

Chemical Reactivity

Organic chemistry encompasses a very large number of compounds (many millions), and our previous discussion and illustrations have focused on their structural characteristics. Now that we can recognize these actors (compounds), we turn to the roles they are inclined to play in the scientific drama staged by the multitude of chemical reactions that define organic chemistry.

We begin by defining some basic terms that will be used frequently as this subject is elaborated.

Chemical Reaction: A transformation resulting in a change of composition, constitution and/or configuration of a compound (referred to as the reactant or substrate).

Reactant or Substrate: The organic compound undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.

Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic; small or large; gas, liquid or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.

Product(s) The final form taken by the major reactant(s) of a reaction.

Reaction Conditions The environmental conditions, such as temperature, pressure, catalysts & solvent, under which a reaction progresses optimally. Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions.

Chemical reactions are commonly written as equations:



Reaction Classification

Classifying Organic Chemical Reactions

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as [functional groups](#), and these constitute one organizational scheme that helps us catalog and remember reactions.

Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

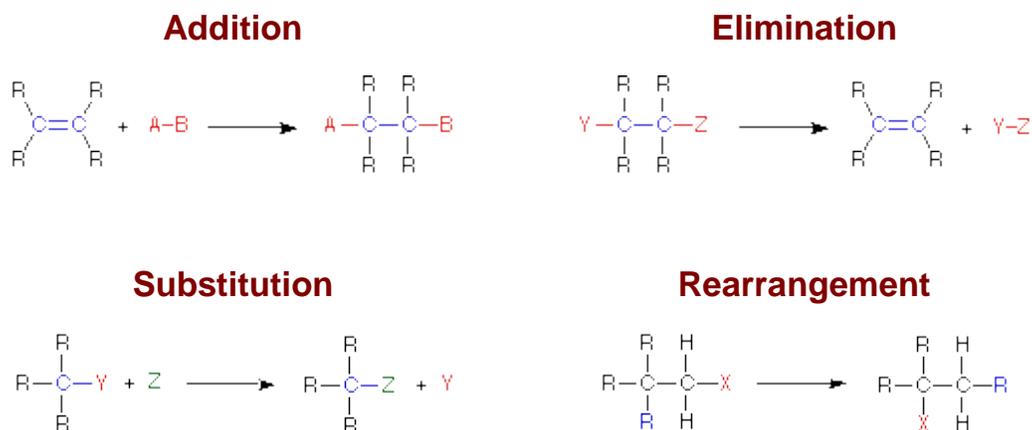
This is best accomplished by perceiving the reaction pathway or mechanism of a reaction.

1. Classification by Structural Change

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms.

The letter **R** in the following illustrations is widely used as a symbol for a generic group. It may stand for simple substituents such as H- or CH₃-, or for complex groups composed of many atoms of carbon and other elements.

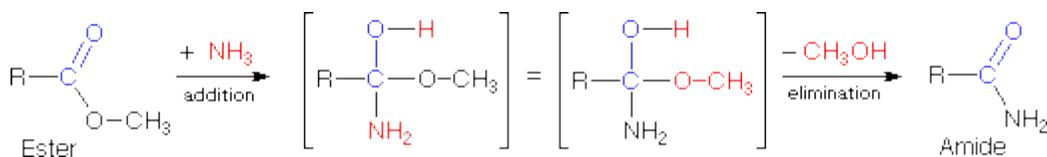
Four Reaction Classes



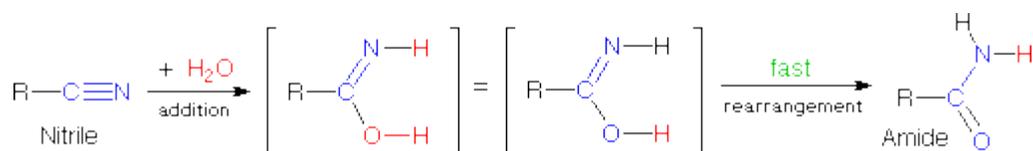
In an addition reaction the number of σ -bonds in the substrate molecule increases, usually at the expense of one or more π -bonds. The reverse is true of elimination reactions, *i.e.* the number of σ -bonds in the substrate decreases, and new π -bonds are often formed.

Substitution reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A rearrangement reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types. The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH₃O & Z = NH₂); however, it is actually two reactions, an addition followed by an elimination.



The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



2. Classification by Reaction Type

At the beginning, it is helpful to identify some common reaction types that will surface repeatedly as the chemical behavior of different compounds is examined. This is not intended to be a complete and comprehensive list, but should set the stage for future elaborations.

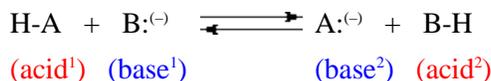
Acidity and Basicity

It is useful to begin a discussion of organic chemical reactions with a review of acid-base chemistry and terminology for several reasons. First, acid-base reactions are among the simplest to recognize and understand. Second, some classes of organic compounds have distinctly acidic properties, and some other classes behave as bases, so we need to identify these aspects of their chemistry. Finally, many organic reactions are catalyzed by acids and/or bases, and although such transformations may seem complex, our understanding of how they occur often begins with the functioning of the catalyst.

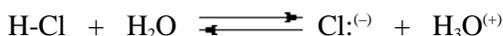
Organic chemists use two acid-base theories for interpreting and planning their work: the *Brønsted theory* and the *Lewis theory*.

Brønsted Theory

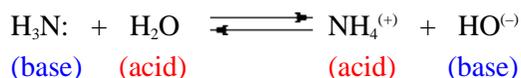
According to the Brønsted theory, **an acid is a proton donor**, and **a base is a proton acceptor**. In an acid-base reaction, each side of the equilibrium has an acid and a base reactant or product, and these may be neutral species or ions.



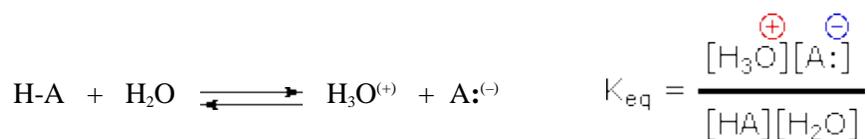
Structurally related acid-base pairs, such as {H-A and A⁽⁻⁾} or {B⁽⁻⁾ and B-H} are called **conjugate pairs**. Substances that can serve as both acids and bases, such as water, are termed **amphoteric**.



(acid) (base) (base) (acid)



The relative strength of a group of acids (or bases) may be evaluated by measuring the extent of reaction that each group member undergoes with a common base (or acid). Water serves nicely as the common base or acid for such determinations. Thus, for an acid H-A, its strength is proportional to the extent of its reaction with the base water, which is given by the **equilibrium constant** K_{eq} .



Since these studies are generally extrapolated to high dilution, the molar concentration of water (55.5) is constant and may be eliminated from the denominator. The resulting K value is called the **acidity constant**, K_a . Clearly, strong acids have larger K_a 's than do weaker acids. Because of the very large range of acid strengths (greater than 10^{40}), a logarithmic scale of acidity ($\text{p}K_a$) is normally employed. Stronger acids have smaller or more negative $\text{p}K_a$ values than do weaker acids.

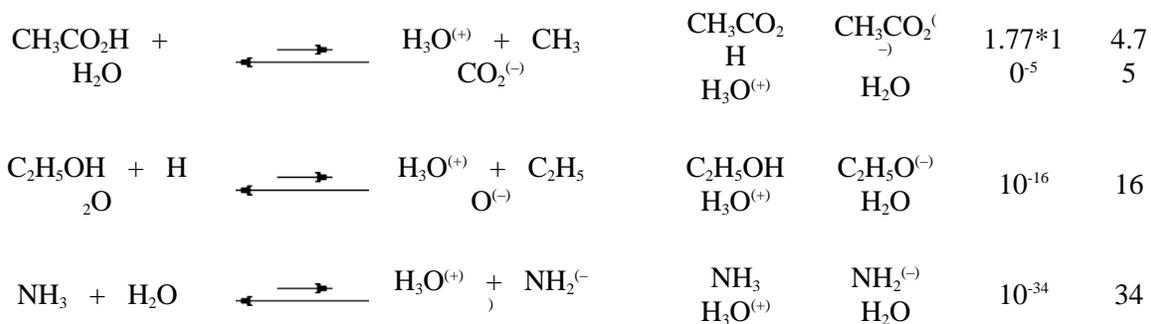
$$K_a = \frac{[\text{H}_3\text{O}^{(+)}][\text{A}^{(-)}]}{[\text{HA}]} \quad \text{p}K_a = -\log K_a = \log \left(\frac{1}{K_a} \right)$$

Some useful principles of acid-base reactions are:

- The stronger the acid the weaker its conjugate base; the stronger the base the weaker its conjugate acid.
- Acid-base equilibria always favor the weakest acid and the weakest base.

Examples of Brønsted Acid-Base Equilibria

Acid-Base Reaction	Conjugate Acids	Conjugate Bases	K_a	$\text{p}K_a$
$\text{HBr} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^{(+)} + \text{Br}^{(-)}$	HBr $\text{H}_3\text{O}^{(+)}$	$\text{Br}^{(-)}$ H_2O	10^5	-5



In all the above examples water acts as a common base. The last example (NH_3) cannot be measured directly in water, since the strongest base that can exist in this solvent is hydroxide ion. Consequently, the value reported here is extrapolated from measurements in much less acidic solvents, such as acetonitrile.

Since many organic reactions either take place in aqueous environments (living cells), or are quenched or worked-up in water, it is important to consider how a conjugate acid-base equilibrium mixture changes with pH. A simple relationship known as the **Henderson-Hasselbalch equation** provides this information.

Henderson-Hasselbalch Equation: $\text{pK}_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^-]}$

When the pH of an aqueous solution or mixture is equal to the pK_a of an acidic component, the concentrations of the acid and base conjugate forms must be equal (the log of 1 is 0). If the pH is lowered by two or more units relative to the pK_a , the acid concentration will be greater than 99%. On the other hand, if the pH (relative to pK_a) is raised by two or more units the conjugate base concentration will be over 99%. Consequently, mixtures of acidic and non-acidic compounds are easily separated by adjusting the pH of the water component in a two phase solvent extraction. For example, if a solution of benzoic acid ($\text{pK}_a = 4.2$) in benzyl alcohol ($\text{pK}_a = 15$) is dissolved in ether and shaken with an excess of 0.1 N sodium hydroxide ($\text{pH} = 13$), the acid is completely converted to its water soluble (ether insoluble) sodium salt, while the alcohol is unaffected. The ether solution of the alcohol may then be separated from the water layer, and pure alcohol recovered by distillation of the volatile ether solvent. The pH of the water solution of sodium benzoate may then be lowered to 1.0 by addition of hydrochloric acid, at which point pure benzoic acid crystallizes, and may be isolated by filtration.

Basicity

The basicity of oxygen, nitrogen, sulfur and phosphorus compounds or ions may be treated in an analogous fashion. Thus, we may write base-acid equilibria, which define a K_b and a corresponding pK_b . However, a more common procedure is to report the acidities of the conjugate acids of the bases (these conjugate acids are often "onium"

cations). The pK_a 's reported for bases in this system are proportional to the base strength of the base. A useful rule here is: $pK_a + pK_b = 14$.

We see this relationship in the following two equilibria:

Acid-Base Reaction	Conjugate Acids	Conjugate Bases	K	pK
$\text{NH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{NH}_4^{(+)} + \text{OH}^{(-)}$	$\text{NH}_4^{(+)}$ H_2O	NH_3 $\text{OH}^{(-)}$	$K_b = 1.8 \times 10^{-5}$	$pK_b = 4.74$
$\text{NH}_4^{(+)} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^{(+)} + \text{NH}_3$	$\text{NH}_4^{(+)}$ $\text{H}_3\text{O}^{(+)}$	NH_3 H_2O	$K_a = 5.5 \times 10^{-10}$	$pK_a = 9.25$

Tables of pK_a values for inorganic and organic acids (and bases) are available in many reference books, and may be examined here by clicking on the appropriate link:

[Inorganic Acidity Constants](#)

[Organic Acidity Constants](#)

[Basicity Constants](#)

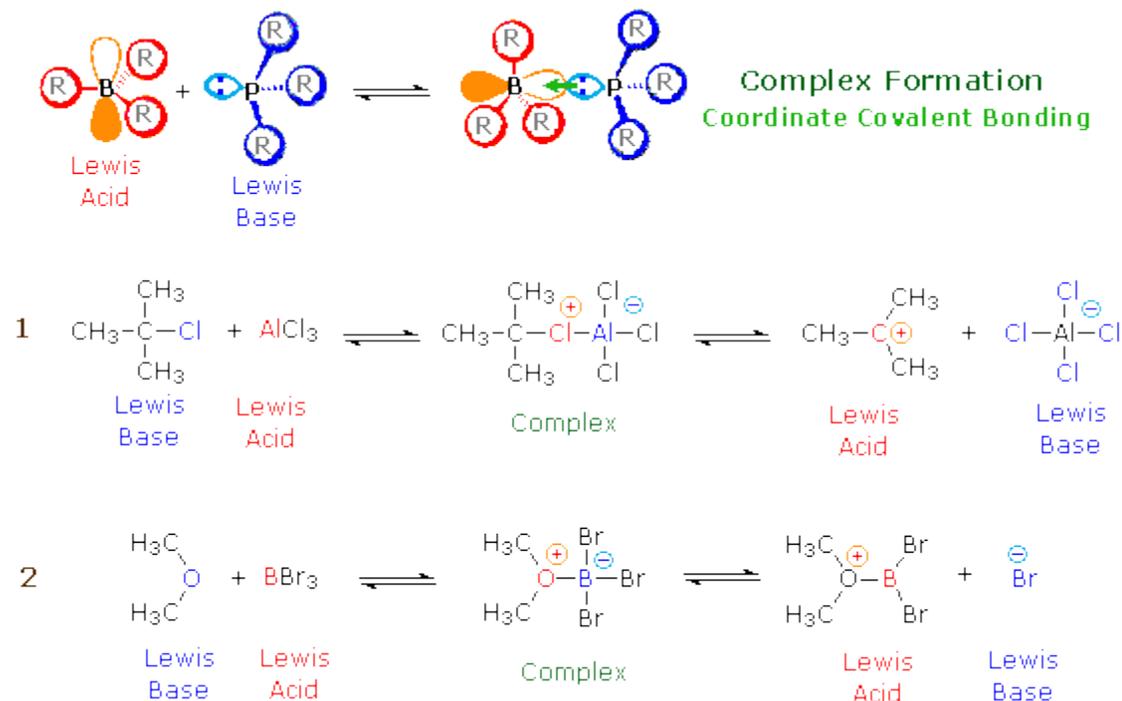
Although it is convenient and informative to express pK_a values for a common solvent system (usually water), there are serious limitations for very strong and very weak acids. Thus acids that are stronger than the hydronium cation, $\text{H}_3\text{O}^{(+)}$, and weak acids having conjugate bases stronger than hydroxide anion, $\text{OH}^{(-)}$, cannot be measured directly in water solution. Solvents such as acetic acid, acetonitrile and nitromethane are often used for studying very strong acids. Relative acidity measurements in these solvents may be extrapolated to water. Likewise, very weakly acidic solvents such as DMSO, acetonitrile, toluene, amines and ammonia may be used to study the acidities of very weak acids. For both these groups, the reported pK_a values extrapolated to water are approximate, and many have large uncertainties. [A useful table of \$pK_a\$ values in DMSO solution has been compiled from the work of F.G. Bordwell, and may be reached](#)

Lewis Theory

According to the Lewis theory, **an acid is an electron pair acceptor**, and **a base is an electron pair donor**. Lewis bases are also Brønsted bases; however, many Lewis acids, such as BF_3 , AlCl_3 and Mg^{2+} , are not Brønsted acids. The product of a Lewis acid-base reaction, is a neutral, dipolar or charged complex, which may be a stable covalent molecule. As shown at the top of the following drawing, coordinate covalent bonding of a phosphorous Lewis base to a boron Lewis acid creates a complex in which the formal charge of boron is negative and that of phosphorous is positive. In this complex, boron acquires a neon valence shell configuration and phosphorous an argon configuration. If the substituents (R) on these atoms are not large, the complex will be favored at equilibrium. However, steric hindrance of bulky substituents may prohibit complex

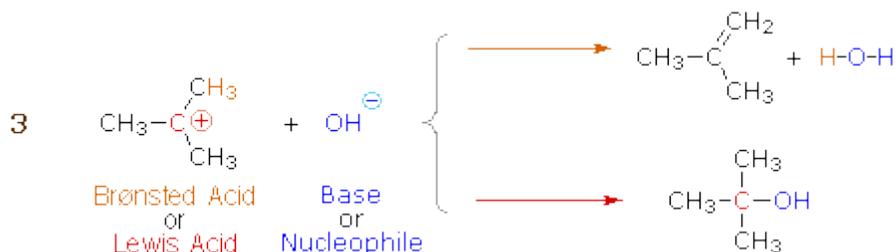
formation. The resulting mixture of non-bonded Lewis acid/base pairs has been termed "frustrated", and exhibits unusual chemical behavior.

Two examples of Lewis acid-base equilibria that play a role in chemical reactions are shown in equations 1 & 2 below.



In the first example, an electron deficient aluminum atom bonds to a covalent chlorine atom by sharing one of its non-bonding valence electron pairs, and thus achieves an argon-like valence shell octet. Because this sharing is unilateral (chlorine contributes both electrons), both the aluminum and the chlorine have formal charges, as shown. If the carbon chlorine bond in this complex breaks with both the bonding electrons remaining with the more electronegative atom (chlorine), the carbon assumes a positive charge. We refer to such carbon species as **carbocations**. Carbocations are also Lewis acids, as the reverse reaction demonstrates.

Many carbocations (but not all) may also function as Brønsted acids. Equation 3 illustrates this dual behavior; the Lewis acidic site is colored red and three of the nine acidic hydrogen atoms are colored orange. In its Brønsted acid role the carbocation donates a proton to the base (hydroxide anion), and is converted to a stable neutral molecule having a carbon-carbon double bond.



A terminology related to the Lewis acid-base nomenclature is often used by organic chemists. Here the term **electrophile** corresponds to a Lewis acid, and **nucleophile** corresponds to a Lewis base.

Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.

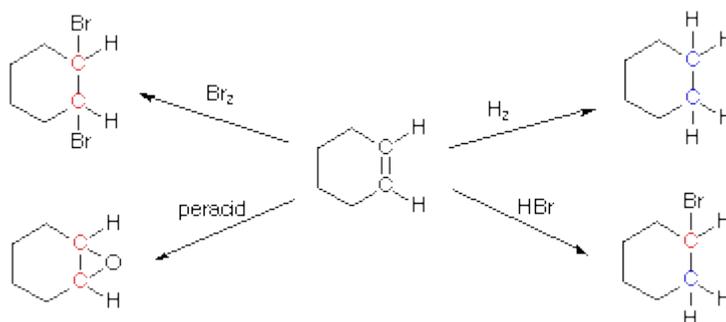
Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Oxidation and Reduction Reactions

A parallel and independent method of characterizing organic reactions is by **oxidation-reduction** terminology. Carbon atoms may have any oxidation state from -4 (e.g. CH_4) to $+4$ (e.g. CO_2), depending upon their substituents. Fortunately, we need not determine the absolute oxidation state of each carbon atom in a molecule, but only the **change in oxidation state** of those carbons involved in a chemical transformation. To determine whether a carbon atom has undergone a redox change during a reaction we simply note any changes in the number of bonds to hydrogen and the number of bonds to more electronegative atoms such as O, N, F, Cl, Br, I, & S that has occurred. Bonds to other carbon atoms are ignored. This count should be conducted for each carbon atom undergoing any change during a reaction.

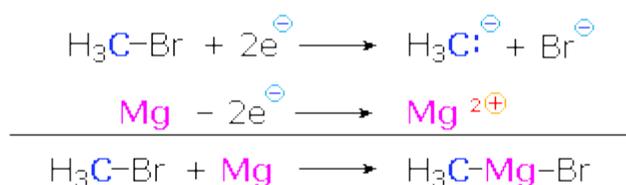
1. If the number of hydrogen atoms bonded to a carbon increases, and/or if the number of bonds to more electronegative atoms decreases, the carbon in question has been **reduced** (i.e. it is in a lower oxidation state).
2. If the number of hydrogen atoms bonded to a carbon decreases, and/or if the number of bonds to more electronegative atoms increases, the carbon in question has been **oxidized** (i.e. it is in a higher oxidation state).
3. If there has been no change in the number of such bonds, then the carbon in question has not changed its oxidation state. In the hydrolysis reaction of a nitrile shown above, the blue colored carbon has not changed its oxidation state.

These rules are illustrated by the following four **addition** reactions involving the same starting material, cyclohexene. Carbon atoms colored blue are reduced, and those colored red are oxidized. In the addition of hydrogen both carbon atoms are reduced, and the overall reaction is termed a reduction. Peracid epoxidation and addition of bromine oxidize both carbon atoms, so these are termed oxidation reactions. Addition of HBr reduces one of the double bond carbon atoms and oxidizes the other; consequently, there is no overall redox change in the substrate molecule.



For a discussion of how oxidation state numbers may be assigned to carbon atoms [Click Here](#).

Since metals such as lithium and magnesium are less electronegative than hydrogen, their covalent bonds to carbon are polarized so that the carbon is negative (reduced) and the metal is positive (oxidized). Thus, Grignard reagent formation from an alkyl halide reduces the substituted carbon atom. In the following equation and half-reactions the carbon atom (blue) is reduced and the magnesium (magenta) is oxidized.



3. Classification by Functional Group

Functional groups are atoms or small groups of atoms (usually two to four) that exhibit a characteristic reactivity when treated with certain reagents. To view a table of the common functional groups and their class names [Click Here](#). A particular functional group will almost always display its characteristic chemical behavior when it is present in a compound. Because of this, the discussion of organic reactions is often organized according to functional groups. The following table summarizes the general chemical behavior of the common functional groups. For reference, the alkanes provide a background of behavior in the absence of more localized functional groups.

Functional Class	Formula	Characteristic Reactions
Alkanes	C-C, C-H	Substitution (of H, commonly by Cl or Br) Combustion (conversion to CO ₂ & H ₂ O)
Alkenes	C=C-C-H	Addition Substitution (of H)
Alkynes	C≡C-H	Addition

		Substitution (of H)
Alkyl Halides	$\text{H}-\text{C}-\text{C}-\text{X}$	Substitution (of X) Elimination (of HX)
Alcohols	$\text{H}-\text{C}-\text{C}-\text{O}-\text{H}$	Substitution (of H); Substitution (of OH) Elimination (of HOH); Oxidation (elimination of 2H)
Ethers	$(\alpha)\text{C}-\text{O}-\text{R}$	Substitution (of OR); Substitution (of α -H)
Amines	$\text{C}-\text{NRH}$	Substitution (of H); Addition (to N); Oxidation (of N)
Benzene Ring	C_6H_6	Substitution (of H)
Aldehydes	$(\alpha)\text{C}-\text{CH}=\text{O}$	Addition Substitution (of H or α -H)
Ketones	$(\alpha)\text{C}-\text{CR}=\text{O}$	Addition Substitution (of α -H)
Carboxylic Acids	$(\alpha)\text{C}-\text{CO}_2\text{H}$	Substitution (of H); Substitution (of OH) Substitution (of α -H); Addition (to C=O)
Carboxylic Derivatives	$(\alpha)\text{C}-\text{CZ}=\text{O}$ (Z = OR, Cl, NHR, etc.)	Substitution (of Z); Substitution (of α -H) Addition (to C=O)

This table does not include any reference to rearrangement, due to the fact that such reactions are found in all functional classes, and are highly dependent on the structure of the reactant. Furthermore, a review of the overall reaction patterns presented in this table discloses only a broad and rather non-specific set of reactivity trends. This is not surprising, since the three remaining categories provide only a coarse discrimination (comparable to identifying an object as animal, vegetable or mineral). Consequently, apparent similarities may fail to reflect important differences. For example, addition reactions to C=C are significantly different from additions to C=O, and substitution reactions of C-X proceed in very different ways, depending on the hybridization state of carbon.

Source : <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/react1.htm#rx2>