

CM1501 Grignard Reactions

Grignard Reagent

Grignard with Epoxides

Grignard with Aldehyde/Ketone

Grignard with Esters

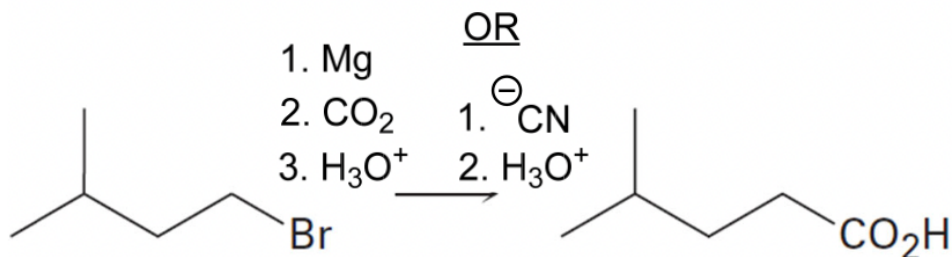
Grignard with Nitriles

Grignard with COOH

Tautomerism

Grignard Reagent

- Increase number of C.
- Alternative method: Nitrile hydrolysis (SN2 with -CN)



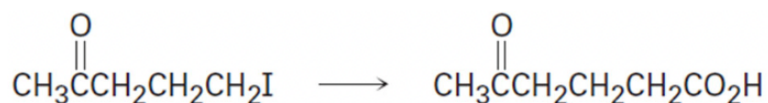
- Grignard reagent cannot be used when there is acidic functional group (e.g. -COOH, -OH, -NH₂, RCCH) in the compound as the Grignard reagent is immediately quenched by the proton source. \Rightarrow use CN hydrolysis

A Grignard reagent cannot be prepared from a compound containing an acidic functional group because the Grignard reagent is immediately quenched by the proton source:

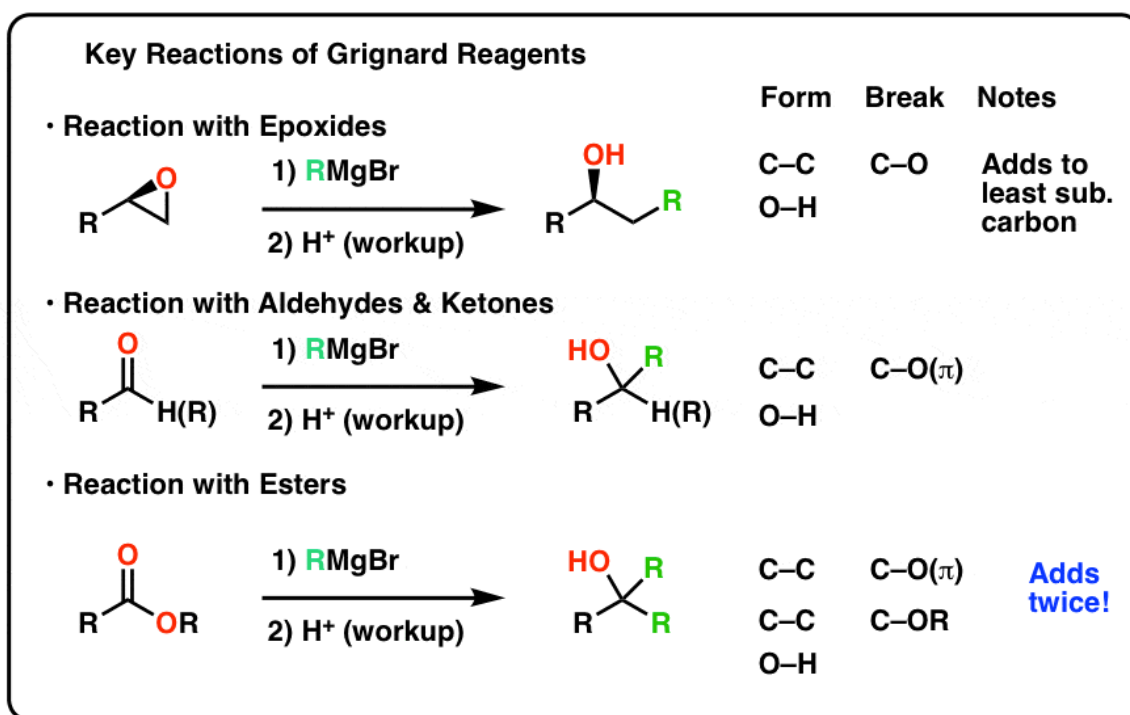


Acidic proton sources include -CO₂H, -OH, -NH₂ and RC \equiv CH,
e.g. BrCH₂CH₂CH₂NH₂ is another compound that does not form a Grignard reagent.

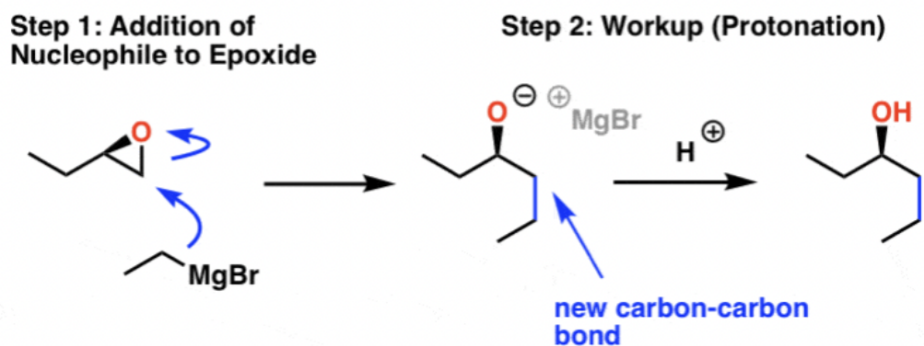
- Use Grignard if the compound does not favour SN2 (e.g. bulky or secondary and above)



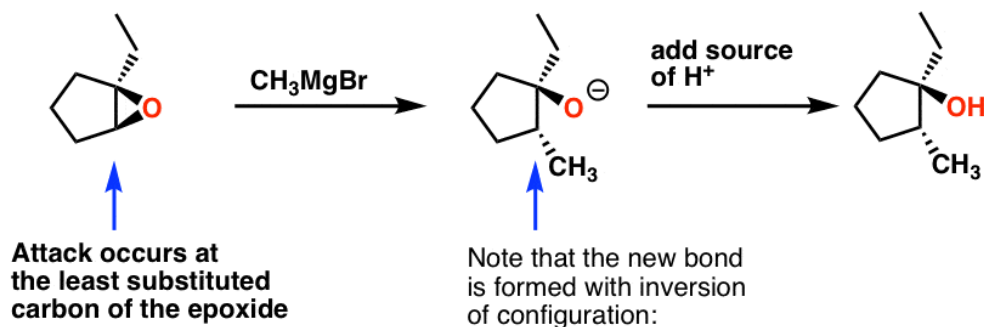
- neither method will yield the desired product as both Grignard and CN will attack -C=O instead of -I



Grignard with Epoxides



This is essentially an S_N2 reaction. Attack occurs with inversion of configuration:



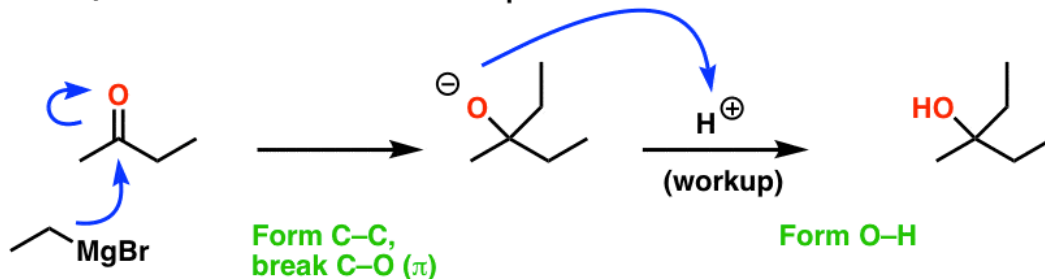
Grignard with Aldehyde/Ketone

Grignard Addition To Aldehydes and Ketones: How It Works

The nucleophilic pair of electrons in the C–Mg bond attack the carbonyl carbon, breaking the C–O (π) bond. In the second step, a proton source is added in workup.

Step 1: Addition

Step 2: Protonation

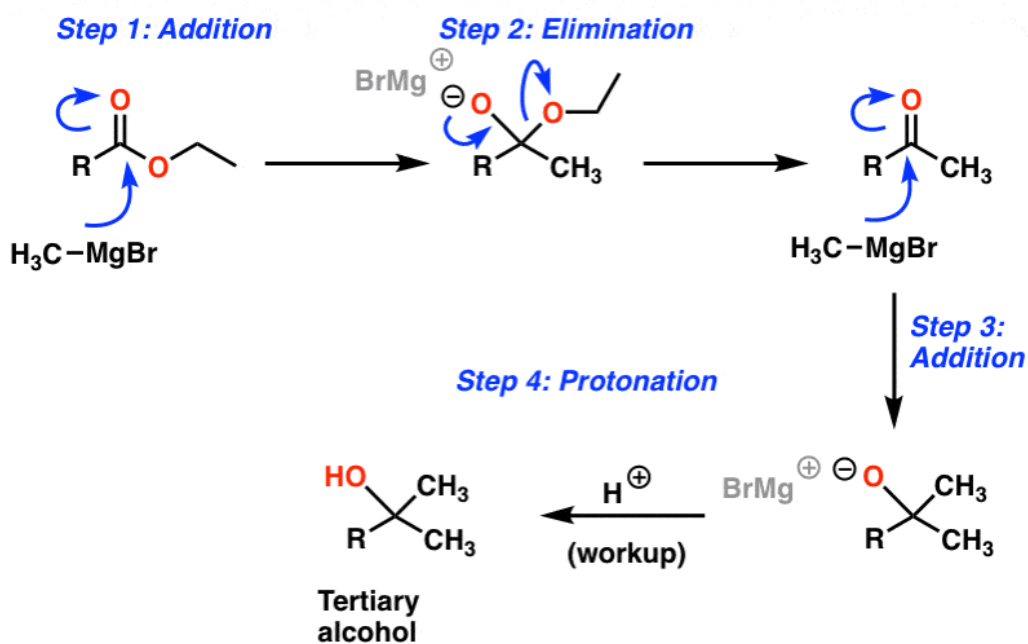


Note: "Addition" is **THE** most important mechanism for carbonyls. Carbonyl carbons are electrophiles, and will react with many different nucleophiles!

Grignard with Esters

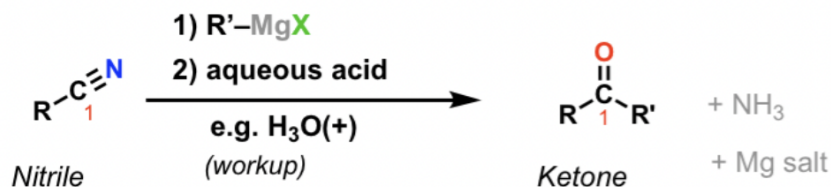
Addition of Grignard Reagents To Esters: How It Works

- In the first step, the nucleophile (Grignard) attacks the carbonyl carbon in an addition reaction (essentially the same step as for ketones/aldehydes).
- THEN, the C–O π bond re-forms, displacing a leaving group (alkoxide, RO⁻). This is a ketone!
- The ketone is then attacked by a second equivalent of nucleophile, leading to formation of a new alkoxide. Workup (addition of water or acid) completes the reaction.

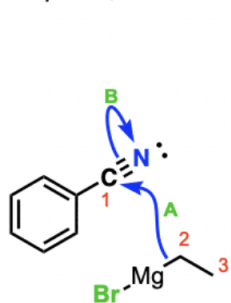


Grignard with Nitriles

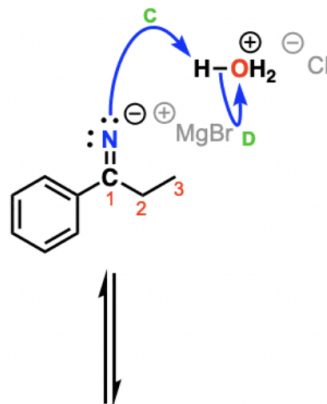
Reaction of Grignard reagents with nitriles to form ketones



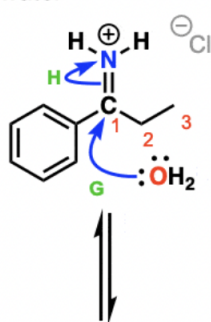
Step 1: 1,2-addition



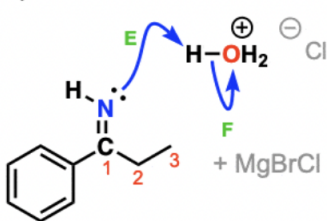
Step 2: Addition of acid; protonation



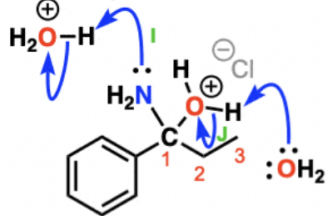
Step 4: 1,2-addition of water



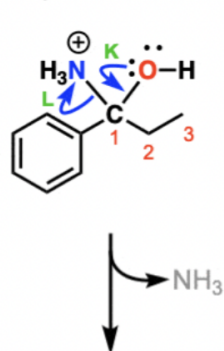
Step 3: Protonation



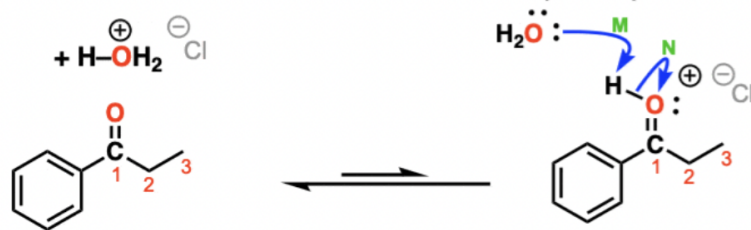
Step 5: Proton transfer



Step 6: 1,2-elimination



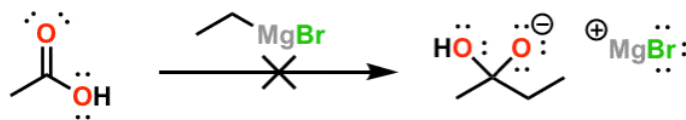
Step 7: Deprotonation



Grignard with COOH

Carboxylic Acids Will Neutralize Strongly Basic Nucleophiles

Reaction you might *think* would happen:



Addition of Grignard reagent to carboxylic acid

What actually happens:



Irreversible Acid base reaction between carboxylic acid and Grignard

Tautomerism

