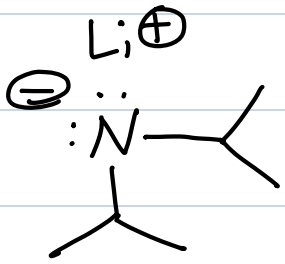
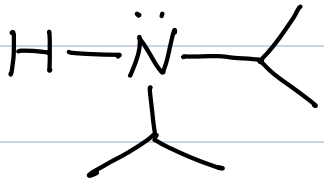
NOVICE
TRICK DOG

The wicked strong base that changes things





Lithium Diisopropylamide

"LDA"

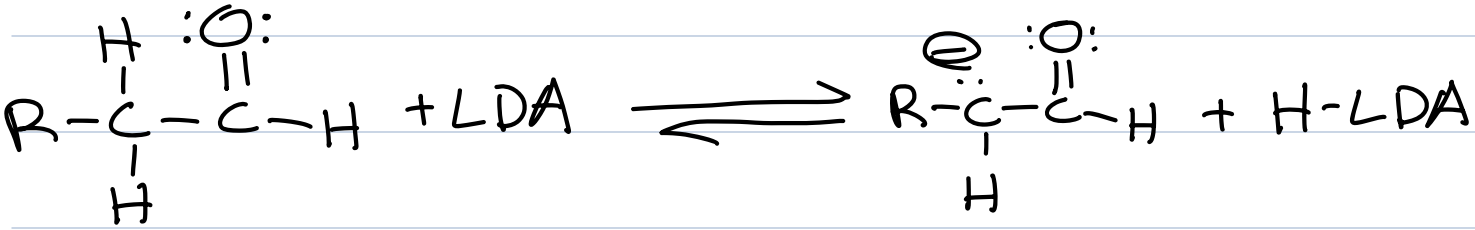
$pK_a \cong 40$

"H-LDA"

Not a nucleophile because of the two isopropyl groups

LDA will quantitatively deprotonate aldehydes, ketones and esters to make enolates!

Aldehydes

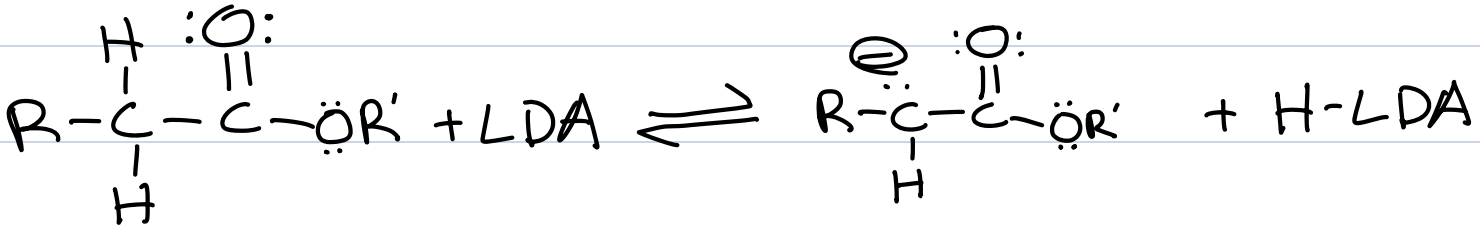


$pK_a = 18\text{-}20$

$pK_a = 40$

This side is favored by $\sim 10^{20}$!

Esters

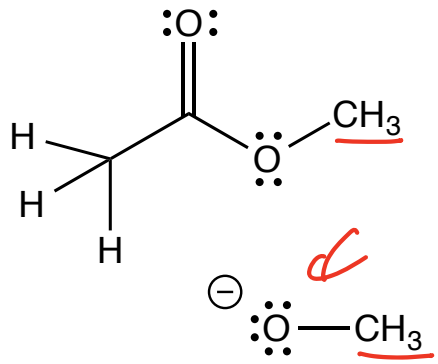


$pK_a = 23\text{-}25$

$pK_a = 40$

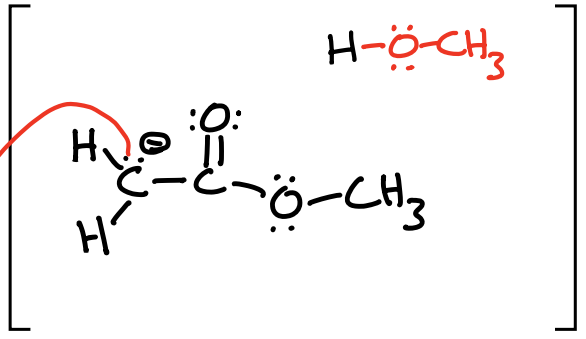
This side is favored by $\sim 10^{15}$!

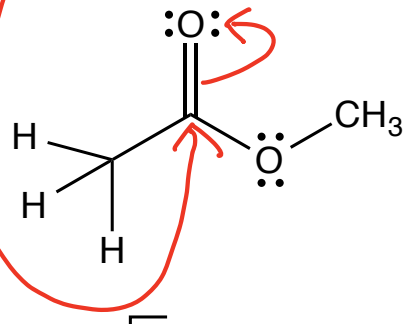
Claisen Condensation → "Aldol with Esters"



The R group of the base must match the ester!!

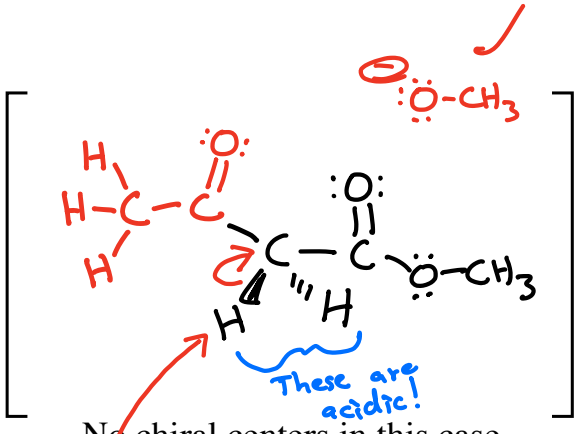
Take a proton away





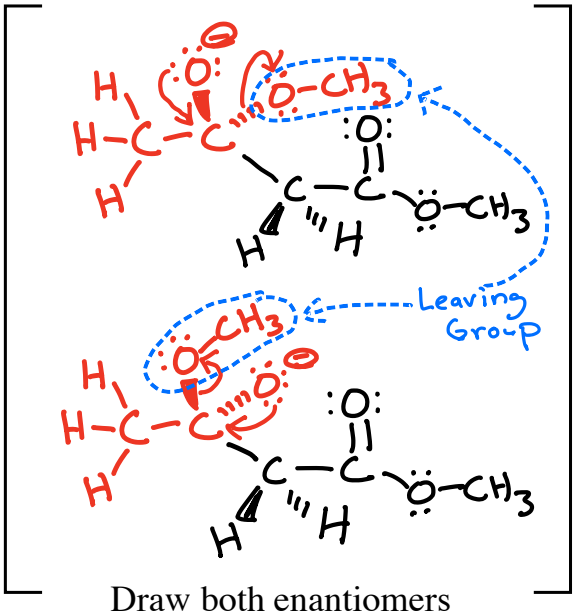
Make a bond

Mechanism B



No chiral centers in this case

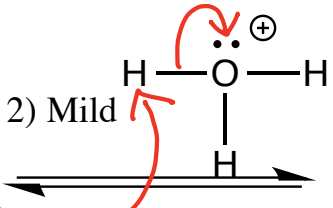
Break a bond

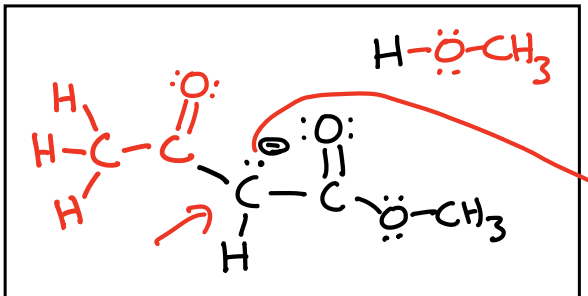


Draw both enantiomers

Take a proton away

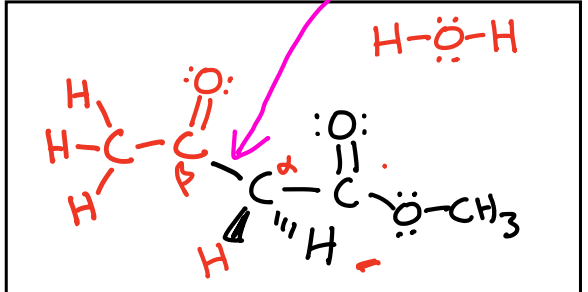
(Chemist opens flask and adds a mild acid)





Initial Products

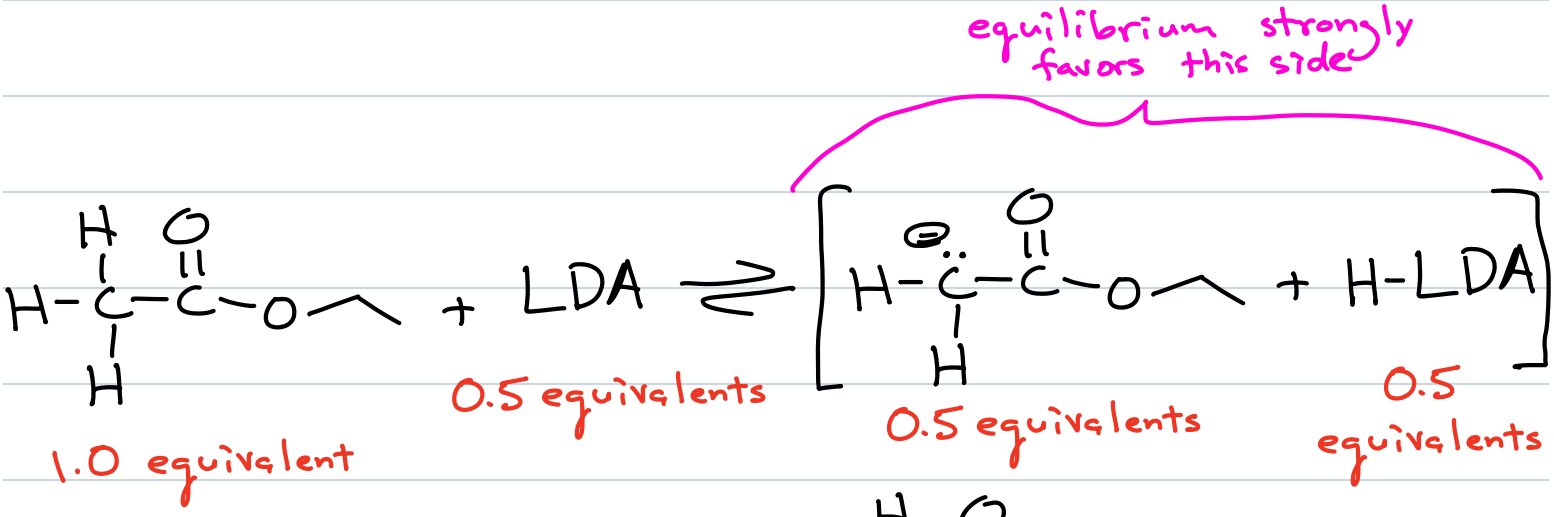
New C-C bond



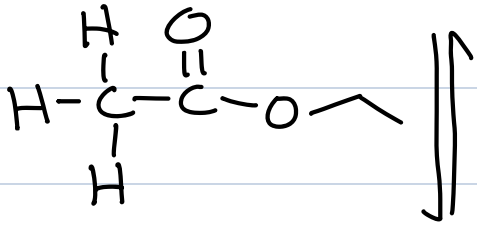
Final Products

This is a much more stable anion compared to $^{\ominus}OCH_3$, providing a strong driving force (motive) for the Claisen condensation reaction

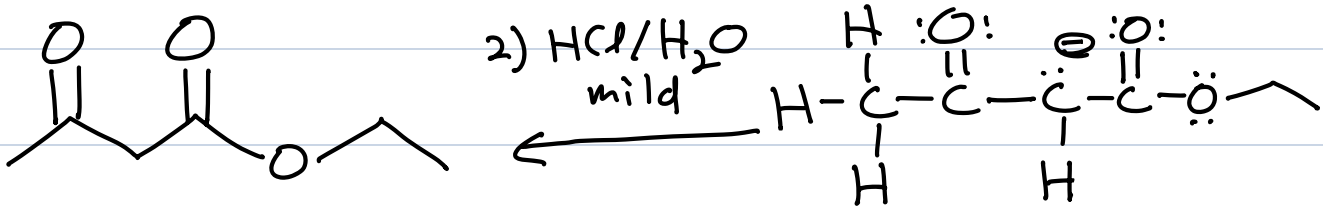
What if we use 0.5 equivalents of LDA with an ester?



Amount of ester left over after 0.5 equivalents of enolate is made



0.5 equivalents

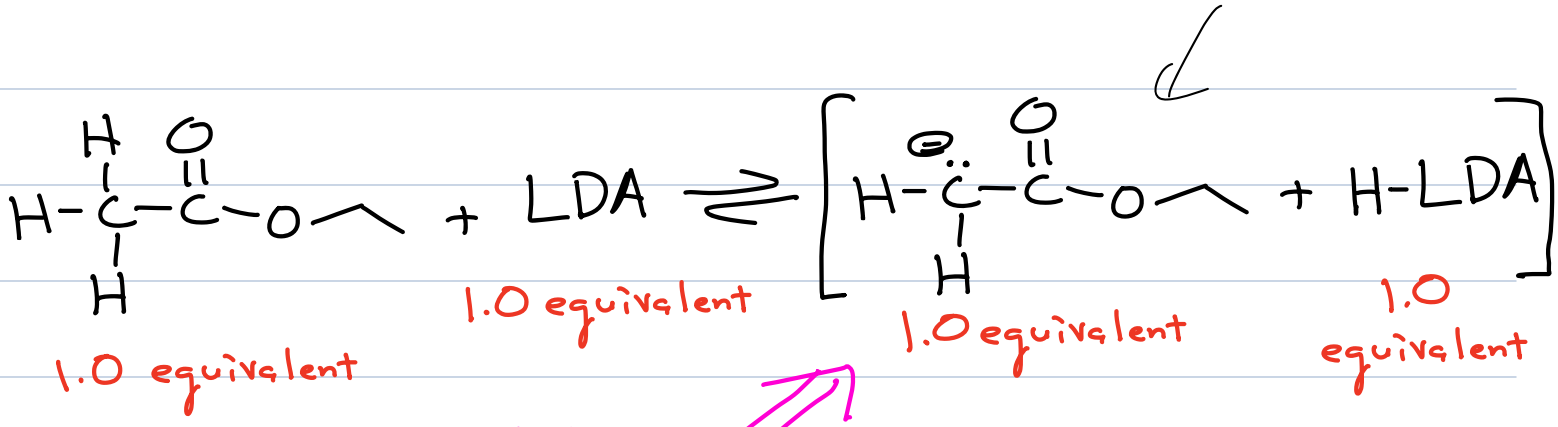


0.5 equivalents

0.5 equivalents

(There are 2 ester molecules used for each product molecule so there can only be half the number of product molecules compared to starting ester molecules)

What if we use 1.0 equivalent of LDA with an ester?



1.0 equivalent

1.0 equivalent

1.0 equivalent

1.0 equivalent

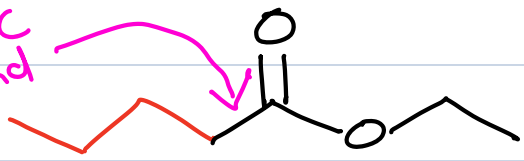
The enolate forms quantitatively so there is no ester left to react with!

2)

1.0 equivalent

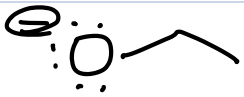
S_N2

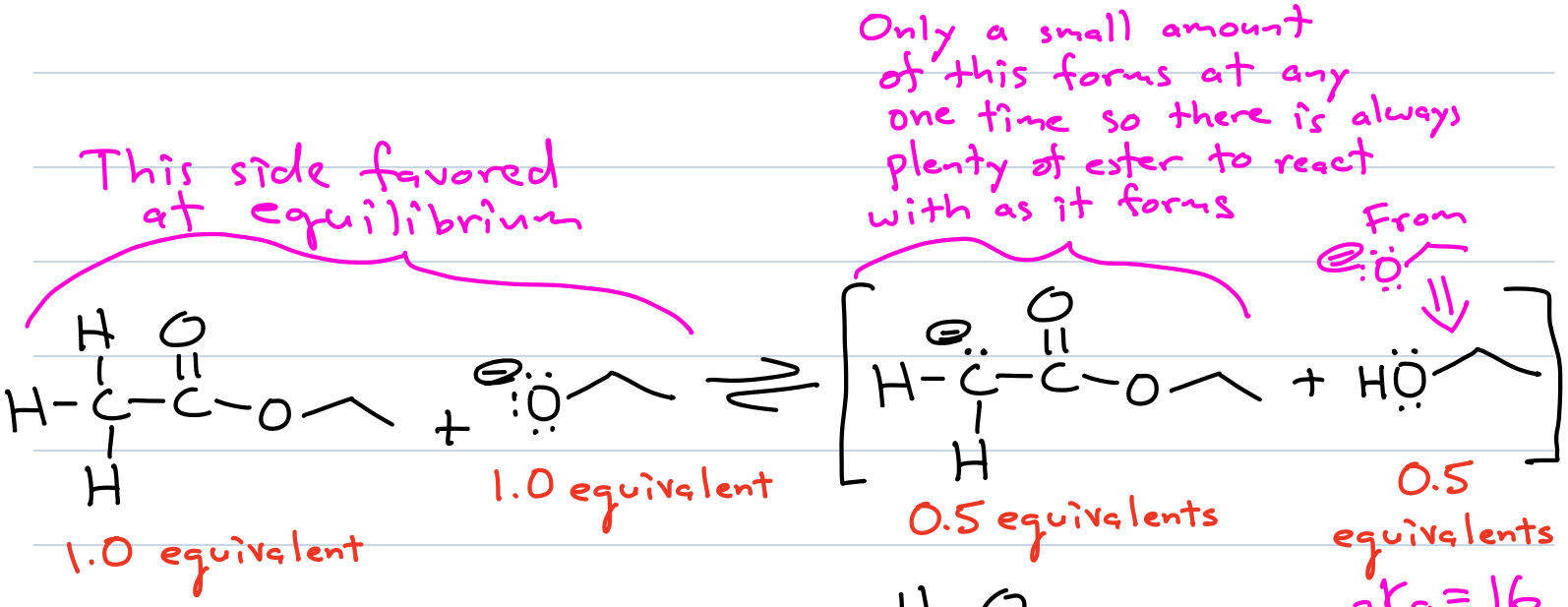
New C-C bond

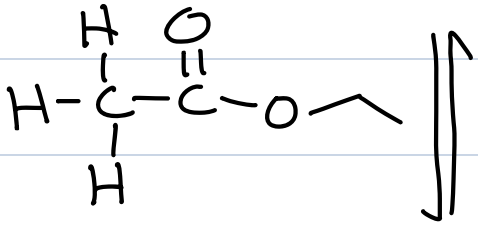


1.0 equivalent

All of the starting ester molecules end up as a the same number of product molecules with a new C-C bond!

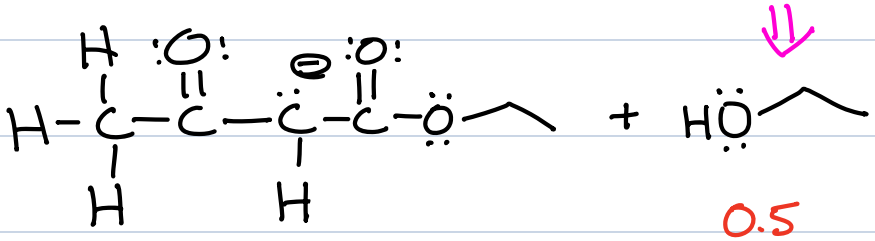
What if we use 1.0 equivalent of  with an ester?





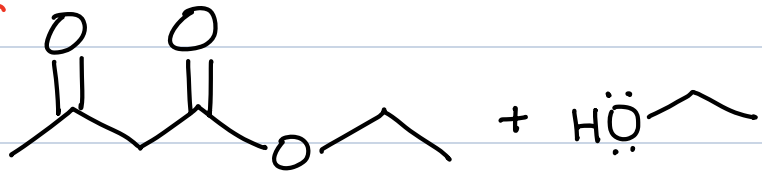
Leaving group from ester

Products from bond-forming step only — not overall process

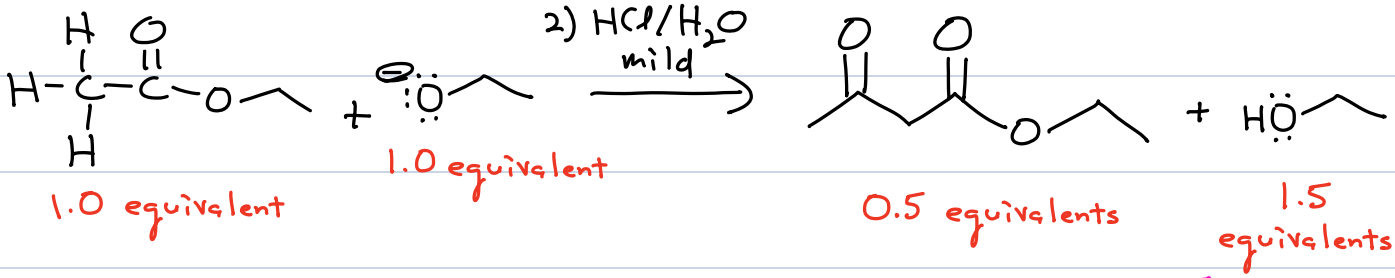


2) HCl/H_2O mild

Overall Products from all steps

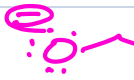


Overall Reaction

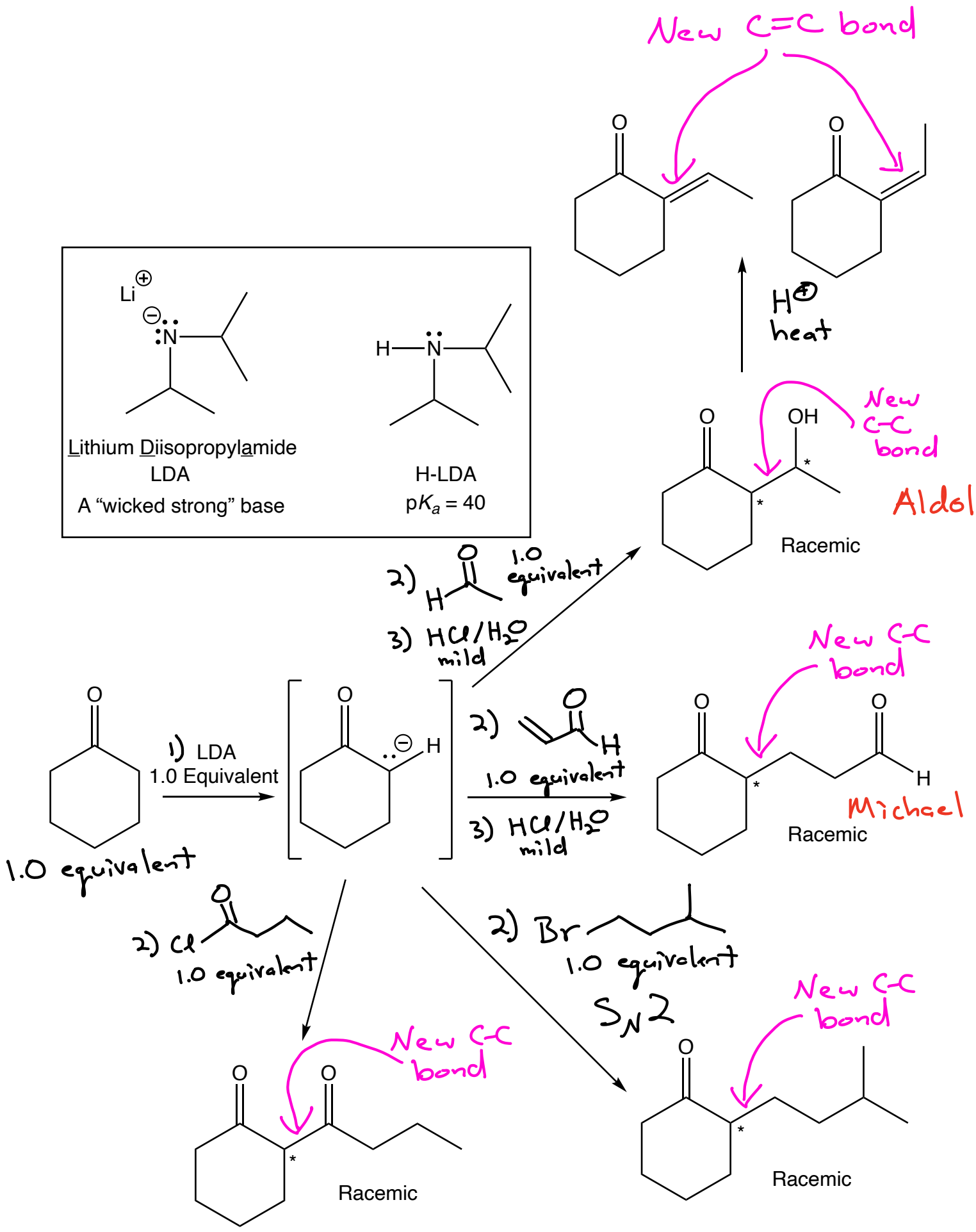


0.5 equivalents comes from first step, formation of the enolate

0.5 equivalents comes from second step, loss of leaving group from ester (see mechanism)

0.5 equivalents is left over from original  that was not used

Note: Considerable detail was added to the preceding four pages compared to what I wrote in lecture — I wanted to capture more of the key points for you to study


New C=C bond
H⊕
heat
New C-C bond
Aldol
Racemic
Lithium Diisopropylamide
LDA
A "wicked strong" base
H-LDA
pKa = 40
2) 1.0 equivalent
3) HCl/H2O mild
1) LDA
1.0 Equivalent
1.0 equivalent
2) 1.0 equivalent
3) HCl/H2O mild
New C-C bond
Michael
Racemic
2) 1.0 equivalent
2) 1.0 equivalent
SN2
New C-C bond
Racemic
New C-C bond
Racemic

α,β-Unsaturated, nitriles, ketones, or esters

β-Substituted aldehydes, nitriles, ketones, or esters

β-Keto esters

α,β-Unsaturated aldehydes

Acid Chlorides

β-Hydroxy aldehydes

Aldehydes

Ketones

Carboxylic esters

β-Ketoaldehyde

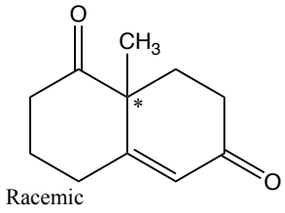
β-Diketone

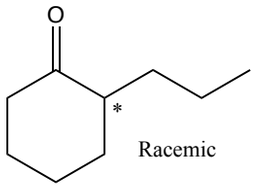
Carboxylic acids

Substituted aldehyde

Substituted ketone

β-Diester


O
CH3
*
O
Racemic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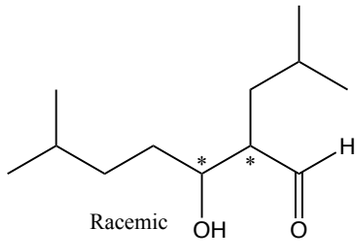
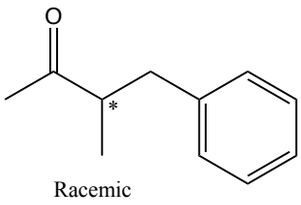
Racemic


*
*
H
Racemic
OH
O


O
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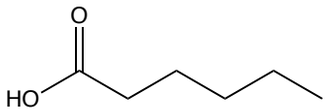
Racemic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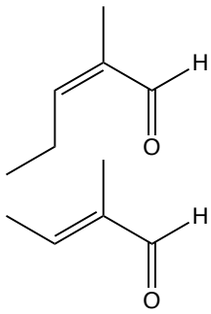
HO


H
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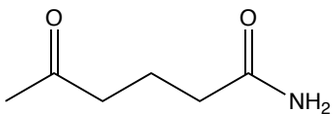
H
O


O
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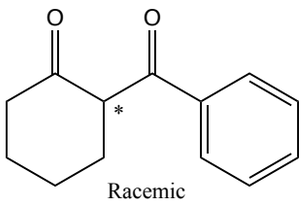
NH2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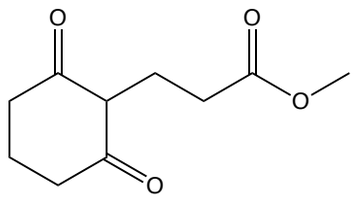
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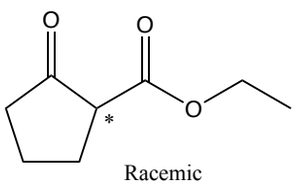
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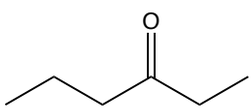
Racemic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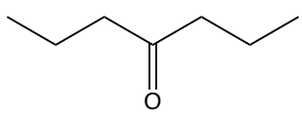
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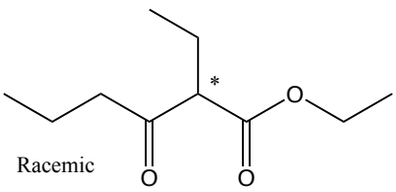
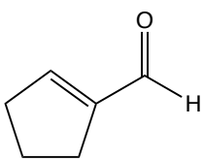

*
O
Racemic
O
O

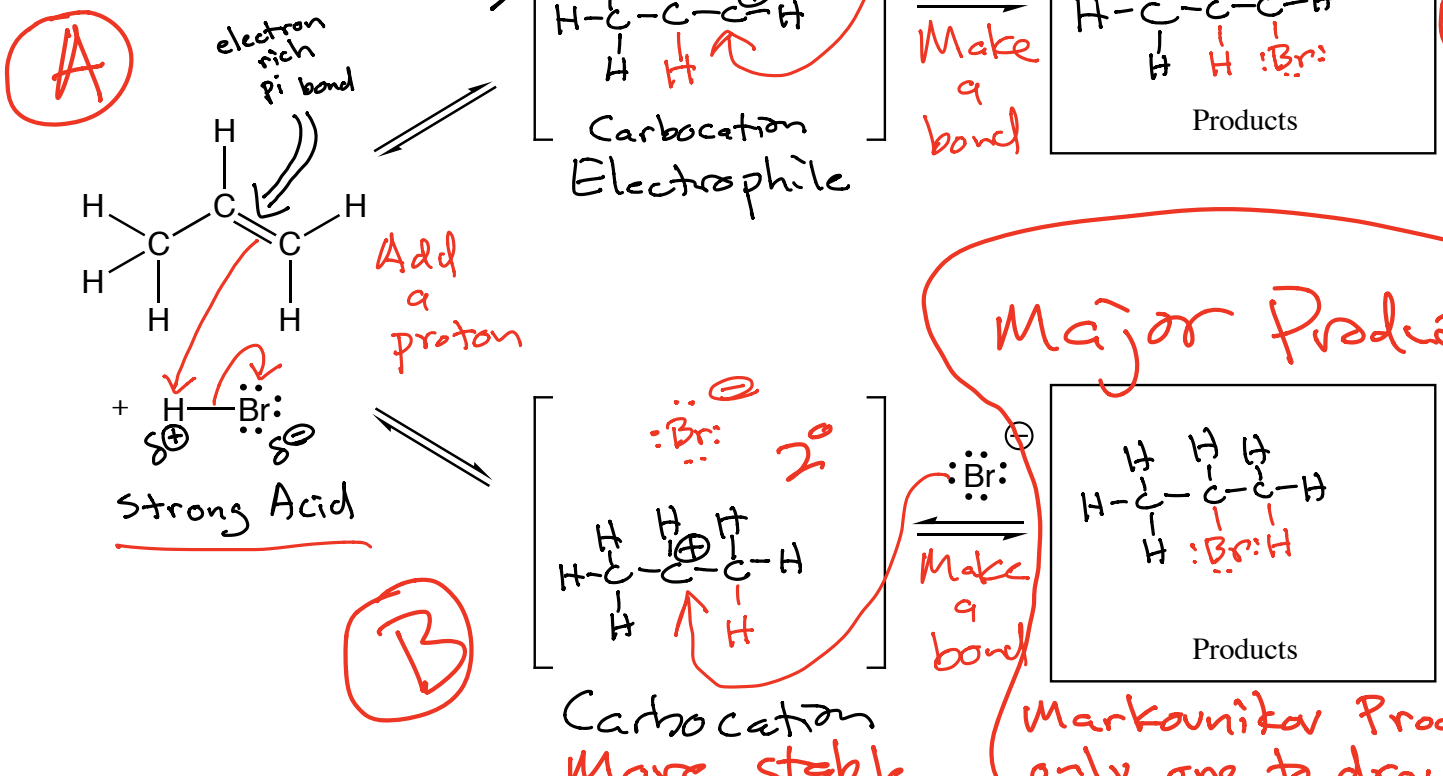

O
H

"X" can be Cl, Br, I
Not F

Addition of H-X to an Alkene

Brackets indicate this is an intermediate

Nucleophile



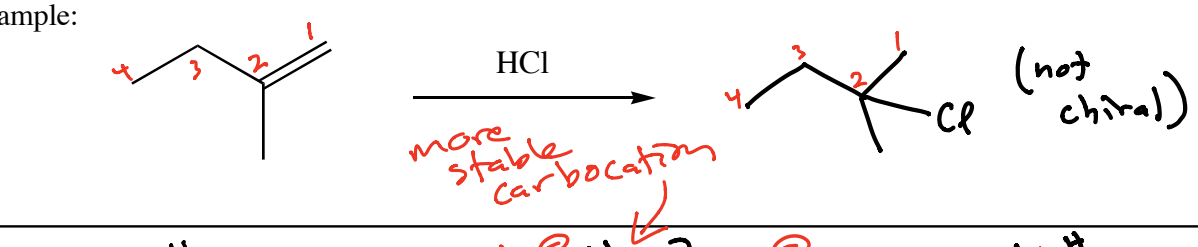
Which constitutional isomer is formed?

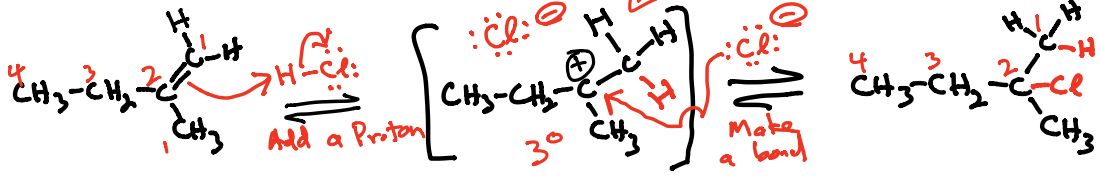
Summary: Alkene pi bond reacts with H-X to add a proton to creat a carbocation intermediate that makes a bond with $X^{\ominus}$ to give the product

Regiochemistry: Markovnikov's Rule

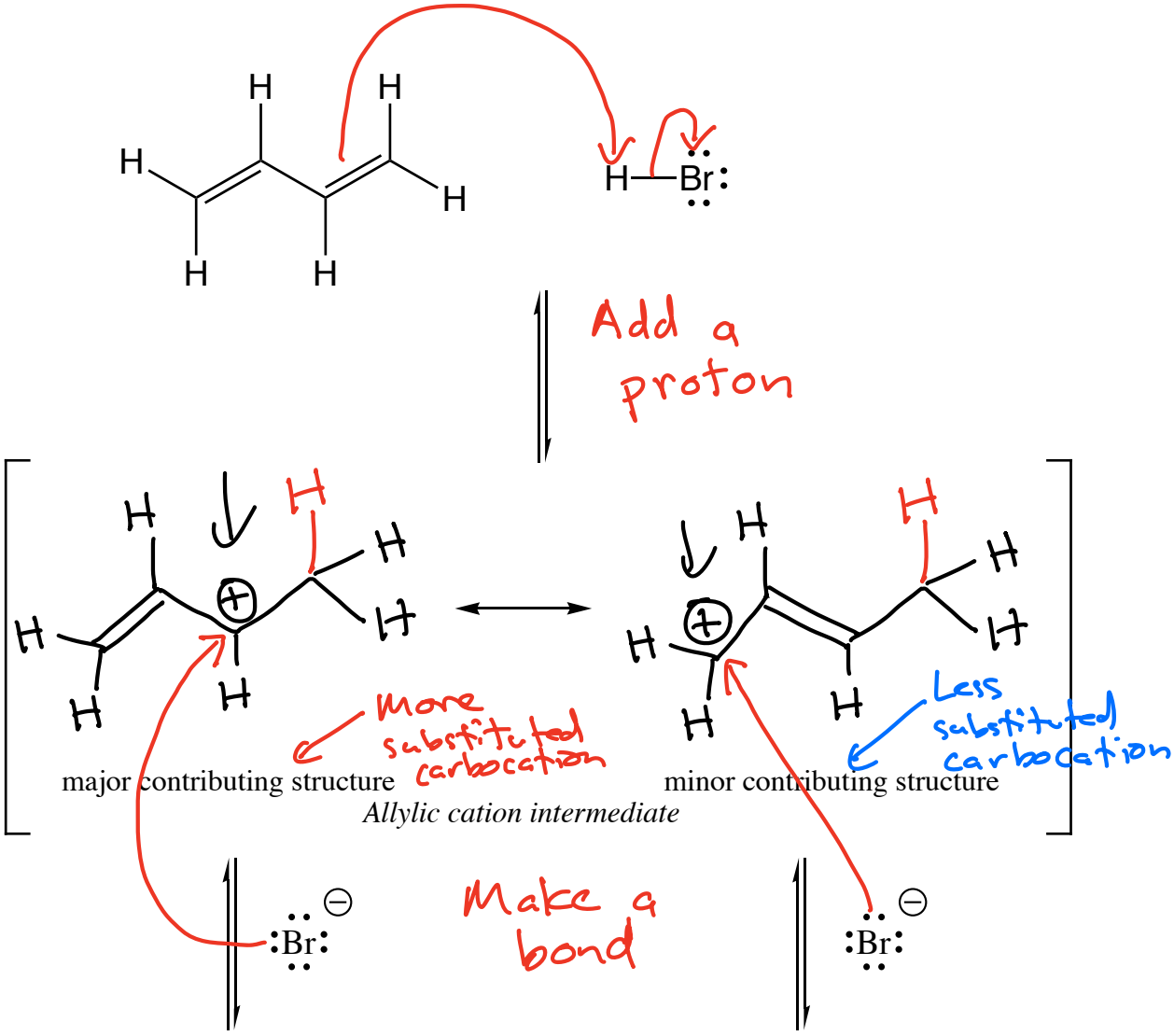
Stereochemistry: Mixed (time capsule) → Racemic Product

Example:

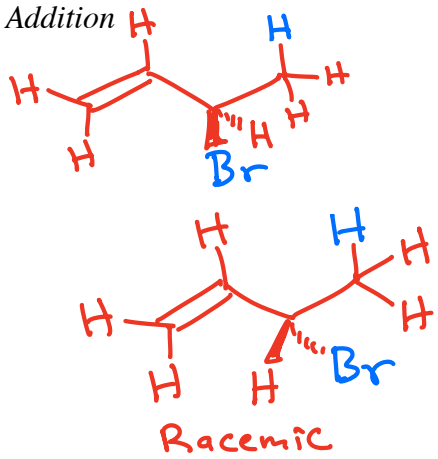




H-X reacting with conjugated dienes

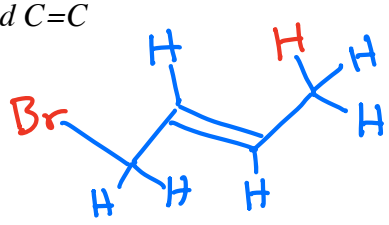


1,2 Addition



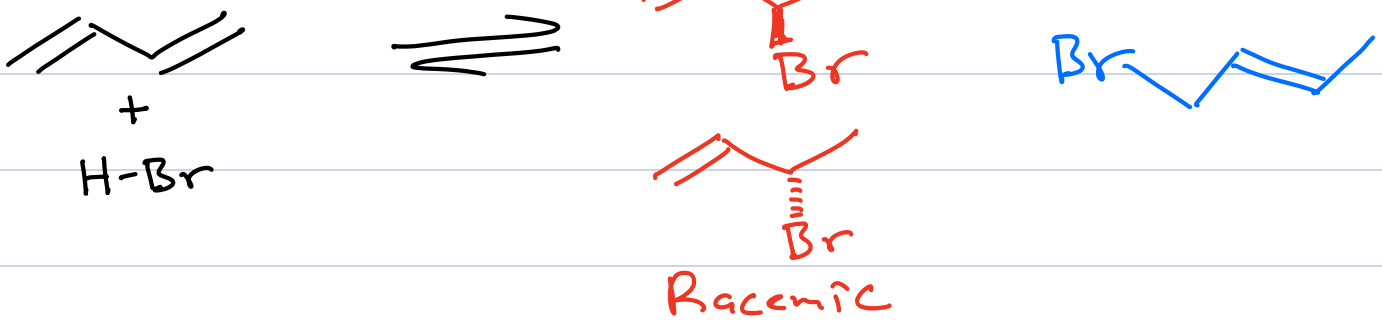
Products

1,4 Addition - more stable, more highly substituted C=C



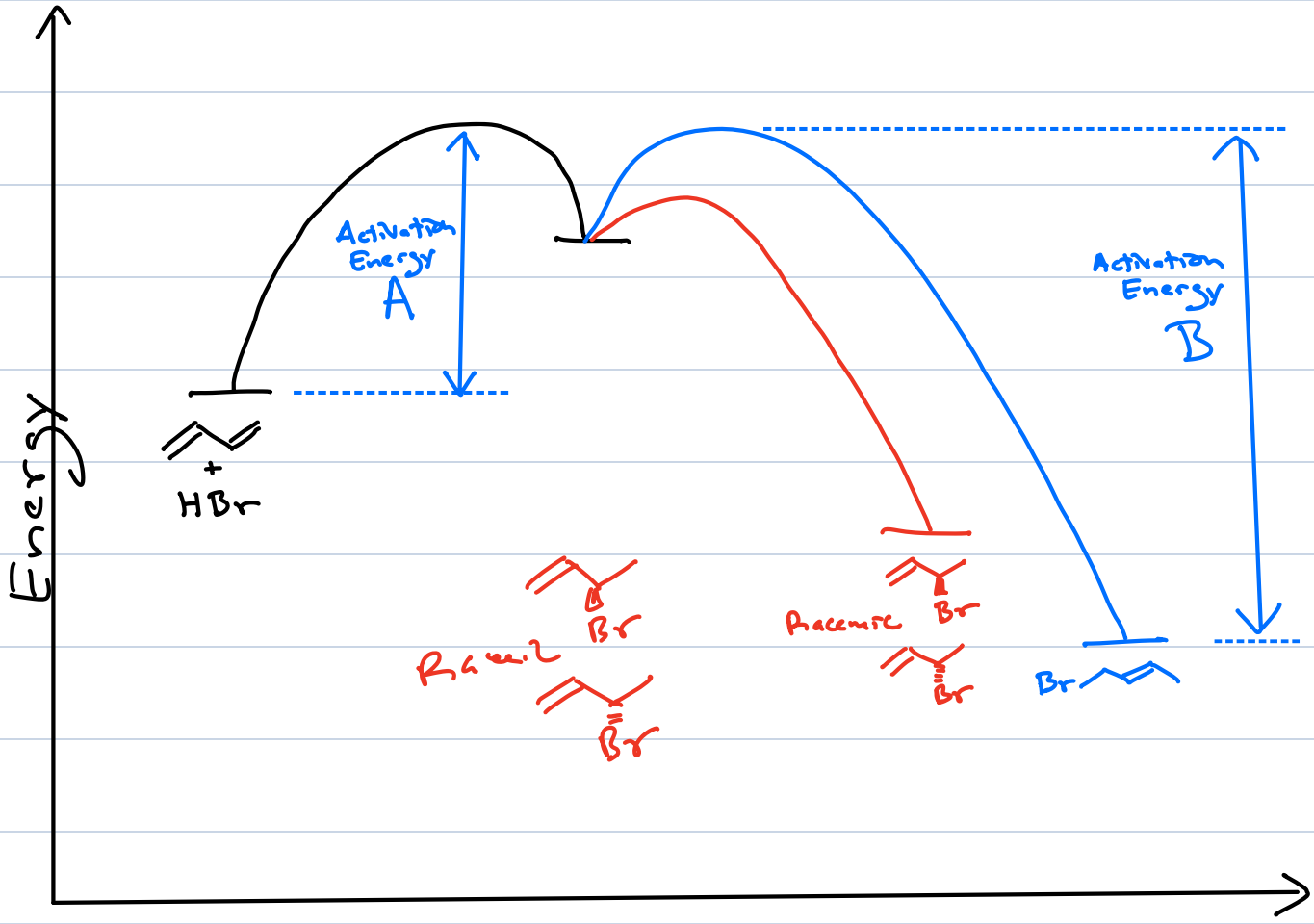
Products

1,2 addition 1,4 addition



Racemic

Temperature of Reaction		
-78°C	90%	10%
+40°C	15%	85%



Low temperature → Molecules have enough energy to get over activation energy A, but not enough energy to get over activation energy B.

Kinetic Control

"Fastest" wins

High temperature → Molecules have enough energy to get over activation energy A and activation energy B

Thermodynamic Control

Most stable product wins