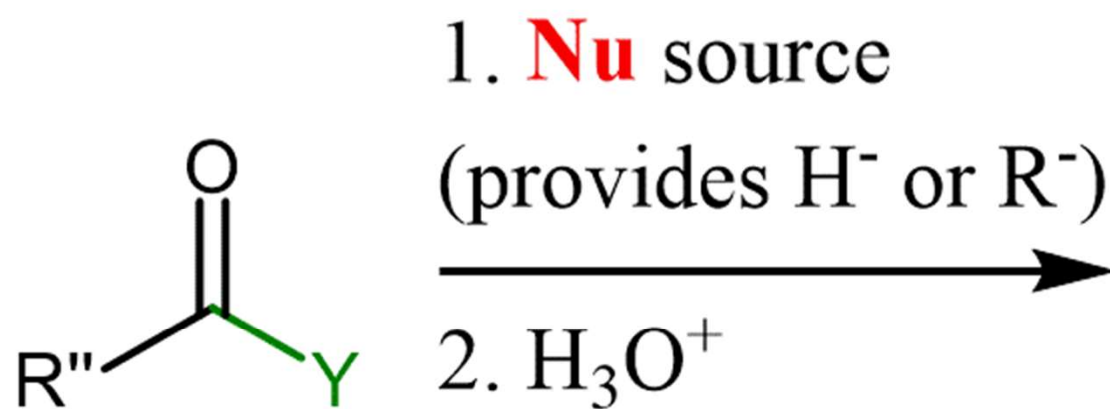


Type A: Single Nucleophilic Addition

The net result is:

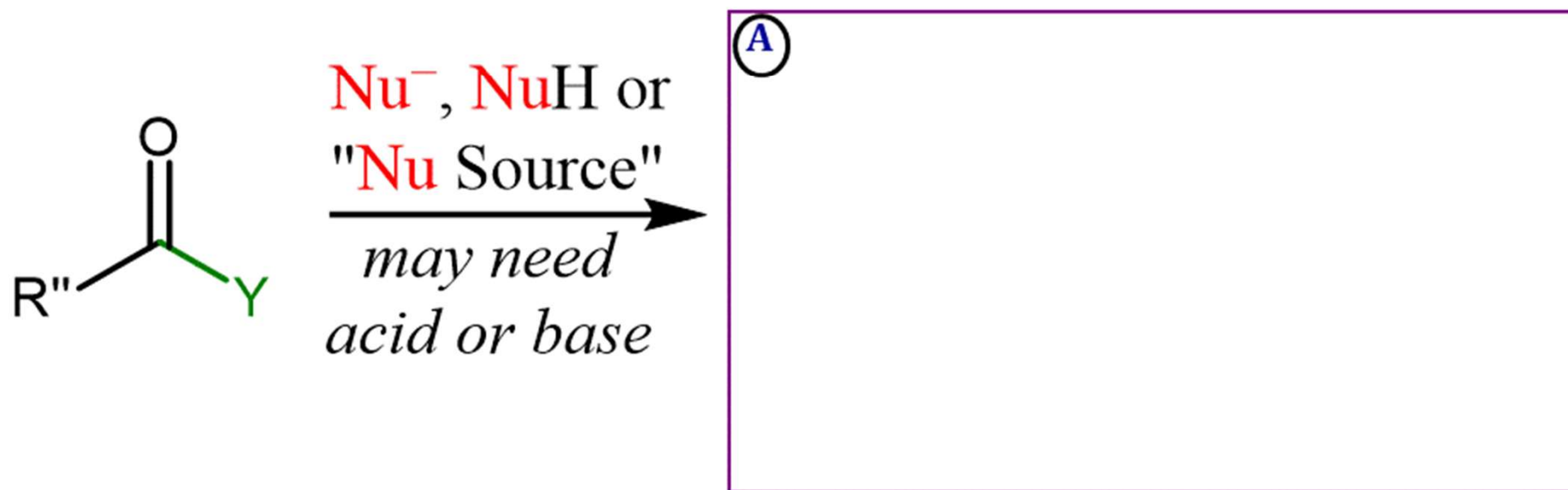
1. Add a nucleophile (Nu) to the carbonyl C to replace the pi bond
2. Protonate the carbonyl O.



Type B: Nucleophilic Acyl Substitution (S_NAc)

The net result is:

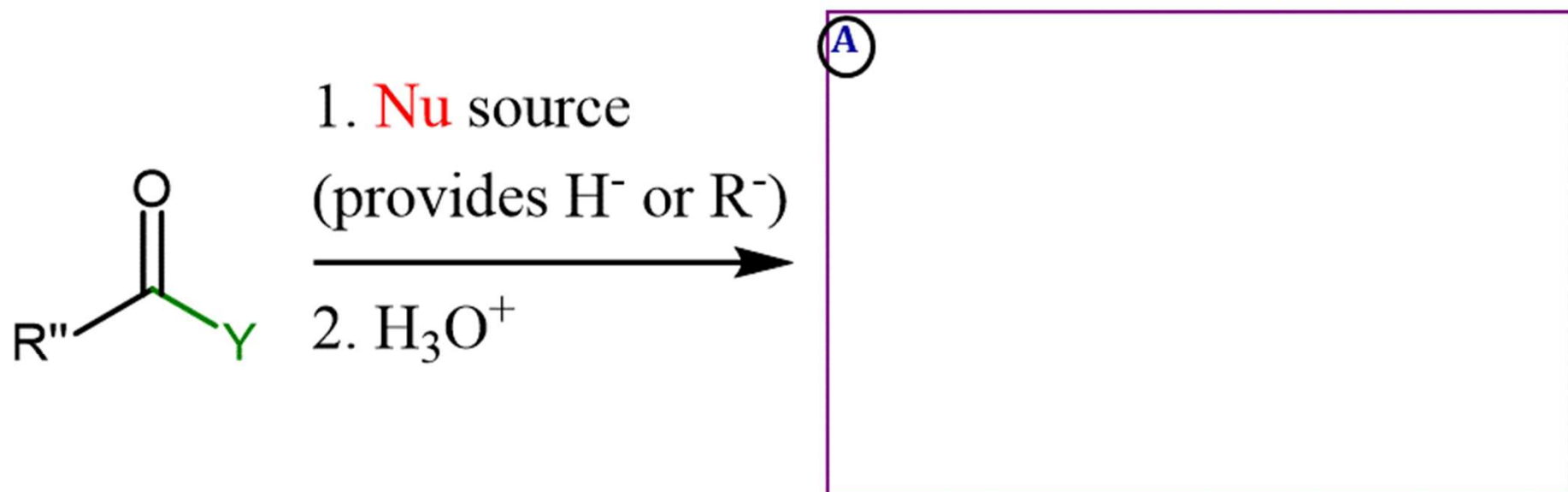
1. Substitute one nucleophile (Nu) for one leaving group (Y) attached to the carbonyl carbon



Type C: S_NAc then Nucleophilic Addition (Type C = B then A!)

The net result is:

1. Replace the pi bond to O and the leaving group with two bonds to nucleophiles.

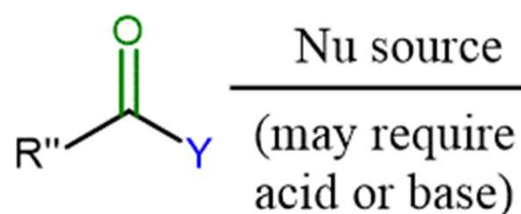


Type D: Replace both Bonds to the Carbonyl O

The net result is:

1. Remove the carbonyl O.
2. Replace the two bonds to carbonyl C. There are four options to replace the two bonds ...

Type D: Replace both Bonds to the Carbonyl O



Option I:

(A)

Option II:

(B)

Option III:

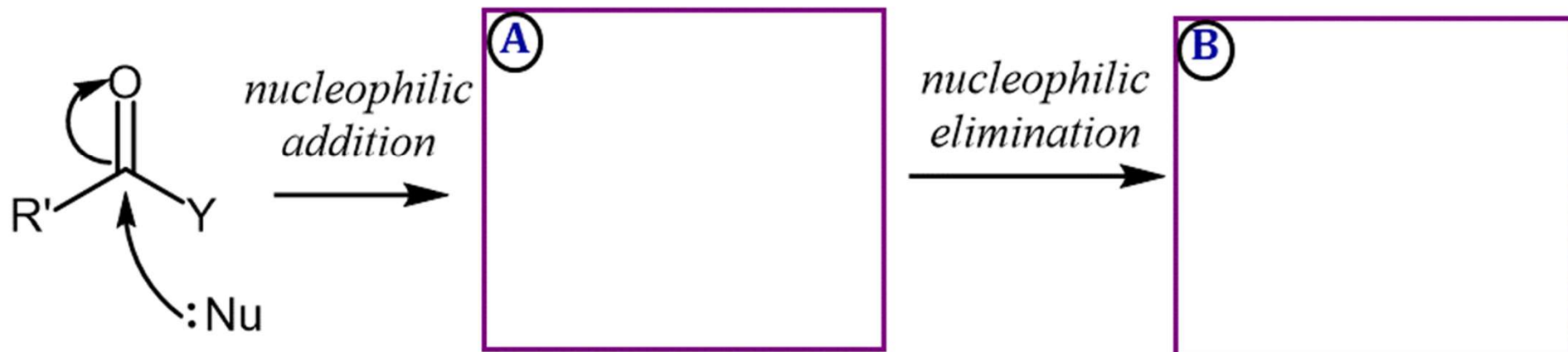
(C)

Option IV:

(D)

VI.8. Introducing Carbonyl Reaction Type B: S_NAc

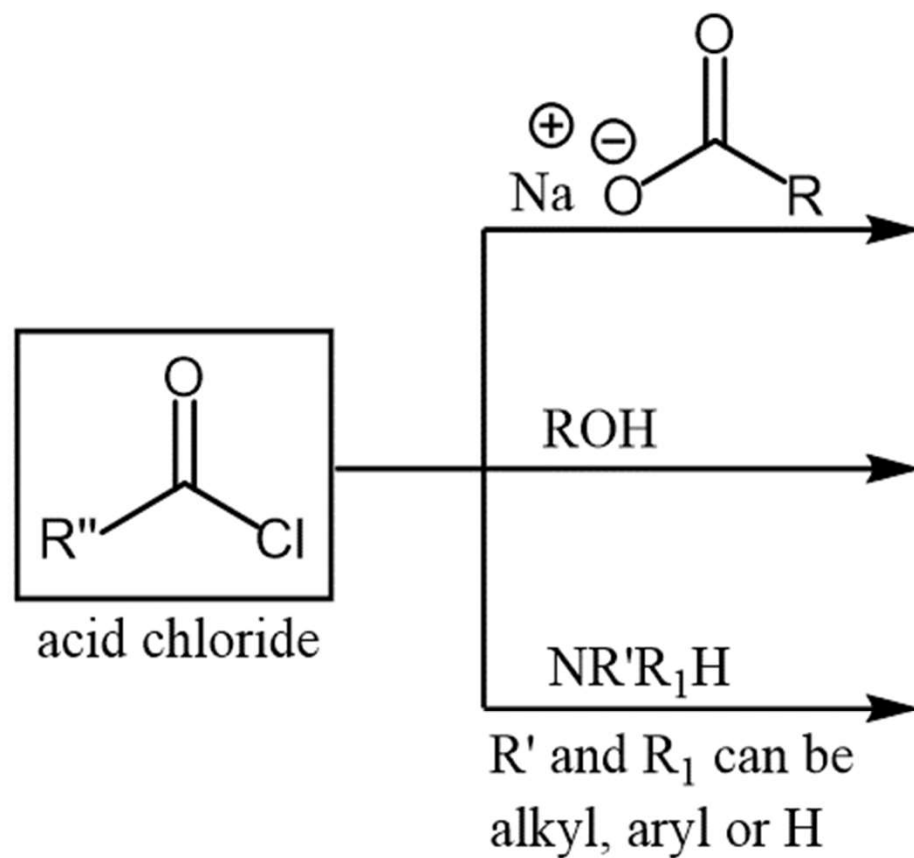
One type of reaction that carbonyl functional groups can undergo consists of two steps: 1) *nucleophilic addition* then 2) *nucleophilic elimination*. These steps comprise **Nucleophilic Acyl Substitution (S_NAc)**. In this Lecture Guide, we also refer to these type of reactions as **carbonyl reaction type B**:



Type B reactions are possible for all of the carbonyl functional groups covered in this Lecture Guide, **except** aldehydes and ketones.

VI.9. S_NAc of Acid Chlorides and Anhydrides

The situation is much simpler when nucleophiles react with acid chlorides or anhydrides. In these cases, there is already a good leaving group on the carbonyl carbon. A variety of nucleophiles react readily with these functional groups. Consider acid chlorides:



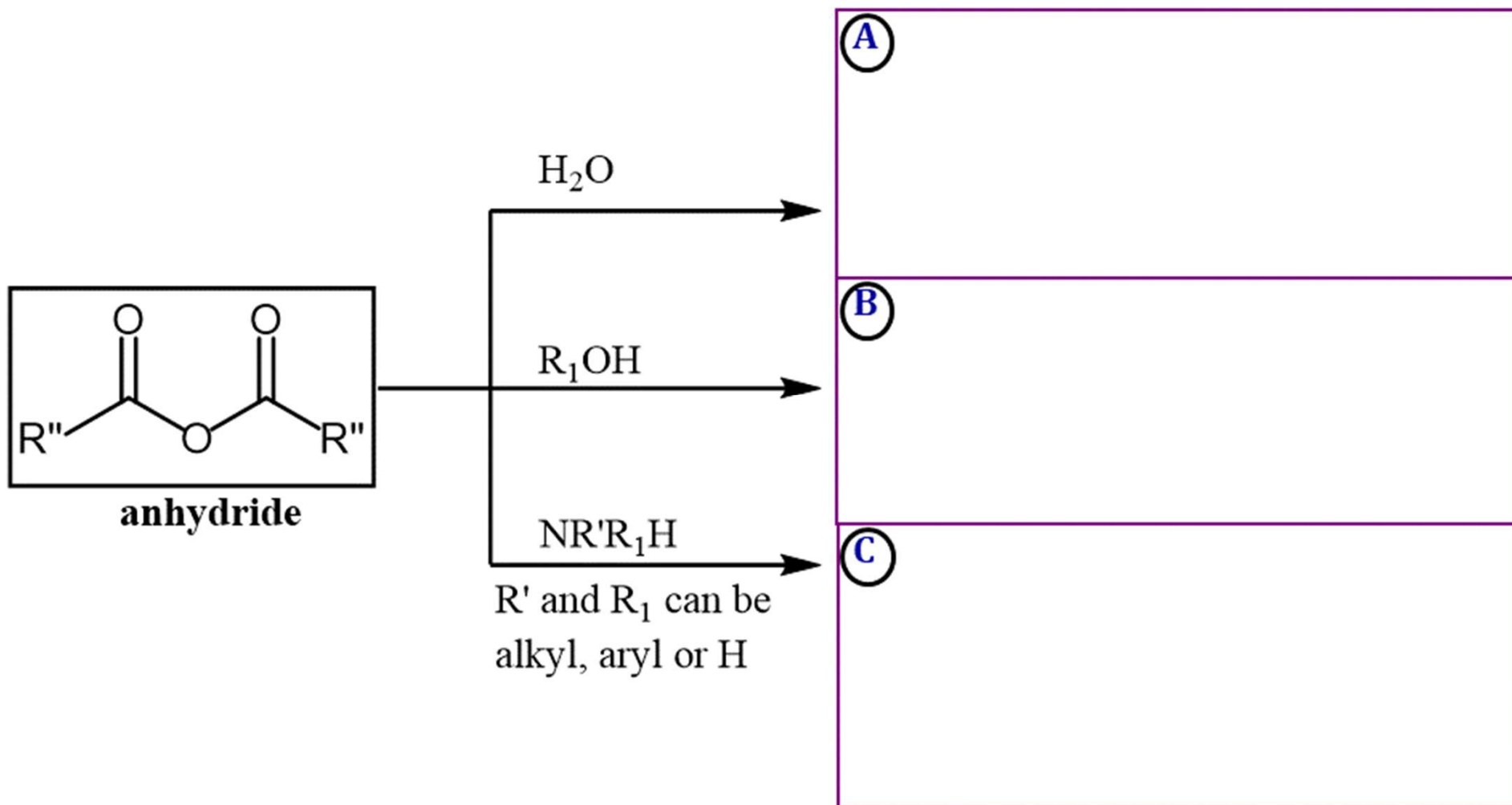
(A)

(B)

(C)

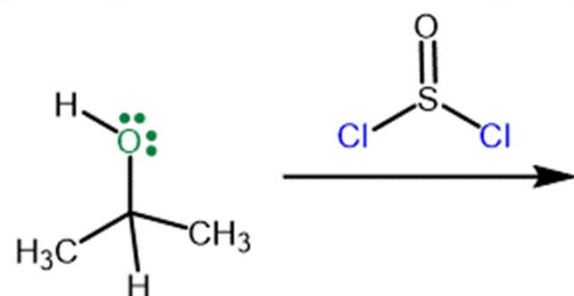
VI.9. S_NAc of Acid Chlorides and Anhydrides

And anhydrides:

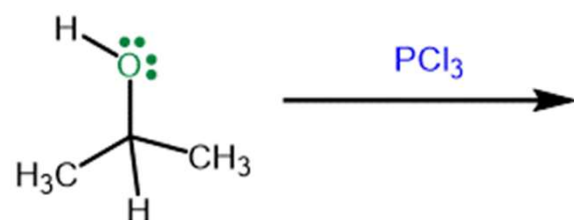


VI.8. Introducing Carbonyl Reaction Type B: S_NAc

Carboxylic acids are not very good substrates for S_NAr. This is because the -OH group is a bad leaving group. For alcohols, we converted the -OH into a good leaving group *before* we did a substitution by using Thionyl chloride (SOCl₂) or phosphorus trihalide (PX₃, X = Cl, Br).

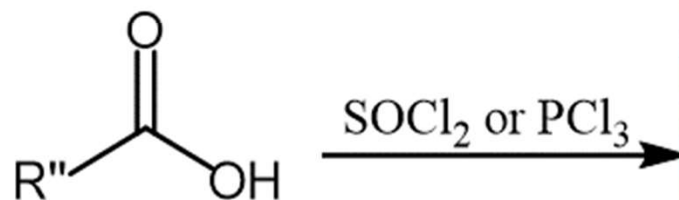


(A)



(B)

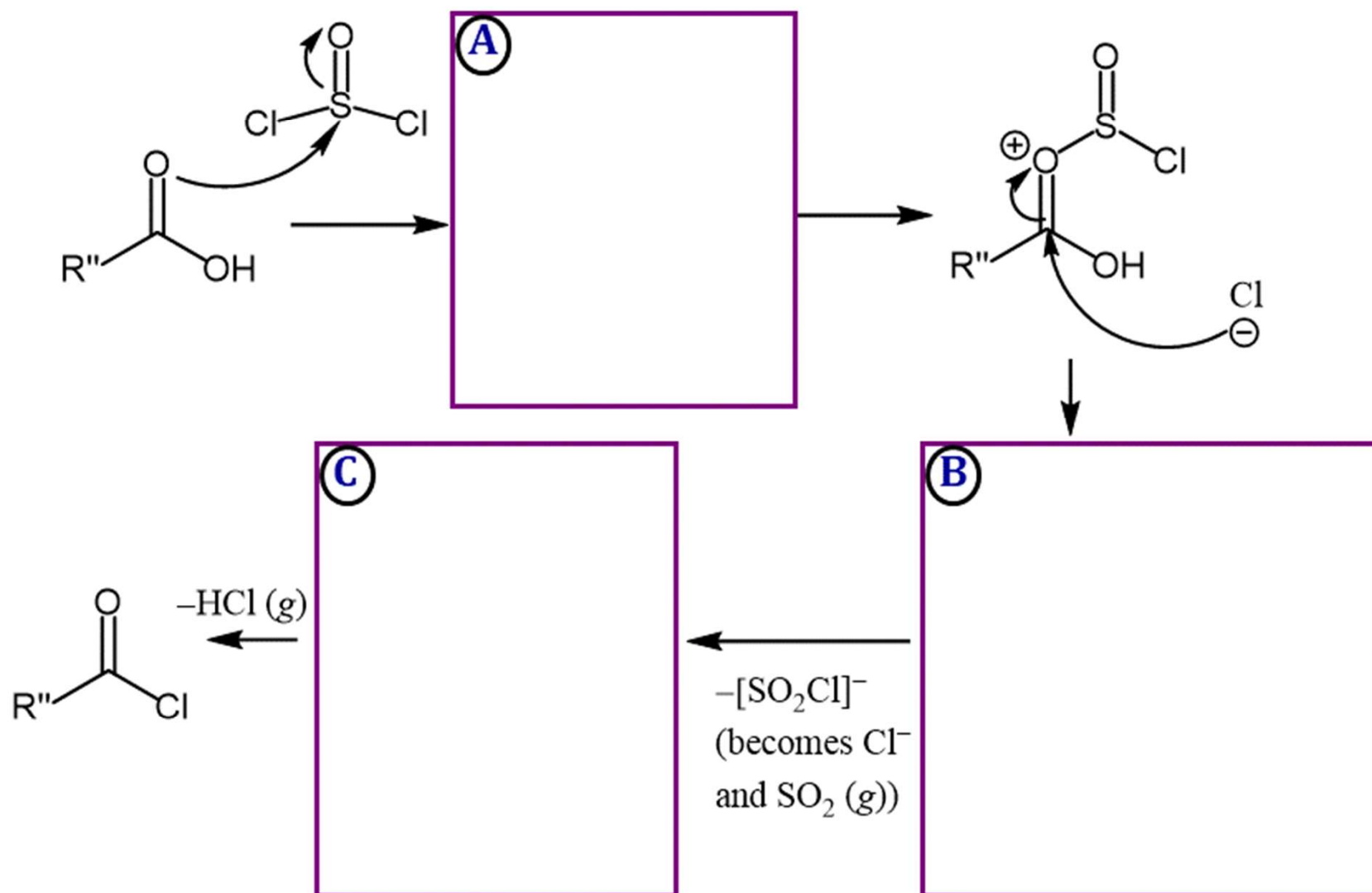
These reagents also work for carboxylic acids:



(C)

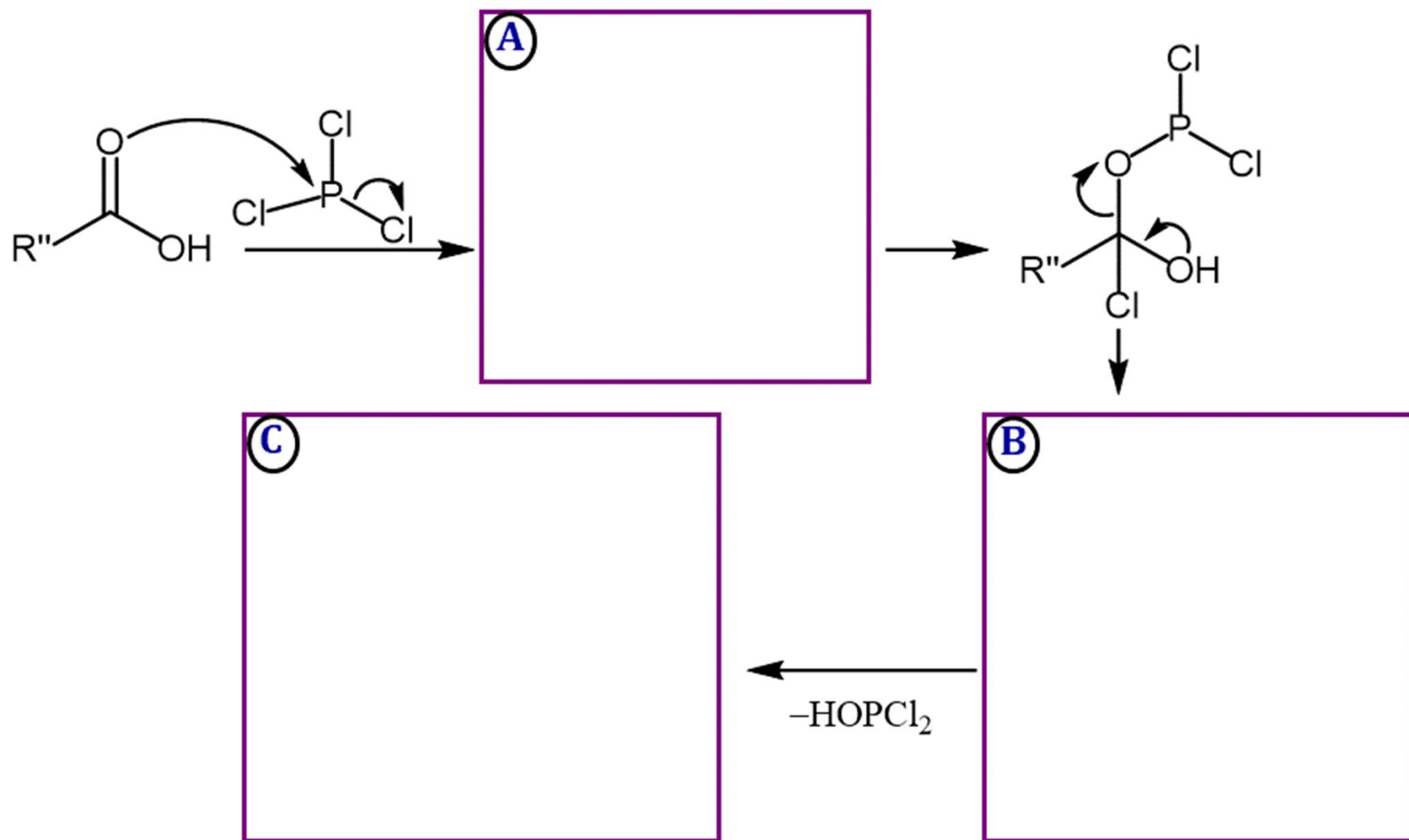
VI.8. Introducing Carbonyl Reaction Type B: S_NAc

Here is the reaction mechanism for a carboxylic acid with thionyl chloride:



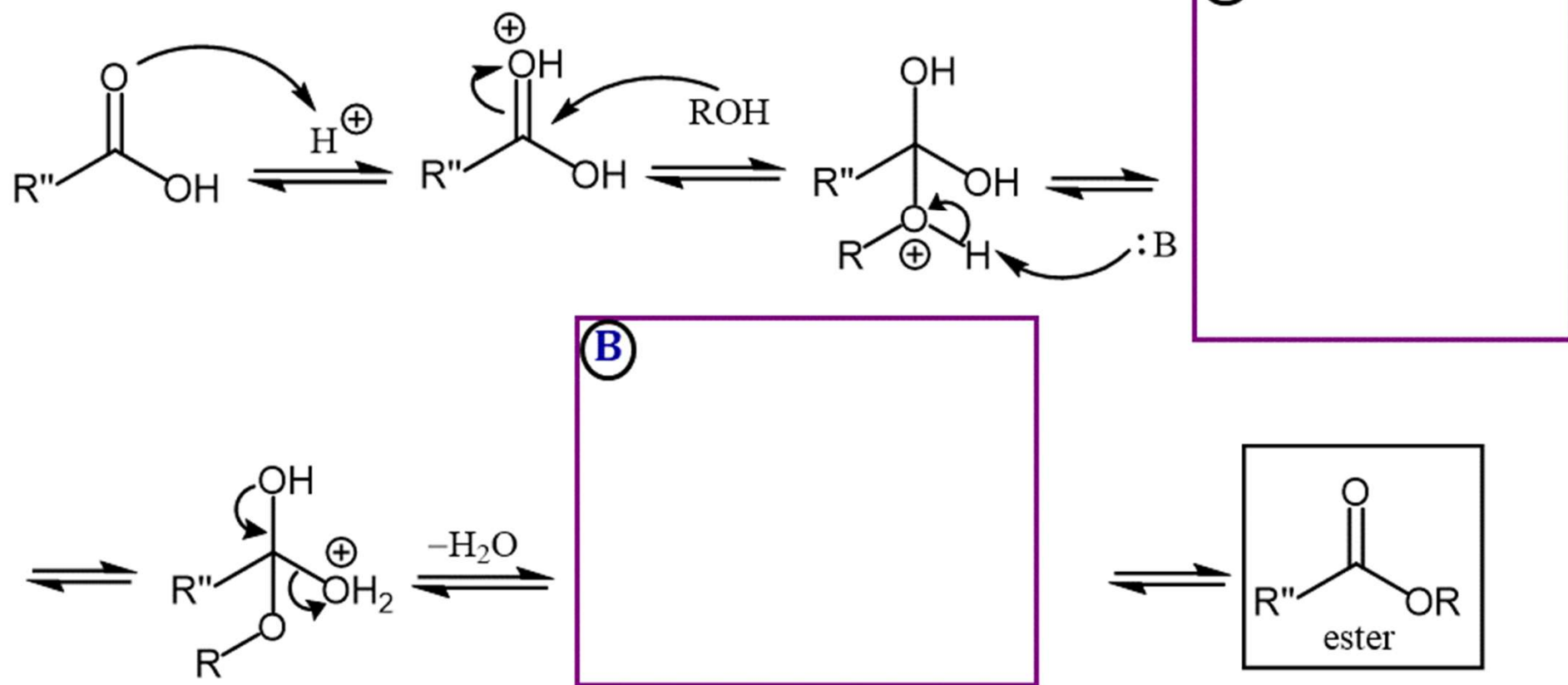
VI.8. Introducing Carbonyl Reaction Type B: S_NAc

Here is the reaction mechanism for a carboxylic acid with phosphorus trichloride:



VI.8. Introducing Carbonyl Reaction Type B: S_NAc

It is possible to convert an $-OH$ group to a good leaving group by protonating it as well, as we saw in reactions of alcohols with HX or H_2SO_4 . If we react a carboxylic acid with an alcohol nucleophile in the presence of an acid catalyst, we will get an ester. This is called **acid-catalyzed esterification** or **Fischer esterification**:



VI.8. Introducing Carbonyl Reaction Type B: S_NAc

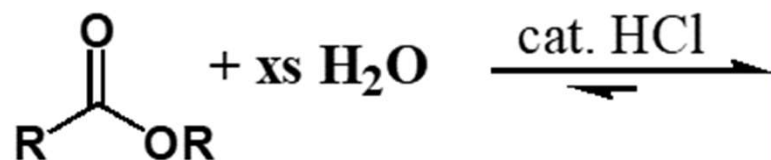
Note that all the steps are reversible, so we can push the reaction to either side of the equation by using LeChatelier's Principle.

LeChatelier's Principle:

(B)

This means that **ester hydrolysis** to convert an ester to a carboxylic acid is also possible:

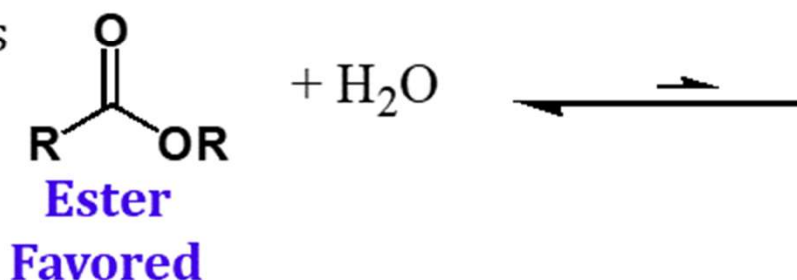
If you add lots of water:



(C)

Carboxylic acid Favored

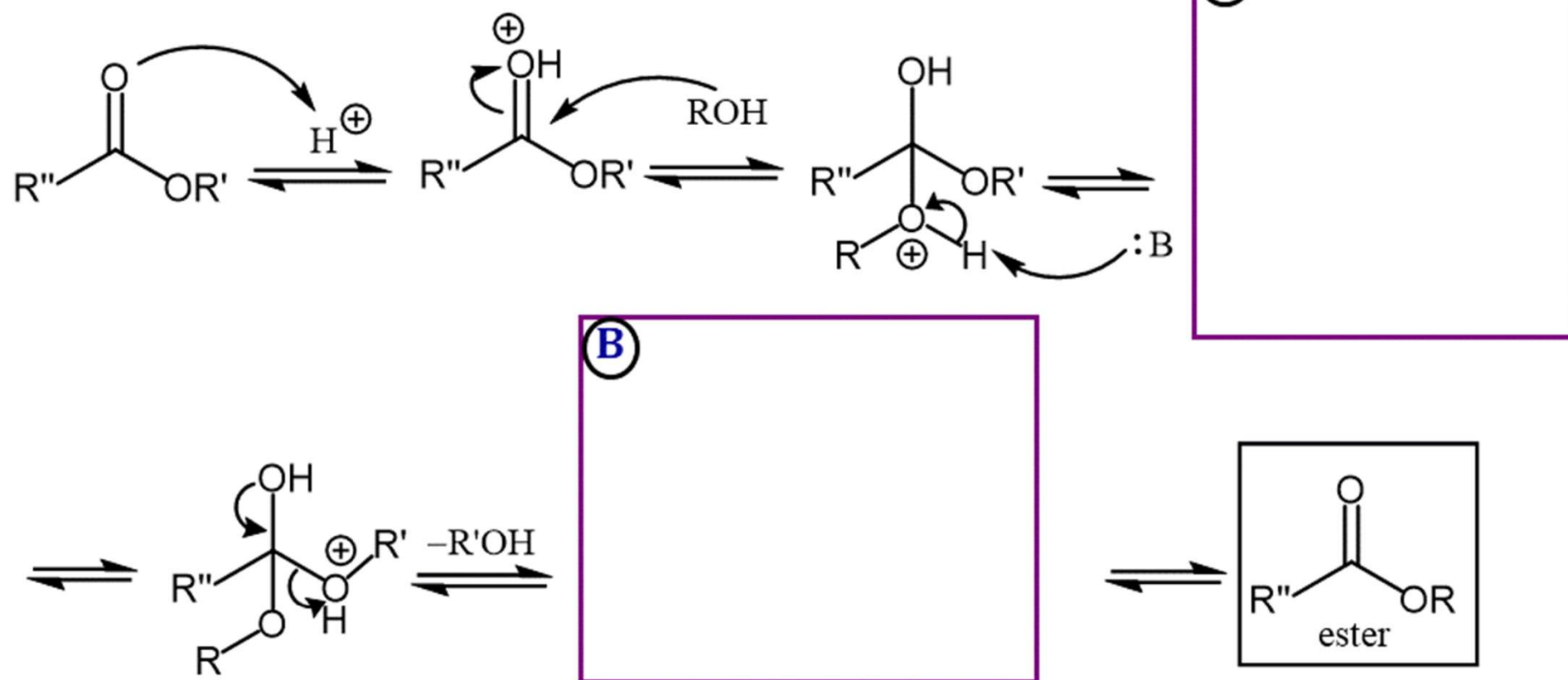
If you add lots of alcohol:



(D)

VI.10. Carbonyl Reaction Type B: S_NAc of Esters

We have seen that esters can undergo acid-catalyzed hydrolysis. If an alcohol is used in place of water for reaction with ether with acid catalysis, **acid-catalyzed transesterification** is possible:



Note that this mechanism mirrors the Fischer esterification of carboxylic acids.

VI.10. Carbonyl Reaction Type B: S_NAc of Esters

Ammonia, primary amines, or secondary amines can also be used as nucleophiles for S_NAc of esters:

