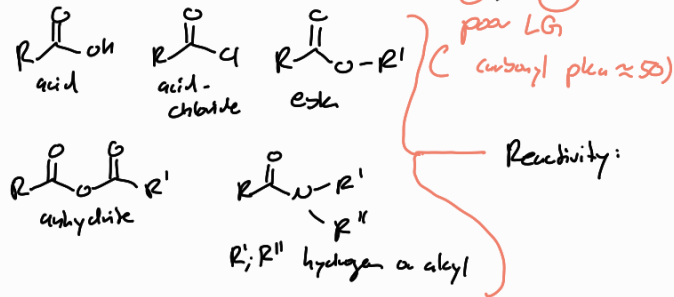


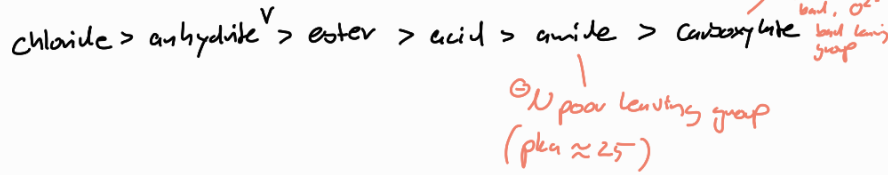
# Nucleophilic Substitution

A leaving group at the carbonyl

Carbonyl ketones/aldehydes

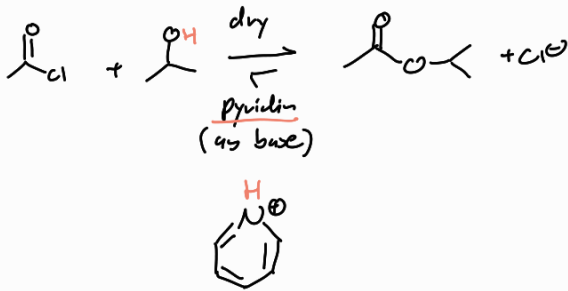


> ketone:

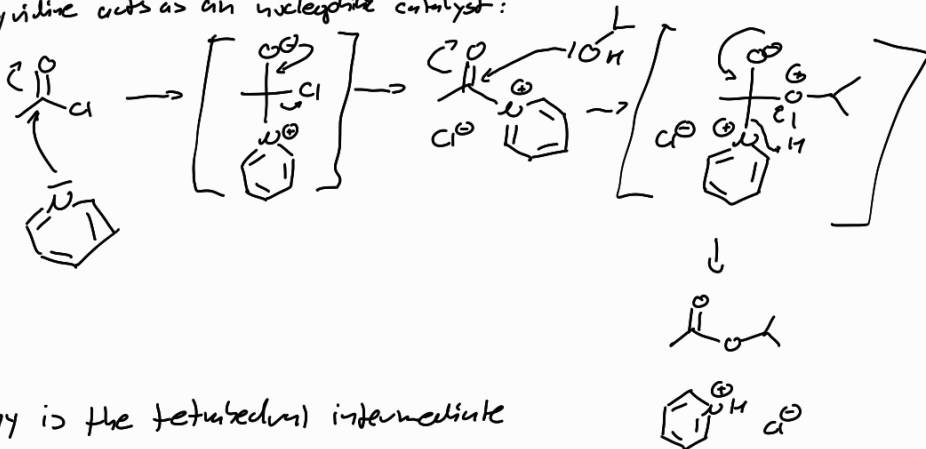


$\Rightarrow$  The more reactive acid chloride and anhydride are useful in synthesis

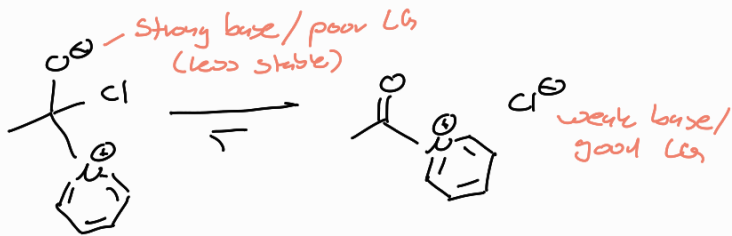
ex conversion into one of the other groups



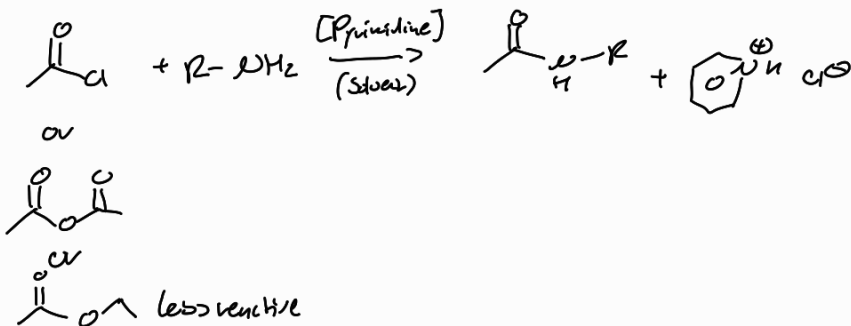
$\oplus$  Pyridine acts as a nucleophilic catalyst:



$\Rightarrow$  Why is the tetrahedral intermediate unstable



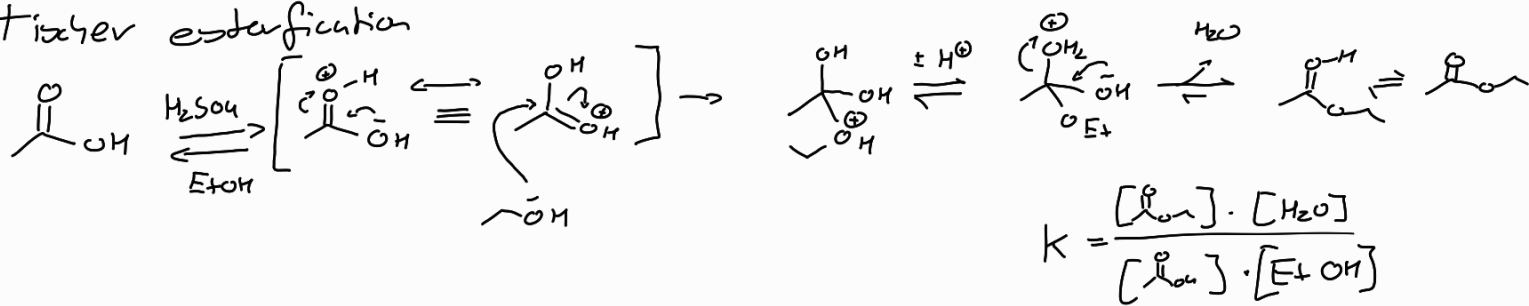
Amides from amines = useful transformation



Alternative to pyridine as catalyst?

# Acid-catalysed substitution at carbonyl

Fischer esterification

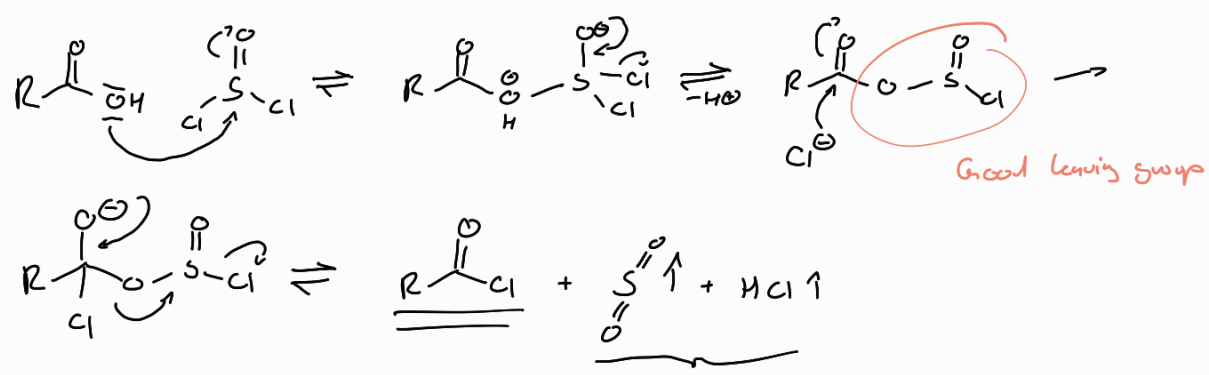


→ use excess of EtOH

How to adjust carbonyl reactivity in synthesis sequence?

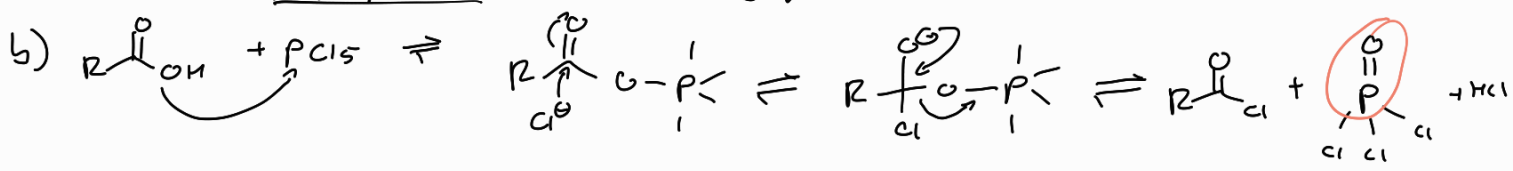
(How to make a acid chloride?)

a) Thionyl chloride SOCl<sub>2</sub>

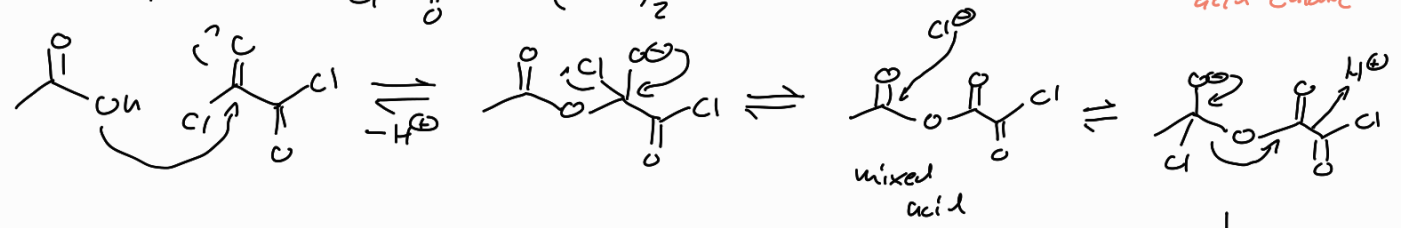
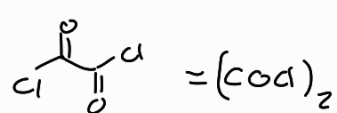


Gases bubble away = driving force of reaction

b) Phosphorus pentachloride



c) Oxalyl chloride



P=O very strong bond, drives the eq towards acid chloride

## Application - synthesis problems

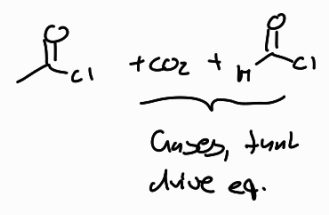
Q1 How to make a ketone from ester?

more reactive



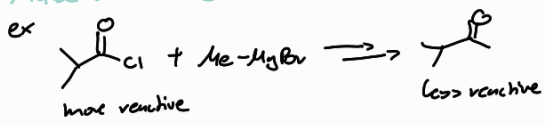
less reactive

Problem: Reactivity ketone > ester  
therefore another addition reaction



Solution 1

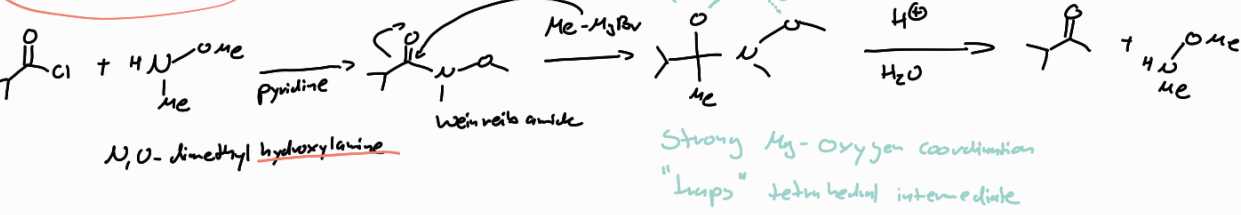
Make the starting material more reactive



Solution 2

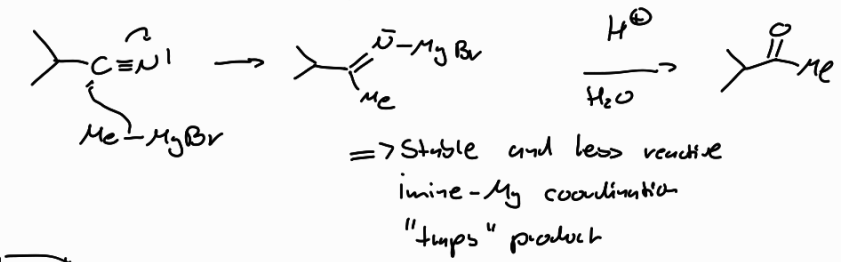
make the product less reactive

Weinreb amides



=> Weinreb amides are very useful and often the method of choice

Solution 3 Reaction with nitriles give less reactive products



[Q2] Adjust ketone/aldehyde reactivity

