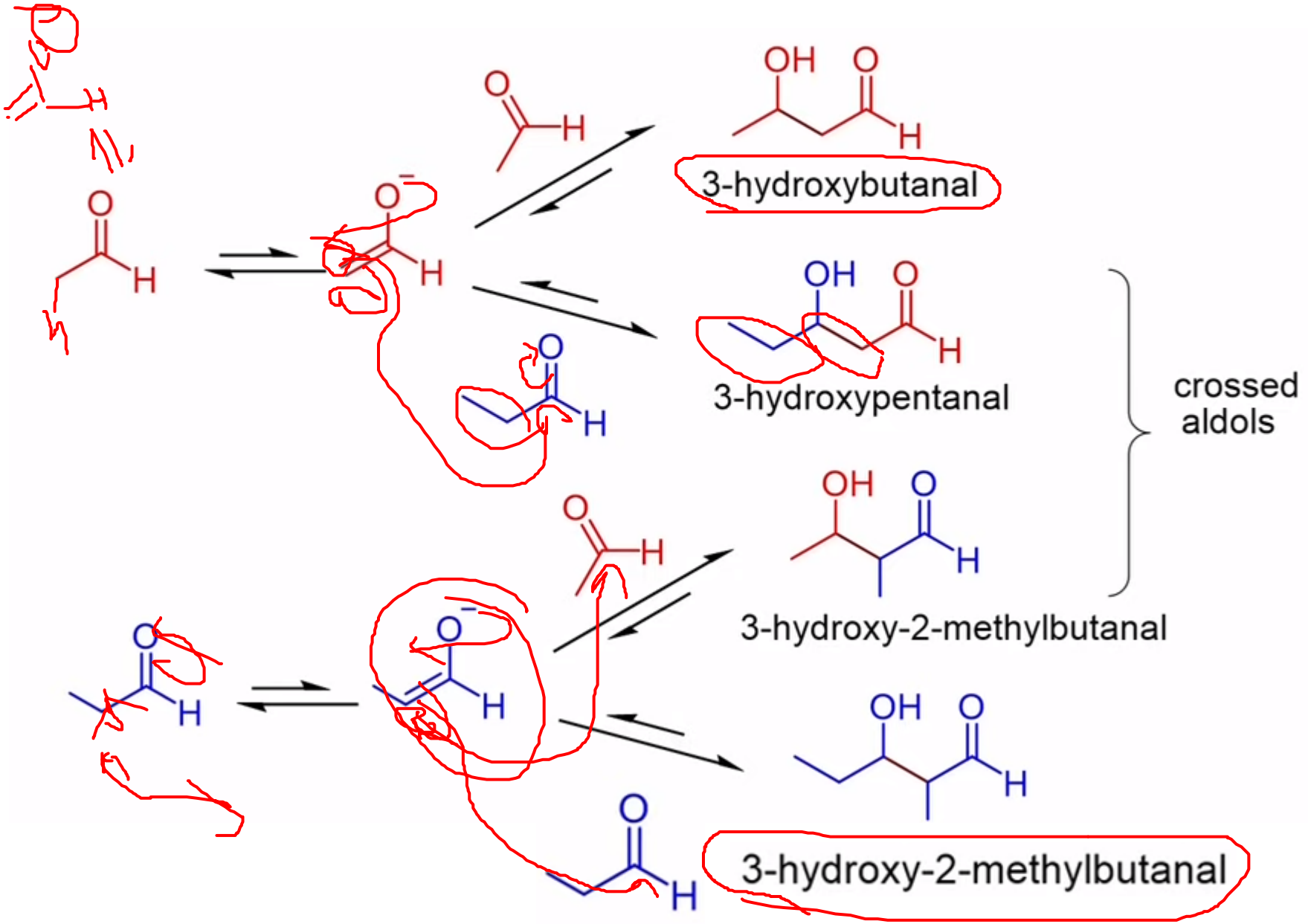
Intramolecular Aldol Condensation



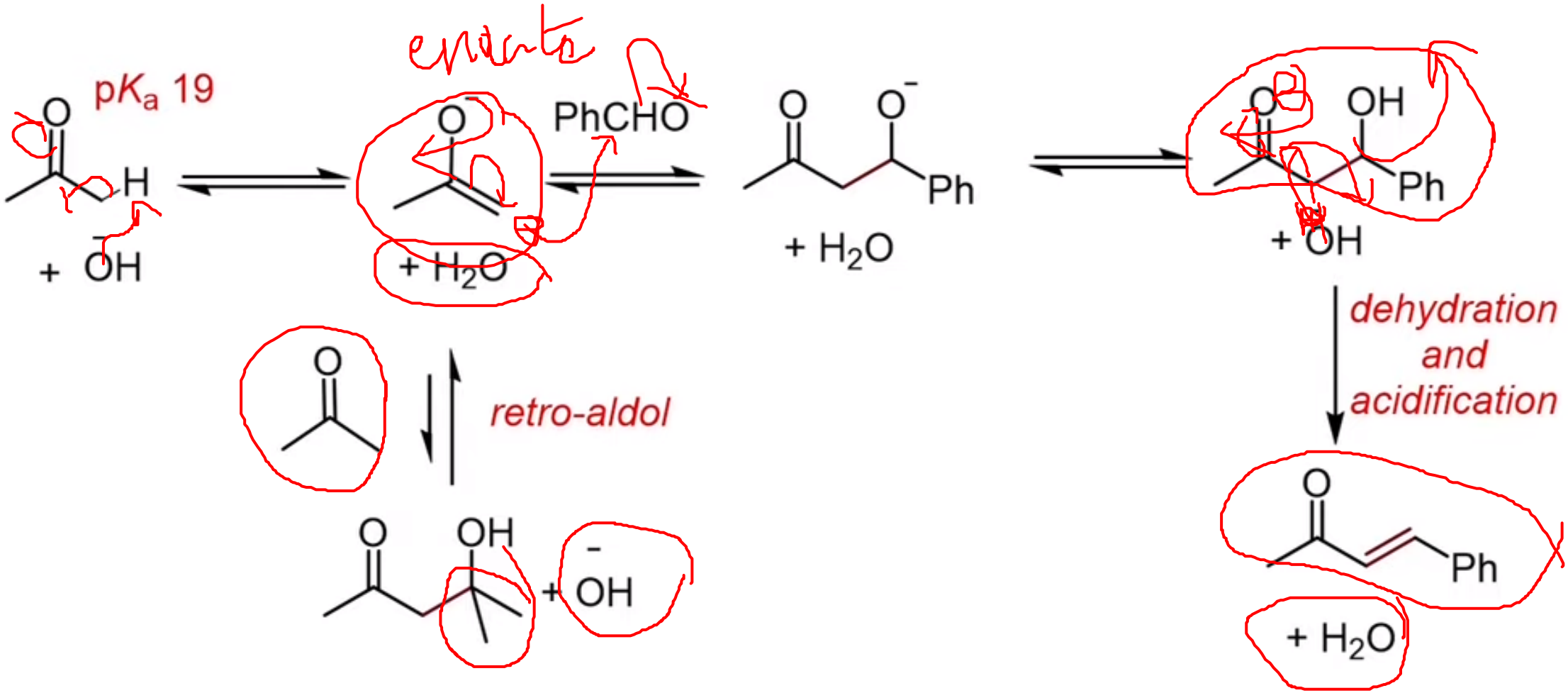




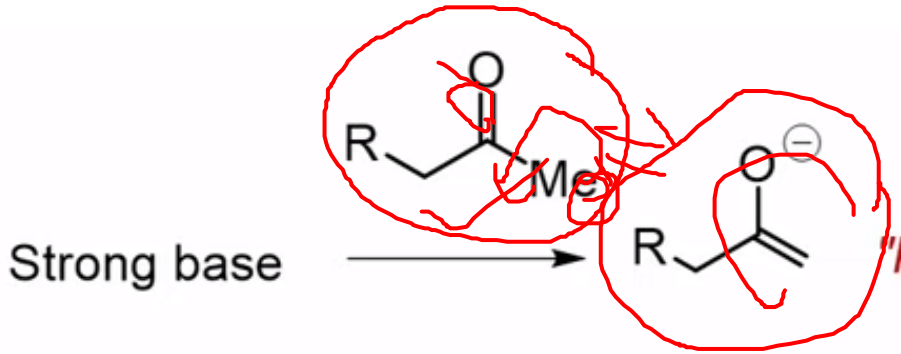
Crossed Aldol Reaction



Crossed Aldol Condensation

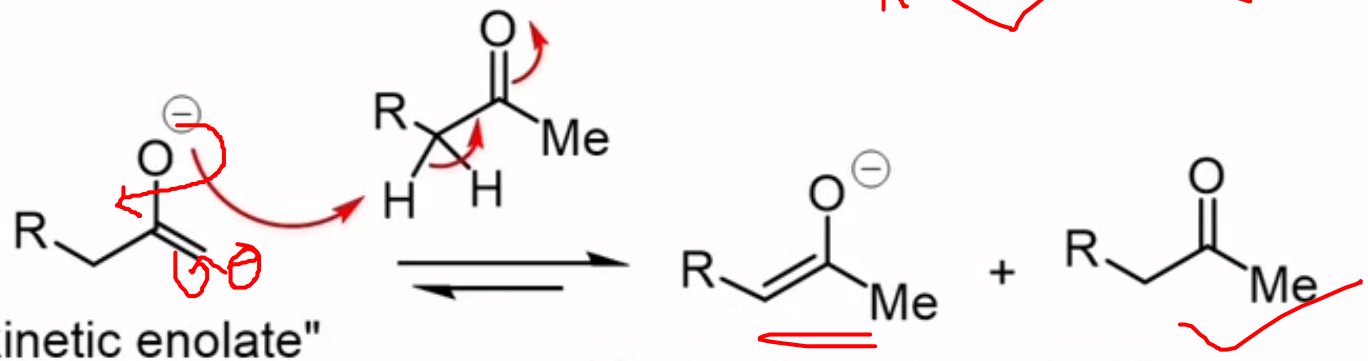


Kinetic Vs Thermodynamic Enolates



"Kinetic enolate"

strong base (eg. LDA)
low temperature
short reaction time

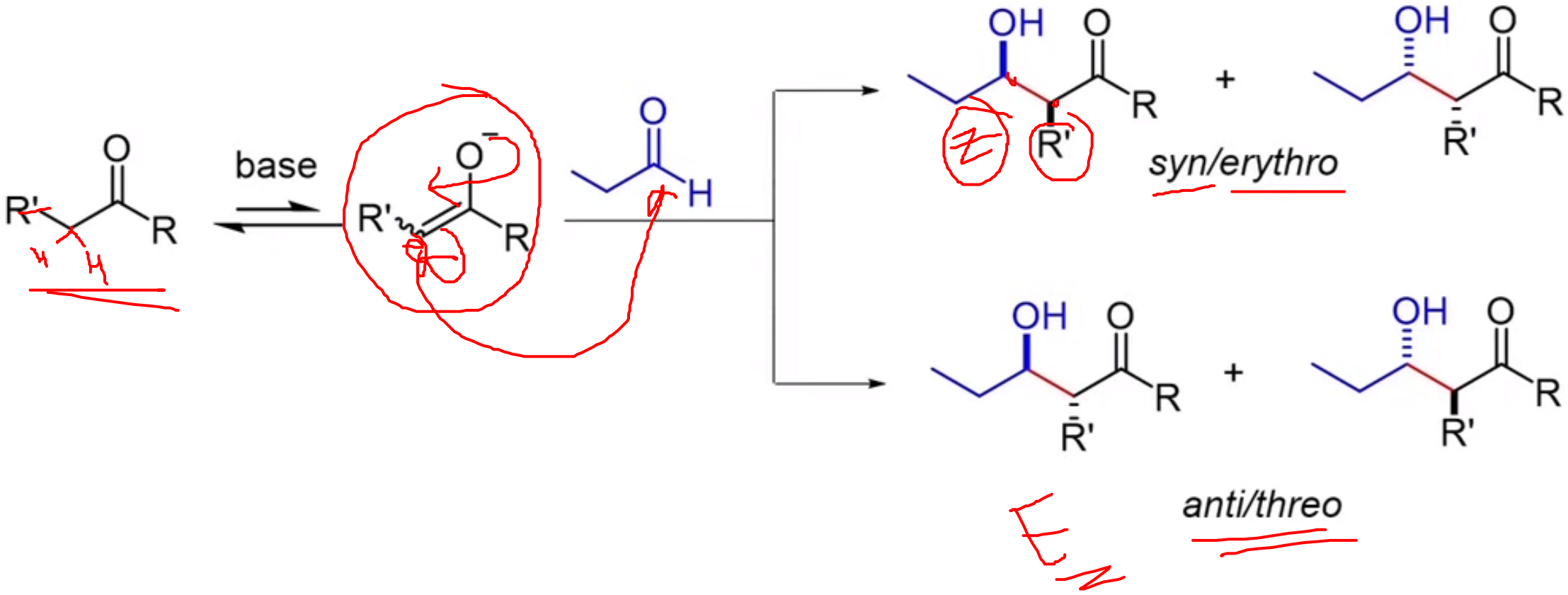


"kinetic enolate"

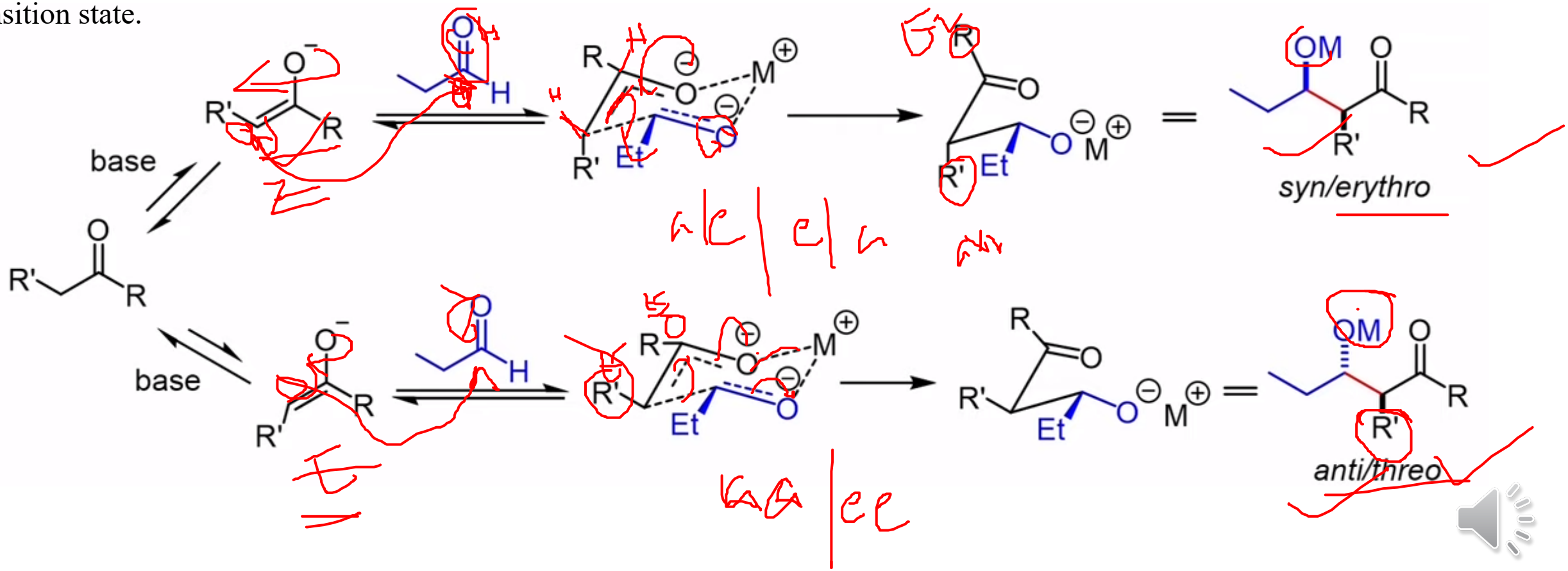
"thermodynamic enolate"

weak base (eg. hydroxide ion)
high temeprature
longer reaction time

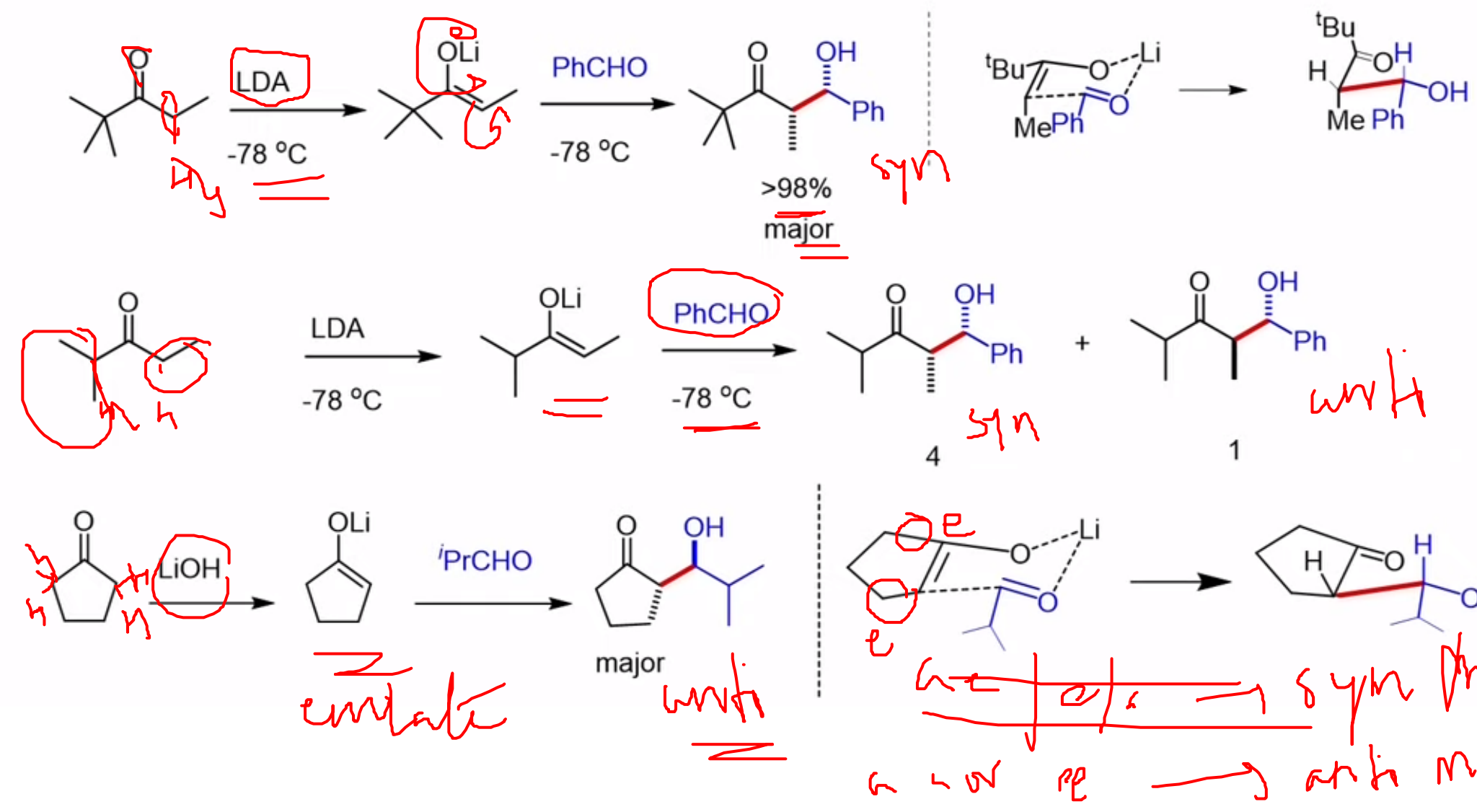
Diastereoselectivity



The mechanism of the classical *acid catalyzed aldol reaction* involves the equilibrium formation of an enol, which functions as a nucleophile. The carbonyl group of the electrophile is activated toward nucleophilic attack by protonation. In the base catalyzed reaction, the enolate is formed by deprotonation followed by the addition of the enolate to the carbonyl group. In both cases, the reaction goes through a number of equilibria, and the formation of the product is reversible. *Aldol reaction* of preformed enolates generally provides the products with high diastereoselectivity, (*Z*)-enolates yielding the *syn* product, (*E*)-enolates forming the *anti* product as the major diastereomer. The stereochemical outcome of the reaction can be rationalized based on the Zimmerman-Traxler model, according to which the reaction proceeds through a six-membered chairlike transition state. The controlling factor according to this model is the avoidance of destabilizing 1,3-diaxial interactions in the cyclic transition state.

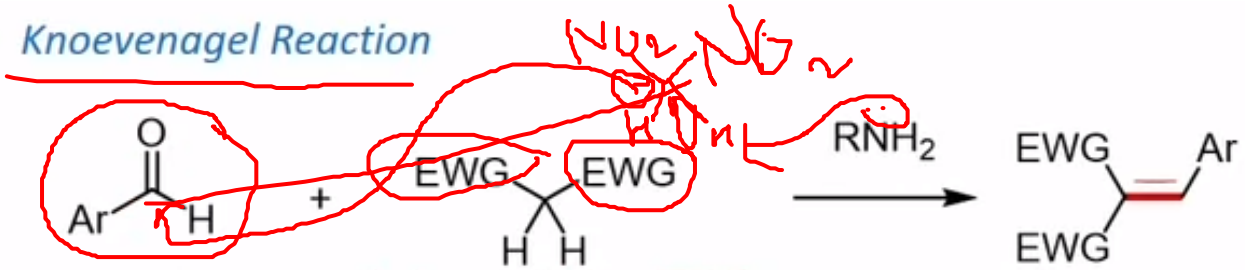


Diastereoselectivity



Reactions Based on Aldol reaction

- *Knoevenagel Reaction*

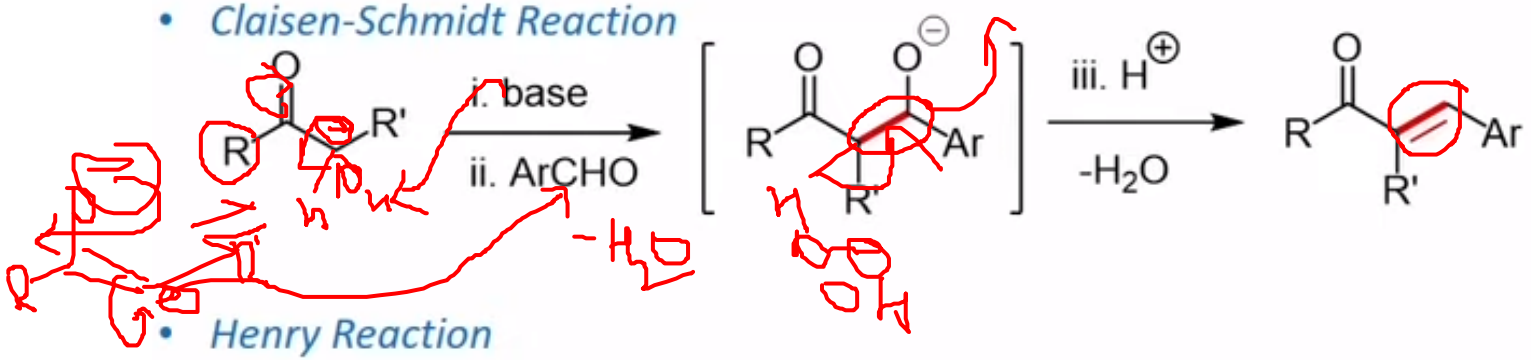


no α protons *methylene with two EWG*

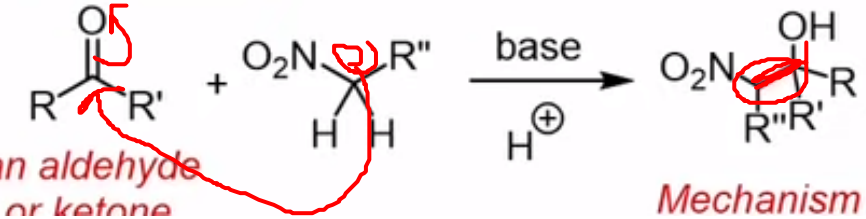
R. Brukner, *Advanced Organic Chemistry*, Harcourt/Academic Press, San Diego, 2002, pp 419-422.

E. Knoevenagel, German Chemist (1865-1921)

- *Claisen-Schmidt Reaction*



- *Henry Reaction*

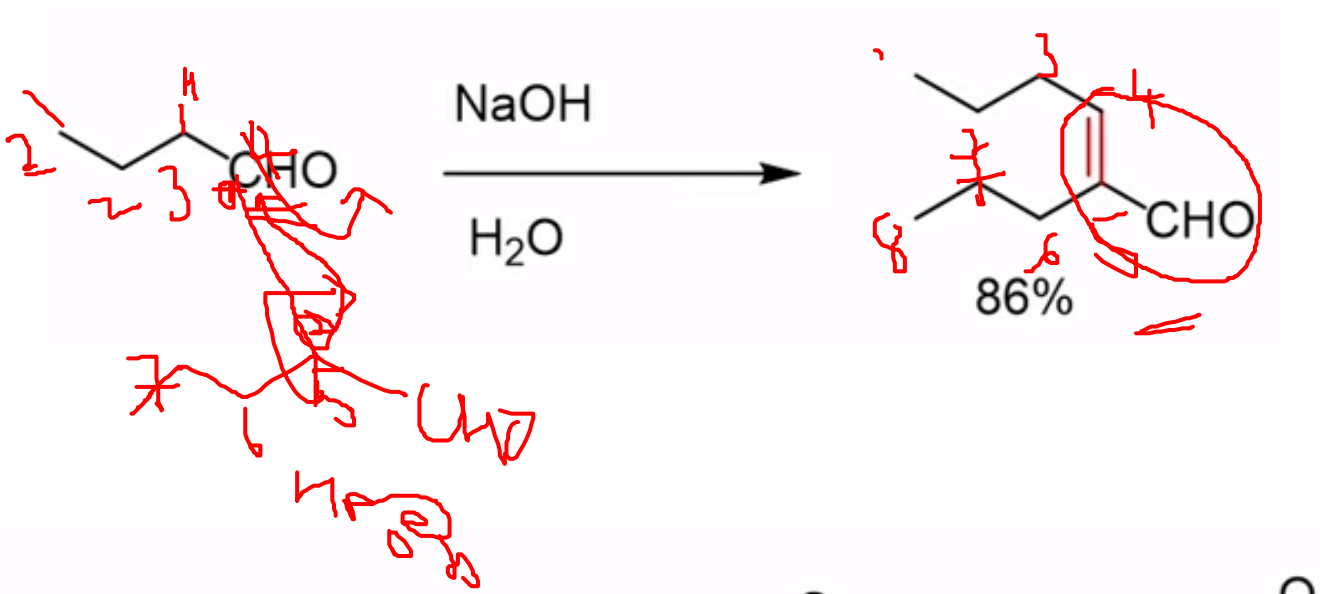


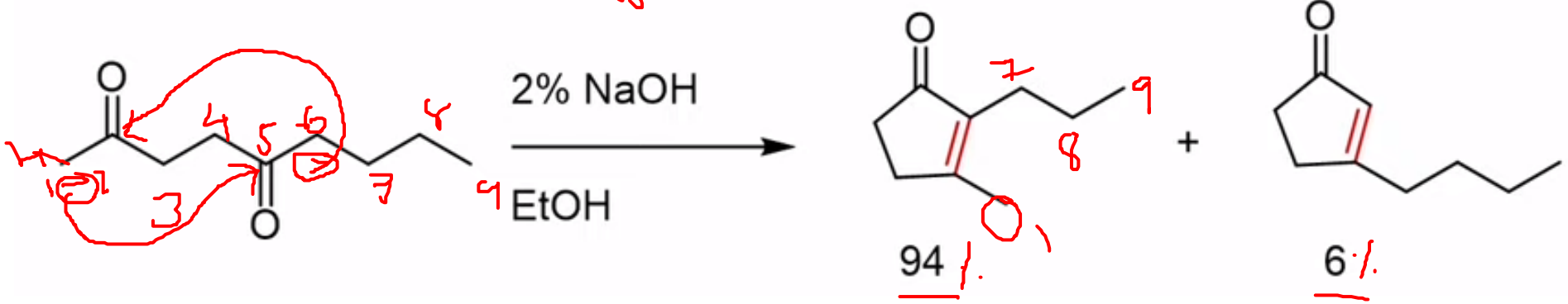
an aldehyde or ketone

Mechanism is similar to Aldol Reaction

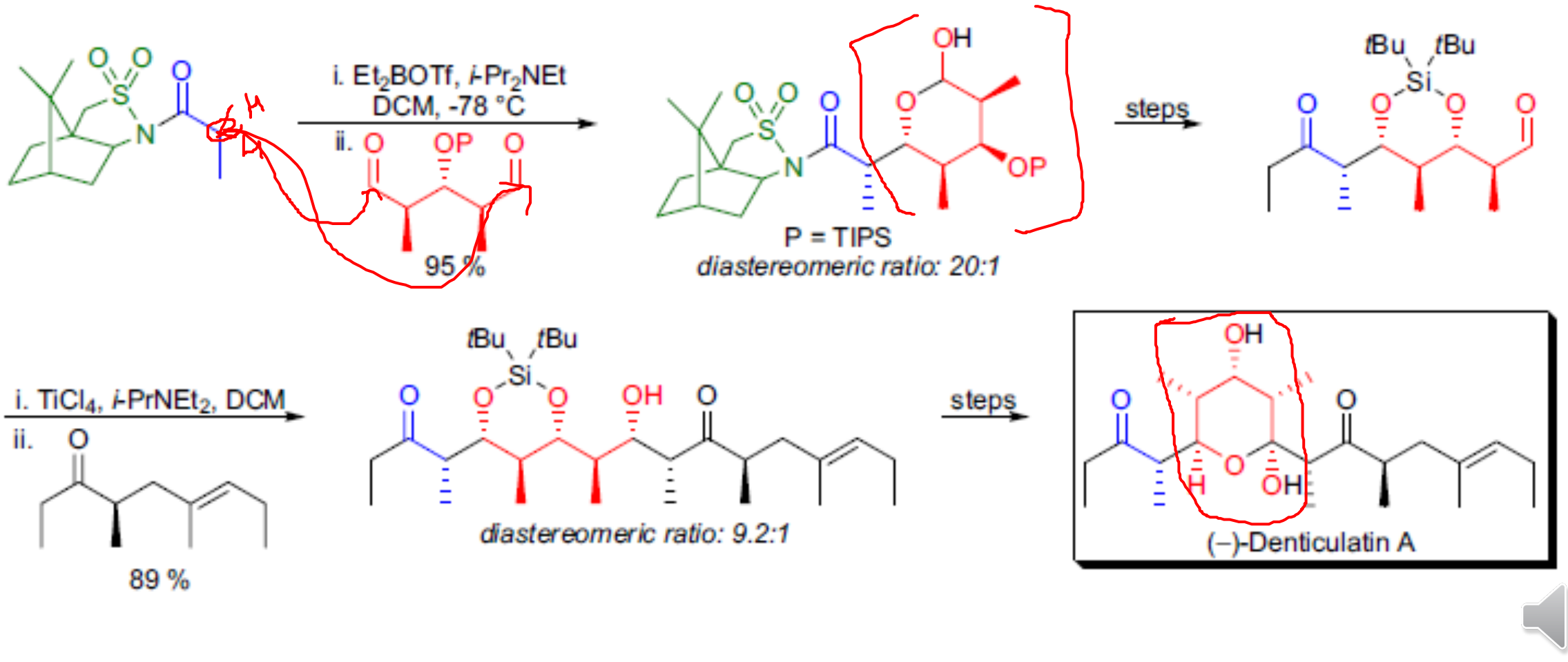
Louis Henry, Belgian Chemist (1834-1913)

Examples

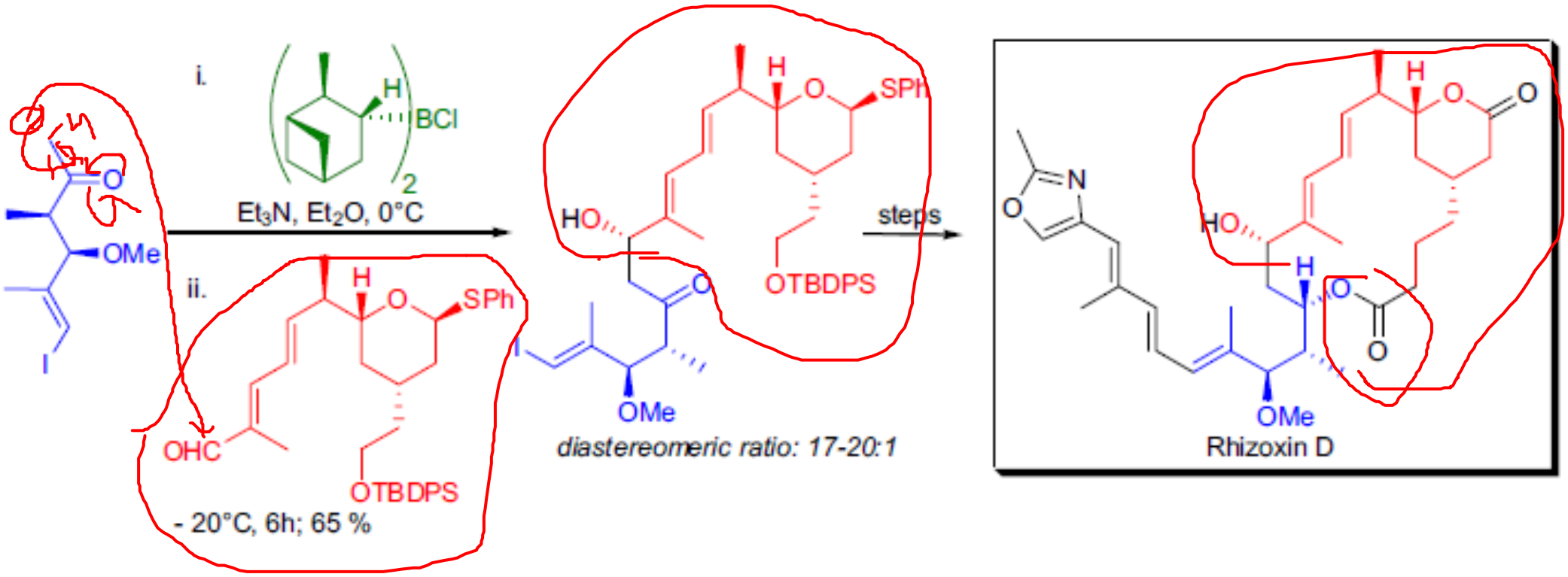




The first enantioselective total synthesis of (–)-denticulatin A was accomplished by W. Oppolzer. The key step in their approach was based on enantiotopic group differentiation in a *meso* dialdehyde by an *aldol reaction*. In the *aldol reaction* they utilized a bornanesultam chiral auxiliary. The enolization of *N*-propionylbornane-10,2-sultam provided the (*Z*)-borylenolate derivative, which underwent an *aldol reaction* with the *meso* dialdehyde to afford the product with high yield and enantiopurity. In the final stages of the synthesis they utilized a second, *doublediastereodifferentiating aldol reaction*. Aldol reaction of the (*Z*)-titanium enolate gave the *anti*-Felkin *syn* product. The stereochemical outcome of the reaction was determined by the α-chiral center in the aldehyde component.



During the total synthesis of rhizoxin D by J.D. White et al., an asymmetric aldol reaction was utilized to achieve the coupling of two key fragments. The aldol reaction of the aldehyde and the chiral enolate derived from (+)-chlorodiisopinocampheylborane afforded the product with a diastereomeric ratio of 17-20:1 at the C13 stereocenter. During their studies, White and co-workers also showed that the stereochemical induction of the chiral boron substituent and the stereocenters present in the enolate reinforce each other thus representing a "matched" aldol reaction.



A possible way to induce enantioselectivity in the aldol reaction is to employ a chiral catalyst. M. Shibasaki and coworkers developed a bifunctional catalyst, (S)-LLB (L=lanthanum; LB=lithium binaphthoxide), which could be successfully applied in direct catalytic asymmetric aldol reactions. An improved version of this catalyst derived from (S)-LLB by the addition of water and KOH was utilized in the formal total synthesis of fostriecin.