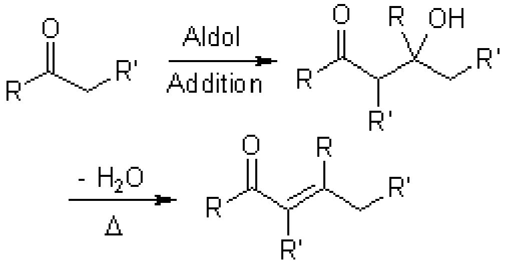
Aldol Condensation



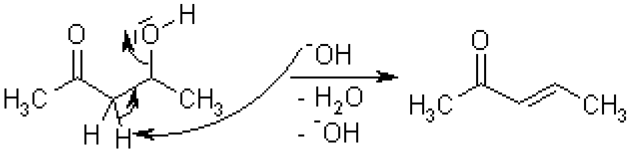
In some cases, the adducts obtained from the Aldol Addition can easily be converted (in situ) to α,β-unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis. The formation of the conjugated system is the driving force for this spontaneous dehydration. Under a variety of protocols, the condensation product can be obtained directly without isolation of the aldol.

The aldol condensation is the second step of the Robinson Annulation.

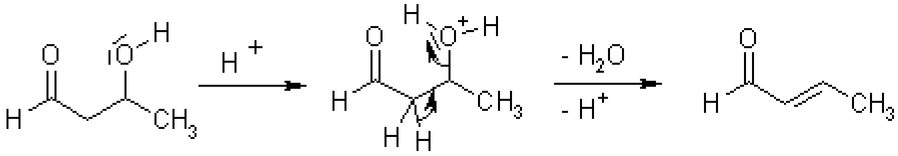
Mechanism of the Aldol Condensation

For the addition step see Aldol Addition

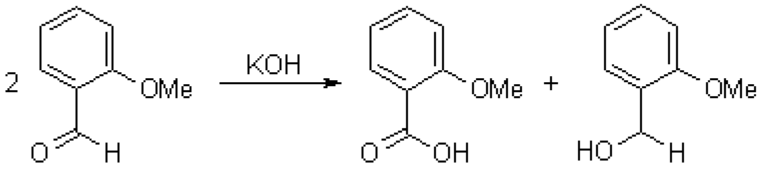
Base catalyzed condensation :



Acid catalyzed condensation :

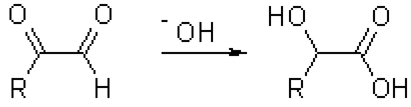


Cannizzaro Reaction

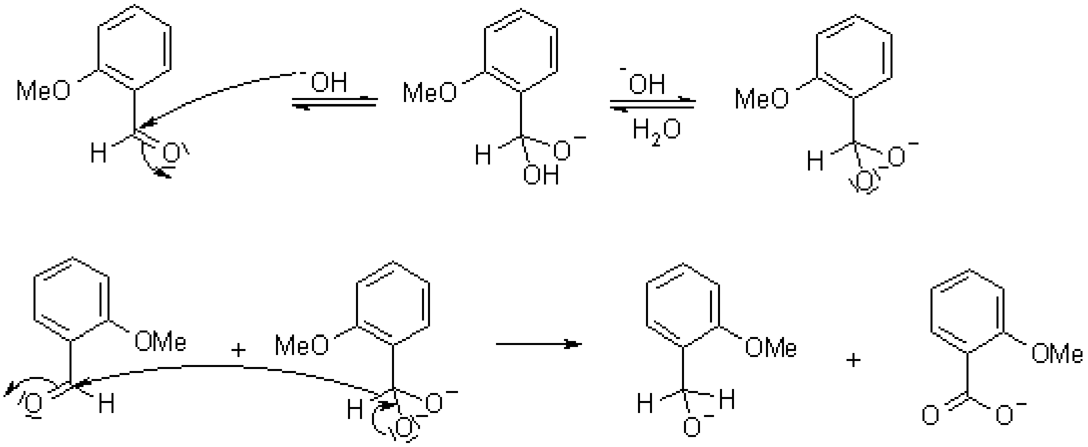


This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base.

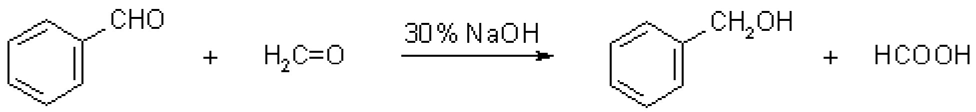
α-Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



Mechanism of the Cannizzaro Reaction



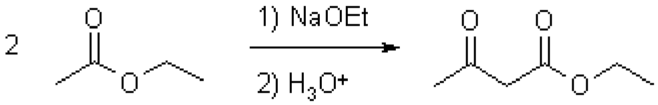
An interesting variant, the Crossed Cannizzaro Reaction, uses formaldehyde as reducing agent:



At the present time, various oxidizing and reducing agents can be used to carry out such conversions (with higher yields), so that today the Cannizzaro Reaction has limited synthetic utility except for the abovementioned conversion of α-keto aldehydes.

The Cannizzaro Reaction should be kept in mind as a source of potential side products when aldehydes are treated under basic conditions.

Acetoacetic-Ester Condensation
Claisen Condensation



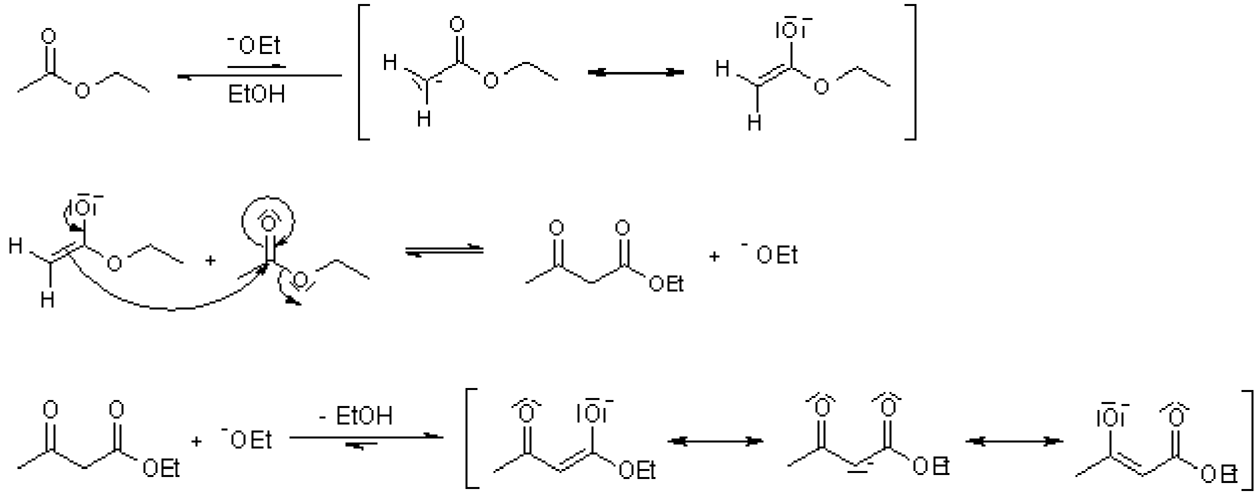
The Claisen Condensation between esters containing α-hydrogens, promoted by a base such as sodium ethoxide, affords β-ketoesters. The driving force is the formation of the stabilized anion of the β-keto ester. If two different esters are used, an essentially statistical mixture of all four products is generally obtained, and the preparation does not have high synthetic utility.

However, if one of the ester partners has enolizable α-hydrogens and the other does not (e.g., aromatic esters or carbonates), the mixed reaction (or crossed Claisen) can be synthetically useful. If ketones or nitriles are used as the donor in this condensation reaction, a β-diketone or a β-ketonitrile is obtained, respectively.

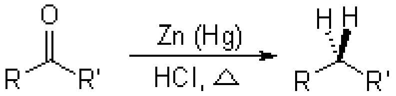
The use of stronger bases, e.g. sodium amide or sodium hydride instead of sodium ethoxide, often increases the yield.

The intramolecular version is known as Dieckmann Condensation.

Mechanism of the Claisen Condensation



Clemmensen Reduction

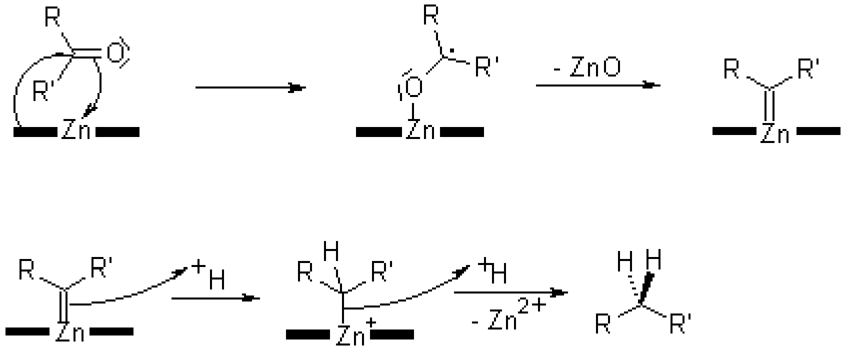


The Clemmensen Reduction allows the deoxygenation of aldehydes or ketones, to produce the corresponding hydrocarbon.

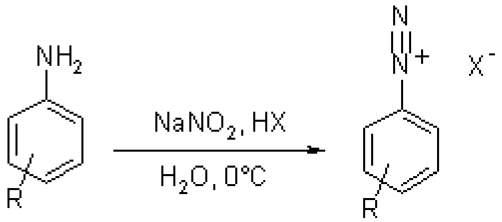
The substrate must be stable to strong acid. The Clemmensen Reduction is complementary to the Wolff-Kishner Reduction, which is run under strongly basic conditions. Acid-labile molecules should be reduced by the Wolff-Kishner protocol.

Mechanism of the Clemmensen Reduction

The reduction takes place at the surface of the zinc catalyst. In this reaction, alcohols are not postulated as intermediates, because subjection of the corresponding alcohols to these same reaction conditions does not lead to alkanes. The following proposal employs the intermediacy of zinc carbenoids to rationalize the mechanism of the Clemmensen Reduction:



Diazotisation

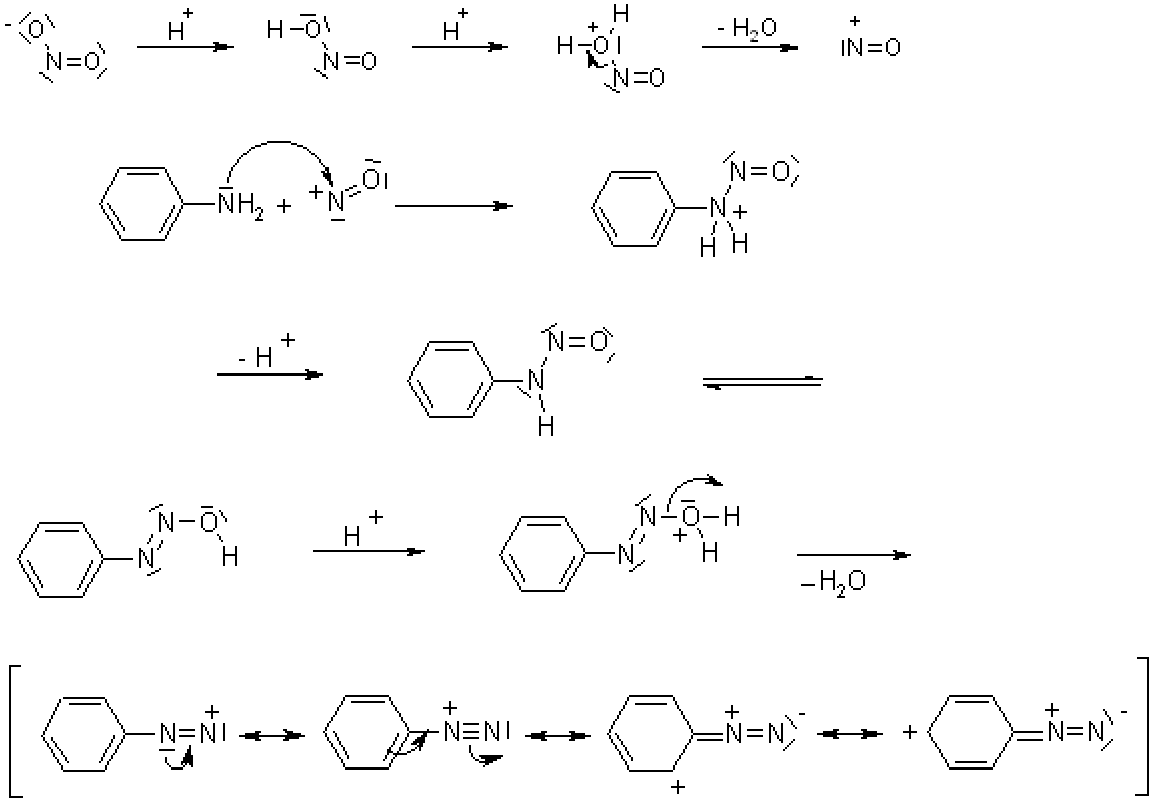


The nitrosation of primary aromatic amines with nitrous acid (generated in situ from sodium nitrite and a strong acid, such as hydrochloric acid, sulfuric acid, or HBF_4) leads to diazonium salts, which can be isolated if the counterion is non-nucleophilic.

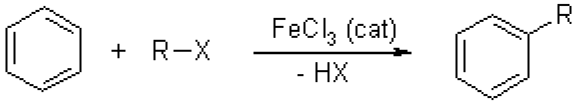
Diazonium salts are important intermediates for the preparation of halides (Sandmeyer Reaction, Schiemann Reaction), and azo compounds. Diazonium salts can react as pseudohalide-type electrophiles, and can therefore be used in specific protocols for the Heck Reaction or Suzuki Coupling.

The intermediates resulting from the diazotization of primary, aliphatic amines are unstable; they are rapidly converted into carbocations after loss of nitrogen, and yield products derived from substitution, elimination or rearrangement processes.

Mechanism of Diazotisation

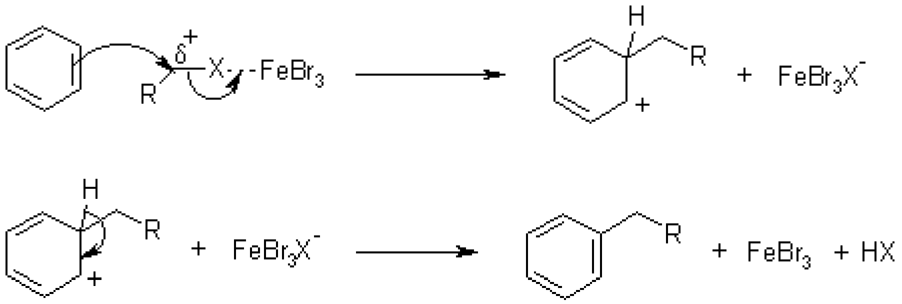


Friedel-Crafts Alkylation

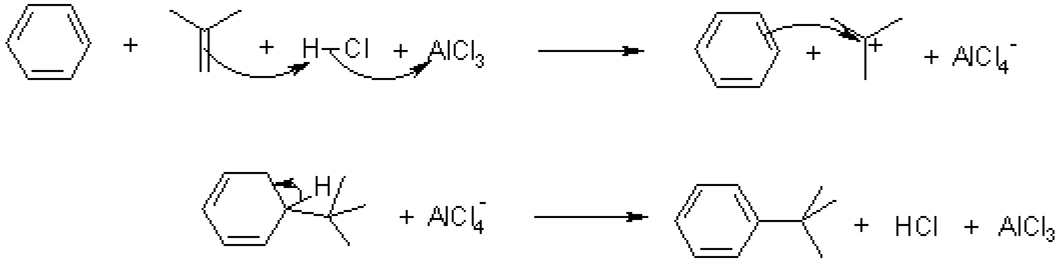


This Lewis acid-catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts Acylation followed by a carbonyl reduction.

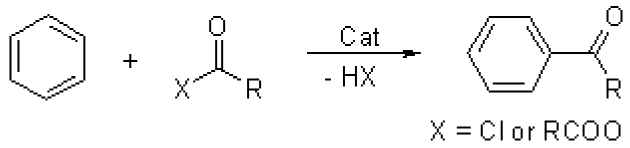
Mechanism of the Friedel-Crafts Alkylation



Using alkenes :

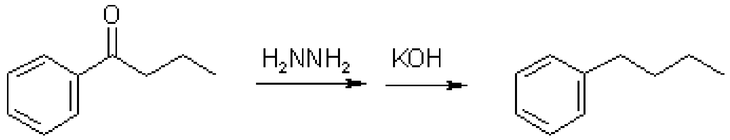


Friedel-Crafts Acylation

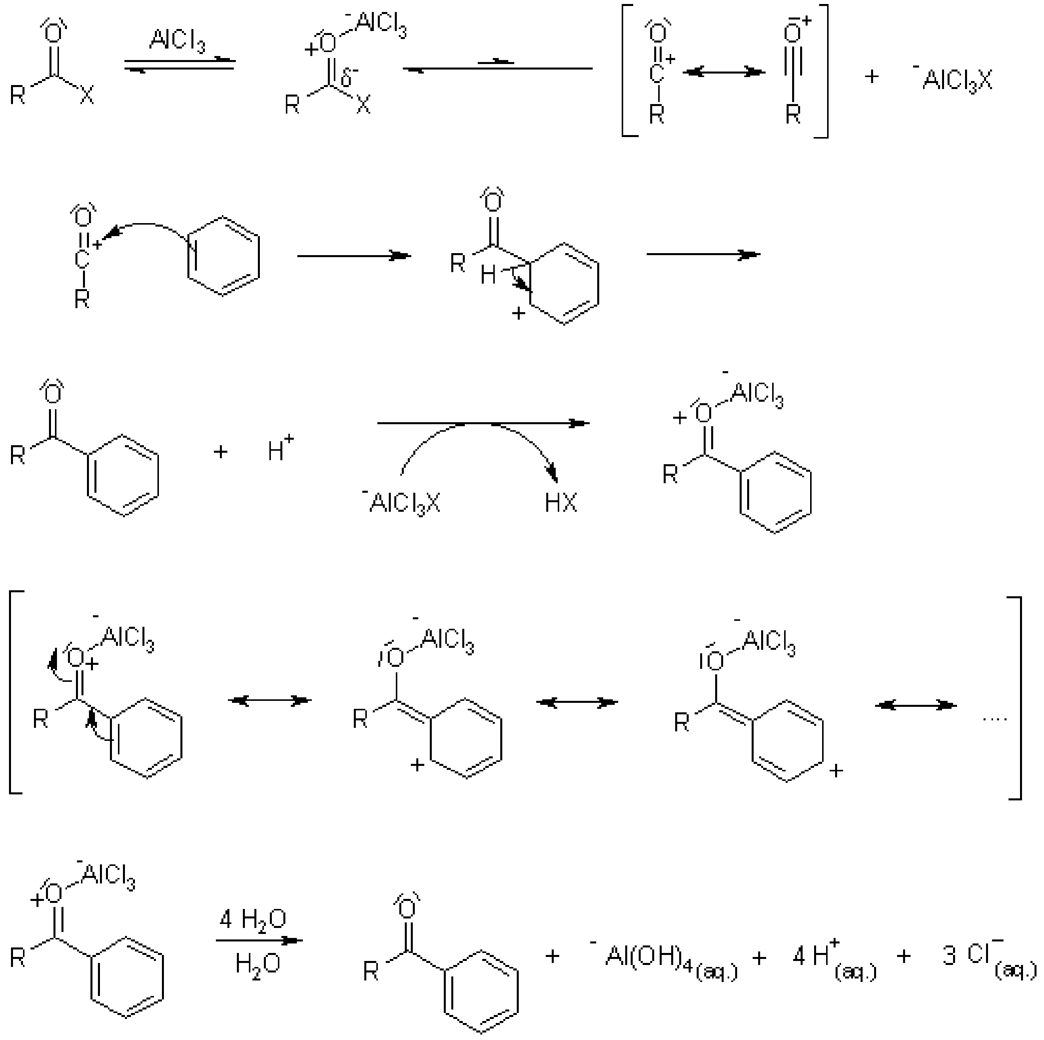


This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. The products are deactivated, and do not undergo a second substitution. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because both the substrate and the product form complexes.

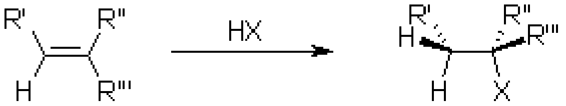
The Friedel-Crafts Alkylation may give polyalkylated products, so the Friedel-Crafts Acylation is a valuable alternative. The acylated products may easily be converted to the corresponding alkanes via Clemmensen Reduction or Wolff-Kishner Reduction.



Mechanism of the Friedel-Crafts Acylation



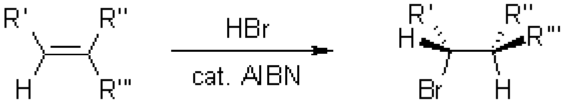
Markovnikov's Rule



Markovnikov Rule predicts the regiochemistry of HX addition to unsymmetrically substituted alkenes.

The halide component of HX bonds preferentially at the more highly substituted carbon, whereas the hydrogen prefers the carbon which already contains more hydrogens.

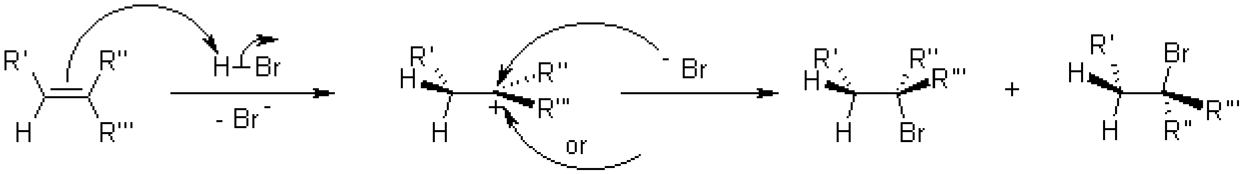
***Anti*-Markovnikov**



Some reactions do not follow Markovnikov's Rule, and *anti*-Markovnikov products are isolated. This is a feature for example of radical induced additions of HX and of Hydroboration.

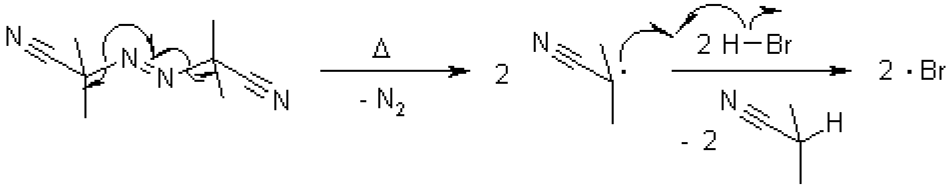
Mechanism

The proton adds first to the carbon-carbon double bond. The carbon bearing more substituents forms a more stable carbenium ion; attack of bromide ion follows in a second step:

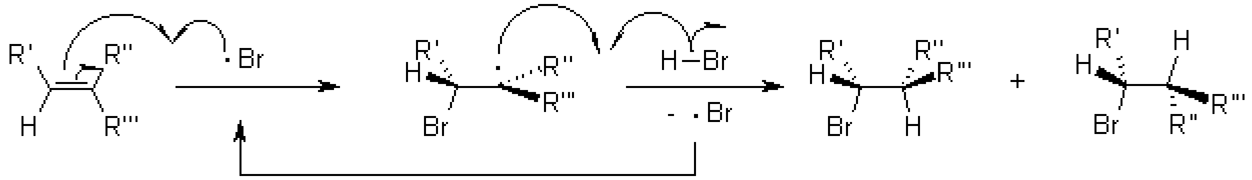


Markovnikov

Radical reactions require an initiation step. In this example, a bromo radical is formed.

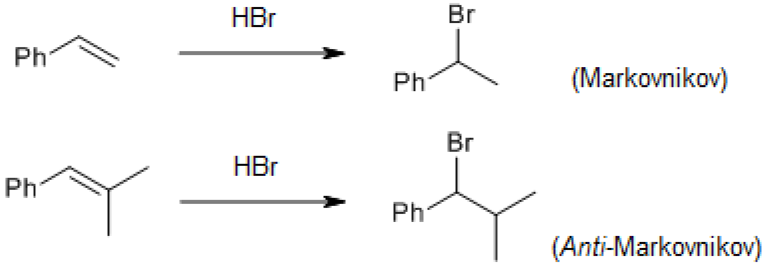


The reversal of the regiochemistry of addition is the result of the reversal of the order in which the two components add to the alkene. Radical addition leads to the formation of the more stable radical, which reacts with HBr to give product and a new bromo radical:

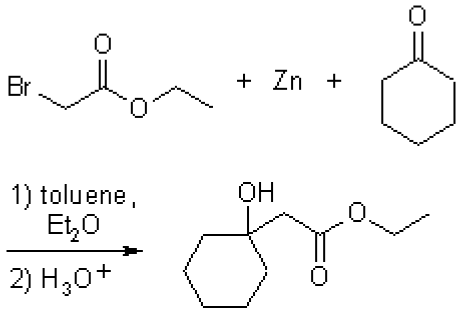


Anti-Markovnikov

The original statement of Markovnikov's rule only takes into account the stabilization of the carbenium ion by alkyl groups. However, a possible mesomeric stabilization of the carbenium ion by suitable functional groups can play a significant role here. Thus, the second reaction, in which the phenyl group offers greater stabilization of an adjacent carbenium ion than do two methyl groups, gives a major product that does not meet the original specification of Markovnikov's Rule:



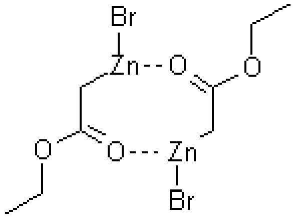
Reformatsky Reaction



The formation of ester-stabilized organozinc reagents and their addition to carbonyl compounds

Mechanism of the Reformatsky Reaction

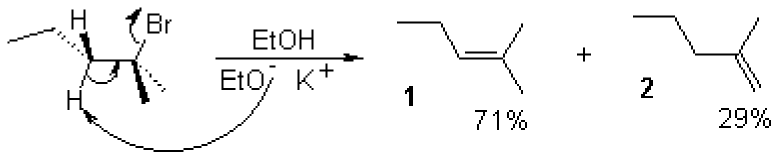
Organozinc compounds are prepared from α-halogenesters in the same manner as Grignard Reagents. This reaction is possible due to the stability of esters against organozincs. Due to the very low basicity of zinc enolates, there is hardly any competition from proton transfer, and the scope of carbonyl addition partners is quite broad. In presence of ketones or aldehydes, the organozinc compounds react as the nucleophilic partner in an addition to give β-hydroxy esters.



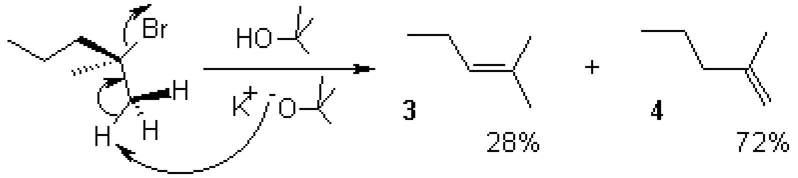
An ester-stabilized organozinc reagent

Compared to organolithiums and organomagnesium halides (Grignard reagents), the organozinc halide reagents used in the Reformatsky Reaction are relatively stable, and many are available commercially.

Saytzeff's Rule

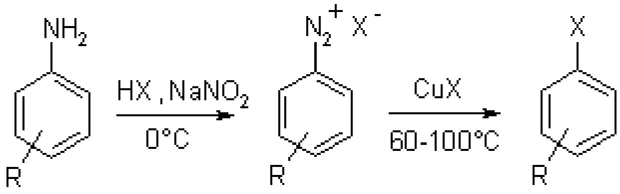


Saytzeff Rule implies that base-induced eliminations (E_2) will lead predominantly to the olefin in which the double bond is more highly substituted, i.e. that the product distribution will be controlled by thermodynamics.



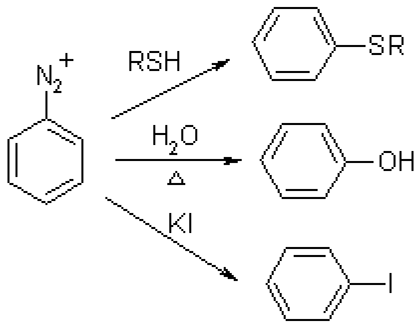
The use of sterically hindered bases raises the activation energy barrier for the pathway to the product predicted by Saytzeff's Rule. Thus, a sterically hindered base will preferentially react with the least hindered protons, and the product distribution will be controlled by kinetics.

Sandmeyer Reaction



X= CN, Br, Cl, SO_3H

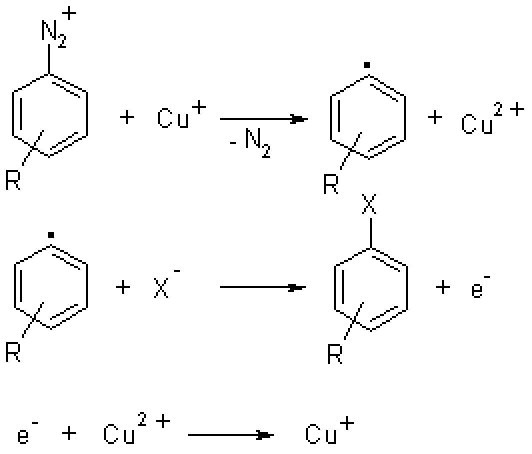
The substitution of an aromatic amino group is possible via preparation of its diazonium salt and subsequent displacement with a nucleophile (Cl-, I-, CN-, RS-, HO-). Many Sandmeyer Reactions proceed under copper(I) catalysis, while the Sandmeyer-type reactions with thiols, water and potassium iodide don't require catalysis.



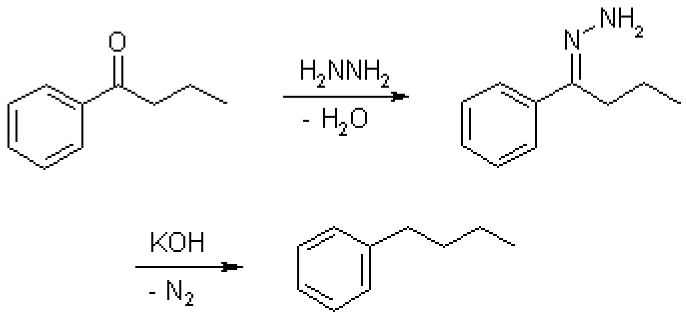
The Sandmeyer Reaction is a very important transformation in aromatic chemistry, because it can result in some substitution patterns that are not achievable by direct substitution.

Fluorination is possible by using the related Schiemann Reaction.

Mechanism of the Sandmeyer Reaction



Wolff-Kishner Reduction



The reduction of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

The Clemmensen Reduction can effect a similar conversion under strongly acidic conditions, and is useful if the starting material is base-labile.

Mechanism of the Wolff-Kishner Reduction