

Named Reactions

in Organic Synthesis

TRANSITION
METAL-CATALYZED
COUPLINGS

REACTIONS
INVOLVING
CARBONYL
COMPOUNDS

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AROMATIC
SUBSTITUTION
REACTIONS

NUCLEOPHILIC
SUBSTITUTION
REACTIONS

REARRANGEMENT
REACTIONS

OXIDATION
REACTIONS



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.

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.



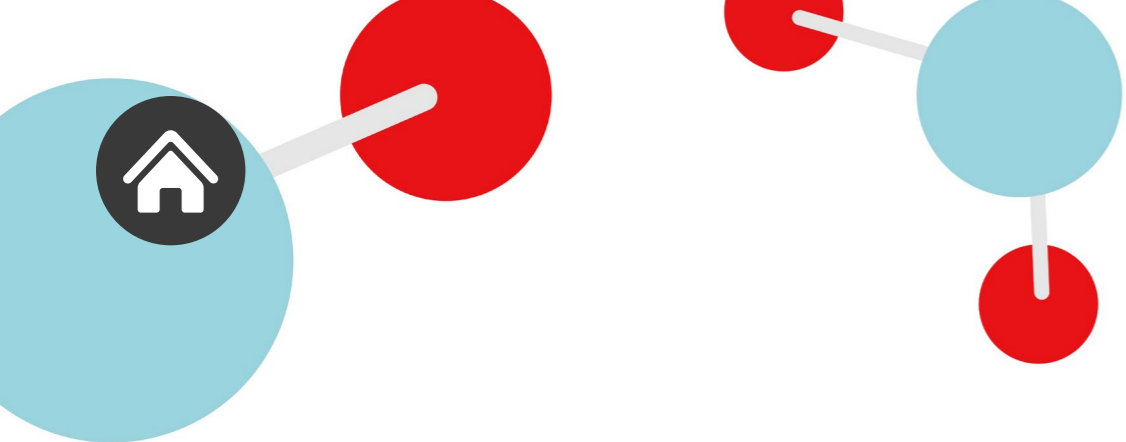
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One of the key features of the Heck reaction is that it tolerates a wide range of different functional groups such as esters, ethers, carboxylic acids, nitriles, phenols and many others.

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

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

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

Negishi Cross-Coupling Reaction

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

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

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

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

Stille Cross-Coupling Reaction

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

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

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

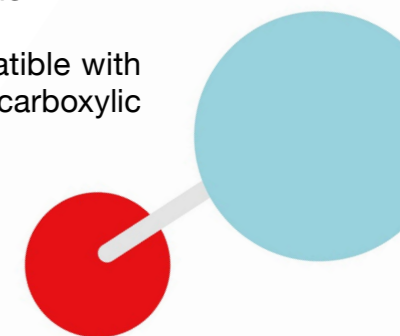


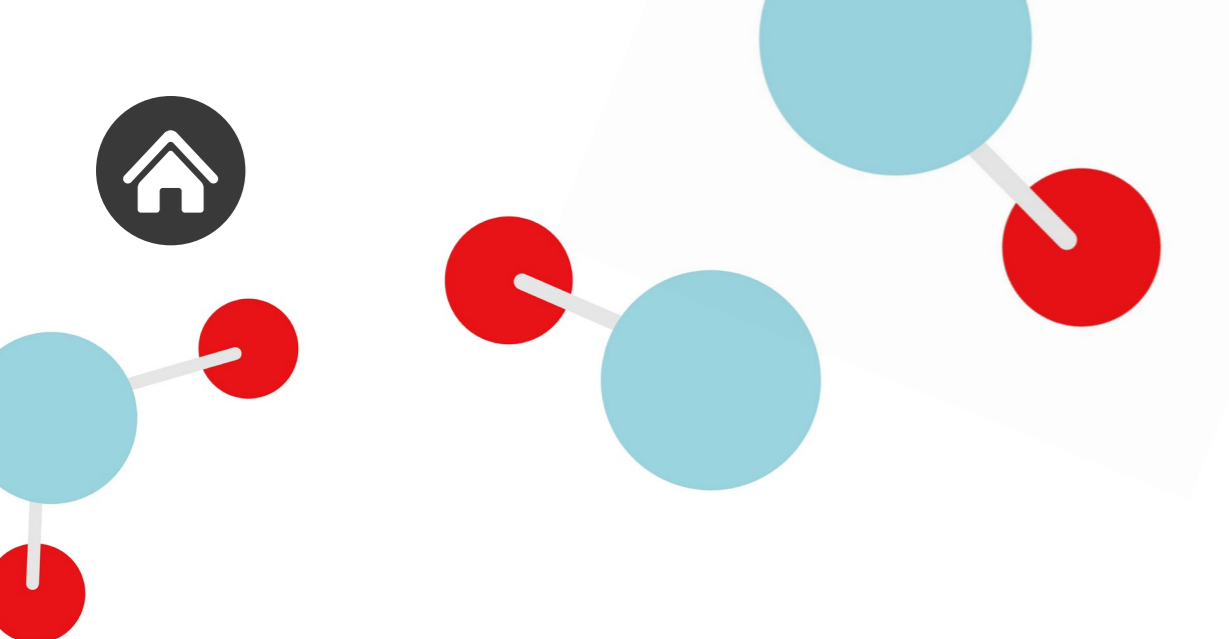
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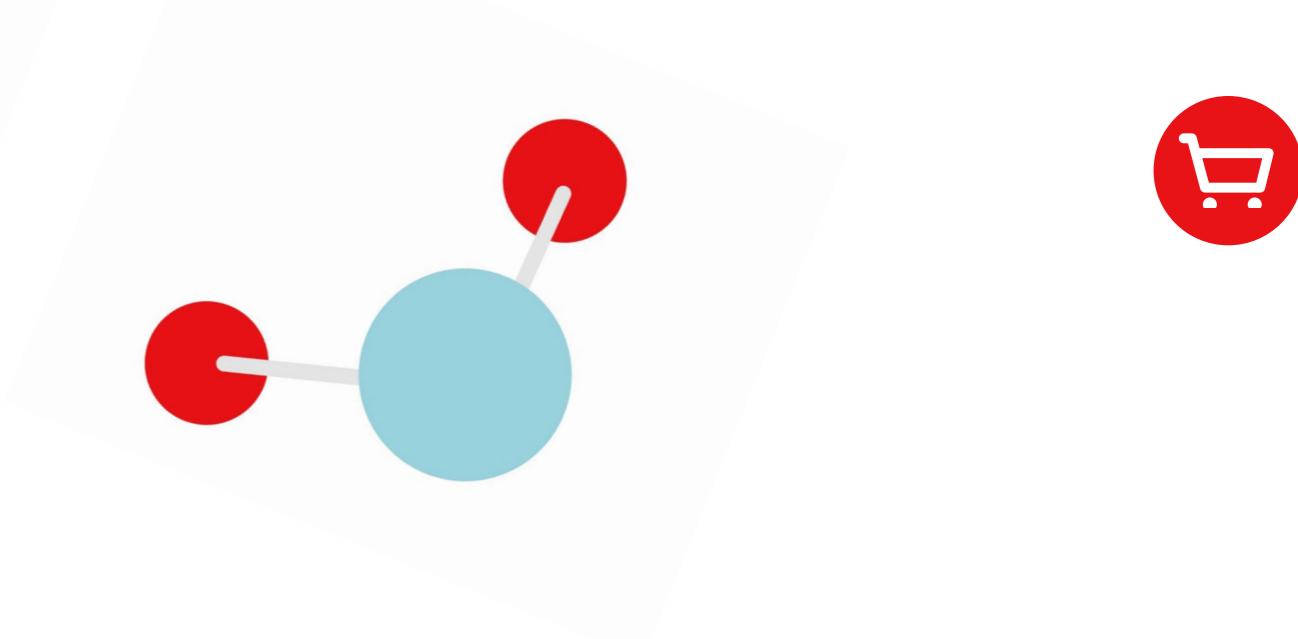
Among the many uses of the Stille cross-coupling reaction in organic synthesis is the total synthesis of natural products, these include the manzamine alkaloid ircinal A and quadrigemine C – another member of the alkaloid family.

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 proteasome inhibitor.

[Click here for a more in-depth look at the Suzuki cross-coupling reaction.](#)

Ullmann Reaction

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

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



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Suzuki-Miyaura Cross-Coupling Reaction

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

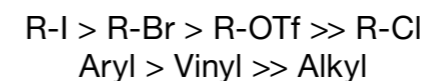
Among the various types of cross-coupling, the Suzuki-Miyaura – usually simply called “Suzuki coupling” – is arguably the one with the broadest utility and applicability. The Suzuki chemistry is based on the Pd(0)-catalyzed coupling of an aryl or vinyl halide with an aryl or vinyl boronic acid.

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

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

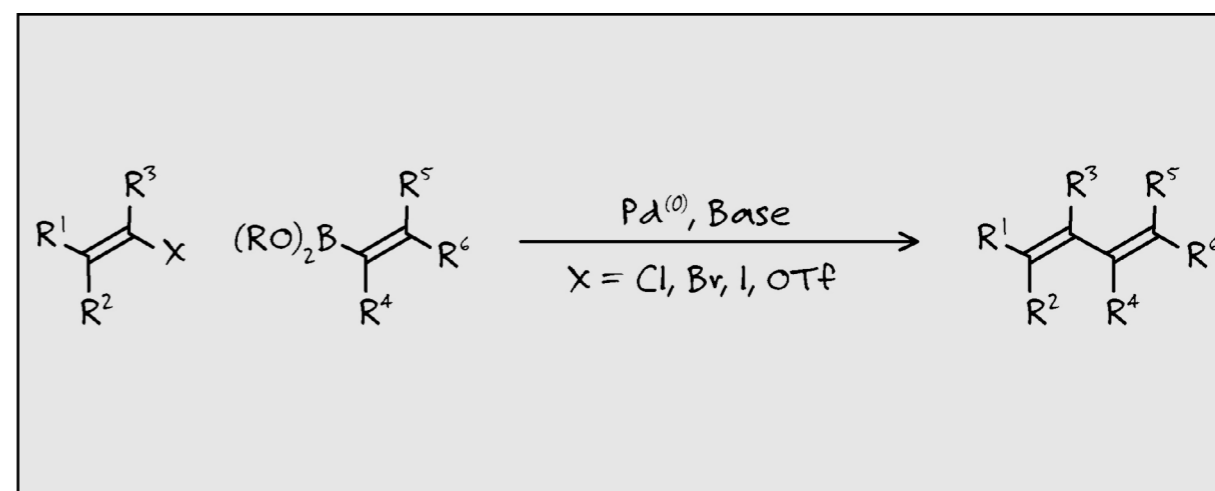
The scope of the other coupling partner has also expanded over time to include pseudo-halides, such as triflates or aryl diazonium salts, and

alkyl halides. The relative reactivity of the halide/pseudo-halide coupling partner is:



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

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



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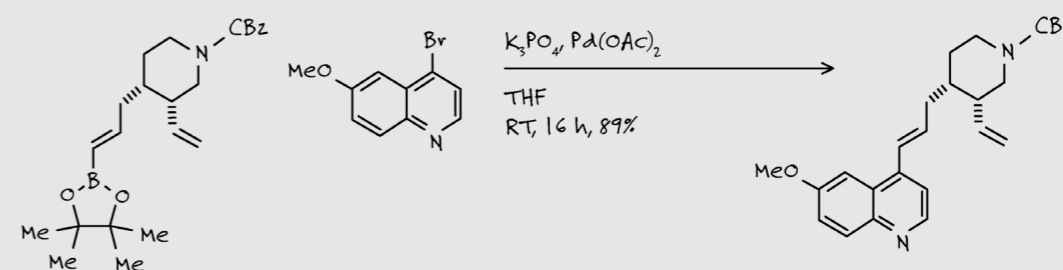
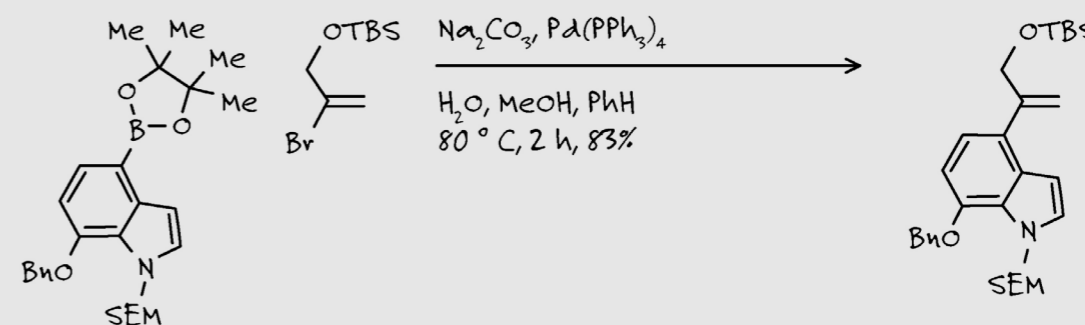
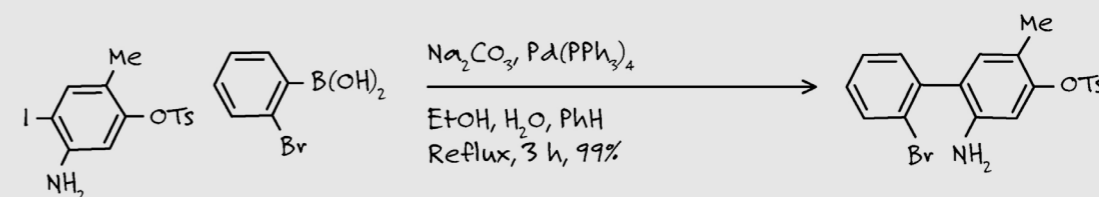
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Suzuki Reaction Examples



Reference Reaction Protocols

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

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



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Product Selection for Suzuki Reaction

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

	Stock Number	Description
Solvents used for downstream/extraction:	39074	Hexanes, for analysis, mixture of isomers
	38917	n-Heptane, 99.5%, for analysis
	17681	Cyclohexane, 99.5%, for analysis
Basic Ingredients/Additives:	041587	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)



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

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



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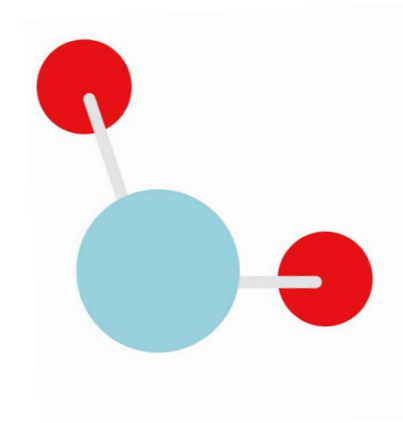
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	Stock Number	Description
Catalysts/ ligands (XPhos Palladacycle 2nd Gen):	44789	Bis[di-tert-butyl(4-dimethylaminophenyl)phosphine] dichloropalladium, 95%
	046665	Dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] palladium(II), Pd 14.1%
	39588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



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Reactions Involving Carbonyl Compounds

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

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

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

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

- Reformatsky reaction
- Stetter reaction
- Wittig reaction

Grignard Reaction

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

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

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

Grignard reagents have been used in the synthesis of several natural products, including the total synthesis of (\pm)-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



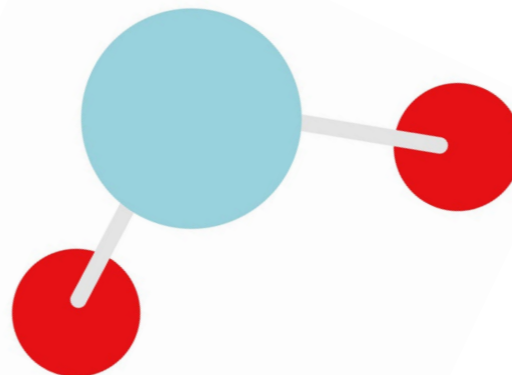
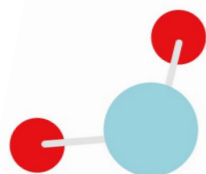
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ethyl benzoylacetate or acetylacetone in the presence of primary and secondary amines. In 1896 he conducted further experiments, reacting benzaldehyde with ethyl acetoacetate at 0 °C using piperidine as the catalyst to form ethyl benzylidene acetoacetate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

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

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

Mannich Reaction

In 1903, German chemist Bernhard Tollens observed that the reaction between acetophenone and formaldehyde in the presence of ammonium

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

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

Reformatsky Reaction

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



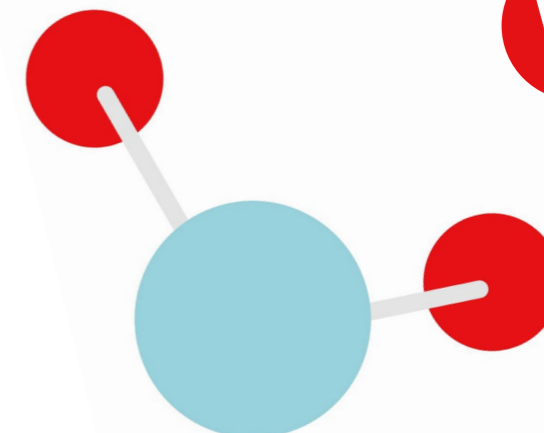
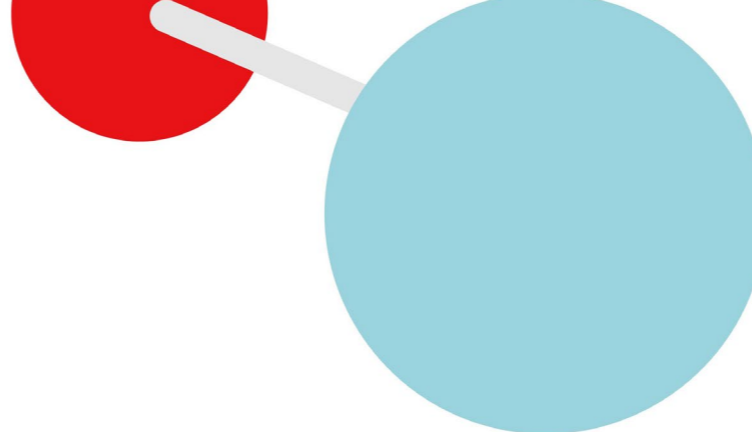
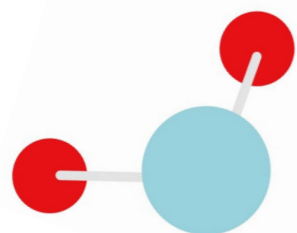
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The reaction proceeds by a two-step process: the zinc metal initially inserts into the carbon-halogen bond to form the zinc enolate Reformatsky reagent, which then reacts with the carbonyl compound in an aldol reaction. In addition to aldehydes and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

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

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

Wittig Reaction

In the early 1950s, chemists Georg Wittig and Georg Geissler reported the reaction of methylenetriphenylphosphorane and benzophenone to

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

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

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



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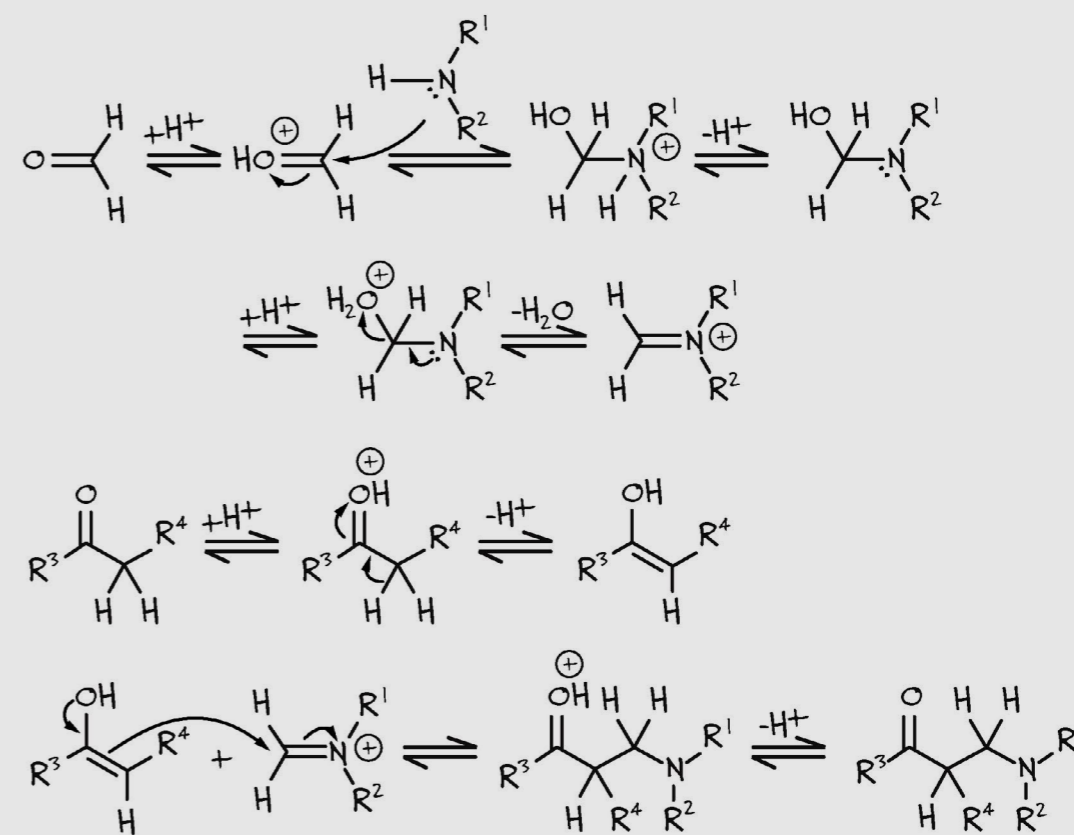
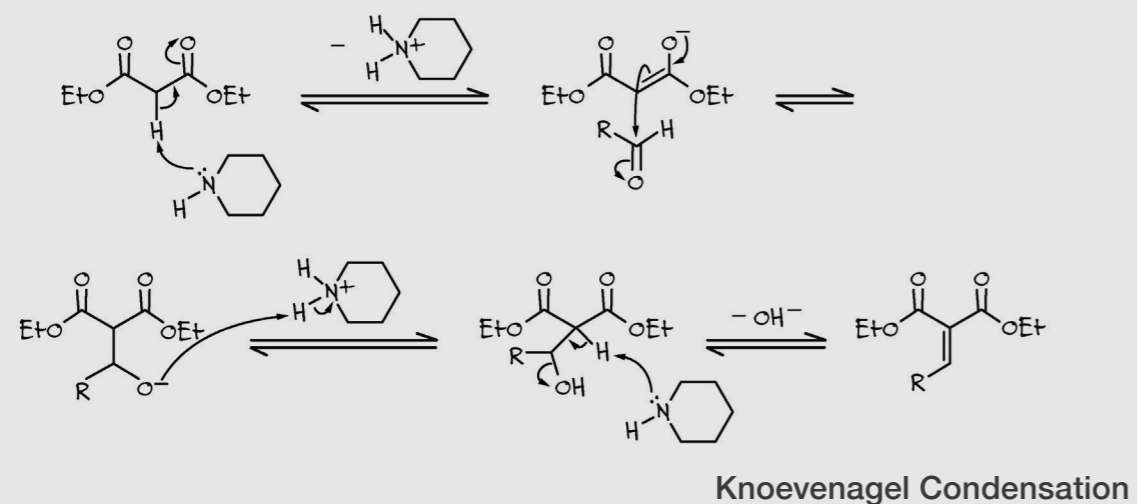
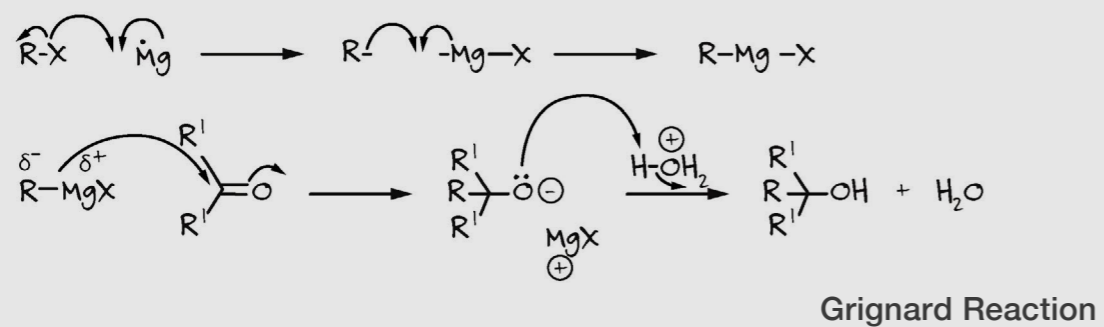
GRIGNARD
REACTION

PRODUCT
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FOR THE GRIGNARD
REACTION





Mechanisms of the Reactions Involving Carbonyl Compounds



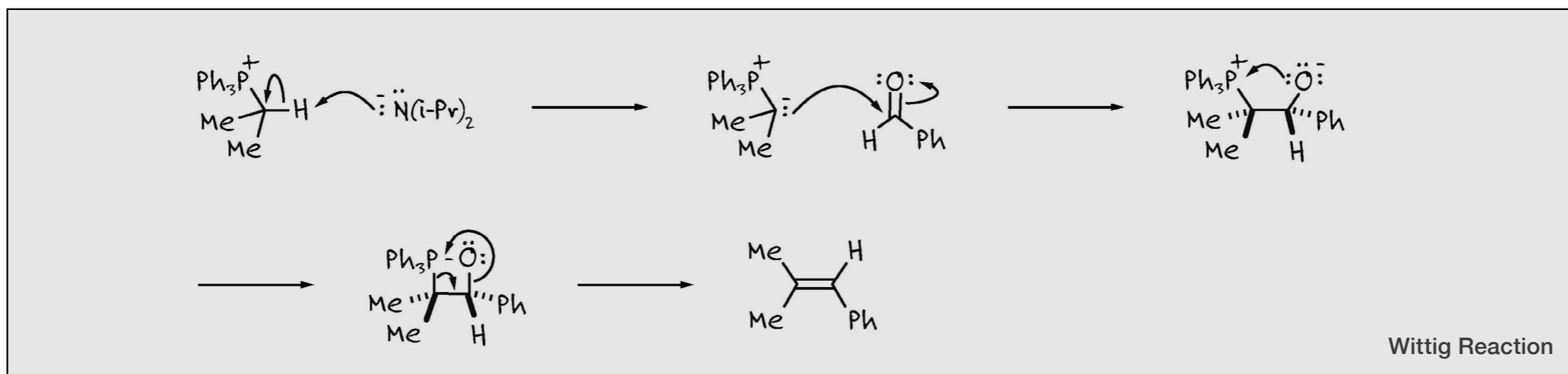
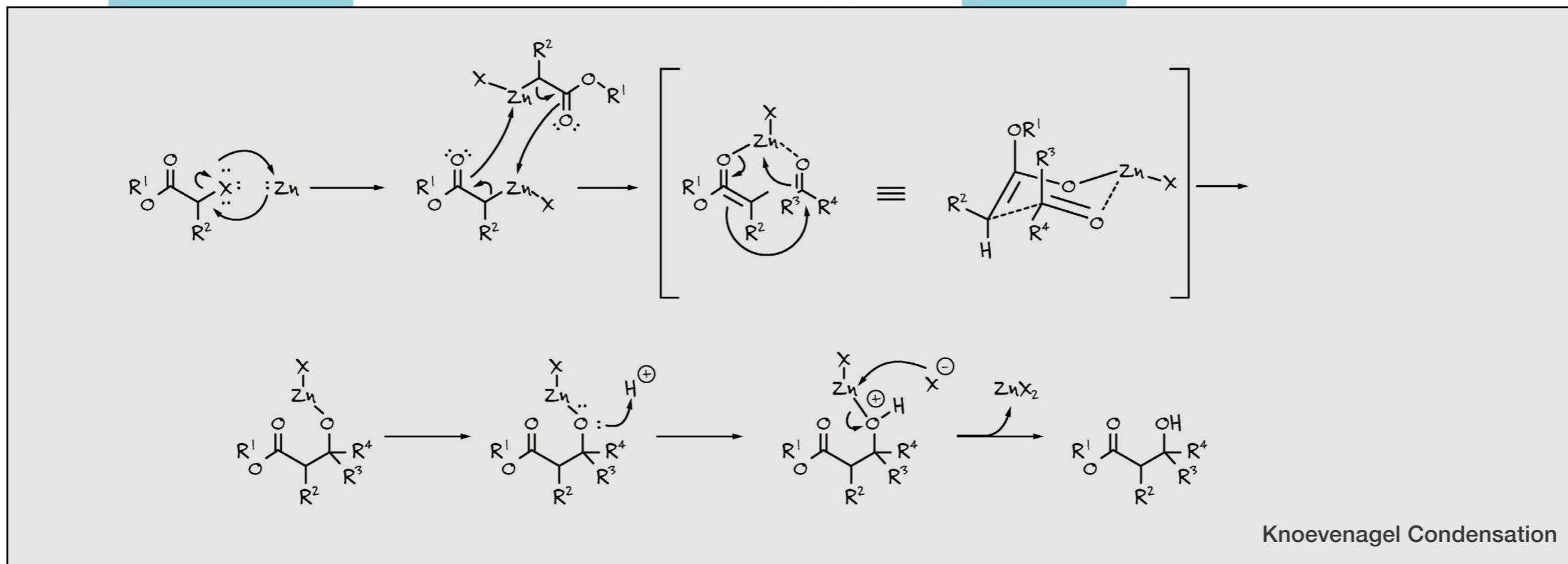
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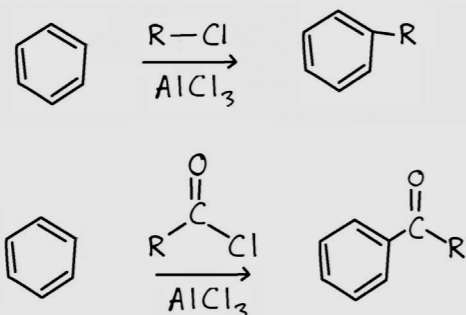
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Grignard Reaction



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

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

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

Preparation of Grignard reagents

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

The reactions protocol is typically very simple, with the halide solution and small magnesium metal bits gently heated in a water bath, with a reflux condenser fitted to the flask. The formation of the Grignard reagents happens with reasonably fast kinetics, reaching full conversion around 30 minutes in most cases. The reaction presents moderate hazards linked to the use of highly volatile and flammable solvents, such as diethyl ether.

It is important to operate in tightly controlled dry conditions, as the Grignard reagents react with water to give the correspondent alkane. This requires a specialized setup, as well as correct reagents and solvent grades.

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

Nucleophilic addition to the carbonyl – Grignard reaction

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

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

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



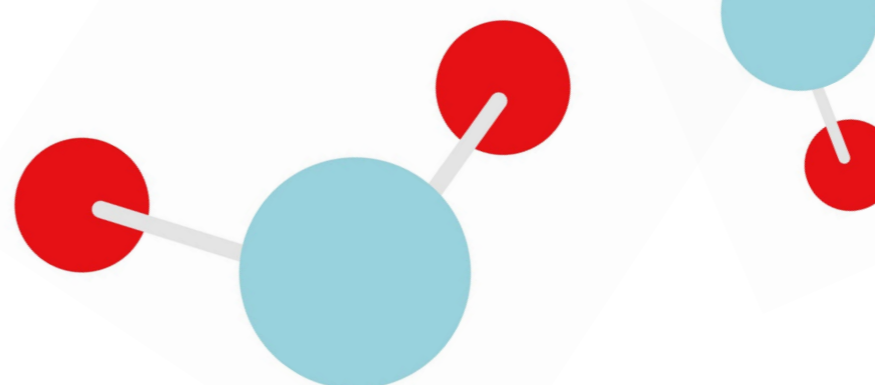
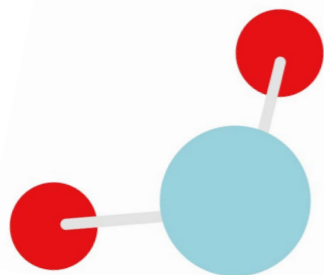
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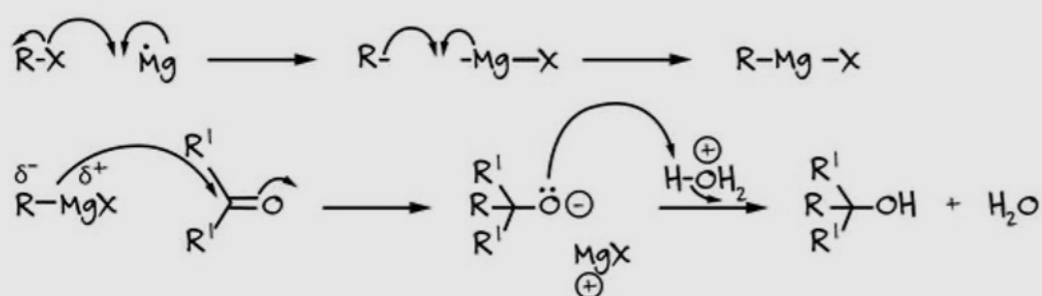
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Grignard reagents have been used in the synthesis of several natural products, including the total synthesis of (\pm)-lepadiformine and several natural and modified cyclotetrapeptide trapoxins.

Mechanism of the Grignard reaction



Reference reaction protocols

Preparation of Grignard reagent

Add 50 mg (2 mmol) of magnesium powder to 3 mL of anhydrous diethyl ether in the reaction vessel, with a reflux condenser and in a water bath at 40°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 maintain the reaction dry). The solution will start turning cloudy, then slowly add the remainder of the bromobenzene solution over a few minutes. Control the reaction temperature to ensure the solution doesn't boil too vigorously. The reaction completion can be detected by the disappearance of the magnesium metal.

Grignard reaction

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

Key literature references

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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.
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Product Selection for the Grignard reaction

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

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



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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 category:

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



Fries Rearrangement

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

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

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

Gattermann and Gattermann-Koch Formylation

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



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

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

Houben-Hoesch Synthesis

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

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

Synthetic applications of the Houben-Hoesch reaction include the total

synthesis of the natural product bostrycoidin and Genistein which is an important nutraceutical molecule found in soybean seeds.

Friedel-Crafts Acylation and Alkylation

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

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

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

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

[Click here for a more in-depth look at the Friedel-Crafts reaction](#)



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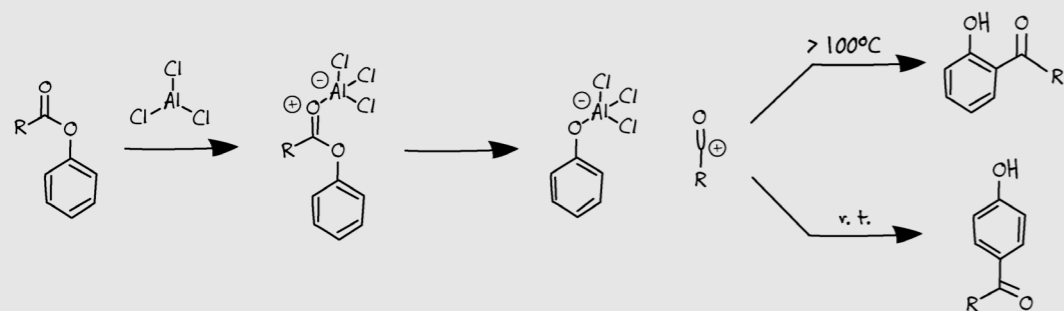
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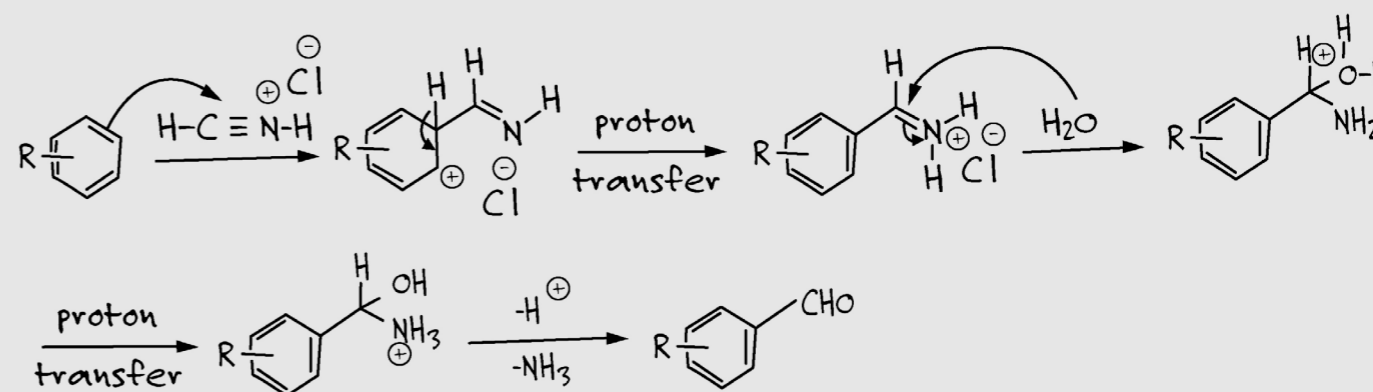
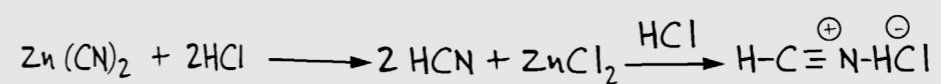




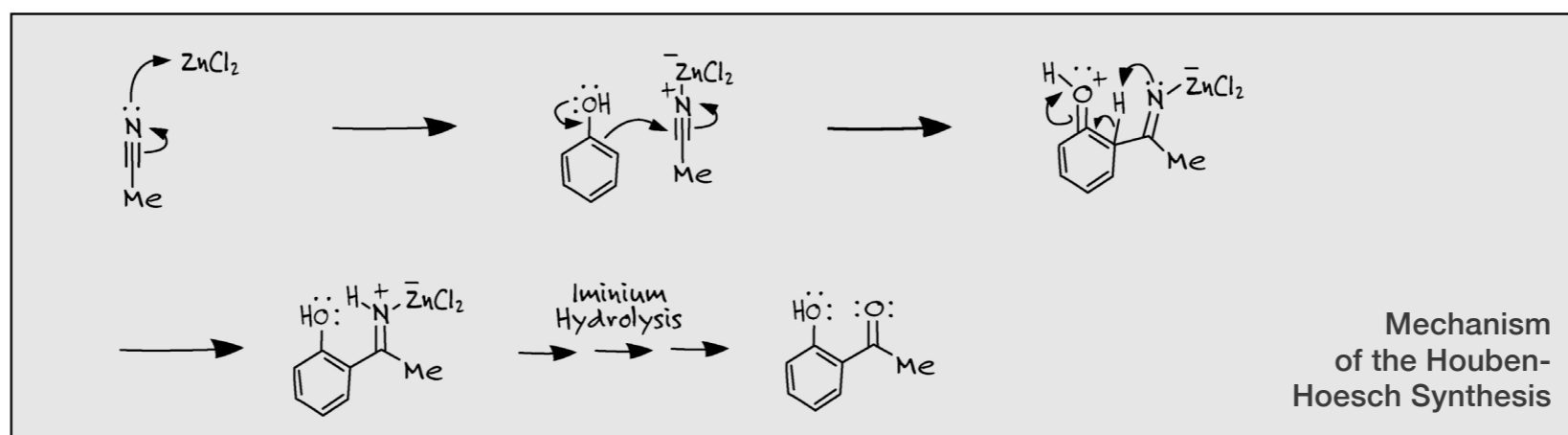
Reaction Mechanism Examples



Mechanism of the Fries Rearrangement



Mechanism of the Gattermann Formylation Using the Adams Modification



Mechanism of the Houben-Hoesch Synthesis



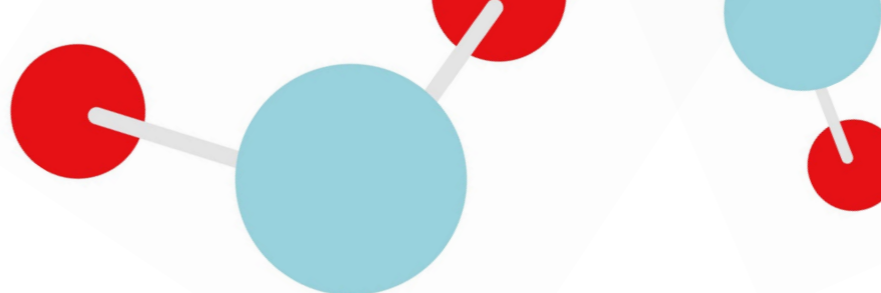
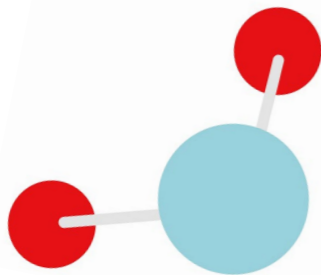
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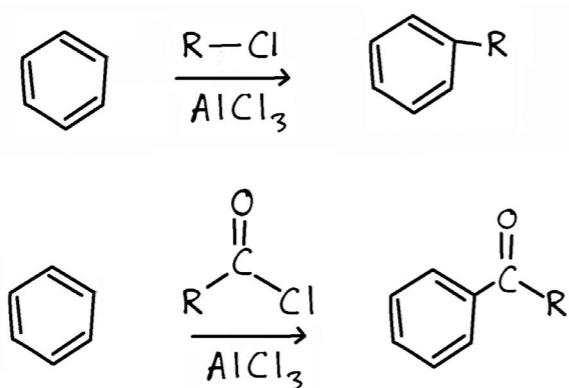




Friedel-Crafts Acylation and Alkylation Reaction

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

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



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

In general terms the alkylation or acylation happens in the presence of a Lewis acid. Besides aluminium chloride (AlCl₃), many others can be used: BeCl₂, CdCl₂, BF₃, BBr₃, GaCl₃, AlBr₃, FeCl₃, TiCl₄, SnCl₄, SbCl₅, lanthanide trihalides, and alkyl aluminium halides.

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

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



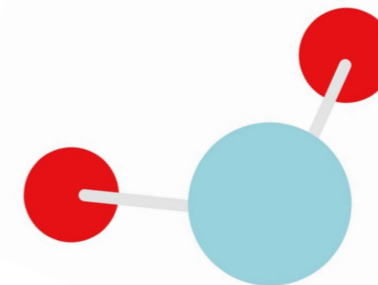
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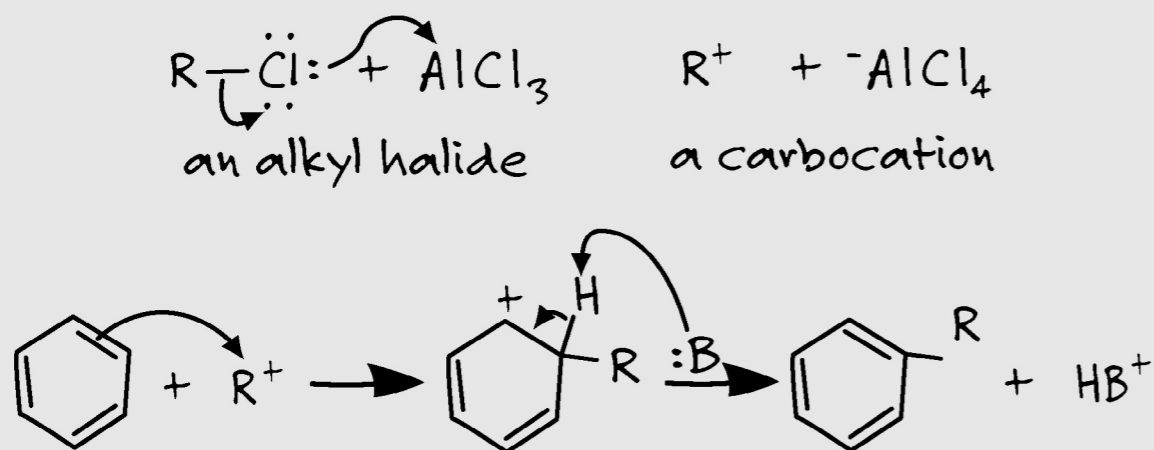




base that forms a strong complex with the Lewis acid catalyst. While this doesn't affect the overall chemistry, it impacts the reaction economics, often preventing industrial applications. There are ways to overcome this by using heterogeneous catalysts, such as zeolites, even though in some cases there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

Mechanism of the Friedel-Crafts Alkylation

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



Reference reaction protocols

Acylation

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

Alkylation

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

Key literature references

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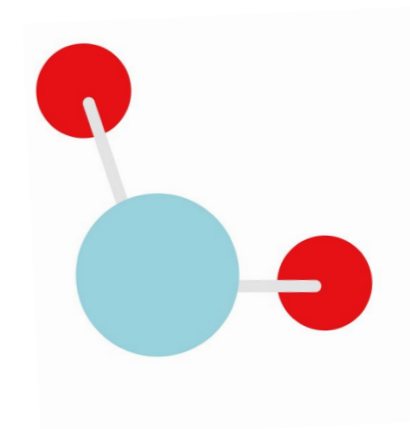
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Product Selection

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



SKU	Description
<i>Popular acetyl halides</i>	
46268	Propionyl chloride, 98%
21947	Acetyl chloride, 99+%
B24472	Isobutyryl chloride, 98%
17347	Chloroacetone, 96%, stabilized
45897	Propionyl chloride, 99.5%, phosgene free

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

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



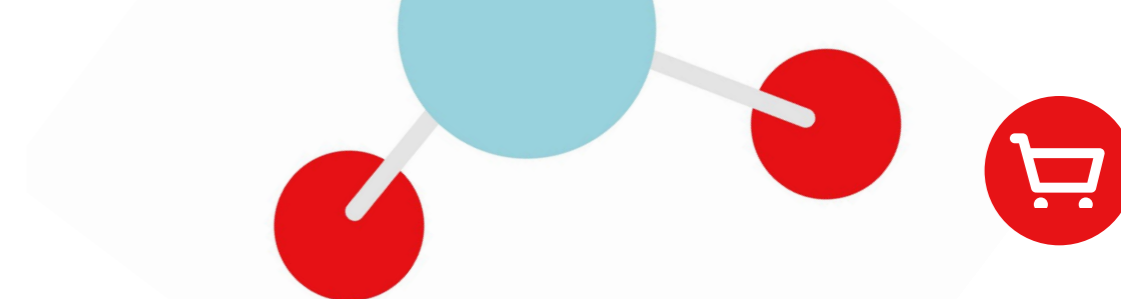
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Nucleophilic Substitution Reactions

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 phosphoramide (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.



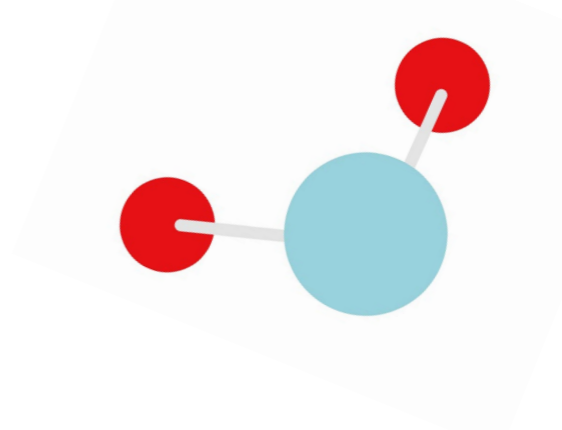
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The total synthesis of peramine, an alkaloid produced by a fungus that protects grasses against grazing by mammals and insects, successfully employed the Gabriel synthesis in the latter stages.

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 > monoperoxymaleic acid > monoperoxiphthalic acid > 3,5-dinitroperbenzoic acid > p-nitroperbenzoic acid > meta chloroperoxybenzoic acid (mCPBA) > performic acid > perbenzoic acid > peracetic acid > Hydrogen peroxide and finally tert-Butyl hydroperoxide (tBuOOH).



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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.

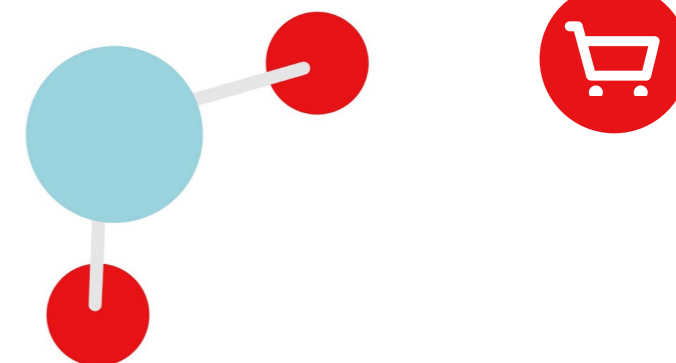
In the latter case, both Dess-Martin and Ley oxidations were tried but the substrate suffered carbon-carbon bond cleavage.

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 β -hydroxy 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.



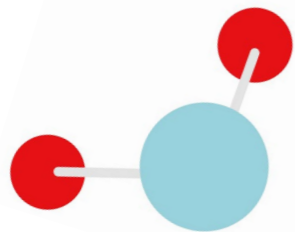
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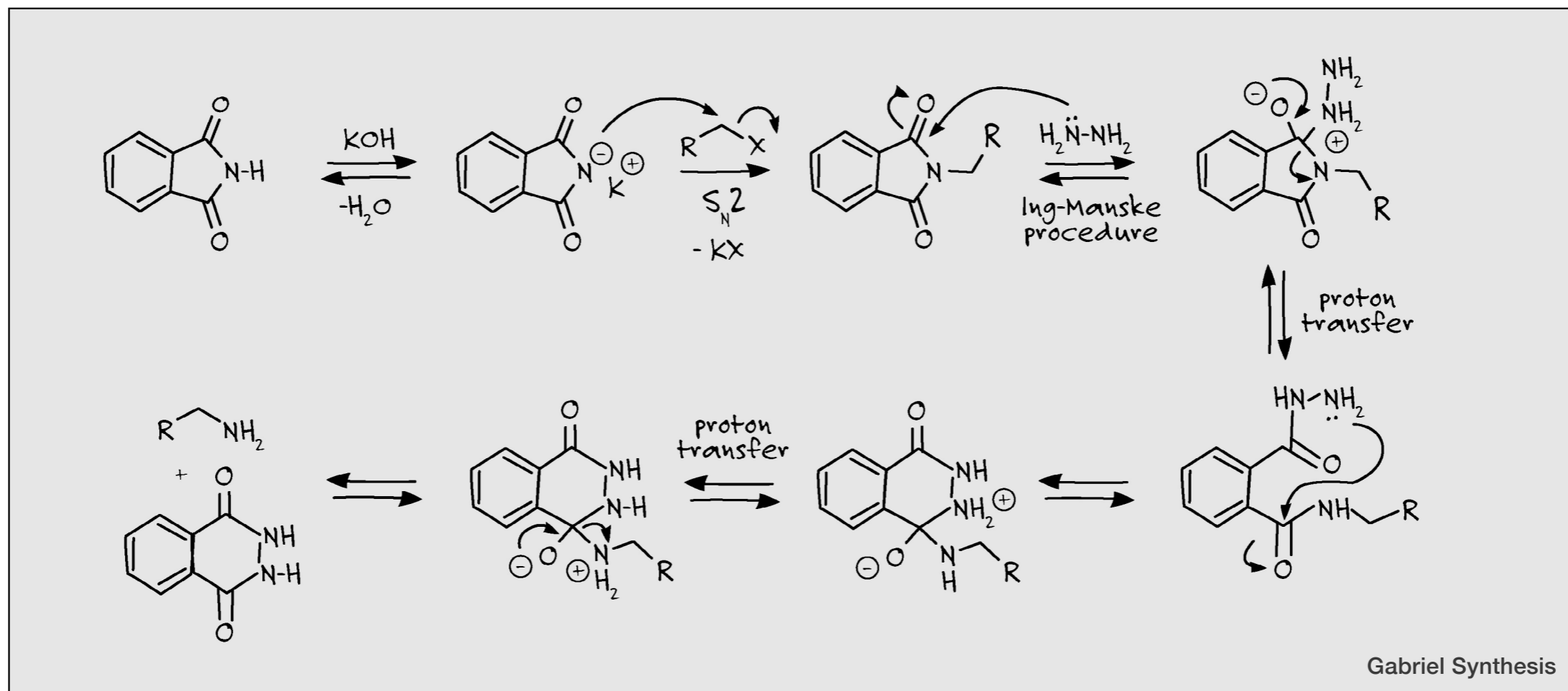
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Reaction Mechanism Examples



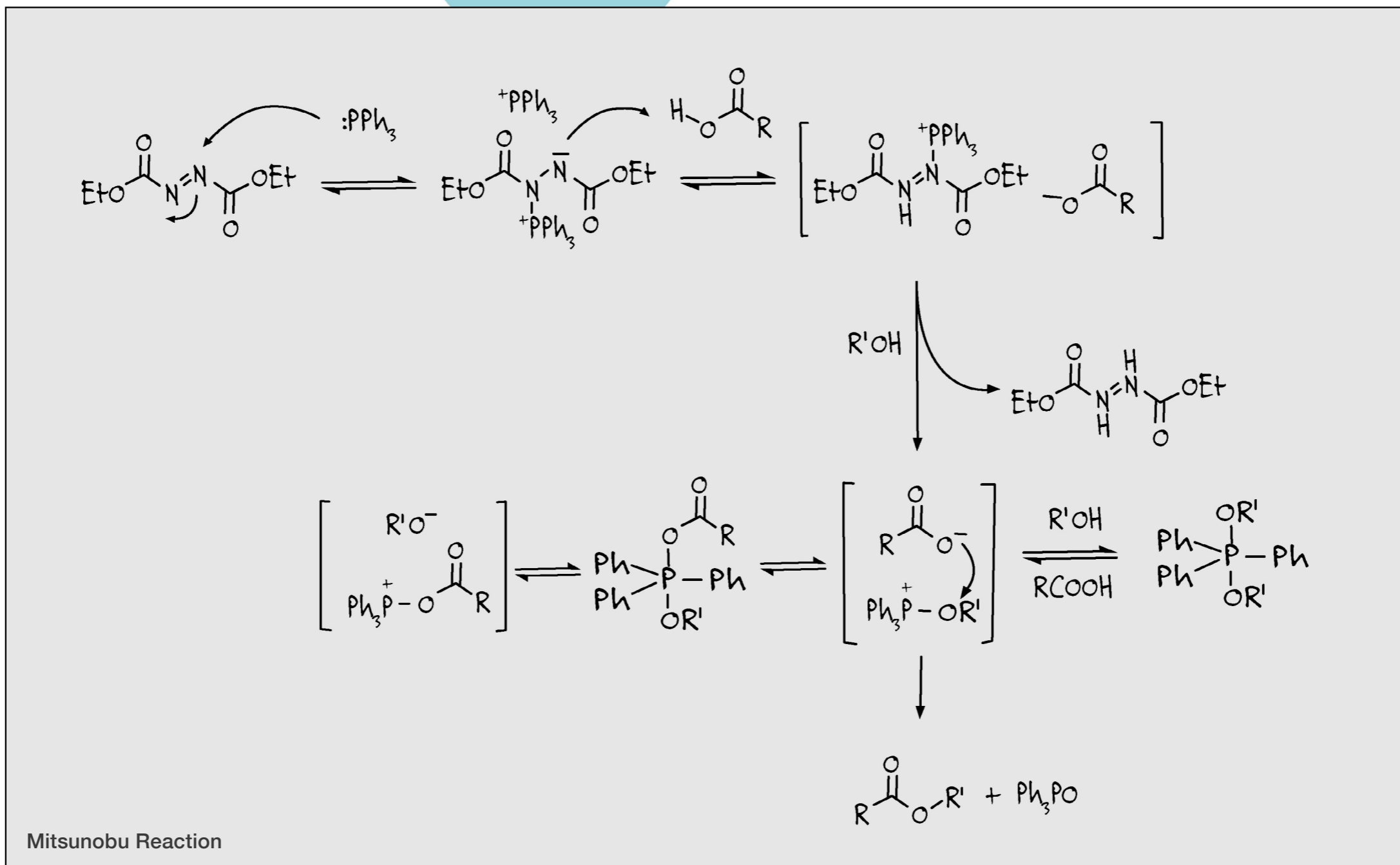
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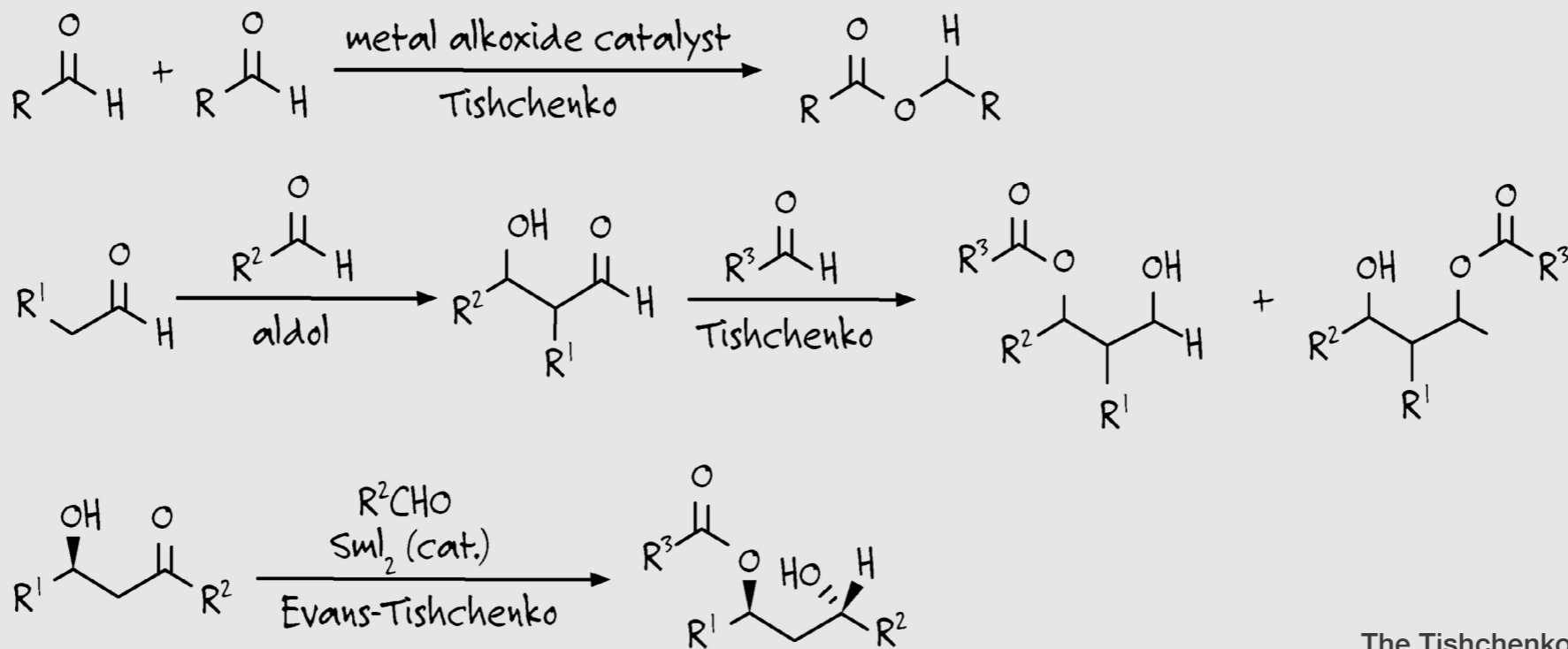
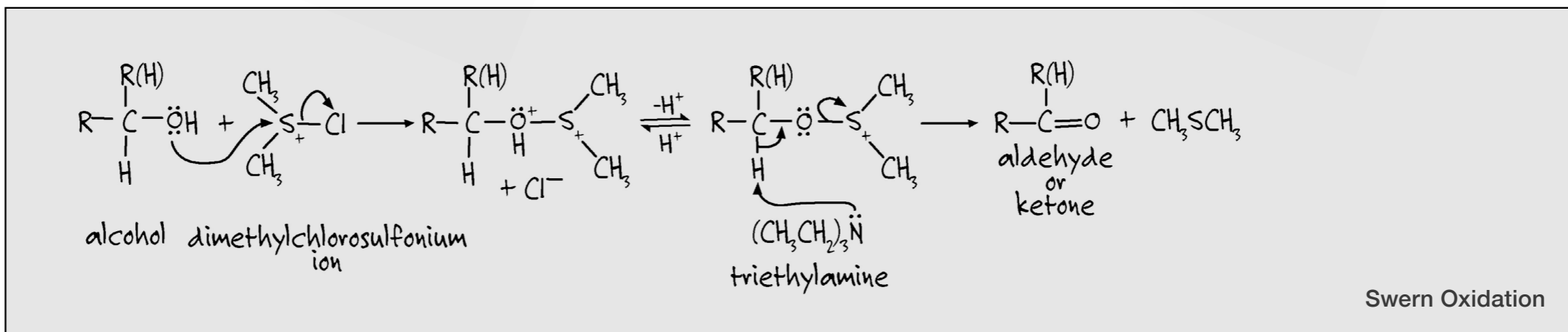
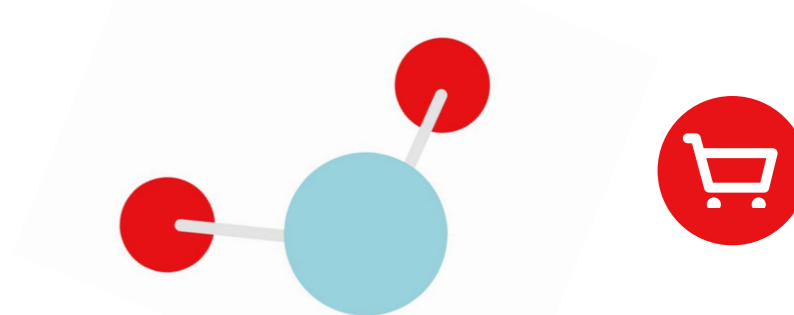
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The Tishchenko and Evans-Tishchenko Reactions



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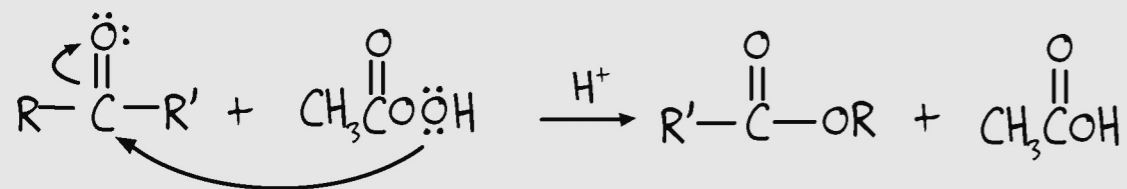
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Baeyer-Villiger reaction



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

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

Mechanism of Baeyer-Villiger reaction

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

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



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Product Selection

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

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

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

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



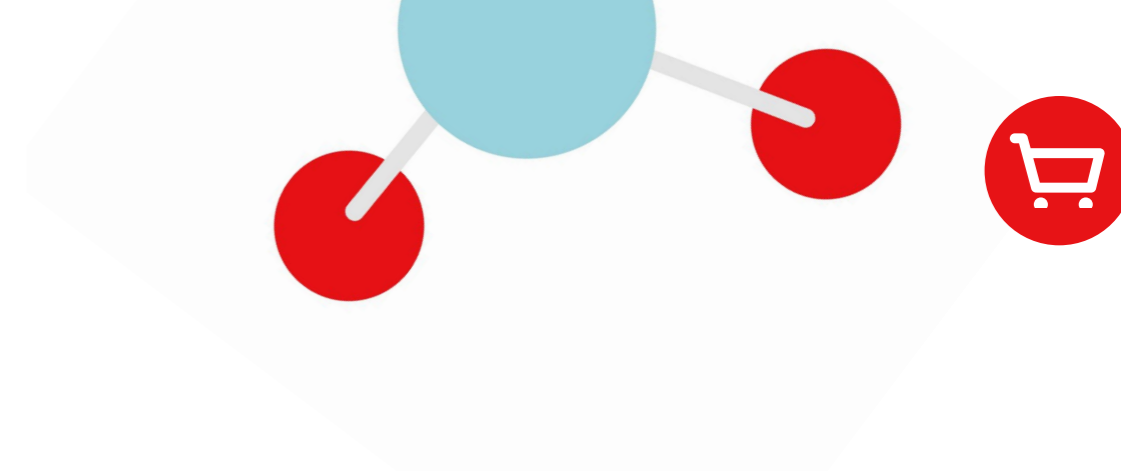
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Rearrangement Reactions

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](#)



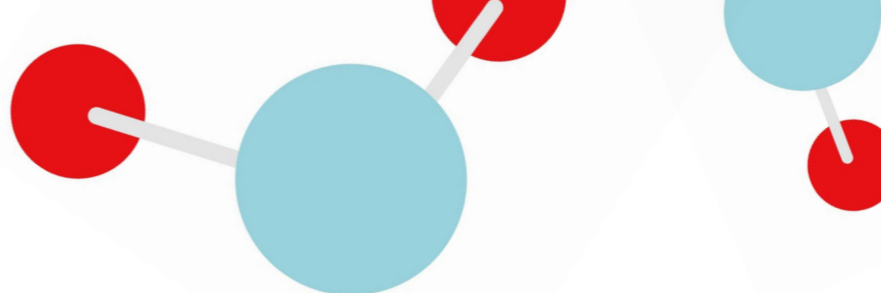
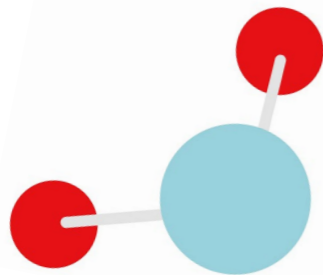
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Curtius rearrangement

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

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

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

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

Claisen rearrangement

In 1912 German chemist Rainer Ludwig Claisen published the rearrangement

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

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

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

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

Ferrier reaction

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



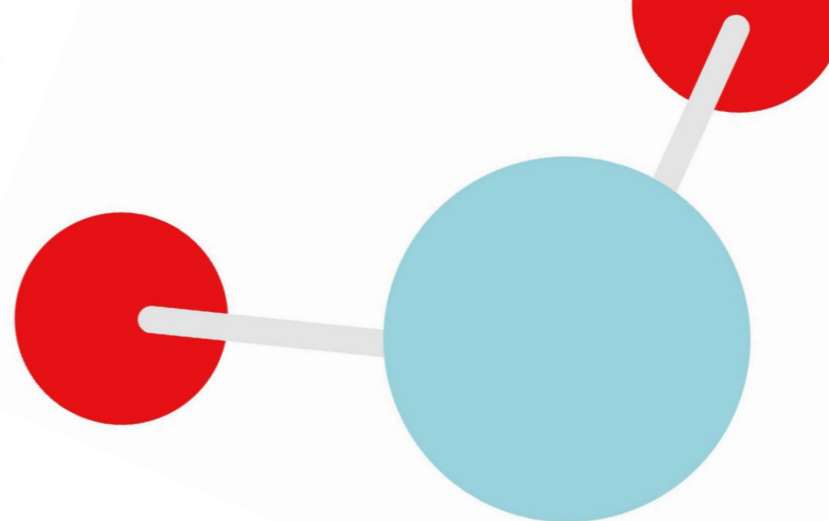
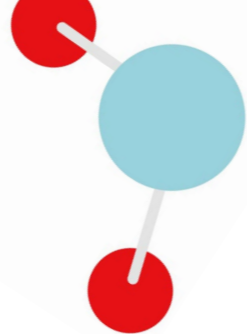
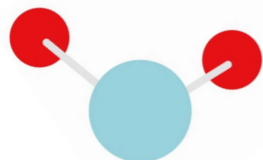
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carbohydrates has become known as the Ferrier reaction/rearrangement.

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 (+)-lycoridine 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.



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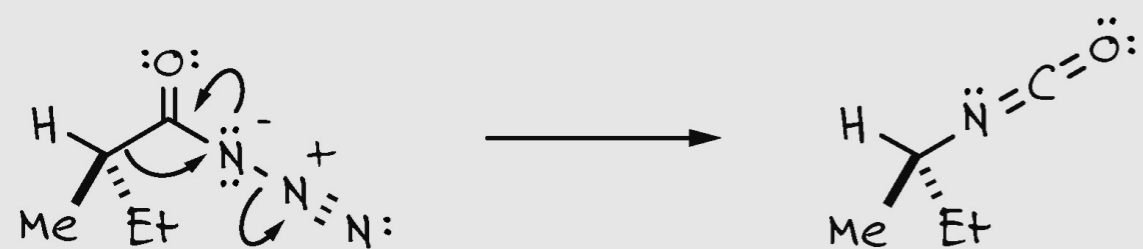
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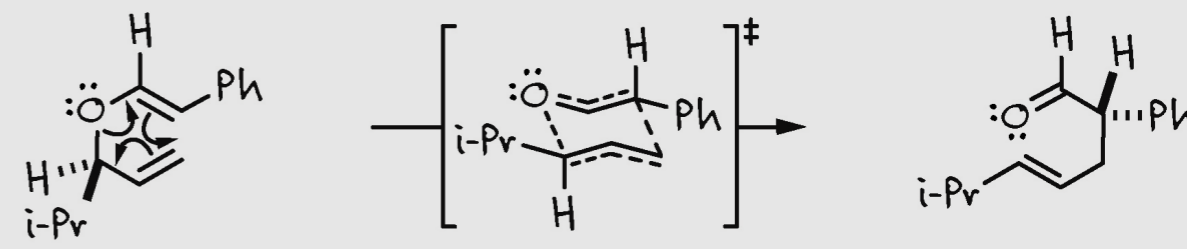




Reaction Mechanism Examples



Curtius rearrangement



Claisen rearrangement



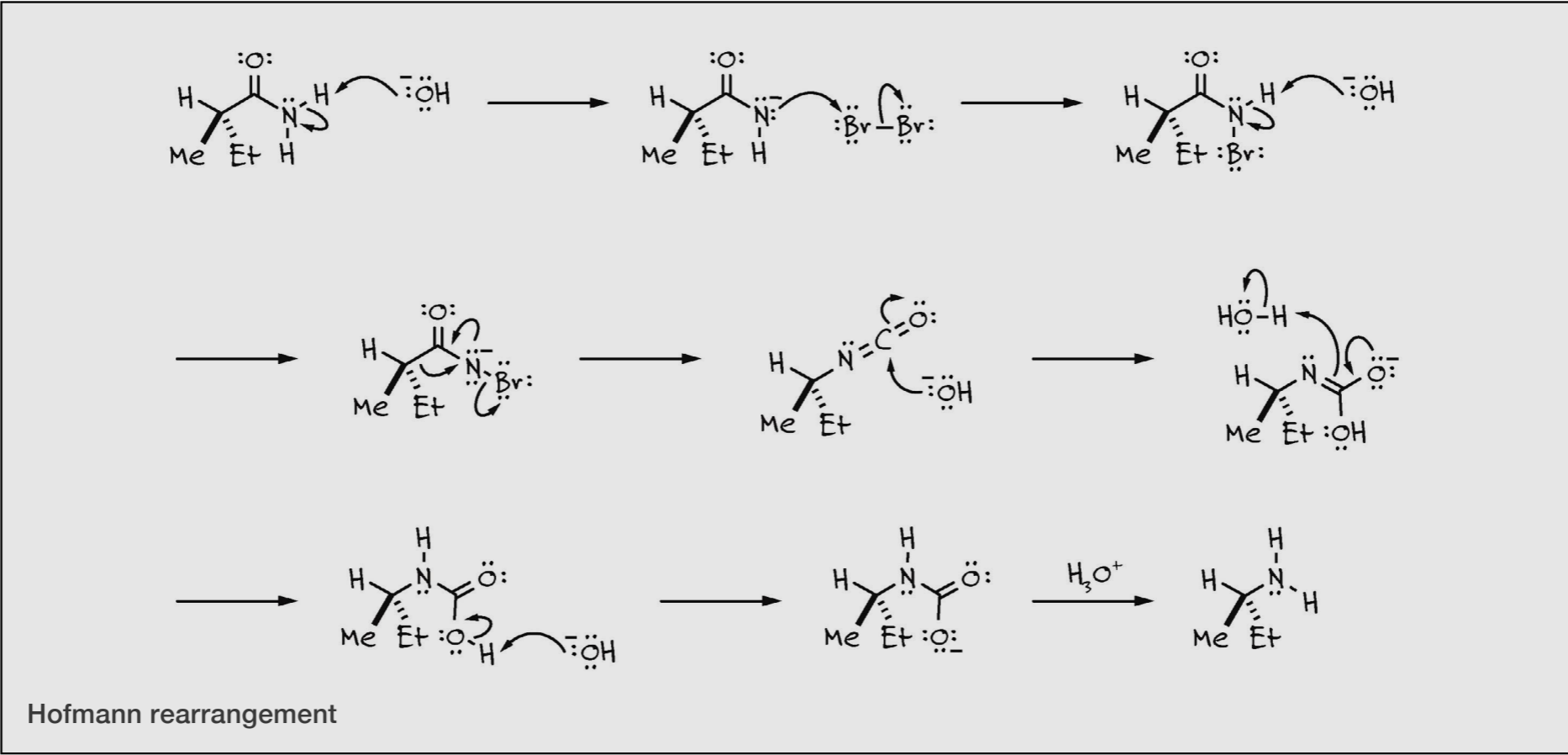
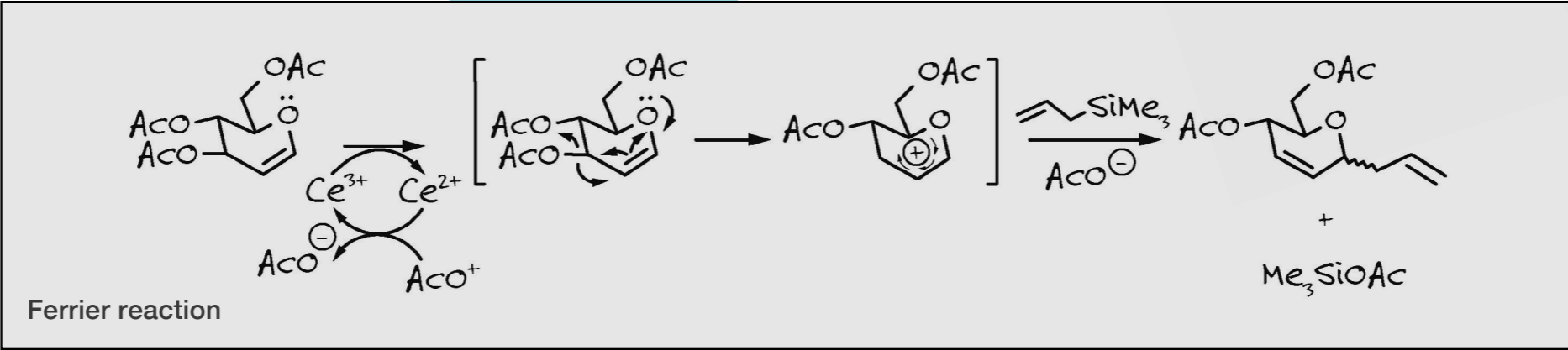
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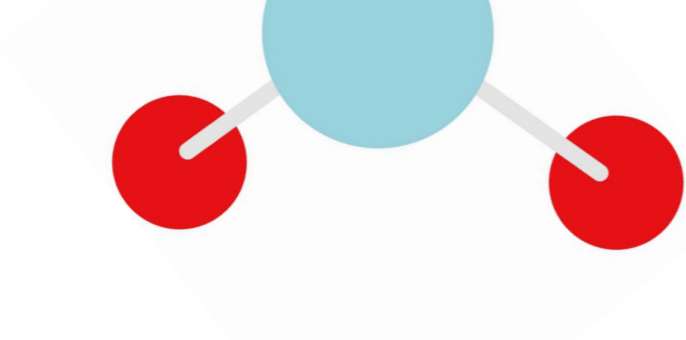
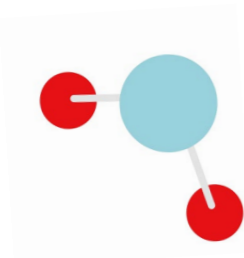
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Beckmann Rearrangement

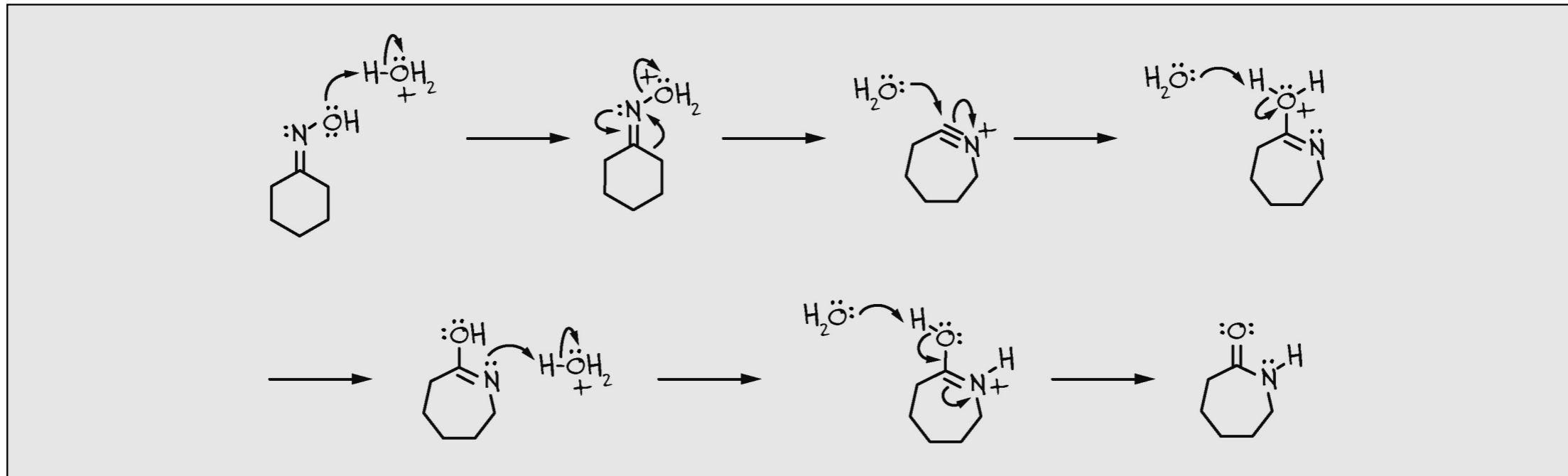
The Beckmann reaction described in 1886 by the German chemist Ernst Otto Beckmann¹ is a rearrangement of an oxime into an amide or a lactam.

The importance of secondary amides in many pharmaceuticals and functional materials illustrates why this reaction is so crucial. One of the best-known

applications involves cyclohexanone reacting with hydroxylamine to give caprolactam, the raw material for nylon production.

The mechanism is well known: under acid-catalyzed conditions, the oxime's OH is converted into a leaving group, followed by the cleavage of a C-C bond to give a new carbon-nitrogen bond in a one-stage mechanism. In general, the oxime nitrogen atom is inserted into the C-oxime 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



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

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

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

Reference reaction protocol

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

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

Key literature references

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



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Product Selection

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

SKU	Description
<i>Oxime Compounds</i>	
10223	Acetaldoxime, 99%, mixture of syn and anti
39053	Acetamide oxime, 95+%
A10802	Acetone oxime, 98%
A11804	Acetophenone oxime, 98%
45328	Benzamide oxime, 97%
A10687	Benzil dioxime, 98%
A10630	alpha-Benzoin oxime, 98+%
34233	Benzophenone oxime, 98%
A17532	p-Benzoquinone dioxime, 95%
A14339	2,3-Butanedione monoxime, 99%
40333	2-Butanone oxime, 99%
H51034	(1R,E)-(+)-Camphorquinone 3-oxime, 99%
A16788	1,2-Cyclohexanedione dioxime, 97%
11120	Cyclohexanone oxime, 97%
A16672	Cyclooctanone oxime, 98+%

SKU	Description
<i>Oxime Compounds</i>	
B24961	Cyclopentanone oxime, 97%
L00914	Dibenzyl ketoxime, 98+%
A12810	Dimethylglyoxime, 99%
33310	Dimethylglyoxime, ACS, 99+%
40834	Dimethylglyoxime, disodium salt octahydrate, 99%
40893	Diphenylglyoxime, 97%
L03950	9-Fluorenone oxime, 98+%
H52232	Methyl 2-pyridyl ketoxime, 97%
39028	2-Octanone oxime, 99%
L17073	1-Phenyl-1,2,3-butanetrione 2-oxime, 98+%
20502	1-Phenyl-1,2-propanedione-2-oxime, 99%
37344	Phenyl 2-pyridyl ketoxime, 98%
13179	syn-2-Pyridinealdoxime, 99+%
20740	Salicylaldoxime, 98%
13262	Salicylhydroxamic acid, 99%

SKU	Description
<i>Protonation agents</i>	
10994	Acetic acid, glacial, 99.9985% (metals basis)
14893	Acetic acid, 99.8%, for biochemistry
22214	Acetic acid, 99.8%, for analysis
33252	Acetic acid, glacial, 99+%
36289	Acetic acid, glacial, ACS, 99.7+%
38739	Acetic acid, Environmental Grade Plus, 99.4% min



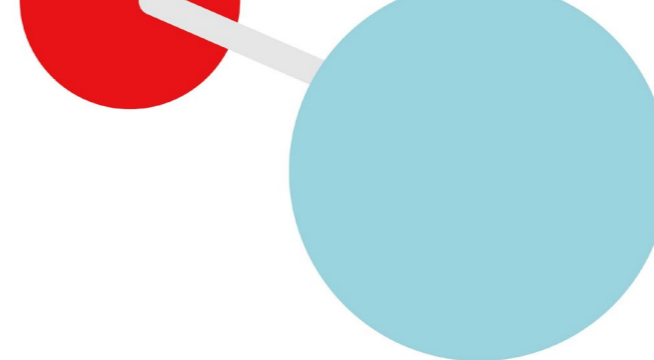
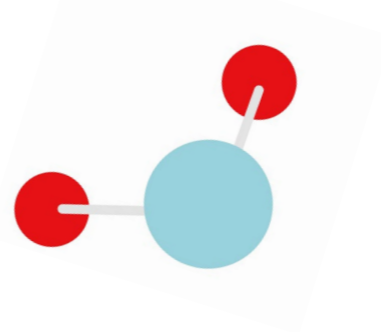
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SKU	Description
<i>Protonation agents</i>	
42322	Acetic acid, 99.7+%, ACS reagent
22213	Acetic anhydride, 99+%, for analysis
42323	Acetic anhydride, 97+%, ACS reagent
L04295	Acetic anhydride, 99+%
10990	Hydrochloric acid, 99.999999% (metals basis),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

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



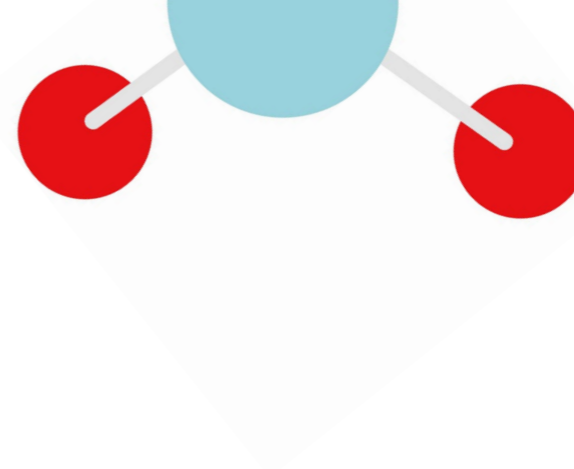
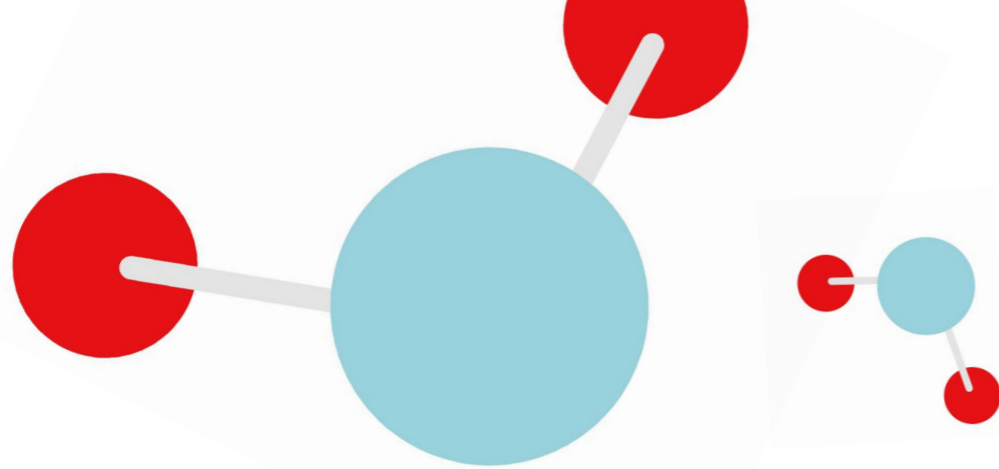
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Oxidation Reactions

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

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

Other oxidation reactions include:

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

Dess–Martin Oxidation

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

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



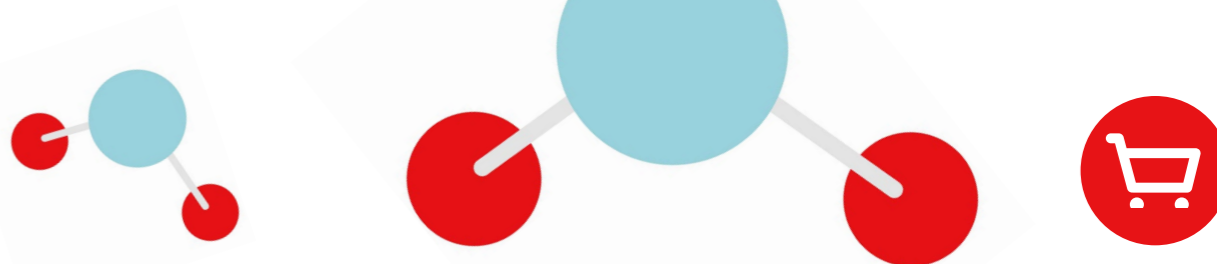
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Jones Oxidation

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

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

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

Oppenauer Oxidation

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

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

One unique feature of this oxidation is that secondary alcohols are oxidized

much faster than primary alcohols, meaning complete chemoselectivity can be achieved.

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

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

Rubottom Oxidation

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

Sharpless Asymmetric Epoxidation

In 1980 K.B. Sharpless and T. Katsuki discovered that the combination of titanium (IV) tetrakisopropoxide, 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.



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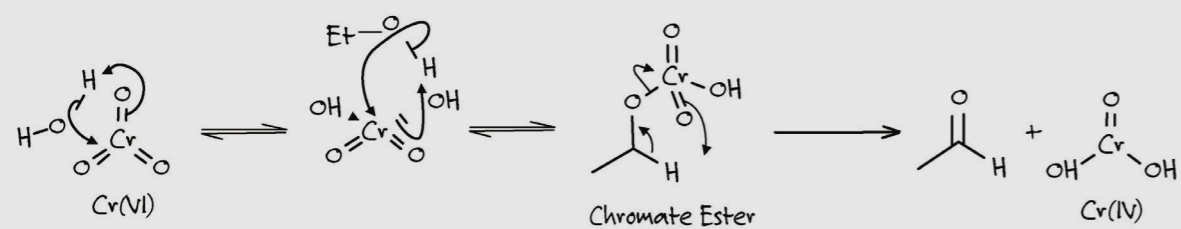
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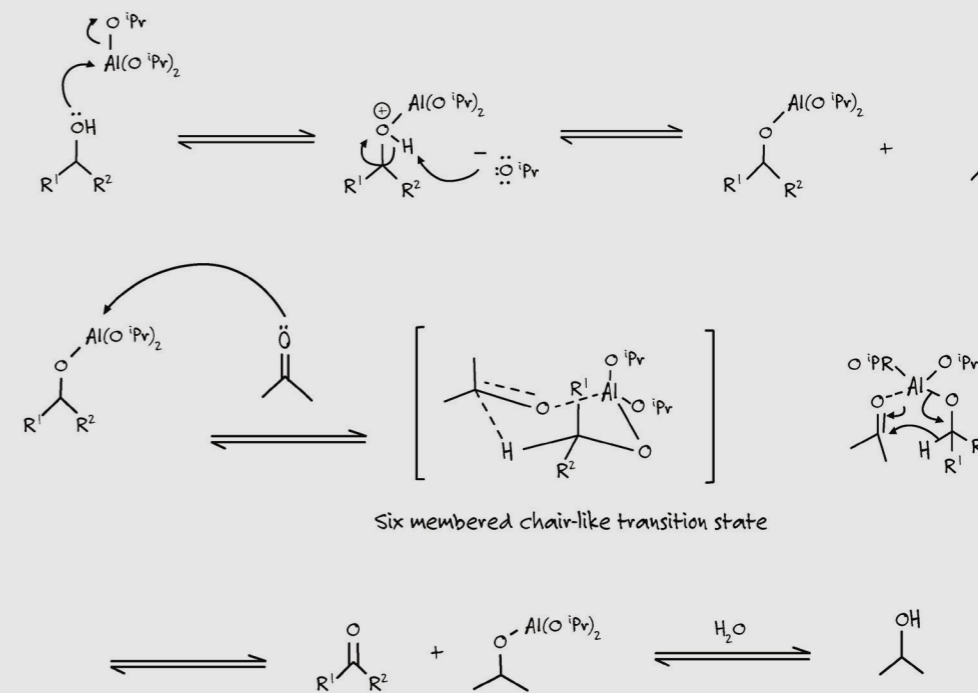




Reaction Mechanism Examples



Jones Oxidation



Oppenauer Oxidation



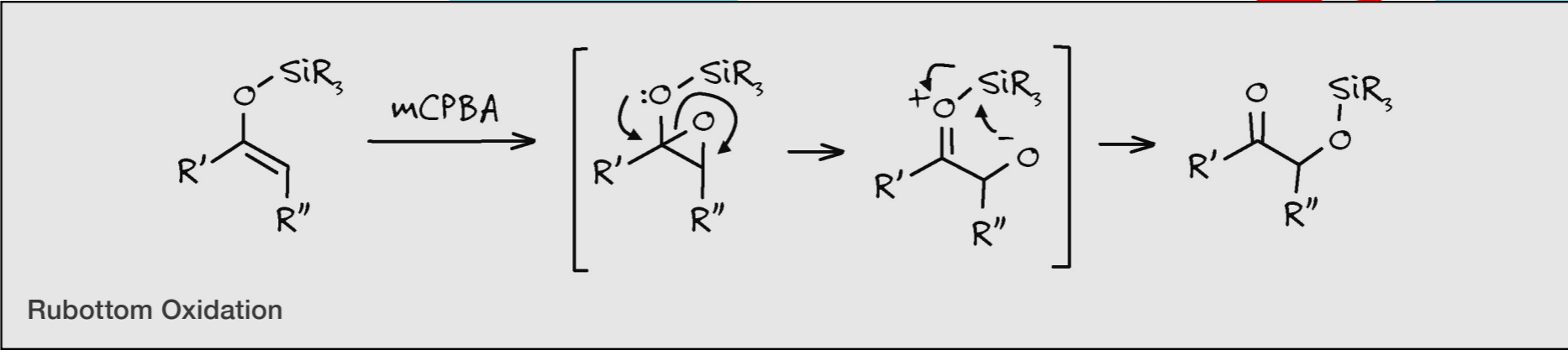
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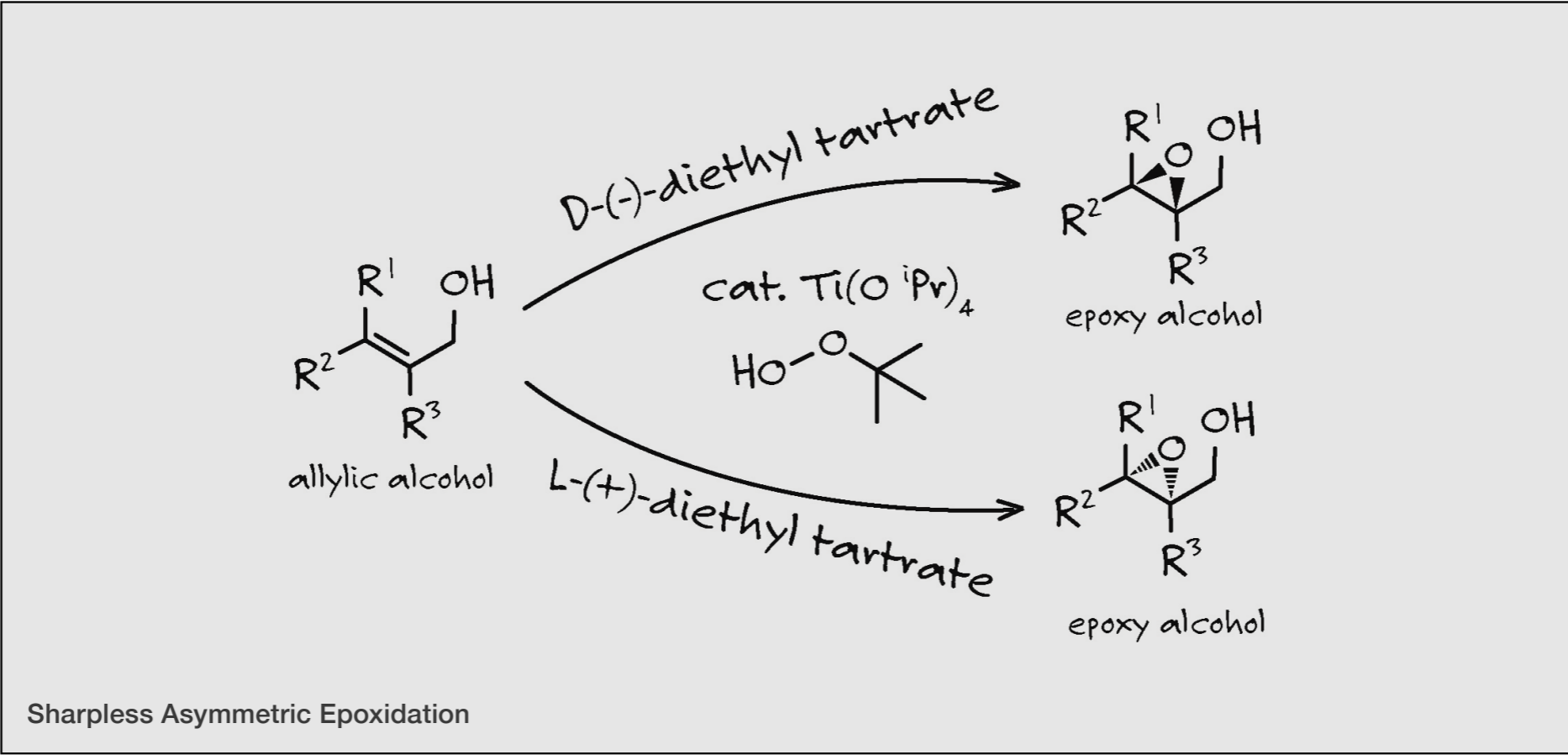
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Rubottom Oxidation



Sharpless Asymmetric Epoxidation

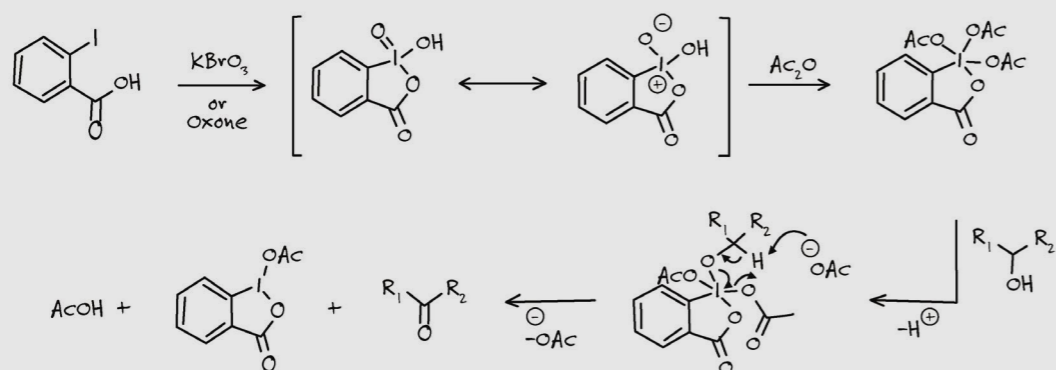




Dess-Martin Reaction

The Dess-Martin reaction, discovered in 1983, is an oxidation of primary or secondary alcohols with triacetoxyperiodinane (DMP) to synthesize aldehydes or ketones, respectively. DMP is obtained by the reaction of 2-iodobenzoic acid with KBrO_3 in H_2SO_4 to give the hydroxyiodinane oxide followed by treatment with a mixture of acetic anhydride and acetic acid at 100°C for 40 min.¹ The reaction could be also performed in oxone ($2\text{KHSO}_5\text{-KHSO}_4\text{-K}_2\text{SO}_4$) to replace KBrO_3 and H_2SO_4 and to reduce the safety risk.² Researchers studied how to facilitate the acetylation and, in 1993, Ireland found that a high yield of Dess Martin periodinane can be achieved by adding a catalytic amount of TsOH to replace HOAc in the second step.³

The oxidation of alcohols with DMP is then performed in dichloromethane at room temperature. In the mechanism, the iodine, bonded to 4 electronegative oxygen atoms, acts as an electrophile and can be attacked by a lone pair of



the alcohol oxygen giving an acetate as leaving group. This one deprotonates the alcohol oxygen positively charged, and, in basic conditions, the final product is generated. Meyer et al. discovered in 1994 that the oxidation is accelerated when DMP is exposed to the atmosphere rather than under inert conditions.⁴

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

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

Reference reaction protocols

Synthesis of N-Fmoc phenylglycinal

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

Key literature references

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



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Product Selection

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

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

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



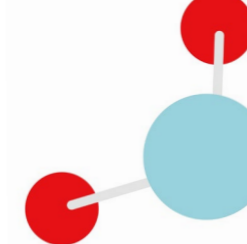
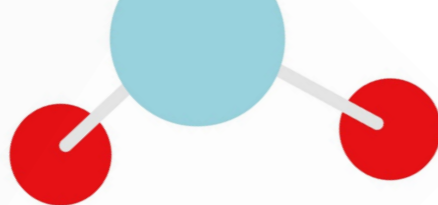
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<i>Primary and secondary alcohols</i>	
L00767	3-Buten-1-ol, 98+%
15433	2-Butoxyethanol, 99%, extra pure
H55285	4-tert-Butyldimethylsiloxy-1-butanol, 97%
A15709	2-Butyn-1-ol, 98%
A11477	3-Butyn-1-ol, 98%
32774	CAPSO, 99%
37100	(2R,3S)-1-Carboxy-4-pentyl-2,3-dihydroxycyclohexa-4,6-diene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

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



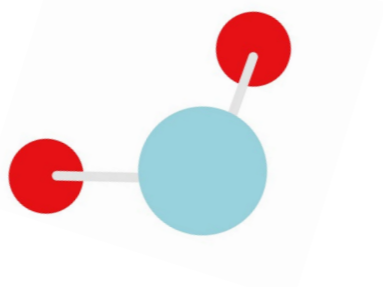
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<i>Primary and secondary alcohols</i>	
A13734	cis-2-Hexen-1-ol, 94%, remainder mainly trans isomer
A13272	trans-2-Hexen-1-ol, 97%
A10313	cis-3-Hexen-1-ol, 98%
L10541	trans-3-Hexen-1-ol, 97%
H54459	4-Hexen-1-ol, predominantly trans, 97%
A19266	cis-4-Hexen-1-ol,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

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



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

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

SKU	Description
<i>Dess-Martin reagents</i>	
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



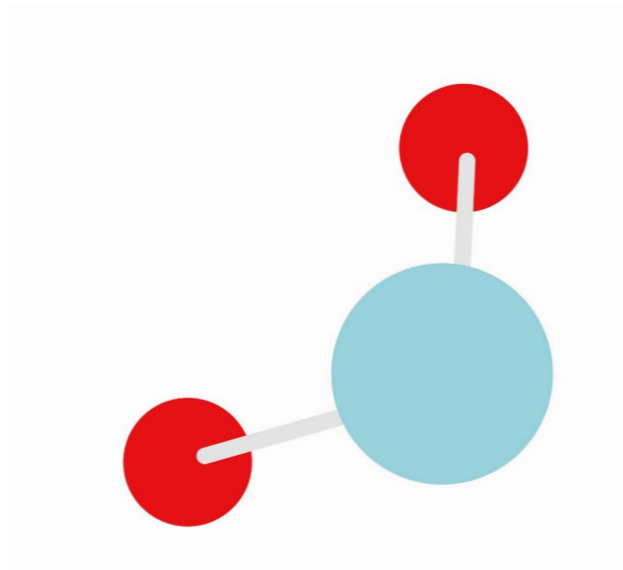
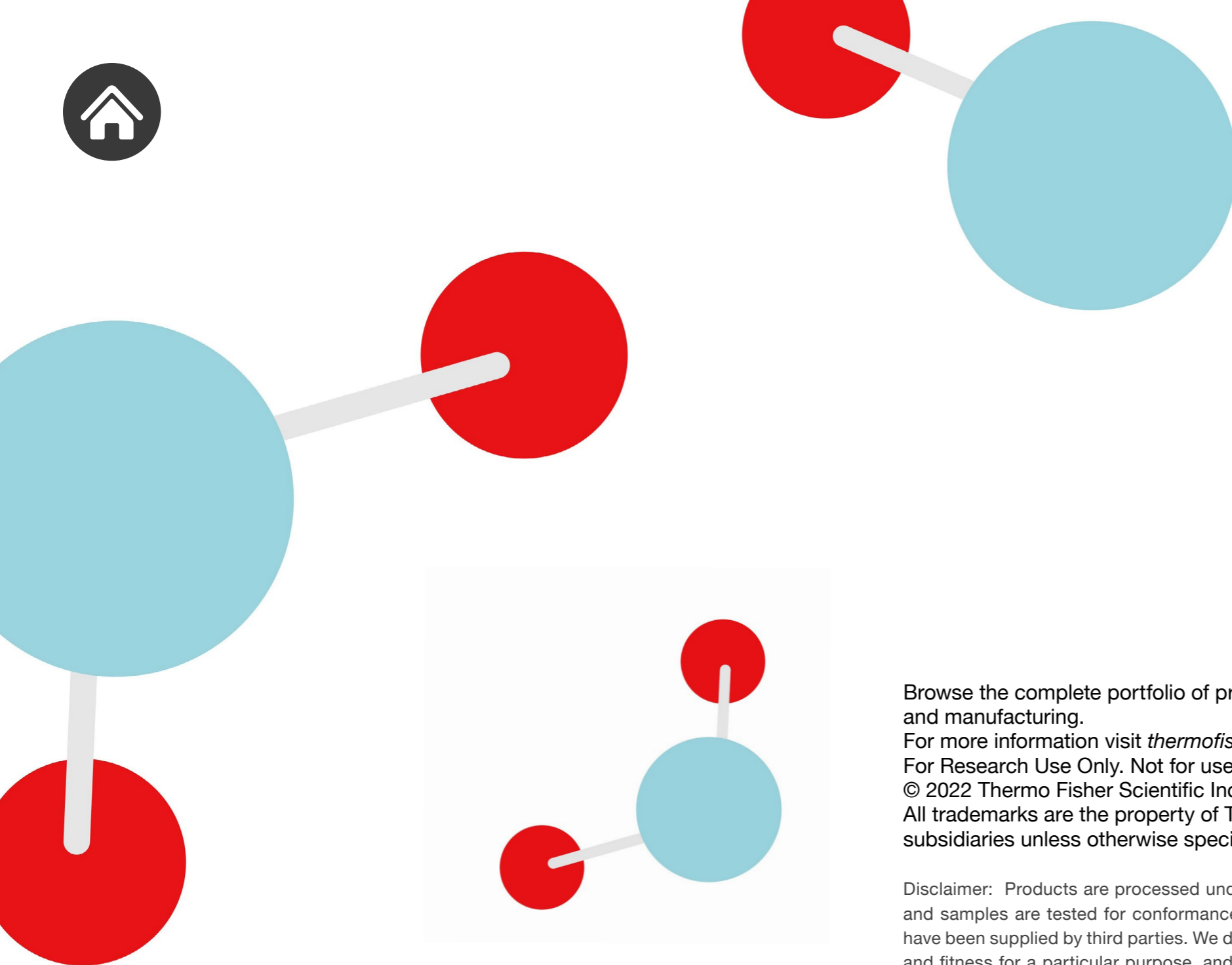
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