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# Named Reactions in Organic Synthesis

TRANSITION METAL-CATALYZED COUPLINGS

REACTIONS INVOLVING CARBONYL COMPOUNDS

ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

NUCLEOPHILIC SUBSTITUTION REACTIONS

REARRANGEMENT REACTIONS

OXIDATION REACTIONS

REDUCTION REACTIONS

## Transition Metal-Catalyzed Couplings

Transition metal-catalyzed cross-coupling reactions have gained widespread use in both academic and industrial synthetic chemistry laboratories as a powerful methodology for the formation of C-C and C-Heteroatom bonds and has subsequently become an indispensable tool in modern organic synthesis.

Reactions using transition metal catalysts have a rich history that led to the awarding of the 2010 Nobel Prize in Chemistry to Professors Suzuki, Heck, and Negishi for their pioneering contributions in this field.

One of the earliest named reactions in this category was discovered in 1901 by Fritz Ullmann when he combined two equivalents of an aryl halide with one of powdered copper at a high temperature and generated the equivalent biaryl compound. Subsequently, the Ullmann reaction has become a convenient method to create numerous biaryl compounds.

Some of the most important named reactions that make use of this technique are:

1. Buchwald-Hartwig coupling
2. Castro-Stevens coupling
3. Glaser coupling
4. Heck reaction
5. Kumada cross-coupling
6. Larock indole synthesis
7. Miyaura boration
8. Negishi cross-coupling
9. Sonagashira cross-coupling
10. Stille cross-coupling
11. Suzuki Reaction
12. Ullmann reaction

### Heck Reaction

During the early 1970s Tsutomu Mizoroki and Richard F. Heck independently discovered that the reaction of aryl, benzyl and styryl halides with alkenes at a high temperature in the presence of a hindered amine base and palladium catalyst resulted in the equivalent substituted alkenes. Nowadays, the palladium-catalyzed arylation or alkenylation of alkenes is known as the Heck reaction – and since it's discovery has become one of the most important synthetic tools for carbon-carbon bond formation.

One of the key features of the Heck reaction is that it tolerates a wide range of different functional groups such as esters, ethers, carboxylic acids, nitriles, phenols and many others.

Despite its flexibility, the Heck reaction does have some drawbacks. For example, substrates cannot contain hydrogen atoms on their β-carbons as corresponding organo-palladium derivatives tend to undergo rapid β-hydride elimination to give alkenes.

During recent decades several modifications have been introduced, such as the use of water as a solvent using water-soluble catalysts.

The Heck reaction has been used in many synthetic routes, including the potent anticancer agent, lasiodiplodin, and the antitumor agent, ecteinascidin.

## Negishi Cross-Coupling Reaction

In 1972, after the discovery of Nickel-catalyzed cross-coupling of alkenyl and aryl halides with Grignard reagents (Kumada cross-coupling), improvements in functional group tolerance were sought. The answer: organometallic substrates with less electropositive metals than lithium and magnesium. From first studies in 1976, extensive research by Ei-ichi Negishi demonstrated that the best results in terms of reactivity, yield and stereoselectivity were obtained when organozincs are used in the presence of palladium catalysts. Since then the palladium or nickel-catalysed cross-coupling of organozincs with aryl, alkenyl or alkynyl halides is known as the Negishi cross-coupling reaction.

The use of organozinc reagents allows for a much greater variety of functional groups to be present in both coupling partners than is possible with Kumada cross-coupling.

Other advantages include high reactivity, high regio- and stereoselectivity, their range of applications, few side reactions and limited toxicity.

The total synthesis of Motuporin, a cyclic pentapeptide that is a potent protein phosphatase-1 inhibitor and cytotoxin, utilized the Negishi cross-coupling reaction.

## Stille Cross-Coupling Reaction

The first palladium-catalyzed cross coupling of organotin compounds was accomplished by Colin Eaborn et al. in 1976. The next year, Masanori Kosugi and Toshihiko Migita described the transition metal-catalyzed cross-coupling of organotins with aryl halides and acid chlorides. Following this, in 1978, John K. Stille used organotin compounds to synthesize ketones using milder reaction conditions than those of Kosugi but giving much improved yields. In the early 1980s, Stille continued to develop and improve on his methodology and thus the palladium-catalyzed coupling reaction between an organostannane and an organic electrophile to form carbon-carbon bonds is known as the Stille cross-coupling reaction.

Despite the main disadvantage of this reaction, the toxicity of the tin compounds, the Stille reaction has developed into one of the most important reactions in organic synthesis. The success of the Stille coupling is primarily down to the ability of the tin precursors to tolerate a wide variety of functional groups, whilst also lacking sensitivity to air and moisture unlike other reactive organometallic compounds.

Indeed the mild reaction conditions of the method are compatible with many types of functional groups including amine, amides, esters, carboxylic acids, hydroxyl, ketone and formyl to name a few.

Among the many uses of the Stille cross-coupling reaction in organic synthesis is the total synthesis of natural products, these include the manzamine alkaloid ircinal A and quadrigemine C – another member of the alkaloid family.

## Suzuki Cross-Coupling Reaction

One of the best known cross-coupling reactions is the Suzuki or Suzuki-Miyaura reaction, where organoboron compounds and organic halides or triflates react in the presence of a palladium catalyst to form carbon-carbon bonds. First reported in 1979, this reaction offers several advantages over other cross-coupling reactions, particularly the Stille reaction, as the boronic acids are much less toxic and environmentally damaging than the organostannanes.

However, like the Stille reaction, the Suzuki cross-coupling reaction offers mild reaction conditions that tolerate a wide range of functional groups and the boronic acids are stable to aqueous conditions.

Since the discovery of this reaction a great many boronic acids and esters have been synthesized, offering a broad selection of differing substituents. More recently, other boron-containing functional groups have been developed, such as trifluoroborates, in place of the boronic acids.

The antitumor natural product epothilone A used Suzuki cross-coupling methodology, as did the total synthesis of TMC-95A – a proteosome inhibitor.

**Click here for a more in-depth looks at the Suzuki cross-coupling reaction.**

## Ullmann Reaction

In 1901, Ullmann discovered that by reacting two equivalents of an aryl halide with one equivalent of copper powder at high temperature a symmetrical biaryl compound was formed. The condensation of two aryl halides in the presence of copper to create biaryl products is now known as the Ullmann reaction. Since then, many differing symmetrical and unsymmetrical biaryls have been synthesized this way. Reaction efficiency can be improved by activating the copper prior to use. This can be achieved by reducing copper iodide with lithium naphthalenide or reducing copper sulphate with zinc powder. Usually temperatures greater than one hundred degrees are required to initiate the coupling, but using activated copper allows lower temperatures to be used. The most common solvent used is dimethyl formamide (DMF), but nitrobenzene or para nitrotoluene can be used for higher temperatures.

The first total synthesis of the natural product Taspine – an alkaloid which acts as a potent acetylcholinesterase inhibitor – by T. Ross Kelly and co-workers utilized the Ullmann reaction to create the central biaryl link.

# Suzuki-Miyaura Cross-Coupling Reaction

Carbon-carbon cross-coupling reactions represent one of the biggest revolutions in organic chemistry and are currently some of the most common reactions in synthetic organic chemistry. Their invention won Akira Suzuki, Ei-Ichi Negishi and Richard Heck the Nobel Prize for Chemistry in 2010.

Among the various types of cross-coupling, the Suzuki-Miyaura – usually simply called “Suzuki coupling” – is arguably the one with the broadest utility and applicability. The Suzuki chemistry is based on the Pd(0)-catalyzed coupling of an aryl or vinyl halide with an aryl or vinyl boronic acid.

Its advantages over similar reactions reside in the mild reaction conditions, common availability of the starting materials and their general low toxicity. Boronic acids are easily prepared, widely available on the market and reasonably cheap. As a matter of fact, they present lower environmental impact and safety hazards than organozinc or organostannane compounds. The inorganic byproducts are easily removed from the mixture. It is also often possible to run the reaction in water with obvious benefits to its green profile, while opening its scope to a wide variety of water-soluble substrates.

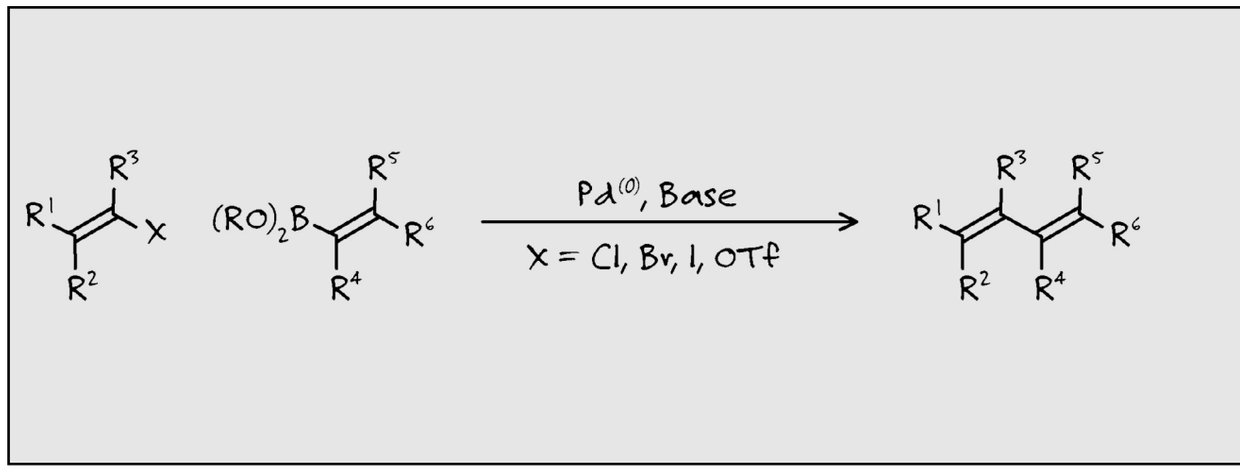
Since its invention in 1979, significant progress has been made and the use of boronic acids, esters and trifluoroborates salts, is widely reported. Even alkyl boronic acids can be considered (with the use of late generation catalysts), despite the lower reactivity.

The scope of the other coupling partner has also expanded over time to include pseudo-halides, such as triflates or aryl diazonium salts, and alkyl halides. The relative reactivity of the halide/pseudo-halide coupling partner is:

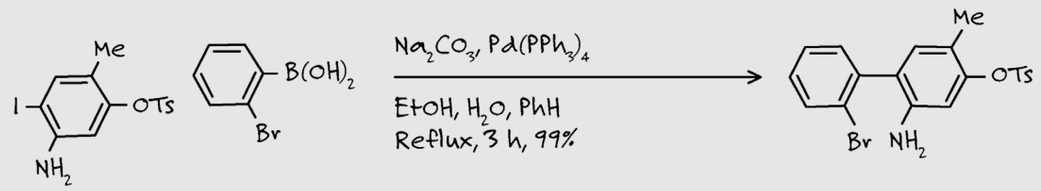
R-I > R-Br > R-OTf >> R-Cl
Aryl > Vinyl >> Alkyl

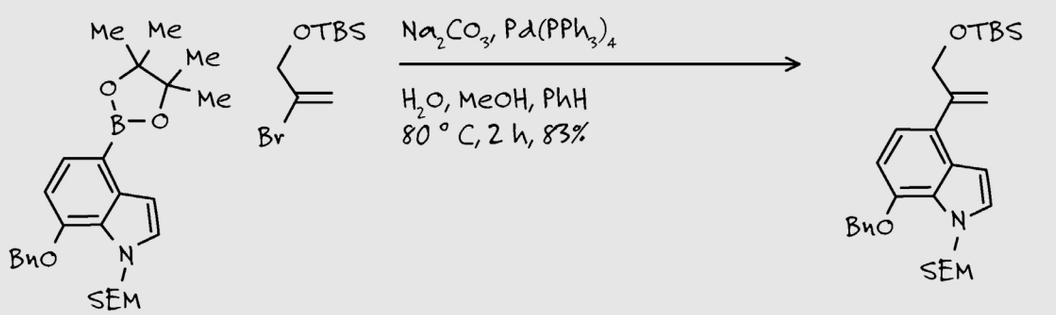
Recent generation homogeneous Pd catalysts have reduced the catalyst loading by orders of magnitude, contributing to the economy of the reaction, now used in numerous commercial processes. It is possible – in fact beneficial – to screen many different catalysts, from relatively simple Pd(0) complexes, such as Pd acetate and Pd tetrakis, or various forms of Pd precatalysts + phosphine ligand and fully formed (pre)catalysts, often as air-stable complexes for an easier handling by the bench chemist.

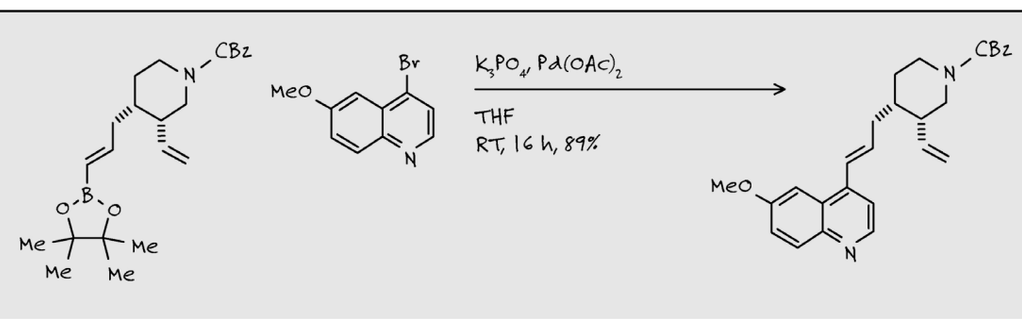
Heterogeneous Pd catalysts can also be used for some simple coupling, although their reactivity is much lower than homogeneous catalysts for highly hindered substrates, or low reactivity electrophiles (e.g. Ar-Cl). The use of aryl diazonium salts, often called “super-electrophiles,” as coupling partners make heterogeneous catalysts quite an attractive option.



## Suzuki Reaction Examples




## Reference Reaction Protocols

Weight aryl/vinyl halide (1 mmol), and the boronic acid/ester (slight excess, 1.1 mmol), palladium catalysts (0.5-10% w/w), tetrabutylammonium bromide (1 mmol) and base (2.5 mmol). Dissolve in distilled water or primary/secondary alcohol in a round bottom flask (with magnetic stirring and reflux apparatus). Heat on a sand bath to the required temperature (coupling reactions can be run from room temperature to 120-150°C). Purge nitrogen gas while stirring. Running the reaction under a nitrogen environment is recommended. Reaction times vary usually between 1-12 h.

The reaction work-up can be based on filtration or extraction depending on the chemical nature of the product.

# Product Selection for Suzuki Reaction

| | Stock Number | Description |
|---|---|---|
| **Solvents:** | 17716 | Toluene, 99+%, extra pure |
| | 18150 | Tetrahydrofuran, 99.9%, extra pure, anhydrous, stabilized with BHT |
| | 10769 | 1-Butanol, 99%, extra pure |
| | B23091 | Isobutanol, 99% |
| | A18232 | 1-Hexanol, 99% |
| | 22023 | 2-Methyl-2-butanol, 99+%, extra pure |
| | 11622 | N,N-Dimethylformamide, 99+%, extra pure |
| | A10924 | N,N-Dimethylacetamide, 99% |
| | 39079 | Xylenes, extra pure, mixture of isomers |
| **Solvents used for downstream/ extraction:** | 42368 | Ethyl acetate, 99.6%, ACS reagent |
| | 17684 | Methanol, 99.9%, for analysis |

| | Stock Number | Description |
|---|---|---|
| **Solvents used for downstream/ extraction:** | 39074 | Hexanes, for analysis, mixture of isomers |
| | 38917 | n-Heptane, 99.5%, for analysis |
| | 17681 | Cyclohexane, 99.5%, for analysis |
| | 041587 | Ethyl acetate, 99.6%, ACS reagent |
| **Basic Ingredients/ Additives:** | 16888 | Potassium tert-butoxide, 98+%, pure |
| | 37122 | Potassium tert-butoxide, pure, 1M solution in THF, AcroSeal® |
| | A16625 | Potassium carbonate, anhydrous, 99% |
| | 012887 | Cesium carbonate, 99% (metals basis) |
| | 14946 | Diisopropylamine, 99% |
| | 11522 | N,N-Diisopropylethylamine, 98+% |
| | 022151 | Lithium chloride monohydrate, 99.95% (metals basis) |
| | 043095 | Cesium acetate, 99% (metals basis) |

| | Stock Number | Description |
|---|---|---|
| **Basic Ingredients/ Additives:** | 014130 | Potassium fluoride, anhydrous, 99% |
| | A12575 | 1-Methylimidazole, 99% |
| | 15753 | 1,10-Phenanthroline, 99+% |
| | 16127 | Tetrabutylammonium iodide, 98% |
| | 43206 | Tetrabutylammonium chloride hydrate, 98% |
| | 18568 | Tetrabutylammonium bromide, 99+% |
| | A12005 | Pyridine, 99+% |
| | 11750 | 2,2’-Dipyridyl, 99+% |
| | 34967 | Celite® 545 |
| | 36005 | Silica gel, for column chrom., ultra pure, 40-60 µm, 60A |
| | 24037 | Silica gel, for chromatography, 0.060-0.200 mm, 60 A |
| **Building blocks:** | H50515 | Ethyl 4-chloro-6-methoxyquinoline-3-carboxylate |
| | 11375 | 4,7-Dichloroquinoline, 98% |
| | A13241 | 2-Bromopyridine, 99% |
| | H55417 | 2-Naphthyl trifluoromethanesulfonate, 97% |
| | L17481 | 4-Nitrophenyl trifluoromethanesulfonate, 99% |
| | 43975 | 3,6-Dihydro-2H-thiopyran-4-yl trifluoromethanesulfonate |

| | Stock Number | Description |
|---|---|---|
| **Building blocks:** | L18581 | 2-Bromobenzeneboronic acid, 98% (example in text) |
| | L17973 | Potassium 4-methyl-beta-styryltrifluoroborate, 95% |
| | L17970 | Potassium vinyltrifluoroborate, 97% |
| | H55315 4 | Nitrobenzenediazonium tetrafluoroborate, 97% |
| | H55827 4 | Methoxybenzenediazonium tetrafluoroborate, 98% |
| | B25670 4 | Bromobenzenediazonium tetrafluoroborate, 96% |
| **Catalysts /ligands:** | 011034 | Palladium(II) chloride, 99.9% (metals basis), Pd 59.0% min |
| | 3010516 | Palladium(II) acetate, Pd 45.9-48.4% |
| | 20238 | Tetrakis(triphenylphosphine)palladium(0), 99% |
| | 039448 | Palladium(II) trifluoroacetate, 97% |
| | 010517 | Palladium(II) 2,4-pentanedionate, Pd 34.7% |
| | 36350 | Bis(tri-tert-butylphosphine)palladium(0), 98% |
| | 31877 | Tris(dibenzylideneacetone)dipalladium(0), 97% |
| | 012760 | Tris(dibenzylideneacetone)dipalladium(0), Pd 21.5% min dichloro[1,1’-bis(di-tert-butylphosphino)ferrocene] palladium(II) (JM’s Pd-118) |
| | 45294 | 1,1’-Bis(di-tert-butylphosphino)ferrocene palladium dichloride |

| | Stock Number | Description |
|---|---|---|
| **Catalysts/ ligands (XPhos Palladacycle 2nd Gen):** | 44789 | Bis[di-tert-butyl(4-dimethylaminophenyl)phosphine] dichloropalladium, 95% |
| | 046665 | Dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] palladium(II), Pd 14.1% |
| | 39588 | Crotyl palladium(II) chloride dimer |
| | 046639 | Chloro(crotyl)[1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino ferrocene]palladium(II) |
| | 04650 | Dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II), Pd 13.0-14.5% |
| | 10005 | Allylpalladium(II) chloride dimer, Pd 56.0% min |
| **Catalysts/ligands (Secondary):** | 20927 | Bis(triphenylphosphine)palladium(II) diacetate, 99% |
| | 36971 | trans-Benzyl(chloro)bis(triphenylphosphine)palladium(II) |
| | 044976 | Dichlorobis(tri-o-tolylphosphine)palladium(II), 98% |
| | 044844 | Dichlorobis(tricyclohexylphosphine)palladium(II), Pd 14.4% |
| | 010493 | Dichloro(1,5-cyclooctadiene)palladium(II), Pd 36.7% |
| | 039233 | Bis[1,2-bis(diphenylphosphino)ethane]palladium(0) |
| | 018779 | Dichloro[1,2-bis(diphenylphosphino)ethane] palladium(II), Pd 18.5% |
| | H26897 | Dichloro[bis(1,3-diphenylphosphino)propane]palladium(II) |
| | 044971 | Dichloro[bis(1,4-diphenylphosphino)butane] palladium(II), Pd 17.6% |

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# Reactions Involving Carbonyl Compounds

A carbonyl group is a functional group consisting of a carbon atom joined to an oxygen atom by a double bond. The carbonyl group is present in many of the most synthetically important functional groups, including those of aldehydes, ketones, esters, amides and other carboxylic acid derivatives. Indeed, the majority of reactions associated with these chemistries directly involve the carbonyl group. Consequently, the carbonyl group plays a key role in a wide range of synthetically important chemical reactions and biological processes.

One of the earliest named reactions involving carbonyl group chemistry is the Aldol reaction, which involves the addition of the enol/enolate of a carbonyl compound to an aldehyde or ketone.

Other well-known named reactions that feature carbonyl groups include:

- Barbier coupling reaction
- Baylis–Hillman reaction
- Corey–Chaykovsky epoxidation
- Corey–Fuchs alkyne synthesis
- Dakin oxidation
- Eschweiler–Clarke methylation
- Evans aldol reaction
- Grignard reaction
- Hantzsch dihydropyridine synthesis
- Mannich reaction
- Pictet–Spengler tetrahydroisoquinoline synthesis
- Reformatsky reaction
- Stetter reaction
- Wittig reaction

## Grignard Reaction

In 1900, French chemist Victor Grignard discovered that when treating an alkyl halide with magnesium metal in diethyl ether, a cloudy solution of an organomagnesium compound was formed. This substance would subsequently react with aldehydes and ketones to produce secondary and tertiary alcohols respectively.

These organomagnesium compounds became known as Grignard reagents and their addition across carbon–heteroatom multiple bonds is now called the Grignard reaction. Very shortly after this discovery, the Grignard reaction became one of the best known and most versatile carbon–carbon bond-forming reactions.

Grignard reagents are typically prepared by reacting alkyl, aryl or vinyl halides with magnesium metal in aprotic nucleophilic solvents such as ethers. The carbon magnesium bond is highly polar, making Grignard reagents excellent carbon nucleophiles. As a result, the subsequent carbon–carbon bond-forming step is straightforward.

Grignard reagents have been used in the synthesis of several natural products, including the total synthesis of (±)-lepadiformine and several natural and modified cyclotetrapeptide trapoxins.

**Click here for a more in-depth look at the Grignard reaction.**

## Knoevenagel Condensation

In 1894, German chemist Emil Knoevenagel reported that diethyl malonate and formaldehyde condensed in the presence of diethylamine to form a bis adduct. He later discovered that the same type of bis adduct was produced when formaldehyde and other aldehydes were condensed with

ethyl benzoylacetate or acetylacetone in the presence of primary and secondary amines. In 1896 he conducted further experiments, reacting benzaldehyde with ethyl acetoacetate at 0 °C using piperidine as the catalyst to form ethyl benzylidene acetoacetate as the single product. The reaction of aldehydes and ketones with active methylene compounds in the presence of a weak base to produce alpha or beta-unsaturated dicarbonyl or related compounds is now known as the Knoevenagel condensation reaction.

One of the general features of this reaction is that aldehydes react much faster than ketones. Additionally, the active methylene groups require two electron withdrawing groups, with typical examples including malonic esters, acetoacetic esters, malonodinitrile or acetylacetone. Both the nature of the catalyst employed and the solvent are important. As the by-product of the reaction is water, removing the generated water by azeotropic distillation or by the addition of molecular sieves helps to shift the equilibrium to favor the formation of the product.

The Knoevenagel reaction has played an important role in the syntheses of several natural products. For example, the total synthesis of the marine-derived diterpenoid sarcodictyin A by Nicolaou and colleagues utilized the Knoevenagel condensation as part of the synthetic route.

## Mannich Reaction

In 1903, German chemist Bernhard Tollens observed that the reaction between acetophenone and formaldehyde in the presence of ammonium chloride led to the formation of a tertiary amine. In 1917, German chemist Carl Mannich also prepared a tertiary amine from antipyrine using the same conditions and recognized that this reaction was general. Since then, the condensation of a CH-activated compound such as an aldehyde or ketone with a primary or secondary amine or ammonia and a non-enolizable aldehyde or ketone to prepare aminoalkylated derivatives has come to be known as the Mannich reaction.

The product of this reaction is a substituted beta-amino carbonyl compound which is often known as a Mannich base. Mannich bases are useful intermediates for synthesis since they can undergo a variety of transformations. These can include beta-elimination to afford alpha or beta-unsaturated carbonyl compounds (Michael acceptors), reaction with organolithium or Grignard reagents to produce beta-amino alcohols, or even substitution of the dialkylamino group with nucleophiles to create functionalized carbonyl compounds. One of the best-known applications of the Mannich reaction is its use in conjunction with an aza-Cope rearrangement to generate heterocycles.

## Reformatsky Reaction

In 1887, Russian chemist Sergey Reformatsky discovered that the ethyl ester of iodoacetic acid reacted with acetone in the presence of metallic zinc to form 3-hydroxy-3-methylbutyric acid ethyl ester. Since then, the zinc-activated reaction between an alpha-halo ester and an aldehyde or ketone has become known as the Reformatsky reaction.

The reaction proceeds by a two-step process: the zinc metal initially inserts into the carbon-halogen bond to form the zinc enolate Reformatsky reagent, which then reacts with the carbonyl compound in an aldol reaction. In addition to aldehydes and ketones, Reformatsky reagents can also react with esters, acid chlorides, epoxides, nitrones, aziridines, imines and nitriles, the latter transformation being known as the Blaise reaction.

The scope of the Reformatsky reaction was further expanded by activating the zinc prior to use. Activated zinc metal can be formed by removal of the deactivating zinc oxide layer through use of reagents such as iodine or 1,2-dibromoethane, or by the reduction of zinc halides in solution using various reducing agents (e.g, Rieke zinc compounds).

The Reformatsky reaction has been applied in the synthesis of several natural products, including a range of macrocyclic cytochalasins – fungal metabolites that exhibit a wide range of biological activities.

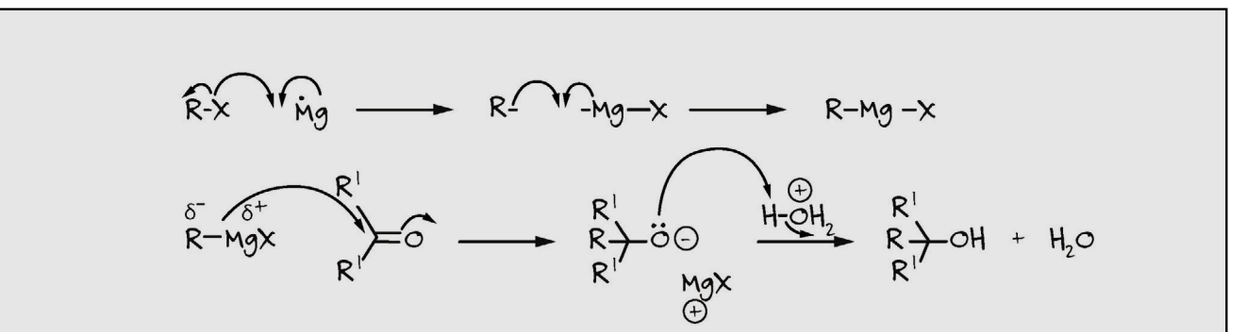
## Wittig Reaction

In the early 1950s, chemists Georg Wittig and Georg Geissler reported the reaction of methylenetriphenylphosphorane and benzophenone to form 1,1-diphenylethene and triphenylphosphine oxide in quantitative yield. Wittig recognized the importance of this reaction and carried out a comprehensive series of experiments in which several phosphoranes were reacted with various aldehydes and ketones to obtain the corresponding olefins. The reaction between carbonyl compounds and phosphoranes to generate carbon–carbon double bonds has subsequently become known as the Wittig reaction. Since its discovery, the Wittig reaction has become one of the most widely used synthetic techniques for the formation of alkenes.

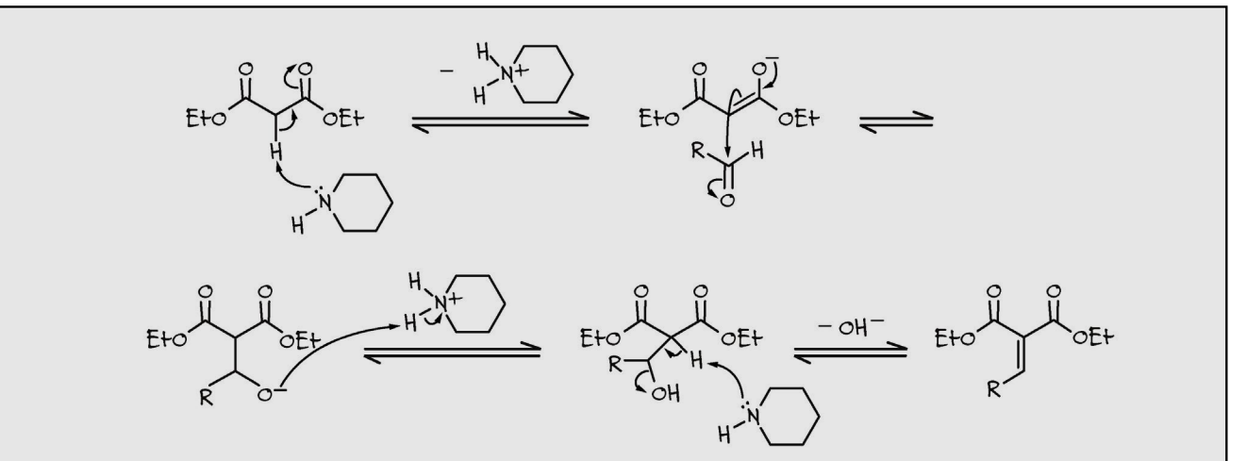
The Wittig reaction has several important variants. One of the most notable is the Horner–Wittig reaction, which occurs when the phosphorus ylides are based on phosphine oxides rather than triarylphosphines. When stabilized alkyl phosphonate carbanions are used to create (E)-alpha, beta-unsaturated esters, the reaction is known as the Horner–Wadsworth–Emmons reaction. Another variant, the Schlosser modification, generates pure E-alkenes when two equivalents of a lithium halide salt is present during the ylide addition step.

The total synthesis of the alkaloid natural product buflavin used the Horner–Wittig reaction between a biaryl aldehyde and a metalated carbamate.

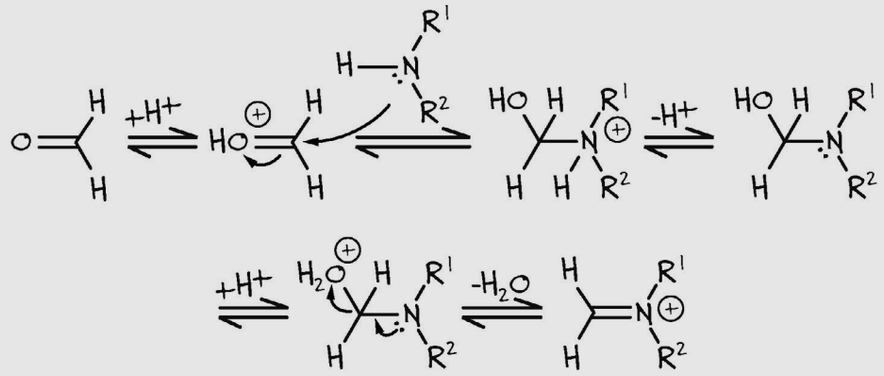
# Mechanisms of the Reactions Involving Carbonyl Compounds

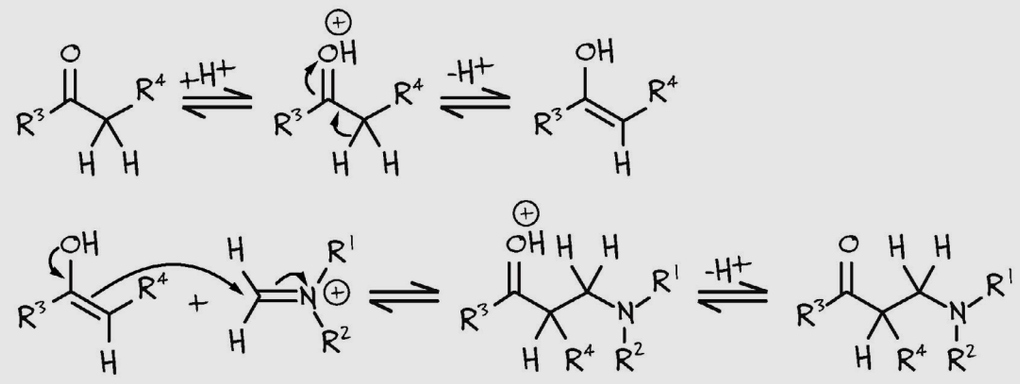


Grignard Reaction

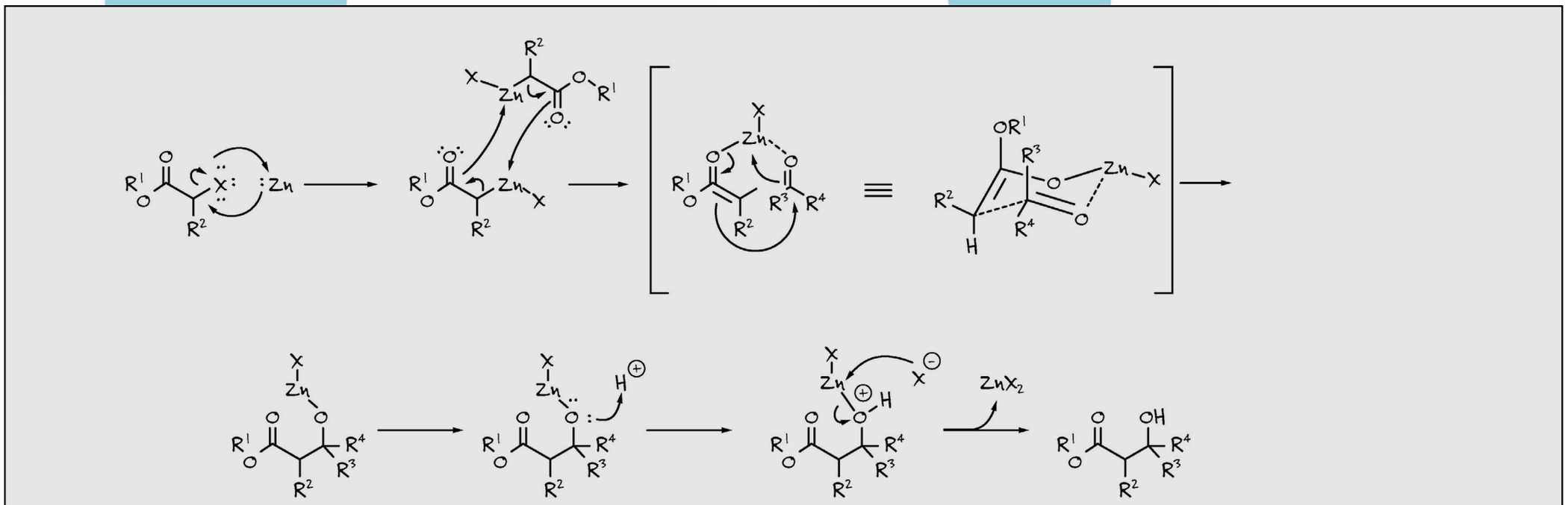


Knoevenagel Condensation

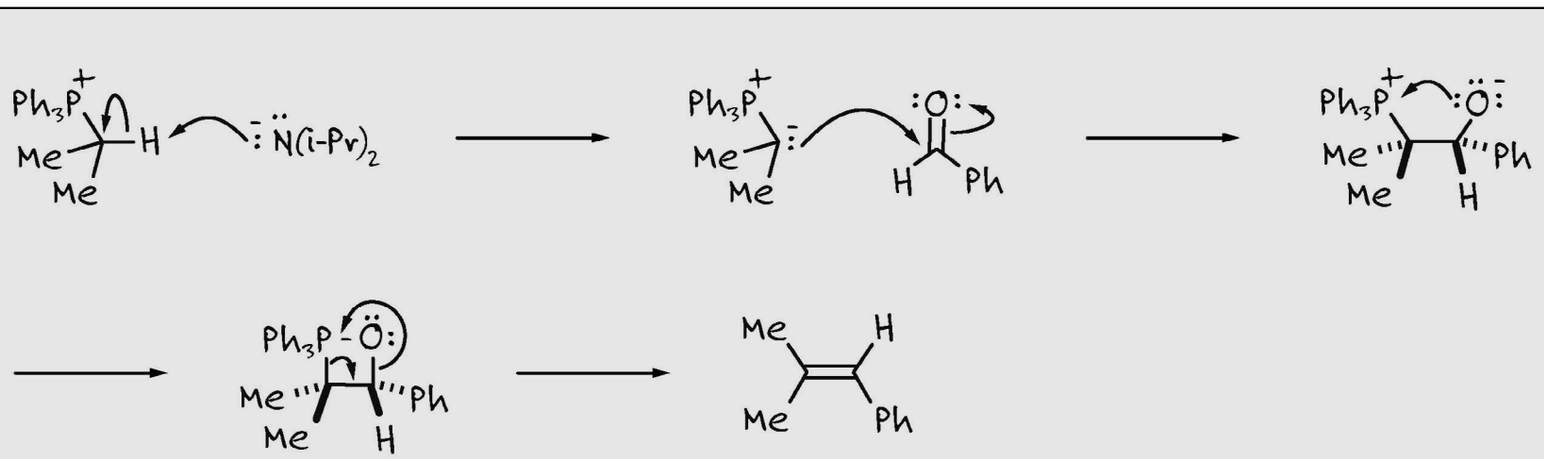




Mannich Reaction

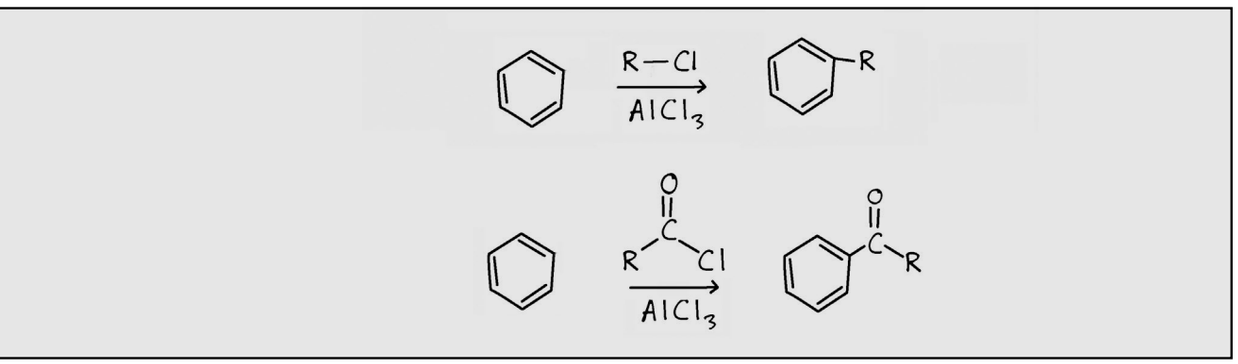


Knoevenagel Condensation



Wittig Reaction

# Grignard Reaction




The Grignard reaction is the nucleophilic addition of an organomagnesium halide to a ketone or an aldehyde to produce tertiary and secondary alcohols respectively.

In 1900, French chemist Victor Grignard discovered that when treating an alkyl halide with magnesium metal in diethyl ether, a cloudy solution of an organomagnesium compound was formed. He also noted the nucleophilicity of these organometallic species, that can easily react with the electrophilic carbonyls.

These organomagnesium compounds became known as Grignard reagents and their addition across carbon–heteroatom multiple bonds is now called the Grignard reaction. Very shortly after this discovery, the Grignard reaction became one of the best known and most versatile carbon–carbon bond forming reactions. This discovery won Victor Grignard the Nobel prize in chemistry in 1912.

## Preparation of Grignard reagents

Grignard reagents are typically prepared by reacting alkyl, aryl or vinyl halides with magnesium metal in aprotic nucleophilic solvents such as ethers. Bromides are most commonly used, but chlorides and iodides are also widely utilized.

The reactions protocol is typically very simple, with the halide solution and small magnesium metal bits gently heated in a water bath, with a reflux condenser fitted to the flask. The formation of the Grignard reagents happens with reasonably fast kinetics, reaching full conversion around 30 minutes in most cases. The reaction presents moderate hazards linked to the use of highly volatile and flammable solvents, such as diethyl ether.
It is important to operate in tightly controlled dry conditions, as the Grignard reagents react with water to give the correspondent alkane. This requires a specialized setup, as well as correct reagents and solvent grades.

Today many Grignard reagents are commercially available and distributed in specialized packaging, such as Thermo Scientific AcroSeal®, preserving their moisture sensitivity and making their handling much easier.

## Nucleophilic addition to the carbonyl – Grignard reaction

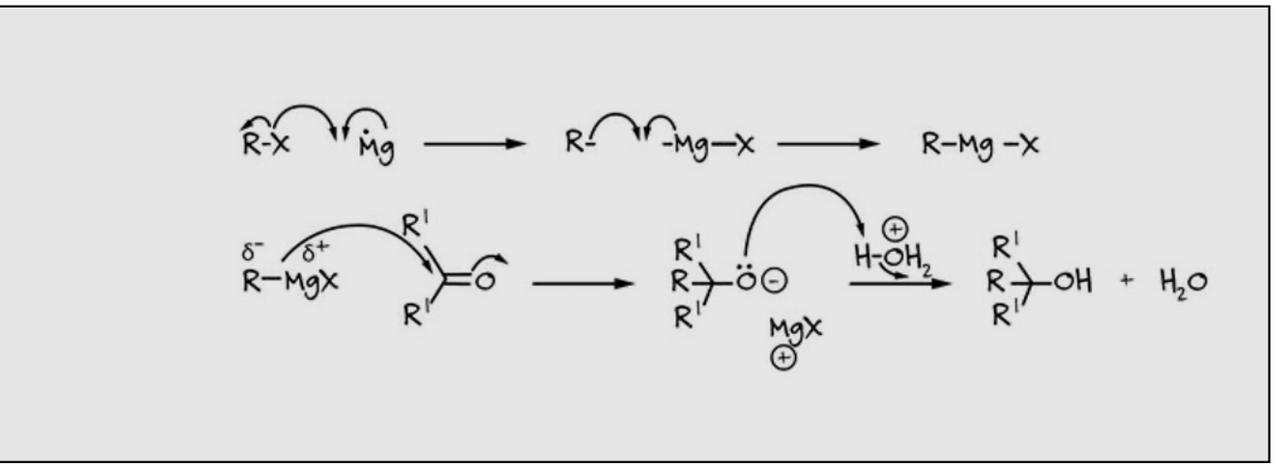
The carbon magnesium bond in the Grignard reagents is highly polar, making them excellent carbon nucleophiles. As a result, the subsequent carbon–carbon bond-forming step in their reaction with ketones or aldehydes is straightforward.

The nucleophilic addition to the carbonyl produces a secondary or tertiary alcohol, depending on whether the starting material is an aldehyde or a ketone. Obviously, the reaction with formaldehyde gives a primary alcohol. Grignard reagents can also react with an ester or a lactone to give a tertiary alcohol by means of a double nucleophilic addition.

While the first stage of the reaction – the nucleophilic addition itself – must be run in aprotic solvents and dry conditions to preserve the organomagnesium compound, Grignard reactions require an aqueous work-up with a diluted acid.

Grignard reagents have been used in the synthesis of several natural products, including the total synthesis of (±)-lepadiformine and several natural and modified cyclotetrapeptide trapoxins.

## Mechanism of the Grignard reaction




## Reference reaction protocols

*Preparation of Grignard reagent*

Add 50 mg (2 mmol) of magnesium powder to 3 mL of anhydrous diethyl ether in the reaction vessel, with a reflux condenser and in a water bath at 40$^0$C. In a separate vial dissolve 330 mg (2.1 mmol) of bromobenzene in 1mL of anhydrous diethyl ether. Using a syringe, transfer 0.1 mL of the bromobenzene solution to the reaction vessel through a septum (to maintain the reaction dry). The solution will start turning cloudy, then slowly add the remainder of the bromobenzene solution over a few minutes. Control the reaction temperature to ensure the solution doesn't boil too vigorously. The reaction completion can be detected by the disappearance of the magnesium metal.

*Grignard reaction*

Dissolve 364 mg of benzophenone (2 mmol) in 1 mL of anhydrous ether. Slowly add the solution to the reaction vessel containing the Grignard reagent, maintaining a gentle reflux for 20 minutes, then allow it to stand at room temperature until the solution decolorizes. Cool the reaction vessel in ice and add drop-wise 2 mL of HCl 3 M. Remove the aqueous layer, wash with a few mL of brine. Collect the ether phase, dry it under vacuum. Progress to further workup as necessary (e.g., recrystallization in IPA).

## Key literature references


1. *Grignard, V. (1900). "Sur quelques nouvelles combinaisons organométaliques du magnésium et leur application à des synthèses d'alcools et d'hydrocabures". Compt. Rend. 130: 1322–25.*
2. *Shirley, D. A. (1954). "The Synthesis of Ketones from Acid Halides and Organometallic Compounds of Magnesium, Zinc, and Cadmium". Org. React. 8: 28–58.*
3. *Maruyama, K.; Katagiri, T. (1989). "Mechanism of the Grignard reaction". J. Phys. Org. Chem. 2 (3): 205–213. doi:10.1002/poc.610020303*
4. *E. C. Ashby and J. T. Laemmle (1975). "Stereochemistry of organometallic compound addition to ketones". Chem. Rev. 75 (4): 521–546.*
5. *K. Colas, A. C. V. D. dos Santos, A. Mendoza, Org. Lett., 2019, 21, 7851-7856.*

# Product Selection for the Grignard reaction

| SKU | Description |
|---|---|
| | *Grignard Reaction* |
| 34729 | Ethylmagnesium bromide, 3M in diethyl ether, AcroSeal® |
| 21285 | Isopropylmagnesium chloride, 2.0M solution in THF, AcroSeal® |
| 25256 | Methylmagnesium chloride, 3M (22 wt.%) solution in THF, AcroSeal® |
| 38628 | Isopropylmagnesium chloride - Lithium chloride complex, 1.3M solution in THF, AcroSeal® |
| H54966 | 2,4-Difluorobenzylmagnesium bromide, 0.25M in 2-MeTHF |
| 18354 | Methylmagnesium bromide, 3M solution in diethyl ether, AcroSeal® |
| 20939 | Vinylmagnesium bromide, 0.7M solution in THF, AcroSeal® |
| 37777 | Di-n-butylmagnesium, 0.5M solution in heptane, AcroSeal® |
| 43912 | Ethynylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 38118 | n-Butylethylmagnesium, 0.9M solution in heptane, AcroSeal® |
| 42745 | Cyclopentylmagnesium bromide, 2.0M solution in diethyl ether, AcroSeal® |
| 20953 | Allylmagnesium bromide, 1M solution in diethyl ether, AcroSeal® |
| 37742 | 4-Methoxyphenylmagnesium bromide, 1M solution in THF, AcroSeal® |
| 42607 | 1-Propynylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 42746 | 3-Butenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 42740 | Methylmagnesium iodide, 3M solution in diethyl ether, AcroSeal® |
| 42775 | Isopropenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 25259 | Vinylmagnesium chloride, 2M (18 wt.%) solution in THF, AcroSeal® |
| 33167 | tert-Butylmagnesium chloride, 1.7M solution in THF, AcroSeal® |
| 20967 | Allylmagnesium chloride, 1.7M solution in THF, AcroSeal® |
| 37746 | (Trimethylsilyl)methylmagnesium chloride, 1.3M solution in THF, AcroSeal® |
| 21073 | 2-Mesitylmagnesium bromide, 1M solution in THF, AcroSeal® |
| 042859 | Phenylmagnesium bromide, 3M in ether, packaged under Argon in resealable ChemSeal® bottles |

| SKU | Description |
|---|---|
| | *Grignard Reaction* |
| 42678 | Isopropylmagnesium bromide, 3M solution in 2-MeTHF, AcroSeal® |
| 39761 | Cyclopropylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 43467 | 1-Propenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| H51156 | Isopropylmagnesium chloride - LiCl complex, 1M in MeTHF |
| 38955 | Benzylmagnesium chloride, 1.4M solution in THF, AcroSeal® |
| 43556 | 2-Methyl-1-propenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 20939 | Vinylmagnesium bromide, 0.7M solution in THF, AcroSeal® |
| 37777 | Di-n-butylmagnesium, 0.5M solution in heptane, AcroSeal® |
| 43912 | 2-Methyl-1-propenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 25257 | Ethylmagnesium chloride, 2.7M (25 wt.%) solution in THF, AcroSeal® |
| 43875 | 2-Methyl-2-phenylpropylmagnesium chloride, 0.5M solution in diethyl ether, AcroSeal® |
| 44078 | Nonylmagnesium bromide, 1M solution in diethyl ether, AcroSeal® |
| 43461 | 2-Thienylmagnesium bromide, 1M solution in THF, AcroSeal® |
| H54625 | 4-Chlorobenzylmagnesium chloride, 0.50M in 2-Me-THF |
| 43555 | Pentylmagnesium bromide, 2M solution in diethyl ether, AcroSeal® |
| 42679 | 4-Fluorobenzylmagnesium chloride, 0.25M solution in THF, AcroSeal® |
| 43886 | (1,3-Dioxolan-2-ylmethyl)magnesium bromide, 0.5M solution in THF, AcroSeal® |
| 42676 | p-Tolylmagnesium bromide, approx. 0.5M solution in diethyl ether, AcroSeal® |
| H54824 | tert-Pentylmagnesium chloride, 1M in 2-MeTHF |
| 43174 | 2-Naphthylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| H51162 | n-Propylmagnesium chloride, 1M in MeTHF |
| 42742 | 4-Methoxybenzylmagnesium chloride, 0.25M solution in THF, AcroSeal® |
| 43193 | 2,3-Dimethylphenylmagnesium bromide, 0.5M solution in THF, AcroSeal® |
| 38895 | Ethynylmagnesium chloride, 0.5M solution in THF/Toluene, AcroSeal® |
| 42741 | 2-Methylallylmagnesium chloride, 0.5M solution in THF, AcroSeal® |
| 45061 | 4-(N,N-Dimethyl)aniline magnesium bromide, 0.5M solution in THF, AcroSeal® |
| | *Magnesium metal* |
| 1023336 | Magnesium powder, -325 mesh, 99.8% |
| 10232A4 | Magnesium turnings, 99.8% (metals basis) |
| 413380250 | Magnesium, Reagent, Ribbon, +99% |

# Electrophilic Aromatic Substitution Reactions

When an atom attached to an aromatic system gets replaced by an electrophile in a chemical reaction this is known as electrophilic aromatic substitution.

Within the category of electrophilic aromatic substitution reactions, there are a number of important chemical reactions which are named after their discoverers. Despite being discovered many years ago, these named reactions continue to play a crucial role in organic synthesis, and in constructing ever more complex and diverse chemical molecules.
One of the earliest and perhaps best known of these named reactions are the Friedel-Crafts Alkylation and Acylation Reactions which are also related to several other classic named reactions in this catergory:

1. Friedel-Crafts acylation and alkylation
2. Fries rearrangement
3. Gattermann and Gattermann-Koch formylation
4. Houben-Hoesch synthesis

## Fries Rearrangement

In the early 1900s, K. Fries and colleagues reacted phenolic esters of acetic and chloroacetic acid with aluminium chloride isolating a mixture of ortho and para-acetyl and chloroacetyl phenols. Fries realized that this rearrangement of phenolic esters was general and for this the transformation of phenolic esters to corresponding ketones and aldehydes in the presence of Lewis or Bronsted acids (e.g. HF; $HClO_4$; PPA) became known as the Fries rearrangement.

There are two main types of Fries rearrangement, the first an anionic reaction where ortho-lithiated O-aryl carbamates are converted to substituted salicylamides, and a photochemical reaction where light-irradiated phenolic esters are converted to the corresponding phenols.

The Friedel-Crafts acylation of phenols is often a two-stage process, formation of the phenolic ester followed by a Fries rearrangement

## Gattermann and Gattermann-Koch Formylation

In 1897 L Gattermann and J.A. Koch successfully introduced an aldehyde group on to toluene by using formyl chloride (HCOCl) as an acylating agent under Friedel-Crafts acylation conditions. Subsequently, the addition of a formyl group into electron-rich aromatic rings by application of CO/HCl/Lewis acid catalysts ($AlX_3$, $FeX_3$, where X = Cl, Br, I) to prepare aromatic aldehydes became known as the Gattermann-Koch formylation.

The scope of the Gattermann-Koch reaction is limited due to the lack of suitable substrates, as it is mostly restricted to alkylbezenes. Therefore, Gattermann introduced a modification which allowed the formylation of phenols, phenolic ethers, and heteroaromatic compounds such as pyrroles and indoles.

The main drawback of the Gattermann formylation was that it called for the use of anhydrous hydrogen cyanide (HCN). To avoid handling HCN, R. Adams generated it *in situ* from zinc cyanide and hydrochloric acid and this became known as the Adams modification; this method has become more widely used in organic synthesis.

## Houben-Hoesch Synthesis

During the early 1900s, the Friedel-Crafts acylation and the Gattermann formylation were widely used to prepare both aromatic aldehydes and ketones. Preparing monoacylated derivatives of highly activated substrates was not possible since it was common to introduce more than one acyl group using the standard Friedel-Crafts acylation conditions.

In 1915, K. Hoesch reported the extension of the Gattermann reaction for the synthesis of aromatic ketones using nitriles instead of hydrogen cyanide, and by replacing the aluminium chloride with the milder zinc chloride. Over ten years later, J. Houben demonstrated that this reaction principally worked for polyphenols or polyphenolic ethers. From this point onwards, the condensation of nitriles with either polyhydroxy- or polyalkoxyphenols to synthesise the corresponding polyhydroxy or polyalkoxyacyloxyphenones was known as the Houben-Hoesch synthesis.

Synthetic applications of the Houben-Hoesch reaction include the total synthesis of the natural product bostrycoidin and Genistein which is an important nutraceutical molecule found in soybean seeds.

## Friedel-Crafts Acylation and Alkylation

In 1877 C. Friedel and J.M. Crafts reacted amyl chloride with aluminium pieces in benzene and formed amyl benzene. The reaction of alkyl halides with benzene was found to be general and aluminium chloride ($AlCl_3$) was identified as the catalyst. Since this discovery, the substitution of both aromatic and aliphatic compounds with a variety of alkylating agents in the presence of a Lewis acid is known as Friedel-Crafts Alkylation.

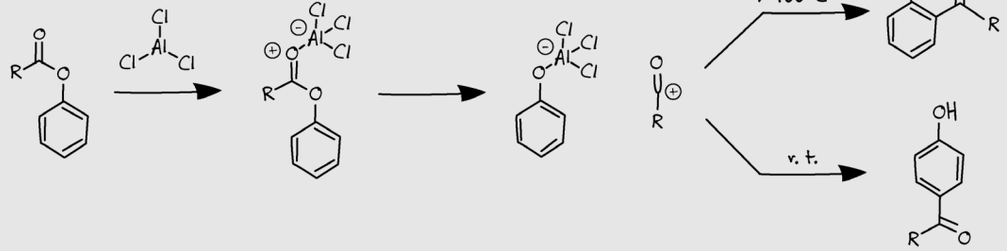
Before the 1940s, the alkylation of aromatic compounds was the foremost application, but later the alkylation of aliphatic systems also gained importance. In addition to aluminium chloride, other Lewis acids can also be used: $BeCl_2$, $CdCl_2$, $BF_3$, $BBr_3$, $GaCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$, lanthanide trihalides, and alkyl aluminium halides.

Closely related to the Friedel-Crafts Alkylation, the introduction of a keto group into an aromatic or aliphatic compound using an acyl halide or anhydride in the presence of a Lewis acid catalyst is known as the Friedel-Crafts Acylation. Compounds that undergo the Friedel-Crafts Alkylation are, in most cases, also easily acylated.

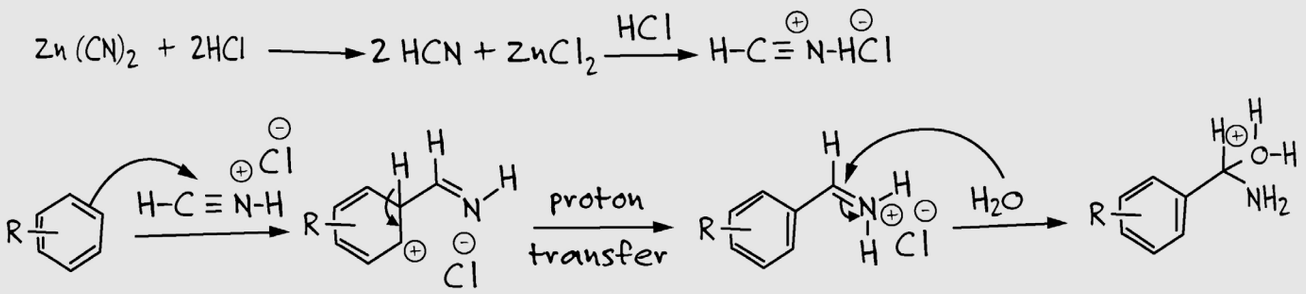
One drawback of the Friedel-Crafts Acylation reaction is that the Lewis acid catalyst often cannot be recovered once the reaction is complete. However heterogeneous catalysts such as zeolites make this reaction more feasible on an industrial scale.

**Click here for a more in-depth look at the Friedel-Crafts reaction**

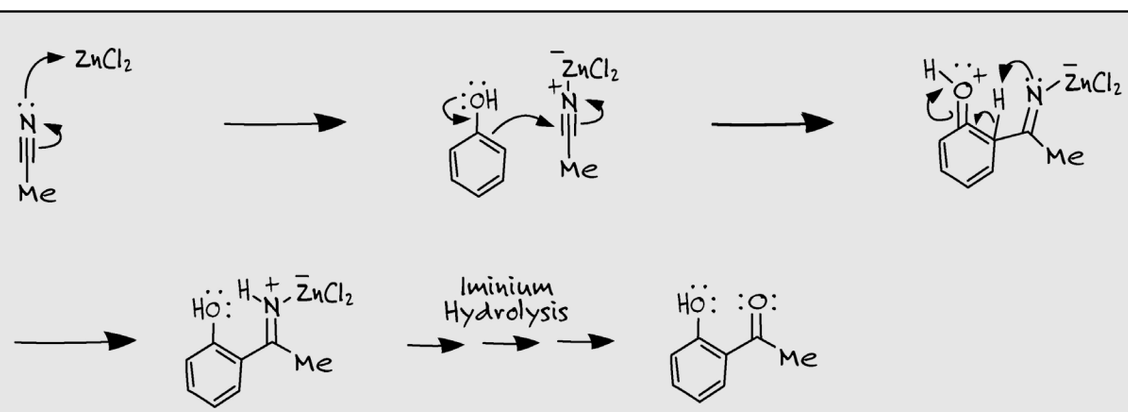
## Reaction Mechanism Examples




Mechanism of the Fries Rearrangement




Mechanism of the Gattermann Formylation Using the Adams Modification

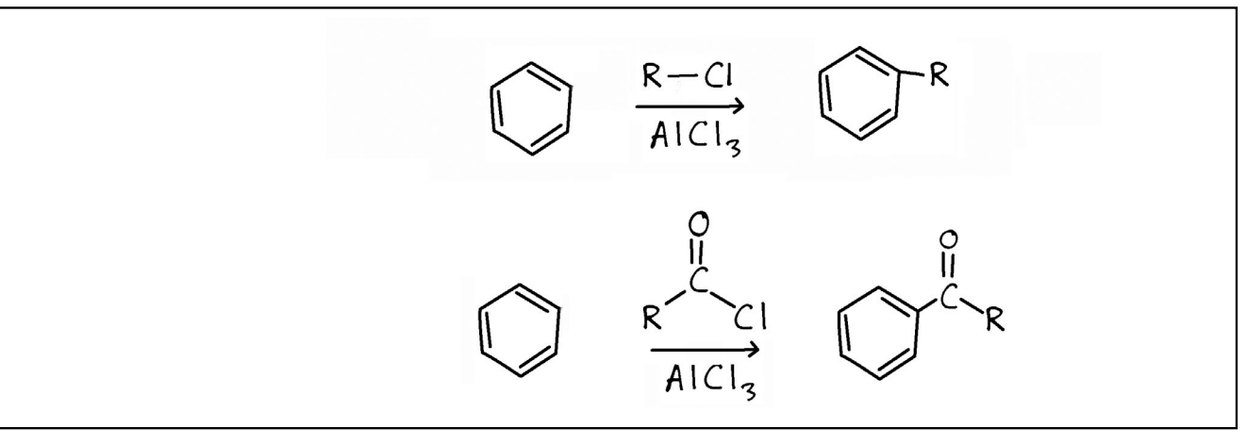



Mechanism of the Houben-Hoesch Synthesis

## Friedel-Crafts Acylation and Alkylation Reaction

The functionalization of aromatic compounds is a staple of organic synthesis. Two of the first and most widely utilized reactions for this purpose are the Friedel-Crafts acylation and alkylation.

It all started in 1877, during a research collaboration stint at the Sorbonne in Paris between Strasbourg-born Charles Friedel and visiting MIT chemistry professor James M. Crafts. They reacted amyl chloride with aluminium pieces in benzene and formed amyl benzene. What they discovered was an electrophilic aromatic substitution of benzene by an alkyl halide, catalyzed by aluminium chloride.




Compounds that undergo Fridel-Crafts alkylation are usually easily acylated by acyl halides, or anhydrides, via the same reaction.

In general terms the alkylation or acylation happens in the presence of a Lewis acid. Besides aluminium chloride (AlCl3), many others can be used: $BeCl_2$, $CdCl_2$, $BF_3$, $BBr_3$, $GaCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$, lanthanide trihalides, and alkyl aluminium halides.

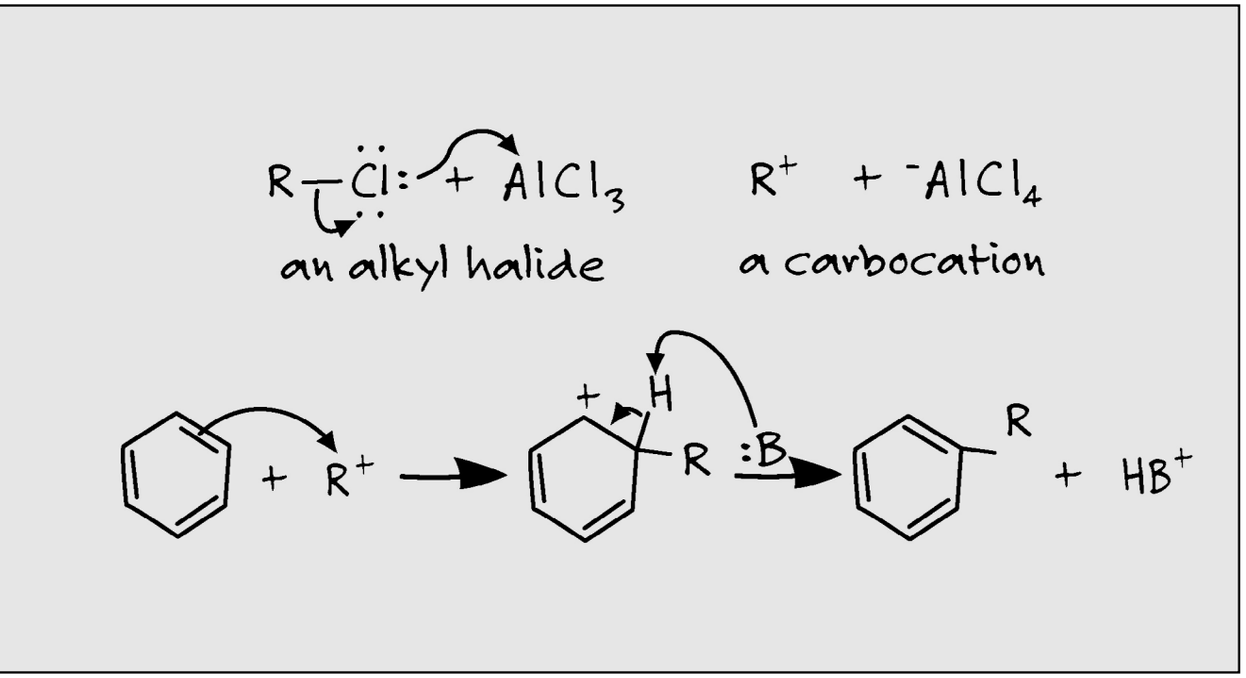
Friedel-Crafts reactions are simple and efficient, do not require harsh conditions and offer the advantage of a broad substrate scope. The reaction is often run solvent-free, as either the aromatic building block and/or the acyl halide can act as solvent, or it requires hydrophobic solvents, such as dichloromethane and ethers, or more polar ones, such as DMF, in case of more polar reagents. The classic Friedel-Crafts acylation and alkylation usually do not require more than moderate heating and can often be run at room temperature under dry conditions, as the Lewis acid catalyst is moisture-sensitive. Despite their several advantages, however, alkylations and acylations present own specific disadvantages. The alkyl substituent on the arene is an activator of the Friedel-Craft reaction, therefore multi-alkylation is a very common occurrence leading to significant amounts of by-products. A possible solution is following a two-step strategy with a Friedel-Crafts acylation of a corresponding acyl halide followed by a carbonyl reduction reaction, such as Clemmensen, or Wolff-Kishner.

The major advantage of the acylation reaction is linked to the electron-withdrawal property of the carbonyl group, which disfavours multiple acylations after the arene is functionalised once. It presents however some disadvantages. One of them is the fact that some acyl halides are intrinsically unstable (e.g., formyl chloride), so they must be generated *in situ* to allow the reaction to occur. Another drawback is that the Lewis acid is often unrecoverable once the reaction reaches completion. This is due to the fact that the ketone reaction product is a moderate Lewis

base that forms a strong complex with the Lewis acid catalyst. While this doesn't affect the overall chemistry, it impacts the reaction economics, often preventing industrial applications. There are ways to overcome this by using heterogeneous catalysts, such as zeolites, even though in some cases there is an efficiency cost to be considered.

## Mechanism of the Friedel-Crafts Alkylation

The reaction mechanism is very similar for the alkylation and the acylation reaction. The alkylation follows the formation of a carbocation, stabilized by complex with the Lewis acid. The acylation typically goes through an acylium center and the formation of the carbocation on the arene scaffold, in the same way as the alkylation.




## Reference reaction protocols

*Acylation*

Flush a round bottom flask and condenser setup with nitrogen. Add 1.1 equivalents of anhydrous aluminium chloride in 15 mL of methylene chloride. Bubble nitrogen in the solution, venting through the condenser. Put the mixture in an ice bath for cooling, then add 1.1 equivalents of acyl chloride in a methylene chloride solution (10 mL) with a syringe, through the addition funnel. Add then 1 equivalent of the arene compound drop-wise to the solution, adjusting the addition rate to avoid violent boiling. Stir for 20 minutes after the addition is complete removing from the ice bath. Pour the mixture slowly onto a aqueous HCl solution and proceed to work-up by extraction, adding anhydrous bicarbonate to neutralize the aqueous phase and collecting the organic layers.

*Alkylation*

Mix/dissolve equimolar amounts of arene and alkyl halide in dimethyl chloride or diethyl ether in a reaction vessel, previously flushed with dry nitrogen. Put the mixture in an ice bath under stirring and add glacial sulfuric acid drop-wise to avoid vigorous boiling of the reaction. At the end of the addition remove from the ice bath and keep under stirring for 15 minutes. Proceed to work-up by adding the mixture to water to dilute the sulfuric acid. Proceed to extraction or crystallization/filtration depending of the physico-chemical characteristics of the reaction product.

## Key literature references


1. *Compt. Rend. 1877, 84, 1450*
2. *Chem. Rev. 1955, 55, 2, 229–281 https://doi.org/10.1021/cr50002a001*
3. *Org. React. 1946, 3, 1. https://doi.org/10.1002/0471264180.or003.01*
4. *J. Org. Chem. 1993, 58, 17, 4656–4661 https://doi.org/10.1021/jo00069a031*
5. *Chem. Soc. Rev. 1972, 1, 73 https://doi.org/10.1039/CS9720100073*

# Product Selection

Safety: Make sure you are aware of the hazards of the materials, read SDS and wear appropriate personal protective equipment before starting a reaction. Always work in properly ventilated areas.

| SKU | Description |
|---|---|
| | *Popular acetyl halides* |
| 46268 | Propionyl chloride, 98% |
| 21947 | Acetyl chloride, 99+% |
| B24472 | Isobutyryl chloride, 98% |
| 17347 | Chloroacetone, 96%, stabilized |
| 45897 | Propionyl chloride, 99.5%, phosgene free |

| SKU | Description |
|---|---|
| | *Popular alkyl halides* |
| 42588 | 1-Chlorobutane, 99.8%, for HPLC |
| 033213 | Phenol, ACS, 99+%, stab. |
| 14934 | Phenol, 99%, extra pure |
| H53476 | 6-Chloro-1-hexyne, 98% |
| 10995 | 1-Chloropropane, 99% |
| B22379 | 1-Chlorohexane, 96% |
| 43382 | 1-Chlorobutane, 99.5%, anhydrous, AcroSeal® |
| B24733 | 1-Chloropentane, 98% |

| SKU | Description |
|---|---|
| | *Catalysts* |
| 46610 | Aluminium chloride, 99%, extra pure, anhydrous, granules |
| 044313 | Aluminum chloride, ultra dry, 99.999% (metals basis) |
| L18489 | Aluminum chloride, 98+%, extra pure, anhydrous powder |
| 42404 | Phosphoric acid, ACS reagent, 85+% solution in water |
| 38902 | Phosphoric acid, 98+%, pure |
| 012357 | Iron(III) chloride, anhydrous, 98% |
| 033273 | Sulfuric acid, ACS, 95.0-98.0% |
| 011000 | Sulfuric acid, 99.9999% (metals basis) |
| 42380 | Hydrofluoric acid, ACS reagent, 48-51% solution in water |
| 41365 | Mercury(II) sulfate, ACS reagent |
| 036286 | Mercury(II) sulfate, ACS, 98.0% min |
| A18067 | Phosphoric acid, 85% aq. soln. |

# Nucleophilic Substitution Reactions

When an electron rich nucleophile reacts with the positive charge of an atom or group of atoms to replace a leaving group, this is known as nucleophilic substitution. The positive or partially positive atom is referred to as an electrophile.

Nucleophilic substitution reactions are important in that they facilitate the interconversion of functional groups, of particular importance are the reactions of alkyl halides (R-X) and alcohols (R-OH)

One of the earliest named reactions using nucleophilic substitution is the Gabriel synthesis. Other well-known named reactions using nucleophilic substitution include:

- Mitsunobu reaction
- Baeyer-Villiger oxidation
- Swern oxidation
- Tishchenko reaction

## Gabriel Synthesis

The alkylation of phthalimide with alkyl halides was first reported in 1884, but in 1887 S. Gabriel realized that the process was a general one and developed a synthesis for primary amines. From this point onwards, a mild two-step process - alkylation followed by solvents - could be used. Solvents include dimethyl sulphoxide (DMSO), hexamethyl phosporamide (HMPA), acetonitrile and ethylene glycol.

Several issues limited the use of the original Gabriel synthesis. Firstly, when the reaction of the potassium phthalimide and alkyl halide required high temperatures, heat sensitive substrates could not be used. Secondly, the hydrolysis step was usually performed in the presence of a strong acid such as sulfuric, hydrobromic or hydroiodic acids, further preventing the use of substrates that were sensitive to acid conditions. Alternatively, where strong alkali could be used for hydrolysis, base sensitive functional groups were excluded.

In 1926 H.R. Ing and R.H.F. Manske developed a modification using hydrazine hydrate in refluxing ethanol to cleave the N-alkylphthalimide under milder and neutral conditions and this became known as the Ing-Manske procedure.

Since then several other modifications have been developed such as the development of novel Gabriel reagents that replace the phthalimide with other nitrogen sources, the addition of catalytic amounts of crown ether or a cryptand to improve yields, and the use of sodium borohydride in IPA for exceptionally mild cleavage of the phthalimide.

The total synthesis of peramine, an alkaloid produced by a fungus that protects grasses against grazing by mammals and insects, successfully employed the Gabriel synthesis in the latter stages.

## Mitsunobu Reaction

In 1967 O. Mitsunobu demonstrated the acylation of secondary alcohols with carboxylic acids in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine. Later it was discovered that optically active secondary alcohols underwent total inversion of configuration under these reaction conditions and this procedure was found to be general for the synthesis of optically active amines, azides, ethers, thioethers and also alkanes. Since then the substitution of primary and secondary alcohols with nucleophiles in the presence of a dialkylazodicarboxylate and a trialkyl- or triaryl phosphine is known as the Mitsunobu reaction.

An important development of this reaction was made by T. Mukaiyama who prepared inverted tert-alkyl carboxylates from chiral tertiary alcohols via alkoxydiphenylphosphines formed *in situ* from 2,6-dimethyl-1,4-benzoquinone.

The synthesis of the potent antitumor antibiotic (+)-duocarmycin A utilised the Mitsunobu reaction during the final stage. This is a special case where the reaction is used to create new carbon-carbon bonds.

## Baeyer-Villiger Oxidation

While exploring the ring cleavage of cyclic ketones in 1899, A. Baeyer and V. Villiger discovered that ketones could be transformed into esters and cyclic ketones into lactones or hydroxy acids by peroxyacids. This reaction became known as the Baeyer-Villiger oxidation. The oxidation of ketones by this method has several benefits:

- It tolerates the presence of many other functional groups
- The rearrangement steps retain the existing stereochemistry at the migrating center
- A wide variety of different peroxyacids can be used as oxidants
- The oxidation can be performed asymmetrically on racemic or prochiral ketones using enzymes or chiral transition metal catalysts
- A wide range of oxidizing agents can be used
- The activity of suitable oxidizing agents can be ranked in the following order: Trifluoroperoxyacetic acid > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > p-nitroperbenzoic acid > meta chloroperoxybenzoic acid (mCPBA) > performic acid > perbenzoic acid > peraceticacid > Hydrogen peroxide and finally tert-Butyl hydroperoxide (tBuOOH).

Only a few methods are known for the synthesis of cage-annulated ethers. A.P Marchand and colleagues used the Baeyer-Villiger oxidation for the preparation of novel cage heterocyclic systems and developed a general process to make cage ethers from cage ketones.

**Click here for a more in-depth look at the Baeyer-Villiger reaction**

## Swern Oxidation

In 1976, when treating dimethyl sulfoxide (DMSO) with trifluoroacetic anhydride (TFAA) below -50°C in dichloromethane, D. Swern and co-workers formed trifluoroacetoxydimethylsulfonium trifluoroacetate which reacted rapidly with primary and secondary amines. When treated with trimethylamine, the resulting alkoxydimethylsulfonium trifluoroacetates formed the corresponding aldehydes and ketones in high yields.

During 1978 oxalyl chloride was found to be more efficient than TFAA as an activating agent for DMSO in the oxidation of alcohols. Since then, the oxidation of primary or secondary alcohols using DMSO and TFAA or oxalyl chloride has been known as the Swern Oxidation.

The total synthesis of the mytotoxic (+)-aseltoxin utilised the Swern oxidation as did that of the marine dolabellane diterpene (+)-deoxyneodolabelline.

In the latter case, both Dess-Martin and Ley oxidations were tried but the substrate suffered carbon-carbon bond cleavage.

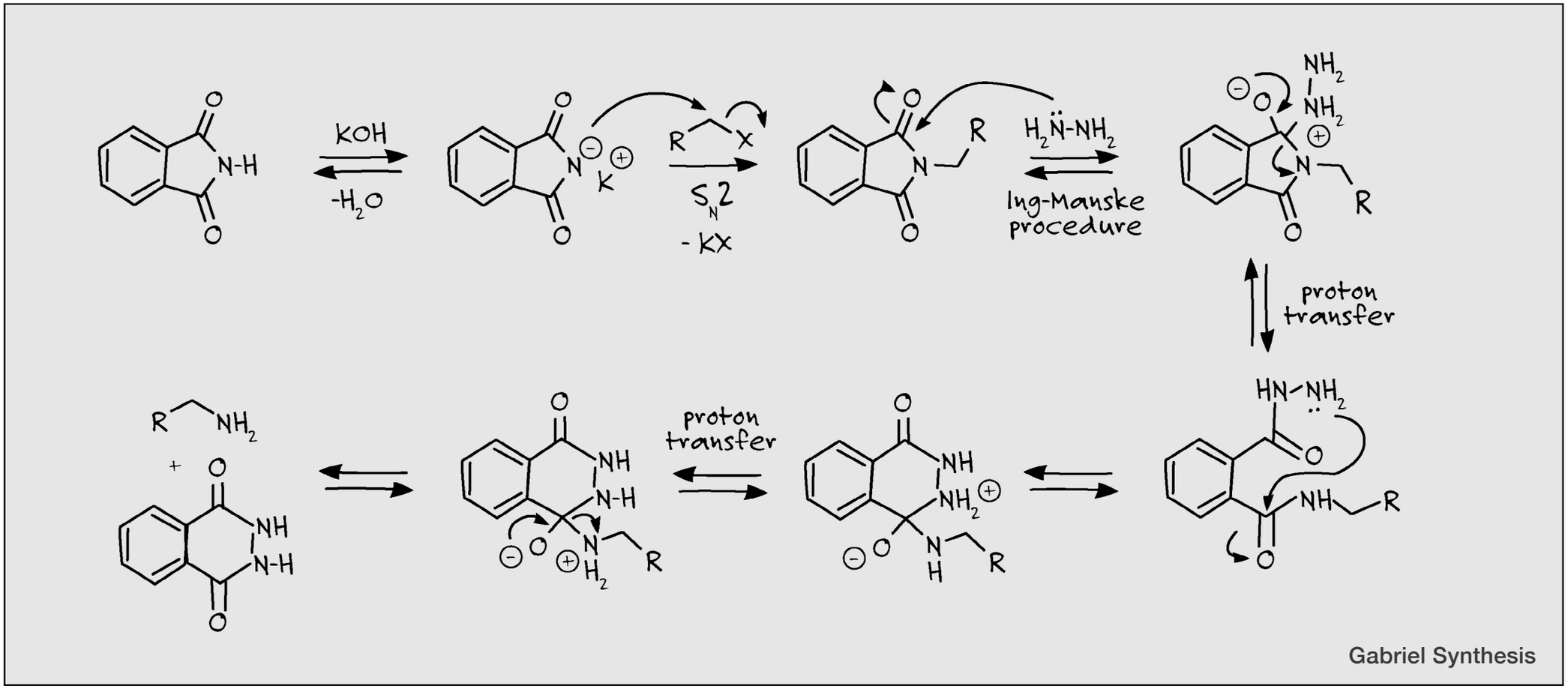
## Tishchenko Reaction

In 1887 L. Claisen discovered the formation of benzyl benzoate from the reaction of benzaldehyde in the presence of sodium alkoxides. Almost thirty years later W.E. Tishchenko found that both enolizable and non-enolizable aldehydes could be converted to their corresponding esters in the presence of magnesium or aluminum alkoxides and this became known as the Tishchenko Reaction. The most common catalysts used are aluminium alkoxides, but a wide variety of other catalysts can be used including alkali- and alkali—earth metal oxides and alkoxides, transition metal-based catalysts such as ruthenium complexes and certain rhodium, iridium and iron complexes.

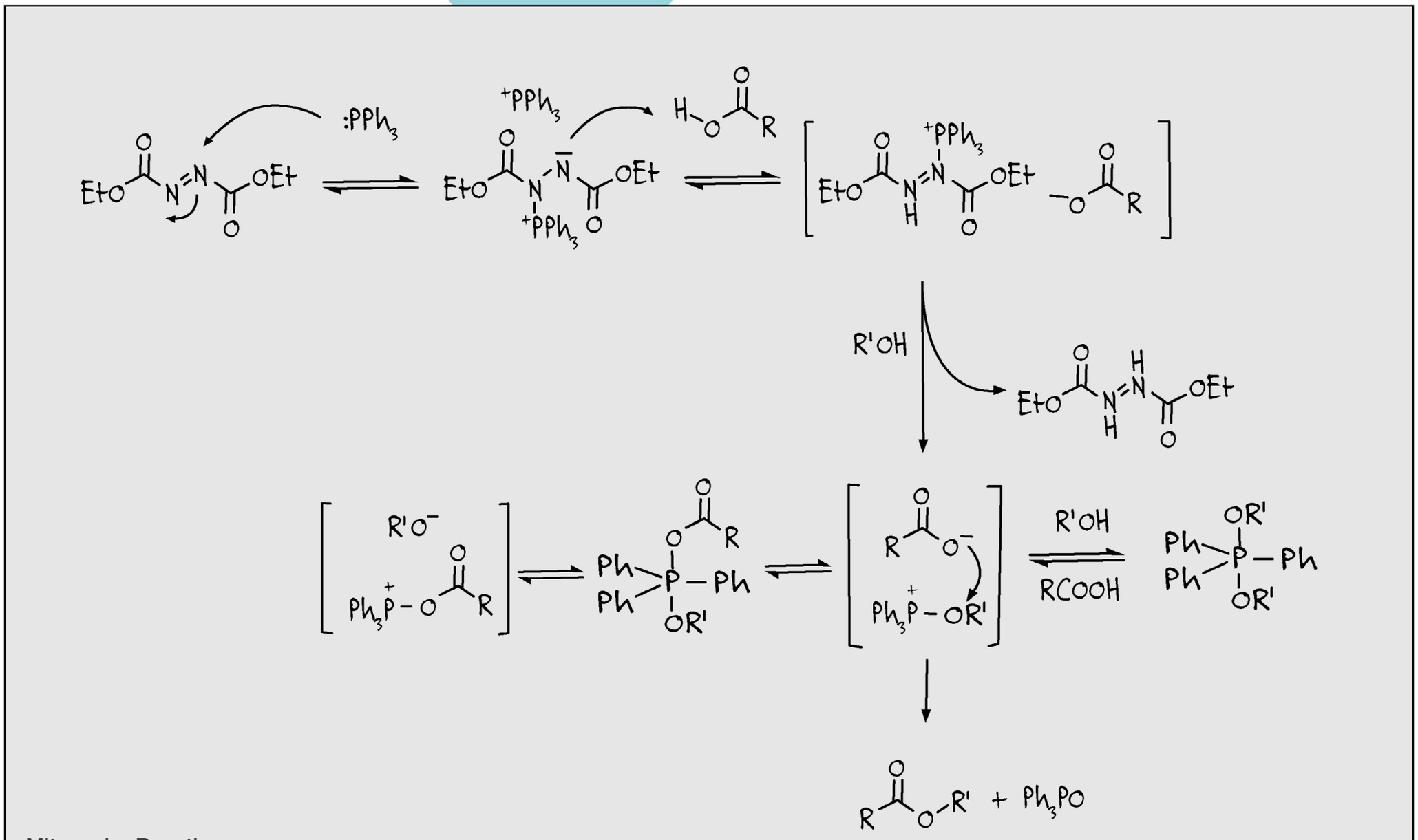
The most widely used modification to the Tishchenko reaction is the Evans-Tishchenko reaction that transforms a chiral betahydroxy ketone in the presence of an aldehyde and catalytic samarium iodide ($SmI_2$) into the anti 1,3-diol monoester with excellent diastereoselectivity.

The natural product Rhizoxin D, a potent antitumor and antifungal compound, was synthesized utilizing the Evans-Tishchenko reaction.

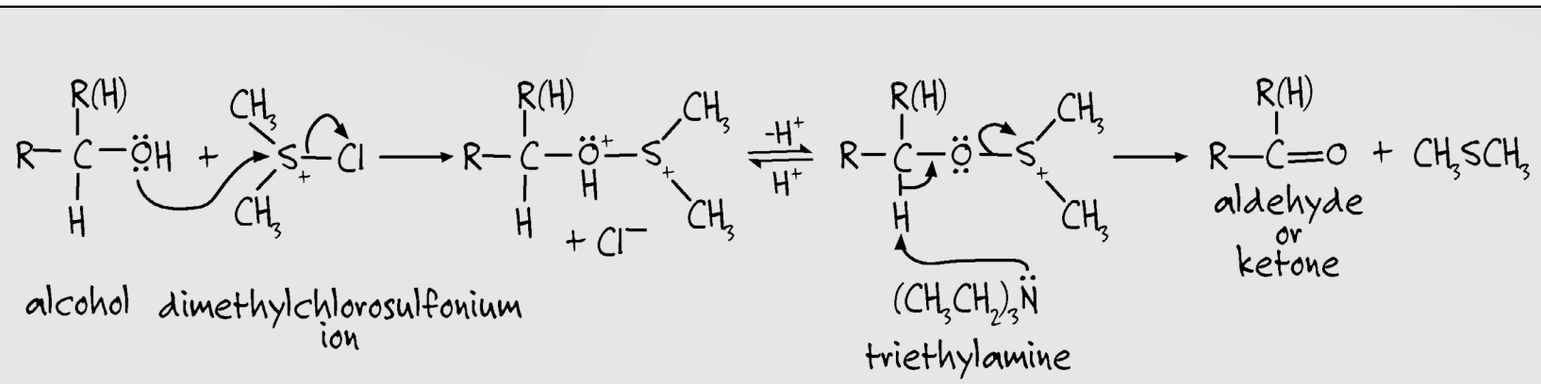
## Reaction Mechanism Examples



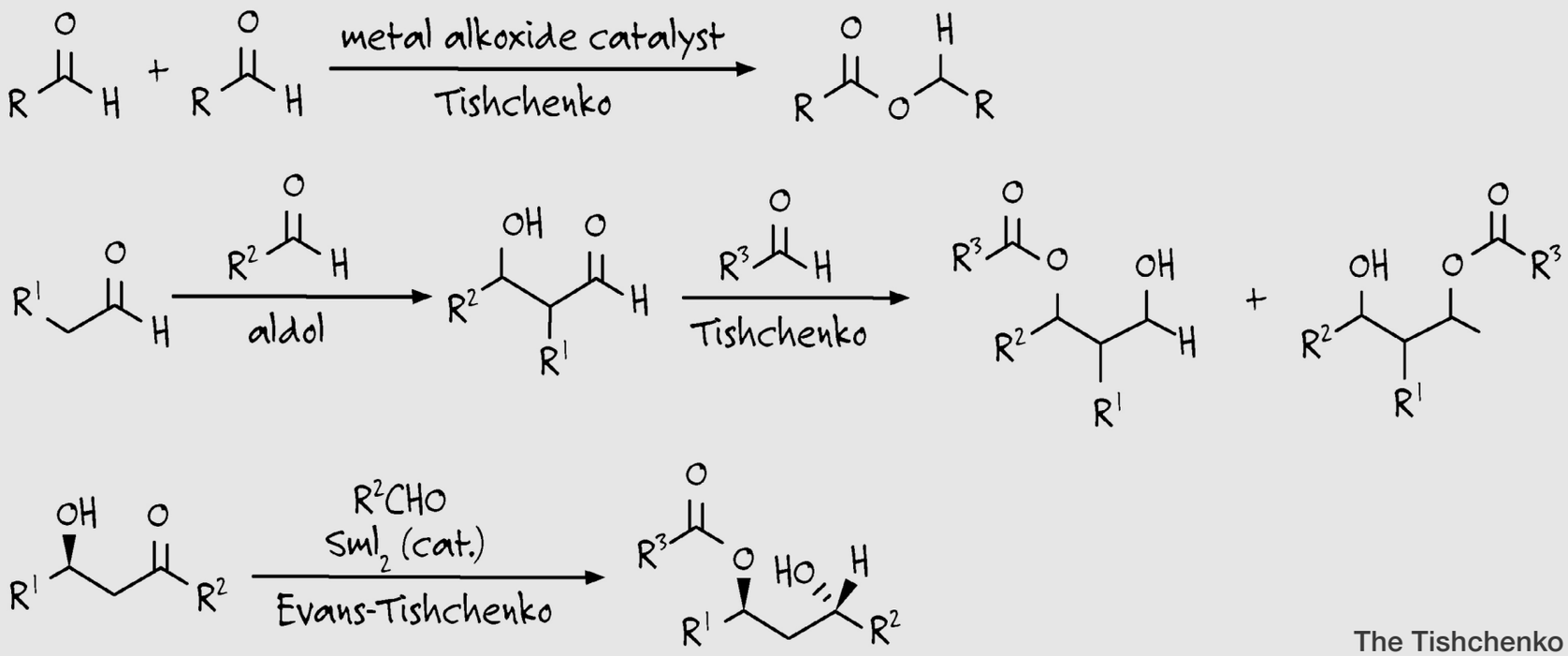

Gabriel Synthesis




Mitsunobu Reaction

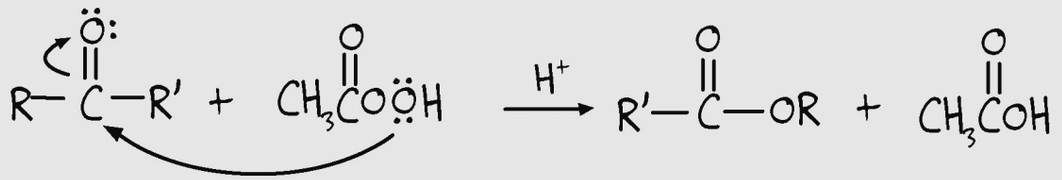



Swern Oxidation




The Tishchenko and Evans-Tishchenko Reactions

# Baeyer-Villiger reaction



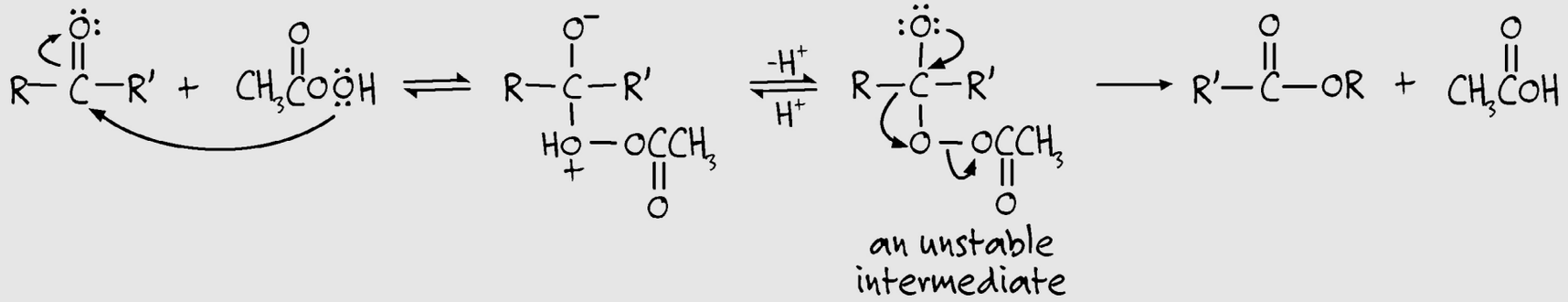

The Baeyer-Villiger reaction is an oxidation of ketone or a cyclic ketone with a peroxyacid to give an ester or a lactone, respectively.

This reaction was discovered in 1899 by Professor Adolf von Baeyer (Nobel prize in chemistry in 1905) and Victor Villiger (BASF Ludwigshafen, Germany), during their studies on the ring cleavage of cyclic ketones with potassium monopersulfate ($KHSO_5$).[1] It occurs without solvent for 24 h at room temperature. Later, $KHSO_5$, known as Caro's reagent, was replaced by an organic peracid obtained by the reaction of dibenzoyl peroxide with sodium ethoxide and treated in acid conditions.[2] Several peroxyacids can be used as oxidants, typical examples are meta-chloroperbenzoic acid (mCPBA), trifluoroperacetic acid (TFPAA) and 4-nitroperbenzoic acid.

## Mechanism of Baeyer-Villiger reaction

The mechanism of this reaction had been discussed for 50 years. Firstly, the hypothesis of the presence of the side product 1,2,4,5-tetraoxocyclohexane as intermediate was rejected by Dilthey; then Criegee suggested a nucleophilic attack on the carbonyl group confirmed in 1953 by von Doering thanks to a [$^{18}$O]benzophenone labeling experiment.[3,4] Since then, the intermediate is known as the Criegee intermediate.

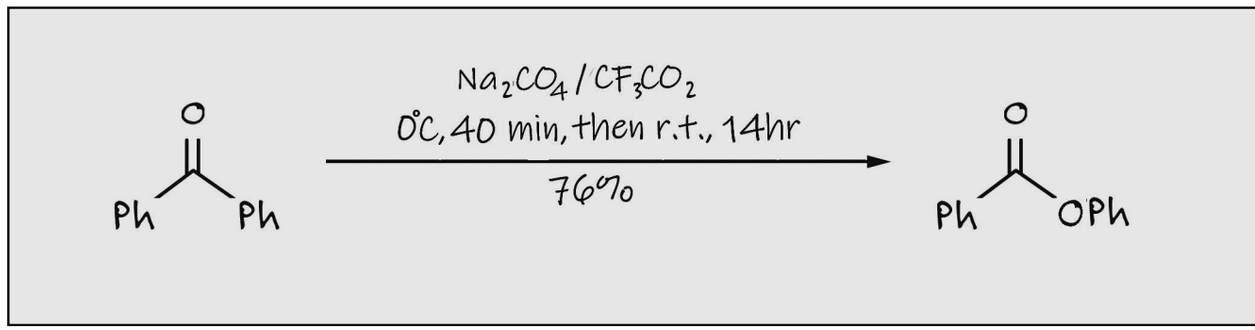
In the first part of the reaction, there is a nucleophilic addition of the peracid to the carbonyl group of the ketone to give rise to the Criegee rearrangement. The adduct formed decomposes then via a cyclic transition




state in which the alkyl group present on the carbonyl carbon migrates to the oxygen to obtain the ester. Later in 1950, the stereoselectivity of the Baeyer-Villiger rearrangement was investigated and Turner demonstrated that the rearrangement took place with retention of configuration at the migrating group.[5] This retention of stereochemistry makes it an useful tool for asymmetric synthesis because one main product is obtained. Studies carried out with organic peracid confirmed that the migratory ability of the substituents of asymmetrical ketones depends on the carbocation character in the transition state of rearrangement: Methyl< Primary Group< Phenyl< Secondary < Cyclohexyl< Tertiary Group. Since 1976, when the Baeyer–Villiger monooxygenases were isolated, the biotechnology approach to the reaction has been considered in order to improve the catalytic activity and to achieve high product concentrations.[6]

*Reference reaction protocols*[7]

Sodium percarbonate (15-20 mmol) is added slowly at 0°C to a solution of benzophenone (10 mmol) and trifluoroacetic acid (20 mL). The mixture is brought to room temperature, stirred for 15 hours, then quenched with 40 mL of ice water. This mixture is extracted with $CH_2Cl_2$, washed with 10% $NaHCO_3$ to remove the acid and purified by recrystallization or distillation.

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3. *R. Criegee, Liebigs Ann. Chem. 1948, 560, 127 –135.*
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5. *M. Renz, B. Meunier Eur. J. Org. Chem. 1999, 737-750*
6. *Ji-Min Woo et al. Nature, Scientific Reports, 2018, 8:10280 DOI:10.1038/s41598-018-28575-8*
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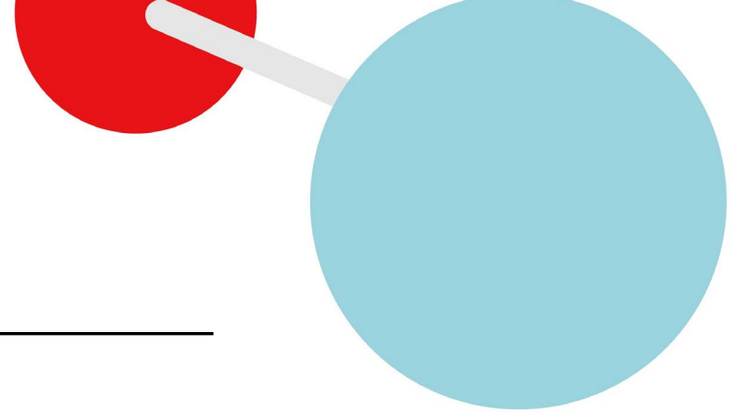
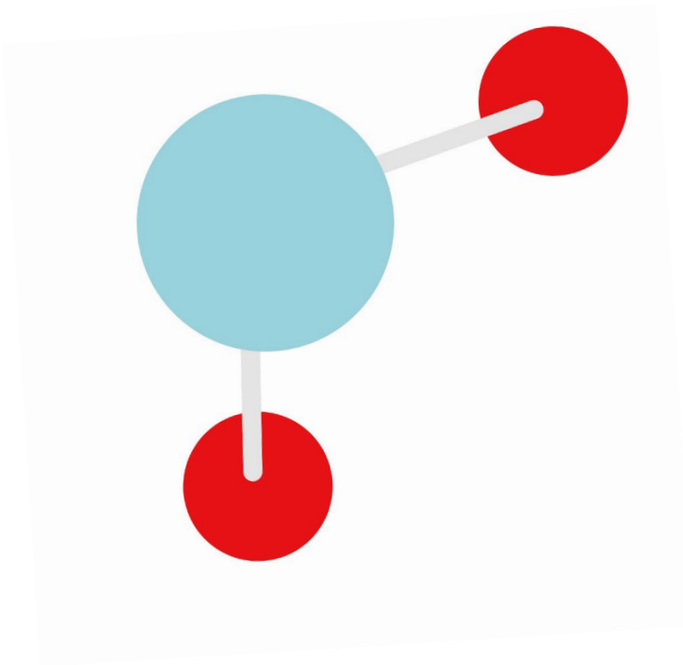




## Product Selection

Safety: Make sure you are aware of the hazards of the materials, read SDS and wear appropriate personal protective equipment before starting a reaction. Always work in properly ventilated areas.

| SKU | Description |
|---|---|
| | *Ketones* |
| 32680 | Acetone, 99.8%, Extra Dry, AcroSeal® |
| 32674 | Acetone, 99.9%, for residue analysis, for trace analysis of polyaromatic hydrocarbons |
| 41734 | D(+)-2-Amino-3-phenyl-1-propanol, 98% |
| 39695 | 2-Butanone, 99.5%, Extra Dry, AcroSeal® |
| 32791 | 2-Butanone, 99+%, for electronic use (MOS), residue free |
| 11093 | Cyclobutanone, 98+% |
| A13068 | Cyclobutanone, 98%, stab. with ca 0.1% BHT |
| 40609 | Cyclohexanone, 99+%, ACS reagent |
| A14222 | Cyclopentanone, 99% |
| A12544 | Ethyl acetoacetate, 99+% |
| A10200 | 2-Heptanone, 99% |
| A16977 | 3-Heptanone, 98% |
| B21222 | 4-Heptanone, 98% |
| 14688 | 2-Hexanone, 98% |
| 14690 | 3-Hexanone, 98% |
| 12148 | 4-Hydroxy-4-methyl-2-pentanone, 99% |
| 14966 | 5-Methyl-2-hexanone, 99% |

| SKU | Description |
|---|---|
| | *Ketones* |
| A11618 | 4-Methyl-2-pentanone, 99% |
| 14878 | 2-Nonanone, 99% |
| A13722 | 5-Nonanone, 98% |
| 12942 | 2-Octanone, 99+% |
| 22413 | 2-Pentanone, 99+%, purified by redistillation, AcroSeal® |
| A15297 | 3-Pentanone, 99% |

| SKU | Description |
|---|---|
| | *Percarboxylic acid* |
| A13926 | tert-Butyl hydroperoxide, 70% aq. soln. |
| 17014 | tert-Butyl peroxybenzoate, 98% |
| 25579 | 3-Chloroperoxybenzoic acid, 70-75%, balance 3-Chlorobenzoic acid and water |
| 34996 | Cumyl hydroperoxide, 80% |
| 25775 | Peroxyacetic acid, ca. 35wt.% sol. in diluted acetic acid, stabilized |

# Rearrangement Reactions

A rearrangement reaction occurs when the carbon skeleton of a molecule is rearranged to provide a structural isomer of the original molecule. Often, a substituent moves from one atom to another atom in the same molecule. Alongside substitution and addition reactions, rearrangements are of fundamental importance within organic synthesis.

One of the earliest named reactions featuring rearrangement is the Lossen rearrangement. In 1872, German chemist Wilhelm Lossen discovered that pyrolysis of benzoyl benzohydroxamate, formed by mixing phenylhydroxamic acid with benzoic acid, gave a mixture of phenyl isocyanate and benzoic acid. Ultimately the conversion of O-acyl hydroxamic acids to their corresponding isocyanates became known as the Lossen rearrangement.

The reaction is still popular today, because despite being closely related to both the Hofmann and Curtius rearrangements, it utilizes much milder reaction conditions and avoids the need to use potentially hazardous azides.

Other rearrangement reactions include:

- Beckmann rearrangement
- Curtius rearrangement
- Claisen rearrangement
- Ferrier reaction
- Hofmann rearrangement

## Beckmann rearrangement

Named after the German chemist Ernst Otto Beckmann, the Beckmann rearrangement involves the conversion of aldoximes and ketoximes into their corresponding amides under acidic conditions. The reaction is usually carried out under relatively high temperatures, usually greater than 130°C, and in the presence of a large excess of strong Brønsted acids such as sulfuric acid or acetic acid. These conditions mean that sensitive substrates are not suitable for this process.

The Beckmann rearrangement is still important in industry today as a key step in the manufacture of caprolactam, a precursor to the synthesis of filaments and fibers such as nylon. The synthesis involves converting cyclohexanone to its oxime, and subsequently treating this with acid to generate caprolactam via a Beckmann rearrangement.

The total synthesis of the non-natural (+)-codeine utilized the Beckmann rearrangement to install a six-membered piperidine ring into the molecule.

**Click here for a more in-depth look at the Beckmann rearrangement**

## Curtius rearrangement

In 1885 German chemist Theodor Curtius reported the thermal decomposition of an acyl azide to an isocyanate with the loss of nitrogen. This reaction subsequently became known as the Curtius rearrangement. Acid catalysis through the use of either protic or Lewis acids significantly lowers the required reaction temperature compared with the uncatalyzed reaction, allowing for the use of more delicate substrates.

The acyl azide precursors can be made through a number of methods, including: reacting acid chlorides or mixed anhydrides with alkali azide or trimethylsilyl azide, treating acylhydrazones with nitrous acid or nitrosonium tetrafluoroborate, or by treating carboxylic acids with diphenyl phosphoryl azide (DPPA). If the reaction is carried out in the presence of water, amines or alcohols then the corresponding amines, ureas and carbamates are formed.

It is possible to induce the Curtius rearrangement through use of photochemical conditions and this is known as the Harger reaction.

The Curtius rearrangement has been successfully employed in several total synthesis campaigns including that of the antitumor and antibacterial antibiotic streptonigrone, as well as pancratistatin, another compound with potent antitumor and antiviral activities.

## Claisen rearrangement

In 1912 German chemist Rainer Ludwig Claisen published the rearrangement of allyl phenyl ethers into their corresponding C-allyl phenols, as well as the conversion of the O-allylated acetoacetic ester to its C-allylated isomer upon treatment with ammonium chloride followed by distillation. Subsequently, the thermal rearrangement of allyl vinyl ethers into their corresponding α,β-unsaturated carbonyl compounds has become known as the Claisen rearrangement.

The precursor allyl vinyl ethers can be prepared in several ways, such as from the allylic alcohols via mercuric ion-catalyzed exchange with ethyl vinyl ether or by Wittig olefination of allyl formates and carbonyl compounds.

A modification is the Johnson–Claisen rearrangement where an allylic alcohol is heated with trialkyl orthoacetate under mildly acidic conditions to produce a α,β-unsaturated ester.

The Claisen rearrangement has been used in many successful total synthesis campaigns including that of 1-O-methylforbesione, via tandem Claisen rearrangement/Diels–Alder reactions by K. C. Nicolaou and colleagues.

## Ferrier reaction

In 1914, German chemist Emil Fischer first noted the allylic rearrangement of tri-O-acetyl-D-glucal to the corresponding 2,3-unsaturated hemiacetal when heated in aqueous conditions. However, the synthetic utility of this reaction was ultimately realized by British chemist Robert Ferrier during the 1960s. Henceforth, the Lewis acid-promoted rearrangement of unsaturated

carbohydrates has become known as the Ferrier reaction/rearrangement.

Commonly-used Lewis acids include boron trifluoride etherate, tin tetrachloride, iodine, iron(III) chloride; and a mixture of trimethylsilyl trifluoromethanesulfonate and silver perchlorate.

In 1979 a second Ferrier rearrangement was identified. Labelled Type II, exocyclic enol ethers are converted to substituted cyclohexanones upon treatment with mercury (II) salts. This form of the rearrangement became synthetically important due to the precursors being readily available from carbohydrates, as well as the fact that the Lewis acids used in catalytic amounts enabled the presence of acid-sensitive functionalities.

The Ferrier reaction has been widely used in total synthesis campaigns, including the stereoselective total synthesis of the antimitotic alkaloid (+)-lycoricidine that made use of the Type II Ferrier rearrangement for the synthesis of the optically active cyclohexanone fragment.

## Hofmann rearrangement

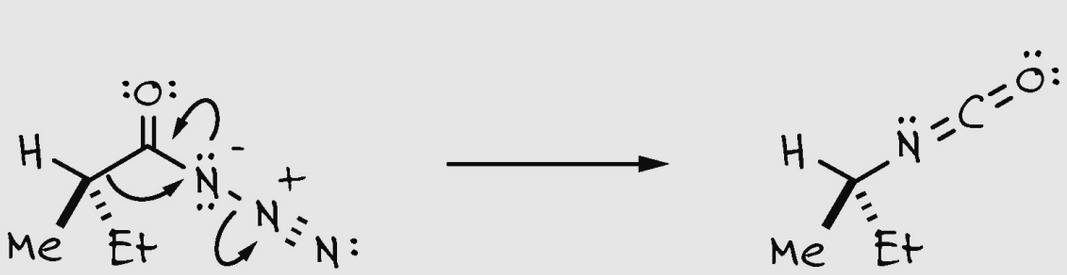
In 1881, German chemist August Wilhelm Hofmann discovered that by treating acetamide with one equivalent of bromine and either sodium or potassium hydroxide, N-bromoacetamide was formed. Upon further deprotonation and heating under anhydrous conditions this afforded methyl isocyanate. However, when aqueous conditions and an excess of base were used, methylamine was the product. Since this discovery the conversion of primary carboxamides to the corresponding one-carbon shorter amines has become known as the Hofmann rearrangement.

Since the original discovery, several modifications have been introduced. For hydrophobic amines, the use of methanolic sodium hypobromite, made from reacting bromine with sodium methoxide in methanol, provides the corresponding methylurethanes in high yields. Where the substrate is either acid- or base-sensitive, the use of a neutral electrochemically-induced Hofmann degradation was developed. To broaden the scope of the reaction for base sensitive substrates, an oxidative rearrangement can be induced using hypervalent iodine reagents such as (diacetoxyiodo)benzene (PIDA).

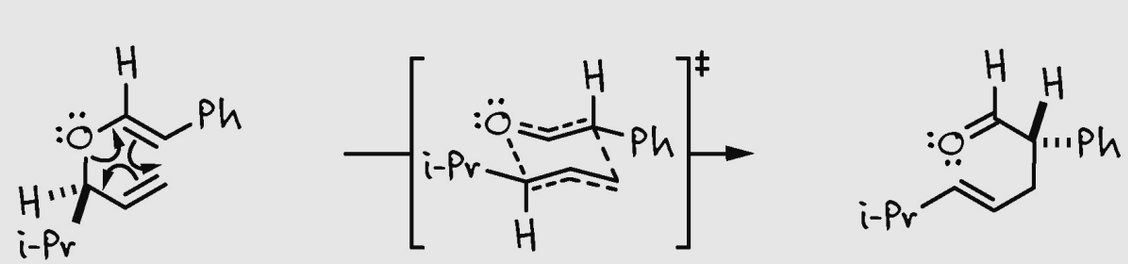
There are many industrial uses for the Hofmann rearrangement including pharmaceutical applications, where it is used in the manufacture of diuretics such as furosemide, for example.

In the total synthesis of the antifungal agent (+)-preussin, a modified version of the Hofmann rearrangement was used as one of the key steps in the final stages of the synthetic route.

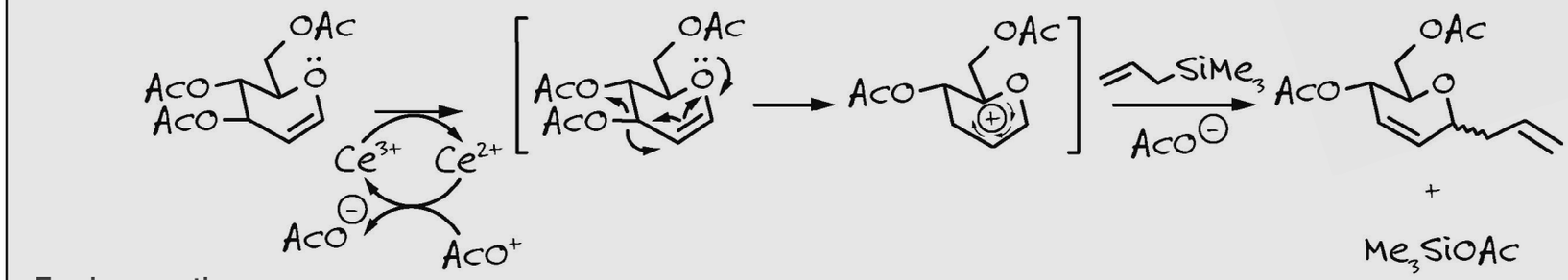
## Reaction Mechanism Examples



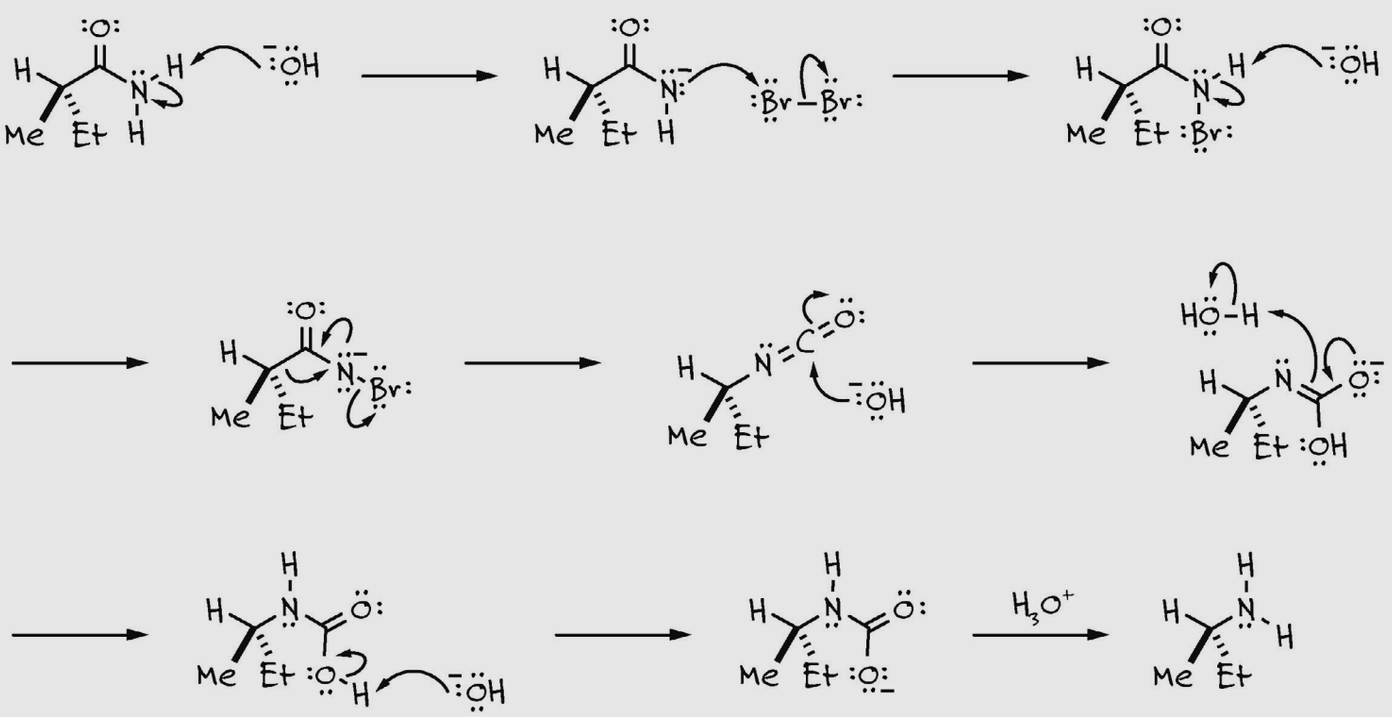

Curtius rearrangement




Claisen rearrangement




Ferrier reaction




Hofmann rearrangement

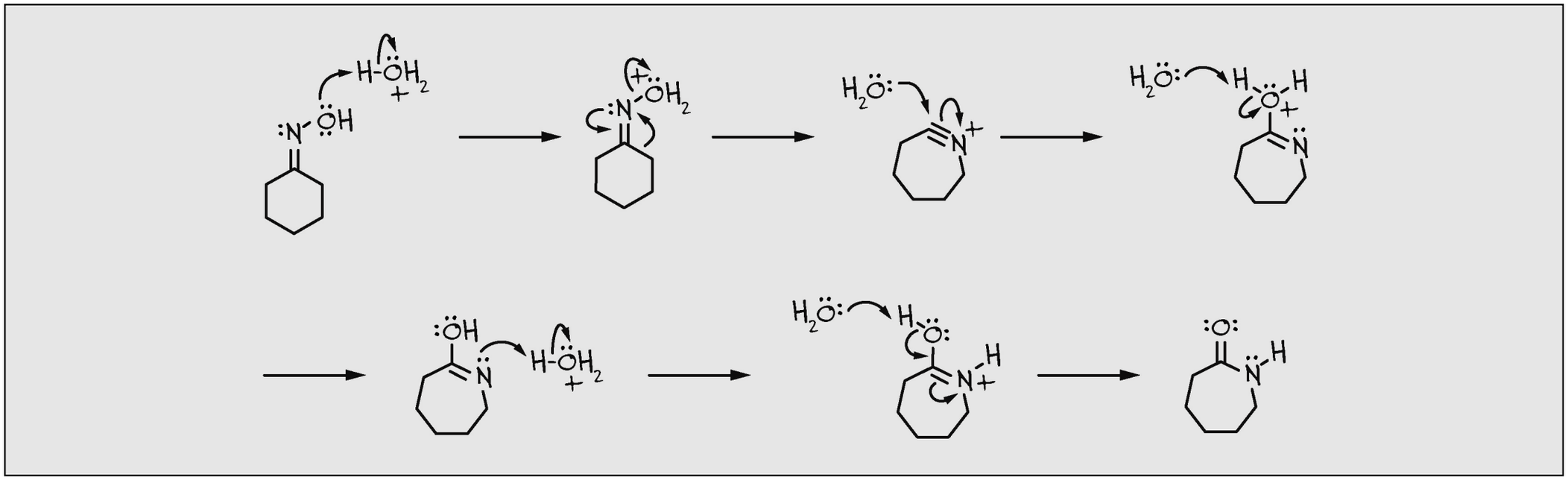
## Beckmann Rearrangement

The Beckmann reaction described in 1886 by the German chemist Ernst Otto Beckmann[1] is a rearrangement of an oxime into an amide or a lactam.

The importance of secondary amides in many pharmaceuticals and functional materials illustrates why this reaction is so crucial. One of the best-known applications involves cyclohexanone reacting with hydroxylamine to give caprolactam, the raw material for nylon production.

The mechanism is well known: under acid-catalyzed conditions, the oxime's OH is converted into a leaving group, followed by the cleavage of a C-C bond to give a new carbon-nitrogen bond in a one-stage mechanism. In general, the oxime nitrogen atom is inserted into the Coxime-Cα bond of aldehydes and ketones. This generates a nitrilium ion that reacts with water and rearranges to the corresponding amide.

The same approach is observed with linear ketones where the migrating group is anti-periplanar to the leaving group on the nitrogen. However, some exceptions could be observed in terms of the migrating group if the isomerization of the oxime occurs faster than the rearrangement. This isomerization depends on the steric and electrostatic effects of the oxime and acid.[2]



A syn-migration is observed when a nitrogen cation is stabilized by neighboring chlorine or bromine. However, in this case, the Beckmann rearrangement doesn't occur even if similar starting materials and reaction conditions are used.[3]

The rate of the rearrangement depends on the temperature, the solvent and the catalyst. Acids commonly used are sulfuric acid, phosphorus pentachloride or Beckman's solution consisting of a mixture of acetic acid, hydrochloric acid and acetic anhydride.

The reaction generally requires high temperature and highly acidic conditions, but this often leads to the production of by-products and difficulty in applying sensitive substrates. For this reason, less aggressive reaction conditions using a complex of 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride) and DMF are also suggested in the literature.[4]

*Reference reaction protocol*

*Synthesis of ε-caprolactam (Nitromethane used as sources of Hydroxylamine)*

305 g of nitromethane were added dropwise to 500 g of concentrated sulfuric acid heated carefully at 125°C followed by 440 g of cyclohexanone. The reaction mixture was then cooled, neutralized with aqueous ammonia and extracted with chloroform. The residue obtained after extraction was distilled to give 79% of ε -caprolactame.[2]

## Key literature references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4. *L. De Luca et al. J. Org. Chem, vol 67, 2002, (17), 6272-6274*

# Product Selection

Safety: Make sure you are aware of the hazards of the materials, read SDS and wear appropriate personal protective equipment before starting a reaction. Always work in properly ventilated areas.

| SKU | Description |
|---|---|
| | *Oxime Compounds* |
| 10223 | Acetaldoxime, 99%, mixture of syn and anti |
| 39053 | Acetamide oxime, 95+% |
| A10802 | Acetone oxime, 98% |
| A11804 | Acetophenone oxime, 98% |
| 45328 | Benzamide oxime, 97% |
| A10687 | Benzil dioxime, 98% |
| A10630 | alpha-Benzoin oxime, 98+% |
| 34233 | Benzophenone oxime, 98% |
| A17532 | p-Benzoquinone dioxime, 95% |
| A14339 | 2,3-Butanedione monoxime, 99% |
| 40333 | 2-Butanone oxime, 99% |
| H51034 | (1R,E)-(+)-Camphorquinone 3-oxime, 99% |
| A16788 | 1,2-Cyclohexanedione dioxime, 97% |
| 11120 | Cyclohexanone oxime, 97% |
| A16672 | Cyclooctanone oxime, 98+% |
| B24961 | Cyclopentanone oxime, 97% |
| L00914 | Dibenzyl ketoxime, 98+% |
| A12810 | Dimethylglyoxime, 99% |
| 33310 | Dimethylglyoxime, ACS, 99+% |
| 40834 | Dimethylglyoxime, disodium salt octahydrate, 99% |
| 40893 | Diphenylglyoxime, 97% |
| L03950 | 9-Fluorenone oxime, 98+% |
| H52232 | Methyl 2-pyridyl ketoxime, 97% |
| 39028 | 2-Octanone oxime, 99% |
| L17073 | 1-Phenyl-1,2,3-butanetrione 2-oxime, 98+% |
| 20502 | 1-Phenyl-1,2-propanedione-2-oxime, 99% |
| 37344 | Phenyl 2-pyridyl ketoxime, 98% |
| 13179 | syn-2-Pyridinealdoxime, 99+% |
| 20740 | Salicylaldoxime, 98% |
| 13262 | Salicylhydroxamic acid, 99% |

| SKU | Description |
|---|---|
| | *Protonation agens* |
| 10994 | Acetic acid, glacial, 99.9985% (metals basis) |
| 14893 | Acetic acid, 99.8%, for biochemistry |
| 22214 | Acetic acid, 99.8%, for analysis |
| 33252 | Acetic acid, glacial, 99+% |
| 36289 | Acetic acid, glacial, ACS, 99.7+% |
| 38739 | Acetic acid, Environmental Grade Plus, 99.4% min |

| SKU | Description |
|---|---|
| | *Protonation agens* |
| 42322 | Acetic acid, 99.7+%, ACS reagent |
| 22213 | Acetic anhydride, 99+%, for analysis |
| 42323 | Acetic anhydride, 97+%, ACS reagent |
| L04295 | Acetic anhydride, 99+% |
| 10990 | Hydrochloric acid, 99.999999% (metals basis), 33% min |
| 12462 | Hydrochloric acid, pure, fuming, 37% solution in water |
| 12463 | Hydrochloric acid, for analysis, fuming, 37% solution in water |
| 33257 | Hydrochloric acid, ACS, HCl 36.5-38.0% |
| 42379 | Hydrochloric acid, ACS reagent, ca. 37% solution in water |
| 45055 | Hydrochloric acid, 37%, for analysis, (max. 0.000001% Hg) |
| 46396 | Hydrochloric acid, for biochemistry, approx. 37% solution in water |
| 87617 | Hydrochloric acid, 99.999% (metals basis), 36.5% min |
| L13091 | Hydrochloric acid, 36% w/w aq. Soln |
| 10989 | Hydrofluoric acid, 99.99% (metals basis) 40% min |
| 22333 | Hydrofluoric acid, for analysis, 48 to 51% solution in water |
| 33258 | Hydrofluoric acid, ACS, 48-51% |
| 38746 | Hydrofluoric acid, Environmental Grade Plus, 47-51% |
| 42380 | Hydrofluoric acid, ACS reagent, 48-51% solution in water |
| 18749 | Iodotrimethylsilane, 95-97%, stabilized |
| 42642 | Iodotrimethylsilane, 95-97%, stabilized, AcroSeal® |

| SKU | Description |
|---|---|
| | *Protonation agens* |
| A12902 | Iodotrimethylsilane, 97%, stab. with copper |
| 16946 | Phosphorus pentachloride, 98% |
| 10524 | Phosphorus(V) oxide, ACS, 98% min |
| 21575 | Phosphorus pentoxide, 99+%, for analysis |
| 31582 | Phosphorus pentoxide, 98+%, ACS reagent |
| 89966 | Phosphorus(V) oxide, 99.99% |
| A13348 | Phosphorus(V) oxide, 98% |
| 19695 | Polyphosphoric acid, pure, > 84% phosphate (as P2O5) |
| L14856 | Polyphosphoric acid, ca 84% (as phosphorus pentoxide) |
| 12464 | Sulfuric acid, for analysis, ca. 96% solution in water |
| 42452 | Sulfuric acid, ACS reagent, 95% solution in water |
| 33273 | Sulfuric acid, ACS, 95.0-98.0% |
| 41997 | Sulfuric acid, extra pure, fuming, 20-30% free SO3 |
| 38266 | Thionyl chloride, 99.7% |
| 13903 | p-Toluenesulfonyl chloride, 99+% |
| A14547 | p-Toluenesulfonyl chloride, 98% |
| 12391 | Triethylamine, 99+% |
| 43228 | Triethylamine, 99.5%, for analysis |
| 46081 | Triethylamine, for HPLC |
| A12646 | Triethylamine, 99% |

## Oxidation Reactions

Historically, the term oxidation referred to the addition of oxygen to a compound. This was because oxygen gas ($O_2$) was the first known oxidizing agent. However, while the addition of oxygen to a compound typically meets the modern criteria of oxidation (electron loss and an increase in oxidation state), the definition of oxidation has been expanded to include other types of chemical reactions that result in an increase in oxidation state.

One of the earliest named oxidation reactions is the Tishchenko reaction, which originated from work by L. Claisen in 1887 on the formation of benzyl benzoate from benzaldehyde in the presence of sodium alkoxides. Almost twenty years later, V.E. Tishchenko discovered that both enolizable and non-enolizable aldehydes can be converted to their corresponding esters in the presence of magnesium or aluminium alkoxides. This became known as the Tishchenko reaction.

Other oxidation reactions include:

- Dess–Martin oxidation
- Jones oxidation
- Oppenauer oxidation
- Rubottom oxidation
- Sharpless asymmetric epoxidation

### Dess–Martin Oxidation

During the 1980s hypervalent iodine reagents were developed as selective, mild and environmentally friendly oxidizing agents for organic synthesis. Perhaps the most important group of these reagents are periodinanes (derivatives of pentacoordinate iodine (V)), and the most well-known of these include the reagents 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP). Whilst IBX had been known since 1893, its insolubility in most organic solvents inhibited its use in organic synthesis. However, in 1983 D.B. Dess and J.C. Martin described the preparation of DMP, a far more soluble alternative. Since this discovery, DMP has become the reagent of choice for the oxidation of alcohols to their corresponding carbonyl compounds, and oxidations using DMP are known as Dess–Martin oxidations.

In the total synthesis of ustiloxin D, a highly potent inhibitor of microtubule assembly, M.M. Joullié and co-workers utilised DMP to convert a macrocyclic primary alcohol into its corresponding aldehyde.

## Jones Oxidation

In 1946 E.R.H. Jones and colleagues reported the synthesis of alkynyl ketones from their corresponding carbinols using chromic acid (chromic trioxide mixed with diluted sulfuric acid) without oxidizing their sensitive triple bond. Since then, the oxidation of primary and secondary alcohols with chromic acid have become known as the Jones oxidation. Chromic acid can be prepared by mixing chromium trioxide ($CrO_3$) or dichromate salts with either sulfuric or acetic acid. The oxidation is generally carried out using acetone as the solvent as it is a very good organic solvent and reacts with excess oxidant to prevent over oxidation of the substrate.

For highly acid-sensitive substrates, several milder chromium oxide-based reactions have been developed, including the Sarett and Collins oxidations. The Sarett oxidation uses pyridine as the solvent, while the Collins oxidation utilizes a complex of chromium (VI) oxide with pyridine in dichloromethane.

The Jones oxidation has been used in a number of successful total synthesis campaigns such as the first synthesis of the polyketide (-)-solanapyrone E and the alkaloid (-)-dendrobine.

## Oppenauer Oxidation

In 1937 R.V. Oppenauer used catalytic amounts of aluminium tert-butoxide to convert steroids with secondary alcohol functionality into their corresponding ketones. Oppenauer's method built on research conducted by other researchers such as H. Meerwein and A. Verley, who described the reduction of carbonyl compounds using aluminium alkoxides.

Oppenauer's method was high yielding and mild compared to other techniques. Today, the oxidation of primary and secondary alcohols to aldehydes and ketones in the presence of metal alkoxides is now known as the Oppenauer oxidation.

One unique feature of this oxidation is that secondary alcohols are oxidized much faster than primary alcohols, meaning complete chemoselectivity can be achieved.

The reverse reaction, the reduction of aldehydes and ketones to alcohols, is called the Meerwein–Ponndorf–Verley reaction.

The Oppenauer oxidation has been used in several total synthesis campaigns including the synthesis of lycopodium alkaloids such as lycodoline.

## Rubottom Oxidation

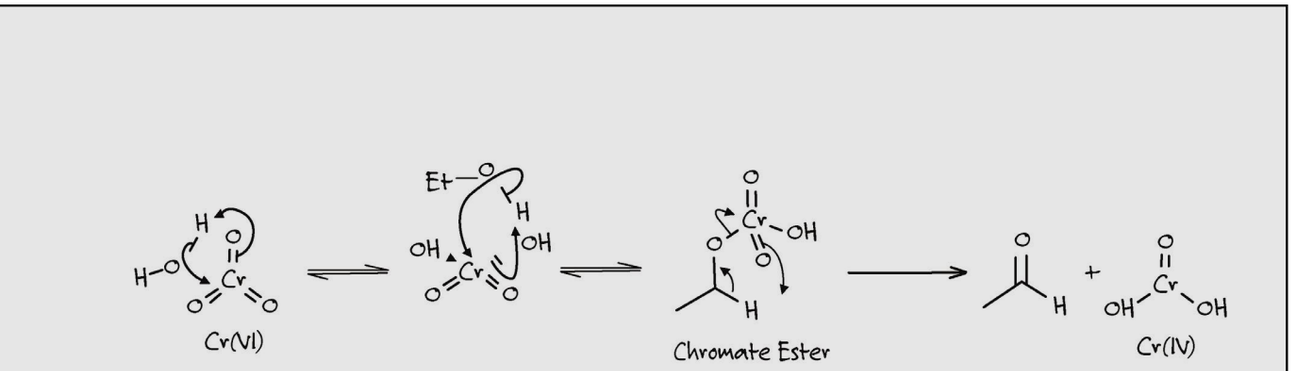
In 1974 G.M. Rubottom, A.G. Brook and A. Hassner independently created a method to prepare alpha-hydroxy aldehydes and ketones through the oxidation of their silyl enol ethers using meta-chloro peroxy benzoic acid (mCPBA). Today the peroxyacid oxidation of silyl enol ether substrates to prepare the corresponding alpha-hydroxy carbonyl compounds is known as the Rubottom oxidation. Synthesis of the potent anti-thrombotic (+/-) rishirilide B utilized the Rubottom oxidation, as did the synthesis of the antitumour antibiotic FR901464.

## Sharpless Asymmetric Epoxidation

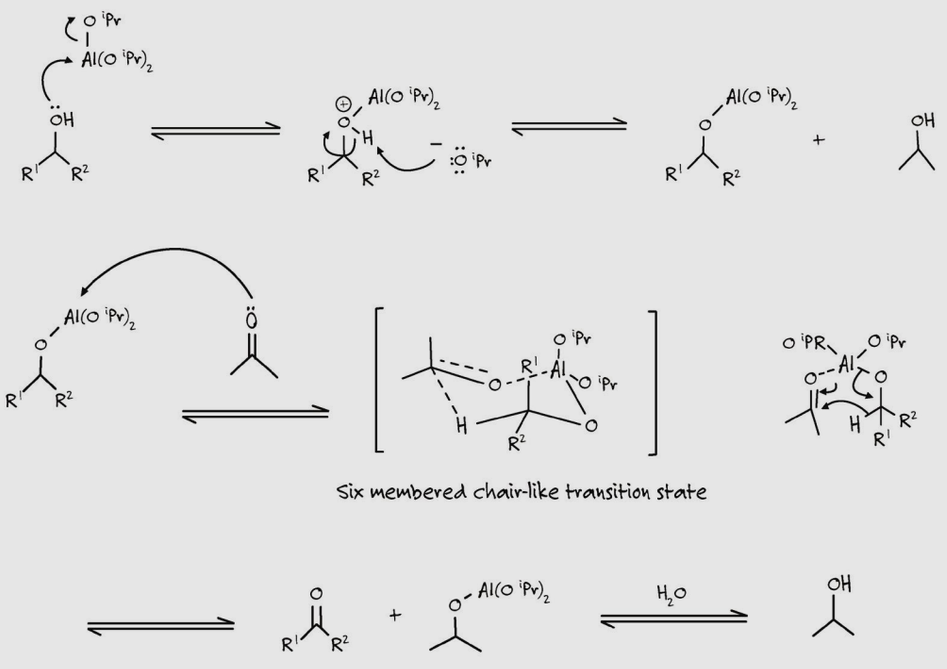
In 1980 K.B. Sharpless and T. Katsuki discovered that the combination of titanium (IV) tetraisopropoxide, optically active diethyl tartrate and tert-butyl hydroperoxide caused a wide variety of allylic alcohols to epoxidize in high yields. Henceforth the titanium (IV) alkoxide-catalyzed epoxidation of prochiral and chiral allylic alcohols in the presence of a chiral tartrate ester and an alkyl hydroperoxide to provide enantiopure 2,3-epoxy alcohols is known as the sharpless asymmetric epoxidation (SAE).

Only allylic alcohols are good substrates for this method as the presence of a hydroxyl group is essential. The addition of catalytic amounts of molecular sieves allows for the use of only catalytic amounts of the titanium–tartrate complex, whereas without the molecular sieves a full equivalent of the complex is required.

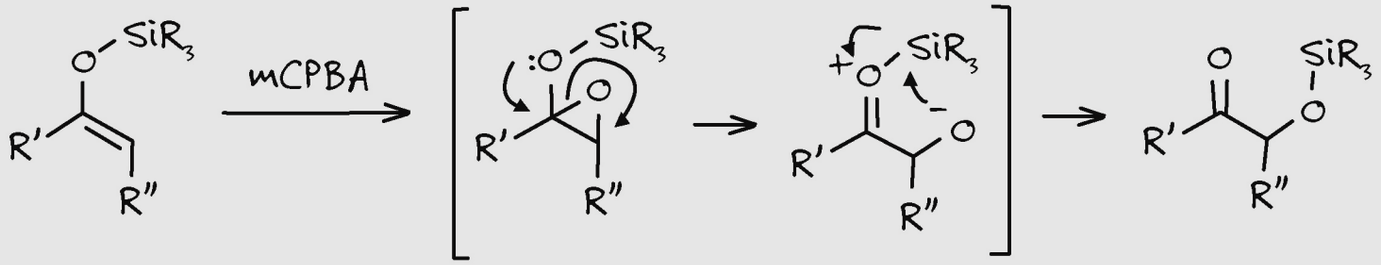
# Reaction Mechanism Examples



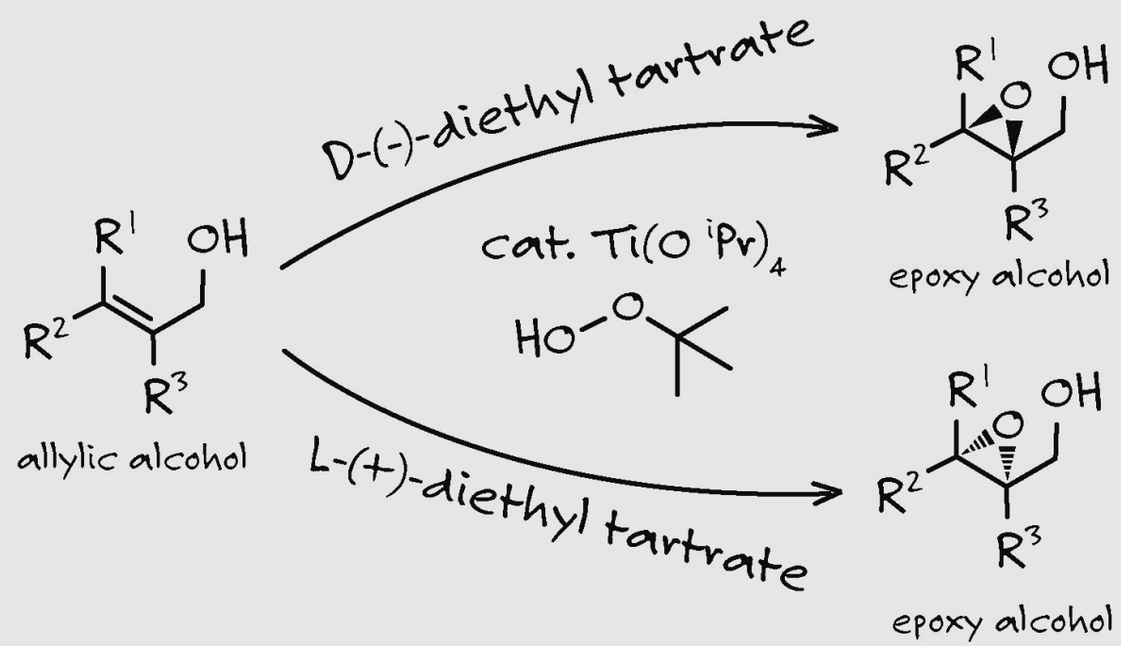

Jones Oxidation




Oppenauer Oxidation




Rubottom Oxidation

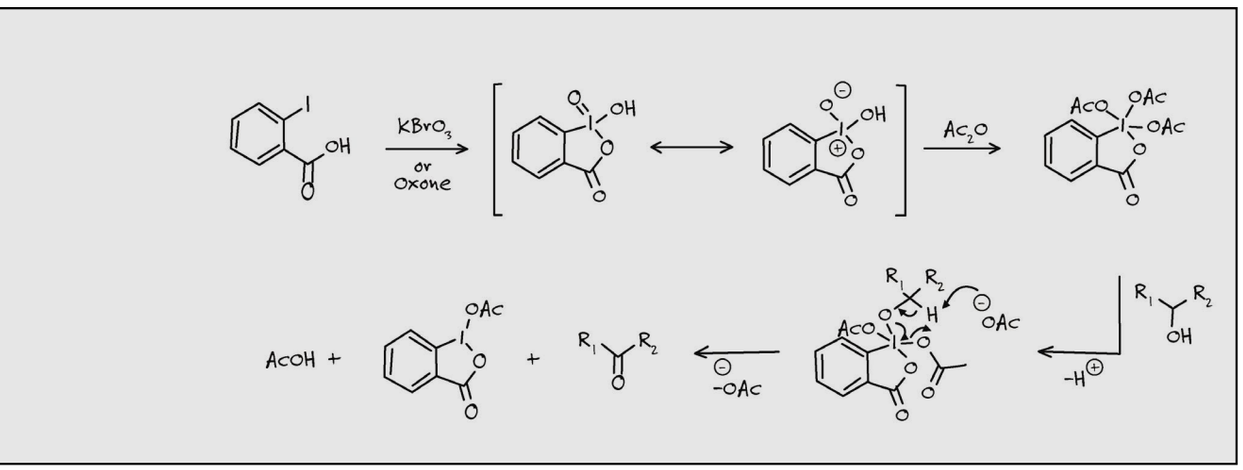



Sharpless Asymmetric Epoxidation

# Dess-Martin Reaction

The Dess-Martin reaction, discovered in 1983, is an oxidation of primary or secondary alcohols with triacetoxyperiodinane (DMP) to synthetize aldehydes or ketones, respectively. DMP is obtained by the reaction of 2-iodobenzoic acid with $KBrO_3$ in $H_2SO_4$ to give the hydroxyiodinane oxide followed by treatment with a mixture of acetic anhydride and acetic acid at 100°C for 40 min.1 The reaction could be also performed in oxone ($2KHSO_5$-$KHSO_4$-$K_2SO_4$) to replace $KBrO_3$ and $H_2SO_4$ and to reduce the safety risk.[2] Researchers studied how to facilitate the acetylation and, in 1993, Ireland found that a high yield of Dess Martin periodinane can be achieved by adding a catalytic amount of TsOH to replace HOAc in the second step.[3]

The oxidation of alcohols with DMP is then performed in dichloromethane at room temperature.  In the mechanism, the iodine, bonded to 4 electronegative oxygen atoms, acts as an electrophile and can be attacked by a lone pair of the alcohol oxygen giving an acetate as leaving group. This one deprotonates the alcohol oxygen positively charged, and, in basic conditions, the final product is generated. Meyer et al. discovered in 1994 that the oxidation is accelerated when DMP is exposed to the atmosphere rather than under inert conditions.[4]




A rate increase was also observed when an extra equivalent of alcohol was added to DMP. The rate of dissociation of the remaining acetate ligand increases thanks to the electron-donating ability of the alkoxy substituent. A similar effect was obtained by adding 1 equivalent of water to obtain an intermediate with hydroxy group in place of alkoxy group.

One of the applications of the Dess-Martin reaction is the synthesis of N-protected α-amino aldehydes, which are intermediates in the pharmaceutical and fine chemical industries.[5]

*Reference reaction protocols*

*Synthesis of N-Fmoc phenylglycinal*

DMP was added to a solution of N-Fmoc-(S)-phenylglycinol in water-saturated dichloromethane. The mixed reaction was stirred at 23°C and water-saturated dichloromethane was added. After 25 min, the solution was diluted with ether and sodium thiosulfate in 80% saturated aqueous sodium bicarbonate solution was added. After extraction with ether and work up with saturated aqueous sodium bicarbonate solution, water and brine, N-Fmoc phenylglycinal is obtained as a white solid.[5]

## Key literature references


1. *Dess, D. B.; Martin, J. C,  J. Org. Chem. 1983, 48, 22, 4155–4156*
2. *Frigerio M; Santagostino M; Sputore S., J. Org. Chem., Vol. 64, No. 12, 1999*
3. *Ireland, R. E.; Liu, L. J. Org. Chem. 1993, 58, 2899.*
4. *Meyer, S. D.; Schreiber, S. L. J. Org. Chem. 1994, 59, 7549-7552*
5. *Myers A. G.;  Zhong B.; Movassaghi M.; Kung D. W.;  Lanman B. A. and Kwon S., Tetrahedron Lett.  41, 2000, 1359–1362*

# Product Selection

Safety: o-iodylbenzoic acid is explosive on heating above 200°C; the Dess–Martin reagent explodes violently on heating under confinement, at 130°C. Make sure you are aware of the hazards of the materials, read SDS and wear appropriate personal protective equipment before starting a reaction. Always work in properly ventilated areas.

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| 18005 | 1-Adamantanemethanol, 99% |
| 16703 | Adonitol, 98% |
| H52304 | (S)-(-)-2-Amino-3-benzyloxy-1-propanol, 98+% |
| B25212 | (R)-(-)-2-Amino-1-butanol, 98% |
| L11449 | (S)-(+)-2-Amino-1-butanol, 98+% |
| B24398 | (±)-2-Amino-1-butanol, 97% |
| A12680 | 4-Amino-1-butanol, 98% |
| 45743 | 3-Amino-2,2-dimethyl-1-propanol, 97% |
| L14157 | 6-Amino-1-hexanol, 97% |
| 29753 | (1R,2S)-(+)-cis-1-Amino-2-indanol, 98% |
| 31565 | (1S,2R)-(-)-cis-1-Amino-2-indanol, 99% |
| 10406 | 2-Amino-2-methyl-1-propanol, 99% |
| L11030 | (R)-(-)-2-Amino-1-propanol, 98% |
| B24916 | (S)-(+)-2-Amino-1-propanol, 98% |
| B23041 | 3-Amino-1-propanol, 99% |
| 45991 | 1,5-Anhydro-D-sorbitol, 97% |
| 30287 | D-Arabitol, 99% |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| 22586 | L(-)-Arabitol, 99% |
| 39688 | Benzyl alcohol, 98+%, Extra Dry, AcroSeal® |
| 44700 | Benzyl alcohol, specified according to requirements of Ph.Eur. |
| H50328 | (R)-(-)-2-Benzylamino-1-butanol, 99% |
| 25484 | (+)-2,3-O-Benzylidene-D-threitol, 98% |
| H26006 | 2-Benzyloxy-2-methyl-1-propanol, 95% |
| 34872 | (3R,4R)-(-)-1-Benzyl-3,4-pyrrolidindiol, 97% |
| 34873 | (3S,4S)-(+)-1-Benzyl-3,4-pyrrolidindiol, 97% |
| L17649 | 5-(Boc-amino)-1-pentanol, 96% |
| NP45209 | 1-BOC-azetidine-3-methanol, 96% |
| 36827 | N-BOC-4-Hydroxypiperidine, 97% |
| H26650 | 1-Boc-4-piperidinemethanol, 97% |
| H32786 | (±)-1-Boc-pyrrolidine-2-methanol, 98% |
| B21483 | 10-Bromo-1-decanol, 95% |
| H54762 | 7-Bromo-1-heptanol, 96% |
| B21803 | 6-Bromo-1-hexanol, 96% |
| H61393 | 9-Bromo-1-nonanol, 98% |
| H27628 | 8-Bromo-1-octanol, 95% |
| H61118 | 3-(4-Bromophenyl)-1-propanol, 98% |
| 34970 | 3-Bromo-1-propanol, 97% |
| L14448 | 11-Bromoundecanol, 97% |
| 10762 | (±)-1,3-Butanediol, 99%, extra pure |
| 24773 | (2S,3S)-(+)-2,3-Butanediol, 99% |
| 39896 | 1-Butanol, 99+%, Extra Dry, AcroSeal® |
| 42349 | 1-Butanol, 99.5%, ACS reagent, meets the requirements of Reag.Ph.Eur. |
| 22029 | sec-Butanol, 99+%, for analysis |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| L00767 | 3-Buten-1-ol, 98+% |
| 15433 | 2-Butoxyethanol, 99%, extra pure |
| H55285 | 4-tert-Butyldimethylsiloxy-1-butanol, 97% |
| A15709 | 2-Butyn-1-ol, 98% |
| A11477 | 3-Butyn-1-ol, 98% |
| 32774 | CAPSO, 99% |
| 37100 | (2R,3S)-1-Carboxy-4-pentyl-2,3-dihydroxycyclohexa-4,6-diene potassium salt, 85%, tech. |
| 35631 | 4-Chloro-1-butanol, 85%, balance THF and HCl |
| 10928 | 1-Chloro-6-hydroxyhexane, 95% |
| A14582 | 6-Chloro-1-hexanol, 97% |
| 10929 | 1-Chloro-3-hydroxypropane, 98%, stabilized |
| A16871 | 3-Chloro-1-propanol, 98%, stab. |
| H28417 | 8-Chloro-1-octanol, 98% |
| L12088 | 5-Chloro-1-pentanol, 95% |
| H31465 | 3-(1,4-Cyclohexadien-1-yl)-1-propanol, 97% |
| 30097 | cis-1,2-Cyclohexanediol, 99% |
| 16165 | trans-1,2-Cyclohexanediol, 98% |
| 11113 | 1,2-Cyclohexanediol, 98%, mixture of cis and trans |
| 31029 | cis-1,2-Cyclopentanediol, 98% |
| 18549 | 1,3-Cyclopentanediol, 95%, mixture of cis and trans |
| A15989 | trans,trans-2,4-Decadien-1-ol, 90%, remainder mainly trans, cis isomer |
| L11768 | trans-5-Decen-1-ol, 96% |
| 15264 | 9-Decen-1-ol, 99% |
| A17288 | 1-Decanol, 98+% |
| H53400 | 5-Decyn-1-ol, 97% |
| L05523 | 2-Decyn-1-ol, 97% |
| 35372 | 1-Deoxy-1-nitro-L-iditol hemihydrate, 99% |
| L13916 | (S)-(+)-2-Dibenzylamino-3-phenyl-1-propanol, 99% |
| A18444 | 2,3-Dichloro-1-propanol, 97+% |
| H53501 | 4,4-Diethylamino-2-butyn-1-ol, 98% |
| 39333 | 1,2:5,6-Di-O-isopropylidene-D-mannitol, 97% |
| H30194 | 3,3-Dimethyl-1-butanol, 97% |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| 11712 | Dipentaerythritol, 85+%, technical |
| H53374 | 1,3-Diphenyl-2-propyn-1-ol, tech. 90% |
| 17166 | Dithioerythritol, 99+% |
| 16568 | DL-1,4-Dithiothreitol, 99%, for biochemistry |
| 32719 | DL-1,4-Dithiothreitol, 99+%, for molecular biology, DNAse, RNAse and Protease free |
| 42638 | DL-1,4-Dithiothreitol, for biochemistry, 1M solution in water |
| B20144 | 1H,1H,7H-Dodecafluoro-1-heptanol, 97% |
| A12228 | 1-Dodecanol, 98% |
| 11770 | Dulcitol, 99+% |
| 21546 | 1-Eicosanol, 98% |
| 11782 | meso-Erythritol, 99% |
| 39769 | Ethanol, 99.5%, Extra Dry, absolute, AcroSeal® |
| 44844 | Ethanol, 99.8%, as ethanol,anhydrous,(denat. with 2% IPA + 2% MEK) |
| 22409 | Ethanol, for spectroscopy, anhydrous, denat. with 5% 2-Propanol + 5% Methanol |
| 27066 | Ethanol, 99.7%, pure, anhydrous, denat. with 3% v/v diethyl ether |
| 36578 | Ethanol, 95+%, pure, denat. with 5% wood spirit |
| 44576 | 2-Ethoxyethanol, for analysis |
| 11789 | 2(2-Ethoxyethoxy)ethanol, 98+% |
| 25905 | 1-Ethoxy-2-propanol, 95% |
| B21026 | 2-Ethyl-1-butanol, 99% |
| 29553 | Ethylene glycol, 99.5%, for analysis |
| 43381 | Ethylene glycol, 99.8%, anhydrous, AcroSeal® |
| A17104 | 2-Ethyl-1-hexanol, 99% |
| A10414 | 2,2,3,3,4,4,4-Heptafluoro-1-butanol, 98% |
| A12793 | 1-Heptanol, 99% |
| A19172 | cis-3-Hepten-1-ol, 97% |
| H61509 | 6-Heptyn-1-ol, 95% |
| A14959 | 2-Heptyn-1-ol, 97% |
| B20884 | 3-Heptyn-1-ol, 98% |
| A11180 | 1-Hexadecanol, 98% |
| B20587 | 2,2,3,4,4,4-Hexafluoro-1-butanol, 95% |
| 29341 | 1,1,1,3,3,3-Hexafluoro-2-propanol, 99.9%, for spectroscopy |
| 35486 | 1,1,1,3,3,3-Hexafluoro-2-propanol, 99.8%, for peptide synthesis |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| A13734 | cis-2-Hexen-1-ol, 94%, remainder mainly trans isomer |
| A13272 | trans-2-Hexen-1-ol, 97% |
| A10313 | cis-3-Hexen-1-ol, 98% |
| L10541 | trans-3-Hexen-1-ol, 97% |
| H54459 | 4-Hexen-1-ol, predominantly trans, 97% |
| A19266 | cis-4-Hexen-1-ol, 97% |
| A15766 | 5-Hexen-1-ol, 98% |
| A18232 | 1-Hexanol, 99% |
| A13339 | 2-Hexyn-1-ol, 97% |
| 36708 | 3-Hydroxypiperidine, 98% |
| 36651 | 4-Hydroxypiperidine, 99+% |
| 12226 | Inositol, 98+% |
| 32696 | Isopropanol, 99.8%, Extra Dry, AcroSeal® |
| 32727 | Isopropanol, 99.5%, for molecular biology, DNAse, RNAse and Protease free |
| 32793 | Isopropanol, 99.8%, for electronic use (MOS), residue free |
| 39698 | Isopropanol, 99+%, specified according to the requirements of Ph.Eur. |
| 42383 | Isopropanol, 99.6%, ACS reagent, meets the requirements of Reag.Ph.Eur. |
| 44708 | Isopropanol, 99%, for biochemistry and histology, AcroSeal® |
| 29580 | Maltitol, 95% |
| 42392 | D-Mannitol, ACS reagent |
| B21965 | 3-Mercapto-1-hexanol, 96% |
| 12479 | Methanol, 99.9%, for biochemistry, AcroSeal® |
| 32574 | Methanol, 99.9%, for HPLC gradient grade |
| 32663 | Methanol, 99.8%, for residue analysis, ECD tested for pesticide analysis |
| 32695 | Methanol, 99.9%, Extra Dry, AcroSeal® |
| 32790 | Methanol, 99.8%, for electronic use (MOS), residue free |
| 42395 | Methanol, >=99.8%, ACS reagent, meets the requirements of Reag.Ph.Eur. |
| H50339 | 4-Methoxy-1-butanol, 98+% |
| 14936 | 2-Methoxyethanol, 99.5+%, for analysis |
| 42878 | 2-Methoxyethanol, for HPLC |
| 24499 | 1-Methoxy-2-propanol, 98.5%, extra pure |
| 33178 | (R)-(-)-1-Methoxy-2-propanol, 98+% |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| 33179 | (S)-(+)-1-Methoxy-2-propanol, 99% |
| H58818 | 3-Methylamino-1-propanol, 95% |
| 15827 | DL-2-Methyl-1-butanol, 98% |
| B21825 | (^+)-2-Methyl-1-butanol, 98% |
| 41272 | 3-Methyl-1-butanol, 99%, for biochemistry, AcroSeal® |
| 41273 | 3-Methyl-1-butanol, ACS reagent |
| 17192 | 3-Methyl-2-buten-1-ol, 99% |
| H64006 | 1-Methyl-2-imidazolemethanol, 98% |
| 25975 | 3-Methyl-3-methoxybutanol, 99% |
| L15953 | 3-Methoxy-3-methyl-1-butanol, 98+% |
| 33532 | 3-Methyl-1-pentanol, 99+% |
| 14938 | 4-Methyl-2-pentanol, 99+% |
| B20729 | 2-Methyl-1-phenyl-1-propanol, 98% |
| B22187 | 1-Methylpiperidine-2-methanol, 98% |
| 16770 | 2-Methyl-1-propanol, 99+%, spectrophotometric grade |
| 39895 | 2-Methyl-1-propanol, 99+%, Extra Dry, AcroSeal® |
| 41265 | 2-Methyl-1-propanol, 99+%, ACS reagent |
| H60502 | 2-Methyl-2-propen-1-ol, 98%. |
| A10403 | 3-Methylthio-1-propanol, 98% |
| H60376 | 3-(4-Morpholinyl)-1-propanol, 95% |
| L01347 | 1-Naphthalenemethanol, 98+% |
| H27218 | 2-(1-Naphthyl)ethanol, 95% |
| L19968 | 1-(4-Nitrophenyl)glycerol, 99% |
| A12510 | 1-Nonanol, 99% |
| A17846 | cis-3-Nonen-1-ol, 97% |
| A18842 | cis-2-Nonen-1-ol, 95% |
| L08387 | cis-6-Nonen-1-ol, 95% |
| L06380 | 2-Nonyn-1-ol, 96% |
| A12020 | 1-Octadecanol, 97% |
| B20108 | 2,2,3,3,4,4,5,5-Octafluoro-1-pentanol, 98% |
| 22018 | 1-Octanol, ACS reagent |
| 43458 | 1-Octanol, 99%, anhydrous, AcroSeal® |
| A19014 | cis-3-Octen-1-ol, 95% |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| A15960 | trans-2-Octen-1-ol, 97% |
| L05596 | 2-Octyn-1-ol, 98% |
| L05414 | 3-Octyn-1-ol, 96% |
| L03673 | 1-Pentadecanol, 99% |
| 12987 | Pentaerythritol, 98% |
| A11846 | 2,2,3,3,3-Pentafluoro-1-propanol, 98% |
| 30086 | 1,2,2,6,6-Pentamethyl-4-piperidinol, 99% |
| 16060 | 1-Pentanol, 99%, pure |
| A14262 | cis-2-Penten-1-ol, 97%, remainder mainly trans-isomer |
| 15001 | 4-Penten-1-ol, 99% |
| A12999 | 2-Pentyn-1-ol, 98% |
| 19733 | 3-Pentyn-1-ol, 99% |
| A10405 | 4-Pentyn-1-ol, 97% |
| L16580 | 1H,1H-Perfluoro-1-decanol, 98% |
| B21407 | 1H,1H,9H-Perfluoro-1-nonanol, 97% |
| L16609 | 1H,1H-Perfluoro-1-tetradecanol, 96% |
| 35188 | DL-sec-Phenethyl alcohol, 97% |
| A13837 | (±)-1-Phenylethanol, 97% |
| A13433 | 4-Phenyl-1-butanol, 97% |
| 13059 | 1-Phenyl-1,2-ethanediol, 97% |
| L04551 | (±)-1-Phenyl-1,2-ethanediol, 97% |
| L12533 | 7-Phenyl-1-heptanol, 97% |
| 18247 | 5-Phenyl-1-pentanol, 98% |
| L13999 | (R)-(+)-2-Phenyl-1-propanol, 98+% |
| L13988 | (S)-(-)-2-Phenyl-1-propanol, 98+% |
| A13022 | 3-Phenyl-1-propanol, 99% |
| 39276 | (±)-1-Phenyl-2-propyn-1-ol, 98+% |
| L09549 | 1-Phenyl-2-propyn-1-ol, 98% |
| 27003 | 3-Phenyl-2-propyn-1-ol, 98% |
| 22087 | 1,2-Propanediol, 99+%, for analysis |
| 44741 | 1,2-Propanediol, ACS reagent |
| 39694 | 1-Propanol, 99.5%, Extra Dry, AcroSeal® |
| 43436 | 1-Propanol, for spectroscopy ACS |

| SKU | Description |
|---|---|
| | *Primary and secondary alcohols* |
| 41840 | 2-Propoxyethanol, 98%, pure |
| 20732 | DL-Propranolol hydrochloride, 99% |
| H50340 | 2-n-Propyl-1-heptanol, 98% |
| 34457 | (R)-(+)-3-Pyrrolidinol, 98% |
| 33943 | (S)-(-)-3-Pyrrolidinol, 98+% |
| 13273 | D-Sorbitol, 97% |
| 18073 | 1-Tetradecanol, 99% |
| 29638 | 2,2,3,3-Tetrafluoro-1-propanol, 99+% |
| 13959 | Triethylene glycol, 99% |
| B21460 | 4,4,4-Trifluoro-1-butanol, 97% |
| 13975 | 2,2,2-Trifluoroethanol, 99.8%, extra pure |
| L16879 | 3,3,3-Trifluoro-1-propanol, 97% |
| H53376 | 4-Trimethylsilyl-3-butyn-1-ol, 98% |
| L04251 | 1-Trimethylsilylmethanol, 95% |
| H53457 | 5-Trimethylsilyl-4-pentyn-1-ol, 97% |
| A14002 | 10-Undecen-1-ol, 99% |
| 22598 | Xylitol, 99+% |

| SKU | Description |
|---|---|
| | *Dess-Martin reagents* |
| L15779 | Dess-Martin periodinane |
| 33311 | Dess-Martin periodinane, 15 wt.% solution in dichloromethane |
| 42900 | Dess-Martin periodinane, 15 wt.% solution in dichloromethane, AcroSeal® |
| 37465 | 2-Iodoxybenzoic acid, stabilized |

# Reduction Reactions

Historically, chemical transformations involving a gain of hydrogen, or a loss of oxygen, were termed “reduction reactions.”

The modern chemical definition of reduction is when a compound gains one or more electrons. It is therefore the opposite of oxidation, where a compound loses one or more electrons.

One of the earliest named reactions featuring reduction is the Tishchenko reaction, named after the Russian organic chemist Vyacheslav Evgen’evich Tishchenko. This reaction is still industrially relevant today as it is used to convert acetaldehyde into the commercially important solvent ethyl acetate.

Other rearrangement reactions include:

- Clemmensen reduction
- Luche reduction
- Meerwein–Ponndorf–Verley reduction
- Staudinger reaction
- Wolff–Kishner reduction

## Clemmensen Reduction

In 1913, the Danish chemist Erik Christian Clemmensen reported that simple ketones and aldehydes reacted with amalgamated zinc (Zn/Hg) in the presence of 40% aqueous hydrochloric acid and in a hydrophobic solvent such as toluene to give the corresponding alkanes after several hours under reflux conditions. Ever since, this method of converting carbonyl groups to the corresponding methylene group has been known as the Clemmensen reduction.

The Clemmensen reduction’s original harsh conditions are not conducive to acid sensitive substrates, so several modifications have been made to increase its synthetic utility by expanding the functional group tolerance. Yamamura and his colleagues developed a milder procedure using organic solvents such as tetrahydrofuran saturated with hydrogen halides such as hydrogen chloride or bromide in the presence of activated zinc dust at ice-bath temperatures. Some carbonyl compounds exhibit poor solubility in the usual solvents, and thus a second solvent such as acetic acid, ethanol, or dioxane is added to increase solubility and facilitate the reaction.

Many heterocyclic 1,3-dicarbonyl compounds possessing alkyl substituents at the electronegative “2” position exhibit interesting biological properties. Synthesis of many of these molecules was expedited by Thomas Kappe and co-workers using a version of the Clemmensen reduction.

**Click here for a more in-depth look at the Clemmensen Reduction**

## Luche Reduction

In 1978, the French chemist Jean Louis Luche reported that using a mixture of lanthanide chlorides and sodium borohydride, alpha beta-unsaturated ketones could be selectively converted to allylic alcohols. It was later determined that a mixture of cerium chloride and sodium borohydride gave the best results. Conversion of enones into the corresponding allylic alcohols by this method became known as the Luche reduction.

This discovery was significant as the reduction of unsaturated carbonyl compounds usually gave a mixture of 1,2- and 1,4- reduction products, while Luche's method provided the 1,2- reduction product exclusively and in good yield. Reactions are conducted at or below room temperature and without the requirement for drying or an inert atmosphere, allowing for the presence of many functional groups. These conditions also provide for the chemoselective reduction of ketones in the presence of aldehydes, as the aldehydes undergo rapid acetalization which prevents their reduction.

The Luche reduction has been utilized in several important total synthesis campaigns, including those of several amaryllidaceae alkaloids such as narciclasine in the laboratory of Tomas Hudlicky.

## Meerwein–Ponndorf–Verley Reduction

In the 1920s, three researchers working independently carried out the reduction of carbonyl compounds using aluminium alkoxides. In 1925 Hans Meerwein successfully reduced aldehydes with ethanol in the presence of aluminium ethoxide, and in the same year Albert Verley reduced ketones using both aluminium ethoxide and isopropoxide. Then in 1926, Wolfgang Ponndorf realized the reduction of both aldehydes and ketones using a variety of metal alkoxides and that this was also generally reversible. Subsequently, the reduction of aldehydes and ketones using metal alkoxides such as aluminium isopropoxide became known as the Meerwein–Ponndorf–Verley reduction (or MPV for short). The reverse reaction, where alcohols are oxidized to aldehydes and ketones, is known as the Oppenauer oxidation.

As the reaction is completely reversible, removal of the lower boiling ketone or addition of excess isopropyl alcohol is required to shift the equilibrium to the right. However, the reaction is very chemoselective for aldehydes and ketones, and other functional groups such as esters and acetals are not changed. This is the great advantage of this reaction versus the use of metal hydride reducing agents.

This highly selective reduction has been used in a myriad of synthesis projects, including that of the furochromone ammiol, and in the determination of the stereochemistry of rutamycin antibiotics through the asymmetric synthesis of the known bicyclic degradation product.

## Staudinger Reaction

In 1919, Hermann Staudinger and Jules Meyer published the reaction

between phenyl azide and triphenylphosphine to generate phosphinimine. It was also found that benzoyl azide reacted in a similar fashion to generate the corresponding benzoyl aza-ylide. Staudinger and Meyer also reacted carbon dioxide with phenyl-aza-ylide to afford phenyl isocyanate and triphenylphosphine oxide, which was the first example of an aza-Wittig reaction. Subsequently the reaction of organic azides with trivalent phosphorus compounds such as triphenylphosphine to generate the corresponding aza-ylides is known as the Staudinger reaction.

The reaction is extremely fast and high-yielding and does not form side products. The iminophosphorane products derived from alkyl or aryl azides reacted with trialkyl- and triarylphosphines are stable and versatile intermediates (e.g., hydrolysis with water gives primary amines). The reaction has been used in the synthesis of a number of natural products including the marine indole alkaloid (+)-hamacanthin B and the antiviral product (–)-hennooxazole A.

## Wolff–Kishner Reduction

In 1911, Nikolai Kishner added a hydrazone dropwise to a mixture of hot potassium hydroxide and a platinized porous plate, forming hydrocarbon. A year later, Ludwig Wolff demonstrated that heating an ethanolic solution of semicarbazones and hydrazones in a sealed tube at approximately 180°C in the presence of sodium ethoxide gave the same result. The deoxygenation of aldehydes and ketones to their corresponding hydrocarbons is now called the Wolff–Kishner reduction.

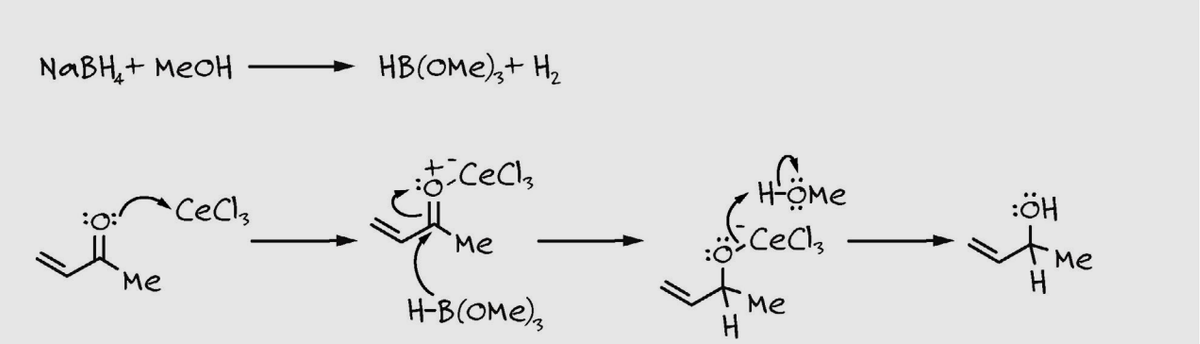
Since the original experiments, the procedure has undergone substantial modifications to allow the use of milder reaction conditions to expand the number of substrates and increase yields. For many years, the standard methodology involved mixing the carbonyl compound with neat hydrazine in a high-boiling solvent such as ethylene glycol in the presence of excess base such as sodium ethoxide. However, the reaction often required refluxing for several days due to the temperature-lowering effects of the water produced as a by-product of hydrazine formation.

The Huang–Minion modification involved removing the water and excess hydrazine via distillation, allowing the reaction temperature to increase once the hydrazine formation was complete. This dramatically shortened the reaction time to just a few hours and allowed the use of the less expensive reagent hydrazine hydrate, along with water soluble bases such as sodium hydroxide.

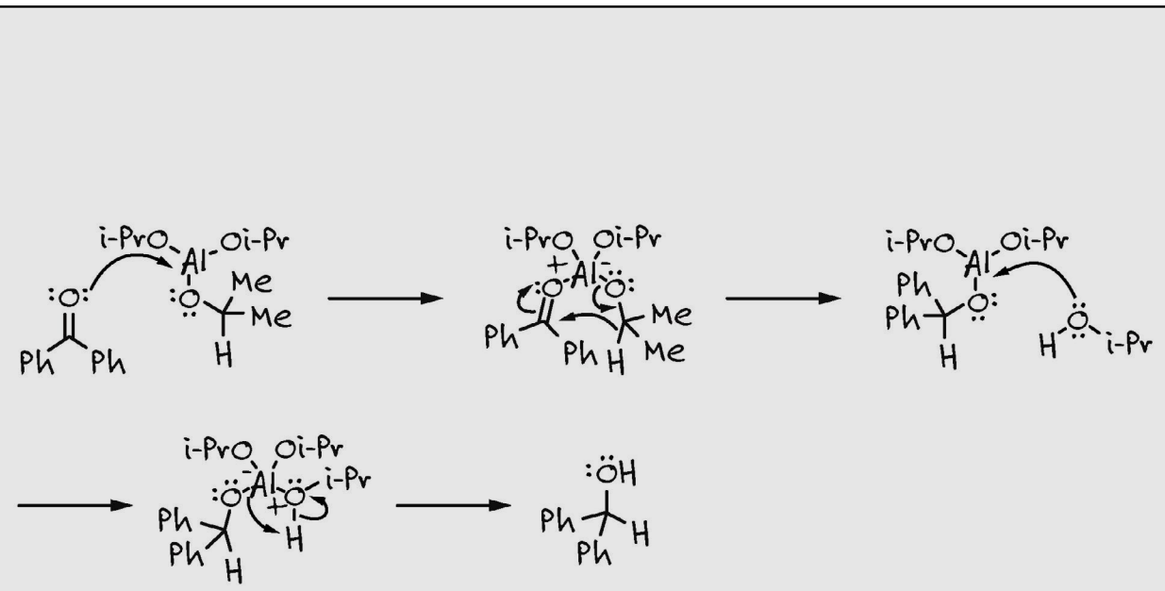
In another modified procedure, known as the Caglioti reaction, tosylhydrazones are used with hydride reagents to obtain the corresponding alkynes.

The total synthesis of dysidiolide, the first compound found to be a natural inhibitor of protein phosphatase cdc25A (essential for cell proliferation), utilized the Wolff–Kishner reduction in the production of an advanced bicyclic intermediate.

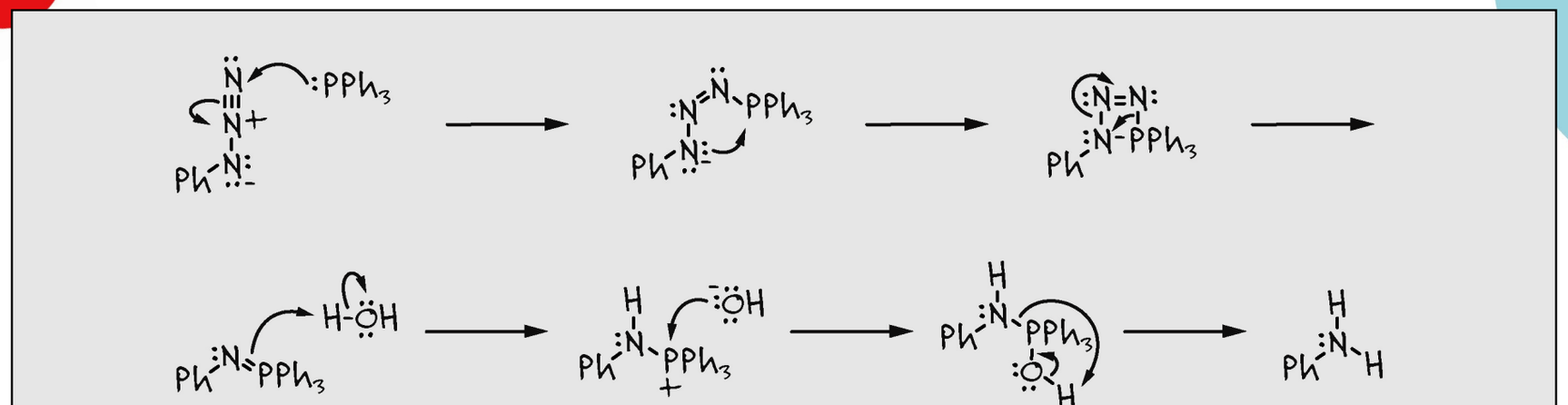
## Reaction Mechanism Examples



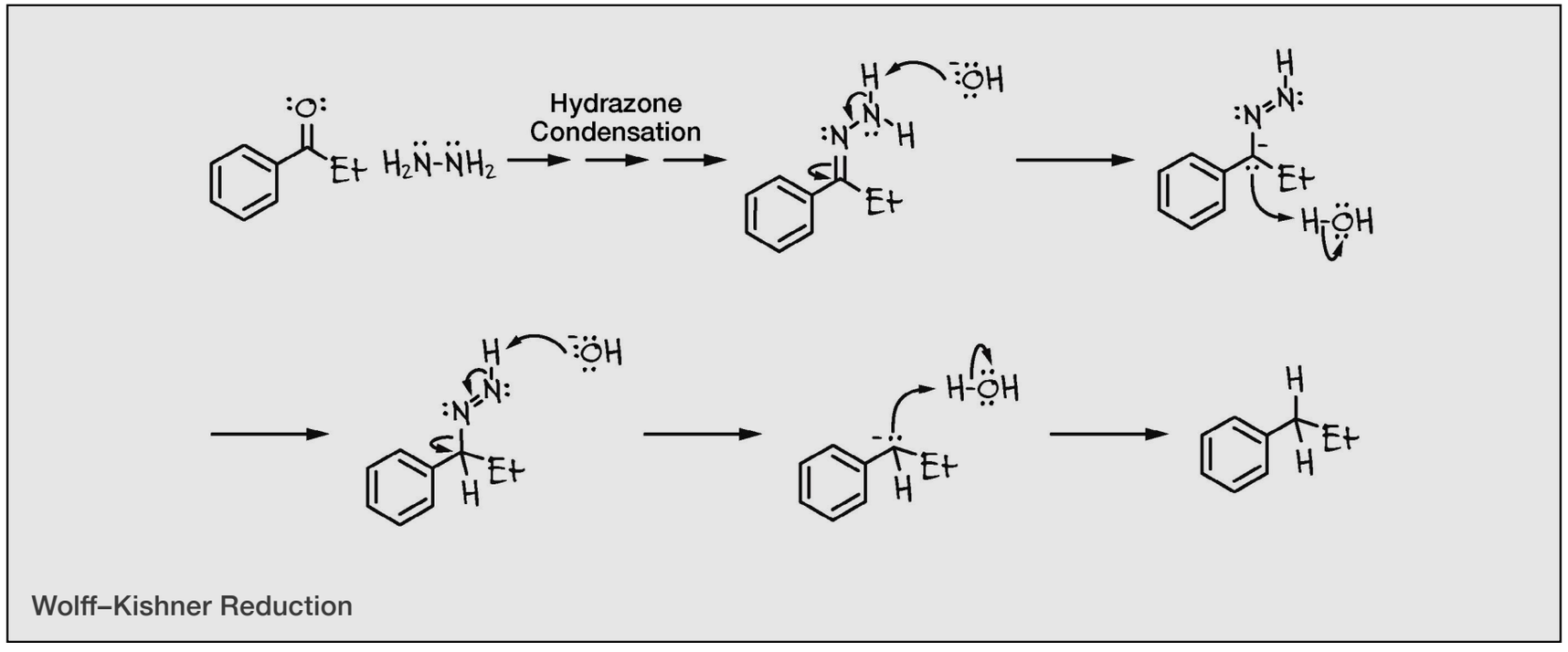

Luche Reduction




Meerwein–Ponndorf–Verley Reduction



Staudinger Reaction




Wolff–Kishner Reduction

# Clemmensen Reduction

Aldehydes and ketones can be converted in the corresponding hydrocarbons in presence of amalgamated zinc, used as reduction reagent, and concentrated hydrochloric acid. This reaction is known as Clemmensen reduction (Figure 1) since its discovery in 1913.[1]

One of the suggested mechanisms can be summarized in a sequence of one electron and one proton transfer. Firstly, an electron is transferred from zinc to the carbonyl group, a zinc carbenoid species is obtained and the oxygen is completely removed from the substrate. Protons are then added and the double bond is cleaved to form the methylene product.[2]

This remains a hypothesis, as the mechanism is still not completely experimentally proven. The consensus is that the alcohol is excluded as intermediate, since it was observed that it cannot be reduced by the Clemmensen reagent.

An alternative mechanism suggested an α-hydroxyalkylzinc chloride as an intermediate. A recent article proposed both a “carboanion” and a “carbene” as intermediates.[3] In this case, the proton transfer is the first step followed the reaction with zinc.

The Clemmensen reaction can be used for several applications: to obtain, for example, aromatics with unbranched hydrocarbon chains. After a Friedel Crafts reaction, it could be used to reduce the carbonyl group and to avoid side products due to a possible rearrangement (Figure 3).

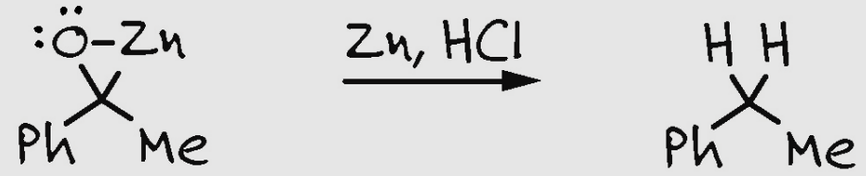



Figure 1. Clemmensen Reaction

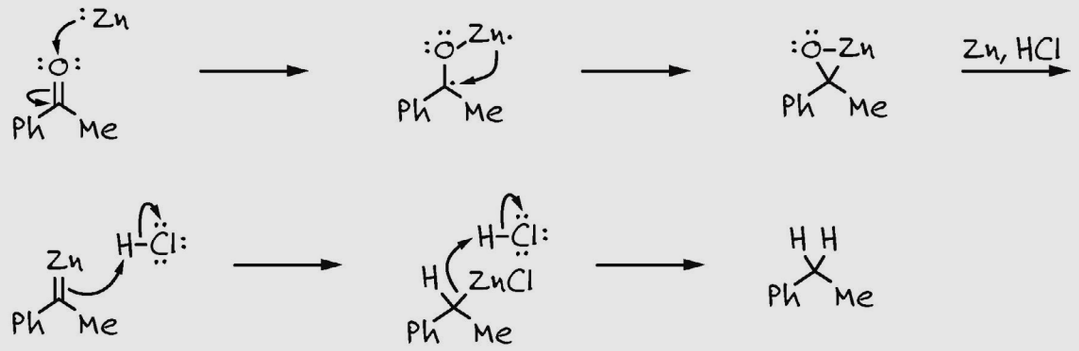



Figure 2. Mechanism of Reaction

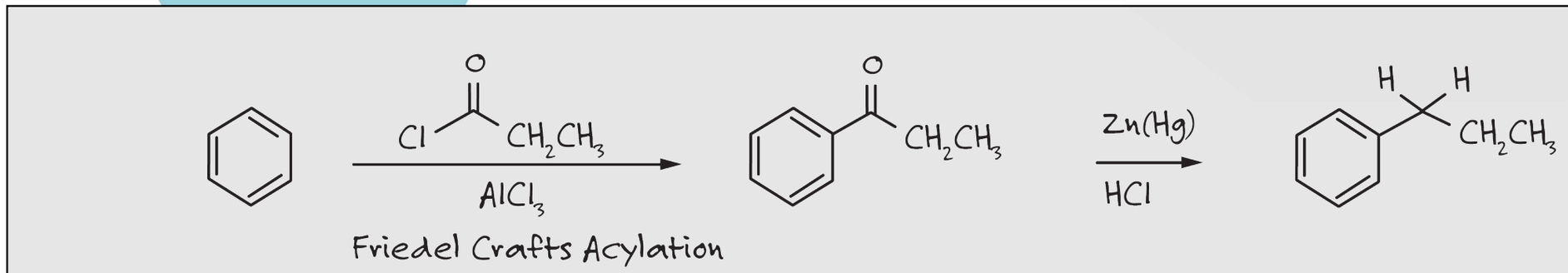



Figure 3. Reduction after Friedel Crafts reaction

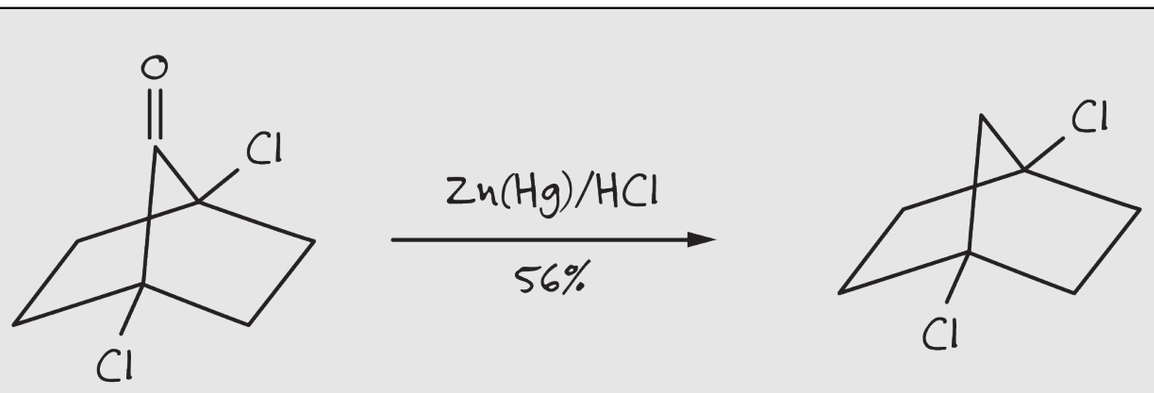



Figure 4. Synthesis of 1,4-dichloronorbonane

Other applications are known, such as the reduction of cyclic ketones, olefinic and carbonyl groups in α,β-unsaturated ketones or carbonyl group in keto acid compounds (carboxylic groups don't react in Clemmensen conditions).

*Reference reaction protocol*[4]

## Synthesis of 1,4-dichloronorbonane

0.10 mol of 1,4-dichloro-7-ketonorbornane in 40 mL of a 3:1 benzene-ethanol solution was added to a mixture of 50 g of zinc amalgam in 30 mL of absolute ethanol and 60 mL of concentrated hydrochloric acid. Five 15-mL portions of concentrated hydrochloric acid were added at the mixture refluxed for 48 h. After the work-up followed by pentane recrystallization at -20°C, 1,4-dichloronorbonane was obtained with a yield of 56%.

## Key literature references


1. *E. Clemmensen Ber. Dtsch. Chem. Ges. 1913, 46, 1837–843.*
2. *J. Burdon; R. C. Price J. Chem. Soc., Chem. Commun. 1986, 893–894.*
3. *F. Sánchez-Viesca*; M. Berros; R. Gómez American Journal of Chemistry 2018, 8(1), 8-12*
4. *A. P. Marchand; W. R. Jr. Weimer J. Org. Chem. 1969, 34, 1109-1112*

# Product Selection

Safety: Make sure you are aware of the hazards of the materials, read SDS and wear appropriate personal protective equipment before starting a reaction. Always work in properly ventilated areas.

| SKU | Description |
|---|---|
| | *Aldehydes* |
| A11987 | 4-Ethoxybenzaldehyde, 97+% |
| B20430 | 4-Acetamidobenzaldehyde, 98% |
| 10480 | p-Anisaldehyde, 99+% |
| A10348 | Benzaldehyde, 99+% |
| H26122 | Benzothiazole-2-carboxaldehyde, 98% |
| 10626 | 4-Biphenylcarboxaldehyde, 99% |
| B20978 | 2,4-Bis(trifluoromethyl)benzaldehyde, 97% |
| A15065 | 2-Bromobenzaldehyde, 98% |
| A11941 | 3-Bromobenzaldehyde, 97% |
| A14237 | 4-Bromobenzaldehyde, 98+% |
| H26109 | 2-Bromo-5-(trifluoromethyl)benzaldehyde, 97% |
| H26986 | 4-Bromo-2-(trifluoromethyl)benzaldehyde, 95% |
| H26256 | 4-Fluoro-3-(trifluoromethoxy)benzaldehyde, 97% |
| A15243 | 4-n-Butoxybenzaldehyde, 98% |
| A15524 | 2-(tert-Butylthio)benzaldehyde, 96% |
| A11201 | 2-Carboxybenzaldehyde, 98+% |
| B21277 | 3-Carboxybenzaldehyde, 97% |

| SKU | Description |
|---|---|
| | *Aldehydes* |
| A15277 | 4-Carboxybenzaldehyde, 98% |
| 10861 | 3-Chlorobenzaldehyde, 99% |
| H26383 | 3-Chloro-2,4-difluorobenzaldehyde, 97% |
| H26444 | 6-Chloro-2-fluoro-3-methoxybenzaldehyde, 97% |
| B22979 | 2-Chloro-6-fluoro-3-methylbenzaldehyde, 97% |
| H26023 | 2-Chloro-6-methylbenzaldehyde, 98% |
| 10960 | 4-Chloro-3-nitrobenzaldehyde, 97% |
| A12852 | 2-(4-Chlorophenylthio)benzaldehyde, 98% |
| H31584 | 5-Chloro-2-(trifluoromethoxy)benzaldehyde, 97% |
| 11035 | trans-Cinnamaldehyde, 99% |
| H29027 | 2-Cyanobenzaldehyde, 98% |
| A14914 | 4-Cyanobenzaldehyde, 98+% |
| 11264 | 3,4-Dibenzyloxybenzaldehyde, 99% |
| H31689 | 2,5-Dibromobenzaldehyde, 97% |
| A13325 | 3,5-Dichlorobenzaldehyde, 97% |
| A13295 | 2,6-Dichlorobenzaldehyde, 97+% |
| H26497 | 2,6-Dichloro-4-(trifluoromethoxy)benzaldehyde, 97% |
| A11825 | 4-Diethylaminobenzaldehyde, 97% |
| H26447 | 2,2-Difluoro-1,3-benzodioxole-4-carboxaldehyde, 97% |
| H26139 | 3,5-Difluoro-4-hydroxybenzaldehyde, 97% |
| A15565 | 2,5-Dihydroxybenzaldehyde, 98+% |
| A11558 | 3,4-Dihydroxybenzaldehyde, 98% |
| A14080 | 2,3-Dimethoxybenzaldehyde, 98+% |
| A12549 | 2,4-Dimethoxybenzaldehyde, 98% |
| A19928 | 2,5-Dimethoxybenzaldehyde, 98+% |
| A11712 | 4-Dimethylaminobenzaldehyde, 98% |

| SKU | Description |
|---|---|
| | *Aldehydes* |
| 11579 | 4-Dimethylaminocinnamaldehyde, 98% |
| B23598 | 4-Dimethylamino-2-methoxybenzaldehyde, 98% |
| A15388 | 3,4-Dimethylbenzaldehyde, 97% |
| A11987 | 4-Ethoxybenzaldehyde, 97+% |
| A15035 | 2-Ethoxybenzaldehyde, 97+% |
| B24762 | 3-Ethoxy-4-methoxybenzaldehyde, 99% |
| A19478 | 3-Ethoxy-4-hydroxybenzaldehyde, 98% |
| B20645 | 4-Ethylbenzaldehyde, 97% |
| A13800 | 2-Fluorobenzaldehyde, 97% |
| 11933 | 3-Fluorobenzaldehyde, 98+% |
| H26729 | 2-Fluoro-3-methoxybenzaldehyde, 97% |
| A18904 | 2-Fluoro-5-methoxybenzaldehyde, 97% |
| B23738 | 2-Fluoro-3-(trifluoromethyl)benzaldehyde, 97% |
| A13287 | 4-n-Hexyloxybenzaldehyde, 98% |
| A13541 | 3-Hydroxybenzaldehyde, 97% |
| A13580 | 4-Hydroxybenzaldehyde, 98% |
| A15753 | 2-Hydroxy-5-methoxybenzaldehyde, 98% |
| A12971 | 2-Hydroxy-4-methoxybenzaldehyde, 98% |
| A10264 | 2-Hydroxy-5-nitrobenzaldehyde, 98% |
| A14019 | 4-Isopropylbenzaldehyde, tech. 90% |
| A15364 | 4-Methoxybenzaldehyde, 98% |
| A13962 | 3-Methoxybenzaldehyde, 98% |
| H26123 | 4-Methoxy-2-(trifluoromethyl)benzaldehyde, 98% |
| H26797 | 2-Methoxy-4-(trifluoromethyl)benzaldehyde, 97% |
| A13594 | 3-Nitrobenzaldehyde, 99% |
| A11501 | 2-Nitrobenzaldehyde, 98+% |
| A11655 | 4-Nitrobenzaldehyde, 99% |
| B22329 | 4-Phenoxybenzaldehyde, 98% |
| B20319 | 2,3,6-Trifluorobenzaldehyde, 97% |
| B20340 | 2,3,5-Trifluorobenzaldehyde, 97% |
| B20943 | 3,4,5-Trifluorobenzaldehyde, 98% |
| B24591 | 2-(Trifluoromethyl)benzaldehyde, 98% |
| A19270 | 3,4,5-Trihydroxybenzaldehyde hydrate, 97% |
| B22792 | 2,4,5-Trimethoxybenzaldehyde, 98% |

| SKU | Description |
|---|---|
| | *Zinc* |
| 000424 | Zinc powder, -100 mesh, 99.9% (metals basis) |
| 000648 | Zinc wire, 0.25mm (0.01in) dia, 99.99+% (metals basis) |
| 010435 | Zinc wire, 3.18mm (0.125in) dia, 99.95% (metals basis) |
| 010440 | Zinc shot, 10mm (0.4in) dia x 2mm (0.08in) thick, 99.99% (metals basis) |
| 010759 | Zinc shot, 1-5mm (0.04-0.2in), 99.999% (metals basis) |
| 010760 | Zinc shot, 1-6mm (0.04-0.24in), Puratronic\|r, 99.9999% (metals basis) |
| 010835 | Zinc powder, average 4-7 micron, 97.5% (metals basis) |
| 011361 | Zinc wire, 1.0mm (0.04in) dia, 99.9997% (metals basis) |
| 012054 | Zinc wire, 0.5mm (0.02in) dia, Puratronic\|r, 99.994% (metals basis) |
| 013256 | Zinc single crystal, 15mm (0.59in) dia, 50mm (2.0in) long, random orientation |
| 013294 | Zinc single crystal, 15mm (0.59in) dia, 50mm (2.0in) long, (0001) orientation, ^+2° |
| 013556 | Zinc single crystal disc, 10mm (0.39in) dia, 2-3mm (0.08-0.1in) thick, (0001) orientation, ^+0.5° |
| 013789 | Zinc flake, -325 mesh, 99.9% (metals basis) |
| 014629 | Zinc mossy, 2.5cm (0.98in) & down, 99% (metals basis) |
| 036602 | Zinc granules, ACS, -20 mesh, 99.8% min |
| 039694 | Zinc powder, -140+325 mesh, 99.9% (metals basis) |
| 041655 | Zinc sputtering target, 50.8mm (2.0in) dia x 3.18mm (0.125in) thick, 99.99% (metals basis) |
| 041657 | Zinc sputtering target, 76.2mm (3.0in) dia x 3.18mm (0.125in) thick, 99.99% (metals basis) |
| 041658 | Zinc sputtering target, 76.2mm (3.0in) dia x 6.35mm (0.250in) thick, 99.99% (metals basis) |
| 042637 | Zinc wire, 2.0mm (0.08in) dia, Puratronic\|r, 99.999% (metals basis) |
| 042704 | Zinc wire, 0.5mm (0.02in) dia, 99.95% (metals basis) |
| 042705 | Zinc wire, 1.0mm (0.04in) dia, 99.95% (metals basis) |
| 042706 | Zinc wire, 2.0mm (0.08in) dia, 99.95% (metals basis) |
| 19450 | Zinc, 99.995%, (trace metal basis), powder |
| 19834 | Zinc, 98+%, dust (stable acc. to UN classification class 4) |
| 20145 | Zinc, 99+%, mossy |
| 22260 | Zinc, granular, 20 mesh |
| 22261 | Zinc, granular, 30 mesh |
| 36726 | Zinc, 99.999%, (trace metal basis), powder, 40 mesh |
| 46373 | Zinc, 10 w/v% suspension in THF |
| L13310 | Zinc powder, -100 mesh, 97+% |

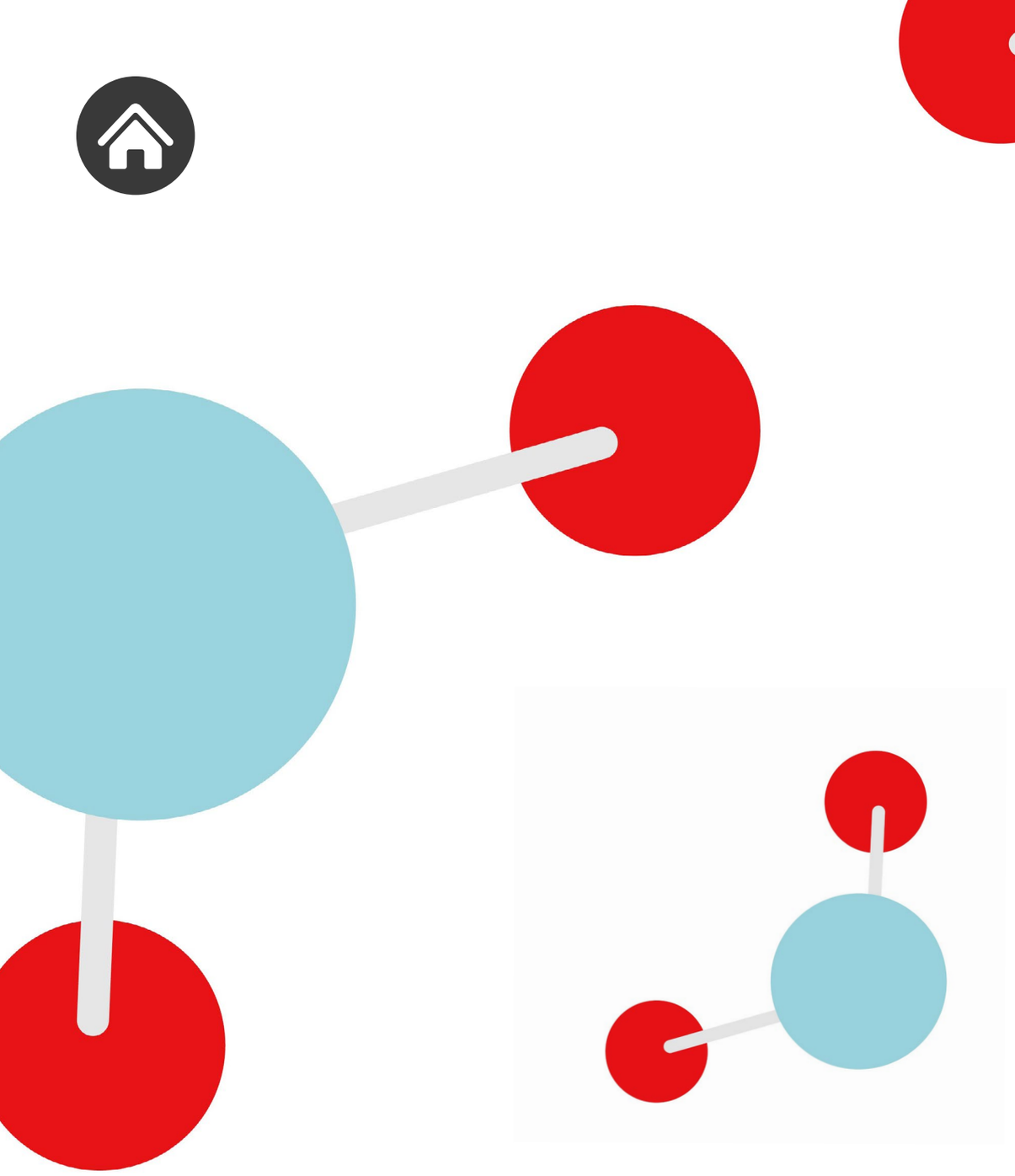
| SKU | Description |
|---|---|
| | *Mercury* |
| 000522 | Mercury, ACS, 99.999% (metals basis) |
| 010242 | Mercury, Electronic Grade, 99.9998% (metals basis) |
| 013625 | Mercury(II) iodide, ultra dry, 99.999% (metals basis) |
| 014497 | Mercury(II) nitrate hydrate, ACS, 98.0% min |
| 036286 | Mercury(II) sulfate, ACS, 98.0% min |
| 036419 | Mercury(I) chloride, ACS, 99.5% min |
| 037106 | Mercury(II) thiocyanate |
| 044816 | Mercury(II) bromide, ACS |
| 087240 | Mercury(I) chloride, 99.5% |
| 19049 | Mercury(II) bromide, 99+% |
| 19348 | Mercury, 99.999%, (trace metal basis) |
| 19350 | Mercury(II) iodide, ACS reagent, red |
| 19689 | Mercury(II) thiocyanate, 99+% |
| 20143 | Mercury(II) chloride, 99.5% |
| 21313 | Mercury(I) nitrate dihydrate, 98%, for analysis |
| 21314 | Mercury(II) nitrate monohydrate, 98+% |
| 38992 | Mercury(I) sulfate, 97% |
| 41365 | Mercury(II) sulfate, ACS reagent |
| 42393 | Mercury(II) chloride, 99.5+%, ACS reagent |
| 42394 | Mercury(II) nitrate monohydrate, ACS reagent |
| 44718 | Mercury(I) nitrate dihydrate, ACS reagent, 9th edition |
| 44759 | Mercury(I) chloride, ACS reagent |
| A11075 | Mercury, redistilled, 99.9+% |
| 20574 | Mercury(II) iodide, red, 99+% |

| SKU | Description |
|---|---|
| | *HCl* |
| 010990 | Hydrochloric acid, 99.999999% (metals basis), 33% min |
| 033257 | Hydrochloric acid, ACS, HCl 36.5-38.0% |
| 035607 | Hydrochloric acid, 50% v/v aq. soln. |
| 038743 | Hydrochloric acid, Environmental Grade, 34-37.5% |
| 087617 | Hydrochloric acid, 99.999% (metals basis), 36.5% min |
| 12463 | Hydrochloric acid, for analysis, fuming, 37% solution in water |
| 38930 | Hydrochloric acid, for analysis, ca. 32% solution in water |
| 42379 | Hydrochloric acid, ACS reagent, ca. 37% solution in water |
| 45055 | Hydrochloric acid, 37%, for analysis, (max. 0.000001% Hg) |
| 46396 | Hydrochloric acid, for biochemistry, approx. 37% solution in water |
| L13091 | Hydrochloric acid, 36% w/w aq. soln. |

| SKU | Description |
|---|---|
| | *Ketone* |
| 10316 | 2-Aminobenzophenone, 98% |
| 10317 | 4-Aminobenzophenone, 98% |
| 10334 | 2-Amino-5-chlorobenzophenone, 98% |
| 10556 | Benzophenone, 99%, pure |
| 10557 | Benzophenone hydrazone, 98+% |
| 10569 | 1-Benzoylacetone, 98% |
| 10658 | 3'-Bromoacetophenone, 97% |
| 10659 | 4'-Bromoacetophenone, 98% |
| 10672 | 4-Bromobenzophenone, 97% |
| 10685 | 4'-Bromo-4-chlorobutyrophenone, 97% |
| 10854 | 4'-Chloroacetophenone, 98+% |
| 10923 | 4-Chloro-4'-fluorobutyrophenone, 97% |
| L02218 | Cyclopropyl phenyl ketone, 97% |
| 11268 | 2,4'-Dibromoacetophenone, 98% |
| 11480 | 2',4'-Dihydroxyacetophenone, 98% |
| 11481 | 2',5'-Dihydroxyacetophenone, 97% |
| 11482 | 2',6'-Dihydroxyacetophenone, 99% |
| 11492 | 4,4'-Dihydroxybenzophenone, 97% |
| 11534 | 2',5'-Dimethoxyacetophenone, 99% |

| SKU | Description |
|---|---|
| | *Diethyl ether* |
| 016767 | Diethyl ether, anhydrous, ACS, 99% min, stab. with BHT |
| 32686 | Diethyl ether, 99.5%, Extra Dry, stabilized, AcroSeal® |
| 36433 | Diethyl ether, 99.5%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal® |

| SKU | Description |
|---|---|
| | *THF* |
| 041820 | Tetrahydrofuran, anhydrous, 99.8+%, unstab., packaged under Argon in resealable ChemSeal bottles |
| 044608 | Tetrahydrofuran, anhydrous, 99.8+%, stab. with 0.025% BHT, packaged under Argon in resealable ChemSeal bottles |
| 047122 | Tetrahydrofuran, anhydrous, 99.8+%, BHT-free, over molecular sieves, packaged under Argon in resealable ChemSeal bottles |
| 34845 | Tetrahydrofuran, 99.5%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal® |



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