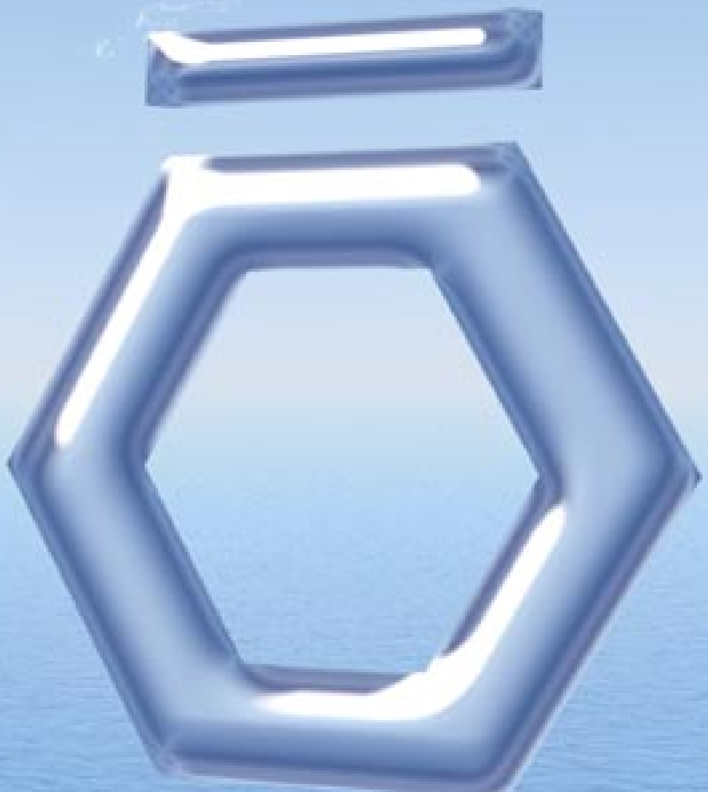
GRIGNARD REAGENTS



ACROS
ORGANICS

Contents

INTRODUCTION

Preparation, general properties and structure

Organomagnesium halides of the general structure R-Mg-X, with R = Alkyl, alkenyl or Aryl and X = Halogen, are called "Grignard" reagents after their inventor.[1,2]

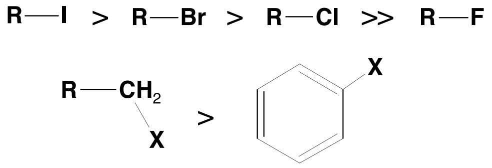
They are extremely valuable and widely-used synthetic tools, mainly as carbanions in nucleophilic additions and substitution-reactions but also in a range of other transformations.

Grignard reagents are generally prepared by the reaction of an organic halide with metallic magnesium ("metallation") in dry diethyl ether[3] or tetrahydrofuran.

In addition to metallation, numerous other methods for the preparation of Grignard reagents have been developed[4]:

- Transmetallation of other organometallic compounds with anhydrous magnesium salts
- Sulfoxide/magnesium exchange[5]
- Carbenoid-homologation[6]
- Reaction with highly active magnesium[7]
- Reaction with magnesium anthracene complex[8]
- Iodine-magnesium exchange[9]
- Exchange reaction using organo magnesium "ate" complexes[10]
- Transition metal-catalyzed Grignard formation[11]
- Mercury-magnesium exchange[12]

Some new methods are very successful in preparing chiral Grignard reagents[13] or reagents with chemical functionalities[9,14,15,16,17] not otherwise accessible by traditional direct metallation.



For direct metallation, relative reactivity of organohalides towards magnesium increases from the fluoride to the iodide. Fluorides are so unreactive that they can only be transferred to Grignard reagents under special conditions. Alkyl halides react easier with magnesium than Aryl halides. The general influence of "R" on the Grignard formation follows the order:

allyl ~ benzyl > primary alkyl > secondary alkyl > cycloalkyl >>tertiary alkyl ~ aromatic > alkenyl/vinyl.

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[1] Victor Grignard and his academic teacher Philippe Barbier invented the "Grignard Reagents" at the University of Lyon (France) in **1901**.

[2] Victor Grignard won the Nobel Prize for chemistry in **1912** (shared with Paul Sabatier).

[3] For a general procedure see i.e. Organikum, 21st ed. Wiley-VCh, Weinheim, Germany, **2001** p. 562

[4] Main Group Metals in Organic Synthesis, H. Yamamoto, K. Oshima (Eds.) Wiley-VCh, Weinheim, **2004**.

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[8] B,Bogdanovic, Angew.Chem. **1985** 97, 253.

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[11] B.Bogdanovic, M.Schwickardi, Angew.Chem. **2000** 112, 4788.

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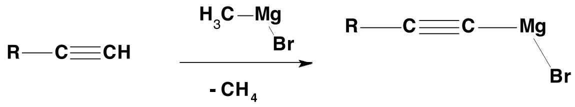
The weaker the carbon-halogen bond is, the easier the Grignard reagent is formed. Unfortunately the ease of Grignard-formation often indicates the likelihood of side reactions such as homocoupling. As a result, yields with very reactive halides are often low.

Strength of carbon-halogen-bonds
C-I< C-Br-< C-Cl and Sp^3-Hal< Sp^2-Hal

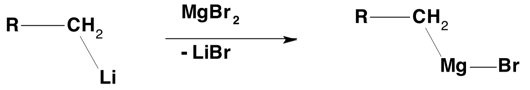
Other ways to make Grignard reagents are the deprotonation of acidic hydrocarbons such as acetylenes (A) or the transmetallation of organolithium compounds with anhydrous magnesium chloride or- bromide (B).

Magnesium, turnings	19801
Magnesium, ribbon	41338
Iodine, ACS	42382
Iodine, p.a.	19656
1,2-Dibromoethane, p.a,	22036
1,2-Dibromoethane,99%	11279
Magnesiumbromide diethyletherate	20970
Magnesiumbromide,anhydrous, 1 M in THF	37998
Magnesiumbromide,anhydrous, 1 M in Diethylether	37997

A:



B:



Although the common Grignard reaction is more than 100 years old, there are still open questions about how these reagents are formed and how the magnesium inserts into the carbon-halogen bond[18],[19].

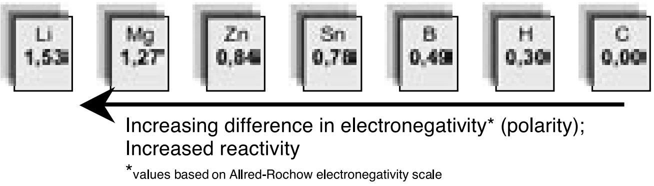
The formation of the Grignard reagent is a heterogeneous reaction at the magnesium surface, and the reactivity of the magnesium[20],[21],[22],[23],[24], the dryness of the solvent[25], the absence of oxygen and other factors all play important roles.

The reaction usually requires an induction period after which the reaction proceeds exothermically.

The chemistry of organomagnesium compounds is characterized by a polarized carbon-magnesium bond, which gives the carbon atom a negative partial charge. Such compounds are frequently called "carbanions", and their dominant chemical properties are their basicity and nucleophilicity,

$C^{\delta-} \blacktriangleright Mg^{\delta+}$

The following scheme illustrates the difference in electronegativity between carbon and other elements based on the Allred-Rochow scale.



The carbon-magnesium-bond is less polarized than the carbon-lithium bond found in organolithium compounds, which makes the Grignard reagents generally less reactive and more selective.

Both organo lithium and organo magnesium compounds are more reactive towards electrophiles than organo-zinc, -boron or tin-compounds.

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[18] H.M.Walborsky, Chemie in unserer Zeit **1991**, 25, 108-116.

[19] a) H.M.Walborsky, Acc.Chem.Res. 1990, 23,286; H. M. Walborsky, C. Zimmermann, J. Am. Chem. Soc. **1992**, 114, 4996;
b) J.F.Garst, Acc.Chem.Res,1991,24,95, c), C.Walling, Acc.Chem.Res. **1991** 24, 255.

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[25] David H. Smith, J. Chem. Ed. 1999,76, 1427-8.

The conformation of Grignard reagents in ethereal solutions is influenced by a dynamic equilibrium, the Schlenk Equilibrium[26] between several species.

In diethylether and tetrahydrofuran all of these species are present, although the Grignard reagent R-MgX dominates. In 1,4-dioxane the equilibrium can shift towards the dialkyl-magnesium[12] species because the magnesium-halides form insoluble complexes with 1,4-dioxane and are removed from the equilibrium. In diethylether the Grignard reagents form monomers when the halogen is bromine or iodine, and dimers when the halogen is chlorine or fluoride. In THF all or these species are predominantly monomeric[27].

The solid state structures of Grignard reagents are often monomeric or dimeric structures with a tetrahedral coordination of the magnesium, whereas solvent free Grignard reagents are often polymeric[28].

Grignard reagents are soluble in a number of aprotic solvents, using oxygen or nitrogen as donor-atoms to form complexes with the magnesium. Compared with alkyllithium compounds the Grignard reagents are less basic, and solutions in ethers are stable at room temperature or even higher. On the other hand a cooled solution of Grignard reagents tends to form precipitates which are very difficult to re-dissolve. A storage temperature around room temperature is suitable and recommended for most compounds[29].

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[26] W.Schlenk, W.Schlenk jr., Chem.Ber. **1929** 62, 920.

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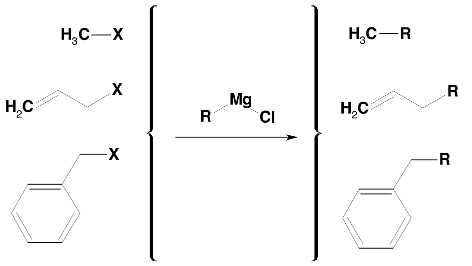
[29] Organomagnesium compounds …., Product brochure of Chemetall GmbH, Frankfurt am Main.

REACTIONS

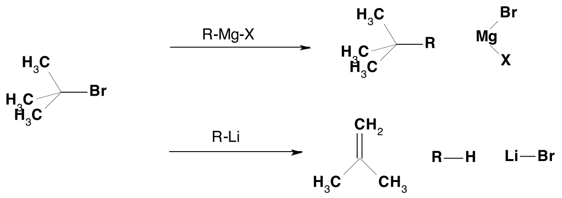
Grignard reagents are very reactive nucleophiles, but compared with organolithium compounds they are softer and their reactivity is more selective[30].

Some general reactions of Grignard reagents are summarized on the following pages:

Substitution and coupling reactions



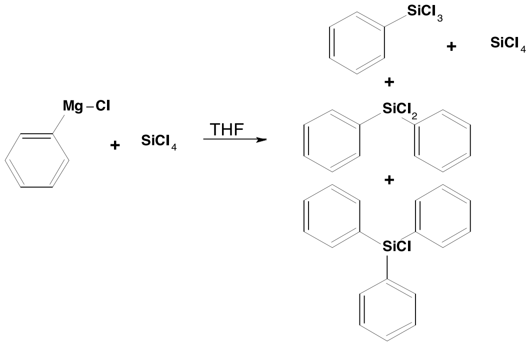
Only very reactive methyl-, allyl and benzylic halides or -tosylates react smoothly with Grignard reagents. Substitution reactions between Grignard reagents and less reactive Alkyl halides usually give poorer results and a mixture of regio- and stereoisomers[31]. Alkylhalides bearing a β–hydrogen often yield predominantly the alkane (from the Grignard) and alkene (from the alkyllithium) as main products.



A significant difference between Grignard reagents and organolithium reagents is their reactivities towards tertiary alkyl halogenides such as tert-butyl bromide.

The strongly basic organolithium reagent deprotonates the tert-alkyl-halide, while the less basic and more lewis-acidic Grignard reagent substitutes the halide according to a S_N1-mechanism[30] with a magnesium -ate complex[10].

Compared with alkylhalides Grignard reagents react easily with halosilanes like tetrachlorosilane, but usually the reaction leads to a mixture of several products. Nevertheless the reaction is a useful approach to access a great number of specialty silanes[32] which cannot be produced otherwise.



Iron(III)acetylacetonate	11913
Iron(III)chloride, anhydrous	16943
Copper(II)chloride anhydrous	20653
Copper(I)iodide 99.995%	20150
Bis(triphenylphosphine)nickel(II)bromide	31632
Bis(triphenylphosphine)nickel(II)chloride	21750
Tetrakis(triphenylphosphine)nickel(0)	22398
Tetrakis(triphenylphosphine)palladium(0)	20238

In addition to the nucleophilic substitution with alkyl substrates, the cross-coupling reactions with alkynyl-, alkenyl- or aryl substrates have received a lot of attention in recent years. Grignard reagents have been widely used in such coupling ractions. The reactions can be greatly improved by the addition of metal catalysts such as copper-[31],[33],[34], silver-[35] iron-[35],[36],[37],[38],[39],[40], and nickel[41],[42]-salts in stoichiometric or catalytical amounts.

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[30] N.Krause, Metallorganische Chemie, Spektrum Akademischer Verlag, Heidelberg **1996**.

[31] E.Erdik, Tetrahedron 40 **1984** 641.

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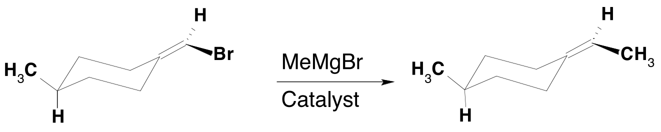
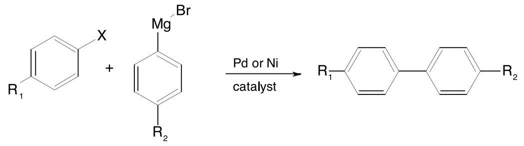
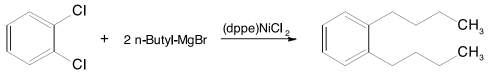
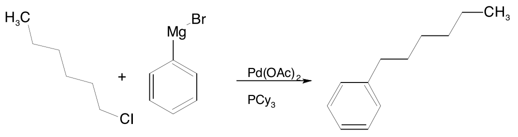
As an example, the reaction of (+)-(S)-(4-methylcyclohexylidene) bromomethane with methylmagnesium-bromide and nickel, iron and cobalt catalysts shows a high retention of configuration[43], whereas the silver catalyst gave complete racemization.



The Kumada-coupling[41,42,44,45], the nickel[46]- or palladium catalyzed reaction between Grignard reagents and aryl- or inylhalides and -tosylates, has attracted a lot of attention as a versatile C-C-coupling reaction. Alkyl-[47] and heteroaryl[48]-halides can also be coupled.







Nickel & Palladium catalysts and ligands

[1,3-Bis-(diphenylphosphino)propane] nickel(II)chloride	29159
Nickel acetylacetonate 96%	12826
Bis(triphenylphosphine)nickel(II)chloride 98%	21750
Tetrakis(triphenylphosphine)nickel(0) 95%	22398
[1,2-Bis(Diphenylphosphino)ethane] nickel (II) chloride	36323
Bis(triphenylphosphine)nickel(II)bromide 99%	31632
Nickel(II) chloride hexahydrate , 99.9999%	19357
Nickel(II) chloride hexahydrate , p.a.	27051
1,2-Bis(dicyclohexylphosphino)ethane nickel(II) chloride	30116
1,1'-Bis-(diphenylphosphino)ferrocene	34801
1,2- Bis-(diphenylphosphino)ethane	14791
1,3-Bis(diphenylphosphino)propane	31005
1,4-Bis-(diphenylphosphino)butane	29646
Bis(triphenylphosphine)palladium(II)chloride 98%	29925
Tetrakis(triphenylphosphine)palladium(0) , 99%	20238
1,1'-Bis(diphenylphosphino)ferrocene palladium(II) chloride,complex with dichloromethane	34868

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[43] H.M.Walborsky, R.B.Banks, J.Org.Chem. **1981** 46, 5074.

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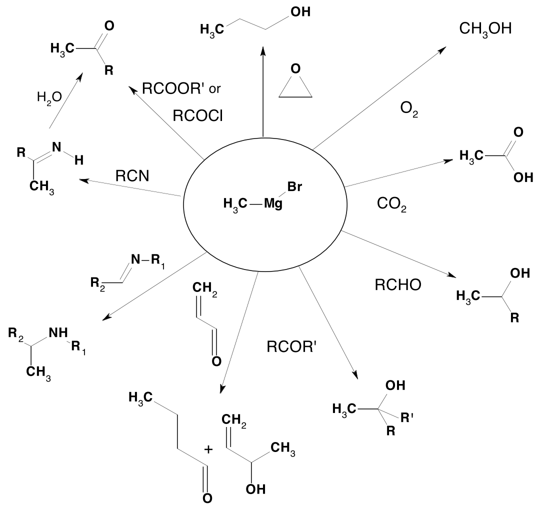
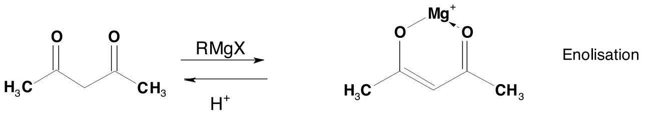
Nucleophilic addition to carbon-heteroatom double bonds

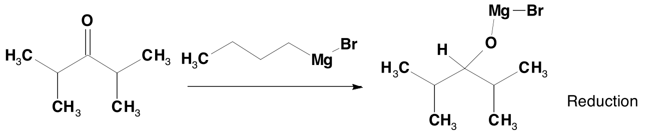


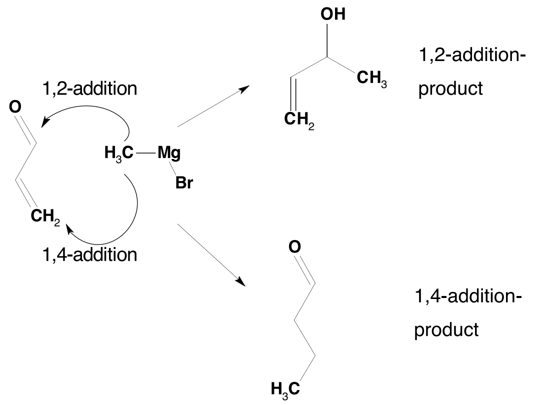
Grignard reagents are strong nucleophiles and react with a broad range of electrophilic substrates. The reactions with aldehydes, ketones[27], esters, acids[49] and acid chlorides is one of the most useful reaction in organic chemistry for the formation of C-C-bonds[50],[51],[52]. The reaction has a very broad scope, and the Grignard reagent can be aliphatic, aromatic or heteroaromatic.

Formaldehyde yields primary alcohols, other aldehydes yield secondary alcohols while ketones yield tertiary alcohols. Other electrophilic chemicals like epoxides and imines react smoothly with Grignard reagents to form alcohols and amines. Oxygen and carbon dioxide as electrophiles yield alcohols and carboxylic acids. Even halogens can be employed[53]. In certain cases, sterically hindered carbonyl compounds or sterically hindered Grignard reagents form side reactions like enolisation, reduction or Wurtz-type coupling[54],[55]. Enolization can be a problem, especially with very acidic β-dicarbonyl compounds and sterically hindered Grignard reagents. Grignard reagents with β-hydrogens can sometimes reduce the carbonyl rather than adding to it.

Especially with very acidic and the can be a problem, whereas Grignard reagents having a β-hydrogen-atom can sometimes reduce the carbonyl-compound instead of adding to it[56].







The reaction of Grignard reagents with carbon dioxide leads to carboxylic acids in moderate to good yields and is one of the most common methods for the synthesis of organic acids.

The addition of Grignard reagents to other double bonds like C=S (i.e. in thioesters) and C=N (i.e. nitriles, imines or carbodiimides) is also a common reaction[55].

The reaction of alkyl-Grignard reagents with α,β-unsaturated carbonyl-compounds usually leads to a mixture of 1,2- and 1,4 addition[30,58], whereas allyl- or phenyl-magnesium halides only offers 1,2 addition with unsaturated ketones[55].

[49] F.Sato, K.Oguro, H.Watanabe, M.Sato, Tetrahedron Lett. 21 (**1980**) 2869.

[50] V.Grignard, Nobel lecture, December 11th, **1912**.

[51] MS Kharash, O. Reinmuth, Grignard Reactions of Nonmetallic Substances, Prentice Hall Inc., New York, **1954**

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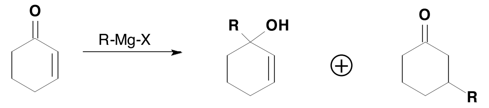


R=		
CH_3	38%	15%
CH_3CH_2	52%	24%
$(CH_3)_2CH$	10%	44%
$(CH_3)_3C$	0%	70%

Generally the nucleophilic addition of Grignard reagents to compounds with a carbon-heteroatom multiple bond is one of the most widely used reactions for C-C bond formation in organic chemistry.

A highly enenatioselective addition of Grignard reagents to prochiral substrates can be achieved by using chiral ligands like spartein[59].

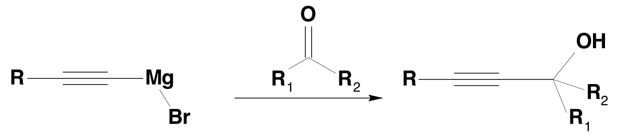
Deprotonation / Metallation

Grignard reagent	pKa
CH_3MgCl	31,2
CH_3CH^2MgCl	30,1
CH_3MgBr	29,5
CH_3CH_2MgBr	29,3
C_6H5CH_2MgCl	24,6
C_6H_5MgCl	23,9
C_6H_5MgBr	22,2

Grignard reagents are valuable bases and can deprotonate a variety of acidic compounds such as water, alcohols and amines to form the corresponding alkane (R-H) and magnesium hydroxides, alcoholates or amides.

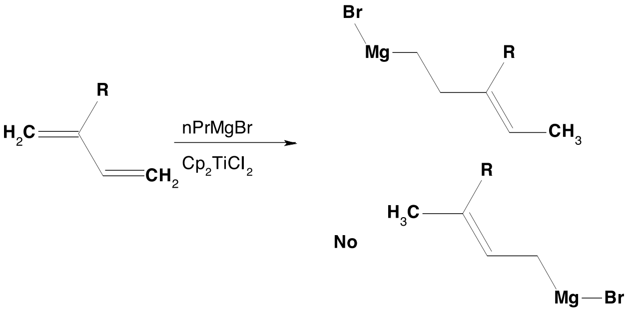
The basicity of Grignard reagents[60] is comparable with Organolithium-reagents, although the latter are more widely used for this purpose.

Synthetically useful is the deprotonation of acetylenes[61] leading to the alkynyl-Grignard reagents, which can act as nucleophiles for reaction with carbonyl compounds[62]. This reaction leads to the important family of propargylic alcohols.



Hydromagnesation

The titanium-catalyzed reaction of organomagnesium halides having a β-hydrogen with olefins[63] is called hydromagnesation, because formally a "HMgX" is added to the double bond. The scope, yield and regioselectivity of the reaction could be increased by changing the catalyst from $TiCl_4$ to Cp_2TiCl_2[64]. The reaction proceeds via the very reactive Cp_2TiClH[30], which is formed by a transmetallation of the Cp_2TiCl_2 with the Grignard reagent and a subsequent β-hydride elimination. The titanium hydride adds regioselectively to the olefin, and a final transmetallation step with a second equivalent of the Grignard reagent recovers the titanium hydride and liberates the reaction product.



Cp_2TiCl_2, 97%	21576
Cp_2TiCl_2, 99%	37246
$TiCl_4$	19723
$TiCl_4$ solution	37774
$TiCl_4$ solution	37816
MgH_2, powder 90%	37845
Cp_2ZrClH	20789
Cp_2ZrCl_2, 98%	18792

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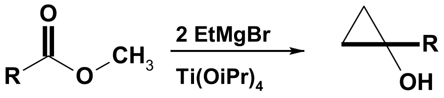
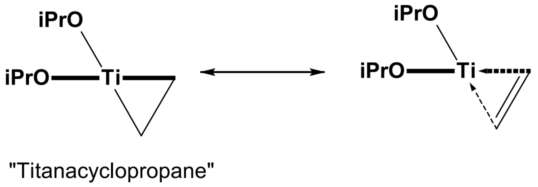
[64] F. Sato and Y. Kobayashi Organic Syntheses, CV 8, 507

Kulinkovich reaction[65]



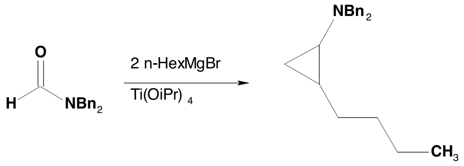


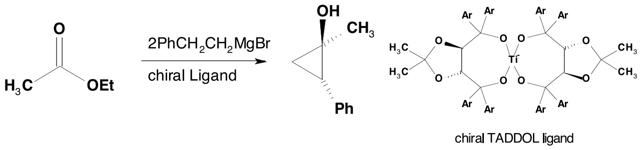
The Kulinkovich reaction is a "hydroxycyclopropanation" of carboxylic esters with a Grignard reagent and titanium tetraisopropoxide. The reaction proceeds via a low-valency "titanacyclopropane".

Other examples with amides or nitriles instead of esters lead to aminocyclopropanes[66].

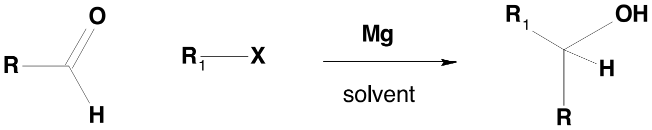
E.J.Corey[67] has used the chiral ligand TADDOL for the first example of an asymmetric Kulinkovich-reaction.

EtMgBr	1M in THF	21047
EtMgBr	0.9M in t-Butylmethylether	34728
EtMgBr	3M in Diethylether	34729
$Ti(O\text{-}iPr)_4$		19470
TADDOL		29634





Barbier reaction[68]



The "Barbier reaction", named after Viktor Grignard's teacher Philippe Barbier, is the "one-step" Grignard reaction, combining the organic halide, the magnesium metal and the electrophilic substrate together in one reaction vessel. Other metals like lithium and zinc[69] can also be used for Barbier-type reactions

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[65] Nachrichten aus der Chemie 7/8 **2004**, 805

[66] V.Chaplinsky A.deMeijere Angew.Chem. 108 (**1996**), 491.

[67] E.J.Corey, S.A.Rao, m.C.Noe, J.Am.Chem.Soc. 116 (**1994**) 9345.

[68] C.Blomberg, F.A.Hartog, Synthesis (**1977**) 18.

[69] A.Jögi, U.Mäeorg, Molecules **2001** 6 964.

Grignard reagents from Acros Organics

Allylmagnesium chloride, 1.7M in THF	20967
Benzylmagnesium chloride, 1.3M solution in THF	33165
Benzylmagnesium chloride, 2M in THF	31737
Benzylmagnesium chloride, 1M in diethyl ether	37739
n-Butylmagnesium chloride, 1.7M solution in THF/toluene	33168
sec-Butylmagnesium chloride, 2.1M solution in THF	33166
tert-Butylmagnesium chloride, 1.7M solution in THF	33167
tert-Butylmagnesium chloride, 2M in diethyl ether	20854
4-Chlorophenylmagnesium bromide, 0.9M in THF/toluene	37725
4-Chlorophenylmagnesium bromide, 1M in diethyl ether	37740
Cyclohexylmagnesium chloride, 1.3M in THF/toluene	37734
Ethynylmagnesium chloride, 1.1M in THF/toluene	37744
Ethylmagnesium chloride, 2.8M solution in THF	25257
Ethylmagnesium chloride, 2M solution in THF	37728
Ethylmagnesium bromide, 3M in diethyl ether	34729
Ethylmagnesium bromide, 1M in THF	21047
Ethylmagnesium bromide, 0.9M in tert.butylmethyl ether	34728
4-Fluorophenylmagnesium bromide, 0.8M in THF	37723
4-Fluorophenylmagnesium bromide, 2M in diethyl ether	37737
Isopropylmagnesium chloride, 2M in THF	21285
4-Methoxyphenylmagnesium bromide, 1M in THF	37742
Methylmagnesium chloride, 3M solution in THF	25256
Methylmagnesium bromide, 3M in diethyl ether	18354
Methylmagnesium bromide, 1.7M in THF/toluene	37733
Methylmagnesium bromide, 1M in THF	37738
Phenylmagnesium chloride, 1.9M solution in THF	25258
Phenylmagnesium bromide, 2.8M in diethyl ether	17398
Phenylmagnesium bromide, 1M in THF	37741
(Trimethylsilylmethyl)magnesium chloride, 1.1M in THF	37746
Vinylmagnesium chloride, 1.7M solution in THF	25259
Vinylmagnesium bromide, 0.7M in THF	20939

Di-alkylmagnesium compounds from Acros Organics

Di-n-butylmagnesium, 0.5M solution in heptane	37777
n-Butylethylmagnesium, 1.3M solution in heptane	37778

Other organomagnesium compounds from Acros Organics

Bis(cyclopentadienyl)magnesium, sublimed 97%	35325

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