# Lecture 3: Forming Carbonyl Groups by Oxidation

***Objectives:***

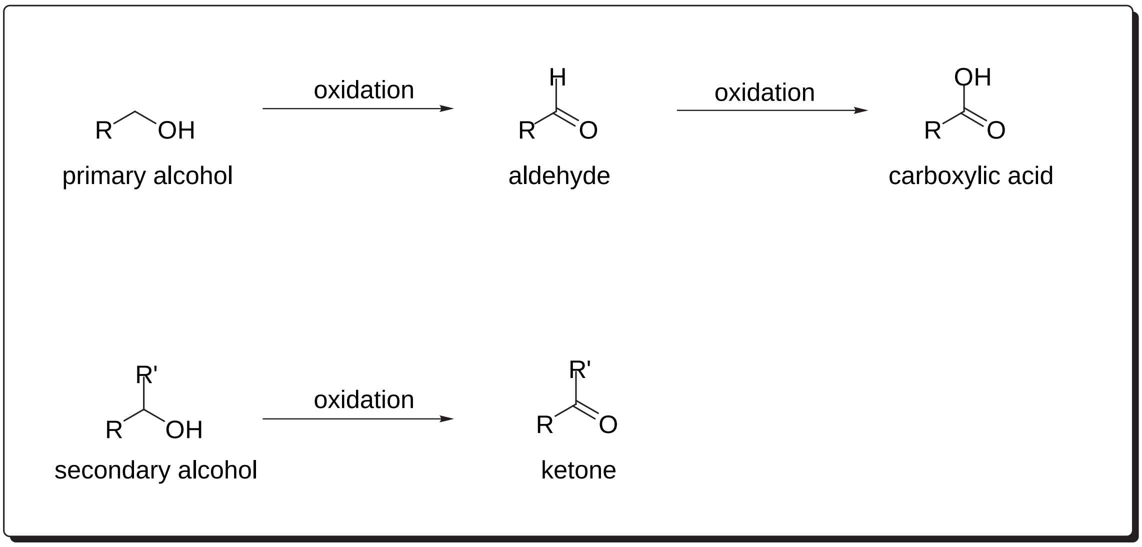
By the end of this lecture you will be able to:

- use chromium-based oxidants to prepare aldehydes, ketones and carboxylic acids;
- draw the mechanism of this oxidation reaction;
- understand some of the selectivity issues involved in using these oxidants;
- use aldehydes and ketones to prepare olefins using the Wittig reaction;
- draw the mechanism of nucleophilic addition to aldehydes and ketones.

## Introduction

The carbonyl functional group is one of the most common in organic molecules. It is also one of the most versatile, providing methods for preparing a wide variety of other functional groups (*e.g.* alcohols, olefins). Its importance has fuelled a large amount of research into efficient methods for preparing this functional group. Oxidising an alcohol remains one of the most useful for accessing carbonyl-containing functional groups at both oxidation levels.

## Oxidation Reactions



Primary alcohols can be oxidised to aldehydes, which in turn can be oxidised to carboxylic acids; secondary alcohols can be oxidised to ketones.

Many types of oxidant can perform these transformations. Middle to late transition metals in high oxidation states are particularly important. We will just consider two types of chromium oxidant.

*An Issue of Chemoselectivity*

Primary alcohols can be oxidised to aldehydes *and/or* carboxylic acids. Ideally we would like methods for *selectively* accessing *either* the aldehyde *or* the carboxylic acid. Such chemoselectivity issues are less important with secondary alcohols, which can only be oxidised to ketones.

*A particularly important problem is the over-oxidation of an aldehyde to the corresponding carboxylic acid*.

Although this chemoselectivity issue has largely been solved by the introduction of new, mild oxidants, there are many cases where it remains a problem; careful choice of the correct oxidant is then important to minimise this unwanted side-reaction.

Oxidants based on chromium in a high (+6) oxidation state are some of the most successful reagents for performing oxidation reactions. Different reagents have different oxidising powers.

- To oxidise a primary alcohol to a carboxylic acid use the **JONES OXIDATION**
- To oxidise a primary alcohol to an aldehyde use **PYRIDINIUM DICHROMATE** (in dichloromethane solvent).

**Jones Oxidation:**

Reaction conditions: Chromium(VI) oxide ($CrO_3$), sulfuric acid ($H_2SO_4$), acetone (solvent).

- Primary alcohols are oxidised to carboxylic acids; the powerful nature of the oxidising system and the reaction conditions ensure that reaction does not stop at the intermediate aldehyde stage.
- Secondary alcohols are oxidised to ketones.
- Tertiary alcohols do not react.
- The reaction conditions are strongly acidic. This can be a severe problem if your molecule has functional groups that are acid-sensitive. In these cases alternative methods need to be found.
- The active oxidant is chromic acid ($H_2CrO_4$)

## Pyridinium dichromate (PDC) oxidation:

*Convince yourself that the chromium atom is in its +6 oxidation state.*

- This oxidation operates under near neutral reaction conditions.
- When dichloromethane is used as the solvent, primary alcohols are oxidised to aldehydes; over-oxidation to the carboxylic acid is (usually!) not a problem.
- Secondary alcohols are oxidised to ketones.
- Tertiary alcohols do not react.

**Mechanism of Oxidation**:

- Reaction proceeds by nucleophilic attack of the alcohol at the highly electrophilic chromium centre (Cr(VI)).

- Two proton transfer steps provide a chromate ester.

- Treatment with base (*e.g.* the solvent) induces collapse of this unstable intermediate through an $E_2$-like reaction mechanism to provide the corresponding carbonyl group. This elimination step is rate-determining.

# Reactions of Aldehydes and Ketones

Ketones and aldehydes are some of the most versatile functional groups; they can be used to prepare a wide variety of other functional groups. We will consider two types of reaction.

## The Wittig Olefination

The Wittig olefination is one of the most widely used methods for preparing olefins. The reaction requires a reactive carbonyl group so aldehydes are very good substrates; ketones are also good; esters and related carboxylic acid derivatives generally do not react.

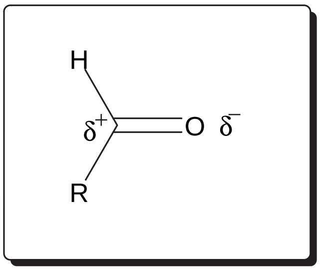
We shall not consider the reaction mechanism in detail - clearly there are issues of stereoselectivity involved.

A basic mechanism:

- The carbonyl compound and phosphorus ylide react to form a four-membered ring intermediate called an oxaphosphetane. This reaction can be highly stereo*selective* depending on the reagents and reaction conditions that are employed.
- The intermediate oxaphosphetane then collapses in a stereo*specific* process to release the olefin and triphenylphosphine oxide.
- Formation of triphenylphosphine oxide ($Ph_3P=O$) provides the thermodynamic driving force for the reaction - the P=O bond is very strong.

**Nucleophilic Addition Reactions with Aldehydes and Ketones**

As we discussed in the first lecture, the carbonyl group is polarised by the strongly electronegative oxygen atom. The net result of this is to withdraw electron density from the carbon centre on to the oxygen centre; the carbon acquires a δ+ charge and the oxygen a δ- charge:



This makes the carbon of a carbonyl group **ELECTROPHILIC** in character and therefore susceptible to attack by nucleophiles. The reaction of nucleophiles with aldehydes and ketones is the most important synthetic transformation for this functional group.

General Mechanism:

We need to be able to understand this reaction mechanism in more detail. By looking at the molecular orbitals involved we can gain further insight into important aspects of the process such as the approach trajectory of the nucleophile on the carbonyl group in the first, rate-determining - and therefore most important - step.

We can gain more information about the Transition State in the rate-determining step by considering an energy diagram of the reaction:

The **Hammond Postulate** states that: *a Transition State more closely resembles the reactive species to which it is closer in energy*; thus in an 'uphill' reaction (*e.g.* step 1 of the nucleophilic addition reaction), the product of this step (in our case the tetrahedral intermediate) is higher in energy than the starting materials. Therefore the T.S. more closely resembles the intermediate - it is said to be *product-like*.

This postulate is very useful - it tells us that anything that stabilises (and therefore lowers the energy of) the intermediate will also lower the energy of the transition state and therefore increase the reaction rate.

Furthermore if the transition state is more similar in energy to the product then we can assume that its structure more closely resembles the product than it does the starting material.

In the case of addition of a nucleophile to a carbonyl group we go from a planar species to one that is tetrahedral. The best approach trajectory along which the nucleophile will follow will be that which requires the *least amount of spatial reorganisation of atoms* (as this requires energy). In its most simple form, the nucleophile will therefore approach at an approach trajectory that is approximately 109°. This is the so-called Bürgi-Dunitz approach trajectory.

Let us consider the important Frontier Orbital interactions involved in this transformation These are those molecular orbital interactions between the Highest Occupied Molecular Orbital, the HOMO, which in our case is on the nucleophile, and the Lowest Unoccupied Molecular Orbital, the LUMO, which is the $\pi^*$-antibonding MO on the carbonyl compound (see Lecture 1).

We can see that the important Frontier Orbital interactions are ideally set up for the nucleophile to approach at a ~109° approach trajectory.  This interaction leads to a lowering in energy which is what you would expect in a bond-forming process:

## Summary

Oxidising alcohols provides one of the best methods for preparing carbonyl functional groups. We have seen how two different chromium oxidants allow chemoselective access to carbonyl groups in either oxidation state:  Jones oxidation is a powerful oxidising system and oxidises alcohols to their maximum oxidation level (primary alcohols to carboxylic acids; secondary alcohols to ketones); PDC is a much milder chromium oxidant and allows the selective preparation of aldehydes from primary alcohols.

Carbonyl groups are very versatile reactive intermediates.  They react with phsophorus ylides in the so-called Wittig reaction to provide olefins.  The electrophilic character of the carbonyl carbon means that they also react with nucleophiles.  We have discussed how the nucleophile approaches the carbonyl carbon along a well-defined approach trajectory, the so-called Bürgi-Dunitz angle, to minimise the energy of the transition state.  Next lecture we will look at the types of nucleophiles that react with aldehydes and ketones.