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Preface

Organic chemistry encompasses a very large number of compounds possessing numerous structure types and characteristics. The structural features and characteristics undergo changes during many complex chemical reactions. These reactions allow the synthesis and inter-conversion of millions of compounds. These chemical reactions involving organic compounds are known as name reactions. Addition reactions, elimination reactions, substitution reactions, pericyclic reactions, rearrangement reactions and redox reactions are some of the important name reactions having vast utility in many fields.

The present book explains how covalent bonds break and form including the processes involved at the outset. The book describes the types of name reactions mentioned above along with their basis and mechanism. Looking to the vast utility of name reactions in the construction of new organic molecules, man-made chemicals, plastics, food additives, fabrics, etc., the book makes sensible suggestions about mechanism and provides step-by-step knowledge on production of intermediates and final compounds. This schematic and picturesque presentation on name reactions will be highly beneficial to students, teachers, chemists and general readers.

K.R. Desai

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Reaction; Haloform Reaction; Hantzsch Dihydropyridine (Pyridine) Synthesis; Heck Reaction; Hell-Volhard-Zelinsky Reaction; Henry Reaction; Hiyama Coupling; Hofmann Elimination; Hofmann's Rule; Hosomi-Sakurai Reaction; Huisgen Cycloaddition; Hunsdiecker Reaction; Ireland-Claisen Rearrangement; Iwanow Reaction (Ivanov Reaction); Jacobsen-Katsuki Epoxidation; Julia-Lythgoe Olefination; Kabachnik-Fields Reaction; Kochi Reaction; Kolbe Electrolysis; Kolbe Nitrile Synthesis; Kolbe-Schmitt Reaction; Kumada Coupling; Lawesson's Reagent; Leuckart Thiophenol Reaction; Luche Reduction; Malonic Ester Synthesis; Mannich Reaction; Markovnikov's Rule; McMurry Reaction; Meerwein-Ponndorf-Verley Reduction; Michael Addition; Mitsunobu Reaction; Miyaura Borylation Reaction; Modified Julia Olefination; Mukaiyama Aldol Addition; Nazarov Cyclization; Nef Reaction; Negishi Coupling; Nozaki-Hiyama Coupling; Nucleophilic Substitution (SN1SN2); Olefin Metathesis; Oppenauer Oxidation; Overman Rearrangement; Oxy-Cope Rearrangement; Paal-Knorr Furan Synthesis; Paal-Knorr Pyrrole Synthesis; Paal-Knorr Thiophene Synthesis; Passerini Reaction; Paterno-Büchi Reaction; Pauson-Khand Reaction; Pechmann Condensation; Petasis Reaction; Peterson Olefination; Pinacol Coupling Reaction; Pinacol Rearrangement; Pinner Reaction; Prevost Reaction; Prilezhaev Reaction; Prins Reaction; Pschorr Reaction; Reformatsky Reaction; Ring Closing Metathesis (RCM); Ring Opening Metathesis (Polymerization) - ROM(P); Ritter Reaction; Robinson Annulation; Rosenmund Reduction; Rosenmund-von Braun Reaction; Rubottom Oxidation; Sandmeyer Reaction; Saytzeff's Rule; Schlosser Modification; Schmidt Reaction; Schotten-Baumann Reaction; Shapiro Reaction; Sharpless Dihydroxylation; Sharpless Epoxidation; Simmons-Smith Reaction; Sonogashira Coupling; Staudinger Synthesis; Staudinger Reaction; Staudinger Reaction; Staudinger Synthesis; Steglich Esterification; Stetter Reaction; Stille Coupling; Strecker Synthesis; Suzuki Coupling; Swern Oxidation; Tamao-Kumada Oxidation; Tebbe Olefination; Tishchenko Reaction; Tsuji-Trost Reaction; Ugi Reaction; Ullmann Reaction; Upjohn Dihydroxylation; Vilsmeier-Haack Reaction; Wacker-Tsuji Oxidation; Weinreb Ketone Synthesis; Wenker-Synthesis; Willgerodt-Kindler Reaction; Williamson Synthesis; Wittig-Horner Reaction; Wittig Reaction; [1,2]-Wittig Rearrangement; [2,3]-Wittig Rearrangement; Wohl-Ziegler Reaction; Wolff-Kishner Reduction; Wolff Rearrangement; Woodward Reaction; Wurtz Reaction; Wurtz-Fittig Reaction; Yamaguchi Esterification.

Organic Reaction Mechanism

CHEMICAL REACTIVITY

Organic chemistry encompasses a very large number of compounds (millions), and our previous discussion and illustrations have focused on their structural characteristics. Now that we can recognize these actors, 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.

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:

$$\text{Reactant}(s) \xrightarrow[\text{Reaction Conditions}]{\text{Reagent(s)}} \text{Product}(s)$$

CLASSIFYING ORGANIC CHEMICAL REACTIONS

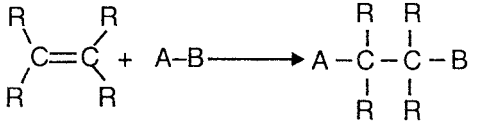
These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions. This is best accomplished by perceiving the reaction pathway or mechanism of a reaction.

CLASSIFICATION BY STRUCTURAL CHANGE

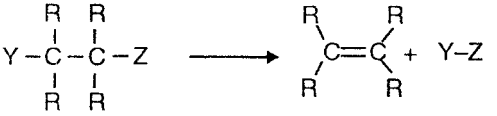
First, we identify four broad classes of reactions based solely on the structural change occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms.

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 CH_3–, or for complex groups composed of many atoms of carbon and other elements.

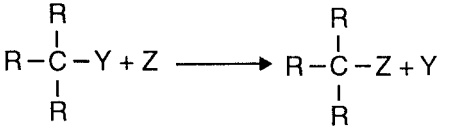
Four Reaction Classes.



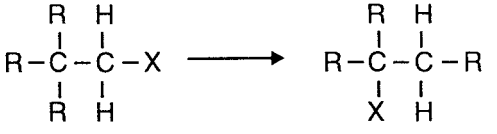
Addition



Elimination



Substitution



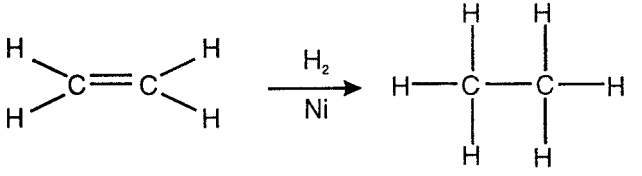
Rearrangement

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.

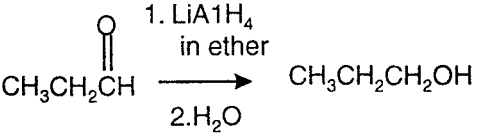
ORGANIC REACTIONS

The Mechanism of Reduction Reactions

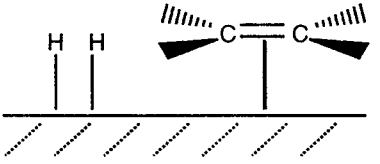
Two fundamentally different reducing agents have been used to add hydrogen across a double bond. A metal can be used to catalyze the reaction between hydrogen gas and the C = C double bond in an alkene.



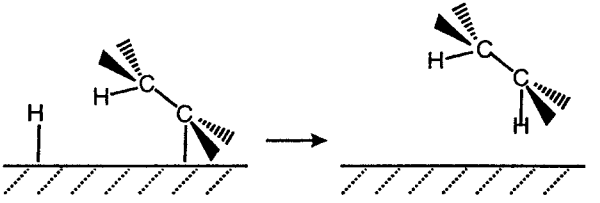
A source of the hydride (H^-) ion, on the other hand, is used to reduce C=O double bonds.



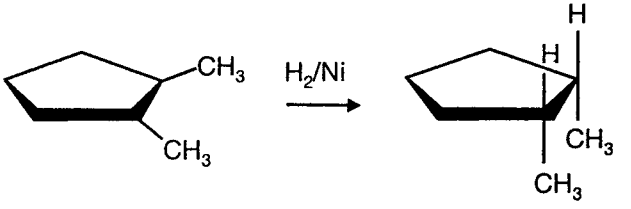
The difference between these reactions is easy to understand. The first reaction uses a nonpolar reagent to reduce a nonpolar double bond. The atoms on the surface of a metal are different from those buried in the body of the solid because they cannot satisfy their tendency to form strong metal-metal bonds. Some metals can satisfy a portion of their combining power by binding hydrogen atoms and/or alkenes to the surface.



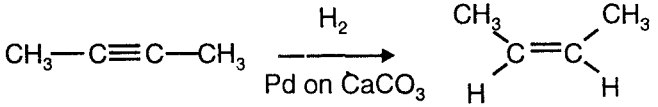
Adding one of the hydrogen atoms to the alkene forms an alkyl group, which can bond to the metal until the second hydrogen atom can be added to form the alkene.



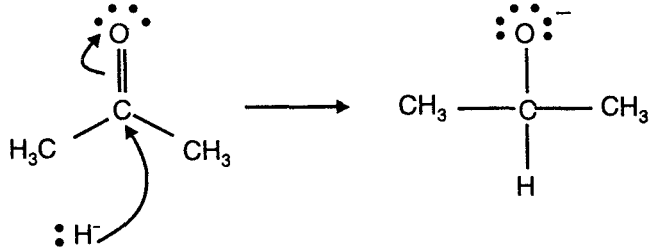
Although the hydrogen atoms are transferred one at a time, this reaction is fast enough that both of these atoms usually end up on the same side of the C=C double bond. This can't be seen in most alkanes produced by this reaction because of the free rotation around C—C bonds. Reduction of a cycloalkene, however, gives a stereoselective product.



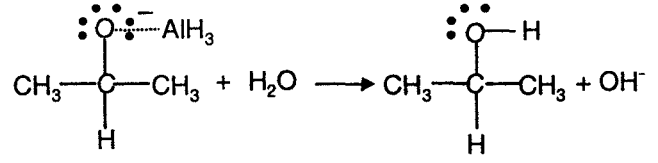
Reduction of an alkyne with hydrogen on a metal catalyst gives the corresponding alkane. By selectively "poisoning" the catalyst it is possible to reduce an alkyne to an alkene. Once again, the reaction is stereoselective, adding both hydrogen atoms from the same side of the C—C bond to form the *cis*-alkene.



Because it is a polar reagent, $LiAlH_4$ won't react with a C=C double bond. It acts as a source of the H^- ion, however, which is a strong Brψnsted base and a strong nucleophile. The H^- ion can therefore attack the $^+$ end of a polar C=O double bond.



The neutral AlH_3 molecule formed when an AlH_4^- ion acts as a hydride donor is a Lewis acid that coordinates to the negatively charged oxygen atom in the product of this reaction. When, in a second step, a protic solvent is added to the reaction, an alcohol is formed.



Nucleophilic Attack by Water

In the early nineties, Dashiell Hammett created the genre of the "hard-boiled". A common occurrence in this literature was a character who "slipped someone a Mickey Finn" a dose of the sedative known as chloral hydrate dissolved in a drink that contains alcohol.

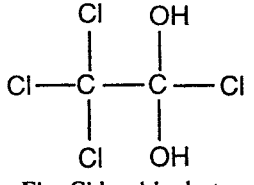
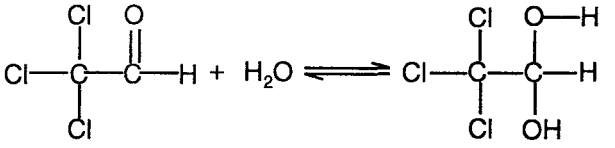


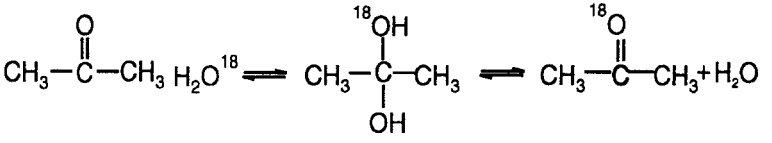
Fig. Chloral hydrate

Chloral hydrate is a white solid formed by adding a molecule of water across the C=O double bond in the corresponding aldehyde.



The equilibrium constant for this reaction is sensitive to the substituents on the C=O double bond. Electron-withdrawing substituents, such as the Cl_3C group in chloral, drive the reaction toward the dialcohol, or diol ($K_a \gg 1$). Electron-donating substituents, such as the pair of CH_3 groups in acetone, pull the equilibrium back toward the aldehyde ($K_a = 2 \times 10^{-3}$).

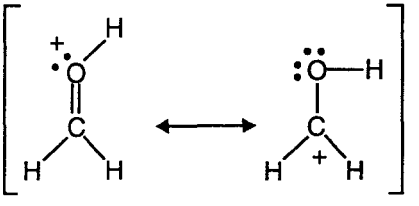
The rate of this reaction can be studied by following the incorporation of isotopically labeled water. The vast majority (99.76%) of water molecules contain ^{16}O, but some contain ^{17}O (0.04%) or ^{18}O (0.2%). When acetone is dissolved in a sample of water that has been enriched in ^{18}O, it gradually picks up the ^{18}O isotope.



The rate of this reaction is infinitesimally slow in a neutral solution (pH 7). But, in the presence of a trace of acid (or base), the reaction occurs very rapidly.

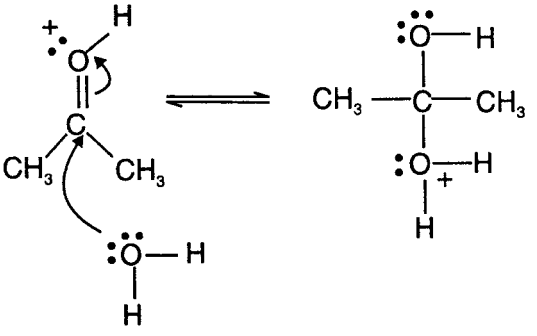
Acid and Base Catalyzed Hydration

The role of the acid catalyst is easy to understand. Protonation of the oxygen atom increases the polarity of the carbonyl bond.



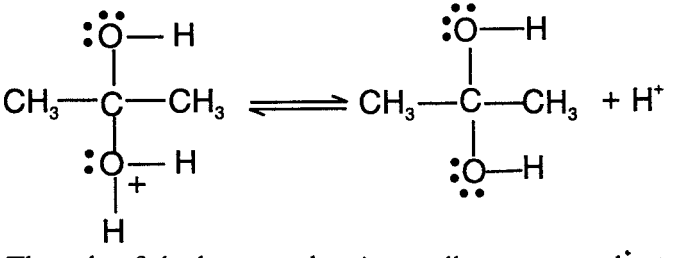
This increases the rate at which a water molecule can act as a nucleophile toward the positive end of the C=O double bond.

Acid-catalyzed hydration: Step 1



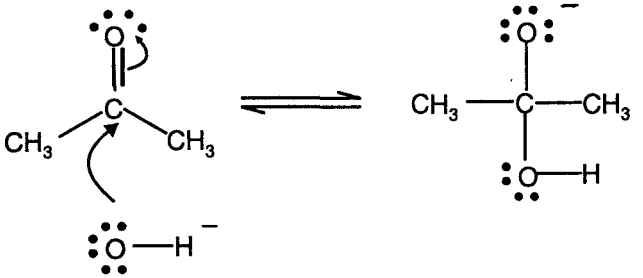
The product of this reaction then loses an H^+ ion to form the diol.

Acid-catalyzed hydration: Step 2



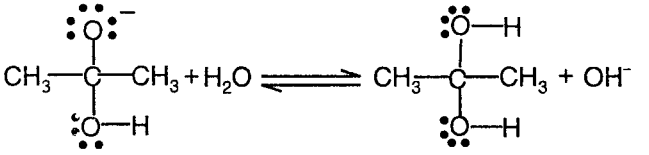
The role of the base catalyst is equally easy to understand. The OH^- ion is a much stronger nucleophile than water; strong enough to attack the carbonyl by itself.

Base-catalyzed hydration: Step 1

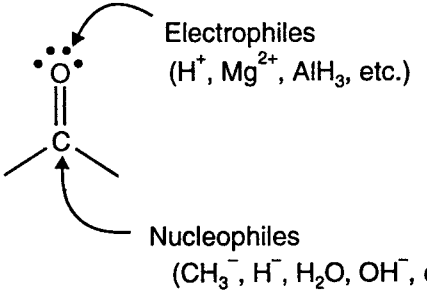


The product of this reaction then picks up a proton from a water molecule to form the diol and regenerate the OH^- ion.

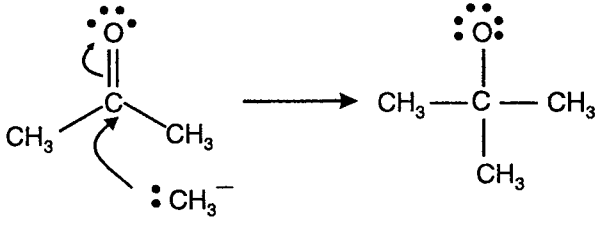
Base-catalyzed hydration: Step 2



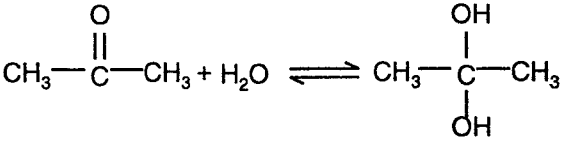
There is a fundamental relationship between the mechanisms of the reactions at the carbonyl group introduced so far. In each case, a nucleophile or Lewis base attacks the positive end of the carbonyl group. And, in each case, the rate of reaction can be increased by coordinating a Lewis acid or electrophile at the other end of the carbonyl.



There is a subtle difference between these reactions, however. Very strong nucleophiles, such as Grignard reagents or the hydride ion, add to the carbonyl in an irreversible reaction.

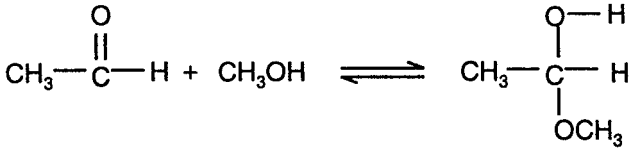


Attack by a weaker nucleophile, such as water, is a reversible reaction that can occur in either direction.



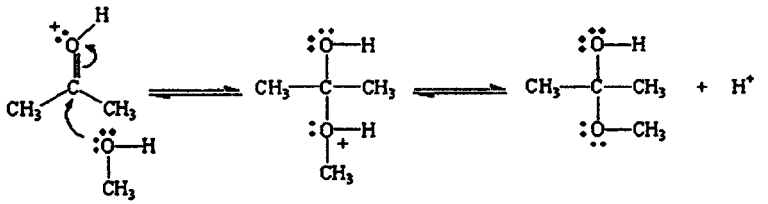
Nucleophilic Attack by an Alcohol

What would happen if we dissolved an aldehyde or ketone in an alcohol, instead of water? We would get a similar reaction, but now an ROH molecule is added across the C=O double bond.

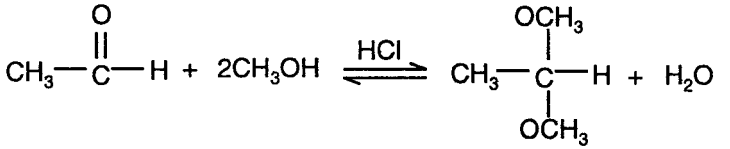


Once again, the reaction is relatively slow in the absence of an acid or base catalyst. If we bubble HCl gas through the solution, or add a small quantity of concentrated H_2SO_4, we get an acid-catalyzed reaction that occurs by a mechanism analogous to that described in the previous section.

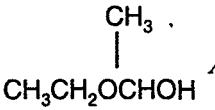
Acid-catalyzed reaction of an alcohol with a carbonyl



The product of this reaction is known as a hemiacetal (literally, "half of an acetal"). If an anhydrous acid is added to a solution of the aldehyde in a large excess of alcohol, the reaction continues to form an acetal.

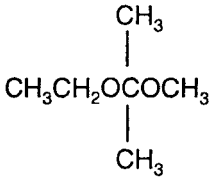


Hemiacetals can be recognized by looking for a carbon atom that has both anOH and an OR group.



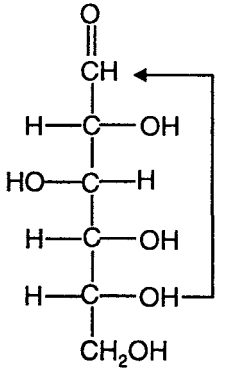
A hemiacetal

Acetals, on the other hand, contain a carbon atom that has two —OR groups.



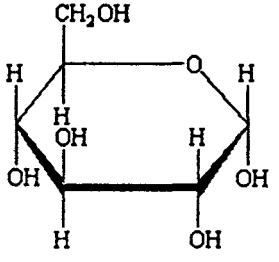
An acetal

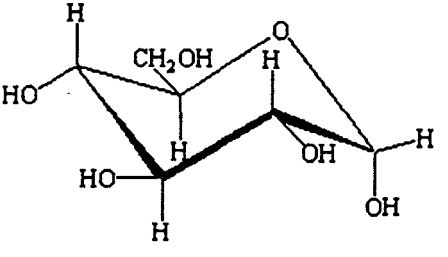
Hemiacetals and acetals play an important role in the chemistry of carbohydrates. Consider what would happen, for example, if the —OH group on the fifth carbon atom in a glucose molecule attacked the aldehyde at other end of this molecule.



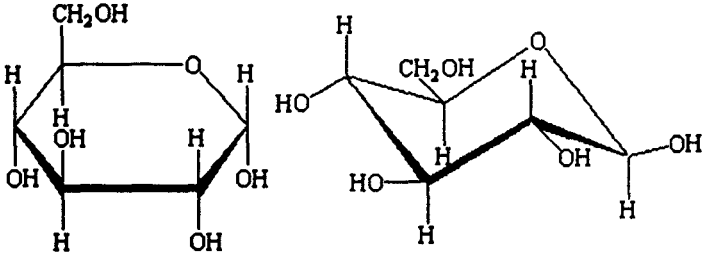
The product of this reaction is a hemiacetal that contains a six-membered ring known as a pyranose. Two isomers of glucopyranose can be formed, depending on whether the OH group attacks from above or below the C=O group.

α-D-Glucopyranose

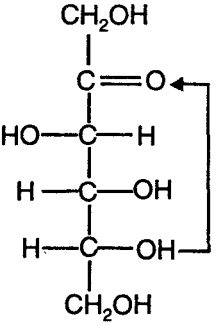




β-D-Glucopyranose

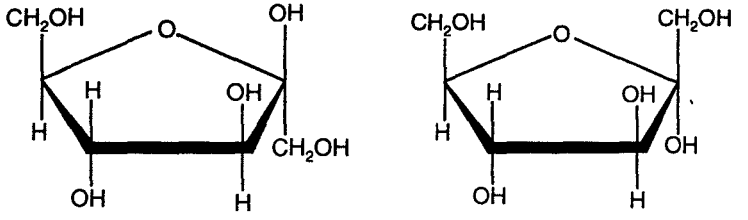


An analogous intramolecular reaction can occur within a fructose molecule.



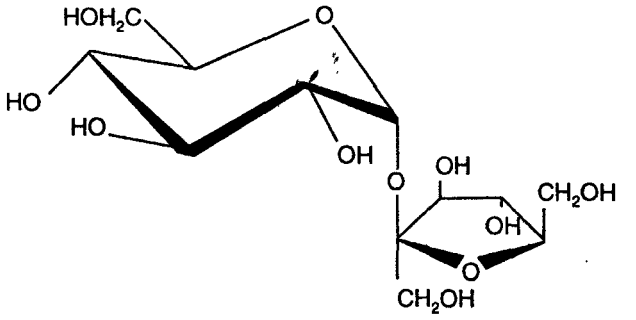
In this case, a hemiacetal is formed that contains a five-membered furanose ring. Once again, there are two isomers, depending on how the OH group attacks the C=O group.

a-D-Fructofuranose b-*D-Fructofuranose*



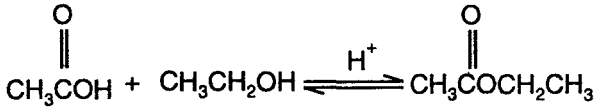
Sugars, such as glucose and fructose, can be linked to form complex carbohydrates by forming an acetal linkage between the OH group on one sugar and the hemiacetal on the other. Sucrose, or cane sugar, for example, is an acetal formed by linking -D-gluco-pyranose and -D-fructofuranose residues.

Sucrose



Addition/Elimination Reactions of Carboxylic Acid Derivatives

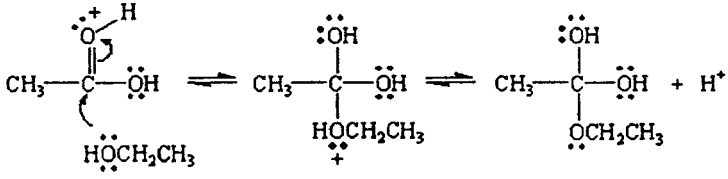
The following reaction can be used to illustrate the synthesis of an ester from a carboxylic acid



These reactions occur very slowly in the absence of a strong acid. When gaseous HCl is bubbled through the solution, or a small quantity of concentrated H_2SO_4 is added, these reactions reach equilibrium within a few hours. Once again, the acid protonates the oxygen of the C=O double bond, thereby increasing the polarity of the carbonyl group, which makes it more susceptible to attack by a nucleophile.

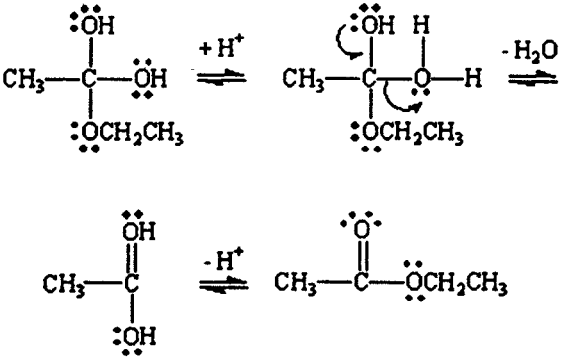
As might be expected, the first step in this reaction involves attack by a nucleophile at the positively charged end of the C=O double bond. A pair of nonbonding electrons on the oxygen atom of the alcohol is donated to the carbon atom of the carbonyl to form a CO bond. As this bond forms, the electrons in the bond of the carbonyl are displaced onto the oxygen atom. A proton is then transferred back to the solvent to give a tetrahedral addition intermediate.

Nucleophilic addition

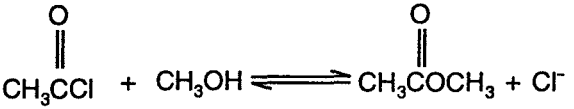


One of the —OH groups in this intermediate picks up a proton, loses a molecule of water, and then transfers a proton back to the solvent to give the ester.

Nucleophilic elimination

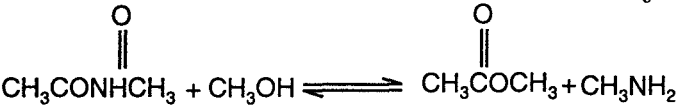


The combination of addition and elimination reactions has the overall effect of substituting one nucleophile for another in this case, substituting an alcohol for water. The rate of these nucleophilic substitution reactions is determined by the ease with which the elimination step occurs. *As a rule, the best leaving groups in nucleophilic substitutions reactions are weak bases.* The most reactive of the carboxylic acid derivatives are the acyl chlorides because the leaving group is a chloride ion, which is a very weak base (K_b 10^{-20}).



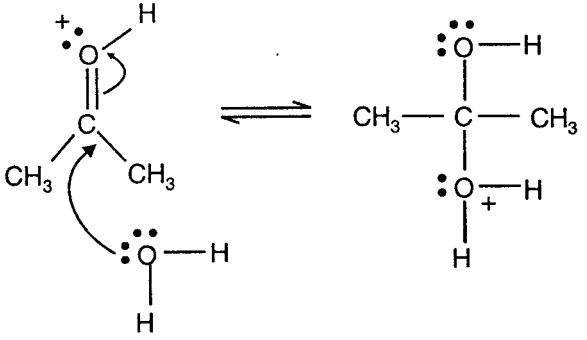
Esters are less reactive because the leaving group is an alcohol, which is a slightly better base (K_b 10^{-14}).

Amides are even less reactive because the leaving group is ammonia or an amine, which are significantly more basic (K_b 10^{-5}).

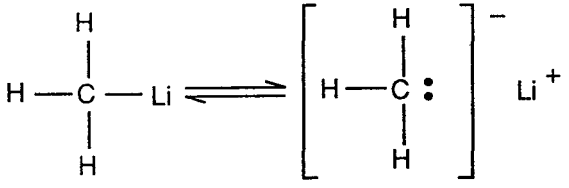


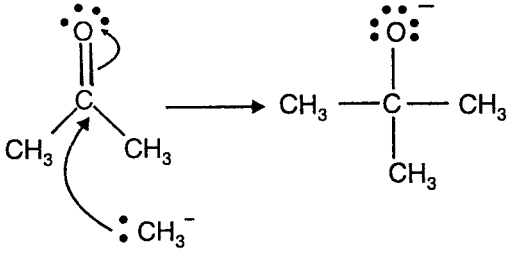
Free Radical Reactions

The starting point for reactions at a carbonyl involves attack by a nucleophile on the carbon atom of the C=O double bond.



Or it involves the heterolytic splitting of a bond to form a nucleophile that can attack the carbonyl group.

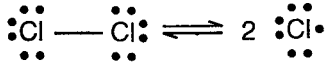




In either case, the reaction is carried by a reagent that donates a pair of electrons to a carbon atom to form a new covalent bond.

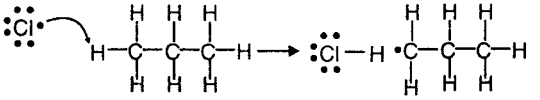
Free-radical halogenation of an alkane occurs by a very different mechanism. The first step in these reactions is the homolytic splitting of a bond to give a pair of free radicals.

Chain initiation



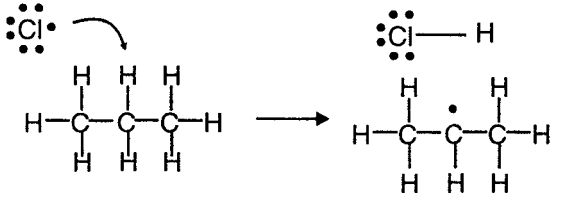
A series of reactions then occurs that involves a chain-reaction. Consider the chlorination of propane, for example. A Cl· atom can attack the CH_3 group at one end of the molecule.

Chain propagation



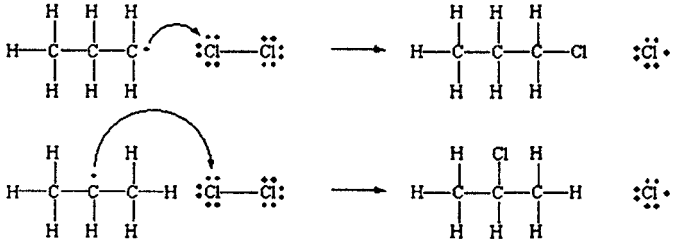
Or it can attack the CH_2 group in the centre of the molecule.

Chain propagation

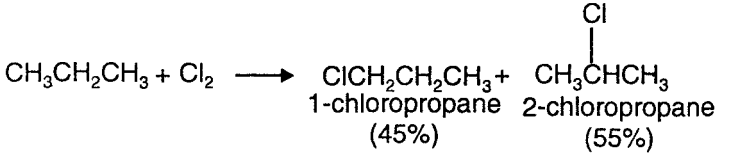


The free radicals generated in these reactions then react with chlorine to form either 1-chloro-propane or 2-chloropropane and regenerate a Cl· radical.

Chain propagation

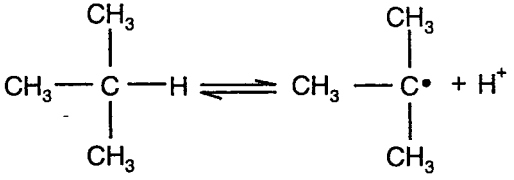


There are six hydrogen atoms in the two CH_3 groups and two hydrogens in the CH_2 group in propane. If attack occurred randomly, six-eighths (or three-quarters) of the product of this reaction would be 1-chloropropane. The distribution of products of this reaction, however, suggests that 1-chloropropane is formed slightly *less often* than 2-chloropropane.

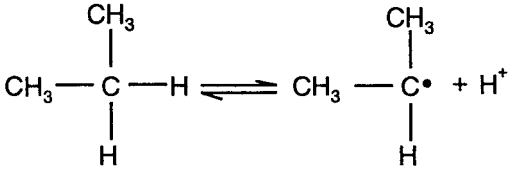


This can be explained by noting that the 2 radical formed by removing a hydrogen atom from the CH_2 group in the centre of the molecule is slightly more stable than the 1 radical produced when a hydrogen atom is removed from one of the CH_3 groups at either end of the molecule.

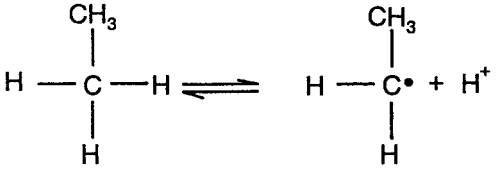
The difference between these radicals can be appreciated by considering the energy it takes to break the CH bond in the following compounds.



$\Delta H = -381$ kJ/mol$_{rxn}$

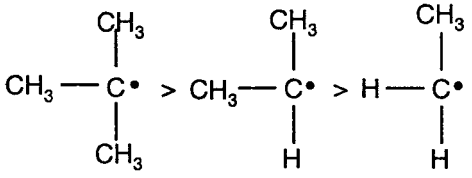


$\Delta H = -395$ kJ/mol$_{rxn}$

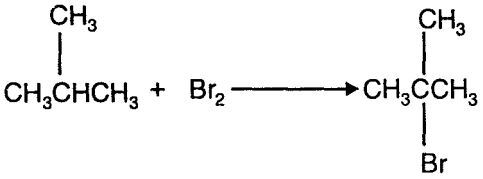


$\Delta H = -410$ kJ/mol$_{rxn}$

These data suggest that it takes *less energy* to break a CH bond as the number of alkyl groups on the carbon atom that contains this bond increases. This can be explained by assuming that the products of the bond-breaking reaction become *more stable* as the number of alkyl groups increases. Or, in other words, 3° radicals are more stable than 2° radicals, which are more stable than 1° radicals.



The activation energy for the chain-propagation steps in free-radical bromination reactions is significantly larger than the activation energy for these steps during chlorination. As a result, free-radical bromination reactions are more selective than chlorination reactions. Bromination reactions are far more likely to give the product predicted from the relative stability of the free-radical intermediate. Bromination of 2-methylpropane, for example, gives almost exclusively 2-bromo-2-methylpropane, not the statistically more likely 1-bromo-2-methylpropane.



Bimolecular Nucleophilic Substitution or S_N2 Reactions

Most of our knowledge of the mechanisms of chemical reactions has come from the study of the factors that influence the rate of these reactions. The type of reaction that has been studied more than any other involves attack by a nucleophile on a saturated carbon atom. Consider the following reaction, for example, which converts an alkyl bromide into an alcohol.

$$CH_3Br + OH^- \rightarrow CH_3OH + Br^-$$

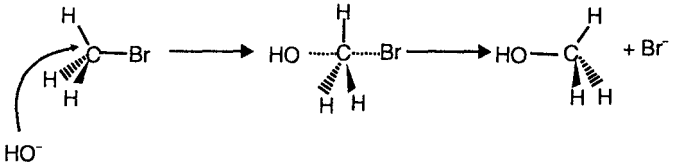
In the course of this reaction, one nucleophile (the OH^- ion) is substituted for another (the Br^- ion). This is therefore a nucleophilic substitution reaction.

The rate of this reaction is first-order in both CH_3Br and the OH^- ion, and second-order overall.

$$\text{Rate} = k(CH_3Br)(OH^-)$$

In the 1930s, Sir Christopher Ingold proposed a mechanism for this reaction in which both the alkyl halide and the hydroxyl ion are involved in the rate-limiting or slowest step of the reaction. The OH^- ion attacks the "backside" of the CH_3Br molecule. (It attacks the carbon atom at a point directly opposite to the Br substituent or leaving group.) When this happens, a pair of nonbonding electrons on the OH^- ion are used to form a covalent bond to the carbon atom

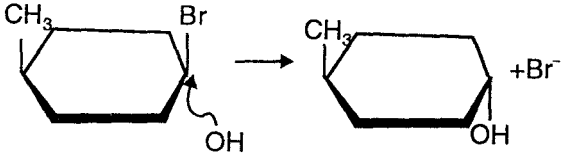
covalent bond to the carbon atom at the same time that the carbon-bromine is broken, as shown in the figure below.



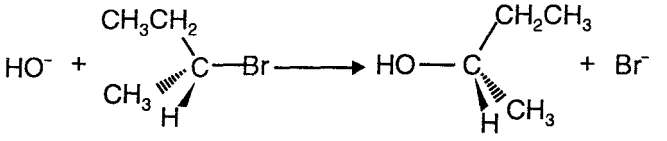
Because the rate-limiting step in this reaction involves both the CH_3Br and OH^- molecules, it is called a bimolecular nucleophilic substitution, or S_N2, reaction.

The most important point to remember about the mechanism of S_N2 reactions is that they occur in a single step. The species in the middle of Figure O3.2 is known as a transition state. If you envision this reaction as an endless series of snapshots that capture the infinitesimally small changes which occur as one bond forms and the other bond breaks, the transition state is the snapshot in this series that has the highest energy and is therefore the least stable. The transition state has an infinitesimally short lifetime, on the order of 10^{-12} seconds.

In the course of an S_N2 reaction, the other three substituents on the carbon atom are "flipped" from one side of the atom to the other. This inevitably leads to inversion of the configuration at a stereocentre. Consider the following reaction, for example, in which *cis*-1-bromo-3-methylcyclopentane is converted into *trans*-3-methylcyclopentanol.



Or the reaction in which the 2-butanol. *R* isomer of 2-bromobutane is transformed into the *S* isomer of



Unimolecular Nucleophilic Substitution or S_N1 Reactions

The kinetics of nucleophilic substitution reactions have been studied in greater detail than any other type of reaction because they don't always proceed through the same mechanism. Consider the reaction between the OH^- ion and *t*-butyl bromide, for example.

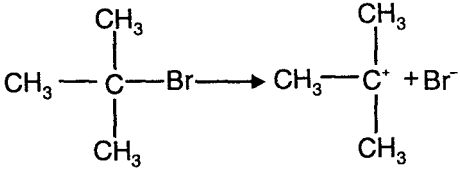
$$(CH_3)CH_3Br + OH^- \rightarrow (CH_3)CH_3OH + Br^-$$

The rate of this reaction depends only on the concentration of the alkyl bromide. (Adding more OH^- ion to the solution has no effect on the rate of reaction.)

$$\text{Rate} = k((CH_3)_3CBr)$$

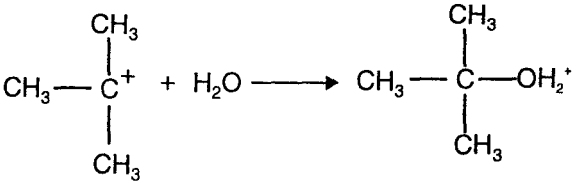
Ingold and coworkers argued that this rate law is consistent with a mechanism in which the rate-limiting or slowest step involves the breaking of the carbon-bromine bond to form a pair of ions. As one might expect, the pair of electrons in the CBr bond end up on the more electronegative bromine atom.

Rate-limiting step:

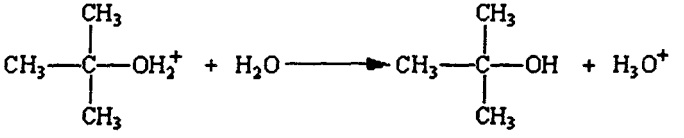


Because the bromine atom has formally gained an electron from the carbon atom, it is now a negatively charged Br^- ion. Because the carbon atom has formally lost an electron, it is now a "carbocation."

The first step in this mechanism is a relatively slow reaction. (The activation energy for this step is roughly 80 kJ/mol.) If this reaction is done in water, the next step is extremely fast. The $(CH_3)_3C^+$ ion is a Lewis acid because it has an empty orbital that can be used to accept a pair of electrons. Water, on the other hand, is a reasonably good Lewis base. A Lewis acid-base reaction therefore rapidly occurs in which a pair of nonbonding electrons on a water molecule are donated to the carbocation to form a covalent C—O bond.

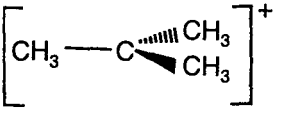


The product of this reaction is a stronger acid than water. As a result, it transfers a proton to water.



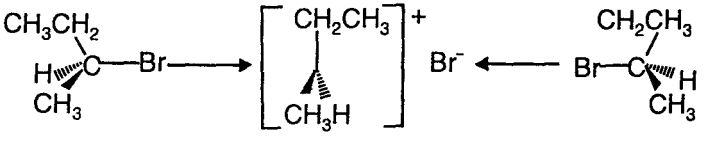
Because the slowest step of this reaction only involves *t*-butyl bromide, the overall rate of reaction only depends on the concentration of this species. This is therefore a unimolecular nucleophilic substitution, or S_N1, reaction.

The central carbon atom in the *t*-butyl carbocation formed in the first step of this reaction is planar, as shown in the figure below.



This means that water can attack this carbocation in the second step with equal probability from either side of the carbon atom. This has no effect on the products of this reaction, because the starting material is not optically active. But what would happen if we started with an optically active halide, such as 2-bromobutane?

Regardless of whether we start with the *R* or *S* isomer, we get the same intermediate when the CBr bond breaks.

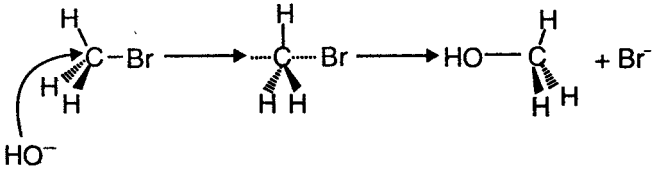


The intermediate formed in the first step in the S_N1 mechanism is therefore *achiral*.

Mixtures of equal quantities of the +/- or *R/S* stereoisomers of a compound are said to be racemic. This term traces back to the Latin

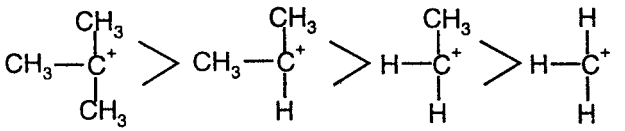
racemus, which means "a cluster of grapes." Just as there is an equal probability of finding grapes on either side of the stem in a cluster of grapes, there is an equal probability of finding the *R* and *S* enantiomers in a racemic mixture. S_N1 reactions are therefore said to *proceed with racemization.* If we start with a pure sample of (R)-2-bromobutane, for example, we expect the product of the S_N1 reaction with the OH^- ion to be a racemic mixture of the two enantiomers of 2-butanol.

We are now ready to address a pair of important questions. First, why does CH_3Br react with the OH^- ion by the S_N2 mechanism if $(CH_3)_3CBr$ does not? The S_N2 mechanism requires direct attack by the OH^- ion on the carbon atom that carries the CBr bond. It is much easier for the OH^- ion to get past the small hydrogen atoms in CH_3Br than it is for this ion to get past the bulkier CH_3 groups in $(CH_3)_3CBr$.



Thus, S_N2 reactions at the 1° carbon atom in CH_3Br are much faster than the analogous reaction at the 3° carbon atom in $(CH_3)_3CBr$.

Why, then, does $(CH_3)_3CBr$ react with the OH^- ion by the S_N1 mechanism if CH_3Br does not? The S_N1 reaction proceeds through a carbocation intermediate, and the stability of these ions decreases in the following order.



Organic chemists explain this by noting that alkyl groups are slightly "electron releasing."

They can donate electron density to a neighbouring group. This tends to delocalize the charge over a larger volume of the molecule, which stabilizes the carbocation.

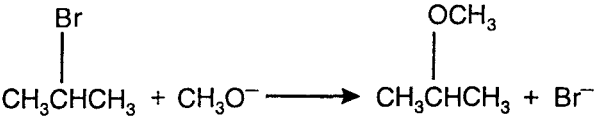
When we encountered a similar phenomenon in the chemistry of free radicals we noted that 3° radicals are roughly 30 kJ/mol more

stable than 1 radicals. In this case, the difference is much larger. A 3° carbocation is 340 kJ/mol more stable than a 1° carbocation! As a result, it is much easier for $(CH_3)_3CBr$ to form a carbocation intermediate than it is for CH_3Br to undergo a similar reaction.

In theory, both starting materials could undergo both reaction mechanisms. But the rate of S_N2 reactions for CH_3Br are much faster than the corresponding S_N1 reactions, whereas the rate of S_N1 reactions for $(CH_3)_3CBr$ are very much faster than S_N2 reactions.

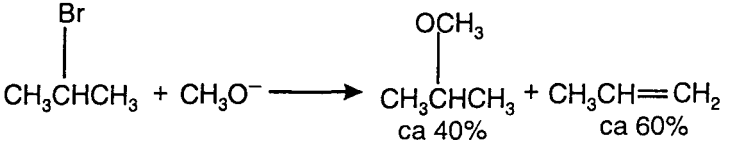
Elimination Reactions

Why do we need to worry about whether a nucleophilic substitution reaction occurs by an S_N1 or S_N2 mechanism? At first glance, it would appear that the same product is obtained regardless of the mechanism of the reaction. Consider the following substitution reaction, for example.



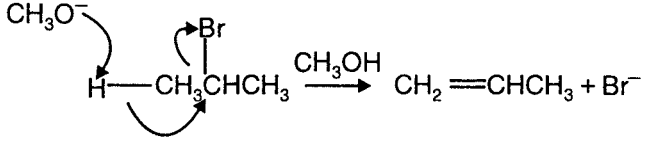
The only apparent difference between the two mechanisms is the stereochemistry of the product. If the reaction proceeds through an S_N2 mechanism, it gives inversion of configuration conversion of an *R* starting material into an *S* product, or vice versa. If the reaction proceeds through a carbocation intermediate via an S_N1 mechanism, we get a racemic mixture.

The importance of understanding the mechanism of nucleophilic substitution reactions can best be appreciated by studying the distribution of products of the example given above. When 2-bromopropane is allowed to react with the methoxide ion in methanol, less than half of the starting material is converted into methyl isopropyl ether; the rest is transformed into 2-propene.



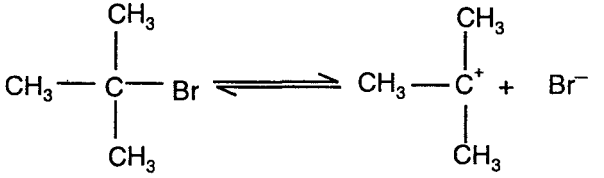
The reaction that produces the alkene involves the loss of an HBr molecule to form a C=C double bond. It is therefore an example of an elimination reaction.

Starting materials that are likely to undergo an bimolecular S_N2 reaction undergo elimination reactions by a bimolecular E_2 mechanism. This is a one-step reaction in which the nucleophile attacks a C—H bond on the carbon atom adjacent to the site of S_N2 reaction.

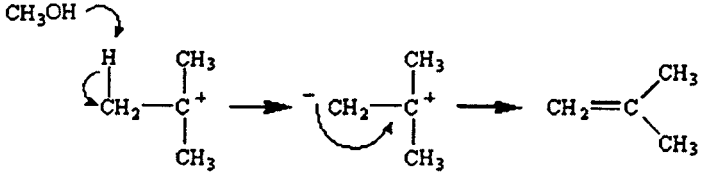


Starting materials that are likely to undergo a unimolecular S_N1 reaction undergo elimination reactions by a unimolecular E_1 mechanism. As might be expected, the rate-limiting step is the formation of the carbocation.

Rate-limiting Step:



The solvent then acts as a base, removing an H^+ ion from one of the alkyl groups adjacent to the carbocation. The electrons in the CH bond that is broken are donated to the empty orbital on the carbocation to form a double bond.



Substitution Versus Elimination Reactions

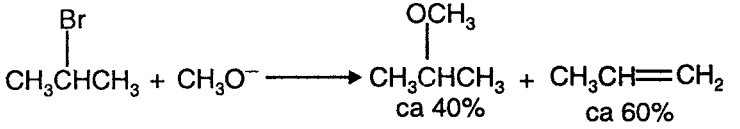
There are three ways of pushing the reaction between an alkyl halide and a nucleophile toward elimination instead of substitution.

- Start with a highly substituted substrate, which is more likely to undergo elimination. Only 10% of a primary alkyl bromide undergoes elimination to form an alkene, for example, when it reacts with an alkoxide

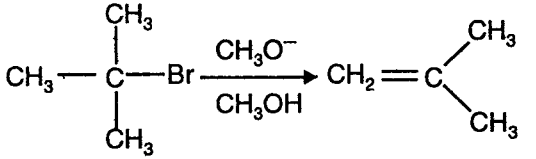
ion dissolved in alcohol. The vast majority of the starting material goes on to form the product expected for an S_N2 reaction.

$$CH_3CH_2CH_2Br \xrightarrow[CH_3OH]{CH_3O^-} CH_3CH_2CH_2OCH_3$$

More than half of a secondary alkyl bromide undergoes elimination under the same conditions, as we have already seen.

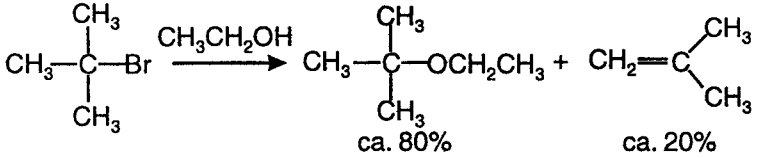


When the starting material is a tertiary alkyl halide, more than 90% of the product is formed by an E_1 elimination reaction.

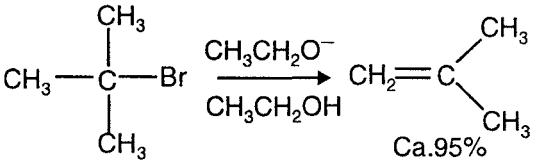


- Use a very strong base as the nucleophile. When we use a relatively weak base, such as ethyl alcohol, only about 20% of *t*-butyl bromide undergoes elimination.

In the presence of the ethoxide ion, which is a much stronger base, the product of the reaction is predominantly the alkene.



- Increase the temperature at which the reaction is run. Because both E_1 and E_2 reactions lead to an increase in the number of particles in the system, they are associated with a positive entropy term. Thus, increasing the temperature of the reaction makes the overall free energy of reaction more negative, and the reaction more favourable.

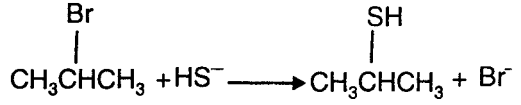


Summary of Substitution/Elimination Reactions

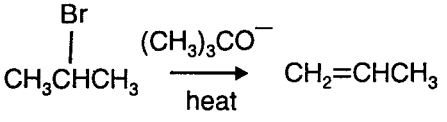
- Methyl halides and primary alkyl halides—such as CH_3CH_2Br—undergo nucleophilic substitution reactions.

$$CH_3CH_2Br + CN \rightarrow CH_3CH_2CN + Br^-$$

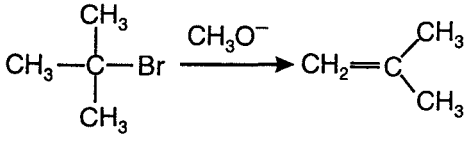
- Secondary alkyl halides undergo S_N2 reactions when handled gently at low temperatures and with moderate strength nucleophiles.



- At high temperatures, or in the presence of a strong base, secondary halides undergo E_2 elimination reactions.



Tertiary halides undergo a combination of S_N1 and E_1 reactions. If the reaction is kept cool, and the nucleophile is a relatively weak base, it is possible to get nucleophilic substitution. At high temperatures, or with strong bases, elimination reactions predominate.



Acids and Bases

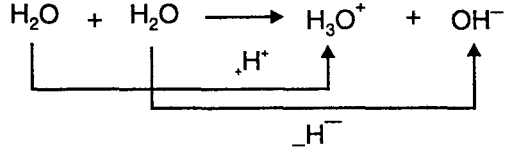
For more than 300 years, substances that behaved like vinegar have been classified as acids, while those that have properties like the ash from a wood fire have been called alkalies or bases. The name "acid" comes from the Latin *acidus*, which means "sour," and

refers to the sharp odor and sour taste of many acids. Vinegar tastes sour because it is a dilute solution of acetic acid in water; lemon juice is sour because it contains citric acid; milk turns sour when it spoils because of the formation of lactic acid; and the sour odor of rotten meat can be attributed to carboxylic acids such as butyric acid formed when fat spoils.

Today, when chemists use the words "acid" or "base" they refer to a model developed independently by Bronsted, Lowry, and Bjerrum. Since the most explicit statement of this theory was contained in the writings of Brψnsted, it is most commonly known as the "Bronsted acid-base" theory.

Bronsted Acid-Base Theory

Bronsted argued that all acid-base reactions involve the transfer of an H^+ ion, or proton. Water reacts with itself, for example, by transferring an H^+ ion from one molecule to another to form an H_3O^+ ion and an OH^- ion.



According to this theory, an acid is a "proton donor" and a base is a "proton acceptor."

Acid-Dissociation Equilibrium Constant

Acids are often divided into categories such as "strong" and "weak." One measure of the strength of an acid is the acid-dissociation equilibrium constant, K_a, for that acid.

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

When K_a is relatively large, we have a strong acid.

HCl: $K_a = 1 \times 10^3$

When it is small, we have a weak acid.

CH_3CO_2H: $K_a = 1.8 \times 10^{-5}$

When it is very small, we have a very weak acid.

H_2O: $K_a = 1.8 \times 10^{-16}$

pH, pOH, and pK_a

In 1909, S. P. L. Sψrenson suggested that the enormous range of concentrations of the H_3O^+ and OH^- ions in aqueous solutions could be compressed into a more manageable set of data by taking advantage of logarithmic mathematics and calculating the pH or pOH of the solution.

$pH = -\log [H_3O^+]$

$pOH = -\log [OH^-]$

The "p" in pH and pOH is an operator that indicates that the negative of the logarithm should be calculated for any quantity to which it is attached. Thus, pK_a is the negative of the logarithm of the acid-dissociation equilibrium constant.

$pK_a = -\log K_a$

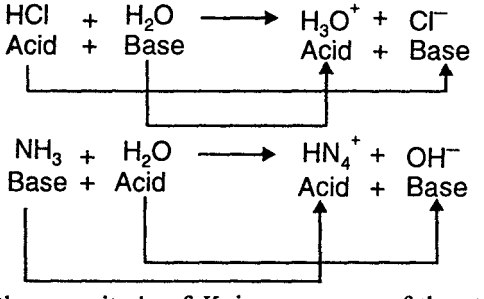
The only disadvantage of using pK_a as a measure of the relative strengths of acids is the fact that large numbers now describe weak acids, and small (negative) numbers describe strong acids.

HCl: $pK_a = -3$

CH_3CO_2H: $pK_a = 4.7$

H_2O: $pK_a = 15.7$

An important features of the Brψnsted theory is the relationship it creates between acids and bases. Every Brψnsted acid has a conjugate base, and vice versa.



Just as the magnitude of K_a is a measure of the strength of an acid, the value of K_b reflects the strength of its conjugate base.

Consider what happens when we multiply the K_a expression for a generic acid (HA) by the K_b expression for its conjugate base (A^-).

$$\frac{[H_3O^+][A^-]}{[HA]} \times \frac{[HA][OH^-]}{[A^-]} = [H_3O^+][OH^-]$$

If we now replace each term in this equation by the appropriate equilibrium constant, we get the following equation.

$$K_aK_b = K_w = 1 \times 10^{-14}$$

Because the product of K_a times K_b is a relatively small number, either the acid or its conjugate base can be "strong." But if one is strong, the other must be weak. Thus, a strong acid must have a weak conjugate base.

$$\underset{\text{Strong acid}}{HCl} + H_2O \longrightarrow H_3O^+ + \underset{\text{Weak base}}{Cl^-}$$

A strong base, on the other hand, must have a weak conjugate acid.

$$NH_4^+ + \underset{\text{Strong base}}{OH^-} \longrightarrow NH_3 + \underset{\text{Weak acid}}{H_2O}$$

Brønsted Acids and Bases in Nonaqueous Solutions

Water has a limiting effect on the strength of acids and bases. All strong acids behave the same in water 1—*M* solutions of the strong acids all behave as 1 *M* solutions of the H_3O^+ ion and very weak acids cannot act as acids in water. Acid-base reactions don't have to occur in water, however. When other solvents are used, the full range of acid-base strength shown in the table below can be observed.

Table: Typical Brψnsted Acids and Their Conjugate Bases

Compound	K_a	pK_a	ConjugateBase	K_b	pK_b
HI	3×10^9	–9.5	I^-	3×10^{-24}	23.5
HCl	1×10^6	–6	Cl^-	1×10^{-20}	20
H_2SO_4	1×10^3	–3	HSO_4^-	1×10^{-17}	17
H_3O^+	55	–1.7	H_2O	1.8×10^{-16}	15.7
HNO_3	28	–1.4	NO_3^-	3.6×10^{-16}	15.4

H_3PO_4	7.1×10^{-3}	2.1	$H_2PO_4^-$	1.4×10^{-12}	11.9
CH_3CO_2H	1.8×10^{-5}	4.7	$CH_3CO_2^-$	5.6×10^{-10}	9.3
H_2S	1.0×10^{-7}	7.0	HS^-	1×10^{-7}	7.0
H_2O	1.8×10^{-16}	15.7	OH^-	55	–1.7
CH_3OH	1×10^{-18}	18	CH_3O^-	1×10^{4}	–4
HCCH	1×10^{-25}	25	HCC^-	1×10^{11}	–11
NH_3	1×10^{-33}	33	NH_2^-	1×10^{19}	–19
H_2	1×10^{-35}	35	H^-	1×10^{21}	–21
$CH_2{=}CH_2$	1×10^{-44}	44	$CH_2{=}CH^-$	1×10^{30}	–30
CH_4	1×10^{-49}	49	CH_3^-	1×10^{35}	–35

The strongest acids are in the upper-left corner of this table; the strongest bases in the bottom-right corner. Each base is strong enough to deprotonate the acid in any line above it. The hydride ion (H^-), for example, can convert an alcohol into its conjugate base

$$CH_3OH + H^- \rightleftharpoons CH_3O^- + H_2$$

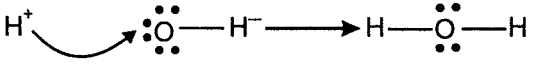
and the amide (NH_2^-) ion can deprotonate an alkyne.

$$CH_3{\equiv}CH + NH_2^- \rightleftharpoons CH_3C{\equiv}C^- + NH_3$$

Lewis Acid-Base Theory

In 1923, G. N. Lewis introduced a theory of acids and bases that is even more powerful than the Brψnsted theory. As a result, it is important to differentiate between the terms "acid" and "base" as they have been used so far and the terms "Lewis acid" and "Lewis base."

Lewis noted that the Brψnsted theory was limited because it focused exclusively on the transfer of a proton (H^+). He argued that a more general definition of acid-base reactions could be obtained by looking at what happens when an H^+ ion combines with an OH^- ion to form water.



Lewis argued that the H^+ ion picks up (or accepts) a pair of electrons from the OH^- ion to form a new covalent bond. As a result, any substance that can act as an electron-pair acceptor is a Lewis acid.

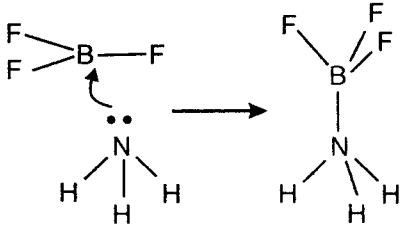
Lewis acid: An electron-pair acceptor, such as the H^+ ion

The pair of electrons that went into the new covalent bond were donated by the OH^- ion. Lewis therefore argued that any substance that can act as an electron-pair donor is a Lewis base.

Lewis base: An electron-pair donor, such as the OH^- ion

The Lewis acid-base theory doesn't affect the category of compounds we have called "bases" because any Brψnsted base must have a pair of nonbonding electrons in order to accept a proton. This theory, however, vastly expanded the family of compounds that can be called "acids." Anything that has one or more empty valence-shell orbitals can now act as an acid

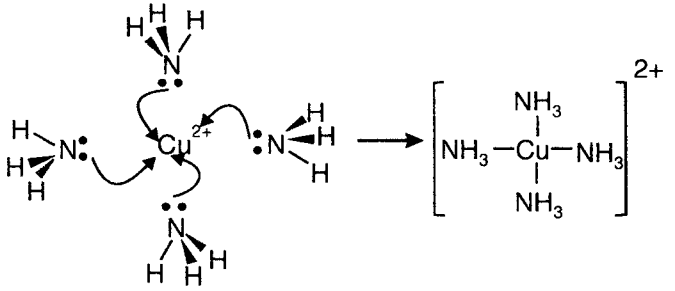
This theory explains why BF_3 reacts instantaneously with NH_3. The nonbonding electrons on the nitrogen in ammonia are donated into an empty orbital on the boron to form a new covalent bond, as shown in the figure below.



It also explains why Cu^{2+} ions pick up ammonia to form the four-coordinate $Cu(NH_3)_4^{2+}$ ion.

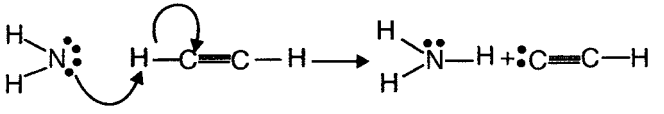
$$Cu^{2+}(aq) + 4\ NH_3(aq) \rightarrow Cu(NH_3)_4^{2+}(aq)$$

In this case, a pair of nonbonding electrons from each of the four NH_3 molecules is donated into an empty orbital on the Cu^{2+} ion to form a covalent Cu—N bond.



Curved Arrow Symbolism

The flow of electrons from a Lewis base to a Lewis acid is often indicated with a curved arrow. The arrow starts on a pair of nonbonding electrons on the Lewis base and points toward the Lewis acid with which it reacts. Because adding a pair of electrons to one point on a molecule often displaces electrons in the molecule, combinations of curved arrows are often used to describe even simple chemical reactions. Consider the following example, in which a pair of electrons on an NH_2^- ion are donated to the H^+ ion formed when the electrons in one of the CH bonds in acetylene are given to the carbon atom instead of being shared by the C and H atoms in this bond.



Using Acids and Bases to Understand Grignard Reagents

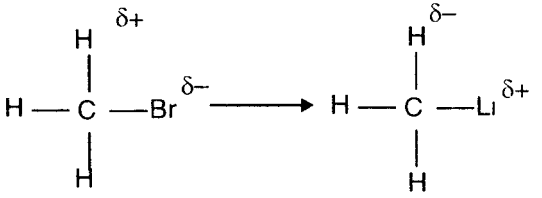
The discussion of acids and bases in the previous section helps us understand the chemistry of the Grignard reagents. Grignard reagents are made by reacting an alkyl bromide with magnesium metal in diethyl ether.

$$CH_3Br \xrightarrow[Et_2O]{Mg} CH_3MgBr$$

An analogous reagent, known as an alkyllithium, can be prepared by reacting the alkyl bromide with lithium metal in diethyl ether.

$$CH_3Br + 2Li \xrightarrow[Et_2O]{} CH_3Li + LiBr$$

In the course of these reactions the carbon atom is reduced from the –2 to the –4 oxidation state. Whereas the starting material contains a carbon atom with a partial positive charge, the carbon atom in the products of these reactions carries a partial negative charge.



CH_3Li and CH_3MgBr can therefore be thought of as a source of the CH_3^- ion.

$$CH_3Li \rightleftharpoons CH_3^- + Li^+$$

The CH_3^- ion is the conjugate base of methane, which is the weakest Brψnsted acid in the table of Brψnsted acids and their conjugate bases.

$$CH_4 \rightleftharpoons CH_3^- + H^+ \quad K_a = 1 \times 10^{-49}$$

The CH_3^- ion is therefore the strongest Brψnsted base in this table.

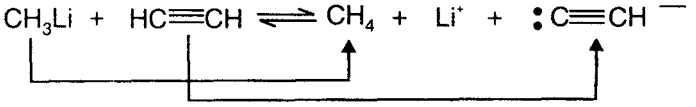
Practice Problem 1:

A graduate student once tried to run the following reaction to prepare a Grignard reagent. Explain what he did wrong, why the yield of the desired product was zero, and predict the product he obtained.

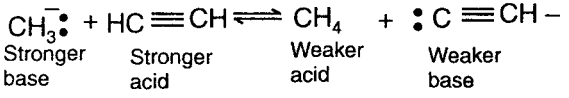
$$CH_3CH_2Br \xrightarrow[CH_3CH_2OH]{Mg} CH_3CH_2MgBr$$

Carbanion Attack at a Carbonyl Group

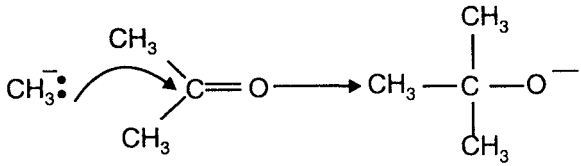
A subtle, but important, point must be made before we can extend our understanding of acid-base chemistry to the reaction between a Grignard or alkyllithium reagent and a carbonyl group. The data in the table of Brψnsted acids and their conjugate bases reflect the strengths of common acids and bases when they act as *Brψnsted acids or bases*. These data predict that methyllithium should react with acetylene to form methane and an acetylide ion, for example.



This reaction should occur because it converts the stronger of a pair of Brψnsted acids and the stronger of a pair of Brψnsted bases into a weaker acid and a weaker base.

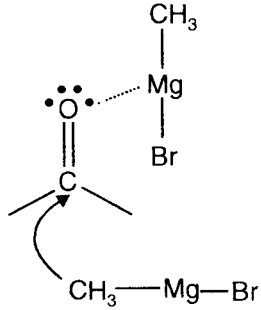


The reaction between a carbonyl and CH_3Li or CH_3MgBr, on the other hand, involves attack by a CH_3^- ion acting as a *Lewis base* or *nucleophile* at the positive end of the carbonyl group.

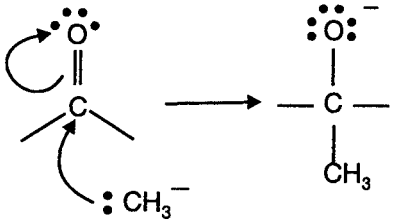


This raises an interesting question: *Is the stronger of a pair of Brψnsted bases always the stronger of a pair of Lewis bases*? Unfortunately, the answer is no, it isn't. At times, the stronger of a pair of Brψnsted bases is the weaker Lewis base or nucleophile. As a rule, however, strong Brψnsted bases are strong nucleophiles, and weak Brψnsted bases are weak nucleophiles.

Despite the enormous utility of the Grignard reagent in organic chemistry, the exact mechanism of the reaction between these reagents and a carbonyl is not known. There is reason to believe that two molecules of the Grignard reagent are involved in this reaction. The magnesium atom of one molecule of this reagent acts as a Lewis acid that interacts with the oxygen atom of the carbonyl group. The alkyl group of the other reagent then acts as a Lewis base, attacking the positive end of the carbonyl.



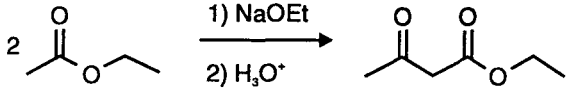
In essence, this reaction involves the attack by a negatively charged CH_3^- ion at the positively charged end of the carbonyl group. When this happens, the pair of nonbonding electrons on the CH_3^- ion are used to from a C—C bond. This, in turn, displaces the pair of electrons in the bond onto the other end of the carbonyl group.



The second molecule of the Grignard reagent, which binds at the oxygen end of the carbonyl, isn't consumed in the reaction. Its function is simple. When it acts as a Lewis acid, binding to the oxygen atom in the C = O double, it increases the polarity of this bond. By making the bond more polar, it increases the rate at which the CH_3^- ion attacks the positive end of the C = O bond.

In the following pages we are discussing ***ORGANIC NAME REACTIONS:***

ACETOACETIC-ESTER CONDENSATION



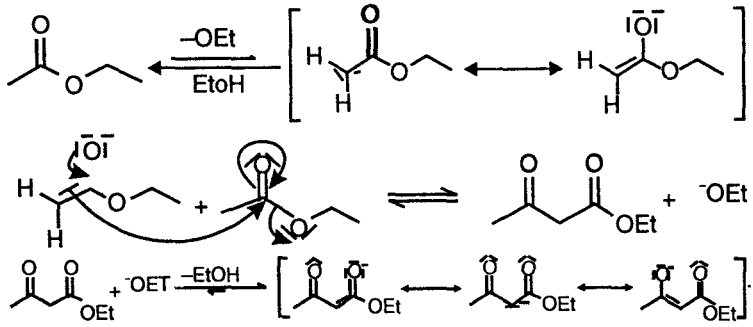
The Claisen Condensation between esters containing α-hydrogens, promoted by a base such as sodium ethoxide, affords β-ketoesters. The driving force is the formation of the stabilized anion of the β-keto ester. If two different esters are used, an essentially statistical mixture of all four products is 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.

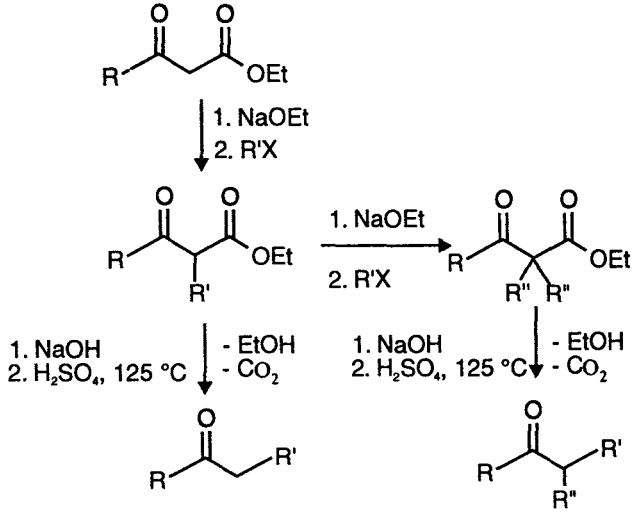
The use of stronger bases, e.g. sodium amide or sodium hydride instead of sodium ethoxide, often increases the yield.

The intramolecular version is known as Dieckmann Condensation.

Mechanism

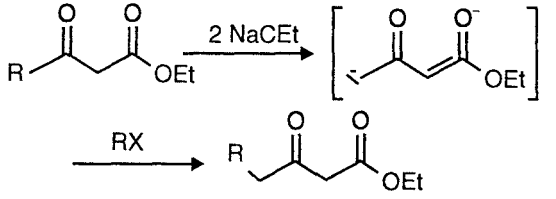


ACETOACETIC ESTER SYNTHESIS



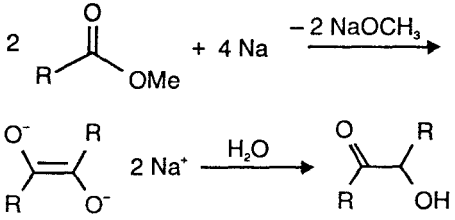
When α-keto acetic acid is treated with one mole of a base, the methylene group which is more acidic reacts with the base. And the reaction with an alkylation reagent gives alkyl products attached to methylene. When this reaction is repeated in the next step, the other hydrogen can also react to a dialkyl product. The two alkylation agents may be the same or different (R',R").

β-Keto esters tend to decarboxylate after hydrolysation to β-keto carboxylic acid and heating to give one or two alkyl-substituted ketones, respectively.

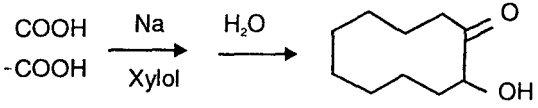


If two moles of a base are added in the first step, the hydrogen of the more acidic methylene group, and in the next step the hydrogen of the methyl group (ambident nucleophiles), reacts with the base. The hydrogenated methyl group is, however, more acidic than the hydrogenated methylene group. The reaction with alkylation agent in the following step gives a product substituted at methyl group. This can be synthetically used to prepare selectively ketones of different types.

ACYLOIN CONDENSATION



The bimolecular reductive coupling of carboxylic esters by reaction with metallic sodium in an inert solvent under reflux gives an α-hydroxyketone, which is known as an acyloin. This reaction is favoured when R is an alkyl. With longer alkyl chains, higher boiling solvents can be used. The intramolecular version of this reaction has been used extensively to close rings of different sizes, e.g. paracyclophanes or catenanes.

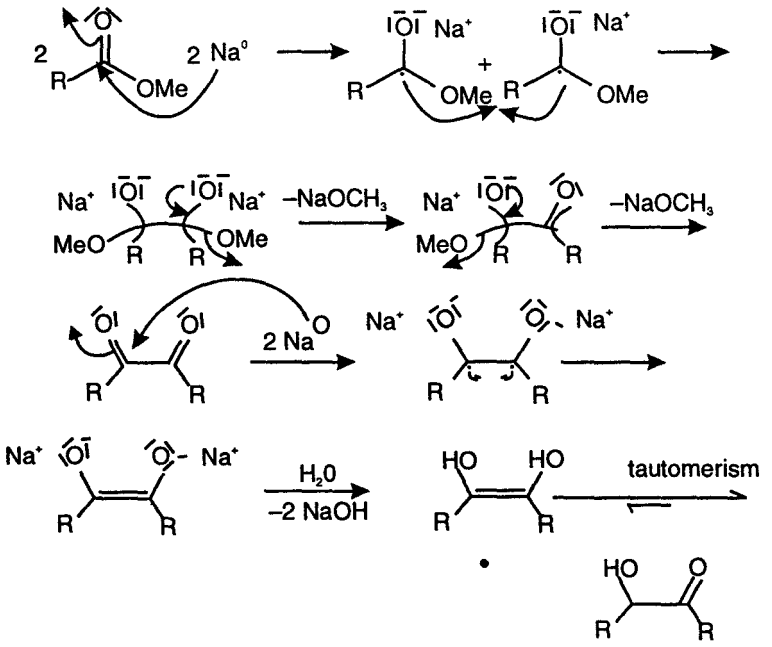


If the reaction is carried out in the presence of a proton donor, such as alcohol, simple reduction of the ester to the alcohol takes place (Bouveault-Blanc Reduction).

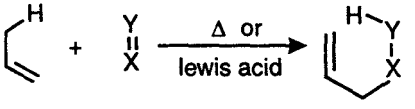
The Benzoin Condensation produces similar products, although with aromatic substituents and under different conditions.

When the acyloin condensation is carried out in the presence of chlorotrimethylsilane, the enediolate intermediate is trapped as the bis-silyl derivative. This can be isolated and subsequently is hydrolysed under acidic condition to the acyloin, which gives a better overall yield.

Mechanism



ALDER-ENE REACTION



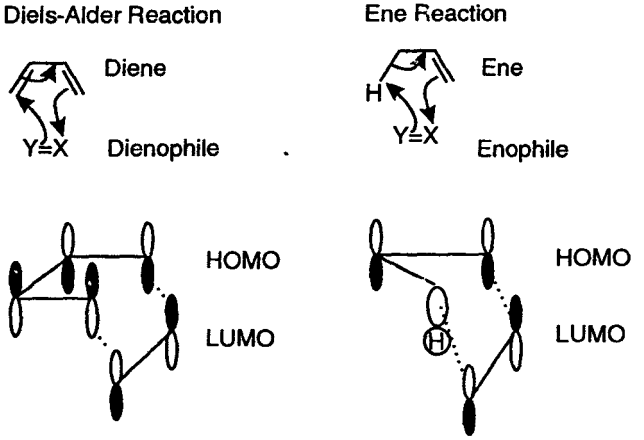
The four-electron system including an alkene π-bond and an allylic C-H σ-bond can participate in a pericyclic reaction in which the double bond shifts and new C-H and C-C σ-bonds are formed. This allylic system reacts similarly to a diene in a Diels-Alder Reaction, while in this case the other partner is called an enophile, analogous to the dienophile in the Diels-Alder. The Alder-Ene Reaction requires higher temperatures because of the higher

activation energy and stereoelectronic requirement of breaking the allylic C-H σ-bond.

The enophile can also be an aldehyde, ketone or imine, in which case β-hydroxy- or β-aminoolefins are obtained. These compounds may be unstable under the reaction conditions, so that at elevated temperature (>400°C) the reverse reaction takes place - the Retro-Ene Reaction.

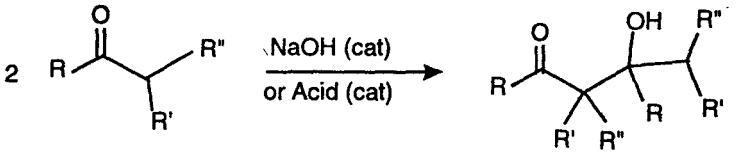
While mechanistically different, the Ene reaction can produce a result similar to the Prins Reaction.

Mechanism



Also like the Diels-Alder, some Ene Reactions can be catalyzed by Lewis Acids. Lewis-Acid catalyzed Ene Reactions are not necessarily concerted (for example: Iron(III) Chloride Catalysis of the Acetal-Ene Reaction).

ALDOL REACTION

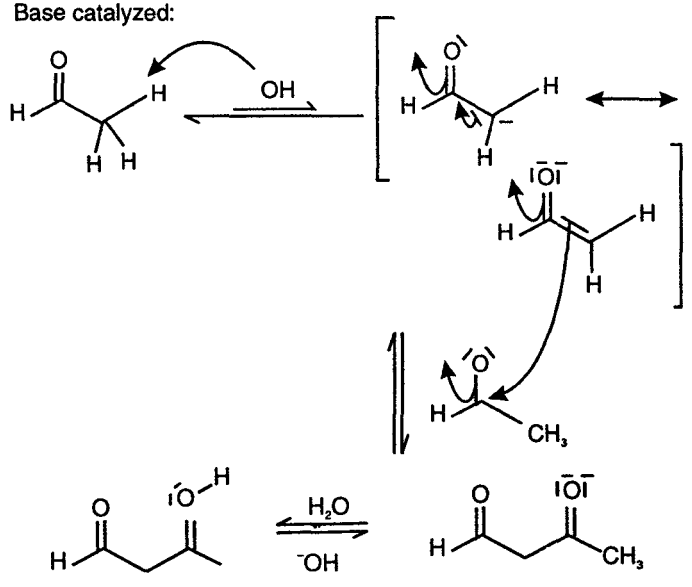


'Aldol' is an abbreviation of aldehyde and alcohol. When the enolate of an aldehyde or a ketone reacts at the α-carbon with the carbonyl of another molecule under basic or acidic conditions to

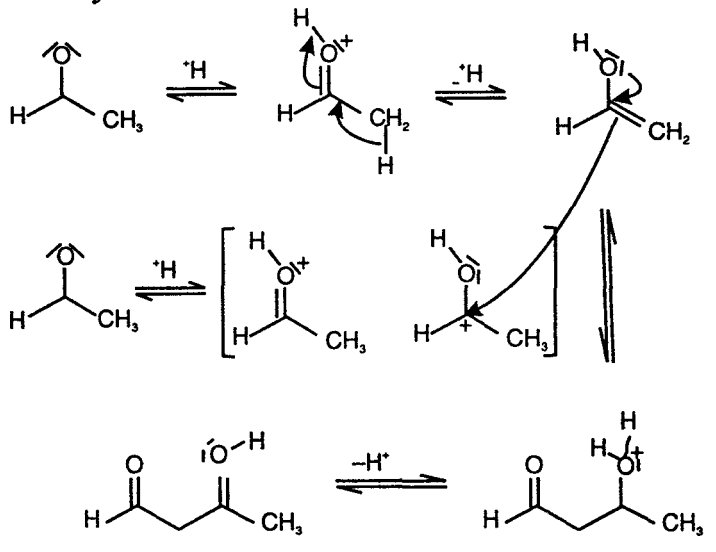
obtain β-hydroxy aldehyde or ketone, this reaction is called Aldol Reaction.

Mechanism

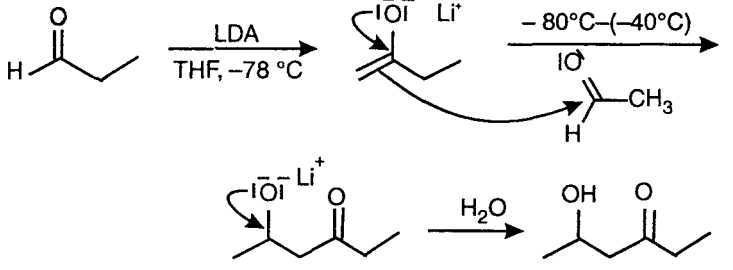
Base catalyzed:



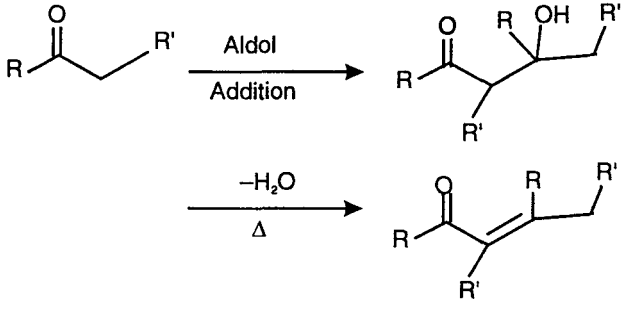
Acid catalyzed



Under conditions of kinetic control, the mixed Aldol Addition can be used to prepare adducts that are otherwise difficult to obtain selectively. This process begins with the irreversible generation of the kinetic enolate, e.g. by employing a sterically hindered lithium amide base such as LDA (lithium diisopropylamide). With an unsymmetrically substituted ketone, such a non-nucleophilic, sterically-demanding, strong base will abstract a proton from the least hindered side. Proton transfer is avoided with lithium enolates at low temperatures in ethereal solvents, so that addition of a second carbonyl partner (ketone or aldehyde) will produce the desired aldol product.



ALDOL CONDENSATION



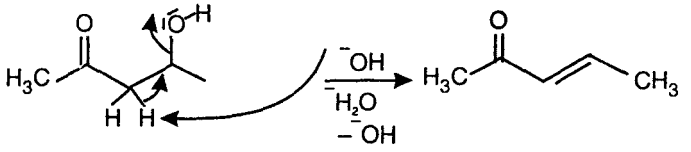
In some cases, the adducts obtained from the Aldol Addition can easily be converted (in situ) to α,β-unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis. The formation of the conjugated system is the driving force for this spontaneous dehydration. Under a variety of protocols,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

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

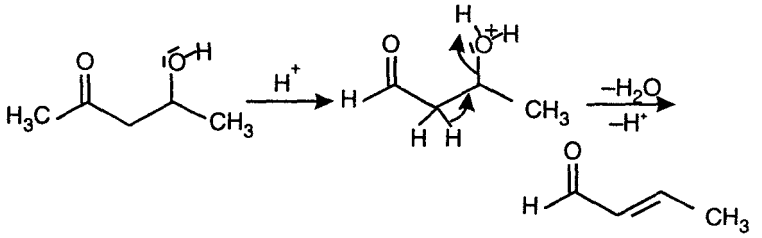
Mechanism

Addition step is same as Aldol Addition

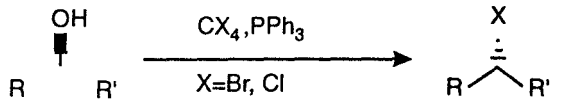
Base catalyzed condensation



Acid catalyzed condensation :



APPEL REACTION



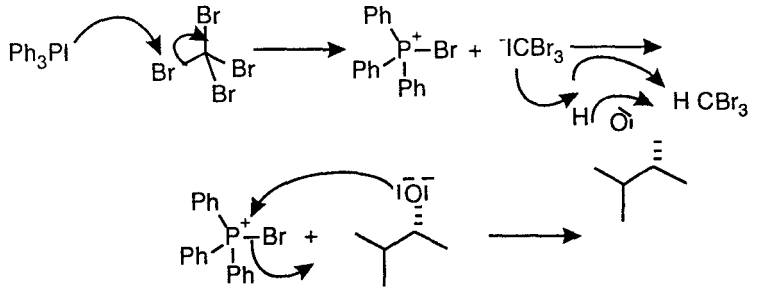
The reaction of triphenylphosphine and tetrahalomethanes (CCl_4, CBr_4) with alcohols is a ready method to convert an alcohol to the corresponding alkyl halide under mild conditions. The yields are normally high.

This reaction is somewhat similar to the Mitsunobu Reaction, where the combination of a phosphine, a diazo compound as a coupling reagent, and a nucleophile are used to invert the stereochemistry of an alcohol or displace it.

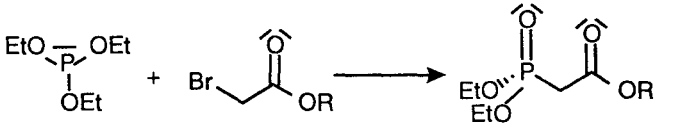
Mechanism

The reaction proceeds by activation of the triphenylphosphine by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group,

and an S_N2 displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric.



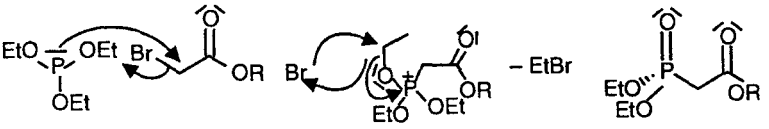
ARBUZOV REACTION



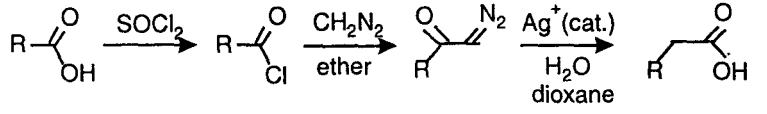
The reaction of a trialkyl phosphate with an alkyl halide to produce an alkyl phosphonate. The first step involves nucleophilic attack by the phosphorus on the alkyl halide, followed by the halide ion dealkylation of the resulting trialkoxyphosphonium salt.

This reaction sees extensive application in the preparation of phosphonate esters for use in the Horner-Emmons Reaction.

Mechanism



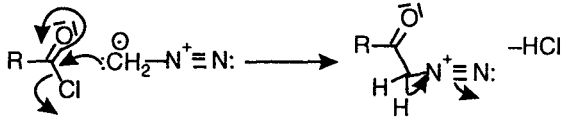
ARNDT-EISTERT SYNTHESIS

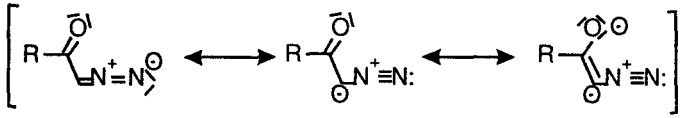


The Arndt-Eistert Synthesis allows the formation of homologated carboxylic acids or their derivatives by reaction of the activated carboxylic acids with diazomethane and subsequent Wolff-Rearrangement of the intermediate diazoketones in the presence of nucleophiles such as water, alcohols, or amines.

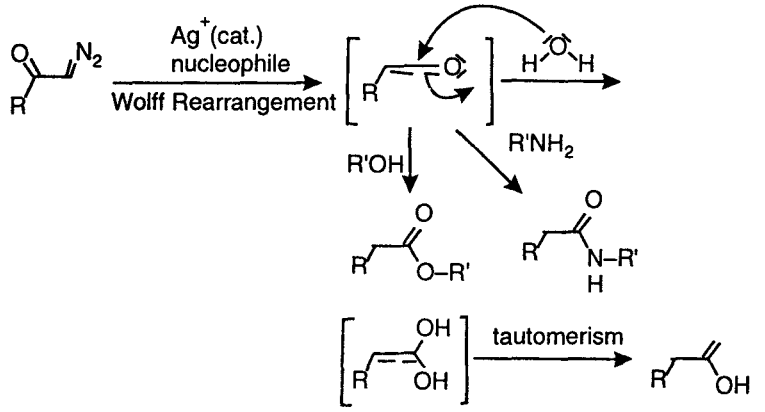
Mechanism

In the first step of this one-carbon homologation, the diazomethane carbon is acylated by an acid chloride or mixed anhydride, to give an α-diazoketone. The excess diazomethane can be destroyed by addition of small amounts of acetic acid or vigourous stirring. Most α-diazoketones are stable and can be isolated and purified by column chromatography.



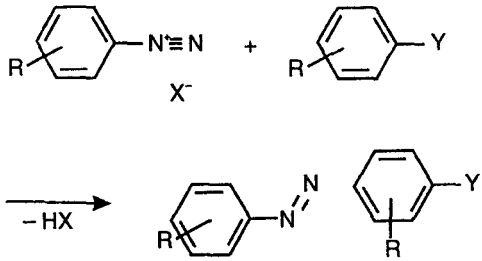


The key step of the Arndt-Eistert Homologation is the Wolff-Rearrangement of the diazoketones to ketenes, which can be accomplished thermally (over the range between r.t. and 750°C, photochemically or by silver(I) catalysis. The reaction is conducted in the presence of nucleophiles such as water (to yield carboxylic acids), alcohols (to give alcohols) or amines (to give amides), to capture the ketene intermediate and avoid the competing formation of diketenes.



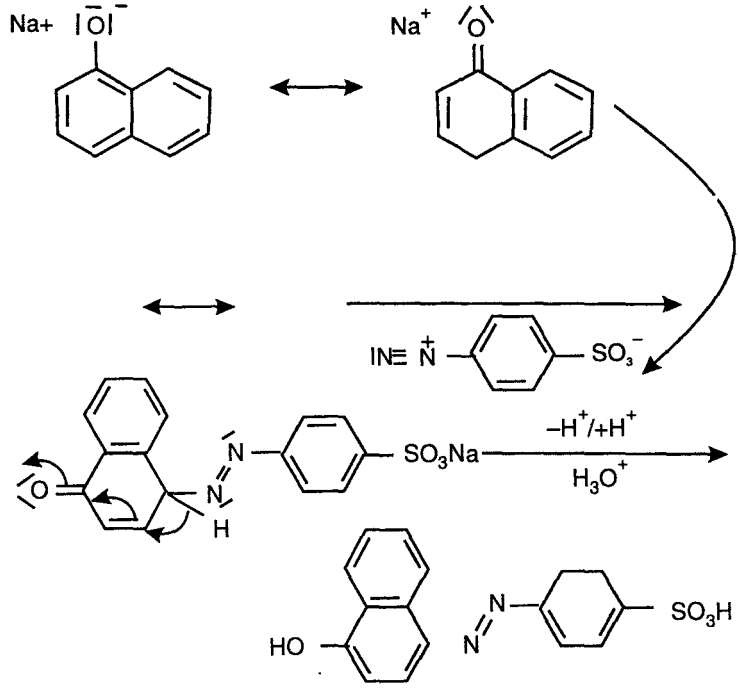
The method is widely used nowadays for the synthesis of β-amino acids. Peptides that contain β-amino acids feature a lower rate of metabolic degradation and are therefore of interest for pharmaceutical applications.

AZO COUPLING

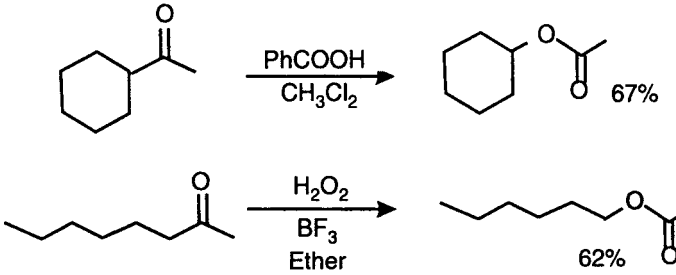


Azo coupling is the most widely used industrial reaction in the production of dyes, lakes and pigments. Aromatic diazonium ions acts as electrophiles in coupling reactions with activated aromatics such as anilines or phenols. The substitution normally occurs at the para position, except when this position is already occupied, in which case *ortho* position is favoured. The pH of solution is quite important; it must be mildly acidic or neutral, since no reaction takes place if the pH is too low.

Mechanism



BAEYER-VILLIGER OXIDATION

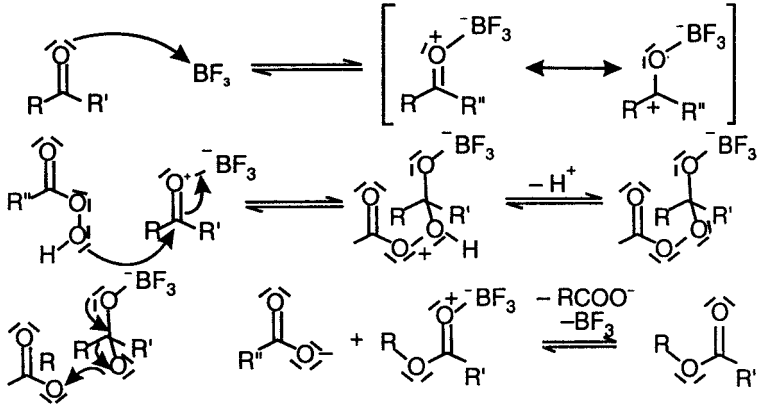


The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The Baeyer-Villiger can be carried out with peracids, such as MCBPA, or with hydrogen peroxide and a Lewis acid.

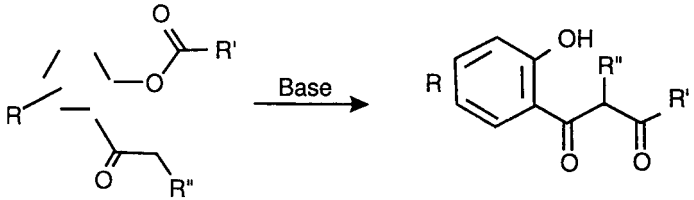
The regiospecificity of the reaction depends on the relative migratory ability of the substituents attached to the carbonyl. Substituents which are able to stabilize a positive charge migrate more readily, so that the order of preference is: tert. alkyl > cyclohexyl > sec. alkyl > phenyl > prim. alkyl > CH_3. In some cases, stereoelectronic or ring strain factors also affect the regiochemical outcome.

The reaction of aldehydes preferably gives formates, but sometimes only the liberated alcohol may be isolated due to the solvolytic instability of the product formate under the reaction conditions.

Mechanism

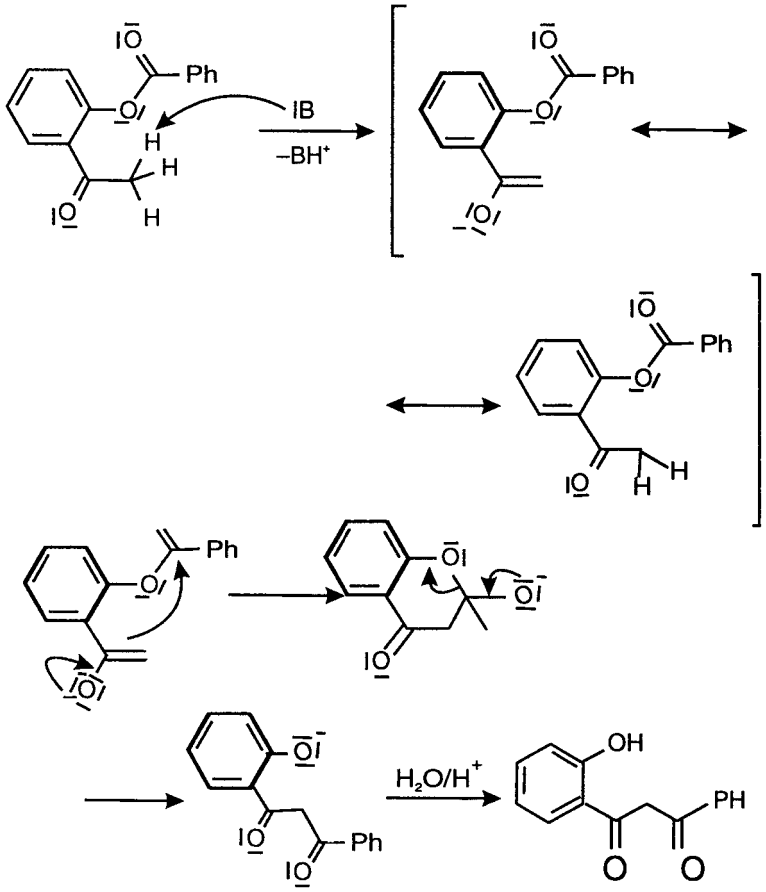


BAKER-VENKATARAMAN REARRANGEMENT

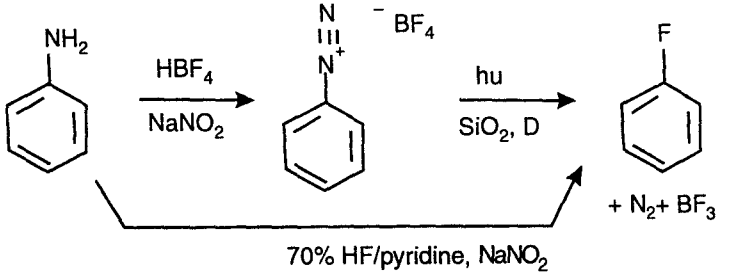


The base-induced transfer of the ester acyl group in an *o*-acylated phenol ester, which leads to a 1,3-diketone. This reaction is related to the Claisen Condensation, and proceeds through the formation of an enolate, followed by intramolecular acyl transfer.

Mechanism



BALZ-SCHIEMANN REACTION

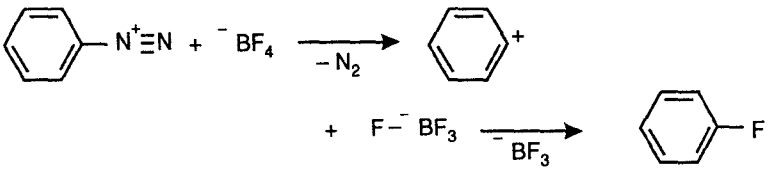


The conversion of aryl amines to aryl fluorides via diazotisation and subsequent thermal decomposition of the derived tetrafluoroborates or hexafluorophosphates. The decomposition may also be induced photochemically.

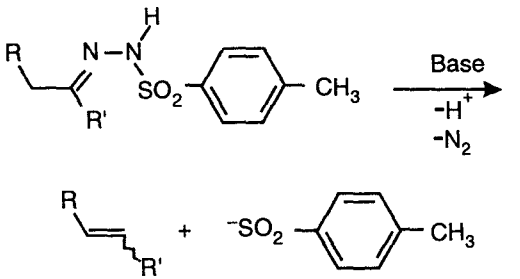
Mechanism

Same as Diazotisation.

The mechanism of the Balz-Schiemann reaction remains obscure. A possible pathway is shown below:



BAMFORD-STEVENS REACTION

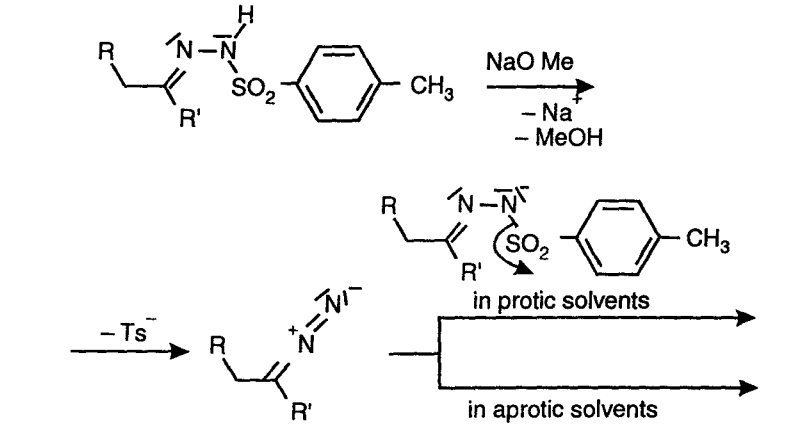


Tosylhydrazones give alkenes upon treatment with strong bases. This reaction is performed in two steps, where the intermediate diazo compound may be isolated. Subsequent reaction with protic or aprotic solvents strongly influences the outcome of the reaction.

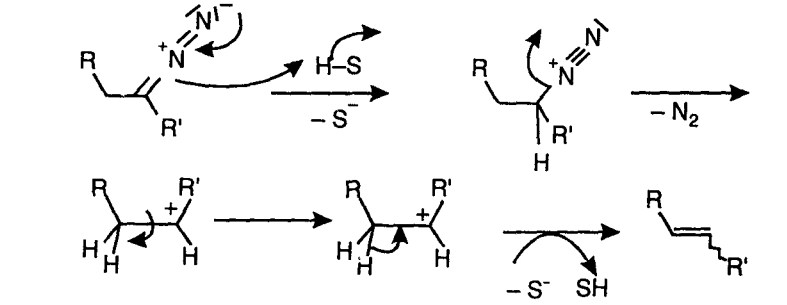
This reaction may be used to effect the overall transformation of a ketone to an alkene.

If an organolithium is used as the base, the reaction follows another mechanism without occurrence of carbenium ions and carbenes.

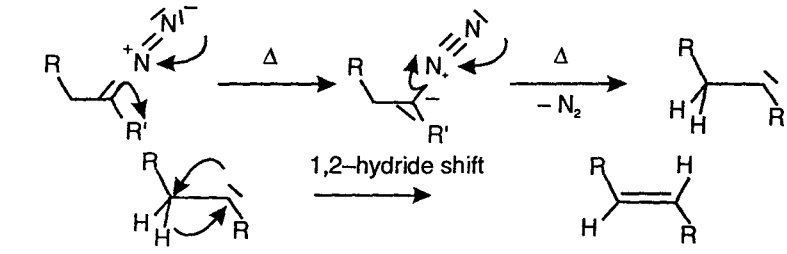
Mechanism



Carbenium ions are formed in protic solvents:

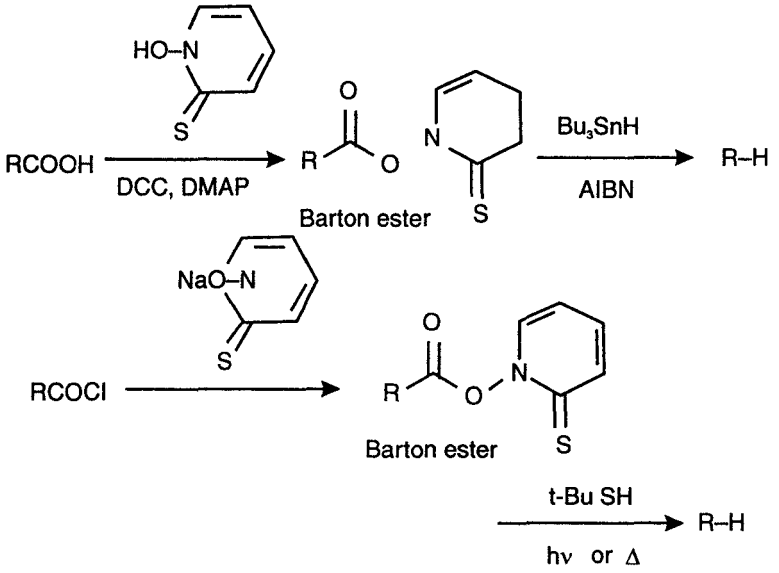


...and carbenes in aprotic solvents:

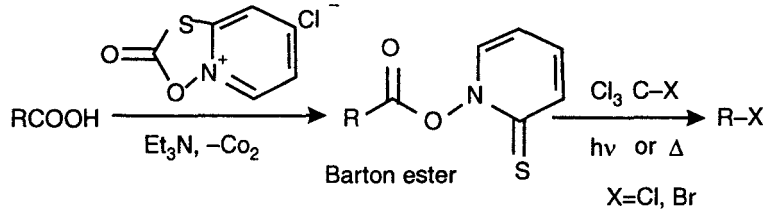


BARTON DECARBOXYLATION

The radical decarboxylation of a Barton ester proceeds to the corresponding alkane after treatment with tributyltin hydride or *t*-butylmercaptan:

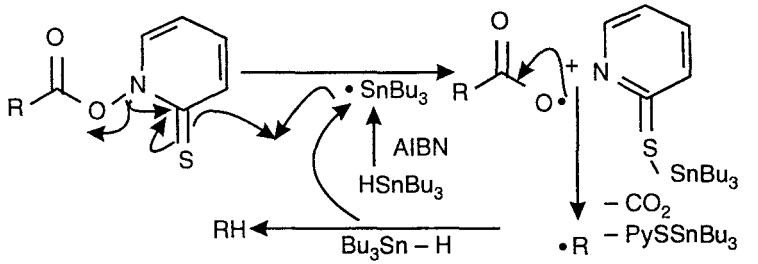


An alternative possibility is the introduction of a substituent by reaction with a suitable radical trapping agent:

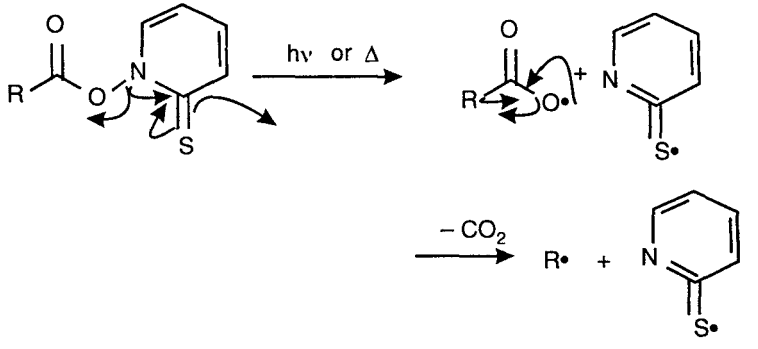


Mechanism

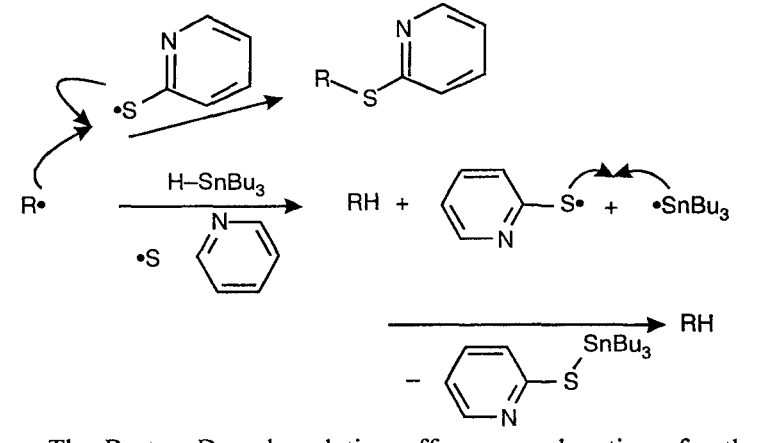
The initiation of the Barton Decarboxylation (Bu_3Sn-H -> Bu_3Sn·) is effected with a radical initiator, and as with the Barton-McCombie Deoxygenation, the driving force for the reaction itself is the formation of the stable S-Sn bond.



In addition, Barton esters can also be cleaved photolytically or thermally:

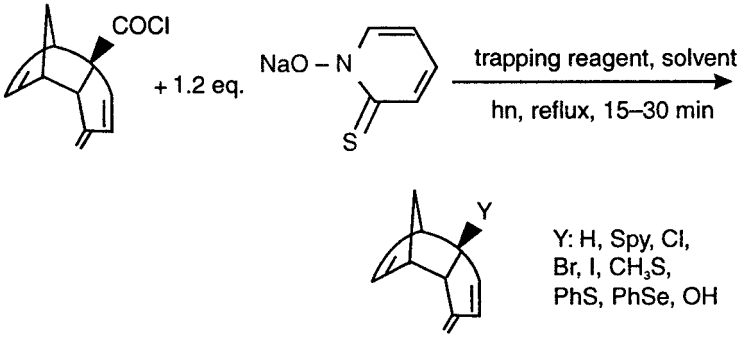


If an excess of a suitable radical trapping agent is present in the reaction medium, substitution will occur; otherwise, radical recombination takes place to give the pyridyl sulfide:

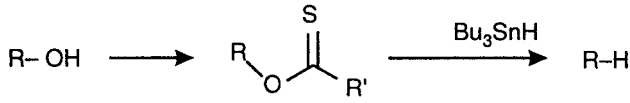


The Barton Decarboxylation offers several options for the introduction of substituents - some examples are shown below:

y	H	SPy	Br	I	PhS
Trapping Reagent	t-BuSH	-	$BrCCl_3$	CHI_3(2 eq.)	PhSSPh (2 eq.)
Solvent	benzene	benzene	$BrCCl_3$	tolune	tolune
t	15 min.	15 min.	15 min.	15 min.	15 min.
Yield (% isol.)	60	90	93	62	42



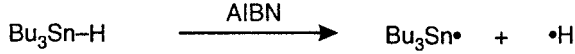
BARTON DEOXYGENATION



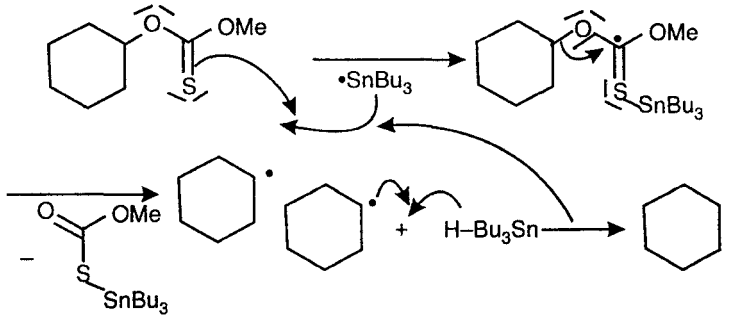
R=Alkyl, R'=H, CH_3, SCH_3, OCH_3Ph, OPH, Imidazolyl

A method for the deoxygenation of alcohols. The alcohol is first converted to the thiocarbonyl derivative, and is then treated with Bu_3SnH. Once the radical chain has been initiated, attack on the Bu_3Sn carrier by sulphur initiates a decomposition yielding the alkyl radical, for which Bu_3SnH serves as hydrogen radical (H·) donor. The driving force for the reaction is the formation of the very stable S-Sn bonds.

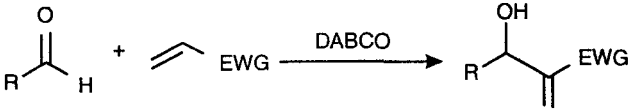
Mechanism



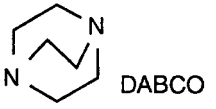
The catalytic cycle, in which low concentration of ·$SnBu_3$ effects the reaction:



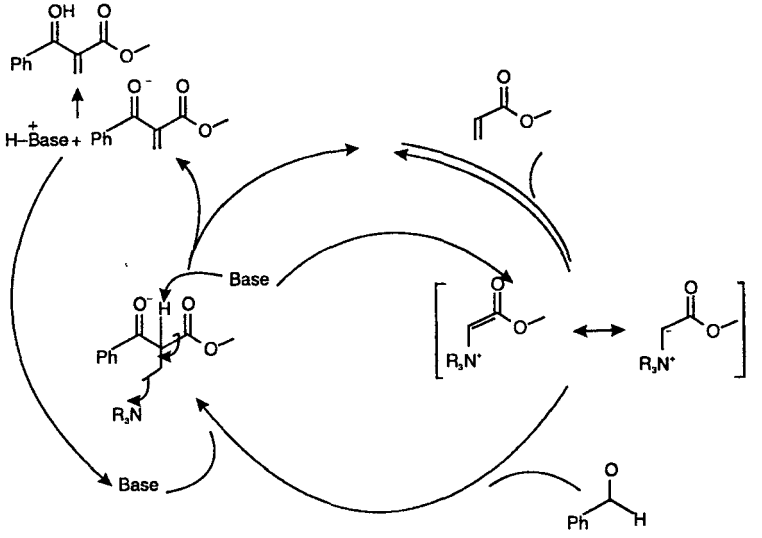
BAYLIS-HILLMAN REACTION



This coupling of an activated alkene derivative with an aldehyde is catalyzed by a tertiary amine (for example: DABCO = 1,4-Diazabicyclo[2.2.2]octane). Phosphines can also be used in this reaction, and enantioselective reactions may be carried out if the amine or phosphine catalyst is asymmetric.

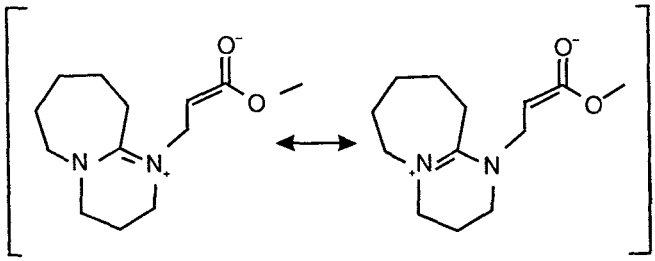


Mechanism



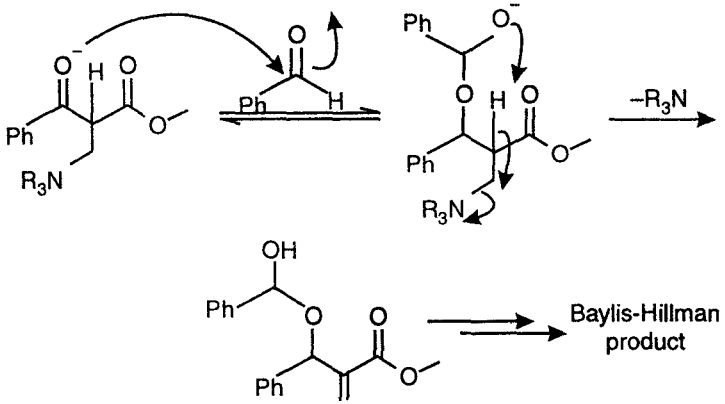
A key step is the addition of the amine catalyst to the activated alkene to form a stabilized nucleophilic anion. This in situ-generated nucleophile then adds to the aldehyde. Subsequent elimination of the catalyst leads to the observed products.

Other activating nitrogen nucleophiles may be suitable too and DMAP and DBU are superior to DABCO in some cases:

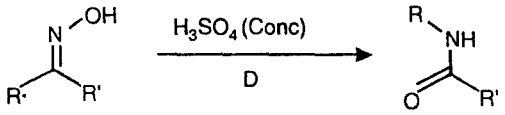


product of the addition of DBU and methylacrylate

For aryl aldehydes under polar, nonpolar, and protic conditions, it has been determined that the rate-determining step is second-order in aldehyde and first-order in DABCO and acrylate. On the basis of this reaction rate data, Tyler McQuade recently proposed the following mechanism involving the formation of a hemiacetal intermediate:



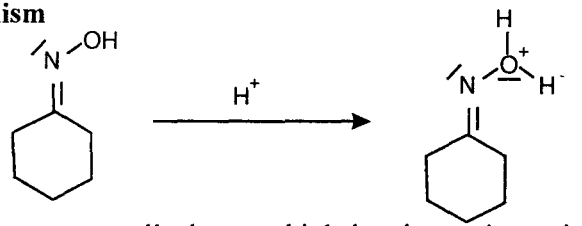
BECKMANN REARRANGEMENT



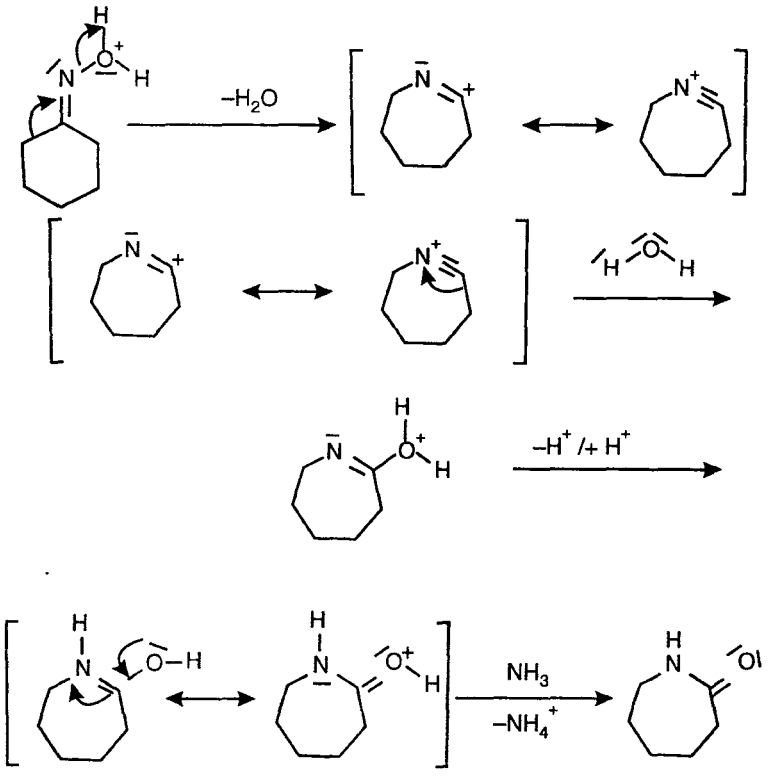
An acid-induced rearrangement of oximes to give amides.

This reaction is related to the Hofmann and Schmidt Reactions and the Curtius Rearrangement, in that an electropositive nitrogen is formed that initiates an alkyl migration.

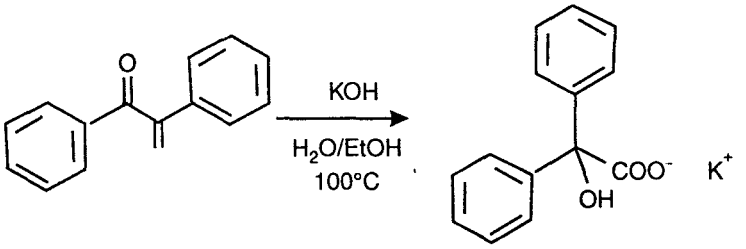
Mechanism



Oximes generally have a high barrier to inversion, and accordingly this reaction is envisioned to proceed by protonation of the oxime hydroxyl, followed by migration of the alkyl substituent "*trans*" to nitrogen. The N-O bond is simultaneously cleaved with the expulsion of water, so that formation of a free nitrene is avoided.

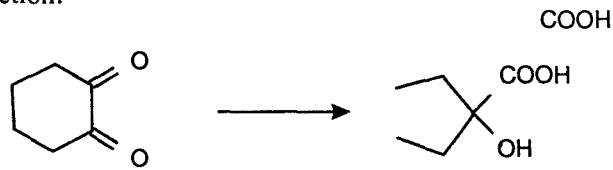


BENZILIC ACID REARRANGEMENT



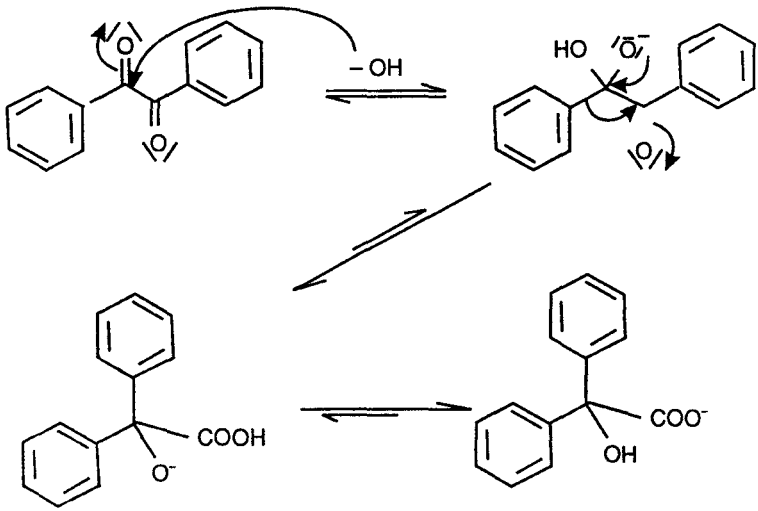
1,2-Diketones undergo a rearrangement in the presence of strong base to yield α-hydroxycarboxylic acids. The best yields are obtained when the subject diketones do not have enolizable protons.

The reaction of a cyclic diketone leads to an interesting ring contraction:

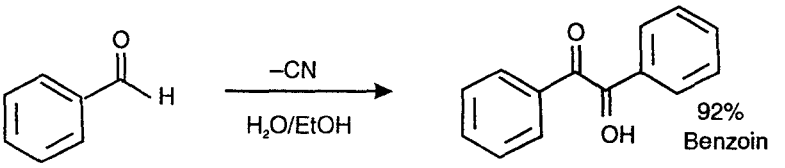


Ketoaldehydes do not react in the same manner, where a hydride shift is preferred.

Mechanism



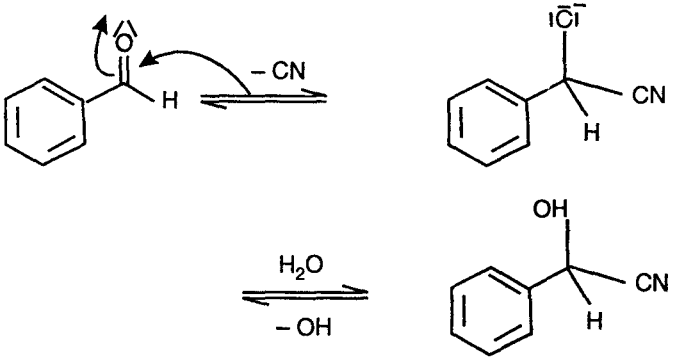
BENZOIN CONDENSATION



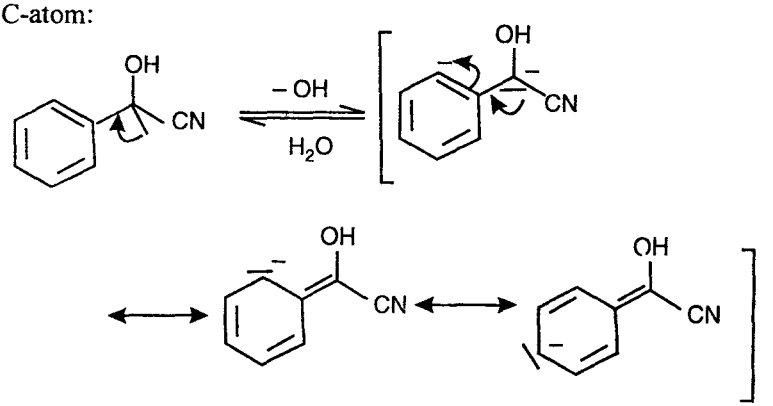
The Benzoin Condensation is a coupling reaction between two aldehydes that allows the preparation of α-hydroxyketones. The first methods were only suitable for the conversion of aromatic aldehydes.

Mechanism

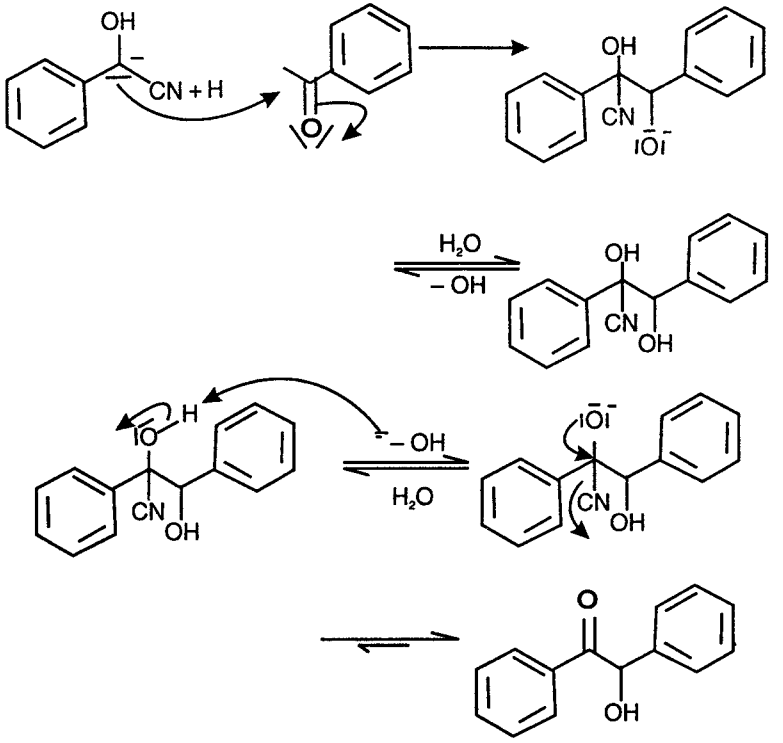
Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation: A thiazolium salt may also be used as the catalyst in this reaction.



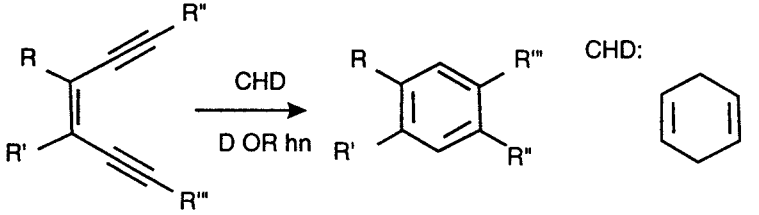
A strong base is now able to deprotonate at the former carbonyl C-atom:



A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction:



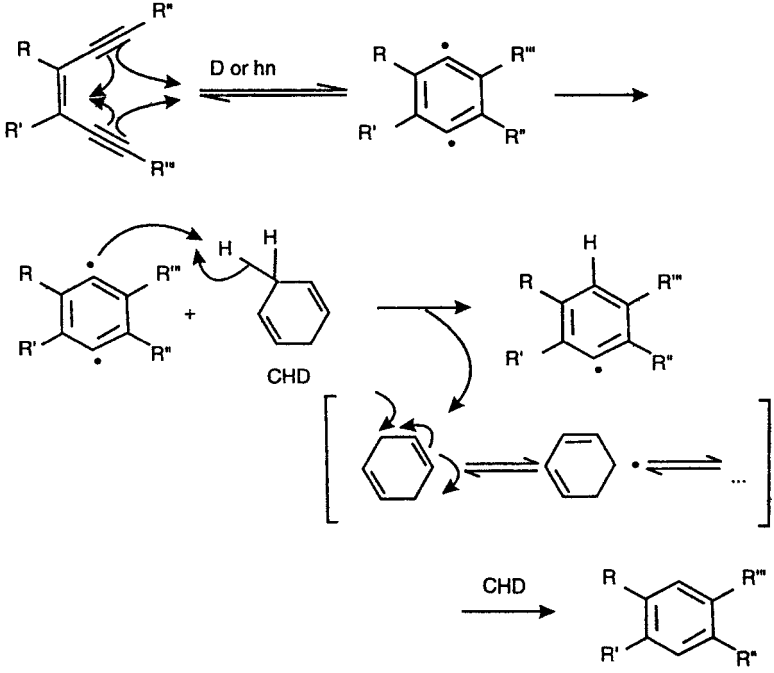
BERGMAN CYCLOAROMATIZATION



The Bergman Cyclization (or Myers-Saito Cyclization) allows the construction of substituted arenes through the thermal or photochemical cycloaromatization of enediynes in the presence of a H• donor such as 1,4-cyclohexadiene.

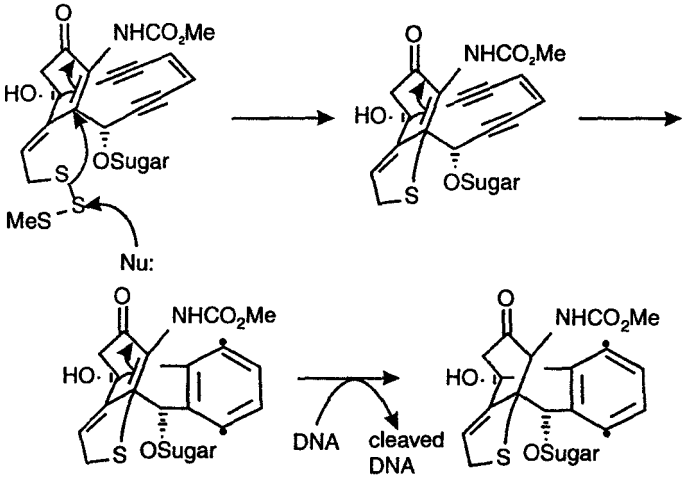
Mechanism

The cyclization is induced thermally or photochemically. Most cyclizations have a high activation energy barrier and therefore temperatures around 200 °C are needed for the cycloaromatization. The Bergman Cyclization forms a 1,4-benzenediyl diradical - a highly reactive species, that reacts with a H• donor to give the corresponding arenes.



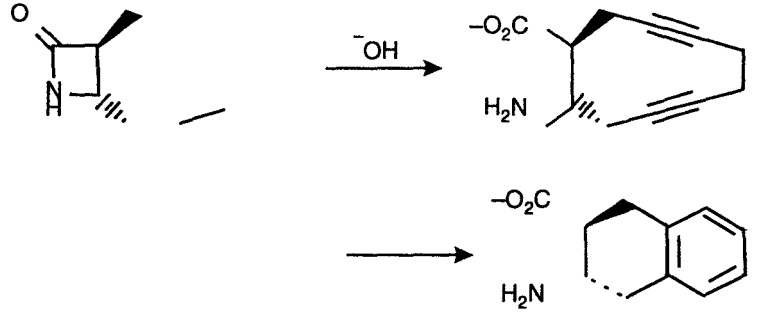
The interest in the Bergman Cyclization was somewhat low, due to its limited substrate scope and the availability of alternative methods for the construction of substituted arenes. However, natural products that contain the enediyne moiety have been discovered recently, and these compounds have cytotoxic activity.

An example is calicheamicin, which is able to form the reactive diradical species even under physiological conditions. Here, the Bergman Cyclization is activated by a triggering reaction. A distinguishing property of this diradical species is that it can effect a dual-strand cleavage of DNA:

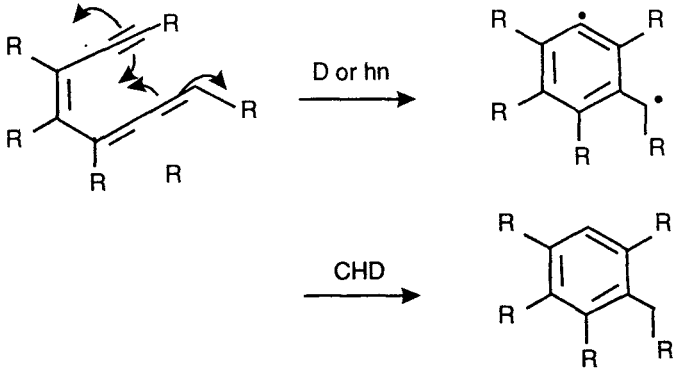


With the discovery of calicheamicin and similar natural products, interest in the Bergman Cyclization has increased. Many enediynes can now be viewed as potential anticancer drugs. Thus, the development of Bergman Cyclization precursors that can undergo cyclization at room temperature has attracted much attention. Now, most publications on this topic deal with the parameters that control the kinetics of the Bergman Cyclization.

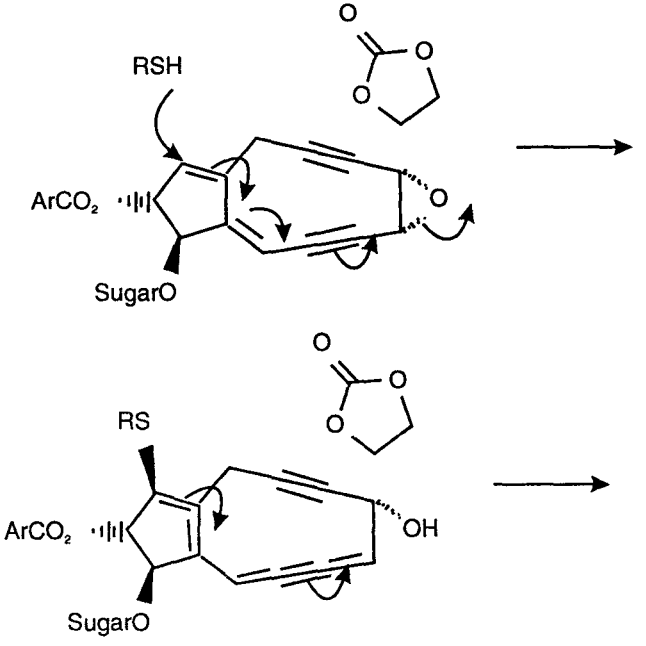
For example, as shown by calicheamicin, cyclic enediynes have a lower activation barrier than acyclic enediynes. As suggested by Nicolaou in 1988, the distance between the acetylenic carbons that form the covalent bond influences the rate of cyclization. Another theory developed by Magnus and Snyder is based on the molecular strain between ground state and transition state; this seems to be more general, especially for strained cyclic systems. Often, as both the distance and the strain are not known, the development of suitable precursors remains difficult, as exemplified by the following enediyne, in which a slight change leads to a cycloaromatization:

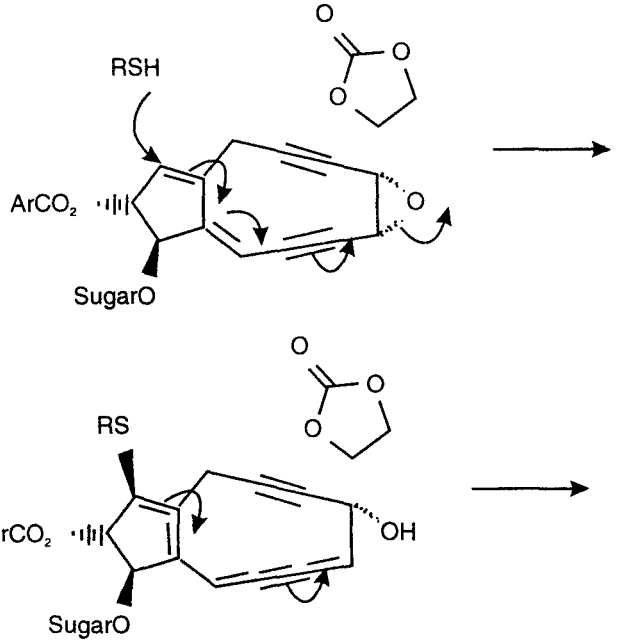


In contrast to the Bergman Cyclization, the Myers-Saito Cyclization of allenyl enynes exhibits a much lower activation temperature while following a similar pathway:

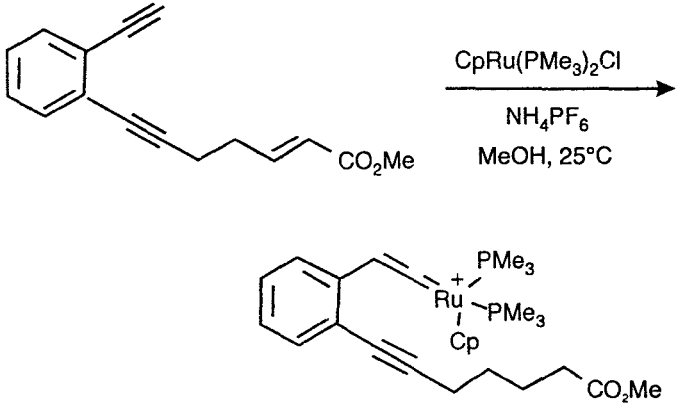


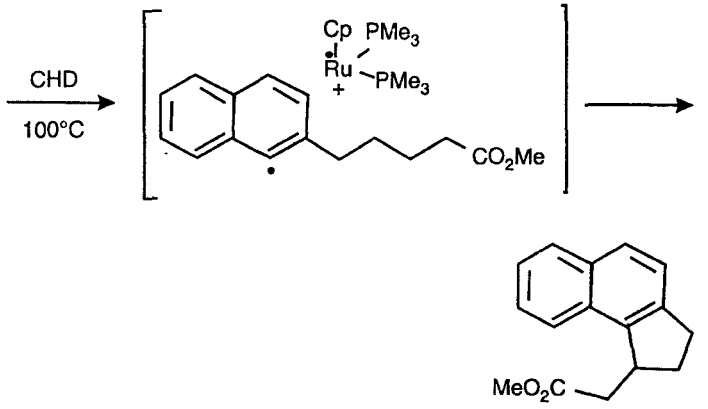
Cyclic enyne allenes are also reactive. Neocarzinostatin is a bacterial antibiotic that also shows antitumor activity. Here, the occurrence of a Myers-Saito Cyclization sets the stage for the cleavage of DNA:



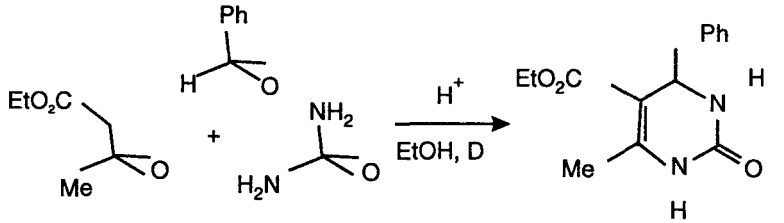


For synthetic purposes, organometallic reagents can be used to generate a precursor to the Bergman Cyclization in which the metal centre forms a part of the cumulated unsaturated system; these cyclizations occur at relatively low temperatures. Here the cyclization can be viewed as a Myers-Saito Cyclization that gives rise to a metal-centreed radical:



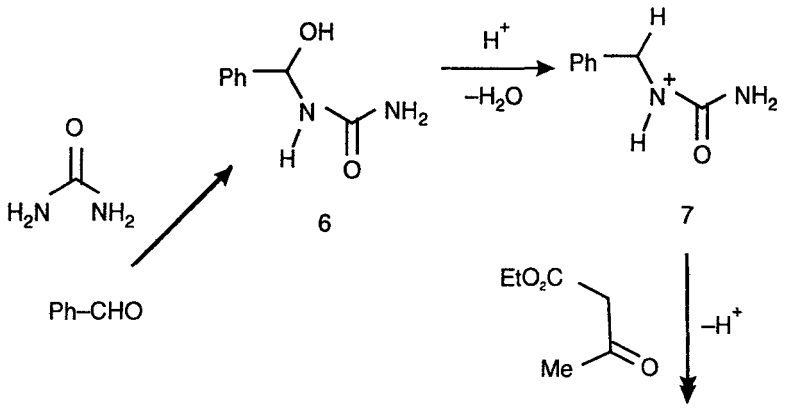


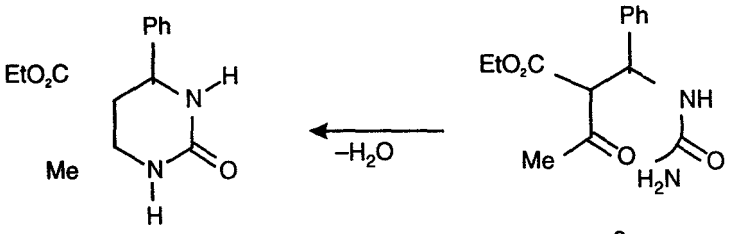
BIGINELLI REACTION



This acid-catalyzed, three-component reaction between an aldehyde, a ĩ-ketoester and urea constitutes a rapid and facile synthesis of dihydropyrimidones, which are interesting compounds with a potential for pharmaceutical application.

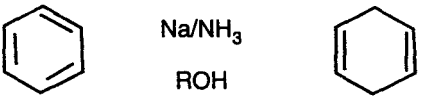
Mechanism





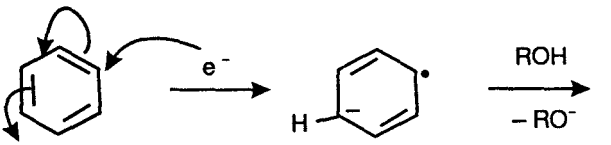
The first step in the mechanism is believed to be the condensation between the aldehyde and urea, with some similarities to the Mannich Condensation. The iminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product.

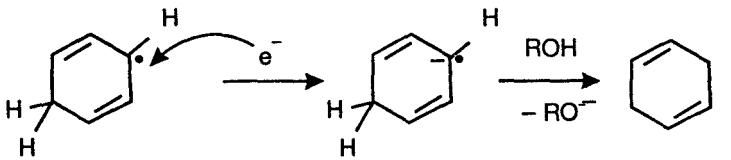
BIRCH REDUCTION



The Birch Reduction offers access to substituted 1,4-cyclohexadienes.

Mechanism

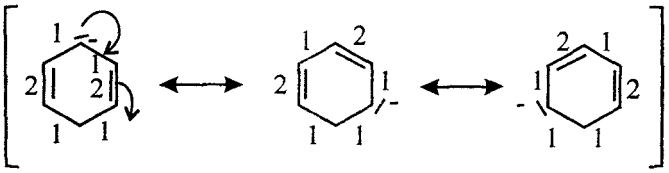




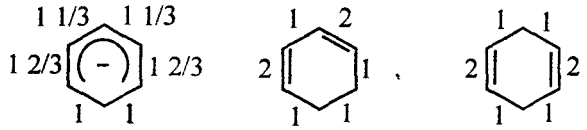
The question of why the 1,3-diene is not formed, even though it would be more stable through conjugation, can be rationalized with a simple mnemonic. When viewed in valence bond terms, electron-electron repulsions in the radical anion will preferentially have the

nonbonding electrons separated as much as possible, in a 1,4-relationship.

This question can also be answered by considering the mesomeric structures of the dienyl carbanion:

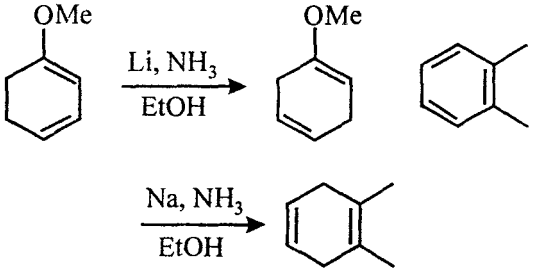


The numbers, which stand for the number of bonds, can be averaged and compared with the 1,3- and the 1,4-diene. The structure on the left is the average of all mesomers depicted above followed by 1,3 and 1,4-diene:



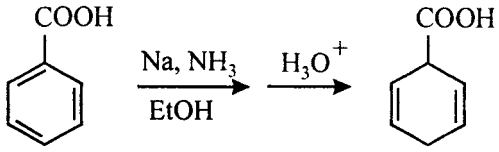
The difference between the dienyl carbanion and 1,3-diene in absolute numbers is 2, and between the dienyl carbanion and 1,4-diene is 4/3. The comparison with the least change in electron distribution will be preferred.

Reactions of arenes with +I- and +M-substituents lead to the products with the most highly substituted double bonds:

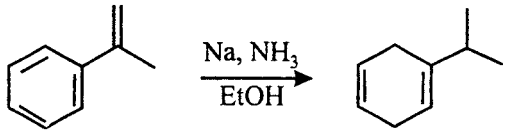


The effect of electron-withdrawing substituents on the Birch Reduction varies. For example, the reaction of benzoic acid leads to

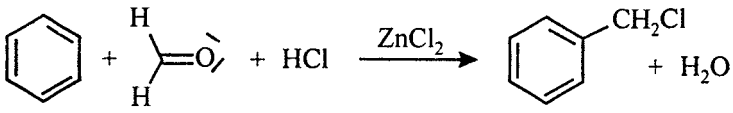
2,5-cyclohexadienecarboxylic acid, which can be rationalized on the basis of the carboxylic acid stabilizing an adjacent anion:



Alkene double bonds are only reduced if they are conjugated with the arene, and occasionally isolated terminal alkenes will be reduced.



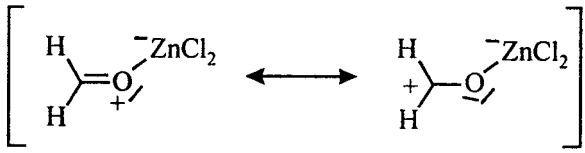
BLANC REACTION

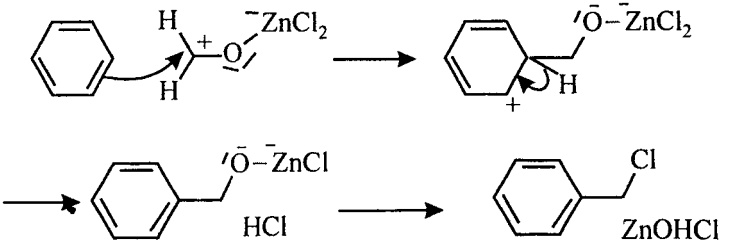


This reaction, which is comparable to a Friedel-Crafts Alkylation, is useful for the preparation of chloromethylated arenes (for example, the Merrifield resin based on polystyrene) from the parent arene with formaldehyde, HCl, and $ZnCl_2$.

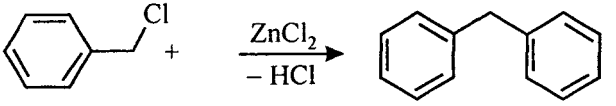
Mechanism

The Lewis acid $ZnCl_2$ effects formation of an oxonium ion which is reactive in electrophilic aromatic substitution. The intermediate zinc alkoxide reacts with the arene to form the chloromethylated product and zinc oxides:

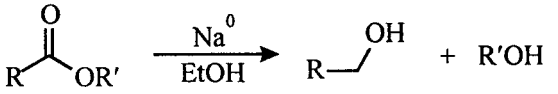




When the concentration (or, effective concentration in the case of polymer residues) is high, the formation of side products due to a second addition are observed:



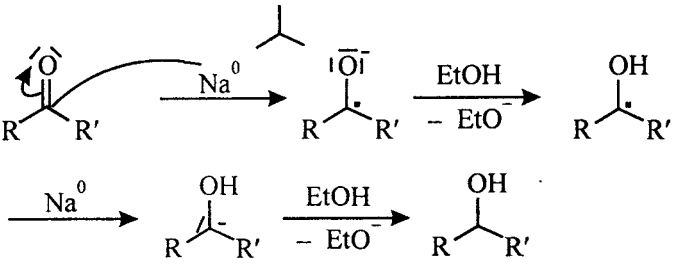
BOUVEAULT-BLANC REDUCTION



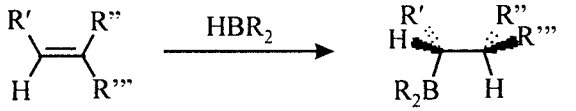
This method is an inexpensive substitute for LAH reductions of esters in industrial production, and was the only alternative prior to the development of the metal hydride reducing agents. This dissolving metal reduction is also related to the Birch Reduction.

Mechanism

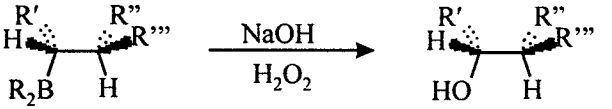
Sodium serves as single electron reducing agent and EtOH is the proton donor. If no proton donor is available, dimerization will take place, as the Acyloin Condensation.



BROWN HYDROBORATION



The *syn*-addition of hydroboranes to alkenes occurs with predictable selectivity, wherein the boron adds preferentially to the least hindered carbon. This selectivity is enhanced if sterically demanding boranes are used.

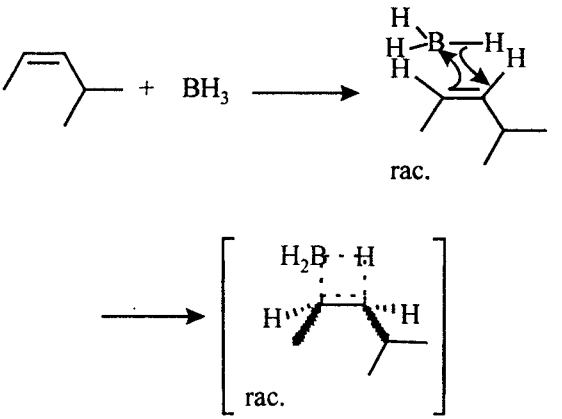


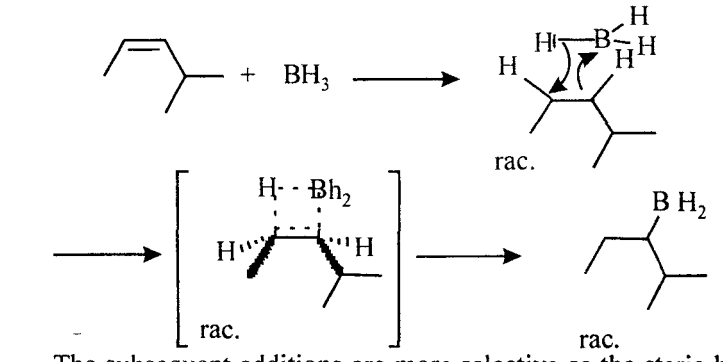
Coupling the hydroboration with a subsequent oxidation of the new formed borane yields *anti*-Markovnikov alcohols. The hydroboration/oxidation sequence constitutes a powerful method for the regio- and stereoselective synthesis of alcohols.

The product boranes may also be used as starting materials for other reactions, such as Suzuki Couplings.

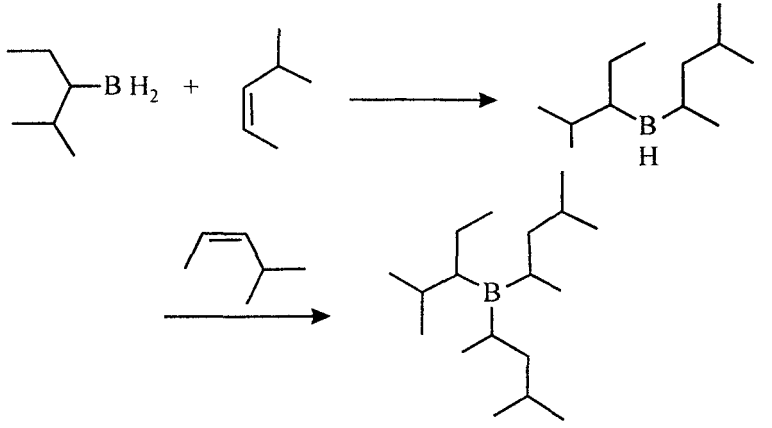
Mechanism

The selectivity of the first addition of borane can be relatively low:

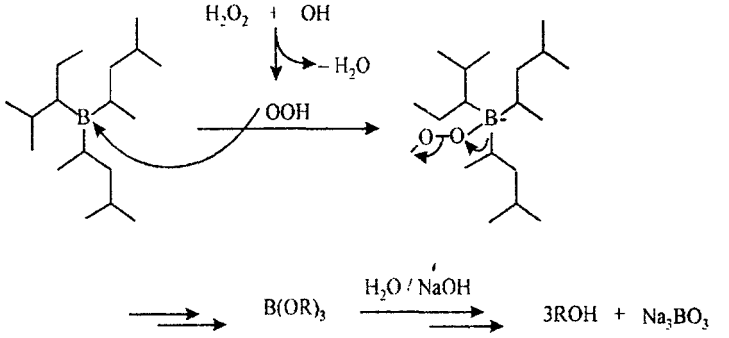




The subsequent additions are more selective as the steric bulk increases, and *anti*-Markovnikov selectivity predominates in the end:

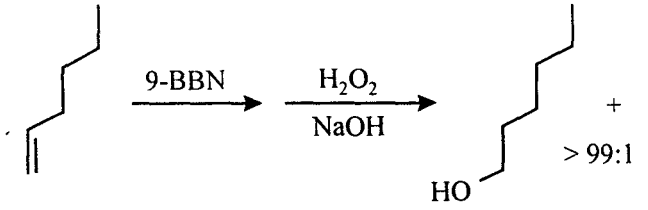


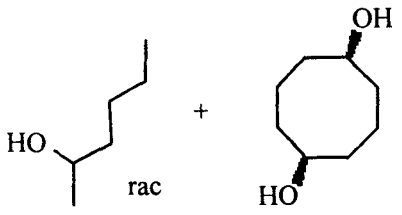
Oxidation with hydrogen peroxide leads to alcohols:

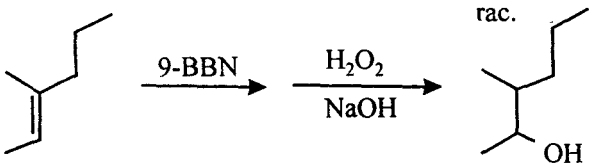


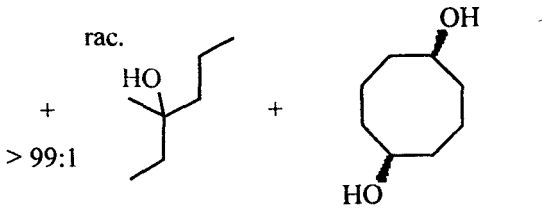
Sterically demanding boranes offer enhanced selectivity. One example of a sterically demanding borane (9-BBN) is generated by the double addition of borane to 1,5-cyclooctadiene:

9-Borabicyclo[3.3.1]nonane





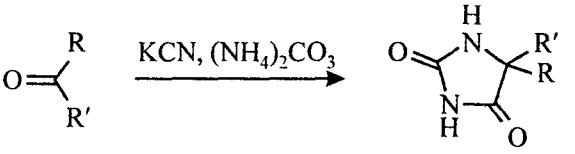




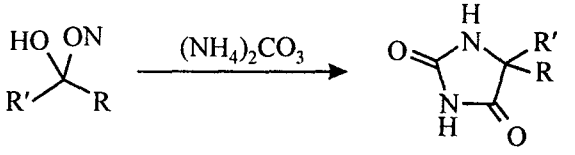
The reactivity and selectivity of the borane reagent may be modified through the use of borane-Lewis base complexes.

BUCHERER-BERGS REACTION

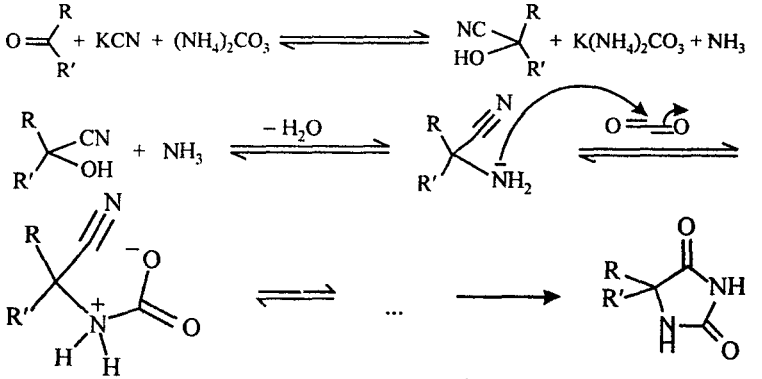
A multi-component reaction between a ketone, potassium cyanide and ammonium carbonate, which leads to the formation of hydantoins.



A pre-formed cyanohydrin can react with ammonium carbonate to give the same product:

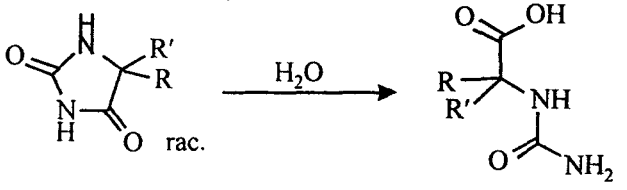


Mechanism

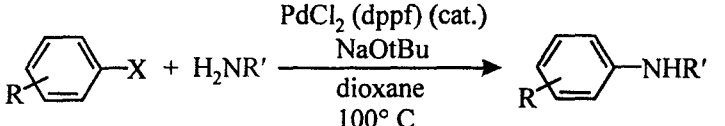


The Bucherer-Bergs Reaction is equivalent to the Strecker

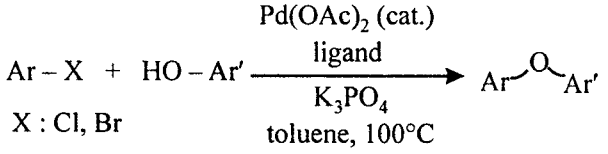
arbamoylamino acids which form amino acids by treatment with acid or with a suitable enzyme:



BUCHWALD-HARTWIG CROSS COUPLING REACTION



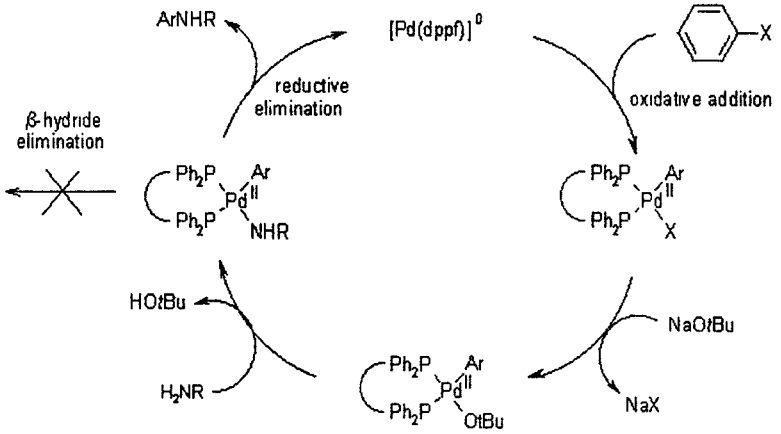
Palladium-catalyzed synthesis of aryl amines. Starting materials are aryl halides or pseudohalides (for example triflates) and primary or secondary amines.



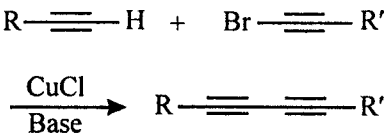
The synthesis of aryl ethers and especially diaryl ethers has recently received much attention as an alternative to the Ullmann Ether Synthesis.

Newer catalysts and methods offer a broad spectrum of interesting conversions.

Mechanism

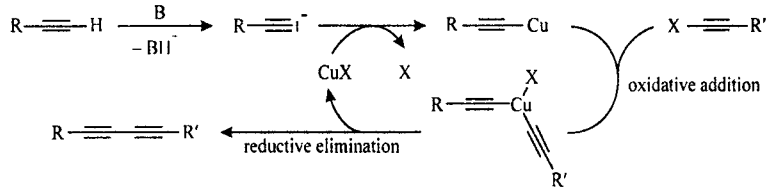


CADIOT-CHODKIEWICZ COUPLING

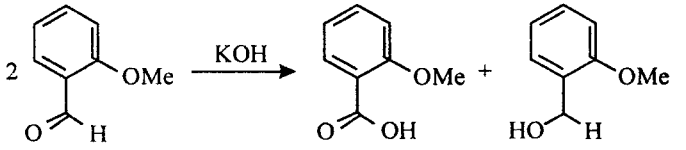


The copper(I)-catalyzed coupling of a terminal alkyne and an alkynyl halide offers access to unsymmetrical bisacetylenes.

Mechanism

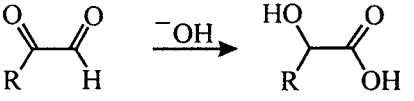


CANNIZZARO REACTION

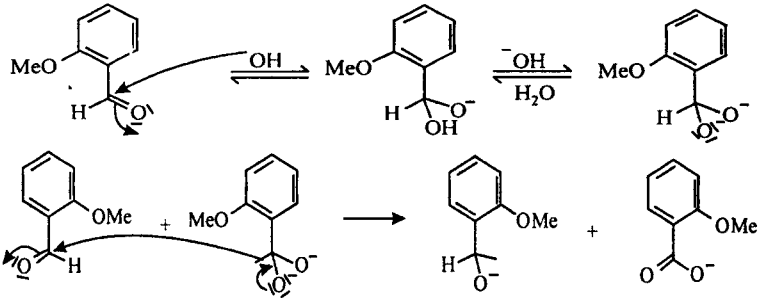


This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base.

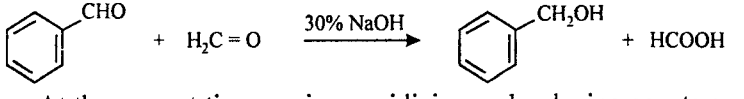
α-Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



Mechanism



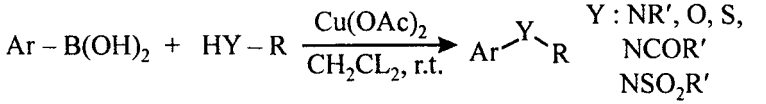
An interesting variant, the Crossed Cannizzaro Reaction, uses formaldehyde as reducing agent:



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.

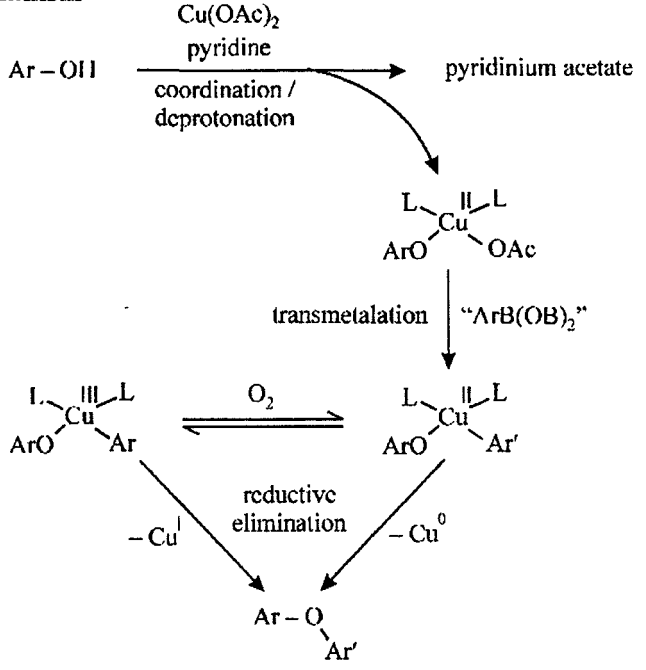
CHAN-LAM COUPLING



This reaction allows aryl carbon-heteroatom bond formation via an oxidative coupling of arylboronic acids, stannanes or siloxanes with N-H or O-H containing compounds in air. Substrates include phenols, amines, anilines, amides, imides, ureas, carbamates, and sulfonamides. The reaction is induced by a stoichiometric amount of copper(II) or a catalytic amount of copper catalyst which is reoxidized by atmospheric oxygen.

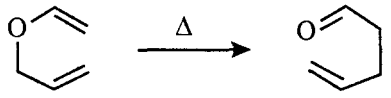
The Chan-Lam Coupling may be conducted at room temperature in air, which gives it a certain advantage over the Buchwald-Hartwig Cross Coupling.

Mechanism



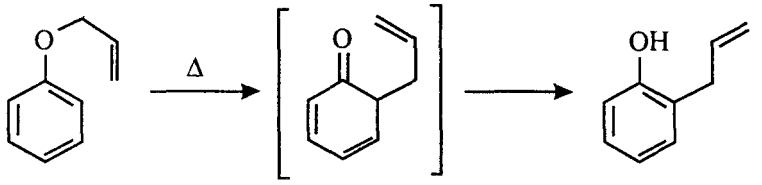
The reaction with a stoichiometric amount of copper(II) is also facilitated by oxygen, because reductive elimination from a copper(III) species is faster.

CLAISEN REARRANGEMENT



The aliphatic Claisen Rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to an unsaturated carbonyl compound.

The aromatic Claisen Rearrangement is accompanied by a rearomatization:

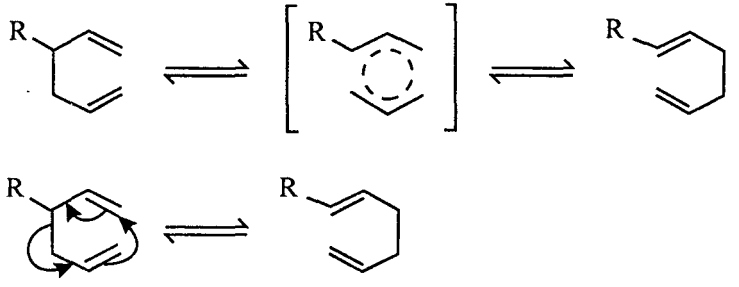


The etherification of alcohols or phenols and their subsequent Claisen Rearrangement under thermal conditions makes possible an extension of the carbon chain of the molecule.

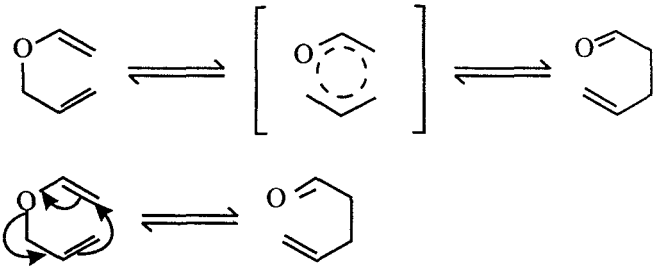
Mechanism

The Claisen Rearrangement may be viewed as the oxa-variant of the Cope Rearrangement:

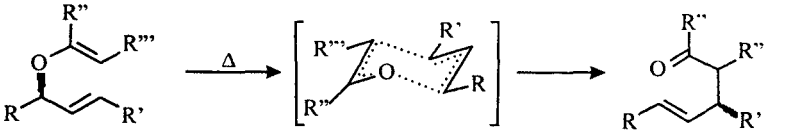
Mechanism of the Cope Rearrangement

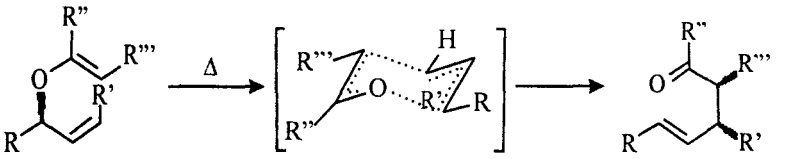


Mechanism of the Claisen Rearrangement

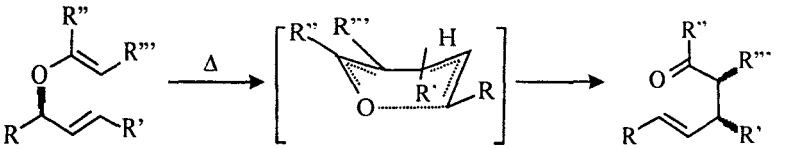


The reaction proceeds preferably *via* a chair transition state. Chiral, enantiomerically enriched starting materials give products of high optical purity.

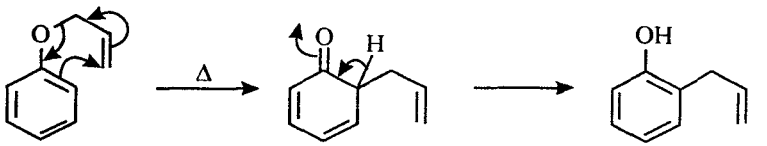




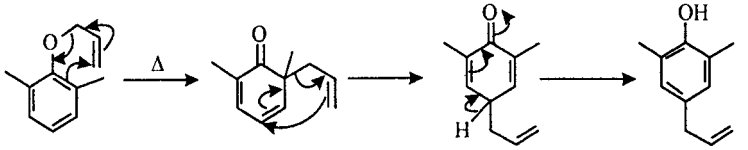
A boat transition state is also possible, and can lead to side products:



The aromatic Claisen Rearrangement is followed by a rearomatization:

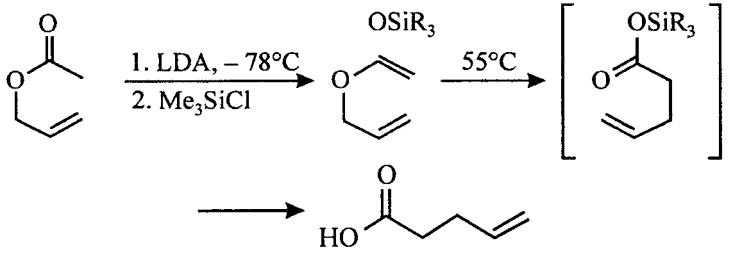


When the *ortho*-position is substituted, rearomatization cannot take place. The allyl group must first undergo a Cope Rearrangement to the *para*-position before tautomerization is possible.

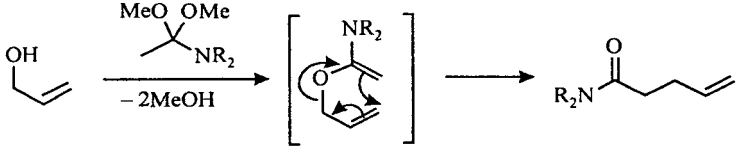


All Claisen Rearrangement reactions described to date require temperatures of > 100 °C if uncatalyzed. The observation that electron withdrawing groups at C-1 of the vinyl moiety exert a positive influence on the reaction rate and the yield has led to the development of the following variations:

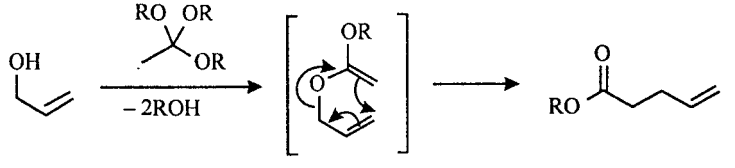
Ireland-Claisen Rearrangement



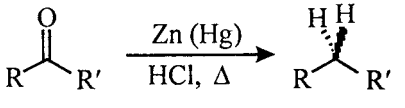
Eschenmoser-Claisen Rearrangement



Johnson-Claisen Rearrangement



CLEMMENSEN REDUCTION

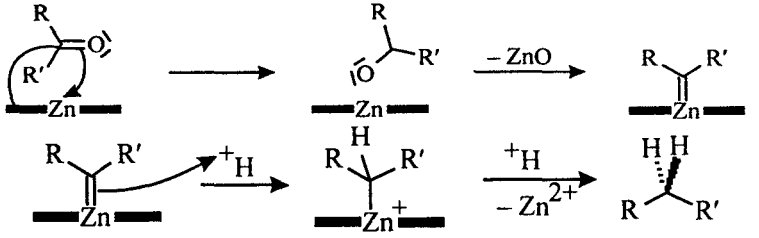


The Clemmensen Reduction allows the deoxygenation of aldehydes or ketones, to produce the corresponding hydrocarbon.

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

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:



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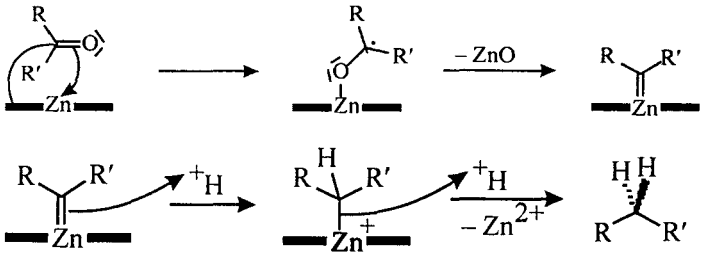
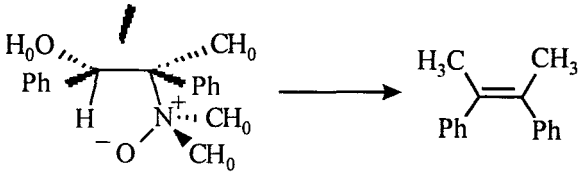
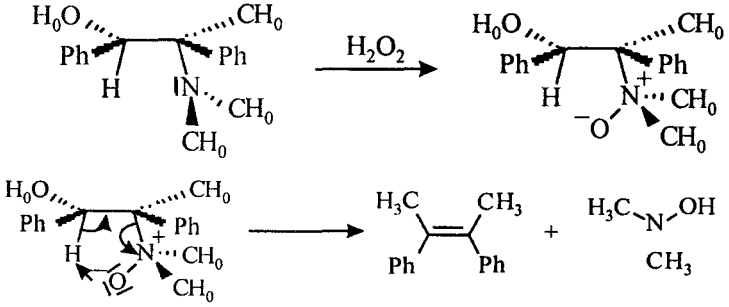


COPE ELIMINATION

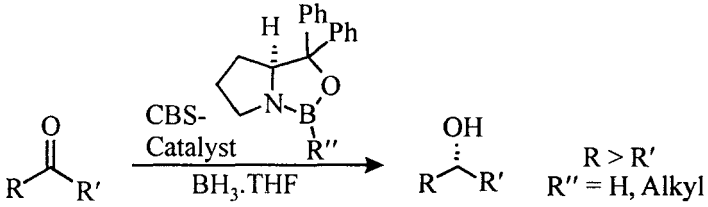


N-Oxides give alkenes via a *syn*-elimination under heating. This reaction obeys Hofmann's Rule.

Mechanism



COREY-BAKSHI-SHIBATA REDUCTION

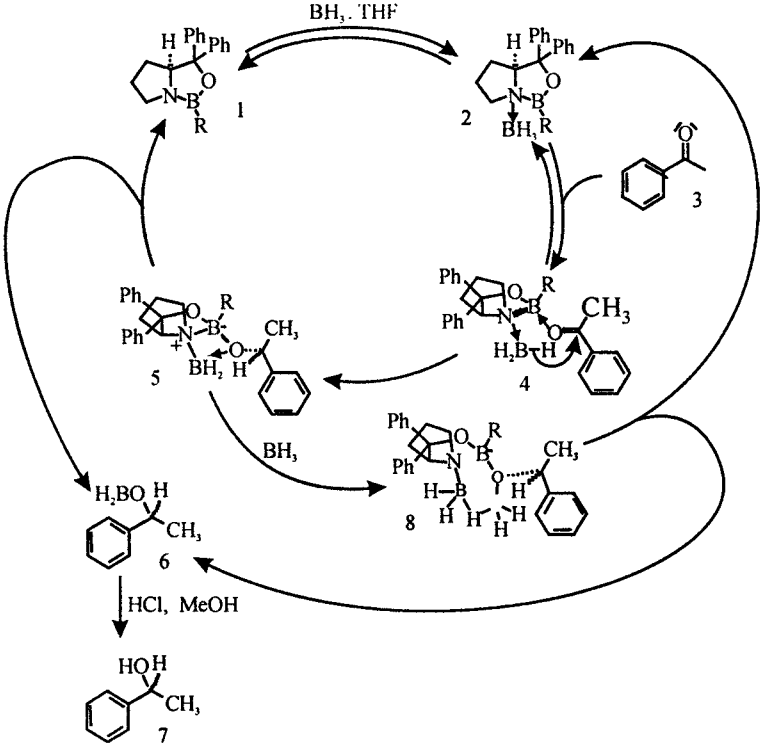


The enantioselective reduction of ketones using borane and a chiral oxazaborolidine as catalyst (CBS Catalyst). Usually, MeCBS

is used (R'' = Me, but selectivity may be increased by varying this substituent).

Mechanism

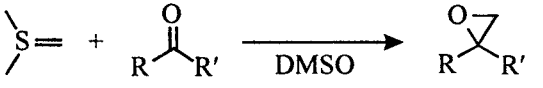
The mechanism depicted portrays the rationale for the enantioselectivity and high reaction rates, which are influenced only by the CBS catalyst. This catalyst is a combination of both a Lewis acid and a chiral auxiliary!



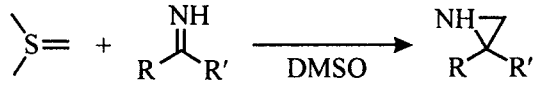
COREY-CHAYKOVSKY REACTION

The reaction of sulfur ylides with carbonyl compounds such as ketones or the related imines leads to the corresponding epoxides or aziridines.

Corey-Chaykovsky Epoxidation

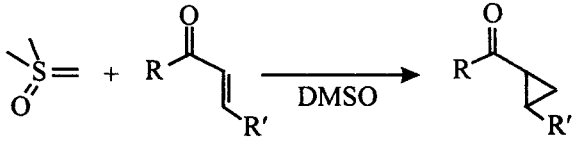


Corey-Chaykovsky Aziridination



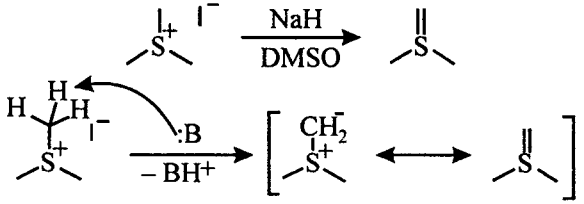
The reaction of sulfur ylides with enones gives cyclopropanes.

Corey-Chaykovsky Cyclopropanation

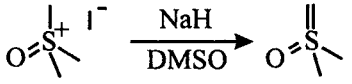


Mechanism

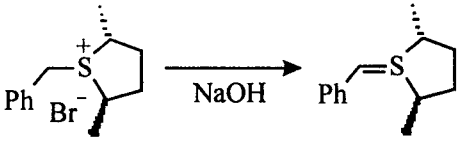
The ylides are generated *in situ* by the deprotonation of sulfonium halides with strong bases.



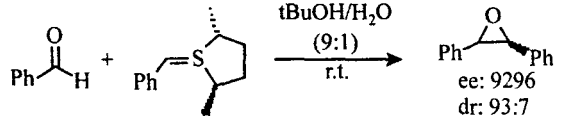
Dimethyloxosulfonium methylide - known as the Corey-Chaykovsky Reagent - is a valuable alternative to dimethylsulfonium methylide and can be generated from trimethylsulfoxonium iodide.



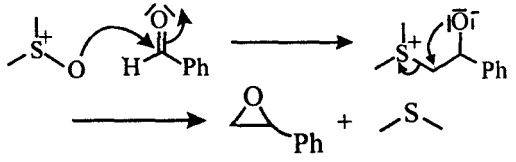
Higher substituted ylides can be generated selectively if one substituent is preferably deprotonated over the others, for example when the negative charge is stabilized or the environment is sterically less demanding:



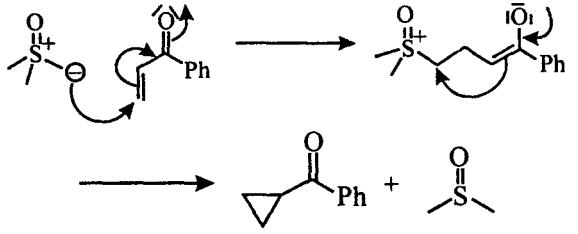
Such ylides are able to transfer more than just a methylene group, and enantioselective induction can be observed if the ylide is chiral:



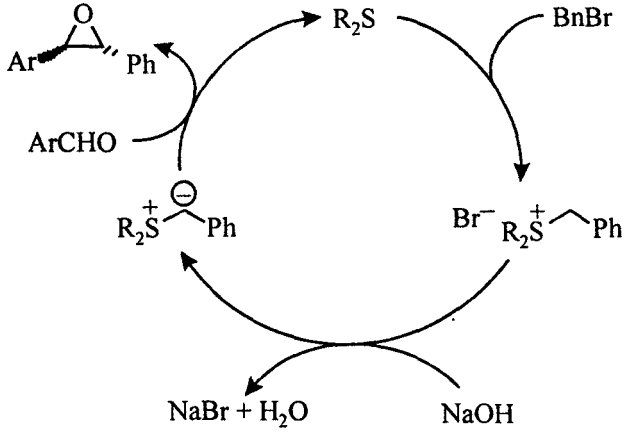
The ylide initially acts as a nucleophile toward the carbonyl compound. The resulting oxygen anion then reacts as an intramolecular nucleophile toward the now electrophilic ylide carbon, which bears a sulfonium cation as a good leaving group:



The reaction of the Corey-Chaykovsky Reagent with enones is a 1,4-addition that is followed by ring closure to give a cyclopropane:

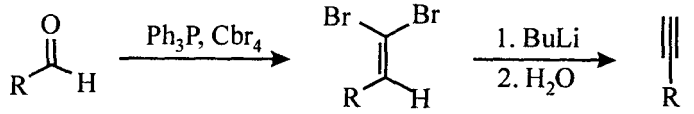


As sulfides are readily alkylated, it is even possible to use them catalytically. Such methods can give very interesting results when expensive chiral sulfides are used for the generation of chiral epoxides.



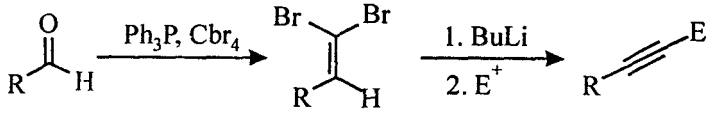
With phosphorus ylides as used for the Wittig Reaction, the phosphorus atom forms a strong double bond with oxygen. This leads the mechanism in a different direction, to effect olefination instead of epoxidation through intermediate oxaphosphetanes.

COREY-FUCHS REACTION



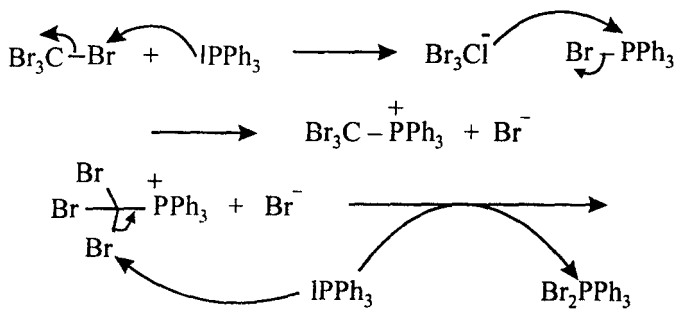
This two step methodology allows the preparation of terminal alkynes by one-carbon homologation of an aldehyde. The first step is comparable to a Wittig Reaction, and leads to a dibromoalkene. Treatment with a lithium base (BuLi, LDA) generates a bromoalkyne intermediate via dehydrohalogenation, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne upon work-up.

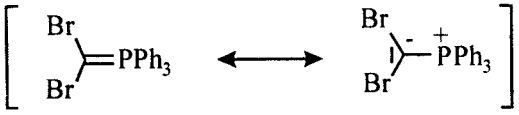
A modification of the Corey-Fuchs Reaction involves the reaction of the intermediate alkynyllithium with an electrophile prior to aqueous work-up, giving a chain extension product:



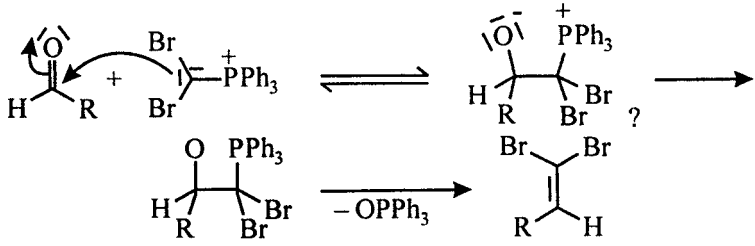
Mechanism

In the formation of the ylide from CBr_4, two equivalents of triphenylphosphine are used. One equivalent forms the ylide while the other acts as reducing agent and bromine scavenger.

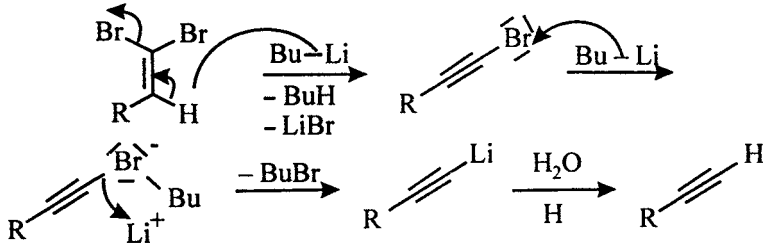




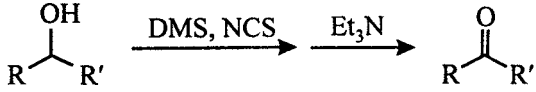
The addition of the ylide to the aldehyde:



Reaction of the dibromoalkene with BuLi:



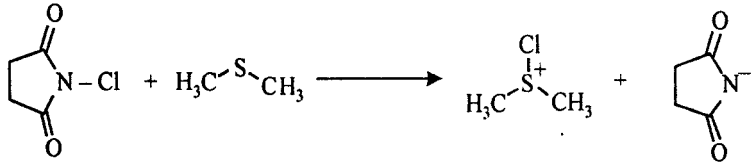
COREY-KIM OXIDATION



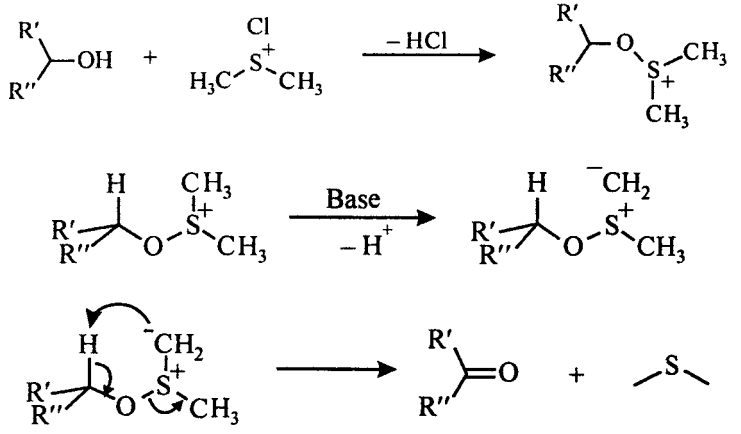
The Corey-Kim Oxidation allows the synthesis of aldehydes and ketones from primary alcohols and secondary alcohols, respectively.

Mechanism

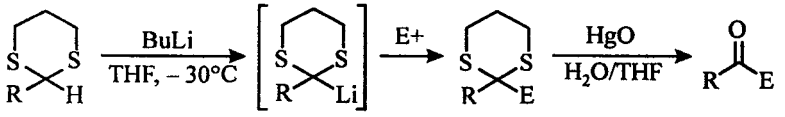
Dimethylchlorosulphonium ion is generated *in situ* from NCS and DMS:



The following steps are comparable to the Swern Oxidation:



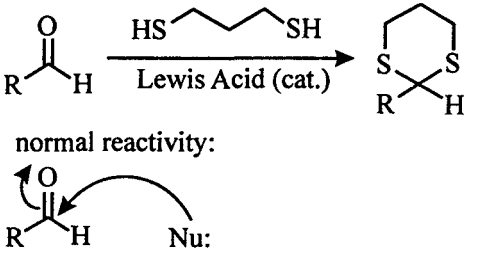
COREY-SEEBACH REACTION

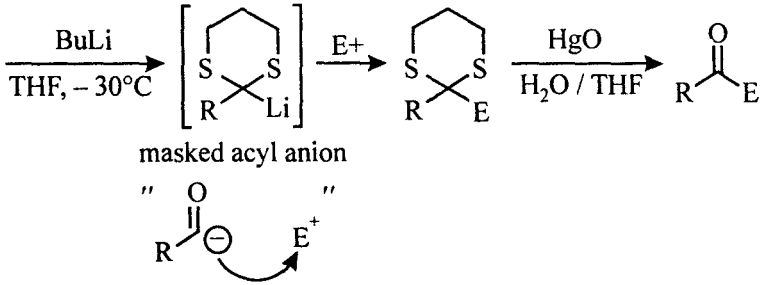


The Corey-Seebach Reaction (or Seebach Umpolung) uses lithiated 1,3-dithianes as nucleophilic acylating agents.

Mechanism

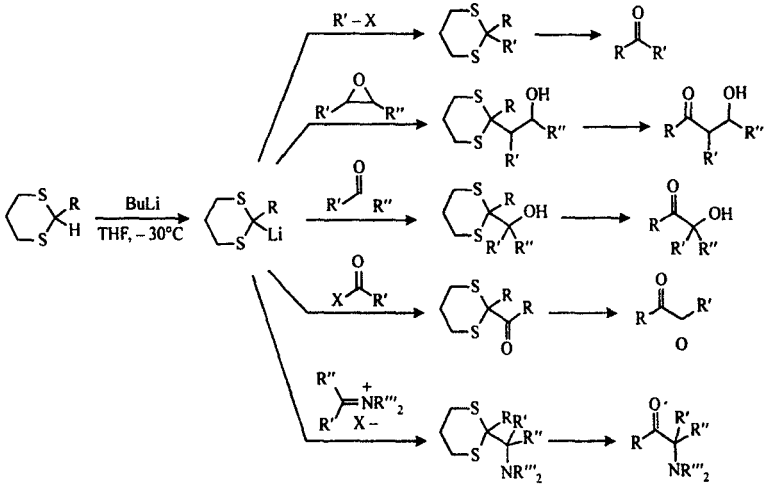
The Corey-Seebach Reaction allows a reversal of the normal reactivity of acyl carbon atoms, which combine only with nucleophiles. The German term "Umpolung" is widely used for this inversion of reactivity.





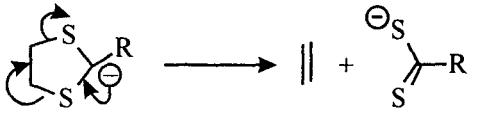
The lithiated 1,3-dithiane can be viewed as an masked acyl anion that is able to react with various electrophiles.

The acidity difference of hydrogen atoms adjacent to divalent sulfur compared to oxygen stems from the greater polarizability of sulfur and the longer C-S-bond length; d-orbitals are not involved. In most cases treatment of dithianes with *n*-BuLi at temperatures of -30 °C is sufficient for the preparation of the lithio-derivatives. With pK_A values of approximately 30, lithiated dithianes can react with aldehydes or ketones, epoxides and acid derivatives, but also with alkyl halides without competing elimination reactions.



Umpolung offers access to a wide range of products, especially 1,2-diketones and α-hydroxy ketones, products that cannot be obtained using the normal reactivity.

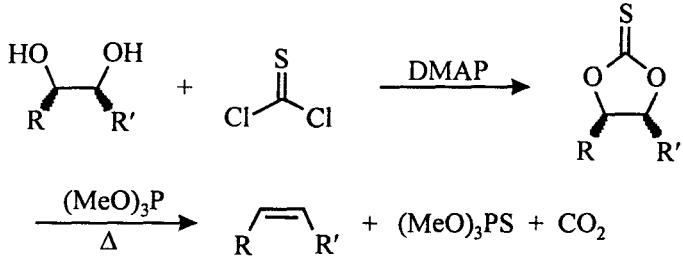
Among the other thioacetals that could be used for Umpolung, metallated dithiolanes undergo fragmentation and disproportionate to ethene and dithiocarboxylates:



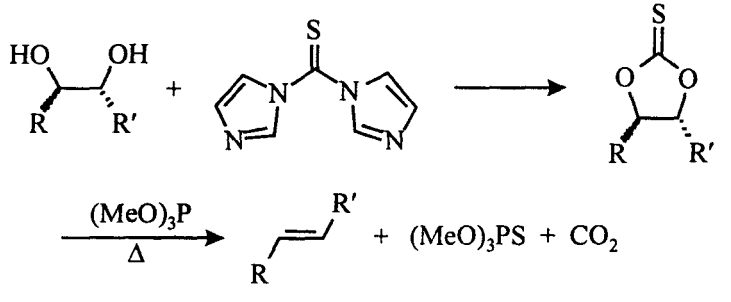
1,3-Dithianes are readily prepared from aldehydes (for an overview, see 1,3-dithianes as protecting group) and offer high stability towards acids and bases. Therefore, use of the S,S-acetal unit is especially useful in multistep synthesis. A crucial step is the hydrolysis of S,S-acetals, the difficulty of which is due to the excellent nucleophilicity of sulfur.

Only irreversible removal of the dithiol or of the solvolysis products can push the equilibrium to the right. Methods of choice are transacetalization to a highly reactive carbonyl derivative, alkylation to sulfide, oxidation of the thiol and formation of metal thiolates, for which mercury(II) salts are frequently used.

COREY-WINTER OLEFIN SYNTHESIS

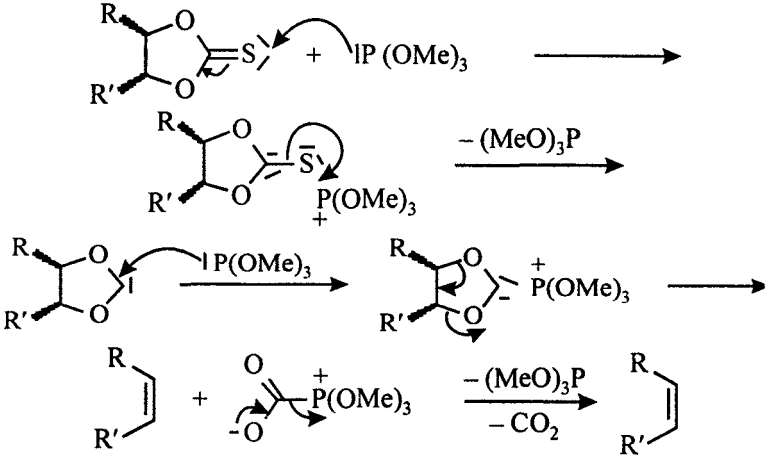


Conversion of 1,2-diols to alkenes. The cyclic thiocarbonate is available from reaction of the diol with thiophosgene or thiocarbonyldiimidazole, and reacts with added trimethylphosphite via a *syn*-elimination to the alkene.

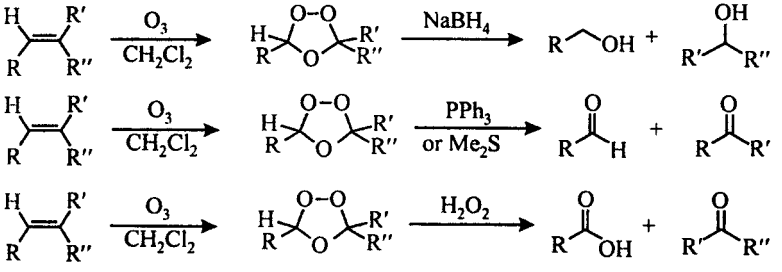


Mechanism

It is assumed that the reaction proceeds with attack of phosphite on sulphur leading to a carbene, which may react with a second equivalent of phosphite during the cycloreversion that splits out carbon dioxide and yields the product alkene.



CRIEGEE MECHANISM

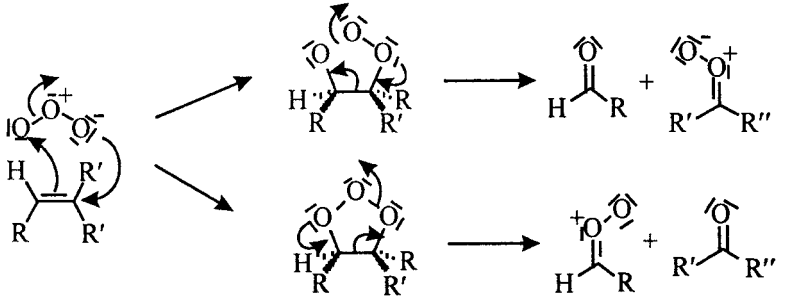


Ozonolysis allows the cleavage of alkene double bonds by reaction with ozone. Depending on the work up, different products may be isolated: reductive work-up gives either alcohols or carbonyl compounds, while oxidative work-up leads to carboxylic acids or ketones.

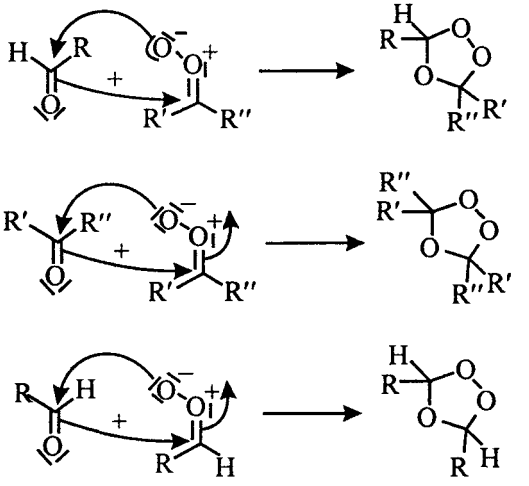
Mechanism

The mechanism was suggested by Criegee and has been recently revisited using ^{17}O-NMR Spectroscopy by the Berger Group.

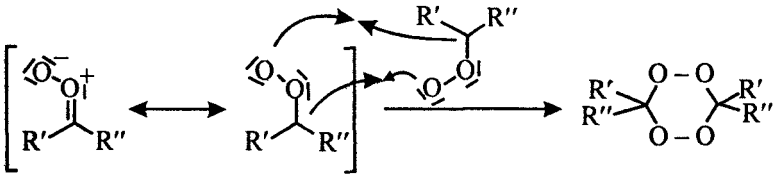
First step is a 1,3-dipolar cycloaddition of ozone to the alkene leading to the primary ozonide (molozonide, 1,2,3-trioxolane, or Criegee intermediate) which decomposes to give a carbonyl oxide and a carbonyl compound:



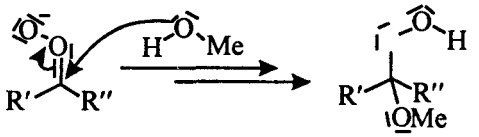
The carbonyl oxides are similar to ozone in being 1,3-dipolar compounds, and undergo 1,3-dipolar cycloaddition to the carbonyl compounds with the reverse regiochemistry, leading to a mixture of three possible secondary ozonides (1,2,4-trioxolanes):



These secondary ozonides are more stable than primary ozonides. Even if the peroxy bridge is shielded by steric demanding groups leading to isolable products, they should not be isolated from an unmodified ozonolysis, because still more explosive side products (tetroxanes) may have been formed:

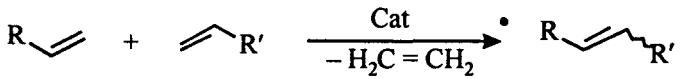


As endoperoxides are investigated as antimalarial compounds, more selective methods have been developed for their preparation (for example the Griesbaum Coozonolysis). The Criegee mechanism is valid for reactions in hydrocarbons, CH_2Cl_2, or other non-interactive solvents. Alcohols react with the carbonyl oxide to give hydroperoxy hemiacetals:



The synthetic value lies in the way the complex mixtures of intermediates can be worked up to give a defined composition of products and a clean conversion of all peroxide species. The three main possibilities are given above, along with examples for the reagents used.

CROSS METATHESIS



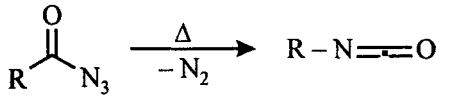
The transalkylidenation of two terminal alkenes under release of ethene, catalyzed by ruthenium carbenoids (Grubbs Catalyst). Statistically, the reaction can lead to three possible pairs of geometric isomers, i.e. *E/Z* pairs for two homocouplings and the cross-coupling (R-CH=CH-R, R'-CH=CH-R', and R-CH=CH-R') - a total of 6 products.

The selectivity of this reaction is currently undergoing further study, but various examples exist in which two alkenes with different reactivity give the cross-coupled product with excellent yields and excellent selectivity.

Mechanism

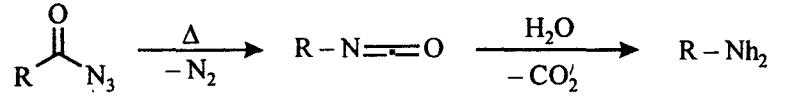
Same as Olefin Metathesis (or Grubbs Reaction).

CURTIUS REARRANGEMENT



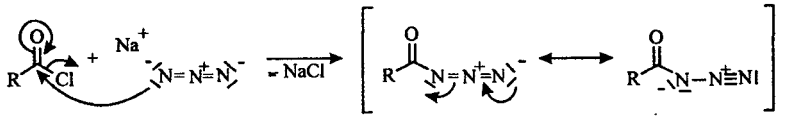
The Curtius Rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.

The reaction sequence - including subsequent reaction with water which leads to amines - is named the Curtius Reaction. This reaction is similar to the Schmidt Reaction with acids, differing in that the acyl azide in the present case is prepared from the acyl halide and an azide salt.

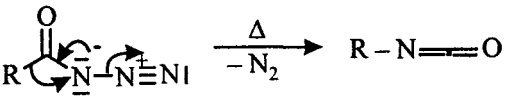


Mechanism

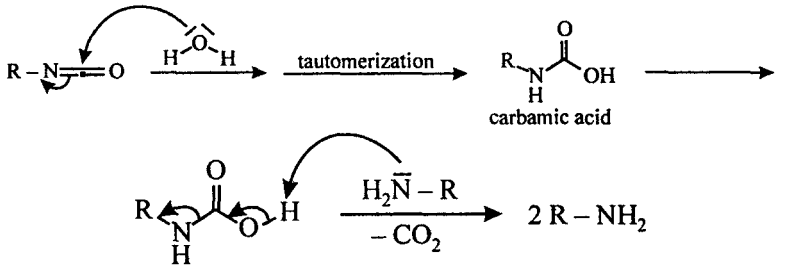
Preparation of azides:



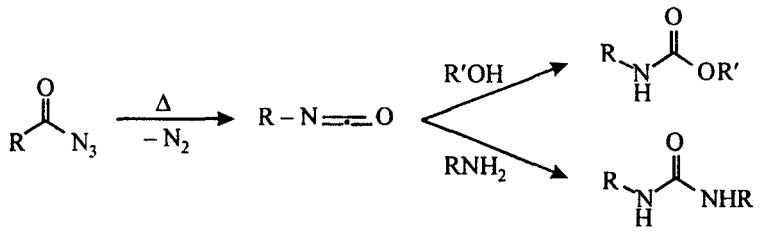
Decomposition:



Reaction with water to the unstable carbamic acid derivative which will undergo spontaneous decarboxylation:

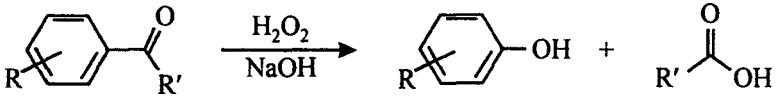


Isocyanates are versatile starting materials:



Isocyanates are also of high interest as monomers for polymerization work and in the derivatisation of biomacromolecules.

DAKIN REACTION



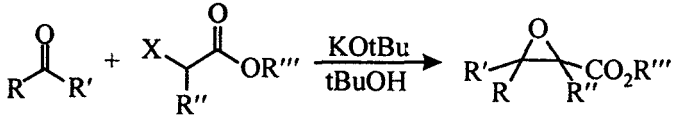
The Dakin Reaction allows the preparation of phenols from aryl aldehydes or aryl ketones via oxidation with hydrogen peroxide in the presence of base. The aryl formate or alkanoate formed as an intermediate is subsequently saponified to yield the substituted phenol product.

Ortho or *para* +M substituents (NH_2, OH) favour this reaction.

Mechanism

Same as Baeyer-Villiger Oxidation for the oxidation step.

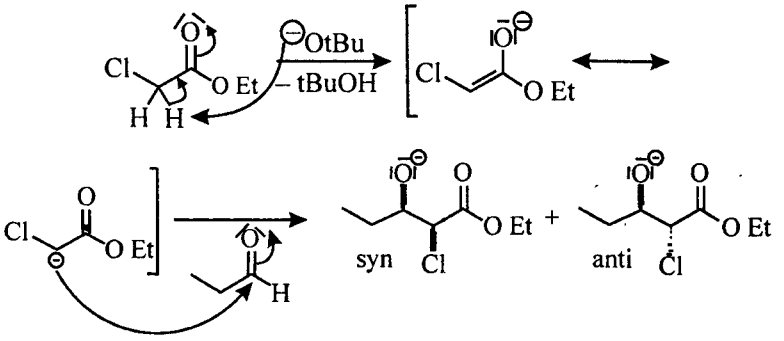
DARZENS CONDENSATION



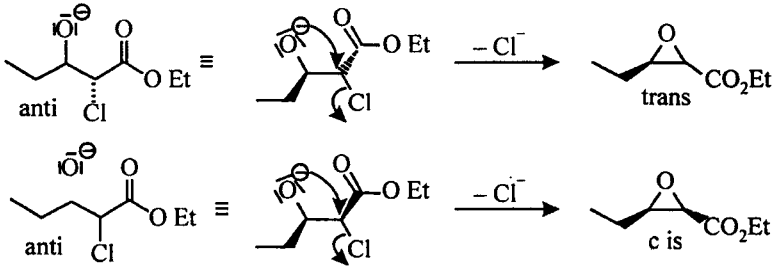
The Darzens Reaction is the condensation of a carbonyl compound with an α-halo ester in the presence of a base to form an α,β-epoxy ester.

Mechanism

After deprotonation, the α-halo ester adds to the carbonyl compound to give *syn* and *anti* diastereomers:

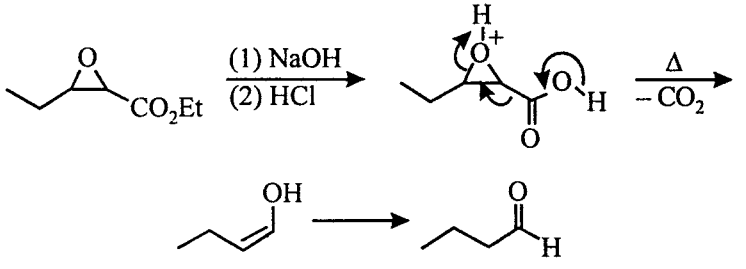


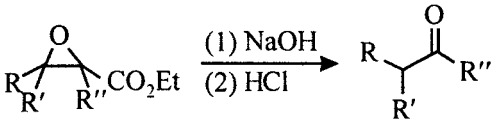
In the subsequent step, an intramolecular S_N2 reaction forms the epoxide:



Typically, the *cis:trans* ratio of the epoxide formation lies between 1:1 and 1:2.

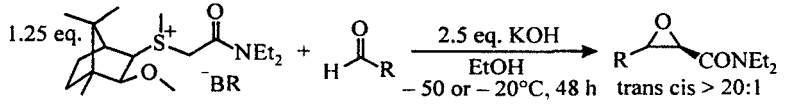
In the past, Darzens methodology was primarily used for the synthesis of aldehydes and ketones, as a homologation reaction without any consideration of stereocontrol in the epoxide formation. For this sequence, saponification of the α,β-epoxy ester followed by decarboxylation gives the substituted carbonyl compound:



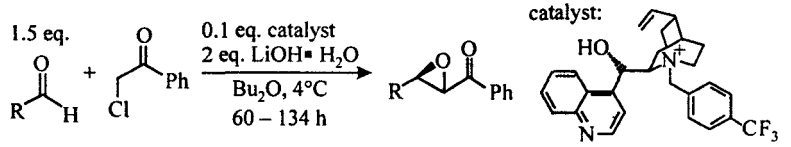


Darzens methodology for the construction of epoxides can also be used for α-halo carbonyl compounds, or similar compounds that can undergo deprotonation and bear electron-withdrawing groups. In addition, the reaction can be carried out with diazoacetate, where N_2 is the leaving group, or with a sulphur ylide with SR_2 as the leaving group.

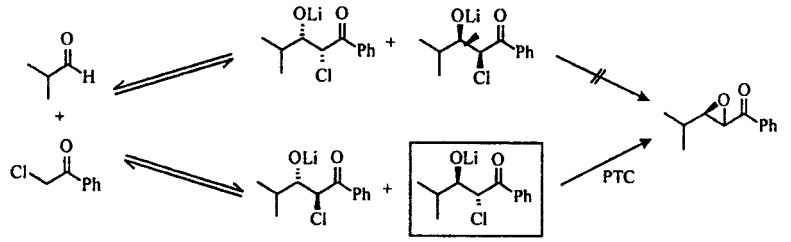
In the following specific substitution pattern, the outcome of the reaction depends on the energy of the transition states of the addition, the rotation and the ring closure, as described by Aggarwal. Although explanations for the diastereoselectivity have been given, the enantioselectivity that is induced by the camphor-derived sulphonium group is not yet fully understood:



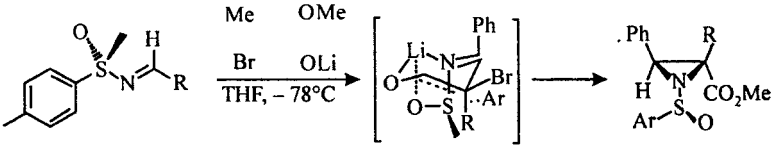
Another concept for highly diastereoselective and enantioselective transformations was developed by Arai:



In this system, the chiral phase transfer catalyst (PTC) is able to recognize one aldolate selectively. There is an equilibrium between *syn*- and *anti*-aldolates via retro-aldol addition, and the formation of a stable, chelated lithium salt blocks the non-catalyzed subsequent reaction from yielding the epoxide product:

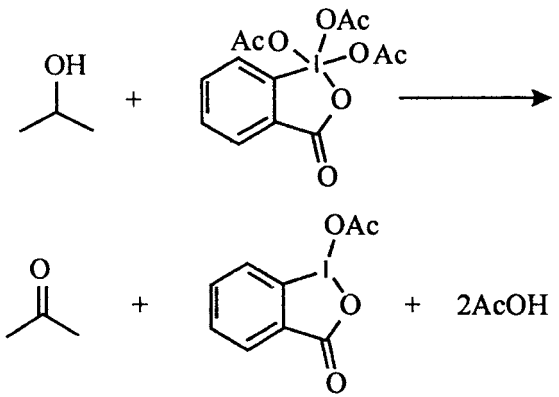


The following aza-Darzens reaction, in which a preformed lithium α-bromoenolate reacts with a sulphinimine to give an aziridine, features a six-membered transition state that accounts for the high diastereoselectivity:



The development of enantioselective methods remains challenging. In principle, any of the methods that are used for stereoselective aldol additions can also be tested in the Darzens Reaction, as the first step is an aldol addition.

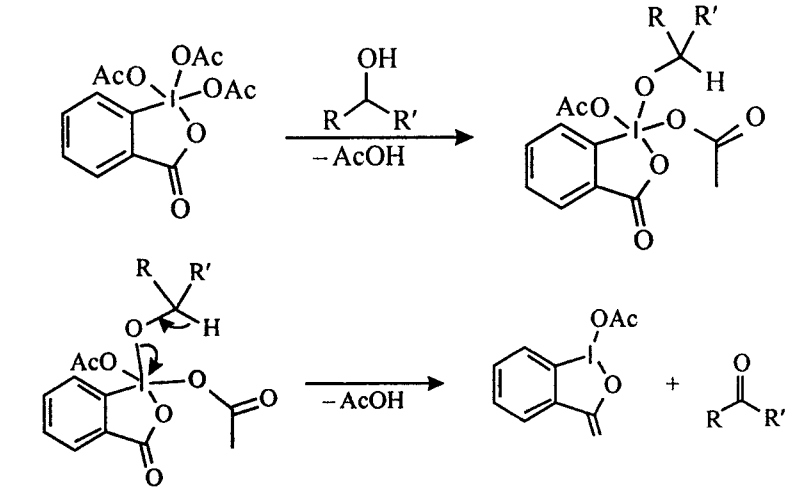
DESS-MARTIN OXIDATION



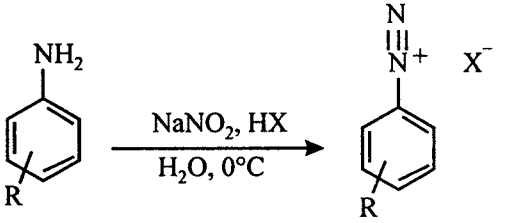
The Dess-Martin Periodinane (DMP), a hypervalent iodine compound, offers selective and very mild oxidation of alcohols to aldehydes or ketones.

The oxidation is performed in dichloromethane or chloroform at room temperature, and is usually complete within 0.5 - 2 hours. Products are easily separated from the iodo-compound byproduct after basic work-up.

Mechanism



DIAZOTISATION

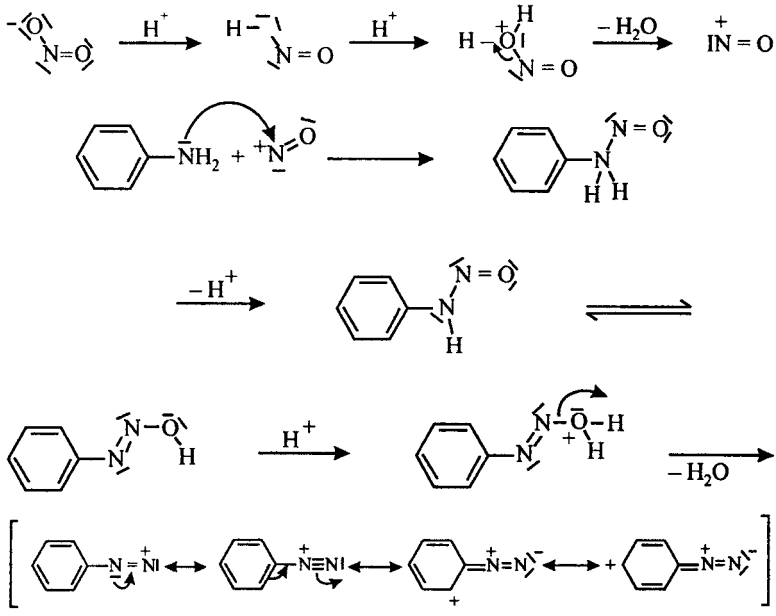


The nitrosation of primary aromatic amines with nitrous acid (generated in situ from sodium nitrite and a strong acid, such as hydrochloric acid, sulfuric acid, or HBF_4) leads to diazonium salts, which can be isolated if the counterion is non-nucleophilic.

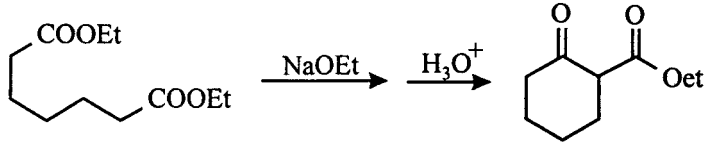
Diazonium salts are important intermediates for the preparation of halides, and azo compounds. Diazonium salts can react as pseudohalide-type electrophiles, and can therefore be used in specific protocols for the Heck Reaction or Suzuki Coupling.

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



DIECKMANN CONDENSATION



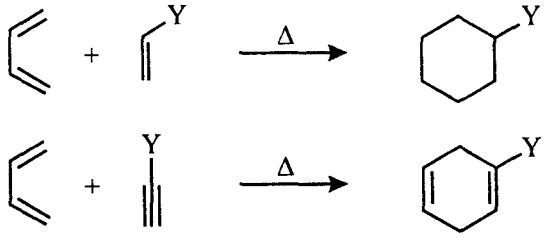
The base-catalyzed intramolecular condensation of a diester. The Dieckmann Condensation works well to produce 5- or 6-membered cyclic ĺ-keto esters, and is usually effected with sodium alkoxide in alcoholic solvent.

The yields are good if the product has an enolizable proton; otherwise, the reverse reaction (cleavage with ring scission) can compete.

Mechanism

Same as The mechanism is similar to the Claisen Condensation.

DIELS-ALDER REACTION



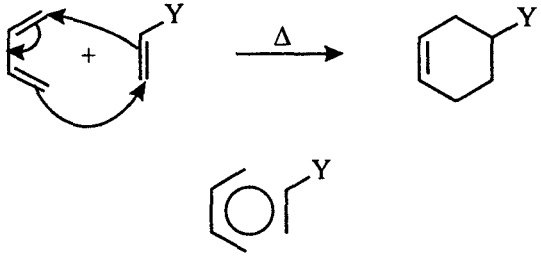
The [4+2]-cycloaddition of a conjugated diene and a dienophile (an alkene or alkyne), an electrocyclic reaction that involves the 4 π-electrons of the diene and 2 π-electrons of the dienophile. The driving force of the reaction is the formation of new σ-bonds, which are energetically more stable than the π-bonds.

In the case of an alkynyl dienophile, the initial adduct can still react as a dienophile if not too sterically hindered. In addition, either the diene or the dienophile can be substituted with cumulated double bonds, such as substituted allenes.

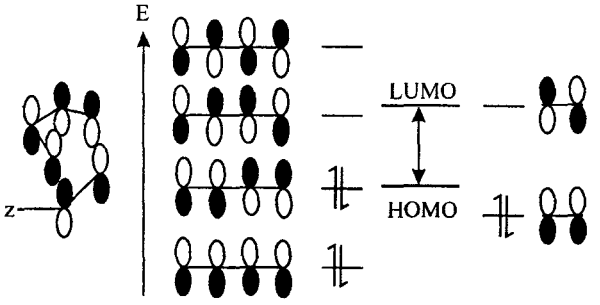
With its broad scope and simplicity of operation, the Diels-Alder is the most powerful synthetic method for unsaturated six-membered rings.

A variant is the hetero-Diels-Alder, in which either the diene or the dienophile contains a heteroatom, most often nitrogen or oxygen. This alternative constitutes a powerful synthesis of six-membered ring heterocycles.

Mechanism

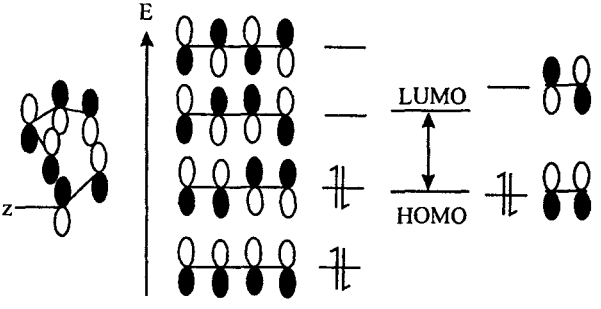


Overlap of the molecular orbitals (MOs) is required:

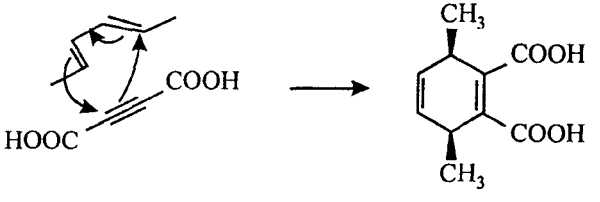


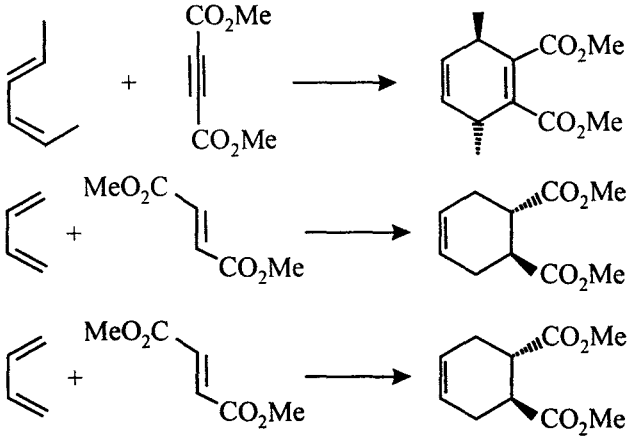
Overlap between the highest occupied MO of the diene (HOMO) and the lowest unoccupied MO of the dienophile (LUMO) is thermally allowed in the Diels Alder Reaction, provided the orbitals are of similar energy. The reaction is facilitated by electron-withdrawing groups on the dienophile, since this will lower the energy of the LUMO. Good dienophiles often bear one or two of the following substituents: CHO, COR, COOR, CN, C=C, Ph, or halogen. The diene component should be as electron-rich as possible.

There are "inverse demand" Diels Alder Reactions that involve the overlap of the HOMO of the dienophile with the unoccupied MO of the diene. This alternative scenario for the reaction is favoured by electron-donating groups on the dienophile and an electron-poor diene.

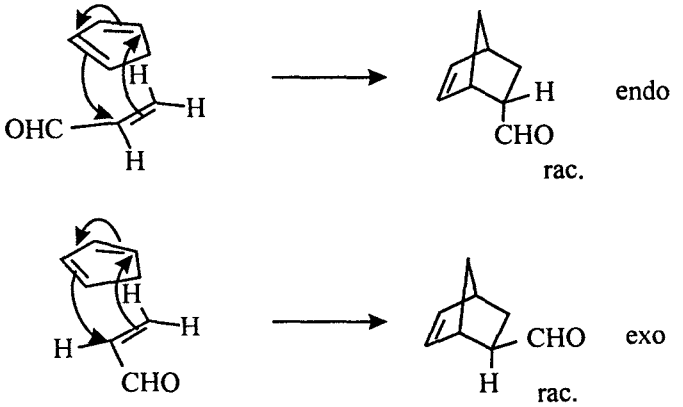


The reaction is diastereoselective.

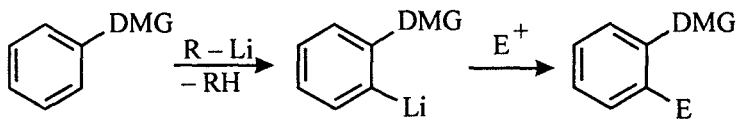




Cyclic dienes give stereoisomeric products. The endo product is usually favoured by kinetic control due to secondary orbital interactions.



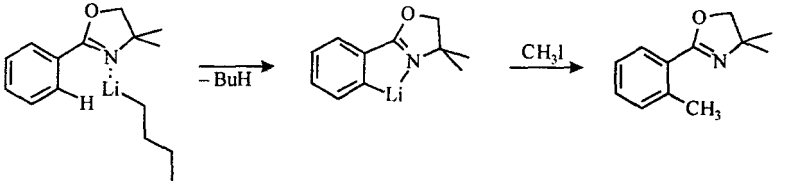
DIRECTED *ORTHO* METALATION



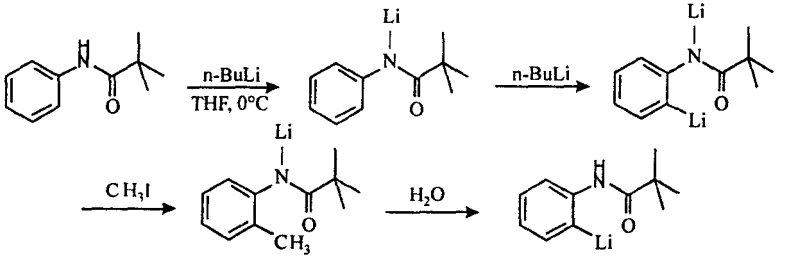
The reaction of an alkyllithium compound with an arene bearing a "Directed Metalation Group" (DMG) normally leads to an *ortho*-metalated intermediate. Good DMG's are strong complexing or chelating groups that have the effect of increasing the kinetic acidity of protons in the *ortho*-position.

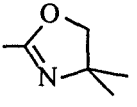
The ortho-metalated intermediate can be reacted with a variety of electrophiles, after which the DMG can be retained if desired, converted to a different functional group; or in some cases removed.

Mechanism

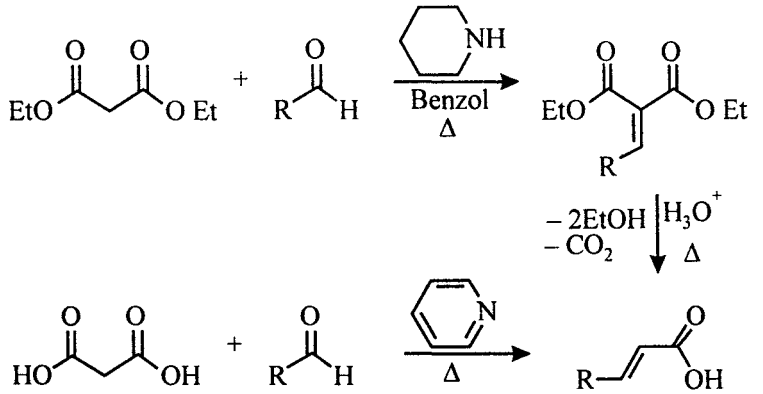


The DMG does not necessarily have to be inert:



Strong DMGs:	$-CON^{-}R$, $-CONR_2$,	$-N^{-}COR$, $-N^{-}CO_2R$
		$-OCONR_2$, $-OMOM$
		$-SO_3R$
	$-CH = NR$	$-SO_2NR_2$
	$-CN$	$-SO_2tBu$
moderate	$-CF_3$	$-NR_2$
		$-NC$
		$-OMe$
		$-F$
		$-Cl$
weak	$-CH_2O^{-}$	$-O^{-}$
	$-CC^{-}$	$-S^{-}$
	Ph	

DOEBNER MODIFICATION

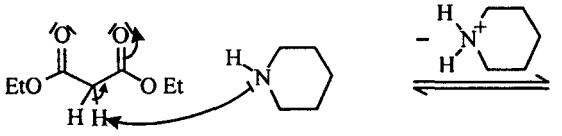


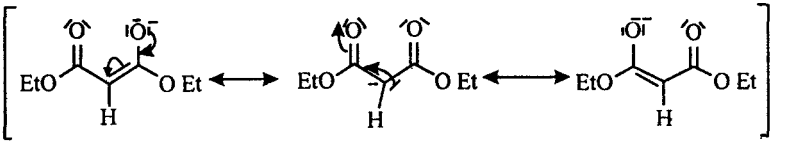
The condensation of carbon acid compounds with aldehydes to afford α,β-unsaturated compounds.

The Doebner Modification (or Knoevenagel Condensation), which is possible in the presence of carboxylic acid groups, includes a pyridine-induced decarboxylation.

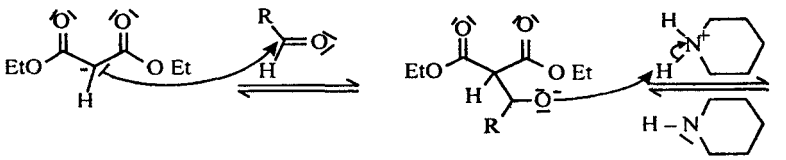
Mechanism

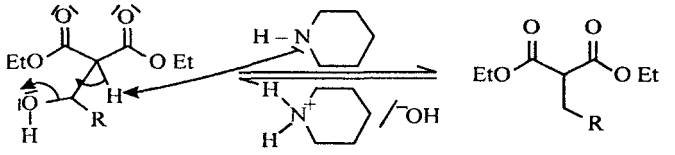
An enol intermediate is formed initially:



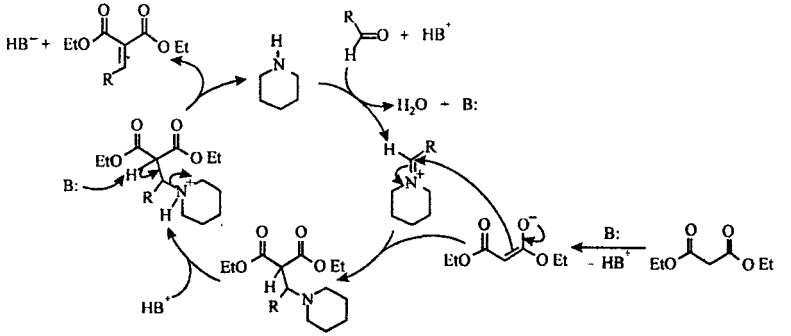


This enol reacts with the aldehyde, and the resulting aldol undergoes subsequent base-induced elimination:

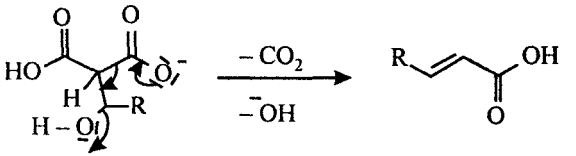




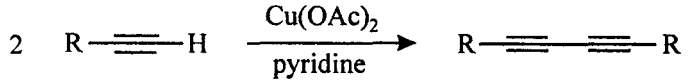
A reasonable variation of the mechanism, in which piperidine acts as organocatalyst, involves the corresponding iminium intermediate as the acceptor:



The Doebner-Modification in refluxing pyridine effects concerted decarboxylation and elimination:

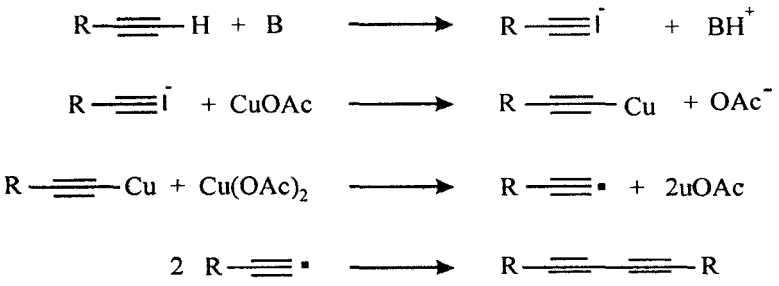


EGLINTON REACTION



The Eglinton Reaction is an oxidative coupling of terminal alkynes, and allows the synthesis of symmetric or cyclic bisacetylenes via reaction of the terminal alkyne with a stoichiometric amount of a copper(II) salt in pyridine.

Mechanism

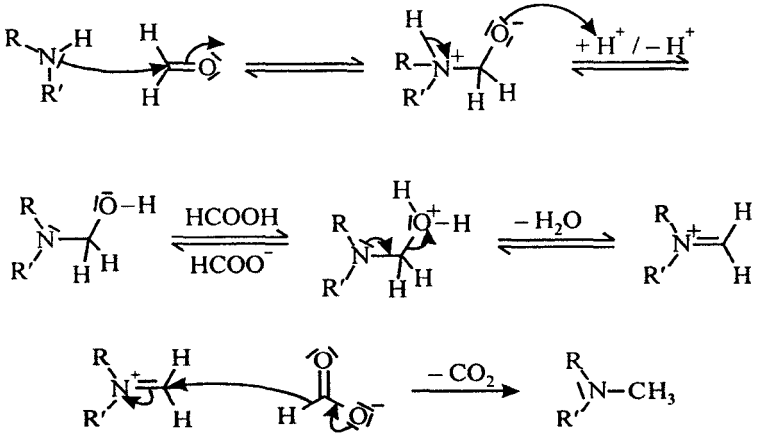


ESCHWEILER-CLARKE REACTION

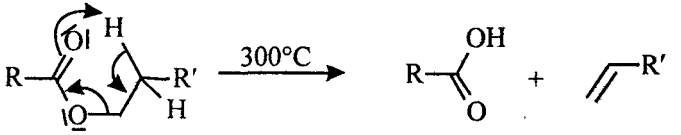
$$R_2N-H \;+\; CH_2=O \xrightarrow[-CO_2]{HCOOH} R_2N-CH_3 \;+\; H_2O$$

This reaction allows the preparation of tertiary methylamines from secondary amines via treatment with formaldehyde in the presence of formic acid. The formate anion acts as hydride donor to reduce the imine or iminium salt, so that the overall process is a reductive amination. The formation of quaternary amines is not possible.

Mechanism

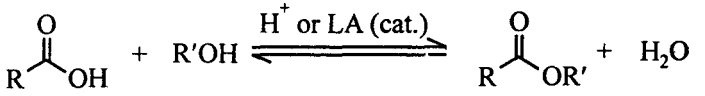


ESTER PYROLYSIS



Ester Pyrolysis is a *syn*-elimination yielding an alkene, similar to the Cope Elimination, for which ĺ-hydrogens are needed. The carboxylic acid corresponding to the ester is a byproduct.The cyclic transition state can only be achieved if the steric environment is not too demanding.

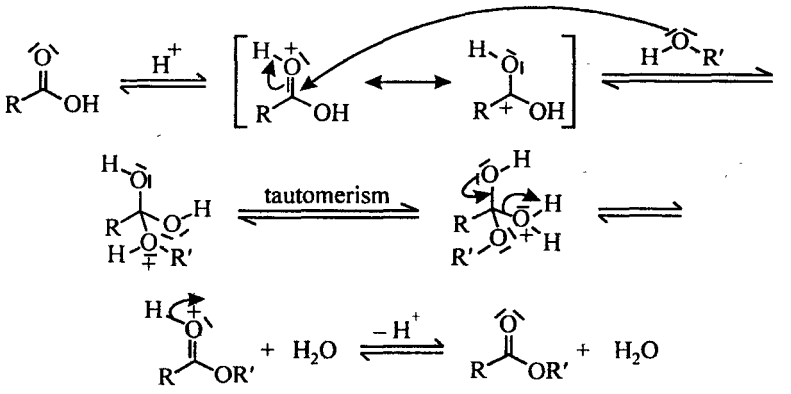
FISCHER-SPEIER ESTERIFICATION



The Lewis or Brψnstedt acid-catalyzed esterification of carboxylic acids with alcohols to give esters is a typical reaction in which the products and reactants are in equilibrium.

The equilibrium may be influenced by either removing one product from the reaction mixture (for example, removal of the water by azeotropic distillation or absorption by molecular sieves) or by employing an excess of one reactant.

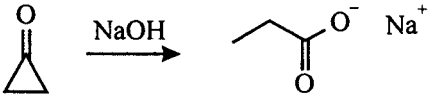
Mechanism



Addition of a proton (e.g.: *p*-TsOH, H_2SO_4) or a Lewis acid leads to a more reactive electrophile. Nucleophilic attack of the alcohol gives a tetrahedral intermediate in which there are two equivalent hydroxyl groups. One of these hydroxyl groups is eliminated after a proton shift (tautomerism) to give water and the ester.

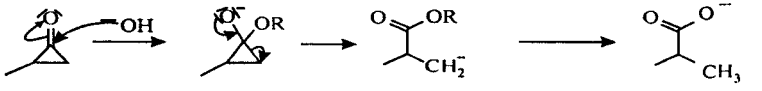
Alternative reactions employ coupling reagents such as DCC (Steglich Esterification), preformed esters (transesterification), carboxylic acid chlorides or anhydrides. These reactions avoid the production of water. Another pathway for the production of esters is the formation of a carboxylate anion, which then reacts as a nucleophile with an electrophile (similar reactions can be found here). Esters may also be produced by oxidations, namely by the Baeyer-Villiger oxidation and oxidative esterifications.

FAVOURSKII REACTION

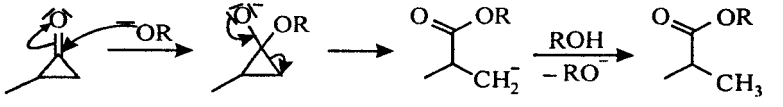


The rearrangement of cyclopropanones, often obtained as intermediates from the base-catalyzed reaction of α-halo ketones, leading to carboxylic acids and derivatives.

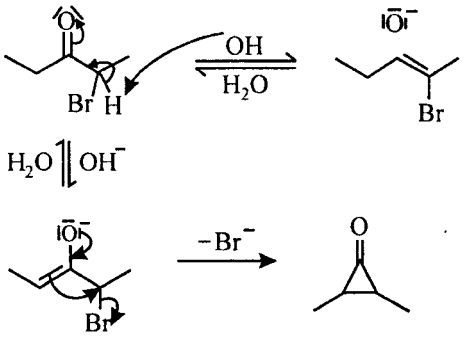
Mechanism



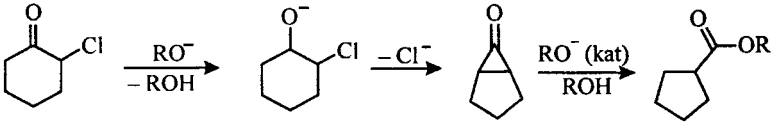
Esters are obtained if alkoxide bases are used:



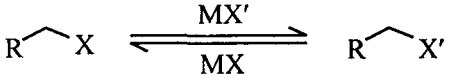
A direct conversion from α-halo ketones is possible:



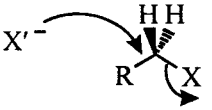
Ring-contraction:



FINKELSTEIN REACTION

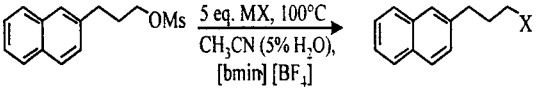


Treatment of a primary alkyl halide or pseudohalide with an alkali metal halide (e.g. KF, KI) leads to replacement of the halogen via an S_N2 Reaction.



Mechanism

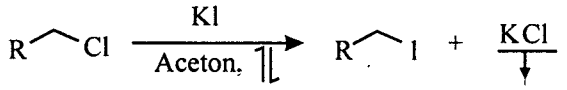
The equilibrium position of the reaction depends on the nucleophilicity of the anion, whether a good leaving group is present, and whether one anion is better stabilized than the other in a given solvent. For example, reactions with KF will thus lead cleanly to fluoroalkanes, because fluoride is such a poor leaving group due to the stability of the C-F bond.



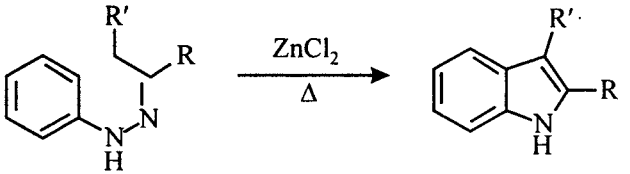
MX	t(min)	yield (%, isol.)
KF	90	93
CsF	20	95
Kcl	30	95
Kbr	30	96
KI	15	96

In general, the reaction is run with an excess of the metal halide. The use of metal salts that have a high lattice energy require the addition of a crown ether.

The equilibrium position of the reaction also depends on the solubility of the metal salt in the solvent used. Thus, the substitution of bromo- and chloroalkanes with KI in acetone leads cleanly to the desired iodoalkane products, since KCl and KBr are insoluble in acetone and are consequently removed from the equilibrium:

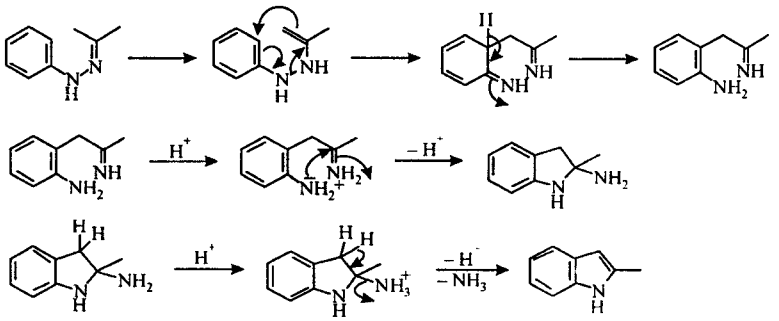


FISCHER INDOLE SYNTHESIS

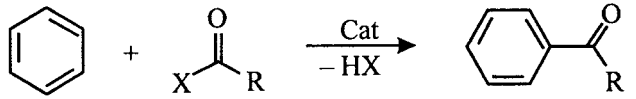


The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brψnsted or Lewis acids. For example a milder conversion when *N*-trifluoroacetyl enehydrazines are used as substrates.

Mechanism



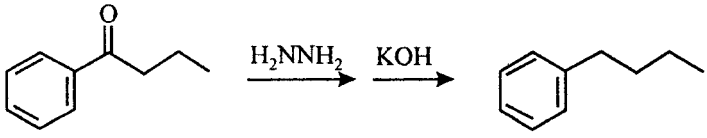
FRIEDEL-CRAFTS ACYLATION



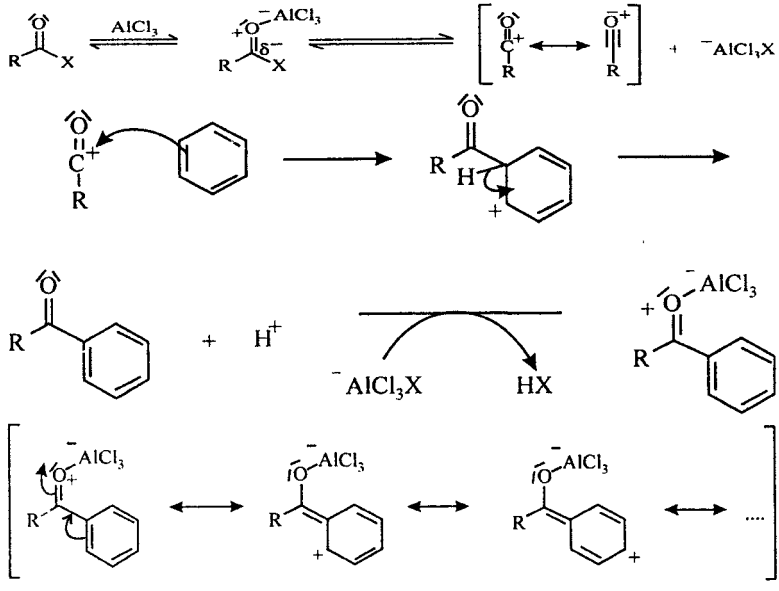
X = Cl or RCOO

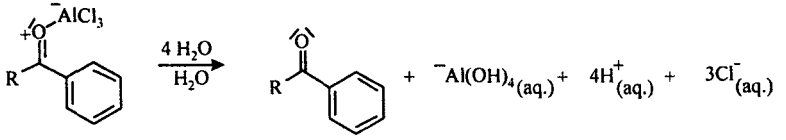
This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. The products are deactivated, and do not undergo a second substitution. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because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

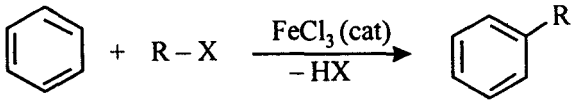


Mechanism



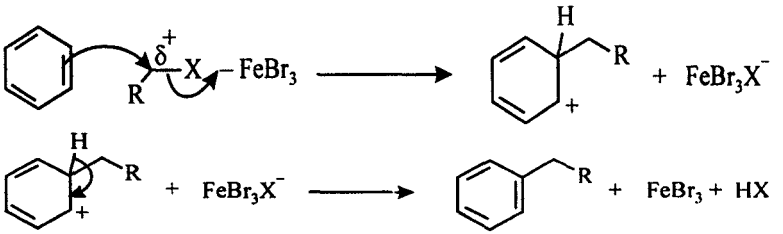


FRIEDEL-CRAFTS ALKYLATION

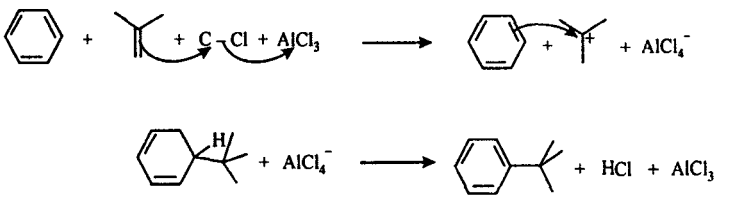


This Lewis acid-catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts Acylation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

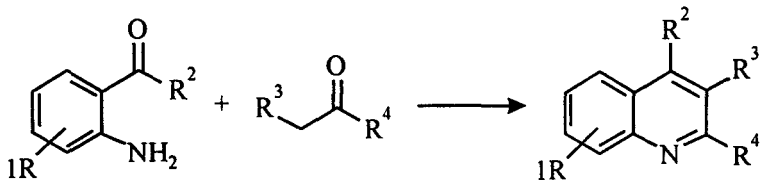
Mechanism



Using alkenes:

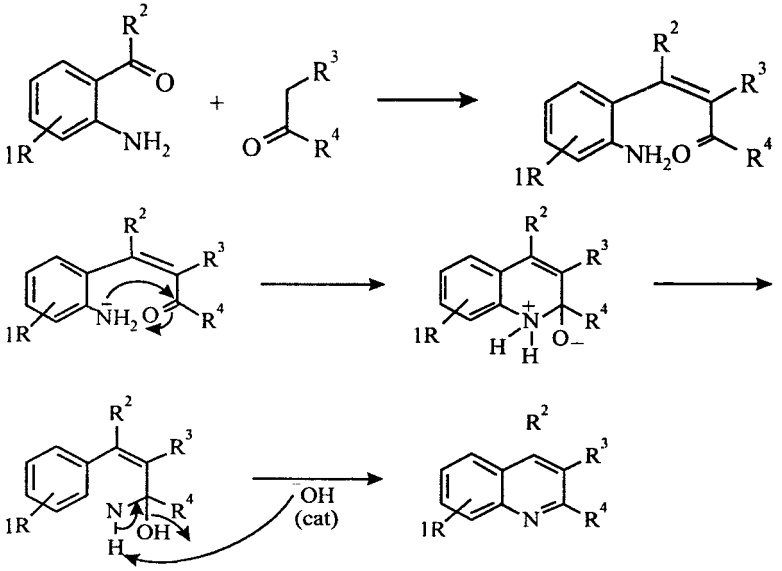


FRIEDLAENDER SYNTHESIS

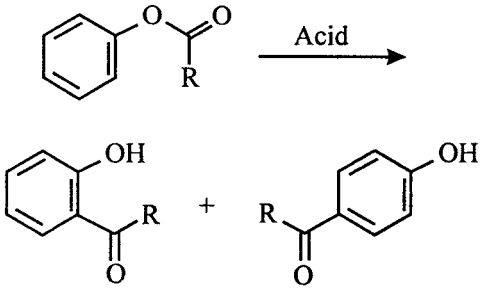


The starting materials for this quinoline synthesis are *o*-aminoaryl aldehydes or ketones and a ketone possessing an α-methylene group. After an initial amino-ketone condensation, the intermediate undergoes base- or acid-catalyzed cyclocondensation to produce a quinoline derivative.

Mechanism



FRIES REARRANGEMENT

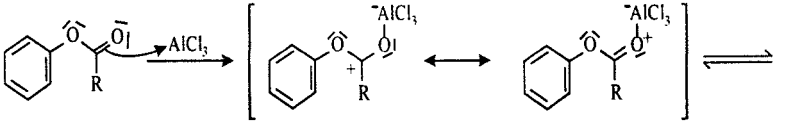


The Fries Rearrangement enables the preparation of acyl phenols.

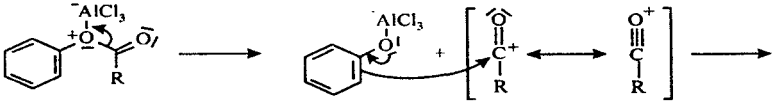
Mechanism

The reaction is catalyzed by Brψnsted or Lewis acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$. The acids are used in excess of the

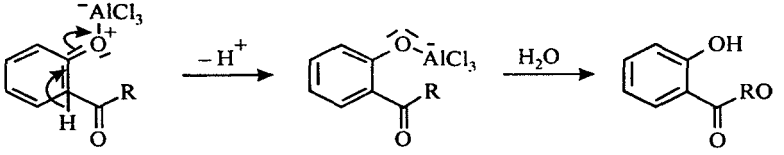
stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products.



The complex can dissociate to form an acylium ion. Depending on the solvent, an ion pair can form, and the ionic species can react with each other within the solvent cage. However, reaction with a more distant molecule is also possible:



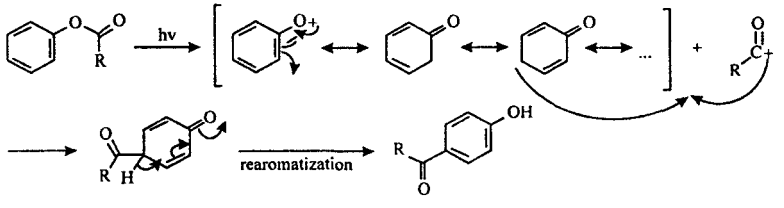
After hydrolysis, the product is liberated.



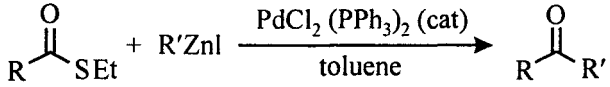
The reaction is *ortho,para*-selective so that, for example, the site of acylation can be regulated by the choice of temperature. Only sterically unhindered arenes are suitable substrates, since substituents will interfere with this reaction.

The requirement for equimolar quantities of the catalyst, the corrosive and toxic conditions (HF), and the violent reaction of the catalyst with water have prompted the development of newer protocols. Zeolites have proven to be unsuitable, since they are deactivated, but strong acids, such as sulfonic acids, provide a reasonable alternative.

An additional option for inducing a Fries Rearrangement is photochemical excitation, but this method is only feasible in the laboratory:



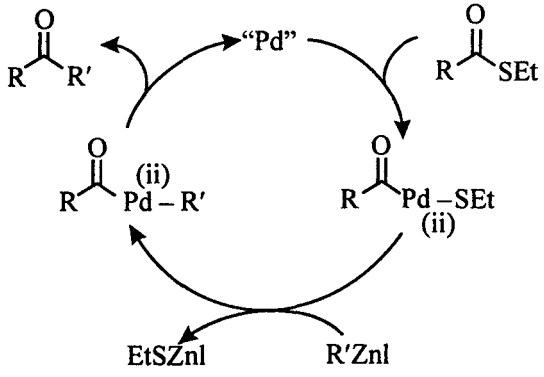
FUKUYAMA COUPLING



The palladium-catalyzed coupling of organozinc compounds with thioesters to form ketones. This reaction tolerates a variety of functional groups due to the low reactivity of the organozinc reagents.

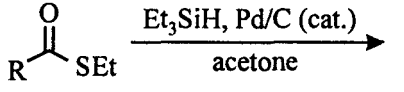
Mechanism

Oxidative addition of the thioester is followed by transmetalation from the zinc compound. Reductive elimination leads to the coupled product.



FUKUYAMA REDUCTION

The conversion of carboxylic acids to aldehydes is normally conducted in two steps by reduction of the acids or their derivatives to the corresponding alcohols followed by mild oxidation.

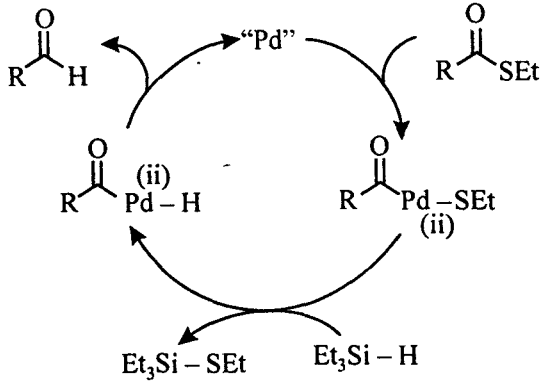


The Fukuyama Reduction allows the convenient and selective reduction of thioesters, which are easily prepared from the corresponding carboxylic acids, for example by the Steglich Esterification.

Mechanism

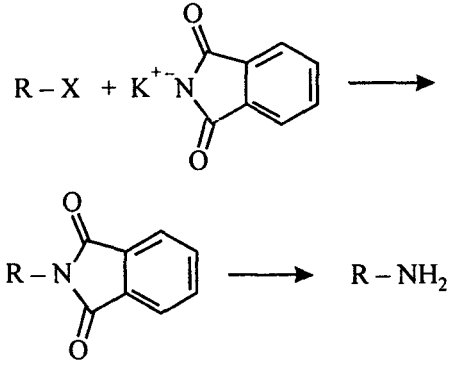
Compared to other direct reductions of carboxylic acids or carboxylic acid derivates such as using DIBAL-H or Rosenmund conditions, the Fukuyama Reduction is a mild alternative, offering outstanding functional group tolerance.

An initial oxidative addition of Pd(0) to the C(sp^2)-S bond is followed by transmetallation of the resultant acylpalladium species with Et_3SiH. Reductive elimination from the acylpalladium hydride leads to the desired aldehyde.



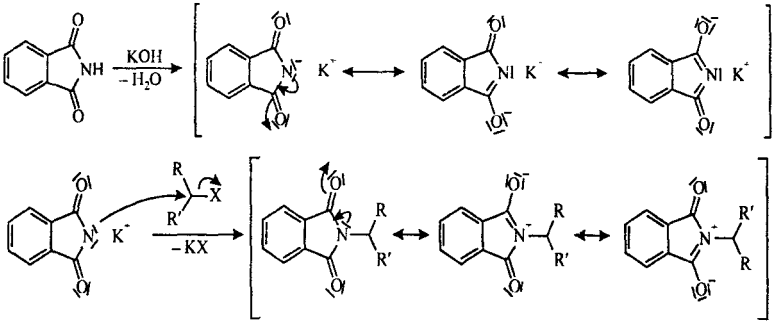
On the basis of this mechanism, it was surmised that substitution of Et_3SiH by an appropriate organometallic reagent would provide access to ketones. Extensive screening of various transition metal catalysts and organometallic reagents have revealed suitable conditions, which are currently used in the Fukuyama-Coupling.

GABRIEL SYNTHESIS

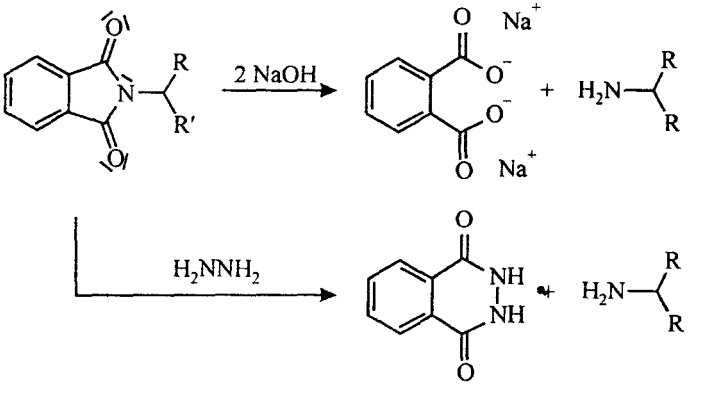


Potassium phthalimide is a $^{-}NH_2$-synthon which allows the preparation of primary amines by reaction with alkyl halides. After alkylation, the phthalimid is not nucleophile and does not react anymore. Product is cleaved by reaction with base or hydrazine, which leads to a stable cyclic product.

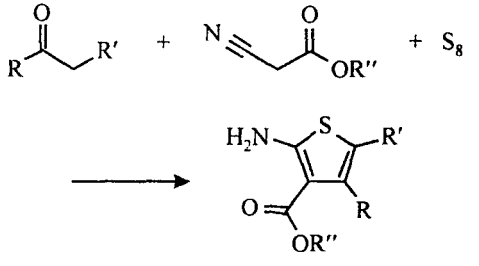
Mechanism



Cleavage:



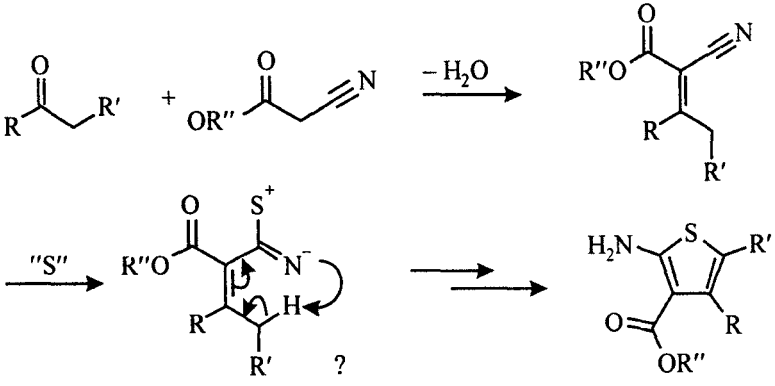
GEWALD REACTION



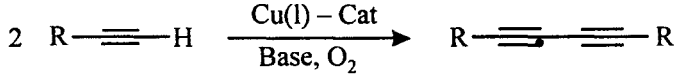
The Gewald Reaction is a synthesis of 2-aminothiophenes via a multi-component condensation between sulfur, an α-methylene carbonyl compound and an α-cyanoester.

Mechanism

First step in the process is a Knoevenagel Condensation, but the remainder of the sequence is not known in detail:

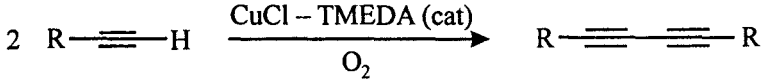


GLASER COUPLING



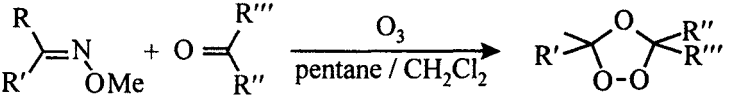
The Glaser Coupling (or Hay Coupling) is a synthesis of symmetric or cyclic bisacetylenes via a coupling reaction of terminal alkynes. Mechanistically, the reaction is similar to the Eglinton Reaction; the difference being the use of catalytic copper(I), which is reoxidized in the catalytic cycle by oxygen in the reaction medium.

The related Hay Coupling has several advantages as compared with the Glaser Coupling. The copper-TMEDA complex used is soluble in a wider range of solvents, so that the reaction is more versatile.



A valuable alternative is the Cadiot-Chodkiewicz Coupling which allows the preparation of asymmetric bisacetylenes.

GRIESBAUM COOZONOLYSIS

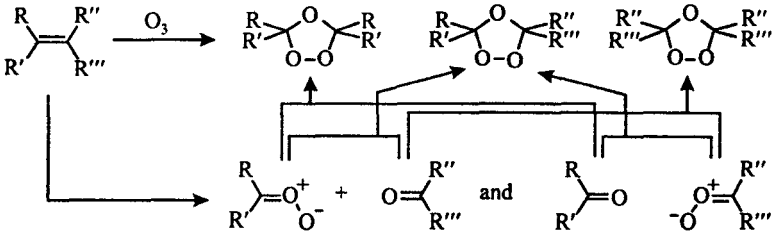


The Griesbaum Coozonolysis allows the preparation of defined, tetrasubsituted ozonides (1,2,4-trioxolanes) by the reaction of *O*-methyl oximes with a carbonyl compound in the presence of ozone. In contrast to their traditional role as intermediates in oxidative alkene cleavage, 1,2,4-trioxolanes with bulky substituents are isolable and relatively stable compounds.

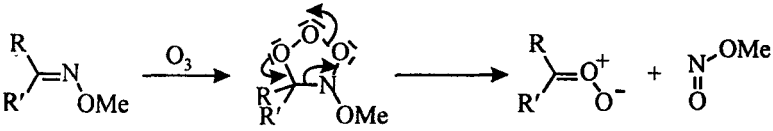
The selective synthesis of substituted 1,2,4-trioxolanes has drawn considerable interest following indications that this heterocycle confers potent pharmacologic activity such as in the antimalarial area.

Mechanism

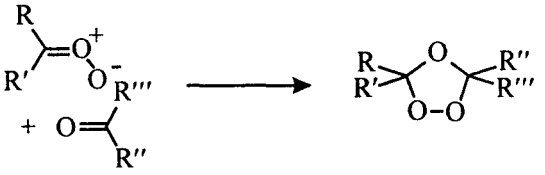
The unmodified ozonolysis of an unsymmetrical alkene produces the intermediate carbonyl compounds and carbonyl oxides nonselectively; these can then react with each other to give a statistical mixture of 1,2,4-trioxolanes.



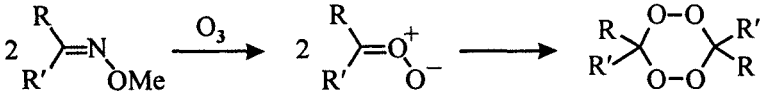
A coozonolysis (two compounds in presence of ozone) is possible if one precursor generates the carbonyl oxide *in situ* that then reacts with the second compound - the carbonyl. *N*-Methyl oximes have been found to be ideal precursors, because they readily react as dipolarophiles in a 1,3-dipolar cycloaddition with ozone. A retro-1,3-dipolar cycloaddition then leads to the formation of the carbonyl oxide and methyl nitrite:



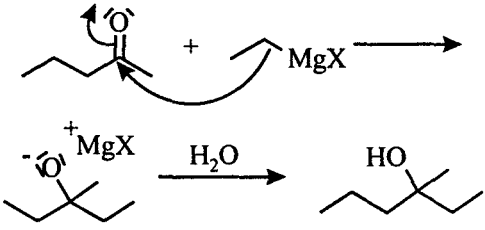
The 1,3-dipolar cycloaddition of the carbonyl oxide with the carbonyl compound gives tetrasubsituted ozonides:



If no carbonyl compound is added, 1,2,4,5-tetraoxanes might be isolated through dimerization of the carbonyl oxide:



GRIGNARD REACTION

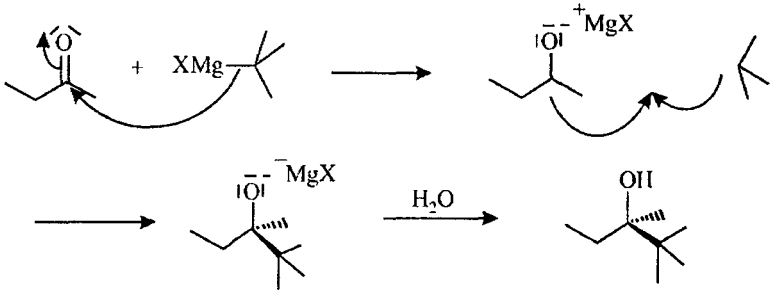


The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate.

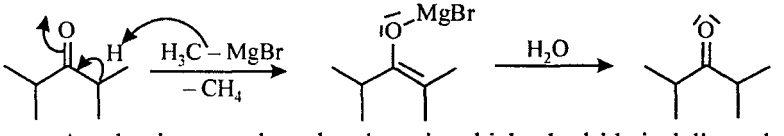
Mechanism

While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism:

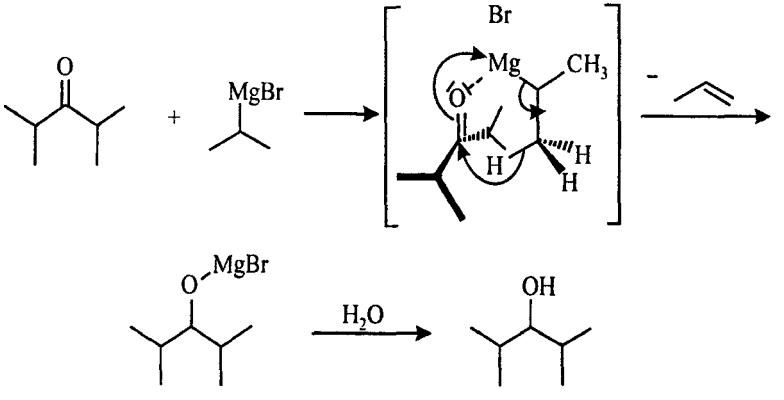


With sterically hindered ketones the following side products are received:

The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered.

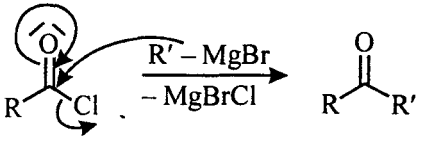


A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state.

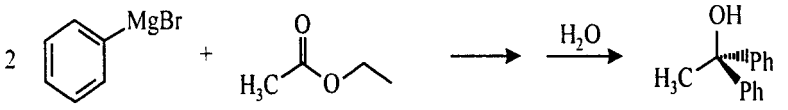


Additional reactions of Grignard Reagents:

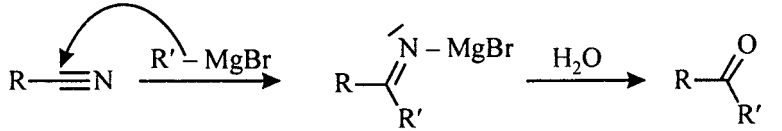
With carboxylic acid chlorides:



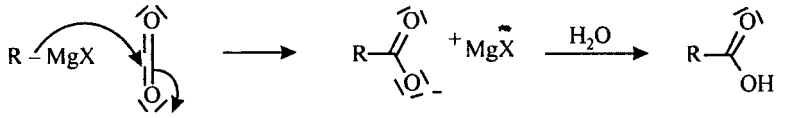
Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent:



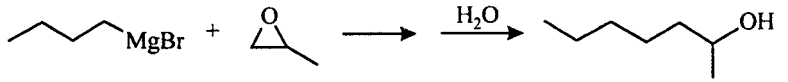
With nitriles:



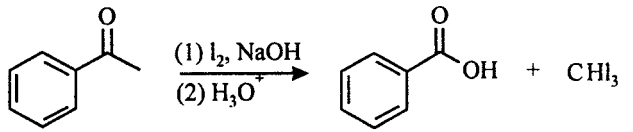
With CO_2 (by adding dry ice to the reaction mixture):



With oxiranes:



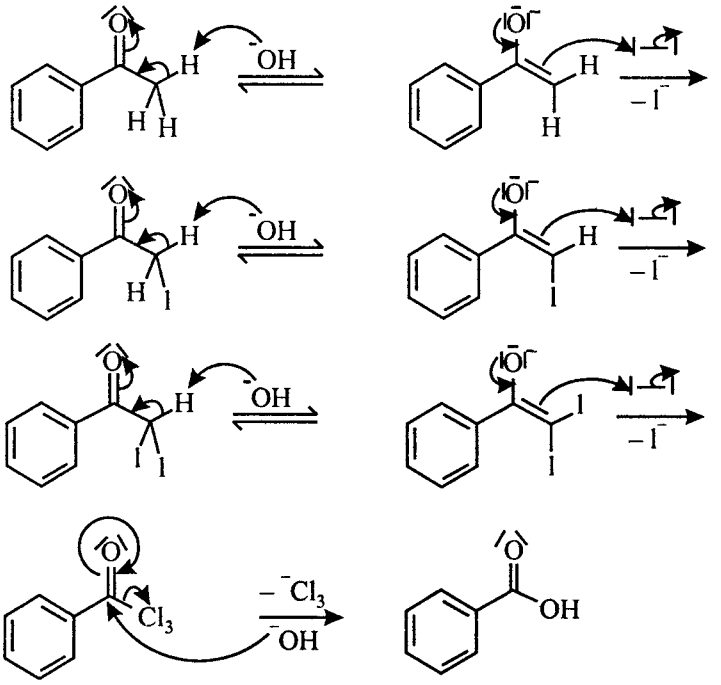
HALOFORM REACTION



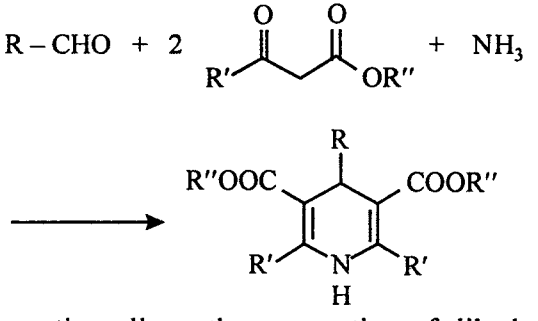
This reaction has been used in qualitative analysis to indicate the presence of a methyl ketone. The product iodoform is yellow and has a characteristic odour. The reaction has some synthetic utility in the oxidative demethylation of methyl ketones if the other substituent on the carbonyl groups bears no enolizable α-protons.

Mechanism

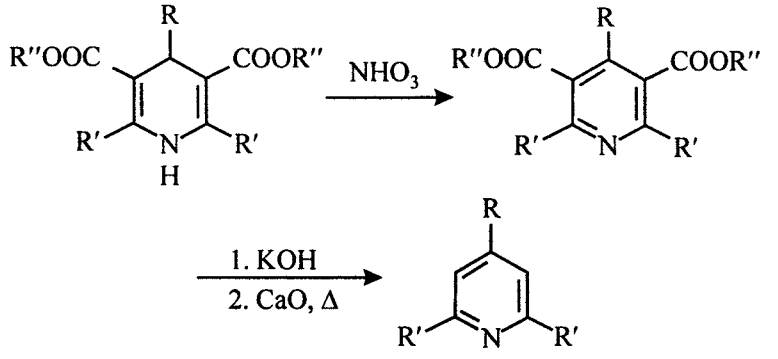
The reaction readily proceeds to completion because of the acidifying effect of the halogen substituents.



HANTZSCH DIHYDROPYRIDINE (PYRIDINE) SYNTHESIS

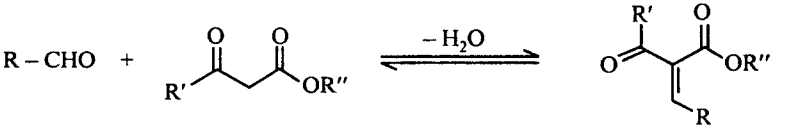


This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

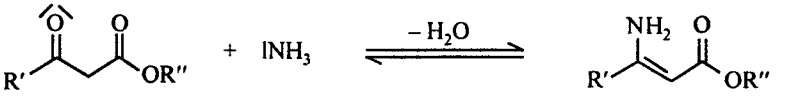


Mechanism

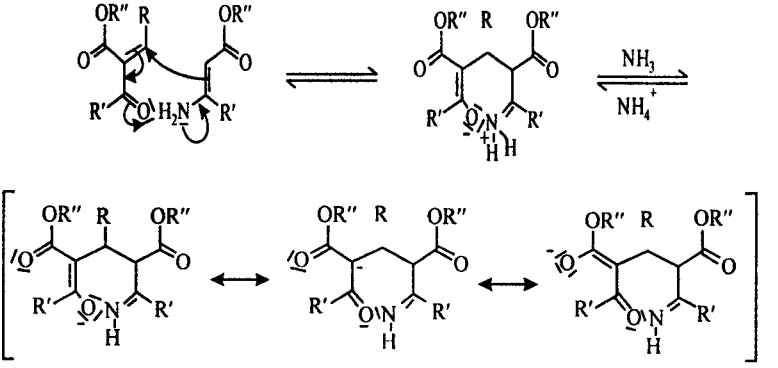
The reaction can be visualized as proceeding through a Knoevenagel Condensation product as a key intermediate:

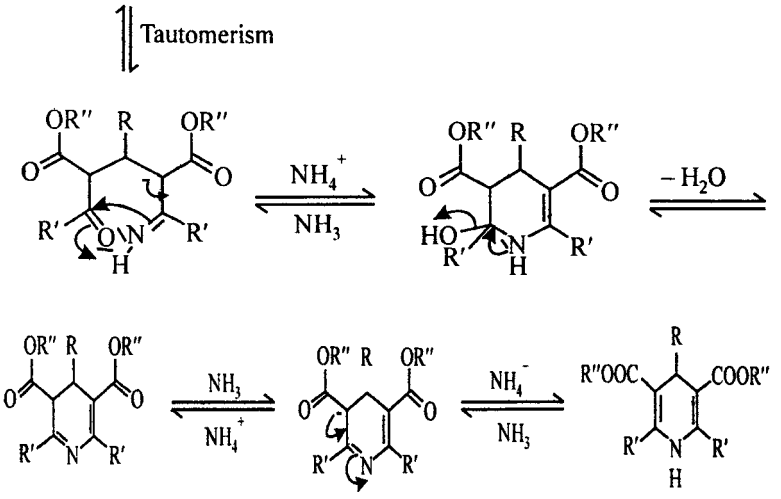


A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β-ketoester with ammonia:

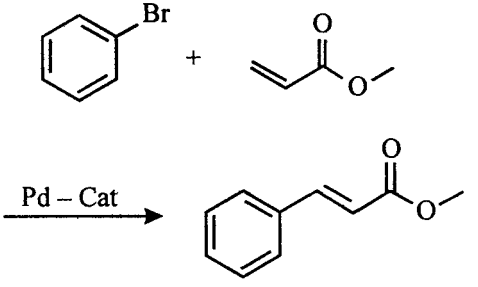


Further condensation between these two fragments gives the dihydropyridine derivative:





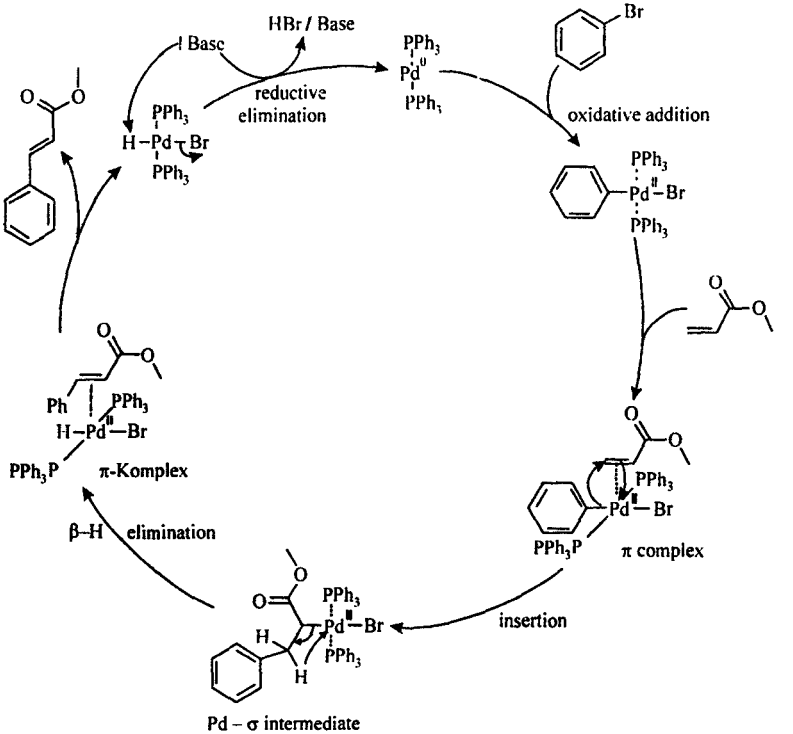
HECK REACTION



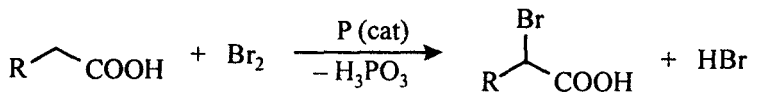
The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the "Heck Reaction". Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.

One of the benefits of the Heck Reaction is its outstanding *trans* selectivity.

Mechanism



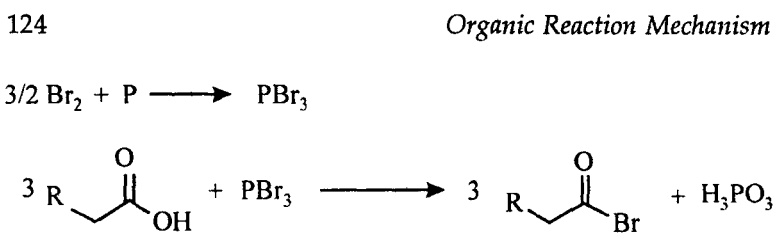
HELL-VOLHARD-ZELINSKY REACTION



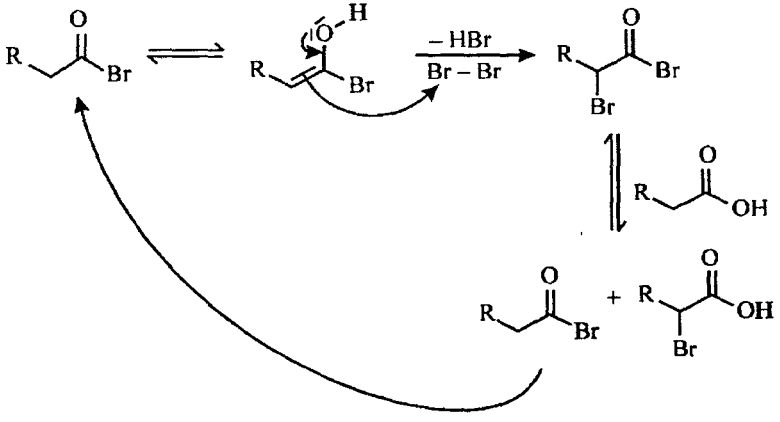
Treatment with bromine and a catalytic amount of phosphorus leads to the selective α-bromination of carboxylic acids.

Mechanism

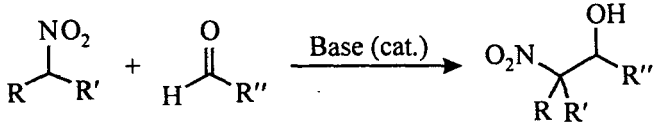
Phosphorus reacts with bromine to give phosphorus tribromide, and in the first step this converts the carboxylic acid into an acyl bromide.



An acyl bromide can readily exist in the enol form, and this tautomer is rapidly brominated at the α-carbon. The monobrominated compound is much less nucleophilic, so the reaction stops at this stage. This acyl intermediate compound can undergo bromide exchange with unreacted carboxylic acid via the anhydride, which allows the catalytic cycle to continue until the conversion is complete.



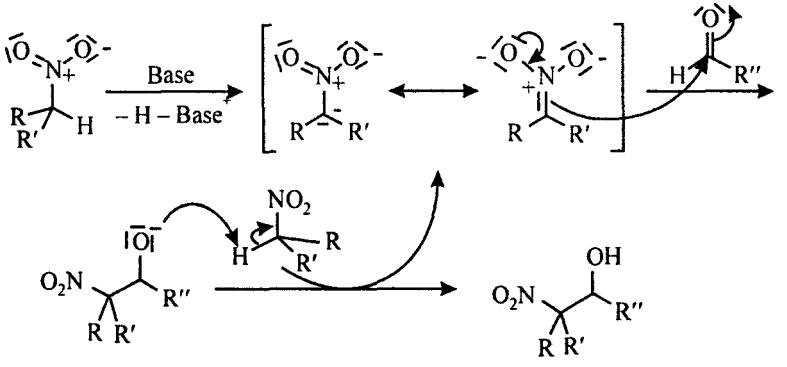
HENRY REACTION



The Henry Reaction is a base-catalyzed C-C bond-forming reaction between nitroalkanes and aldehydes or ketones. It is similar to the Aldol Addition, and also referred to as the Nitro Aldol Reaction.

If acidic protons are available (i.e. when R = H), the products tend to eliminate water to give nitroalkenes. Therefore, only small amounts of base should be used if the isolation of the β-hydroxy nitro-compounds is desired.

Mechanism



HIYAMA COUPLING

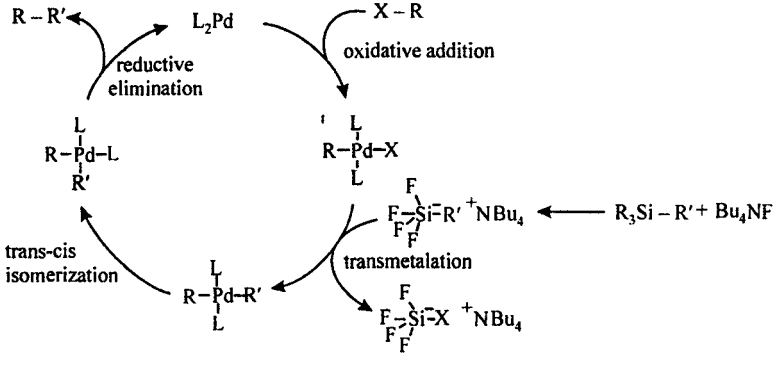
$$R-X \;+\; R''_3Si-R' \xrightarrow[F^- \text{ or base}]{\text{Pd (cat.)}} R-R'$$

R''_3Si: $(RO)_3Si$, $Me_{(3-n)}F_nSi$

The Hiyama Coupling is the palladium-catalyzed C-C bond formation between aryl, alkenyl, or alkyl halides or pseudohalides and organosilanes. This reaction is comparable to the Suzuki Coupling and also requires an activating agent such as fluoride ion or a base.

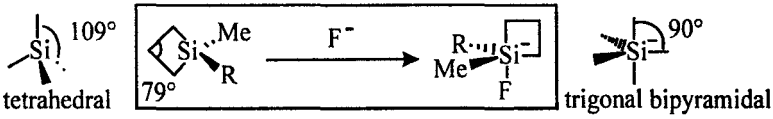
Mechanism

Crucial for the success of the Hiyama Coupling is the polarization of the Si-C bond. Activation of the silane with base or fluoride ions (TASF, TBAF) leading to a pentavalent silicon compound is a first necessary step.



However, the reaction rate is also increased by using silanes with R" groups such as fluoro or alkoxy instead of alkyl. In fact, there are only a few successful examples of coupling reactions using trimethylsilane derivatives.

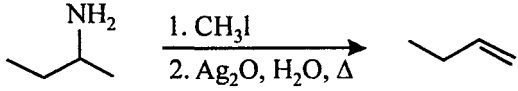
Another approach uses silacyclobutanes. These small-ring silanes offer enhanced Lewis acidity because angle strain is released when the silicon transitions from tetrahedral to pentavalent, which favours the activation.



Lewis acidity enhanced by strain release

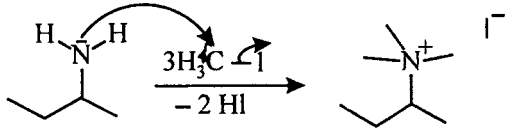
Organosilanes are stable and easily prepared compounds with low toxicity. With the many improvements in the reaction conditions that have been reported, the Hiyama Coupling has become an interesting alternative to the Suzuki Coupling that offers a comparable scope of conversions. On the other hand, the broad commercial availability of boronic acids and boronates currently makes the Suzuki Coupling the more convenient choice.

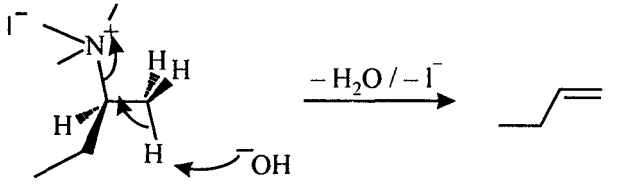
HOFMANN ELIMINATION



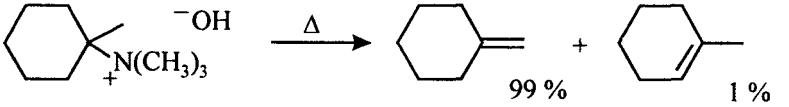
Sometimes referred to as the Hofmann Degradation. This elimination reaction of alkyl trimethyl amines proceeds with *anti*-stereochemistry, and is generally suitable for producing alkenes with one or two substituents. The reaction follows the Hofmann Rule.

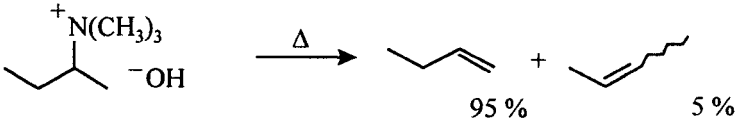
Mechanism





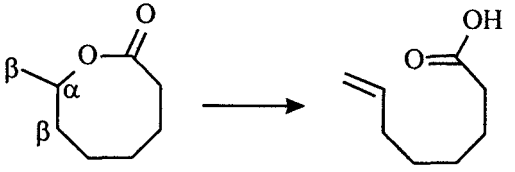
HOFMANN'S RULE





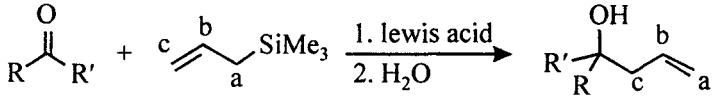
Hofmann's Rule implies that steric effects have the greatest influence on the outcome of the Hofmann or similar eliminations. The loss of the β-hydrogen occurs preferably from the most unhindered (least substituted) position [$-CH_3 > -CH_2-R > -CH(R_2)$]. The product alkene with fewer substitutents will predominate.

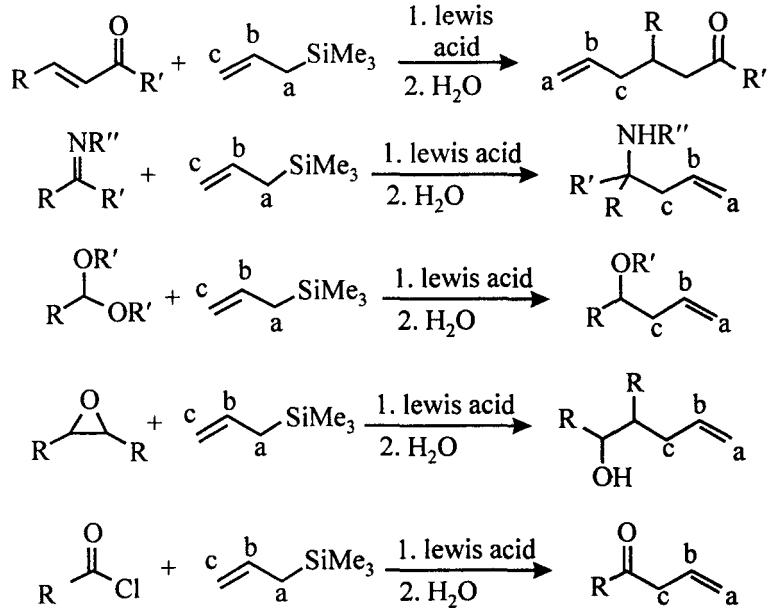
Ester Pyrolysis also obeys this preference, and the Hofmann Rule is generally followed whenever a reaction passes through a cyclic transition state.



Hofmann's Rule is valid for all intramolecular eliminations and for the Hofmann Elimination. Most bimolecular eliminations will follow Saytzeff's Rule.

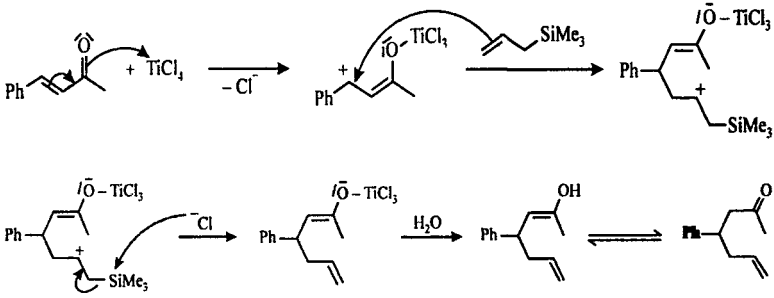
HOSOMI-SAKURAI REACTION





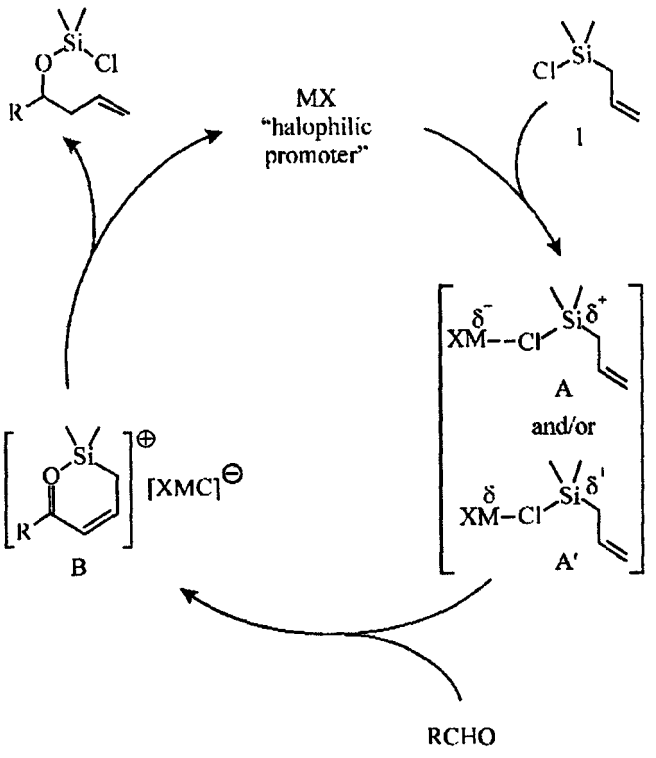
The Hosomi Sakurai Reaction involves the Lewis acid-promoted allylation of various electrophiles with allyltrimethysilane. Activation by Lewis acids is critical for an efficient allylation to take place.

Mechanism

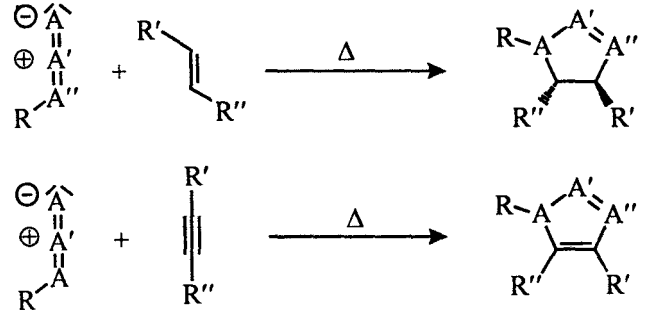


Note: Silicon stabilizes β carbocations (β effect)

Only catalytic amounts of Lewis acid are needed in the newer protocols. Note the use of allylsilyl chlorides instead of allyltrimethylsilane:

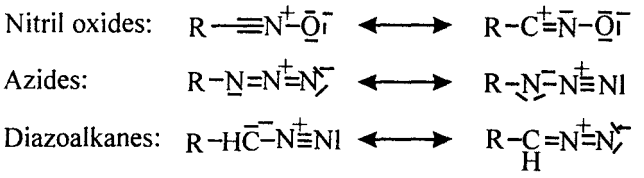


HUISGEN CYCLOADDITION

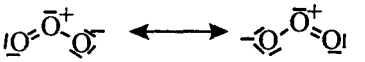


The Huisgen Cycloaddition (or 1,3-Dipolar Cycloaddition) is the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5-membered (hetero)cycles. Examples of dipolarophiles are alkenes and alkynes and molecules that possess related heteroatom

functional groups (such as carbonyls and nitriles). 1,3-Dipolar compounds contain one or more heteroatoms and can be described as having at least one mesomeric structure that represents a charged dipole.

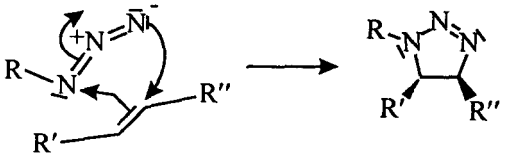


Examples of linear, propargyl-allenyl-type dipoles



An example of an allyl-type dipole is Ozonolysis

Mechanism

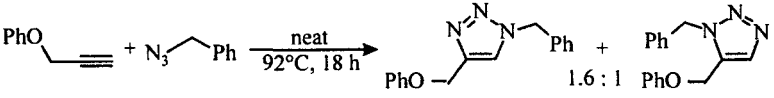


2 π-electrons of the dipolarophile and 4 electrons of the dipolar compound participate in a concerted, pericyclic shift. The addition is stereoconservative (suprafacial), and the reaction is therefore a $[_2s+_4s]$ cycloaddition similar to the Diels-Alder Reaction. Attention: many authors still use "[2+3] cycloaddition", which counts the number of involved atoms but does not follow IUPAC recommendations. IUPAC recommends the use of "(2+3)" for the number of involved atoms instead.

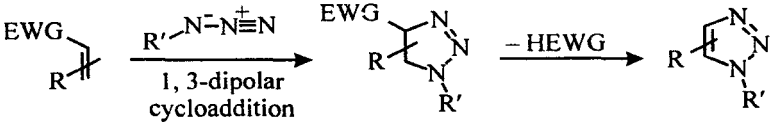
A condition for such a reaction to take place is a certain similarity of the interacting HOMO and LUMO orbitals, depending on the relative orbital energies of both the dipolarophile and the dipole. Electron-withdrawing groups on the dipolarophile normally favour an interaction of the LUMO of the dipolarophile with the HOMO of the dipole that leads to the formation of the new bonds, whereas electron donating groups on the dipolarophile normally

favour the inverse of this interaction. Diazomethane as an electron-rich dipolar compound therefore rapidly reacts with electron-poor alkenes, such as acrylates. Relative reactivity patterns may be found in the literature.

The regioselectivity of the reaction depends on electronic and steric effects and is somewhat predictable. For example, the addition of alkynes to azides, which is an interesting reaction for the generation of 1,2,3-triazole libraries by the simple reaction of two molecules leads to regioisomers:

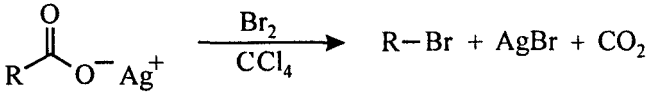


The reaction has been modified to a more regioselective, copper-catalyzed stepwise process by the Sharpless group, which is no longer a classic Huisgen Cycloaddition. Another approach prefers the use of a directing electron withdrawing group, which is removable later:



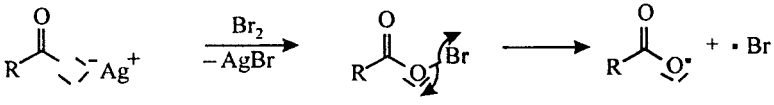
In summary, the 1,3-dipolar cycloaddition allows the production of various 5-membered heterocycles. Many reactions can be performed with high regioselectivity and even enantioselective transformations of prochiral substrates.

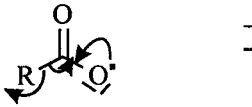
HUNSDIECKER REACTION

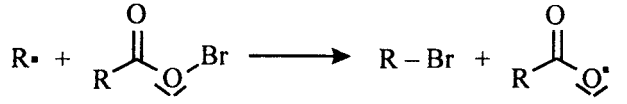


The silver(I) salts of carboxylic acids react with halogens to give unstable intermediates which readily decarboxylate thermally to yield alkyl halides. The reaction is believed to involve homolysis of the C-C bond and a radical chain mechanism.

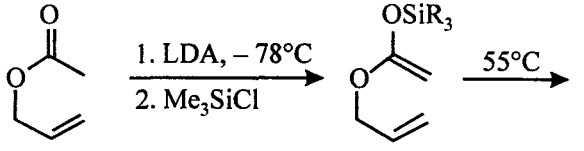
Mechanism

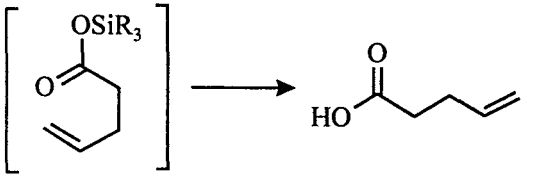






IRELAND-CLAISEN REARRANGEMENT



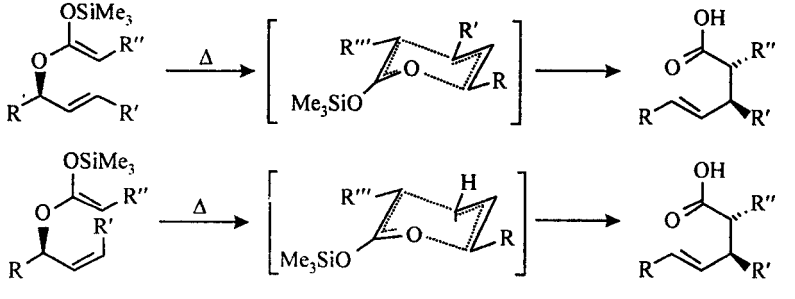


This gentle variant of the Claisen Rearrangement employs the allyl ester of a carboxylic acid instead of an allyl vinyl ether. The ester is converted to its silyl-stabilized enolate (silyl ketene acetal), which rearranges at temperatures below 100 °C.

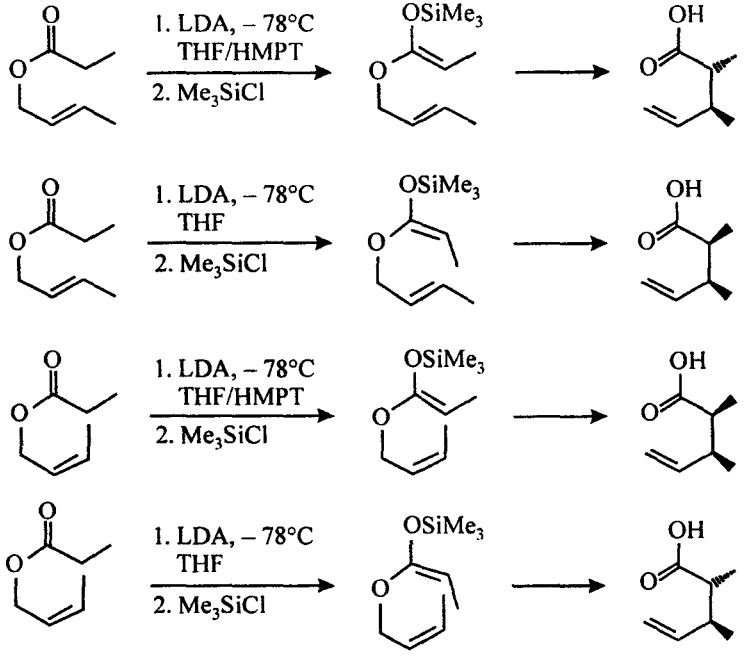
The immediate product of the rearrangement, a carboxylic acid silyl ester, cannot be isolated and is hydrolyzed during workup. The Ireland-Claisen Rearrangement thus offers ready access to chain-extended carboxylic acids.

Mechanism

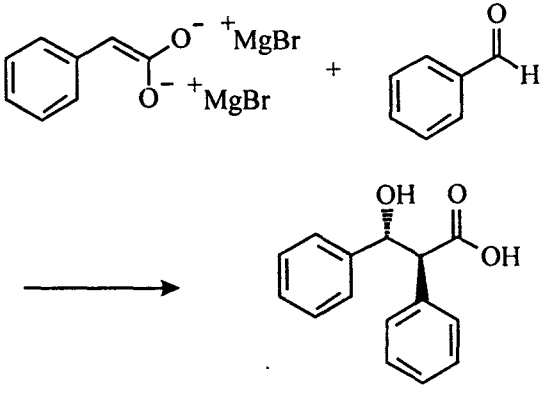
As with the Claisen Rearrangement, the Ireland modification also proceeds with a high degree of stereoselectivity:



An advantage of the Ireland-Claisen Rearrangement is the option of controlling the enolate geometry through the judicious choice of solvent:



IWANOW REACTION (IVANOV REACTION)

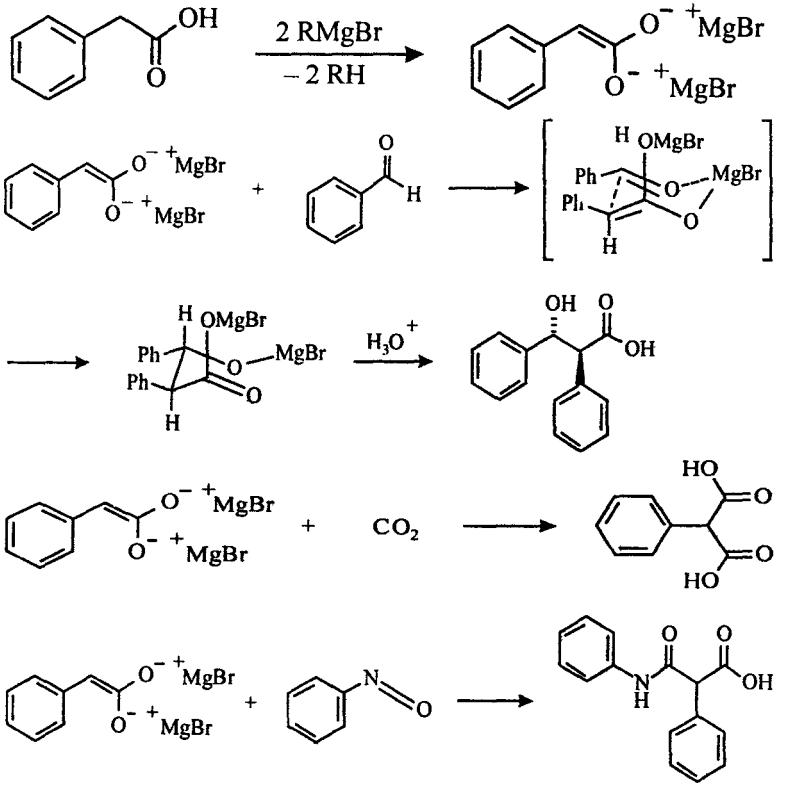


Ivanov Reagents are carboxylate enolates (enediolates, or carboxylic acid dianions) derived from phenyl acetic acid or

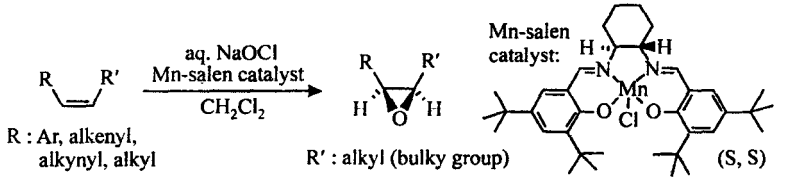
substituted analogs, and react with aldehydes to give β-hydroxy acids, similar to the Aldol Addition.

The stereoselectivity can be explained with the Zimmerman-Traxler Model, which predicts a six-membered cyclic transition state leading to excellent stereoselectivity for *anti*-substituted products.

Mechanism



JACOBSEN-KATSUKI EPOXIDATION

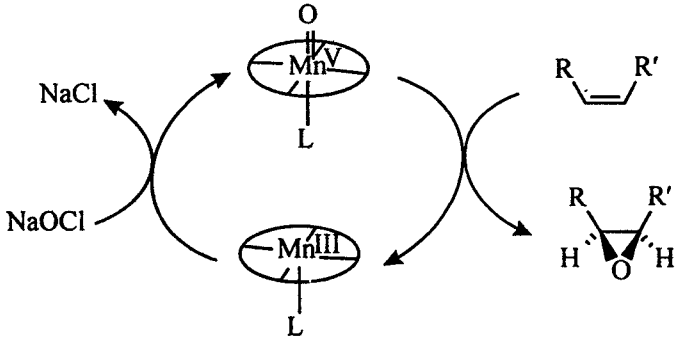


The Jacobsen Epoxidation allows the enantioselective formation of epoxides from various *cis*-substituted olefins by using a chiral Mn-salen catalyst and a stoichiometric oxidant such as bleach.

Compared to the Sharpless Epoxidation, the Jacobsen Epoxidation allows a broader substrate scope for the transformation: good substrates are conjugated *cis*-olefins or alkyl-substituted *cis*-olefins bearing one bulky alkyl group.

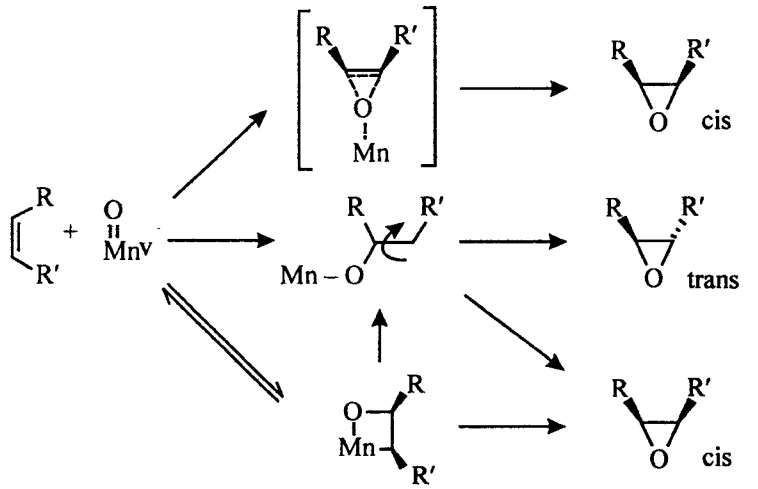
Mechanism

A simplified catalytic cycle shows the formation of an Mn(V)-oxo complex. L could be a counterion or an amine *N*-oxide ligand, the addition of which has a slight beneficial effect on enantioselectivity, reaction rate and product yield:

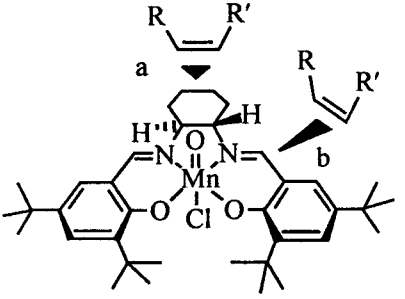


Discussions of the mechanism of the oxygen transfer to the double bond have led to controversy. Depending on the substrate and additives, the formation of side products with *trans* stereochemistry points to a radical mechanism, whereas alkyl-substituted olefins stereoselectively give only *cis* products via a concerted mechanism.

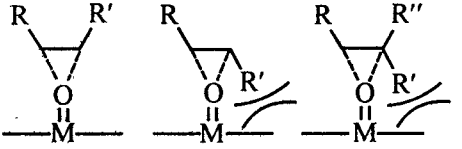
The suggested formation of manganaoxetanes receives support from calculations on a theoretical level, and from experiments reported by Katsuki using derivatives of the Jacobsen catalyst.



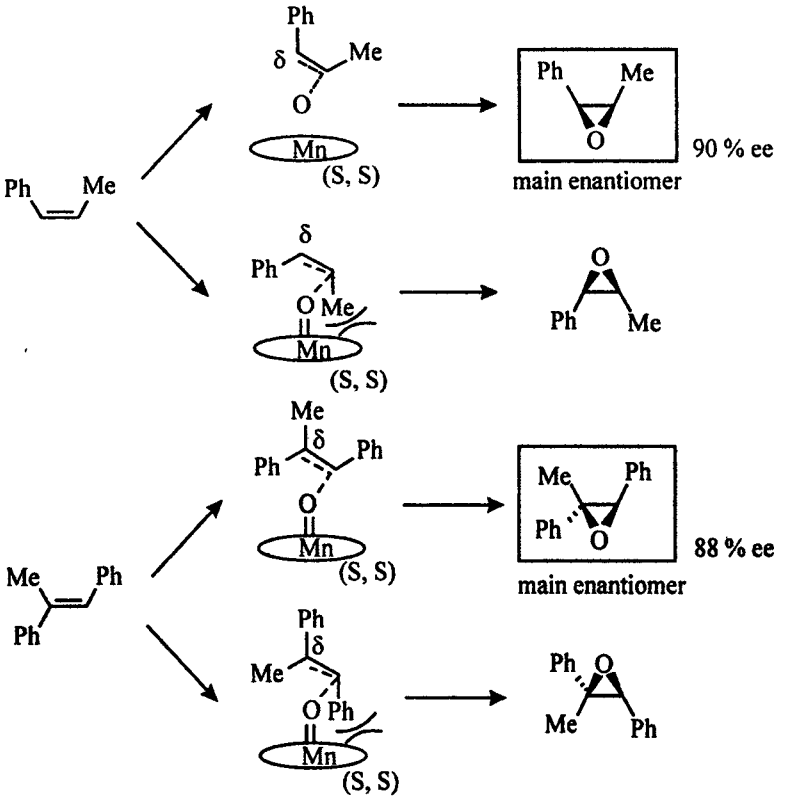
Two different models exist for the approach of the substrate, which help to explain the stereoselectivity of the nearby flat catalyst.



In a simple model, steric repulsion accounts for rate differences and lowered selectivity:



However, Jacobsen was able to show that, after addition of a pyridine *N*-oxide derivative, trisubstituted alkenes are in fact excellent substrates. The dissymmetry of the chiral salen ligand can effectively orient the radical selectivity:

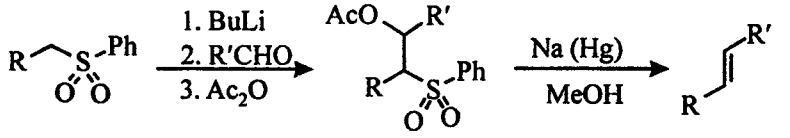


Many oxene, nitrene and carbene transfer reactions using well-designed chiral first- and second-generation metallosalen complexes as catalysts.

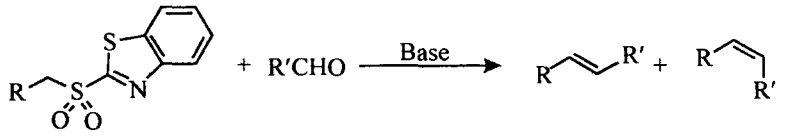
JULIA-LYTHGOE OLEFINATION

This multistep synthesis enables the preparation of (*E*)-alkenes.

The addition of a phenylsulfonyl carbanion to an aldehyde or ketone leads to an intermediate alcohol, which is esterified in situ. The reductive elimination with sodium amalgam to furnish the alkene takes place in a second step.

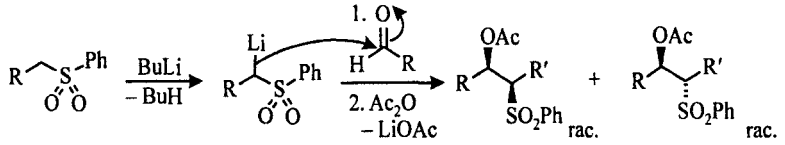


The Julia-Kociensky Olefination is an alternative procedure, which leads to the olefin in one step.

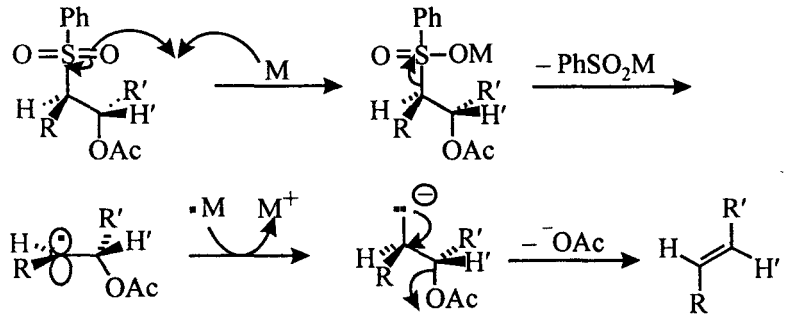


Mechanism

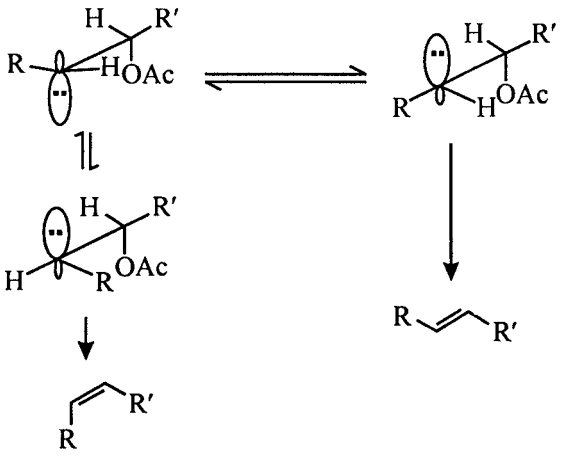
The acetoxysulfone synthesis produces diastereomers:



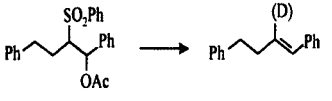
A first possible mechanism proceeds through a planar radical that can rotate freely about the C-C bond. Both diastereomers would thus pass through the same radical intermediate, which can be used to explain the (*E*)-selectivity.



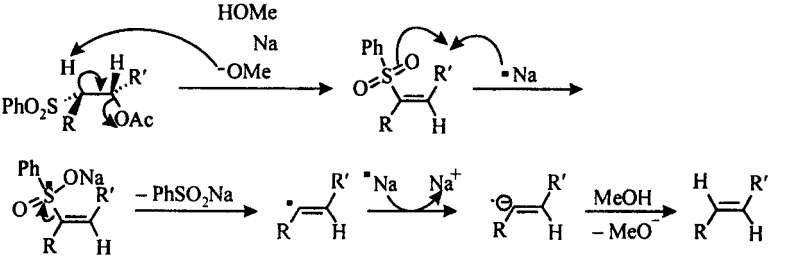
Even though the carbanion is not configurationally or conformationally stable, it will prefer an arrangement with the R-groups further apart that will later lead to the (*E*)-alkene:



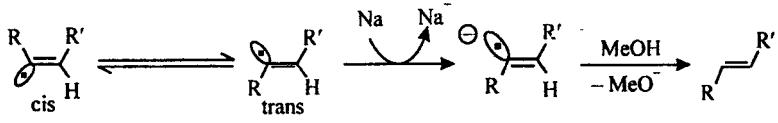
Keck demonstrated in 1995 that when the sodium amalgam reaction is run in MeOD as solvent, deuterium is incorporated into the product, in contrast to the absence of incorporation seen in the SmI_2 reduction. Thus, the mechanism proposed above is completely consistent with the SmI_2 reduction (M = SmI_2).

Deuterium Incorporation in Reductions of Acetoxy Sulfones	Reaction conditions	E : Z	Deuterium incorpn (%)
	8 eq. SmI_2, THF DMPU, CD_3OD. 60 min	2.3 : 1	0
	5% Na/Hg, Na_2HPO_4. THF/CD_3OD (4:1)	9.1 : 1	91

The classical Julia Olefination with sodium amalgam might possibly proceed via an initial elimination to an alkenyl sulfone, which would then undergo homolytic cleavage involving single electron transfer.

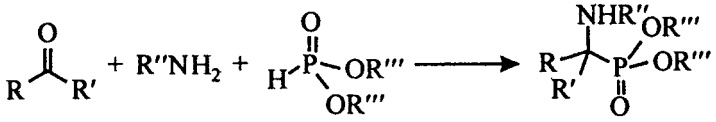


Since the *cis*- and *trans*-vinyl radicals can equilibrate at this stage and the *trans*-radical is the more stable of the two, both diastereomeric acetoxy sulfones would still lead selectively to the same product.



A disadvantage of the Julia Olefination is its low tolerance for reducible functional groups. The (*E*)-selectivity is generally good to very good for alkenes with a low degree of substitution, while the selectivity improves as a function of increased branching in the substitutents.

KABACHNIK-FIELDS REACTION

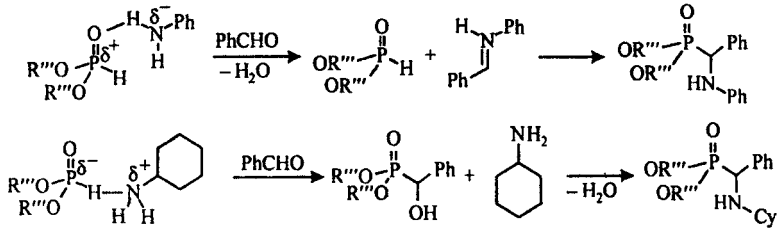


This three-component coupling of a carbonyl, an amine and a hydrophosphoryl compound leads to α-aminophosphonates. The Kabachnik-Fields Reaction is very important in drug discovery research for generating peptidomimetic compounds.

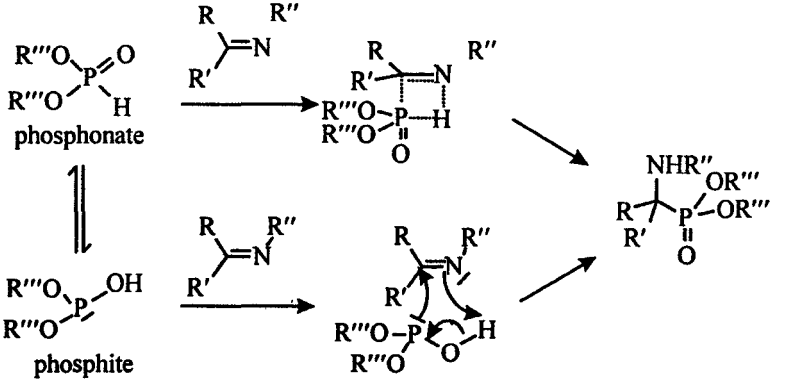
Early protocols were limited to simple starting materials (for example aldehydes) but newer methods permit reactions to take place even with sterically demanding starting materials.

Mechanism

The pathway of the Kabachnik-Fields reaction depends on the nature of the substrates. The amine and hydrophosphoryl compound form a complex in which either one of the partners may react with the carbonyl compound. Often, the basicity of the amine determines the reaction pathway. Weakly basic amines such as anilines, which can act as proton donors, favour the formation of an imine, whereas alkylamines such as cyclohexylamines do not form imines:

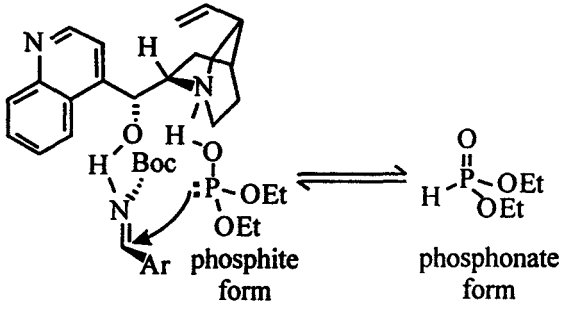


If additional catalysts are used, both acids and bases can have a positive influence on the reaction rate. Sometimes, the chemical yield and the diastereoselectivity of the formation of α-aminophosphonates are higher in two-component systems using preformed imines. In this case, due to the phosphonate <-> phosphite tautomerism, the addition to the imine could occur by either a four- or five-membered transition state:



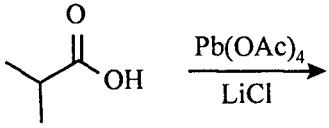
A more detailed discussion of the mechanism of the Kabachnik-Fields reaction, its synthetic potential and the biological activity of the α-aminophosphonates.

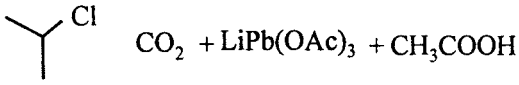
An interesting recent publication of an enantioselective transformation using quinine as an organocatalyst suggests the following transition state:



As this example shows a high degree of complexity, one can imagine that the design of an enantioselective three-component reaction would be somewhat more difficult, and it is clear that some basic investigation into the stereocontrol of the Kabachnik-Fields reaction is still needed.

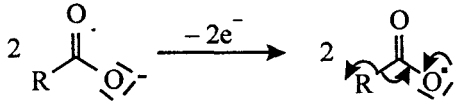
KOCHI REACTION





The Kochi Reaction is a one-carbon oxidative degradation of carboxylic acids, and is a valuable alternative to the Hunsdiecker Reaction. A Pb(IV) reagent is the oxidant, and this reaction is suitable for synthesis of secondary and tertiary chlorides.

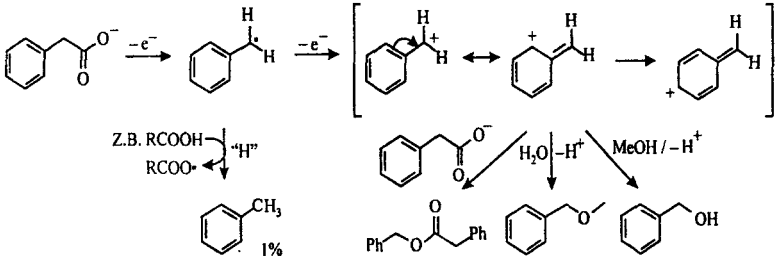
KOLBE ELECTROLYSIS



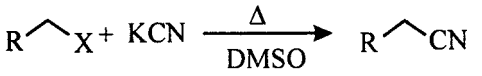
The electrochemical oxidative decarboxylation of carboxylic acid salts that leads to radicals, which dimerize. It is best applied to the synthesis of symmetrical dimers, but in some cases can be used with a mixture of two carboxylic acids to furnish unsymmetrical dimers.

Mechanism

The formation of side products depends on the ease of the follow-up oxidation which leads to carbenium ions, and their subsequent rearrangement:



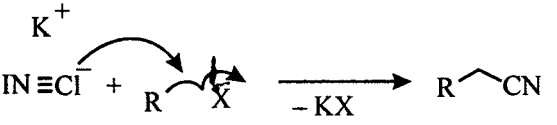
KOLBE NITRILE SYNTHESIS



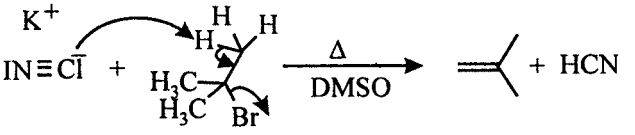
The reaction of primary aliphatic halides and alkali metal cyanides - the Kolbe Nitrile Synthesis - gives nitriles in good yields.

Mechanism

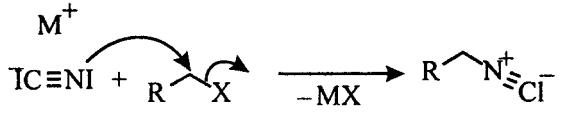
The Kolbe Nitrile Synthesis is a typical S_N2 reaction, which runs best in polar aprotic solvents (DMSO, acetone):



Primary alkylating agents work best, while secondary bromides and chlorides react in moderate yields to give the desired nitriles. Tertiary halides mainly undergo side reactions, one of which is the E2 elimination:



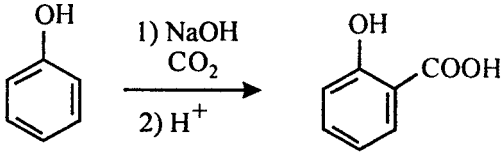
Cyanide is an ambident nucleophile, and can also react on nitrogen to yield isonitriles.



According the HSAB principles, the carbon centre is more basic and more nucleophilic. When protic solvents are used, the resulting greater solvation of this carbon centre is thought to favour the competing reaction at the weaker nitrogen centre. A similar rationale explains why the more covalent cyanide salts such as silver cyanides and cuprous cyanides also give isonitriles as main product.

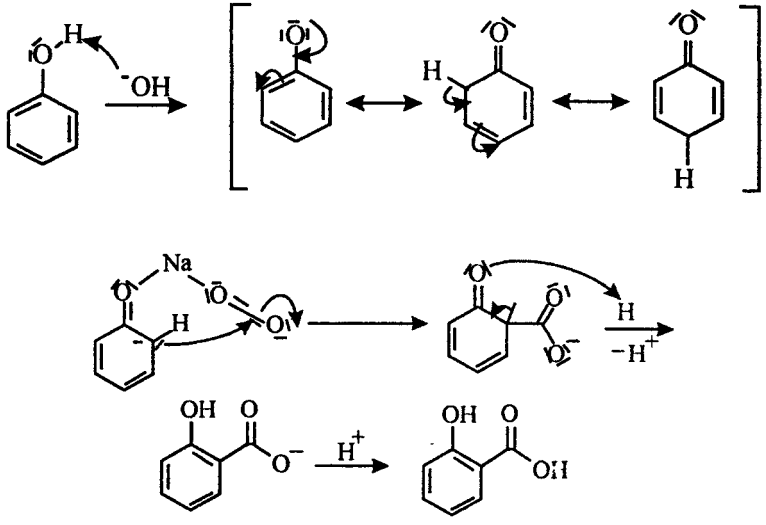
As the isonitriles are rapidly hydrolyzed to amines and formic acid, an extraction step with hydrochloric acid is normally sufficient in practice to remove these impurities from a desired nitrile product.

KOLBE-SCHMITT REACTION



A base-promoted carboxylation of phenols that allows the synthesis of salicylic acid derivatives.

Mechanism



KUMADA COUPLING

$$RX + RMgX \xrightarrow[Pd(PPh_3)_4]{Ni(dp\ pb)\ Cl_2\ or} R' - R$$

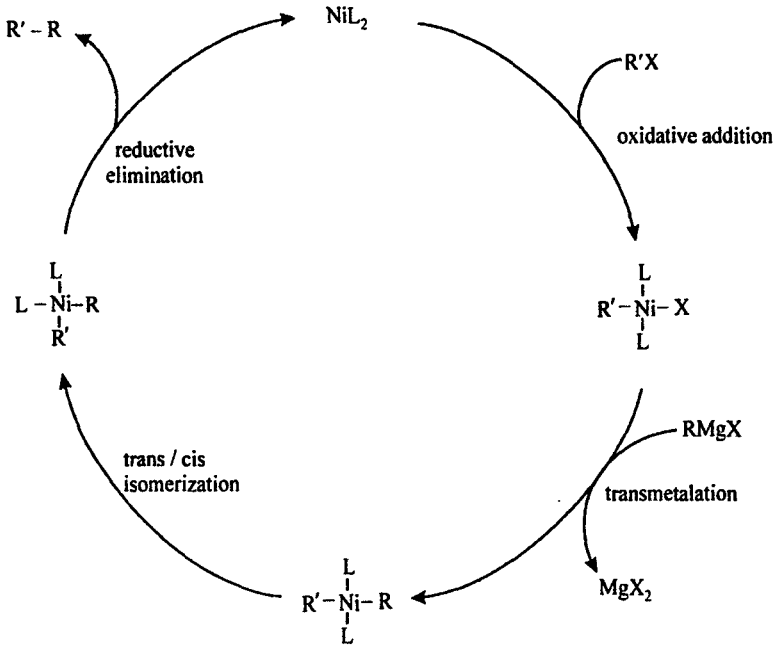
R = Aryl, Vinyl, Alkyl
R′ = Aryl, Vinyl X = Cl > Br > I

The Kumada Coupling was the first Pd or Ni-catalyzed cross coupling reaction, developed in 1972.

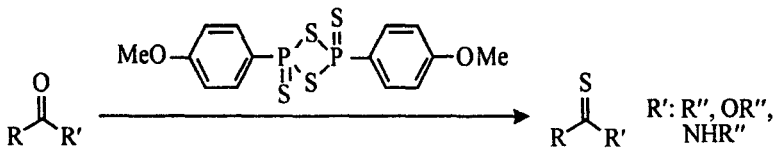
The coupling of Grignard reagents with alkyl, vinyl or aryl halides under Ni-catalysis provides an economic transformation, but the reaction is limited to halide partners that do not react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives, and the Kumada Coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls.

The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of Grignard reagents to zinc compounds for the starting materials in the Negishi Coupling.

Mechanism



LAWESSON'S REAGENT

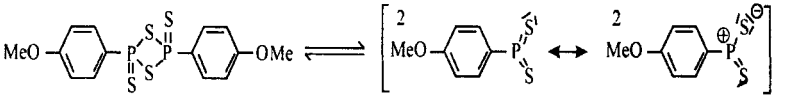


Lawesson's Reagent is a mild and convenient thionating agent for ketones, esters, and amides that allows the preparation of thioketones, thioesters and thioamides in good yields.

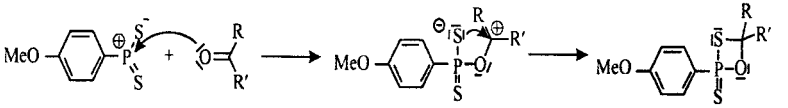
Reactions using the comparable reagent P_4S_{10} normally need higher temperatures and a large excess of the thionating agent.

Mechanism

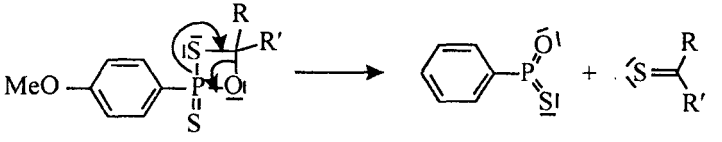
Lawesson's Reagent in solution is in equilibrium with a more reactive dithiophosphine ylide:



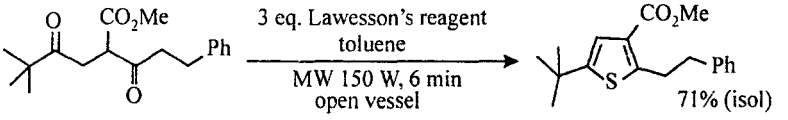
The reaction with a carbonyl gives rise to a thiaoxaphosphetane intermediate:



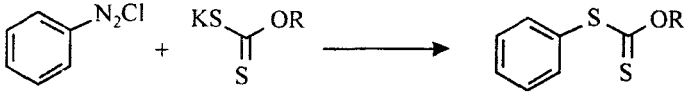
The driving force is the formation of a stable P=O bond in a cycloreversion step that resembles a portion of the mechanism known for the Wittig Reaction:

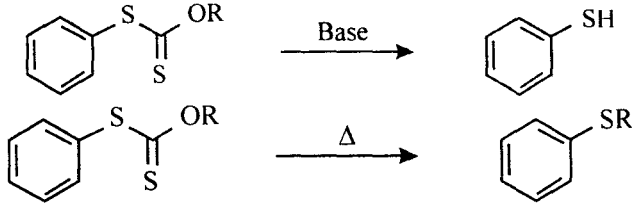


Reactions of ketones, amides, lactams and lactones are normally faster than reactions of esters. Esters are unreactive depending on the reaction conditions, which allows selective transformations:



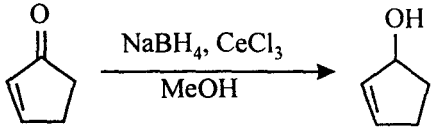
LEUCKART THIOPHENOL REACTION





The Leuckart Thiophenol Reaction allows the preparation of thiophenols and corresponding thioethers from anilines or their corresponding diazonium salts. The first step is the reaction of an aryl diazonium salt with a potassium alkyl xanthate to give an aryl xanthate, which affords an aryl mercaptan upon basic hydrolysis or an aryl thioether upon warming.

LUCHE REDUCTION



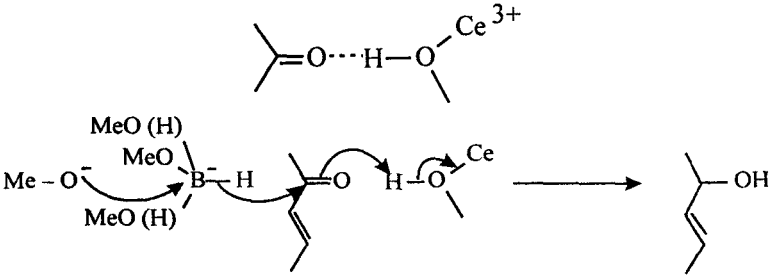
The selective 1,2-reduction of enones with sodium borohydride is achieved in combination with $CeCl_3$.

Mechanism

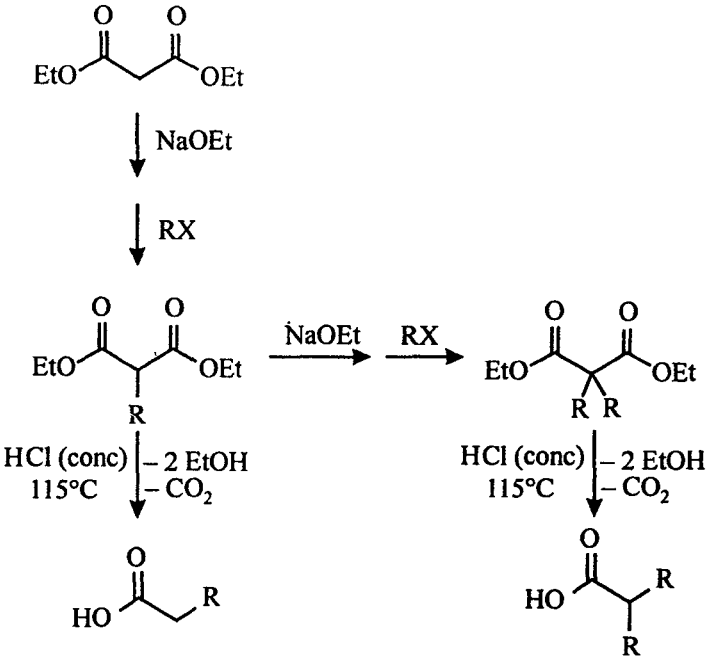
$CeCl_3$ is a selective Lewis acid catalyst for the methanolysis of sodium borohydride. The resulting reagents, various sodium methoxyborohydrides, are harder reducing agents and therefore effect an 1,2-reduction with higher selectivity.

$$NaBH_4 + nMeOH \xrightarrow{CeCl_3\,(cat.)} NaBH_{(4n)}(OMe)_n + nH_2$$

Furthermore, $CeCl_3$ activates methanol.

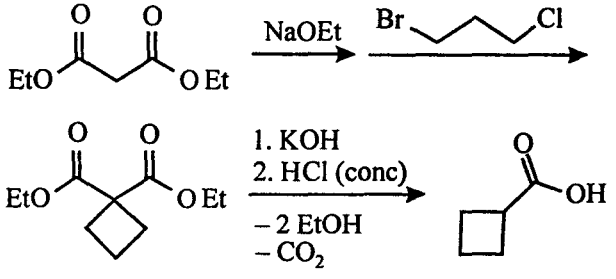


MALONIC ESTER SYNTHESIS

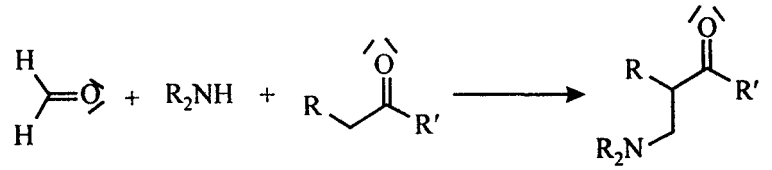


Malonic esters are more acidic than simple esters, so that alkylations can be carried out via enolate formation promoted by relatively mild bases such as sodium alkoxide, and subsequent alkylation with halides. An excess of ester must be used to prevent dialkylated products. Carboxylic acids may optionally be obtained after hydrolysis and decarboxylation.

Intramolecular dialkylation can lead to interesting products such as cyclobutanes:



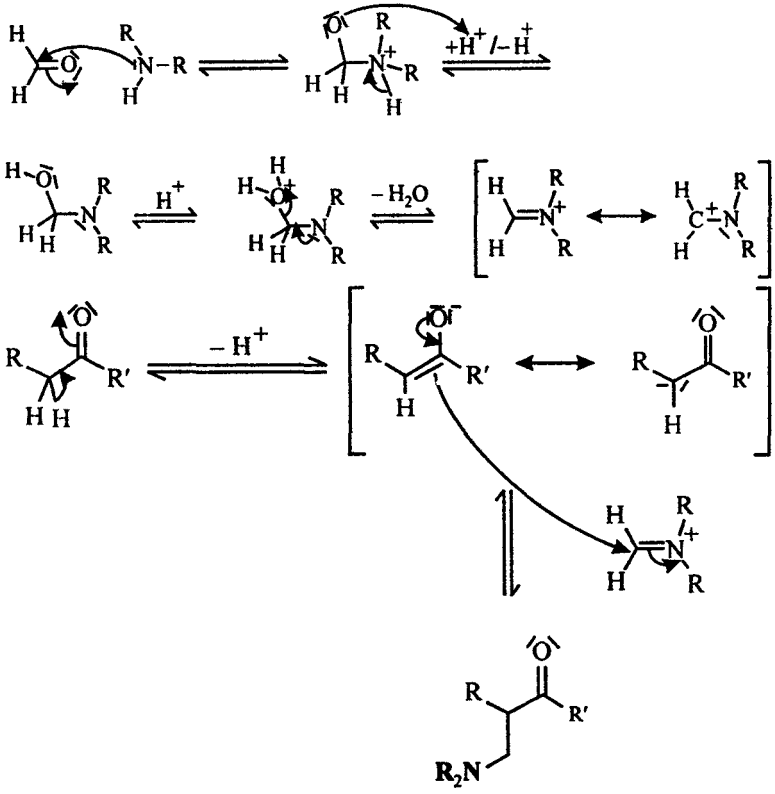
MANNICH REACTION



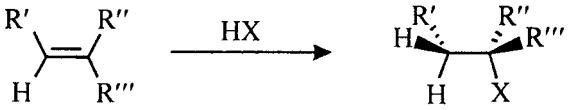
This multi-component condensation of a nonenolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminomethylated products. The iminium derivative of the aldehyde is the acceptor in the reaction.

The involvement of the Mannich Reaction has been proposed in many biosynthetic pathways, especially for alkaloids.

Mechanism



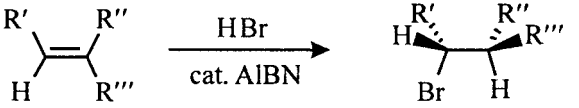
MARKOVNIKOV'S RULE



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

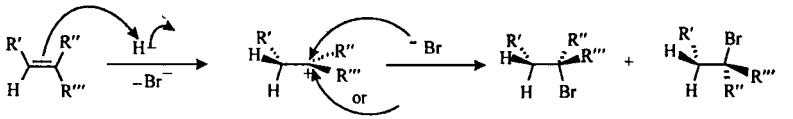


Some reactions do not follow Markovnikov's Rule, and *anti*-Markovnikov products are isolated. This is a feature for example of radical induced additions of HX and of Hydroboration.

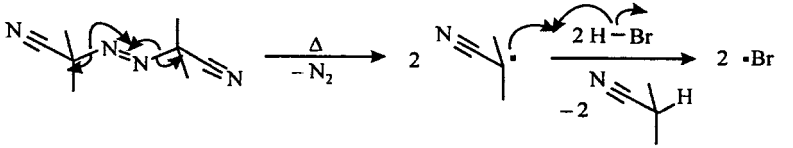
Mechanism

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



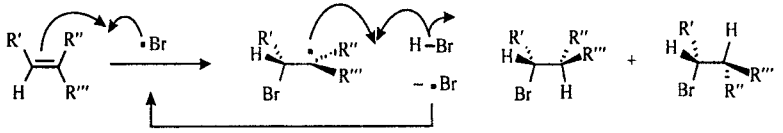
Radical reactions require an initiation step. In this example, a bromo radical is formed.



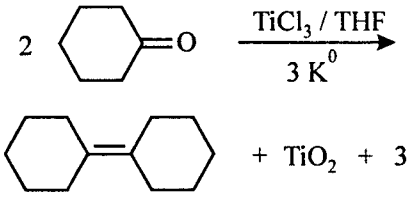
The reversal of the regiochemistry of addition is the result of the reversal of the order in which the two components add to the alkene. Radical addition leads to the formation of the more stable

radical, which reacts with HBr to give product and a new bromo radical:

Anti-Markovnikov

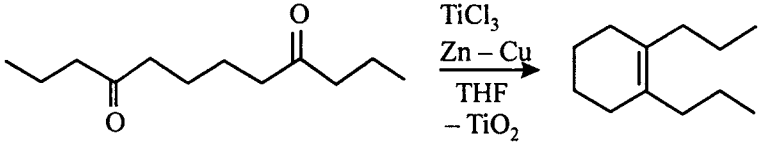


MCMURRY REACTION

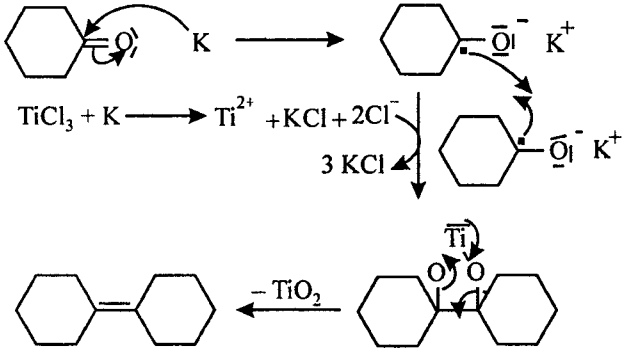


This reductive coupling involves two steps. The coupling is induced by single electron transfer to the carbonyl groups from alkali metal, followed by deoxygenation of the 1,2-diol with low-valent titanium to yield the alkene.

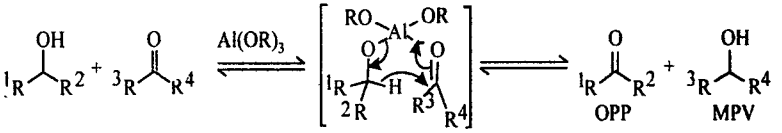
The McMurry Reaction works well to produce symmetric products or rings:



Mechanism



MEERWEIN-PONNDORF-VERLEY REDUCTION

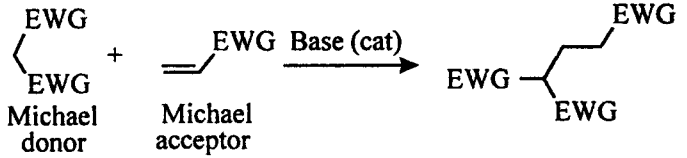


The aluminium-catalyzed hydride shift from the a-carbon of an alcohol component to the carbonyl carbon of a second component, which proceeds via a six-membered transition state, is referred to as the Meerwein-Ponndorf-Verley Reduction (MPV) or the Oppenauer Oxidation, depending on which component is the desired product. If the alcohol is the desired product, the reaction is viewed as the Meerwein-Ponndorf-Verley Reduction.

Isopropanol is useful as a hydride donor because the resulting acetone may be continuously removed from the reaction mixture by distillation.

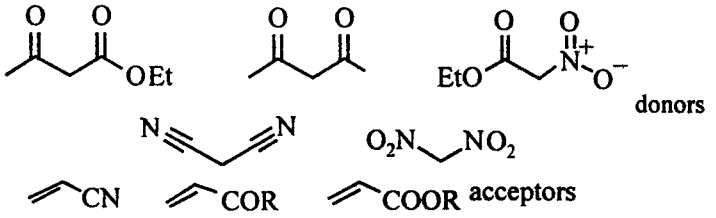
Grignard Reagents will sometimes yield the result of an MPV reduction if the carbonyl carbon is too hindered for nucleophilic addition.

MICHAEL ADDITION

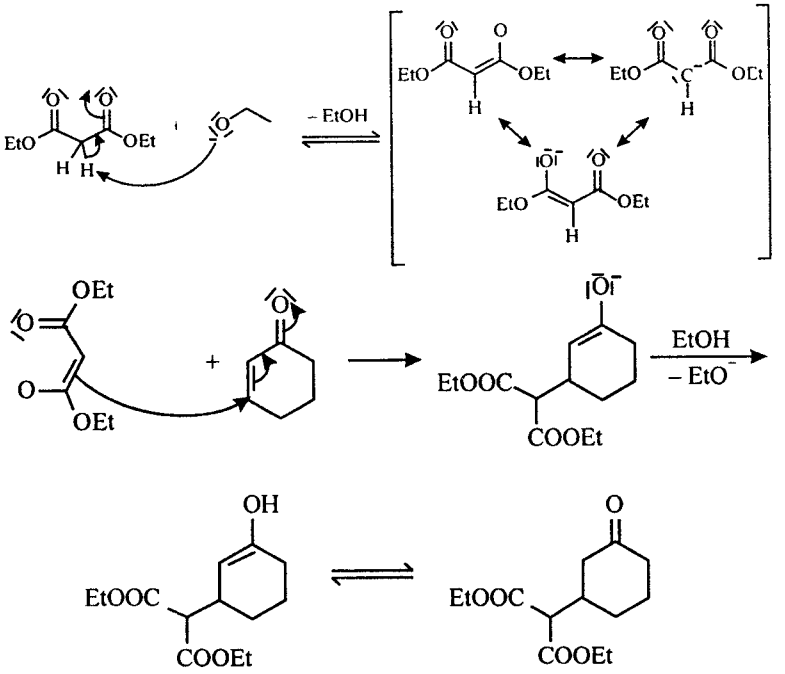


The 1,4-addition (or conjugate addition) of resonance-stabilized carbanions. The Michael Addition is thermodynamically controlled; the reaction donors are active methylenes such as malonates and nitroalkanes, and the acceptors are activated olefins such as α,β-unsaturated carbonyl compounds.

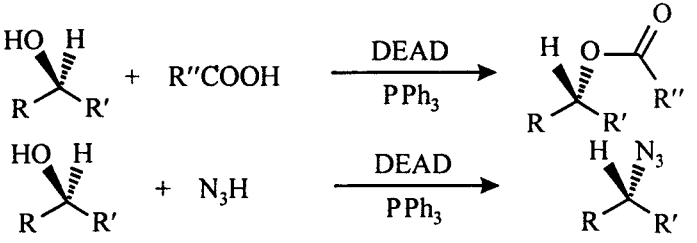
Examples:



Mechanism



MITSUNOBU REACTION

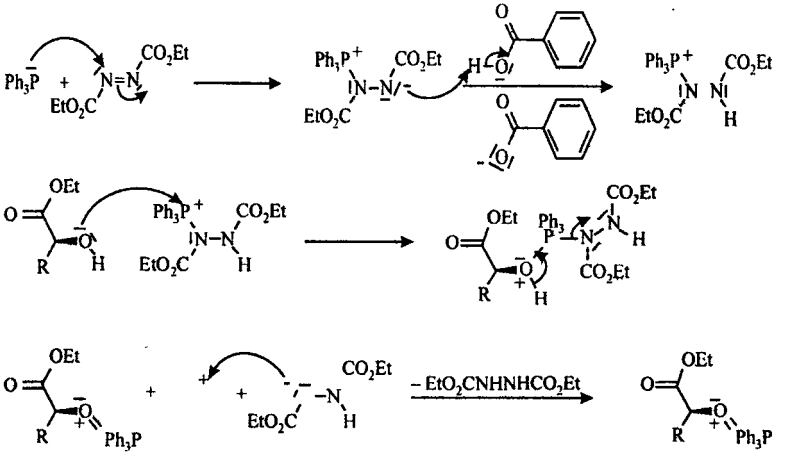


The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds. The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate) must be protonated during the course of the reaction to prevent from side reactions.

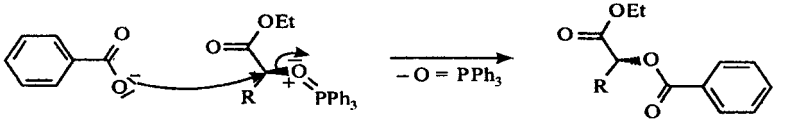
Suitable nitrogen nucleophiles include phthalimide or hydrogen azide; subsequent hydrolysis or selective reduction makes the corresponding amines accessible.

Mechanism

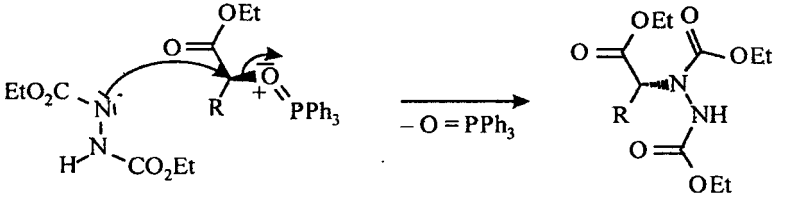
The triphenylphosphine combines with DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Substitution by the carboxylate, mercaptyl, or other nucleophile completes the process.



The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a powerful method for the inversion of stereogenic centres in natural product synthesis.

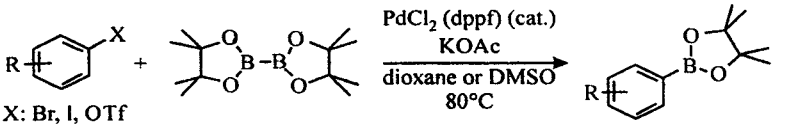


Side Reaction:

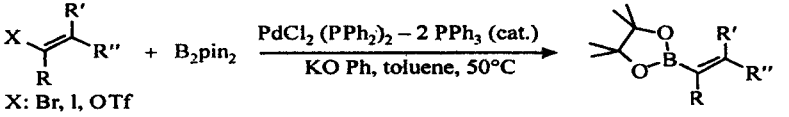


New protocols have been developed which allow better removal of side products and/or the conversion of more basic nucleophiles.

MIYAURA BORYLATION REACTION

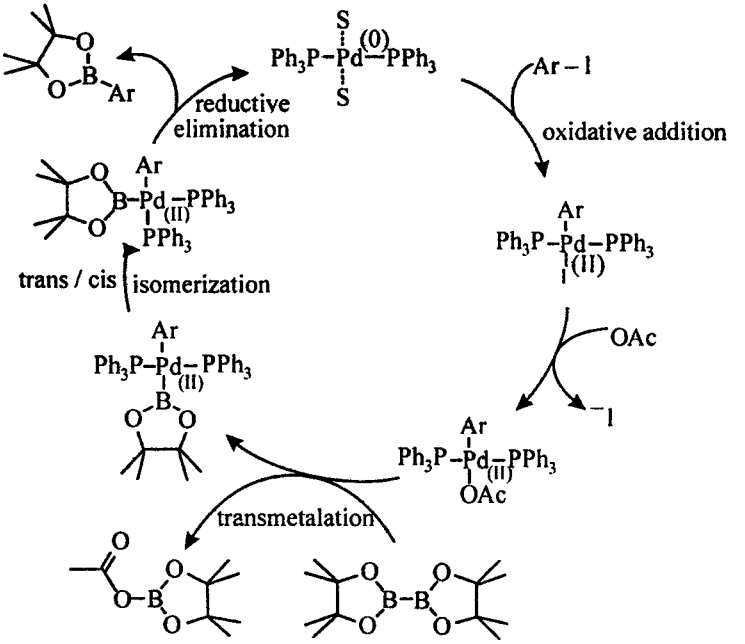


The Miyaura borylation reaction enables the synthesis of boronates by cross-coupling of bis(pinacolato)diboron (B_2pin_2) with aryl halides and vinyl halides.



Borylated products derived from B_2pin_2 allow normal work up including chromatographic purification and are stable towards air. Pinacol esters are difficult to hydrolyze, but they may serve as coupling partners in the Suzuki Coupling and similar reactions without prior hydrolysis.

Mechanism



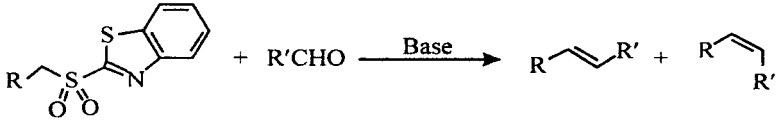
Crucial for the success of the borylation reaction is the choice of an appropriate base, as strong activation of the product enables the competing Suzuki Coupling. The use of KOAc and KOPh is actually the result of a screening of different reaction conditions by the Miyaura group.

The starting material bis(pinacolato)diboron is a poor Lewis acid and ^{11}B-NMR of KOAc and B_2bin_2 in DMSO-d6 shows no evidence of the coordination of the acetoxy anion to a boron atom leading to a tetrahedral activated species. However, the formation of an (acetato)palladium(II) complex after the oxidative addition of the halide influences the reaction rate of the transmetalation step. The Pd-O bond, which consists of a hard Lewis base with a soft Lewis acid, is more reactive than a Pd-X (X=Br, I) bond. In addition, the high oxophilicity of boron has to be considered as a driving force for the transmetalation step, which involves an acetato ligand.

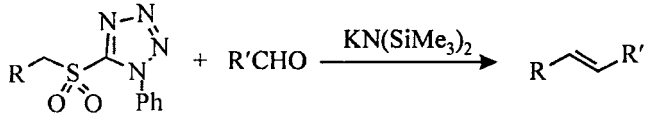
The mild reaction conditions allow the preparation of boronates which are not accessible via lithium or Grignard intermediates followed by borylation. The use of HBPin instead of B_2Pin_2 allows similar reactions in large scale synthesis, and also tolerates various reducible functional groups, although side products may arise due to dehalogenation of the aryl halide.

MODIFIED JULIA OLEFINATION

The Modified Julia Olefination (or Julia-Kocienski Olefination) enables the preparation of alkenes from benzothiazol-2-yl sulfones and aldehydes in a single step:

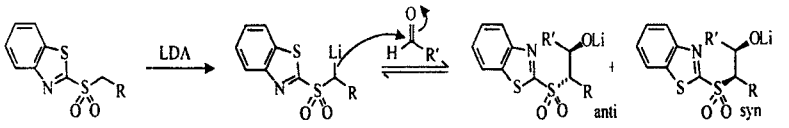


The Julia-Kochienski Olefination - a further refinement of the Modified Julia Olefination - offers very good *E*-selectivity.

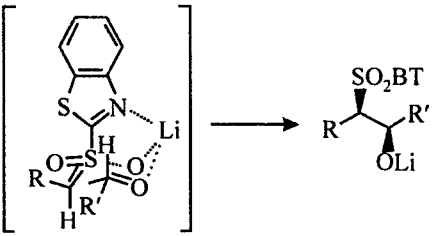


Mechanism

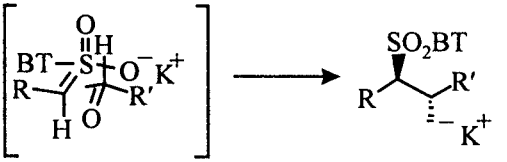
The initial addition of the sulfonyl anion to the aldehyde is reversible:



Whether the anti or syn intermediate is generated can be influenced to some extent by the choice of reaction conditions:

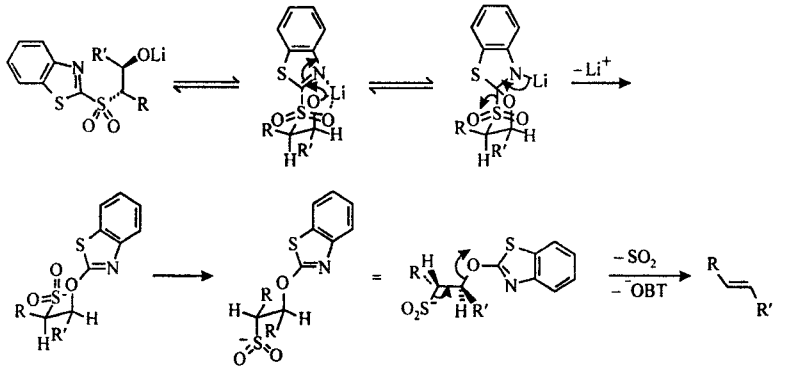


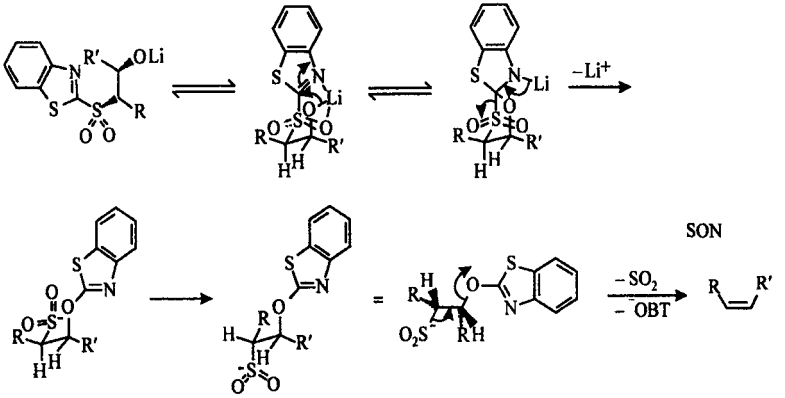
A chelate will form with small counterions (Li) and in apolar solvents, leading to a closed transition state.



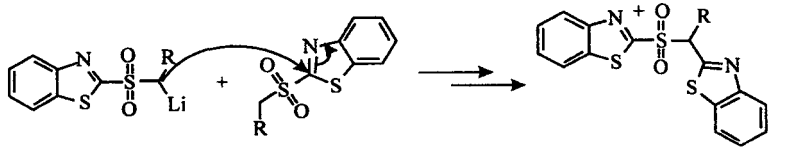
With larger counterions (K) and polar solvents, an open transition state becomes possible.

The intermediates that form react further to give *E*- and *Z*-isomers of the alkene:



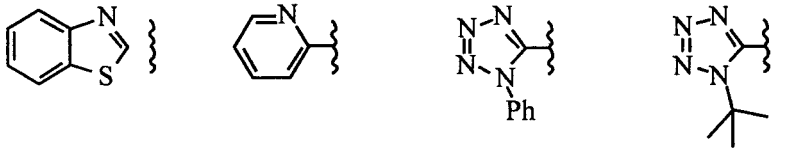


A mechanistically related nucleophilic addition of the sulfonyl carbanion to a second equivalent of the BT sulfone leads to a side product.



Since the reaction with the aldehyde occurs faster, it is best to carry out this reaction under "Barbier-like conditions": in general, the base is added to a mixture of the aldehyde and sulfone.

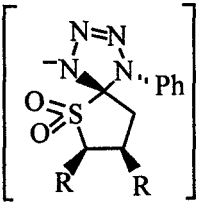
The benzothiazolyl group (BT) can play several roles: in one, it enables a more or less strongly pronounced complexation that influences the selectivity; on the other hand, it can also undergo nucleophilic substitution at the carbon attached to the sulfonyl group, which then becomes a leaving group. Other (hetero)cyclic substituents can assume these roles, and offer somewhat different selectivity:



BT Py PT TBT

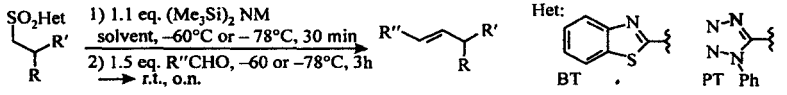
Specifically, the pyridinyl sulfone exhibits high *Z*-selectivity, while the 1-phenyl-1*H*-tetrazol-5-yl sulfone (PT-SO_2R) gives somewhat better *E*-selectivity than the BT sulfones. The reason for

this is the sterically demanding phenyl group, which favours the following transition state:

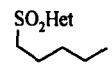
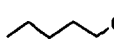


The 1-phenyl-1*H*-tetrazol-5-yl sulfones do not have a tendency to self-condense, so they can first be deprotonated with base and then reacted with the aldehyde. This makes possible a far milder reaction process, including reactions with base-sensitive aldehydes.

The following Table shows the selectivity and yields for BT and PT sulfones in various solvents, where they are first metalated with various bases and then reacted with an aldehyde.

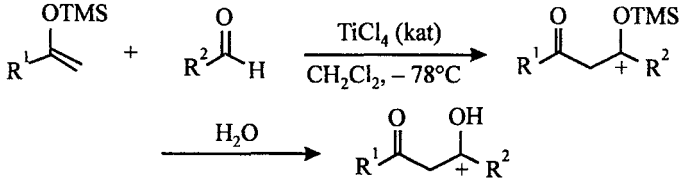


In contrast to the classical Julia Olefination, the Modified Julia Olefination offers the possibility of saving one or two synthesis steps. In addition, there are fewer problems with scale-up than with the classical variant. The *E/Z*-selectivity can be controlled by varying the sulfonyl group, solvent and base.

	Solvent	T (°C)	M	Benzothiazole (BT) Yield (%, GC)	E:Z (GC)	Phenyltetrazole(PT) Yield (%, GC)	E:Z (GC)
	PhMe	–78	Li	8	40:60	55	57:43
			Na	29	51:49	80	59:41
			K	15	47:53	13	64:36
	Et_2O	–78	Li	7	43:57	76	73:27
			Na	17	53:47	90	57:43
			K	68	51:49	30	72:28
	THF	–78	Li	42	60:40	97	75:25
			Na	0	–	89	76:24
			K	24	55:45	71	86:14
	DME	–60	Li	3	55:45	95	77:23
			Na	27	77:23	92	86:14
			K	6	75:25	71	94:6

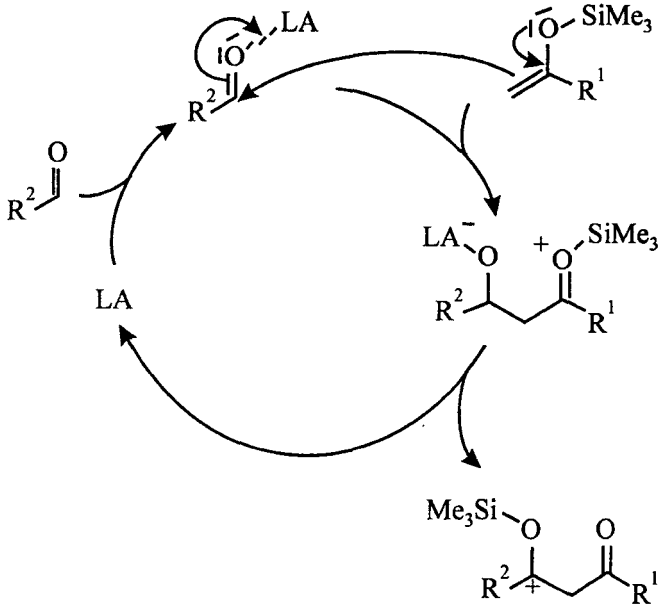
In contrast to the classical Julia Olefination, the Modified Julia Olefination offers the possibility of saving one or two synthesis steps. In addition, there are fewer problems with scale-up than with the classical variant. The *E/Z*-selectivity can be controlled by varying the sulfonyl group, solvent and base.

MUKAIYAMA ALDOL ADDITION



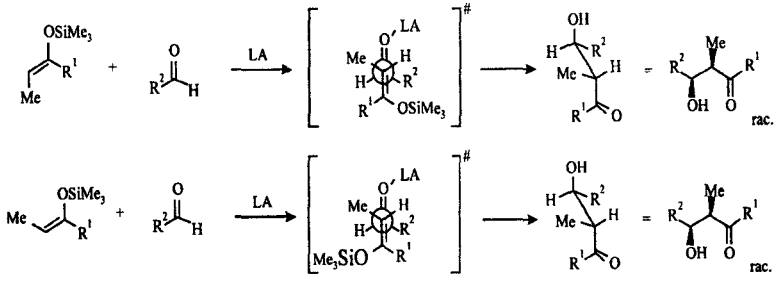
The use of silyl enol ethers as an enolate equivalent in Lewis acid-catalyzed aldol additions. The trimethylsilyl group is thought of as a sterically demanding hydrogen equivalent that activates the enol and traps the aldol hydroxyl.

Mechanism

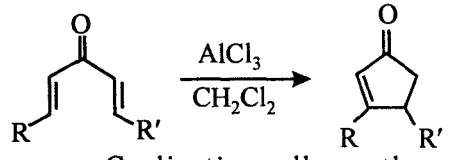


The open transition state is preferred, but the outcome of the reaction (*syn/anti*) depends on the size of substituents and on the Lewis acid. New modified protocols allow *syn*- or *anti*-selective transformations and even the selective preparation of enantiomers.

Transition-state for *syn*-selective transformations:



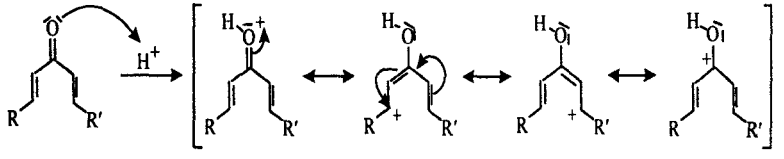
NAZAROV CYCLIZATION



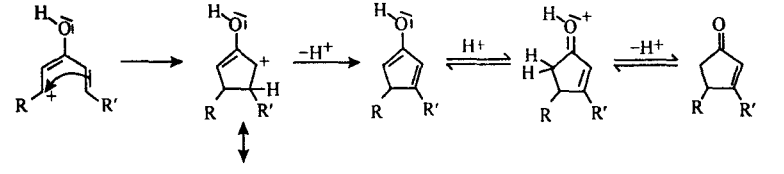
The Nazarov Cyclization allows the synthesis of cyclopentenones from divinyl ketones.

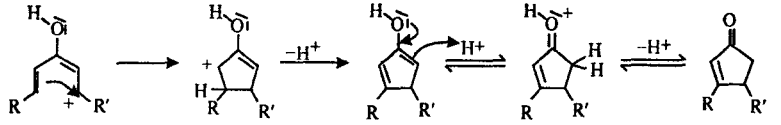
Mechanism

The reaction is catalyzed by strong Lewis or Brψnstedt acids, and one or more equivalents of the Lewis acid are normally necessary:

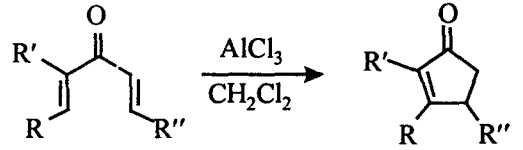


The regioselectivity of the cyclization is quite low if the side chains have a similar degree of substitution.

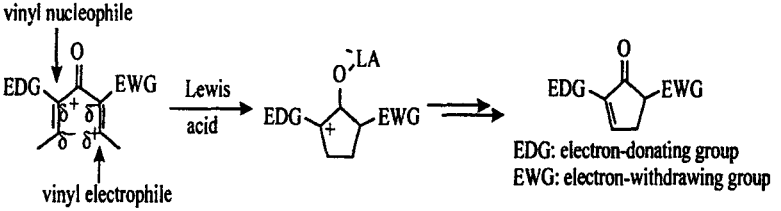


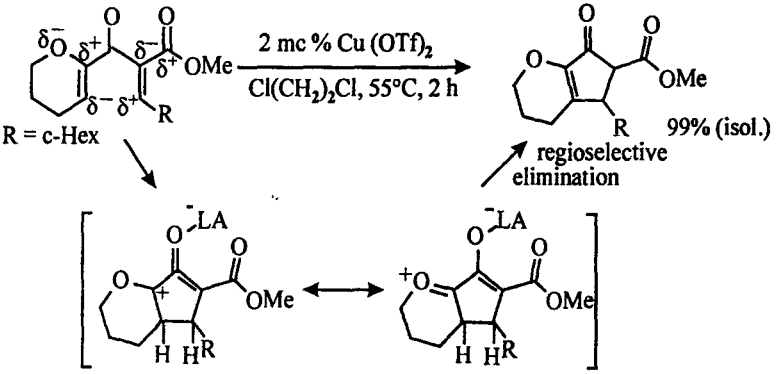


Nazarov reactions with more highly substituted substrates generate the product having the double bond with the highest degree of substitution:

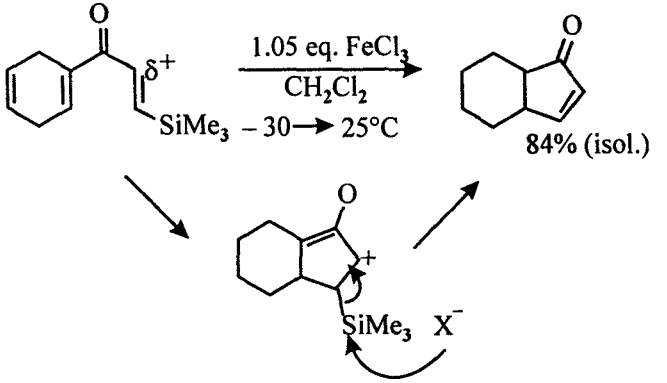


Electron-donating and -withdrawing substituents can polarize the conjugated system in the Nazarov Reaction, which facilitates the cyclization and gives better regioselectivity:

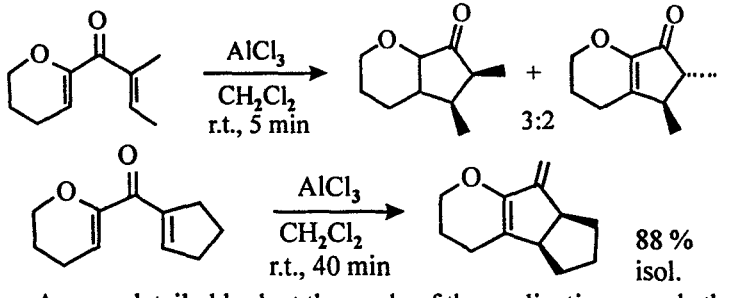




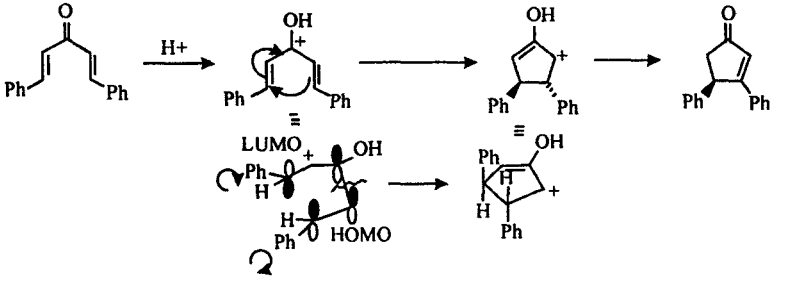
Another approach uses silicon's ability to stabilize β-carbocations (β-effect). In addition, the TMS group behaves like a proton and is removed after nucleophilic activation:



A limiting factor is also the stereoselectivity. As the substituents α to the keto group are prone to racemization using strong Lewis or Brønstedt acids due to equilibria involving proton transfer, the diastereoselectivity is often low:

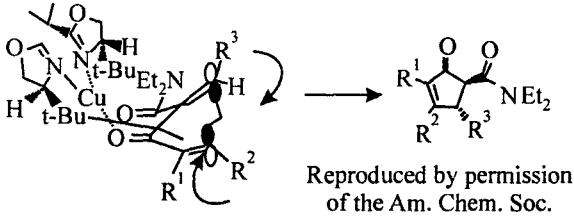


A more detailed look at the mode of the cyclization reveals that 4 π electrons are involved in a conrotatory mechanism, but any diastereoselectivity involving the new formed σ bond is lost after elimination of the proton:



The Nazarov Cyclization is a rare example of a Lewis acid-catalyzed 4-π conrotatory electrocyclic reaction. Asymmetric

induction could be achieved if a chiral Lewis acid were able to control the direction of the conrotatory closure. However, only a few such reactions have been reported. Common drawbacks are low enantioselectivity and the use of nearly stoichiometric amounts of the chiral Lewis acids, which must still be overcome.



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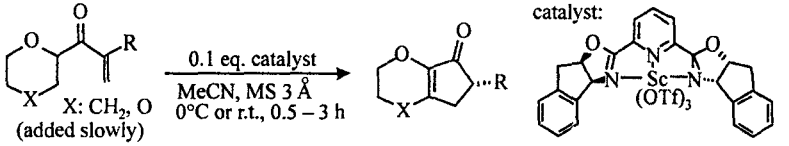
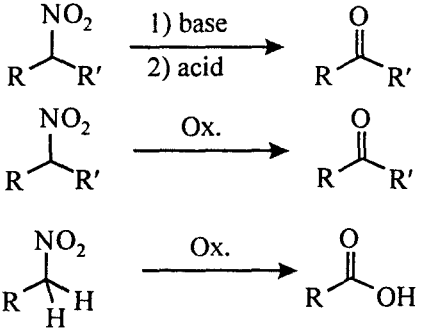
The catalyst shown below to the right induces an asymmetric proton transfer, which generates the stereogenic centre α to the keto group:



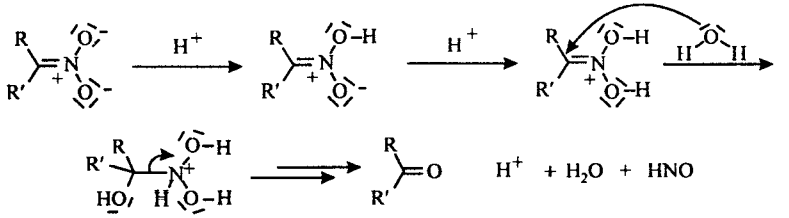
NEF REACTION



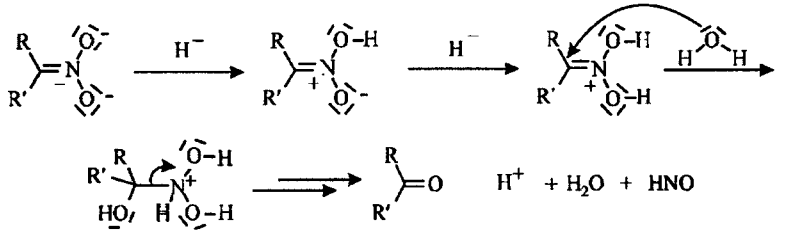
The conversion of nitro compounds into carbonyls is known as the Nef Reaction. Various methodologies have been developed, but the most important is the standard procedure: a preformed nitronate salt is poured into strong aqueous acid (pH < 1). Some oxidative variations have also found wide application, and some reductive methods have even been developed.

Mechanism

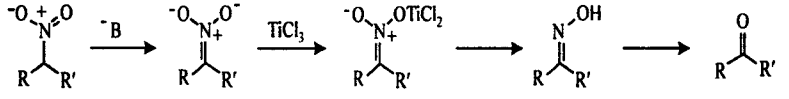
Nitroalkanes are relatively strong carbon acids, and deprotonation leads to the nitronate salt. The hydrolysis of this intermediate must take place in strong acid, to prevent the formation of side products such as oximes or hydroxynitroso compounds:



The procedure using the commercial reagent Oxone is mechanistically interesting:



The reductive method leads to oximes, which may be hydrolyzed to the corresponding carbonyl compound. Ti(III) serves to reduce the N-O bond, and titanium's strong affinity towards oxygen facilitates the hydrolysis to complete the conversion:



NEGISHI COUPLING

$$RX + R'ZnX \xrightarrow[Cl_2Pd(PPh_3)_2 + 2(i\text{-}Bu)_2\dot{A}lH]{Ni(PPh_3)_4 \quad or} R-R'$$

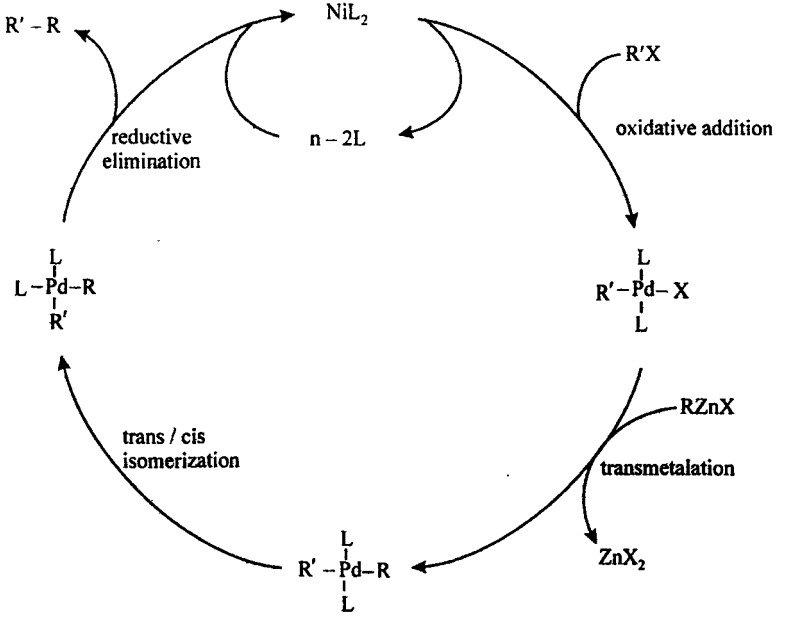
R = alkenyl, aryl, allyl, benzyl, propargyl

R′ = alkenyl, aryl, alkynyl, alkyl, benzyl, allyl

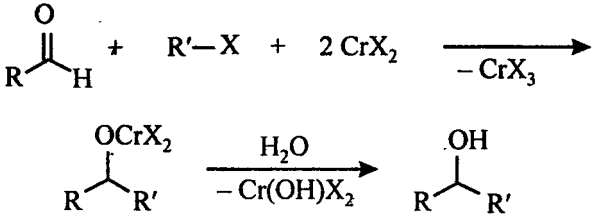
The Negishi Coupling was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. The versatile nickel- or palladium-catalyzed coupling of organozinc compounds

with various halides (aryl, vinyl, benzyl, or allyl) has broad scope, and is not restricted to the formation of biaryls.

Mechanism



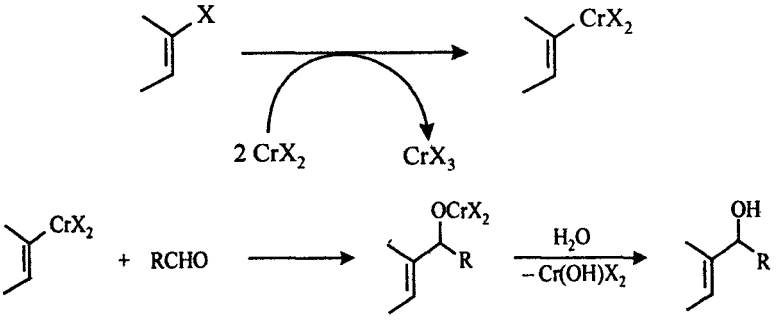
NOZAKI-HIYAMA COUPLING



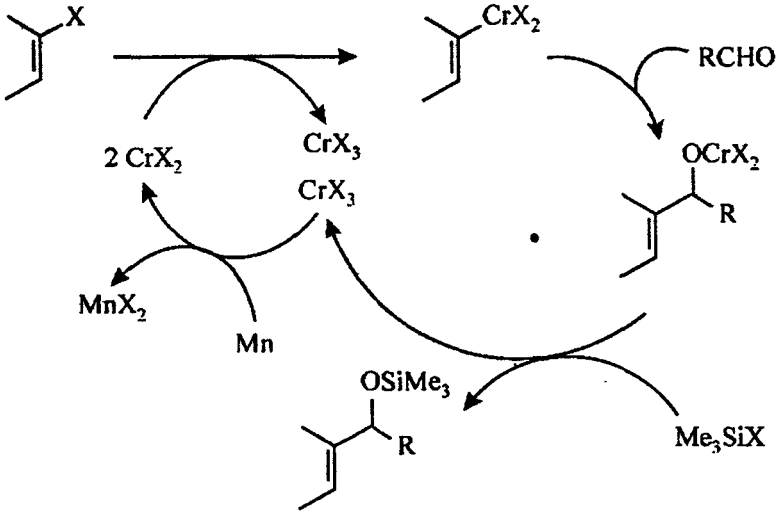
This coupling between halides and aldehydes is a chromium-induced redox reaction. A key advantage is the high chemoselectivity toward aldehydes. A disadvantage is the use of excess toxic chromium salts.

Newer methods allow the use of catalytic amounts chromium(II), which is regenerated by reduction with manganese or via electrochemical reduction.

Mechanism



Catalyzed Reaction:

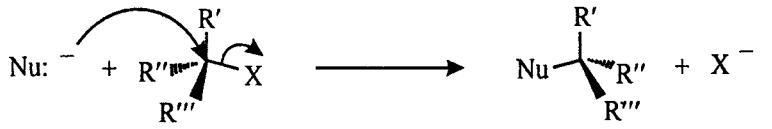


NUCLEOPHILIC SUBSTITUTION (S_N1S_N2)

Nucleophilic substitution is the reaction of an electron pair donor (the nucleophile, Nu) with an electron pair acceptor (the electrophile). An sp^3-hybridized electrophile must have a leaving group (X) in order for the reaction to take place.

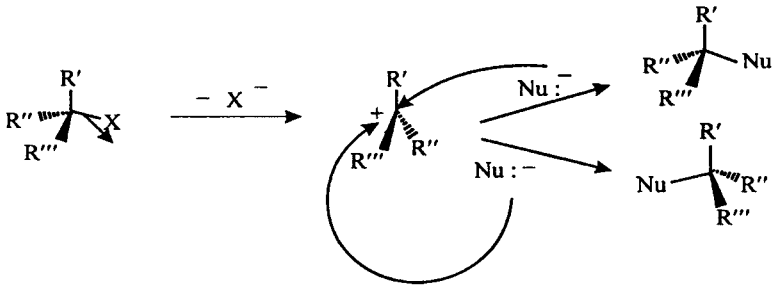
Mechanism

The term S_N2 means that two molecules are involved in the actual transition state:



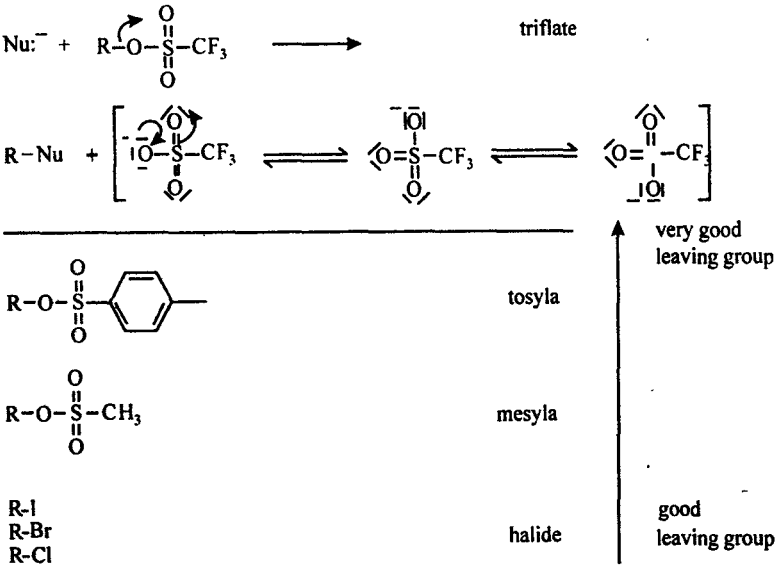
The departure of the leaving group occurs simultaneously with the backside attack by the nucleophile. The S_N2 reaction thus leads to a predictable configuration of the stereocentre - it proceeds with inversion (reversal of the configuration).

In the S_N1 reaction, a planar carbenium ion is formed first, which then reacts further with the nucleophile. Since the nucleophile is free to attack from either side, this reaction is associated with racemization.

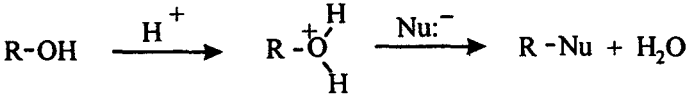


In both reactions, the nucleophile competes with the leaving group. Because of this, one must realise what properties a leaving group should have, and what constitutes a good nucleophile. For this reason, it is worthwhile to know which factors will determine whether a reaction follows an S_N1 or S_N2 pathway.

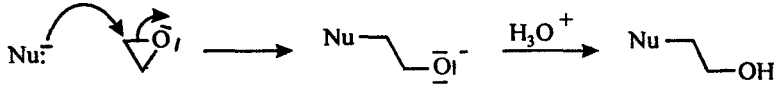
Very good leaving groups, such as triflate, tosylate and mesylate, stabilize an incipient negative charge. The delocalization of this charge is reflected in the fact that these ions are not considered to be nucleophilic.



Hydroxide and alkoxide ions are not good leaving groups; however, they can be activated by means of Lewis or Brψnsted acids.

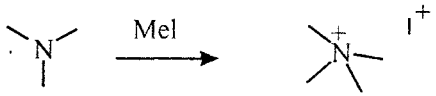


Epoxides are an exception, since they relieve their ring strain when they undergo nucleophilic substitution, with activation by acid being optional:

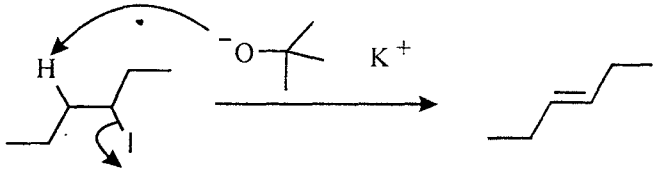


Triflate, tosylate and mesylate are the anions of strong acids. The weak conjugate bases are poor nucleophiles. Nucleophilicity increases in parallel with the base strength. Thus, amines, alcohols and alkoxides are very good nucleophiles. Base strength is a rough measure of how reactive the nonbonding electron pair is; thus, it is not necessary for a nucleophile to be anionic.

Under substitution conditions, amines proceed all the way to form quaternary salts, which makes it difficult to control the extent of the reaction.

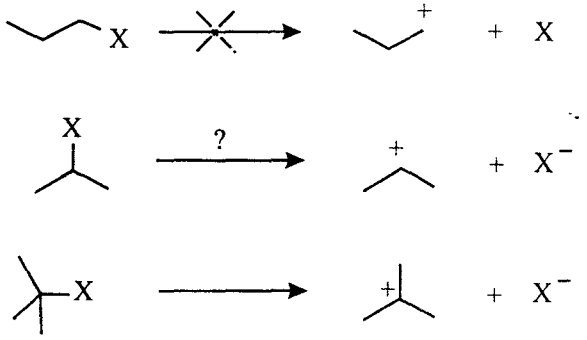


However, as a nucleophile's base strength and steric hindrance increase, its basicity tends to be accentuated. If there are abstractable protons at the β-position of the electrophile, an elimination pathway can compete with the nucleophilic substitution.



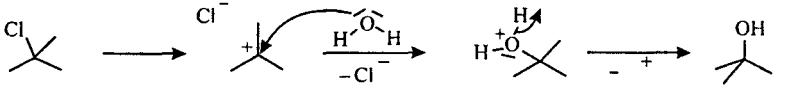
An additional factor that plays a role is the character of the solvent. Increasing stabilization of the nucleophile by the solvent results in decreasing reactivity. Thus, polar protic solvents will stabilize the chloride and bromide ions through the formation of hydrogen bonds to these smaller anions. Iodide is a comparatively better nucleophile in these solvents. The reverse behaviour predominates in aprotic polar media.

The solvent also plays an important role in determining which pathway the reaction will take, S_N1 versus S_N2. It may safely be assumed that a primary-substituted leaving group will follow an S_N2 pathway in any case, since the formation of the corresponding unstable primary carbenium ion is disfavoured. Reaction by the S_N1 pathway is highly probable for compounds with tertiary substitution, since the corresponding tertiary carbenium ion is stabilized through hyperconjugation:



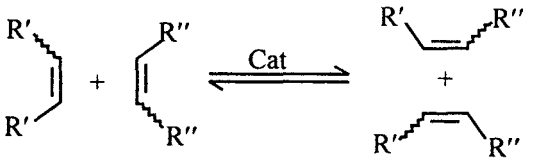
The better the solvent stabilizes the ions, the more probable that the reaction will follow an S_N1 pathway (e.g., in polar protic solvents such as water/acetone). The more highly substituted is the incipient carbenium ion, the more probable that the reaction will follow an S_N1 pathway. The more unreactive the nucleophile, the more probable it becomes that a reaction with secondary and tertiary electrophiles will follow an S_N1 pathway. A weaker nucleophile is not as effective in the backside attack, since this location is sterically shielded, especially in the case of tertiary substrates. Carbenium ions are planar and therefore less sterically hindered, and are naturally more reactive as electrophiles than the uncharged parent compound.

The hydrolysis of *tert*-butyl chloride is a typical S_N1 reaction:



OLEFIN METATHESIS

Olefin Metathesis (Grubbs Reaction) allows the exchange of substituents between different olefins - a transalkylidenation.

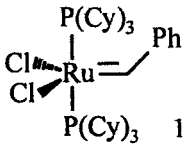


This reaction was first used in petroleum reformation for the synthesis of higher olefins (Shell higher olefin process - SHOP), with nickel catalysts under high pressure and high temperatures. Nowadays, even polyenes with MW > 250,000 are produced industrially in this way.

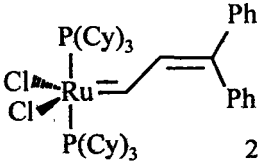
Synthetically useful, high-yield procedures for lab use include ring closure between terminal vinyl groups, cross metathesis - the intermolecular reaction of terminal vinyl groups - and ring opening of strained alkenes. When molecules with terminal vinyl groups are used, the equilibrium can be driven by the ready removal of the product ethene from the reaction mixture. Ring opening metathesis can employ an excess of a second alkene (for example ethene), but can also be conducted as a homo- or co-polymerization reaction. The driving force in this case is the loss of ring strain.

All of these applications have been made possible by the development of new homogeneous catalysts. Shown below are some of these catalysts, which tolerate more functional groups and are more stable and easy to handle.

Grubbs

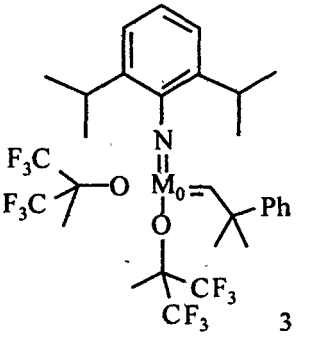


1



2

Schrock

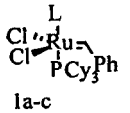


3

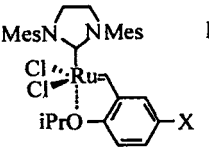
The Schrock catalysts are more active and are useful in the conversion of sterically demanding substrates, while the Grubbs catalysts tolerate a wide variety of functional groups.

The second generation Grubbs catalysts are even more stable and more active than the original versions. Some of these are depicted:

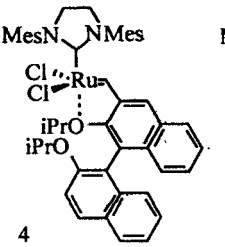
Activity: 2 < 1b < 4 < 5 ⟹



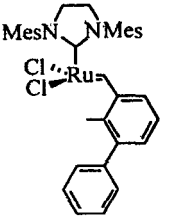
1a-c



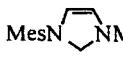
2 X = H
3 X = Br



4

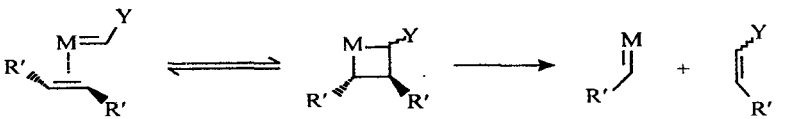


5

ac L = PCy_3 bc L =  cL = 

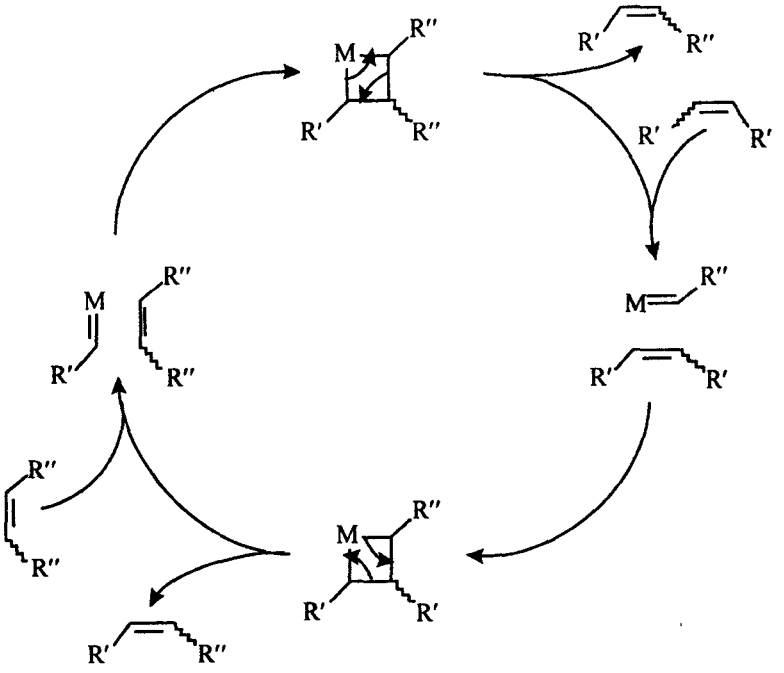
Mechanism

Initiation:

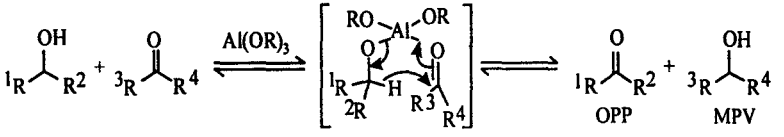


Catalytic Cycle:

Chauvin Mechanism



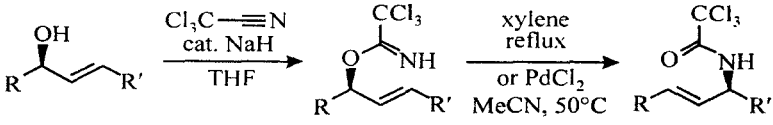
OPPENAUER OXIDATION



The aluminium-catalyzed hydride shift from the α-carbon of an alcohol component to the carbonyl carbon of a second component, which proceeds over a six-membered transition state, is named Meerwein-Ponndorf-Verley-Reduction (MPV) or Oppenauer Oxidation (OPP) depending on the isolated product. If aldehydes or ketones are the desired products, the reaction is viewed as the Oppenauer Oxidation.

Non-enolizable ketones with a relatively low reduction potential, such as benzophenone, can serve as the carbonyl component used as the hydride acceptor in this oxidation.

OVERMAN REARRANGEMENT

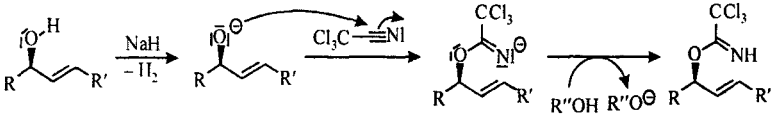


The Overman Rearrangement allows the conversion of readily available allylic alcohols into allylic amines by a two-step synthesis involving the rearrangement of an allylic trichloroacetimidate to an allylic trichloroacetamide with clean 1,3-transposition of the alkenyl moiety.

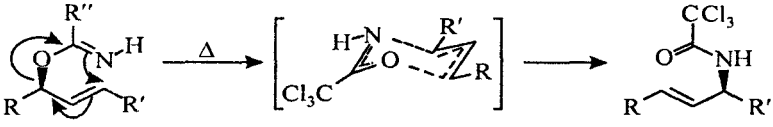
Allylic amines are useful precursor of a variety of nitrogen-containing molecules, such as alkaloids, antibiotics and unnatural amino acids.

Mechanism

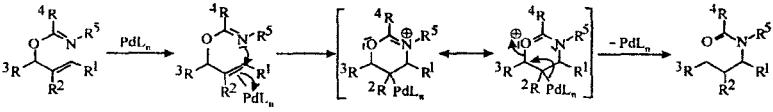
The deprotonated alcohol ads to trichloroacetonitrile to give a trichloroacetimidate anion. As this latter intermediate can readily deprotonate the starting alcohol, only a catalytic amount of a strong base is needed.



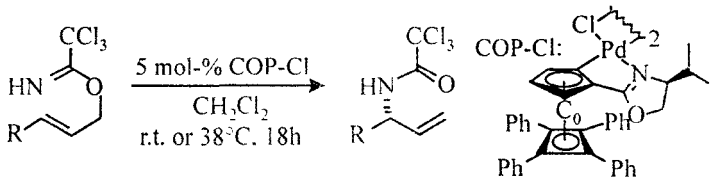
The formation of the allylic amine can involve a thermal [3,3]-sigmatropic rearrangement - comparable to the Claisen Rearrangement - that prefers to proceed *via* a chair-like transition state:



Alternatively, the rearrangement can be induced by a transition metal catalyst such as Pd(II) or Hg(II):



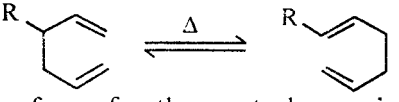
Some chiral transition metal catalysts bind with face-selectivity toward the substrate, which enables the enantioselective conversion of prochiral starting materials:



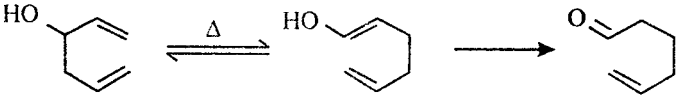
The detailed explanation of the reaction mechanism and the stereoselection induced by transition metal catalysts along with some early examples of Pd-catalyzed chiral conversions.

OXY-COPE REARRANGEMENT

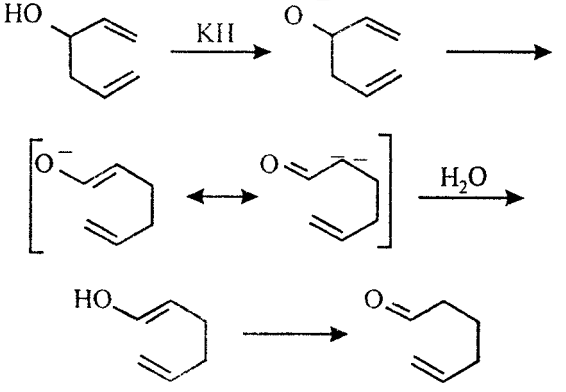
The Cope Rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1.5-diene. The main product is the thermodynamically more stable regioisomer. The Oxy-Cope has a hydroxyl substituent on an sp^3-hybridized carbon of the starting isomer.



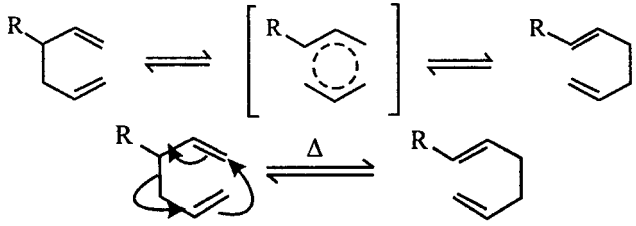
The driving force for the neutral or anionic Oxy-Cope Rearrangement is that the product is an enol or enolate (resp.), which can tautomerize to the corresponding carbonyl compound. This product will not equilibrate back to the other regioisomer.



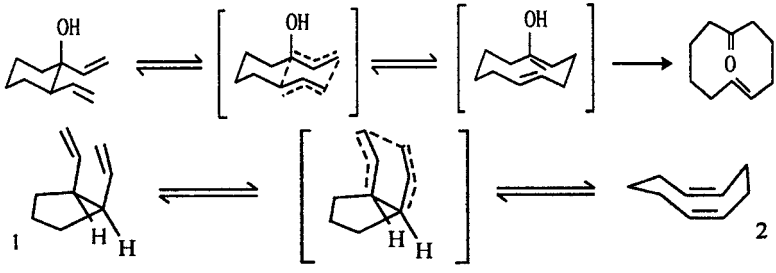
The Oxy-Cope Rearrangement proceeds at a much faster rate when the starting alcohol is deprotonated, e.g. with KH. The reaction is then up to 10^{17} times faster. and may be conducted at room temperature. Aqueous work up then gives the carbonyl compound.



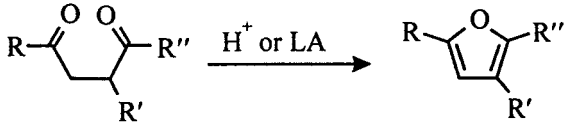
Mechanism



Two transition states are possible, and the outcome of the reaction can be predicted on the basis of the most favourable overlap of the orbitals of the double bond, as influenced by stereoelectronic factors:

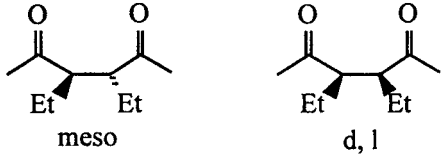


PAAL-KNORR FURAN SYNTHESIS

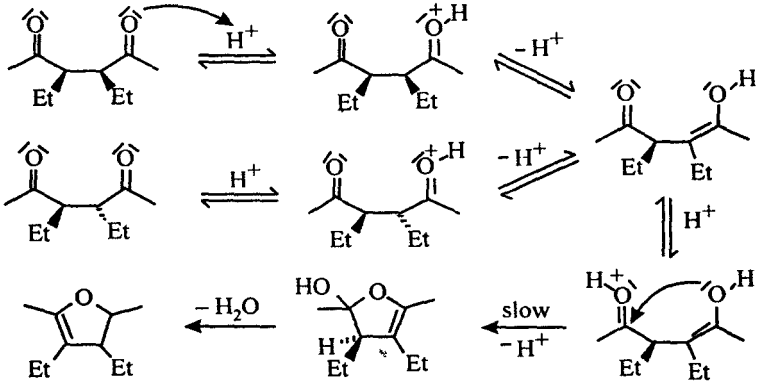


The acid-catalyzed cyclization of 1,4-dicarbonyl compounds known as the Paal-Knorr synthesis is one of the most important methods for the preparation of furans. As many methods for the synthesis of 1,4-diones have recently been developed, the synthetic utility of the Paal-Knorr reaction has improved.

Mechanism

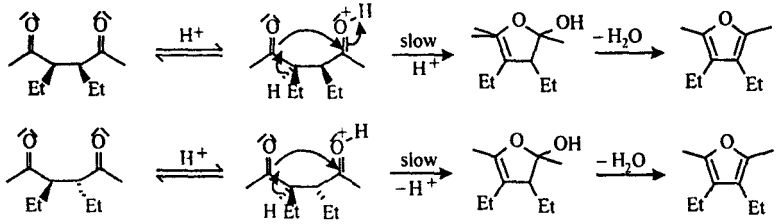


A comparison of the cyclizations of *meso*- and *dl*-3,4-diethyl-2,5-hexanediones showed that these compounds cyclize at unequal rates, and that the stereochemical configuration of unchanged dione is preserved during the reaction. These findings are at odds with the commonly accepted mechanism that involves the ring closure of a rapidly formed monoenol.



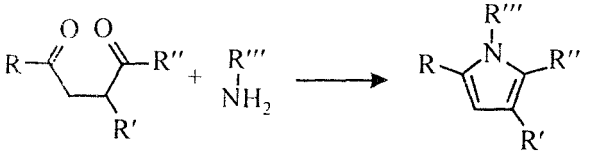
The rate of acid-catalyzed enolization is known not to be very sensitive to the structure of the ketone. Since the rate-determining step would be the same for both substrates, the differences in the reaction rate cannot be explained by this mechanism.

A mechanism in which the substituents would interfere differently in the rate-determining step is shown below. The ease of achieving a suitable conformation for the cyclization is not the same for both molecules:



A more detailed description can be found in the work by Amarath and Amarath, and references cited therein.

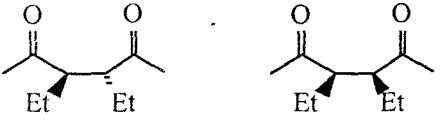
PAAL-KNORR PYRROLE SYNTHESIS



The Paal-Knorr Pyrrole Synthesis is the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to give a pyrrole.

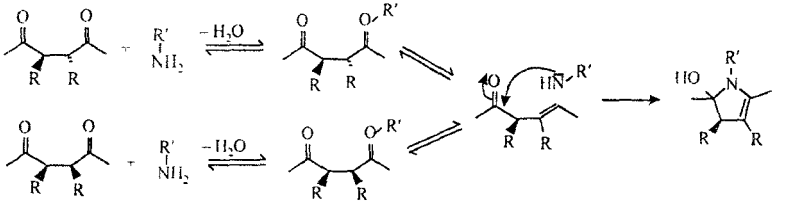
The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at pH < 3 lead to furans as main products.

Mechanism

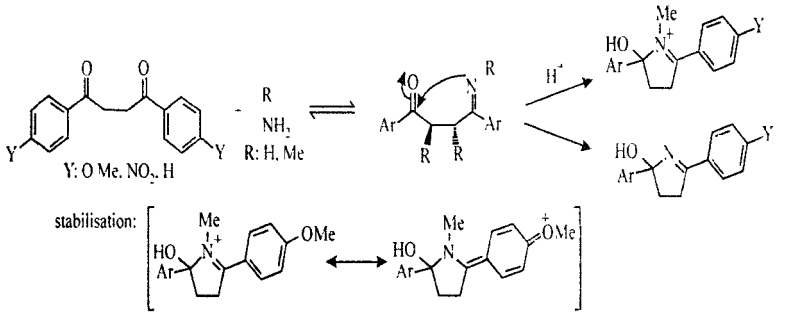


meso d, l

Amarath has shown that *meso*- and *dl*-3,4-diethyl-2,5-hexanediones cyclize at unequal rates, and that the stereochemical configuration of the unchanged dione is preserved during the reaction. Any mechanism that involves the formation of an enamine before the rate-determining step - the cyclization - must be ruled out.

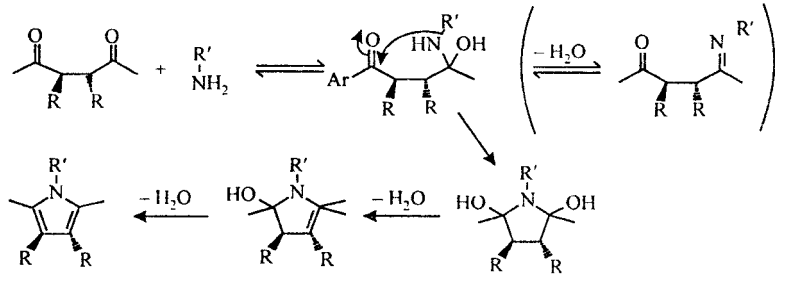


If the ring is formed from an imine that is generated from a primary amine, a charged immonium ion must be an intermediate. Amarath tried to stabilize or destabilize the immonium ion with different aryl groups as substituents:



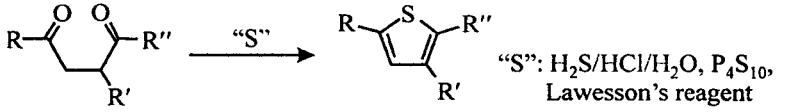
The use of ammonia should give an uncharged intermediate and is therefore less affected by the choice of substitutents. The substituents also influence the basicity of the imine, with the nitro group leading to a more basic nucleophile. The rates of cyclization have been compared using ammonia and methylamine. The nitro group has in every situation had a positive effect on the reaction rate. The methoxy group has a negative effect on the cyclization rate in each case. Comparison of the relative reaction rates of all substrates (R: H, Me) showed no specific stabilization/destabilization effect for a possible mechanism involving an immonium ion.

A mechanism that accounts for the influence of different substitution patterns (*meso*, *dl*) and explains the influence of a *p*-nitrophenyl group making a nucleophile more reactive (although not as the imine) includes the cyclization of a hemiacetal which is followed by different dehydration steps:



A more detailed description can be found in the work by Amarath, and references cited therein.

PAAL-KNORR THIOPHENE SYNTHESIS

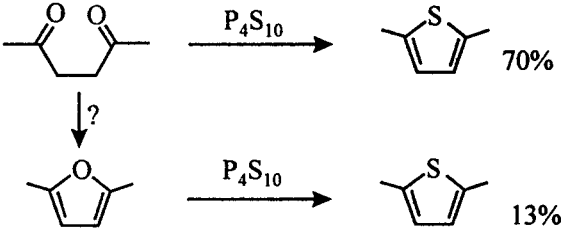


The Paal-Knorr Thiophene Synthesis allows the generation of thiophenes by condensation of a 1,4-dicarbonyl compound in the presence of an excess of a source of sulfur such as phosphorous pentasulfide or Lawesson's reagent.

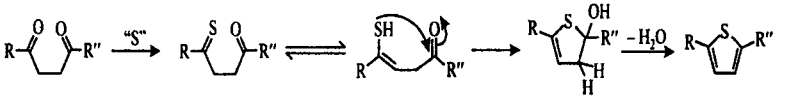
Attention: some toxic H_2S is formed as a side product regardless of the sulfur source.

Mechanism

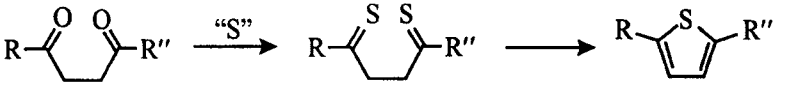
Reagents such as phosphorus pentasulfide or Lawesson's reagent act as sulfurizing agents as well as dehydrating agents, allowing a reaction pathway that could lead first to the formation of furans. This hypothesis was tested by Foye by treatment of different 1,4-dicarbonyl compounds and the corresponding possible furan intermediates (such as acetonylacetone and 2,5-dimethylfuran) with phosphorus pentasulfide. Using the same reaction conditions, the differences in the yields of 2,5-dimethylthiophene excludes the possibility that a predominant reaction pathway could lead through furan intermediates:



Foye suggested the following reaction pathway:

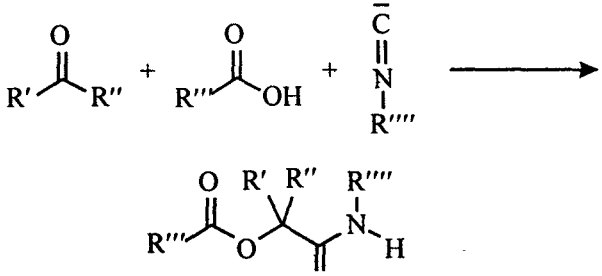


The occurrence of a bis-thioketone intermediate is assumed to be possible but not necessary



The reaction mechanism still needs further elucidation before it is fully understood.

PASSERINI REACTION

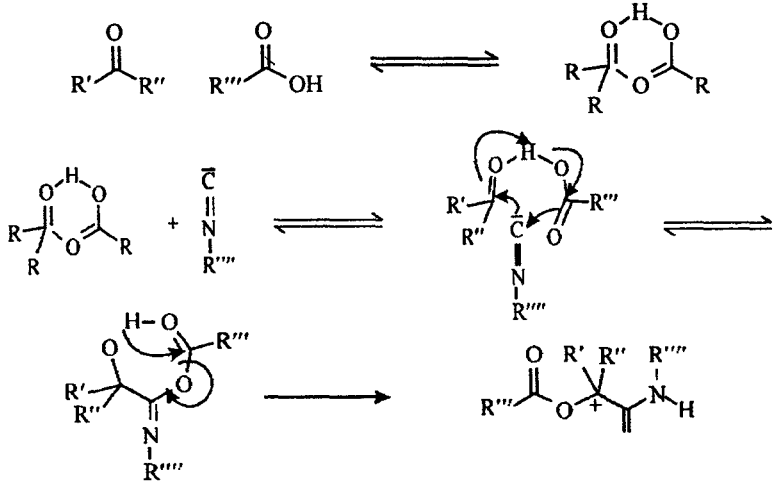


This three-component reaction between a carboxylic acid, a carbonyl compound such as a ketone or aldehyde, and an isocyanide, offers direct access to α-hydroxy carboxamides.

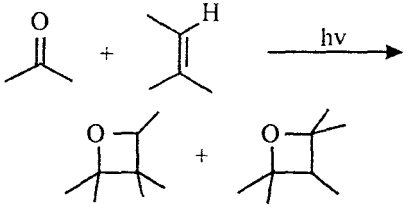
Mechanism

The Passerini Reaction proceeds rapidly if the reaction is performed in aprotic solvents at room temperature. High yields are obtained with high concentrations of the starting materials in the reaction mixture.

From these findings, it is assumed that the Passerini Reaction does not follow an ionic pathway. Hydrogen bonding is believed to play a crucial role in the formation of the presumed cyclic transition state for this reaction.



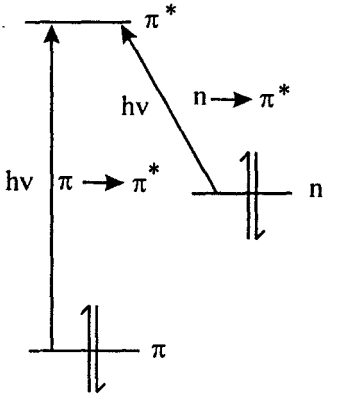
PATERNO-BÜCHI REACTION



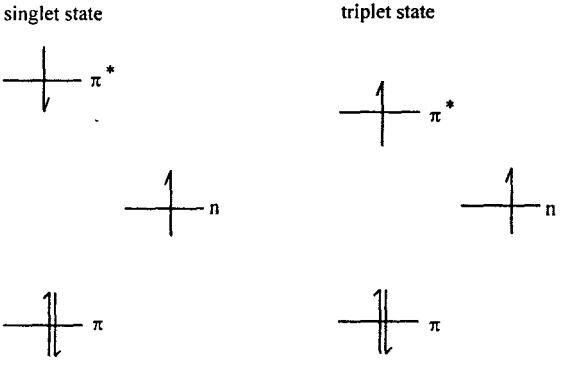
The photochemical [2+2] cycloaddition of a carbonyl with an olefin to give an oxetane.

Mechanism

The possible transitions (C=O) are shown below:

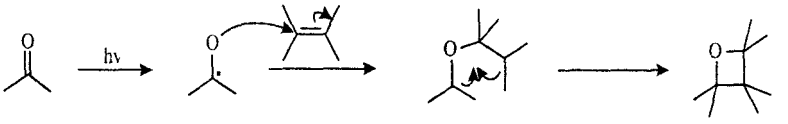


Once the carbonyl ground state has been photoexcited, either a singlet or triplet state may be formed:



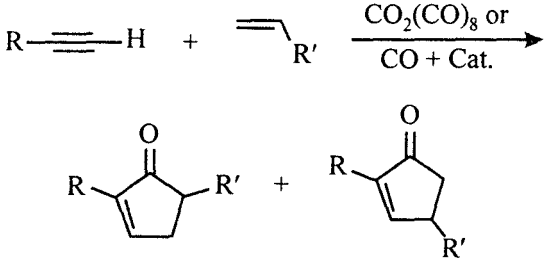
n,π*-transition

Either type of transition (n,π* and π,π*) and electronic state (singlet, triplet) may participate in the first stage of this reaction, which is rationalized by invoking diradical intermediates:



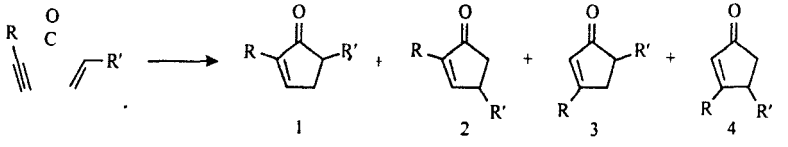
Breaking of the new σ-bonds requires more energy, and the reverse reaction is not possible using same light frequency.

PAUSON-KHAND REACTION



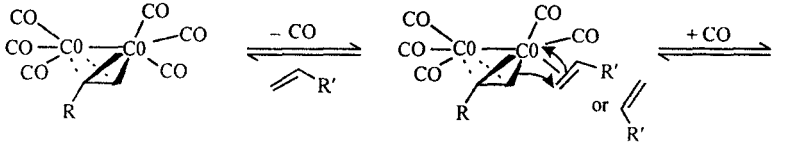
The Pauson-Khand Reaction is a [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide.

Mechanism

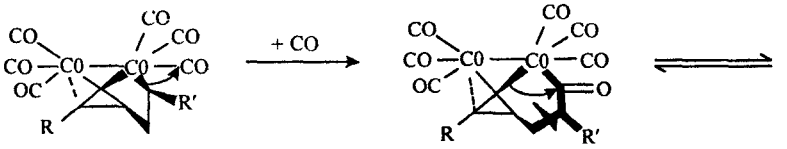


The following mechanism is postulated, although only the stable alkyne $Co_2(CO)_6$ complex has been isolated.

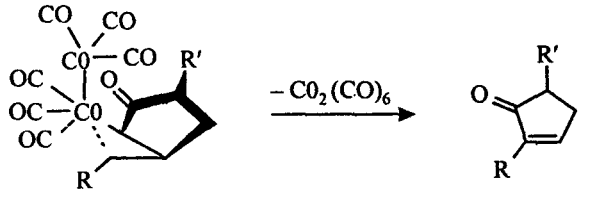
The stereochemistry of the complexation of the alkene at cobalt is guided by steric repulsions between the R and R' groups, so that isomers **1** and **2** are favoured.



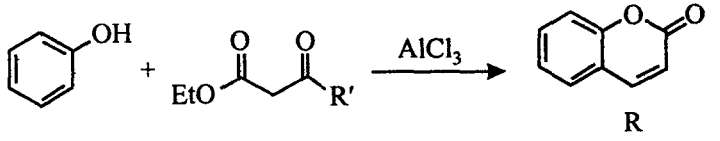
The insertion of the alkene is followed by insertion of carbon monoxide and reductive elimination of one Co unit:



Dissociation of the second Co unit gives the resulting cyclopentenone product:



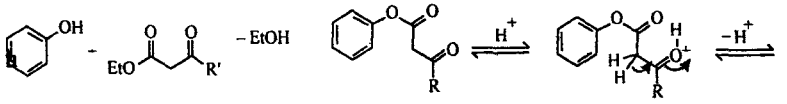
PECHMANN CONDENSATION



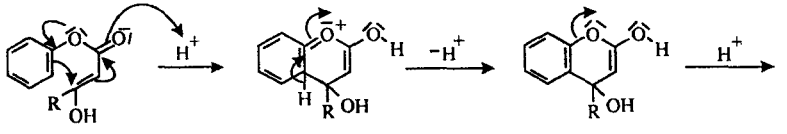
The Pechmann Condensation (or Coumarin Synthesis) allows the synthesis of coumarins by reaction of phenols with β-keto esters.

Mechanism

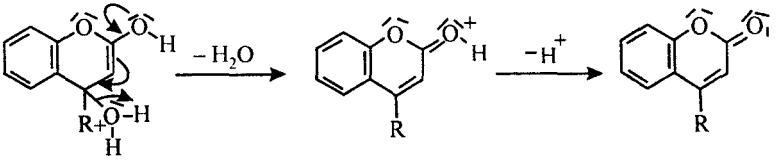
The reaction is conducted with a strong Brønstedt acid



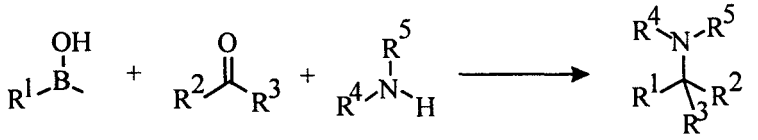
as methanesulfonic acid or a Lewis acid such as $AlCl_3$. The acid catalyses transesterification as well as keto-enol tautomerisation:



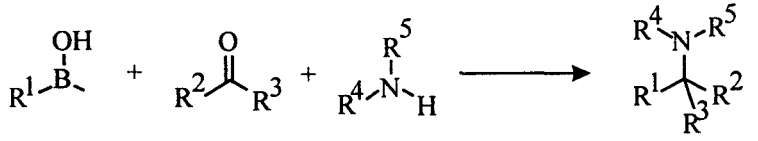
A Michael Addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation:

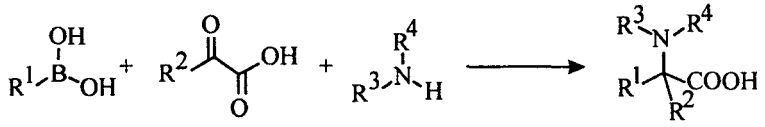


Subsequent acid-induced elimination of water gives the product:



PETASIS REACTION



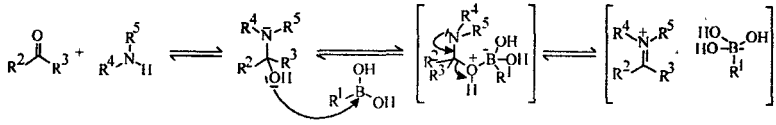


The Petasis Reaction is a multicomponent reaction (MCR) that enables the preparation of amines and their derivatives such as α-amino acids.

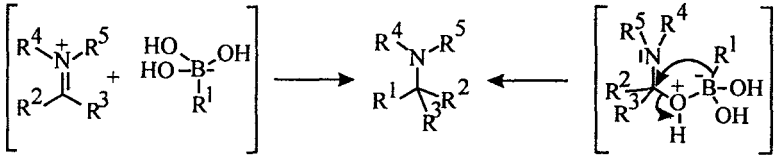
The reaction is also referred to as the Boronic Acid Mannich Reaction, since it proceeds via an imine with the organic ligand of the boronic acid acting as the nucleophile, similar to the role of the enolizable ketone component in the original Mannich Reaction.

Mechanism

As in the classical reaction that it resembles, the Petasis Reaction also involves a large number of interdependent equilibrium steps, some of them identical to those in the Mannich Reaction.

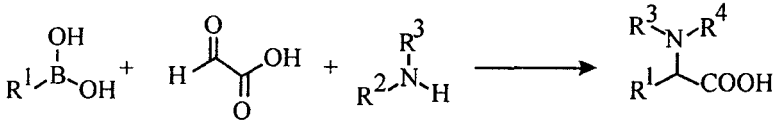


Little is known with certainty in connection with the key step that involves the nucleophilic addition of the organic ligand from the boronate to the imine. One proposal is that the transfer is actually intramolecular, and takes place via the adduct pictured above:



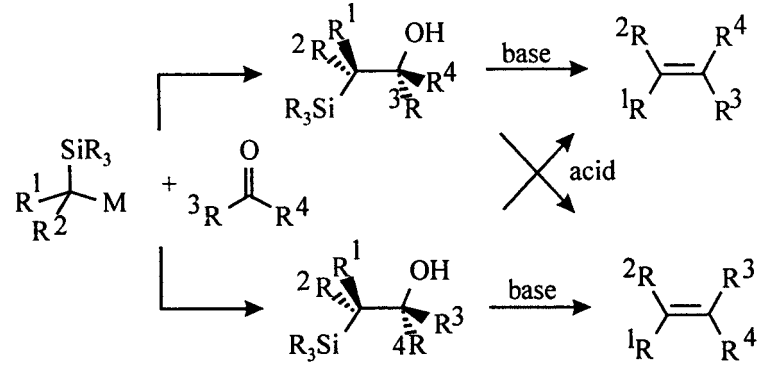
Regardless of how it does take place, the fact that this addition is irreversible certainly imparts a clear advantage. In the classical Mannich, the reversibility of the final step limits the number of cases where the yields are synthetically useful. By comparison, the Boronic Acid Mannich Reaction permits a much broader scope of conversions to be carried out.

The direct reaction with glyoxylic acid merits particular mention, since it leads to interesting, unnatural α-amino acids in a single step, while avoiding the appearance of toxic byproducts such as seen with the Strecker Synthesis.



This reaction can be carried out with secondary amines, sterically hindered primary amines, hydrazines or anilines in dichloromethane at room temperature. The range of potential nucleophilic partners includes alkenylboronic acids, and electroneutral as well as electron-rich (hetero-)arylboronic acids. The conversion of electron-poor boronic acids can be effected at elevated temperatures (MW) in suitable solvents.

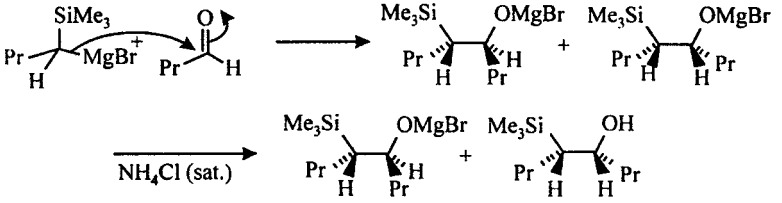
PETERSON OLEFINATION



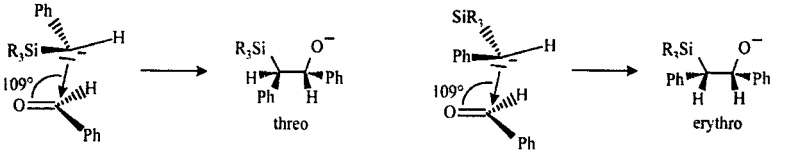
The Peterson Reaction allows the preparation of alkenes from α-silylcarbanions. The intermediate β-hydroxy silane may be isolated, and the elimination step - the Peterson Elimination - can be performed later. As the outcome of acid or base-induced elimination is different, the Peterson Olefination offers the possibility of improving the yield of the desired alkene stereoisomer by careful separation of the two diastereomeric β-hydroxy silanes and subsequently performing two different eliminations.

Mechanism

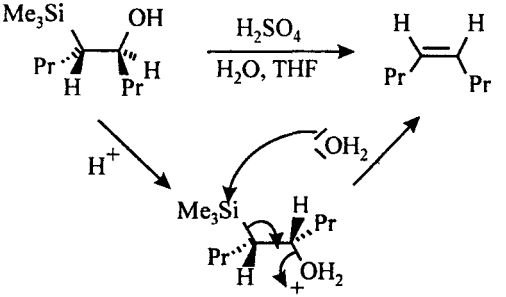
In the first step of the Peterson Olefination, addition of the silylcarbanion to a carbonyl compound and subsequent aqueous work up leads to diastereomeric adducts.



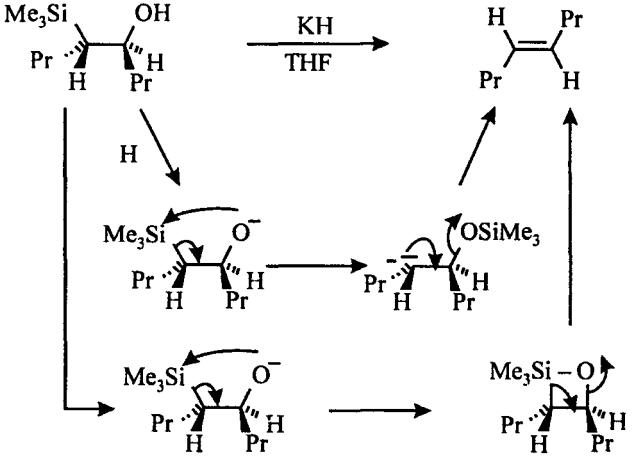
Some of these reactions are stereoselective and may be rationalized with simple models: The reaction of benzaldehyde and a silylcarbanion gives the *threo*-product if the silyl group is small. This implies that in the transition state, the two sterically demanding groups are *anti*. As the silyl group becomes more sterically demanding than trimethylsilyl, the selectivity shifts towards the *erythro*-isomer.



Acidic hydrolysis proceeds via an *anti*-elimination:



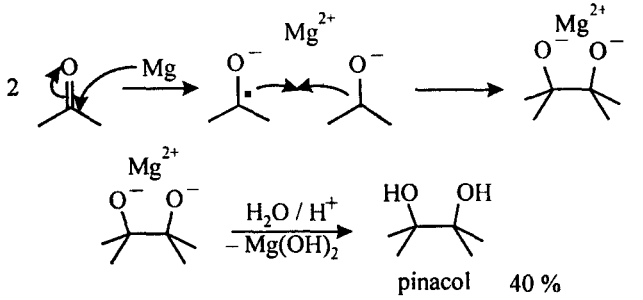
In contrast, the base-catalyzed elimination may proceed via a 1,3-shift of the silyl group after deprotonation, or with the formation of a pentacoordinate 1,2-oxasiletanide that subsequently undergoes cycloreversion:



The use of α-silyl organomagnesium compounds is helpful for the isolation of the intermediate β-hydroxysilanes, because magnesium strongly binds with oxygen, making the immediate elimination impossible. If excess organolithium or lithium amide base is used to generate the α-silyl carbanion, this base can effect the deprotonation as well, and since the lithium-oxygen bond is not as

strong as magnesium-oxygen, the reaction leads directly to the alkene. Some reactions proceed with good diastereoselectivity, so the direct conversion can be an attractive option.

PINACOL COUPLING REACTION

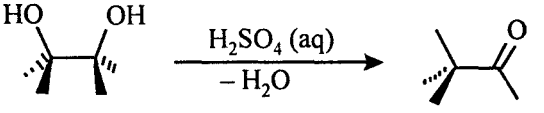


pinacol 40 %

This reaction involves the reductive homo-coupling of a carbonyl compound to produce a symmetrically substituted 1,2-diol. The first step is single electron transfer of the carbonyl bond, which generates radical ion intermediates that couple via carbon-carbon bond formation to give a 1,2-diol. The example depicted above shows the preparation of pinacol itself.

Pinacol and other highly substituted 1,2-diols tend to undergo dehydration with rearrangement under acid-catalysis.

PINACOL REARRANGEMENT



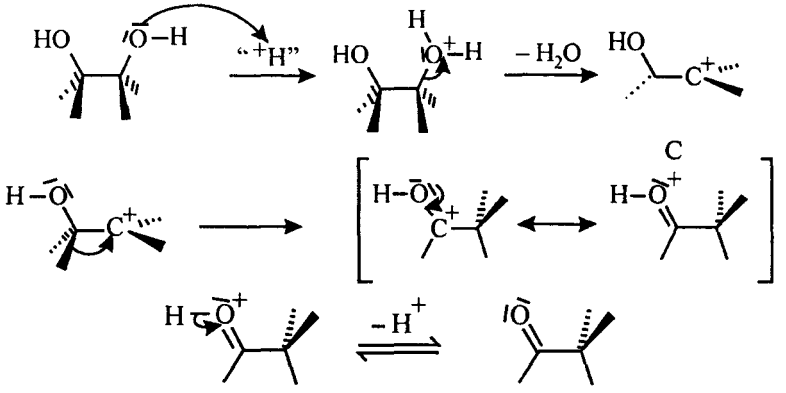
pinacol

In the conversion that gave its name to this reaction, the acid-catalyzed elimination of water from pinacol gives *t*-butyl methyl ketone.

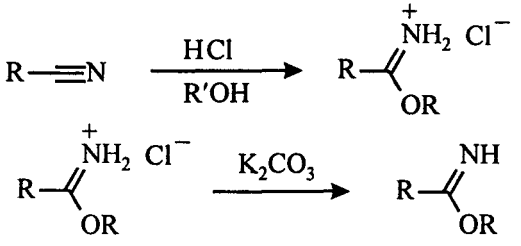
Mechanism

This reaction occurs with a variety of fully substituted 1,2-diols, and can be understood to involve the formation of a carbenium ion intermediate that subsequently undergoes a rearrangement. The first generated intermediate, an α-hydroxycarbenium ion, rearranges through a 1,2-alkyl shift to produce the carbonyl compound. If two

of the substituents form a ring, the Pinacol Rearrangement can constitute a ring-expansion or ring-contraction reaction.

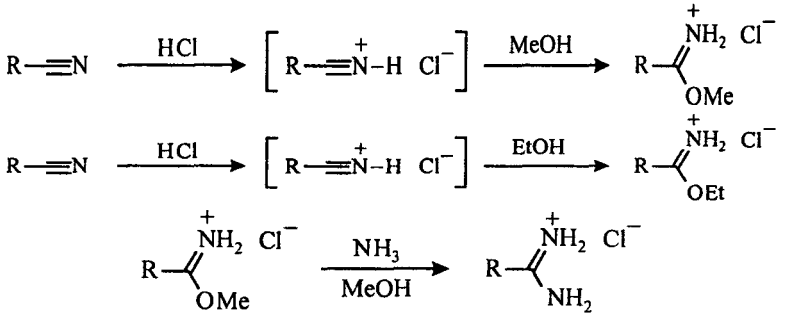


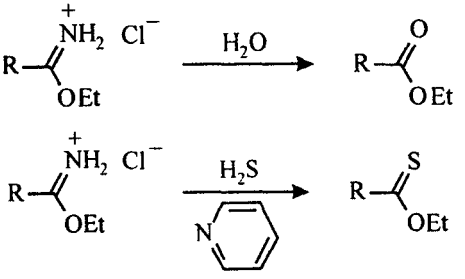
PINNER REACTION



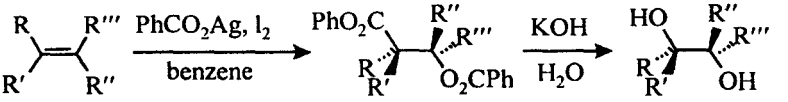
The Pinner Reaction is the partial solvolysis of a nitrile to yield an iminoether. Treatment of the nitrile with gaseous HCl in a mixture of anhydrous chloroform and an alcohol produces the imino ether hydrochloride. These salts are known as Pinner Salts, and may react further with various nucleophiles.

Mechanism





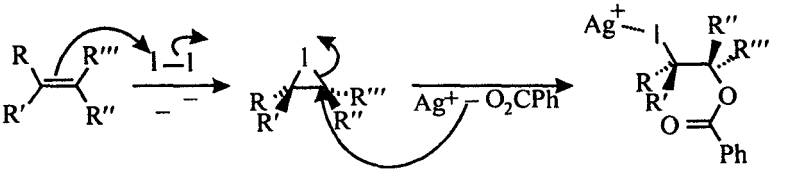
PREVOST REACTION



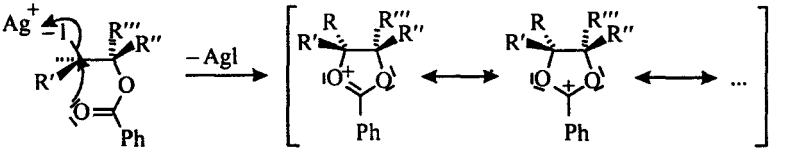
The Prevost Reaction allows the synthesis of *anti*-diols from alkenes by the addition of iodine followed by nucleophilic displacement with benzoate in the absence of water. Hydrolysis of the intermediate diester gives the desired diol.The Woodward Modification of the Prevost Reaction gives *syn*-diols.

Mechanism

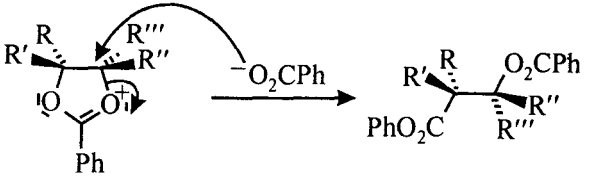
The initial addition of iodine leads to a cyclic iodonium ion, which is opened through nucleophilic substitution by benzoate anion:



A neighbouring-group participation mechanism prevents the immediate nucleophilic substitution of iodine by a second equivalent of benzoate that would lead to a *syn*-substituted product. Instead, a cyclic benzoxonium ion intermediate is formed:



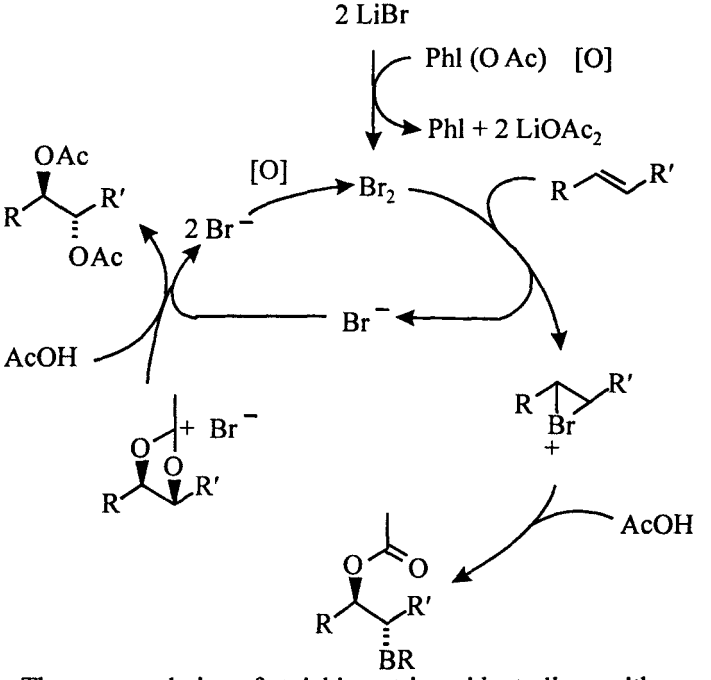
Opening of this intermediate by a second addition of benzoate gives the *anti*-substituted dibenzoate:



Hydrolysis then delivers the diol.

In the Woodward-Modification, added water decomposes the above benzoxonium intermediate directly to a *syn*-substituted diol.

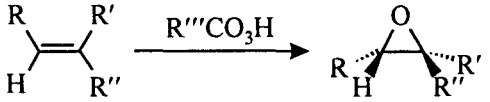
The use of expensive silver salts, the requirement for a stoichiometric amount of molecular halogen, and the formation of a relatively large amount of organic and inorganic wastes are definite drawbacks to this reaction. Sudalai recently reported on catalytic versions of both the Prevost Reaction and the Woodward-Modification.



The proper choice of stoichiometric oxidant allows either *syn*- or *anti*-selective dihydroxylations. $NaIO_4$ as the oxidizing agent generates H_2O as a side product of the oxidation and therefore enables the Woodward Reaction to take place.

High-valent iodine reagents are still relatively expensive, and the identification of a less costly stoichiometric oxidant would be a significant improvement for this process.

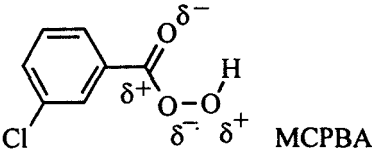
PRILEZHAEV REACTION



The epoxidation of an alkene with peracid to give an oxirane. The commercial available mCPBA is a widely used reagent for this conversion, while magnesium mono-perphthalate and peracetic acid are also employed.

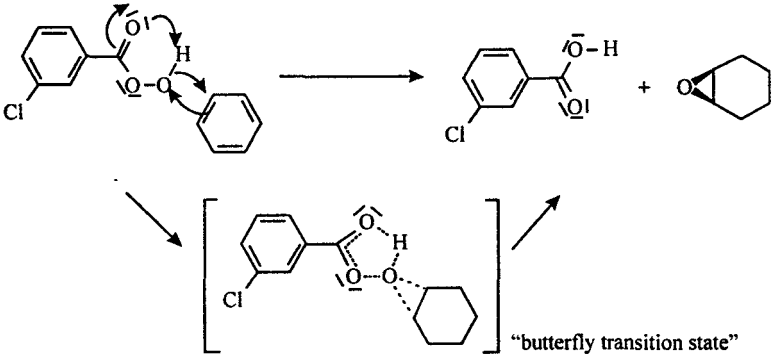
Mechanism

Peracids tend to adopt an intramolecularly hydrogen-bonded conformation in solution, and the high degree of polarisation results in an electrophilic oxygen atom that is able to add to alkenes.



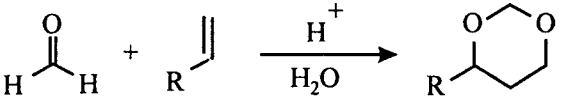
Hydrogen peroxide in combination with various additional catalysts may also be used in these epoxidations.

The transition state, in which oxygen is added and the proton is shifted simultaneously, resembles a butterfly and is known as the "Butterfly Mechanism":

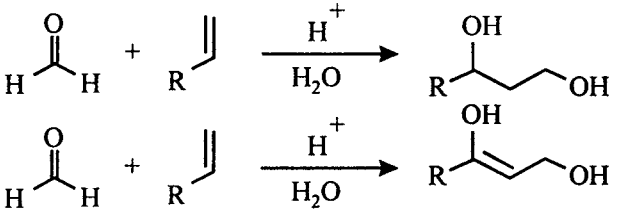


PRINS REACTION

The Prins Reaction is the acid-catalyzed of addition aldehydes to alkenes, and gives different products depending on the reaction conditions. It can be thought of conceptually as the addition of the elements of the gem-diol carbonyl hydrate of the aldehyde across the double bond.

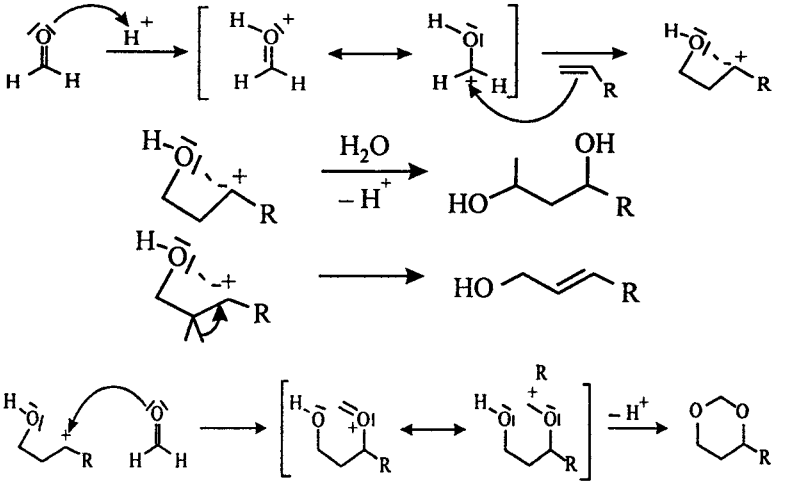


An excess of aldehyde and temperatures < 70 °C lead to the formation of acetals. When one equivalent of aldehyde is used and temperatures are > 70 °C diols or allylic alcohols may be isolated.

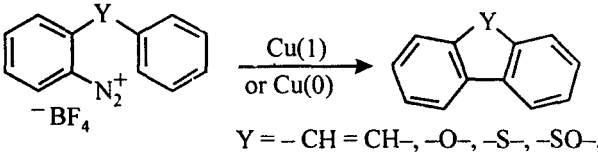


Although the mechanism is different, a Prins allylic alcohol product is equivalent to the result of an Ene Reaction.

Mechanism



PSCHORR REACTION

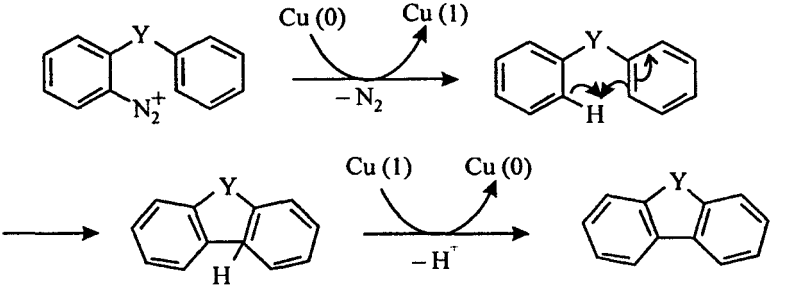


Y = – CH = CH–, –O–, –S–, –SO–,...

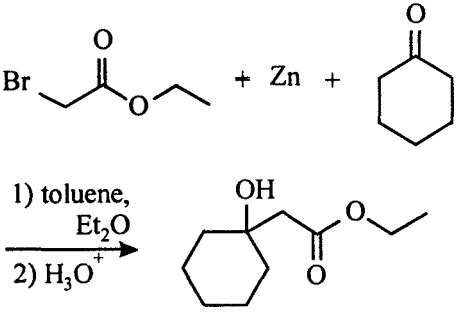
The Pschorr Reaction allows the preparation of biaryl tricyclics by intramolecular substitution of one arene by an aryl radical. This radical is generated in situ from an aryl diazonium salt by copper catalysis. Although excess copper salts are used, the yield is normally moderate.

Alternative one-electron donors that are more soluble have recently been discovered. The reported method leads to improved yields in a shorter reaction time.

Mechanism



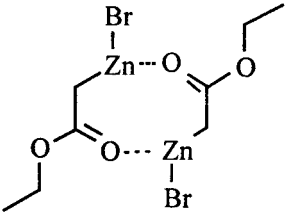
REFORMATSKY REACTION



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

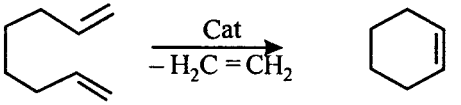
Mechanism

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

RING CLOSING METATHESIS (RCM)

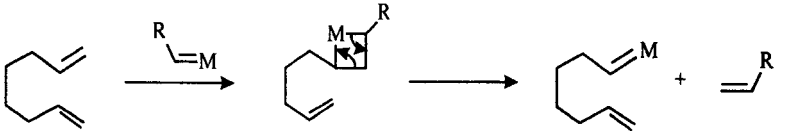


The Ring-Closing Metathesis (RCM) allows synthesis of 5- up to 30-membered cyclic alkenes. The *E/Z*-selectivity depends on the ring strain.

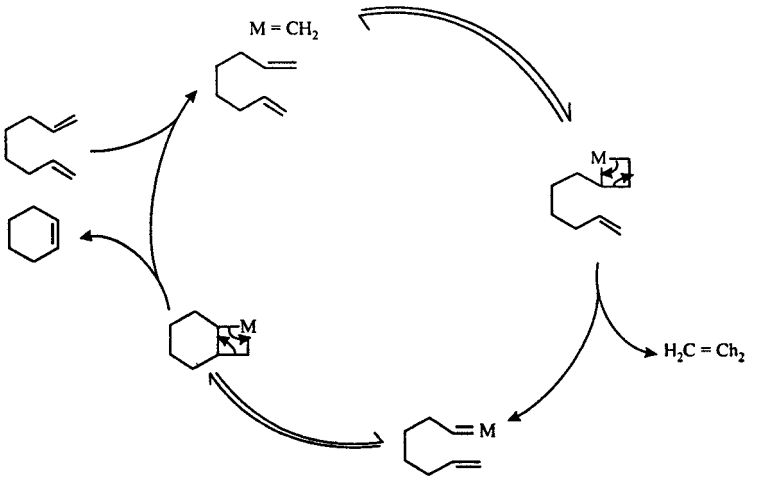
The Ru-catalysts used tolerate a variety of functional groups, but normally the molecule must have polar side chains that are able to build a template for the catalyst. The modern Second Generation Grubb's Catalysts are more versatile.

Mechanism

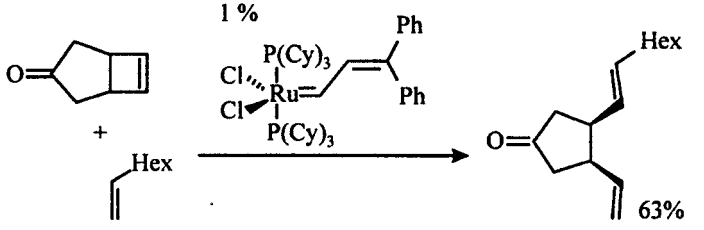
The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to starting materials. When the olefins of the substrate are terminal, the driving force for RCM is the removal of ethene from the reaction mixture.



Chauvin's Mechanism



RING OPENING METATHESIS (POLYMERIZATION) - ROM(P)



Strained rings may be opened by a ruthenium carbene-catalyzed reaction with a second alkene following the mechanism of the Cross Metathesis. The driving force is the relief of ring strain. As the products contain terminal vinyl groups, further reactions of the Cross Metathesis variety may occur. Therefore, the reaction conditions must be optimized to favour the desired product.

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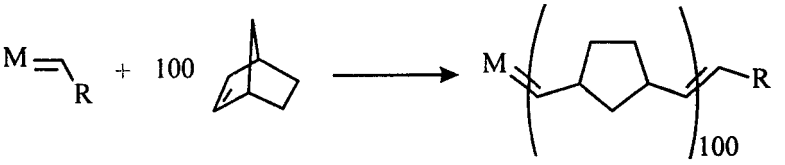
In absence of excess of a second reaction partner, polymerization occurs (ROMP):

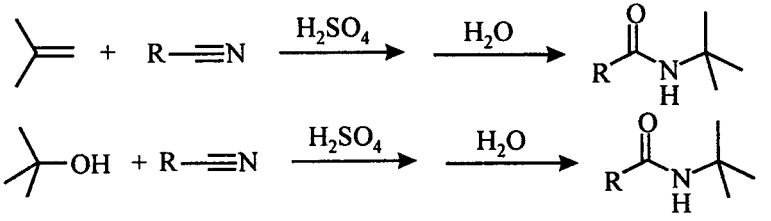


The reverse reaction the Ring Closing Metathesis is a valuable synthesis tool for preparing from 5- up to 30-membered rings.

Mechanism

Same as Olefin Metathesis.

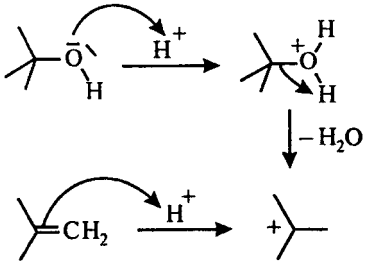
RITTER REACTION



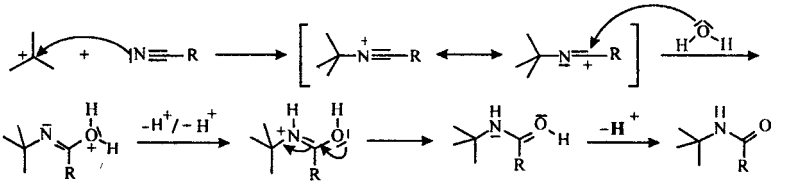
The acid-induced nucleophilic addition of a nitrile to a carbenium ion, followed by hydrolysis to the corresponding amide.

Mechanism

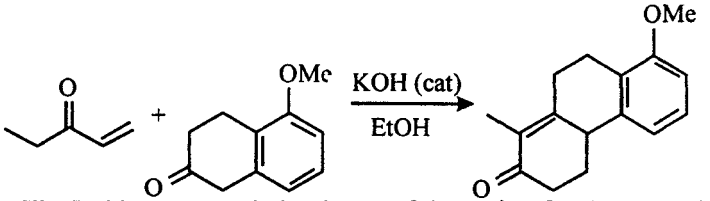
Any substrate capable of generating a stable carbenium ion is a suitable starting material; primary alcohols do not react under these conditions, with exception of benzylic alcohols:



The carbenium ion adds to the nitrile nitrogen to give a nitrilium ion intermediate, which undergoes hydrolysis to the corresponding amide upon aqueous work-up.



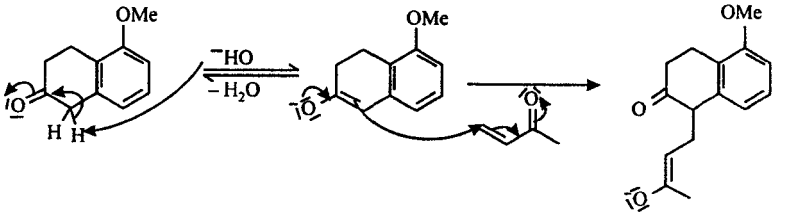
ROBINSON ANNULATION



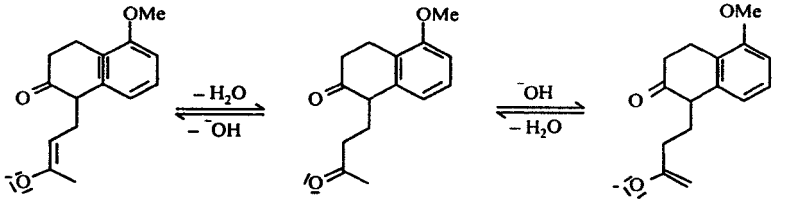
The Robinson Annulation is a useful reaction for the formation of six-membered rings in polycyclic compounds, such as steroids. It combines two reactions: the Michael Addition and the Aldol Condensation

Mechanism

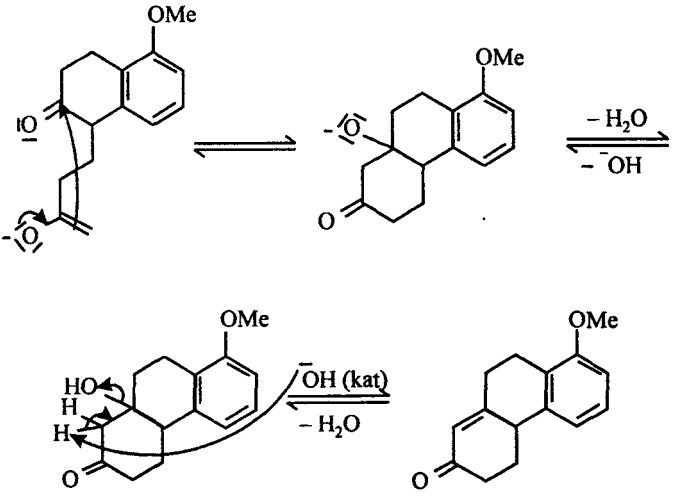
The first step in the process is the Michael Addition to an α,β-unsaturated ketone, such as methyl vinyl ketone:



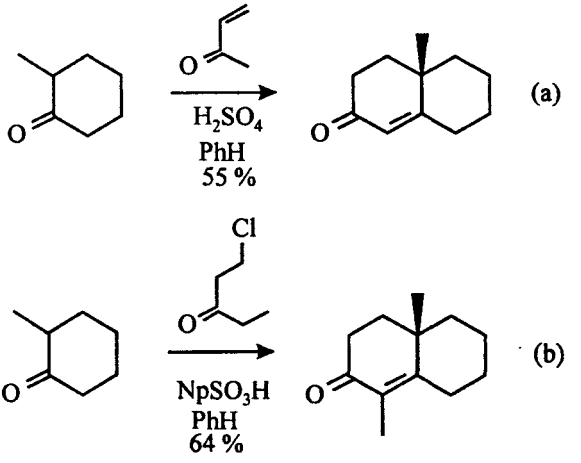
The newly formed enolate intermediate must first tautomerize for the conversion to continue:



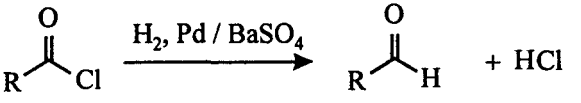
The subsequent cyclization via Aldol Addition is followed by a condensation to form a six-membered ring enone:



The Robinson Annulation can also proceed under acidic catalysis, with the entire process occurring in one pot, as shown below. The use of a precursor of the α,β-unsaturated ketone, such as a β-chloroketone, can reduce the steady-state concentration of enone and decrease the side reaction of polymerization.

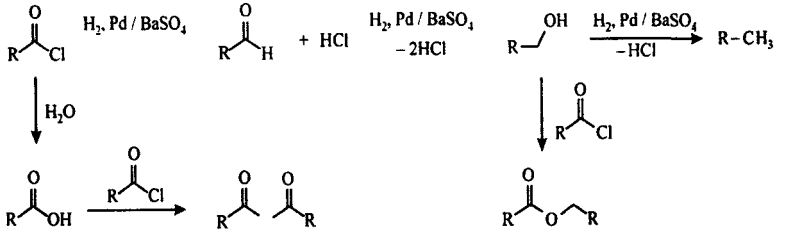


ROSENMUND REDUCTION



The catalytic hydrogenation of acid chlorides allows the formation of aldehydes.

Mechanism



The Pd catalyst must be poisoned, for example with $BaSO_4$, because the untreated catalyst is too reactive and will give some overreduction. Some of the side products can be avoided if the reaction is conducted in strictly anhydrous solvents.

ROSENMUND-VON BRAUN REACTION

$$Ar-X+CuCN \xrightarrow[DMF]{\Delta} Ar-CN$$

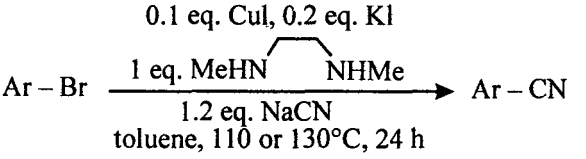
Aryl nitriles can be prepared by the cyanation of aryl halides with an excess of copper(I) cyanide in a polar high-boiling solvent such as DMF, nitrobenzene, or pyridine at reflux temperature.

Mechanism

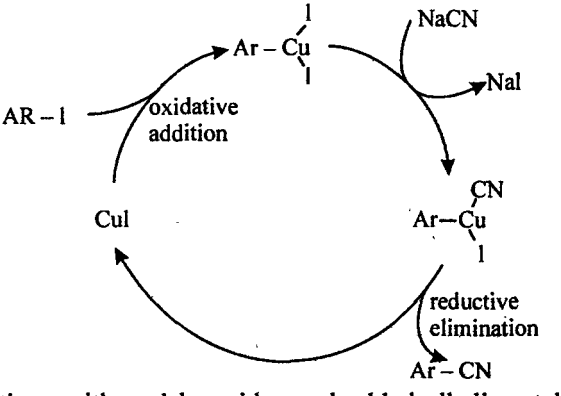
The mechanism probably involves the formation of a Cu(III) species through oxidative addition of the aryl halide. Subsequent reductive elimination then leads to the product:

$$Ar-X+Cu-CN \xrightarrow[addition]{oxidative} \begin{matrix} Ar \\ | \\ NC-Cu-X \end{matrix} \xrightarrow[-CuX]{reductive\ elimination} Ar-CN$$

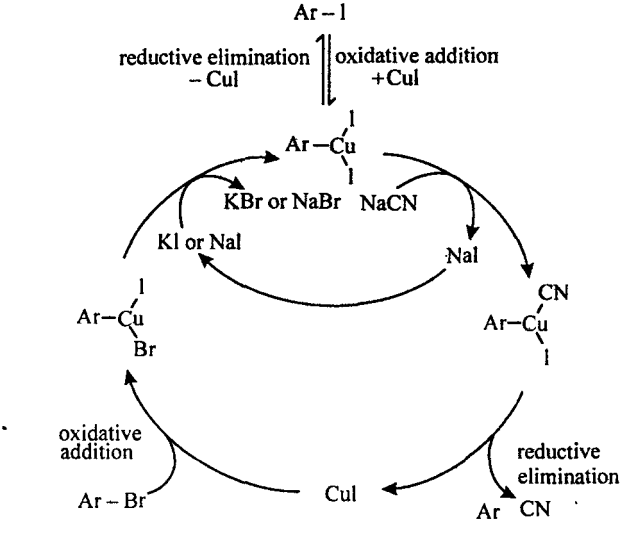
The excess of copper cyanide and the use of a polar, high-boiling point solvent makes the purification of the products difficult. In addition, elevated temperatures (up to 200°C) lower the functional group tolerance. The use of alkali metal cyanides or cyanation reagents such as cyanohydrins, a catalytic amount of copper(I) iodide and kalium iodide, allows a mild, catalytic cyanation of various aryl bromides.



If aryl iodides, sodium cyanide and copper(I) iodide are used, a simple mechanism similar to that of an Ullmann-type reaction can be proposed:

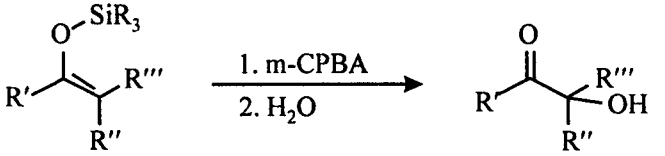


Reactions with aryl bromides and added alkali metal iodides involve additional equilibria in which aryl bromides give the more reactive aryl iodides:



The formation of a copper(III) species and the use of cyanohydrins.

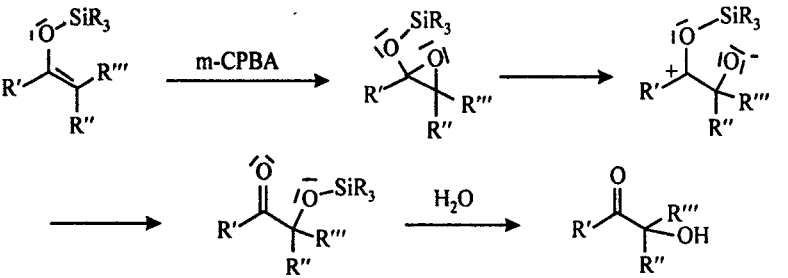
RUBOTTOM OXIDATION



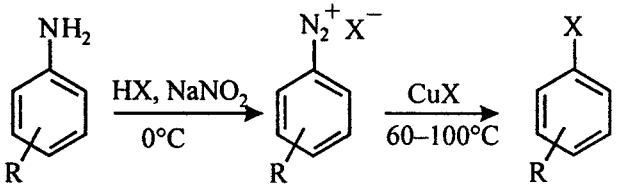
The synthesis of α-hydroxy ketones is achieved by reaction of silyl enol ethers with mCPBA, with subsequent rearrangement. Aqueous work up or reaction with TBAF (fluoride ions) gives the desired product after desilylation

Mechanism

The enol ether double bond is epoxidized by the peracid. Relief of the epoxide ring strain drives the rearrangement with migration of the silyl group to give the silylated α-hydroxy ketone product.



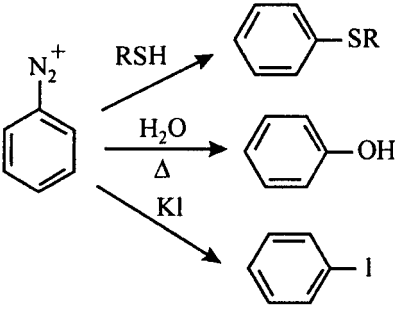
SANDMEYER REACTION



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

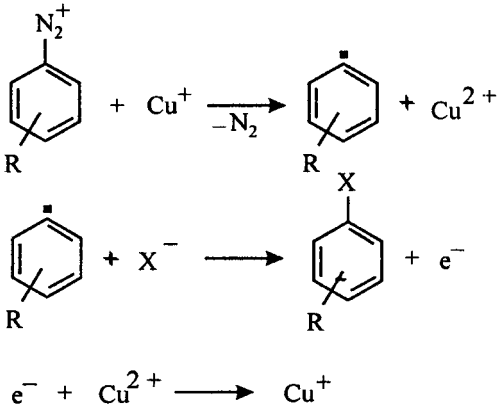
a nucleophile (Cl-, I-, CN-, RS-, HO-). Many Sandmeyer Reactions proceed under copper(I) catalysis, while the Sandmeyer-type reactions with thiols, water and potassium iodide don't require catalysis.



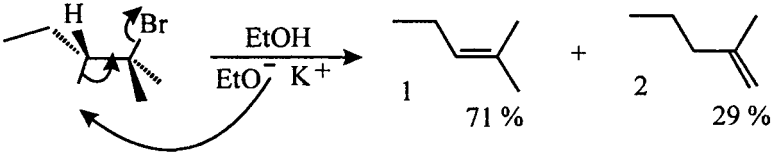
The Sandmeyer Reaction is a very important transformation in aromatic chemistry, because it can result in some substitution patterns that are not achievable by direct substitution.

Fluorination is possible by using the related Schiemann Reaction.

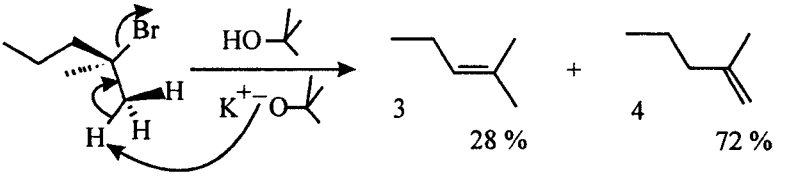
Mechanism



SAYTZEFF'S RULE

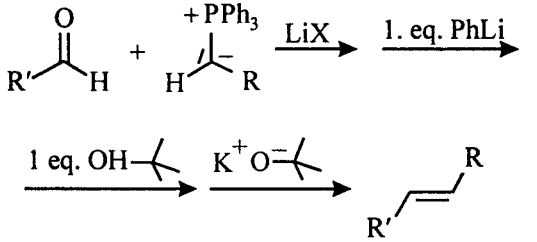


Saytzeff Rule implies that base-induced eliminations (E2) will lead predominantly to the olefin in which the double bond is more highly substituted, i.e. that the product distribution will be controlled by thermodynamics.



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.

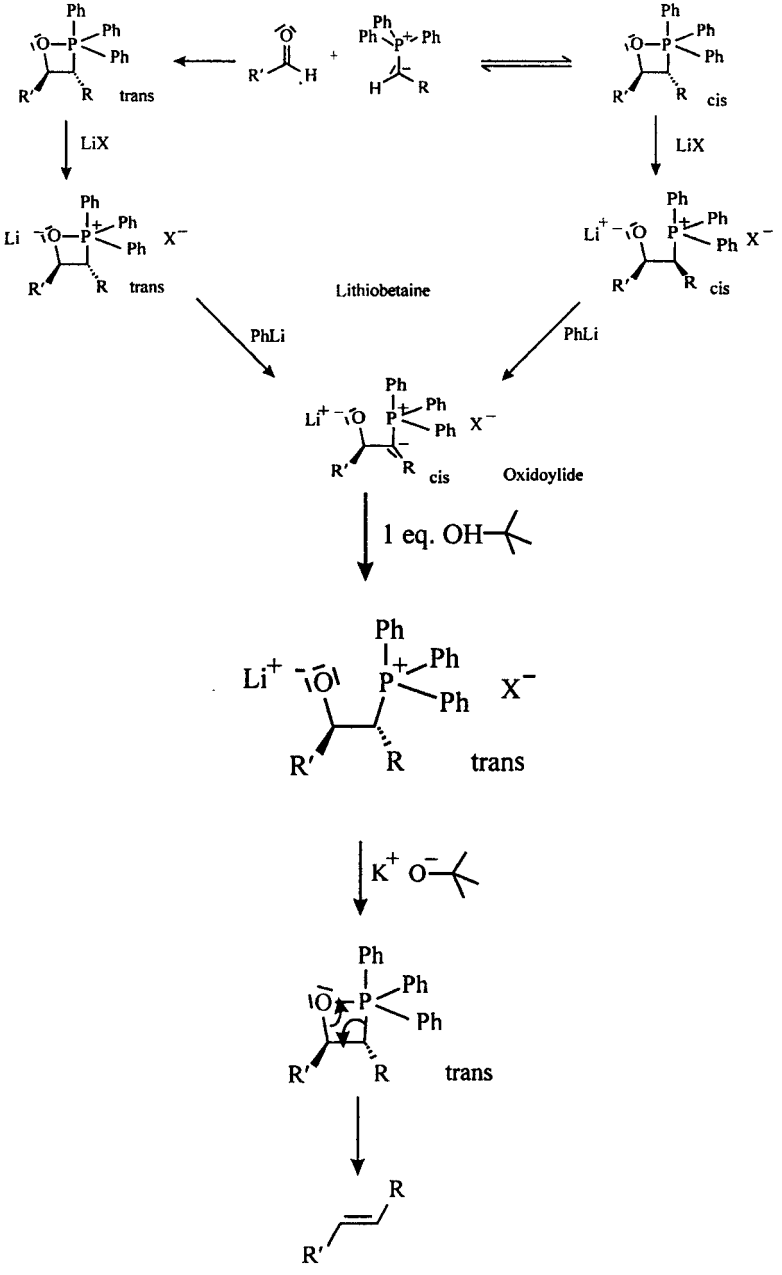
SCHLOSSER MODIFICATION



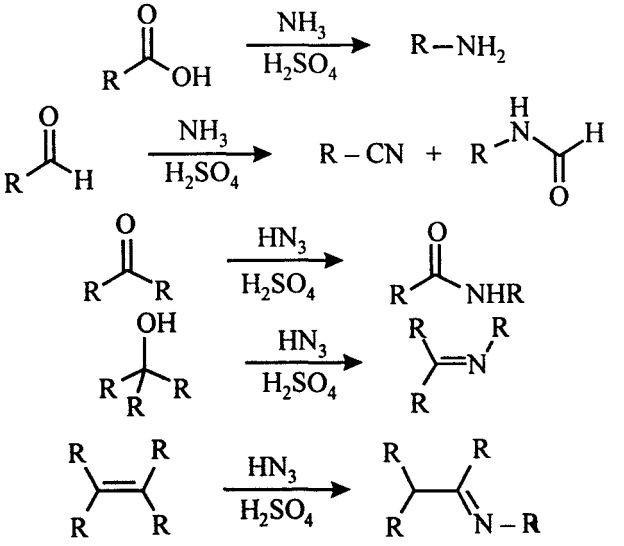
The Schlosser Modification of the Wittig Reaction allows the selective formation of *E*-alkenes through the use of excess lithium salts during the addition step of the ylide and subsequent deprotonation/protonation steps.

Mechanism

Lithium salts effect, that the intermediate betaines do not react further. These lithiobetaines which are quite stable may be deprotonated. Deprotonation is equal to the lost of one stereogenic centre. Use of a steric hindered proton donator then leads to the *trans* lithiobetaine. The reaction takes "normal" course, if lithium is exchanged by potassium.


trans
cis
LiX
Lithiobetaine
PhLi
Oxidoylide
1 eq. OH
trans
K+ O
trans

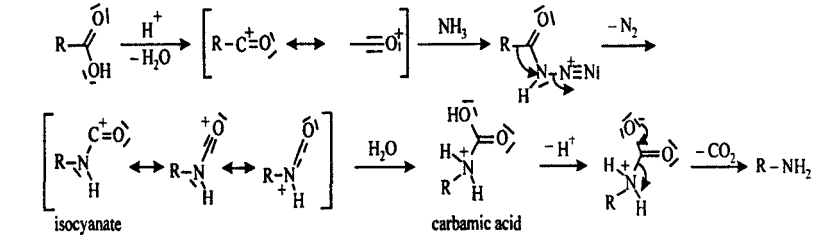
SCHMIDT REACTION



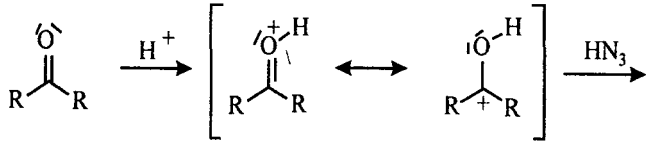
The acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced.

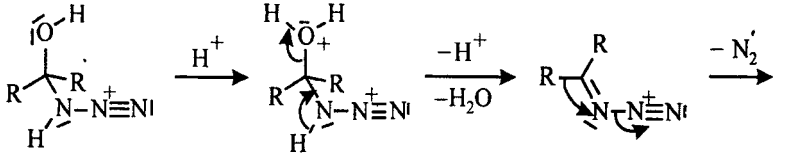
Mechanism

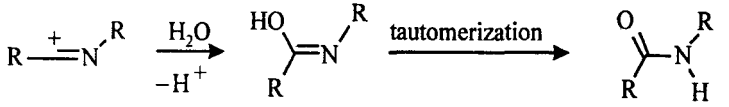
Reaction of carboxylic acids gives acyl azides, which rearrange to isocyanates, and these may be hydrolyzed to carbamic acid or solvolysed to carbamates. Decarboxylation leads to amines.



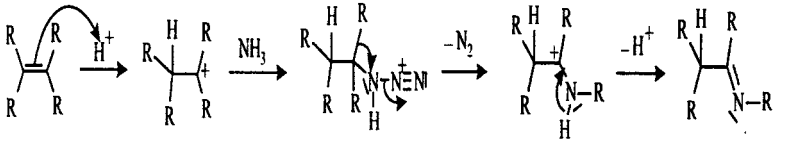
The reaction with a ketone gives an azidohydrin intermediate, which rearranges to form an amide:





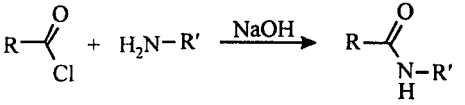


Alkenes are able to undergo addition of HN_3 as with any HX reagent, and the resulting alkyl azide can rearrange to form an imine:



Tertiary alcohols give substitution by azide via a carbenium ion, and the resulting alkyl azide can rearrange to form an imine.

SCHOTTEN-BAUMANN REACTION

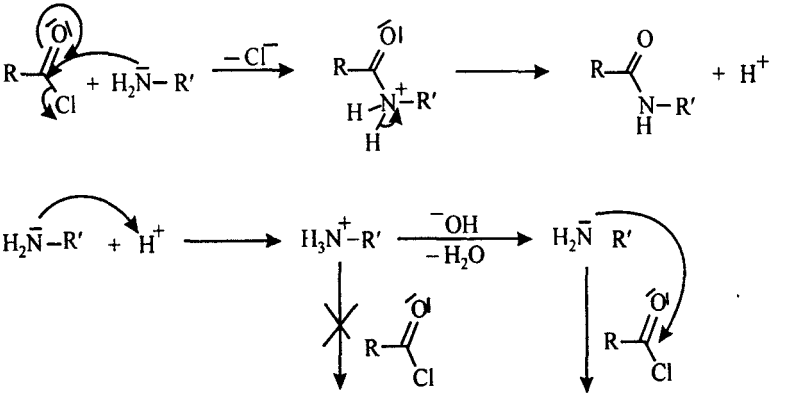


The use of added base to drive the equilibrium in the formation of amides from amines and acid chlorides.

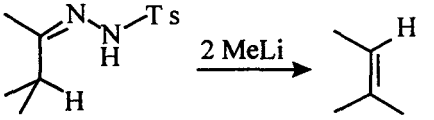
The acylation of amines with carboxylic acid chlorides leads to the production of one equivalent acid, which will form a salt with unreacted amine and diminish the yield. The addition of an additional equivalent of base to neutralise this acid is a way to optimise the conditions. Normally, aqueous base is slowly added to the reaction mixture.

In general, the use of biphasic aqueous basic conditions is often named "Schotten-Baumann conditions".

Mechanism



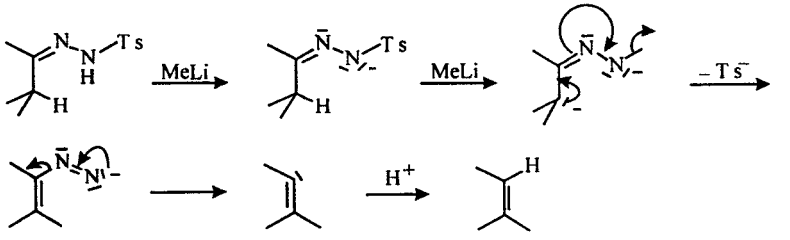
SHAPIRO REACTION



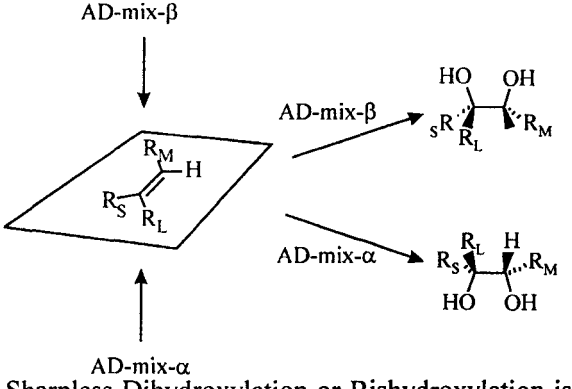
The Shapiro Reaction, a variation on the Bamford-Stevens Reaction, is the base-induced reaction of tosylhydrazones to afford alkenes. This reaction is carried out with two equivalents of an organolithium compound.

Mechanism

The advantage of the Shapiro over Bamford-Stevens Reaction is, that the resulting dianion does not tend to rearrange, which can occur with intermediate carbenes and carbenium ions. However, the Shapiro reaction does not lead to high stereoselectivity between the *E-/Z*-isomers.

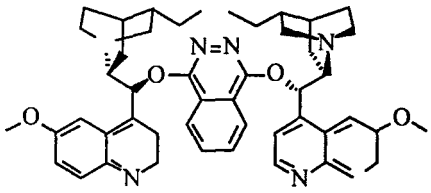


SHARPLESS DIHYDROXYLATION

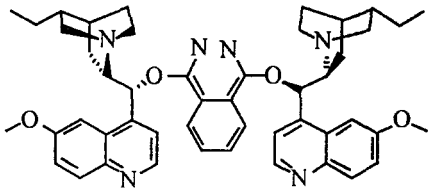


The Sharpless Dihydroxylation or Bishydroxylation is used in the enantioselective preparation of 1,2-diols from prochiral olefins. This procedure is performed with an osmium catalyst and a stoichiometric oxidant [e.g. $K_3Fe(CN)_6$ or *N*-methylmorpholine oxide (NMO)]; it is carried out in a buffered solution to ensure a stable pH, since the reaction proceeds more rapidly under slightly basic conditions. Enantioselectivity is achieved through the addition of enantiomerically-enriched chiral ligands [$(DHQD)_2PHAL$, $(DHQ)_2PHAL$ or their derivatives]. These reagents are also available as stable, prepackaged mixtures (AD-mix α and AD-mix β, AD = asymmetric dihydroxylation) for either enantiopreference.

Ad-mix-β:
$K_2OsO_2(OH)_4$(cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$ (cat):

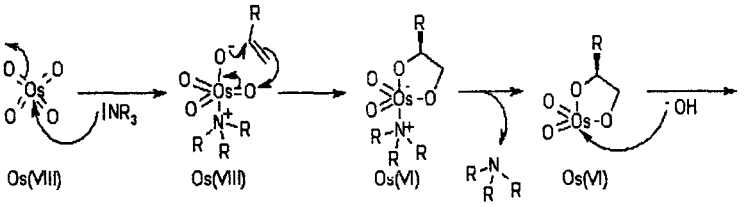


Ad-mix-α:
$K_2OsO_2(OH)_4$(cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$ (cat):



Mechanism

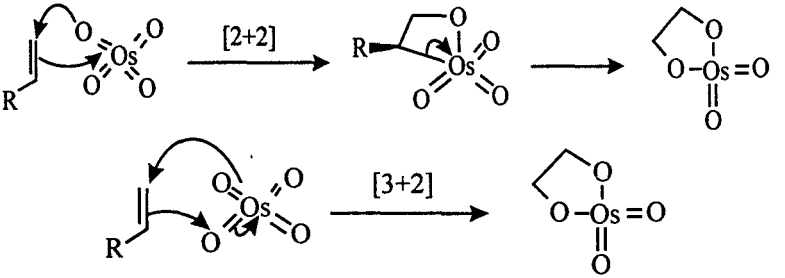
The ligand accelerates the reaction and transfers the chiral information.



After the dihydroxylated product is released from the complex through hydrolysis, reoxidation of the metal takes place - sodium chlorite is used in this example, which can regenerate two equivalents of the catalyst.

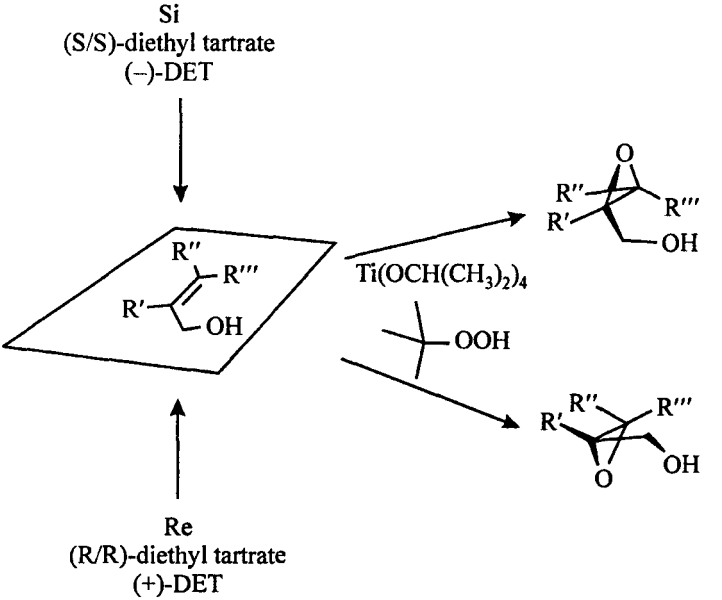
If the olefin concentration is too high, a second equivalent of the substrate might bind to the catalytic centre in the absence of the chiral ligand, and undergo a dihydroxylation. This side reaction will decrease the enantioselectivity.

There has been some speculation regarding the actual addition step, for which experimental data suggest the possible involvement of two separate steps. Thus, the question arises during these discussions of whether the key step takes place via an initial [3+2]-addition, or by a [2+2]-addition followed by expansion of the metallacycle.



Quantum chemical calculations have shown an initial [3+2]-addition of the OsO_4 to be energetically more favourable. However, this energy difference is substantially smaller in the related Re(VII) oxide additions.

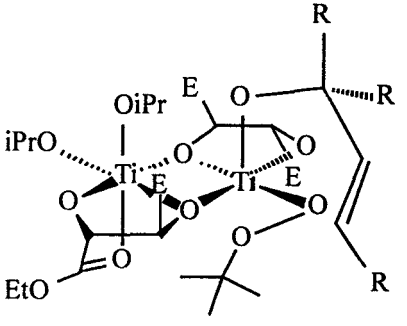
SHARPLESS EPOXIDATION



The Sharpless Epoxidation allows the enantioselective epoxidation of prochiral allylic alcohols. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative.

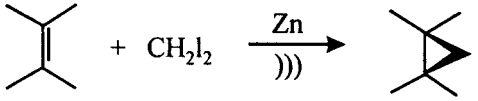
Mechanism

The oxidant for the epoxidation is *tert*-Butyl hydroperoxide. The reaction is catalyzed by Ti(O*i*Pr)$_4$, which binds the hydroperoxide, the allylic alcohol group, and the asymmetric tartrate ligand via oxygen atoms (putative transition state depicted below).



E = COOEt

SIMMONS-SMITH REACTION



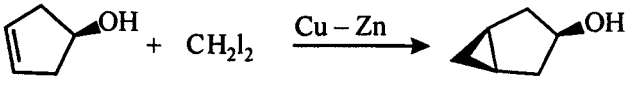
This reaction affords the cyclopropanation of olefins.

Mechanism

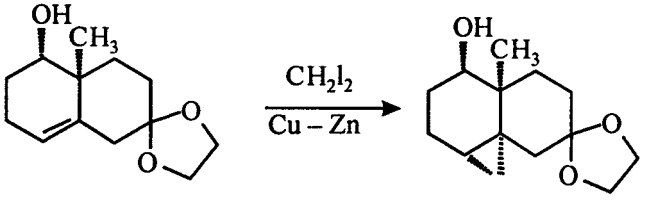
Ultrasonication improves the rate of formation of these organozinc compounds, as with many organometallic reactions occurring at a surface.

$$2\,CH_2I_2 + 2\,Zn \longrightarrow 2\,|CH_2Zn| \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

The mechanism has not been fully clarified, but pure carbenes can be excluded, and a metal carbenoid is likely to be involved. The following results may be interpreted to indicate a possible complexation of the active species by hydroxy groups leading to reaction on the same face as this substituent. This would only be possible if an organozinc reagent is present.

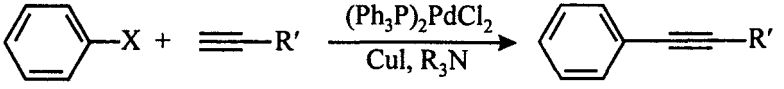


66 %

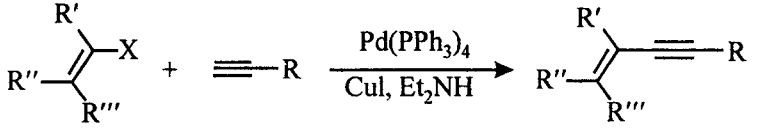


76 %

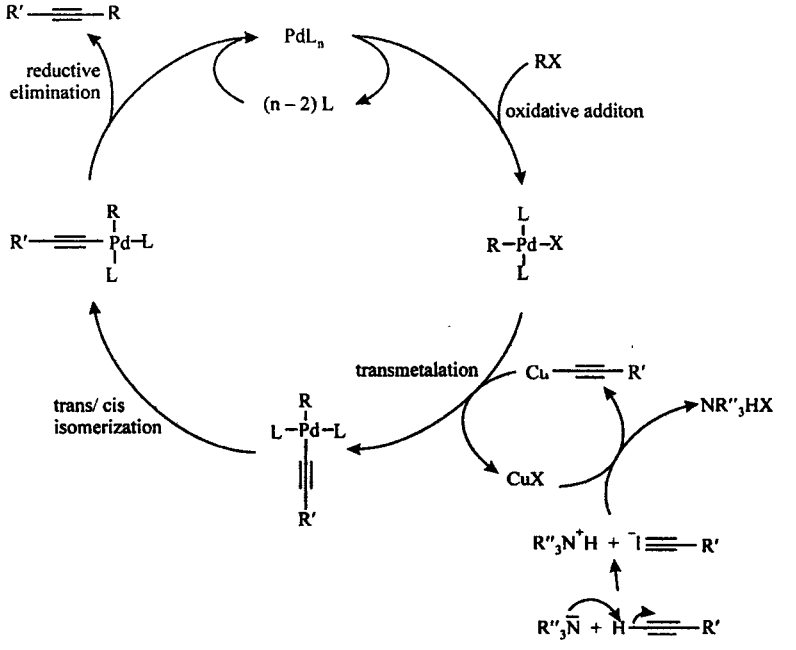
SONOGASHIRA COUPLING



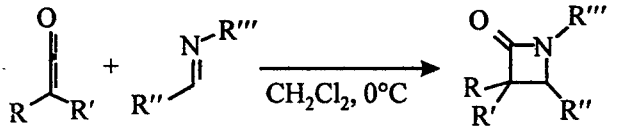
This coupling of terminal alkynes with aryl or vinyl halides is performed with a palladium catalyst, a copper(I) cocatalyst, and an amine base. Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions are not important.



Mechanism



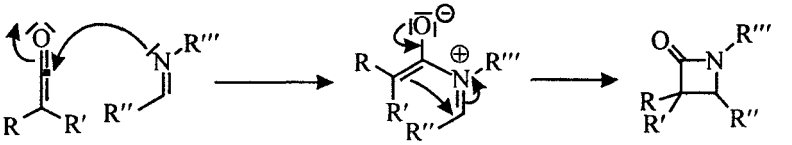
STAUDINGER SYNTHESIS



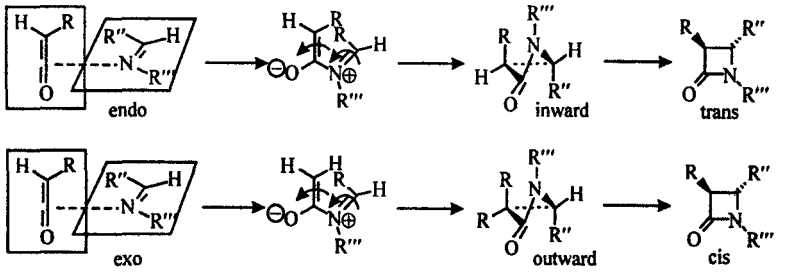
The formal [2+2]-cycloaddition of imines to ketenes forms β-lactams.

Mechanism

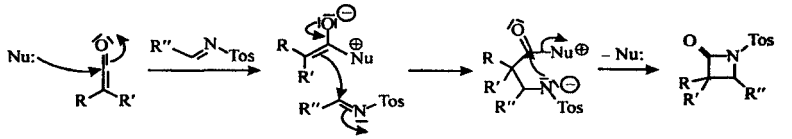
Both the ketene and the imine are molecules that can act as either nucleophiles or electrophiles. In the first step, the imine adds to the ketene as a nucleophile. The subsequent cycloaddition delivers the β-lactam:



The zwitterionic intermediate undergoes an electrocyclic conrotatory ring closure to give the β-lactam ring. In general, (*E*)-imines lead preferentially to *cis*-β-lactams. Ab initio calculations have shown a correlation between stereochemistry of the lactam closure and the donor/acceptor character of the substituents. If R is electrodonating, the conrotatory closure via an "outward rotation" that produces a *cis*-stereochemistry is preferred by ~10 kcal/mol, whereas electron-withdrawing groups favour an "inward"-rotation:

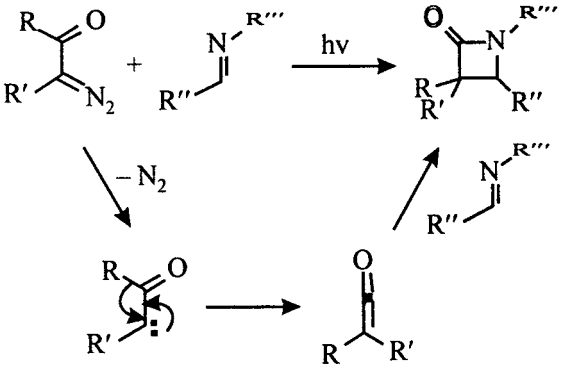


At lower temperatures, a catalytic version involves the use of non-nucleophilic imines and the Umpolung of the ketene substrate using tertiary amines or other suitable nucleophiles, making the ketene nucleophilic:

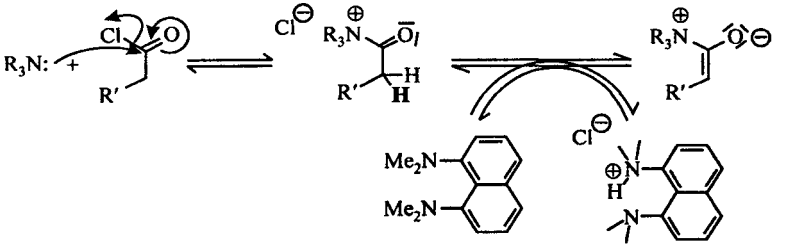


This reversed reactivity mode allows the use of chiral nucleophilic catalysts for enantioselective induction.

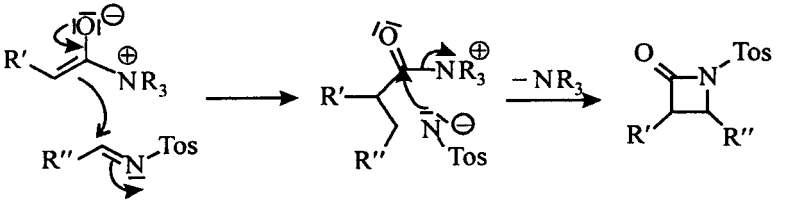
Diphenylketene is quite stable, but other ketenes readily polymerise and must be prepared immediately before the reaction. Ketenes can also be formed *in situ* in the presence of the imine by a light- or heat-induced Wolff-Rearrangement:



Using the reversed mode strategy, the reaction of acid chlorides with a tertiary amine in the presence of a proton sponge readily produces ketenes:



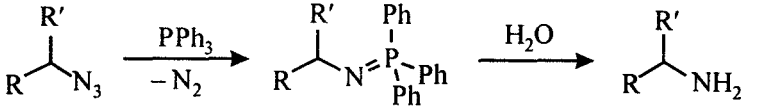
R_3N could be an expensive chiral amine catalyst such as a chinchona alkaloid, whereas the proton sponge is used stoichiometrically. For achiral reactions, NEt_3 can serve both functions. The subsequent reaction follows the pathway known from the reverse mode reactions, with the catalyst recovered unchanged:



A general overview about advances in the catalytic, asymmetric synthesis of β-lactams can be found in an article written by Thomas Lectka, whereas a publication by Claudio Palomo discusses reactions of acyl chlorides with imines, including diastereoselectivites and mechanistic insights of the ring closure leading to *cis* or *trans*

substituted β-lactams and asymmetric induction from the ketene component. The influence of solvents and additives and the pathways of ketene generations and addition modes on the stereoselectivity.

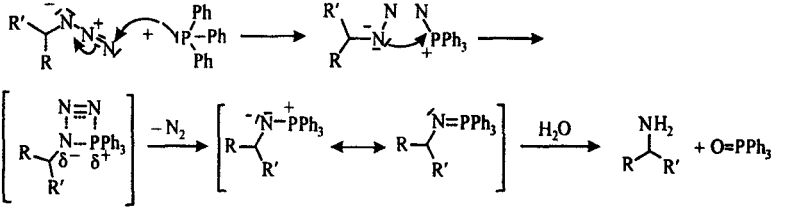
STAUDINGER REACTION



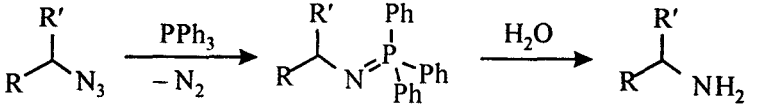
Azides may be converted to amines by hydrogenation, but another possibility is the Staudinger Reaction, which is a very mild azide reduction. As there are a variety of methods for preparing azides readily, the Staudinger Reaction makes it possible to use $^-N_3$ as an $^-NH_2$ synthon.

Mechanism

Triphenylphosphine reacts with the azide to generate a phosphazide, which loses N_2 to form an iminophosphorane. Aqueous work up leads to the amine and the very stable phosphine oxide.



STAUDINGER REACTION



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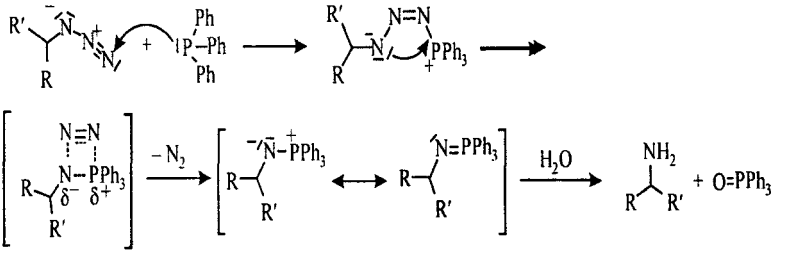
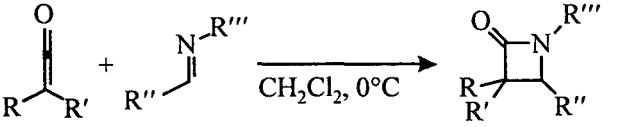


STAUDINGER SYNTHESIS



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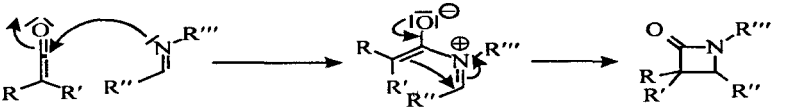
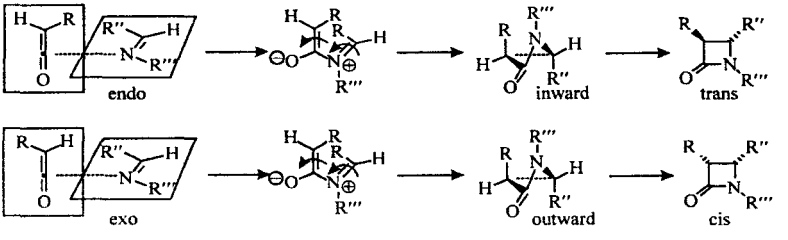
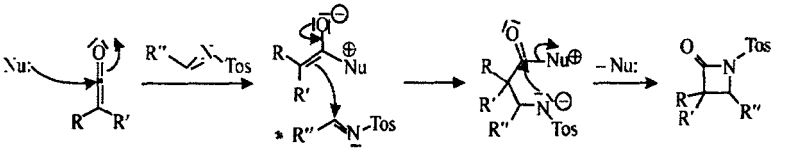
Both the ketene and the imine are molecules that can act as either nucleophiles or electrophiles. In the first step, the imine adds to the ketene as a nucleophile. The subsequent cycloaddition delivers the β-lactam:



The zwitterionic intermediate undergoes an electrocyclic conrotatory ring closure to give the β-lactam ring. In general, (*E*)-imines lead preferentially to *cis*-β-lactams. Ab initio calculations have shown a correlation between stereochemistry of the lactam closure and the donor/acceptor character of the substituents. If R is electrodonating, the conrotatory closure via an "outward rotation" that produces a *cis*-stereochemistry is preferred by ~10 kcal/mol, whereas electron-withdrawing groups favour an "inward"-rotation:

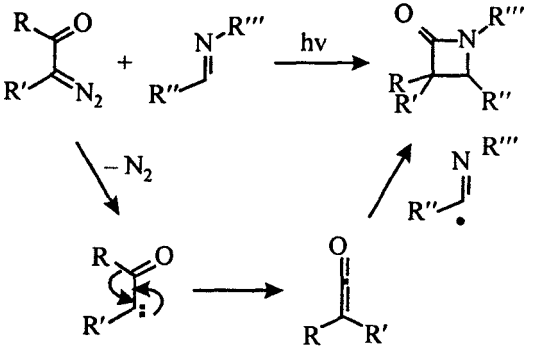


At lower temperatures, a catalytic version involves the use of non-nucleophilic imines (for example tosylated imines) and the Umpolung of the ketene substrate using tertiary amines or other suitable nucleophiles, making the ketene nucleophilic:

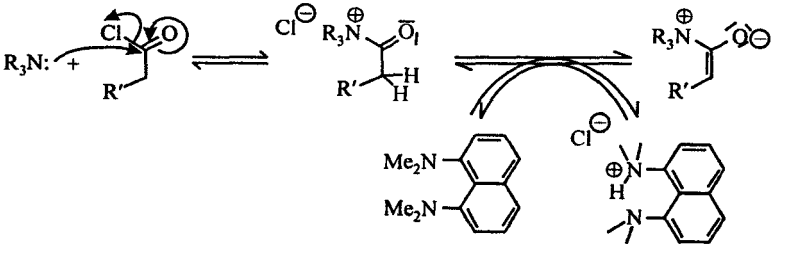


This reversed reactivity mode allows the use of chiral nucleophilic catalysts for enantioselective induction.

Diphenylketene is quite stable, but other ketenes readily polymerise and must be prepared immediately before the reaction. Ketenes can also be formed *in situ* in the presence of the imine by a light- or heat-induced Wolff-Rearrangement:

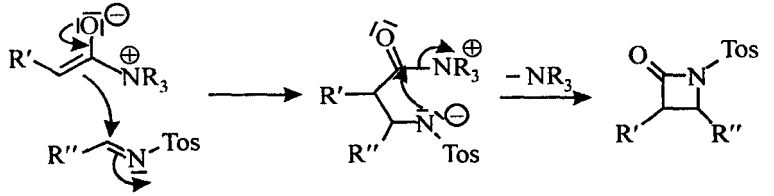


Using the reversed mode strategy, the reaction of acid chlorides with a tertiary amine in the presence of a proton sponge readily produces ketenes:



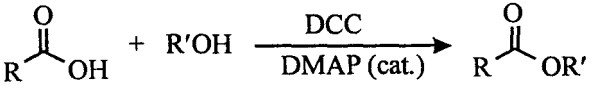
R_3N could be an expensive chiral amine catalyst such as a chinchona alkaloid, whereas the proton sponge is used

stoichiometrically. For achiral reactions, NEt_3 can serve both functions. The subsequent reaction follows the pathway known from the reverse mode reactions, with the catalyst recovered unchanged:



A general overview about advances in the catalytic, asymmetric synthesis of β-lactams can be found in an article written by Thomas Lectka, whereas a publication by Claudio Palomo discusses reactions of acyl chlorides with imines, including diastereoselectivites and mechanistic insights of the ring closure leading to *cis* or *trans* substituted β-lactams and asymmetric induction from the ketene component. The influence of solvents and additives and the pathways of ketene generations and addition modes on the stereoselectivity.

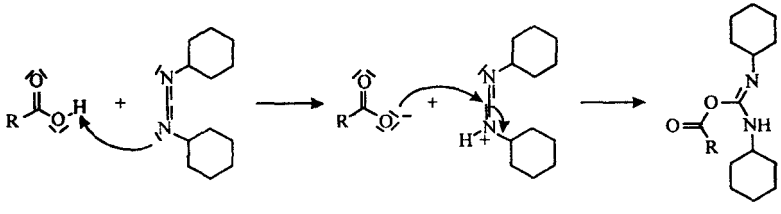
STEGLICH ESTERIFICATION



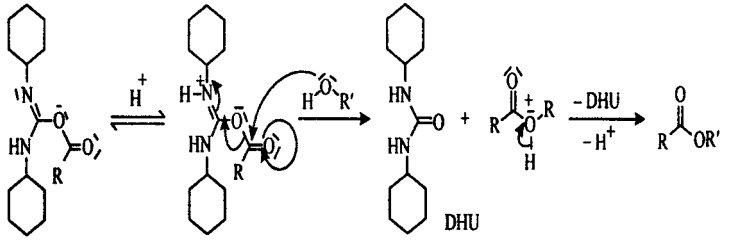
The Steglich Esterification is a mild reaction, which allows the conversion of sterically demanding and acid labile substrates. It's one of the convenient methods for the formation of *tert*-butyl esters because *t*-BuOH tends to form carbocations and isobutene after a subsequent elimination under the conditions employed in the Fischer Esterification.

Mechanism

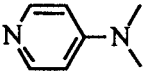
DCC (dicyclohexylcarbodiimide) and the carboxylic acid are able to form an *O*-acylisourea intermediate, which offers reactivity similar to the corresponding carboxylic acid anhydride:



The alcohol may now add to the activated carboxylic acid to form the stable dicyclohexylurea (DHU) and the ester:



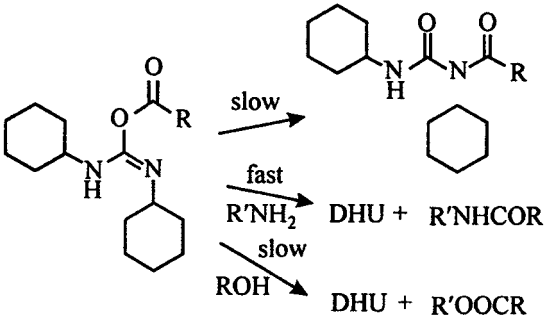
In practice, the reaction with carboxylic acids, DCC and amines leads to amides without problems, while the addition of approximately 5 mol-% DMAP is crucial for the efficient formation of esters.



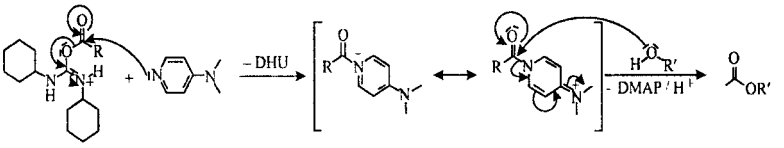
DMAP

4-N, N-dimethylaminopyridine

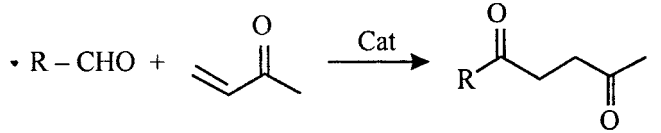
N-Acylureas, which may be quantitatively isolated in the absence of any nucleophile, are the side products of an acyl migration that takes place slowly. Strong nucleophiles such as amines react readily with the *O*-acylisourea and therefore need no additives:



A common explanation of the DMAP acceleration suggests that DMAP, as a stronger nucleophile than the alcohol, reacts with the *O*-acylisourea leading to a reactive amide ("active ester"). This intermediate cannot form intramolecular side products but reacts rapidly with alcohols. DMAP acts as an acyl transfer reagent in this way, and subsequent reaction with the alcohol gives the ester.

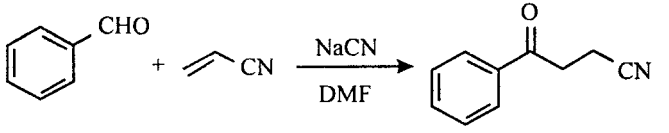


STETTER REACTION



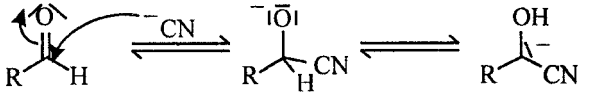
The Stetter Reaction is a 1,4-addition (conjugate addition) of an aldehyde to an a,β-unsaturated compound, catalyzed by cyanide or a thiazolium salt. This reaction competes with the corresponding 1,2-addition, which is the Benzoin Condensation. However, the Benzoin-Condensation is reversible, and since the Stetter Reaction leads to more stable products, the main product will be derived from 1,4-addition.

Some of the possible products are: 1,4-diketones, 4-ketocarboxylic acids and the corresponding nitriles.

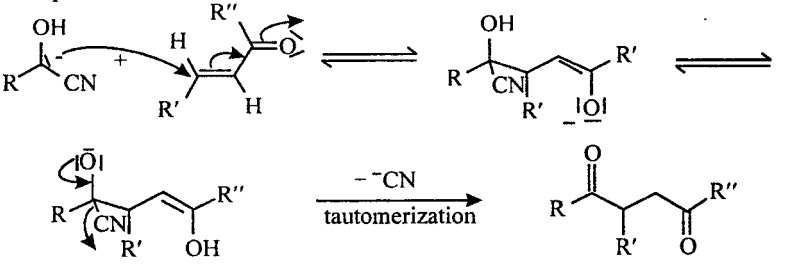


Mechanism

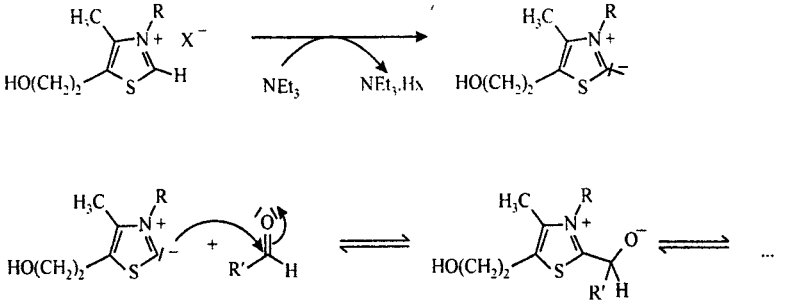
The cyanide ion effects an *umpolung* of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation:



This *in situ* generated nucleophile reacts with the unsaturated compound:



The thiazolium salts may be converted into ylides by deprotonation. These ylides are comparable to the cyanide adducts in their ability to catalyze the Stetter Reaction effectively.

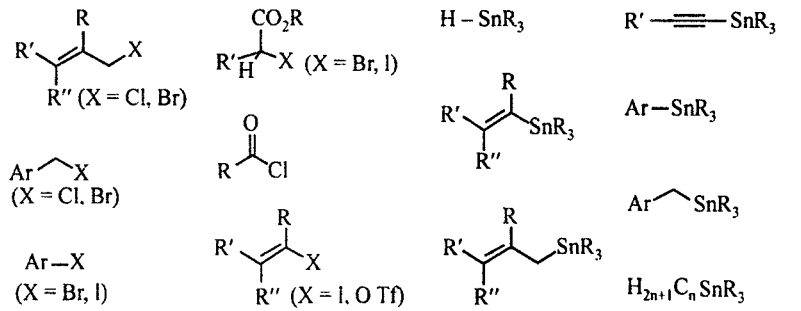


STILLE COUPLING

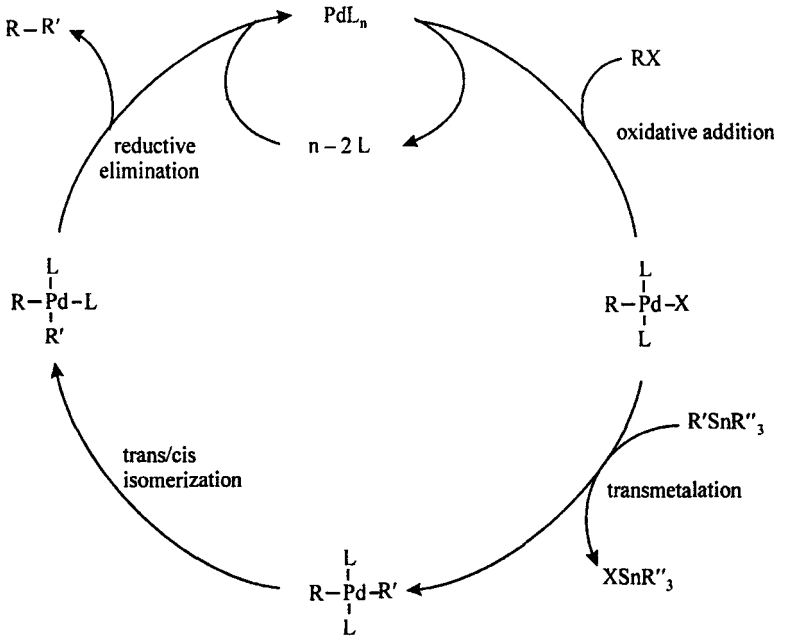
$$R' - X + RSnBu_3 \xrightarrow{Pd - Cat} R' - R + XSnBu_3$$

The Stille Coupling is a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, with very few limitations on the R-groups. Well-elaborated methods allow the preparation of differen. products from all of the combinations of halides and stannanes depicted below. The main drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki Coupling. Improvements in the Suzuki Coupling may soon lead to the same versatility without the drawbacks of using tin compounds.

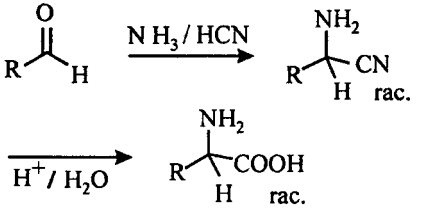
Convenient electrophiles and stannanes:



Mechanism



STRECKER SYNTHESIS



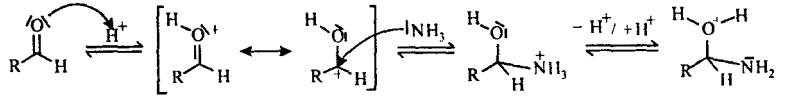
The Strecker Synthesis is a preparation of α-aminonitriles, which are versatile intermediates for the synthesis of amino acids via hydrolysis of the nitrile.

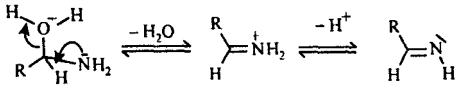
Mechanism

The reaction is promoted by acid, and HCN must be supplied or generated *in situ* from cyanide salts - in the latter case, one equivalent of acid is consumed in the reaction.

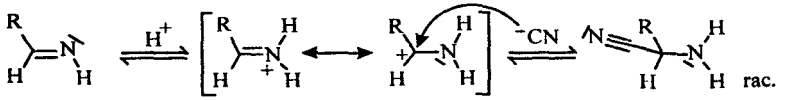
$$NH_4Cl + NaCN \rightleftharpoons NH_3 + HCN + NaCl$$

The first step is probably the condensation of ammonia with the aldehyde to form an imine:

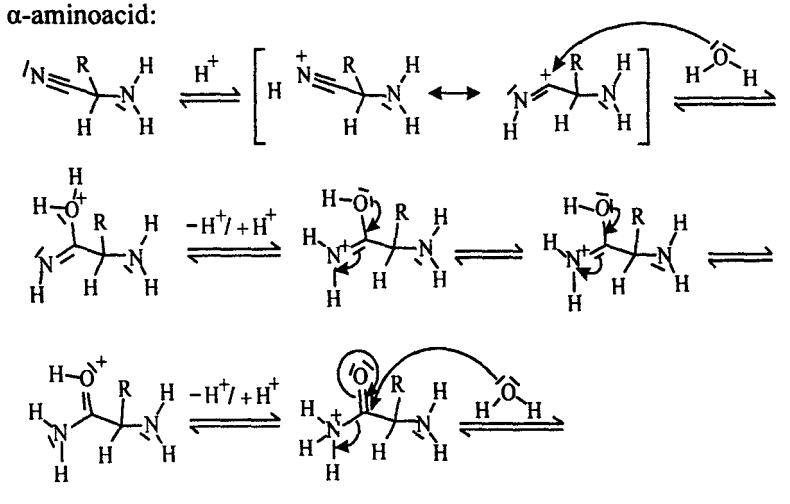


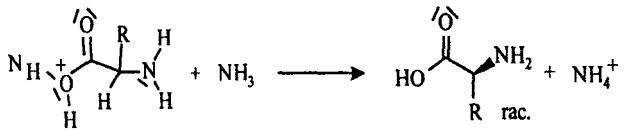


The cyanide adds as a nucleophile to the imine carbon, generating the α-aminonitrile:

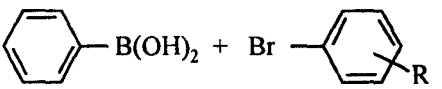


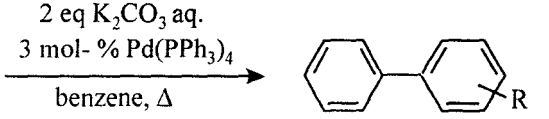
This product may optionally be hydrolysed to the corresponding α-aminoacid:





SUZUKI COUPLING

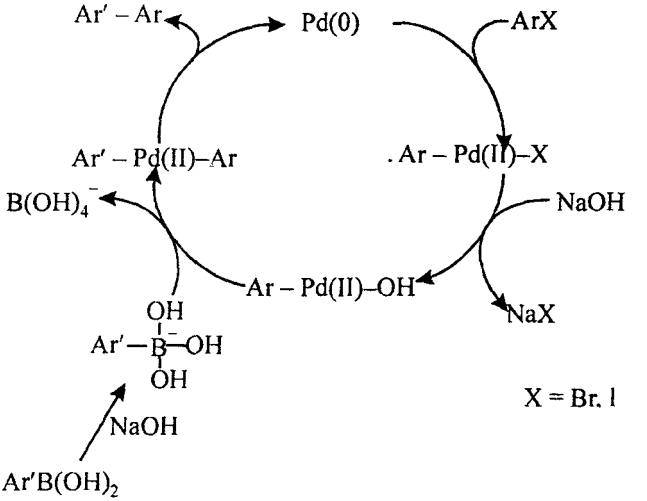




The Suzuki Coupling, which is the palladium-catalysed cross coupling between organoboronic acid and halides. Recent catalyst and methods developments have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners.

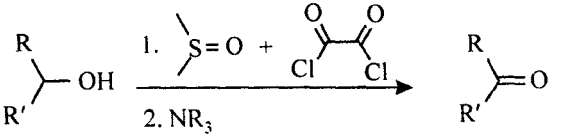
Mechanism

One difference between the Suzuki mechanism and that of the Stille Coupling is that the boronic acid must be activated, for example with base. This activation of the boron atom enhances the polarisation of the organic ligand, and facilitates transmetallation. If starting materials are substituted with base labile groups (for example esters), powdered KF effects this activation while leaving base labile groups unaffected.



In part due to the stability, ease of preparation and low toxicity of the boronic acid compounds, there is currently widespread interest in applications of the Suzuki Coupling, with new developments and refinements being reported constantly.

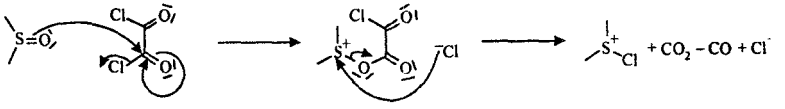
SWERN OXIDATION



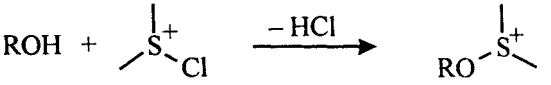
The Swern Oxidation of alcohols avoids the use of toxic metals such as chromium, and can be carried out under very mild conditions. This reaction allows the preparation of aldehydes and ketones from primary and secondary alcohols, resp. Aldehydes do not react further to give carboxylic acids. A drawback is the production of the malodorous side product dimethyl sulphide.

Mechanism

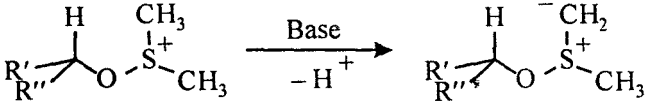
Dimethylchlorosulphonium ion is generated in situ from DMSO and oxalyl chloride.



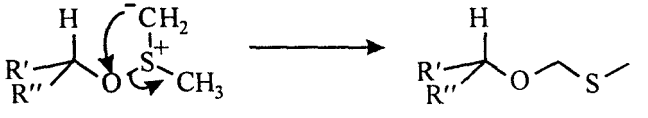
The reaction with an alcohol at -78°C leads to an alkoxysulphonium ion:



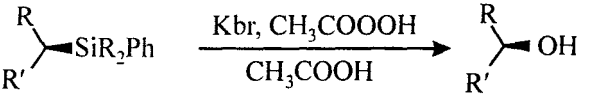
Deprotonation of this intermediate gives a sulphur ylide, which undergoes intramolecular deprotonation via a five-membered ring transition state and fragmentation to yield the product and DMS (odour!):



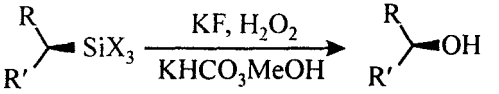
If the temperature is not kept near -78°C, mixed thioacetals may result:



TAMAO-KUMADA OXIDATION



Fleming (-Tamao) Oxidation



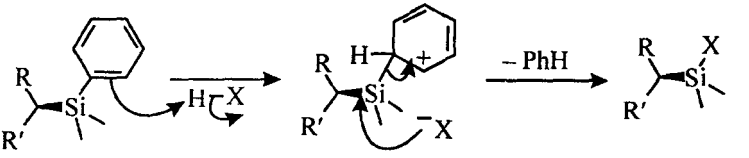
(Fleming-) Tamao (-Kumada) Oxidation

Parallel procedures for the oxidation of silyl groups to hydroxy groups were developed by Fleming and Tamao. The conversion of a dimethylphenylsilyl group, which involves a specific reaction mechanism, was pioneered by Fleming.

Mechanism

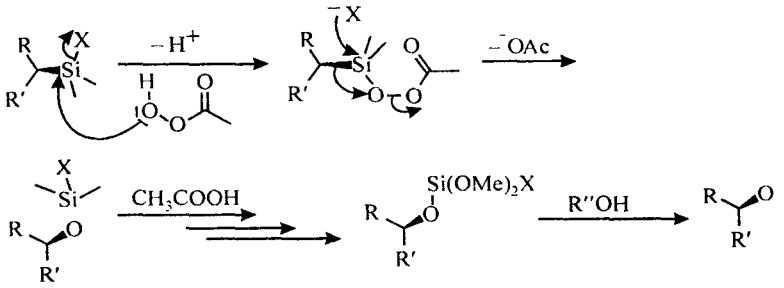
Silyl groups, which are non-polar electropositive groups without lone pairs, tolerate many chemical reactions that would not be possible in presence of hydroxy groups. The Fleming-Tamao Oxidation permits silyl groups to be used as "masked hydroxy groups", which has found broad application in total syntheses. In addition, enantioselective hydrosilylation of alkenes followed by Fleming-Tamao oxidation allows the preparation of chiral alcohols.

The first step of the Fleming Oxidation is the removal of the phenyl group in which the very stable phenylsilane group is converted into a more reactive halosilane after electrophilic aromatic substitution:

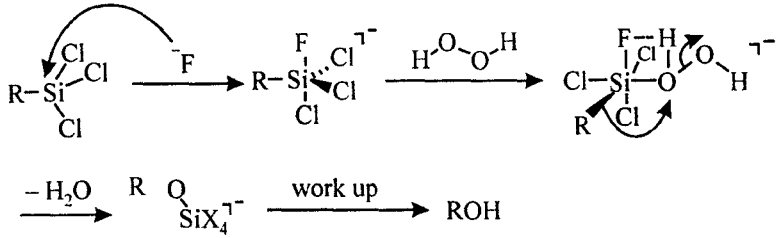


The removal may be done as separate step followed by the addition of the oxidation reagents or in one of the more convenient one-pot procedures. The phenyl group can also be activated through bromination using excess bromine or a bromide source leading to phenyl bromide as by-product.

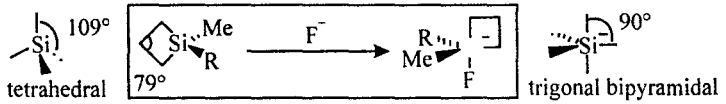
The displacement of the halide by peracetic acid leads to an intermediate that rearranges to give a silanol. Protic work-up gives the desired alcohol:



The Tamao Oxidation uses the more reactive fluoro- or chlorosilanes ($RSiMe_nX_{(2-n)}$), in which the silicon is a stronger Lewis acid and shows more metallic character than the substrates used in the Fleming oxidation. Further activation by a fluoride ion then leads to a pentavalent intermediate which is able to bind hydrogen peroxide. The transition state is also stabilized through hydrogen bonding between fluorine and hydrogen:

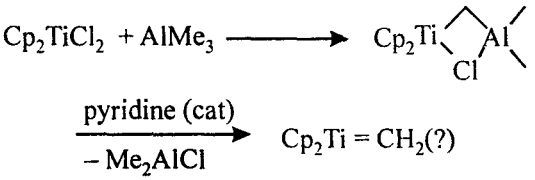


Strained siletanes may also be used in the Tamao Oxidation instead of halosilanes; these intermediates offer a comparable Lewis acidity because coordination of the fluoride ion releases angle strain.

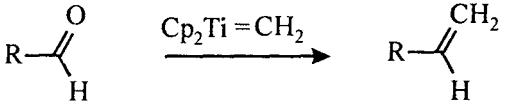


Lewis acidity enhanced by strain release

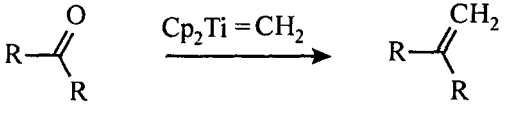
TEBBE OLEFINATION



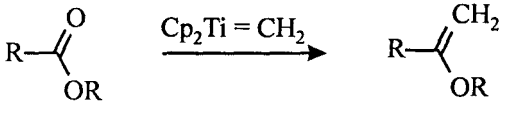
The Tebbe Reagent is a metal carbenoid prepared from the dimetallomethylene species derived by the reaction of trimethyl aluminium with titanocene dichloride; this reagent exhibits carbenoid behaviour after the addition of a catalytic amount of pyridine. The Tebbe Reagent reacts with various carbonyl partners to give the product of methylenation:



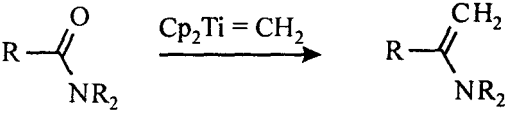
Aldehydes to alkenes



Ketones to alkenes

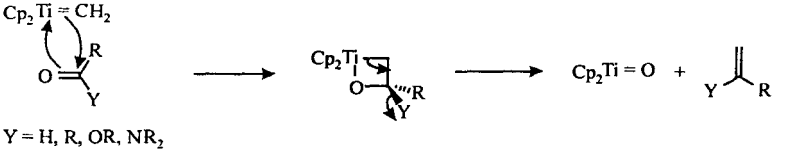


Esters to enol ethers

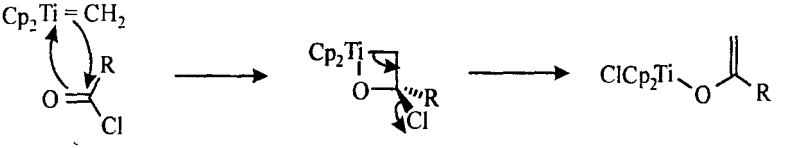


Amides to enamines

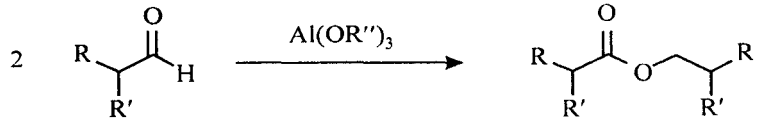
Mechanism



Y = H, R, OR, NR_2



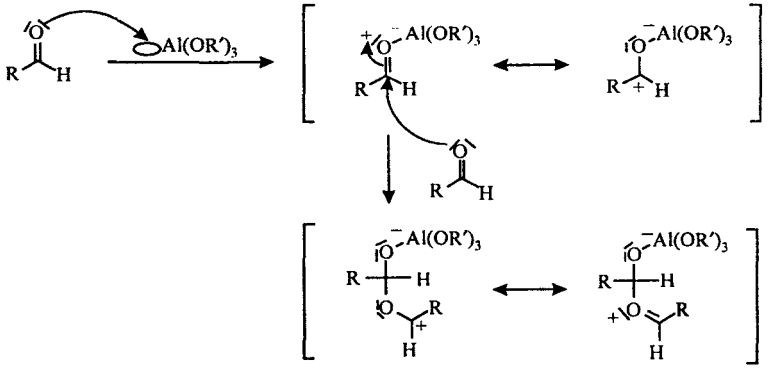
TISHCHENKO REACTION



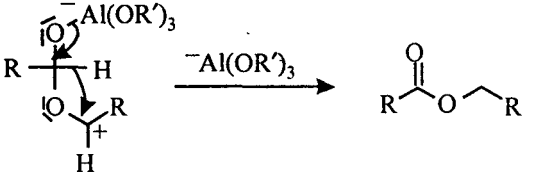
The Tishchenko Reaction is a disproportionation reaction that allows the preparation of esters from two equivalents of an aldehyde.

Mechanism

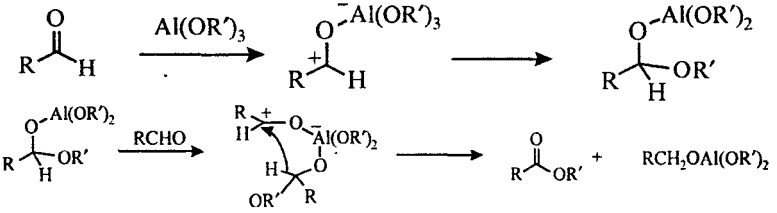
The aluminium alkoxide acts as a Lewis acid to coordinate with one molecule of the aldehyde, and to facilitate the addition of a second equivalent of aldehyde, generating a hemiacetal intermediate:



This species undergoes an intramolecular 1,3-hydride shift that results in the production of the aluminium-coordinated ester.

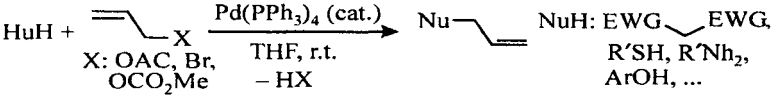


A potential side reaction is the involvement of one of the alkoxide groups from the catalyst:



This can be minimised, if the reaction is conducted at low temperatures and low catalyst loadings.

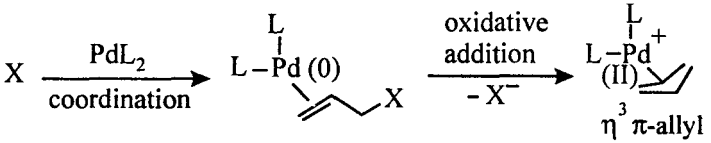
TSUJI-TROST REACTION



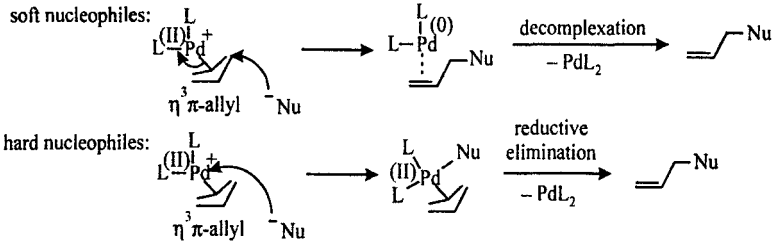
The Tsuji-Trost Reaction (or Trost Allylation) is the palladium-catalyzed allylation of nucleophiles such as active methylenes, enolates, amines and phenols with allylic compounds such as allyl acetates and allyl bromides.

Mechanism

The coordination of the Pd(0)-catalyst to the double bond forms an η^2 π-allyl complex. An oxidative addition, during which the leaving group is expelled, gives an η^3 π-allyl complex. This step is also called ionization:

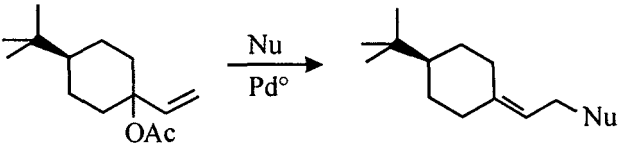


Depending on the strength of the nucleophile, the reaction can take two different pathways. Soft nucleophiles, such as those derived from conjugate acids with a pKa < 25, normally add directly to the allyl moiety, whereas hard nucleophiles first attack the metal centre, followed by reductive elimination to give the allylation product:



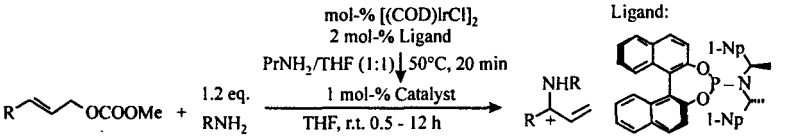
These two mechanistic modes have an impact on the development of asymmetric variants of the Tsuji-Trost Reaction.

Nonsymmetric allyl substrates normally undergo substitution at the least hindered allylic position, with a selectivity that depends on the size of the nucleophile:

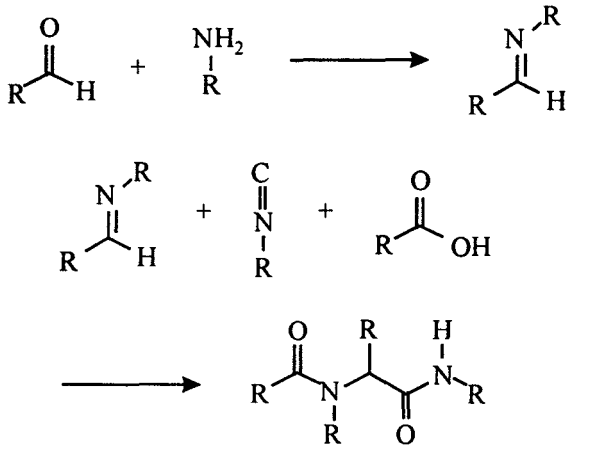


Sterically unhindered nucleophiles such as phenol give the more branched product.

Similar reactions can be conducted using catalysts based on molybdenum or iridium. These reactions offer - as an alternative to the Tsuji-Trost Reaction - access to branched regioisomers:



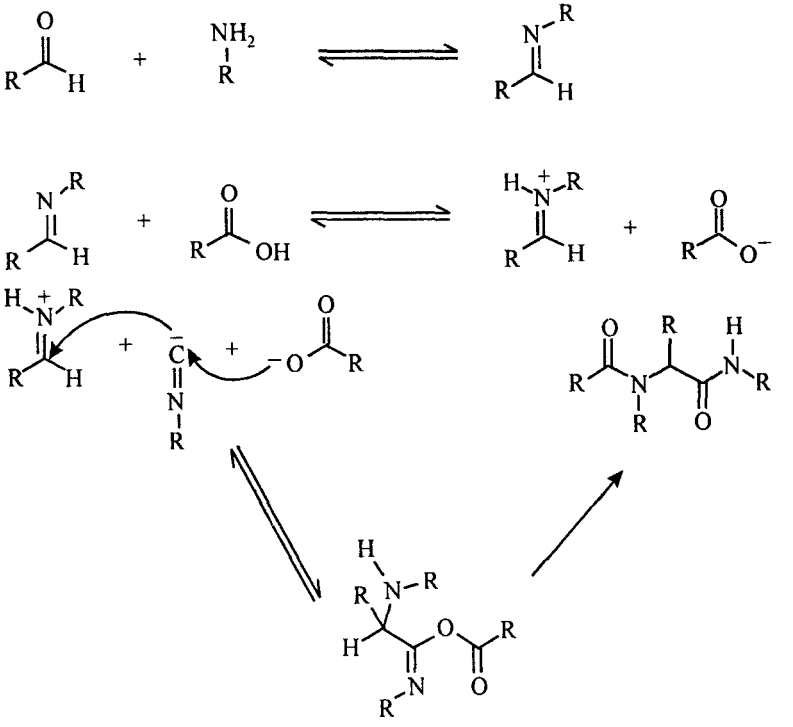
UGI REACTION



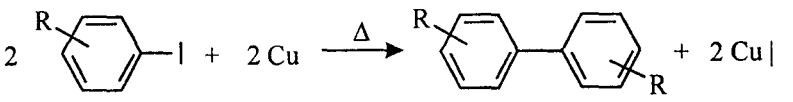
The Ugi four-component condensation (U-4CC) between an aldehyde, an amine, a carboxylic acid and an isocyanide allows the rapid preparation of α-aminoacyl amide derivatives. The Ugi Reaction products can exemplify a wide variety of substitution patterns, and constitute peptidomimetics that have potential pharmaceutical applications. This reaction is thus very important for generating compound libraries for screening purposes.

Mechanism

The mechanism is believed to involve a prior formation of an imine by condensation of the amine with the aldehyde, followed by addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon; the resulting acylated isoamide rearranges by acyl transfer to generate the final product.

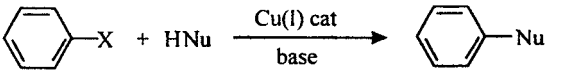


ULLMANN REACTION



There are two different transformations referred as the Ullmann Reaction. The "classic" Ullmann Reaction is the synthesis of symmetric biaryls via copper-catalyzed coupling. The "Ullmann-type" Reactions include copper-catalyzed Nucleophilic Aromatic

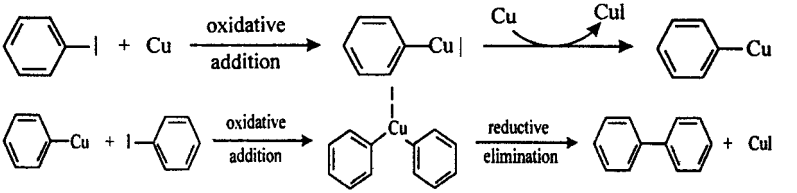
Substitution between various nucleophiles (e.g. substituted phenoxides) with aryl halides. The most common of these is the Ullmann Ether Synthesis.



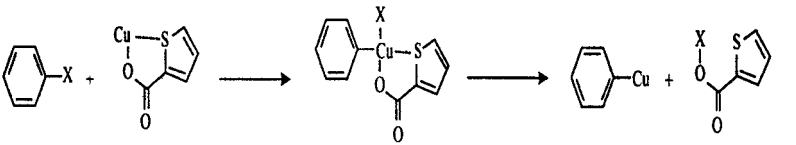
HNu= NHR', HOAr, HSR, ...

Mechanism

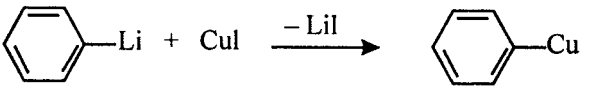
Biaryls are available through coupling of the aryl halide with an excess of copper at elevated temperatures (200 °C). The active species is a copper(I)-compound which undergoes oxidative addition with the second equivalent of halide, followed by reductive elimination and the formation of the aryl-aryl carbon bond.



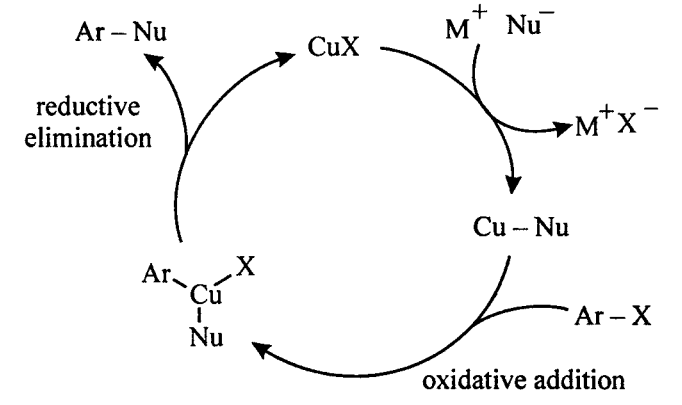
The organocopper intermediate can be generated at a more moderate 70 °C using a novel thiophenecarboxylate reagent. The reaction otherwise follows the same reaction path as above.

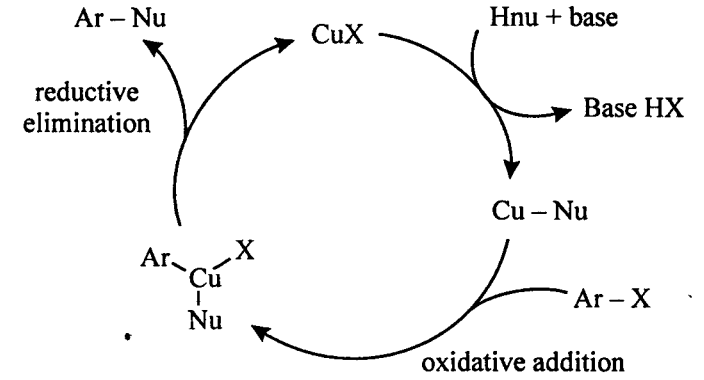


Another possibility is the use of Cu(I) for the oxidative coupling of aryllithium compounds at low temperatures. This method can also be used to generate asymmetric biaryls, after addition of the appropriate halide.

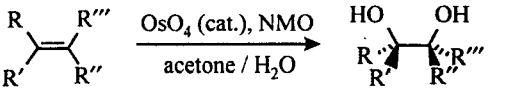


Ullmann-type reactions proceed through a catalytic cycle, and in one mechanism the copper is postulated to undergo oxidation to Cu(III). As some Cu(III) salts have been prepared.





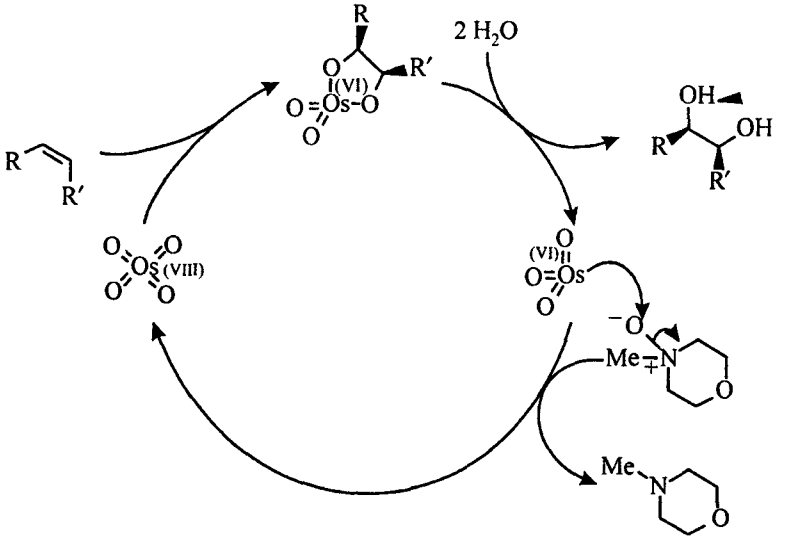
UPJOHN DIHYDROXYLATION



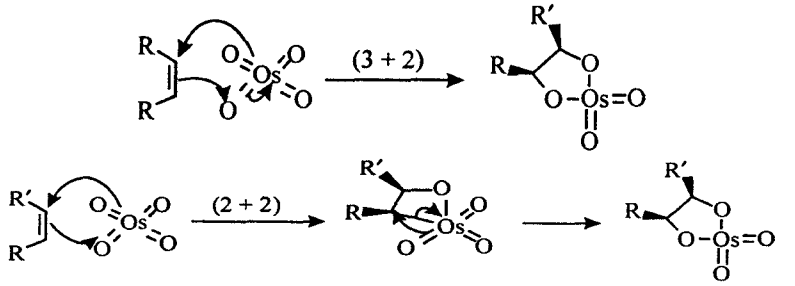
The Upjohn Dihydroxylation allows the *syn*-selective preparation of 1,2-diols from alkenes by the use of OsO_4 as a catalyst and a stoichiometric amount of an oxidant such as NMO (*N*-methyl morpholine-*N*-Oxide).

Mechanism

The toxic and volatile OsO_4 can also be prepared *in situ* by the oxidation of $K_2OsO_2(OH)_4$ with NMO. NMO is also the cooxidant that enables the use of a catalytic amount of OsO_4, because this reagent is able to reoxidize an Os(VI) species to an Os(VIII) species:

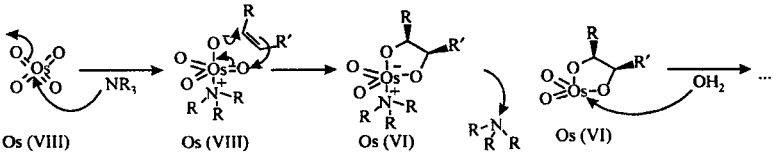


The key step is the cycloaddition of OsO_4 to the olefin. There has been some speculation regarding the actual addition step, for which experimental data suggest the possible involvement of two separate steps. Thus, the question arises during these discussions of whether the key step takes place via an initial (3+2)-addition (1,3-dipolar cycloaddition), or by a (2+2)-addition followed by expansion of the metallacycle.



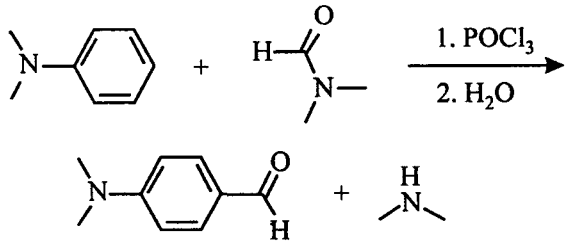
Quantum chemical calculations have shown an initial (3+2)-addition of OsO_4 to be energetically more favourable. However, this energy difference is substantially smaller in the related Re(VII) oxide additions.

Tertiary amines such as DMAP and pyridine accelerate the addition reaction.



The use of chiral amines enables enantioselective conversions, such as $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL in the Sharpless Dihydroxylation.

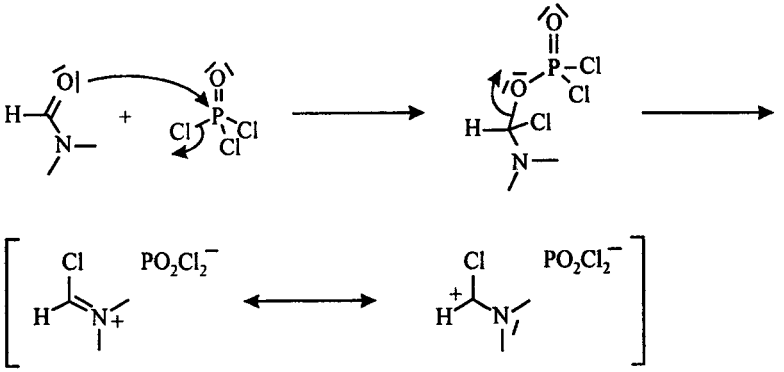
VILSMEIER-HAACK REACTION



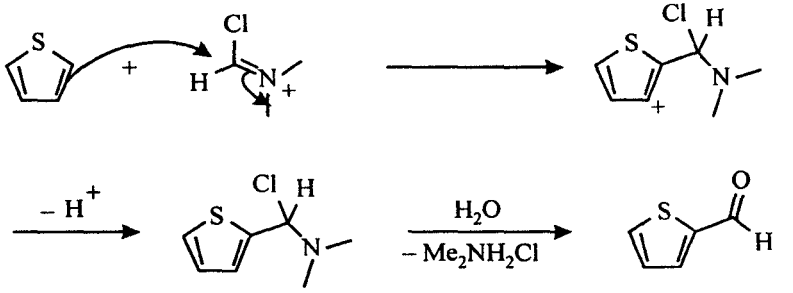
The Vilsmeier Reaction allows the formylation of electron-rich arenes.

Mechanism

The formylating agent, also known as the Vilsmeyer-Haack Reagent, is formed *in situ* from DMF and phosphorus oxychlorid:



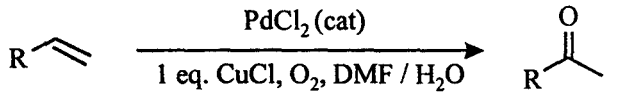
An electrophilic aromatic substitution leads to α-chloro amines, which are rapidly hydrolyzed during work up to give the aldehyde:



WACKER-TSUJI OXIDATION

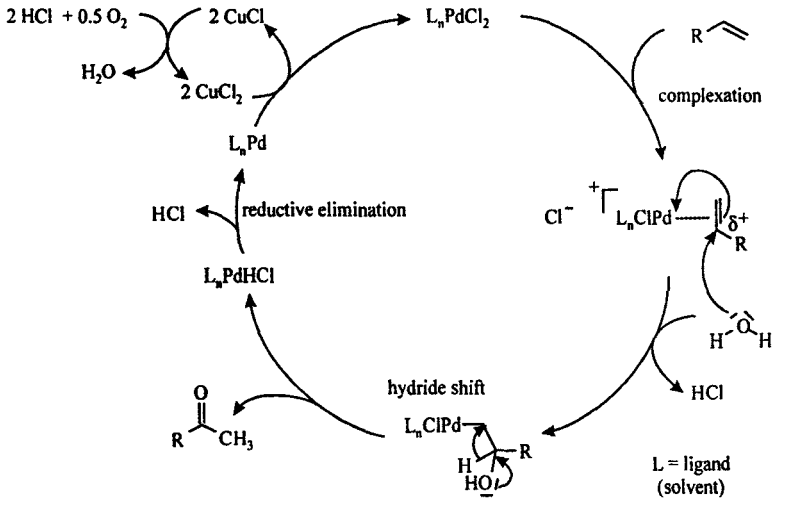
$$H_2C = CH_2 \xrightarrow[CuCl_2\,(cat),\,O_2,\,H_2O]{PdCl_2\,(cat)} \text{CH}_3\text{CHO}$$

The Wacker Oxidation is an industrial process, which allows the synthesis of ethanal from ethene by palladium-catalyzed oxidation with oxygen. Copper serves as redox cocatalyst.



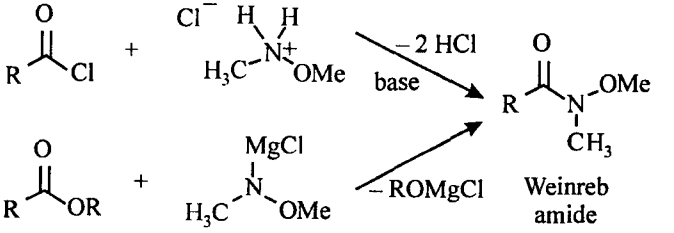
The lab scale modification - the Wacker-Tsuji Oxidation - is useful for the synthesis of various ketones.

Mechanism

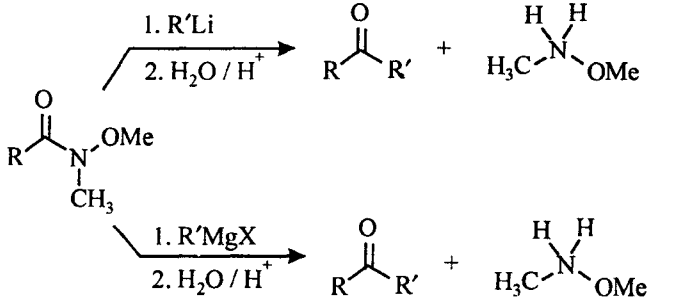


The mechanism is typical of palladium olefin chemistry, and water serves as the oxygen source; the reduced palladium is reoxidized by Cu(II) and ultimately by atmospheric oxygen.

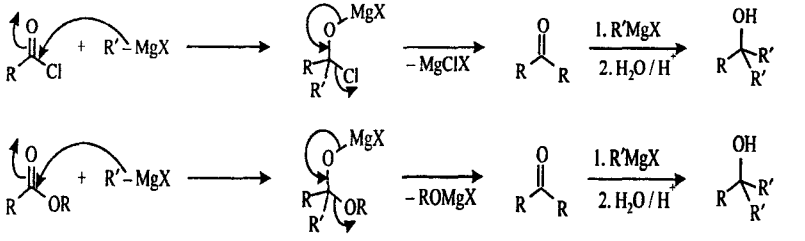
WEINREB KETONE SYNTHESIS



The reaction of esters and carboxylic acid chlorides with organolithium and organomagnesium compounds does not lead to ketones in high yields, because the intermediate ketones are still highly reactive toward the organometallic reagent. However, after derivatisation to the corresponding Weinreb Amide, reaction with organometallics does give the desired ketones, as the initial adduct is stabilized and doesn't undergo further reaction.

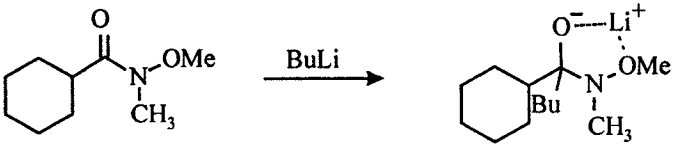


Mechanism

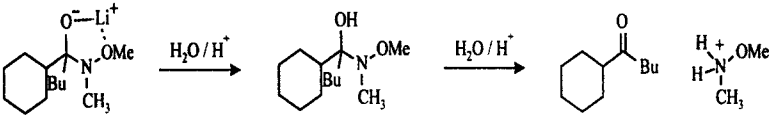


With the usual reaction of organometallic reagents with acid derivatives (ester or acid chloride), the starting materials can add two equivalents of organometallic compound. The ketone generated after the first addition is quite reactive, and there is quite no selectivity between it and the starting acid derivative:

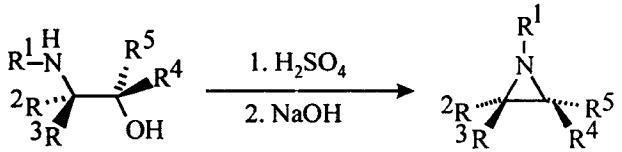
The organometallic adducts of Weinreb Amides are able to form stable chelates, and do not regenerate an electrophilic carbonyl group *in situ* for further reaction:



Aqueous work up liberates the ketone from this chelate:



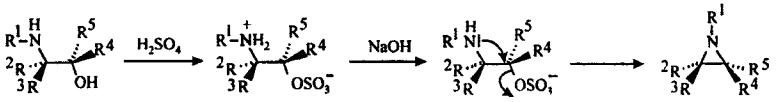
WENKER-SYNTHESIS



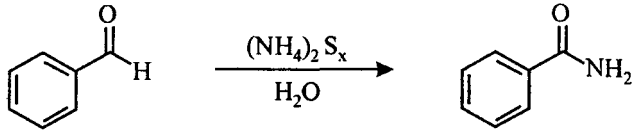
This reaction sequence allows the preparation of aziridines from 1,2-amino alcohols.

Mechanism

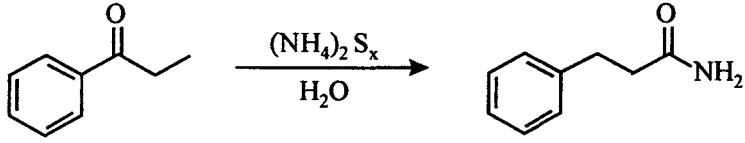
After preparation of sulphonate salt, a second deprotonation step effects the ring closure:



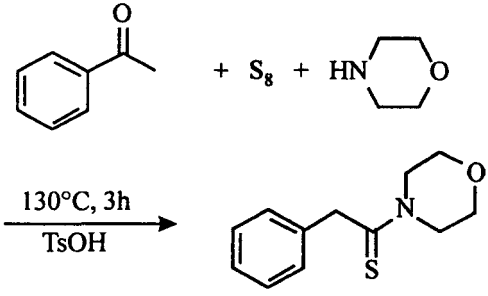
WILLGERODT-KINDLER REACTION



The Willgerodt Reaction allows the synthesis of amides from aryl ketones under the influence of a secondary amine and a thiating agent. The mechanism involves the formation of an enamine which undergoes thiation, and the carbonyl group migrates to the end of the chain via a cascade of thio-substituted iminium-aziridinium rearrangements.

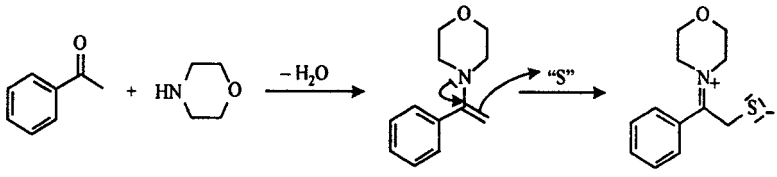


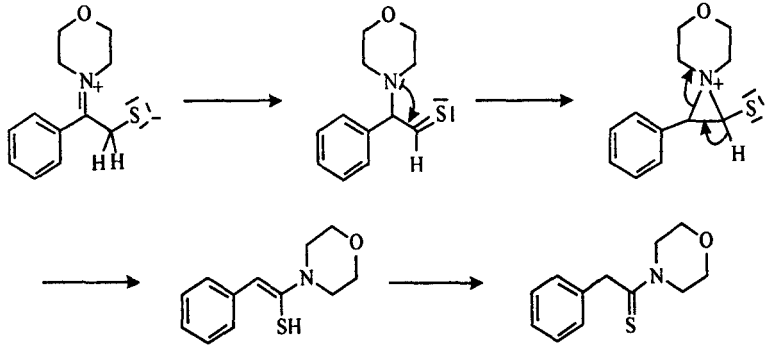
The Kindler Modification is more convenient:



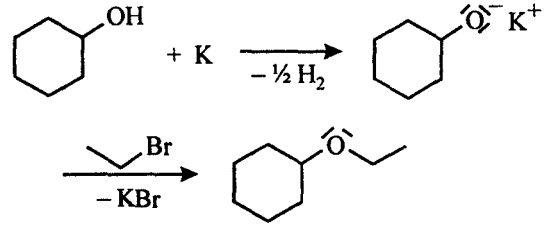
Hydrolysis of the thioamide provides the amide.

Mechanism





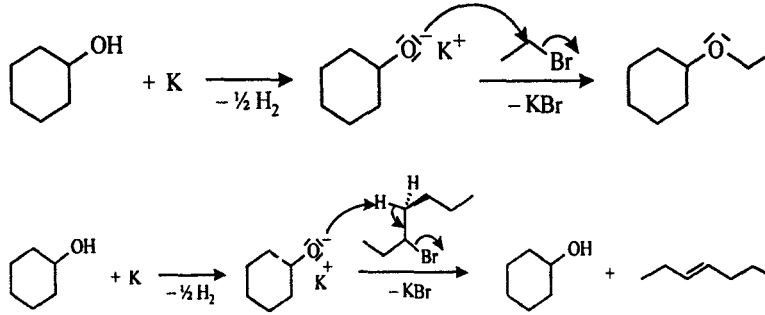
WILLIAMSON SYNTHESIS



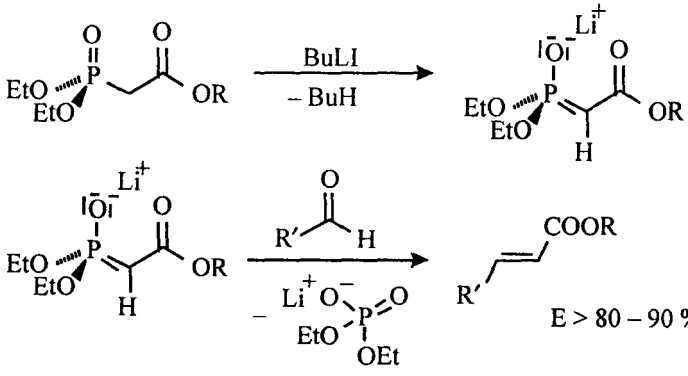
This method is suitable for the preparation of a wide variety of unsymmetric ethers. The nucleophilic substitution of halides with alkoxides leads to the desired products.

If the halides are sterically demanding and there are accessible protons in the β-position, the alkoxide will act as a base, and side products derived from elimination are isolated instead.

Mechanism



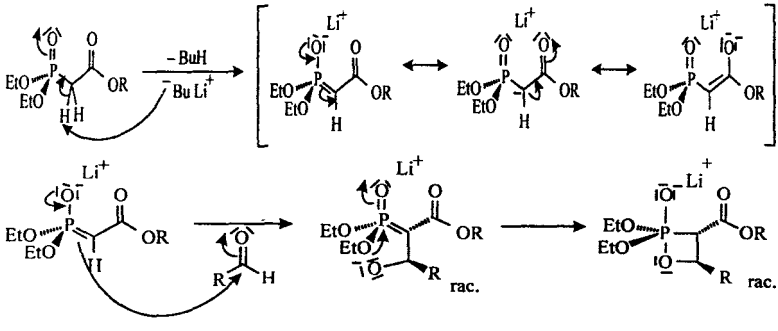
WITTIG-HORNER REACTION

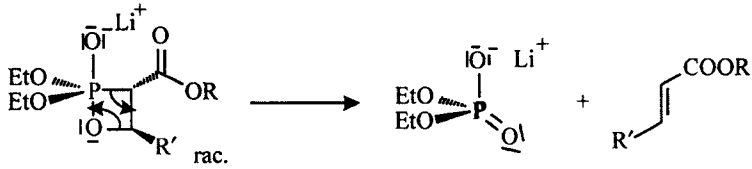


The reaction of aldehydes or ketones with stabilized phosphorus ylides (phosphonate carbanions) leads to olefins with excellent *E*-selectivity.

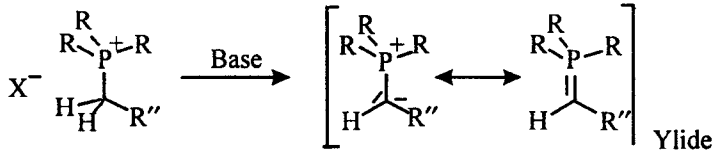
Mechanism

The reaction mechanism is similar to the mechanism of the Wittig Reaction. The stereochemistry is set by steric approach control, where the antiperiplanar approach of the carbanion to the carbon of the carbonyl group is favoured when the smaller aldehydic hydrogen eclipses the bulky phosphoranyl moiety. This places the ester group syn to the aldehyde R group, but the incipient alkene assumes an *E*-orientation of these groups after rotation to form the oxaphosphetane. As the lithium counterion does not interfere with oxaphosphetane formation, use of BuLi is possible, but NaH and NaOMe are also suitable bases for forming the ylide. The resulting phosphate byproduct is readily separated from the desired products by simply washing with water.





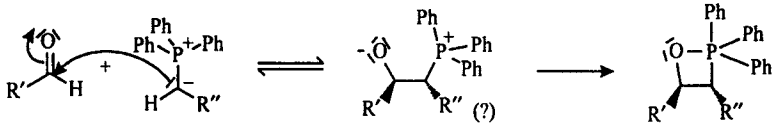
WITTIG REACTION



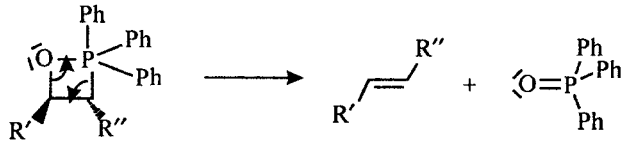
The Wittig Reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. The geometry of the resulting alkene depends on the reactivity of the ylide. If R is Ph, then the ylide is stabilized and is not as reactive as when R = alkyl. Stabilized ylides give (*E*)-alkenes whereas non-stabilized ylides lead to (*Z*)-alkenes.

Mechanism

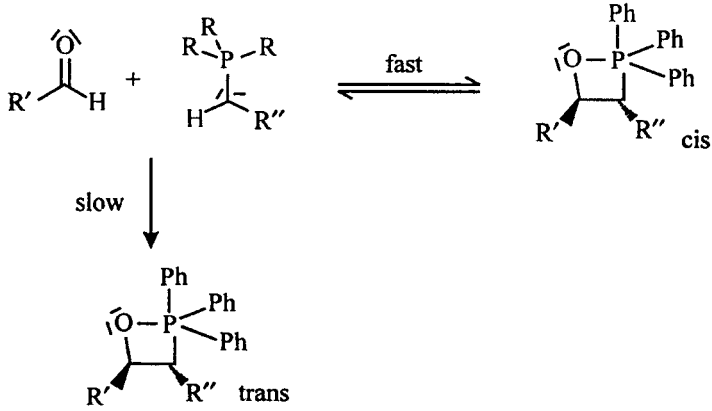
Addition of the ylide to the carbonyl is postulated to lead first to the zwitterionic intermediate betaine, which would then close to form a four-membered cyclic intermediate, an oxaphosphetane. The existence of the betaine hasn't been fully established, although its intermediacy plays an important role in the Schlosser Modification. Betaines may be stabilized by lithium salts leading to side products; therefore, suitable bases in the Wittig Reaction are for example: NaH, NaOMe, NEt_3).



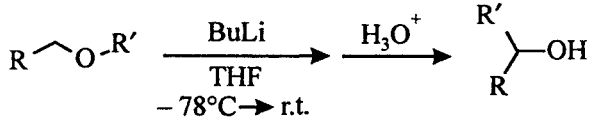
The driving force is the formation of a very stable phosphine oxide:



Reactive ylides give rapid reaction and subsequent rapid ring opening to give the (Z)-alkene:



[1,2]-WITTIG REARRANGEMENT

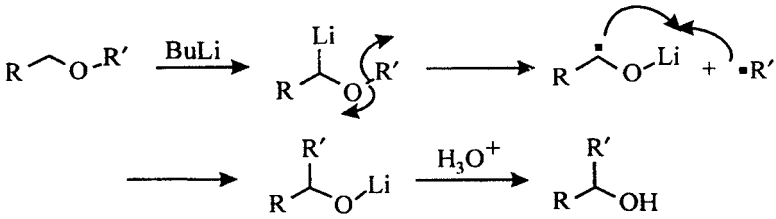


The [1,2]-Wittig Rearrangement is the base-promoted reaction of ethers to yield secondary or tertiary alcohols.

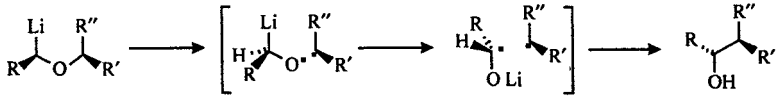
Mechanism

Compared to the [2,3]-Wittig Rearrangement, the [1,2]-rearrangement has received little attention because of the somewhat limited substrate scope and moderate yields.

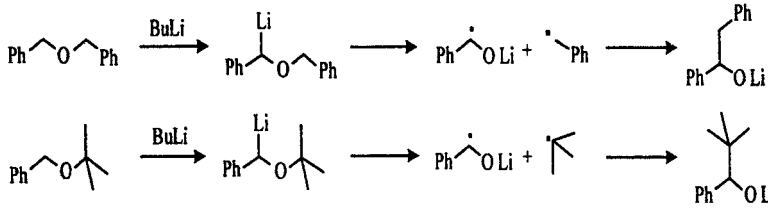
The [1,2]-Wittig Rearrangement is a carbanion rearrangement that proceeds via a radical dissociation-recombination mechanism. The lithiated intermediate forms a ketyl radical and a carbon radical, which give an alcoholate after fast recombination within the solvent cage:



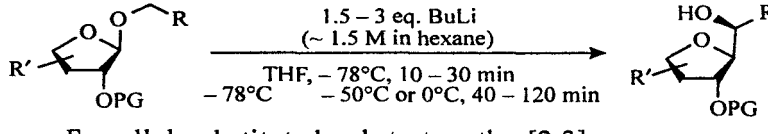
Despite its radical character, the integrity of the two radical stereocentres is retained to an appreciable extent, with retention of configuration at the migrating carbon and inversion at the lithium-bearing centre:



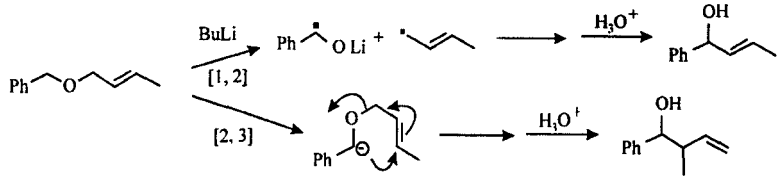
Regioselectivity and ease of reaction are determined by the substituents. The R-groups must be able to stabilize either an anion for the lithiation step, or a radical to facilitate the migration step. For example benzyl groups are able to stabilize both the anionic charge and the radical. Tertiary alkyl groups are able to stabilize radicals, and the combination with a benzyl group thus gives an ideal substrate:



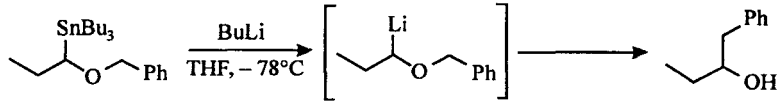
Some other very suitable substrates have been reported; for example, *O*-glycosides can be selectively converted in high yields to the *C*-glycosides:



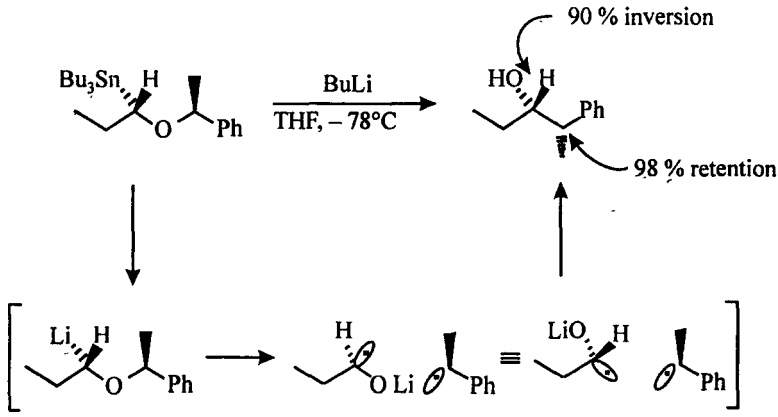
For allyl-substituted substrates, the [2,3]-rearrangement competes with [1,2]-rearrangement. Normally in these cases, the [1,2]-rearrangement is only a source of side products. Keeping the temperature as low as possible avoids contamination with these [1,2]-rearrangement products:



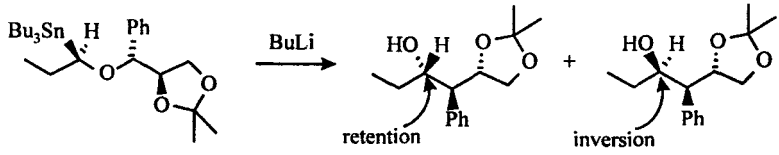
The regioselectivity can be better controlled if α-alkoxystannanes are used as substrates. This modification is named the "Wittig-Still Rearrangement". Here, the intermediate organolithium compound is produced through transmetallation:



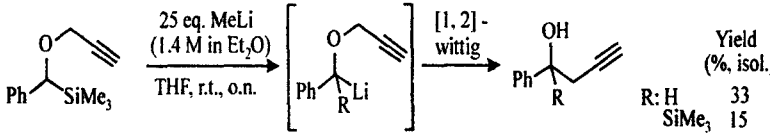
The Wittig-Still Rearrangement is also a suitable starting point for performing mechanistic studies about the stereospecificity of this process, and Maleczka and Feng have reported on the stereochemical outcome of the [1,2]-Wittig Rearrangement.



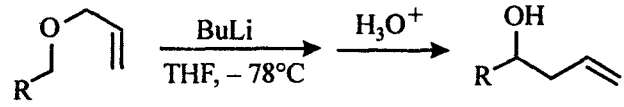
They found that the "normal" stereochemical tendency can be overcome by specific intramolecular chelation effects:



Similar reactions can be performed using the less toxic α-alkoxysilanes as starting materials:



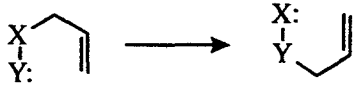
[2,3]-WITTIG REARRANGEMENT



The [2,3]-Wittig Rearrangement allows the synthesis of homoallylic alcohols by the base-induced rearrangement of allyl ethers at low temperatures.

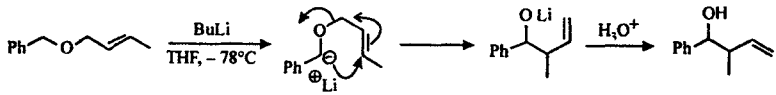
Mechanism

The [2,3]-Wittig Rearrangement is a [2,3]-sigmatropic reaction, a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state. A general scheme for [2,3]-sigmatropic reactions is given here:



[2,3]-Sigmatropic reactions encompass a vast number of synthetically useful variants in terms of both the atom pair involved (X, Y) and the electronic state (Y: anions, non-bonding electron pairs, ylides).

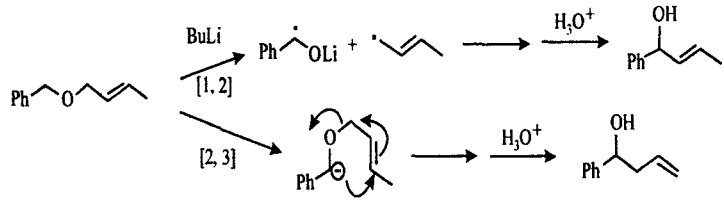
The transformation of deprotonated allyl ethers into homoallylic alcohols is the [2,3]-sigmatropic version of the [1,2]-Wittig Rearrangement, and is therefore termed [2,3]-Wittig Rearrangement:



These [2,3]-rearrangements feature regioselective carbon-carbon bond formation with allylic transposition of the oxygen, generation of specific olefin geometries and transfer of chirality. A discussion

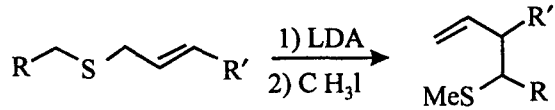
of the mechanism, scope and limitations, stereochemical control and synthetic applications.

The concerted [2,3]-shift competes with the [1,2]-shift in many cases:



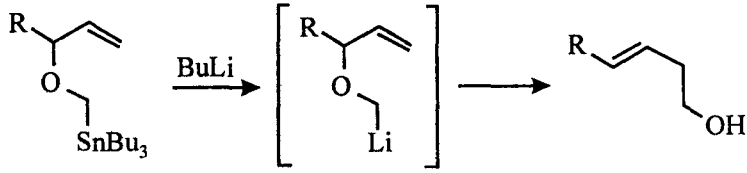
The product ratio varies as a function of the temperature and structural environment. The [2,3]-Wittig Rearrangement should be conducted at a low temperature to avoid contamination by the [1,2]-product.

The reaction rate depends on the energy gap between HOMO (anion) and LUMO (allyl). Roughly speaking, the less stable the carbanion, the faster the rearrangement.

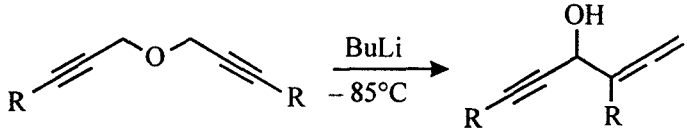


For the Thio-[2,3]-Wittig Rearrangement, Nakai reported the following relative reaction rates: R = Ph > CO_2Li > CN > CO_2Et > COMe, and for R' = Ph > H > CH_3. Reactions in this series were conducted at temperatures of from -80 °C to +60 °C.

The scope of the [2,3]-Wittig Rearrangement is mainly defined by the availability of methods for generating carbanions at temperatures low enough to minimize the occurrence of the [1,2]-rearrangement. Tin-lithium exchange, for example, allows the selective preparation of extremely unstable carbanions in a reaction known as the [2,3]-Wittig-Still rearrangement:

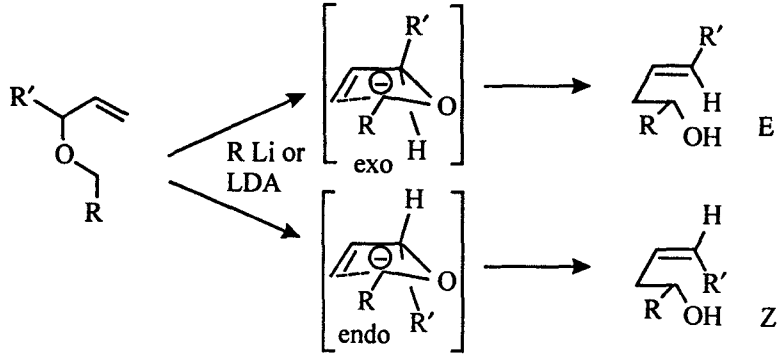


[2,3]-Wittig Rearrangements of propargyl ethers can afford allenic alcohols, but the scope is relatively limited and the process is not general.



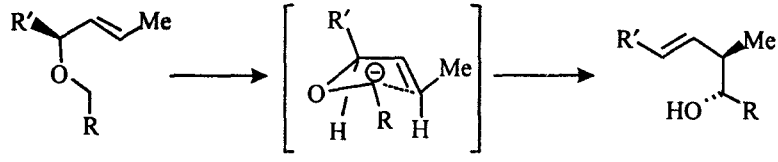
Terminal alkynyl groups, for example, are deprotonated; the use of a second equivalent of base allows the generation of 1,2-rearrangement products via dianion intermediates.

Many diastereoselective rearrangements have been reported and chirality transfer with the generation of new stereocentres can be explained by models for the transition state based on an envelope conformation. The two putative pathways are shown below:



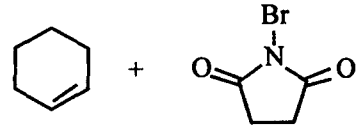
A strong preference for *E* products has been confirmed by numerous experiments.

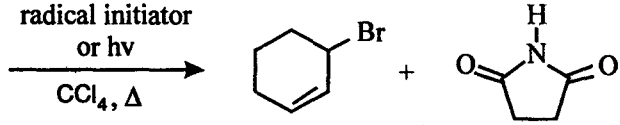
An originally chiral carbon becomes a planar sp^2 centre in the course of the rearrangement of some asymmetric substrates, while simultaneously new chiral centres are generated at an originally sp^2 centre and the anionic carbon:



Properly designed strategies based on the [2,3]-Wittig Rearrangement are powerful tools for asymmetric synthesis as exemplified by the many examples presented.

WOHL-ZIEGLER REACTION



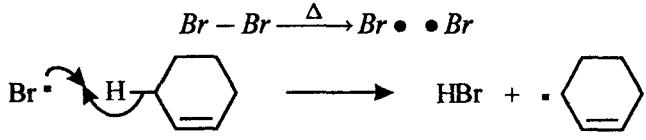


The bromination of allylic positions with *N*-bromosuccinimide (NBS) follows a radical pathway.

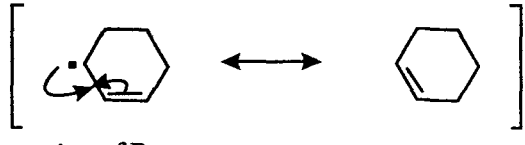
Mechanism

It is very important to keep the concentration of Br_2 and HBr low to prevent side reactions derived from simple ionic addition with the alkene. These reagents are therefore generated in situ from NBS. The catalytically active species is Br_2, which is almost always present in NBS samples (red colour).

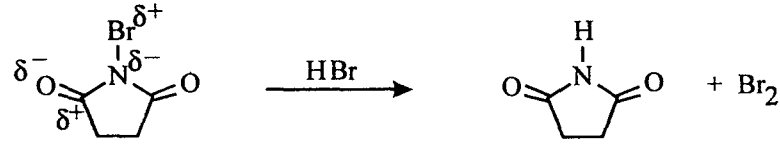
A radical initiator (UV, AIBN) is needed for the homolytic bond cleavage of Br_2:



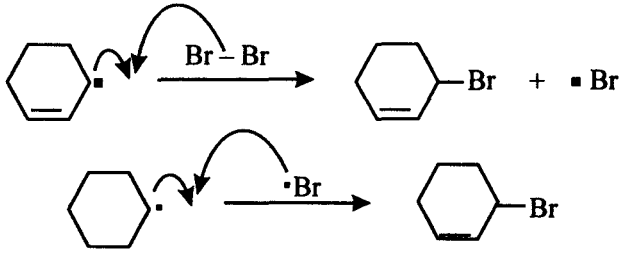
The allylic position is favoured for hydrogen abstraction, because the resulting radical intermediate is resonance stabilized:□



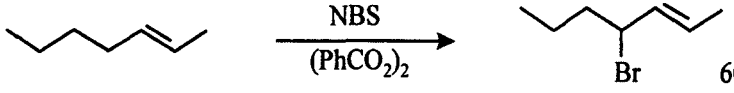
Regeneration of Br_2:



Bromination:



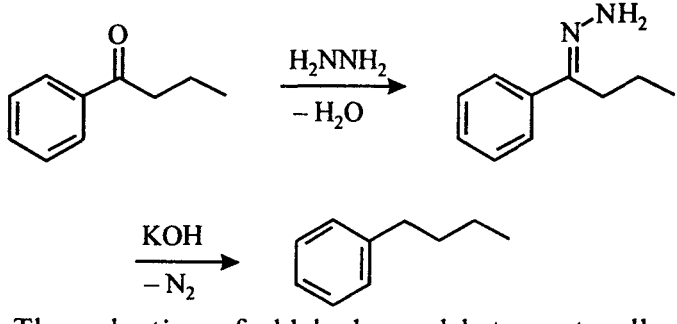
Bromination is favoured to occur at the more highly substituted position, because the corresponding intermediate radicals are better stabilized.



CCl_4 is the solvent of choice, because NBS is poorly soluble and resulting succinimide is insoluble and floats at the surface. This keeps the concentration of reagents low and is a signal that the reaction is finished.

However, environmental concerns have all but eliminated the use of CCl_4, and its replacement, CH_2Cl_2, is being restricted as well. Many other solvents are reactive toward NBS, and are thus unsuitable, but acetonitrile can be used to good effect.

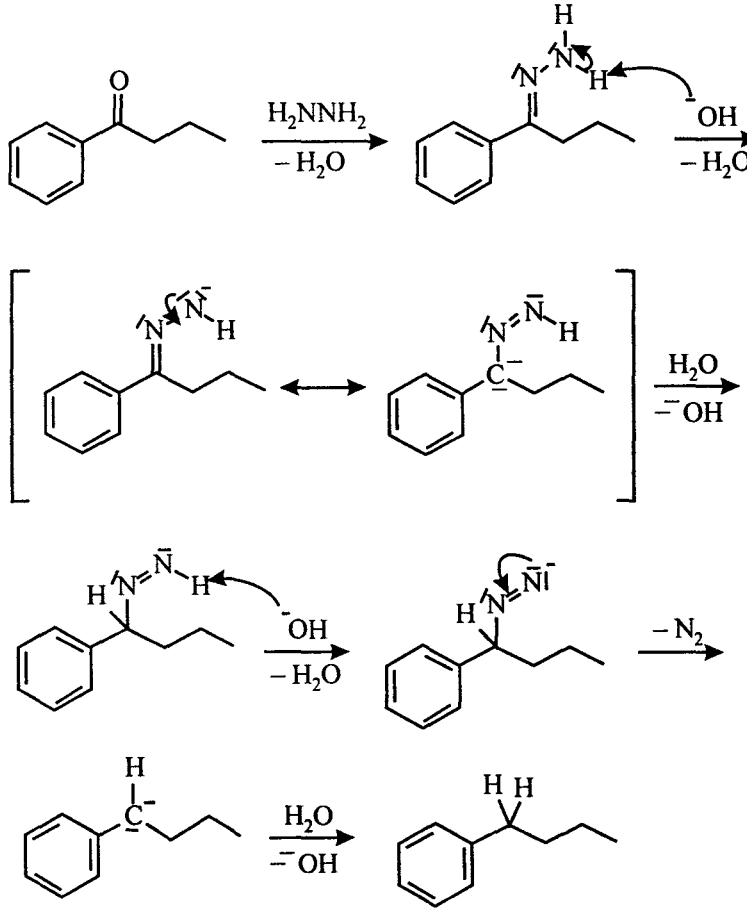
WOLFF-KISHNER REDUCTION



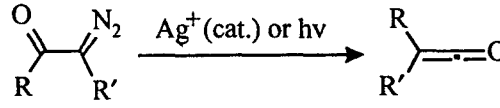
The reduction of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

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

Mechanism

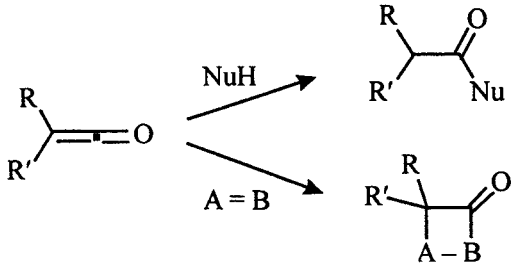


WOLFF REARRANGEMENT



The Wolff Rearrangement allows the generation of ketenes from α-diazoketones. Normally, these ketenes are not isolated, due to their high reactivity to form diketenes.

Wolff rearrangements that are conducted in the presence of nucleophiles generate derivatives of carboxylic acids, and in the presence of unsaturated compounds can undergo [2+2] cycloadditions.



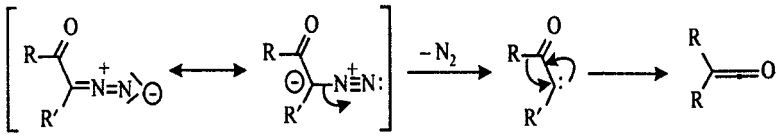
The formation of α-diazoketones from carboxylic acids (via the acyl chloride or an anhydride) and the subsequent Wolff Rearrangement in the presence of nucleophiles results in a one-carbon homologation of carboxylic acids. This reaction sequence.

Mechanism

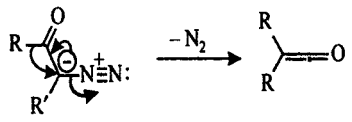
α-Diazoketones undergo the Wolff Rearrangement thermally in the range between room temperature and 750 °C in gas phase pyrolysis. Due to competing reactions at elevated temperatures, the photochemical and metal-catalyzed variants that feature a significantly lowered reaction temperature are often preferred.

Nitrogen extrusion and the 1,2-shift can occur either in a concerted manner or stepwise via a carbene intermediate:

stepwise:

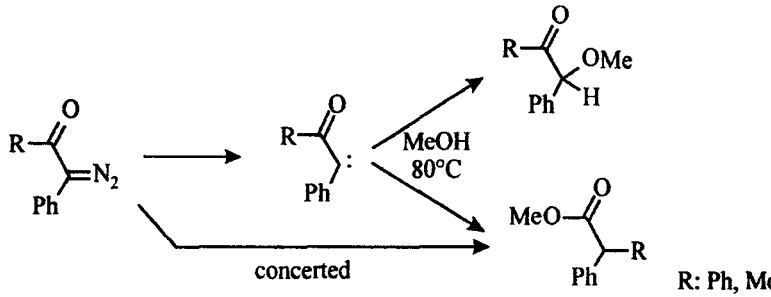


concerted:



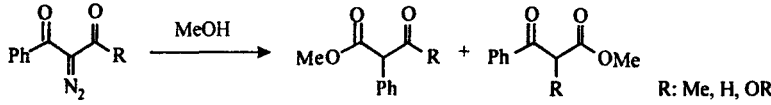
Silver ion catalysis fails with sterically hindered substrates, pointing to the requisite formation of a substrate complex with the ion. In these cases, photochemical excitation is the method of choice.

The solvent can affect the course of the reaction. If Wolff-Rearrangements are conducted in MeOH as solvent, the occurrence of side products derived from an O-H insertion point to the intermediacy of carbenes:



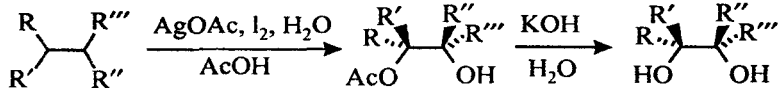
The course of the reaction and the migratory preferences can depend on the conditions (thermal, photochemical, metal ion catalysis) of the reaction. Analysis of the product distribution helps to determine different degrees of concertedness or the migratory aptitude of the group that rearranges. If R is phenyl, the main product comes from the rearrangement, whereas the methyl group gives more of the insertion side product.

The reactions of 2-diazo-1,3-diones also help to determine the migratory aptitude:



In a photolysis, methyl is preferred for rearrangement, whereas under thermolysis conditions the phenyl substituent migrates preferentially. Hydrogen always exceeds the migratory aptitude of phenyl groups. The alkoxy group in aryl or alkyl 2-diazoketocarboxylates never migrates.

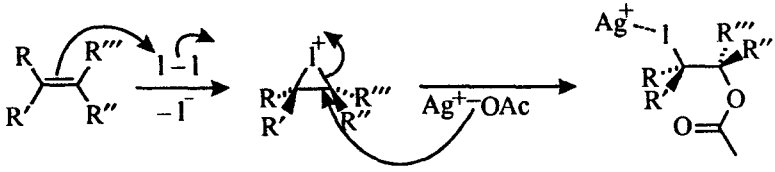
WOODWARD REACTION



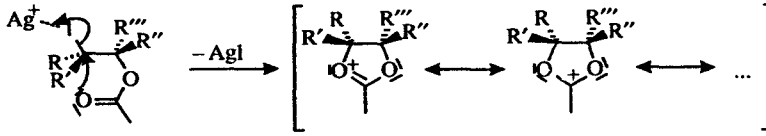
The Woodward Reaction (or Woodward *cis*-Hydroxylation) allows the synthesis of *syn*-diols from alkenes by the addition of iodine followed by nucleophilic displacement with acetate in the presence of water. Hydrolysis of the intermediate ester gives the desired diol. The Prevost Reaction gives *anti*-diols.

Mechanism

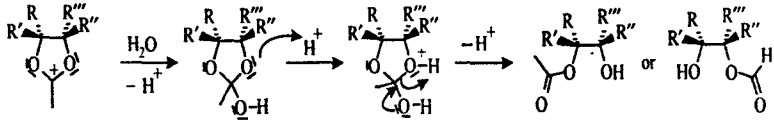
Similar to the Prevost Reaction, initial addition of iodine leads to a cyclic iodonium ion, that is opened through nucleophilic substitution by acetate anion:



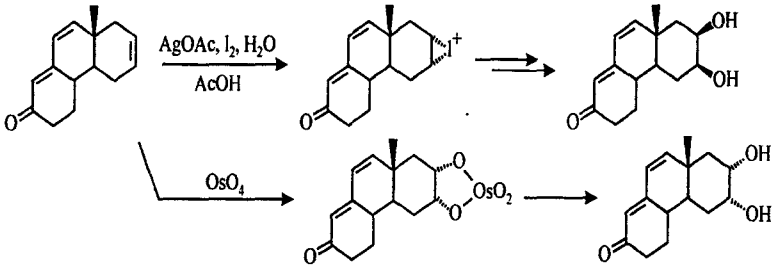
A cyclic acetoxonium ion is then formed:



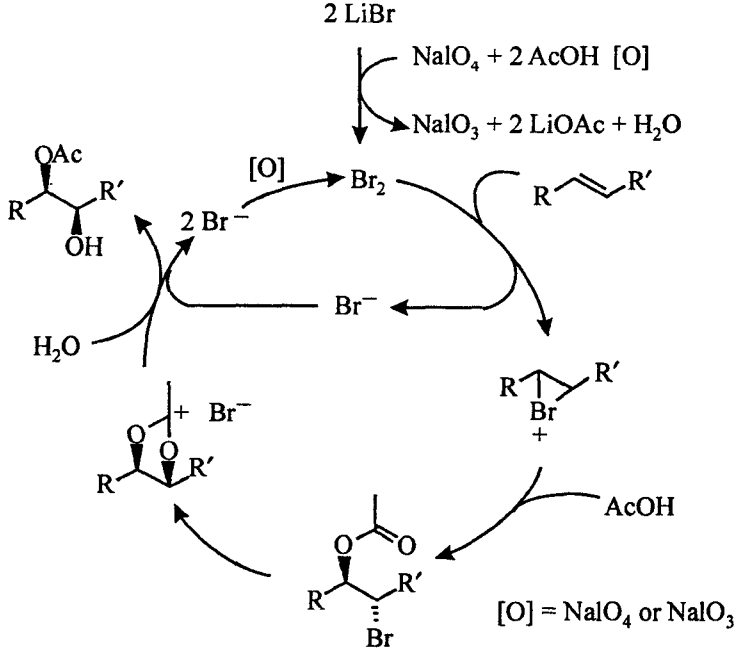
In contrast to the course of the Prevost Reaction, water appears to add readily as a nucleophile to the partially positive carbon atom of the intermediate. The cyclic orthoacetate is then cleaved to a monoacylated diol:



The desired diol can be isolated after hydrolysis. Woodward noted, that his modification of the Prevost reaction offers the opposite facial selectivity as compared to oxidations with OsO_4 in the hydroxylation of synthetic steroid intermediates. Here, the steric approach factors first direct the stereochemistry of the iodination, which is followed by hydroxylation from the opposite face, whereas OsO_4 leads to the isomeric *cis*-diol by direct attack from the most accessible face.



In a recent modification described by Sudalai, $NaIO_4$ acts both as the stoichiometric oxidant and as a source of water:



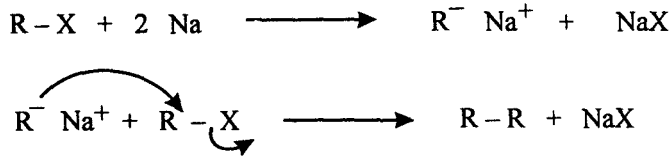
WURTZ REACTION

$$2\,R-X+2\,Na \longrightarrow 2\,R-R+2\,NaX$$

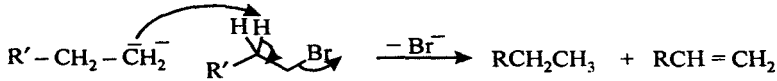
The Wurtz Coupling is one of the oldest organic reactions, and produces the simple dimer derived from two equivalents of alkyl halide. The intramolecular version of the reaction has also found application in the preparation of strained ring compounds:

Using two different alkyl halides will lead to an approximately statistical mixture of products. A more selective unsymmetric modification is possible if starting materials have different rates of reactivity.

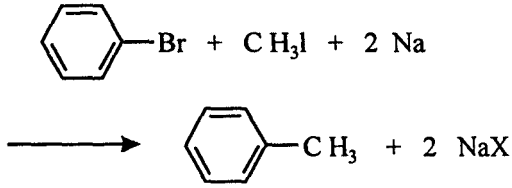
Mechanism



Side products:



WURTZ-FITTIG REACTION

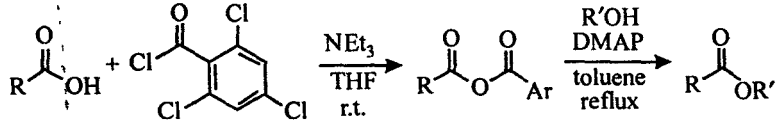


This reaction allows the alkylation of aryl halides. The more reactive alkyl halide forms an organosodium first, and this reacts as a nucleophile with an aryl halide as the electrophile. Excess alkyl halide and sodium may be used if the symmetric coupled alkanes formed as a side product may be separated readily.

Mechanism

Same as Wurtz Reaction.

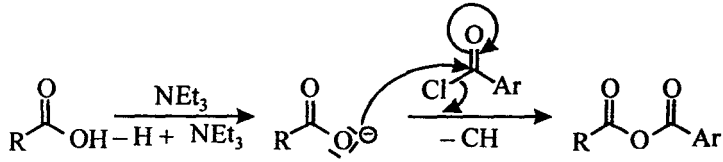
YAMAGUCHI ESTERIFICATION



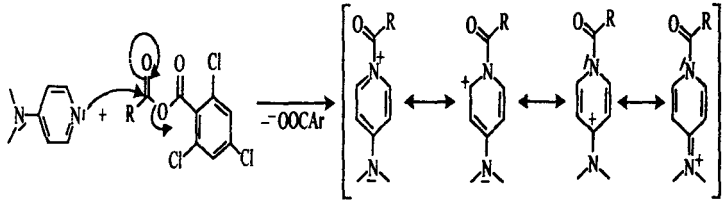
The Yamaguchi Esterification allows the mild synthesis of highly functionalized esters. After formation of a mixed anhydride between the Yamaguchi Reagent (2,4,6-trichlorobenzoyl chloride) and the carboxylic acid, the volatiles are removed and the reaction of the anhydride with an alcohol in presence of a stoichiometric amount of DMAP generates the desired ester.

Mechanism

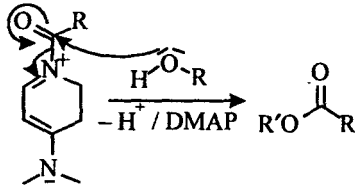
Addition of the carboxylate to the carboxylic acid chloride forms the mixed anhydride:



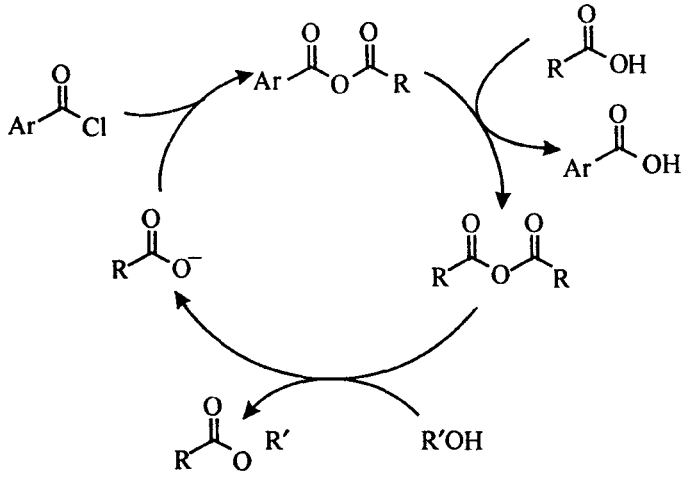
DMAP is an acyl transfer reagent that reacts regioselectively at the less hindered carbonyl site:



DMAP is a stronger nucleophile than the alcohol. The newly formed intermediate is less hindered, the acyl group is still polarized and DMAP is a good leaving group, all of which enable a fast reaction with the alcohol.



In reactions with aliphatic carboxylic acids, there is no need for a two step-procedure. It has been shown, that slight reactivity differences in this case can even lead to the formation of the symmetric aliphatic anhydrides, as shown in the following reaction pathway:



The assumption is that aliphatic carboxylates are better nucleophiles than either aromatic carboxylates or alcohols. However, the aliphatic anhydride is also more electrophilic towards DMAP (not shown in the scheme) or the alcohol than is the aromatic carbonyl of the mixed anhydride produced in situ.

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