ThermoFisher SCIENTIFIC

TRANSITION METAL-CATALYZED COUPLINGS

REACTIONS INVOLVING CARBONYL COMPOUNDS

TITLE
(COMING SOON...)

Transition Metal-Catalyzed Couplings

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

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

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

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

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

Heck Reaction

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

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

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

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

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

Negishi Cross-Coupling Reaction

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

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

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

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

Stille Cross-Coupling Reaction

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

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

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

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

Suzuki Cross-Coupling Reaction

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

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

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

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

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

Ullmann Reaction

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

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

Suzuki-Miyaura Cross-Coupling Reaction

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

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

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

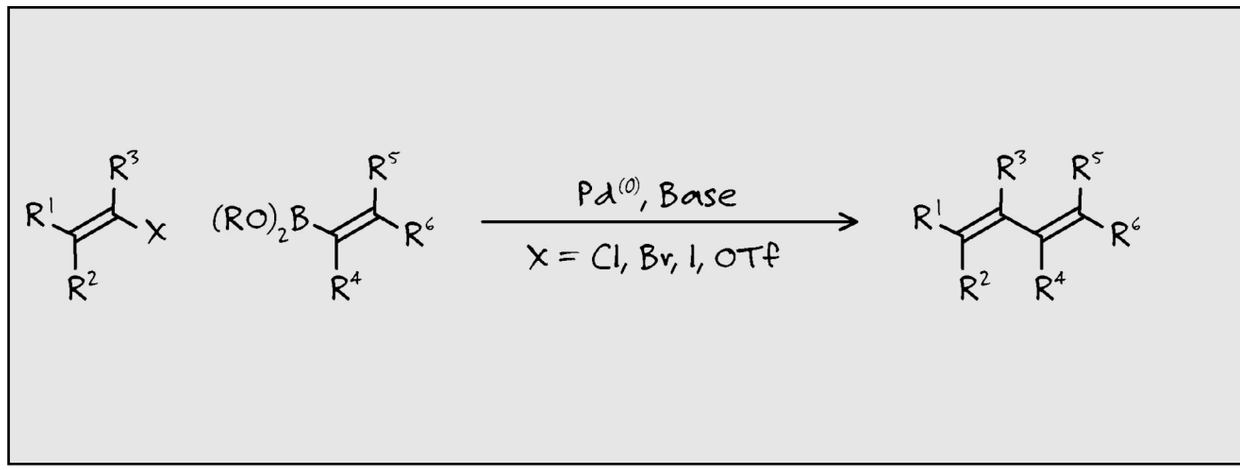
Since its invention in 1979, significant progress has been made and the use of boronic acids, esters and trifluoroborates salts, is widely reported. Even alkyl boronic acids can be considered (with the use of late generation catalysts), despite the lower reactivity.

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

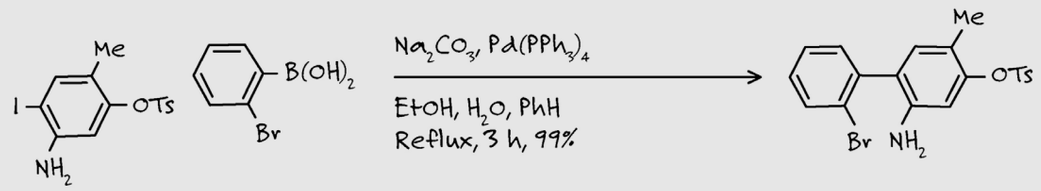
R-I > R-Br > R-OTf >> R-Cl
Aryl > Vinyl >> Alkyl

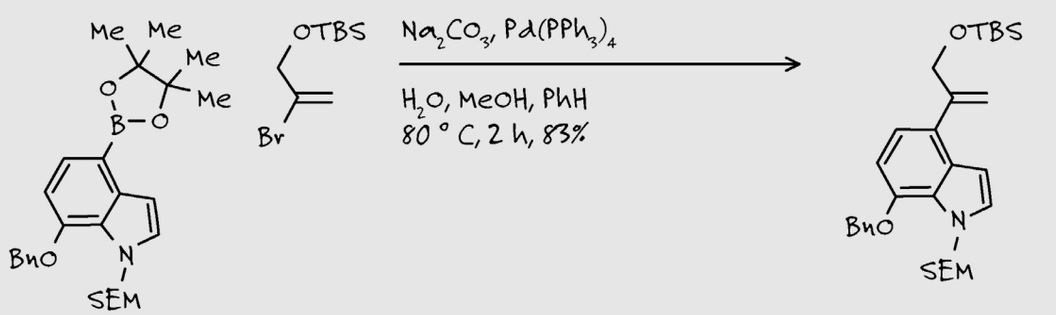
Recent generation homogeneous Pd catalysts have reduced the catalyst loading by orders of magnitude, contributing to the economy of the reaction, now used in numerous commercial processes. It is possible – in fact beneficial – to screen many different catalysts, from relatively simple Pd(0) complexes,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

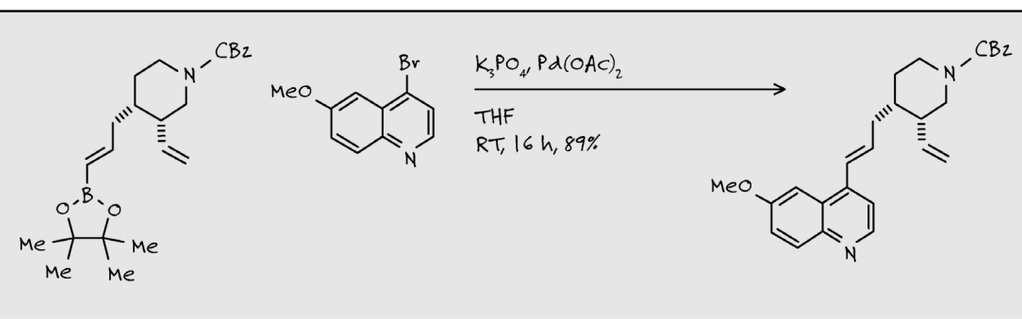
Heterogeneous Pd catalysts can also be used for some simple coupling, although their reactivity is much lower than homogeneous catalysts for highly hindered substrates, or low reactivity electrophiles (e.g. Ar-Cl). The use of aryl diazonium salts, often called “super-electrophiles,” as coupling partners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



Suzuki Reaction Examples







Reference Reaction Protocols

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

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

Product Selection for Suzuki Reaction

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

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

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

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

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

Key literature references

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Reactions Involving Carbonyl Compounds

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

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

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

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

Grignard Reaction

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

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

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

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

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

Knoevenagel Condensation

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

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

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

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

Mannich Reaction

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

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

Reformatsky Reaction

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

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

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

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

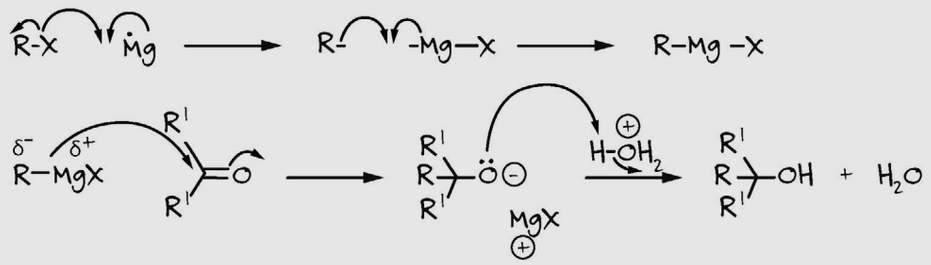
Wittig Reaction

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

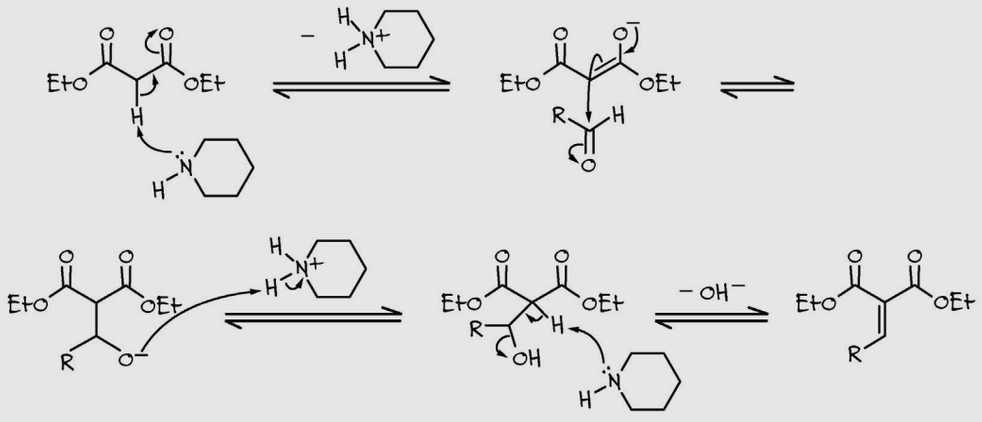
The Wittig reaction has several important variants. One of the most notable is the Horner–Wittig reaction, which occurs when the phosphorus ylides are based on phosphine oxides rather than triarylphosphines. When stabilized alkyl phosphonate carbanions are used to create (E)-alpha, beta-unsaturated esters,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

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

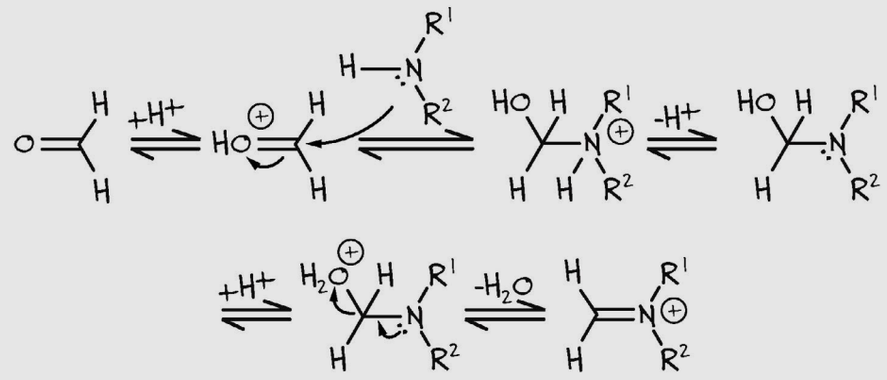
Mechanisms of the reactions involving carbonyl compounds

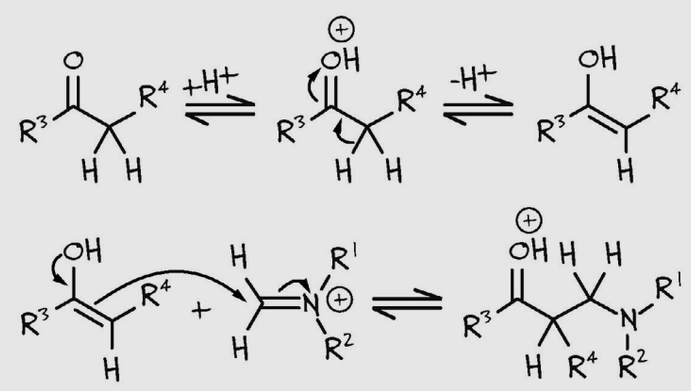


Grignard Reaction

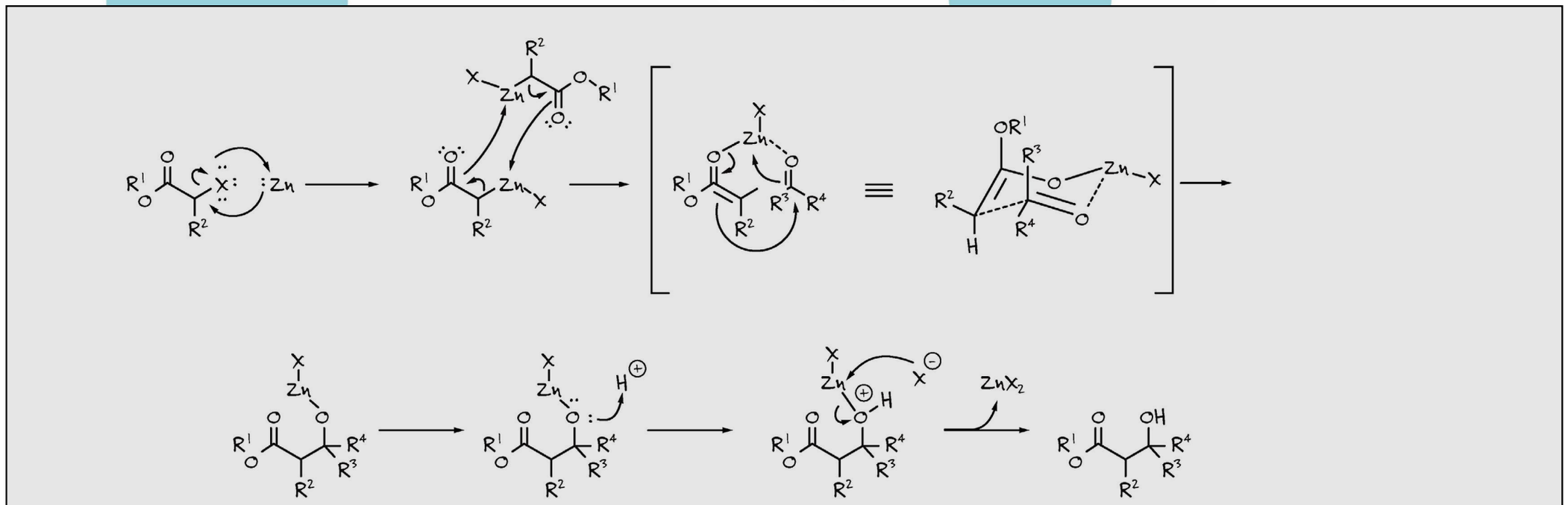


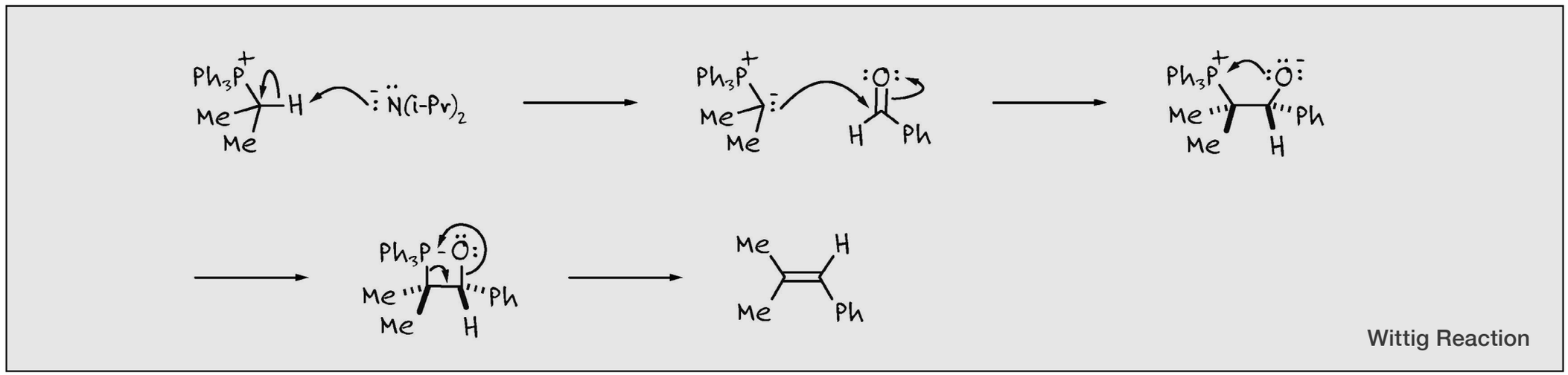
Knoevenagel Condensation



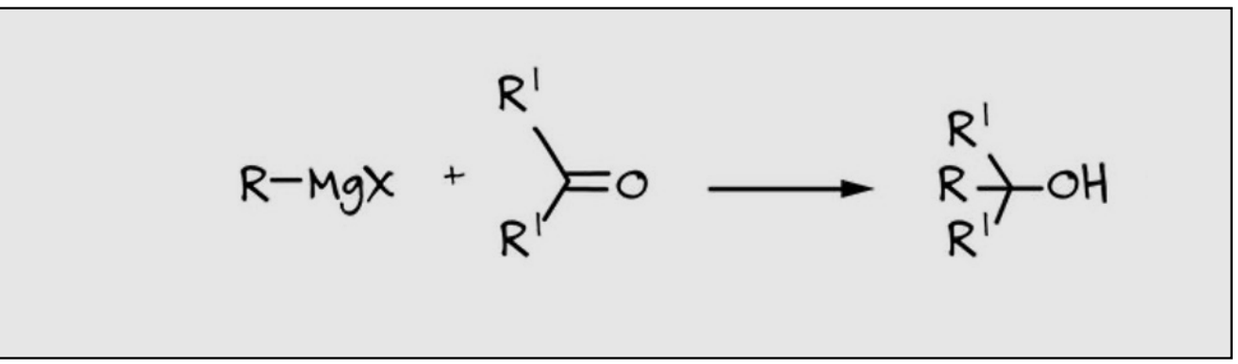


Mannich Reaction


Knoevenagel Condensation


Wittig Reaction

Grignard Reaction



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

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

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

Preparation of Grignard reagents

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

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

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

Nucleophilic addition to the carbonyl – Grignard reaction

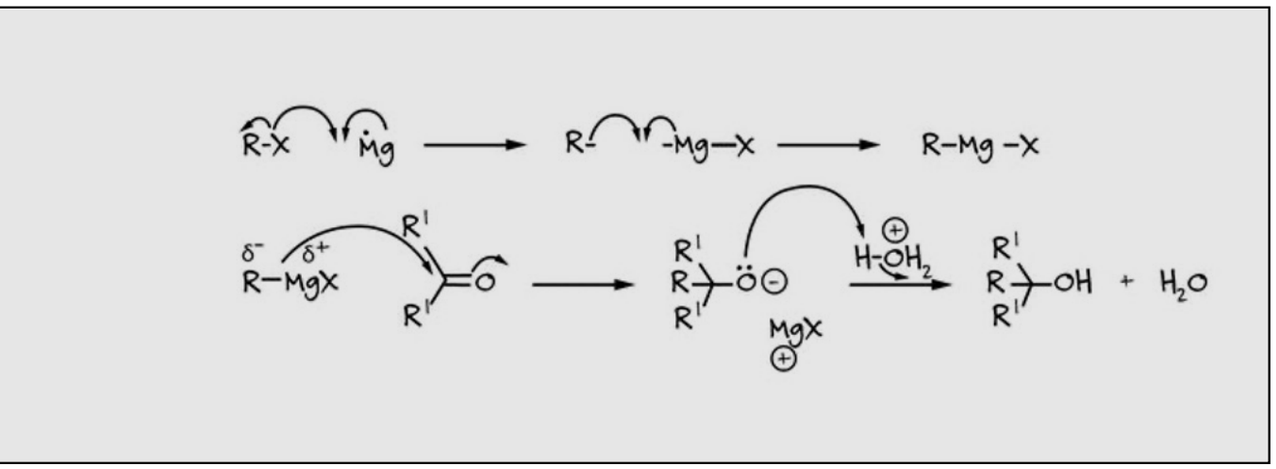
The carbon magnesium bond in the Grignard reagents is highly polar, making them excellent carbon nucleophiles. As a result, the subsequent carbon–carbon bond-forming step in their reaction with ketones or aldehydes is straightforward.

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

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

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

Mechanism of the Grignard reaction



Reference reaction protocols

Preparation of Grignard reagent

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

Grignard reaction

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

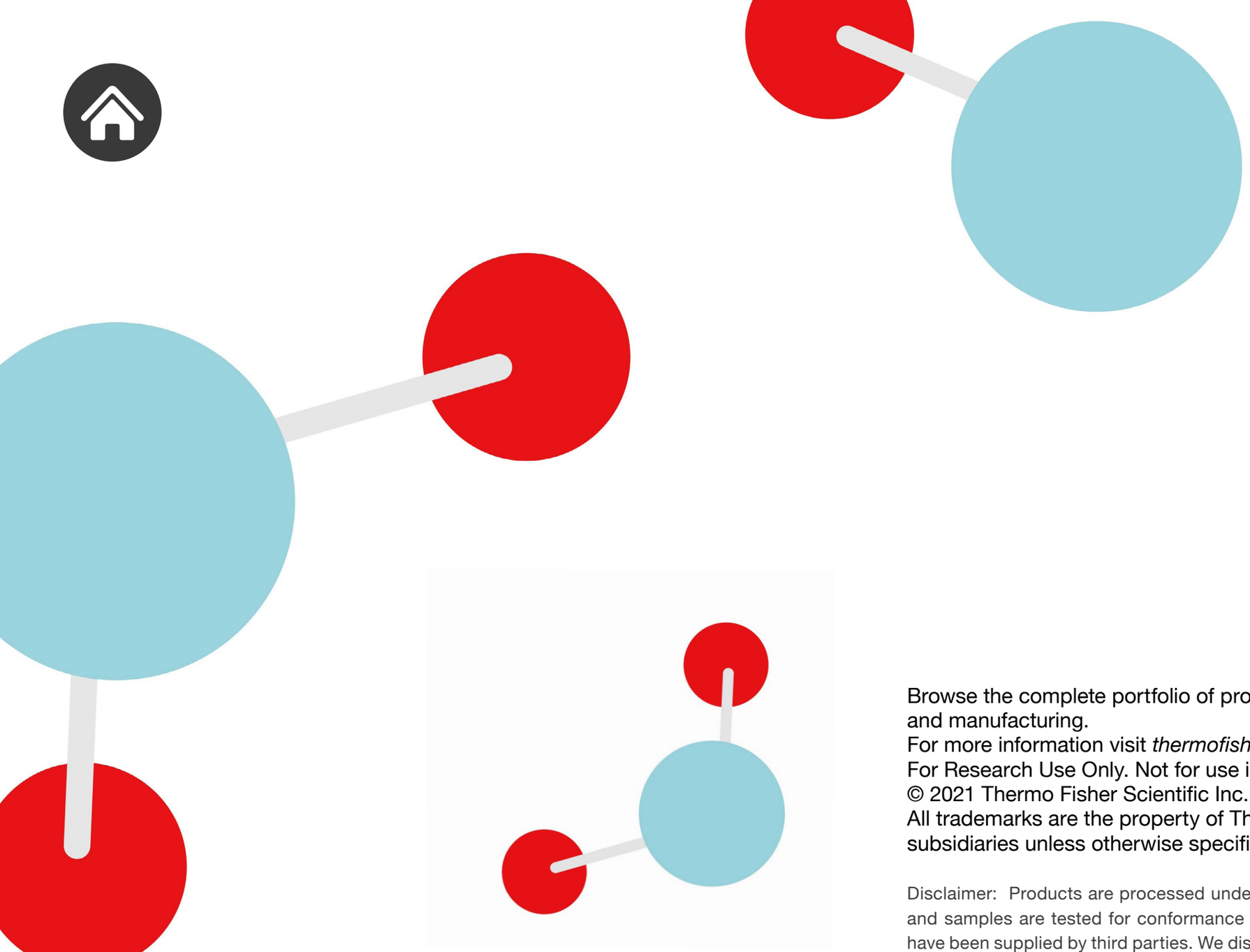
Key literature references

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

Product Selection for the Grignard reaction

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

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



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