C/P SECTION REFERENCE

# High Yield Organic Chemistry Reactions for the MCAT

All reactions categorised by how often they appear on the exam. Spend 60% of your time on Tier 1, 30% on Tier 2, and 10% on Tier 3.

**8**
**TIER 1 • MUST KNOW**
Appear on nearly every exam. Know cold.

**9**
**TIER 2 • KNOW WELL**
Appear regularly. Conceptual understanding.

**8**
**TIER 3 • RECOGNISE**
Can appear. Know the concept & product.

## REACTIONS COVERED

1 SN1 & SN2 Substitution
2 E1 & E2 Elimination
3 Carbonyl Nucleophilic Addition
4 Nucleophilic Acyl Substitution
5 Aldol Reaction & Condensation
6 Oxidation & Reduction
7 Hydrolysis & Condensation
8 Keto-Enol Tautomerism
9 Electrophilic Addition to Alkenes
10 Electrophilic Aromatic Sub.
11 Epoxide Ring Opening
12 Transesterification
13 Acetal / Hemiacetal Formation
14 Claisen Condensation
15 Conjugate (Michael) Addition
16 Free Radical Halogenation
17 Decarboxylation
18 Diels-Alder Reaction
19 Wittig Reaction
20 Wolff-Kishner / Clemmensen
21 Hofmann Elimination
22 Strecker / Gabriel Synthesis
23 Haloform Reaction
24 Acetoacetic / Malonic Ester
25 Nitrile Reactions

TIER 1

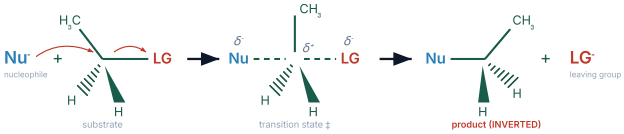
# Must Know Cold

These appear on nearly every MCAT. Know the mechanism, products, stereochemistry, and conditions.

## 1 Nucleophilic Substitution — SN1 & SN2

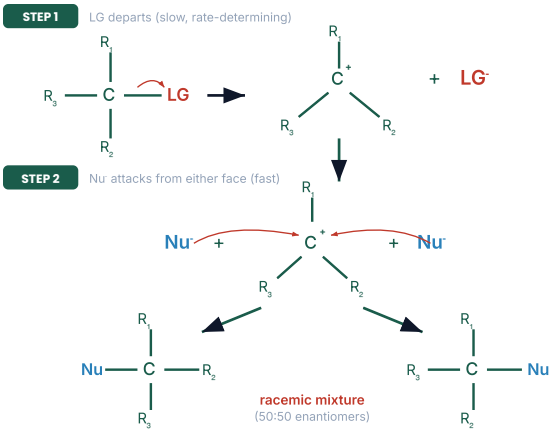
A nucleophile replaces a leaving group on carbon. **The single most tested organic chemistry topic on the MCAT.**

### SN2 — One Step (Concerted)




Strong Nu attacks from behind, 1°/methyl substrate, polar aprotic solvent. Rate = k[Sub][Nu] — 2nd order, hence $S_N2$

### SN1 — Two Steps (Carbocation)




Weak Nu, 3° substrate, polar protic solvent. Rearrangements possible. Rate = k[Sub] — 1st order, hence $S_N1$.

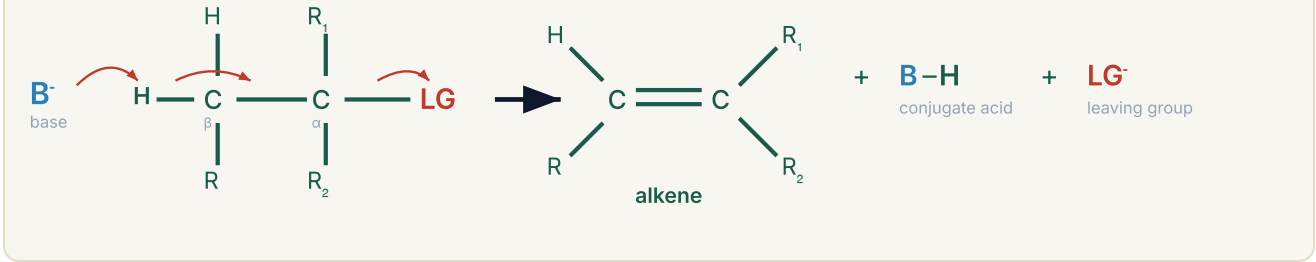
Key Decision: **Substrate → 1° = SN2, 3° = SN1, 2° = look at nucleophile strength & solvent**

## 2 Elimination — E1 & E2

A leaving group departs and a π bond (double bond) forms. Almost always tested alongside SN1/SN2.

### E2 — One Step (Concerted)

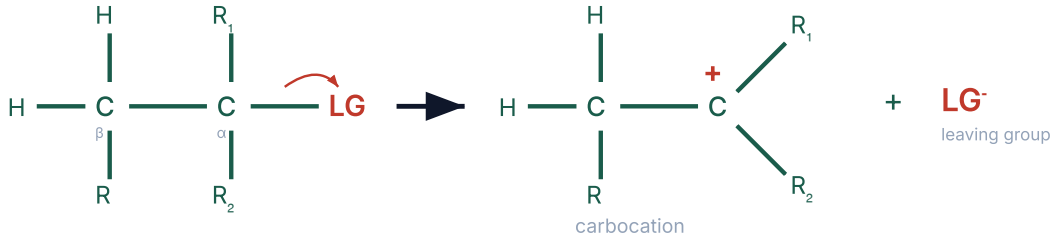
$B^-$ removes H from $C_\beta$ while LG departs from $C_\alpha$ simultaneously — electrons from the C–H bond form the new C=C π bond.



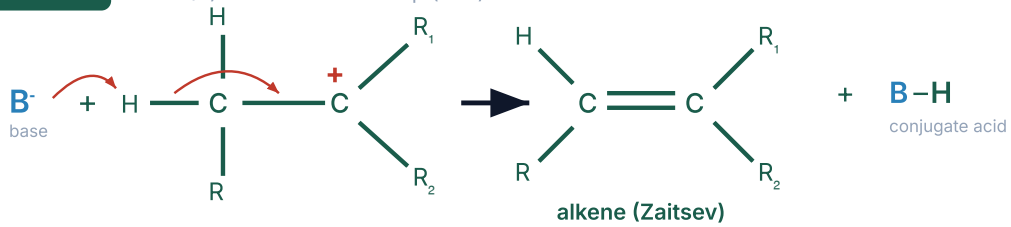

Strong/bulky base (e.g. $OH^-$, t-$BuO^-$, LDA), high temp. **Anti-periplanar** = H and LG must be 180° apart. **Zaitsev's rule**: more substituted alkene favoured. Rate = k[Sub][$B^-$] — 2nd order, hence E**2**.

## E1 — Two Steps (via Carbocation)

**STEP 1** LG departs (slow) — forms carbocation




**STEP 2** Base (B) removes H from Cβ (fast) — alkene forms

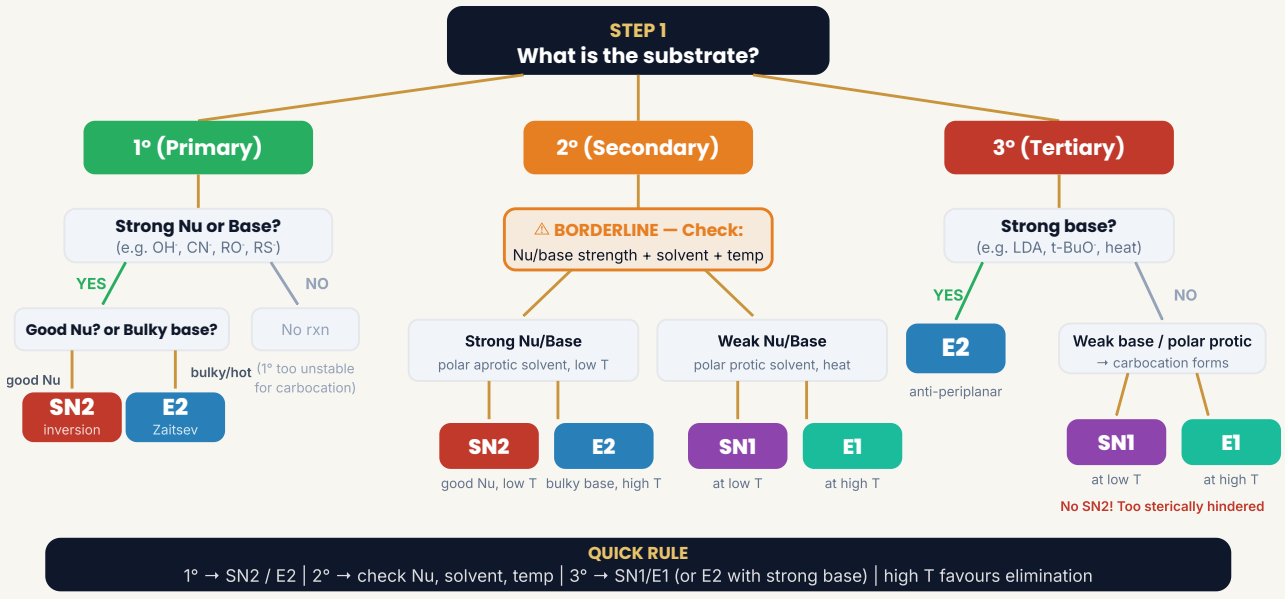



E1: no anti-periplanar requirement, carbocation can rearrange, Zaitsev product favoured

Weak base, 3° substrate, polar protic solvent, heat. Rate = k[Sub] — 1st order, hence $E_1$. Competes with SN1.

**Dr. Donnelly's tip:** On the MCAT, you're rarely asked "draw the mechanism." Instead, you must *predict which pathway* (SN1/SN2/E1/E2) dominates. Use the decision tree below.

### The SN1/SN2/E1/E2 Decision Tree

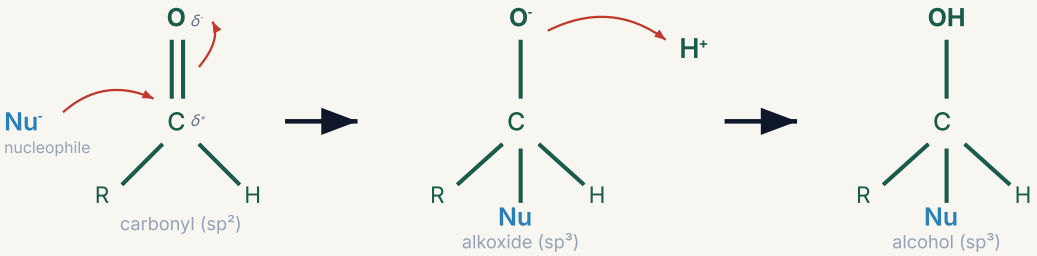


## 3 Nucleophilic Addition to Carbonyls

**The carbonyl (C=O) is the most important functional group on the MCAT.** Nucleophile attacks electrophilic carbonyl carbon of aldehydes/ketones.

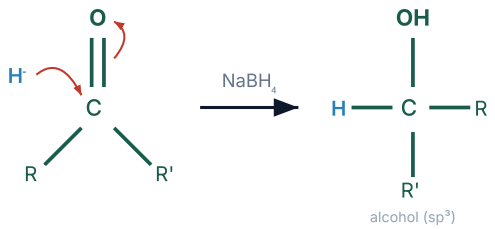
### Nucleophilic Addition to C=O

$Nu^-$ attacks the electrophilic carbonyl C ($sp^2$), π bond breaks, electrons go to O. The tetrahedral alkoxide intermediate is then protonated.



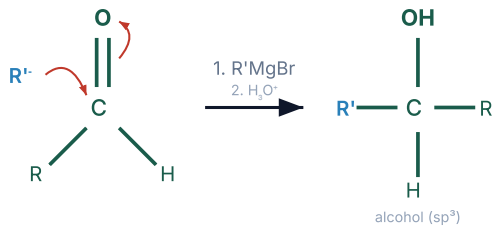

**Key sub-reactions you must know:**

#### $NaBH_4$ / $LiAlH_4$ Reduction



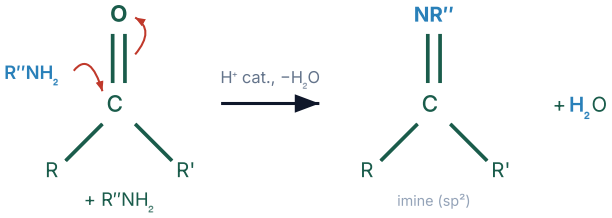

$H^-$ delivered to carbonyl C. $NaBH_4$ = mild (ketones/aldehydes). $LiAlH_4$ = strong (also esters, acids).

#### Grignard Reaction (RMgBr)



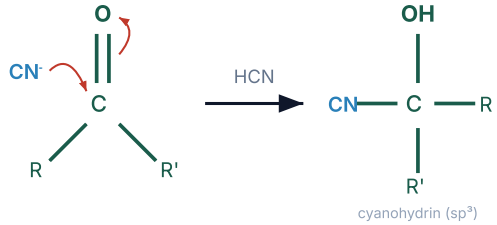

$R^{:-}$ (carbanion) attacks C=O, adding a new C–C bond. Formaldehyde → 1° alcohol. Aldehyde → 2° alcohol. Ketone → 3° alcohol.

#### Imine (Schiff Base) Formation




1° amine attacks C=O → carbinolamine → loses $H_2O$ → C=N (imine). 2° amine → enamine instead.

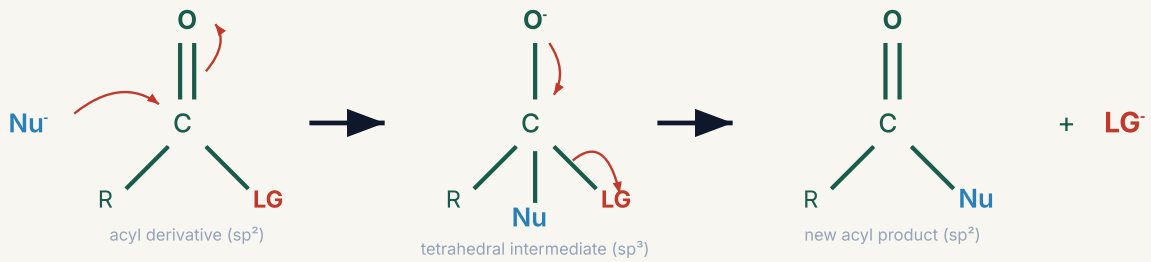
#### Cyanohydrin Formation




$CN^-$ attacks C=O → tetrahedral product with both OH and CN. Important for amino acid synthesis.

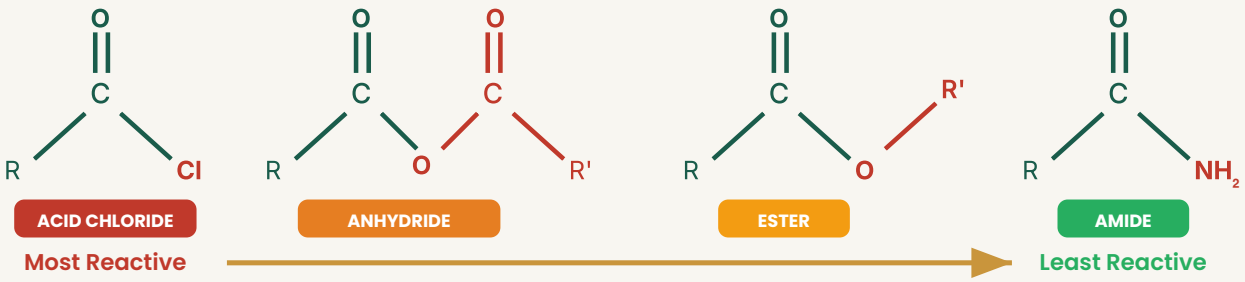
## 4 Nucleophilic Acyl Substitution

Nucleophile attacks carbonyl of a carboxylic acid derivative; the leaving group departs (addition-elimination). **Directly connects to biochemistry** (peptide bonds, ester bonds in lipids).




Addition-elimination: Nu attacks → tetrahedral intermediate → LG departs. C=O reforms.

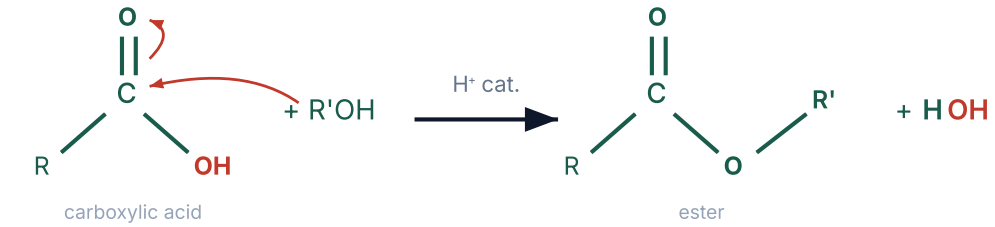
**Reactivity order (know this cold):**




Better leaving group = more reactive • N lone pair donates into C=O = least reactive

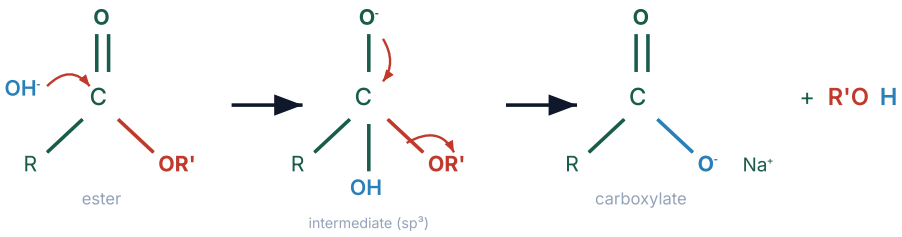
**Key reactions:**

### Fischer Esterification



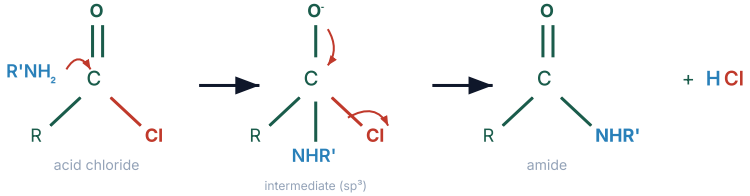

Reversible. Acid-catalysed. Driven forward by excess alcohol or removal of $H_2O$.

### Saponification




Irreversible ($OH^-$ is a strong nucleophile). This is how soap is made from fats.

### Amide Formation (from Acid Chloride)




Acid chlorides are the most reactive acyl derivatives — react rapidly with amines. $Cl^-$ is an excellent leaving group.

## 5 Aldol Reaction & Aldol Condensation

Enolate attacks a carbonyl, forming a β-hydroxy carbonyl. With heat, dehydration gives an α,β-unsaturated carbonyl. **Key C–C bond-forming reaction.**

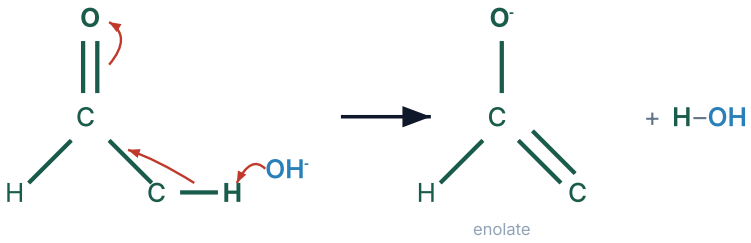
$$2 \times R{-}CH_2{-}CHO \longrightarrow \beta\text{-hydroxy aldehyde} \longrightarrow \alpha,\beta\text{-unsaturated aldehyde} + H_2O$$

**Step 1: base (enolate forms) • Step 2: nucleophilic attack • Step 3: heat (dehydration)**

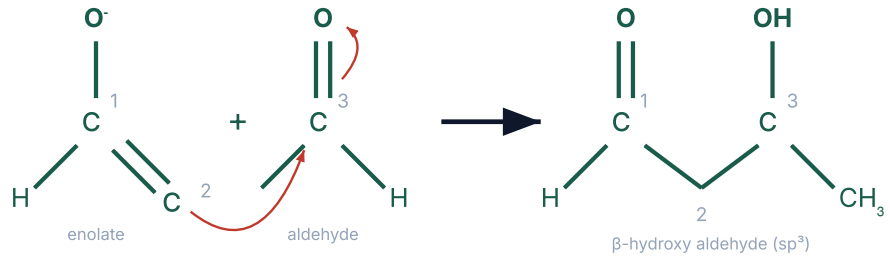
MCAT focus: **Recognise aldol products, understand enolate formation, identify crossed aldol situations**

### Aldol Reaction — 3 Steps

**STEP 1** Base removes α-H → enolate forms

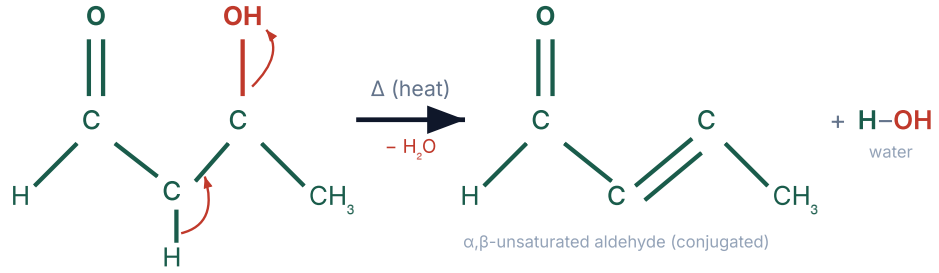



**STEP 2** Enolate attacks second carbonyl




Step 1: base removes α-H → enolate. Step 2: enolate $C_2$ attacks carbonyl $C_3$ (new C–C). Step 3: protonation → β-hydroxy aldehyde.

### Aldol Condensation (Dehydration)

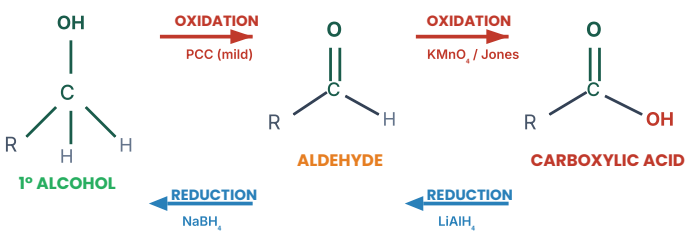



Heat drives dehydration: –OH and α–H lost as $H_2O$. Conjugated C=C–C=O system is thermodynamically stable (irreversible).

## 6 Oxidation & Reduction of Alcohols / Carbonyls

Fundamental to both organic chemistry and metabolism. Know which reagents are mild vs. strong.

### The Oxidation Ladder (Primary Carbon)




PCC = stops at aldehyde
Jones/$KMnO_4$ = all the way

$NaBH_4$ = C=O to alcohol
$LiAlH_4$ = also esters, acids

Also: 2° alcohol → ketone (any oxidising agent). Ketones cannot be further oxidised (no H on carbonyl C).
3° alcohols cannot be oxidised (no C–H bond on the carbon bearing OH).

## 7 Hydrolysis & Dehydration Synthesis (Condensation)

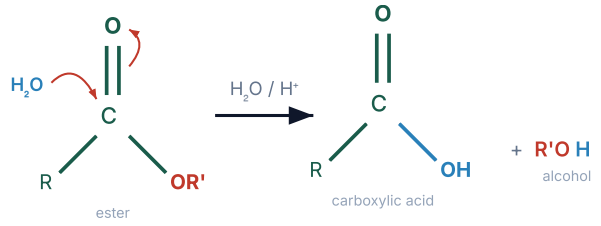
**Directly tested in biochemistry:** peptide bonds, disaccharides, triglycerides. Two sides of the same coin.

**Hydrolysis:** Water breaks a bond.
Ester + $H_2O$ → acid + alcohol
Amide + $H_2O$ → acid + amine
Glycosidic bond → 2 sugars

**Condensation:** Two molecules join, losing $H_2O$.
Acid + alcohol → ester + $H_2O$
Acid + amine → amide + $H_2O$
2 sugars → glycosidic bond + $H_2O$

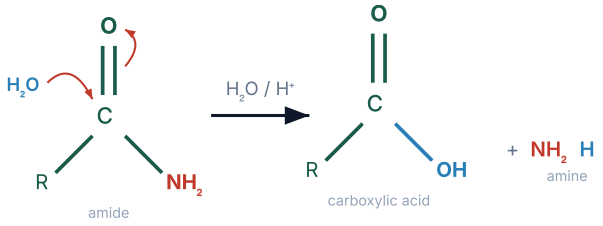
**Key reaction diagrams:**

### Ester Hydrolysis



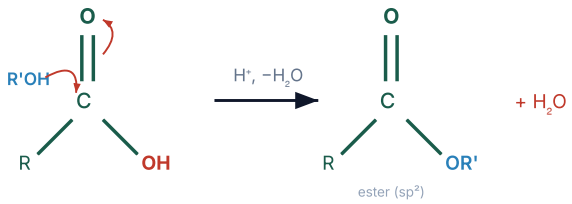

Water breaks the ester bond. Acid or base catalysed. Reverse of Fischer esterification.

### Amide Hydrolysis



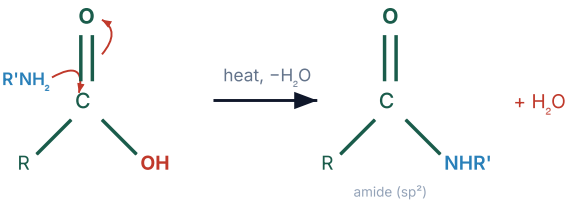

Requires strong acid/base + heat (amide bond is very stable). Key for peptide digestion.

### Ester Condensation (Fischer)



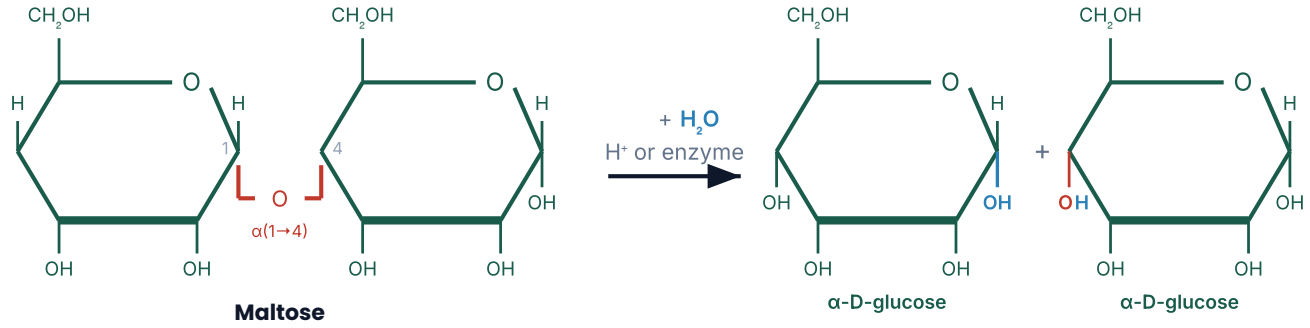

Acid + alcohol condense, losing $H_2O$. Acid-catalysed, reversible. Same as Fischer esterification.

### Amide Condensation (Peptide Bond)



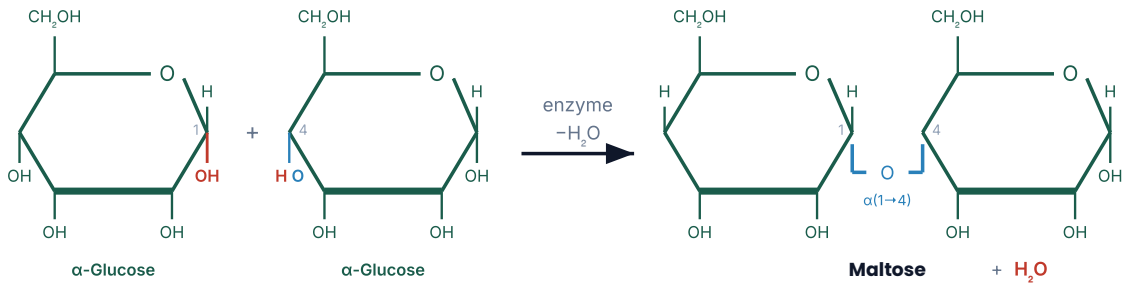

Acid + amine condense to form amide (peptide bond). Fundamental to protein synthesis.

### Glycosidic Bond Hydrolysis (Maltose → 2 Glucose)




$H_2O$ breaks the glycosidic bond. C1 gets **OH** from water. The glycosidic **O** stays on C4, picking up **H** from water. Catalysed by acid or enzymes (e.g. maltase).

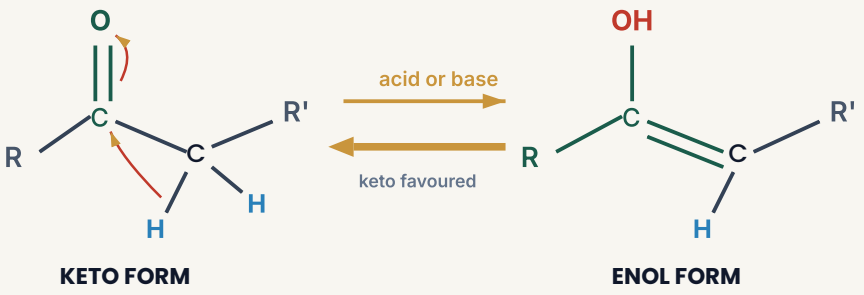
### Glycosidic Bond Formation (2 Glucose → Maltose + $H_2O$)




**OH** from C1 + **H** from C4 leave as $H_2O$. C4's **O** stays as the glycosidic bridge. Reverse = hydrolysis.

## 8 Keto-Enol Tautomerism

Interconversion between keto form (C=O, C–H) and enol form (C=C, O–H). Acid or base catalysed. **Foundation for aldol, α-halogenation, and all enolate chemistry.**




KETO FORM

ENOL FORM

**Enol = reactive form**

Foundation for aldol, α-halogenation, and all enolate chemistry

MCAT focus: **Keto form is thermodynamically favoured. Enol is the reactive form. α-hydrogens are acidic because of resonance stabilisation of the enolate.**

TIER 2

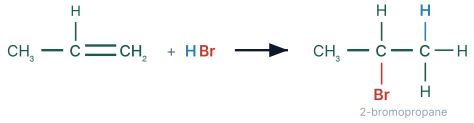
# Know Well

Tested regularly. Conceptual understanding is usually sufficient — you won't be asked to draw full mechanisms.

## 9 Electrophilic Addition to Alkenes

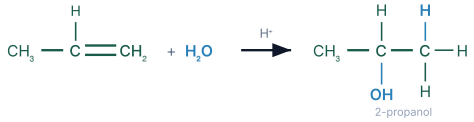
Electrophile ($H^+$) adds across C=C double bond. **Markovnikov:** H adds to the less substituted C, placing the nucleophile ($Br^-$, OH) on the more substituted C (via the more stable carbocation intermediate).

### HBr Addition (Markovnikov)



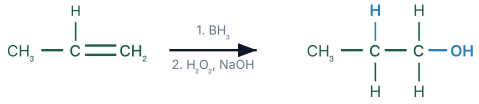

2-bromopropane

### Acid-Catalysed Hydration (Markovnikov)



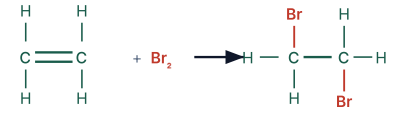

2-propanol

### Hydroboration-Oxidation (Anti-Markovnikov, syn)




1-propanol

### Halogenation (anti addition via bromonium ion)

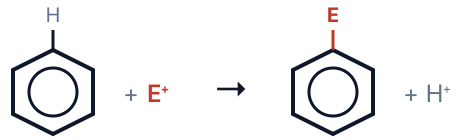



1,2-dibromoethane (anti)

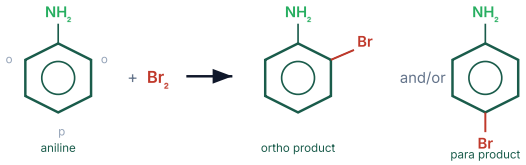
Anti-Markovnikov ($BH_3/H_2O_2$): **B adds to the less substituted C, while H adds to the more substituted C, followed by oxidation that replaces boron with an –OH group on the same face (syn addition).**
Halogenation ($Br_2$): **Br atoms add to opposite faces via a bromonium ion intermediate (anti addition).**

## 10 Electrophilic Aromatic Substitution

Electrophile replaces H on benzene ring. Know directing effects.



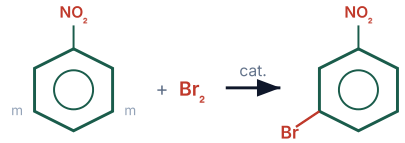

### Activating / Ortho-Para Directors: –$NH_2$, –OH, –OR, –alkyl




aniline — ortho product — para product

$NH_2$ donates electron density into the ring (activating), directing $E^+$ to ortho and para positions.

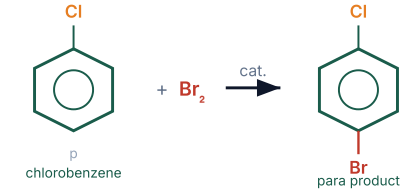
### Deactivating / Meta Directors: –$NO_2$, –CN, –COR, –COOH




nitrobenzene — meta product

Electron-withdrawing groups deactivate the ring and direct $E^+$ to the meta position.

### Halogens (–F, –Cl, –Br): Deactivating but Ortho-Para Directing



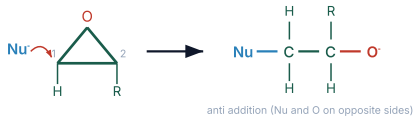

chlorobenzene — para product

Halogens are the exception: they withdraw electron density (deactivating) but their lone pairs donate into the ring, directing ortho/para.

## 11 Epoxide Ring Opening

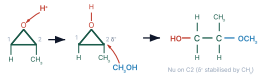
Nucleophile attacks the strained 3-membered ring (anti/backside). In base, $Nu^-$ does an SN2 attack on the less substituted C (less steric hindrance). In acid, $H^+$ protonates O first, building $\delta^+$ on the more substituted C, so the weaker nucleophile attacks there instead.

### General Mechanism



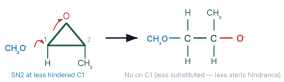

anti addition (Nu and O on opposite sides)

### Acid Conditions: $H^+$ protonates the epoxide O



Step 1: $H^+$ protonates the epoxide O, weakening C–O bonds. Step 2: $\delta^+$ builds on the more substituted C2, so the nucleophile attacks there.

### Base Conditions: Nu attacks less substituted C (SN2 backside)

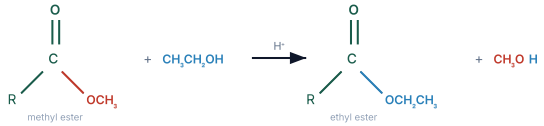


## 12 Transesterification

One ester is converted to another by swapping the alcohol portion. Reversible — driven by excess of new alcohol.

**R–CO–OR′ + R″OH → R–CO–OR″ + R′OH**

### Example: Methyl ester → Ethyl ester




methyl ester — ethyl ester

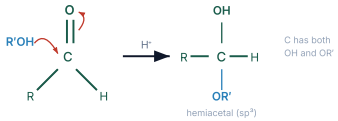
The $OCH_3$ leaves and is replaced by $OCH_2CH_3$ from the incoming alcohol. Key in lipid/biodiesel chemistry.

## 13 Acetal & Hemiacetal Formation

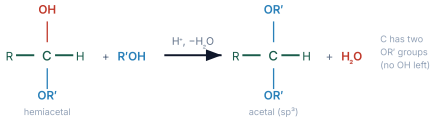
Aldehyde/ketone + alcohol → hemiacetal (1 equiv) or acetal (2 equiv). Acid-catalysed, reversible.

**RCHO + R′OH [H⁺] → hemiacetal [+ R′OH] → acetal + $H_2O$**

### Step 1: Hemiacetal Formation (1 equiv R′OH)




### Step 2: Acetal Formation (2nd equiv R′OH replaces OH)




**Biochem link:** Cyclic sugars are hemiacetals/hemiketals. Glycosidic bonds are acetals. Acetal formation is reversible in acid but stable in base (protecting group strategy).

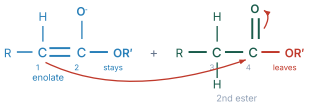
## 14 Claisen Condensation

Two esters react (strong base) to form a β-keto ester. Ester analogue of the aldol reaction.

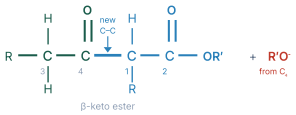
**2 × R–$CH_2$–COOR′ [base] → β-keto ester + R′OH**

**STEP 1** Base removes α-H → enolate


**STEP 2** Enolate attacks carbonyl C of 2nd ester (new C–C bond)




**STEP 3** OR′ leaves, C=O reforms → β-keto ester

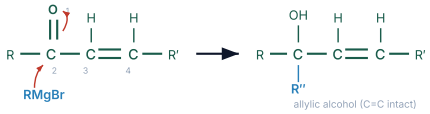



**Biochem link:** Fatty acid synthesis uses Claisen-type condensation (via thioester — the thiolate is a better leaving group than alkoxide).

## 15 Conjugate (Michael) Addition

With α,β-unsaturated carbonyls, the nucleophile can attack the carbonyl C (1,2-addition) or the β-C (1,4-addition). Which pathway dominates depends on the nucleophile strength.

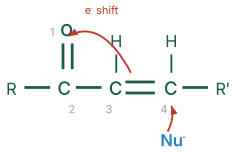
### Strong Nu⁻ (RMgBr, RLi) → 1,2-Addition (direct to C=O)



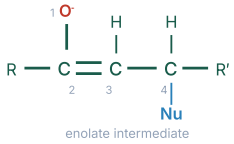

Strong Nu attacks C=O directly (kinetic control). C=C double bond is unchanged.

### Weak Nu⁻ (enolates, cuprates, amines, thiols) → 1,4-Addition (Michael)

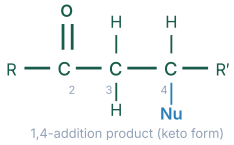
**STEP 1** Nu⁻ attacks β-C (position 4), electrons shift through conjugated system




**STEP 2** Enolate intermediate forms (O⁻ at position 1)




**STEP 3** Tautomerisation: enolate → keto form (H adds to C3, C=O reforms)




Called "1,4" because overall: H adds to O (position 1) and Nu adds to β-C (position 4). The enolate intermediate tautomerises to the more stable keto form.

Key point: **Strong Nu (RLi, RMgBr) → 1,2 (C=C intact, new bond to C=O carbon). Weak Nu (enolates, cuprates, RSH, amines) → 1,4 Michael (C=O intact, new bond to β-C).**

## 16 Free Radical Halogenation

Radical chain reaction: alkane C–H replaced by C–X. Three phases: initiation, propagation, termination.

**$R–H + X_2$ [hv or heat] → $R–X + HX$**

**INITIATION** Homolytic cleavage of X–X by light or heat


**PROPAGATION** Two steps that repeat in a chain

**Step 1:** X• abstracts H from R–H


**Step 2:** R• abstracts X from X–X (regenerates X•)


**TERMINATION** Two radicals combine — chain stops

R• + R• → R–R  R• + X• → R–X  X• + X• → X–X

Any two radicals can combine to end the chain

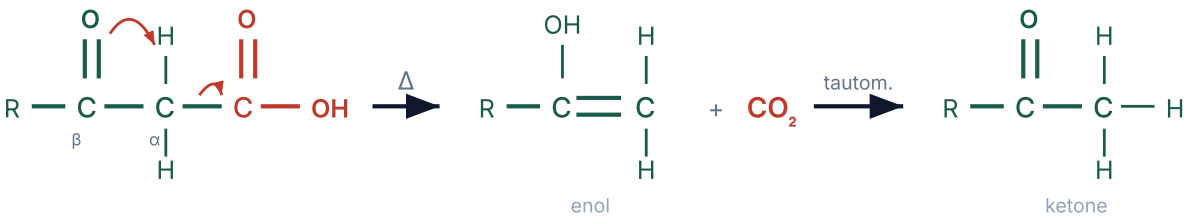
Selectivity: **$Br_2$ is highly selective (favours 3° C–H, more stable radical). $Cl_2$ is less selective (reacts with almost any C–H). Radical stability: 3° > 2° > 1° > methyl.**

## 17 Decarboxylation

Loss of $CO_2$ from a carboxylic acid. Requires C=O at the β-position for the six-membered cyclic transition state.

**β-keto acid [heat] → ketone + $CO_2$**

### Mechanism




The β-C=O oxygen grabs the α-H. The C–COOH bond breaks simultaneously, releasing $CO_2$ as gas. The enol tautomerises to the more stable ketone.

Biochem link: **Pyruvate → acetaldehyde + $CO_2$ (requires TPP cofactor). Isocitrate → α-ketoglutarate + $CO_2$ in Krebs cycle. Acetoacetate → acetone + $CO_2$ in ketone body metabolism.**

TIER 3

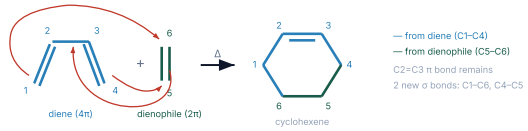
# Recognise the Concept

Can appear on the MCAT but less frequently. Know the product and key concept — you won't need full mechanisms.

## 18 Diels-Alder Reaction

[4+2] cycloaddition. Conjugated diene (4 π electrons) + dienophile (2 π electrons) → cyclohexene. Concerted, syn addition — no intermediates.

### Mechanism




All 3 pairs of π electrons move simultaneously (concerted): C1=C2 π → new C1–C6 σ bond, C3=C4 π → new C4–C5 σ bond, C5=C6 π → new C2=C3 π bond. Two new σ bonds form (closing the ring), one π bond remains (C2=C3). Diene must be in s-cis conformation. Works best with electron-rich diene + electron-poor dienophile (e.g. with C=O or CN).

## 19 Wittig Reaction

Phosphorus ylide + aldehyde/ketone → alkene. Converts C=O to C=C at the exact same position.

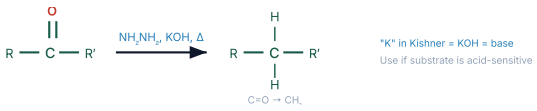
$$R_2C{=}O + Ph_3P{=}CHR' \rightarrow R_2C{=}CHR' + Ph_3P{=}O$$

The ylide C becomes part of the new C=C. $Ph_3P{=}O$ byproduct (very stable P=O bond drives the reaction).

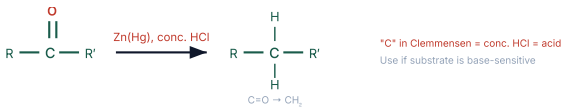
## 20 Wolff-Kishner & Clemmensen Reduction

Both reduce C=O all the way to $CH_2$ (complete deoxygenation). Same product, different conditions — **know which is acid vs base!**

### Wolff-Kishner — BASIC conditions




### Clemmensen — ACIDIC conditions




## 21 Hofmann Elimination & Rearrangement

**Elimination:** Quaternary ammonium + base → *less* substituted alkene (anti-Zaitsev). **Rearrangement:** Amide + $Br_2$/NaOH → amine (one fewer carbon).

## 22 Strecker & Gabriel Synthesis

**Strecker:** Aldehyde + $NH_3$ + HCN → α-amino acid. **Gabriel:** Phthalimide alkylation + hydrolysis → 1° amine. Listed under amino acid synthesis in AAMC outline.

## 23 Haloform Reaction

Methyl ketone + excess halogen (base) → carboxylate + haloform ($CHX_3$).

$$R{-}CO{-}CH_3 + 3X_2\ [NaOH] \rightarrow RCOO^- + CHX_3$$

Tests α-halogenation and enolate reactivity understanding.

## 24 Acetoacetic & Malonic Ester Synthesis

Use stabilised enolates for C–C bond formation, then decarboxylation. **Acetoacetic** → substituted ketones. **Malonic** → substituted acetic acids. Conceptual understanding sufficient.

## 25 Nitrile Reactions

**Hydrolysis:** R–CN + $H_2O/H^+$ → RCOOH. **Reduction:** R–CN + $LiAlH_4$ → $RCH_2NH_2$. Straightforward transformations that occasionally appear.

**Tier 3 study strategy:** Don't spend more than 10% of your organic chemistry study time here. If you see one of these on the MCAT, the passage will usually explain the reaction — your job is to *interpret* it using Tier 1 concepts (nucleophilic attack, leaving group quality, thermodynamics vs. kinetics).

## Master Reference: All 25 Reactions at a Glance

| TIER | # | REACTION | WHAT IT DOES | KEY REAGENTS / CONDITIONS |
|---|---|---|---|---|
| T1 | 1 | SN1 / SN2 | Nucleophile replaces leaving group | Nu strength, substrate, solvent |
| T1 | 2 | E1 / E2 | Leaving group departs, π bond forms | Base strength, temp, substrate |
| T1 | 3 | Nuc. Addition (C=O) | Nu attacks aldehyde/ketone | $NaBH_4$, $LiAlH_4$, RMgBr, HCN |
| T1 | 4 | Nuc. Acyl Sub. | Nu replaces LG on acid derivative | Acid chloride > anhydride > ester > amide |
| T1 | 5 | Aldol | Enolate + carbonyl → β-hydroxy C=O | Base (NaOH, LDA); heat for condensation |
| T1 | 6 | Oxidation / Reduction | Alcohol ↔ carbonyl ↔ acid | PCC, $KMnO_4$, $NaBH_4$, $LiAlH_4$ |
| T1 | 7 | Hydrolysis / Condensation | $H_2O$ breaks or forms bonds | $H^+$ or $OH^-$ catalyst; heat |
| T1 | 8 | Keto-Enol Tautomerism | C=O ↔ C=C(OH) | Acid or base catalyst |
| T2 | 9 | Electrophilic Addition | $E^+$ adds across C=C | HBr, $H_2O/H^+$, $Br_2$, $BH_3$ |
| T2 | 10 | EAS | $E^+$ replaces H on aromatic ring | Directing groups, Lewis acid catalyst |
| T2 | 11 | Epoxide Opening | Nu attacks strained ring | Acid vs. base = different regio |
| T2 | 12 | Transesterification | Swap alcohol portion of ester | Excess alcohol, $H^+$ catalyst |
| T2 | 13 | Acetal / Hemiacetal | C=O + ROH → hemiacetal → acetal | $H^+$ catalyst; links to sugar chemistry |
| T2 | 14 | Claisen Condensation | 2 esters → β-keto ester | Strong base; ester aldol analogue |
| T2 | 15 | Michael Addition | 1,4-conjugate addition | Weak Nu + α,β-unsaturated C=O |
| T2 | 16 | Radical Halogenation | Alkane C–H → C–X | $X_2$ + hv; radical chain mechanism |
| T2 | 17 | Decarboxylation | β-keto acid loses $CO_2$ | Heat; biochem: pyruvate, Krebs cycle |
| T3 | 18 | Diels-Alder | [4+2] cycloaddition → ring | Diene + dienophile; concerted |
| T3 | 19 | Wittig | C=O → C=C | Phosphorus ylide |
| T3 | 20 | Wolff-Kishner / Clemmensen | C=O → $CH_2$ (full reduction) | $NH_2NH_2$/KOH or Zn(Hg)/HCl |
| T3 | 21 | Hofmann | Anti-Zaitsev elimination | Quaternary ammonium + base |
| T3 | 22 | Strecker / Gabriel | Amino acid / amine synthesis | Aldehyde + $NH_3$ + HCN |
| T3 | 23 | Haloform | Methyl ketone → carboxylate + $CHX_3$ | Excess $X_2$ + NaOH |
| T3 | 24 | Acetoacetic / Malonic Ester | C–C bond + decarboxylation | Stabilised enolates |
| T3 | 25 | Nitrile Reactions | CN → COOH or CN → $CH_2NH_2$ | $H_2O/H^+$ or $LiAlH_4$ |

### Study Time Allocation


Master Tier 1 first. Only move to Tier 2 when you can identify all 8 Tier 1 reactions, their products, mechanisms, and stereochemistry from memory. Tier 3 reactions are low-probability — the passage will usually explain them.