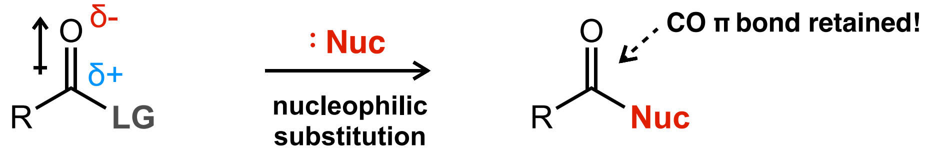
Carbonyl Substitutions - Carboxylic Acid Derivatives

This Core Concept Sheet describes the general reactivity observed when carboxylic acids and their derivatives undergo **nucleophilic substitution**.

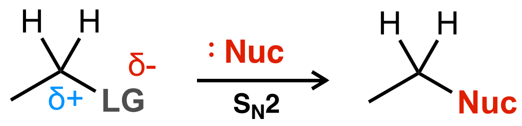


carboxylic acid derivative

New carboxylic acid derivative

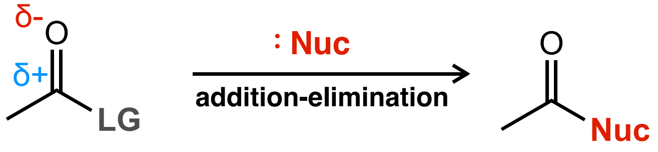
Overall, the reaction substitutes a **nucleophile** for a **leaving group**. The net transformation is similar to S_N2 reactions of alkyl halides in organic chemistry 1, but **the mechanism of substitution at carbonyls does not proceed through S_N2.**

Alkyl halide substitution (S_N2)



alkyl halide

Carbonyl substitution

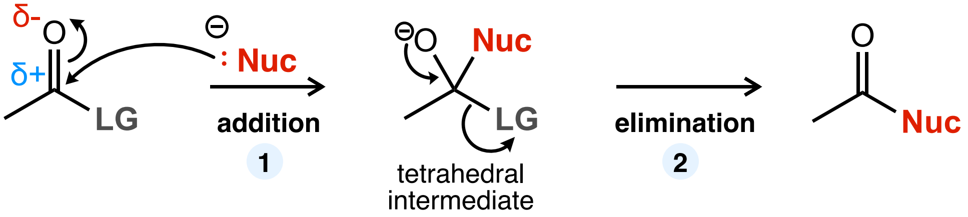


carboxylic acid derivative

In general, the mechanism of carbonyl substitution reactions proceeds through an **addition of the nucleophile** to the carbonyl, then **elimination of the LG to reform the CO π bond.**

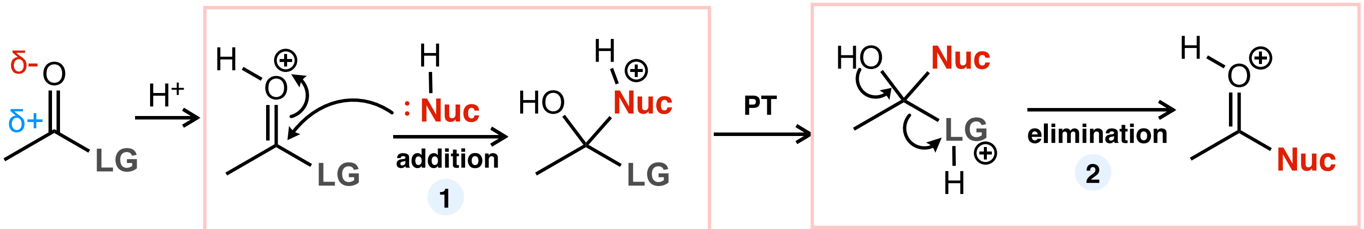
Depending on the nucleophile and conditions (acidic or not), the mechanism may also involve a series of protonations and deprotonations, referred to as **proton transfer** (**PT**).

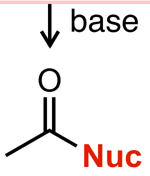
A. With a strong nucleophile (basic conditions)



B. With a weak nucleophile (acidic conditions)

With a weak nucleophile, we often need to use acid to protonate the carbonyl making it more electrophilic.

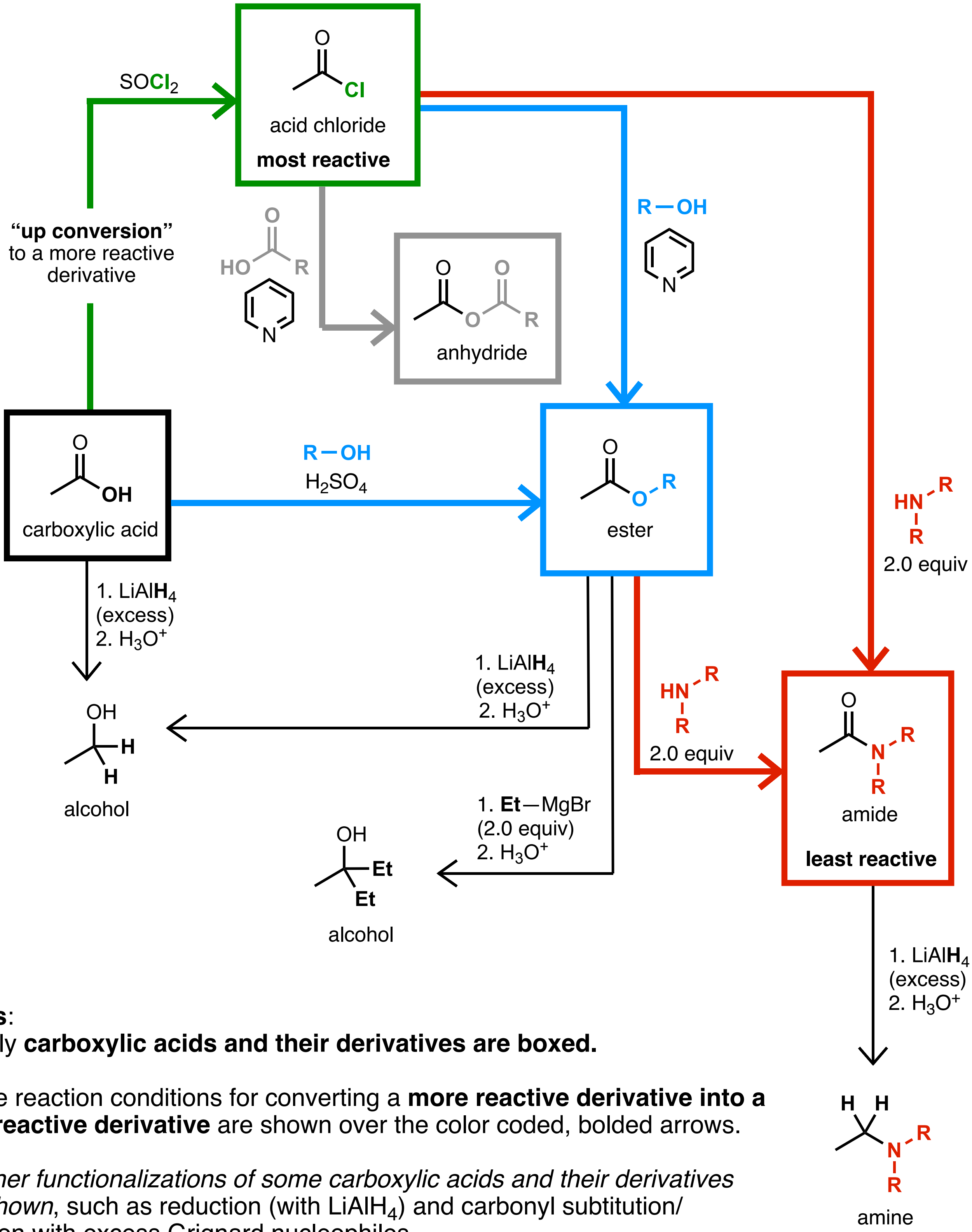




It is important to recognize that although the mechanisms seem different, **both mechanisms fundamentally involve an addition, then an elimination.**

The reactivity of carboxylic acid derivatives is often illustrated as a **reaction waterfall** that mirrors an energy diagram. While carboxylic acids are abundant and inexpensive, they typically are not reactive enough for subsitution reactions. Therefore, we "up convert" our carboxylic acid to a **more reactive derivative** first.

*Acetic acid is shown as the carboxylic acid



Notes:

1. Only **carboxylic acids and their derivatives are boxed.**

2. The reaction conditions for converting a **more reactive derivative into a less reactive derivative** are shown over the color coded, bolded arrows.

2. *Other functionalizations of some carboxylic acids and their derivatives are shown*, such as reduction (with $LiAlH_4$) and carbonyl subtitution/ addition with excess Grignard nucleophiles.