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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

ELECTROPHILIC ADDITION REACTIONS

FREE RADICAL REACTIONS

HETEROCYCLE FORMATION

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 its 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 (i.e., Kumada cross-coupling), improvements in functional group tolerance were sought. The answer turned out to be 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-catalyzed 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 stereo-selectivity, few side reactions, and limited toxicity, all of which support a wide range of applications.

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 disadvantage of toxicity of the tin compounds, the Stille reaction has developed into one of the most important reactions in organic synthesis. Its success is primarily driven by the ability of the tin precursors to tolerate a wide variety of functional groups while 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 its discovery, 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 coworkers 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 catalytic cycle of this cross-coupling reaction includes a sequence of oxidative addition, transmetalation, and finally the reductive elimination step. The reaction starts with the *oxidative addition* of the electrophile (Figure 1.1) to the zero valent metal Pd(0) to form Pd(II).

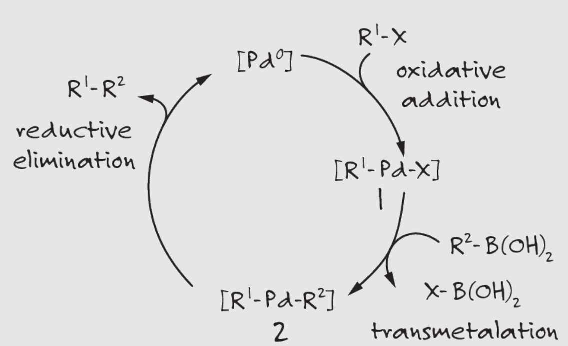


Figure 1.1 Catalytic cycle for the Suzuki–Miyaura reaction

In the *transmetalation*, the organoborane compound reacts with intermediate 1 to obtain the intermediate 2. The weak nucleophilic character of boron-bonded organic groups makes this step difficult, but it can be accelerated by using simple bases like sodium hydroxide, and sodium carbonate.

In the *reductive elimination* process, the formation of the C-C bond occurs and the oxidation state on the metal is restored to 0 to continue the catalytic cycle.

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 affordable. 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, despite their lower reactivity, can be considered with the use of late generation catalysts.

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, and even beneficial, to screen many different catalysts for air stability and easier handling by bench chemists. This applies to Pd(0) complexes such as Pd acetate and Pd tetrakis, as well as various forms of Pd precatalysts + phosphine ligand and fully formed (pre)catalysts.

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.

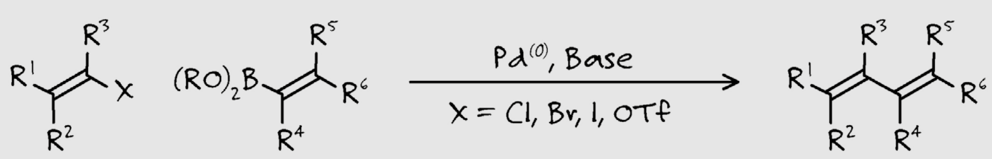


Figure 1.2. Generalized example of the Suzuki reaction

Reference Reaction Protocols

Weigh 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.

Suzuki Reaction Examples

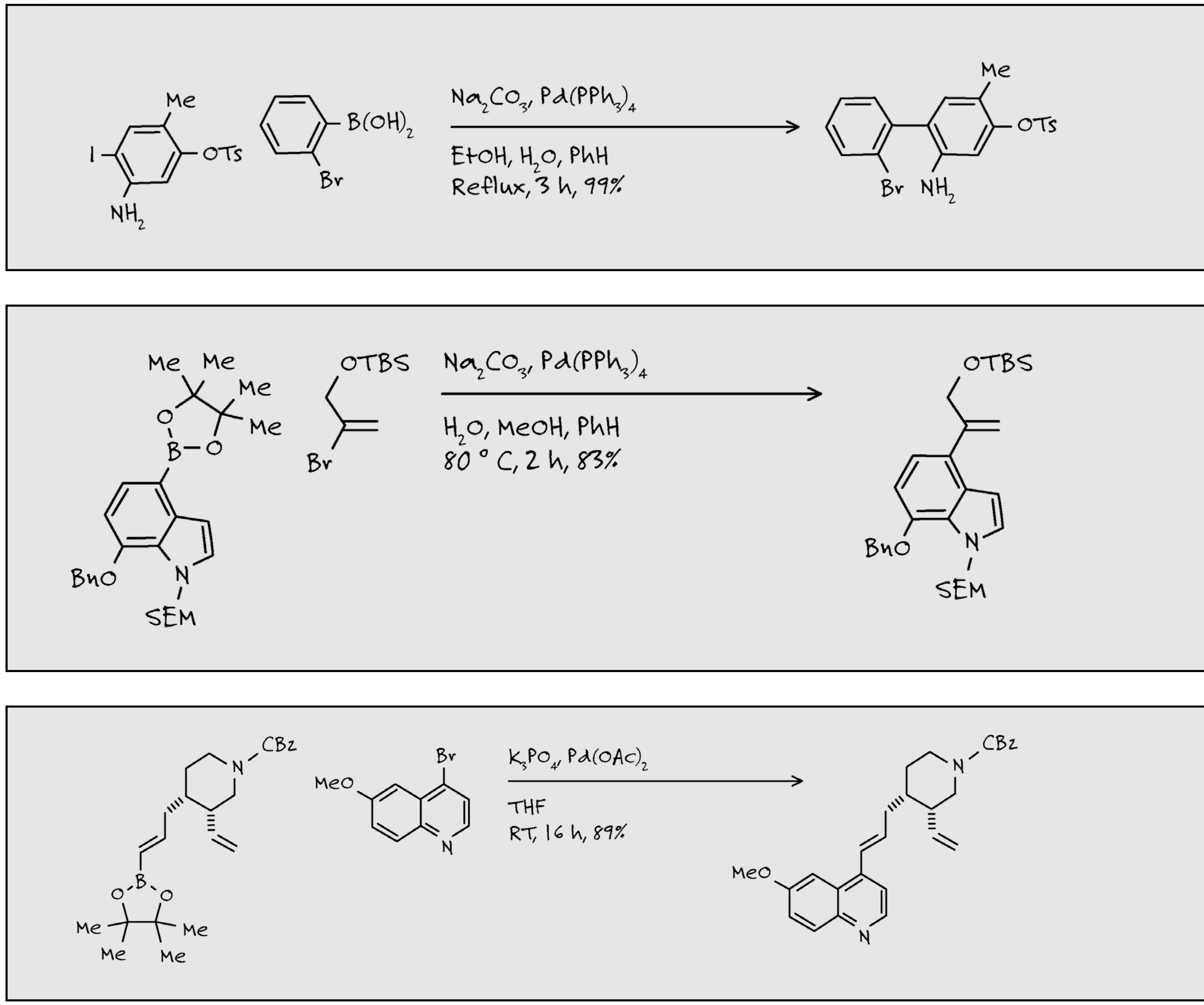
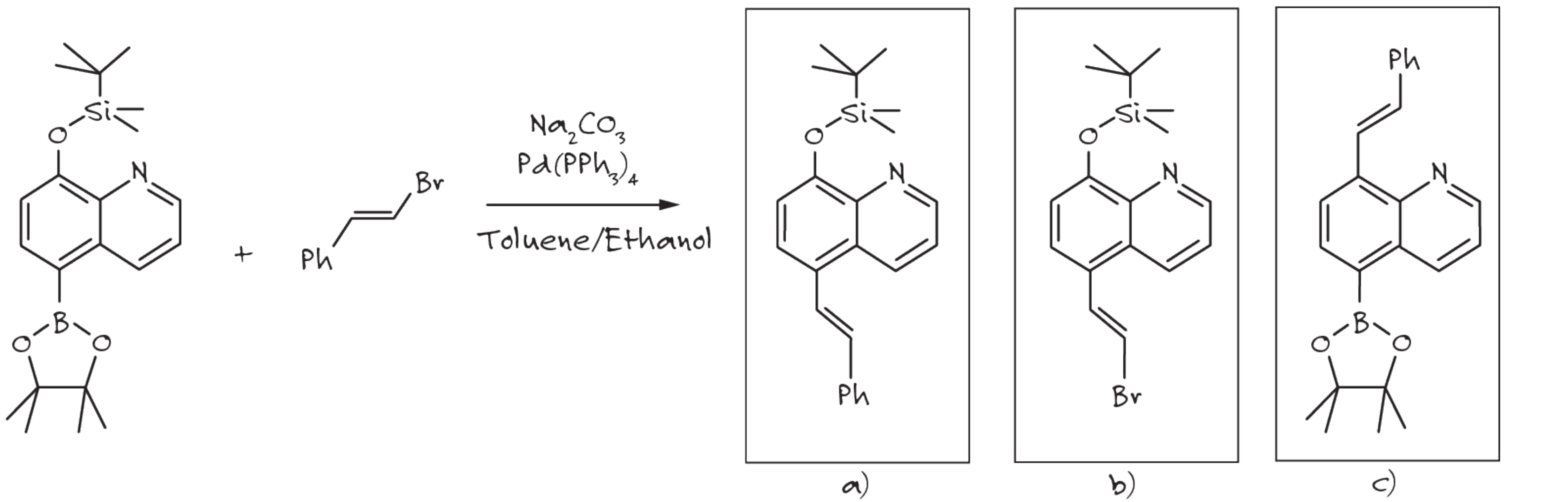


Figure 1.3. Specific examples of the Suzuki reaction

TEST YOUR KNOWLEDGE — SUZUKI REACTION

Identify the correct final product(s) produced in the cross coupling reaction below.



Product Selection for Suzuki Reaction

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.

Stock Number	Description
	Solvents
18150	Tetrahydrofuran, 99.9%, extra pure, anhydrous, stabilized with BHT
10769	1-Butanol, 99%, extra pure
B23091	Isobutanol, 99%
A18232	1-Hexanol, 99%
16662	2-Methyl-2-butanol, 99%, pure, Thermo Scientific™
A10924	N,N-Dimethylacetamide, 99%
39079	Xylenes, extra pure, mixture of isomers
A12986	1,2-Dimethoxyethane, 99+%, stab. with BHT
40882	1,4-Dioxane, 99+%, ACS reagent, stabilized, Thermo Scientific™
16424	1,4-Dioxane, 99+%, ACS reagent, stabilized, Thermo Scientific™
	Solvents Used for Downstream/Extraction
42368	Ethyl acetate, 99.6%, ACS reagent
40692	Dichloromethane, 99.6%, ACS reagent, stabilized with amylene, Thermo Scientific™
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
	Basic Ingredients/Additives
42368	Ethyl acetate, 99.6%, ACS reagent
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)

Click descriptions for product details and ordering information

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
38768	Potassium phosphate, tribasic, 97%, pure, anhydrous, Thermo Scientific™
15791	Triethylamine, 99%, pure, Thermo Scientific™
42433	Sodium hydroxide, 97+%, ACS reagent, pellets, Thermo Scientific™
011552	Sodium carbonate, anhydrous, ACS, 99.5% min, Thermo Scientific™
A12714	Barium hydroxide octahydrate, 97%, Thermo Scientific™

Stock Number	Description
	Building Blocks
L18581	2-Bromobenzeneboronic acid, 98% (example in text)
11375	4,7-Dichloroquinoline, 98%
A13241	2-Bromopyridine, 99%
L17481	4-Nitrophenyl trifluoromethanesulfonate, 99%
43975	3,6-Dihydro-2H-thiopyran-4-yl trifluoromethanesulfonate
L17973	Potassium 4-methyl-beta-styryltrifluoroborate, 95%
L17970	Potassium vinyltrifluoroborate, 97%
H55315	Nitrobenzenediazonium tetrafluoroborate, 97%
H55827	Methoxybenzenediazonium tetrafluoroborate, 98%
B25670	Bromobenzenediazonium tetrafluoroborate, 96%
	Catalysts/Ligands
011034	Palladium(II) chloride, 99.9% (metals basis), Pd 59.0% min
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%
45294	1,1'-Bis(di-tert-butylphosphino)ferrocene palladium dichloride

Stock Number	Description
	Catalysts/Ligands
041225	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II), complex with dichloromethane (1:1), Pd 13%, Thermo Scientific™
36934	Tris(dibenzylideneacetone)dipalladium-chloroform adduct, 97%, Thermo Scientific™
29197	Bis(dibenzylideneacetone)palladium, Thermo Scientific™
29925	Bis(triphenylphosphine)palladium(II) chloride, 98%, Thermo Scientific™
14042	Triphenylphosphine, 99%, Thermo Scientific™
A12093	Tri(o-tolyl)phosphine, 98+%, Thermo Scientific™
38683	Tricyclohexylphosphonium tetrafluoroborate, 99%, Thermo Scientific™
36694	Tri-tert-butylphosphonium tetrafluoroborate, 97+%, Thermo Scientific™
	Catalysts/Catalyst Precursors
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%
041225	Dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II)
010005	Allylpalladium(II) chloride dimer, Pd 56.0% min

Stock Number	Description
	Catalysts
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%
039233	Bis[1,2-bis(diphenylphosphino)ethane]palladium(0)
H26897	Dichloro[bis(1,3-diphenylphosphino)propane]palladium(II)
044971	Dichloro[bis(1,4-diphenylphosphino)butane] palladium(II), Pd 17.6%

Key Literature References

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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 (e.g., 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 (i.e., 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 reactoin 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.

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

Mechanisms of the Reactions Involving Carbonyl Compounds

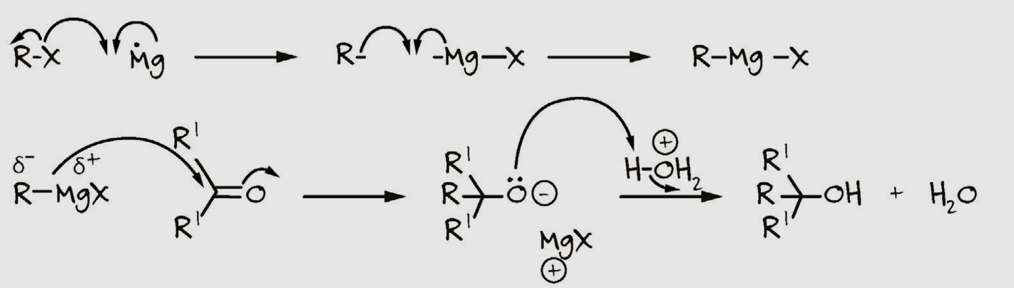


Figure 2.1. Grignard reaction mechanism

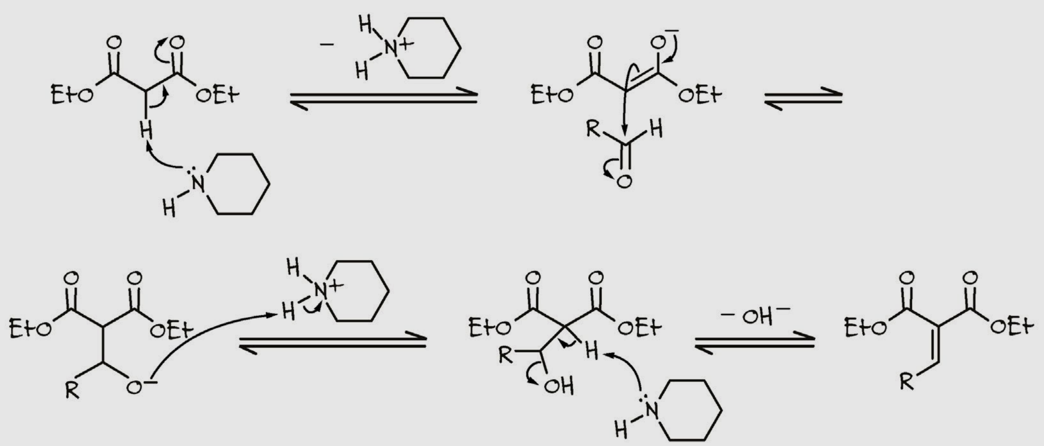


Figure 2.2. Knoevenagel condensation reaction mechanism

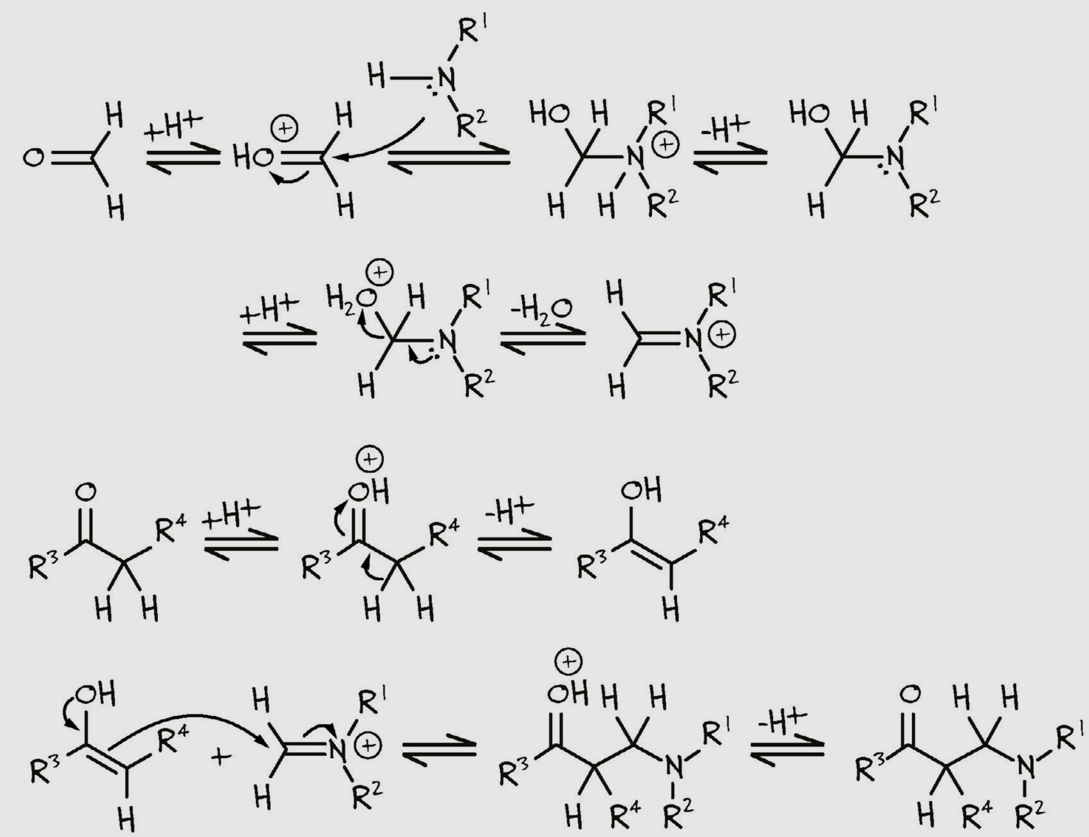


Figure 2.3. Mannich reaction mechanism

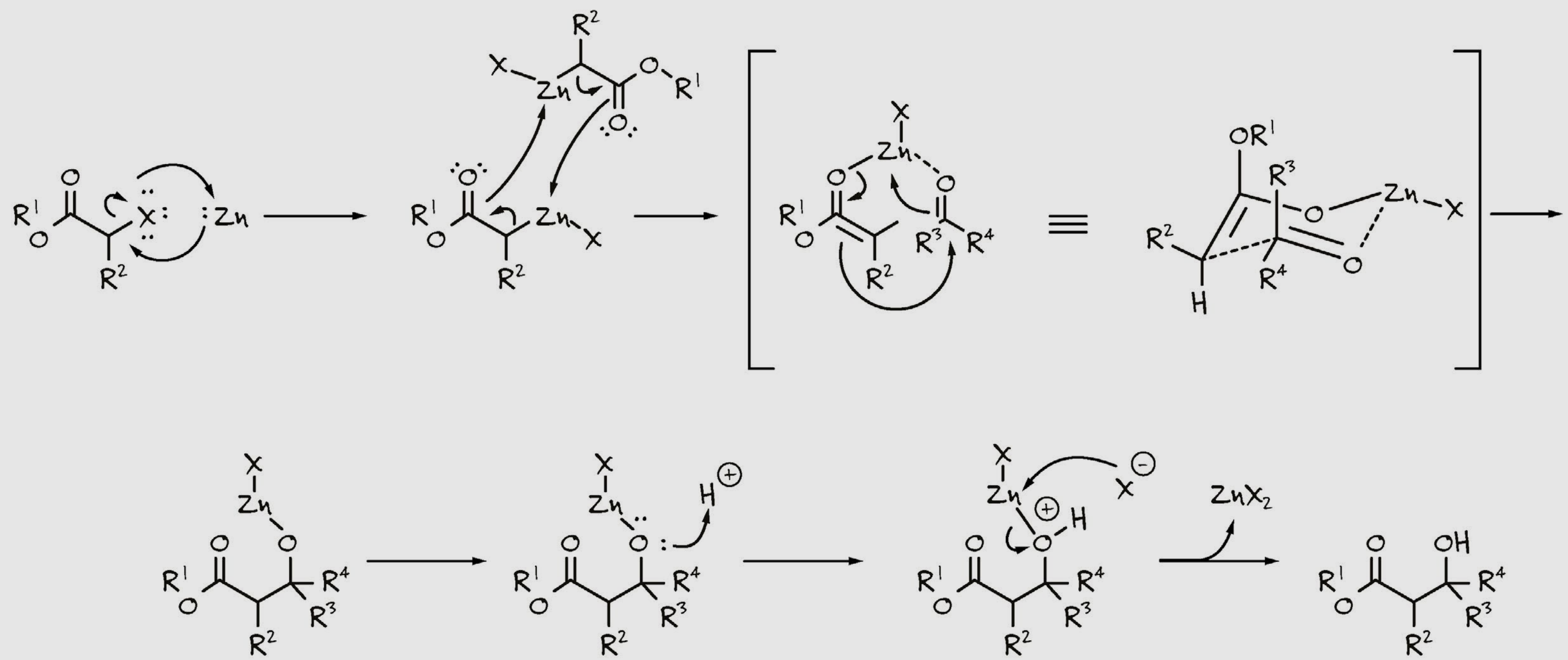


Figure 2.4. Reformatsky reaction mechanism

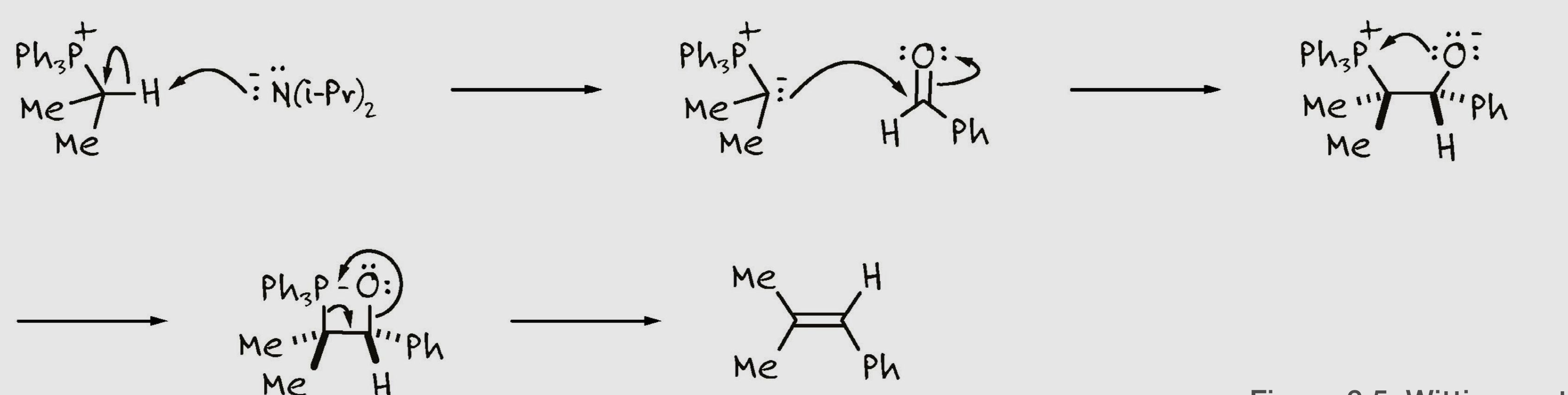


Figure 2.5. Wittig reaction mechanism

Grignard Reaction

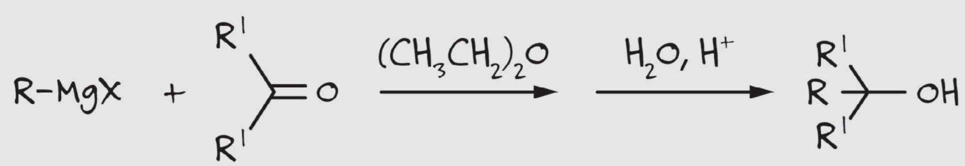


Figure 2.6. Simplified Grignard reaction mechanism

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 reaction 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. For example, 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 nucleophilic addition stage of the reaction must be run in aprotic solvents and dry conditions to preserve the organomagnesium compound, Gignard reactions otherwise 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

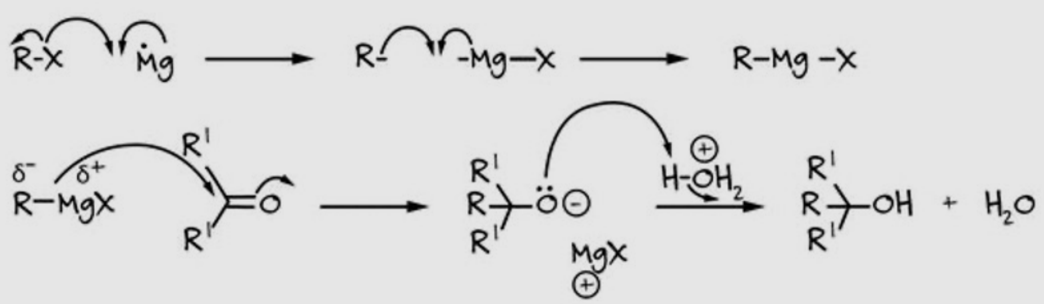


Figure 2.7. Detailed Grignard reaction mechanism

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 °C. In a separate vial dissolve 330 mg (2.1 mmol) of bromobenzene in 1 mL of anhydrous diethyl ether. Using a syringe, transfer 0.1 mL of the bromobenzene solution to the reaction vessel through a septum to keep 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

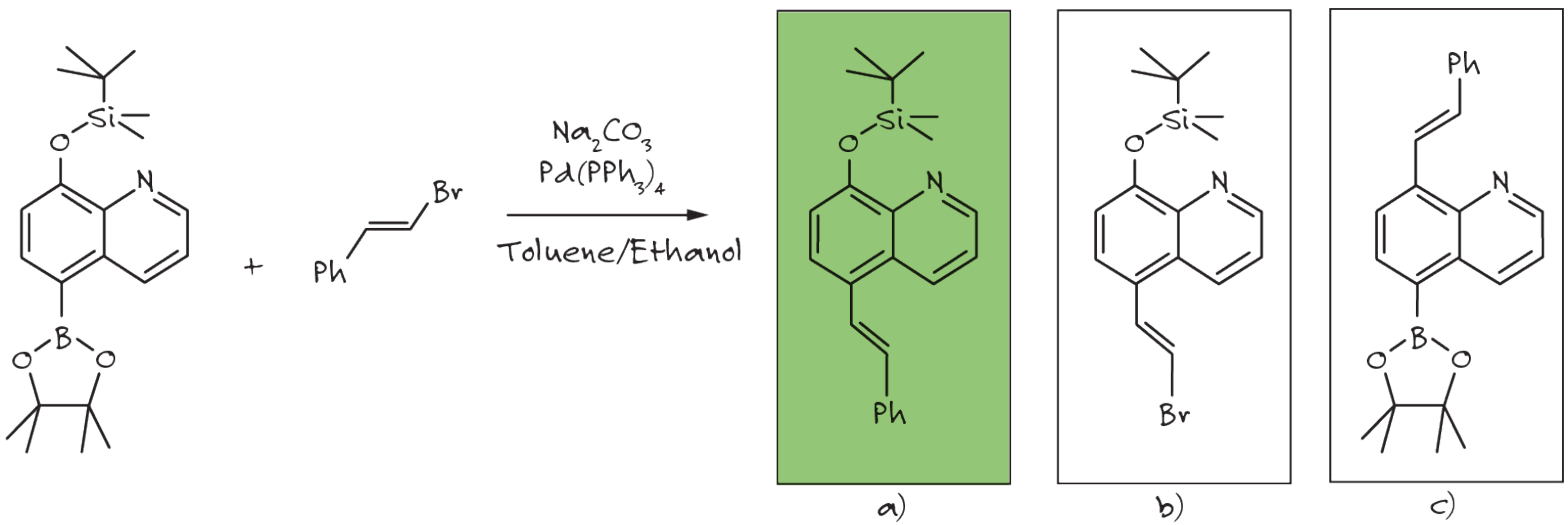
Dissolve 364 mg of benzophenone (2 mmol) in 1 mL of anhydrous ether. Slowly add the solution to the reaction vessel containing the Grignard reagent, maintaining a gentle reflux for 20 minutes, then allow it to stand at room temperature until the solution decolorizes. Cool the reaction vessel in ice and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

QUIZ ANSWER — SUZUKI REACTION

The correct final product produced in the cross coupling reaction below is choice a).



Reference

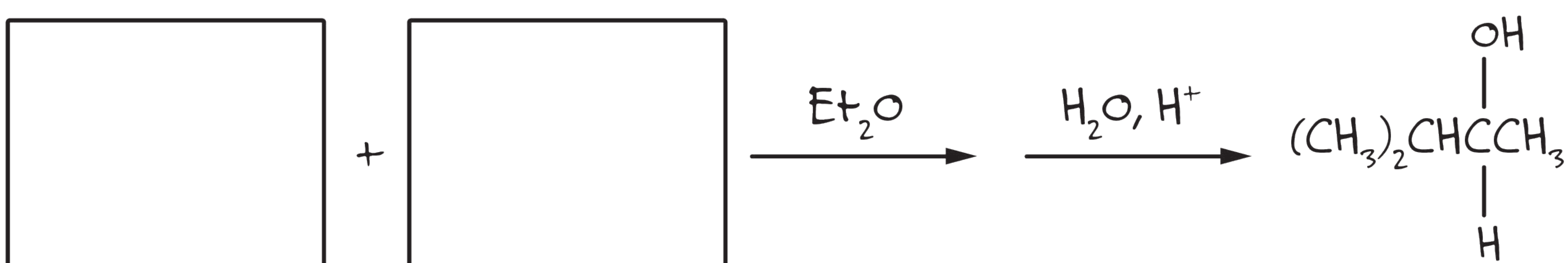
1. *F. Babudri and al. Synthesis, 2006 No 8, 1325-1332.*

JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — GRIGNARD REACTION

What two reagents would be needed to obtain the indicated alcohol from the Grignard reaction?



JUMP TO THE PREVIOUS QUIZ QUESTION
CLICK TO SEE THE ANSWER TO THIS QUESTION
JUMP TO THE NEXT QUIZ QUESTION

Product Selection for the Grignard Reaction

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
	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

Click descriptions for product details and ordering information

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™
43556	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™
H54237	3-Chlorobenzylmagnesium chloride, 0.50M in 2-MeTHF
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
010233	Magnesium powder, -325 mesh, 99.8%
010232	Magnesium turnings, 99.8% (metals basis)
012811	Magnesium, Reagent, Ribbon, +99%

Wittig Reaction

The Wittig reaction is a well-known method to obtain an alkene by the reaction of an aldehyde or a ketone with a triphenyl phosphonium ylides (Figure 2.8).[1]

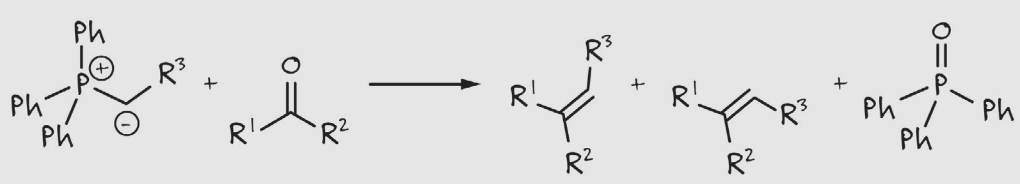


Figure 2.8. Simplified Wittig reaction mechanism

Ylides are obtained by deprotonation of the phosphonium salt (Figure 2.9).

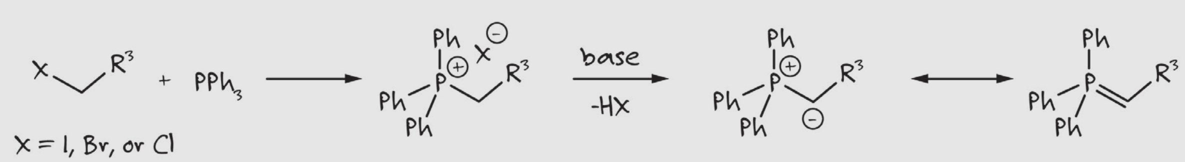


Figure 2.9. Synthesis of substituted triphenyl phosphonium ylides

The R substituent of the ylide plays a key role in the Wittig reaction because the ylide's reactivity with the phosphonium salt is dramatically affected by it. When the substituent group is an alkyl group that is not able to stabilize the negative charge, ylides are classified as non-stabilized. When R is an aryl, vinyl, halo, or alkoxy group, able to slightly stabilize the carbanion, ylides are considered semi-stabilized. Stabilized ylides are obtained with a strong electron-withdrawing group as the substituent (i.e., when R is a carbonyl, an ester, a sulfone, cyano group).[2]

Strong bases such as LDA, n-BuLi, $NaNH_2$, NaHMDS, or t-BuOK are used to generate the non-stabilized and semi-stabilized ylides and the reaction is carried out at low temperatures and under inert conditions. On the other hand, stabilized ylides are prepared in presence of weaker bases such as aqueous NaOH. Generally, ylides are prepared in situ and only stabilized ones can be stocked.

Mechanism of the Wittig Reaction

First the triphenylphosphonium salt is deprotonated to give the corresponding ylide, as commented previously. The latter contains a negatively charged carbon that attacks the carbonyl group of the aldehyde or the ketone during a nucleophilic addition to yield a betaine (i.e., a dipolar charged intermediate). The next step is a cyclization forming a heterocyclic 4-membered ring known as an oxaphosphetane. Finally, a reverse two-plus-two cycloaddition occurs, where the oxaphosphetane decomposes leading to the formation of a carbon-carbon double bond and triphenylphosphine oxide. The alkene, as final product, is formed (Figure 2.10).

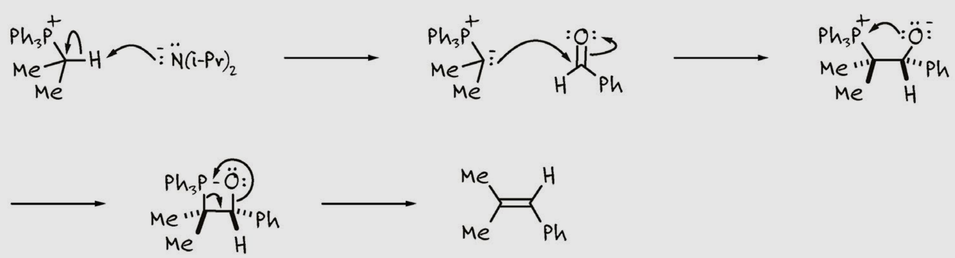


Figure 2.10. Detailed mechanism of the Wittig reaction

The nature of the phosphonium ylide involved in the Wittig reaction, affects the stoichiometry of the isomers present in the final alkene. Non-stabilized ylides yield Z-alkenes isomers (Figure 2.11).[3]

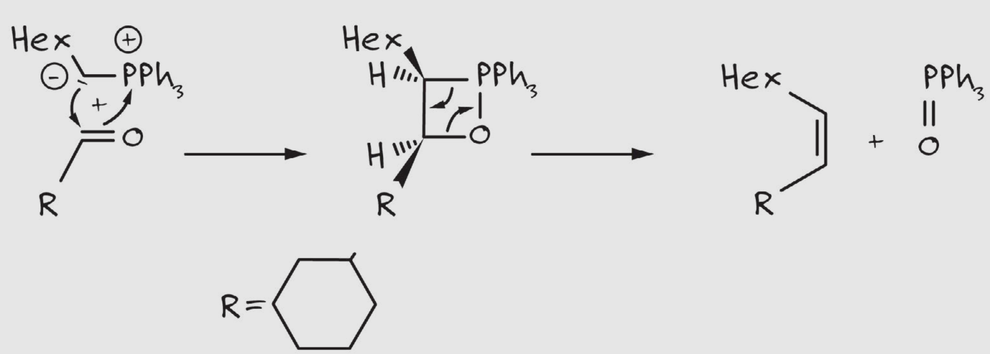


Figure 2.11. Synthesis of Z-alkene isomer

E-alkene isomers are obtained from stabilized ylides (Figure 2.12), and a product mixture of Z- and E-isomers is formed for semi-stabilized ylides (Table 1 and Table 2).[3]

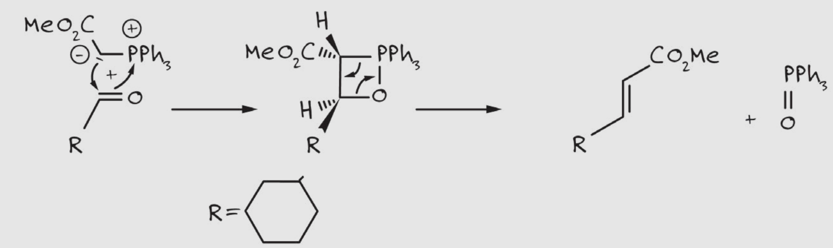


Figure 2.12. Synthesis of E-alkene isomer

A selective formation of E-alkenes from non-stabilized ylides is observed when Li-halide salt (e.g., LiBr) is used in the reaction mixture to form a lithiobetaine, known as the Schlosser modification (Figure 2.13).[3,4]

Table 1. Resulting isomer effect of ylide involved in Wittig reaction

Ylide substituent group	Ylides classification	Synthesis conditions	Resulting isomer
Alkyl	Non-stabilized	Strong base	Z
Aryl, vinyl, halo, alkoxy	Semi-stabilized	Strong base	E,Z
Carbonyl, ester, sulfone, cyano	Stabilized	Weak base	E

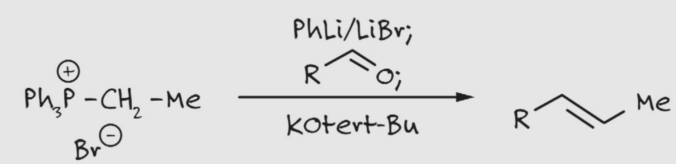


Figure 2.13. Schlosser modification

Table 2. Percentage of E-alkenes based on Wittg ylide substituent group

Ylide substituent group	% E -alkenes
R = pent	~99
R = Ph	~97

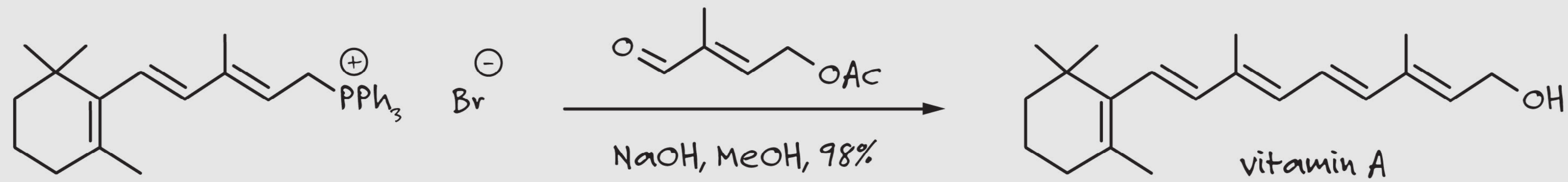


Figure 2.14. Synthesis of vitamin A

Applications of the Wittig Reaction

The Wittig reaction is a powerful method that has contributed to the advancement of the total synthesis of natural products for the drug discovery area. It is one of the key steps in the synthesis of vitamin A (i.e., retinol), which is an essential micronutrient essential for good vision, growth, and the reproduction and differentiation of epithelial tissues (Figure 2.14). Furthermore, Vitamin A deficiency is an important cause of child mortality.

The Wittig reaction was also investigated in aqueous media involving semi-stabilized ylides to obtain 1,3-dienes and 1,3,5-trienes. The 1,3-diene sub-unit is used in a wide range of bioactive materials and as π-component in the Diels–Alder cycloaddition leading to a wide range of intermediates.[6] The use of water as a solvent is an important step towards more green chemistry.

Reference Reaction Protocols

Synthesis of Trans-9-(2-Phenylethenyl)anthracene (Figure 2.15).[7]

Benzyltriphenyl-phosphonium chloride and 9-anthracenecarboxyaldehyde were solubilized in dimethylformamide. 50% NaOH solution was added dropwise, and the reaction mixture was stirred for 30 min. The product was precipitated by 4 mL of a 1:1 mixture of 1- propanol/H_2O. After crystallization, a yellow product is obtained (50%-70% yield).

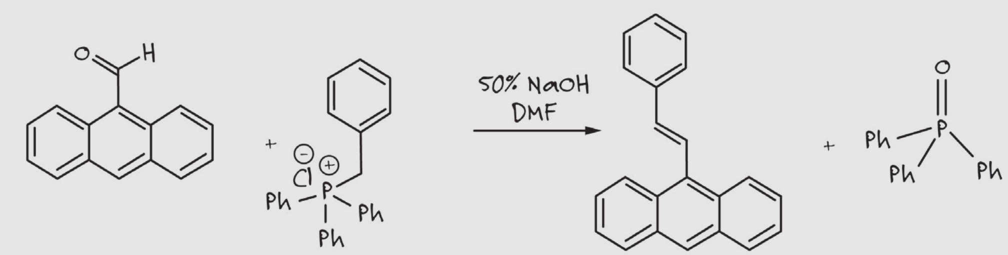


Figure 2.15. Synthesis of Trans-9-(2-Phenylethenyl)anthracene

Key Literature References

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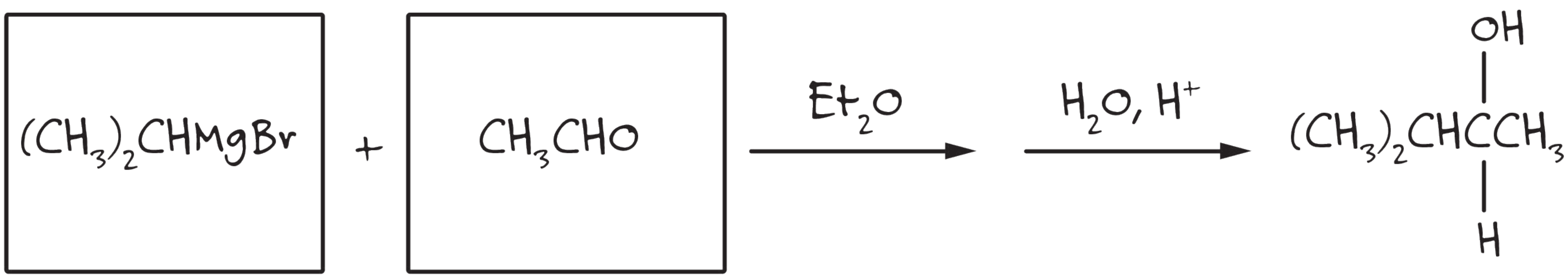
2. *P. A. Byrne; D. G. Gilheany* Chem. Soc. Rev., 2013, 42, 6670-6696.*
3. *R. Brückner, Mécanismes réactionnels en chimie organique, DeBoeck Université, 1999.*
4. *Dr. M. Schlosser; K. F. Christmann Angew. Chem., Int. Ed. Eng. 1966, 5, 126.*
5. *G. L. Parker; L. K. Smith *; I. R. Baxendale Tetrahedron, 2016, 72, 1645-1652.*
6. *J. McNulty *; P. Das Tetrahedron Letters 50 (2009) 5737–5740.*
7. *C. Jaworek; S. Iacobucci Journal of Chemical Education 2002, 79, 111.*

QUIZ ANSWER — GRIGNARD REACTION

Below are the **correct** two reagents that would produce the indicated alcohol using the Grignard reaction.



JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

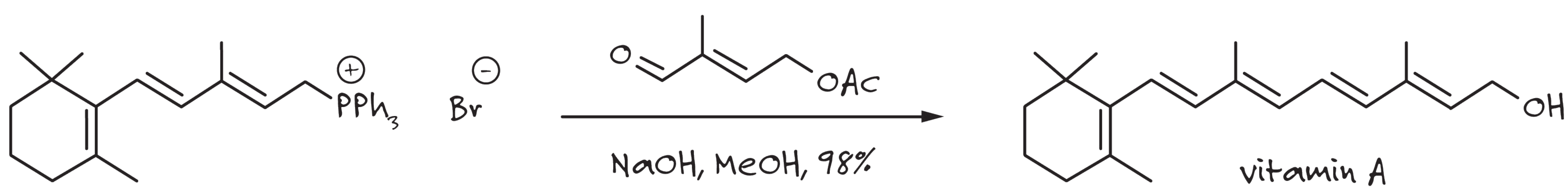
TEST YOUR KNOWLEDGE — WITTIG REACTION

How would you **classify the ylide** used in the synthesis of vitamin A below?

a) Stabilized

b) Semi-stabilized

c) Non-stabilized



JUMP TO THE PREVIOUS QUIZ QUESTION

CLICK TO SEE THE ANSWER TO THIS QUESTION

JUMP TO THE NEXT QUIZ QUESTION

Product Selection for the Wittig Reaction

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
	Solvents
61508	Diethyl ether, ACS reagent, anhydrous, Thermo Scientific™
34845	Tetrahydrofuran, 99.5%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal™
36441	Toluene, 99.8%, Extra Dry, AcroSeal™, Thermo Scientific™
61046	Ethylene glycol dimethyl ether, 99.5%, Extra Dry over Molecular Sieve, AcroSeal™, stabilized
34846	Dichloromethane, 99.8%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal™

SKU	Description
	Reagents
A10739	Benzophenone, 99%, Thermo Scientific™
A10739	Benzophenone, 99%, Thermo Scientific™
L02502	Triphenylphosphine, powder, 99%, Thermo Scientific™
A14089	Triphenylphosphine, flake, 99%, Thermo Scientific™
H36949	n-Butyllithium, 2.5M in hexane, packaged under Nitrogen in resealable AcroSeal™ bottles, Thermo Scientific™
20955	Lithium bis(trimethylsilyl)amide, 1M solution in THF, AcroSeal™
41823	Potassium bis(trimethylsilyl)amide, 0.7M in toluene, AcroSeal™
42879	Potassium tert-butoxide, pure, 1.6-1.7M (20 wt.%) solution in THF, AcroSeal™
26883	Lithium diisopropylamide, 2M sol. in THF/n-heptane/ethylbenzene, AcroSeal™
14601	(Methoxymethyl)triphenylphosphonium chloride, 98%
10830	(Carbethoxymethyl)triphenylphosphonium bromide, 98%
A13096	(Cyanomethyl)triphenylphosphonium chloride, 98+%
37062	(tert-Butoxycarbonylmethylene)triphenylphosphorane, 97%
16956	Methyl (triphenylphosphoranylidene)acetate, 98%
16997	1-Triphenylphosphoranylidene-2-propanone, 99%
A11709	(Formylmethylene)triphenylphosphorane, 97%
B24567	Benzyltriphenylphosphonium bromide, 98%
39911	2-(Triphenylphosphoranylidene)propionaldehyde, 98%
A18882	(1,3-Dioxolan-2-ylmethyl)triphenylphosphonium bromide

Click descriptions for product details and ordering information

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. In recognition of Fries realizing that this rearrangement of phenolic esters was general, the transformation of phenolic ester 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. First is an anionic reaction where ortho-lithiated O-aryl carbamates are converted to substituted salicylamides. Second is 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 (i.e., 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 (e.g., $BeCl_2$, $CdCl_2$, 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

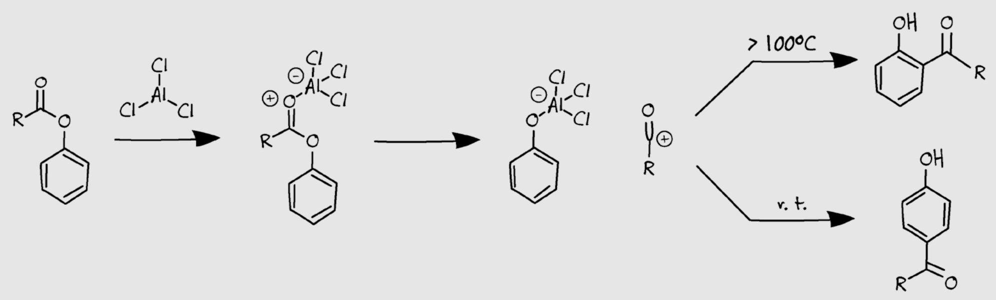


Figure 3.1. Mechanism of the Fries rearrangement

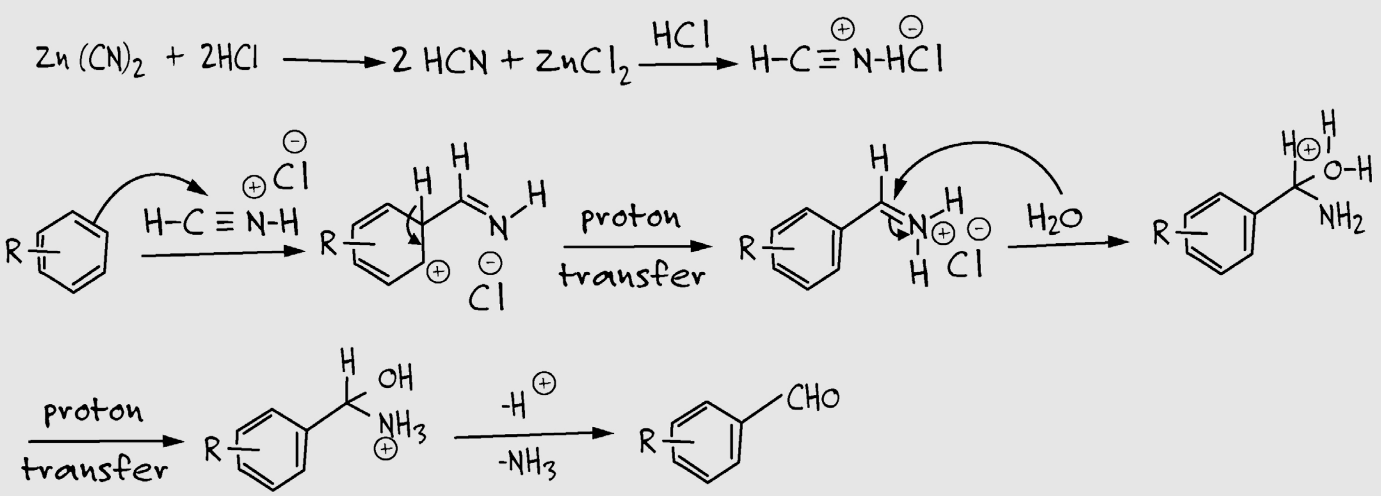


Figure 3.2. Mechanism of the Gattermann formylation using the adams modification

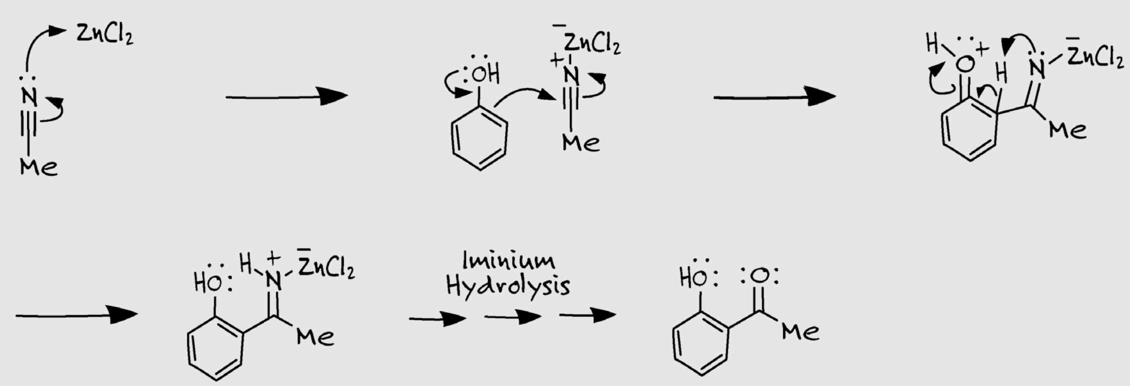


Figure 3.3. Mechanism of the Houben-Hoesch synthesis

ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS
REACTION MECHANISMS EXAMPLES
FRIEDEL-CRAFTS ACYLATION AND ALKYLATION REACTION
PRODUCT SELECTION FOR FRIEDEL-CRAFTS ACYLATION AND ALKYLATION REACTION

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.

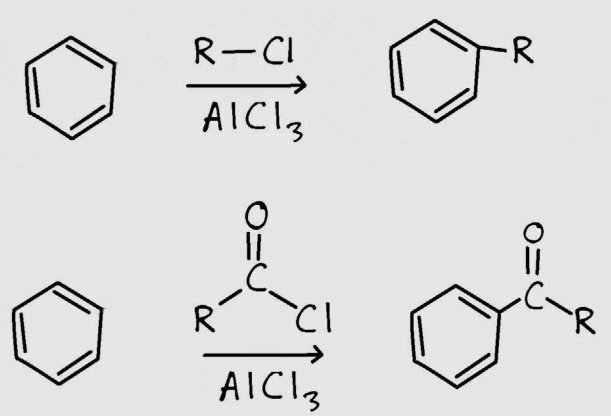


Figure 3.4. Simplified Friedel-Crafts reaction

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 ($AlCl_3$), many others an be used (e.g., $BeCl_2$, $CdCl_2$, 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, where 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 several advantages, however, alkylations and acylations present their 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.

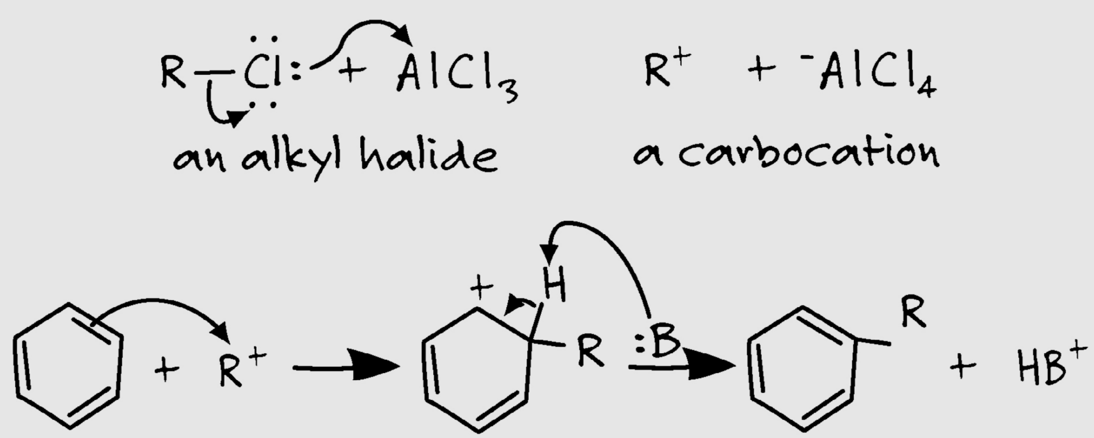


Figure 3.5. Friedel-Crafts reaction mechanism

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 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

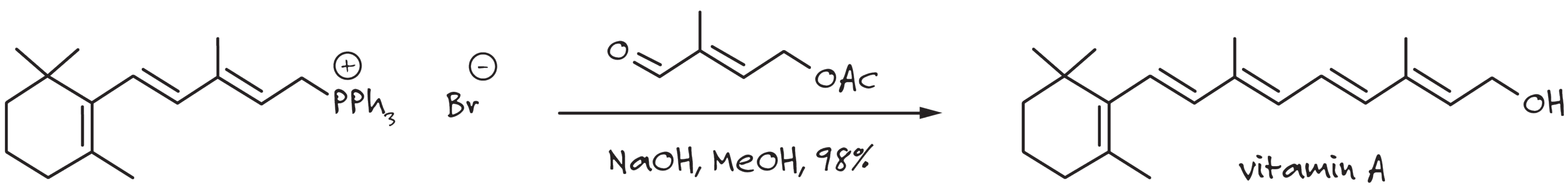
Mix/dissolve equimolar amounts of arene and alkyl halide in dimethyl chloride or diethyl ether in a reaction vessel, previously flushed with dry nitrogen. Put the mixture in an ice bath under stirring and add glacial sulfuric acid drop-wise to avoid vigorous boiling of the reaction. At the end of the 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.*

QUIZ ANSWER — WITTIG REACTION

The ylide involved in the synthesis of vitamin A is classified as **stabilized.** It's stabilized because the negative charge of the ylide is stabilized by the conjugated allylic system.



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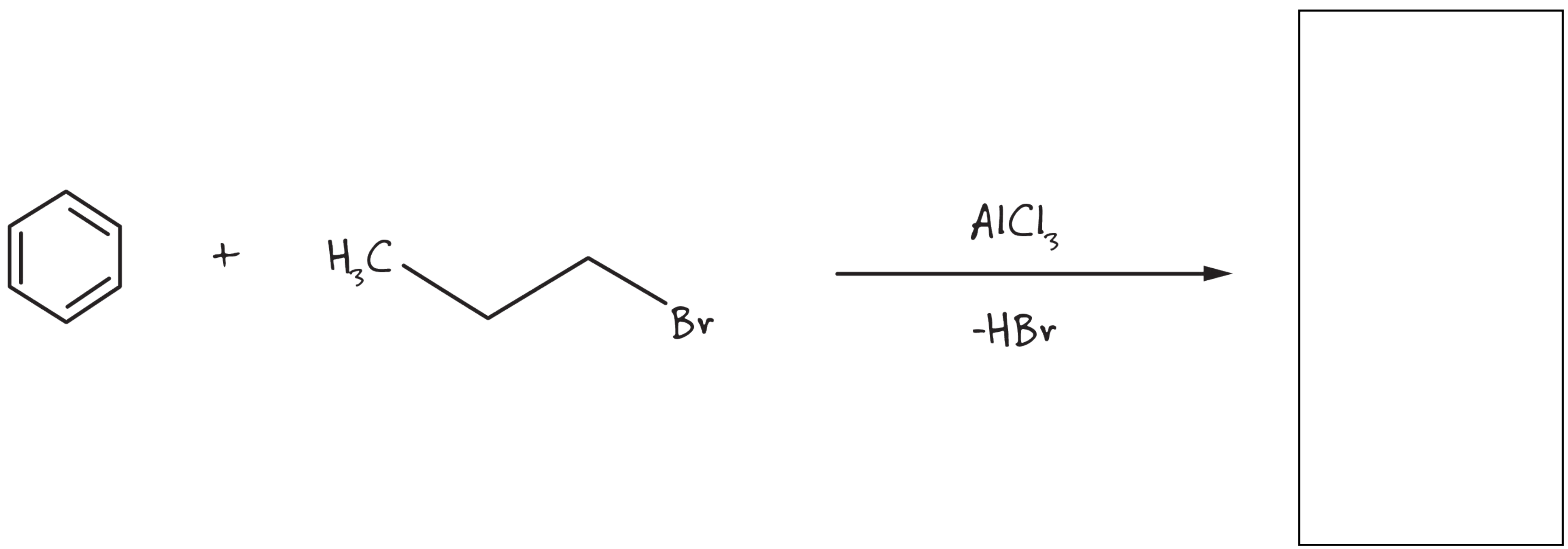
TEST YOUR KNOWLEDGE — FRIEDEL-CRAFTS REACTION

What is the major **final product** of this reaction?



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Product Selection for the Friedel-Crafts Reaction

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
	Acetyl halides
21947	Acetyl chloride, 99+%, Thermo Scientific Chemicals
A17575	Butyryl chloride, 98%, Thermo Scientific Chemicals
B24472	Isobutyryl chloride, 98%
16912	Valeryl chloride, 98%, Thermo Scientific Chemicals
B23027	Hexanoyl chloride, 98%, Thermo Scientific Chemicals
L03315	Heptanoyl chloride, 99%, Thermo Scientific Chemicals
40203	Benzoyl chloride, 98+%, ACS reagent, Thermo Scientific Chemicals
A14142	Cyclopentanecarbonyl chloride, 98%, Thermo Scientific Chemicals
A19824	Cyclohexanecarbonyl chloride, 97+%, Thermo Scientific Chemicals

SKU	Description
	Alkyl halides
A10461	1-Bromopropane, 99%, Thermo Scientific Chemicals
42588	1-Chlorobutane, 99.8%, for HPLC
10883	2-Chlorobutane, 99+%, Thermo Scientific Chemicals
B24733	1-Chloropentane, 98%
10732	2-Bromopropane, 99%, Thermo Scientific Chemicals
A13004	tert-Butyl chloride, 98+%, Thermo Scientific Chemicals
17347	Chloroacetone, 96%, stabilized
A12481	Benzyl chloride, 99%, stab., Thermo Scientific Chemicals

SKU	Description
	Catalysts
21746	Aluminum chloride, 98.5%, extra pure, anhydrous, powder, Thermo Scientific Chemicals
19578	Aluminum chloride, 99%, extra pure, anhydrous, granules, Thermo Scientific Chemicals
42711	Boron trifluoride etherate, ca. 48% BF3, AcroSeal™, Thermo Scientific Chemicals
011113	Aluminum bromide, 98%, Thermo Scientific Chemicals
089065	Aluminum bromide, 99.997% (metals basis), Thermo Scientific Chemicals
29520	Boron tribromide, 99.9%, Thermo Scientific Chemicals
L14880	Boron tribromide, 1M soln. in dichloromethane, Thermo Scientific Chemicals
A16281	Zinc chloride, anhydrous, 98+%, Thermo Scientific Chemicals
42459	Zinc chloride, 97+%, ACS reagent, Thermo Scientific Chemicals
21914	Cadmium chloride, 99%, for analysis, anhydrous, Thermo Scientific Chemicals
012357	Iron(III) chloride, anhydrous, 98%, Thermo Scientific Chemicals
011571	Tin(IV) chloride, anhydrous, 98% (metals basis), Thermo Scientific Chemicals
022979	Titanium(IV) chloride, 99.99% (metals basis), Thermo Scientific Chemicals
035677	Antimony(V) chloride, ultra dry, 99.999% (metals basis), Thermo Scientific Chemicals
043879	Gallium(III) chloride, ultra dry, 99.999% (metals basis), Thermo Scientific Chemicals
040566	Scandium(III) trifluoromethanesulfonate, 98%, Thermo Scientific Chemicals
30417	Ytterbium(III) triflate hydrate, 99.9%, (trace metal basis), Thermo Scientific Chemicals
42404	Phosphoric acid, ACS reagent, 85+% solution in water
38902	Phosphoric acid, 98+%, pure

Click descriptions for product details and ordering information

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

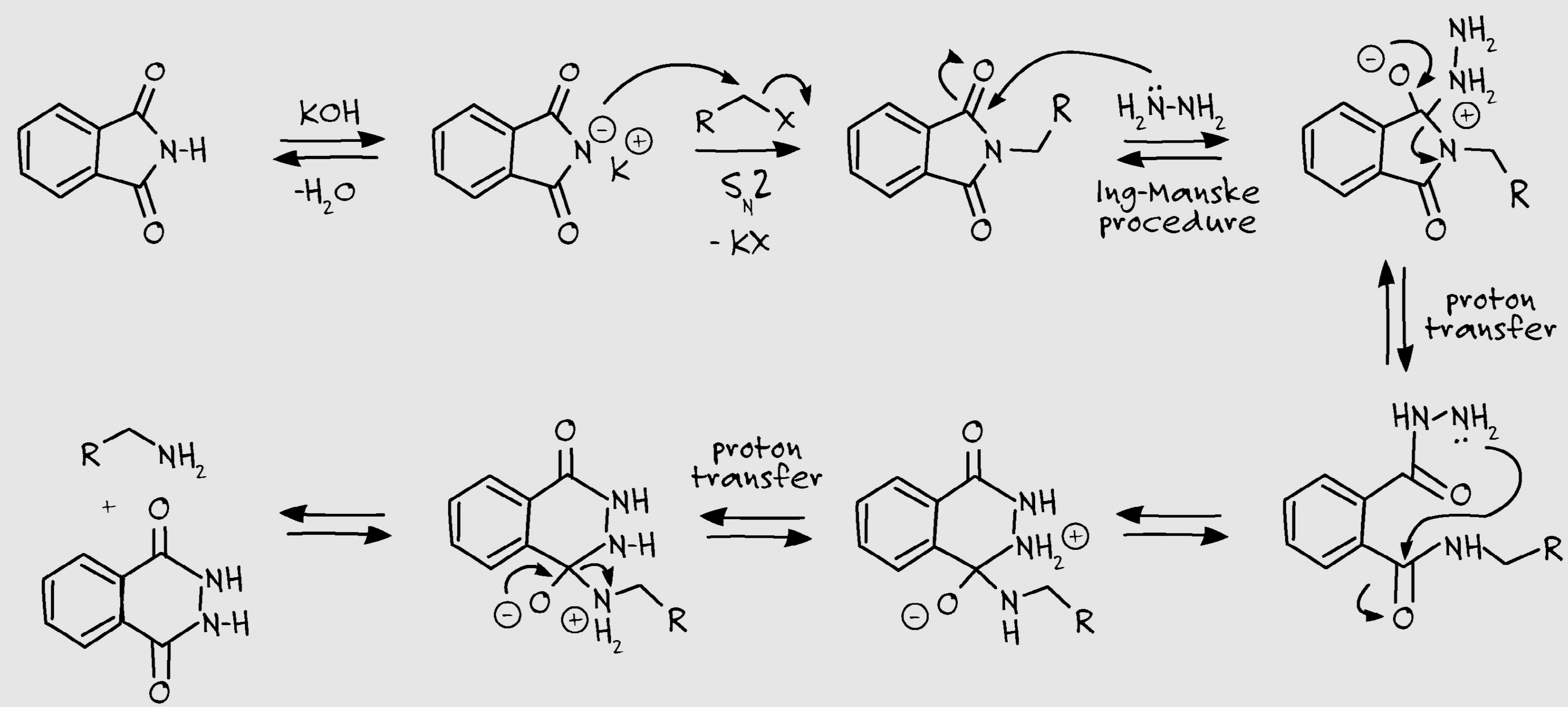


Figure 4.1. Gabriel synthesis mechanism

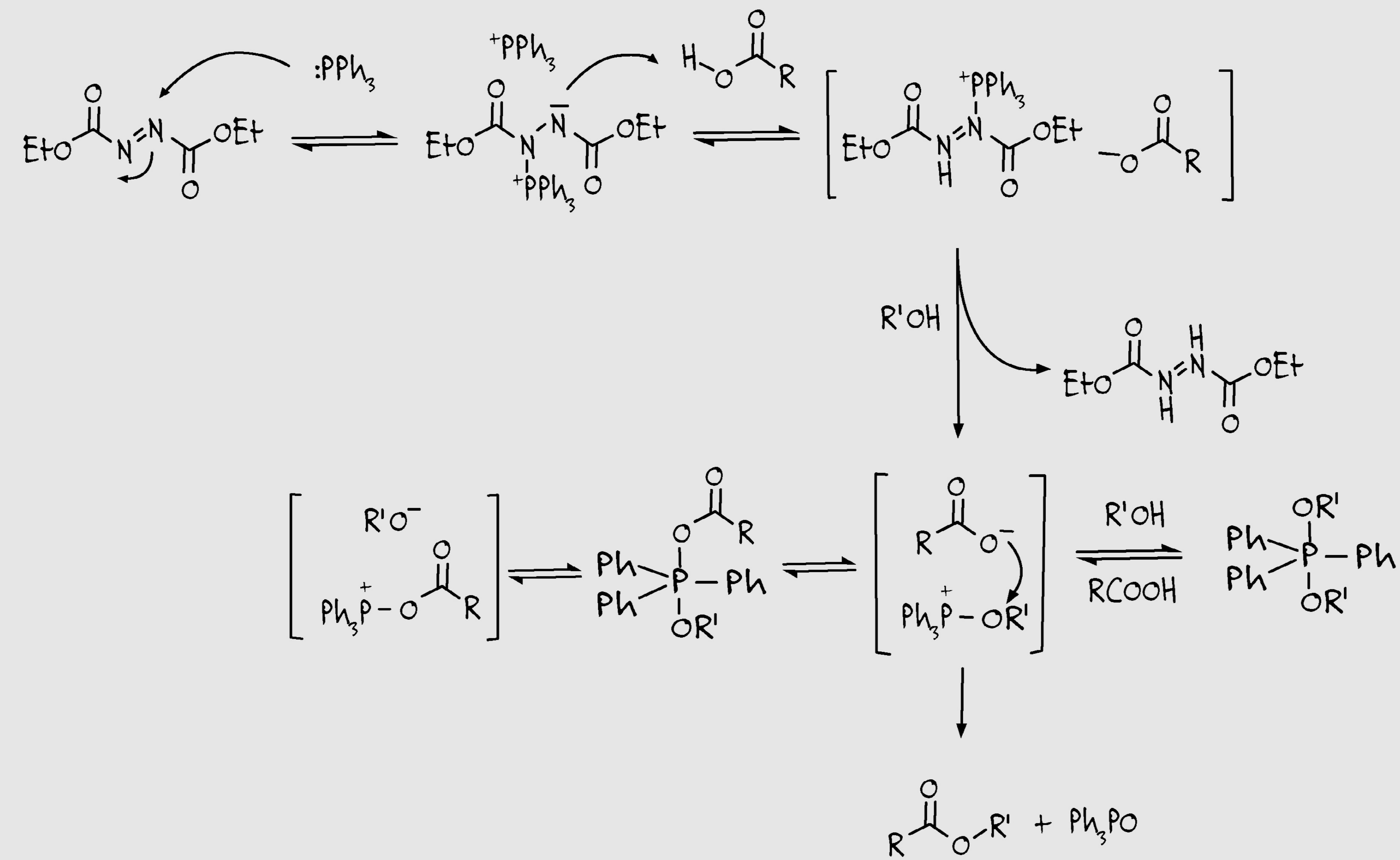


Figure 4.2. Mitsunobu mechanism

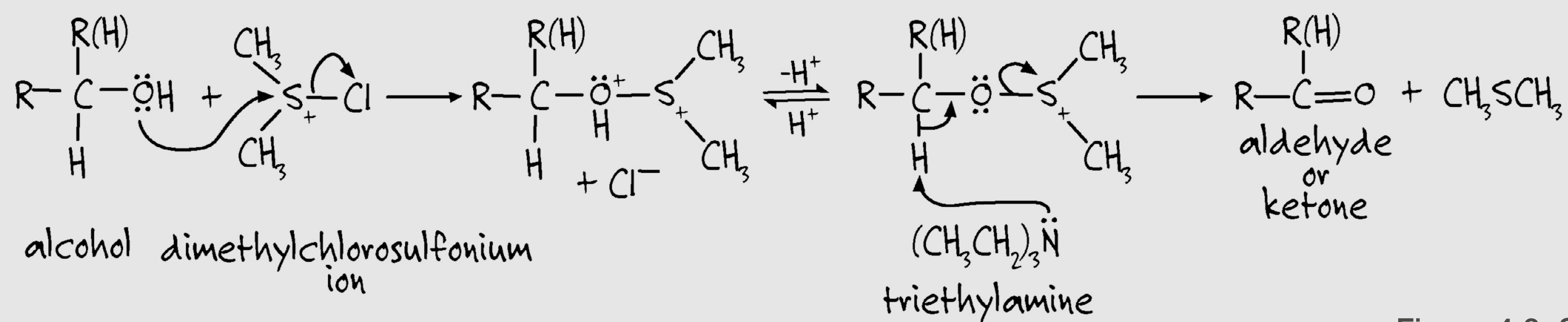


Figure 4.3. Swern oxidation mechanism

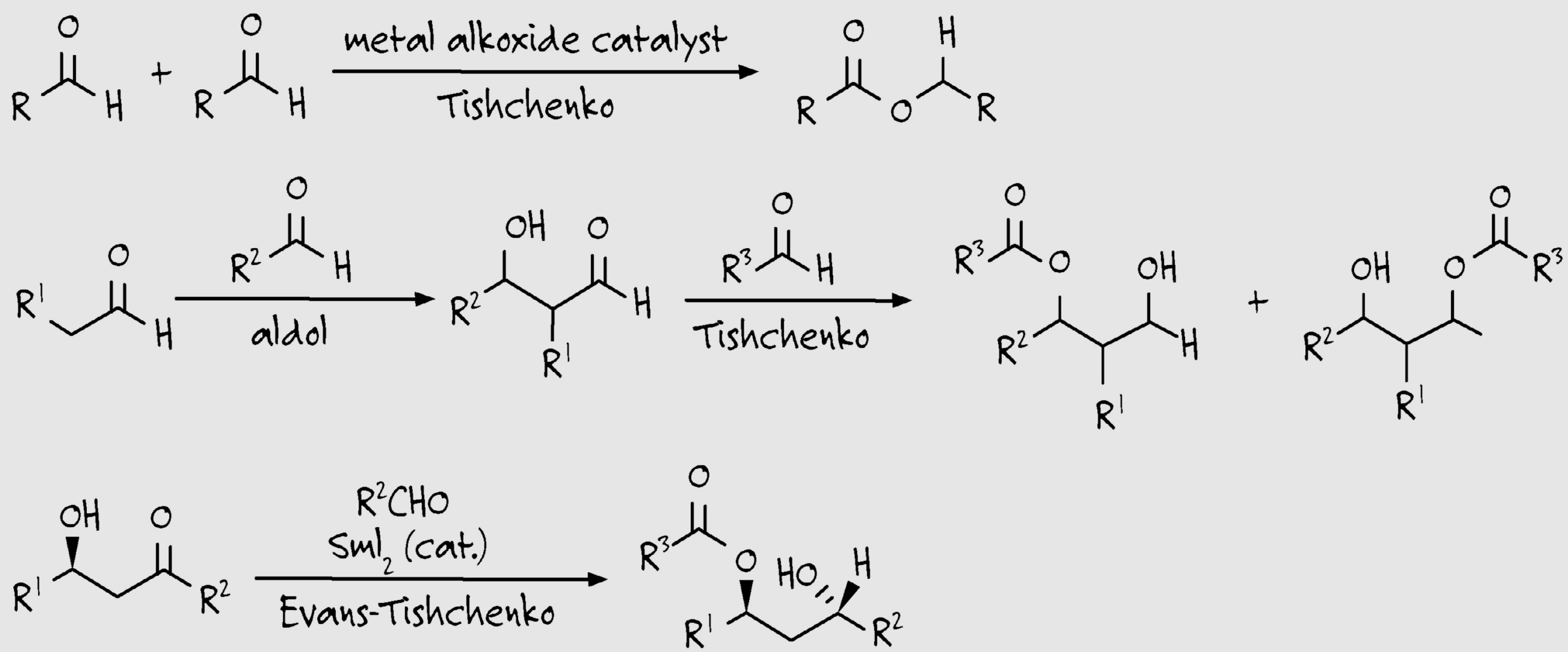


Figure 4.4. Mechanisms of the Tishchenko and Evans-Tishchenko reactions

Baeyer-Villiger reaction

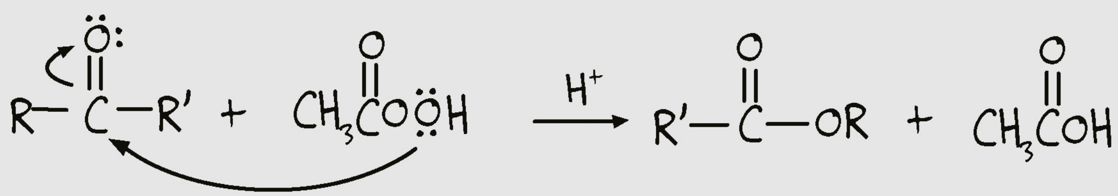


Figure 4.5. Simplified Baeyer-Villiger reaction mechanism

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, which was 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

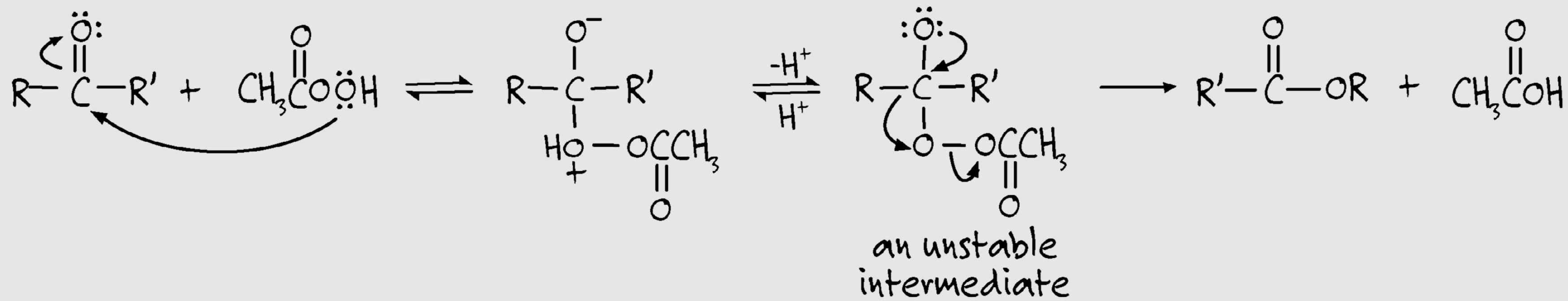


Figure 4.6. Detailed Baeyer-Villiger reaction mechanism

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, where methyl < primary group < phenyl < secondary group < 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

Sodium percarbonate (15-20 mmol) is added slowly at 0 °C to a solution of benzophenone (10 mmol) and trifluoroacetic acid (20 mL)[7]. 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.

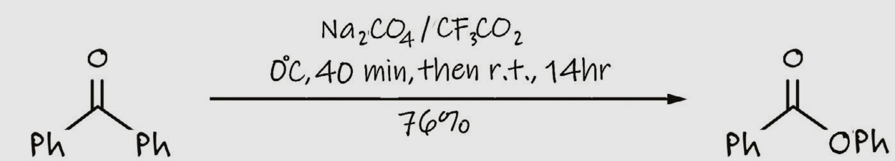


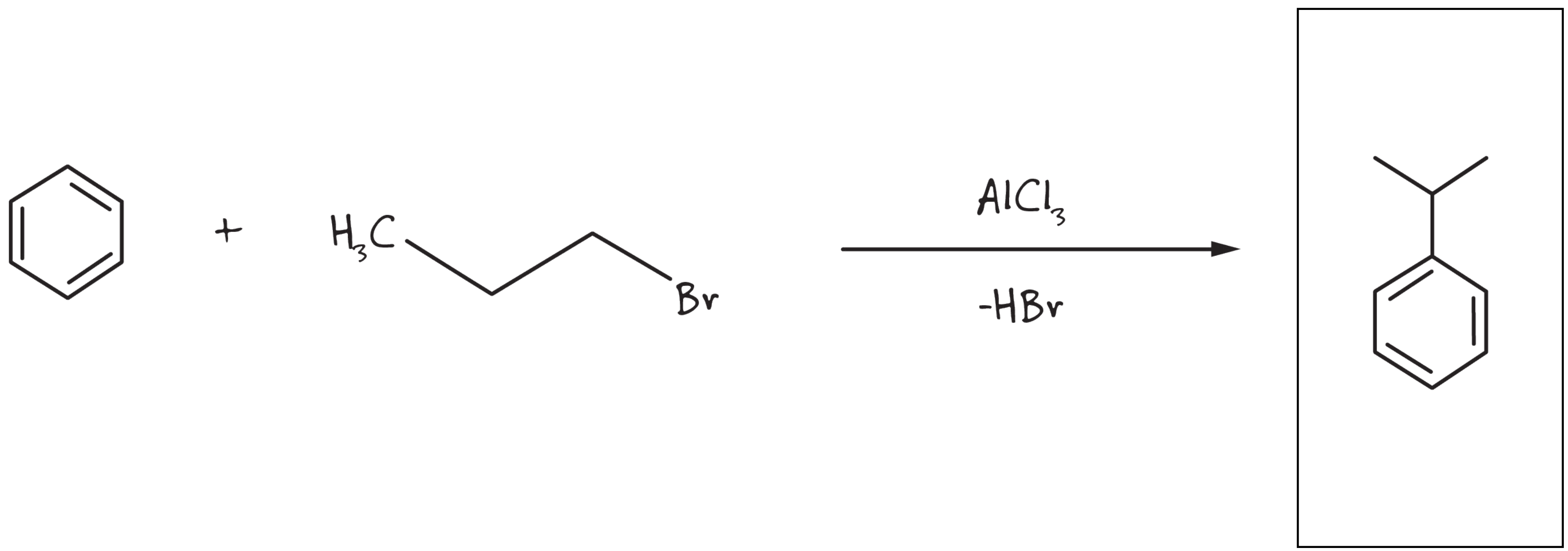
Figure 4.7. Synthesis of phenyl benzoate from benzophenone

Key Literature References

1. A. Baeyer, V. Villiger, Ber. Dtsch. Chem. Ges. 1899, 32, 3625 –3633.
2. A. Baeyer, V. Villiger, Ber. Dtsch. Chem. Ges. 1900, 33, 858-864.
3. R. Criegee, Liebigs Ann. Chem. 1948, 560, 127 –135.
4. W. v. E. Doering, E. Dorfman, J. Am. Chem. Soc. 1953, 75, 5595-5598.
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.
7. G. A. Olah, Q. Wan, N. J; Trivedi, G.K. S. Prakash, Synthesis, 1991, 9, 739-740 DOI: 10.1055/s-1991-26561.

QUIZ ANSWER — FRIDEL-CRAFTS REACTION

The final major product of the reaction below is cumene.
While n-propylbenzene is a product, it will undergo rearrangement to cumene, which is more stable and is thus the major product.



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TEST YOUR KNOWLEDGE — BAYER-VILLIGER REACTION

Select the answer(s) that are **TRUE** about the **Bayer-Villiger reaction:**

a) 3-Chloroperoxybenzoic acid is used in the Bayer-Villiger oxidation

b) This reaction can be catalyzed by Pd

c) This reaction can be performed using dichloromethane as a solvent

d) The Bayer-Villiger reaction can be used as a one-step reaction to produce Testolactone, an anti-cancer drug

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JUMP TO THE NEXT QUIZ QUESTION

Product Selection for the Baeyer-Villiger Reaction

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
	Oxidants/Additives
25579	3-Chloroperoxybenzoic acid, 70-75%, balance 3-Chlorobenzoic acid and water, Thermo Scientific Chemicals
L13940	Urea hydrogen peroxide adduct, 97%, Thermo Scientific Chemicals
L06866	Cumyl hydroperoxide, tech. 80%, Thermo Scientific Chemicals
37073	Sodium percarbonate, 13-14% active oxygen, Thermo Scientific Chemicals
18034	tert-Butyl hydroperoxide, 70% Solution in water, Thermo Scientific Chemicals
25775	Peroxyacetic acid, ca. 35wt.% sol. in diluted acetic acid, stabilized
13972	Trifluoroacetic acid, 99%, extra pure, Thermo Scientific Chemicals
14781	Trifluoroacetic anhydride, 99+%, Thermo Scientific Chemicals

Click descriptions for product details and ordering information

SKU	Description
	Ketones
A13068	Cyclobutanone, 98+%
A14222	Cyclopentanone, 99%
39940	2,2-Dimethylcyclopentanone, 97%, Thermo Scientific Chemicals
40609	Cyclohexanone, 99+%, ACS reagent
12661	2-Methylcyclohexanone, 98%, Thermo Scientific Chemicals
17426	4-Methylcyclohexanone, 98%, Thermo Scientific Chemicals
A17340	2-Phenylcyclohexanone, 98%, Thermo Scientific Chemicals
L08614	4-Phenylcyclohexanone, 98+%, Thermo Scientific Chemicals
B21000	Cyclohexyl methyl ketone, 95%, Thermo Scientific Chemicals
A17665	Menthone, mixture of isomers, 98%, Thermo Scientific Chemicals
H55889	1-Adamantyl methyl ketone, 99%, Thermo Scientific Chemicals
A14275	2-Adamantanone, 98%, Thermo Scientific Chemicals
10241	Acetophenone, 98%, pure, Thermo Scientific Chemicals
A11162	4'-Methoxyacetophenone, 99%, Thermo Scientific Chemicals
15201	2-Bromoacetophenone, 98%, Thermo Scientific Chemicals
12211	1-Indanone, 99+%, Thermo Scientific Chemicals
A13303	1-Tetralone, 97%, Thermo Scientific Chemicals
10556	Benzophenone, 99%, pure, Thermo Scientific Chemicals
11920	9-Fluorenone, 99+%, Thermo Scientific Chemicals
12925	Norcamphor, 99%, Thermo Scientific Chemicals
B22472	Bicyclo[3.2.0]hept-2-en-6-one, 97%, Thermo Scientific Chemicals
16464	DL-Camphor, 96%, Thermo Scientific Chemicals

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 reaction.

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 by 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, including 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

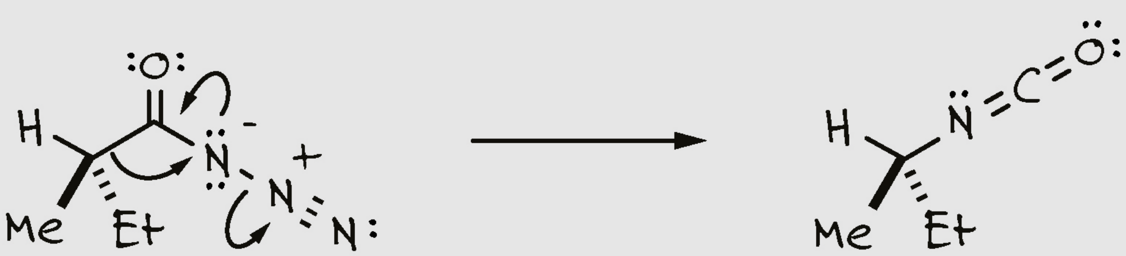


Figure 5.1. Curtius reaction mechanism

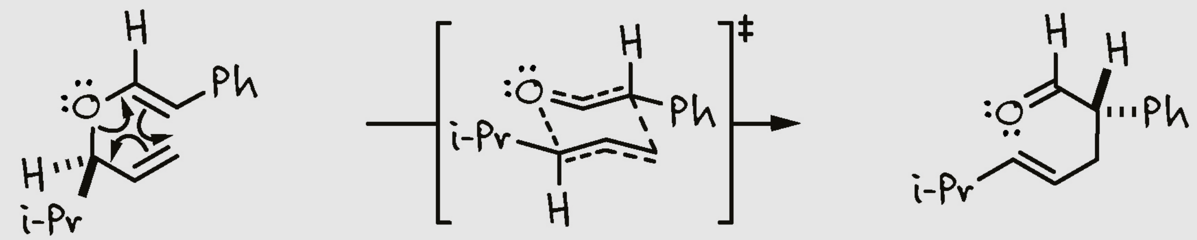


Figure 5.2. Claisen reaction mechanism

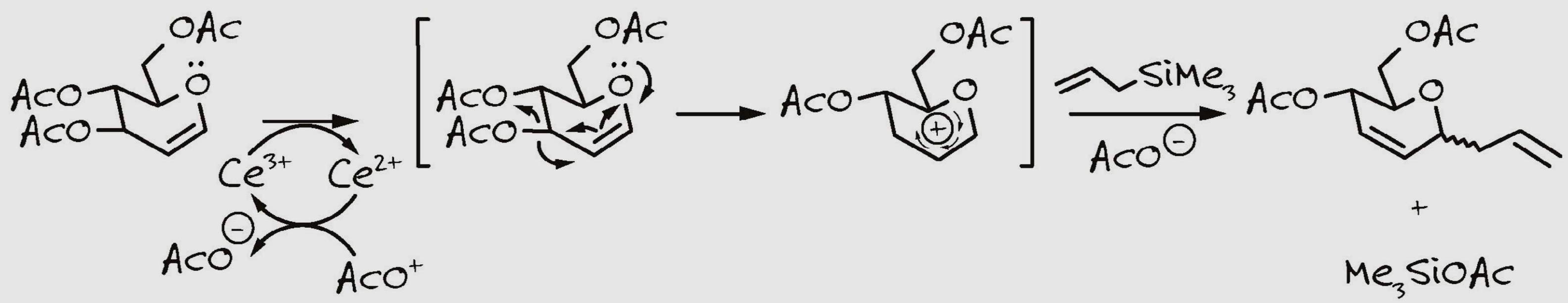


Figure 5.3. Ferrier reaction mechanism

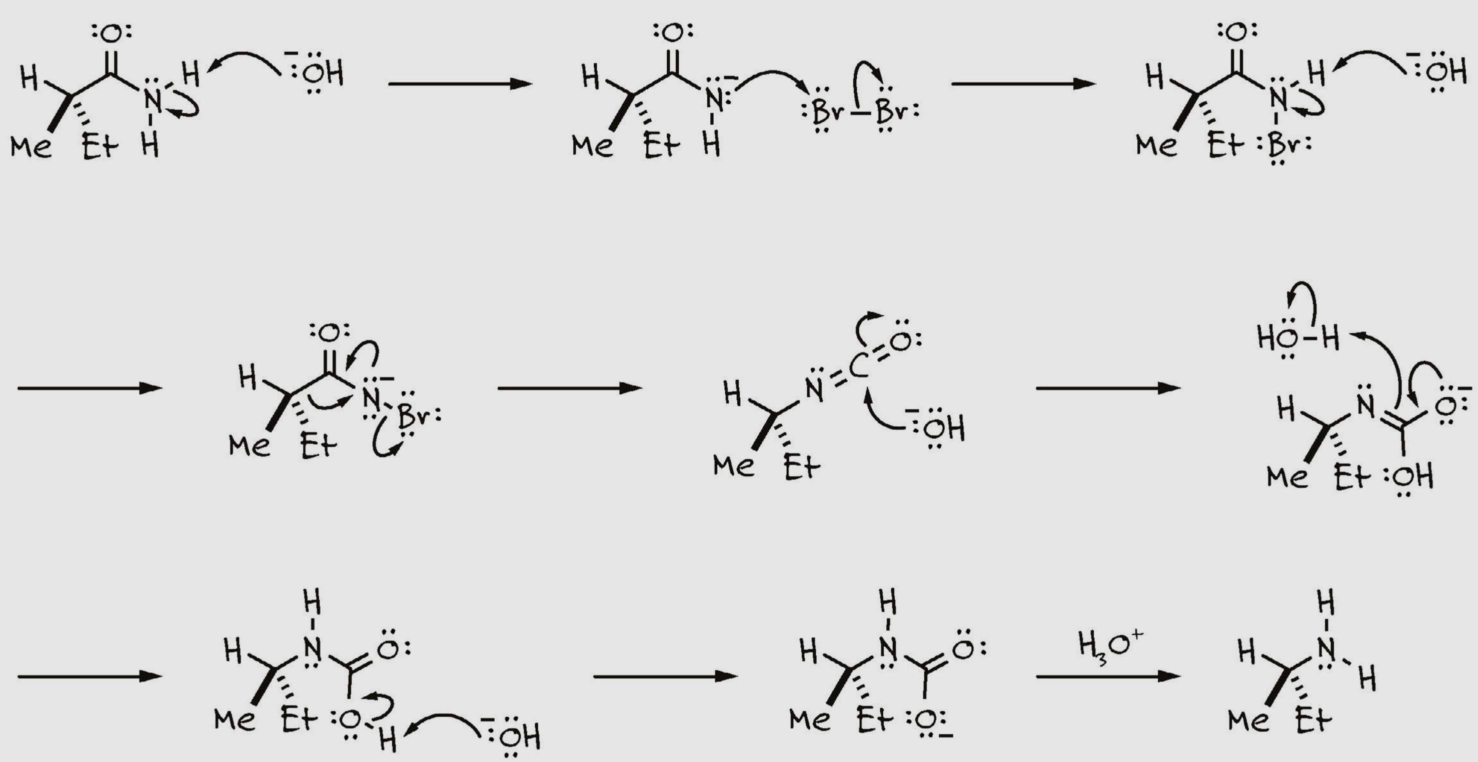


Figure 5.4. Hofmann reaction mechanism

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, where 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]

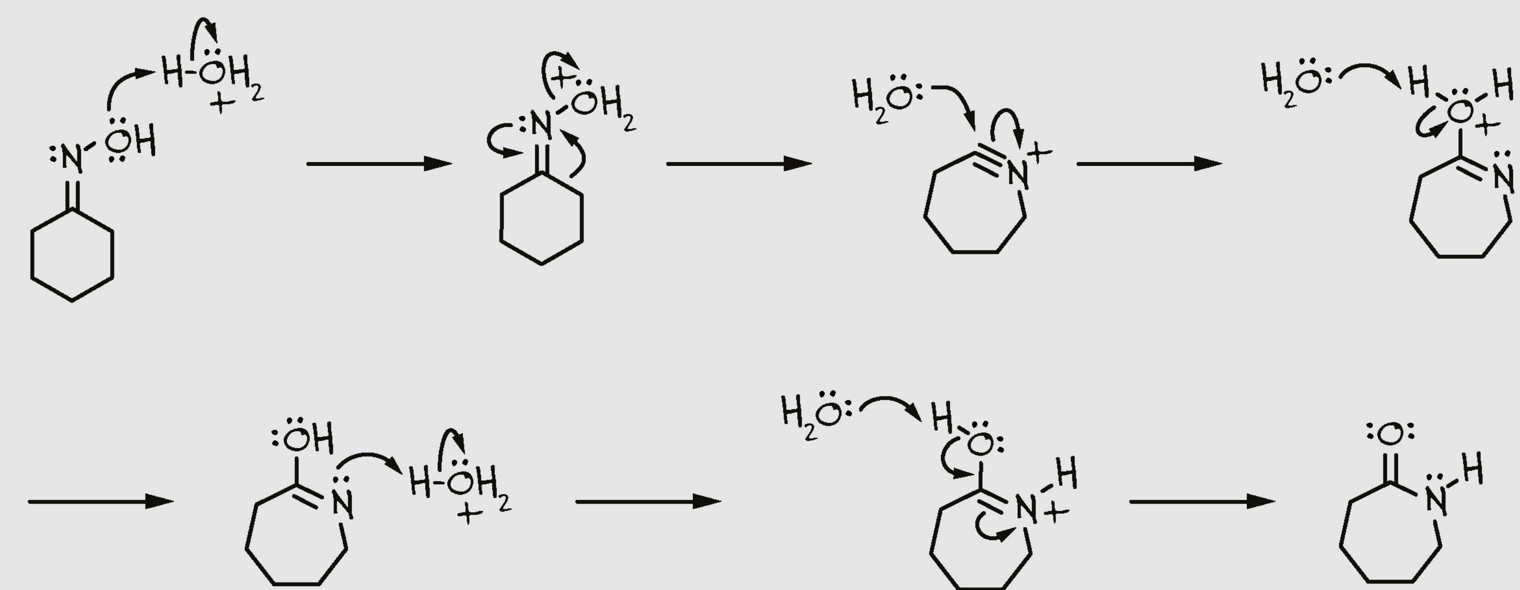


Figure 5.5. Beckmann reaction mechanism

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 Beckann's solution, which consists 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 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

1. *E. Beckmann Berichte der Deutschen Chemischen Gesellschaft, vol. 19, 1886, pp. 988-993, DOI:10.1002/cber.188601901222.*
2. *L.G. Donaruma; W. Z. Heldt (review) Org. React. 1960 (11), 1-156.*
3. *T. Ohwada et al. PNAS, vol. 110, 2013, (11), 4206-4211.*
4. *L. De Luca et al. J. Org. Chem, vol 67, 2002, (17), 6272-6274.*

QUIZ ANSWER — BAYER-VILLIGER REACTION

All of the following are actually true for the Bayer-Villiger reaction!

a) 3-Chloroperoxybenzoic acid can be used in the Bayer-Villiger-Oxidation

Visit our products selection.

b) This reaction can be catalyzed by Pd

J. Org. Chem. 2008, 73, 11, 3996–4003. For other reactions calatyzed by Pd, visit our previous chapter.

c) The reaction can be performed in Dichloromethane as solvent

Visit the reaction in Chemdex.

d) The Bayer Villiger Oxidation is one step used to produce Testolactone (anticancer drug)

See the video **HERE!**

JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — BECKMANN REARRANGEMENT REACTION

Make selections from the options in **each sentence** below to make each statement **true** for the Beckmann rearrangement reaction:

1. An *(acid / base)* catalyzed reaction is used to convert an *(oxime / amide)* to an *(oxime / amide)* functional group.
2. During this reaction, the cleavage of the *(C–C bond / C–N bond)* and formation of the *(C–C bond / C–N bond)* take place.
3. It is generally performed at *(high / low)* temperature and a *(nitronium / nitrilium)* ion is generated.
4. The *(nitronium / nitrilium)* reacts with *(water / triethylamine)* leading to the final product.
5. The Beckmann reaction was used to produce *(Caprolactam / Caprolactone)*.
6. *(Caprolactam / Caprolactone)* is the starting material in the manufacture of *(nylon-6 / nylon-6,6)*.

JUMP TO THE PREVIOUS QUIZ QUESTION | CLICK TO SEE THE ANSWER TO THIS QUESTION | JUMP TO THE NEXT QUIZ QUESTION

Product Selection for the Beckmann Reaction

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
	Promoters
42459	Zinc chloride, 97+%, ACS reagent
19684	Zinc chloride, 98+%, extra pure
A11892	Aluminum chloride, anhydrous, granular, 99%
012298.	Aluminum chloride, anhydrous, Reagent Grade
A15275	Boron trifluoride diethyl etherate, 98+%, Thermo Scientific Chemicals
42711	Boron trifluoride etherate, ca. 48% BF3, AcroSeal™, Thermo Scientific Chemicals
L03442	Cyanuric chloride, 98%, Thermo Scientific Chemicals
17428	Phosphonitrilic chloride trimer, 98%
L08775	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 97%, Thermo Scientific Chemicals
38266	Thionyl chloride, 99.7%
20901	1-Propanephosphonic acid cyclic anhydride, 50 wt.% sol. in ethyl acetate
13903	p-Toluenesulfonyl chloride, 99+%
18749	Iodotrimethylsilane, 95-97%
42642	Iodotrimethylsilane, 95-97%, stabilized, AcroSeal™
16946	Phosphorus pentachloride, 98%
010524	Phosphorus(V) oxide, ACS, 98% min
21575	Phosphorus pentoxide, 99+%
19695	Polyphosphoric acid, pure, >84% phosphate (as P2O5)
34393	Gallium(III) trifluoromethanesulfonate, 99%

SKU	Description
	Oxime compounds
A10640	Acetaldoxime, syn + anti, 98%, Thermo Scientific Chemicals
A10802	Acetone oxime, 98%, Thermo Scientific Chemicals
A11804	Acetophenone oxime, 98%
34233	Benzophenone oxime, 98%
40333	2-Butanone oxime, 99%
A16788	1,2-Cyclohexanedione dioxime, 97%
A19820	Cyclohexanone oxime, 97%
A16672	1,2-Cyclohexanedione dioxime, 97%
B24961	Cyclopentanone oxime, 97%
A16672	Cyclooctanone oxime, 98+%
L00914	Dibenzyl ketoxime, 98+%
L03950	9-Fluorenone oxime, 98+%
20740	Salicylaldoxime, 98%
H52232	Methyl 2-pyridyl ketoxime, 97%
13179	syn-2-Pyridinealdoxime, 99+%
A15525	4-Nitrobenzaldoxime, 98%
A11351	2,6-Dichlorobenzaldoxime, 97%
L14719	2-Chloro-6-fluorobenzaldoxime, 97%

Click descriptions for product details and ordering information

SKU	Description
	Single step reagents
40542	Copper(II) Trifluoromethanesulfonate, 98%
040133	Copper(II) trifluoromethanesulfonate, 99%
32594	Hydroxylamine-O-sulfonic acid, 97%
42274	Zinc oxide, ACS reagent
044264	Zinc oxide, 99.9% (metals basis)
423705	Iron(III) chloride hexahydrate, 97+%, ACS reagent
12503	Iron(III) chloride hexahydrate, 99+%, extra pure
41205	Hydroxylamine hydrochloride, ACS reagent
27010	Hydroxylamine hydrochloride, 99+%, Thermo Scientific Chemicals
17013	Acetohydroxamic acid, 98+%

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 (i.e., 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 (i.e., 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.

Click here for a more in-depth look at the Dess-Martin reaction.

Jones Oxidation

In 1946, E.R.H. Jones and colleagues reported the synthesis of alkynyl ketones from their corresponding carbinols using chromic acid (i.e., 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

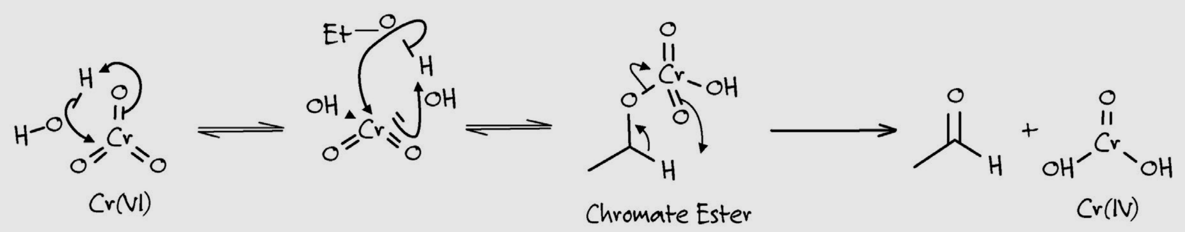


Figure 6.1. Jones reaction mechanism

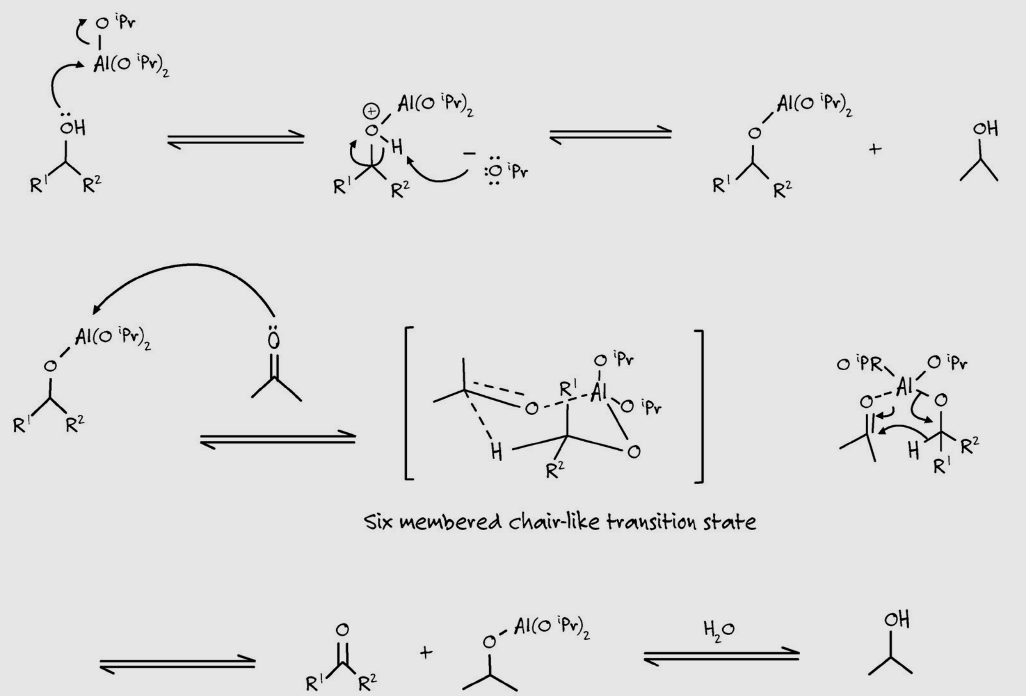


Figure 6.2. Oppenauer reaction mechanism

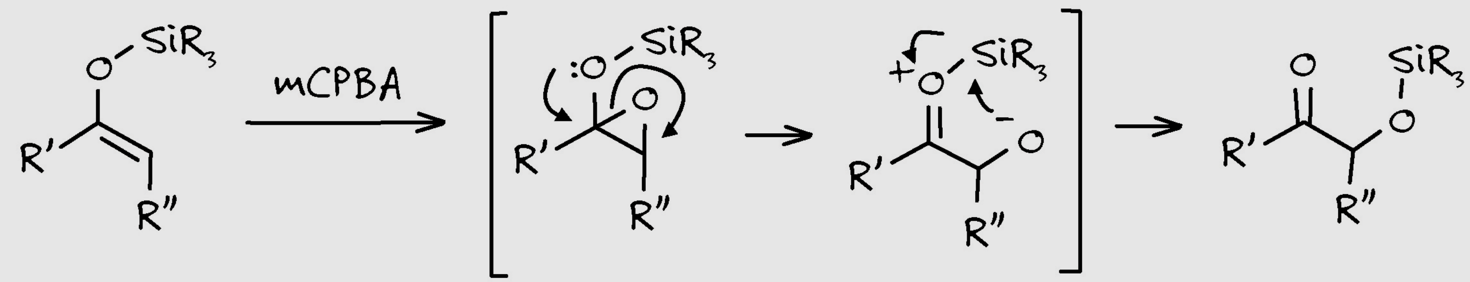


Figure 6.3. Rubottom reaction mechanism

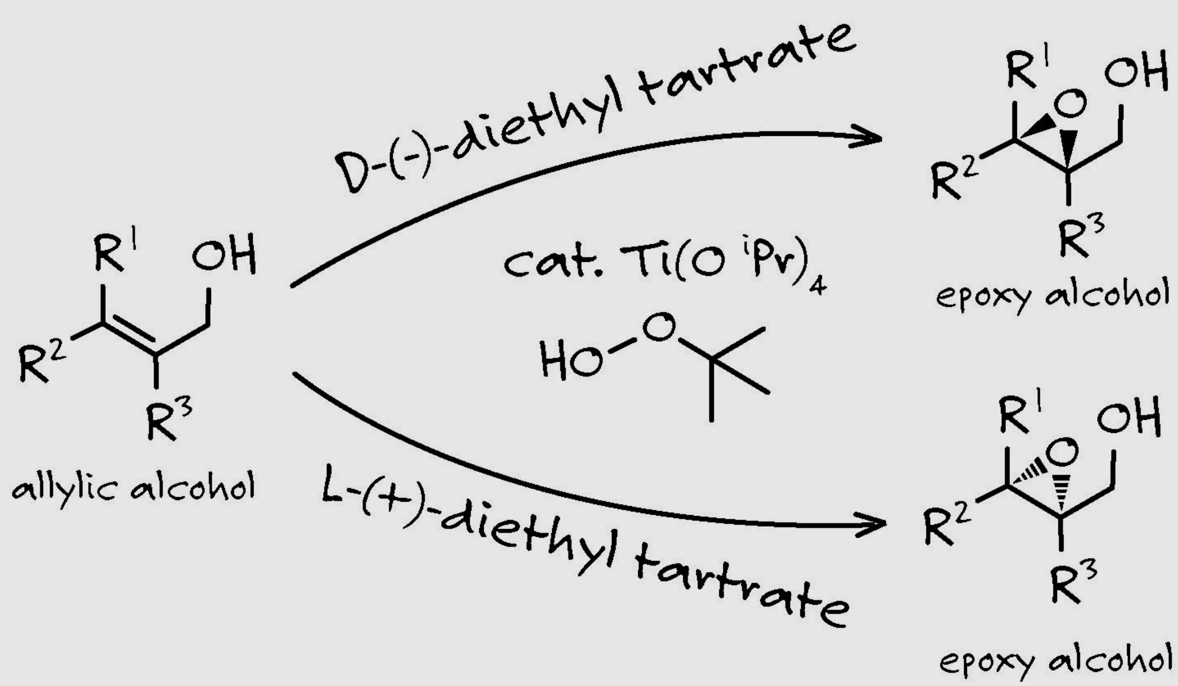


Figure 6.4. Sharpless asymmetric epoxidation reaction mechanism

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 can also be 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 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]

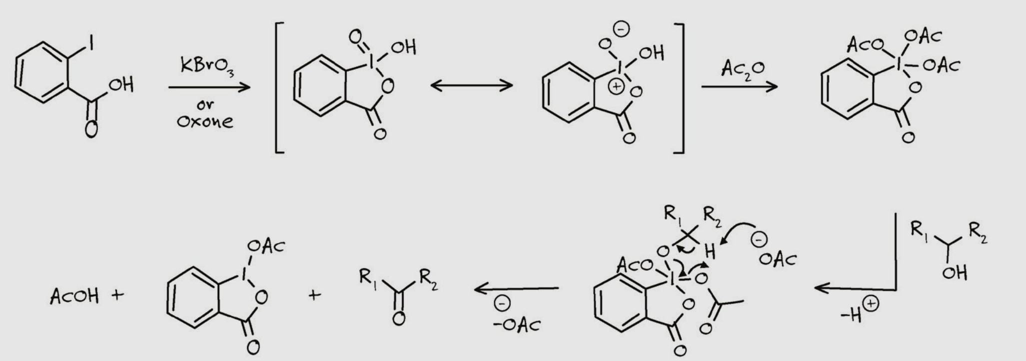


Figure 6.5. Dess-Martin reaction mechanism

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.*

QUIZ ANSWER — BECKMANN REARRANGEMENT REACTION

Correct answers are in **green/bold**. How did you do?

1. An (**acid** / base) catalyzed reaction is used to convert an (**oxime** / amide) to an (oxime / **amide**) functional group.
2. During this reaction, the cleavage of the (**C–C bond** / C–N bond) and formation of the (C–C bond / **C–N bond**) take place.
3. It is generally performed at (**high** / low) temperature and a (nitronium / **nitrilium**) ion is generated.
4. The (nitronium / **nitrilium**) reacts with (**water** / triethylamine) leading to the final product.
5. The Beckmann reaction was used to produce (**Caprolactam** / Caprolactone).
6. (**Caprolactam** / Caprolactone) is the starting material in the manufacture of (**nylon-6** / nylon-6,6).

JUMP TO THE QUIZ QUESTION
JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — DESS-MARTIN REACTION

Answer the questions below about the **Dess-Martin oxidation reaction:**

1. Question: When conducting this reaction with a secondary alcohol, the product will be an aldehyde. True or false?

2. Question: What does exposure of Dess–Martin periodinane (DMP) to the atmosphere vs. inert conditions do to this reaction?

3. Question: What are some ways to increase the rate of this reaction?

4. Question: What is the primary limitation of using 2-iodoxybenzoic acid (IBX) as the oxidizing agent in this reaction?

5. Question: Will use of acetic acid (HOAc) or tosylic acid (TsOH) produce a higher yield of DMP in this reaction?

JUMP TO THE PREVIOUS QUIZ QUESTION

CLICK TO SEE THE ANSWER TO THIS QUESTION

JUMP TO NEXT QUIZ QUESTIOIN

Product Selection for the Dess-Martin Reaction

Safety: 2-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
L09318	1-Adamantaneethanol, 98%
18005	1-Adamantanemethanol, 99%
B23831	1-Adamantanemethanol, 98%
16703	Adonitol, 98%
H52304	(S)-(-)-2-Amino-3-benzyloxy-1-propanol, 98+%
24403	(R)-(-)-2-Amino-1-butanol, 98%
B25212	(R)-(-)-2-Amino-1-butanol, 98%
L11449	(S)-(+)-2-Amino-1-butanol, 98+%
B24398	(±)-2-Amino-1-butanol, 97%
17635	4-Amino-1-butanol, 98%
A12680	4-Amino-1-butanol, 98%
L10429	3-Amino-2,2-dimethyl-1-propanol, 95%
29460	6-Amino-1-hexanol, 94%
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%
A17814	2-Amino-2-methyl-1-propanol, 95%, may cont. ca 5% water

SKU	Description
	Primary and secondary alcohols
40044	(R)-(-)-2-Amino-1-propanol, 98%
L11030	(R)-(-)-2-Amino-1-propanol, 98%
10445	(S)-(+)-2-Amino-1-propanol, 98%
B24916	(S)-(+)-2-Amino-1-propanol, 98%
L03608	(±)-2-Amino-1-propanol, 98%
10446	3-Amino-1-propanol, 99%
45991	1,5-Anhydro-D-sorbitol, 97%
30287	D-Arabitol, 99%
22586	L(-)-Arabitol, 99%
14839	Benzyl alcohol, 99%, pure
39122	Benzyl alcohol, for analysis
39688	Benzyl alcohol, 98+%, Extra Dry, AcroSeal®
44700	Benzyl alcohol, specified according to requirements of Ph.Eur.
44772	Benzyl alcohol, ACS reagent
H50328	(R)-(-)-2-Benzylamino-1-butanol, 99%
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%
45209	1-BOC-azetidine-3-methanol, 96%
36827	N-BOC-4-Hydroxypiperidine, 97%
39772	N-BOC-4-Piperidinemethanol, 97%
H26650	1-Boc-4-piperidinemethanol, 97%
H32786	(±)-1-Boc-pyrrolidine-2-methanol, 98%
38459	10-Bromo-1-decanol, 95%
B21483	10-Bromo-1-decanol, 95%

Click descriptions for product details and ordering information

SKU	Description
	Primary and secondary alcohols
H54762	7-Bromo-1-heptanol, 96%
27009	6-Bromo-1-hexanol, 95%
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%
40320	3-Bromo-1-propanol, 92%
B22857	3-Bromo-1-propanol, 95%
29344	11-Bromo-1-undecanol, 97%
L14448	11-Bromoundecanol, 97%
10762	(±)-1,3-Butanediol, 99%, extra pure
10764	2,3-Butanediol, 98%, mixture of racemic and meso forms, techn.
21798	(2R,3R)-(-)-2,3-Butanediol, 98+%, 99+% ee
24773	(2S,3S)-(+)-2,3-Butanediol, 99%
10769	1-Butanol, 99%, extra pure
16769	1-Butanol, 99+%, for spectroscopy
23208	1-Butanol, 99.5%, for analysis
39375	1-Butanol, for HPLC
39896	1-Butanol, 99+%, Extra Dry, AcroSeal®
42349	1-Butanol, 99.5%, ACS reagent, meets the requirements of Reag.Ph.Eur.
L13171	1-Butanol, 99%
10770	sec-Butanol, 99%, extra pure
22029	sec-Butanol, 99+%, for analysis
29575	3-Buten-1-ol, 98+%
L00767	3-Buten-1-ol, 98+%
15433	2-Butoxyethanol, 99%, extra pure
H55285	4-tert-Butyldimethylsiloxy-1-butanol, 97%
22340	2-Butyn-1-ol, 98%
A15709	2-Butyn-1-ol, 98%
15733	3-Butyn-1-ol, 97%
A11477	3-Butyn-1-ol, 98%
32774	CAPSO, 99%

SKU	Description
	Primary and secondary alcohols
35631	4-Chloro-1-butanol, 85%, balance THF and HCl
L04042	4-Chloro-1-butanol, tech. 85%
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%
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%
A19490	9-Decen-1-ol, 90+%
16576	Decyl alcohol, 98+%
A17288	1-Decanol, 98+%
H53400	5-Decyn-1-ol, 97%
L05523	2-Decyn-1-ol, 97%
L13916	(S)-(+)-2-Dibenzylamino-3-phenyl-1-propanol, 99%
36509	2,3-Dichloro-1-propanol, 97%
A18444	2,3-Dichloro-1-propanol, 97+%
H53501	4,4-Diethylamino-2-butyn-1-ol, 98%
H30194	3,3-Dimethyl-1-butanol, 97%
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
40919	DL-1,4-Dithiothreitol, 98%, pure
42638	DL-1,4-Dithiothreitol, for biochemistry, 1M solution in water

Click descriptions for product details and ordering information

SKU	Description
	Primary and secondary alcohols
B20144	1H,1H,7H-Dodecafluoro-1-heptanol, 97%
15545	1-Dodecanol, 98%
A12228	1-Dodecanol, 98%
11770	Dulcitol, 99+%
21546	1-Eicosanol, 98%
L08807	1-Eicosanol, 96%
11782	meso-Erythritol, 99%
15602	2-Ethoxyethanol, 99%, extra pure
11789	2(2-Ethoxyethoxy)ethanol, 98+%
25905	1-Ethoxy-2-propanol, 95%
B21026	2-Ethyl-1-butanol, 99%
14675	Ethylene glycol, 99+%, extra pure
29553	Ethylene glycol, 99.5%, for analysis
41001	Ethylene glycol, 95%, pure
43381	Ethylene glycol, 99.8%, anhydrous, AcroSeal®
44423	Ethylene glycol, technical
11853	2-Ethyl-1-hexanol, 99%
A17104	2-Ethyl-1-hexanol, 99%
A10414	2,2,3,3,4,4,4-Heptafluoro-1-butanol, 98%
12036	1-Heptanol, 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%
12048	1-Hexadecanol, 96%
A11180	1-Hexadecanol, 98%
B20587	2,2,3,4,4,4-Hexafluoro-1-butanol, 95%
14754	1,1,1,3,3,3-Hexafluoro-2-propanol, 99.5+%, pure
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
44582	1,1,1,3,3,3-Hexafluoro-2-propanol, 99%, for analysis
A13734	cis-2-Hexen-1-ol, 94%, remainder mainly trans isomer

SKU	Description
	Primary and secondary alcohols
15814	trans-2-Hexen-1-ol, 96%
A13272	trans-2-Hexen-1-ol, 97%
12077	cis-3-Hexen-1-ol, 98%
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%
21304	5-Hexen-1-ol, 99%
A15766	5-Hexen-1-ol, 98%
12079	Hexyl alcohol, 98%, pure
43386	Hexyl alcohol, 99%, anhydrous, AcroSeal®
A18232	1-Hexanol, 99%
A13339	2-Hexyn-1-ol, 97%
36708	3-Hydroxypiperidine, 98%
36651	4-Hydroxypiperidine, 99+%
12226	Inositol, 98+%
14932	Isopropanol, 99.5+%, pure
16788	Isopropanol, 99+%, for spectroscopy
18413	Isopropanol, 99.5%, for analysis
32696	Isopropanol, 99.8%, Extra Dry, AcroSeal®
32727	Isopropanol, 99.5%, for molecular biology, DNAse, RNAse and Protease free
36440	Isopropanol, 99.5%, Extra Dry over Molecular Sieve, AcroSeal®
38391	Isopropanol, 99.5%, for HPLC
38392	Isopropanol, 99.5%, for HPLC gradient grade
38971	Isopropanol, 99.5+%, extra pure
39698	Isopropanol, 99+%, specified according to the requirements of Ph.Eur.
41279	Isopropanol, 99.5%, for spectroscopy ACS
42383	Isopropanol, 99.6%, ACS reagent, meets the requirements of Reag.Ph.Eur.
44425	Isopropanol, technical
44708	Isopropanol, 99%, for biochemistry and histology, AcroSeal®
29580	Maltitol, 95%
12534	D-Mannitol, 98+%
42392	D-Mannitol, ACS reagent

Click descriptions for product details and ordering information

SKU	Description
	Primary and secondary alcohols
34756	3-Mercapto-1-hexanol, 96%
12479	Methanol, 99.9%, for biochemistry, AcroSeal®
16783	Methanol, 99.9%, for spectroscopy
17684	Methanol, 99.9%, for analysis
17715	Methanol, 99+%, extra pure
26828	Methanol, 99.8%, for HPLC
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®
32695	Methanol, 99.9%, Extra Dry, AcroSeal®
32790	Methanol, 99.8%, for electronic use (MOS), residue free
36439	Methanol, 99.8%, Extra Dry over Molecular Sieve, AcroSeal®
41377	Methanol, >=99.8%, for spectroscopy ACS
42395	Methanol, >=99.8%, ACS reagent, meets the requirements of Reag.Ph.Eur.
44431	Methanol, technical
14936	2-Methoxyethanol, 99.5+%, for analysis
16858	2-Methoxyethanol, 99+%, for spectroscopy
18079	2-Methoxyethanol, 99+%, extra pure
39689	2-Methoxyethanol, 99+%, Extra Dry, AcroSeal®
42878	2-Methoxyethanol, for HPLC
44748	2-Methoxyethanol, ACS reagent
24499	1-Methoxy-2-propanol, 98.5%, extra pure
33178	(R)-(-)-1-Methoxy-2-propanol, 98+%
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%
12648	3-Methyl-1-butanol, 98%, pure
41272	3-Methyl-1-butanol, 99%, for biochemistry, AcroSeal®
41273	3-Methyl-1-butanol, ACS reagent
L13660	3-Methyl-1-butanol, mixture of isomers, 99%
17192	3-Methyl-2-buten-1-ol, 99%
A16089	3-Methyl-2-buten-1-ol, 98+%

SKU	Description
	Primary and secondary alcohols
H36436	3-Methyl-2-buten-1-ol, 97%
15663	3-Methyl-3-buten-1-ol, 97%
B23398	3-Methyl-3-buten-1-ol, 97%
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+%
B22356	3-Methyl-1-pentanol, 98%
14938	4-Methyl-2-pentanol, 99+%
B20729	2-Methyl-1-phenyl-1-propanol, 98%
B20936	2-Methyl-1-phenyl-2-propen-1-ol, tech. 85%
B22187	1-Methylpiperidine-2-methanol, 98%
15828	2-Methyl-1-propanol, 99+%, extra pure
16770	2-Methyl-1-propanol, 99+%, spectrophotometric grade
39895	2-Methyl-1-propanol, 99+%, Extra Dry, AcroSeal®
41264	2-Methyl-1-propanol, for HPLC
41265	2-Methyl-1-propanol, 99+%, ACS reagent
15029	2-Methyl-2-propen-1-ol, 98%
H60502	2-Methyl-2-propen-1-ol, 98%.
A10403	3-Methylthio-1-propanol, 98%
H60376	3-(4-Morpholinyl)-1-propanol, 95%
18011	1-Naphthalenemethanol, 98%
L01347	1-Naphthalenemethanol, 98+%
H27218	2-(1-Naphthyl)ethanol, 95%
L19968	1-(4-Nitrophenyl)glycerol, 99%
15747	1-Nonanol, 97%
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%
12930	1-Octadecanol, 95%
A12020	1-Octadecanol, 97%

Click descriptions for product details and ordering information

SKU	Description
Primary and secondary alcohols	
B20108	2,2,3,3,4,4,5,5-Octafluoro-1-pentanol, 98%
15063	1-Octanol, 99%, pure
22018	1-Octanol, ACS reagent
43458	1-Octanol, 99%, anhydrous, AcroSeal®
A15977	1-Octanol, 99%
H36188	1-Octanol, natural, 98%
A19014	cis-3-Octen-1-ol, 95%
A15960	trans-2-Octen-1-ol, 97%
38703	2-Octyn-1-ol, 98%
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
A13093	1-Pentanol, 98+%
A14262	cis-2-Penten-1-ol, 97%, remainder mainly trans-isomer
15001	4-Penten-1-ol, 99%
A11178	4-Penten-1-ol, 98+%
A12999	2-Pentyn-1-ol, 98%
19733	3-Pentyn-1-ol, 99%
L02951	3-Pentyn-1-ol, 98%
33043	4-Pentyn-1-ol, 95%
A10405	4-Pentyn-1-ol, 97%
L16580	1H,1H-Perfluoro-1-decanol, 98%
L16590	1H,1H-Perfluoro-1-dodecanol, tech. 90%
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%
18037	4-Phenyl-1-butanol, 97%
A13433	4-Phenyl-1-butanol, 97%

SKU	Description
Primary and secondary alcohols	
13059	1-Phenyl-1,2-ethanediol, 97%
L04551	(±)-1-Phenyl-1,2-ethanediol, 97%
L12533	7-Phenyl-1-heptanol, 97%
L12070	5-Phenyl-1-pentanol, 97%
A10830	(±)-1-Phenyl-1-propanol, 98+%
L13999	(R)-(+)-2-Phenyl-1-propanol, 98+%
L13988	(S)-(-)-2-Phenyl-1-propanol, 98+%
B23473	(±)-2-Phenyl-1-propanol, 97%
16131	3-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%
L06337	3-Phenyl-2-propyn-1-ol, 97%
15872	1,2-Propanediol, 99%, extra pure
22087	1,2-Propanediol, 99+%, for analysis
44741	1,2-Propanediol, ACS reagent
14948	1-Propanol, 99+%, extra pure
23207	1-Propanol, 99.5%, for analysis
38960	1-Propanol, for HPLC
39694	1-Propanol, 99.5%, Extra Dry, AcroSeal®
43436	1-Propanol, for spectroscopy ACS
44577	1-Propanol, ACS reagent
44627	1-Propanol, specified according to the requirements of Ph.Eur.
A19902	1-Propanol, 99+%
41840	2-Propoxyethanol, 98%, pure
20732	DL-Propranolol hydrochloride, 99%
H50340	2-n-Propyl-1-heptanol, 98%
H57954	2-n-Propyl-1-pentanol, 97%
34457	(R)-(+)-3-Pyrrolidinol, 98%
33943	(S)-(-)-3-Pyrrolidinol, 98+%
13273	D-Sorbitol, 97%
18073	1-Tetradecanol, 99%

Click descriptions for product details and ordering information

SKU	Description
	Primary and secondary alcohols
A19638	1-Tetradecanol, 97+%
29638	2,2,3,3-Tetrafluoro-1-propanol, 99+%
B21594	2,2,3,3-Tetrafluoro-1-propanol, 97%
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%
38132	4-Trimethylsilyl-3-butyn-1-ol, 98%
L04251	1-Trimethylsilylmethanol, 95%
H53457	5-Trimethylsilyl-4-pentyn-1-ol, 97%
38899	10-Undecen-1-ol, 98+%, stabilized
A14002	10-Undecen-1-ol, 99%
L11807	10-Undecyn-1-ol, 96%
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

Click descriptions for product details and ordering information

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 (e.g., HCl or HBr) 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 (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.

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.

Click here for a more in-depth look at the Wolff-Kishner reduction.

Reaction Mechanism Examples

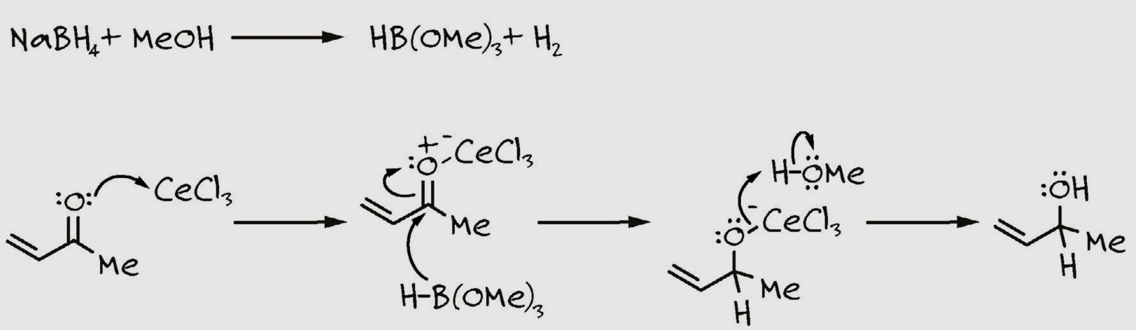


Figure 7.1. Luche reaction mechanism

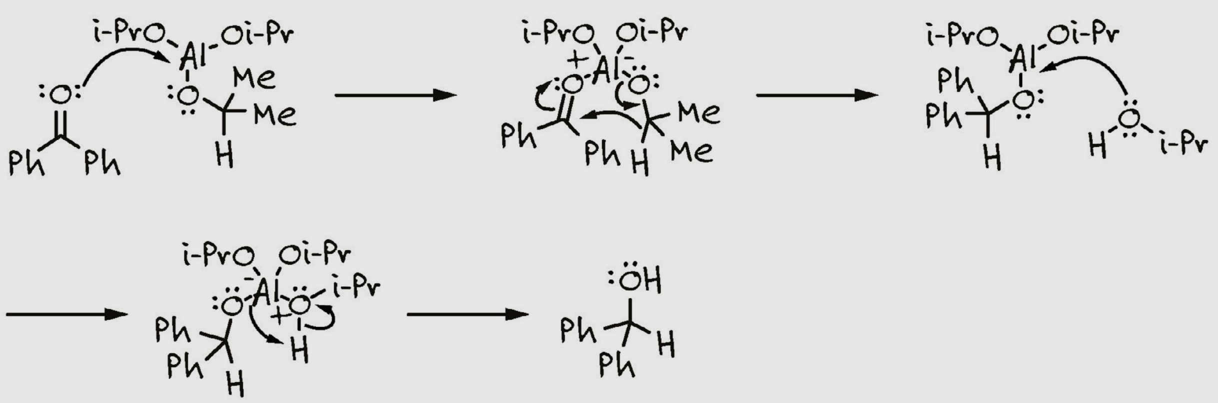


Figure 7.2. Meerwein-Ponndorf-Verley reaction mechanism

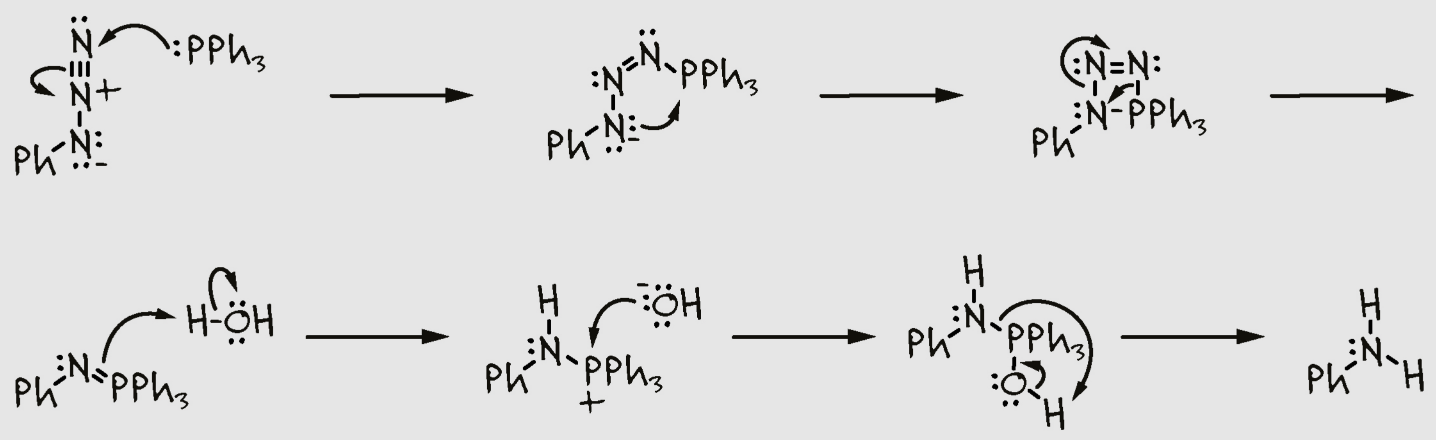


Figure 7.3. Staudinger reaction mechanism

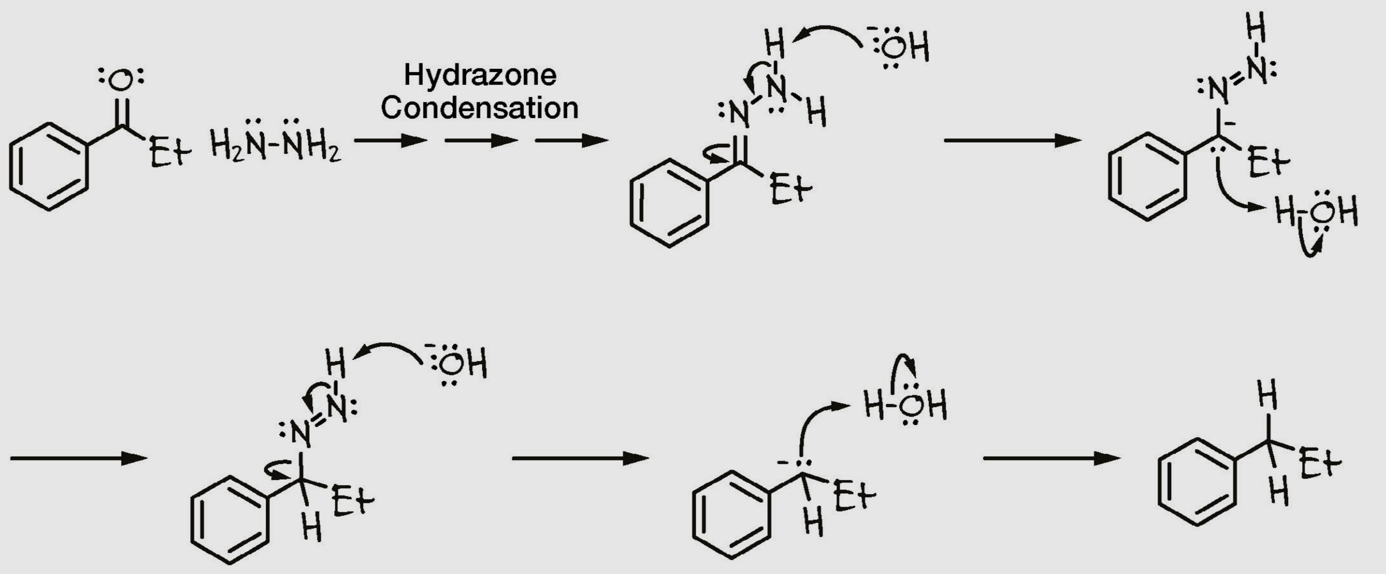


Figure 7.4. Wolff-Kishner reaction mechanism

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 7.5) since its discovery in 1913.[1]

One of the suggested mechanisms can be summarized in a sequence of one-electron and one-proton transfers. First, 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 carbeneas 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, including synthesis of 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 7.7).

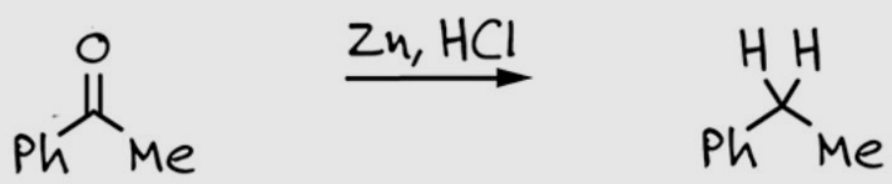


Figure 7.5. Simplified Clemmensen reaction

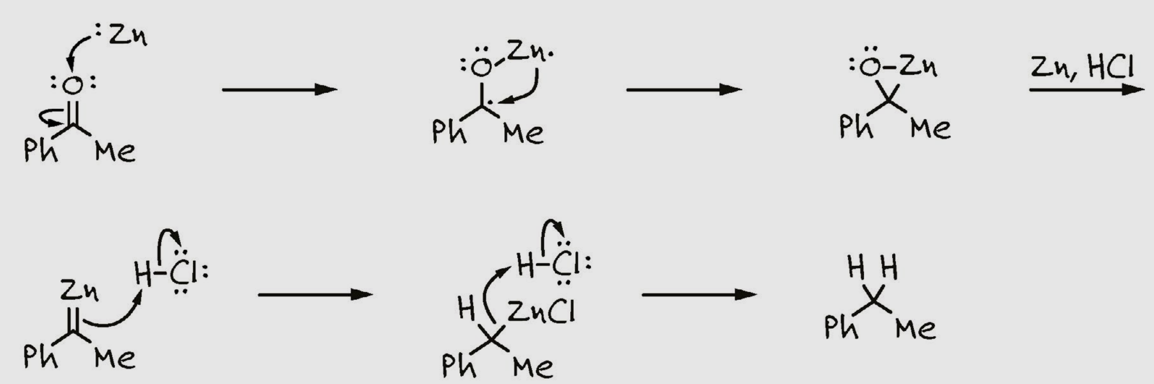


Figure 7.6. Detailed Clemmensen reaction mechanism

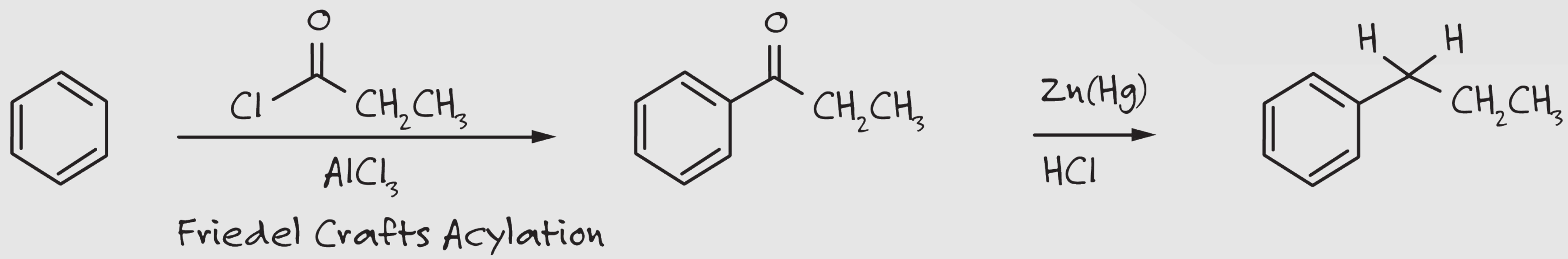


Figure 7.7. Reduction after Friedel Crafts reaction

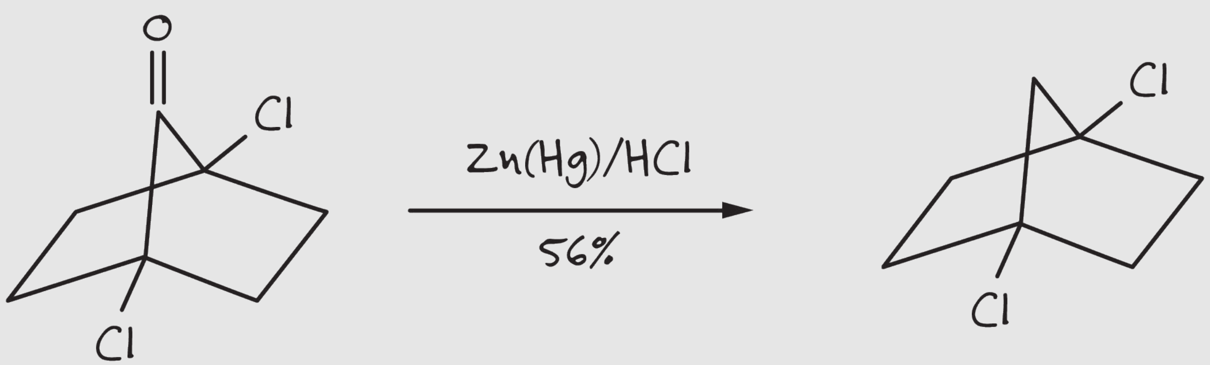


Figure 7.8. Synthesis of 1,4-dichloronorbonane

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

Reference Reaction Protocol

Synthesis of 1,4-dichloronorbonane[4]

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 and 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.

QUIZ ANSWER — DESS-MARTIN REACTION

Below are **answers** to each question regarding the **Dess-Martin oxidation reaction**.

1. **Question:** When conducting this reaction with a secondary alcohol, the product will be an aldehyde. True or false?
   Answer: False. Aldehydes are the product when conducted on a primary alcohol. Ketones are the product when this reaction is conducted on a secondary alcohol.

2. **Question**: What does exposure of Dess–Martin periodinane (DMP) to the atmosphere vs. inert conditions do to this reaction?
   Answer: Exposure of DMP to atmosphere accelerates this reaction, as discovered by Meyer et al. in 1994.

3. **Question:** What are some ways to increase the rate of this reaction?
   Answer: As noted above, exposure of DMP to the atmosphere can accelerate this reaction. Adding an extra equivalent of alcohol to DMP can also accelerate this reaction. Adding an equivalent of water is yet another way to accelerate this reaction.

4. **Question:** What is the primary limitation of using 2-iodoxybenzoic acid (IBX) as the oxidizing agent in this reaction?
   Answer: IBX is insoluble, or has very low solubility, in most organic solvents, which limits it use in organic synthesis.

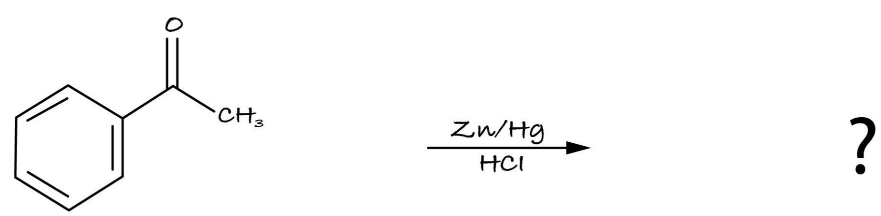
5. **Question:** Will use of acetic acid (HOAc) or tosylic acid (TsOH) produce a higher yield of DMP in this reaction?
   Answer: Ireland et al, discovered in 1993 that use of a catalytic amount of TsOH will produce a higher yield of DMP.

JUMP TO THE QUIZ QUESTION

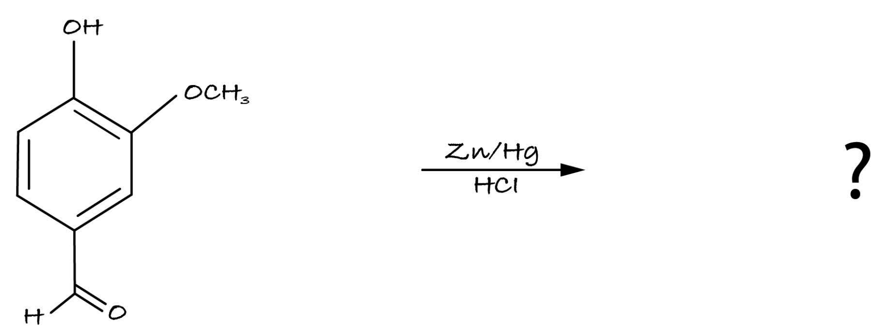
JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — CLEMMENSEN REDUCTION REACTION

Draw and name the Clemmensen reduction reaction product for each reaction shown below.



1. Acetophenone



2. 4-hydroxy-3-methoxy-benzaldehyde

JUMP TO THE PREVIOUS QUIZ QUESTION
CLICK TO SEE THE ANSWER TO THIS QUESTION
JUMP TO NEXT QUIZ QUESTIOIN

Product Selection for the Clemmensen Reaction

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
11538	2,4-Dimethoxybenzaldehyde, 98%
A12549	2,4-Dimethoxybenzaldehyde, 98%
A19928	2,5-Dimethoxybenzaldehyde, 98+%
036684	4-Dimethylaminobenzaldehyde, ACS
A11712	4-Dimethylaminobenzaldehyde, 98%
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%
11932	2-Fluorobenzaldehyde, 97%
A13800	2-Fluorobenzaldehyde, 97%
11933	3-Fluorobenzaldehyde, 98+%
A18904	2-Fluoro-5-methoxybenzaldehyde, 97%

SKU	Description
	Aldehydes
A13287	4-n-Hexyloxybenzaldehyde, 98%
A13541	3-Hydroxybenzaldehyde, 97%
A13580	4-Hydroxybenzaldehyde, 98%
A12971	2-Hydroxy-4-methoxybenzaldehyde, 98%
A15753	2-Hydroxy-5-methoxybenzaldehyde, 98%
A10264	2-Hydroxy-5-nitrobenzaldehyde, 98%
A14019	4-Isopropylbenzaldehyde, tech. 90%
A13962	3-Methoxybenzaldehyde, 98%
A15364	4-Methoxybenzaldehyde, 98%
A13594	3-Nitrobenzaldehyde, 99%
A11501	2-Nitrobenzaldehyde, 98+%
A11655	4-Nitrobenzaldehyde, 99%
B22329	4-Phenoxybenzaldehyde, 98%
B24591	2-(Trifluoromethyl)benzaldehyde, 98%
A19270	3,4,5-Trihydroxybenzaldehyde hydrate, 97%
B22792	2,4,5-Trimethoxybenzaldehyde, 98%

Click descriptions for product details and ordering information

SKU	Description
	Mercury
000522	Mercury, ACS, 99.999% (metals basis)
010242	Mercury, Electronic Grade, 99.9998% (metals basis)
044816	Mercury(II) bromide, ACS
19049	Mercury(II) bromide, 99+%
44812	Mercury(II) bromide, ACS reagent
036419	Mercury(I) chloride, ACS, 99.5% min
087240	Mercury(I) chloride, 99.5%
21312	Mercury(I) chloride, 99+%, extra pure
44759	Mercury(I) chloride, ACS reagent
012289	Mercury(II) iodide, ACS, 99.0% min (Assay-dried basis)
20574	Mercury(II) iodide, red, 99+%
A16130	Mercury(II) iodide, 99+%
21313	Mercury(I) nitrate dihydrate, 98%, for analysis
44718	Mercury(I) nitrate dihydrate, ACS reagent, 9th edition
014497	Mercury(II) nitrate hydrate, ACS, 98.0% min
21314	Mercury(II) nitrate monohydrate, 98+%
42394	Mercury(II) nitrate monohydrate, ACS reagent
38992	Mercury(I) sulfate, 97%
036286	Mercury(II) sulfate, ACS, 98.0% min
19050	Mercury(II) sulfate, 99+%
41365	Mercury(II) sulfate, ACS reagent
A16330	Mercury(II) sulfate, 98+%
037106	Mercury(II) thiocyanate
19689	Mercury(II) thiocyanate, 99+%

SKU	Description
	HCl
035607	Hydrochloric acid, 50% v/v aq. soln.
033257	Hydrochloric acid, ACS, HCl 36.5-38.0%
087617	Hydrochloric acid, 99.999% (metals basis), 36.5% min
L13091	Hydrochloric acid, 36% w/w aq. soln.
010990	Hydrochloric acid, 99.999999% (metals basis), 33% min

SKU	Description
	Zinc
19834	Zinc, 98+%, dust (stable acc. to UN classification class 4)
013789	Zinc flake, -325 mesh, 99.9% (metals basis)
000424	Zinc powder, -100 mesh, 99.9% (metals basis)
010835	Zinc powder, average 4-7 micron, 97.5% (metals basis)
036602	Zinc granules, ACS, -20 mesh, 99.8% min
039694	Zinc powder, -140+325 mesh, 99.9% (metals basis)
19450	Zinc, 99.995%, (trace metal basis), powder
22260	Zinc, granular, 20 mesh
22261	Zinc, granular, 30 mesh
36726	Zinc, 99.999%, (trace metal basis), powder, 40 mesh
L13310	Zinc powder, -100 mesh, 97+%
014629	Zinc mossy, 2.5cm (0.98in) & down, 99% (metals basis)
20145	Zinc, 99+%, mossy
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)
000648	Zinc wire, 0.25mm (0.01in) dia, 99.99+% (metals basis)
010435	Zinc wire, 3.18mm (0.125in) dia, 99.95% (metals basis)
011361	Zinc wire, 1.0mm (0.04in) dia, 99.9997% (metals basis)
012053	Zinc wire, 1.0mm (0.04in) dia, Puratronic|r, 99.9985% (metals basis)
012054	Zinc wire, 0.5mm (0.02in) dia, Puratronic|r, 99.994% (metals basis)
012055	Zinc wire, 0.25mm (0.01in) dia, Puratronic|r, 99.994% (metals basis)
042637	Zinc wire, 2.0mm (0.08in) dia, Puratronic|r, 99.999% (metals basis)
042703	Zinc wire, 0.25mm (0.01in) dia, 99.95% (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)

SKU	Description
	Ketone
10241	Acetophenone, 98%, pure
H55889	1-Adamantyl methyl ketone, 99%
10309	4'-Aminoacetophenone, 99%
10310	2-Aminoacetophenone hydrochloride, 96%
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%
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
	Et-O-Et
016767	Diethyl ether, anhydrous, ACS, 99% min, stab. with BHT

SKU	Description
	THF
32697	Tetrahydrofuran, 99.85%, Extra Dry, stabilized, AcroSeal®
34845	Tetrahydrofuran, 99.5%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal®
44836	Tetrahydrofuran, 99.85%, Extra Dry, stabilized, AcroSeal®, package of 4x25ML bottles
044608	Tetrahydrofuran, anhydrous, 99.8+%, stab. with 0.025% BHT, packaged under Argon in resealable ChemSeal bottles
047382	Tetrahydrofuran, anhydrous, 99.8+%, stab. with 0.025% BHT, packaged under Argon in resealable AcroSeal® bottles
047122	Tetrahydrofuran, anhydrous, 99.8+%, BHT-free, over molecular sieves, packaged under Argon in resealable ChemSeal bottles
047327	Tetrahydrofuran, anhydrous, 99.8+%, BHT-free, over molecular sieves, packed with Argon in resealable AcroSeal® bottles
041820	Tetrahydrofuran, anhydrous, 99.8+%, unstab., packaged under Argon in resealable ChemSeal bottles
042254	Tetrahydrofuran, anhydrous, 99.8+%, unstab.
45707	Tetrahydrofuran, 99.85%, Extra Dry, Unstabilized, AcroSeal®

Wolff–Kishner Reaction

While the previously described Clemmensen reaction covers reduction of aldehydes and ketones to the corresponding methylene, the Wolff–Kishner reaction is a complementary method carried out under basic conditions that allows the reduction of carbonyl functionalities into methylene groups in the presence of acid-sensitive substrates.

The Wolff-Kishner reduction was first carried out using sodium alkoxide in anhydrous alcohol.[1] In 1945, Soffer et al.[2] reported the use of a high-boiling solvent (e.g., diethylene or diethylene glycol) with metallic sodium or sodium methoxide. Some disadvantages of this method were soon noted by Huang–Minlon. Specifically, it was noted to require the use of an expensive 100% hydrazine hydrate, to use large amounts of solvent and sodium, and to require very long reaction times (i.e., 50-100 hours).[3]

In 1946, Huang–Minlon proposed a new variant where the aldehyde or ketone is heated with a reduced amount of hydrazine hydrate (85%), in the presence of alkali hydroxide, with diethylene glycol as the solvent. This improved process requires distillation to remove some water and excess hydrazine hydrate once the formation of hydrazone is considered completed, before the temperature is then raised to 180–200 °C. In this way, it is not necessary to use a large excess of sodium and the reaction time is also significantly reduced.[3]

Mechanism of the Wolff-Kishner Reaction

The first step of the reaction consists of the condensation of the hydrazine with aldehydes or ketones to obtain in situ the corresponding hydrazone. First, a nucleophilic addition occurs, followed by a proton transfer, and then the loss of water.

Following formation of the hydrazone, the Wolff–Kishner mechanism then involves deprotonation of the terminal nitrogen at a high temperature, in the presence of a base. It is in this step that the double bond between adjacent nitrogen atoms and the negative charge on the carbon is formed.

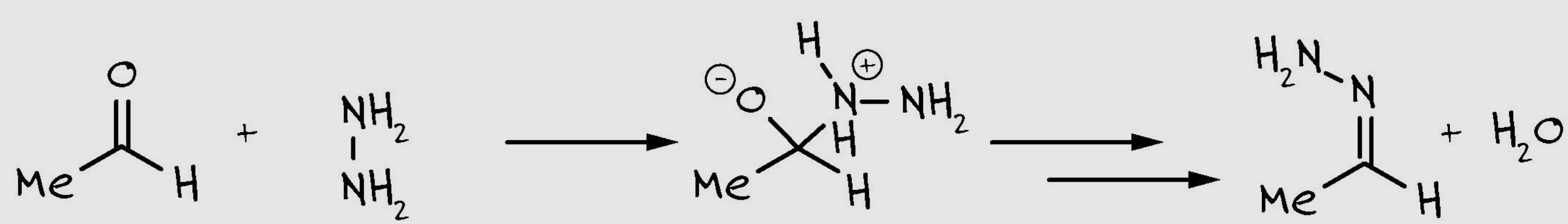


Figure 7.9. Formation of hydrazone

This carbanion is then protonated by water in the next step. The base–induced hydrogen shift is performed again and nitrogen (N_2) and water are then released, leading to the anionic species. A final protonation by the solvent then yields the hydrocarbon product.

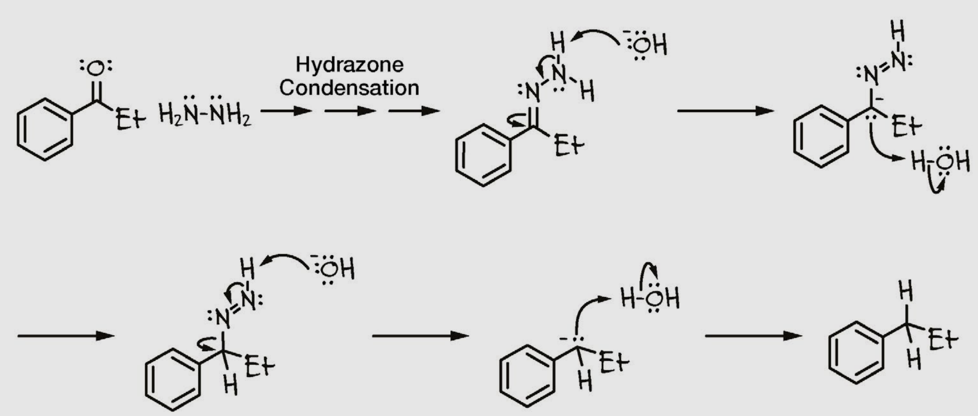


Figure 7.10. The Wolff-Kishner mechanism

A further improvement was later observed that involves use of a preformed hydrazone that is added slowly to potassium tert-butoxide, used as the base, and dimethyl sulfoxide (DMSO), used as solvent.[4] This variant, known as Cram modification, proceeds readily at room temperature and has served as the precursor to other variants that use more mild reaction conditions.[5]

Reaction Variant	Reagent	Base	Solvent	Temp (°C)
Soffer et al.	hydrazine (100%)	sodium methoxide	diethyleneglycol	180–200
Huang-Minlon	hydrazine (85%)	alkali hydroxide	diethyleneglycol	180–200
Cram	derived hydrazones	potassium tert-butoxide	dimethyl sulfoxide (DMSO)	room temperature

The Wolff-Kishner reaction is used in the reduction of camphor to comphane (Figure 7.11).

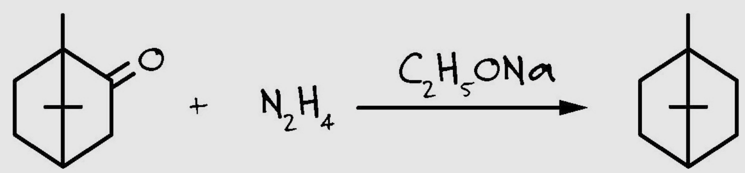


Figure 7.11. Reduction of camphor

Furthermore, this reduction method is widely used to obtain 3-alkylpyrroles starting from 4-acyl-2-pyrrolethiolcarboxylates (Figure 7.12).[6] This synthetic route, combined with the hydrolysis and decarboxylation of the thioester group, leads to a higher yield and avoids the formation of by-products observed with other methods.

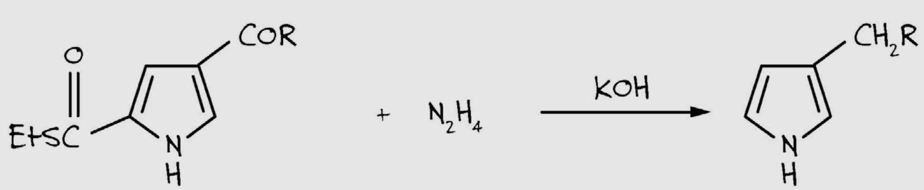


Figure 7.12. Synthesis of 3-alkylpyrroles

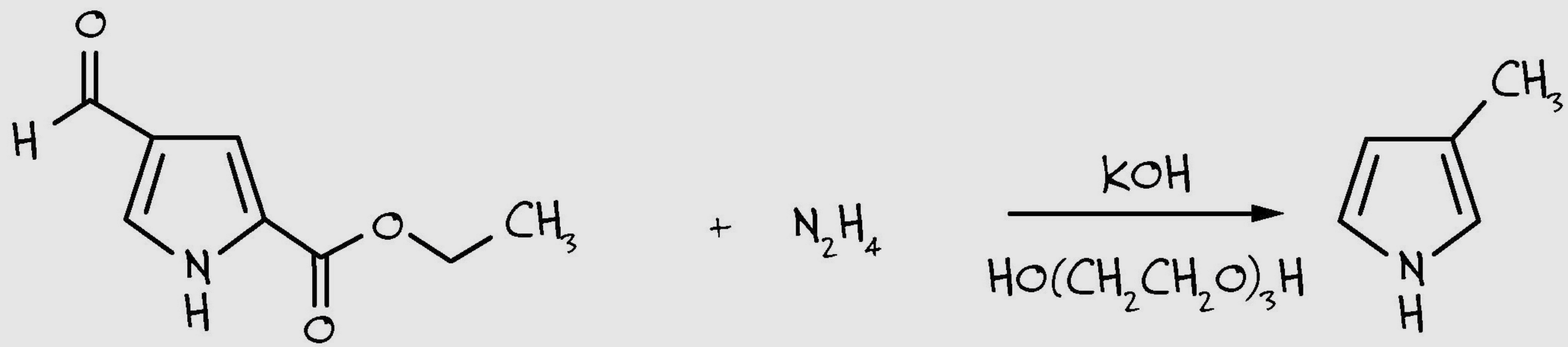


Figure 7.10. The Wolff-Kishner mechanism

Reference Reaction Protocols

Synthesis of 3-Methylpyrrole[6]

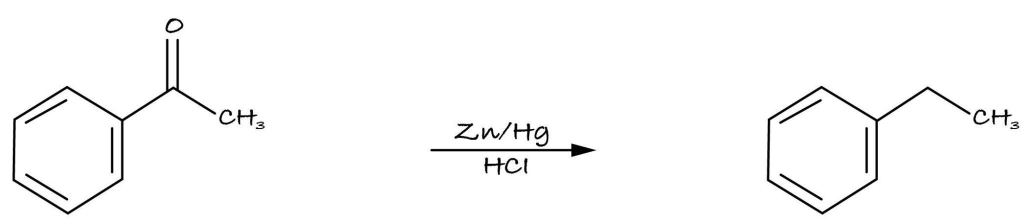
Ethyl 4-formyl-2-pyrrolethiolcarboxylate, potassium hydroxide, hydrazine, and triethylene glycol were stirred at 125 °C for 90 min. The temperature was then raised to 220 °C for 4 h. After extraction, purification by chromatography, and distillation, 3-methylpyrrole (44%) was obtained.

Key Literature References

1. *H. H. Szmanti Angew. Chem. internat. Edit. 1968, 7, 120-128.*
2. *M. D. Soffer; M. Soffer; K.W. Sherk J. Am. Chem. Soc. 1945, 67, 9, 1435–1436; C. H. Herr; F. C. Whitmore ; R. W. Schiessler J. Am. Chem. Soc. 1945, 67, 12, 2061–2063.*
3. *Huang-Minlon J. Am. Chem. Soc. 1946, 68, 2487–2488.*
4. *M. E. Furrow; A. G. Myers J. Am. Chem. Soc. 2004, 126, 5436-5445.*
5. *L. Caglioti; M. Magi Tetrahedron. 1963, 19, 1127-1131.*
6. *J. K. Grovesh; U. J. Anderson; H. Nagy Canadian Journal of Chemistry 1971, 49, 2427-2433.*

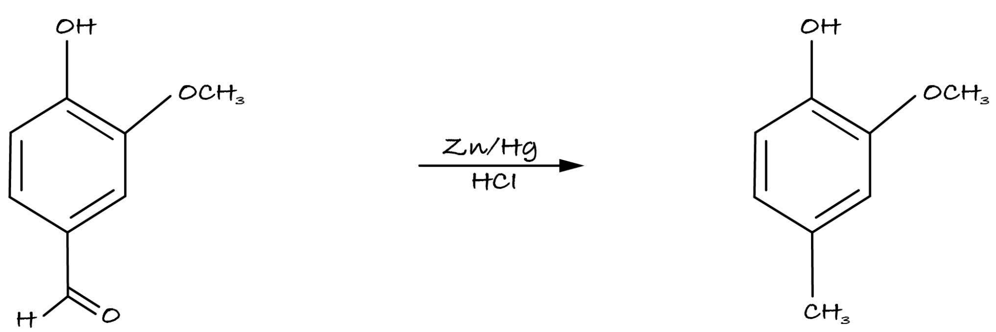
QUIZ ANSWER — CLEMMENSEN REACTION

Below are the structure and name of the Clemmensen reduction reaction products for each reaction shown.



1. Acetophenone

Ethylbenzene, or 1-phenyl ethane



2. 4-hydroxy-3-methoxy-benzaldehyde

2-methoxy-4methyl phenol

JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

REDUCTION REACTIONS

REACTION EXAMPLES

CLEMMENSEN REDUCTION

PRODUCT SELECTION FOR CLEMMENSEN REDUCTION

WOLFF–KISHNER REACTION

PRODUCT SELECTION FOR WOLFF–KISHNER REACTION

TEST YOUR KNOWLEDGE — WOLFF-KISCHNER REACTION

Determine if each of the following is true or false, relative to the Wolff-Kischner reaction.

1. The Wolff-Kischner reaction is carried out under acidic conditions and oxidizes aldehydes and ketones to the corresponding methylene. **True** OR **False**?

2. The first mechanistic step of the Wolff-Kischner reaction is an in situ formation of a hydrazone via condensation of thehydrazine with aldehydes or ketones. **True** OR **False**?

3. The Cram variation of the Wolff-Kischner reaction is performed at high temperatures (180-200 °C). **True** OR **False**?

JUMP TO THE PREVIOUS QUIZ QUESTION
CLICK TO SEE THE ANSWER TO THIS QUESTION
JUMP TO NEXT QUIZ QUESTIOIN

Product Selection for the Wolff-Kishner Reaction

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
	Hydrazine
19671	Hydrazine hydrate, 100% (Hydrazine, 64%)
20959	Hydrazine hydrate, 80% (Hydrazine, 51%)

SKU	Description
	KOH
013451	Potassium hydroxide, ACS, 85% min, K{2}CO{3} 2.0% max
42414	Potassium hydroxide, ca. 85%, ACS reagent, pellets
23255	Potassium hydroxide, ca. 85%, extra pure, flakes
A16199	Potassium hydroxide, flake, 85%
A18854	Potassium hydroxide, pellets, 85%

SKU	Description
	Diethylene glycol
12116	Diethylene glycol, 99%, extra pure
A14728	Diethylene glycol, 99%

SKU	Description
	Methyl sulfoxide
036480	Dimethyl sulfoxide, ACS, 99.9% min
043998	Dimethyl sulfoxide, anhydrous, 99.8+%, packaged under inert gas in resealable ChemSeal^t bottles
61042	Methyl sulfoxide, 99.7+%, Extra Dry, AcroSeal®
37522	Methyl sulfoxide, 99.7+%, Extra Dry over Molecular Sieve, AcroSeal®

SKU	Description
	Potassium tert-butoxide
16888	Potassium tert-butoxide, 98+%, pure
36499	Potassium tert-butoxide, pure, 20 wt.% solution in THF
42879	Potassium tert-butoxide, pure, 1.6-1.7M (20 wt.%) solution in THF, AcroSeal®
37122	Potassium tert-butoxide, pure, 1M solution in THF, AcroSeal®
42612	Potassium tert-butoxide, 1M solution in tert-butanol, AcroSeal®
44583	Potassium tert-butoxide, 2M (25% w/w) solution in 2-MeTHF, AcroSeal®

SKU	Description
	Sodium borohydride
038788	Sodium borohydride, 98%
088983	Sodium borohydride, 98% min
013432	Sodium borohydride, 98+%
38993	Sodium borohydride, 12% solution in 40% aq. sodium hydroxide solution
087659	Sodium borohydride, stable aq. soln., 4.4M in 14M NaOH
19113	Sodium borohydride, 0.5M solution in diglyme, AcroSeal®

Click descriptions for product details and ordering information

Electrophilic Addition Reactions

An addition reaction occurs when two molecules are joined to create a more complex compound, where all of the atoms in the original molecules are usually incorporated into the larger one. Electrophilic addition involves the attack of a primary substrate by an electrophile. The substrate generally possesses a carbon-carbon double or triple bond.

One of the first named reactions featuring electrophilic addition was the Prilezhaev reaction, named after the Russian chemist Nikolai Alexandrovich Prilezhaev who, in 1909, was the first to use peroxycarboxylic acids to oxidize isolated double bonds to the corresponding oxiranes (i.e., epoxides). Because of its wide utility, epoxidation is one of the most frequently used reactions in organic chemistry. Epoxides, such as epichlorohydrin, are used in the manufacture of epoxy resins, a group of adhesives.

Some of the most common named electrophilic addition reactions are:

- Noyori asymmetric hydrogenation
- Prilezhaev reaction
- Schwartz hydrozirconation
- Shi asymmetric epoxidation
- Simmons-Smith cyclopropanation

Noyori Asymmetric Hydrogenation Reaction

In 1980, the Japanese Nobel prize-winning chemist Ryoji Noyori reported that BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) complexed with ruthenium [BINAP-Ru(II)] catalyzed the asymmetric hydrogenation of alpha-(acylamino) acrylic acids or esters to give the corresponding amino acid derivatives in excellent enantiomeric yields. Several years later, it was discovered that asymmetric hydrogenation of a wide variety of functionalized olefins could be achieved utilizing BINAP-Ru(II) dicarboxylate complexes. Subsequently, it was found that oligomeric halogen-containing BINAP-Ru(II) complexes were efficient catalysts for the asymmetric hydrogenation of functionalized ketones. Following these discoveries, the reduction of both functionalized olefins and ketones using BINAP-Ru(II) in the presence of hydrogen gas became known as Noyori asymmetric hydrogenation.

Industrial uses of this technique include the synthesis of the anti-inflammatory drug naproxen and the antibacterial agent levofloxacin.

Prilezhaev Reaction

In 1909, Russian chemist Nikolai Alexandrovich Prilezhaev demonstrated the oxidation of isolated double bonds to the corresponding epoxides using peroxycarboxylic acids. The reaction subsequently became known as the Prilezhaev reaction. This method of using peroxycarboxylic acids to prepare epoxides is among the most widely used, unless an enantiomerically pure form is required, for which other methods such as the Shi asymmetric epoxidation can be utilized.

The most commonly used reagent for this reaction is the commercially available meta-chloroperoxybenzoic acid (mCPBA). However, other possible reagents include magnesium monoperphthalate and peracetic acid.

Epoxidation is one of the most frequently used reactions in organic chemistry. It is commercially important because epoxidation followed by polymerizaton gives glycols or polyoxoalkylenes, which are used as detergents, lubricants, waxes, and components of hydraulic liquids.

Schwartz Hydrozirconation Reaction

In 1970, Helmut Weigold and Peter C. Wailes first prepared the reagent zirconocene hydrochloride. However, it was not until 1974 that Donald W. Hart and Jeffrey Schwartz demonstrated how this reagent could be used in organic synthesis. Hart and Schwartz reacted the organozirconium intermediates with electrophiles such as hydrochloric acid, bromine, and acid chlorides to generate the corresponding alkane, bromoalkanes, and ketones. Subsequently, the reaction of zirconocene hydrochloride ($(C_5H_5)_2ZrHCl$), also known as Schwartz's reagent, with multiple bonds to create alkenylzirconium compounds became known as the Schwartz hydrozirconation.

The reagent is commercially available but can also be readily prepared by the reduction of zirconocene dichloride with lithium aluminium hydride. Schwartz's reagent is used in the synthesis of some macrolides, a class of natural products that show antibiotic and antifungal activity that have been used to produce several drugs. It was also used in the total synthesis of apoptolidin by Kyriacos Nicolaou to prepare an important vinyl iodide fragment of the molecule.

Shi Asymmetric Epoxidation Reaction

There had been many previous attempts to create an efficient non-metal catalyst for asymmetric epoxidations. In 1996, Yian Shi of Colorado State University developed a fructose-derived ketone catalyst that demonstrated excellent enantioselectivity. Since this discovery, the use of Shi's catalyst has become known as the Shi asymmetric epoxidation.

The Shi epoxidation involves treating alkenes with oxone (potassium peroxymonosulfate) in the presence of the Shi catalyst. The reaction is believed to proceed via a dioxirane intermediate generated from the ketone catalyst by the oxone. One potential side reaction that can occur is the Baeyer-Villiger oxidation, where rearrangement of the peroxy group results in the formation of an ester. However, this can be mitigated by maintaining the pH at an optimum level of 10.5.

The Shi epoxidation has been used in the key step of several total synthesis campaigns, including the synthesis of glabrescol, a chiral C2-symmetric pentacyclic oxasqualenoid, by Elias J. Corey and colleagues.

Simmons-Smith Cyclopropanation Reaction

In 1958, Howard Ensign Simmons Jr. and Ronald D. Smith stereospecifically converted unfunctionalized alkenes such as cyclohexene to cyclopropanes using diiodomethane (CH_2I_2) in the presence of a zinc-copper couple. This reaction proved to be general, and has since become an important method of preparing cyclopropanes. This is known today as the Simmons-Smith cyclopropanation.

The zinc-copper couple can be prepared by reacting zinc powder with copper sulfate solution. However, a zinc-silver couple often gives better yields and shorter reaction times. The use of diethylzinc with diiodomethane also gives excellent results and is known as the Furukawa modification. The use of iodo- or chloromethyl samarium iodide for the cyclopropanation of allylic alcohols in the presence of other olefins is known as the Molander modification.

The Simmons-Smith cyclopropanation reaction was used in the total synthesis of the antimitotic agent (+)-curacin A by Shigeo Iwasaki's team to generate the cyclopropane ring.

Click here for a more in-depth look at the Simmons-Smith cyclopropanation reaction.

Reaction Mechanism Examples

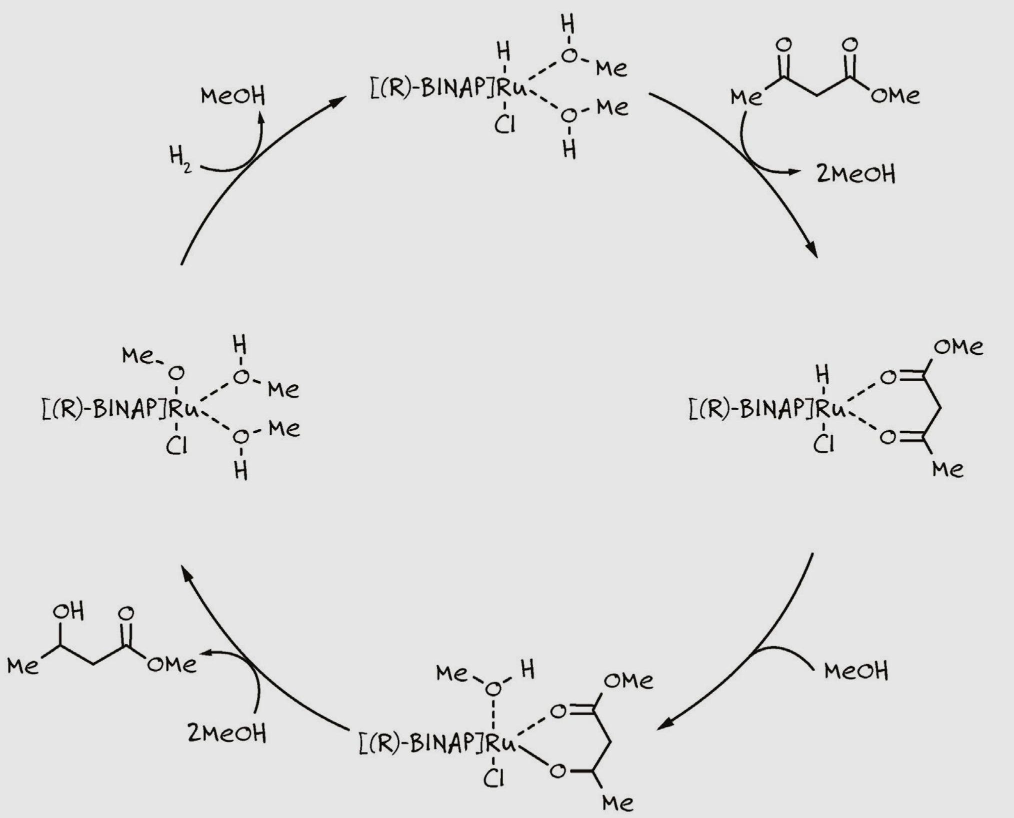


Figure 8.1. Noyori asymmetric hydrogenation mechanism

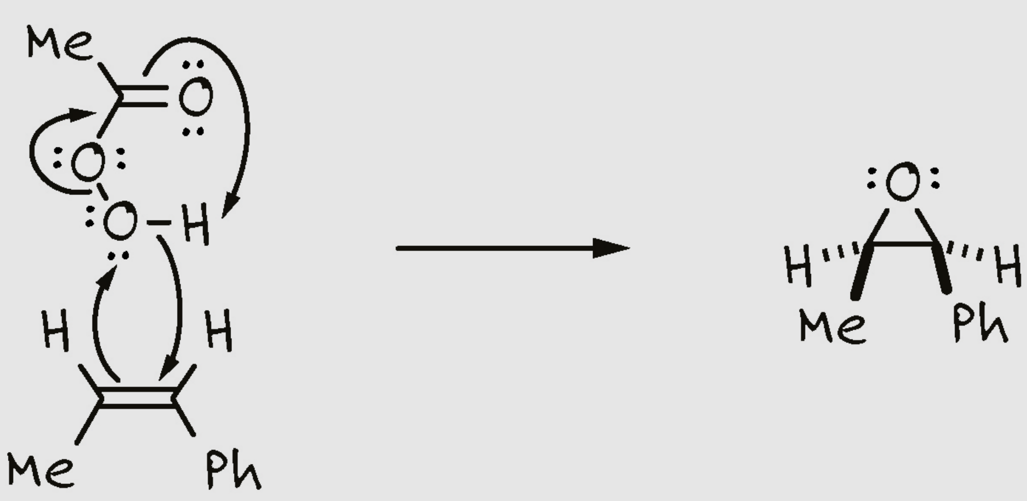


Figure 8.2. Prilezhaev reaction mechanism

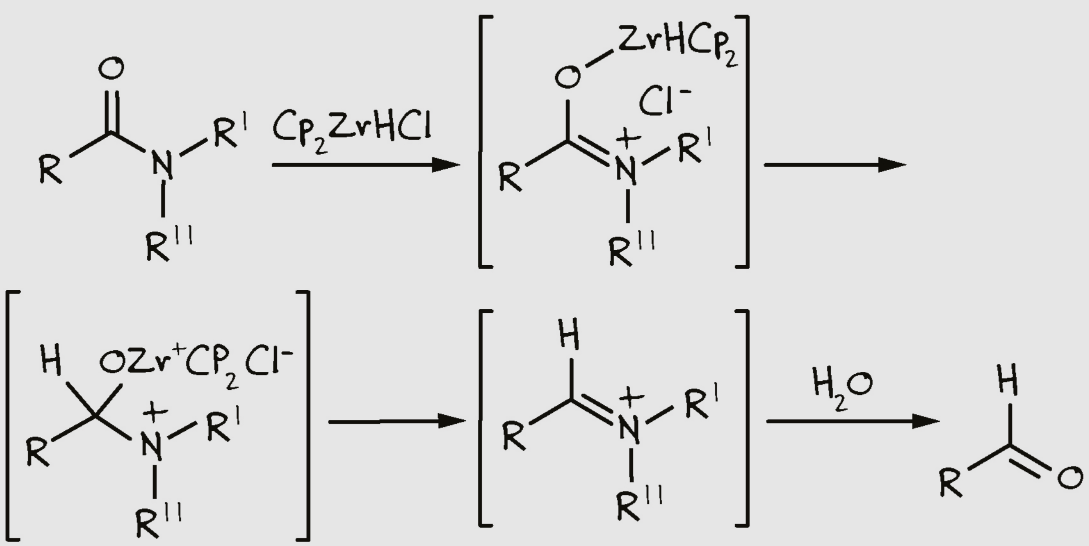


Figure 8.3. Schwartz hydrozirconation mechanism

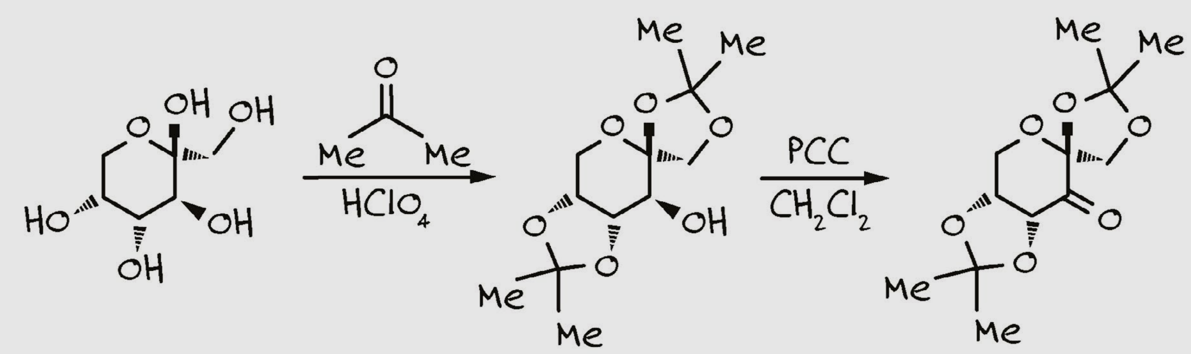


Figure 8.4. Shi asymmetric epoxidation mechanism

Simmons-Smith Cyclopropanation Reaction

In 1958, Howard Ensign Simmons Jr. and Ronald Smith from DuPont Company reported a reaction between an olefin with Zn/Cu (zinc–copper couple) and CH_2I_2 (diiodomethane) to form the corresponding cyclopropane (see Figure 8.5).[1]

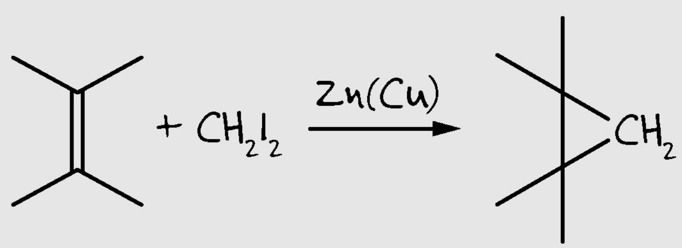


Figure 8.5. Simplified Simmons-Smith reaction

This is a typical electrophilic addition where a pi bond is cleaved, and two covalent bonds are formed by the addition of an electrophile.

The organozinc, obtained by the reaction of zinc-copper couple and diiodomethane, respects the Schlenk equilibrium (see Figure 8.6), already observed in Grignard reagents.

$$2\ CH_2I_2 + 2\ Zn \longrightarrow 2\ ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

Figure 8.6. Schlenk equilibrium

Regarding the monoalkylzinc carbenoid ICH_2ZnI and the dialkylzinc carbenoid ICH_2ZnCH_2I, it is still unknown as is which is the reactive species. However, the use of this reagent avoids handling diazomethane, a toxic and unstable gas. The addition of the methylene occurs in a concerted mechanism since all bonds are broken and are formed in only one step. (see Figure 8.7).

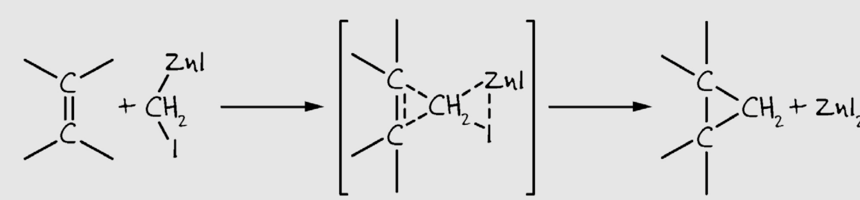


Figure 8.7. Simmons-Smith reaction mechanism

This is a syn addition and it takes place on the less hindered side of the alkene. However, the stereochemistry can be controlled by coordinating organozinc reagent (i.e., with oxygen). In 1978, in fact, Pereyre and coworkers observed that the cyclopropane ring is formed on the same side of the hydroxyl group after the reaction of cyclic allylic alcohol with Simmons–Smith reagent.[2] A variant of this reaction has been introduced later by Furukawa et al. who used commercially available diethylzinc as reactive agent.[3] Furthermore, researchers observed that an alkene with an electron donor substituent used as starting material, gives a final product in high yield.

The biggest advantages of Simmons–Smith reaction are the broad variety of substrates, the control of stereochemistry and the wide range of functional groups that can be used. Asymmetric cyclopropanations have attracted a lot of interest due to the fact that they are an important step in the synthesis of natural products. R-muscone, for example, is used in fragrances for its typical smell of musk. In nature, the muscone can be extracted by musk deer, but the synthesis of this product is more efficient and less costly.

Reference reaction protocol

Synthesis of (R)-muscone[4]

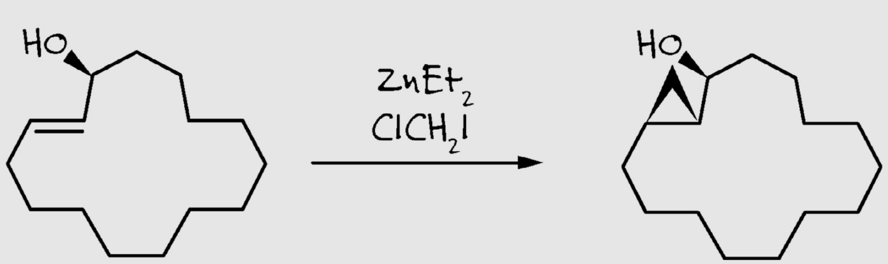


Figure 8.8. Synthesis of (R)-muscone

A solution of Et_2Zn (0.4 M) in 1,2-dichloroethane was prepared and cooled to 0 °C, then 4 equivivalents of chloroiodomethane were added and stirred for 10 min. A solution of (lS,2E)-2~cyclopentadecenol (3.5 mmol) in 1,2- dichloroethane was added slowly and stirred for 30 min at 0 °C. After the work-up, the target molecule was obtained with 91% yield.

Key Literature References

1. *Simmons, H.E. and Smith, R.D. (1958) J. Am. Chem. Soc., (1958), 80, 5323-5324.*
2. *Ratier, M., Castaing, M., Godet, J.-Y., and Pereyre, M. (1978) J. Chem. Res. Miniprint, (1978), 2309-2318.*
3. *J. Furukawa, N. Kawabata and J. Nishimura, Tetrahedron Letters, 1966, 3353.*
4. *Oppolzer W;, and Radinov R.N. J. Am. Chem. Soc., (1993), 115 (4), 1593-1594.*

QUIZ ANSWER — WOLFF-KISCHNER REACTION

Below are **correct** answers to each question, relative to the Wolff-Kischner reaction.

1. The Wolff-Kischner reaction is carried out under acidic conditions and oxidizes aldehydes and ketones to the corresponding methylene. **True** OR **False**?

   False. The Wolff-Kischner reaction is carried out under basic conditions and reduces carbonyls in methylene groups.

2. The first mechanistic step of the Wolff-Kischner reaction is an in situ formation of a hydrazone via condensation of thehydrazine with aldehydes or ketones. **True** OR **False**?

   True. This is the first step of the mechanism, which is followed by a proton transfer and loss of water.

3. The Cram variation of the Wolff-Kischner reaction is performed at high temperatures (180-200 °C). **True** OR **False**?

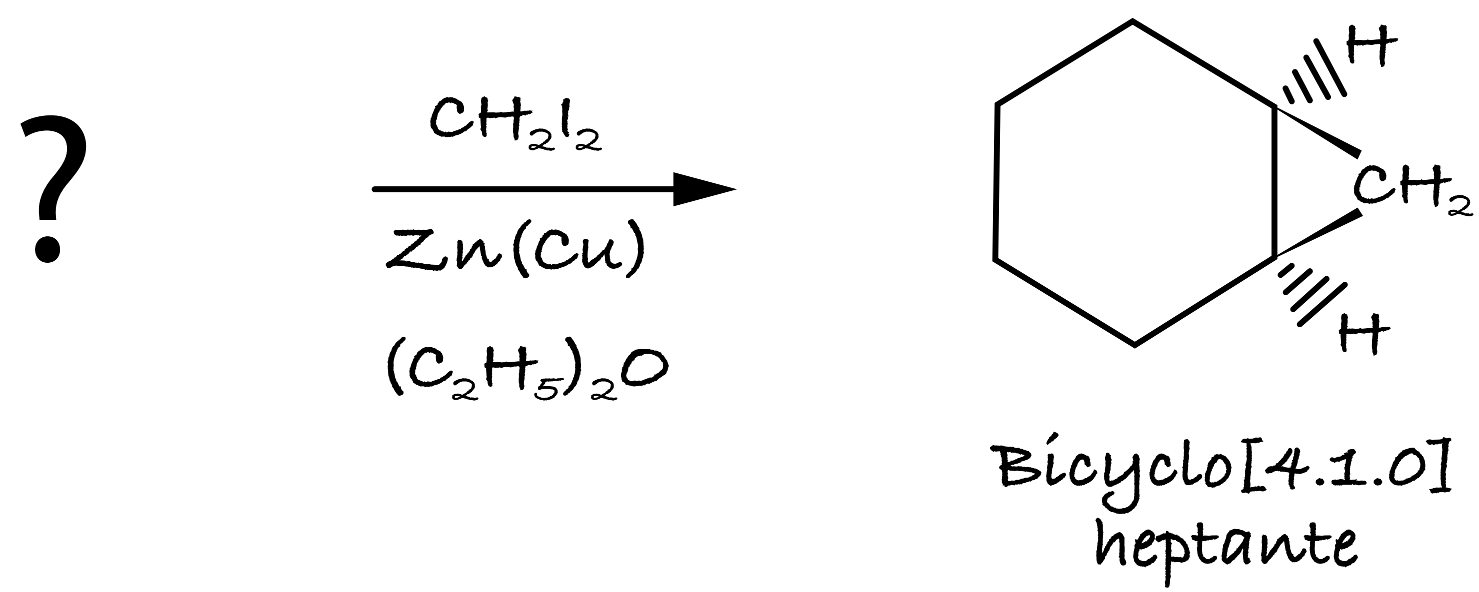
   False. The Cram variation uses a preformed hydrazone, potassium tert-butoxide as the base, and DMSO as the solvent, which allows it to be performed at room temperature.

JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — SIMMONS-SMITH REACTION

What starting material or substrate will produce the product shown when using the **Simmons-Smith reaction?**



JUMP TO THE PREVIOUS QUIZ QUESTION

CLICK TO SEE THE ANSWER TO THIS QUESTION

JUMP TO NEXT QUIZ QUESTIOIN

Product Selection for the Simmons-Smith Reaction

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
	Zn + Zn compounds
000648	Zinc wire, 0.25mm (0.01in) dia, 99.99+% (metals basis)
000682	Zinc ingot, 345mm (13.6in) long, 99.99% (metals basis)
010435	Zinc wire, 3.18mm (0.125in) dia, 99.95% (metals basis)
011361	Zinc wire, 1.0mm (0.04in) dia, 99.9997% (metals basis)
012053	Zinc wire, 1.0mm (0.04in) dia, Puratronic|r, 99.9985% (metals basis)
012054	Zinc wire, 0.5mm (0.02in) dia, Puratronic|r, 99.994% (metals basis)
012055	Zinc wire, 0.25mm (0.01in) dia, Puratronic|r, 99.994% (metals basis)
014629	Zinc mossy, 2.5cm (0.98in) & down, 99% (metals basis)
041655	Zinc sputtering target, 50.8mm (2.0in) dia x 3.18mm (0.125in) thick, 99.99% (metals basis)
041656	Zinc sputtering target, 50.8mm (2.0in) dia x 6.35mm (0.250in) thick, 99.99% (metals basis)
041657	Zinc sputtering target, 76.2mm (3.0in) dia x 3.18mm (0.125in) thick, 99.99% (metals basis)
042637	Zinc wire, 2.0mm (0.08in) dia, Puratronic|r, 99.999% (metals basis)
042703	Zinc wire, 0.25mm (0.01in) dia, 99.95% (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

SKU	Description
	Zn + Zn compounds
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
L13310	Zinc powder, -100 mesh, 97+%
20806	Zinc iodide, 98+%, pure
21276	Zinc iodide, 99.999%, (trace metal basis), extra pure
011661	Zinc iodide, 98%
035727	Zinc iodide, ultra dry, 99.995% (metals basis)
37731	Diethylzinc, 1.5M solution in toluene, AcroSeal®
H37734	Diethylzinc, nominally 15% w/w in hexane, packaged under Nitrogen in resealable AcroSeal[t bottles

SKU	Description
	Diiodomethane
16983	Diiodomethane, 99+%, stabilized
A15457	Diiodomethane, 99%, stab.

Click descriptions for product details and ordering information

SKU	Description
	Dibromomethane
A10456	Dibromomethane, 99%

SKU	Description
	Hexene compounds
10250	1-Acetylcyclohexene, 97%
33512	3-Bromocyclohexene, 95%
A10370	3-Bromocyclohexene, 95%
36470	6-Bromo-1-hexene, 97%
L12909	6-Bromo-1-hexene, 95%
H53396	6-Chloro-1-hexene, 97%
15484	Cyclohexene, 99%, pure, stabilized
A11359	Cyclohexene, 99% stab.
019462	1-Cyclohexene-1-acetic acid
L10284	1-Cyclohexene-1-carbonitrile, 98%
29175	1-Cyclohexene-1-carboxylic acid, 96%
A10741	1-Cyclohexene-1-carboxylic acid, 97%
29439	3-Cyclohexenecarboxylic acid, 97%
A15229	3-Cyclohexene-1-carboxylic acid, 98%
L09392	cis-4-Cyclohexene-1,2-dicarboxylic acid, 98%
H25950	(1S,2R)-cis-4-Cyclohexene-1,2-dicarboxylic acid 1-monomethyl ester, 98%
B21431	cis-4-Cyclohexene-1,2-dicarboxylic anhydride, 95%
H56929	1-Cyclohexene-1,2-dicarboxylic anhydride, 97+%
37258	1,2-Epoxy-5-hexene, 98%
12075	1-Hexene, 99%, AcroSeal®

SKU	Description
	Hexene compounds
21321	1-Hexene, 97%
B20271	1-Hexene, 98%
14990	trans-2-Hexene, 98+%
B22289	trans-2-Hexene, 99%
H53472	2-Hexene, cis + trans, tech. 85%
H53485	cis-3-Hexene, 97%
H53506	cis-2-Hexene, 96%
14991	trans-3-Hexene, 98%
L10311	trans-3-Hexene, 98%
15684	1-Methyl-1-cyclohexene, 98+%, stabilized
L15014	1-Methyl-1-cyclohexene, 96%
30431	3-Methyl-1-cyclohexene, 90%, tech.
21371	Methyl 1-cyclohexene-1-carboxylate, 98%
B25568	Methyl 1-cyclohexene-1-carboxylate, 97%
H29100	4-Methyl-1,2-cyclohexene oxide, cis + trans, 97%
L14622	Methyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate, 99%
B20602	1-Phenylcyclohexene, 96%
33483	1-Pyrrolidino-1-cyclohexene, 95%
14088	4-Vinyl-1-cyclohexene, 97%, stabilized

Free Radical Reactions

An organic free radical is a free radical form of carbon possessing three single bonds and a single unpaired electron. The existence of such a species was long thought impossible. But in 1900, Russian chemist Moses Gomberg discovered the first organic free radical, and now many free radical organic chemistry researchers consider Gomberg the founder of their field. It wasn't until the 1930s that free radical chemistry began to grow in importance. We now know that organic free radicals, initially viewed as a curiosity, play a fundamental role in the way enzymes function in the human body. These highly reactive species are implicated in the aging process as well as in the development of cancer and other diseases. Understanding organic free radicals has helped us to explain DNA synthesis and many other natural phenomena. Free radical reactions have become an increasingly important tool in organic synthesis in the last two decades, because of their selectivity and specificity as well as their mild nature. They play a key role in the production of plastics, synthetic rubber, and other widely used synthetic materials.

Common, well-known free radical reactions include:

- Hunsdiecker reaction
- Keck radical allylation
- Meerwein arylation
- Sandmeyer reaction
- Wohl-Ziegler bromination

Hunsdiecker Reaction

In 1861, Russian chemist Alexander Borodin prepared methyl bromide from silver acetate in a combined decarboxylation and halogenation reaction. Building on this work in 1939, German chemists Cläre and Heinz Hunsdiecker demonstrated that when silver salts of carboxylic acids react with a halogen, an alkyl halide is formed which possesses one fewer carbon atoms than the substrate. Subsequently, this reaction became known as the Hunsdiecker reaction or sometimes the Hunsdiecker–Borodin reaction, referencing Borodin's earlier work.

The silver salts are usually prepared from the corresponding carboxylic acid by treatment with silver oxide. However, in order to obtain high yields, the salts must be pure and extremely dry, which can be challenging to achieve. Subsequently, several modifications were introduced, including the use of acid chlorides as a more reactive functional group and the use of thallium(I) carboxylates in place of silver. The Cristol-Firth modification employs an excess of red mercuric oxide and one equivalent of the halogen, while the Suarez modification treats the acid with hypervalent iodine reagents.

Another derivation, known as the Barton modification, exploits the thermal or photolytic decomposition of thiohydroxamate esters in halogen donor solvents. This modification is compatible with almost all functional groups, and was used in the asymmetric total synthesis of antimitotic agents (+)- and (-)-spirotryprostatin B.

Keck Radical Allylation

First reported separately by Masanori Kosugi and Jean Grignon in 1973, the coupling of an alkyl halide with allyltributyltin under radical conditions to insert an allyl group was employed in the total synthesis of perhydrohistrionicotoxin by Gary Keck and colleagues. After he had determined the scope of this reaction, it became known as the Keck radical allylation. Azobisisobutyronitrile (AIBN) was found to be the most efficient catalyst in initiating the process, and the reaction was found to be general for primary, secondary, and tertiary alkyl bromides. The reaction is highly chemoselective, tolerates a wide range of functional groups, and is tolerant of steric hindrance.

This reaction has been utilized successfully in a number of total synthesis campaigns, including that of the Stemona alkaloid (-)-tuberostemonine (by Peter Wipf), and the anti-cancer alkaloid manzamine A (by David J. Hart).

Meerwein Arylation

In 1939, German chemist Hans Meerwein and colleagues studied the reaction of diazo compounds with α, β-unsaturated carbonyl compounds, in which the aryl group was added across the double bond and a molecule of nitrogen was lost. In one such experiment, coumarin was reacted with p-chlorodiazonium chloride in the presence of a copper (II) chloride catalyst to produce 3-(p-chlorophenyl)coumarin. Subsequently, the arylation of substituted alkenes with aryldiazonium halides in the presence of a metal catalyst became known as the Meerwein arylation.

Generally, the aryldiazonium halides are prepared through the diazotization of the aromatic amines using sodium nitrite and aqueous hydrohalic acids, and then reacted immediately with the alkenes in an organic solvent such as acetone or acetonitrile.

The Meerwein arylation reaction has been used in many successful synthesis campaigns, including the preparation of a series of peptide mimetic aldehyde inhibitors of calpain by Ron Bihovsky, and in the first successful process for the synthesis of N(5)-ergolines by the research group of Jack E. Baldwin.

Sandmeyer Reaction

In 1884, Swiss chemist Traugott Sandmeyer attempted to synthesize phenylacetylene from benzenediazonium chloride and copper(I) acetylide. However, the main product isolated was chlorobenzene, and no trace of the desired product was found. On careful examination of the reaction, it was discovered that copper(I) chloride was formed in situ, which catalyzed the replacement of the diazonium group with a chlorine atom. Following this discovery, the substitution of aryldiazonium salts with halides or pseudo halides became known as the Sandmeyer reaction.

The required aryldiazonium halides are generally prepared from the corresponding arylamines via diazotization using either sodium nitrite and aqueous hydrochloric acid, or alkyl nitrites such as tert-butyl nitrite under anhydrous conditions. These aryldiazonium compounds are prepared and reacted in situ with copper(I) chloride, bromide, or cyanide to obtain the corresponding aryl halide or nitrile.

The Sandmeyer reaction has been used in many successful synthesis campaigns, including the preparation of the anti-psychotic drug flupentixol as well as neoamphimedine, a compound that has anti-cancer properties.

Wohl-Ziegler Bromination

In 1919, German chemist Alfred Wohl investigated the reaction between 2,3-dimethyl-2-butene and N-bromoacetamide in diethyl ether and discovered that the double bond of the substrate remained unchanged and one of the methyl groups was replaced by bromine. This discovery was interesting, as the reaction was previously thought to require the use of bromine at high temperatures to react with the alkenes. In 1942, Karl Ziegler carried out a comprehensive study of the utility of N-bromosuccinimide (NBS) in the allylic bromination of olefins and demonstrated the synthetic value of the process. Subsequently, the addition of bromine at the allylic position of olefins or at the benzylic position of alkylated aromatic or heteroaromatic compounds became known as the Wohl-Ziegler bromination.

NBS is the commercially available reagent that is by far the most effective, giving the least amount of side products.

Click here for a more in-depth look at the Wohl-Ziegler reaction.

Reaction Mechanism Examples

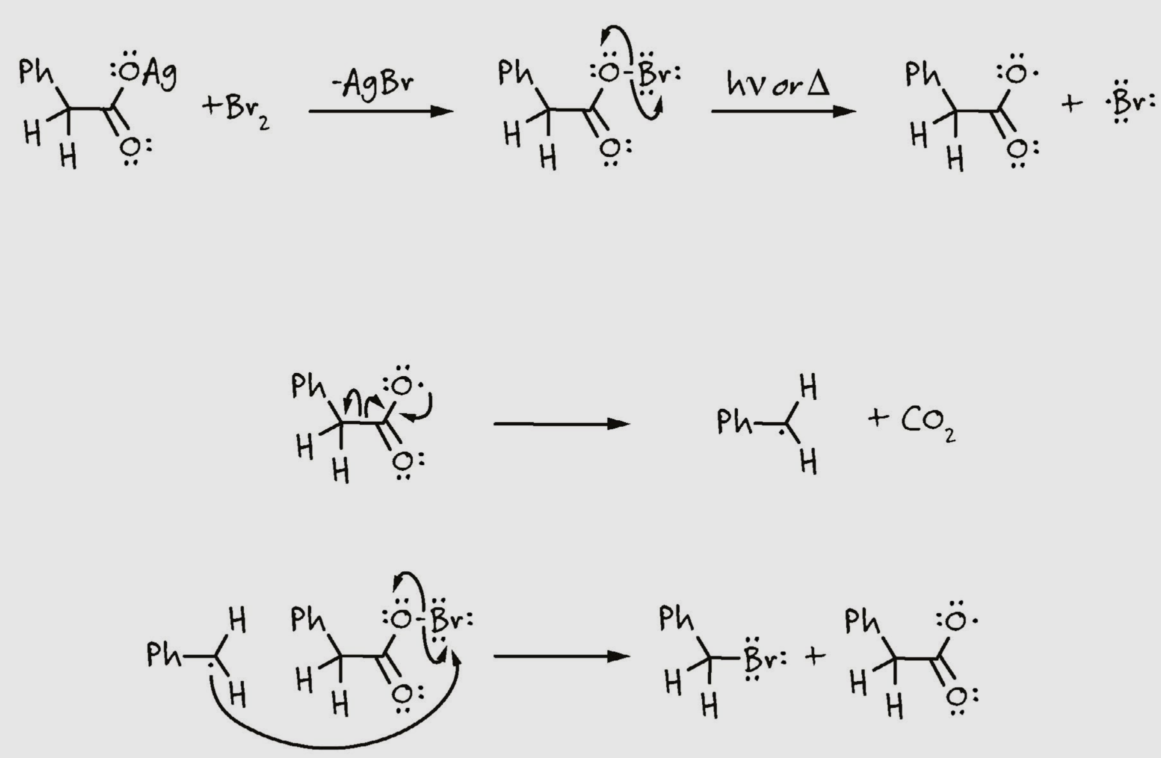


Figure 9.1. Hunsdiecker reaction mechanism

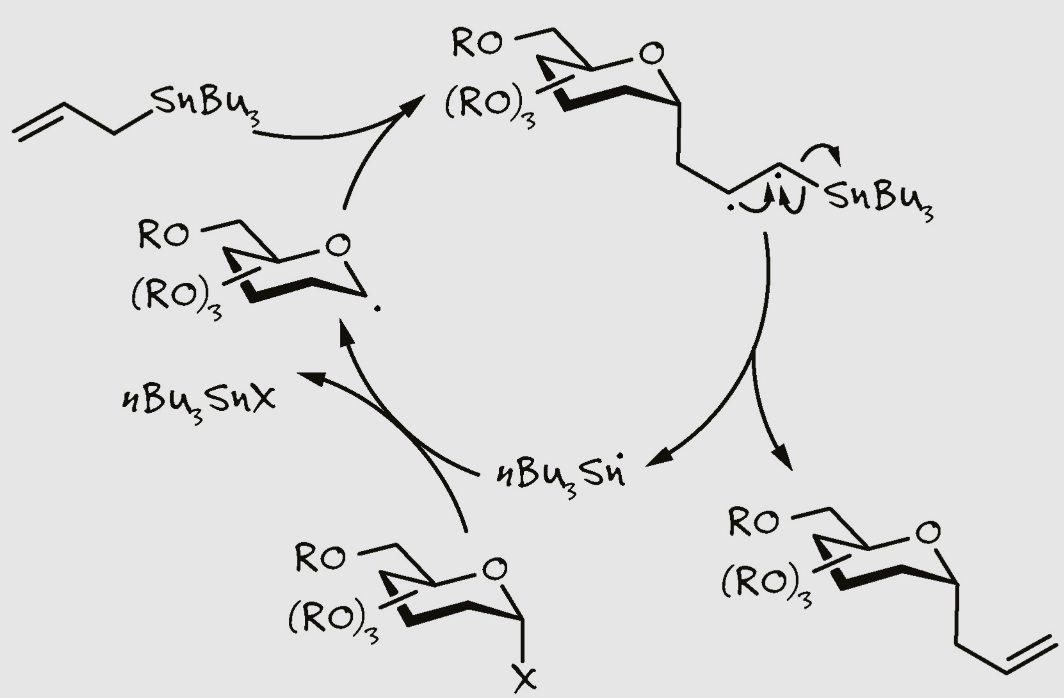
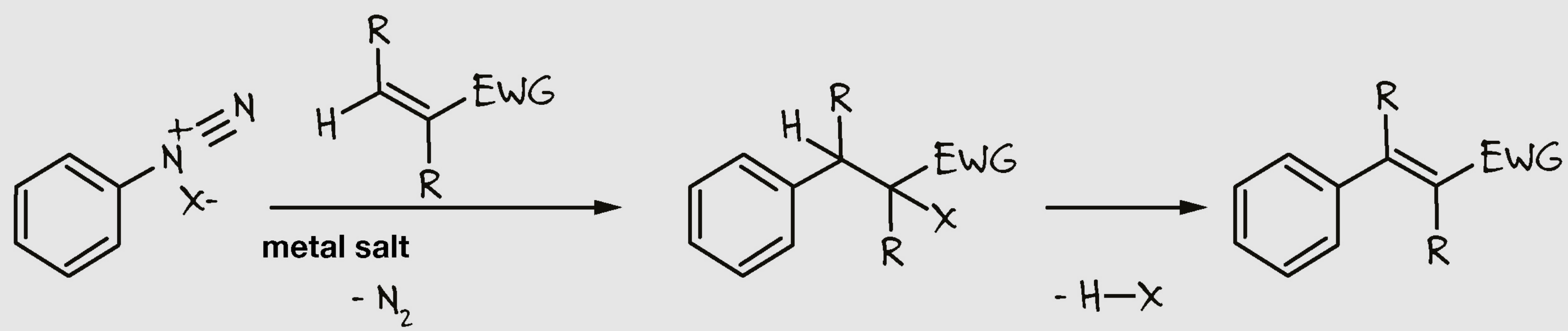


Figure 9.2. Keck radical allylation mechanism



EWG = electron withdrawing group

Figure 9.3. Meerwein arylation mechanism

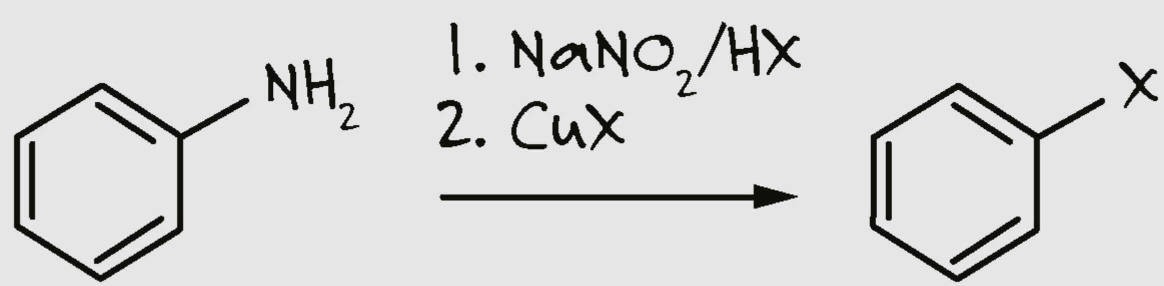


Figure 9.4. Sandmeyer reaction mechanism

Wohl-Ziegler Bromination

The field of natural organohalogen products expands as more of these compounds are found to exhibit potentially useful biological activities. Here, bromination is an extremely important step in these synthetic pathways.

The Wohl-Ziegler reaction is the addition of bromine at the allylic position of olefins or at the benzylic position of aromatic compounds (see Figure 9.5).

In 1919, Alfred Wohl reported first the bromination at the allylic position when studying the reaction between 2,3-dimethyl-2-butene and N-bromoacetamide.[1] Later, in 1942, Karl Ziegler showed the importance to use N-bromo-succinimide known simply as NBS) as a brominating reagent.[2]

The mechanism of this reaction was a topic of discussion for several years. In 1944, Bloomfield suggested that succinimidyl radicals directly participate in the bromination.[3] Finally, in 1953, Goldfinger developed an alternative mechanism where the reaction occurs in the presence of a radical initiator and a small amount of bromine.[4] Schmid and Karrer proposed the use of dibenzoyl peroxide as the catalyst.[5] The Goldfinger mechanism of the Wohl-Ziegler bromination reaction can be described in 3 steps. In the first step, known as initiation, the initiator decomposes into a radical species when heated or irradiated andthe Br radical is formed. In the second step, known as propagation, the Br radical abstracts the hydrogen from the olefin and generates HBr and the allylic radical. The latter reacts with another bromine molecule to give the final product. In the last step, known as termination, HBr reacts with NBS to generate a new molecule of bromine and succinimide.

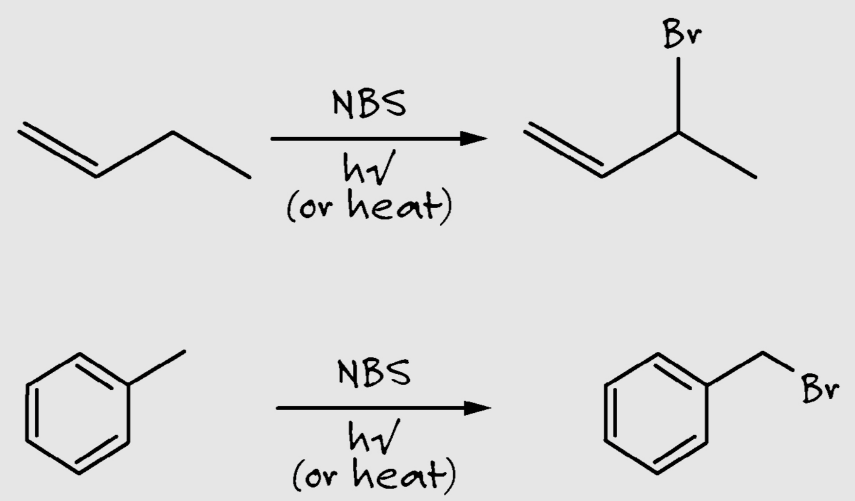


Figure 9.5. Simplified Wohl-Ziegler reaction

The Goldfinger mechanism was confirmed by Day, Lindstrom, and Skell when they compared the hydrogen abstraction selectivity of Br, Cl and succinimidyl radicals and reported that the last one is not an intermediate in the propagation step.[6] The completion of the reaction is indicated by the presence of the insoluble imide floating on top of the vessel. In Figure 9.6 the mechanism is depicted using the azobisisobutyronitrile, normally know as AIBN, as the radical initiator.

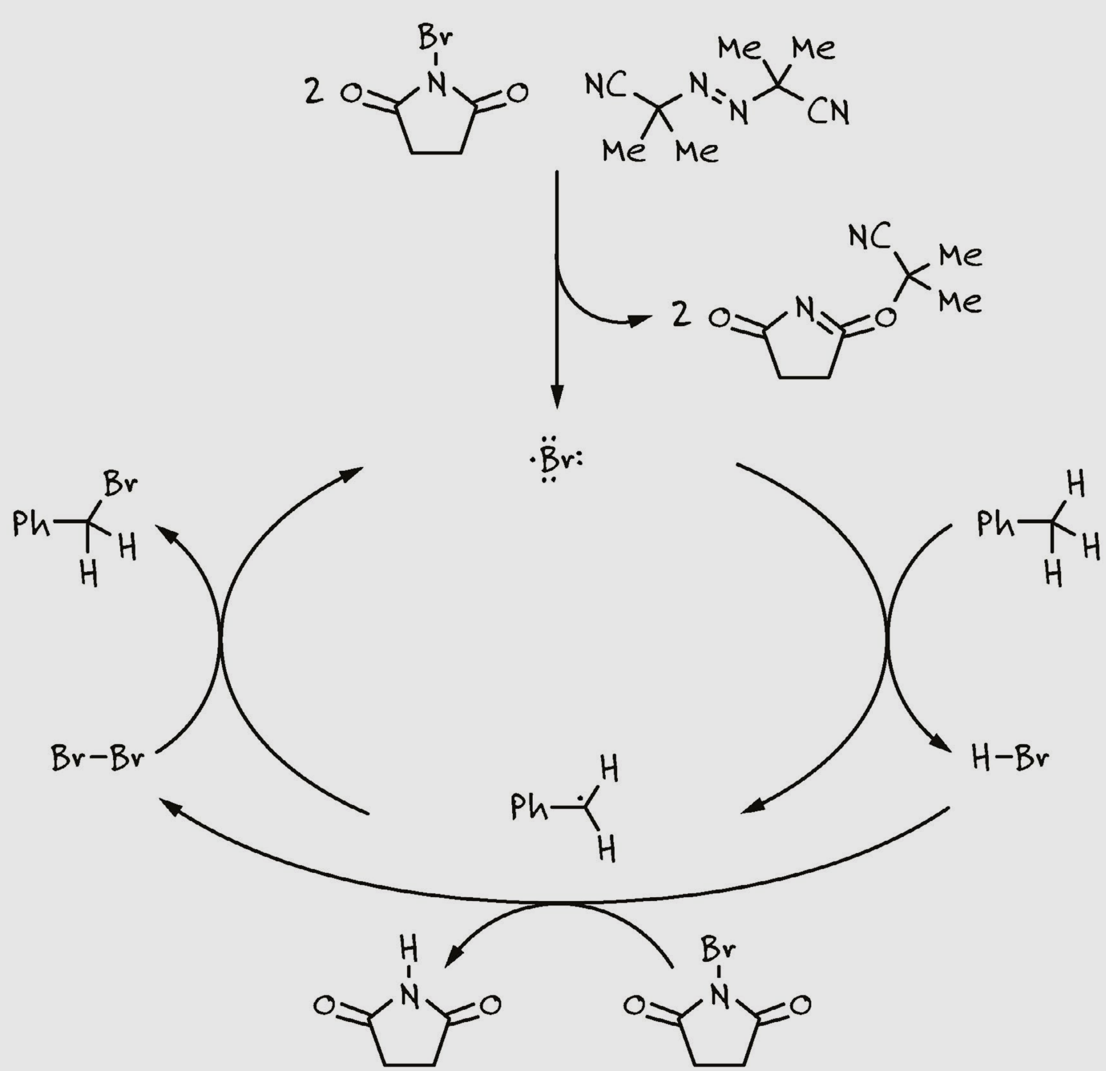


Figure 9.6. Wohl-Ziegler reaction mechanism

In the reaction, it is important to use only a small amount of bromine to avoid side products or dibromination.

The Wohl-Ziegler mechanism reaction has two main advantages, which are that NBS is commercially available, and that the reaction can be performed in environmentally friendly conditions when ionic liquids or solvent-free systems are used. Rahman for example, developed the bromination of diquilonine using the solid-solid Wohl-Ziegler reaction.[7]

The Wohl-Ziegler reaction has several applications. For example, one of the main steps to synthetize (-)-Tryprostatine A, a natural product isolated from the *Aspergillus fumigatus* that is used to overcome multi-drug resistance in cancer (see Figure 9.7).

Reference Reaction Protocol

Reaction protocol[8] used in Figure 9.8:[8]

A mixture of ethyl p-toluate (6 mmol), NBS (6.3 mmol), benzoyl peroxide (0.24 mmol), and 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF_6), was heated at 90 °C under an argon atmosphere until the starting ethyl p-toluate was consumed completely. After the workup, the final product was obtained with a yield of 76%.

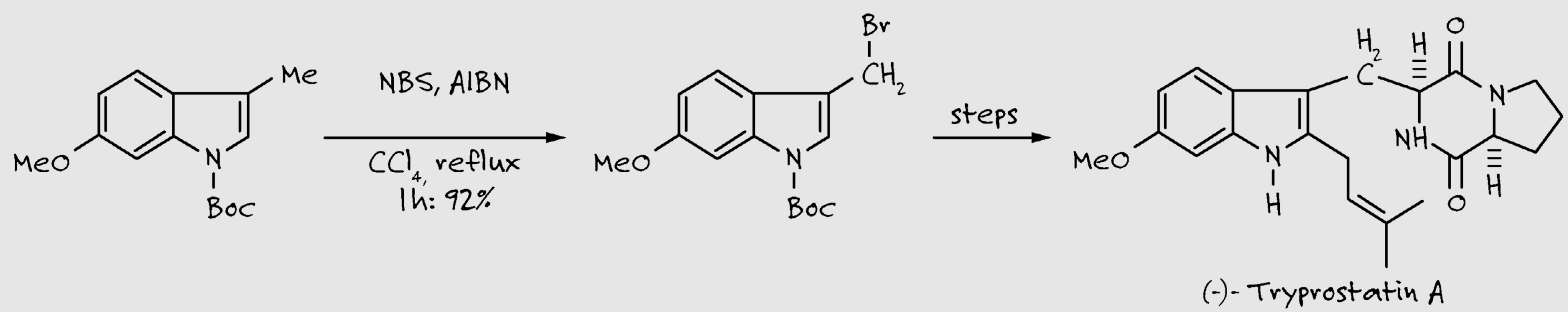


Figure 9.7. Synthesis of (-)-Tryprostatine A

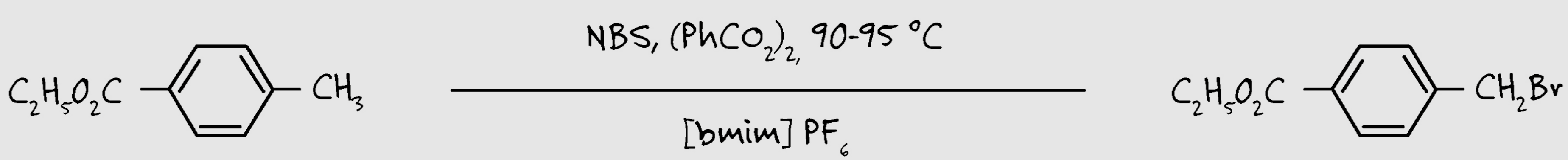


Figure 9.8. The Wohl-Ziegler reaction using ionic liquid as solvent

Key Literature References

1. *Wohl, A. Chem. Ber., 1919, 52, 51.*
2. *Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. Ann. 1942, 551, 80.*
3. *Bloomfield, G. F. J. Chem. Soc. 1944, 114.*
4. *Adam, J.; Gosselain, P.A.; Goldfinger, P. Nature 1953,17,4355: 704–705.*
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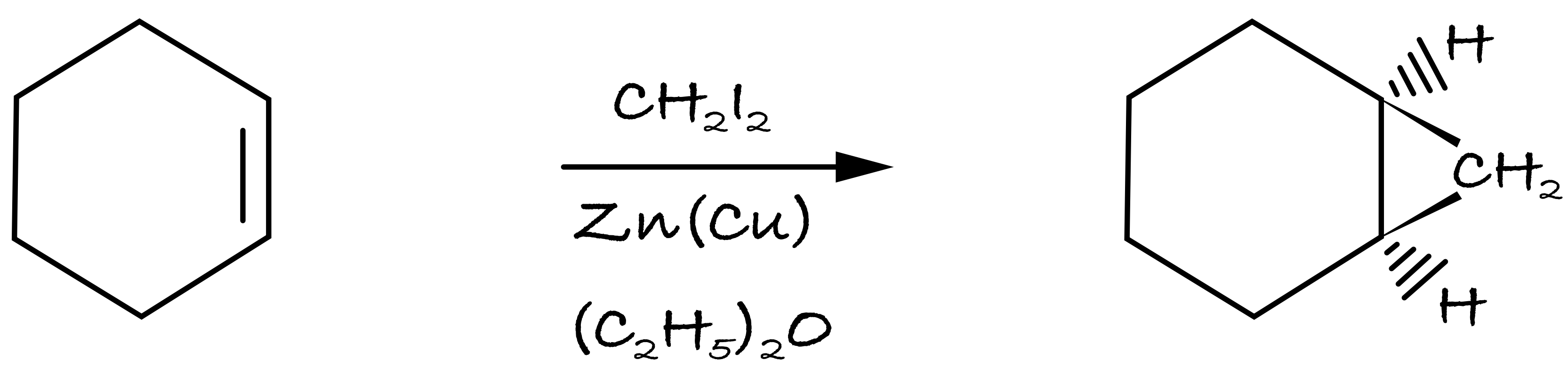
8. *Togo H., Hirai T. Synlett 2003, 5, 702–704.*

QUIZ ANSWER — SIMMONS-SMITH REACTION

Cyclohexene is the starting material or substrate that will produce the product shown when using the Simmons-Smith reaction.



Cyclohexene

Bicyclo[4.1.0] heptante

JUMP TO THE QUIZ QUESTION

JUMP TO THE NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — WOHL-ZIEGLER REACTION

Make selections from the options in each sentence below to make **each statement true** for the Wohl-Ziegler reaction.

1. Bromination reactions are growing in use because halogenated compounds are *(commonly used / excluded from)* biological processes.
2. The free radical generated in the propagation step of this reaction is a (*allylic / bromine*) radical.
3. A *(limiting / excess)* amount of bromine is used to avoid side products and dibromination.
4. The Wohl-Ziegler reaction *(can / cannot)* be conducted using ionic liquids as solvent.
5. The Wohl-Ziegler reaction was discovered by Alfred Wohl in *(1919 / 1939)* but then studied and improved by Karl Ziegler in *(1928 / 1942)*.

JUMP TO THE PREVIOUS QUIZ QUESTION
CLICK TO SEE THE ANSWER TO THIS QUESTION
JUMP TO NEXT QUIZ QUESTIOIN

Product Selection for the Wohl-Ziegler Reaction

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
	Alkene
031213	1-Decene, 96%, remainder isomers
11191	1-Decene, ca. 95%
L06800	1-Decene, 94%
16343	2,3-Dimethyl-1,3-butadiene, 98%, stabilized with BHT
L04207	2,3-Dimethyl-1,3-butadiene, 98%, stab. with 100ppm BHT
15659	2,3-Dimethyl-2-butene, 98%
15272	3,3-Dimethyl-1-butene, 95%
43872	2,3-Dimethyl-2-butene, 1M solution in THF, AcroSeal®
15536	2,4-Dimethyl-1,3-pentadiene, 98%
H35300	2,4-Dimethyl-1,3-pentadiene, 98%
42627	4,4-Dimethyl-1-pentene, 99%
A14992	1-Dodecene, 96%
11763	1-Dodecene, 93-95%
L11487	1-Heptene, 98+%
12039	1-Heptene, 98%
12050	1-Hexadecene, 92%, tech.
L02637	1-Hexadecene, 90+%
34667	2,4-Hexadiene, 90%, tech., mixture of isomers
B20271	1-Hexene, 98%
12075	1-Hexene, 99%, AcroSeal®

SKU	Description
	Alkene
21321	1-Hexene, 97%
B20271	1-Hexene, 98%
B22289	trans-2-Hexene, 99%
14990	trans-2-Hexene, 98+%
L14619	Isoprene, 99%, stab. with ca 0.02% 4-tert-butylcatechol
12267	Isoprene, 98%, stabilized
12649	2-Methyl-2-butene, 99+%
031853	2-Methyl-2-butene, tech. 90%, remainder mainly 2-methyl-1-butene
12649	2-Methyl-2-butene, 99+%
41409	2-Methyl-2-butene, 90%, balance 2-Methyl-1-butene
42639	2-Methyl-2-butene, 2M solution in THF, AcroSeal®
12740	2-Methyl-1-pentene, 99%
H53373	2-Methyl-1-pentene, 97%
033029	4-Methyl-1-pentene, 98+%
12742	4-Methyl-1-pentene, 97%
12808	Myrcene, 90%, tech., stabilized
12931	1-Octadecene, 90%, tech.
L11004	1-Octadecene, tech. 90%
12935	1,7-Octadiene, 98.5%
L07659	1,7-Octadiene, 97%
30125	1-Octene, 99+%
A11146	1-Octene, 97+%
12986	1,4-Pentadiene, 99%
26866	1-Pentene, 97%
43073	1-Pentene, 97%, AcroSeal®
A16723	1-Pentene, 97%
21535	Squalane, 99%
A17931	Squalane, 98%
B20944	Squalene, 98%
A13201	Tetramethylethylene, 97%
14013	2,3,3-Trimethyl-1-butene, 99+%
14018	2,4,4-Trimethyl-1-pentene, 99%
B20187	2,4,4-Trimethyl-1-pentene, 99%
16263	2,4,4-Trimethyl-2-pentene, 98%
B20773	2,4,4-Trimethyl-2-pentene, 97%

Click descriptions for product details and ordering information

SKU	Description
	THF
041820	Tetrahydrofuran, anhydrous, 99.8+%, unstab., packaged under Argon in resealable ChemSeal^t bottles
042254	Tetrahydrofuran, anhydrous, 99.8+%, unstab.
044608	Tetrahydrofuran, anhydrous, 99.8+%, stab. with 0.025% BHT, packaged under Argon in resealable ChemSeal^t bottles
047122	Tetrahydrofuran, anhydrous, 99.8+%, BHT-free, over molecular sieves, packaged under Argon in resealable ChemSeal bottles
047327	Tetrahydrofuran, anhydrous, 99.8+%, BHT-free, over molecular sieves, packed with Argon in resealable AcroSeal|r bottles
047382	Tetrahydrofuran, anhydrous, 99.8+%, stab. with 0.025% BHT, packaged under Argon in resealable AcroSeal|r bottles
18150	Tetrahydrofuran, 99.9%, extra pure, anhydrous, stabilized with BHT
44640	Tetrahydrofuran, 99.5%, for analysis, stabilized with BHT
032468	Tetrahydrofuran, Spectrophotometric Grade, 99.7+%, unstab.
041819	Tetrahydrofuran, Spectrophotometric grade, 99.7+%, unstab., packaged under Argon in resealable ChemSeal^t bottles
047329	Tetrahydrofuran, Spectrophotometric grade, 99.7+%, unstab., packaged under Argon in resealable AcroSeal|r bottles
22216	Tetrahydrofuran, 99.5+%, for spectroscopy
45053	Tetrahydrofuran, 99.8%, for biochemistry, unstabilized, AcroSeal®
030760	Tetrahydrofuran, ACS, 99+%, stab. with 250ppm BHT
16424	Tetrahydrofuran, 99.6%, ACS reagent, stabilized with BHT
17663	Tetrahydrofuran, 99+%, extra pure, stabilized with BHT
32697	Tetrahydrofuran, 99.85%, Extra Dry, stabilized, AcroSeal®
34845	Tetrahydrofuran, 99.5%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal®
44836	Tetrahydrofuran, 99.85%, Extra Dry, stabilized, AcroSeal®, package of 4x25ML bottles
L13304	Tetrahydrofuran, 99%, stab. with 250-350ppm BHT
038994	Tetrahydrofuran, non-UV, HPLC Grade, 99.7+%, stab. with 250ppm BHT
022904	Tetrahydrofuran, UV, HPLC Grade, 99.7+% min, unstab.
26829	Tetrahydrofuran, 99.8%, for HPLC, unstabilized
45707	Tetrahydrofuran, 99.85%, Extra Dry, Unstabilized, AcroSeal®
044505	Tetrahydrofuran, Biograde, 99.8%, unstab.

SKU	Description
	DCM
12779	Methyl sulfoxide, 99.7%, pure
16785	Methyl sulfoxide, 99.9%, for spectroscopy
29552	Methyl sulfoxide, 99.8+%, extra pure
29552	Methyl sulfoxide, 99.8+%, extra pure
32718	Methyl sulfoxide, 99.8+%, for molecular biology, DNAse, RNAse and Protease free
022914	Dimethyl sulfoxide, HPLC Grade, 99.9+%
032434	Dimethyl sulfoxide, Spectrophotometric Grade, 99.9+%
036480	Dimethyl sulfoxide, ACS, 99.9% min
042780	Dimethyl sulfoxide, HPLC grade, 99.9+%, packaged under Argon in resealable ChemSeal^t bottles
043998	Dimethyl sulfoxide, anhydrous, 99.8+%, packaged under Argon in resealable ChemSeal^t bottles
A13280	Dimethyl sulfoxide, 99+%
J66650	Dimethyl sulfoxide, Bioreagent

SKU	Description
	TEA
12391	Triethylamine, 99+%
15791	Triethylamine, 99%, pure
21951	Triethylamine, 99.7%, extra pure
43228	Triethylamine, 99.5%, for analysis
46081	Triethylamine, for HPLC
A12646	Triethylamine, 99%

SKU	Description
	NBS
A15922	NN-Bromosuccinimide, 99%

SKU	Description
	DCM
032440	Dichloromethane, Spectrophotometric Grade, 99.7+%, stab. with amylene
039116	Dichloromethane, ACS, 99.5+%, stab. with amylene
042006	Dichloromethane, Environmental Grade, 99.8+%, stab. with amylene
16777	Dichloromethane, 99.8%, for spectroscopy, stabilized with amylene
32660	Dichloromethane, for residue and pestic. anal., stab. with amylene
32676	Dichloromethane, 99.9%, for residue analysis, for anal.of polyarom.hydrocarb., stab.with amylene
32685	Dichloromethane, 99.9%, Extra Dry, stabilized, AcroSeal®
34846	Dichloromethane, 99.8%, Extra Dry over Molecular Sieve, Stabilized, AcroSeal®
35480	Dichloromethane, 99.9%, for peptide synthesis, stabilized with amylene
40691	Dichloromethane, 99.9%, for biochemistry, stabilized with approx. 50 ppm amylene, AcroSeal®
40692	Dichloromethane, 99.6%, ACS reagent, stabilized with amylene
40693	Dichloromethane, 99.5%, for spectroscopy ACS, stabilized with amylene
44837	Dichloromethane, 99.9%, Extra Dry, stabilized, AcroSeal®, package of 4x25ML bottles
041835	Dichloromethane, anhydrous, 99.7+%, packaged under Argon in resealable ChemSeal^t bottles, stab. with amylene
047352	Dichloromethane, anhydrous, 99.7+%, packaged under Argon in resealable AcroSeal|r bottles, stab. with amylene
022917	Dichloromethane, HPLC Grade, 99.7+%, stab. with amylene
11346	Dichloromethane, 99.8+%, for analysis, stabilized with amylene
26833	Dichloromethane, 99.8%, for HPLC, stabilized with amylene
38378	Dichloromethane, 99+%, extra pure, stabilized with amylene
12405	Dichloromethane, 99+%, extra pure, stabilized with ethanol
39070	Dichloromethane, 99.5%, for analysis, stabilized with ethanol
L13089	Dichloromethane, 99+%, stab. with ca. 50ppm amylene
36423	Dichloromethane, 99.8%, for HPLC, stabilized with methanol

SKU	Description
	(PhCOO)2
21178	Dibenzoyl peroxide, 75%, remainder water
L13174	Dibenzoyl peroxide, 97% (dry wt.), wet with 25% water

SKU	Description
	BTF
13977	alpha,alpha,alpha-Trifluorotoluene, 99+%
B21340	Benzotrifluoride, 99%

SKU	Description
	Et-O-Et
016767	Diethyl ether, anhydrous, ACS, 99% min, stab. with BHT

Heterocycle Formation

A heterocyclic compound is a cyclic compound that has at least one element other than carbon (e.g., nitrogen, oxygen, or sulfur) as part of its ring structure. Its general structure resembles that of cyclic organic compounds containing only carbon. However, the presence of heteroatoms gives heterocyclic compounds distinct physical and chemical properties.

One of the earliest named reactions in this category was discovered in 1882 by A. Hantzsch, who condensed two equivalents of ethyl acetoacetate with one of acetaldehyde and ammonia to obtain a fully-substituted symmetrical dihydropyridine.

Some of the best known heterocycle formation reactions, named for the chemists that discovered them, are:

- Fischer indole synthesis
- Hantzsch dihydropyridine synthesis
- Knorr pyrrole synthesis
- Pictet-Spengler tetrahydroisoquinoline synthesis
- Pomeranz-Fritsch reaction

Fischer Indole Synthesis

In 1883, E. Fischer and F. Jourdan treated an arylhydrazone (pyruvic acid 1-methylphenylhydrazone) with alcoholic hydrogen chloride and generated 1-methylindole-2-carboxylic acid. The synthesis of indoles from the hydrazones of enolizable ketones, or aldehydes, in the presence of an acid catalyst is now known as the Fisher indole synthesis.

The Fischer indole synthesis is mechanistically complex but simple to carry out. The arylhydrazones do not need to be isolated and can be generated in situ by condensation of the hydrazine and the carbonyl compound. A significant problem is the poor regioselectivity observed when preparing indoles from unsymmetrical ketones or hydrazines. The regiochemical outcome of the reaction is determined by various factors including electronic effects of arylhydrazine substituents, steric effects of ketone substituents, and the strength of the acid used to catalyze the indolization.

Despite its limitations, the Fischer indole synthesis is still widely used and was applied to the synthesis of peduncularine, an alkaloid that shows cytotoxic activity towards breast cancer cell lines.

Click here for a more in-depth look at the Fisher Indole synthesis reaction.

Hantzsch Dihydropyridine Synthesis

In 1882, A. Hantzsch condensed two equivalents of ethyl acetoacetate with one of acetaldehyde and ammonia to obtain what he believed at the time to be a 2,3-dihydropyridine but was later found to be a 1,4-dihydropyridine. Since then, the one-pot condensation of a beta-keto ester or a 1,3-dicarbonyl compound with an aldehyde and ammonia to prepare 1,4-dihydropyridines is known as the Hantzsch dihydropyridine synthesis.

Often the 1,4-dihydropyridines spontaneously oxidize to the corresponding substituted pyridines, but in the case of more stable variants, oxidizing agents (e.g., HNO_2, HNO_3, MnO_2, etc.) can be used, as necessary, to drive oxidation.

While the original procedure only provided symmetrical products, several modifications afford unsymmetrical dihydropyridines. For example, utilizing the Knoevenagel modification, various substituted 1,5-dicarbonyl compounds can be prepared.

Making use of the Hantzsch dihydropyridine synthesis, M. Baley reported the first synthesis of an unsymmetrical 2,2':6',2"-terpyridine.

This reaction has many applications. Commercially, 1,4-dihydropyridines are an important class of calcium channel blockers (e.g., nifedipine) that help reduce blood pressure in patients with hypertension.

Knorr Pyrrole Synthesis

In 1886, L. Knorr heated a mixture of α-nitroso ethyl acetoacetate and ethyl acetoacetate together in glacial acetic acid in the presence of zinc dust, forming a tetra-substituted pyrrole. Ever since, the condensation of an α-amino ketone or α-amino-β ketoester with an active methylene compound has been known as the Knorr pyrrole synthesis.

The Neber rearrangement can be used to prepare the precursor α-aminoketones from the corresponding oxime by reaction with tosyl chloride.

Because α-aminoketones are often quite labile and can undergo self-condensation to form a pyrazine, they are often prepared by first nitrosating the ketone, and then reducing it in situ. An example applied use of the Knorr pyrrole reaction is H.E. Rosenberg's and R.W. Ward's synthesis of the anti-inflammatory analgesic compound, 4,5,8,9-tetrahydro-8-methyl-9-oxothieno[3'3':5,6]cyclohepta[1,2-b]-pyrrole-7-acetic acid.

Pictet-Spengler Tetrahydroisoquinoline Synthesis

In 1911, A. Pictet and T. Spengler condensed phenylethylamine and dimethoxymethane in concentrated hydrochloric acid to give 1,2,3,4-tetrahydroisoquinoline. They also observed a similar reaction when tyrosine and phenylalanine were treated in the same way. Since then, the condensation of a β-arylethylamine with a carbonyl compound in the presence of a protic or Lewis acid to create a substituted tetrahydroisoquinoline has been known as the Pictet-Spengler tetrahydroisoquinoline synthesis, or the Pictet-Spengler reaction.

A variation of the Pictet-Spengler reaction utilizes an indole as the aromatic substrate. P.D. Bailey accomplished the total synthesis of the alkaloid (—)–suaveoline using this approach. Total synthesis of the natural product pyranonaphthoquinone was also accomplished utilizing the Pictet-Spengler reaction to generate the precursor naphthopyran intermediate.

Pomeranz-Fritsch Reaction

In 1893, C. Pomeranz and P. Fritsch independently described a new synthesis of isoquinoline. This was prepared by heating a benzalaminoacetal, generated through the condensation of benzaldehyde and 2,2-diethoxyethylamine, in concentrated sulfuric acid.

Over the course of that decade, the authors used this technique to create a broad range of structurally diverse isoquinolines. From then on, the acid-catalyzed cyclization of benzalaminoacetals (i.e., Schiff bases) to give substituted isoquinolines has been known as the Pomeranz-Fritsch reaction.

Two of the more important modifications are:
- The Schlittler-Muller modification, where a substituted benzylamine is condensed with glyoxal hemiacetal to provide the corresponding C1-substituted isoquinoline.
- The Bobbitt-modification, where hydrogenation of the benzalaminoacetal and subsequent acid-catalyzed cyclization of the resulting amine generates a tetrahydroisoquinoline.

Reaction Mechanism Examples

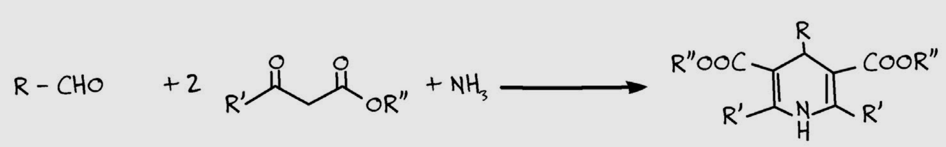


Figure 10.1. Hantzsch dihydropyridine synthesis mechanism

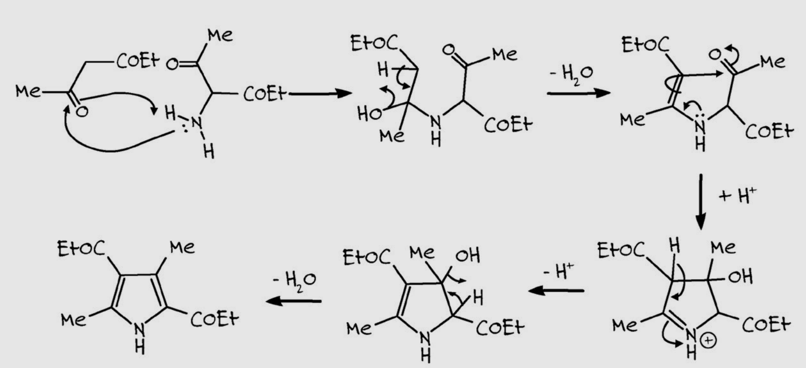


Figure 10.2. Knorr pyrrole synthesis mechanism

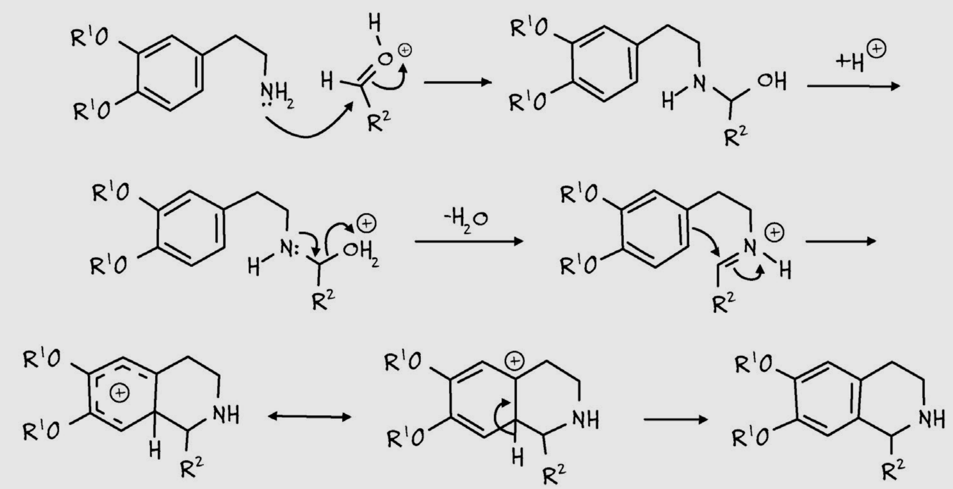


Figure 10.3. Pictet-Spengler tetrahydroisoquinoline synthesis mechanism

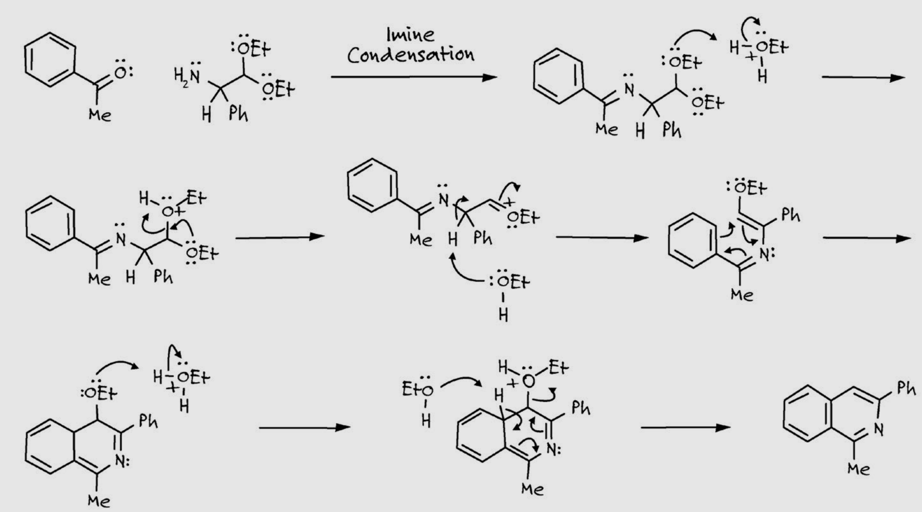


Figure 10.4. Pomeranz-Fritsch mechanism

Fischer Indole Synthesis

The Fischer indole synthesis is one of the oldest reactions in organic synthesis and is considered a reliable and versatile method for the preparation of substituted indoles. These considerations make it the most commonly used reaction for indole synthesis.

Frequently used catalysts for the Fischer indole synthesis include protic acids (e.g., PTSA, PPA, HCl, AcOH and H_2SO_4) and Lewis acids (e.g., $ZnCl_2$, $BF_3.Et_2O$, PCl_3 and $AlCl_3$). Indolizations catalyzed by Lewis acids generally occur at lower temperatures than those using protic acids, but in general the reaction conditions are quite harsh. Hydrazines are often used as their hydrochloride salts, which are relatively stable, and aldehydes are used in a protected form to prevent low yields.

Milder conditions are desirable and have been developed. An example is the use of a tartaric acid-dimethylurea melt (at 70 °C) which acts as the catalyst and the solvent for the reaction.[1] Sensitive functional groups (e.g., N-Cbz, azide, nitrile and ester) are tolerated, and the acid-labile N-Boc protecting group survives the reaction conditions.

The structure of the hydrazine can affect the efficiency of the reaction. The presence of electron withdrawing groups, or ortho-substituents, on the aryl hydrazine slows the reaction down. Formation of azaindoles from pyridylhydrazines does not work well due to protonation of the pyridyl nitrogen by the catalyst.[2] To avoid this, azaindolization can be attempted without using an acid catalyst. Unfortunately, this approach requires elevated temperatures in high boiling solvents (e.g., diethylene glycol at >200 °C) and has limited scope.

Mechanism of the Fischer Indole Synthesis

The mechanism (Figure 10.5), first proposed by R. Robinson in 1924, begins with acid catalyzed condensation of a ketone, or an aldehyde, with an arylhydrazine to form a hydrazone.[3] The imine nitrogen of the hydrazone is protonated and tautomerizes to an ene-hydrazine. This intermediate then undergoes a [3,3] sigmatropic rearrangement that, after re-aromatization, gives an imine. 5-exo-trig cyclisation of the imine forms an aminal, which eliminates ammonia, to produce the indole ring system.

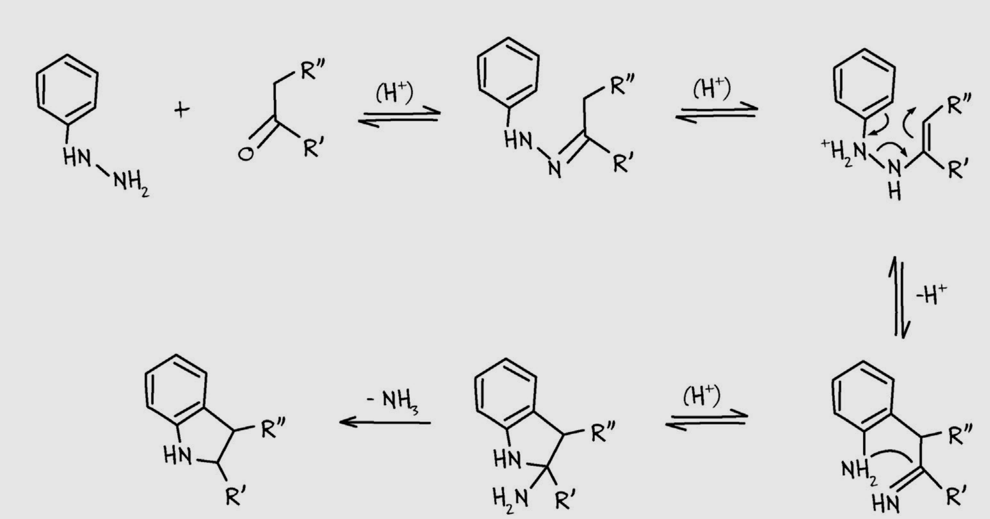


Figure 10.5. Fischer indole synthesis mechanism

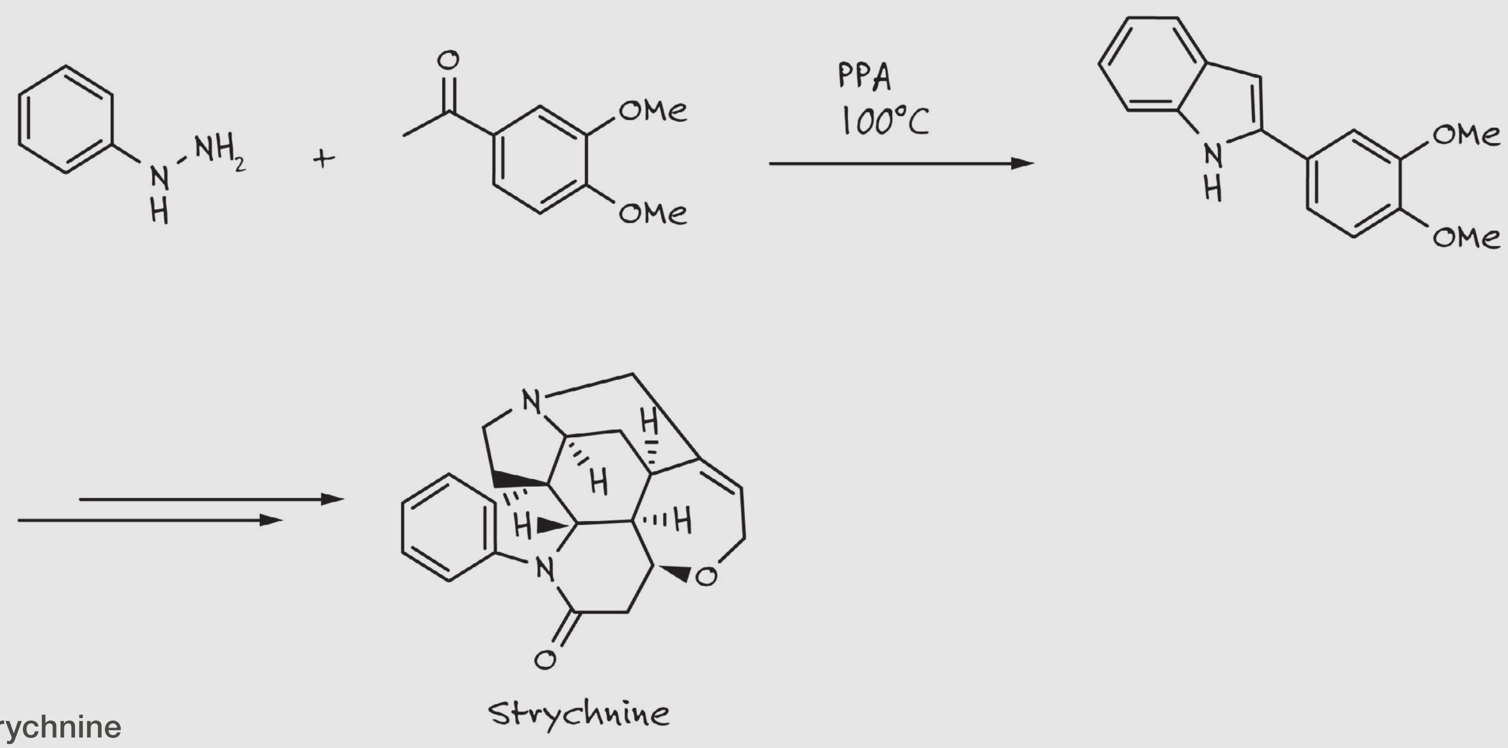


Figure 10.6. Synthesis of strychnine

Indoles are considered privileged scaffolds in drug discovery as they are found in a wide range of biologically active compounds, and many natural products contain the indole nucleus.[4,5] The Fischer indole synthesis has been extensively applied to the synthesis of natural products and pharmaceutical compounds.

R. B. Woodward's first total synthesis of Strychnine in 1954 (Figure 10.6) is considered a milestone in organic chemistry due to the complexity of its molecular structure.[6] The Fischer indole synthesis, using phenylhydrazine and acetoveratrone,,in the presence of polyphosphoric acid (PPA), was used to produce 2-veratrylindole, the starting material for the 29–step linear route.

GSK's serotonin receptor modulator, Sumatriptan (Figure 10.7), was prepared by late-stage indolization of a protected aldehyde, and a pre-functionalized arylhydrazine, in modest yield (30%).[7]

Using a similar approach to Sumatriptan, the 4-azaindole analogue of melatonin (Figure 10.8) was synthesized in good yield (69%). This work showed that, despite its reputation, some substituted 4- and 6-azaindoles are accessible using the Fischer indole synthesis.[8] The successful azaindolization of these systems has been attributed to the methoxy group lowering the basicity of the nitrogen.[2] If a relatively basic pyridyl nitrogen was present then competing protonation would make the desired reaction pathway (i.e., imine protonation, tautomerization followed by [3,3] sigmatropic rearrangement) to the desired indole unfavorable.

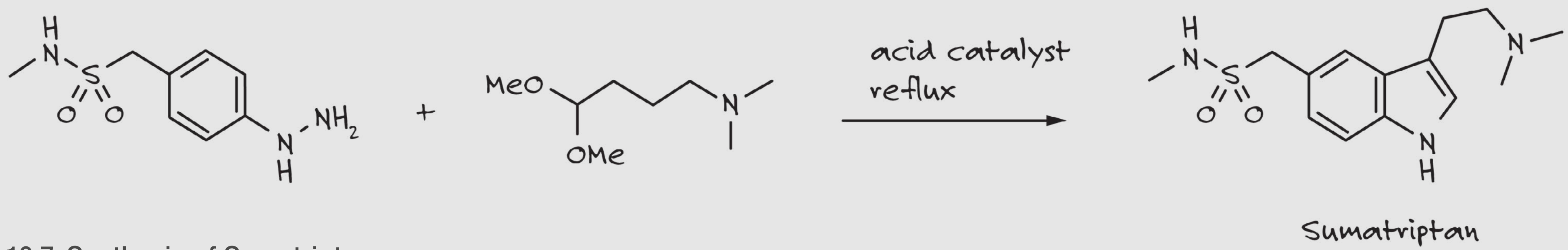


Figure 10.7. Synthesis of Sumatriptan

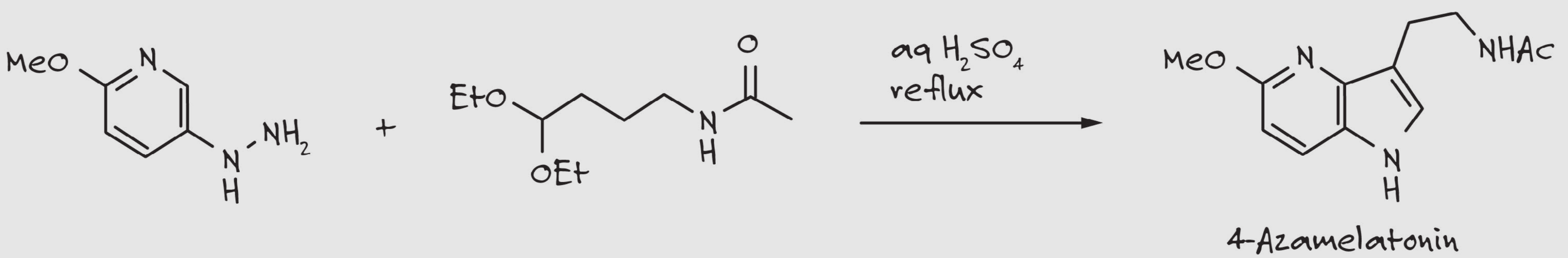


Figure 10.8. Synthesis of 4-azamelotonin

Reference Reaction Protocols

Synthesis of 2-phenylindole derivatives

Phenyl hydrazine (15 mmol) and $ZnCl_2$ (28 mmol) were added to a solution of the acetophenone (15 mmol) in 35 mL acetic acid. The reaction was heated to 70 °C for 4 hours and allowed to cool. The reaction mixture was filtered, to remove the $ZnCl_2$, and then concentrated. The residue was dissolved in EtOAc, subjected to an aqueous work-up, dried and concentrated to give the crude 2-phenyl indole which was purified by silica gel chromatography.

Key Literature References

1. *S. Gore et al., Org. Lett., 2012, 14, 4568-4571.*
2. *B. J. Simmons et a.l, J. Am. Chem. Soc., 2017, 139, 14833–14836.*
3. *G. M. Robinson and R. Robinson, J. Chem. Soc., Trans., 1924,125, 827-840.*
4. *T. V. Sravanthi and S.L Manju, Euro. J. Pharm. Sci., 2016, 91, 1–10.*
5. *M. M. Heravi et al., RSC Adv., 2017, 7, 52852-52887.*
6. *R. B. Woodward et al., J. Am. Chem. Soc., 1954, 76, 4749-4751.*
7. *M. Baumann et al., Beilstein J. Org. Chem., 2011, 7, 442–495.*
8. *M. Jeanty et al., Org. Lett., 2009, 11, 5142-5145.*

QUIZ ANSWER — WOHL-ZIEGLER REACTION

Below are the correct options that make each sentence below **true** for the Wohl-Ziegler reaction.

1. Bromination reactions are growing in use because halogenated compounds are (***commonly used*** / *excluded from)* biological processes.
2. The free radical generated in the propagation step of this reaction is a *(**allylic / bromine**)* radical.

   Both! A Br radical is formed that abstracts the hydrogen from the olefine to generate HBr and an allylic radical.
3. A *(**limiting*** / *excess)* amount of bromine is used to avoid side products and dibromination.
4. The Wohl-Ziegler reaction *(**can*** / *cannot)* be conducted using ionic liquids as solvent).

   It can be, and the reaction is generally more environmentally friendly when ionic liquids are used as solvent.
5. The Wohl-Ziegler reaction was discovered by Alfred Wohl in (***1919*** / *1939*) but then studied and improved by Karl Ziegler in (***1928*** / *1942*).

JUMP TO THE QUIZ QUESTION

JUMP TO NEXT QUIZ QUESTION

TEST YOUR KNOWLEDGE — FISCHER INDOLE SYNTHESIS

Select which answer(s) are correct for each question below about the Fischer indole reaction.

1. The following acids can be used at catalysts for the Fischer indole synthesis:

   i. $ZnCl_2$
   ii. Et_2O
   iii. H_2SO_4
   iv. HCl

2. Which of the following structures on the hydrazine can slow the reaction or negatively affect its efficiency?

   i. Electron withdrawing groups
   ii. Ortho substituents

3. Which of the following can be synthesized using this reaction?

   i. Strychnine
   ii. Sumatriptan
   iii. 4-azamelatonin
   iv. 2-phenylindole derivatives

4. This is one of the oldest oldest named reactions in organic synthesis given its discovery by E. Fischer and F Jourdan in what year?

   i. 1812
   ii. 1854
   iii. 1883
   iv. 1901

Product Selection for the Fischer Indole Reaction

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
	H2SO4
011000	Sulfuric acid, 99.9999% (metals basis), 92% min
033273	Sulfuric acid, ACS, 95.0-98.0%
035606	Sulfuric acid, 5% v/v aq. soln.
038751	Sulfuric acid, Environmental Grade, 93-98%
039668	Sulfuric acid, 50% v/v aq. soln.
039669	Sulfuric acid, 20% v/v aq. soln.
042552	Sulfuric acid, 10% v/v aq. soln.
042554	Sulfuric acid, 15% v/v aq. soln.
042555	Sulfuric acid, 75% v/v aq. soln.
045596	Sulfuric acid, 72% w/w aq. soln.

SKU	Description
	HCl
035607	Hydrochloric acid, 50% v/v aq. soln.
033257	Hydrochloric acid, ACS, HCl 36.5-38.0%
087617	Hydrochloric acid, 99.999% (metals basis), 36.5% min
L13091	Hydrochloric acid, 36% w/w aq. soln.
010990	Hydrochloric acid, 99.999999% (metals basis), 33% min

SKU	Description
	Ketones
10241	Acetophenone, 98%, pure
H55889	1-Adamantyl methyl ketone, 99%
10309	4'-Aminoacetophenone, 99%
10310	2-Aminoacetophenone hydrochloride, 96%
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%
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
	Aldehydes
A11987	4-Ethoxybenzaldehyde, 97+%
B20430	4-Acetamidobenzaldehyde, 98%
030749	Benzaldehyde, 98%
A10348	Benzaldehyde, 99+%
10626	4-Biphenylcarboxaldehyde, 99%
10665	2-Bromobenzaldehyde, 97%
A15065	2-Bromobenzaldehyde, 98%
10666	3-Bromobenzaldehyde, 96%
A11941	3-Bromobenzaldehyde, 97%
10667	4-Bromobenzaldehyde, 99%
A14237	4-Bromobenzaldehyde, 98+%
H26109	2-Bromo-5-(trifluoromethyl)benzaldehyde, 97%
A11201	2-Carboxybenzaldehyde, 98+%
B21277	3-Carboxybenzaldehyde, 97%
A15277	4-Carboxybenzaldehyde, 98%
A12757	4-Chlorobenzaldehyde, 98%
10861	3-Chlorobenzaldehyde, 99%
A13254	3-Chlorobenzaldehyde, 97%
H26023	2-Chloro-6-methylbenzaldehyde, 98%
10960	4-Chloro-3-nitrobenzaldehyde, 97%
A12852	2-(4-Chlorophenylthio)benzaldehyde, 98%
11035	trans-Cinnamaldehyde, 99%
H29027	2-Cyanobenzaldehyde, 98%
11072	4-Cyanobenzaldehyde, 98%
A14914	4-Cyanobenzaldehyde, 98+%
11264	3,4-Dibenzyloxybenzaldehyde, 99%
H31689	2,5-Dibromobenzaldehyde, 97%
A13325	3,5-Dichlorobenzaldehyde, 97%
11316	2,6-Dichlorobenzaldehyde, 99%
A13295	2,6-Dichlorobenzaldehyde, 97+%
11400	4-(Diethylamino)benzaldehyde, 99%
A11825	4-Diethylaminobenzaldehyde, 97%
H26139	3,5-Difluoro-4-hydroxybenzaldehyde, 97%
11484	2,5-Dihydroxybenzaldehyde, 99%
A15565	2,5-Dihydroxybenzaldehyde, 98+%
11485	3,4-Dihydroxybenzaldehyde, 97%

SKU	Description
	Aldehydes
A11558	3,4-Dihydroxybenzaldehyde, 98%
11537	2,3-Dimethoxybenzaldehyde, 97%
A14080	2,3-Dimethoxybenzaldehyde, 98+%
11538	2,4-Dimethoxybenzaldehyde, 98%
A12549	2,4-Dimethoxybenzaldehyde, 98%
A19928	2,5-Dimethoxybenzaldehyde, 98+%
036684	4-Dimethylaminobenzaldehyde, ACS
A11712	4-Dimethylaminobenzaldehyde, 98%
11579	4-Dimethylaminocinnamaldehyde, 98%
B23598	4-Dimethylamino-2-methoxybenzaldehyde, 98%
A15388	3,4-Dimethylbenzaldehyde, 97%
A15035	2-Ethoxybenzaldehyde, 97+%
B24762	3-Ethoxy-4-methoxybenzaldehyde, 99%
A19478	3-Ethoxy-4-hydroxybenzaldehyde, 98%
B20645	4-Ethylbenzaldehyde, 97%
11932	2-Fluorobenzaldehyde, 97%
A13800	2-Fluorobenzaldehyde, 97%
11933	3-Fluorobenzaldehyde, 98+%
A18904	2-Fluoro-5-methoxybenzaldehyde, 97%
A13287	4-n-Hexyloxybenzaldehyde, 98%
A13541	3-Hydroxybenzaldehyde, 97%
A13580	4-Hydroxybenzaldehyde, 98%
A12971	2-Hydroxy-4-methoxybenzaldehyde, 98%
A15753	2-Hydroxy-5-methoxybenzaldehyde, 98%
A10264	2-Hydroxy-5-nitrobenzaldehyde, 98%
A14019	4-Isopropylbenzaldehyde, tech. 90%
A13962	3-Methoxybenzaldehyde, 98%
A15364	4-Methoxybenzaldehyde, 98%
A13594	3-Nitrobenzaldehyde, 99%
A11501	2-Nitrobenzaldehyde, 98+%
A11655	4-Nitrobenzaldehyde, 99%
B22329	4-Phenoxybenzaldehyde, 98%
B24591	2-(Trifluoromethyl)benzaldehyde, 98%
A19270	3,4,5-Trihydroxybenzaldehyde hydrate, 97%
B22792	2,4,5-Trimethoxybenzaldehyde, 98%

SKU	Description
	Ph-Hydrazines
A14446	N-Acetyl-N'-phenylhydrazine, 98%
39402	3-Benzyloxyphenylhydrazine hydrochloride, 98%
39403	4-Benzyloxyphenylhydrazine hydrochloride, 98%
A17367	N-Benzyl-N-phenylhydrazine hydrochloride, 98+%
H32975	3,5-Bis(trifluoromethyl)phenylhydrazine hydrochloride, 98%
B23966	2-Bromophenylhydrazine hydrochloride, 94%
16735	3-Bromophenylhydrazine hydrochloride, 98%
B23510	3-Bromophenylhydrazine hydrochloride, 98%
16231	4-Bromophenylhydrazine hydrochloride, 99%
A15590	4-Bromophenylhydrazine hydrochloride, 97%
A10175	3-Chloro-4-fluorophenylhydrazine hydrochloride, 98%
14914	2-Chlorophenylhydrazine hydrochloride, 97%
A14136	2-Chlorophenylhydrazine hydrochloride, 97%
16736	3-Chlorophenylhydrazine hydrochloride, 97%
A14770	3-Chlorophenylhydrazine hydrochloride, 97%
40495	4-Chlorophenylhydrazine hydrochloride, 97%
A14518	4-Chlorophenylhydrazine hydrochloride, 97%
39230	4-Cyanophenylhydrazine hydrochloride, 97+%
B22157	4-Cyanophenylhydrazine hydrochloride, 97%
A10717	2,3-Dichlorophenylhydrazine hydrochloride, 97%
A11968	2,6-Dichlorophenylhydrazine hydrochloride, 98+%
A13906	3,4-Dichlorophenylhydrazine hydrochloride, 98+%
A15127	3,5-Dichlorophenylhydrazine hydrochloride, 95%
A11625	2,4-Difluorophenylhydrazine hydrochloride, 97%
H26189	3,5-Difluorophenylhydrazine hydrochloride, 97%
A16526	2,3-Dimethylphenylhydrazine hydrochloride, 97%
B21009	2,4-Dimethylphenylhydrazine hydrochloride, 95%
A13027	3,4-Dimethylphenylhydrazine hydrochloride, 98%
A11336	3,5-Dimethylphenylhydrazine hydrochloride, 98%
A11289	1,1-Diphenylhydrazine hydrochloride, 98%

SKU	Description
	Ph-Hydrazines
A16853	2-Ethylphenylhydrazine hydrochloride, 98%
A13716	2-Fluorophenylhydrazine hydrochloride, 98%
16737	3-Fluorophenylhydrazine hydrochloride, 97%
L07418	3-Fluorophenylhydrazine hydrochloride, 98%
11959	4-Fluorophenylhydrazine hydrochloride, 97%
A15624	4-Fluorophenylhydrazine hydrochloride, 97%
39905	4-Iodophenylhydrazine, 95%
L14806	4-Iodophenylhydrazine, 95%
A12416	4-Isopropylphenylhydrazine hydrochloride, 98%
L14810	4-Methoxy-2-methylphenylhydrazine hydrochloride, 96%
16649	4-Methoxyphenylhydrazine hydrochloride, 98%
L06076	4-Methoxyphenylhydrazine hydrochloride, 98%
B22440	1-Methyl-1-phenylhydrazine, 97%
42496	4-(Methylsulfonyl)phenylhydrazine hydrochloride, 95%
12883	2-Nitrophenylhydrazine, 97%, moistened with ca 30% water
L09273	4-Nitrophenylhydrazine mono and dihydrochloride, 98%
29668	Phenylhydrazine, 97%
A11246	Phenylhydrazine, 97%
15155	Phenylhydrazine hydrochloride, 99+%
A14645	Phenylhydrazine hydrochloride, 99%
B20015	4-Sulfonamidophenylhydrazine hydrochloride, 97%
39704	4-(Trifluoromethoxy)phenylhydrazine hydrochloride, 97%
H26180	4-(Trifluoromethoxy)phenylhydrazine hydrochloride, 98%
A14781	2-(Trifluoromethyl)phenylhydrazine, 97%
L11996	3-(Trifluoromethyl)phenylhydrazine, 95%
L12436	4-(Trifluoromethyl)phenylhydrazine, 95%
B25182	2-(Trifluoromethyl)phenylhydrazine hydrochloride, 98%
H32340	4-(Trifluoromethyl)phenylhydrazine hydrochloride, 96%
L10958	2,4,6-Trimethylphenylhydrazine hydrochloride, 97%

QUIZ ANSWER — FISHER INDOLE REACTION

Below are correct answer(s) for each question regarding the Fisher indole reaction.

1. The following acids can be used at catalysts for the Fisher indole synthesis:

   i. $ZnCl_2$
   ii. Et_2O
   iii. H_2SO_4
   iv. HCl

Answer: All of the above! The reaction can use a variety of both protic and Lewis acids.

2. Which of the following structures on the hydrazine can slow the reaction or negatively affect its efficiency?

   i. Electron withdrawing groups
   ii. Ortho substituents

Answer: Both can negatively affect the reaction

3. Which of the following can be synthesized using this reaction?

   i. Strychnine
   ii. Sumatriptan
   iii. 4-azamelatonin
   iv. 2-phenylindole derivatives

Answer: All of the above can be produced using this reaction!

4. This is one of the oldest oldest named reactions in organic synthesis given its discovery by E. Fischer and F Jourdan in what year?

   i. 1812
   ii. 1854
   iii. 1883
   iv. 1901

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JUMP TO THE FIRST QUIZ QUESTION

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