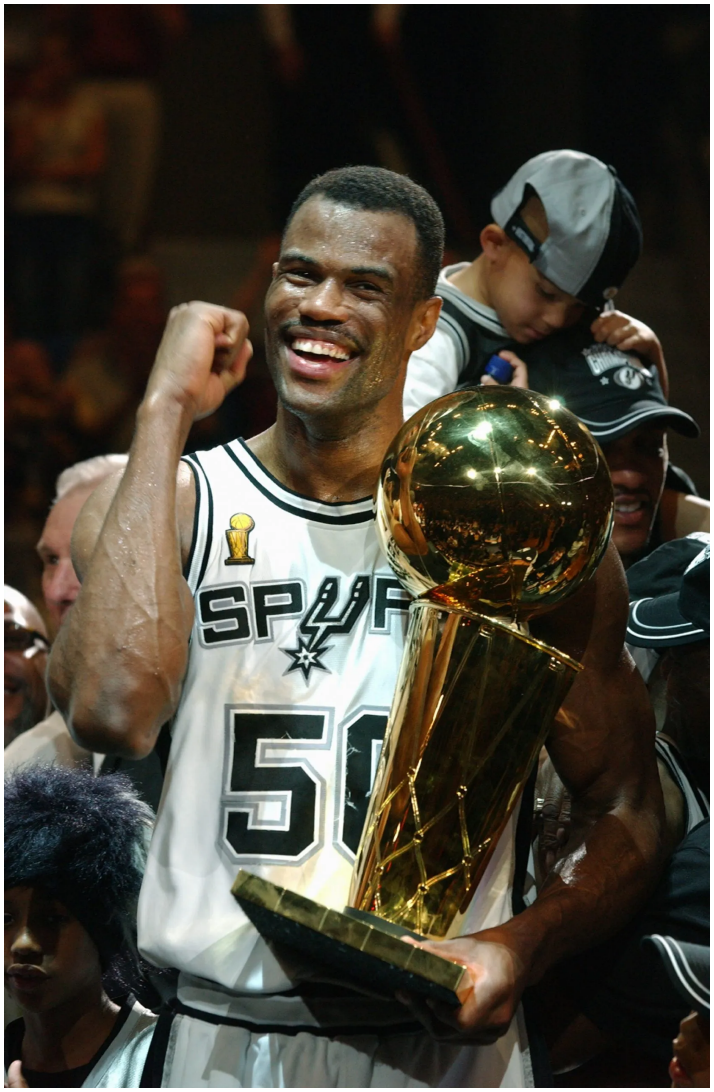
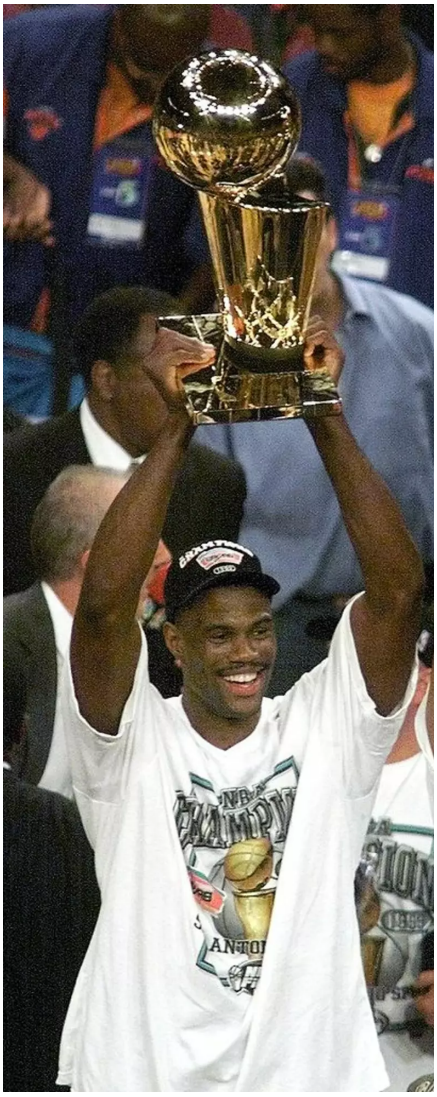
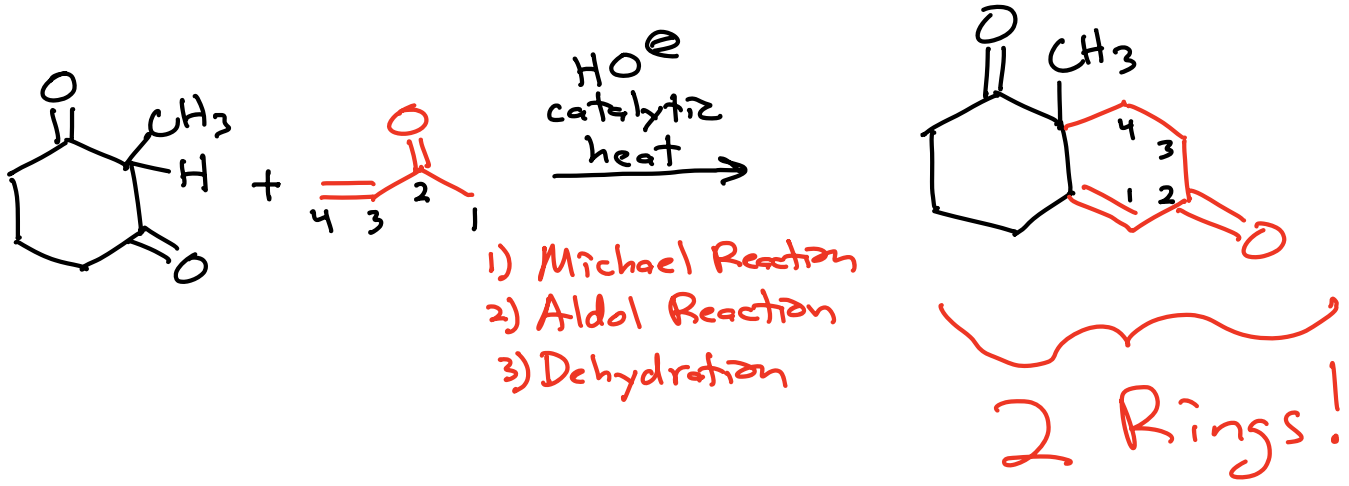




David Robinson earned 2 NBA Championship Rings!

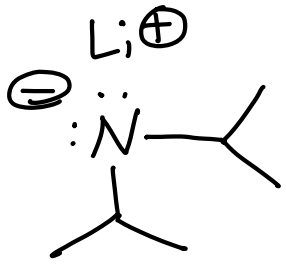
This is the only Robinson annulation reaction you will see on exams

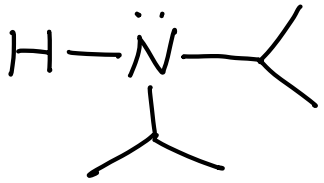


Note how the only Robinson annulation you will see in this class creates a product with

2 Rings!

The wicked strong base that changes things





Lithium Diisopropylamide

"LDA"

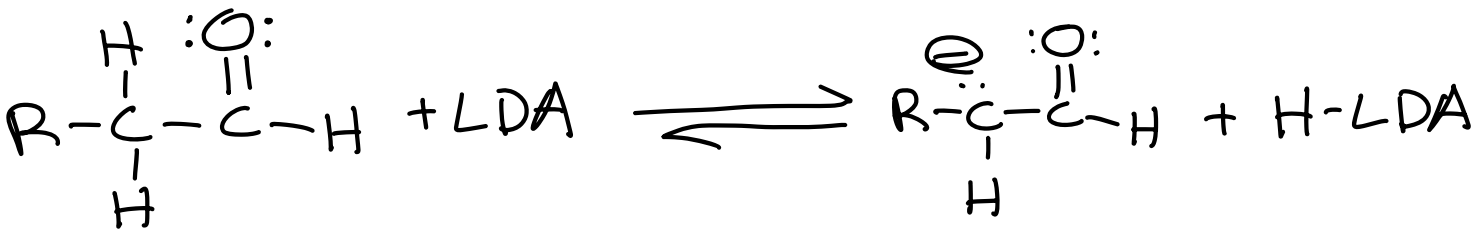
$pK_a \cong 40$

"H-LDA"

Not a nucleophile because of the two isopropyl groups

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

Aldehydes

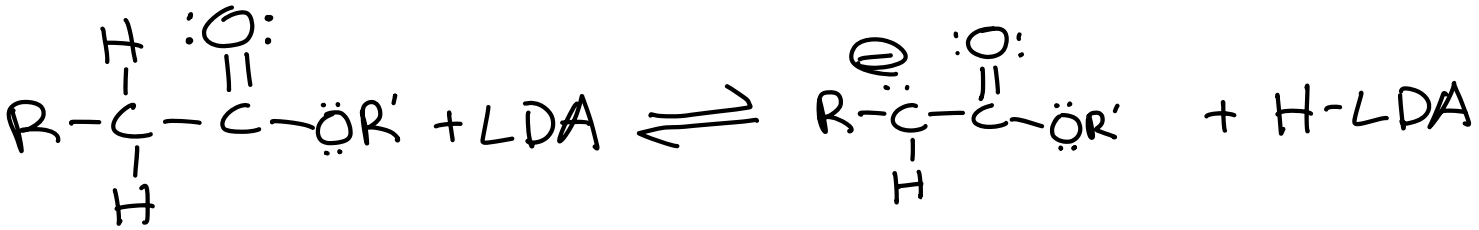


$pK_a = 18\text{-}20$

$pK_a = 40$

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

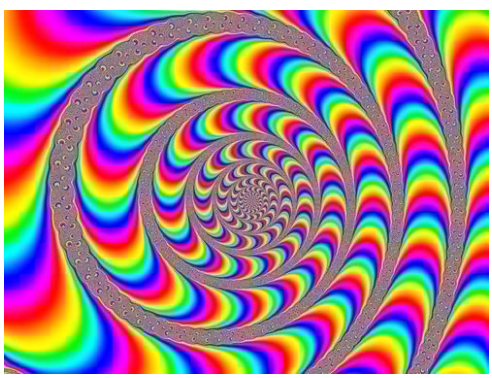
Esters

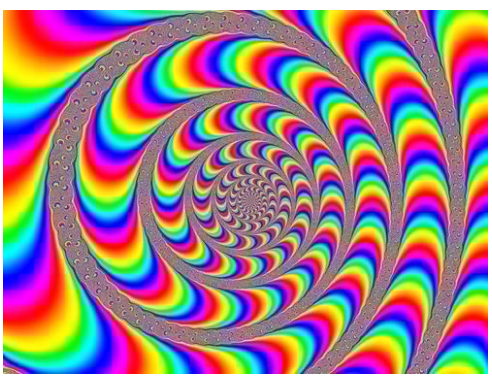


$pK_a = 23\text{-}25$

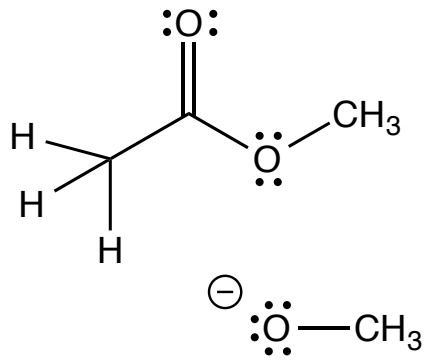
$pK_a = 40$

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

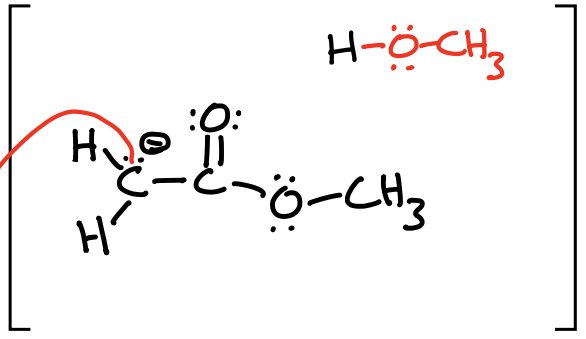




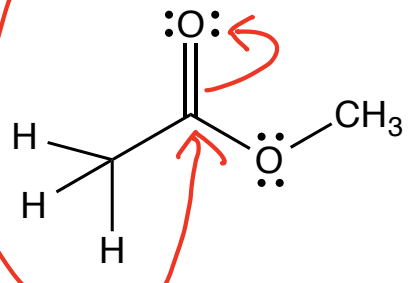
Claisen Condensation → "Aldol with Esters"



Take a proton away

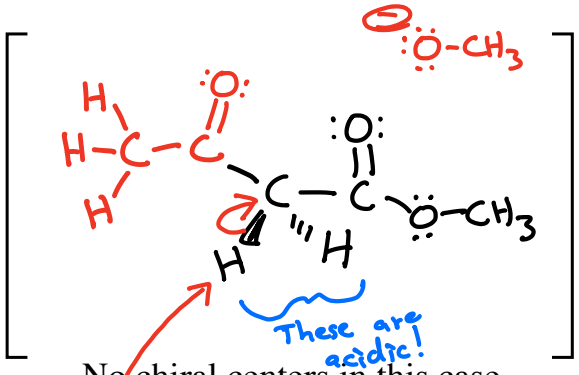


The R group of the base must match the ester!!



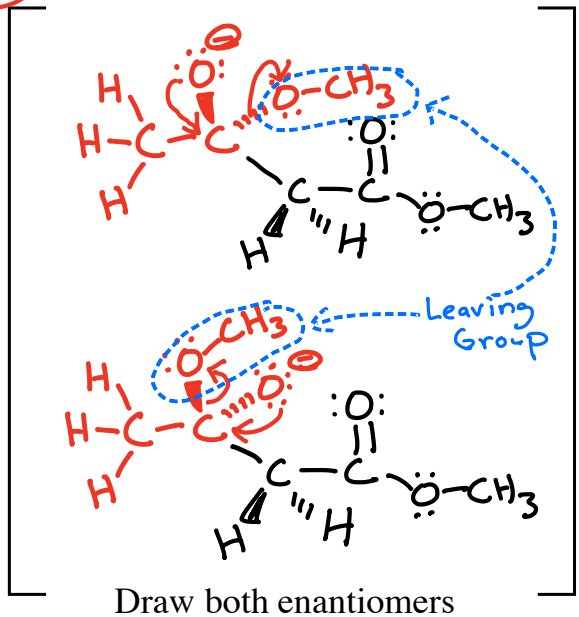
Make a bond

Mechanism B

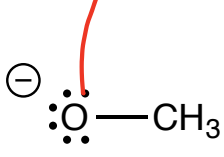


No chiral centers in this case

Break a bond

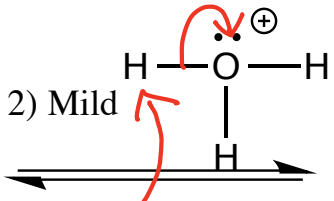


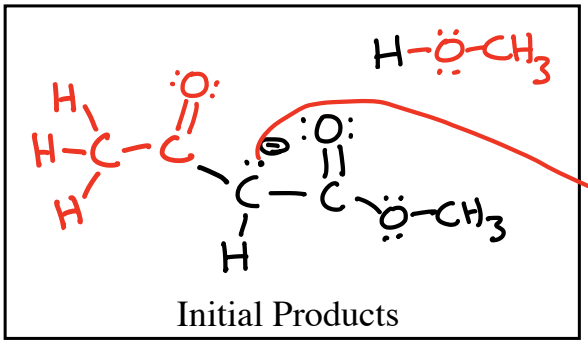
Draw both enantiomers



Take a proton away

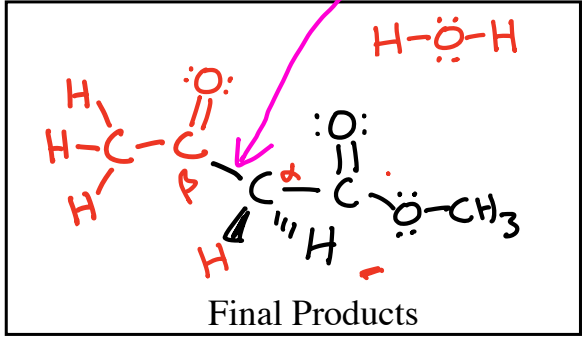
(Chemist opens flask and adds a mild acid)





Initial Products

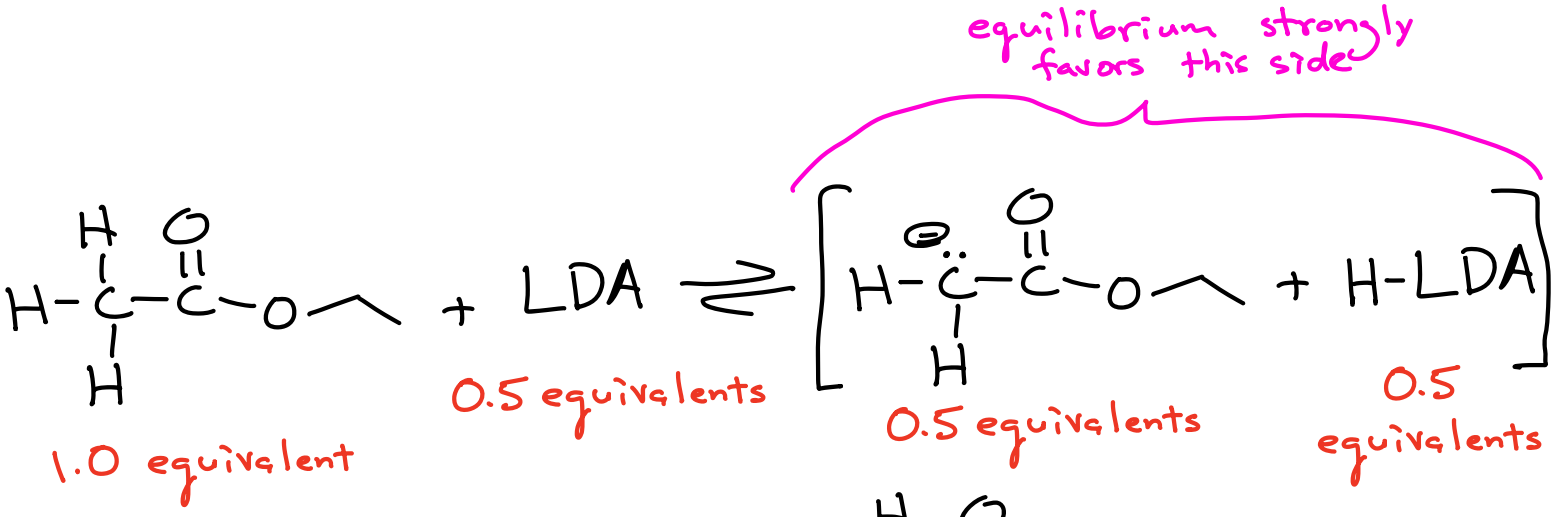
New C–C bond



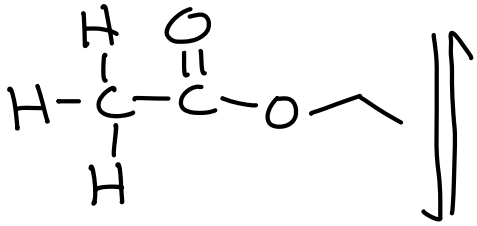
Final Products

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

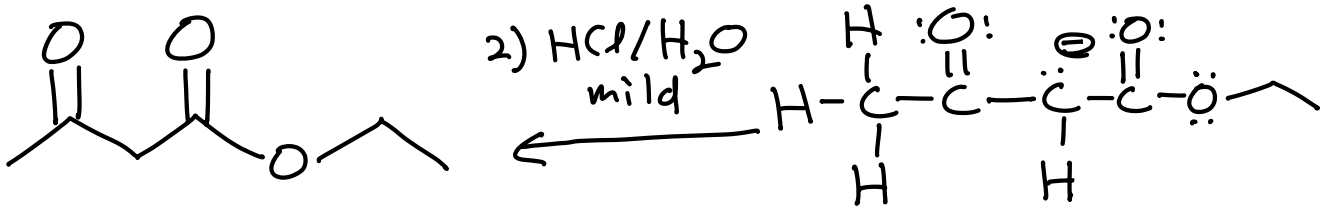
What if we use 0.5 equivalents of LDA with an ester?



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



0.5 equivalents

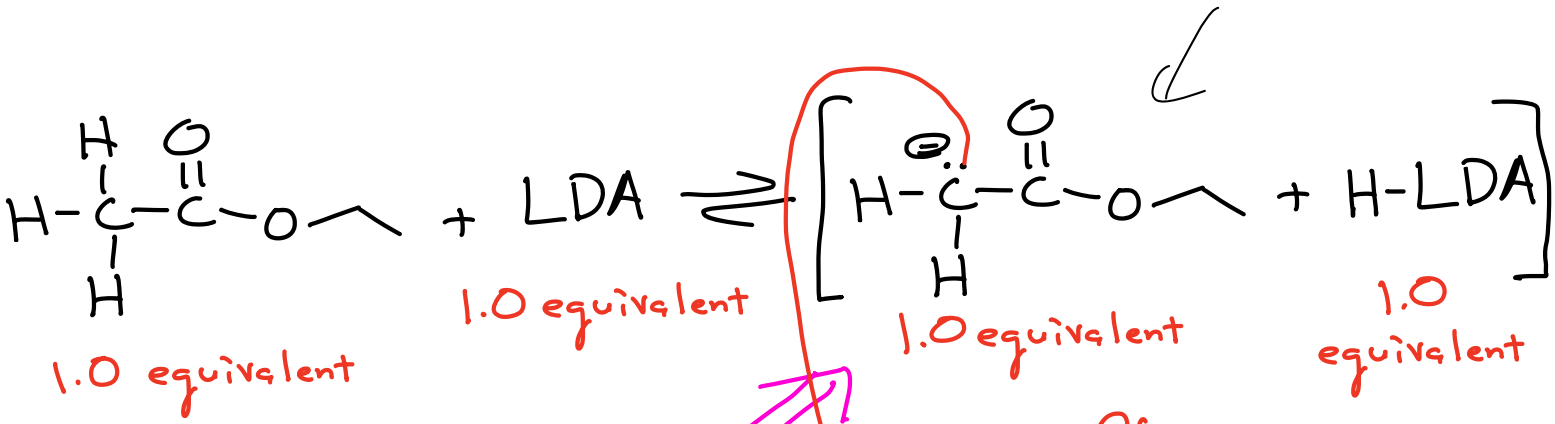


0.5 equivalents

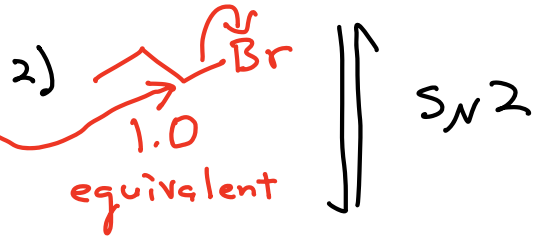
0.5 equivalents

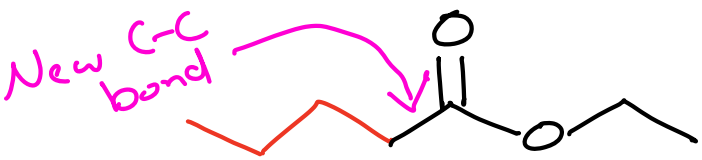
(There are 2 ester molecules used for each product molecule so there can only be half the number of product molecules compared to starting ester molecules)

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



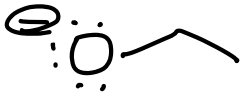
The enolate forms quantitatively so there is no ester left to react with!





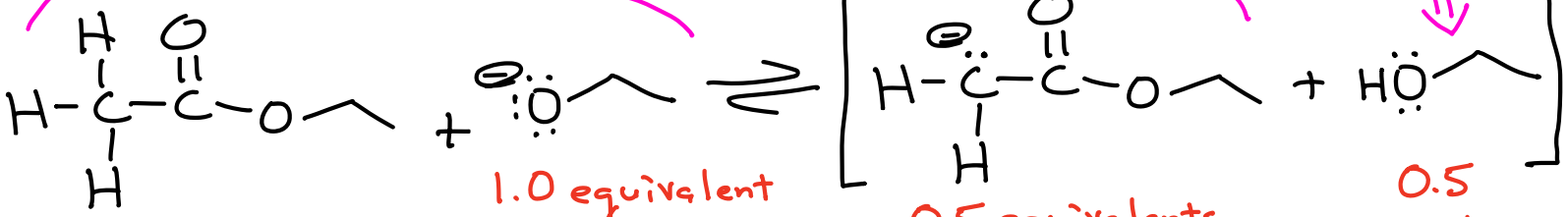
1.0 equivalent

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?

This side favored at equilibrium

Only a small amount of this forms at any one time so there is always plenty of ester to react with as it forms



1.0 equivalent

1.0 equivalent

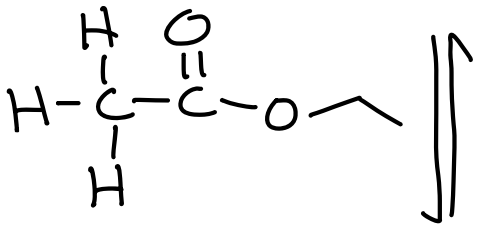
0.5 equivalents

From 

0.5 equivalents

pKa = 23-25

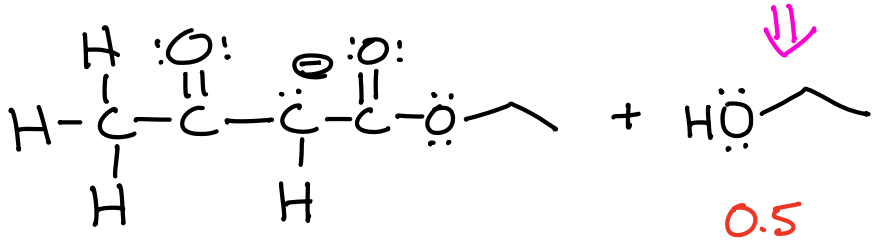
pKa = 16



0.5 equivalents

Leaving group from ester

Products from bond-forming step only — not overall process

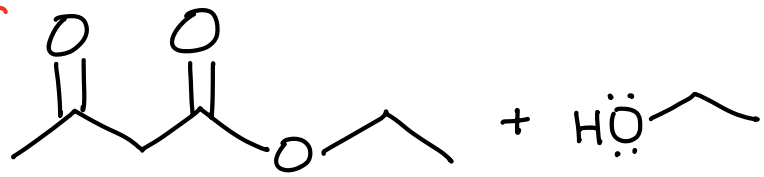


0.5 equivalents

0.5 equivalents

2) HCl/H_2O mild

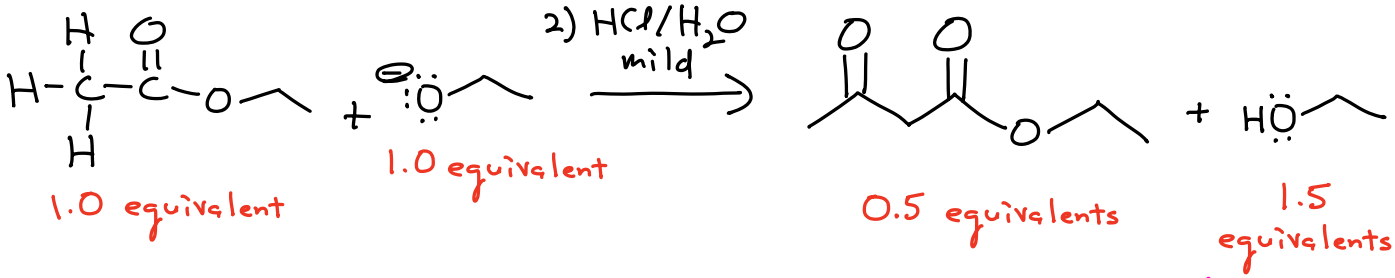
Overall Products from all steps



0.5 equivalents

1.5 equivalents

Overall Reaction

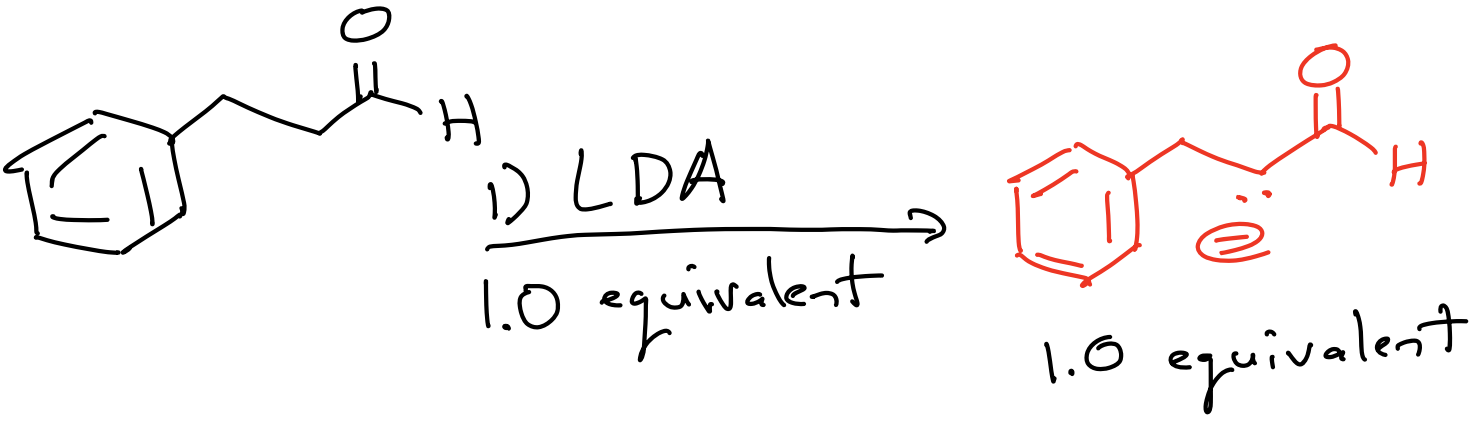


0.5 equivalents comes from first step, formation of the enolate

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

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



This enolate will just sit in the reaction until a chemist opens the flask and adds an electrophile!

NAME (Print): _____

EID _____

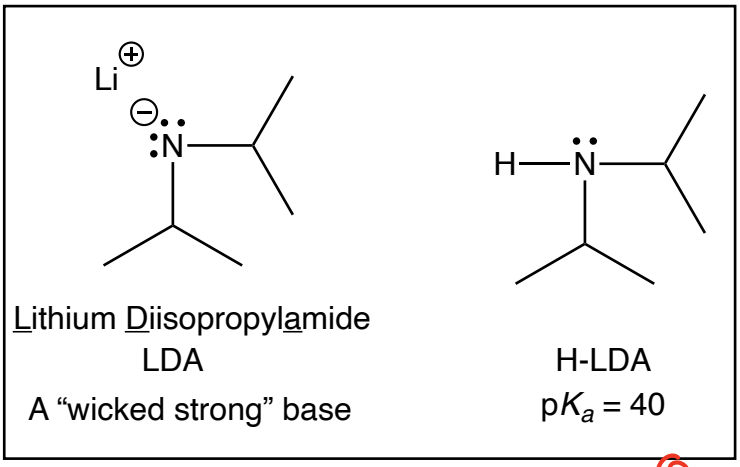
SIGNATURE: _____

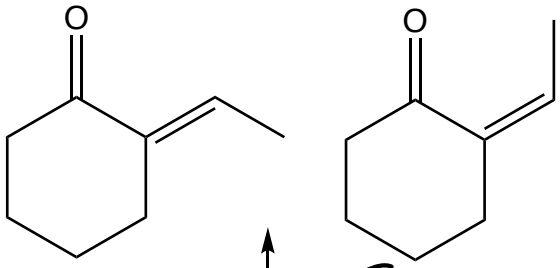
Chemistry 320N
In-class Quiz
Mar. 13, 2025

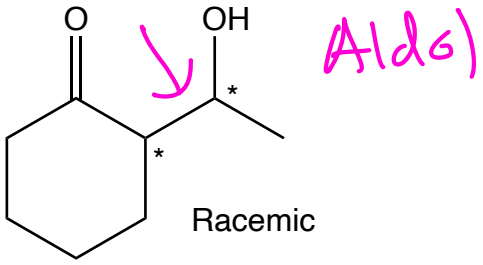
Please print the first three letters of your last name in the three boxes

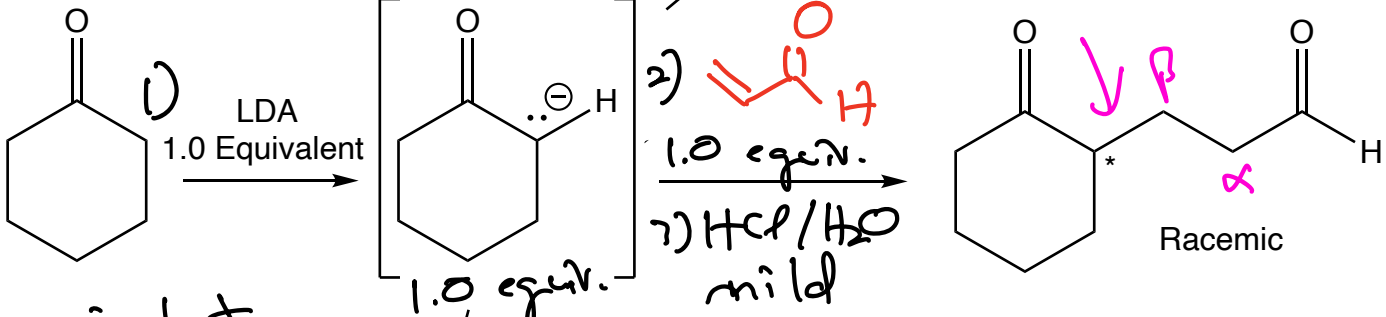
The pKa of a typical aldehyde is 18 – 20. What happens when we add 1.0 equivalent of LDA to an aldehyde?

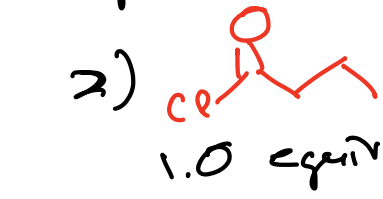
- ○ We will get an aldol reaction without having to add any further reagents.
- ● All of the aldehyde will make an enolate, so there will be no further reaction until an electrophile is added by the chemist.

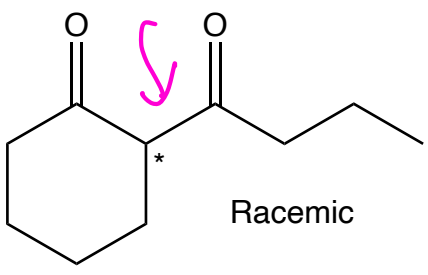

Li
N
H
N
Lithium Diisopropylamide
LDA
A "wicked strong" base
H-LDA
pKa = 40

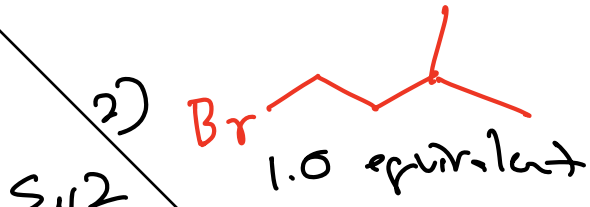

O
O
H⊕
heat

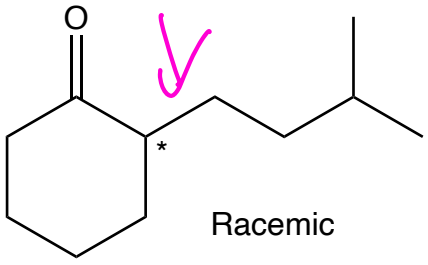

O
OH
Aldol
Racemic


O
1)
LDA
1.0 Equivalent
O
H
1.0 equiv.
2)
1.0 equiv.
3) HCl/H2O
mild
O
O
β
α
H
Racemic


1.0 equivalent
2)
Cl
1.0 equiv.


O
O
Racemic


SN2
2)
Br
1.0 equivalent


O
Racemic

Roadmap for OChem II!

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

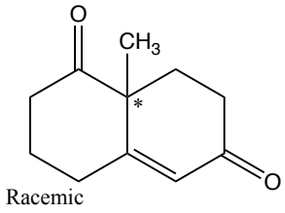
Carboxylic acids

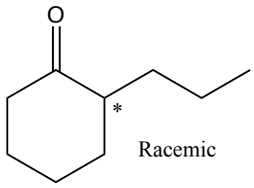
Substituted aldehyde

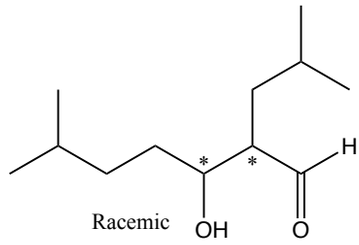
Substituted ketone

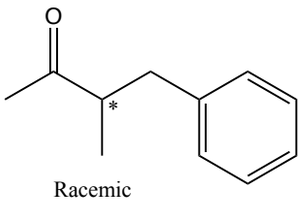
β-Diester

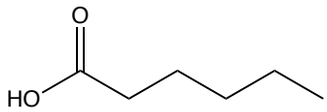
All of these have a FRE you should be able to recognize!

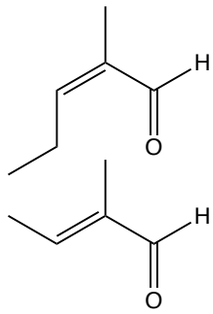


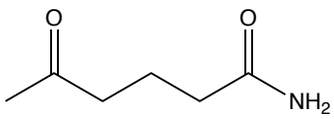


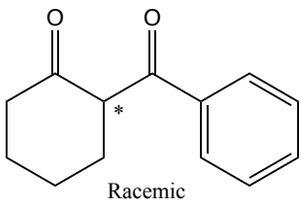


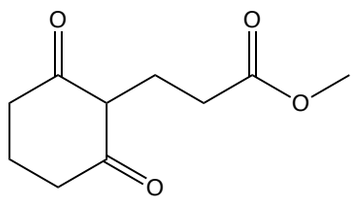


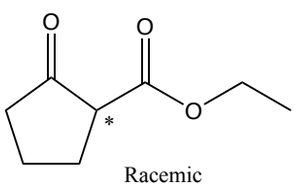


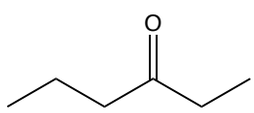


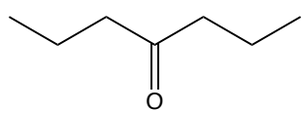


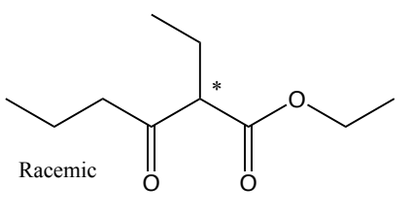


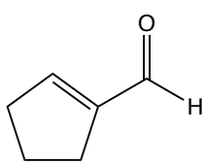


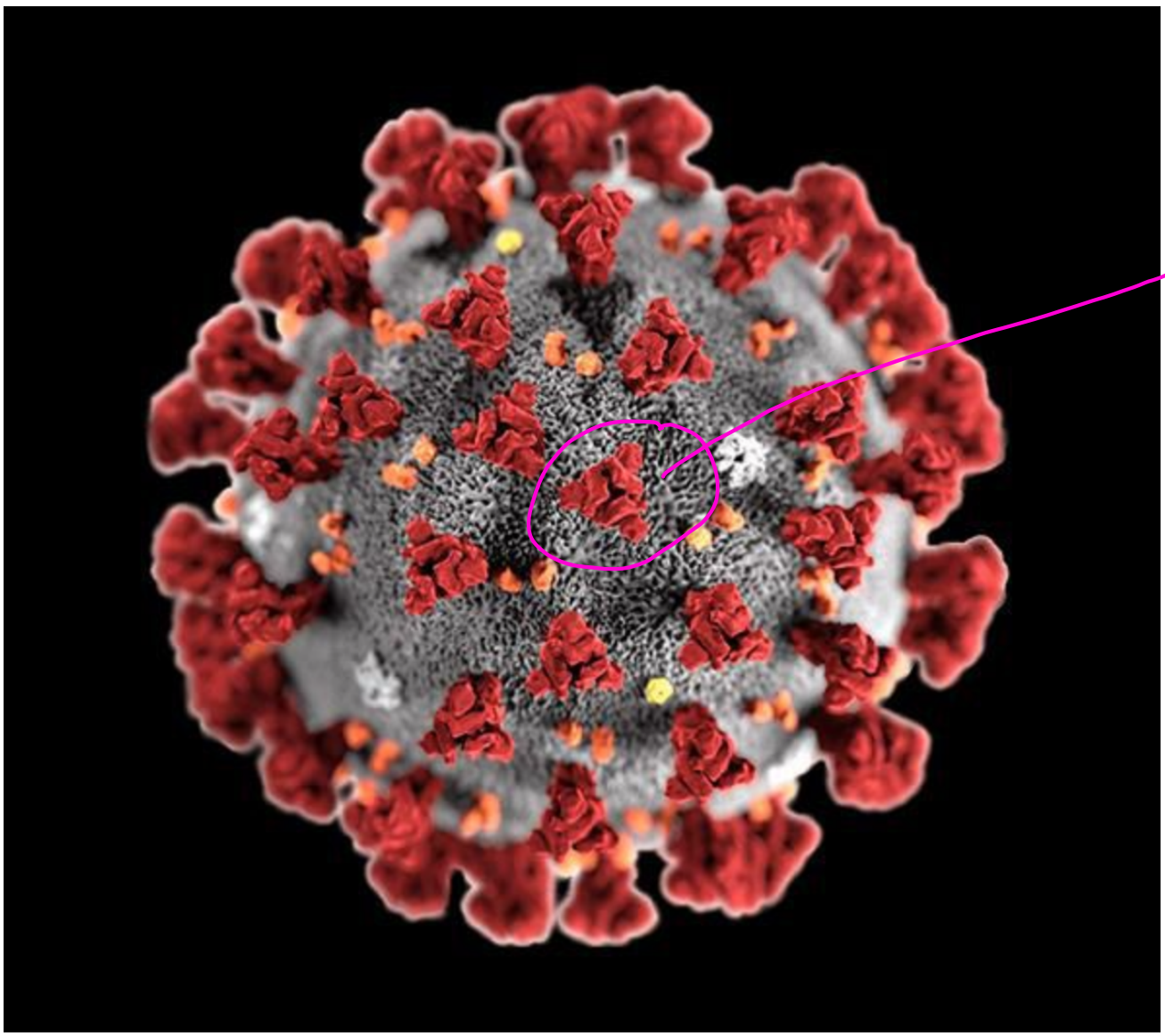











Spike protein

New UT cases

The University of Texas said two people in its community, an unnamed student and the Dean of Undergraduate Studies Brent Iverson, had tested positive for the virus. It is unclear if the pair are included in Travis County's count of confirmed cases.

immunobiology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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1-10 Each developing lymphocyte generates a unique antigen receptor by rearranging its receptor genes.

How are antigen receptors with an almost infinite range of specificities encoded by a finite number of genes? This question was answered in 1976, when **Susumu Tonegawa** discovered that the genes for immunoglobulin variable regions are inherited as sets of **gene segments**, each encoding a part of the variable region of one of the immunoglobulin polypeptide chains (Fig. 1.18). During B-cell development in the bone marrow, these gene segments are irreversibly joined by DNA recombination to form a stretch of DNA encoding a complete variable region. Because there are many different gene segments in each set, and different gene segments are joined together in different cells, each cell generates unique genes for the variable regions of the heavy and light chains of the immunoglobulin molecule. Once these recombination events have succeeded in producing a functional receptor, further rearrangement is prohibited. Thus each lymphocyte expresses only one receptor specificity.

This mechanism has three important consequences. First, it enables a limited number of gene segments to generate a vast number of different proteins. Second, because each cell assembles a different set of gene segments, each cell expresses a unique receptor specificity. Third, because gene rearrangement involves an irreversible change in a cell's DNA, all the progeny of that cell will inherit genes encoding the same receptor specificity. This general scheme was later also confirmed for the genes encoding the antigen receptor on T lymphocytes. The main distinctions between B- and T-lymphocyte receptors are that the immunoglobulin that serves as the B-cell antigen receptor has two identical antigen-recognition sites and can also be secreted, whereas the T-cell antigen receptor has a single antigen-recognition site and is always a cell-surface molecule. We shall see later that these receptors also recognize antigen in very different ways.

The potential diversity of lymphocyte receptors generated in this way is enormous. Just a few hundred different gene segments can combine in different ways to generate thousands of different receptor chains. The diversity of lymphocyte receptors is further amplified by junctional diversity, created by adding or subtracting nucleotides in the process of joining the gene segments, and by the fact that each receptor is made by pairing two different variable chains, each encoded in distinct sets of gene segments. A thousand different chains of each type could thus generate 10^6 distinct antigen receptors through this **combinatorial diversity**. Thus a small amount of genetic material can encode a truly staggering diversity of receptors. Only a subset of these randomly generated receptor specificities survive the selective processes that shape the peripheral lymphocyte repertoire; nevertheless, there are lymphocytes of at least 10^8 different specificities in an individual at any one time. These provide the raw material on which clonal selection acts.

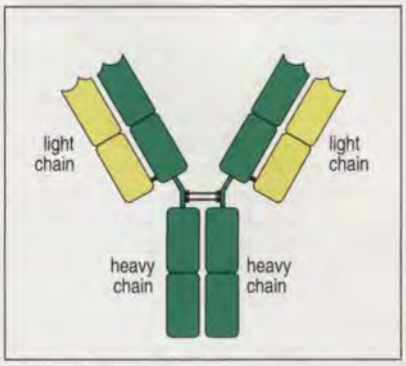

Fig. 1.17 Antibodies are made up of four protein chains. There are two types of chain in an antibody molecule: a larger chain called the heavy chain (green), and a smaller one called the light chain (yellow). Each chain has both a variable and a constant region, and there are two identical light chains and two identical heavy chains in each antibody molecule.

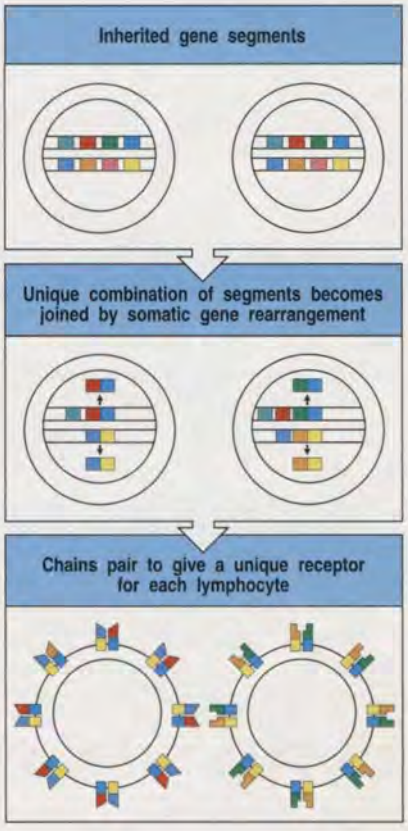

Fig. 1.18 The diversity of lymphocyte antigen receptors is generated by somatic gene rearrangements. Different parts of the variable regions of antigen receptors are encoded by sets of gene segments. During a lymphocyte's development, one member of each set of gene segments is joined randomly to the others by an irreversible process of DNA recombination. The juxtaposed gene segments make up a complete gene that encodes the variable part of one chain of the receptor, and is unique to that cell. This random rearrangement is repeated for the set of gene segments encoding the other chain. The rearranged genes are expressed to produce the two types of polypeptide chain. These come together to form a unique antigen receptor on the lymphocyte surface. Each lymphocyte bears many copies of its unique receptor.

CORONAVIRUS

Prevalent, protective, and convergent IgG recognition of SARS-CoV-2 non-RBD spike epitopes

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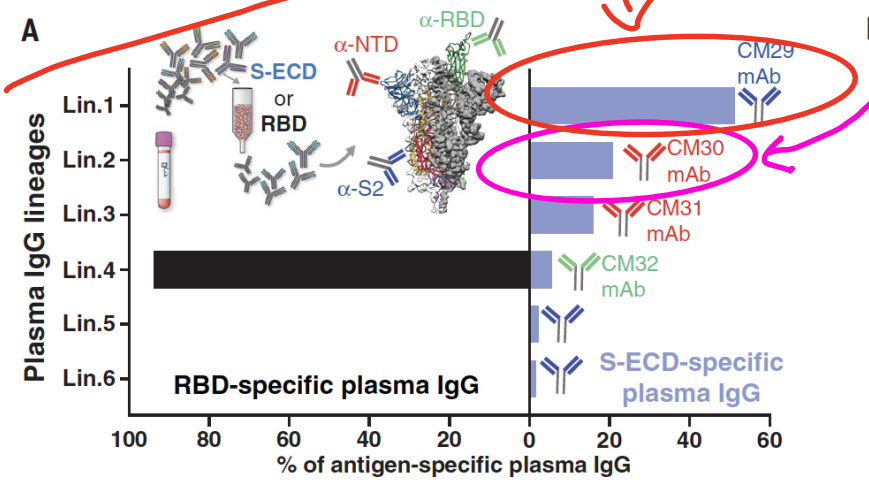
Voss *et al.*, *Science* **372**, 1108–1112 (2021) 4 June 2021

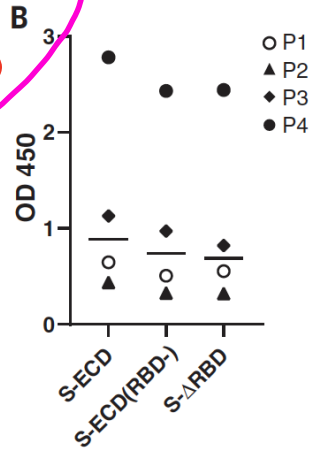
CORONAVIRUS

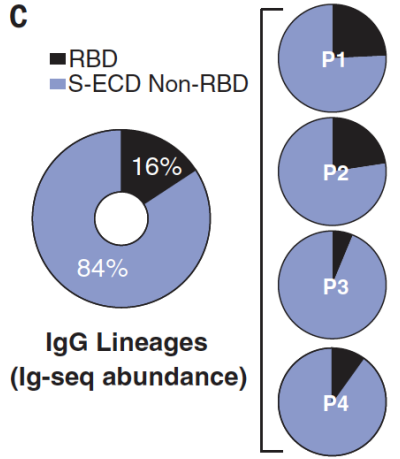
Prevalent, protective, and convergent IgG recognition of SARS-CoV-2 non-RBD spike epitopes

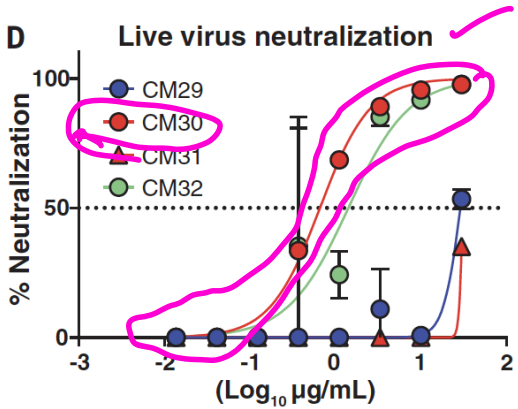
This one came from a cold I must have had

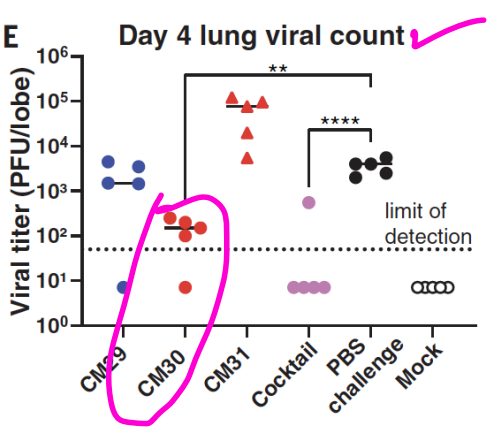
This antibody saved me!

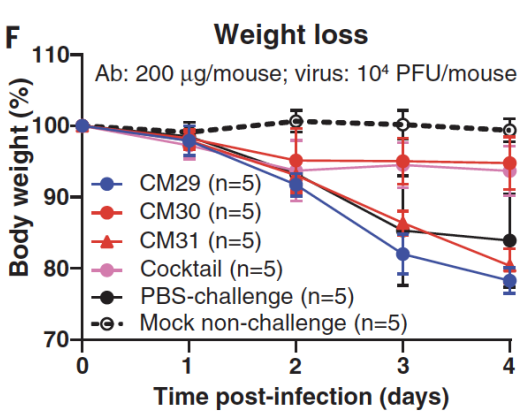










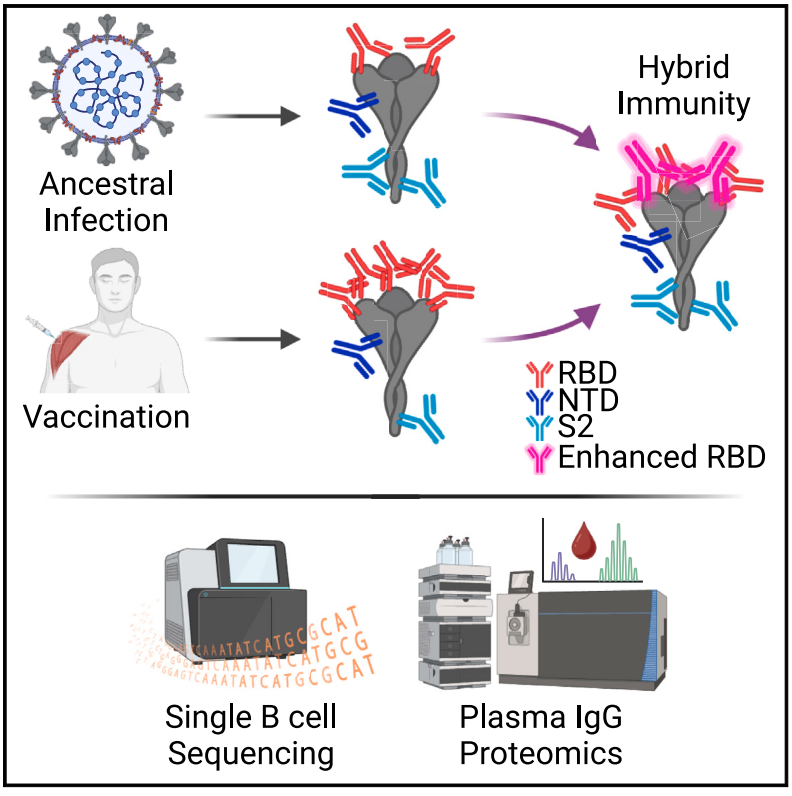


Cell Reports
Medicine

Article

Hybrid immunity to SARS-CoV-2 arises from serological recall of IgG antibodies distinctly imprinted by infection or vaccination

Graphical abstract



Highlights

- Infection and vaccination imprint distinct IgG responses at the molecular level
- Immunological imprinting varies between infection (S2/NTD) and vaccination (RBD)
- Over 60% of the IgG recall in hybrid immunity originates from the initial exposure
- Hybrid immune IgG plasma mAbs have superior neutralization potency and breadth

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In brief

Voss et al. demonstrate that hybrid immunity to SARS-CoV-2 arises from distinct immunological imprints left by infection and vaccination. Plasma antibodies maintain these initial imprints, with over 60% of the response derived from the initial exposure, but with enhanced potency and breadth, highlighted by the broadly neutralizing mAb SC27.

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The vaccine protected me from COVID AND a common cold!

CellPress
OPEN ACCESS

CM 29 That P3 me!

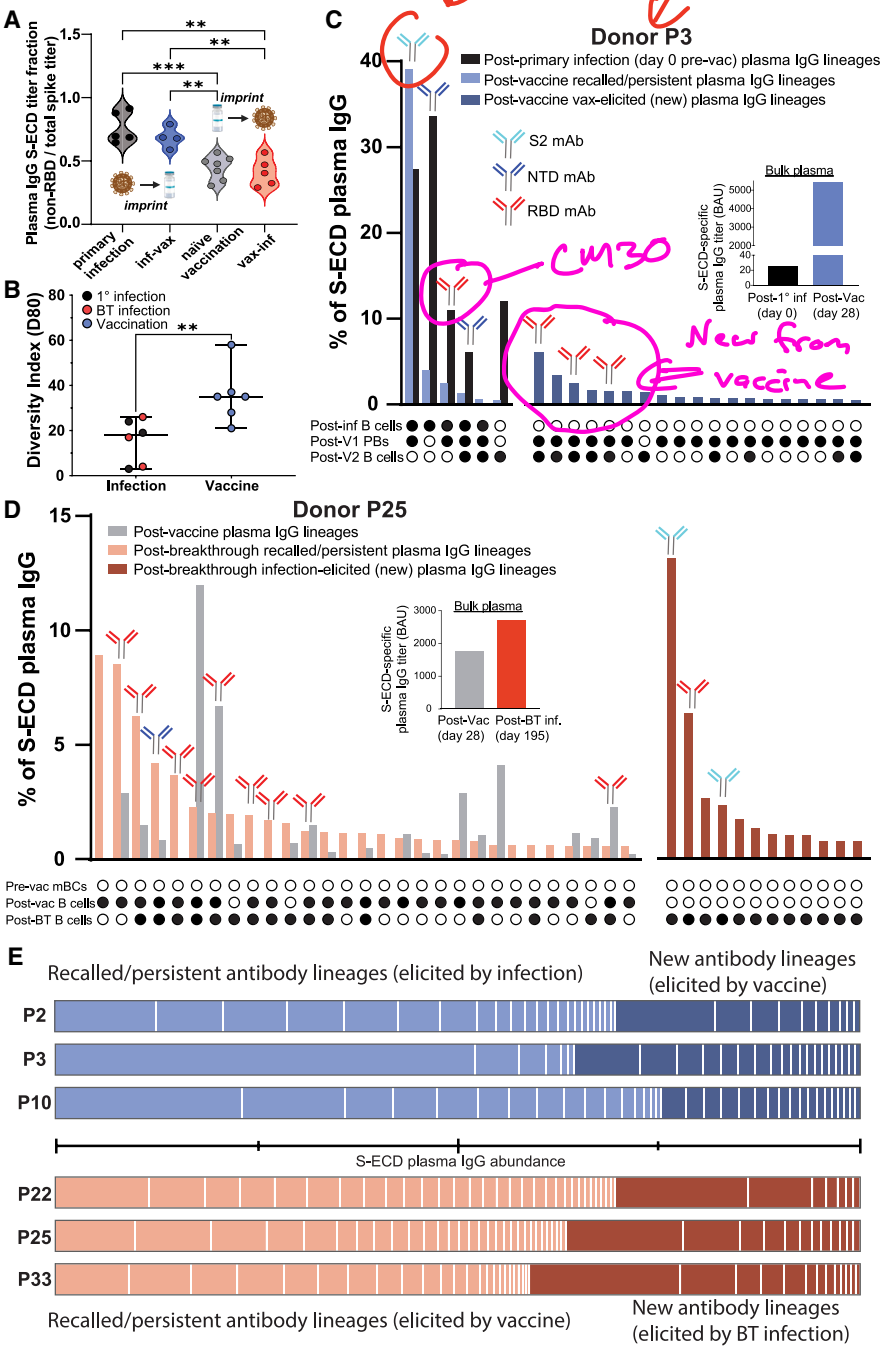

Figure 1. IgG serological recall and hybrid immunity are predetermined by the initial immunological imprint set by infection or vaccination

(A) Plasma RBD competition ELISA reveals that mode and order of exposure to SARS-CoV-2 S result in differential persistent antibody orientation, with infection and vaccination imprinting non-RBD and RBD epitopes, respectively. Results are based on two technical replicates.

(B) Comparison of post-infection and post-vaccination anti-S plasma IgG repertoire diversity (D80). D80, diversity index 80%: the number of lineages that comprise 80% of the S-reactive plasma IgG repertoire by abundance. Error bars represent 95% CI about the median.

(C) Donor P3 plasma IgG repertoire elicited by primary infection (black bars), recalled by subsequent vaccination (light blue bars), and newly elicited by subsequent vaccination (dark blue bars). Each bar represents an individual plasma IgG lineage. Antibody symbols above bars indicate S domain specificity of recombinantly cloned mAbs representative of each lineage. The insert shows anti-S plasma binding titers at each time point, and the UpSet plot below the repertoire bar plot indicates whether the plasma lineage was detected (filled circle) in total B cells, sorted MBCs, and sorted PBs. "Post-V1," following the first vaccine dose and "Post-V2," following the second vaccine dose.

(D) Donor P25 plasma IgG repertoire elicited by naive vaccination (gray bars), recalled by subsequent BT infection (pink bars), and newly elicited by subsequent vaccination (red bars). Insert and UpSet plot as described in C.

(E) Hybrid immunity: proportion of plasma IgG anti-S lineages following secondary exposure, across the cohort, which are recalled from lineages originally imprinted by the initial exposure. The horizontal line between the plots denotes each quartile of the plasma IgG repertoire by relative abundance. Plasma IgG limit of quantitation = 15 ng/mL.[30] Significant differences calculated using the Mann-Whitney U test linked by horizontal lines are indicated by asterisks: $^{**}p < 0.01$, $^{***}p < 0.001$.

IgG anti-S binding profiles and antibody diversity differ at the molecular level between infection and vaccination

Quantitative assessment of antibody levels using analytical methods like ELISA lacks the ability to distinguish abundances at the lineage (family) or clonal (individual) level. Thus, we sought to establish at the molecular level whether the bulk increases in binding and neutralization titers observed in the hybrid immune individuals stem from an augmentation in pre-existing plasma antibody lineages or if newly elicited antibody lineages with novel specificities are the determining factor. The lineage composition and relative abundance of IgG antibodies comprising the polyclonal plasma response to stabilized HexaPro S-ECD were determined using the Ig-seq pipeline[30,35–37] that integrates liquid chromatography-tandem mass spectrometry (LC-MS/MS) proteomics of chromatographically enriched antigen-reactive polyclonal IgG with high-throughput sequencing of B cell heavy-chain (VH), light-chain (VL), and single B cell VH:VL variable region repertoires (B cell receptor [BCR] sequencing [BCR-seq]).

Overall, the repertoire diversity index (D80, Figure 1B) of anti-S-ECD plasma IgG lineages varied significantly between post-infection and post-vaccination ($p < 0.01$). Infection, whether primary or BT, resulted in more polarized (i.e., top-heavy in terms of relative abundance of IgG lineages) plasma IgG repertoires with