Conjugate Addition

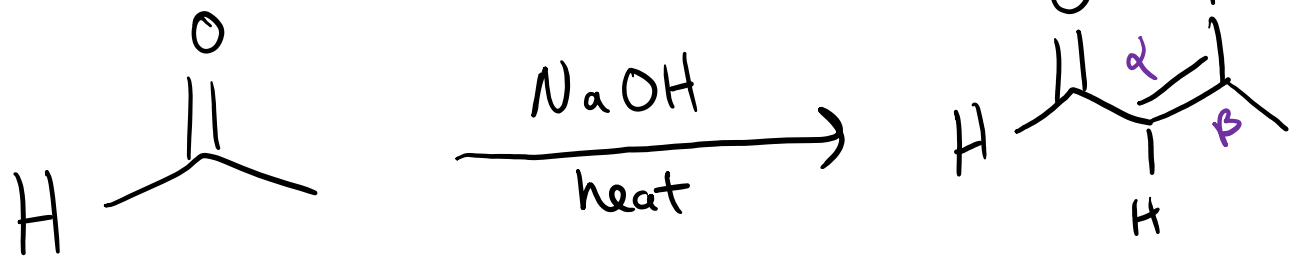
on Exam 3

Exam 2 Review

3/29/2023

Conjugate Addition (21.6)

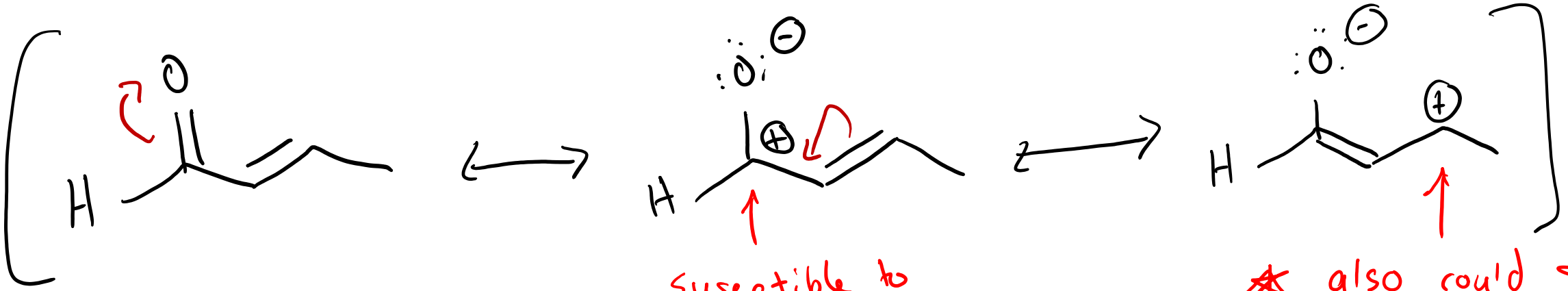
Remember Aldol condensation:



E isomer

α,β unsaturated carbonyl

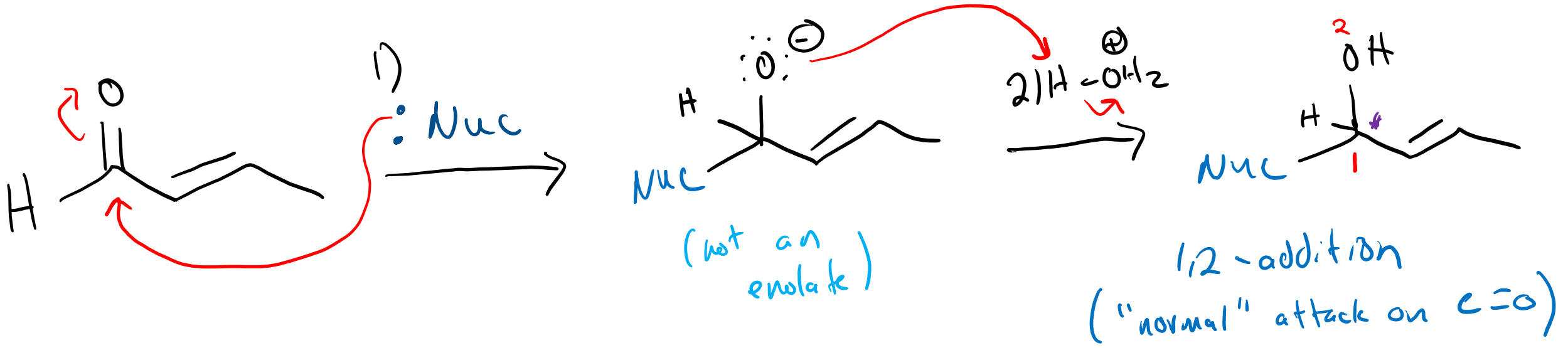
can be very useful in synthesis

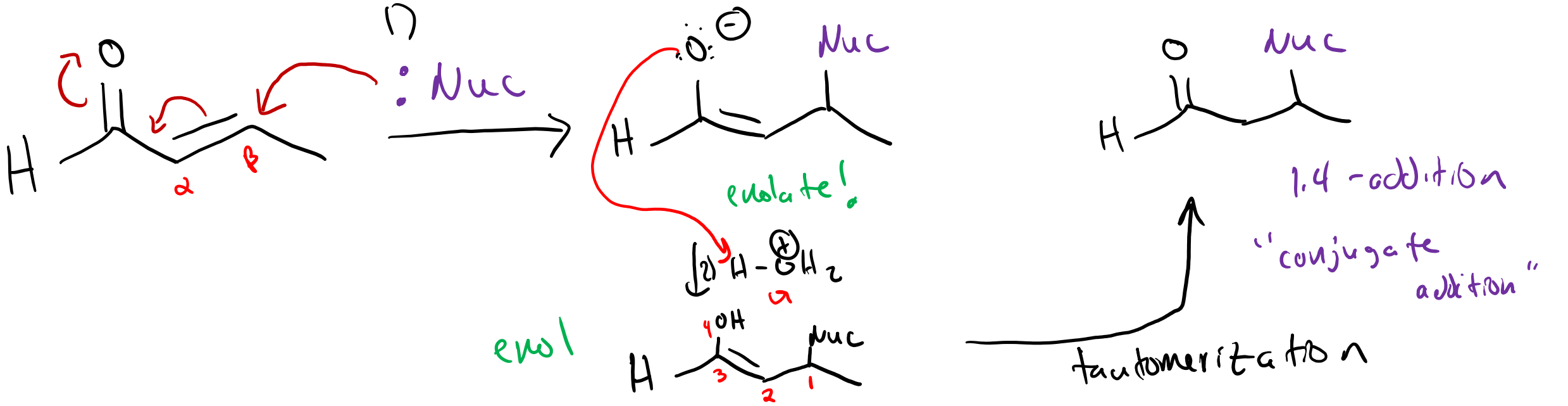


susceptible to :Nuc attack here!

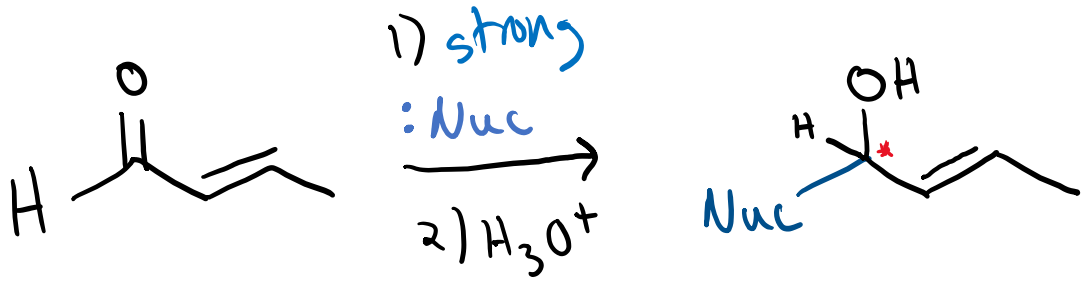
★ also could be attacked! ★

1,2- vs 1,4-addition





1,2- vs 1,4-addition: Strength of Nucleophiles and Regioselectivity



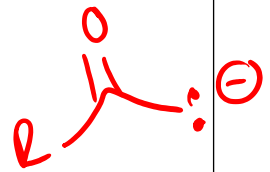
strong nuc → 1,2 -addition favored

$LiAlH_4$ "$H:^{\ominus}$" $pK_{aH} \approx 38$

$RMgBr$ "$R:^{\ominus}$" $pK_{aH} = 50$

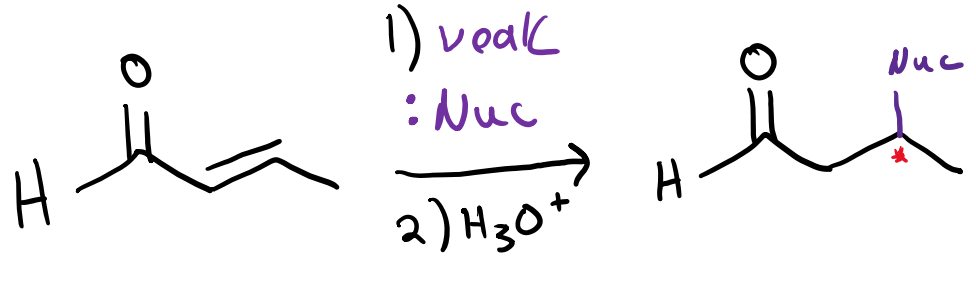
moderate

$pK_{aH} = 20$



enolate

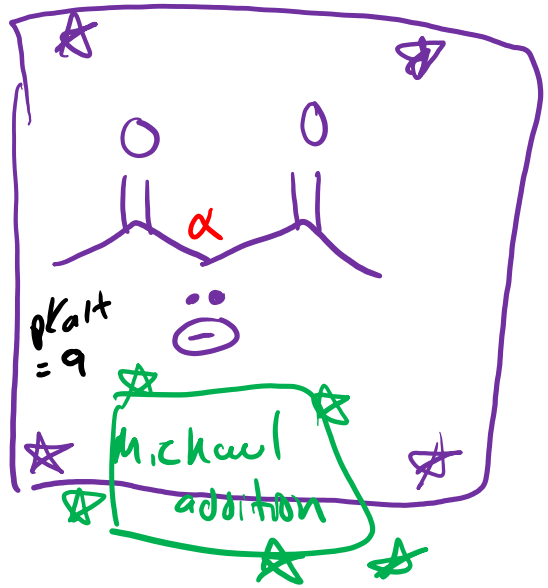
(mix of 1,2- vs 1,4)



weak nuc → 1,4 addition

$:\ddot{O}R$ $pK_{aH} \approx 16$

$H\ddot{N}R_2$ $pK_{aH} = 10$



R_2CuLi N/A

↳ weaker C:⊖ nuc. than Grignard

Ch 19: Wittig Reaction

- Overall reaction/recipe
- Stereochemistry (E vs Z) and dependence on ylide structure

- Reduction (Hydride transfer) & reaction of Grignard reagents with aldehydes and ketones may be relevant!

Ch 20: Carboxylic Acid Derivatives

- Synthesis of carboxylic acids (including oxidation of alcohols, hydrolysis of nitriles, & haloform reaction)
- Acyl transfer reaction mechanisms (general)
  - Neutral nucleophile + weak acid
  - Neutral nucleophile + weak base
  - Anionic nucleophile
  - I will *not* ask about any of the "weird" mechanisms with carboxylic acids – (BH_3-THF, $LiAlH_4$, and $SOCl_2$)

- Synthesis of Esters (via Sn2, Fischer Esterification, alcoholysis)

- Synthesis of Acid Chlorides
- Synthesis of Anhydrides
- Reactions of Acid Chlorides/~~Acid Chlorides~~ (react in the same way)
  - Hydrolysis, alcoholysis, aminolysis

anhydrides

Ch 20: Carboxylic Acid Derivatives

- Hydrolysis of Esters (acidic and basic conditions)
- LeChatelier's principle
- Synthesis (ammonolysis of Acid Chloride/Anhydride) and hydrolysis of Amides
- Weinreb Amides – reactions with hydride and carbon nucleophiles and difference vs regular Amide
- Hydride transfer reagents with: Aldehyde/ketone, Amide, Weinreb Amide, Acid chloride/Anhydride, Ester, and Carboxylic Acid
  - Know which F.G.'s use which reducing reagents
  - Know the difference in outcomes for each F.G.! They don't all have C=O become C-OH….
    - Final slide of 3/1 handout (Friday before spring break)
- Grignard and Gilman reagents with all of the above F.G.'s
  - Except Carboxylic Acids (why not?) and ***regular*** Amides
  - Know the difference in outcomes! The F.G.'s don't all react the same way!
- I will not count off for leaving out the quenching step " 2)H_3O^+ " *only if* it doesn't actually show up in the mechanism (i.e. with a Gilman reagent)

Ch 21: Alpha-carbon reactions (*all* mechanisms are fair game)

- Using pKa table to compare acidity of various functional groups
- Using pKa table to predict K_{eq} of an acid-base reaction
- Comparing acidity: qualitatively (charge stability)
- Keto-enol tautomerism (acidic and basic conditions)

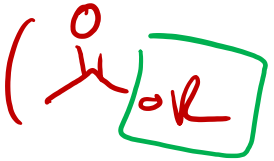
- Alpha-halogenation (acidic and basic conditions)
  - Regioselectivity under acidic conditions
  - E2 reaction of mono-halogenated product from acidic conditions
  - Difference in outcomes acidic vs basic mechanism (and why)
  - Haloform reaction & mechanism

- Acidity of alpha-carbons (and "double-alpha" protons between two C=O groups)

Ch 21: Alpha-carbon reactions (***all*** mechanisms are fair game)

- ("self")-Aldol and retro-Aldol reactions
  - Choice of base and why
- Cross-Aldol reactions and mechanism
  - Backtracking steps from product (who was enolate, who was electrophile etc)
  - Choice of base and why
- Aldol condensation reaction and stereochem (least hindered product)
- Intramolecular Aldol
  - Ring strain! 5- or 6- member rings are the least strained

- Claisen Condensation – all the same things as Aldol
  - Reaction, mechanism, backtracking from product
  - Choice of base and why
  - Crossed-Claisen and Intramolecular Claisen

aldol chem w/ leaving group ()

- Alpha-alkylation
  - Choice of base – regioselectivity and why
  - Malonic Ester Synthesis and why we care about it (alpha-alkylated carboxylic acid)
  - Acetoacetic ester synthesis and why we care about it (alpha-alkylated acetone but with 2° R-X)

Exam Format

- A *bunch* of fill-in-the-blank reaction schemes
- 1-2 Flawed Synthesis
- 2-3 Mechanisms* (see previous slides)
- Guided and less-guided synthesis
  - No fully “open ended” synthesis – closest I would give to that is like the practice exam question
- Random assorted conceptual things

- Approx 5-6 pages, designed to be completed in about 1 hr 20 minutes total.