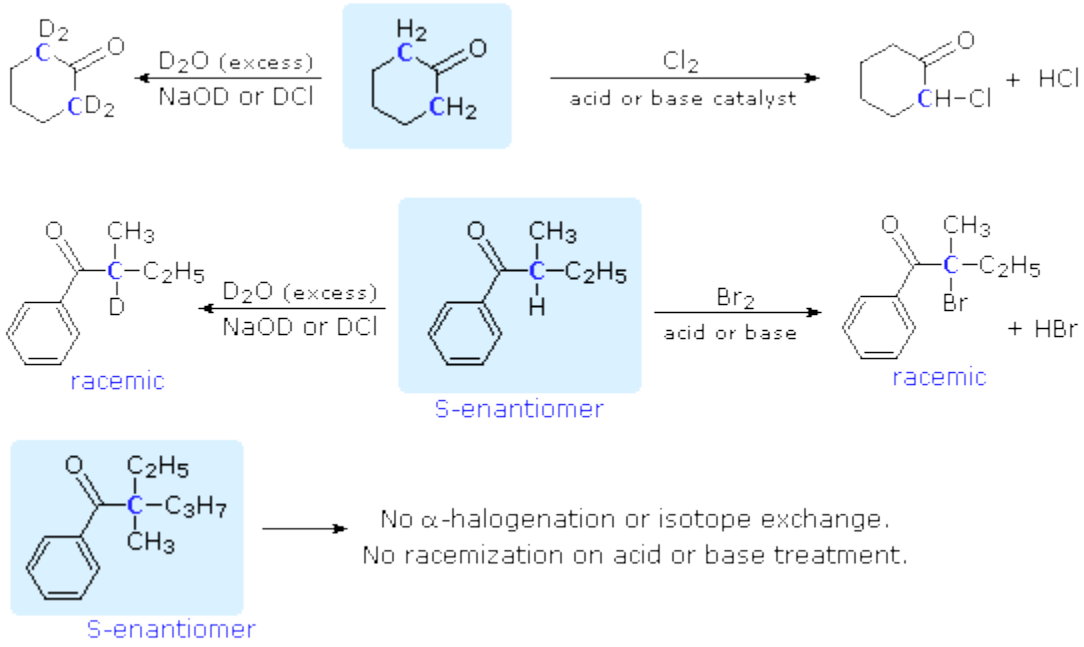
Reactions at the α-Carbon

Many aldehydes and ketones undergo substitution reactions at an alpha carbon, as shown in the following diagram (alpha-carbon atoms are colored blue). These reactions are acid or base catalyzed, but in the case of halogenation the reaction generates an acid as one of the products, and is therefore autocatalytic. If the alpha-carbon is a chiral center, as in the second example, the products of halogenation and isotopic exchange are racemic. Indeed, treatment of this ketone reactant with acid or base alone serves to racemize it. Not all carbonyl compounds exhibit these characteristics, the third ketone being an example.



Two important conclusions may be drawn from these examples. **First**, these substitutions are limited to carbon atoms alpha to the carbonyl group. Cyclohexanone (the first ketone) has two alpha-carbons and four potential substitutions (the alpha-hydrogens). Depending on the reaction conditions, one or all four of these hydrogens may be substituted, but none of the remaining six hydrogens on the ring react. The second ketone confirms this fact, only the alpha-carbon undergoing substitution, despite the presence of many other sites. **Second**, the substitutions are limited to hydrogen atoms. This is demonstrated convincingly by the third ketone, which is structurally similar to the second but has no alpha-hydrogen.

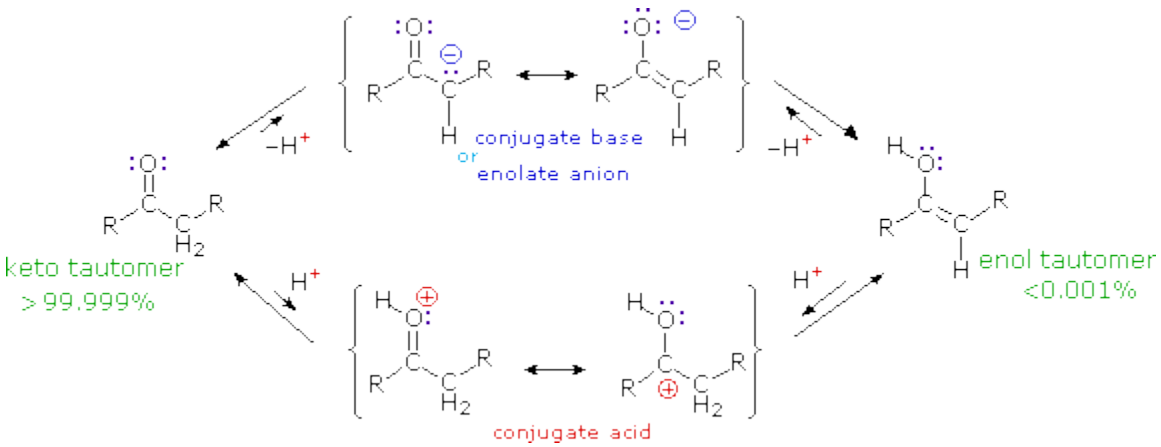
1. Mechanism of Electrophilic α-Substitution

Kinetic studies of these reactions provide additional information. The rates of halogenation and isotope exchange are essentially the same (assuming similar catalysts and concentrations), and are identical to the rate of racemization for those reactants having chiral alpha-carbon units. At low to moderate halogen concentrations, the rate of halogen

substitution is proportional (i.e. first order) to aldehyde or ketone concentration, but independent of halogen concentration. This suggests the existence of a common reaction intermediate, formed in a slow (rate-determining step) prior to the final substitution. Acid and base catalysts act to increase the rate at which the common intermediate is formed, and their concentration also influences the overall rate of substitution. From previous knowledge and experience, we surmise that the common intermediate is an enol tautomer of the carbonyl reactant. Several facts support this proposal:

(i) Compounds that do not have any α-hydrogen atoms cannot enolize and do not undergo any of the reactions described above.
(ii) The carbon-carbon double bond of an enol is planar, so any chirality that existed at the α carbon is lost on enolization. If chiral products are obtained from enol intermediates they will necessarily be racemic.
(iii) In simple aldehydes and ketones enol tautomers are present in very low concentration. Reactions that involve enol reactants will therefore be limited in rate by the enol concentration. Increasing the amounts of other reactants will have little effect on the reaction rate.
(iv) Enolization is catalyzed by acids and bases. These catalysts will therefore catalyze reactions proceeding via enol intermediates.

The reactions shown above, and others to be described, may be characterized as an electrophilic attack on the electron rich double bond of an enol tautomer. This resembles closely the first step in theaddition of acids and other electrophiles to alkenes. Therefore, if electrophilic substitution reactions of this kind are to take place it is necessary that nucleophilic character be established at the alpha-carbon. A full description of the acid and base-catalyzed keto-enol tautomerization process (shown below) discloses that only two intermediate species satisfy this requirement. These are the **enol tautomer** itself and its conjugate base (common with that of the keto tautomer), usually referred to as an **enolate anion**.



Clearly, the proportion of enol tautomer present at equilibrium is a critical factor in alpha substitution reactions. In the case of simple aldehydes and ketones this is very small, as

noted above. A complementary property, the acidity of carbonyl compounds is also important, since this influences the concentration of the more nucleophilic enolate anion in a reaction system. Ketones such as cyclohexanone are much more acidic than their parent hydrocarbons (by at least 25 powers of ten); nevertheless they are still very weak acids (pK_a = 17 to 21) compared with water. Together with some related acidities, this is listed in the following table. Even though enol tautomers are about a million times more acidic than their keto isomers, their low concentration makes this feature relatively unimportant for many simple aldehydes and ketones.

Acidity of α-Hydrogens in Some Activated Compounds

Compound	$RCH_2–NO_2$	$RCH_2–COR$	$RCH_2–C{\equiv}N$	$RCH_2–SO_2R$
pK_a	9	20	25	25

In cases where more than one activating function influences a given set of alpha-hydrogens, the enol concentration and acidity is increased. Examples of such doubly (and higher) activated carbon acids aregiven elsewhere.

In view of these facts it may seem surprising that alpha-substitution reactions occur at all. However, we often fail to appreciate the way in which a rapid equilibrium involving a minor reactive component may spread the consequences of its behavior throughout a much larger population. Consider, for example, a large group of hungry, active hamsters running about in a big cage. Opening onto the cage there is a small annex that can hold a maximum of three hamsters. Out of two hundred hamsters in the cage, there are an average of two hamsters in the annex at any given time. The hamsters are free to enter and exit the annex, but any hamster that does so is marked by a bright red dye. Although the hamster concentration in the annex is small relative to the whole population, it will not be long before all the hamsters are dyed red. If we substitute molecules for hamsters, their numbers will be extraordinarily large (recall the size of Avogadro's number), but the equilibrium between keto tautomers (hamsters in the cage) and enol tautomers (hamsters in the annex) is so rapid that complete turnover of all the molecules in a sample may occur in fractions of a second rather than minutes or hours. The principle is the same in both cases. Racemization and isotope exchange are due to the rapid equilibrium between chiral keto tautomers and achiral enol tautomers, as well as statistical competition between hydrogen and its deuterium isotope. For halogenation there is also a thermodynamic driving force, resulting from increased bond energy in the products. For example, the alpha-chlorination of cyclohexane, shown above, is exothermic by over 10 kcal/mole.

Source : http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/aldket2.htm#rx5