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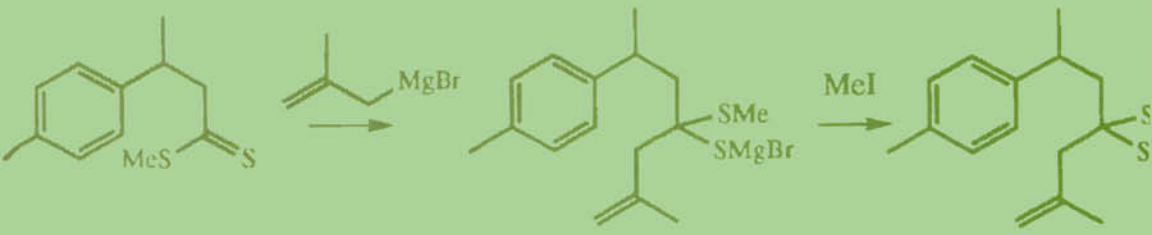
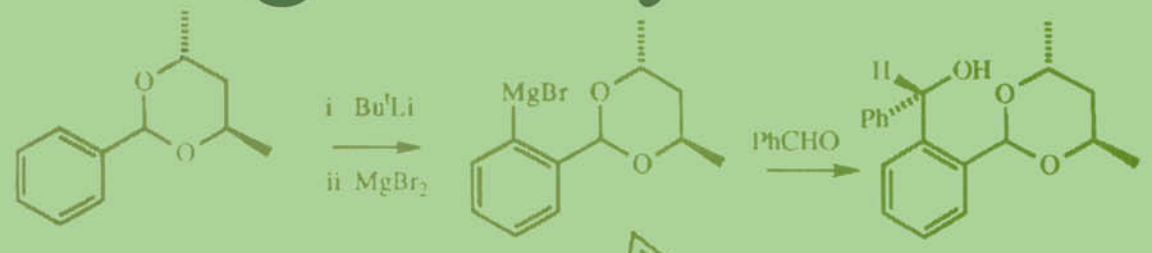
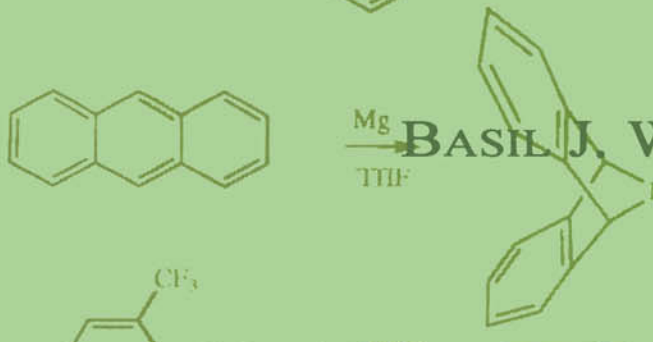



# Organomagnesium Methods in Organic Synthesis





BASIL J. WAKEFIELD

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# Organomagnesium Methods in Organic Synthesis

# BEST SYNTHETIC METHODS

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# Organomagnesium Methods in Organic Synthesis

Basil J. Wakefield

*Department of Chemistry and Applied Chemistry,*
*University of Salford, Salford M5 4WT,*
*UK*

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This book is a guide providing general information concerning its subject matter; it is not a procedural manual. Synthesis of chemicals is a rapidly changing field. The readers should consult current procedural manuals for state-of-the-art instructions and applicable government safety regulations. The publisher and the authors do not accept responsibility for any misuse of this book, including its use as a procedural manual or as a source of specific instructions.

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# Foreword

There is a vast and often bewildering array of synthetic methods and reagents available to organic chemists today. Many chemists have their own favoured methods, old and new, for standard transformations, and these can vary considerably from one laboratory to another. New and unfamiliar methods may well allow a particular synthetic step to be done more readily and in higher yield, but there is always some energy barrier associated with their use for the first time. Furthermore, the very wealth of possibilities creates an information-retrieval problem. How can we choose between all the alternatives, and what are their real advantages and limitations? Where can we find the precise experimental details, so often taken for granted by the experts? There is therefore a constant demand for books on synthetic methods, especially the more practical ones like *Organic Syntheses, Organic Reactions,* and *Reagents for Organic Synthesis,* which are found in most chemistry laboratories. We are convinced that there is a further need, still largely unfulfilled, for a uniform series of books, each dealing concisely with a particular topic from a *practical* point of view—a need, that is, for books full of preparations, practical hints and detailed examples, all critically assessed, and giving just the information needed to smooth our way painlessly into the unfamiliar territory. Such books would obviously be a great help to research students as well as to established organic chemists.

We have been very fortunate with the highly experienced and expert organic chemists, who, agreeing with our objective, have written the first group of volumes in this series, *Best Synthetic Methods.* We shall always be pleased to receive comments from readers and suggestions for future volumes.

A. R. K., O. M.-C., C. W. R.

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# Preface

Despite the wealth of documentation, noted in Chapter 1, there is a need for a collected source of *practical* information, covering newer developments as well as the "classical" preparations of Grignard reagents. Noteworthy among the more recent advances are the use of special forms of magnesium, ultrasonic activation, and magnesium–diene compounds.

I have been gratified by the response to *Organolithium Methods*, and I have therefore adopted a similar scope and organization for *Organomagnesium Methods*, and my criteria for the selection of procedures have been the same. Once again, I am very grateful to colleagues both at Salford and in other institutions who have generously provided me with experimental details and comments on their experience with published procedures. I also thank Dr Ke-Dong Li for translations from Chinese.

B. J. WAKEFIELD

After studying at Imperial College, Basil Wakefield held appointments in the USA and UK, and worked in industry, before moving to Salford, where he has spent most of his academic career. At Salford he made academic links with many countries, including Egypt, Jordan, Papua New Guinea and Tanzania, and has always maintained contact with industry. He is now director of Ultrafine Chemicals Ltd.

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# Abbreviations

| | |
|---|---|
| acac | pentane-2,4-dione, acetylacetone |
| Cp | cyclopentadienyl |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| ether | diethyl ether |
| hexametapol* | hexamethylphosphoric triamide, tris(dimethylamino)phosphine oxide |
| THF | tetrahydrofuran |
| TMEDA | *N,N,N′,N′*-tetramethyl-1,2-ethanediamine, tetramethylethylenediamine |
| ° | °C |

*Confusion has been caused by the inconsistent use of the abbreviations HMPT/HMPA for $(Me_2N)_3P/(Me_2N)_3PO$. The use of Normant's trivial name, "hexametapol" for the phosphorus (v) compound avoids ambiguity

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# —1—

# Introduction and General References

The history of organomagnesium compounds is long, and a vast amount of work on their chemistry was carried out during the first half of this century. There are not many fields of chemistry where a book published in 1954 is still an important source of information, but the mammoth work of Kharasch and Reinmuth [A] provides the best summary of this early work. This classic was followed by the book by Ioffe and Nesmeyanov [B] (originally published in Russian), and by substantial chapters in *Houben–Weyl* [C] and *Comprehensive Organometallic Chemistry* [D, E]. Organomagnesium compounds feature in the Specialist Periodical Reports of the Royal Society of Chemistry and in the Annual Surveys issues of the *Journal of Organometallic Chemistry*. Information on individual compounds may be found in the *Dictionary of Organometallic Compounds* [F] and its annual supplements.

Despite this wealth of documentation, there is a need for a collected source of *practical* information, covering newer developments as well as the "classical" preparations of Grignard reagents. Noteworthy among the more recent advances are the use of the special forms of magnesium, ultrasonic activation, and magnesium–diene compounds.

Because of the frequent need to make comparisons between organomagnesium compounds and organolithium compounds, the companion volume, *Organolithium Methods*, is cited as General Ref. [G].

## A NOTE ON NOMENCLATURE

To an organic chemist, the traditional naming of a Grignard reagent as an alkylmagnesium halide has seemed acceptable and unambiguous, even though he or she has become aware that this name (or the formula RMgX) is likely to be an inadequate representation of the molecular species being dealt with. Other commonly encountered ways of naming such a compound include "halomagnesioalkane", "magnesium(alkyl) halide" and "alkyl(halo)magnesium". The last is used by *Chemical Abstracts*, but

with the parentheses omitted, which the author finds confusing. Similarly, the formulation Mg(X)R seems contrived to an organic chemist. Some *Chemical Abstracts* names (for example "dibromo-μ-1,4-butanediyldimagnesium" for $BrMgCH_2CH_2CH_2CH_2MgBr$) are clearly designed to be understood by computers rather than by human beings. Any attempt to be fully consistent and systematic would probably fail, and would please few if any readers. The author has therefore, for his own convenience, adopted a fairly "traditional" approach.

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# —2—

# General Considerations in the Application of Organomagnesium Compounds in Organic and Organometallic Synthesis

## 2.1 TYPES OF ORGANOMAGNESIUM COMPOUND; CONSTITUTION AND REACTIVITY

### 2.1.1 Types of organomagnesium compound

Magnesium can form one or two covalent bonds to carbon. In the former case, the other valency is available to form bonds to a variety of other groups. (For a discussion of coordination to Mg(II), see Section 2.1.2.) Some of the resulting types of organomagnesium(II) compounds are listed in Table 2.1. Of these compounds, only the chlorides, bromides and iodides, and to a lesser extent the dialkylmagnesium compounds, are widely used in synthesis, and almost all the examples described in this book involve these classes. (Some of the others may be important as intermediates in certain reactions; see, for example, Section 6.1.) Accounts of the chemistry of the other classes of compounds may be found in General Ref. [D] and in Refs [1] and [2]; other references are given in Table 2.1.

In addition to the types of compounds listed in Table 2.1, cyclopentadienyl compounds and 'ate complexes should be noted.*

Di(cyclopentadienyl)magnesium (magnesocene) is easily prepared (see p. 48) and is a valuable starting material for the preparation of cyclopentadienyl derivatives of other metals (see Chapter 15).

'Ate complexes of magnesium are less commonly encountered than those of, for example, aluminum, and they have not yet found many applications in synthesis.† However, there are indications that they may be useful reagents when electron transfer reaction pathways are desired.

*The compounds obtained by reactions of magnesium with dienes (and anthracene) are classified as special cases of dialkylmagnesium compounds; see, for example, p. 40.

†For a recent example see Ref. [3].

TABLE 2.1

Types of organomagnesium(II) compounds, RMgX

| Nature of X | Common name[a] | *Chemical Abstracts* name[a] |
|---|---|---|
| H | Alkylmagnesium hydride | Alkylhydromagnesium |
| R | Dialkylmagnesium | Dialkylmagnesium |
| NR′R″ | Alkylmagnesium dialkylamide | Alkyl(dialkylamino)magnesium or alkyl(*N*,*N*-dialkylaminato)magnesium |
| OR′ | Alkylmagnesium alkoxide | Alkoxyalkylmagnesium or alkanolatoalkylmagnesium |
| OCOR′ | Alkylmagnesium carboxylate [4, 5] | |
| R′COCHCOR″ | Alkylmagnesium β-diketonate [6] | |
| $OSO_2R'$ | Alkylmagnesium sulfonate [5] | |
| SR′ | Alkylmagnesium thiolate | Alkyl(alkylthio)magnesium or alkanethiolatoalkylmagnesium |
| SCN/NCS | Alkylmagnesium thiocyanate [7] | |
| F | Alkylmagnesium fluoride | Alkylfluoromagnesium |
| Cl | Alkylmagnesium chloride | Alkylchloromagnesium |
| Br | Alkylmagnesium bromide | Alkylbromomagnesium |
| I | Alkylmagnesium iodide | Alkyliodomagnesium |

[a]The organic group is designated "alkyl" for convenience.
[b]For other references, see text.

### 2.1.2 Constitution and reactivity

Although it is convenient to formulate Grignard reagents simply as "RMgX", the solutions obtained by the reaction of magnesium with an organic halogen compound usually contain an equilibrium mixture of a variety of species. The ratio of the species in solution varies with the organic group, the halogen, the solvent, the concentration and the temperature. A relatively simple example is "phenylmagnesium bromide". When this Grignard reagent in diethyl ether is concentrated, crystals of a monomeric dietherate are obtained, which has the simple structure shown in Fig. 2.1, in which the magnesium is tetracoordinate, with the ligands

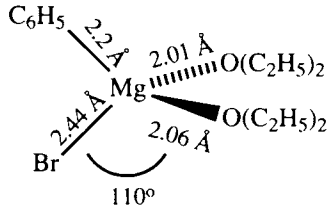



FIG. 2.1. The structure of phenylmagnesium bromide dietherate.

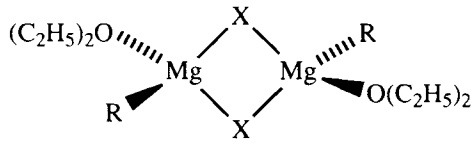
arranged in a distorted tetrahedron [8].* However, this is certainly not the only species in solution. Although there is little association in dilute solutions, oligomeric species are present at higher concentrations, the degree of association reaching about 3.7 at 1.5 M [2]. Moreover, there is good evidence for an equilibrium of the type shown — the Schlenk equilibrium [10]:

$$R_2Mg + MgX_2 \rightleftharpoons 2RMgX \quad (1)$$
(solvation omitted for simplicity)

For phenylmagnesium bromide in diethyl ether at 25° the equilibrium constant has been estimated as 55–62 ($\Delta H^\circ = -8.4$ kJ mol$^{-1}$ and $\Delta S^\circ = 5.0$ J mol$^{-1}$ K$^{-1}$) [11]. Solutions of phenylmagnesium bromide in diethyl ether do conduct electricity, but the degree of ionization is low; presumably ionization to give $RMg^+$ and $X^-$ (and corresponding associated and/or solvated species) is involved [12].

For simple alkyl- and arylmagnesium chlorides, bromides and iodides, the following broad generalizations may be made:

(i) For the chlorides in diethyl ether, the predominant species over a wide range of concentrations is a solvated, halogen-bridged dimer **(1)**, (X=Cl). For the bromides and iodides there is more variation of degree of association with concentration.




**(1)**

(ii) In more strongly coordinating solvents such as THF the degree of association is lower. In THF, monomeric species predominate, and there are significant concentrations of all three species in the Schlenk equilibrium. In the presence of the more strongly coordinating hexametapol, the degree of association falls below one, owing to ionization of the Mg–Br bond (cf. above) [13]. (For precipitation of magnesium halide complexes from solutions containing dioxane, see p. 66).

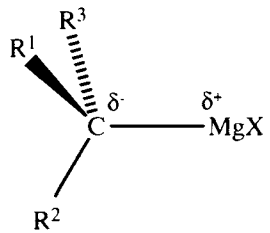
*Note, however, that although tetracoordinate magnesium is the norm, higher coordination numbers are possible for arylmagnesium halides, particularly where intramolecular coordination is involved [9].

(iii) In less strongly coordinating solvents the degree of association increases. Solutions in hydrocarbons tend to precipitate magnesium halide. For example, phenylmagnesium chloride in tetralin deposits magnesium chloride, leaving the solute with the stoichiometry $Ph_3Mg_2Cl$ [14]. (The structure of crystals with analogous composition derived from neopentylmagnesium bromide, has recently been determined [15].*

Dimethylmagnesium and diethylmagnesium are highly associated in solution, and precipitate/crystallize from diethyl ether as linear polymers (they are insoluble in hydrocarbons) [17]. With strongly chelating ligands such as TMEDA they are depolymerized to form solvated monomers [D]. Homologues are less highly associated in donor solvents. Some of the longer-chain alkyl derivatives are appreciably soluble in hydrocarbons; they are presumably associated, but little information on their constitution is available. (The mixed butyl(s-butyl)magnesium is of particular importance: see p. 62–3).

Detailed reviews on the structures of organomagnesium compounds and the constitution of their solutions have been published [D, 1, 2]. These references, especially the first two, also cover alkylmagnesium hydrides, amides, alkoxides and thiolates. However, while all of these compounds are of intrinsic interest, they are little used in synthesis.

The complexities of their constitution in solution make studies of the mechanism of reactions of organomagnesium compounds extraordinarily difficult. Few reactions have stimulated such a wealth of elegantly planned and meticulously executed experiments as those of Grignard reagents with carbonyl compounds (see Section 6.1). Fortunately an admittedly grossly oversimplified rationale for the reactivity of organomagnesium compounds, and in particular for the influence of solvation, is adequate for most applications in organic synthesis. In a monomeric, unsolvated species **(2)**,




**(2)**

*Ill-characterized materials with the composition $PhMg_nX$) have recently been reported as the product of solid phase reactions between halobenzenes and magnesium [16].

the carbon–magnesium bond is polarized, so that the carbon atom is nucleophilic (and Brønsted-basic), while the magnesium atom is electrophilic (coordinatively unsaturated, Lewis-acidic). In a Lewis-basic solvent such as diethyl ether, solvation of the magnesium *decreases* its electrophilicity, but the polarization of the carbon–magnesium bond increases, thus increasing the carbanionic character of the organic ligand. A more strongly Lewis basic solvent such as THF further decreases the electrophilicity of magnesium and increases the nucleophilicity of carbon. It is important to realize that the rate-limiting step of, for example, nucleophilic additions to carbonyl groups may be electrophilic attack at oxygen rather than (as assumed by virtually all elementary textbooks) nucleophilic attack on carbon (see Section 6.1).

Organomagnesium compounds sometimes behave as single-electron donors. Such behaviour is most likely to be observed in highly polar, cation-solvating media and/or when steric hindrance inhibits alternative pathways. 'Ate complexes of magnesium can also act as single electron donors (see p. 97). It should be noted that the presence of traces of transition metals may lead to electron transfer processes [2].

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## 2.2 PRACTICAL CONSIDERATIONS

### 2.2.1 Choice of solvent

The "practical" factors affecting the choice of solvents for organomagnesium reactions are similar to those for organolithium reactions [G], but their relative importance is somewhat different. The most commonly used solvents, diethyl ether and THF, are much less readily attacked by organomagnesium than by organolithium reagents; hydrocarbons are less usually satisfactory solvents for organomagnesium compounds; and very low temperatures (below −78°) are rarely employed for organomagnesium reactions, so low freezing points for solvents are not often a requisite.

The physical properties of some solvents which have been employed for organomagnesium compounds are listed in Table 2.2 (see also General Ref. [A], p. 45), and notes on the solvent types follow.

TABLE 2.2

Solvents for organomagnesium reactions

| Solvent | b.p.° | m.p.° |
|---|---|---|
| Benzene | 80 | 5.5 |
| Heptane | 98 | −90.5 |
| Methylcyclohexane | 100 | −126 |
| Diethyl ether | 34.5 | −116 |
| THF | 64–65 | −65 |
| Diisopropyl ether | 69 | −60 |
| DME | 82–83 | −58 |
| 1,4-Dioxane | 101.5 | 12 |
| Dibutyl ether | 142 | −95 |
| Triethylamine | 89 | −115 |
| TMEDA | 122 | −55 |
| Hexametapol | 232 | 7 |
| Dichloromethane | 40 | −97 |

*Hydrocarbons.* Contrary to popular belief, some Grignard reagents are appreciably soluble in hydrocarbons, but their solubility is often low, and the composition of the solutes is variable, so purely hydrocarbon solvents

have rarely been used unless an unsolvated reagent is required. Recently, however, it has been discovered that mixed n-butyl-s-butylmagnesium reagents are soluble in hydrocarbons, and solutions in heptane are commercially available.

Solutions of *solvated* organomagnesium compounds in largely hydrocarbon media have also been obtained by the use of hydrocarbon solvents containing small proportions of donors such as THF.

It should be noted that an active form of magnesium chloride, formed during the reaction of magnesium with alkyl chlorides, may catalyse Friedel–Crafts alkylation of aromatic solvents [1].

*Ethers.* Diethyl ether is the most commonly used solvent for organomagnesium compounds, and almost all the classical studies involved Grignard reagents in diethyl ether. It continues to be a good general-purpose choice. Most organomagnesium compounds are soluble in it, and it is a convenient solvent for conventional work-up procedures, though its low boiling point is sometimes a disadvantage. For many reactions it is adequately dried by sodium wire, and its high vapour pressure at room temperature creates a "blanket" over the surface of the solution, which sometimes makes the provision of a nitrogen or argon atmosphere unnecessary. Nevertheless, for low concentrations of organomagnesium compounds or for work at low temperatures, drying and handling procedures like those described below must be used. The hazardous properties of diethyl ether — its flammability, proneness to the formation of peroxides, and toxicity — are well known, and appropriate safety precautions should be taken.

When a more strongly Lewis-basic solvent is required, THF is the most widely used alternative to diethyl ether, and this is also the solvent of choice for the preparation of Grignard reagents from vinylic and many aryl halides (see Section 3.1.1). This solvent is much less easily dried, and more hygroscopic, than diethyl ether. Drying procedures that have been found satisfactory for THF include distillation from lithium aluminum hydride, from Grignard reagents (or organolithium compounds) or from benzophenone ketyl. The last, used in a "THF still" is favoured by the present author. Various designs of THF still (which may be used or adapted for other solvents) are available. Two good ones are shown in Fig. 2.2.

It is important that the THF used in the still should not be too wet; unless freshly opened commercial dry THF is used, it should be predried with, for example, anhydrous magnesium sulfate followed by sodium wire. The predried THF is placed in flask A, together with benzophenone. Sodium or, better, potassium chips are added. When any initial effervescence has subsided, the flask is heated, and refluxing THF is returned to flask A via the three-way tap B. When the THF is dry, the

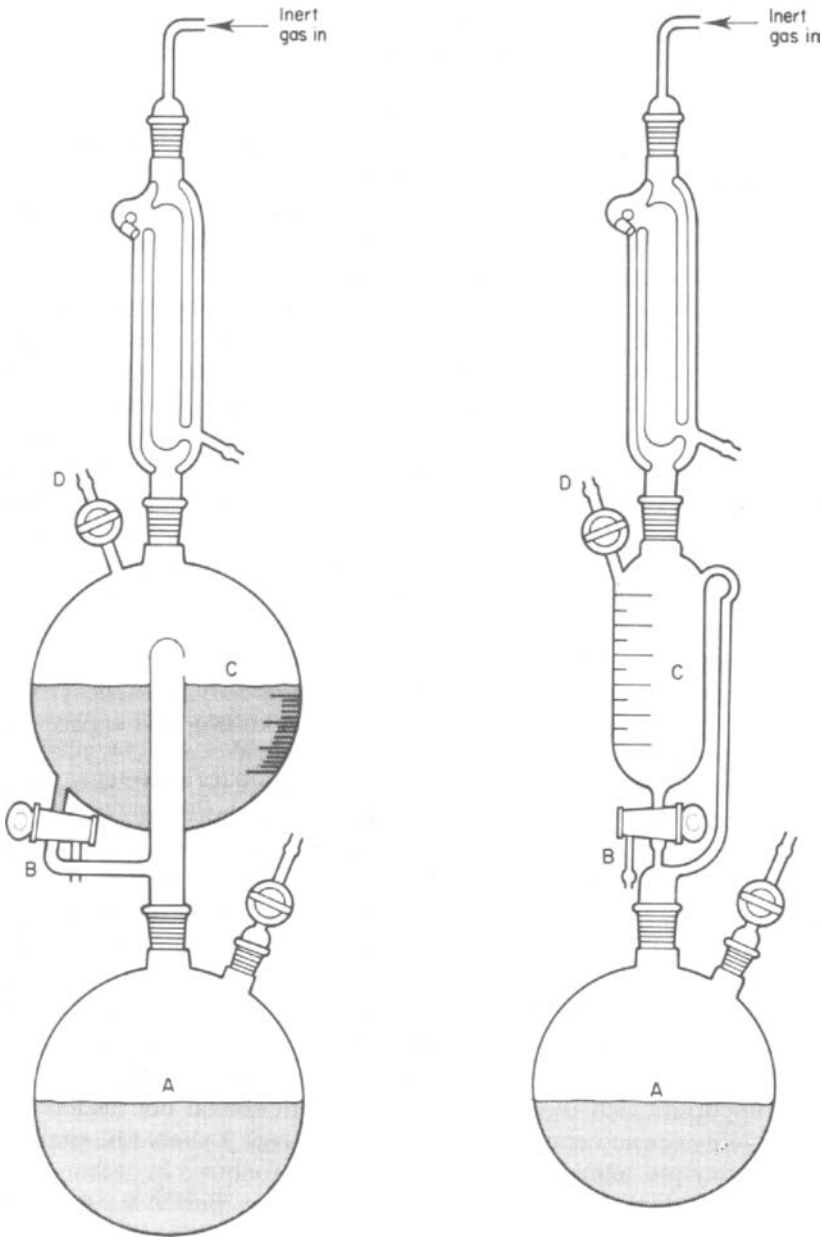


FIG. 2.2. Stills for preparing dry THF and other solvents.

intense blue colour of benzophenone ketyl develops, and the remaining pieces of sodium or potassium should have a bright surface. Tap B is then shut, and dry THF collects in reservoir C. When reservoir C is full, condensate overflows and returns to flask A. The second outlet from tap B is connected to the apparatus to be used for the reaction, and the required volume of THF is transferred. Alternatively, small volumes of THF may be transferred via septum D.

Dibutyl ether is an alternative to diethyl ether when a high reaction temperature is required; it has also been found useful by laboratories in the tropics or at high altitude, where the low boiling point of diethyl ether is a problem. Diisopropyl ether has also been used, but is notorious for its tendency to form peroxides.

Chelating diethers such as DME and 1,4-dioxane are useful, but their use tends to result in precipitation of a magnesium halide complex; this phenomenon is made use of in the most commonly used procedure for obtaining solutions of dialkylmagnesium compounds.

*Tertiary amines* have been comparatively little used as solvents for organomagnesium compounds, though triethylamine shows some promise [2]. TMEDA is more commonly used as an additive than as a solvent: one molar equivalent is normally sufficient to exert the required activating effect. Pyridine is less reactive towards organomagnesium compounds than towards organolithium compounds (see p. 96), and has been used as an alternative to 1,4-dioxane in the preparation of dialkylmagnesium compounds (see p. 65).

*Hexametapol* is difficult to purify and dry [3] and it is a SUSPECTED CARCINOGEN, but it is a particularly good promotor of electron transfer reactions.

*Dichloromethane.* Most of the common chlorinated solvents react with both organomagnesium and organolithium compounds, often at low temperatures (see, for example, Section 3.2.2 for metal–halogen exchange reactions). The exception is dichloromethane, which has a useful combination of low freezing point and boiling point, and moderate polarity, with no tendency to solvate magnesium, and which is not significantly attacked by organomagnesium compounds under mild conditions. An example of its use is noted on p. 52–3.

### 2.2.2 Reactions at low temperatures

Besides ice baths and solid carbon dioxide–acetone baths, convenient cooling baths contain solvents cooled to a slush by stirring with liquid nitrogen. A selection is listed in Table 2.3 (and see also Table 2.2 and Ref [4]). It should be noted that published experimental details do not always

specify whether the temperature reported is the true internal temperature of a reaction vessel, or merely the temperature of the external cooling bath; in the experimental procedures recorded in this book, the statements in the primary literature have had perforce to be repeated, but with honourable exceptions they should be regarded with some reservations.

TABLE 2.3

Solvents for cooling slush baths

| Solvent | Temperature of slush(°) |
|---|---|
| Tetrachloromethane | −23 |
| Chlorobenzene | −45 |
| Chloroform | −63 |
| Ethyl acetate | −84 |
| Hexane | −94 |
| Methanol | −126 |
| Pentane | −131 |

### 2.2.3 Inert atmospheres

For many routine reactions involving Grignard reagents in diethyl ether, the solvent vapour forms a protective blanket over the solution (cf. Ref. [5]), and drying tubes are adequate to exclude moisture. Nevertheless, the use of closed systems with inert atmospheres is recommended even for preparative work, and for physicochemical studies, where traces of alkoxides may have significant effects, it may be necessary to employ vacuum line techniques, rigorously purified atmospheres in glove boxes, and the like.* The cheapest form of inert atmosphere is "white spot"

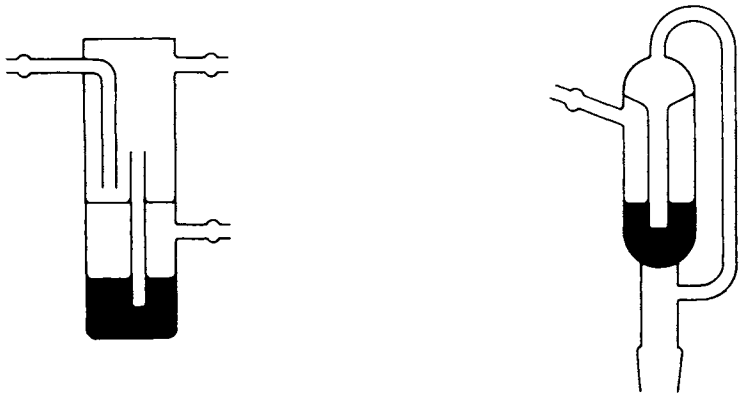

FIG. 2.3. Inert-gas bubblers.

nitrogen, used directly from the cylinder without purification, and this is satisfactory for most experiments. To preserve an inert atmosphere in apparatus, it is best to maintain the internal pressure at slightly above atmospheric. An excess pressure of 1–2 cm of mineral oil is usually sufficient, and this is conveniently ensured by means of a bubbler, such as those shown in Fig. 2.3, attached to the apparatus. This is designed in such a way that if the internal pressure should inadvertently fall below atmospheric (eg. on rapid cooling), oil is not sucked into the apparatus and ingress of oxygen is minimized.

For small-scale work, a very simple device is a balloon connected to a

*For information on such techniques see Ref. [6]. The painstaking work of the Amsterdam group is exemplary [7].

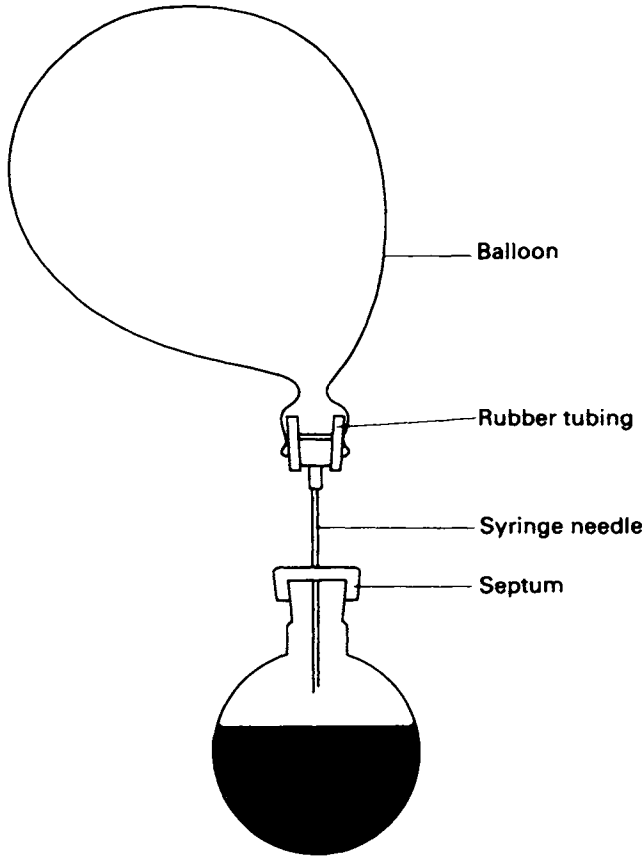


FIG. 2.4. Balloon method for maintaining an inert atmosphere.

syringe needle and inflated by the inert gas. The apparatus is flushed with the inert gas, the septum fitted, and the needle inserted, as shown in Fig. 2.4. However, the use of a balloon is *not* recommended for prolonged reactions, since oxygen can diffuse into the balloon.

### 2.2.4 Storage and transfer of organomagnesium compounds; safety precautions

Organomagnesium compounds are not usually pyrophoric. However, they do react vigorously, or even violently, with water and oxygen, so they must be stored or transferred out of contact with both. As noted above, this is most easily accomplished by handling them under a blanket of nitrogen. Whenever possible, solutions should be stored at room temperature, since storage in refrigerators gives rise to the risk of contamination via condensation or ice build-up on the container, as well as reduction in internal pressure as the container is cooled. In order to transfer solutions of organomagnesium compounds from the vessels in which they have been made, or from containers such as bottles fitted with sealed caps containing septa, in which commercial organomagnesium reagents are often supplied,* use may be made of the pressure of the inert atmosphere. The vessels are interconnected by a tube (a "cannula"), which can be flushed with nitrogen and then dipped below the surface of the solution, which is forced over by nitrogen pressure or syphoned (Fig. 2.5). A very convenient form of cannula for fairly small quantities is a flexible double-ended

*When large amounts of the reagent are supplied in cylinders or tanks, manufacturers provide detailed procedures.

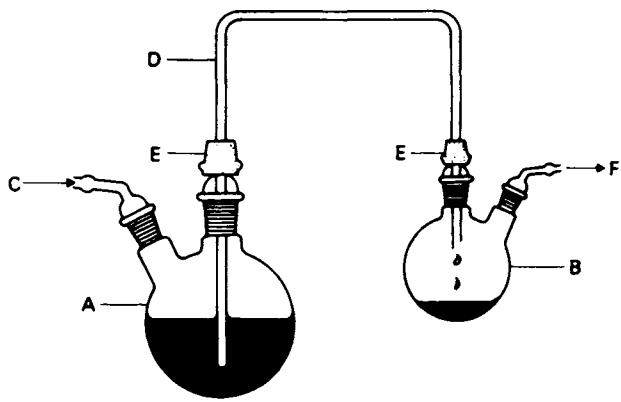


FIG. 2.5. Transfer of organomagnesium solution under inert atmosphere: A, storage flask; B, receiving flask; C, inert gas in; D, transfer tube; E, sleeve; F, to bubbler.

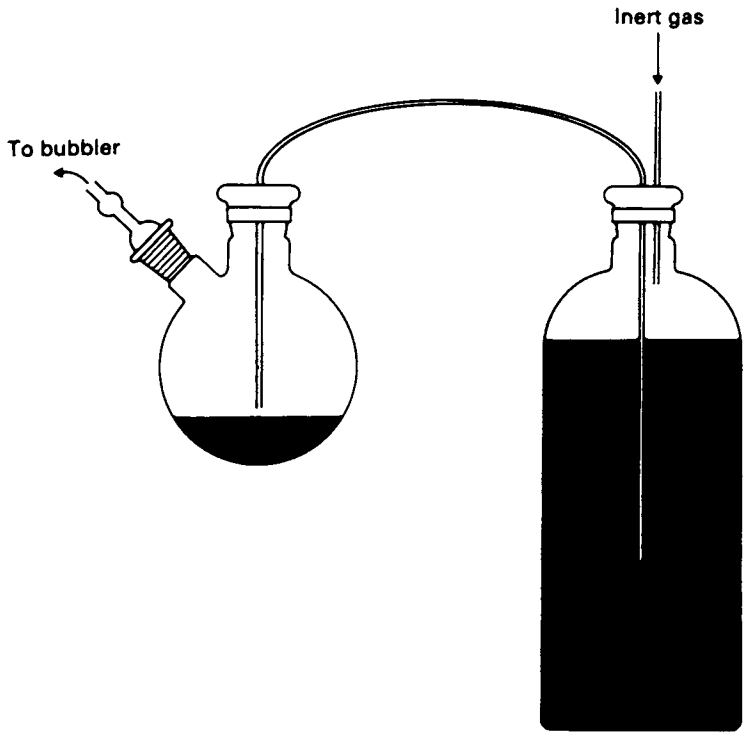


FIG. 2.6. Transfer by means of a double-ended needle.

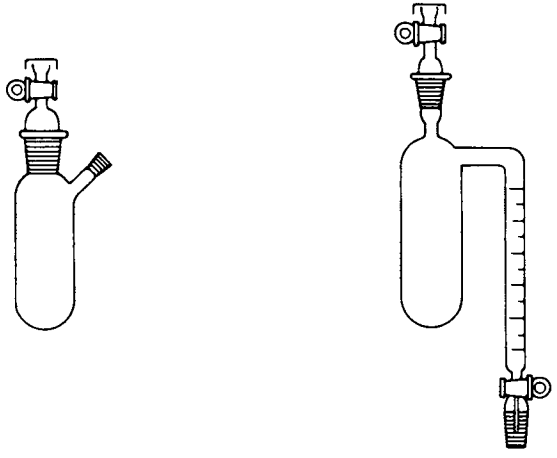

FIG. 2.7. Modified Schlenk tubes.

hollow needle, which can be passed through septa at each end (Fig. 2.6).

For intermediate storage, modified Schlenk tubes (Fig. 2.7) may be used. The version with a burette side-arm is particularly convenient for dispensing a measured volume to a reaction vessel.

For small-scale transfer the syringe-and-septum method is routinely used. The following procedure is recommended:

(i) The syringe is flushed with inert gas.
(ii) If the organomagnesium solution is being withdrawn from a closed vessel, a positive internal pressure is maintained by passing inert gas through the septum. (Alternatively, the syringe is filled with inert gas, which is forced into the vessel before the solution is withdrawn).
(iii) Slightly more than the required volume of solution is drawn into the syringe. The tip of the needle is then raised above the surface of the solution, and some inert gas is drawn into the syringe.
(iv) The syringe is withdrawn and immediately inverted, and the

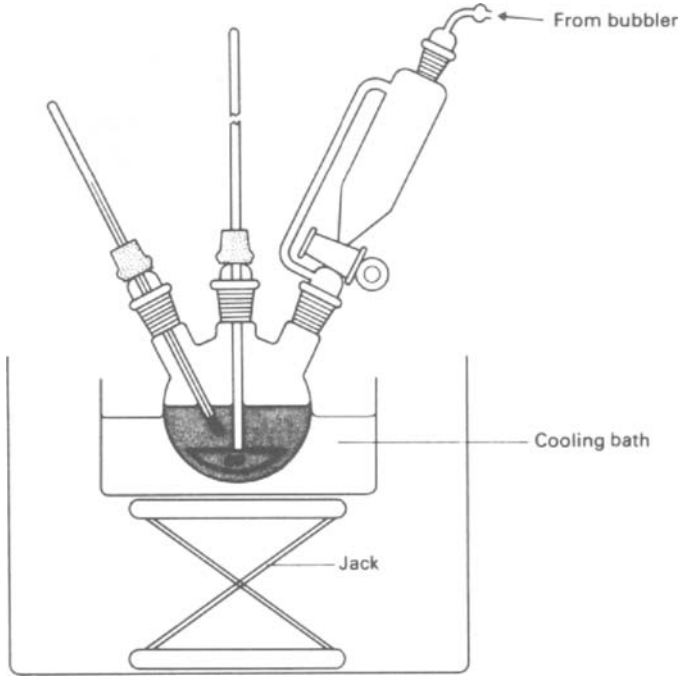


FIG. 2.8. Typical assembly for an organomagnesium reaction. For reactions in boiling solvent the thermometer is replaced by a condenser.

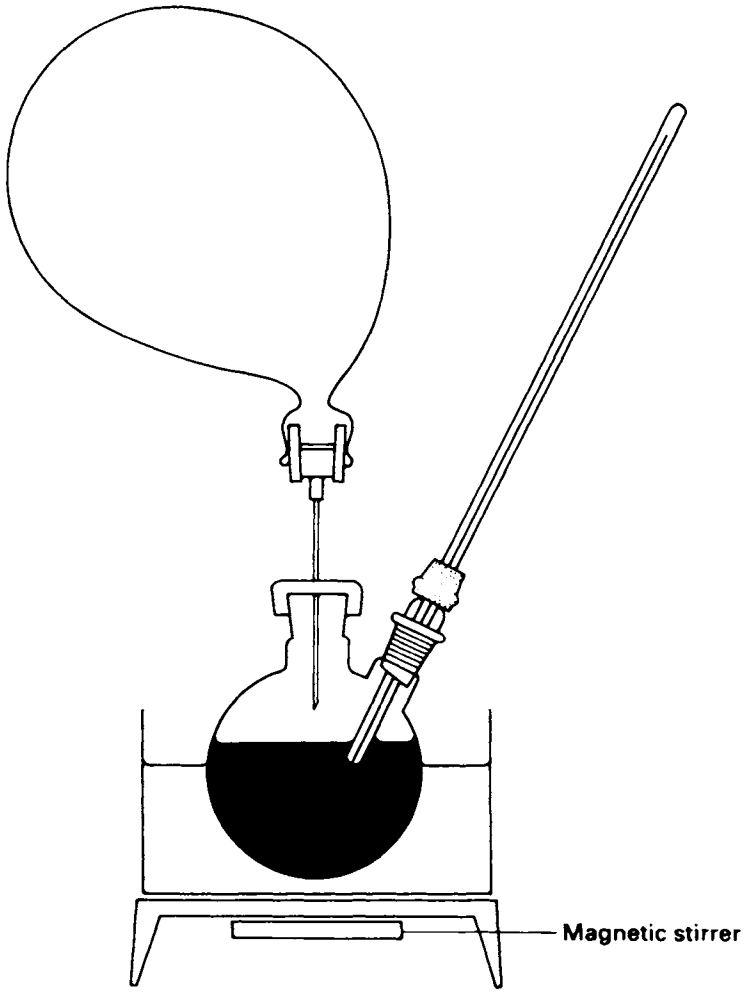


FIG. 2.9. Typical assembly for a small-scale organomagnesium reaction.

plunger is advanced until the barrel is just filled by the solution.

(v) The required amount of the solution is dispensed into the receiver.

(vi) The excess of solution is discharged into a quenching medium (e.g. an ethyl acetate or acetone–hydrocarbon mixture) and the syringe is immediately flushed out, disassembled, cleaned and dried. (Hydrolysis and oxidation products of organomagnesium

compounds can rapidly "seize" syringes, taps, stoppers, etc.).

Despite the greatest care in keeping and using organomagnesium compounds safely, accidents may happen. Appropriate precautions must therefore always be taken. Personal protective clothing and safety spectacles should be worn. Experiments should be conducted behind screens. Dishes to catch spillages should be provided. In case of fire, EXTINGUISHERS USING WATER OR HALOGENATED HYDROCARBONS MUST NOT BE USED. For small laboratory fires, carbon dioxide extinguishers may be usable, but THE USE OF CARBON DIOXIDE EXTINGUISHERS ON BURNING MAGNESIUM IS DANGEROUS. The most generally satisfactory extinguishers for organomagnesium fires are the dry-powder type.

### 2.2.5 Typical assemblies for reactions

Two typical assemblies for reactions are shown in Figs 2.8 and 2.9. Assemblies of these types can be readily adapted to accommodate variations in procedures and the particular models of equipment available.

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## 2.3 DETECTION AND ESTIMATION OF ORGANOMAGNESIUM COMPOUNDS

### 2.3.1 Detection

For detecting the presence of an organomagnesium compound, Gilman's colour test 1 is convenient:

$$(4\text{-}Me_2NC_6H_4)_2C{=}O + RMgX \longrightarrow (4\text{-}Me_2NC_6H_4)_2C(R)OMgX \longrightarrow [(4\text{-}Me_2NC_6H_4)_2CR]^+ I^-$$

A sample (0.5–1 ml) of the test solution is added to an equal volume of 4,4′-bis(dimethylamino)benzophenone (Michler's ketone) in dry toluene. A few drops of water are added, and the mixture is shaken.* A few drops of a 0.2% solution of iodine in glacial acetic acid are added, resulting in the formation of a blue or green colour. A recent variation employs tris(4-dimethylaminophenyl)methane (leuco crystal violet, LCV), followed by aerial oxidation [1].

Gaidis [2] devised two modifications, to distinguish between alkyl- and arylmagnesium compounds:

(a) Following hydrolysis, the solution is buffered to pH 9 by the addition of 20% aqueous catechol (1–2 ml). A few drops of 0.5% iodine in benzene are added and the solution is shaken. A green to blue colour in the organic layer indicates the presence of an arylmagnesium compound (and a pale-green colour also slowly develops with vinylmagnesium chloride). The mixture is then acidified with acetic acid to reveal the presence of an alkylmagnesium compound.

(b) Following hydrolysis the solution is acidified with acetic acid (5–15 drops). Aqueous sodium bisulfite (20%) is added; with aryl- (and vinyl-) magnesium compounds the blue or green colour persists, but with alkylmagnesium compounds it is discharged.

Gilman's colour test 2, which depends on rapid metal–halogen exchange with 4-bromo-*N*,*N*-dimethylaniline, is positive for alkyllithium compounds [3], but not for organomagnesium compounds.

*Aerial oxidation often leads to the formation of the blue–green colour at this stage.

### 2.3.2 Estimation

The most important determination is normally the concentration of carbon–magnesium-bonded species in solution. For routine estimation of this concentration for freshly prepared solutions of organomagnesium compounds, an aliquot of the test solution may be added to an excess of standard acid, and then back-titrated with sodium hydroxide. However, this simple determination of total base will give a high estimate of organomagnesium content if products of hydrolysis or oxidation are present. Analytical methods based on the determination of the hydrocarbon formed on hydrolysis of the organomagnesium compound

have been used [4, 5], but are of limited applicability and low precision. Accordingly, several methods have been devised for determining organomagnesium content by titration, using indicators which give intense colours in the presence of reactive organomagnesium compounds.* The most widely used involve titration of the test solution with s-butanol using 1,10-phenanthroline, 2,2′-biquinoline, or *N*-phenyl-1-naphthylamine as the indicator [6, 7]. Recently, direct titration against the red-coloured diphenyl ditelluride has been described [8], and titration against pyrene-1-acetic acid has been used to estimate methylmagnesium iodide [9].

When estimation of the concentration of magnesium, halide, etc., in organomagnesium compounds is required, hydrolysis followed by standard analytical methods is normally satisfactory.

*Alkynylmagnesium compounds may give unsatisfactory results [6].

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# —3—

# Preparation of Organomagnesium Compounds

By far the commonest method for preparing organomagnesium compounds remains the classical Grignard reaction of magnesium with organic halides, and the majority of those commercially available are solutions prepared in this way. Several manufacturers have facilities for preparing Grignard reagents on a "fine chemicals" scale, and a surprising number are offered for sale as laboratory chemicals. A selection of Grignard reagents and other organomagnesium compounds currently available is listed in Table 3.1.

## 3.1 BY REACTIONS OF METALLIC MAGNESIUM

A variety of methods for preparing organomagnesium compounds utilize elemental magnesium, and for many of them the purity and form of the metal is important or even critical.

(CAUTION: The flammability of magnesium is well known, and appropriate precautions must be taken when handling it (see note concerning fire extinguishers on p. 18). The more finely divided the magnesium, the greater the hazard, and the very reactive forms, especially the slurries described below, are PYROPHORIC in contact with air).

*Purity.* Magnesium is readily available in a purity of 99.8%, and this grade is satisfactory for many routine purposes. However, impurities may be detrimental to the yield of organomagnesium compounds, and some, particularly transition metals, may have a profound effect on certain reactions even in low concentrations. Sublimed magnesium is also commercially available, typically with less than 10 ppm impurities; magnesium containing only zinc at over 1 ppm has been obtained by this method [1]. "Ultrapure" magnesium, estimated to contain less than $10^{-2}$ ppm impurities, has been described [2]. Equipment for subliming magnesium is shown schematically in Fig. 3.1 [3]. The bottom of the outer vessel is covered with a layer of about 2 cm of Grignard-grade magnesium turnings. The vessel is evacuated and filled to atmospheric pressure with

TABLE 3.1

Commercially available organomagnesium reagents

| Organomagnesium compound | Solvent | Concentration (M) | Supplier[a] |
|---|---|---|---|
| Allylmagnesium bromide | Diethyl ether | 1–1.5 | a, e, f |
| Allylmagnesium chloride | THF | 1–2.5 | a, e |
| Benzylmagnesium chloride | Diethyl ether | 1 | a[b] |
| | THF | 1–2 | a, e, f |
| Bis(pentamethylcyclopentadienyl)magnesium (decamethylmagnesocene) | *c* | | f |
| n-Butyl-s-butylmagnesium[d] | Heptanes | 1 | c |
| n-Butylmagnesium chloride | Diethyl ether | 2 | a |
| | THF | 1.5–2.5 | a, e, f |
| s-Butylmagnesium chloride | Diethyl ether | 1.5–2.5 | a, e |
| t-Butylmagnesium chloride | Diethyl ether | 2–3 | a, e |
| | THF | 1.5–2.5 | a, e |
| 4-t-Butylphenylmagnesium bromide | Diethyl ether | 2 | a |
| 4-Chlorophenylmagnesium bromide | Diethyl ether | 1 | a |
| Cyclohexylmagnesium chloride | Diethyl ether | 2 | a, e |
| Cyclopentylmagnesium chloride | Diethyl ether | 2 | a |
| Decylmagnesium bromide | Diethyl ether | ≈ 1 | a, e |
| Di(cyclopentadienyl)magnesium(magnesocene) | *c* | | f |
| Di-n-hexylmagnesium | Hydrocarbon | ≈ 1 | e |
| Diethylmagnesium | Diethyl ether | 1–1.5 | e |
| Dimethylmagnesium | Diethyl ether | 1 | e |
| 1,1-Dimethylpropylmagnesium chloride | Diethyl ether | 1 | a |
| Dodecylmagnesium bromide | Diethyl ether | 1 | a |
| Ethylmagnesium bromide | Diethyl ether | 3 | a, e, f |
| | THF | 2 | a |
| | t-Butyl methyl ether | 1 | a |
| Ethylmagnesium chloride | Diethyl ether | 1.5–2 | a, e, f |
| | THF | 1.5–3 | a, b, d, e |
| Ethynylmagnesium bromide | THF | 0.5 | a |
| 4-Fluoro-3-methylphenylmagnesium bromide | THF | 1 | a |
| 4-Fluorophenylmagnesium bromide | Diethyl ether | 2 | a |
| | THF | 1 | a |
| n-Heptylmagnesium bromide | Diethyl ether | 2–3 | e |
| n-Hexylmagnesium bromide | Diethyl ether | 2–3 | a, e |
| Isobutylmagnesium bromide (2-methylpropylmagnesium bromide) | Diethyl ether | 2 | a |
| Isobutylmagnesium chloride (2-methylpropylmagnesium chloride) | Diethyl ether | 1.5–2.5 | a, e |
| Isopropylmagnesium chloride | Diethyl ether | 2–3 | a, e, f |
| | THF | 2 | a |
| Magnesium anthracenide (9,10-dihydro-9,10-anthracenediyl)tris(tetrahydrofuran)magnesium) | *e* | | |
| Mesitylmagnesium bromide (2,4,6-trimethylphenylmagnesium bromide) | Diethyl ether | 1 | a |
| | THF | 1 | a |
| 4-Methoxyphenylmagnesium bromide | THF | 1–2 | e |
| Methylmagnesium bromide | Dibutyl ether | 1–2 | a, e |
| | Diethyl ether | 3 | a, e, f |
| | Toluene–THF | 1.5 | a |
| Methylmagnesium chloride | THF | 3 | a, b, d, e, f |

TABLE 3.1 *(continued)*

| Organomagnesium compound | Solvent | Concentration (M) | Supplier[a] |
|---|---|---|---|
| Methylmagnesium iodide | Diethyl ether | 2–3 | a[b], e |
| Neopentylmagnesium chloride (2,2-dimethylpropylmagnesium chloride) | Diethyl ether | 0.5–1 | e |
| Octadecylmagnesium chloride | THF | 1 | a |
| Octylmagnesium chloride | THF | 2 | a |
| Pentamethylenebis(magnesium bromide) (1,5-bis(bromomagnesio)pentane) | THF | 0.5 | a |
| n-Pentylmagnesium bromide | Diethyl ether | 1.5–2.5 | a, e |
| Phenylmagnesium bromide | Diethyl ether | 3 | a[b], e, f |
| | THF | 1 | a[b] |
| Phenylmagnesium chloride | THF | 2–3 | a, b, d, e, f |
| n-Propylmagnesium chloride | Diethyl ether | 2–3 | a, e |
| Tetradecylmagnesium chloride | THF | 1 | a |
| *o*-Tolylmagnesium bromide | Diethyl ether | 2 | a |
| *p*-Tolylmagnesium bromide | Diethyl ether | 1–2.5 | a, e |
| Trimethylsilylmethylmagnesium chloride | Diethyl ether | 1–1.5 | a, e |
| Vinylmagnesium bromide | THF | 1–1.5 | a, e, f |
| Vinylmagnesium chloride | THF | 1–1.5 | b, d, e |

[a]a, Aldrich Chemical Company; b, Chemetall GmbH; c, FMC, Lithium Division; d, Acros (formerly Janssen Chimica; e, Johnson Matthey Alfa Products; f, Strem Chemicals Company. [b]Also available deuterium-labelled. [c]Solid. [d]See p. 63. [e]Solid THF complex; see p. 40.

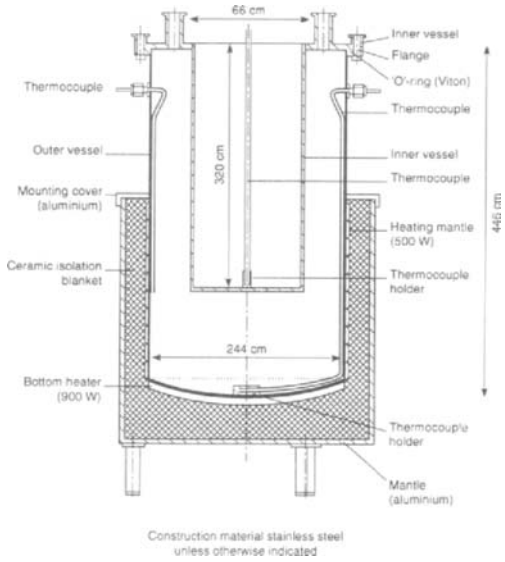



FIG. 3.1 Apparatus for the sublimation of magnesium. (Based on detailed drawings of apparatus developed by the workshop of the Scheikundig Laboratorium, Vrije Universiteit, Amsterdam).

argon three times. It is evacuated to about 1 mbar, and the bottom is heated to 700° and the wall to 500° for 8 h. The evacuated vessel is allowed to cool to room temperature and flushed with argon. The sublimed magnesium is removed from the inner vessel ("cold finger") by scraping with a glass rod.

It must be emphasized that when high purity magnesium is converted into turnings, chips or powder, special precautions have to be taken in order to avoid contamination [2]. It should also be noted that magnesium surfaces, exposed to air, rapidly become covered with an oxide film. Methods for activating magnesium (see below) usually depend on the removal or penetration of this surface film.

*Turnings.* Magnesium turnings are often sold as "for Grignard reagents", and are convenient to use and sufficiently reactive in many cases. Their reactivity is enhanced by the presence of surface dislocations resulting from their preparation.

*Chips.* Sublimed magnesium is usually supplied in the form of chips, but often has a large effective surface area.

*Powder.* In many cases the advantage of using magnesium powder (large surface area) is outweighed by the disadvantage of increased susceptibility to surface contamination, but this form of magnesium has been found particularly useful for reactions in hydrocarbon media [4]. Powder prepared by "scratching" a billet of magnesium is especially reactive, again because of the presence of surface dislocations.

*Slurries.* Several techniques have been used to prepare slurries of highly reactive magnesium, but some are difficult to carry out without special equipment. For example, magnesium vapour has been co-condensed with a solvent at 77 K [5]. Similarly reactive slurries were made much more readily available by Rieke (hence the name "Rieke magnesium"), who reduced magnesium halides to the metal by alkali metals, for example from magnesium chloride and potassium in the presence of potassium iodide, with THF as the medium [6]. However, this procedure is still somewhat hazardous, and a more recent procedure, where the magnesium halide is reduced by lithium, with naphthahlene as an electron carrier, is safer as well as giving a slurry of comparable activity to the original Rieke magnesium [7].

*Rieke magnesium by reduction of magnesium chloride with lithium naphthalene* [7,8]. Lithium (224 mg, 3.3 mmol)*, anhydrous magnesium chloride (1.57 g, 16.5 mmol)†, naphthalene (436 mg, 3.4 mmol) and dry

*Lithium (99.9%, rod) is cut into chips under oil, rinsed with hexane, and transferred to a tared weighing adapter filled with argon. The adapter is evacuated and refilled with argon several times to remove the solvent, and weighed. The lithium is transferred to the reaction flask under a stream of argon.

†Weighed and transferred under argon.

THF (~ 20 ml) are placed in a 50 ml round-bottomed flask furnished with a septum, condenser, magnetic stirrer, and an atmosphere of argon. The mixture is stirred *vigorously* at room temperature for 24 h. (If the reaction stops, because the lithium surface becomes coated with magnesium, it can be restarted by rubbing the piece of lithium against the wall of the flask with a metal spatula). The reactive magnesium suspension is dark grey to black, and slowly settles when stirring is stopped.

For an example of the use of "Rieke magnesium", see p. 35.

The highly reactive form of magnesium obtained by "dry stirring" (see under "Activation of magnesium", below, may also be regarded as a slurry.

*Magnesium anthracene.* Syntheses of organomagnesium compounds from the magnesium–anthracene adduct (see p. 40) proceed via dissociation of the adduct to give magnesium in a highly reactive form [9, 10].* Indeed, anthracene may be used to catalyse the reactions of other forms of magnesium (see below).

*Catalytically prepared magnesium hydride has been used as an alternative to magnesium anthracene [10].

*Activation of magnesium.* Numerous procedures have been used, whereby the surface of magnesium is activated [A, D]; in many cases the procedures are empirical — it is not known whether they work merely by cleaning or etching the metal surface, or whether the formation of some intermediate reactive magnesium compound is involved. A selection of better-known procedures follows; examples are described or listed in Section 3.1.1.

(a) Mechanical activation. Various more or less elaborate procedures for mechanically exposing fresh magnesium surfaces in a reaction medium have been described [A, 11]. However, comparable activation may be obtained much more simply. For example, prolonged dry stirring of magnesium turnings in an inert atmosphere leads to a high degree of activation [12]. Simply crushing magnesium turnings with a glass rod is sometimes sufficient to start a recalcitrant reaction. Ultrasonic irradiation is also effective [13, 14], and may be regarded as a means of mechanical activation, though other effects may also be involved.

(b) Activation by halogens. One of the most convenient methods of activating magnesium, introduced by Grignard himself [15], is reaction of the metal surface with iodine. Most commonly, a reaction is initiated simply by adding a small crystal of iodine to magnesium in the reaction mixture. Alternatively, magnesium is

preactivated by heating with iodine [A]. Disadvantages of activation by iodine are slightly reduced yields and coloured solutions. Bromine has been much less used than iodine, but appears to be equally effective [A].

(c) Activation by alloying. Activation of magnesium by amalgamation or by alloying with copper or various transition metals has been reported [A, D], but these means of activation rarely offer advantages over other methods, while involving toxicity hazards and/or the risk of promoting side-reactions. They are therefore not generally recommended, though the amalgamation method may be useful in particular cases [16–18].

(d) Activation by "entrainment". The "entrainment" method, in which an otherwise unreactive organic halide is caused to react with magnesium in the presence of a reactive halide such as iodomethane or bromoethane, was introduced by Grignard [19], and has been frequently used. It can also suppress side-reactions [20], but has the disadvantage that *two* organomagnesium compounds are formed. A commonly used modification employs 1,2-dibromoethane as the coreactant; in this case the by-products are magnesium bromide and ethene, which do not usually interfere with subsequent reactions [21].

### 3.1.1 By reaction of organic halides with magnesium

The mechanism of the reaction between organic halides and magnesium, leading to organomagnesium compounds, has been the subject of much speculation and study, and no little controversy. For the chemist wishing to prepare and use the organomagnesium compounds, information on the mechanism is especially relevant to two matters: the nature and amount of by-products, and the stereochemistry of the organomagnesium product.

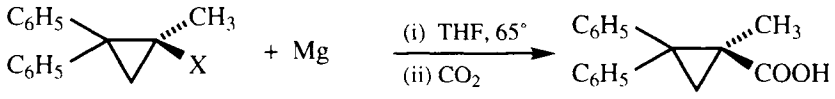
Following the prophetic speculations of Kharasch and Reinmuth [A] and the crucial CIDNP experiments of the Amsterdam group [22], the main features of the mechanism are now clear. Electron transfer from the magnesium surface to adsorbed organic halide gives rise to alkyl radicals and halide ions. Further recombination steps lead to the alkylmagnesium halide. Two matters especially remain controversial: whether the electron transfer step involves a discrete radical anion intermediate, and to what extent radicals leave the metal surface to diffuse into the solution. Recent arguments have been summarized [23, 24], commented on [25], and pursued [26]. The implications for practical work may be summarized briefly as follows:

(i) Frequently observed by-products from the preparation of a Grignard reagent from an organic halide, RX, and magnesium are those expected

from radical processes, notably coupling products (R–R), products from hydrogen abstraction from the solvent, etc., (R–H), and in appropriate cases disproportionation products (R–H again, and the corresponding alkene). References to these and other radical-derived products are given in the reviews cited [23, 24]. It must be emphasized that the formation of such by-products may be promoted by even small traces of transition metals [D, 2].

(ii) The implications of observations on the extent to which the configuration of alkyl halides is retained on reaction with magnesium to form organomagnesium compounds are debatable [23–25]. The observations themselves may be summarized as follows:

(a) Molecules containing magnesium bound to an asymmetric carbon atom are not generally configurationally stable. However, there are some exceptions to this generalization, notably some cyclopropylmagnesium halides [23], and in these cases reaction of the halide with magnesium proceeds with a significant amount of retention of configuration, e.g. [23]




| | | |
|---|---|---|
| X = Cl | 0.5 h | 81% (optical purity 27%) |
| | 3 h | 89% (optical purity 26%) |
| X = Br | 0.5 h | 70% (optical purity 19%) |
| | 3 h | 79% (optical purity 11%) |

(b) Alk-1-enylmagnesium halides are often configurationally stable, and the reaction of halides with magnesium again proceeds largely with retention of geometry (for a review, see Ref. [23]). For example, the reaction of (*Z*)-1-bromo-2-phenylethene with magnesium in ether gave the Grignard reagent with 68% retention of configuration, and the corresponding reaction of the (*E*) isomer proceeded with 59% retention of configuration [27].

The following selection of preparations is representative of the main types of procedure for preparing organomagnesium compounds by the reaction of magnesium with organic halides. Other well-described preparations are listed in Table 3.2. Yields are not listed in Table 3.2, since in many cases only the yields of subsequent reactions are recorded; they are in general high unless otherwise stated.

TABLE 3.2

Preparation of Grignard reagents by the reaction of magnesium with organic halides

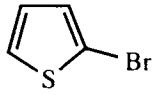
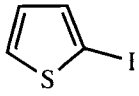
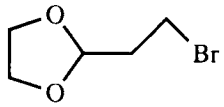
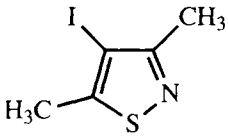
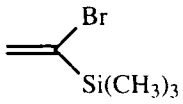
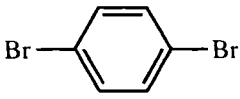
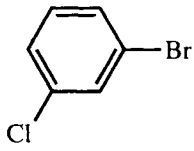
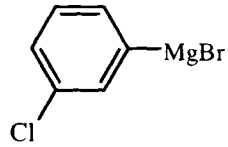
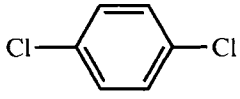
| Halide | General technique[a] | Ref. | Notes |
|---|---|---|---|
| $CH_2Br_2$ | N | [20] | Di-Grignard reagent obtained using magnesium amalgam in diisopropyl ether, and vacuum line technique. Yield ~ 80% |
| $CH_3Br$ | A | [39, 40] | See also procedure in text |
| $CH_3Cl$ | A | [41] | Use of gaseous reagent |
| $CH_3I$ | A | [42] | |
| $CF_2=CFBr$ | B | [43] | |
| $CH_2=CHBr$ | B | [44, 45] | See also procedure in text |
| $CH_2=CHCl$ | B | [46] | |
| $CH_3CH_2Br$ | A | [47–49] | |
| | B | [50] | |
| $HC\equiv CCH_2Br$ | A | [51, 52] | Product reacts as $CH_2=C=CHMgBr$ |
| $CH_2=CHCH_2Br$ | A | [53–55] | |
| $CH_2=CHCH_2Cl$ | A | [56, 57] | See also Refs. [12] and [58] |
| $ClMgOCH_2CH_2CH_2Cl$ | B | [59] | By reaction of $HOCH_2CH_2CH_2Cl$ with $CH_3MgCl$, then Mg |
| $(CH_3)_2CHBr$ | A | [60] | |
|  | A<br>B | [61]<br>[62] | |
|  | A | [63] | |
| $CH_2=CHCH_2CH_2Cl$ | A | [64] | |
| $BrCH_2CH_2CH_2CH_2Br$ | B | [65, 66] | Di-Grignard reagent. |
| $ClCH_2CH_2CH_2CH_2Br$ | A | [67] | Mono-Grignard reagent, $ClCH_2CH_2CH_2CH_2MgBr$ |
|  | B | [68–70] | Temperature kept below 35°, and preferably below 25° [70] to prevent decomposition |
| $CH_3CH_2CH_2CH_2Br$ | A | [71–74] | |
| $CH_3CH_2CH_2CH_2Cl$ | B | [75] | See also procedure in text |
| $(CH_3)_2CHCH_2Cl$ | A | [76] | |

TABLE 3.2 *(continued)*

| Halide | General technique[a] | Ref. | Notes |
|---|---|---|---|
| $CH_3CH_2CH(Cl)CH_3$ | A | [77] | |
| $(CH_3)_3CCl$ | B | [78] | |
| | C | [79] | 200 mesh powder |
| $(CH_3)_3SiCH_2Cl$ | A | [80, 81] | |
|  | E | [82] | Entrainment with bromoethane but may proceed via metal–halogen exchange |
| $BrCH_2C(CH_3)_2CH_2Br$ | N | [83] | Doubly sublimed magnesium; high dilution, vacuum line technique. Yield ~ 14% |
| $(CH_3)_2NCH_2CH_2CH_2Cl$ | B | [84] | |
| $CH_3CH_2CH_2CH_2CH_2Br$ | A | [85] | |
| $(CH_3)_2CHCH_2CH_2Br$ | A | [86] | |
| $CH_3CH_2CH_2CH(Br)CH_3$ | D | [87] | |
| $(CH_3)_3CCH_2Cl$ | A | [88] | Difficult to initiate; inert atmosphere and pure neopentyl chloride needed |
| | E | [89] | |
|  | B | [31] | |
| $C_6BrF_5$ | A | [90] | |
| $C_6ClF_5$ | B | [91] | |
|  | A | [92] | Mono-Grignard reagent |
|  | A | [93] | Product is  |
|  | F | [94] | Mono- or di-Grignard reagent obtainable |

*(continued on next page)*

TABLE 3.2 *(continued from previous page)*

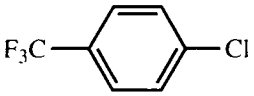
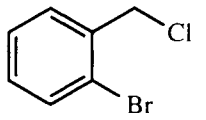
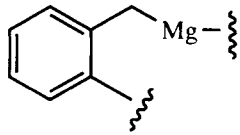
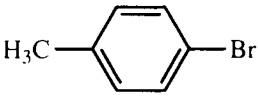
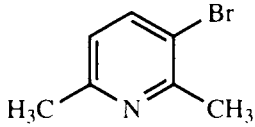
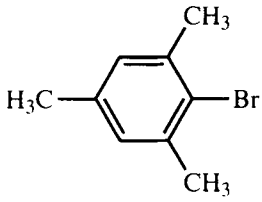
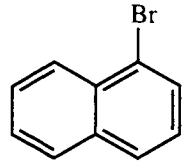
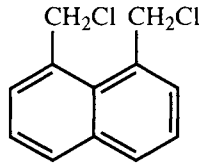
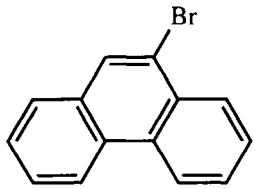
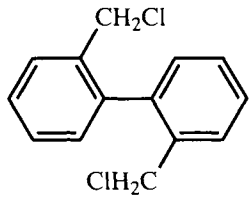
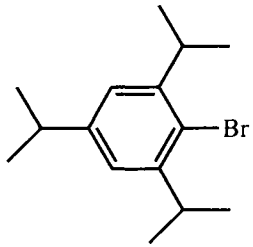
| Halide | General technique[a] | Ref. | Notes |
|---|---|---|---|
| $C_6H_5Br$ | A | [95, 96, 97] | |
| | B | [98] | |
| 4-$CH_3$–$C_6H_4F$ | H | [99] | |
| cyclo-$C_5H_{11}Br$ | A | [100] | See also procedure in text for cyclohexylmagnesium chloride |
| $(CH_3)_2CHSi(CH_3)_2CH_2Cl$ | B | [101] | |
|  | – | [102] | Reactions of halogenobenzotrifluorides with magnesium are HAZARDOUS |
|  | C,E | [103] | Product is mainly oligomer of  |
|  | B | [104] | |
| $C_6H_5CH_2Cl$ | A | [105–107] | |
|  | B | [108] | |
| $C_6H_5CH_2CH_2Cl$ | B | [109] | |
| $C_6H_5CH(Cl)CH_3$ | G | [12] | |
|  | A<br>E | [110, 111]<br>[112] | Entrainment with bromoethane gave higher yield |

TABLE 3.2 *(continued)*

| Halide | General technique[a] | Ref. | Notes |
|---|---|---|---|
|  | A | [113] | Grignard reagent sparingly soluble; benzene (HAZARD) added to dissolve it |
| $n\text{-}C_{11}H_{23}Br$ | A | [114] | |
|  | F[b] | [115] | Many other examples described |
|  | A | [116] | |
|  | C | [117] | Di-Grignard reagent |
|  | B | [118] | Yield of subsequent reaction 34% (not optimized), but illustrates formation of Grignard reagent despite steric hindrance |
| $C_6H_5CH_2O(CH_2)_{11}Br$ | E | [119] | With sonication |

[a]A, magnesium turnings, ether; B, magnesium turnings, THF; C, magnesium powder; D, dibutyl ether; E, entrainment; F, magnesium anthracenide or activation by anthracene; G, magnesium activated by dry stirring; H, Rieke magnesium; N, special technique. [b]Using 9-trimethylsilylanthracene.

(CAUTION: It will be noted that in most of the following procedures, only a small proportion of the organic halide is added initially. Except for reactions on the smallest scale, it is important that this procedure is followed, and that no more organic halide is added until the reaction has started. There is often an induction period [119a], but when the reaction does start it is often HIGHLY EXOTHERMIC, and may be UNCONTROLLABLE if too much organic halide is added at once. The start of the reaction is usually manifested by changes at the magnesium surface ("hot spots", gas evolution*, colour or brightness changes) and/or by heat evolution. In case of uncertainty, the formation of Grignard reagent may be checked by a Gilman colour test (see p. 18–19).)

*Commercial magnesium often contains dissolved gases, notably hydrogen, which are released when the metal dissolves.

The first preparation, of cyclomagnesium chloride, exemplifies the traditional procedure [29], using magnesium turnings, with diethyl ether as the solvent, and no provision of an inert atmosphere other than the solvent vapour. This type of procedure is satisfactory for most primary and many secondary and tertiary alkyl chlorides and bromides and for many aryl bromides. Iodides may also be used, but the additional expense is rarely justified, particularly as they tend to suffer more side-reactions such as Wurtz-type coupling. Early work on the factors affecting such reactions has been thoroughly reviewed [A].

*Cyclohexylmagnesium chloride* (traditional Grignard reagent) [28, A] Magnesium turnings ("Grignard grade"; 26.7 g, 1.1 mol) and sodium-dried ether (100 ml) are placed in a 1 litre flask, fitted with a dropping funnel, condenser, and stirrer, and with calcium chloride guard tubes protecting the dropping funnel and condenser. Redistilled chlorocyclohexane (15 ml) and a crystal of iodine are added, and the mixture is heated gently *without stirring* until the reaction starts (~ 5–10 min). Ether (125 ml) is added, and the stirrer is started. A cooling bath is prepared. The remainder of a total of 118.5 g (121 ml, 1.0 mol) of chlorocyclohexane, mixed with dry ether (225 ml) is added from the dropping funnel during 30–45 min, with cooling if necessary. The mixture is stirred and heated under reflux for 15–20 min after the addition is complete. The resulting solution is approximately 2 M in cyclohexylmagnesium chloride.

THF is higher-boiling and more Lewis-basic than ether, and Grignard reagent preparations in this solvent are often successful with halides which react only with difficulty or not at all in ether, notably vinyl halides and

aryl chlorides (and alkyl fluorides [32]). On the other hand, side-reactions such as Wurtz-type coupling are more troublesome in THF than in ether for more reactive halides.

*Vinylmagnesium bromide (ethenylmagnesium bromide)* (reaction in THF, under an inert atmosphere) [30, 31] A 2 litre three-necked flask is fitted with a reflux condenser (preferably cooled by solid carbon dioxide in acetone), a 500 ml pressure-equalizing dropping funnel and a mechanical stirrer, and furnished with an atmosphere of nitrogen or argon. Magnesium turnings (26.4 g, 1.09 mol) and dry THF (800 ml) are placed in the flask. Vinyl bromide (107 g, 70.5 ml, 1.0 mol) is condensed in a 500 ml flask cooled in solid carbon dioxide/acetone and diluted with dry THF (200 ml); the mixture is transferred to the dropping funnel. The vinyl bromide solution (~ 70 ml) is added dropwise. When the reaction has started (iodomethane (0.5 ml) is added as initiator if necessary), the mixture is stirred as the remainder of the vinyl bromide solution is added dropwise at such a rate that a gentle reflux is maintained. After the addition is complete, the mixture is stirred and heated under reflux for a further 30–60 min. The yield is high.

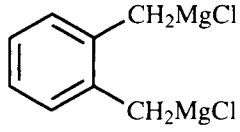
*Methylmagnesium bromide* (use of dibutyl ether as high-boiling solvent to facilitate subsequent reaction (see p. 223) [33] A 3 litre three-necked round-bottomed flask is equipped with a mechanical stirrer and a jacketed 250 ml pressure-equalizing dropping funnel, and furnished with an atmosphere of nitrogen. Magnesium turnings (101 g, 4.15 mol) and dry, peroxide-free dibutyl ether (~ 1.5 litre) are placed in the flask, and the mixture is cooled in ice–water. The jacket of the dropping funnel is filled with solid carbon dioxide in acetone, and bromomethane (200 ml, 365.6 g, 3.85 mol) is transferred to the dropping funnel.* Bromomethane (5–10 ml) is added to the stirred suspension. If the reaction does not start, a few crystals of iodine are added. The remainder of the bromomethane is added dropwise during 2 h, the dropping funnel is replaced by a stopper, the ice–water bath is removed, and the mixture is stirred at room temperature for several hours. The yield, based on the yield of the subsequent reaction, is greater than 85%.

*Liquid bromomethane may be withdrawn from a metal cylinder fitted with a needle valve by inverting the cylinder.

The preparation of benzylmagnesium halides requires special care, owing to the susceptibility of the halides to Wurtz-type coupling. The formation of di-Grignard reagents from 1,2-bis(halomethyl)benzenes is particularly tricky, but may be accomplished by the use of an excess of

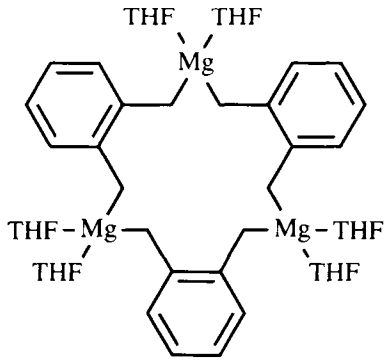
magnesium powder in conjunction with the chloromethylbenzene and dilute solutions.

*1,2-Bis(chloromagnesiomethyl)benzene* (use of magnesium powder) [34]




Magnesium powder (May and Baker or Alfa, 50 mesh; 1.20 g, 49 mmol) is placed in a 500 ml three-necked flask fitted with a 250 ml pressure-equalizing dropping funnel and a filtration tube attached to a 250 ml Schlenk flask, and furnished with an inert atmosphere. A mixture of 1,2-dibromoethane (CARCINOGEN) (0.1 ml) and THF (5 ml) is added, and the flask is warmed until gas evolution is apparent, and then for a further 2 min. The THF is removed by syringe, and replaced by fresh THF (12.5 ml). A mixture of freshly purified 1,2-bis(chloromethyl)benzene (LACHRYMATOR) (2.14 g, 12.2 mmol) and THF (150 ml) is added from the dropping funnel dropwise, with stirring, during 3.5 h. The mixture is stirred at about 20° for approximately 15 h and filtered. The concentration of the di-Grignard reagent in the yellow filtrate is typically 0.073 M, representing almost quantitative yield.

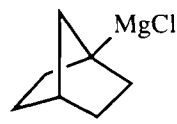
(On cooling to −40° overnight, the solution of the di-Grignard reagent deposits crystals of the trimetallacycle **(1)**.)




**(1)**

*Unsolvated n-butylmagnesium chloride* (use of hydrocarbon solvent and magnesium powder) [35] Magnesium powder (particle size 64–76 μm; see note on p. 24) (3.22 g, 0.132 mol) and methylcyclohexane (60 ml) are placed in a 250 ml round-bottomed flask fitted with a thermometer, a pressure-equalizing dropping funnel, a reflux condenser, and a mechanical stirrer (glass link or PTFE), and furnished with an inert atmosphere. The methylcyclohexane is heated to reflux and the mixture is stirred vigorously as approximately one-fifth of a mixture of 1-chlorobutane (9.26 g, 0.1 mol) and methylcyclohexane (20 ml) is added. With recently prepared magnesium powder, the reaction usually starts (grey turbidity) within a few minutes; if not, it may be initiated by addition of a crystal of iodine to the *unstirred* mixture. (The reaction is also promoted by the presence of certain alkoxides, but the properties of the product may be modified.) When the reaction has started, the remainder of the chlorobutane solution is added during about 12 min, at such a rate that a steady refluxing is maintained. When the addition is complete, stirring and heating are continued for a further 15 min. The constitution of the product is unknown, but the carbon–magnesium bonds formed represent approximately 75% yield.

*1-Norbornylmagnesium chloride* (use of Rieke magnesium) [6c]

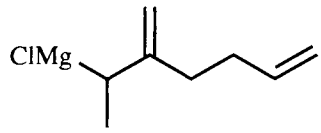



Rieke magnesium (~ 0.020 mmol) is prepared as described on p. 24 in a 200 ml three-necked round-bottomed flask equipped with a PTFE-coated magnetic stirrer bar, stopper, septum and reflux condenser, and furnished with an atmosphere of argon, and allowed to cool to room temperature. 1-Chloronorbornane (1.25 g, 9.58 mmol) is injected by means of a warm syringe. The mixture is heated under reflux for 6 h, and allowed to cool to room temperature.

*Pentachlorophenylmagnesium halide* (entrainment technique) [36] Magnesium turnings (39 g, 1.6 mol), hexachlorobenzene (142.4 g, 0.5 mol) and diethyl ether (1 litre) are placed in a 3 litre three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel for slow addition or a syringe pump, and protected by drying tubes. The mixture is warmed to gentle reflux and stirred as a mixture of 1,2-dibromoethane (188 g, 1.0 mol) and benzene (200 ml) (CAUTION: both components of the mixture

are volatile and highly toxic — it would be preferable to substitute toluene for benzene) is added during 48 h (~ 1 drop/25 s). The resultant mixture containing the Grignard reagent is dark brown and heterogeneous.

*2-(Chloromagnesio)-3-methylenehept-6-ene* (use of magnesium anthracene) [37]

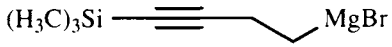



Magnesium powder (2.5 g, 103 mmol), anthracene (250 mg, 1.4 mmol) and dry, oxygen-free THF are placed in a flask under an atmosphere of argon and subjected to ultrasonic irradiation for 5 min. More THF (75 ml) is added, and ultrasonic irradiation is continued for 15 h, during which time the temperature rises to 60°. The supernatant orange solution is removed by syringe, and the residue is washed with dry THF and then suspended in THF (150 ml). The suspension is cooled to −78° and stirred as a mixture of 2-chloro-3-methylenehept-6-ene (1.14 g, 7.9 mmol) and THF (15 ml) is added by syringe pump during 5 h, and the mixture is allowed to warm to room temperature.

(For subsequent reactions see p. 78.)

The following preparation is an example of the procedure described by Brown [12]. Attempts to prepare the Grignard reagent using conventional activation with iodine were unsatisfactory.

*1-Trimethylsilyl-4-bromomagnesio-1-butyne* (activation of magnesium by dry stirring) [38]

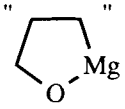



Magnesium turnings (1.27 g, 52 mmol) are stirred in an argon atmosphere for 48 h in a 100 ml three-necked round-bottomed flask [12]. Dry THF (20 ml) is added, followed dropwise by a solution of 4-bromo-1-trimethylsilyl-1-butyne (2.56 g, 12.5 mmol) in dry THF (20 ml). After the initial exothermic reaction has subsided, the mixture is stirred at room temperature for 1 h.

The yield of a subsequent copper-catalysed reaction with 2-cyclohexenone was 81%.

### 3.1.2 By reactions of ethers and thioethers with magnesium

Saturated ethers do not normally react with magnesium, though THF is cleaved by Rieke magnesium [120] or active magnesium from magnesium hydride [10] to give **(2)**. Allyl and benzyl ethers are more reactive towards

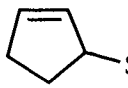
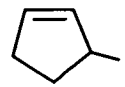



**(2)**

magnesium, and reactions of magnesium with allyl aryl ethers in THF readily give allylmagnesium alkoxides. A procedure follows, and other examples are listed in Table 3.3. Analogous reactions of thioethers have been reported, and examples of these are also listed in Table 3.3.

TABLE 3.3

Reactions of allyl and benzyl ethers and thioethers with magnesium

| Ether | Form of magnesium[a] | Product | Yield (%) | Ref. |
|---|---|---|---|---|
| $CH_2=CHCH_2OCH_3$ | A | $CH_2=CHCH_2MgOCH_3$ | 55 | [122] |
| $CH_2=CHCH_2O-\alpha-C_{10}H_8$ | B | $CH_2=CHCH_2MgO-\alpha-C_{10}H_8$ | 86 | [123] |
| $CH_3CH=CHCH_2O-\beta-C_{10}H_8$ | A | $CH_3CH=CHCH_2MgO-\beta-C_{10}H_8$ | 79 | [122] |
| $C_6H_5CH_2OCH_3$ | A | $C_6H_5CH_2MgOCH_3$ | 88 | [122] |
| $C_6H_5CH_2OC_6H_5$ | A | $C_6H_5CH_2MgOC_6H_5$ | 91 | [122] |
| $(C_6H_5CH_2)_2O$ | B | $C_6H_5CH_2OMgCH_2C_6H_5$ | 42 | [7] |
| $CH_2=CHCH_2SC_6H_5$ | | $CH_2=CHCH_2MgSC_6H_5$ | 67 | [124] |
|  | B |  | 45 | [124] |

[a]A, Rieke; B, turnings.

*3-Phenylprop-2-enylmagnesium phenoxide* [121]

$$C_6H_5CH=CHCH_2OC_6H_5 \rightarrow C_6H_5CH=CHCH_2MgOC_6H_5$$

Magnesium turnings (1.0 g, 41 mmol), 1-phenyl-3-phenoxyprop-1-ene (2.1 g, 10 mmol) and dry THF (20 ml) are placed in a 50 ml two-necked flask fitted with a reflux condenser and a magnetic stirrer, and furnished with an inert atmosphere. The mixture is warmed and a few drops of 1,2-

dibromoethene are added. When the reaction has started (dark-green colour, positive Gilman test) the mixture is heated under reflux for 4 h. The yield, based on reaction with carbon dioxide, is 90%.

### 3.1.3 By reactions of dialkylmercury compounds with magnesium

The reaction of dialkylmercury compounds with magnesium is valuable for preparing dialkylmagnesium compounds, free from traces of halide, and either as solids or in a variety of solvents.

$$R_2Hg + Mg \rightarrow R_2Mg + Hg$$

It has been used particularly to prepare samples for physicochemical studies [125–127]. The reaction may be carried out in the absence of solvent, in which case the product is extracted from the magnesium amalgam formed by a suitable solvent [128, 129]. In a solvent such as diethyl ether the reaction may be very slow, but proceeds in virtually quantatitive yield [130, 131].

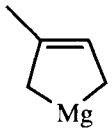
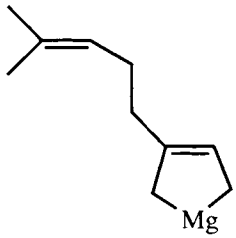
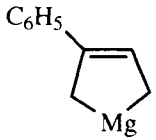
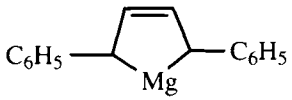
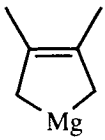
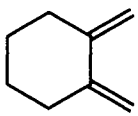
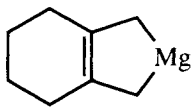
*Diarylmagnesium compounds (general procedure)* [132] Magnesium (2.4 g, 100 mmol), diarylmercury (20 mmol) and diethyl ether (200 ml) are sealed *in vacuo* in glass apparatus and the mixture is stirred for 2–3 weeks. (In case of incomplete reaction, more magnesium is added, and stirring is continued for a further 1–2 weeks.) The suspension is allowed to settle, and the clear solution, containing the diarylmagnesium, is decanted.

### 3.1.4 By reactions of hydrocarbons with magnesium

It has been known for many years that magnesium adds to 1,3-dienes, and the reagents thus produced have been the subject of increasing interest [133]. A complication in the use of these reagents for organic or organometallic synthesis is that they may be of varying stoichiometry, with rearrangement as well as oligomerization occurring [133]. Nevertheless, under defined conditions mainly 1:1 adducts, which react as magnesacyclopentenes,* may be obtained. In the earlier work, various catalysts were employed, but with reactive forms of magnesium in THF, catalysts are unnecessary. The preparation of the 1:1 adduct of magnesium and butadiene is described below, and other examples are listed in Table 3.4.

*In at least one case the adduct does indeed have a monomeric structure [134].

TABLE 3.4
1:1 adducts of magnesium with 1,3-dienes

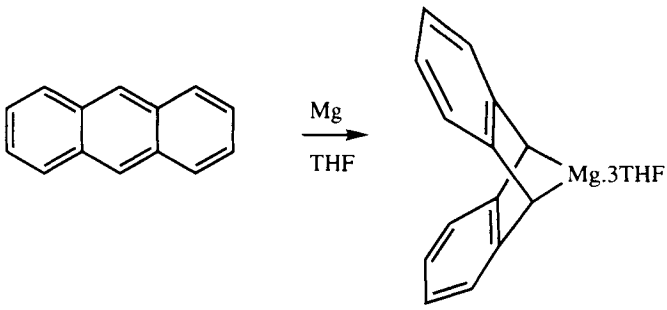
| Diene | Conditions[a] | Product[b] | Yield (%) | Ref. |
|---|---|---|---|---|
| Isoprene | A<br>C |  | 86[c]<br>High | [136]<br>[137] |
| Myrcene | B<br>C |  | ~ 90<br>High | [138, 139]<br>[137] |
| 2-Phenyl-1,3-butadiene | C |  | High | [137] |
| 1,4-Diphenyl-1,3-butadiene | C |  | High | [140] |
| 2,3-Dimethyl-1,3-butadiene | D<br>C |  | 77<br>High | [141]<br>[137] |
|  | C |  | High | [142] |

[a]A, magnesium powder, THF ($FeCl_3$ + EtMgBr catalyst); B, magnesium powder, THF ($FeCl_3$ catalyst); C, Rieke magnesium, THF; D, activated magnesium turnings, THF.
[b]Formulated as the magnesacyclopentene for convenience. [c]~ 70% 1:1 adduct.

*Magnesium butadiene 1:1 adduct (magnesacyclopentene)* [135] Butadiene (6.75 g, 0.125 mol) is distilled into a suspension of magnesium turnings (6.08 g, 0.25 mol) in THF (80 ml) cooled to −78°. Iodobenzene (0.28 ml) is added, and the tube is sealed and shaken at 40° for 15 h. The tube is opened under nitrogen and the suspension of the product in THF is removed from the residual magnesium by syringe. The suspension is filtered, and the solid is washed with THF and dried *in vacuo* (0.1 mmHg) at 70° for 3 h, to give the adduct (~ 51%), with the composition $C_4H_6Mg{\cdot}2THF$.

Magnesium transfers an electron to various aromatic hydrocarbons to give radical anions, and in a number of cases isolable complexes are formed, but they have not found significant use in synthesis [D]. On the other hand the magnesium salt of the dianion of cyclooctatetraene is isolable as the THF complex, and has been used to make cyclooctatetraene complexes of other metals [143–145]. The adduct of magnesium with anthracene, isolated as an orange–red THF complex, is a useful source of reactive magnesium (see p. 25). Various analogues [144, 146] and a polymer-supported version of the complex [147, 148] have been described.

*Magnesium anthracene THF complex* [149]




Magnesium powder (50 mesh) (24.3 g, 1 mol) and anthracene (200 g, 1.12 mol) are placed in a three-necked 2 litre flask and heated in an oven at 110° for 10 min. The flask is fitted with a stirrer, reflux condenser and three-way tap, evacuated, and filled with argon or nitrogen. Dry THF (1 litre) is added, followed by a few drops of bromoethane (or a little magnesium anthracene), and the mixture is stirred at 60° for 24 h. By this time the magnesium has dissolved and a voluminous orange precipitate has formed. Stirring is continued at room temperature for 12 h. The suspension is filtered through a glass sinter, and the product is washed with THF (2 × 300 ml) and dried *in vacuo* to give the complex as fine, orange crystals (373 g, 89%).

Reactions of hydrocarbon acids with magnesium, with displacement of hydrogen, have been used preparatively only for the synthesis of cyclopentadienyl and related compounds. The reaction of cyclopentadiene vapour with magnesium at 500–600°C gives good yields of magnesocene [150]. In the presence of a catalytic amount of trichloro(cyclopentadienyl)titanium the reaction proceeds in THF at 0° to room temperature [151], and it can also be carried out under mild conditions with Rieke magnesium [145]. The reaction with Rieke magnesium has also been used to prepare diindenylmagnesium and difluorenylmagnesium [145].

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## 3.2 PREPARATION FROM OTHER ORGANOMAGNESIUM COMPOUNDS

### 3.2.1 By metallation

$$RMgX + R'H \rightarrow R'MgX + RH$$

Until recently, the preparation of organomagnesium compounds by metallation was only of value in the case of quite strong carbon acids ($pK_a < \sim 25$) such as alkynes and cyclopentadienes, which are metallated by Grignard reagents. Dialkylmagnesium compounds are also reactive towards these types of substrate, the n-butyl-s-butylmagnesium reagent (see p. 63) being particularly useful. Grignard reagents are also effective with some polyhalogenated compounds, but reactions such as the versatile *ortho* metallation of substituted aromatic compounds by organolithium compounds [G] were poor with organomagnesium compounds.* However, it has now been reported that sterically hindered magnesium amides, analogous to lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) are effective metallating reagents. They are probably less powerful than the lithium reagents, but have the

*A special case is described in Ref. [1].

advantage of being stable even in boiling THF [2]. α-Metallation of carbonyl compounds (enolization) and other α-metallations by organomagnesium compounds also occur, but their use has been overshadowed by the corresponding reactions of LDA and organolithium compounds [G]; however, enolization by hindered magnesium amides such as BrMgTMP [3] promises to be useful. The longer-established [4] bis-deprotonation of arylacetic acids by Grignard reagents should also be noted [5]:

$$ArCH_2COOH + 2RMgX \rightarrow ArCH{=}C(OMgX)_2$$

The reference cited [5] also gives procedures for related magnesiations of other carboxylic acids, phenylacetronitrile, t-butyl acetate, acetophenone, methyl phenyl sulfone, and diethyl phenylmethanephosphonate.

Representative procedures for some of the more important types of reaction are described below.

Extensive studies have been made of the metallation of 1-alkynes by organomagnesium compounds [D]. For preparative purposes, metallation by Grignard reagents (commonly ethylmagnesium bromide) in diethyl ether or THF is usually straightforward and convenient. Magnesiation of acetylene itself has special features and is described separately.

*Alkynylmagnesium bromides (general procedure for metallation of 1-alkynes by ethylmagnesium bromide)* [6]

$$RC{\equiv}CH + C_2H_5MgBr \rightarrow RC{\equiv}CMgBr + C_2H_6$$

A 1 litre three-necked round-bottomed flask is equipped with a gas inlet tube, a mechanical stirrer, and an efficient reflux condenser (in the case of volatile acetylenes, a solid carbon dioxide–acetone cold finger condenser) with the top of the condenser connected to a cold trap, and furnished with an inert atmosphere. (CAUTION: particularly in the case of volatile acetylenes, all connections, and the stirrer seal, must be gas-tight). The alkyne (0.5–0.6 mol) is introduced into a solution of ethylmagnesium bromide (approximately equimolar) in ether or THF, as a gas or from the dropping funnel, under the conditions summarized in Table 3.5; this table also specifies the conditions required to complete the metallation.

The problem with the magnesiation of acetylene itself is that ethynylmagnesium bromide tends to disproportionate to give the

TABLE 3.5

Metallation of 1-alkynes by ethylmagnesium bromide

$$RC{\equiv}CH + C_2H_5MgBr \rightarrow RC{\equiv}CMgBr + C_2H_6$$

| R | Solvent | Procedure |
|---|---|---|
| $CH_3$[a], $C_2H_5$, $H_2C{=}CH$ | $Et_2O$ | Reaction mixture at 30–35°. Alkyne distilled in during 1.5 h. Contents of cold trap after condenser distilled in during 2 h |
| | THF | Reaction mixture at ~ 45°. Alkyne distilled in during 30 min. Cold traps interchanged and contents of trap after condenser distilled in during 30 min; interchange, etc. repeated twice |
| $(CH_3)_3C$ | THF | Reaction mixture at 50°. Alkyne added dropwise during 30 min. Heating continued for 15 min. Contents of cold trap diluted with THF (30 ml) and added during 5 min. Heated for 30 min. Operation with cold trap repeated. Heating continued for 15 min. |
| $R'C{\equiv}C$, $Me_3Si$, R'O, R'S | $Et_2O$ | Alkyne added to refluxing mixture dropwise during 45 min. Refluxing continued for 30 min |
| | THF | Reaction mixture held at 0–5° as alkyne added dropwise during 20 min. Mixture allowed to warm to 20°. Stirring continued for 15 min |
| Others | $Et_2O$ | Alkyne added to refluxing mixture dropwise during 45 min. Refluxing continued for 2 h |
| | THF | Reaction mixture heated to 50° as alkyne added dropwise during 30 min. Stirring continued for 1 h |

[a]A similar preparation of prop-1-ynylmagnesium bromide has been described in *Organic Syntheses* [7].

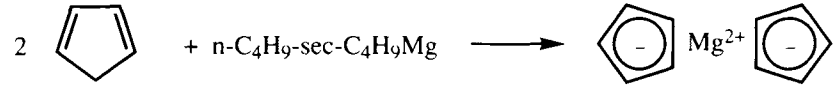
di-Grignard reagent, which precipitates. Thus, in order to obtain ethynylmagnesium bromide, an excess of acetylene must be maintained in the reaction mixture. The procedure described below has been successfully carried out on a 2–3 M scale [9]. For smaller-scale preparations (< 0.3 M) a simplified procedure in which a rapid stream of acetylene is passed into the Grignard reagent at 5–20° is adequate [9].

*Ethynylmagnesium bromide* [8] A 1 litre three-necked flask is equipped with a sealed mechanical stirrer, a gas inlet (which will dip below the surface of 200 ml of liquid in the flask), a 500 ml pressure-equalizing dropping funnel, and a gas outlet tube through which the excess of acetylene will issue (HAZARD). The apparatus is purged with nitrogen, a solution of ethylmagnesium bromide (~ 0.5 mol) in THF (300 ml) is placed in the dropping funnel, and THF (200 ml) is placed in the flask. Purified acetylene is passed through the gas inlet tube at the rate of 15–20 1 $h^{-1}$, and the stirrer is started. After 5 min, the ethylmagnesium bromide solution (5 ml) is added in one portion. When the frothing (ethane evolution) subsides, the remainder of the ethylmagnesium bromide is added similarly in 5 ml portions (~ 3 h; the temperature rises to 5–10° above ambient). The resulting solution of ethynylmagnesium bromide is homogeneous at 30°.

If the di-Grignard reagent is required, it is readily prepared (as a gelatinous suspension) by passing acetylene into a solution of ethylmagnesium bromide (~ 1 M in THF) at 50° [9].

The metallation of cyclopentadienes and related compounds by Grignard reagents is slow and often requires high temperatures [A, D], though it is faster in the presence of solvents such as hexametapol [11]. Dialkylmagnesium compounds are more reactive, and metallation of cyclopentadiene itself by the n-butyl-s-butylmagnesium reagent occurs at a convenient rate at 25°.

*Magnesocene* (use of dialkylmagnesium compound to metallate cyclopentadienes, etc.) [10]

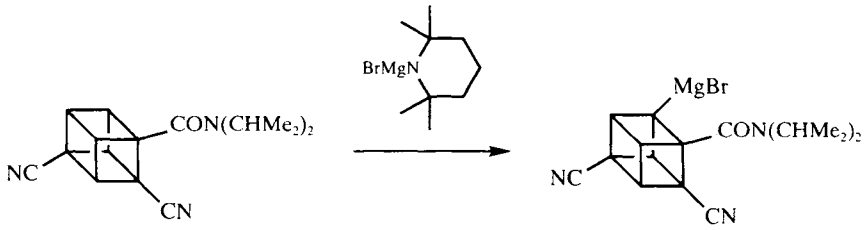



A 250 ml two-necked flask is equipped with a magnetic stirrer bar, a three-way stopcock in one neck and a septum on the other, and filled with nitrogen. n-Butyl-s-butylmagnesium reagent (~ 0.75 M in heptane or similar aliphatic hydrocarbon solvent; 45.6 mmol) is added by syringe. The solution is stirred at 25° as freshly distilled cyclopentadiene (6.6 g, 100 mmol) is added dropwise by syringe during 30 min. (Gas is evolved, and the mixture becomes turbid after about one-third of the cyclopentadiene

has been added). Under a positive pressure of nitrogen the septum is replaced by a stopper, and stirring is continued for 1 h. The resulting white precipitate of magnesocene (5.8 g, 82%) is isolated by filtration through a glass sinter under nitrogen.

Metallation by magnesium diisopropylamides or tetramethylpiperidides is relatively undeveloped [2, 12–14], but appears a promising alternative to metallation by the corresponding lithium amides. The reagents may be prepared by reaction of the amide with ethylmagnesium bromide [13] or, as in this example, by reaction of the lithium amide with magnesium bromide. Both the bromomagnesioamide and the magnesium bis-amide have been used.

*1-Bromomagnesio-3,5-dicyanocubane-2-(*N,N*-diisopropyl)carboxamide* (metallation by sterically hindered magnesium amide) [12]




A solution of 2,2,6,6-tetramethylpiperidine (17 ml, 0.10 mol) in THF (80 ml) is cooled to −78° as butyllithium (2.5 M in hexanes, 40 ml) is added slowly. The mixture is allowed to warm to 0° for 20 min, then recooled to −78°, and transferred by cannula to a stirred suspension of magnesium bromide etherate (26 g, 0.1 mol) in THF (60 ml) at −78°. The mixture is stirred at 0° until homogeneous, then at room temperature for 1 h, to give a solution approximately 0.5 M in bromomagnesium tetramethylpiperidide. Part of this solution (110 ml, ~10 equivalents) is added slowly to a suspension of 2,4-dicyanocubane-*N,N*-diisopropylcarboxamide (1.48 g, 5.26 mmol) in THF (30 ml) at −78°. The mixture is stirred at room temperature for 40 min.

Subsequent reaction with carbon dioxide at −78° gave the carboxylic acid (98%).

References to other selected procedures are listed in Table 3.6.

TABLE 3.6

Metallation by organomagnesium compounds

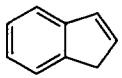
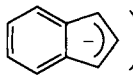
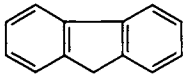
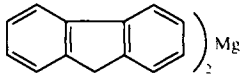
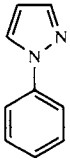
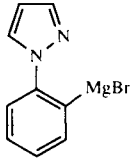
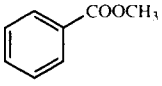
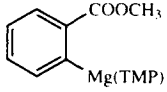
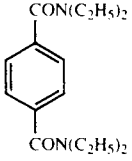
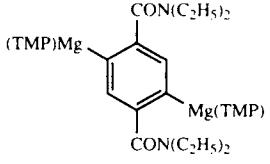
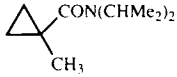
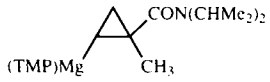
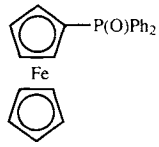
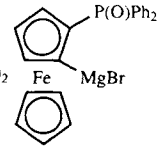
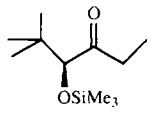
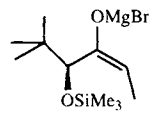
| Substrate | Metallating reagent | Product | Yield (%) | Ref. |
|---|---|---|---|---|
| $PhC{\equiv}CH$ | $Bu^nBu^sMg$ | $(PhC{\equiv}C)_2Mg$ | 93 | [15] |
| | EtMgBr | $PhC{\equiv}CMgBr$ | >75 | [16] |
| | $Pr^iMgCl$ | $PhC{\equiv}CMgCl$ | Almost quantitative | [17] |
| $CpBu^t$ | $Et_2Mg$ | $(Bu^tC_5H_4)_2Mg$ | 62 | [18][a] |
| | $Bu^nBu^sMg$ | | 40 | [19] |
| $CpSiMe_3$ | $Bu^nBu^sMg$ | $(Me_3SiC_5H_4)_2Mg$ | 88 | [20][a] |
| $C_5H_2(SiMe_3)_3$ | $Me_2Mg$ (+ TMEDA) | $(Me_3Si)_3C_5H_2MgMe{\cdot}TMEDA$ | 77 | [21][a] |
| $C_5H_2(SiMe_3)_3$ | MeMgBr (+ TMEDA) | $(Me_3Si)_3C_5H_2MgBr{\cdot}TMEDA$ | 59.5 | [21] |
| $Me_5C_5H$ | $Pr^iMgCl$ | $Me_5C_5MgCl{\cdot}THF$ | 80–90 | [22] |
|  | $Bu^nBu^sMg$ |  | 87 | [23] |
|  | $Bu^nBu^sMg$ |  | 52<br>95 | [24]<br>[25] |
| $CHCl_3$ | $Pr^iMgCl$ | $Cl_3CMgCl$ | 70[b] | [26] |
| $CHBr_3$ | $Pr^iMgCl$ | $Br_3CMgCl$ | 50[b] | [26] |
| $C_6F_5H$ | EtMgBr | $C_6F_5MgBr$ | 85[b] | [27] |
|  | EtMgBr |  | 80[b] | [28] |
|  | $Mg(TMP)_2$[c] |  | 81[b] | [2] |
|  | $Mg(TMP)_2$[c] (excess) |  | 87[b] | [2] |
|  | $Mg(TMP)_2$[c] |  | 85[b] | [2] |

TABLE 3.6 *(continued)*

| Substrate | Metallating reagent | Product | Yield (%) | Ref. |
|---|---|---|---|---|
|  | $BrMgN(CHMe_2)_2$ |  | 70[b] | [29] |
|  | BrMgTMP[c] |  | 66[b] | [3] |

[a] Other examples also described. [b] Yield of subsequent reaction. [c] TMP, 2,2,6,6-tetramethylpiperidide.

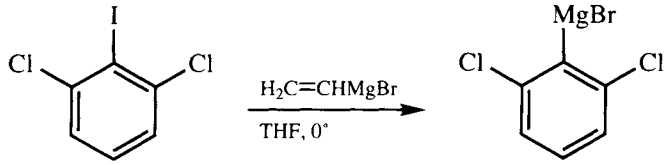
### 3.2.2 By metal–halogen exchange

$$RX + R'MgX' \rightarrow RMgX' + R'X$$

The preparation of organomagnesium compounds by metal–halogen exchange between Grignard reagents and organic halides is much less widely used than the corresponding reaction of organolithium compounds [G]. Nevertheless, it does work well for certain classes of compound, notably aryl (especially heteroaryl) bromides and iodides and 1,1-dihaloalkyl halides, $RCX_2Y$, where Y is usually Br or I, although reactions where Y is Cl are known.* As in the case of organolithium compounds [G], the reactions often proceed under conditions mild enough to preserve unstable carbenoid (or arynoid) products; an example, also involving a reactive functional group, is given below.

For the Grignard reagent, ethylmagnesium bromide or isopropylmagnesium chloride has usually been employed. In order to avoid Wurtz-type coupling, vinylmagnesium bromide has been advocated, the vinyl halide formed being unreactive towards the arylmagnesium halide formed [31]. Surprisingly, the use of two equivalents of t-butylmagnesium halide, leading to "self-destruction" of the

*The formation of "α-haloenolates" by metal–halogen exchange between isopropylmagnesium chloride and α,α-dichlorocarbonyl compounds such as $XCl_2CCOOR$, where X = Cl, COR or COOR [30] may be noted.




halide produced, has not been explored in the case of Grignard reagents (cf. reactions with t-butyllithium [32]).

$$RX + 2Bu^tMgX' \rightarrow RMgX' + Bu^tX + Bu^tMgX'$$
$$Bu^tX + Bu^tMgX' \rightarrow CH_2{=}C(CH_3)_2 + Bu^tH + MgXX'$$

Most reactions have been carried out in diethyl ether or THF, but the use of dichloromethane has been advocated [33].

Representative procedures follow, and other examples are listed in Table 3.7.

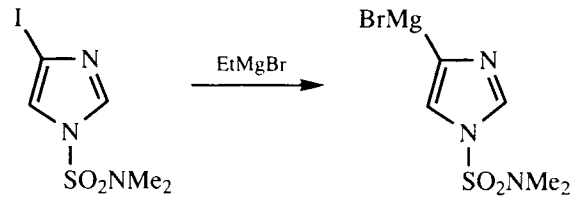
*An ω-fluorosulfonylmagnesium bromide (perfluoro-5-fluorosulfonyl-3-oxapentylmagnesium bromide)* [34]

$$FSO_2CF_2CF_2OCF_2CF_2I + EtMgBr \rightarrow FSO_2CF_2CF_2OCF_2CF_2MgBr + EtI$$

A solution of ethylmagnesium bromide (20 mmol) in diethyl ether (180 ml), is placed in a three-necked round-bottomed flask, fitted with a stirrer and a pressure-equalizing dropping funnel and furnished with an inert atmosphere. The solution is cooled to −78° and stirred as tetrafluoro-1-fluorosulfonyl-5-iodo-3-oxapentane (6.0 g, 14 mmol) is added dropwise at such a rate that the temperature does not exceed −70°. Stirring is continued for 3 h, after which time the metal–halogen exchange is complete. The resulting Grignard reagent is stable at −30° for at least 3 h.

As well as illustrating the preparation of a heterocyclic Grignard reagent by metal–halogen exchange, the following procedure is an example of the use of dichloromethane as the solvent.

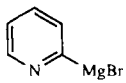
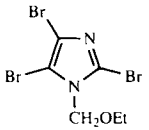
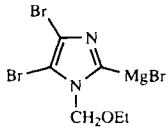
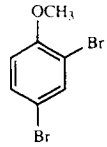
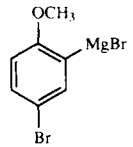
*1-(Dimethylsulfamoyl)imidazol-4-ylmagnesium bromide* [35]



Ethylmagnesium bromide (3 M in ether, 13.3 ml, 39.9 mmol) is introduced during 5 min into a solution of 1-dimethylsulfamoyl-4-iodoimidazole (10.0 g, 33.2 mmol) in dichloromethane (100 ml) at room temperature, and the mixture is left for 1 h.

TABLE 3.7

Metal–halogen exchange between Grignard reagents and organic halides

| Organic halide | Grignard reagent (solvent) | Product (yield, %) | Ref. |
|---|---|---|---|
| $CCl_4$ | $Pr^iMgCl$ (THF) | $Cl_3CMgCl$ (60) | [26] |
| $CHI_3$ | $Pr^iMgCl$ (THF) | $I_2CHMgCl$ (72) | [36] |
| $CH_2I_2$ | $Pr^iMgCl$ (THF) | $ICH_2MgCl$ (70) | [26] |
| $F_2C{=}CFI$ | EtMgBr ($Et_2O$) | $F_2C{=}CF_2MgBr$ (high) | [37] |
| $C_2F_5I$ | EtMgBr ($Et_2O$) | $C_2F_5MgBr$ (80) | [38] |
| $Me_3SiCBr_3$ | $Pr^iMgCl$ (THF) | $Me_3SiCBr_2MgCl$ (50–60) | [39] |
|  | EtMgBr(THF) |  (91)[a,b] | [40] |
| $C_6Br_6$ | PhMgBr (THF) | $C_6Br_5MgBr$ (high)[c] | [41] |
| $C_6F_5Cl$ | EtMgBr (THF) | $C_6F_5MgBr$ (85) | [42] |
|  | EtMgBr($Et_2O$) |  (80) | [43] |
|  | $Pr^iMgCl$(THF) |  (93) | [44] |
| n-$C_6H_{13}CF{=}CFBr$ | PhMgBr ($Et_2O$) | n-$C_6H_{13}CF{=}CFMgBr$ (80) | [45] |
| n-$C_8F_{17}I$ | PhMgBr ($Et_2O$) | n-$C_8F_{17}MgBr$ (almost quantitive) | [37, 46] |

[a]Preparation of 3- and 4-pyridylmagnesium halides also described. [b]Grignard reagents have been prepared similarly by metal–halogen exchange between isopropylmagnesium bromide and various bromofurans, thiophenes and selenophenes [47]. Solid pyridylmagnesium halides have been isolated following metal–halogen exchange reactions of halopyridines with phenylmagnesium bromide [48]. [c]With an excess of ethylmagnesium bromide, some 1,4-di-Grignard reagent was obtained [49].

A subsequent reaction with benzaldehyde gave 1-[1-(dimethylsulfamoyl)imidazol-4-yl]-1-phenylmethanol (83%).

### 3.2.3 By hydromagnesiation

Thirty years ago it was reported that reactions of Grignard reagents with 1-alkenes, catalysed by titanium tetrachloride, lead to organomagnesium compounds, formally derived by addition of HMgX to the carbon–carbon double bond [50, 51], e.g.

$$CH_3CH_2CH_2CH=CH_2 \xrightarrow[TiCl_4]{PrMgBr} CH_3CH_2CH_2CH_2CH_2MgX$$

The reaction has since been extended to a variety of alkenes (including dienes and styrenes) and alkynes [52, 53], and it has been established that the hydrogen atoms transferred are β-hydrogen atoms from the Grignard reagent.

Dicyclopentadienyltitanium dichloride is possibly superior to titanium tetrachloride as a catalyst. Nickel(II) compounds are also active, but with these catalysts concurrent addition of the organomagnesium compounds to carbon–carbon multiple bonds (see Section 4.1) causes complications. Examples of hydromagnesiation by Grignard reagents are listed in Table 3.8. As will be seen from entries in Table 3.8, the stereochemistry of addition to alkynes is *syn*. The regiochemistry is also usually predictable; in the relevant examples in Table 3.8, one regioisomer is obtained mainly or exclusively. In other cases, however, mixtures are formed [54].

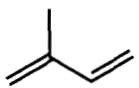
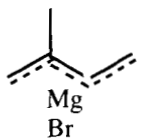
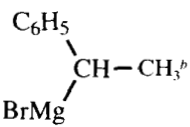
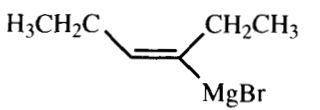
More recently, a related reaction has been reported, in which active forms of magnesium hydride, prepared *in situ* or pre-prepared, undergo addition to alkenes, catalysed by titanium or zirconium(IV) halides, to give dialkylmagnesium compounds [56, 59, 64]:

$$2RCH=CH_2 + MgH_2 \xrightarrow[\text{or } Cp_2TiCl_2]{ZrCl_4} (RCH_2CH_2)_2Mg$$

These reactions give high yields with 1-alkenes, as shown, but are less satisfactory with alkynes or non-terminal alkenes. Examples of these reactions are also given in Table 3.8, and procedures for hydromagnesation by both Grignard reagents and magnesium hydride follow.

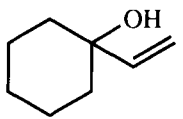
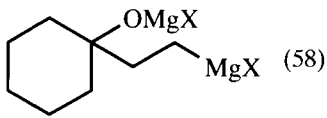
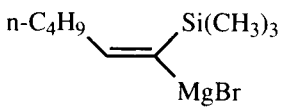
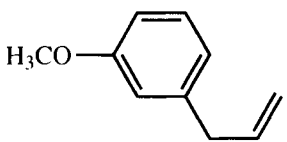
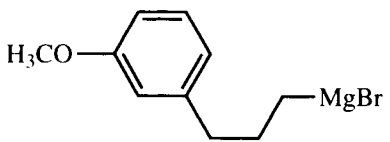
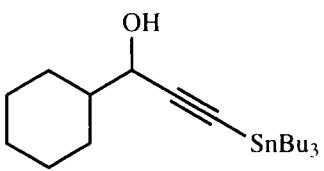
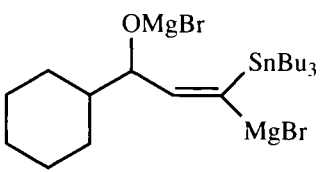
TABLE 3.8

Preparation of organomagnesium compounds by hydromagnesiation[a]

| Substrate | Source of "HMgX" | Catalyst | Product (yield, %) | Ref. |
|---|---|---|---|---|
| $CH_2=CH_2$ | $MgH_2$ | $TiCl_4$ | $(CH_3CH_2)_2Mg$ (97) | [55, 56] |
| $CH_3CH_2CH=CH_2$ | $MgH_2$ | $TiCl_4$ | $(CH_3CH_2CH_2CH_2)_2Mg$ (86) | [55, 56] |
|  | $Pr^nMgBr$ | $Cp_2TiCl_2$ |  (95) | [57] |
| $CH_3OCH_2CH_2CH=CH_2$ | $MgH_2$ | $ZrCl_4$ | $(CH_3OCH_2CH_2CH_2CH_2)_2Mg$ (35) | [58] |
| $(CH_3)_2NCH_2CH_2CH=CH_2$ | $MgH_2$ | $ZrCl_4$ | $[(CH_3)_2NCH_2CH_2CH_2CH_2]_2Mg$ (51) | [58] |
| $C_6H_5CH=CH_2$ | $MgH_2$ | $Cp_2TiCl_2$ |  (high) | [57, 59] |
| $CH_3CH_2C{\equiv}CCH_2CH_3$ | $Bu^iMgBr$ | $CpTiCl_2$ |  (90) | [54] |

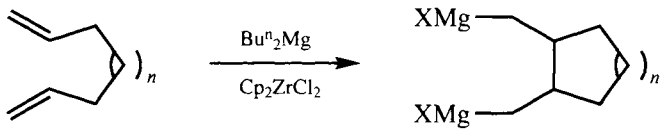
*(continued on next page)*

TABLE 3.8 *(continued from previous page)*

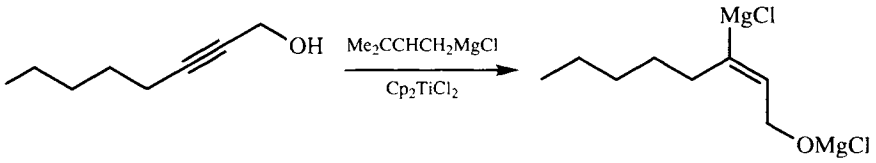
| Substrate | Source of "HMgX" | Catalyst | Product (yield, %) | Ref. |
|---|---|---|---|---|
|  | EtMgBr | $Cp_2TiCl_2$ |  (58) | [60] |
| $n\text{-}C_6H_{13}CH{=}CH_2$ | $MgH_2$ | $ZrCl_4$ | $(n\text{-}C_8H_{17})_2Mg$ (87) | [55, 56] |
| $n\text{-}C_4H_9C{\equiv}CSi(CH_3)_3$ | $Bu^tMgBr$ | $Cp_2TiCl_2$ |  (87) | [61] |
|  | $Pr^nMgBr$ | $TiCl_4$ |  (60)[c] | [62] |
|  | $Bu^tMgBr$ | $Cp_2TiCl_2$ |  (75) | [63] |

[a] See also table in ref. [53]. [b] Together with ~ 10% of regioisomer. [c] Some isomerization also observed

In an interesting extension, hydromagnesiation of 1,6-heptadiene and 1,7-octadiene is reported, though without full experimental details, to result in cyclization [65]:




*Hydromagnesiation of oct-2-yn-1-ol* [53]




A 500 ml three-necked flask is fitted with a pressure-equalizing dropping funnel and a stopper, and furnished with a magnetic stirrer bar and an inert atmosphere. Isobutylmagnesium chloride (0.75 M in ether, 320 mol, 240 mmol) is placed in the flask and cooled by means of an ice-water bath. Dicyclopentadienyltitanium dichloride (1.3 g, 5.2 mmol) is added, and the solution is stirred at 0° for 10 min. A solution of oct-2-yn-1-ol (13.2 g, 105 mmol) is added to the cooled solution dropwise from the dropping funnel during 20 min, and the resulting solution is stirred at room temperature for 4 h.

The yield of a subsequent reaction was 86%.

*Bis[3-(*N,N*-dimethylamino)propyl]magnesium* [58]

$$2Me_2NCH_2CH{=}CH_2 + MgH_2 \longrightarrow (Me_2NCH_2CH_2CH_2)_2Mg$$

A 250 ml three-necked flask is fitted with an efficient reflux condenser and furnished with a magnetic stirrer bar and an inert atmosphere. A suspension of magnesium hydride (100 mmol) in THF (~ 50 ml), prepared by catalytic hydrogenation of magnesium, is placed in the flask by means of a metal U tube. Zirconium tetrachloride (0.23 g) and 3-dimethylaminoprop-1-ene (allyldimethylamine) (18.8 g, 220 mmol) are added and the mixture is stirred and heated under reflux for 48 h. The suspension is filtered through a glass sinter, and THF and unreacted amine are evaporated from the filtrate *in vacuo*. Sublimation from the dark,

viscous residue ($10^{-3}$ mbar, 60°) gives the title compound as white, extremely air-sensitive needles (8.5 g, 43%), m.p. 113–115°.

### 3.2.4 Miscellaneous preparations from other organomagnesium compounds

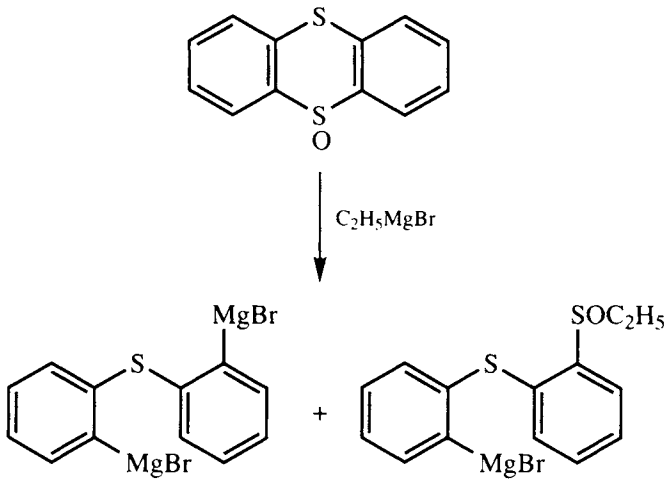
Reactions between organomagnesium compounds and sulfoxides can be complex (see Sections 8.3.3, 13.2), but in favourable cases the equilibrium

$$R^1S(O)R^2 + R^3MgX \rightleftharpoons R^1MgX + R^3S(O)R^2$$

can give useful yields of the new Grignard reagent, $R^3MgX$. Experimental details are sparse, but the reaction has been applied to the preparation of 3- and 4-pyridyl- and 4-quinolylmagnesium bromides [66], 2-bromo- and 2-chlorophenylmagnesium bromides [67] and 2-phenylthio, 2-phenylsulfinyl- and 2-phenylsulfonylphenylmagnesium bromides [68]. The equilibrium also lies to the right with alkynyl sulfoxides [69]:

$$R^1C{\equiv}CS(O)R^2 + R^3MgBr \longrightarrow R^1C{\equiv}CMgBr + R^2S(O)R^3$$

This type of reaction has been used to prepare a di-Grignard reagent, though in this case a side-reaction competes [68]:




(up to 55%)

Transmetallation reactions of Grignard reagents with other organometallic compounds are rare. An example is shown here [70]; other transmetallations have been briefly reported [71].

$$(C_6H_5)_2SiHMe \xrightarrow{2RMgX} C_6H_5MgX + C_6H_5SiH(Me)R + R_2SiHMe$$

up to 73%

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## 3.3 PREPARATION FROM ORGANOALKALI METAL COMPOUNDS

The reactions covered in this section may be represented for convenience by equations (1)–(3). It should be emphasized, however, that these equations are in many cases oversimplified; indeed, in many of the examples reported, the reagent produced is used *in situ*, and its constitution is undetermined.

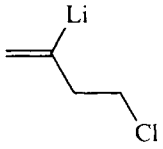
$$RM + MgX_2 \longrightarrow RMgX + MX \quad (1)$$

$$RM + R'MgX \longrightarrow RMgR' + MX \quad (2a)$$
$$\text{or } 2RM + MgX_2 \longrightarrow R_2Mg + 2MX \quad (2b)$$

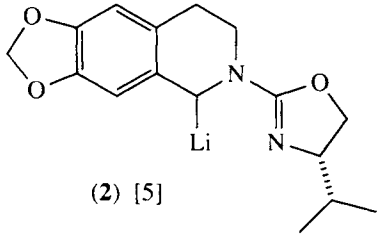
$$RM + R'_2Mg \longrightarrow MMgRR'_2 \quad (3)$$

### 3.3.1 Preparation of "Grignard reagents" (equation (1))

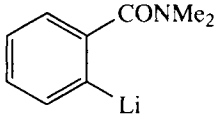
The preparation of organomagnesium reagents by the addition of one equivalent of a magnesium halide to a solution of an organoalkali metal compound is a commonly used procedure, giving products which certainly resemble conventional Grignard reagents in their reactions. The procedure is most commonly applied to organolithium compounds [G], though examples involving organosodium [1] and organopotassium compounds [2, 3] have been described. Some recent examples of organolithium compounds which have been converted into "Grignard reagents" are represented by formulae **(1)–(4)**. For these examples,



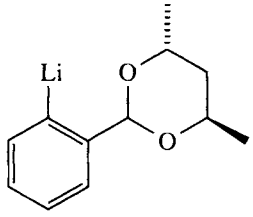

(**1**) [4]




(**2**) [5]




(**3**) [6]




(**4**) [7]

magnesium bromide was used; the use of magnesium chloride [2, 8] and magnesium iodide [9] has been described, but for practical purposes magnesium bromide is preferred, since it is readily prepared in anhydrous form (often *in situ*). Three methods for this preparation are available: from bromine and magnesium (e.g. in ether [10] or THF [11]), from mercury (II) bromide and magnesium (e.g in ether–benzene [12] or THF [13]), and from 1,2-dibromo+ethane and magnesium (e.g. in ether [14] or ether–benzene [15]).

*Magnesium bromide, THF complex* [11] A solution of bromine (1.45 g, 9.1 mmol) in dry THF is added by syringe to a suspension of magnesium turnings (0.33 g, 13.8 mmol) in dry THF (10 ml) under an inert atmosphere. A vigorous reaction occurs, and a two-phase system develops, with a clear upper layer and pale-orange lower layer. The entire mixture may be used, or alternatively the upper layer is removed by syringe and its volume noted. The remaining orange layer typically contains magnesium bromide (~ 5 mmol) in THF (~ 4 ml).

### 3.3.2 Preparation of dialkylmagnesium compounds (equations (2) and (2a))

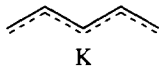
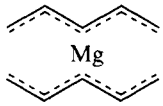
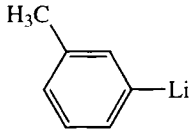
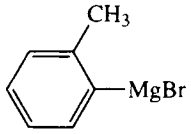
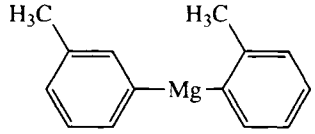
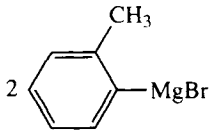
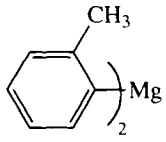
The reactions represented by equations (2) and (2a) have both been used to prepare symmetrical dialkylmagnesium compounds; examples are listed in Table 3.9. Under suitable conditions good results may be obtained, though alternative routes are available for these compounds (see for example Section 3.4.1). The reaction of equation (2) may also be used to prepare *unsymmetrical* dialkylmagnesium compounds, for which few alternative methods are available. Examples of these reactions are also included in Table 3.9. It must be noted, however, that the products of such reactions may consist of mixtures, resulting from ligand exchange processes.* For example, while the product of the procedure described below is largely n-butyl(s-butyl)magnesium, both di-n-butylmagnesium and di-s-butylmagnesium are also present (together with small amounts of octylmagnesium species).

The following procedure gives the useful hydrocarbon-soluble metallating reagent referred to in Section 3.2.1 (see also Table 3.1, p. 22). It is more complicated than procedures described earlier [18], but gives a reagent which is less liable to precipitation on storage.

*Possibly via 'ate complexes; it is noteworthy that the reverse of equation (3) has been reported [16].

TABLE 3.9

Preparation of dialkylmagnesium compounds from organoalkali metal compounds

| Organoalkali metal compound | Magnesium component[a] | Product | Ref. |
|---|---|---|---|
| $Bu^SLi$ | $MgCl_2$ | $Bu^S{}_2Mg$ | [18] |
|  | $MgBr_2$ |  | [2] |
| PhLi | PhMgBr | $Ph_2Mg$ | [19] |
|  |  |  | [19] |
|  | $MgCl_2$ |  | [19] |

[a]An interesting example of the use of a hindered magnesium phenoxide has been reported, though without experimental details [20].

*"n-Butyl(s-butyl)magnesium"* [17] A 1 litre four-necked flask is fitted with an efficient sealed mechanical stirrer, a condenser, a pressure-equalizing dropping funnel and a thermometer, and furnished with an inert atmosphere. A mixture of 1-chlorobutane (66.3 ml, 58.3 g, 0.63 mol) and 1-chlorooctane (11.65 ml, 10.4 g, 0.07 mol) and an aliphatic hydrocarbon solvent (e.g. octanes, 78 ml) is placed in the dropping funnel. Magnesium powder (preferably ~ 100 mesh; 20 g) and the aliphatic hydrocarbon solvent (500 ml) are placed in the flask, together with a small amount of s-butyllithium solution or of the product from a previous run. The mixture is heated to boiling and the heat is turned off. When refluxing has ceased, 10 ml of the mixture from the funnel is added rapidly. When an exothermic reaction starts, the remainder of the mixture from the funnel is added at such a rate as to maintain refluxing. When the addition is complete, the mixture is stirred and heated under reflux for 45 min. The

viscous mixture is allowed to cool to 50–60°, and s-butyllithium (~ 1.1 M in hydrocarbon, 0.56 mol) is added during 30 min. The resulting mixture is stirred for 45 min, and filtered through a glass sinter under an inert atmosphere. The filter is washed with the hydrocarbon solvent. In the run described [17], the combined filtrate and washings (1385 ml) were 0.77 M in Mg, representing a yield of 85%.

### 3.3.3 Preparation of magnesium 'ate complexes (equation (3))

The reaction represented by equation (3) is fairly general, and several complexes with the stoichiometry $MMgR_3$ have been isolated and characterized [D]; an example is $LiMgPh_3$, as a dimeric TMEDA complex [21]. An alternative method for preparing such complexes in solution is the reaction of an alkali metal with a dialkylmagnesium [22]:

$$2M + 3MgR_2 \longrightarrow 2MMgR_3 + Mg$$

However, a range of other stoichiometries is possible [D], and $Na_2MgPh_4$, for example, has been characterized as its PMDETA complex [23]. Remarkably, some magnesium 'ate complexes, e.g. $NaMgBu^nBu^s_2$, are soluble in hydrocarbons [24].

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## 3.4 PREPARATION BY LIGAND EXCHANGE ON RMgX

Covered in this section are processes which result in the substitution of the ligand X in an organomagnesium compound, RMgX:

$$RMgX \longrightarrow RMgY$$

For application in synthesis, the most important of these are those where X = halogen and Y = alkyl: the transformation of Grignard reagents into dialkylmagnesium compounds. Other transformations of this type are valuable for preparing alkylmagnesium hydrides (Y = H), alkoxides (Y = OR′), carboxylates (Y = OCOR′), amides (Y = $NR'_2$, thiolates (Y = SR′), etc., but since most of these products are not extensively employed in synthesis these transformations are summarized only briefly.

### 3.4.1 Preparation of dialkylmagnesium compounds

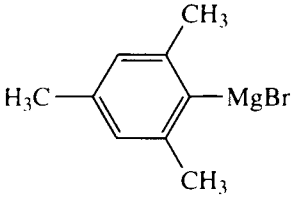
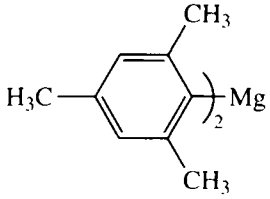
As noted in Section 2.1.2, Grignard reagents in solution may be described in terms of the Schlenk equilibrium (or modifications), represented in its simplest form by

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

If this type of equilibrium is displaced to the right by selective precipitation of magnesium halide, a solution of the dialkylmagnesium compound should result. Such selective precipitation does sometimes occur, notably from hydrocarbon solutions (see, for example, p. 6 [1]), but it is rarely sufficiently selective and/or complete to provide a useful method for obtaining dialkylmagnesium compounds. However, certain additives have been found to achieve the desired result. Of these, pyridine [2] is not recommended because of the risk of attack on the pyridine ring

TABLE 3.10

Preparation of dialkylmagnesium compounds by dioxane precipitation

| Grignard reagent | Product | Ref. |
|---|---|---|
| $CH_3CH_2MgBr$ | $(CH_3CH_2)_2Mg$ | [8–10] |
| $CH_2{=}C(CH_3)CH_2MgCl$ | $(CH_2{=}C(CH_3)CH_2)_2Mg$ | [11] |
| $(CH_3)_3CMgCl$ | $[(CH_3)_3C]_2Mg$ | [12] |
| $(CH_3)_3CCH_2MgCl$ | $[(CH_3)_3CCH_2]_2Mg$ | [13] |
| $C_6H_5MgBr$ | $(C_6H_5)Mg$ | [8] |
| n-$C_8H_{17}MgCl$[a] | (n-$C_8H_{17})_2Mg$ | [1] |
|  |  | [14] |
| $C_6H_5C(CH_3)_2CH_2MgCl$ | $(C_6H_5C(CH_3)_2CH_2)_2Mg$ | [13] |

[a] The Grignard reagent, prepared in heptane, had a low chloride content, but this was reduced still further by the addition of dioxane.

(see p. 96); TMEDA [3] probably has only limited applicability; glymes ($MeO(CH_2CH_2O)_nMe$) appear to be good, but are still relatively untried [4, 5]; only 1,4-dioxane so far gives consistently acceptable results for a range of organic groups, as listed in Table 3.10.* Two aspects of the dioxane precipitation method should be noted: some organomagnesium species may be initially coprecipitated, and prolonged stirring may be required to achieve the desired result; and the precipitated magnesium halide complex may be very finely divided, necessitating centrifugation before filtration or decantation. It should also be noted that traces of halide may remain in solution.

*A variant is the interaction of dioxane with a di-Grignard reagent, giving a solution of a 'magnesacycloalkane' [6].

*Bis(trimethylsilylmethyl)magnesium* [7] (CAUTION: 1,4-dioxane is a suspected carcinogen.) Trimethylsilylmagnesium chloride (0.45 mol) in diethyl ether (~ 500 ml) is placed in a 1 litre three-necked flask, equipped with a pressure-equalizing dropping funnel, a mechanical stirrer and a stopper, and furnished with an inert atmosphere. 1,4-Dioxane (freshly distilled from sodium under nitrogen) (45 ml, 0.52 mol) is added dropwise with rapid stirring during 1–2 h. The dropping funnel is replaced by the inert gas inlet, and the white suspension is stirred rapidly for 12 h. The suspension is transferred to centrifuge tubes via 2.5 mm stainless steel tubing and centrifuged (~ 2500 rpm, 30 min). The colourless supernatant liquid is transferred via stainless steel tubing to a 500 ml flask equipped with a magnetic stirrer bar, and the diethyl ether is evaporated from the stirred solution *in vacuo*. Diethyl ether (100 ml) is added to the white solid in the centrifuge tubes, and the resulting suspension is centrifuged, and the supernatant liquid is transferred to the 500 ml flask. The ether is removed *in vacuo* to leave the product as a white, solid dioxanate. The dioxane is removed if the solid is heated at 100–140°/$10^{-2}$ torr for 24 h. The residue may then be dissolved in diethyl ether (200 ml) to give a solution containing 70–80% yield of bis(trimethylsilylmethyl)magnesium.

### 3.4.2 Ligand exchange between dialkylmagnesium compounds

Exchange of organic ligands between dialkylmagnesium compounds occurs more or less rapidly, depending on the conditions and on the presence of, for example, metal salts [15]:

$$R_2Mg + R'_2Mg \rightleftharpoons 2RMgR'$$

In a few cases the equilibrium lies (or is displaced by precipitation) well to the right, and the reaction becomes of preparative value:

$$Cp_2Mg + R_2Mg \longrightarrow 2CpMgR$$

(R = $CH_3$ [15], $CH_3CH_2$ [16], $CH_2{=}CHCH_2$ [16], $(CH_3)_3CCH_2$ [17], $C_6H_5$ [15])

$$(CH_3CH_2)_2Mg + (ROCH_2CH_2CH_2CH_2)_2Mg \longrightarrow 2CH_3CH_2MgCH_2CH_2CH_2CH_2OR \text{ [18]}$$

$$(CH_3CH_2)_2Mg + (R_2NC_nH_{2n})_2Mg \longrightarrow 2CH_3CH_2MgC_nH_{2n}NR_2 \text{ [18]}$$

### 3.4.3 Preparation of alkylmagnesium hydrides

Although alkylmagnesium hydrides may well be intermediates in a number of reactions of organomagnesium compounds [19, D], methods for preparing them in pure form, even in solution, are limited. Reduction of organomagnesium compounds by compounds such as lithium aluminum hydride commonly gives mainly magnesium hydride, though in THF, solutions containing $CH_3MgH$, $C_6H_5MgH$ or $C_6H_5Mg_2H_3$ may be obtained [20, 21].

$$4R_2Mg + LiAlH_4 \longrightarrow 4RMgH = LiAlR_4$$

$$2(C_6H_5)_2Mg + LiAlH_4 \longrightarrow C_6H_5Mg_2H_3 + LiAlH(C_6H_5)_3$$

The pure hydrides may be obtained by reactions of dialkylmagnesium compounds with active magnesium hydride, and isolated as solvated solids [21].

### 3.4.4 Preparation of RMgX, where X is an oxygen, nitrogen or sulfur ligand

Although other methods are available for synthesizing alkylmagnesium dialkylamides, alkoxides and thiolates, the reaction of a dialkylmagnesium compound with a secondary amine, an alcohol, or a thiol, provides a convenient general method. Some examples are summarized in Table 3.11.

$$R_2Mg + HX \longrightarrow RMgX + RH$$
$$(X = NR'_2, OR', SR')$$

A convenient alternative procedure for alkylmagnesium alkoxides, which avoids the sometimes tedious preparation of a dialkylmagnesium compound, is the reaction of an alkyl chloride, magnesium and an alcohol, in a medium (such as a hydrocarbon) in which magnesium chloride is insoluble [28].

$$2RCl + 2Mg + R'OH \longrightarrow RMgOR' + RH + MgCl_2$$

The Schlenk-type equilibrium

$$R_2Mg + MgX_2 \rightleftharpoons 2RMgX$$
$$(X = NR'_2, OR', SR')$$

TABLE 3.11

Preparation of alkylmagnesium dialkylamides, alkoxides and thiolates

$$R_2Mg + HX \longrightarrow RMgX^a + RH$$
$$(X = NR'_2, OR', SR')$$

| R | X | Ref. |
|---|---|---|
| $CH_3$ | Various $NR'_2$ | [22] |
| $CH_3$ | $N(CH_3)CH_2CH_2N(CH_3)_2$ | [23] |
| $CH_3CH_2$ | Various $NR'_2$[b] | [24] |
| $(CH_3)_2CH$ | Various $NR'_2$ | [24] |
| $C_6H_5$ | Various $NR'_2$[c] | [22] |
| $C_6H_5CH_2$ | Various $NR'_2$ | [22] |
| $CH_3$ | $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OC(CH_3)_3$[d] | [25] |
| $CH_3CH_2$ | Various OR' | [26] |
| $(CH_3)_2CH$ | $OCH_3$,$OCH_2CH_3$,$OCH(CH_3)_2$ | [26] |
| $CH_3$ | $SC(CH_3)_3$,$SCH_2CH_2N(CH_3)_2$ | [27] |
| $CH_3CH_2$ | $SC(CH_3)_3$ | [27] |
| $(CH_3)_3C$ | $SCH(CH_3)_2$,$SCH_2CH_2N(CH_3)_2$ | [27] |

[a]This formula merely indicates the stoichiometry; the products are almost invariably associated and/or solvated. [b]With dimethylamine, only magnesium bis(dimethylamide) is obtained. [c]Full experimental details given for phenylmagnesium diisopropylamide. [d]Disproportionates in dilute solution in benzene [26].

often lies to the left (see, for example, footnotes *b* and *d* to Table 3.11). However, one or two examples have been reported where the equilibrium lies to the right, giving alkylmagnesium alkoxides:

$$(CH_3)_2Mg + Mg(OC(CH_2CH_3)_2CH_3)_2 \longrightarrow 2CH_3MgOC(CH_2CH_3)_2CH_3 \quad [15]$$

$$Cp_2Mg + Mg(OCH_2CH_3)_2 \longrightarrow 2CpMgOCH_2CH_3 \quad [16]$$

Another general method is the reaction of Grignard reagent with an anion:

$$RMgX + M^+Y^- \longrightarrow RMgY + MX$$

This method has been applied to the preparation of alkylmagnesium alkoxides (with sodium alkoxides) [29], carboxylates (with sodium carboxylates) [30], acetylacetonates (with sodium acetylacetonate) [29],

and thiocyanates and selenocyanates (with potassium thiocyanate or selenocyanate) [31].

Recently, the reaction of organolithium compounds with magnesium carboxylates or sulfonates has been used to prepare organomagnesium compounds with increased selectivity towards carbonyl compounds (see Section 6.1) [32].

$$\mathrm{RLi} + \mathrm{MgY_2} \longrightarrow \mathrm{RMgY} + \mathrm{LiY}$$
$$(\mathrm{Y} = \mathrm{OCOR'}, \mathrm{OSO_2R'})$$

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30. See Section 2.1, Ref. [4].
31. See Section 2.1, Ref. [7].
32. See Section 2.1, Ref. [5].

## 3.5 OTHER METHODS FOR PREPARING ORGANOMAGNESIUM COMPOUNDS

A number of reactions of organomagnesium compounds, giving rise to new organomagnesium compounds, are covered in other chapters. They include addition to carbon–carbon multiple bonds (see Chapter 4), addition to isonitriles (see Section 5.4), addition to carbon monoxide (see Section 6.5), thiophilic addition to carbon–sulfur double bonds (see Chapter 7) and addition to carbenes (see Section 9.1).

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# —4—

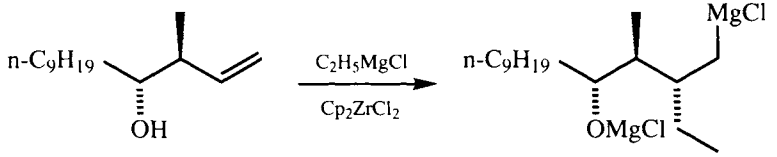
# Addition of Organomagnesium Compounds to Carbon–Carbon Multiple Bonds

## 4.1 ADDITION TO ALKENES AND ALKYNES

Although some uncatalysed addition reactions of organomagnesium compounds with ethene, non-conjugated terminal ethenes and alkynes have been reported [D, E, 1–5], they are of limited use in synthesis, with certain exceptions, described below. Moreover, organomagnesium compounds, in contrast to organolithium compounds [E, 6], have not been much used as initiators for polymerizing dienes.* Attempts to catalyse the addition of organomagnesium compounds to alkenes and alkynes by titanium, zirconium and nickel derivatives were not very successful: with alkylmagnesium compounds bearing β-hydrogen atoms, hydromagnesiation tended to predominate (see Section 3.2.3), and with other organomagnesium compounds low yields and/or mixtures were usually obtained [11]. However, it now appears that under catalysis by dicyclopentadienylzirconium dichloride, carbomagnesiation of 1-alkenes by ethylmagnesium compounds is fairly general [12], and can give good yields under carefully controlled conditions [13, 14]. Neighbouring group participation by hydroxyl groups may be observed, and can influence both the regiochemistry and the stereochemistry of the addition [15, 16], and recently asymmetric addition catalysed by a chiral zirconium catalyst has been reported [17].

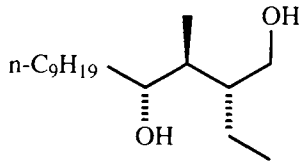
*Active polymerization catalysts have been derived from organomagnesium compounds, for example by reaction with titanium (IV) chloride [7]; the polymerization of various vinyl monomers has been initiated by organomagnesium compounds [8]; and recently polymerization initiated by magnesium 'ate complexes has been described [9, 10].

*4-(Chloromagnesiooxy)-2-ethyl-3-methyltridecylmagnesium chloride* [16]



A solution of *anti*-4-hydroxy-3-methyltridec-1-ene (850 mg, 4.0 mmol) in ether (20 ml) is cooled to 0° as ethylmagnesium chloride (1 M, 20 ml, 20 mmol) is added dropwise by syringe. The mixture is allowed to warm to 20° and dicyclopentadienylzirconium dichloride (58.4 mg, 0.2 mmol) is added. The mixture is stirred at about 25° for 12 h.

A subsequent reaction with trimethyl borate followed by hydrogen peroxide (see Section 15.1) gave the alcohol **(1)** (72%), with over 95% with the relative stereochemistry shown [16].



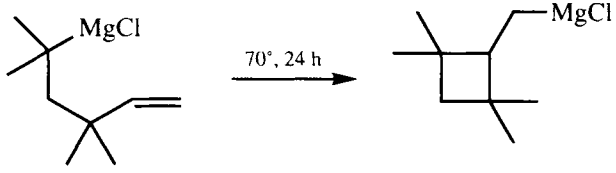

**(1)**

Copper(I) catalysis of the addition of organomagnesium compounds to alkynes has been observed, but stoichiometric organocopper reagents, derived from organomagnesium compounds, are more effective in the absence of other activating features [4].

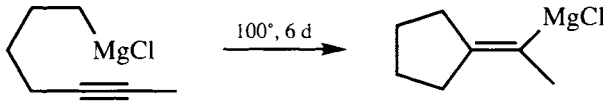
Reactions involving conjugate addition of organomagnesium compounds to α,β-unsaturated carbonyl compounds, nitriles, etc., are of course useful, and are described in connection with the relevant functional groups. (On the other hand, addition to aromatic rings, conjugated with electron-withdrawing groups, is covered in Section 4.2).

There are three important exceptions to the generalization which opens this chapter: (a) intramolecular additions, (b) additions to alkenes and alkynes bearing n-donor substituents able to provide anchimeric assistance, and (c) addition of allymagnesium derivatives. These beneficial features may operate alone or together.

(a) Intramolecular addition of non-allylic organomagnesium groups to carbon–carbon multiple bonds often gives rise to mixtures of cyclized products and/or rearranged open-chain products [D, E, 4, 18, 19]. However, in favourable cases one product may be obtained in high yield, though slowly, as in the example reactions shown. (Intramolecular additions of *allylic* organomagnesium groups are discussed under paragraph (c)).

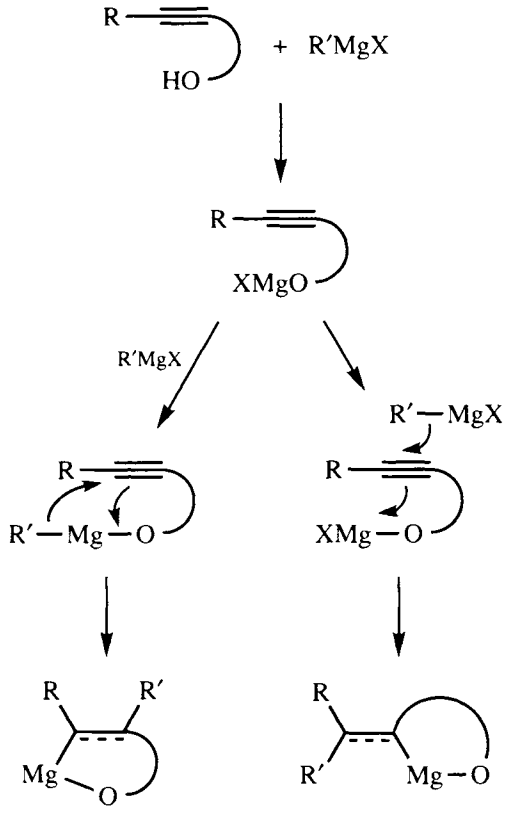



[20]



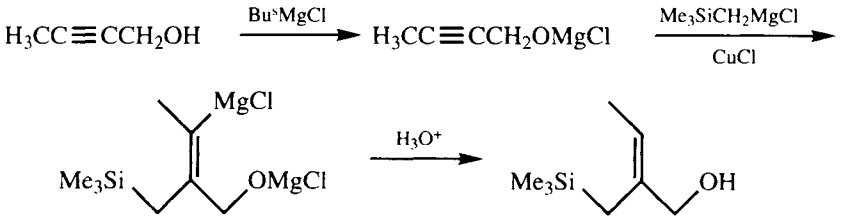

[21]

(b) Some activation of carbon–carbon bonds to addition by organomagnesium compounds is provided by suitably placed substituents, capable of coordination to magnesium. The most effective activating subtituents are α-oxide groups (arising from deprotonation of allyl/propargyl alcohols) [22–25]. α-Dialkylamino groups are moderately effective [24, 26–28], α-alkoxy groups are less so [27, 29], and α-alkylthio groups are only weakly activating [29]. β-Oxido groups are weakly activating [22, 23, 30], but more remote substituents have little or no effect in acyclic systems [23, 25]. In these reactions, allylmagnesium compounds are more reactive than alkyl- or vinyl magnesium compounds, but in the last cases, copper(I) catalysis is effective, as in the following procedure.



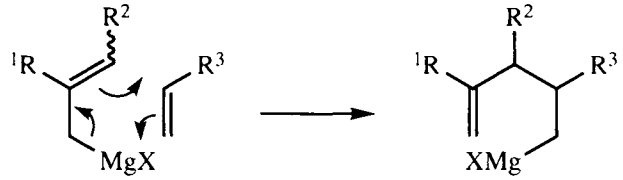
For the uncatalysed reactions of the propargyl alkoxides in weakly electron-donating solvents, the regiochemistry is largely determined by the effect of the oxido group, and the products are formulated as oxamagnesiacyclopentanes. However, both *syn* and *anti* stereochemistry have been reported, and rationalized by the mechanisms shown. Under the influence of copper(I) catalysis, however, both the regio- and the stereochemistry may be modified. (When small amounts of the regioisomer are formed, elimination leads to an allene).

*(Z)-2-(Trimethylsilylmethyl)but-2-en-1-ol* [31]

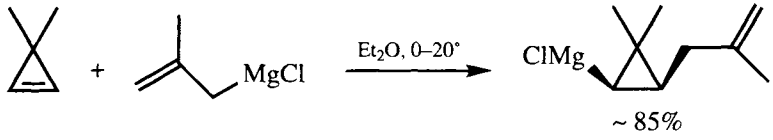



s-Butylmagnesium chloride (2.0 M in diethyl ether, 25 ml, 50 mmol) is added to ether (120 ml). The solution is cooled to −20° as but-2-yn-1-ol (3.5 g, 3.8 ml, 50 mmol) is added slowly by syringe, and the solution is stirred at −20° for 10 min. Stirring and cooling is continued as copper(I) chloride (0.50 g, 5 mmol) is added in one portion, quickly followed by trimethylsilylmethylmagnesium chloride (~ 0.7 M in diethyl ether, 50 mmol), by cannula. The mixture is stirred at room temperature for 3 d, and then poured into ice-cold pH 9 buffer solution (saturated aqueous ammonium chloride (450 ml) + concentrated ammonium hydroxide (50 ml)). The aqueous phase is separated and extracted with ether (6 × 70 ml), and the combined organic layers are dried ($MgSO_4$), filtered and concentrated under reduced pressure. Distillation of the residue (Kugelrohr, 76°, 5 torr) gives (*Z*)-2-(trimethylsilylmethyl)but-2-en-1-ol (5.03 g, 64%).

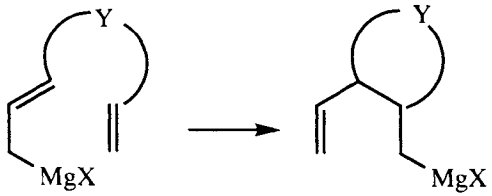
(c) The high reactivity of allylmagnesium compounds towards carbon–carbon multiple bonds has been attributed to a mechanism involving a cyclic transition state, termed a magnesium–ene reaction [1, 32]:



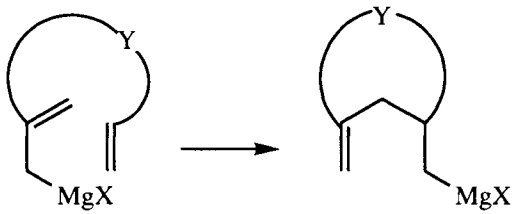
Intermolecular reactions of this type suffer from variable yields and regio- and/or stereoselectivity, though they can give good results in favourable cases. Some examples have been noted in paragraph (b), above, and another is shown in the following equation [33]:




On the other hand, *Intramolecular* versions of the magnesium–ene reaction commonly proceed in high yield, with good regio- and stereoselectivity, and have furnished elegant syntheses of the carbon skeleton of natural products. Oppolzer [32] has classified intramolecular magnesium–ene reactions as type I, in which the enophile becomes linked to the terminal carbon atom of the magnesium–ene unit, or type II, in




Type I




Type II

which the enophile becomes linked to the central carbon atom of the magnesium–ene unit. (In both cases, substituents are omitted for clarity). The following generalizations may be made [32].

(i) The ease of cyclization decreases in the following order of size of

the developing ring:

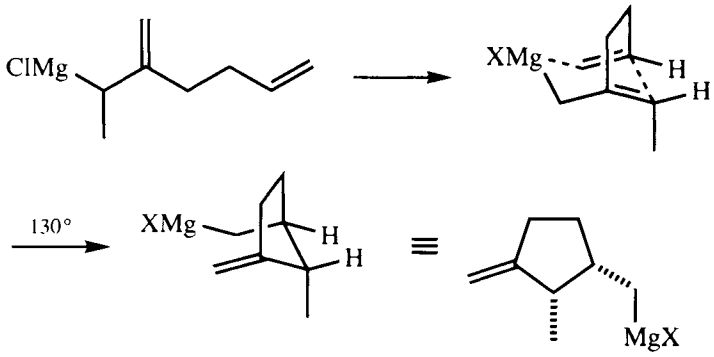
Type I: 5>6>>7
Type II: 6>5, 7>>8

(ii) Carbon–carbon bonds are preferentially formed between the proximal sites of the ene and enophile in the type I process and between the more substituted terminal and the proximal enophile site in the type II process.

(iii) Type I cyclizations usually furnish, under kinetic control, predominantly five- and six-membered rings carrying *cis*-disposed magnesium donor and acceptor units even when a quaternary centre is generated. Dialkyl-substituted allylmagnesium groups react preferentially in their (*Z*) form, inducing a *cis* relationship of the 3-substituent and the magnesium acceptor site in type II cyclization products. (Note, however, that the stereoselectivity of both types of cyclization may be diminished by severe steric hindrance).

(iv) These reactions only proceed satisfactorily with terminal (or strained) olefinic enophile units. Heteroatoms in the developing ring may also cause complications* (see also Ref. [28]).

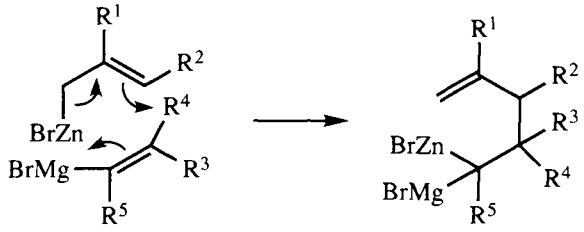
The stereoselectivity of these processes has proved useful in the synthesis of natural products. For example, a key step in an elegant synthesis of (±)-chokol-A was achieved by heating the Grignard reagent whose synthesis is described on p. 36 at 130° for 6 h [35]:




It is convenient, if not strictly systematic, to note here the intriguing and potentially useful bimetallic reagents obtained by the addition of allylzinc

*Some of these limitations may be overcome if the organomagnesium compound is converted into an organozinc compound (see Chapter 16) [34].

bromides to 1-alkenylmagnesium halides [36]:

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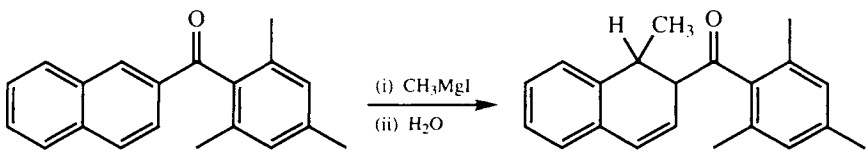
## 4.2 ADDITION TO AROMATIC RINGS

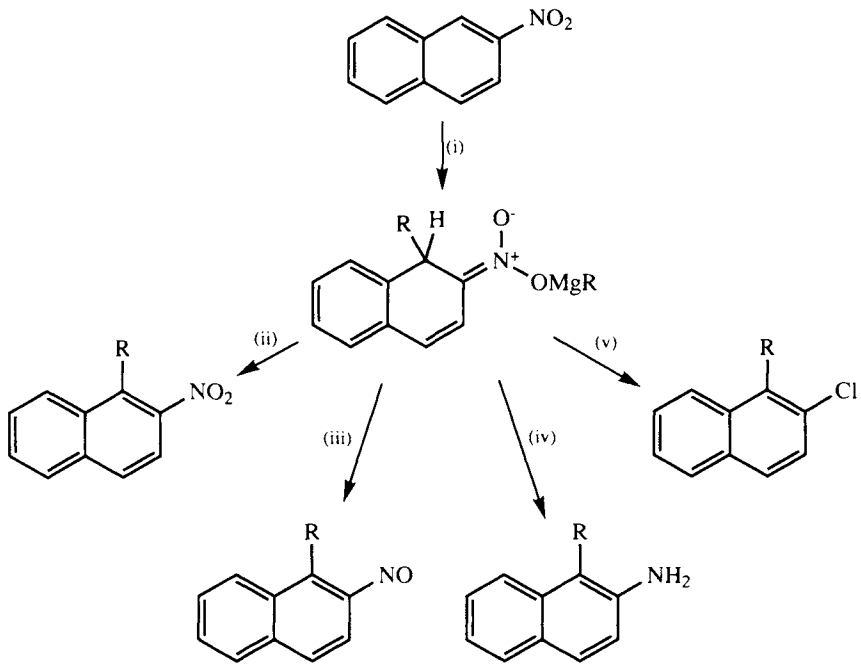
Organomagnesium compounds add to unsubstituted arenes only under forcing or "Barbier" conditions [1]. On the other hand, aromatic rings substituted by electron-withdrawing groups are surprisingly susceptible to attack by organomagnesium compounds. The early work on reactions of hindered aryl ketones [2] has been little further developed [3], despite some reports which should surely be followed up, e.g. [4].




up to 74%

Reactions in which methoxy groups, *ortho* to keto, ester or oxazoline groups, are displaced by organomagnesium compounds presumably proceed by an addition–elimination pathway, and are covered in Section 8.2).

Early investigations of reactions of organomagnesium compounds with nitro compounds led to mixtures of products, and gave little indication that they might be useful [5]. However, it has now been established that with two equivalents of an alkylmagnesium halide in THF, nucleophilic addition to the ring of a variety of nitroaromatic compounds occurs, as summarized in Table 4.1. The product of the addition is a nitronate anion, which may be converted into various products, as illustrated by the example of 2-nitronaphthalene.




(i) 2RMgX; (ii) DDQ or $KMnO_4$ or $Br_2/Et_3N$ [6] and see Ref. [7]; (iii) $BF_3$ or conc. HCl [8]; (iv) excess RMgX, CuI [9]; (v) NaOCl (see procedure) [10]

TABLE 4.1

Nucleophilic addition of organomagnesium compounds to nitroaromatic compounds

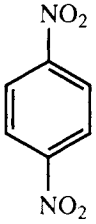
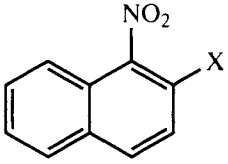
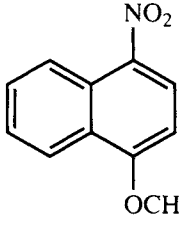
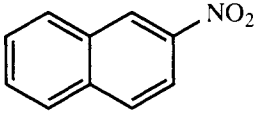
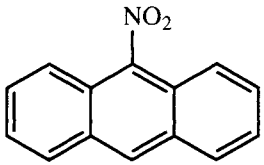
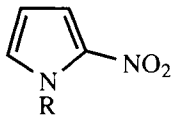
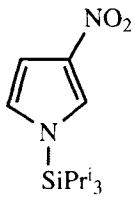
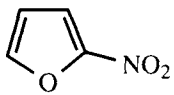
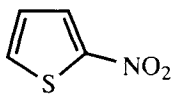
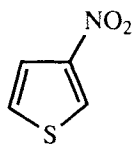
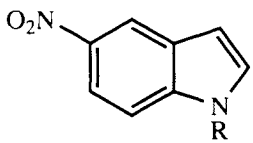
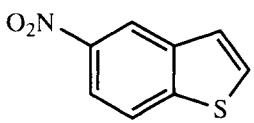
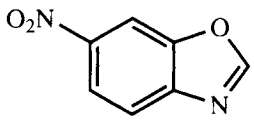
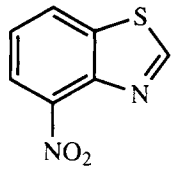
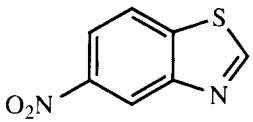
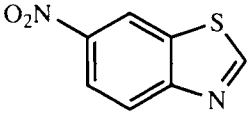
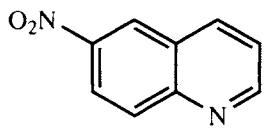
| Nitro compound | Position of attack | Ref. |
|---|---|---|
|  X=Cl,I,CN,CHO,COOMe,COPh, $CH_2Cl$,$CH_2CH_2COMe$,$CH(OR)_2$,$OSiMe_3$ | *ortho* to $NO_2$[a] | [6, 11, 12] |
|  | Mainly 2,3-di | [13] |
|  X=$CH_3$,$OCH_3$ | 4 | [6, 7, 11] |
|  | 2 (+ a little 4) | [6, 14] |
|  | 1[b] | [6–10] |

TABLE 4.1 *(continued)*

| Nitro compound | Position of attack | Ref. |
|---|---|---|
|  | 10 | [11] |
|  | 3 and 5 | [15] |
|  | 2 | [15] |
|  | 3 and 5 | [16] |
|  | 3 and 5 | [15] |
|  | 2 | [15] |
|  | 4 | [6, 11] |
|  | 4 | [8, 9] |

*(continued on next page)*

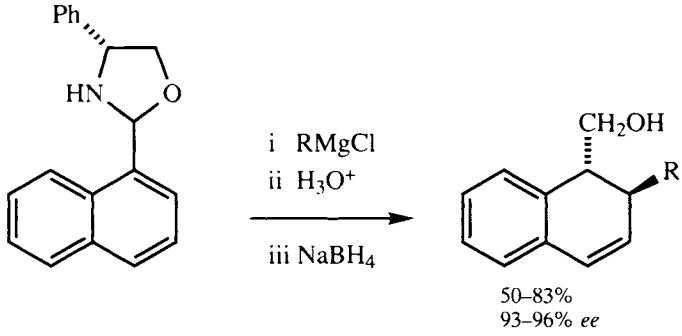
TABLE 4.1 *(continued)*

| Nitro compound | Position of attack | Ref. |
|---|---|---|
|  | 7 | [8] |
|  | 7 | [17] |
|  | 4 | [17] |
|  | 7 | [8, 9, 11, 17] |
|  | 4 and 6 | [17] |
|  | 5 | [8, 10, 11] |

[a]Some attack *para* to $NO_2$ also observed in some cases, with or without diplacement of X [18]. [b]The 1-position is attacked even in the case of, for example, 1-methyl-2-nitronaphthalene [19].

*6-Chloro-5-methylquinoline* [10] A solution of 6-nitroquinoline (1.86 g, 10 mmol) in THF (50 ml) is stirred at about 20° under nitrogen as methylmagnesium chloride (1 M in THF, 20 mmol) is added dropwise. The mixture is stirred for 10 min and then added dropwise to a vigorously stirred solution, freshly prepared by adding 8% aqueous sodium hypochlorite (40 ml) to a solution of potassium hydroxide (2.16 g) in ethanol. The mixture is stirred for 10 min and then extracted with dichloromethane (3 × 50 ml), and the combined organic layers are filtered, washed with water (3 × 100 ml) and dried. The solvents are evaporated under reduced pressure. Chromatography of the residue (silica, 4:1 cyclohexane–ethyl acetate) gives 6-chloro-5-methylquinoline (0.75 g, 73%). (Further elution with 1:1 cyclohexane–ethyl acetate gives a little 5-methyl-6-nitroquinoline).

A most remarkable reaction of Grignard reagents with a 1-(oxazolidin-2-yl)naphthalene has been described, in which addition to the aromatic ring occurs, whereas organolithium, organocerium or organocopper reagents all attack the oxazolidine 2-position [20]:

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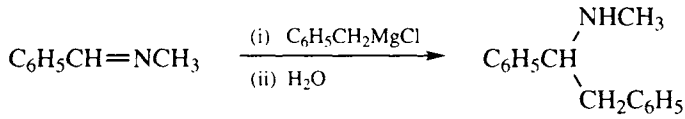
# —5—

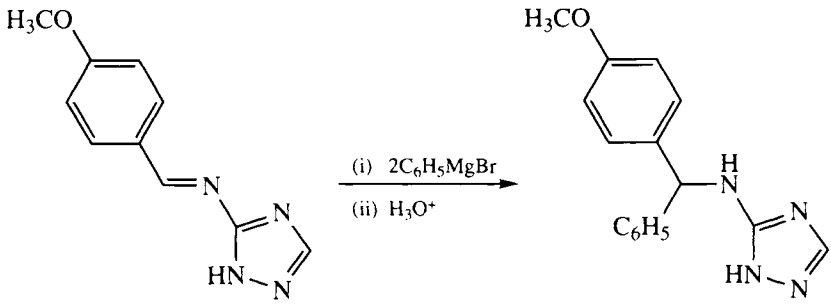
# Addition of Organomagnesium Compounds to Carbon–Nitrogen Multiple Bonds

## 5.1 ADDITION TO IMINES, IMINIUM SALTS AND RELATED COMPOUNDS

Unconjugated carbon–nitrogen double bonds are less reactive than might have been predicted towards addition of organomagnesium compounds, and when imines possess hydrogen atoms α to carbon or nitrogen, deprotonation may compete with addition [1]. However, addition to aromatic aldimines can give good yields, with or without hydrogen atoms α to nitrogen [2]:

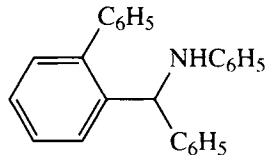



91–96% [3]




60% [4]

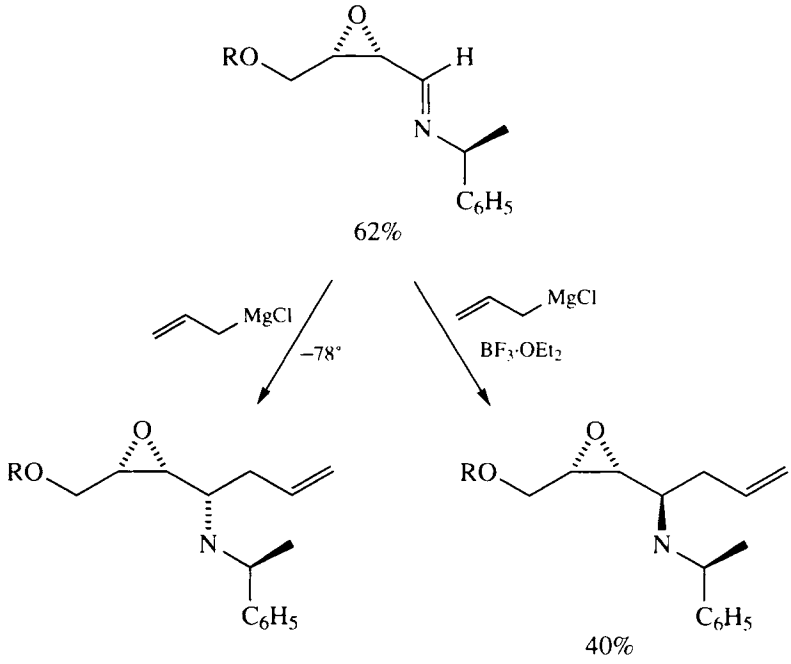
On the other hand, benzophenone imines undergo addition only under forcing conditions, to give products such as (1) resulting from attack at a ring [5].



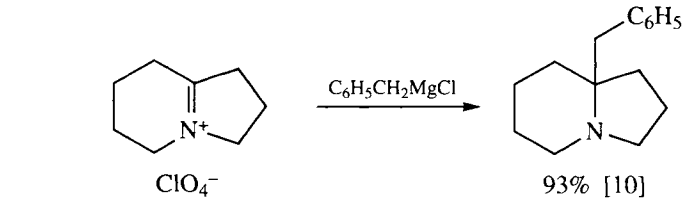
(1)

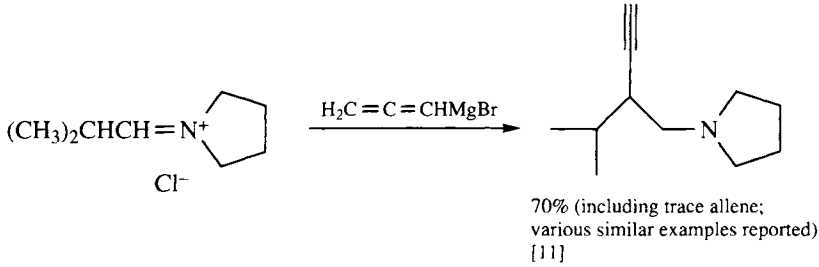
Imines may be activated by complexation with Lewis acids, but this also increases the acidity of α-hydrogen atoms. A combination of copper(I) halide and boron trifluoride etherate is a possible solution to the problem [6, 7]. Activation by trimethylsilyl triflate is also effective with aldimines (though not with ketimines) [7, 8].

It should be noted that in cases where the stereochemistry of the addition is dependent on chelation control, the presence of Lewis acids may profoundly influence the selectivity, e.g. [9].

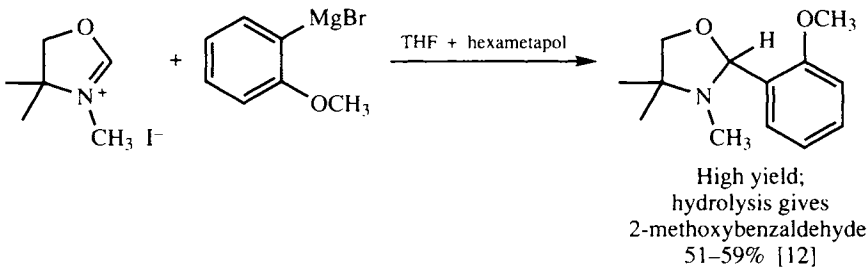



The above additions to activated imines presumably involve iminium salt/complex intermediates. Addition to preformed iminium salts can also be effective, as in the examples given here.



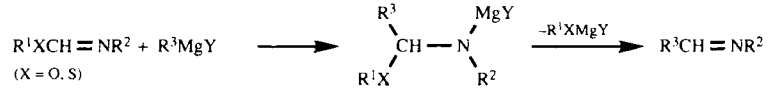

A related reaction involves addition to a quaternized oxazoline.*




From the limited number of examples reported, *N*-sulfonation of aldimines appears to promote smooth addition of Grignard reagents [13, 14]:

$$R^1CH{=}NSO_2Ar \xrightarrow[(ii)\ H_3O^+]{(i)\ R^2MgX} R^1R^2CHNHSO_2Ar$$

*Note that the unquaternized oxazoline is an imidoester; addition to imidoesters and thioesters is usually followed by elimination, so that the overall result is substitution:



The products of the analogous reactions with sulfams are relatively easily hydrolysed to the free amine [15]:

$$(ArCH{=}N)_2SO_2 \xrightarrow{RMgX} (ArCH(R){-}NH)_2SO_2 \xrightarrow[\text{(ii) aq. NaOH}]{\text{(i) } H_2O\text{, pyridine}} ArCH(R)NH_2$$

The related reactions of *N*-sulfonyl- [16], *N*-diphenylphosphinyl- [17] and *N*-diethoxyphosphoryl- [18] formamidoesters must involve addition, elimination, and a second addition (see footnote on p. 89).

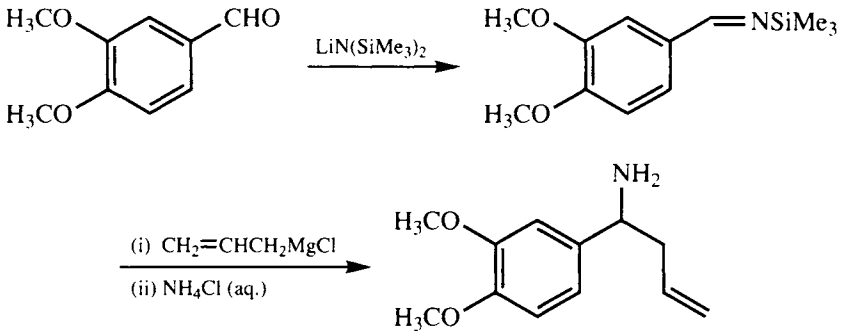
$$C_2H_5OCH{=}NSO_2C_6H_5 + 2RMgBr \longrightarrow R_2CHNHSO_2C_6H_5$$
or $C_2H_5OCH{=}NP(O)(C_6H_5)_2$
or $C_2H_5OCH{=}NP(O)(OC_2H_5)_2$

Primary amines have also been prepared via addition of Grignard reagents to various *N*-metalloaldimines, followed by hydrolysis.

$$R^1CH{=}NML_n \xrightarrow[\text{(ii) hydrolysis}]{\text{(i) } R^2MgX} R^1R^2CHNH_2$$

$ML_n = SiMe_3$ [19–21], $AlBu^i_2$ [22], $BR_nH_{2-n}$ [23]

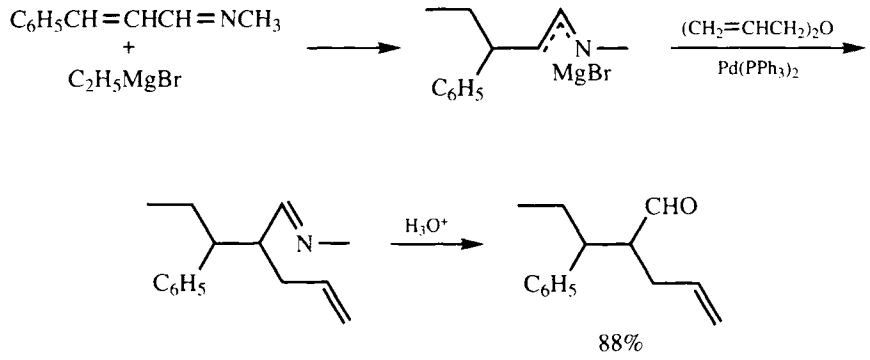
*4-Amino-4-(3,4-dimethyoxyphenyl)but-1-ene* [19]




A solution of 3,4-dimethoxybenzaldehyde (5.0 g, 30 mmol) in THF (10 ml), under an inert atmosphere, is cooled in an ice–water bath and stirred

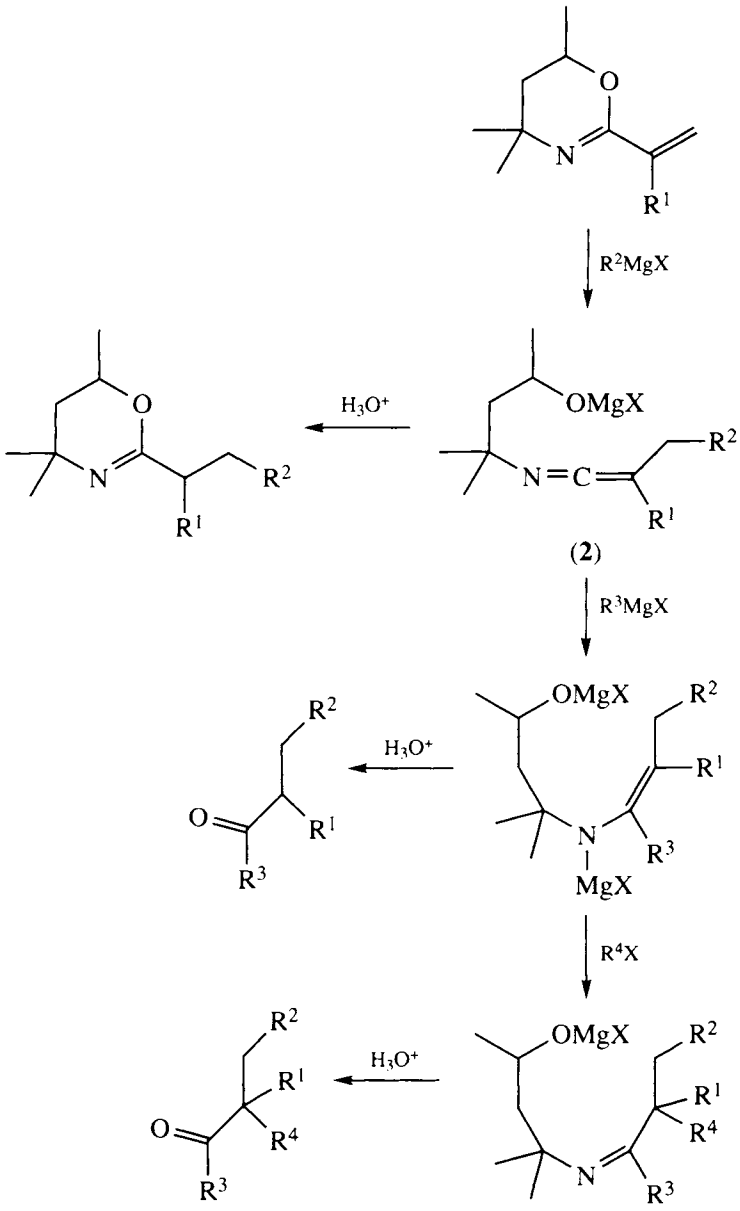
as lithium bis(trimethylsilyl)amide (prepared from hexamethyldisilazane (8.2 ml, 39 mmol) and n-butyllithium (~ 1.5 M in hexane, 36 mmol) in THF (10 ml)) is added. To the resulting solution is added allylmagnesium chloride (~ 0.6 M in diethyl ether, 36 mmol). The mixture is stirred at room temperature for 30 min, poured into saturated aqueous ammonium chloride (200 ml) and extracted with dichloromethane (3 × 30 ml). The combined extracts are concentrated *in vacuo*. Chromatography of the residue (silica, chloroform–methanol–saturated aqueous ammonium chloride (250:10:1)) followed by recrystallization from hexane gives 4-amino-4-(3,4-dimethoxyphenyl)but-1-ene (5.92 g, 95%), m.p. 56–57°.

Both 1,2- and 1,4-addition of organomagnesium compounds to α,β-ethylenic imines has been reported [E, 24]. The latter has been used in tandem addition–alkylation sequences, e.g. [25].

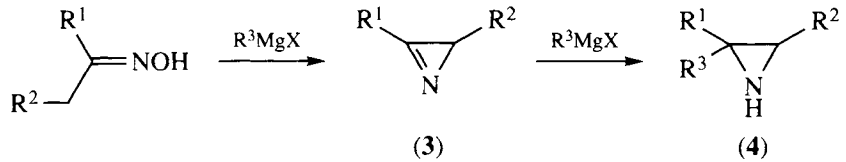



Conjugated addition is also the first step in Meyers' strategy for multiple carbon–carbon bond formation, shown in Scheme 5.1; the ketenimine **(2)** formed by ring opening of the initial adduct of a Grignard reagent to a 2-alkenyldihydro-1,3-oxazine can itself undergo addition of a Grignard reagent [26].

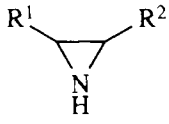
Oximes, hydrazones, semicarbazones, diazines and carbodiimides all undergo reactions involving addition to a carbon–nitrogen double bond [A, D], but these reactions are of limited value, with the exception of the reaction with ketoximes. This last reaction, with an excess of Grignard at elevated temperatures, is a useful route to aziridines, **(4)**, although yields are rarely high. In some cases, reduction of the intermediate azirine **(2)** leads to an alternative aziridine **(5)**.




**Scheme 5.1**



(3) (4)



(5)

Examples of reactions giving both types of aziridine are listed in Table 5.1.

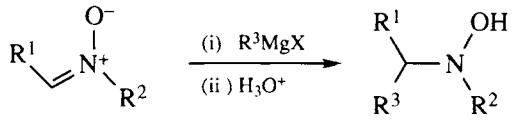
TABLE 5.1

Synthesis of aziridines from ketoximes and Grignard reagents

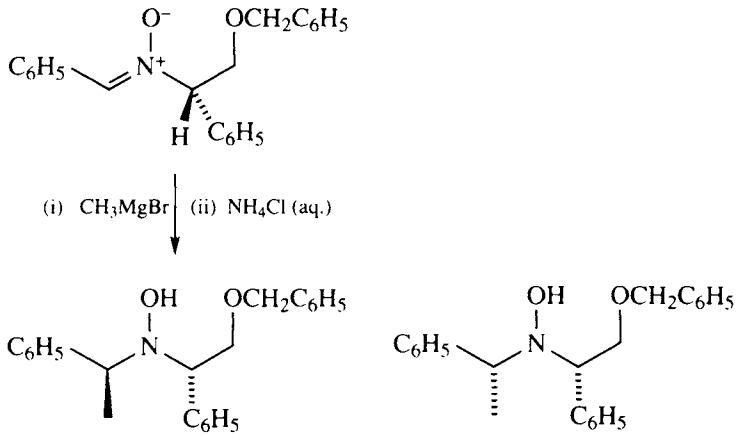
| Oxime, $R^1C(=NOH)CH_2R^2$ | | Grignard reagent, $R^3MgX$ | Aziridine **(4)**, yield (%) | Aziridine **(5)** yield (%) | Ref. |
|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | | | |
| $CH_3$ | H | n-$C_4H_9$ | 16 | | [27] |
| $(CH_3)_3C$ | H | $C_6H_5$ | 90 | | [28] |
| $C_6H_5$ | H | $CH_3CH_2$ | 20–60 | | [29, 30] |
| $C_6H_5$ | D[a] | $C_6H_5$ | 65 | | [28] |
| $CF_3$ | $C_6H_5$ | $CH_3$[b] | 21 | | [31][c] |
| $CF_3$ | $C_6H_5$ | $CH_3CH_2$[b] | | 95 | [31][c] |
| $CH_3CH_2$ | $CH_3$ | $CH_3CH_2$ | 14 | | [27] |
| $(CH_3)_2C(OH)$ | $CH_3$ | $C_6H_5$ | 30 | | [32][d] |
| $C_6H_5$ | $CH_3$ | $CH_3CH_2$ | 50 | | [29] |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | Up to 45 | | [33] |
| $C_6H_5$ | $CH_3$ | $C_6H_5CH_2CH_2$ | 42 | 15 | [34] |
| $C_6H_5$ | $CH_3CH_2$ | $CH_3CH_2CH_2$ | 43 | | [27] |
| $C_6H_5CH_2$ | $C_6H_5$ | $(CH_3)_2CHCH_2$ | | 47 | [34] |

[a] "$R^2CH_2$" = $CD_3$. [b] With sonication. [c] Alternative reactions occur with allymagnesium halides [35]. [d] Stereoselectivity of analogous reactions studied.

While the addition of organomagnesium compounds to nitrones was reported over 80 years ago [36], only occasional examples were described until recently [37–40]:




However, two factors are likely to lead to the further exploitation of this reaction in synthesis: (a) the addition may proceed with a useful degree of stereoselectivity, and (b) the initial adducts may be readily converted into amines (for example by acylation followed by reduction [41] or by reaction with carbon disulfide [42]). An example of a diastereoselective addition is shown in the following equation [41]; others have been described [41, 43, 44]:

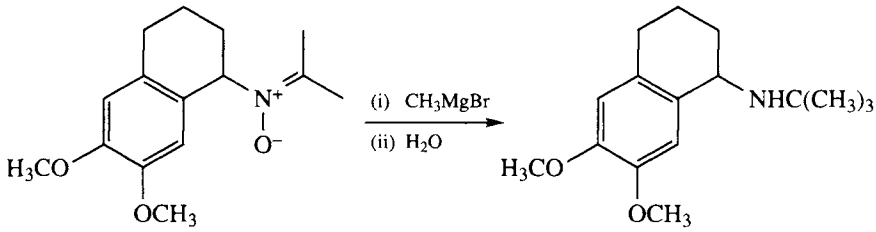



91 : 9

Analogous reactions with ketonitrones proceed less readily, and are more liable to side-reactions involving deprotonation [45], but may give good results under optimized conditions (particularly in relatively non-polar solvents) [42].

N-*t-Butyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-naphthaleneamine* [42] The crude nitrone **(6)*** (3.00 g, 13.6 mmol) is dissolved in dry benzene (150 ml) (HAZARD) under an inert atmosphere. The solution is cooled in an ice

*Prepared by autoxidation of the corresponding hydroxylamine [42].




(6)

bath, and methylmagnesium bromide (~ 3.6 M in diethyl ether, 36.5 mmol) is added by syringe. The ice bath is removed, and the mixture is stirred as it warms to room temperature (30 min). Water is added, and the mixture is extracted with dichloromethane. The extract is dried ($Na_2SO_4$) and evaporated, and the residue is recrystallized from ethyl acetate–hexane to give *N*-t-butyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-naphthaleneamine (3.15 g, 92%), m.p. 115–116°.

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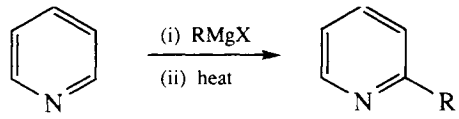
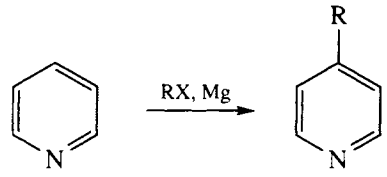
## 5.2 ADDITION TO NITROGEN HETEROCYCLIC AROMATIC COMPOUNDS

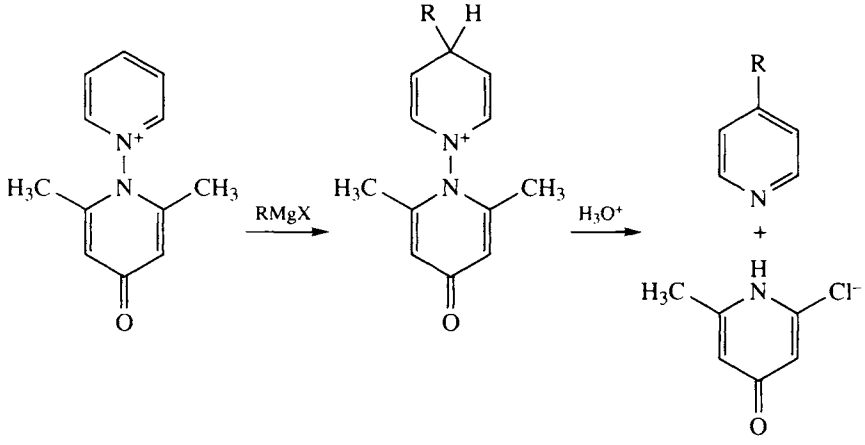
Organomagnesium compounds usually resemble organolithium compounds in their reactions with nitrogen heterocyclic aromatic compounds [E, G], but they generally give inferior results for preparative purposes. Thus, as in the case of organolithium compounds, addition normally occurs at the 2-position of pyridine, and subsequent elimination or oxidation gives the 2-substituted pyridine [1]:



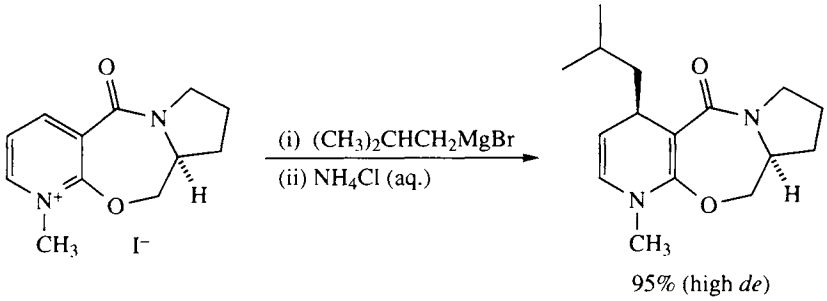

On the other hand, circumstances have been found where 4-substitution occurs as well as, or even instead of, 2-substitution. These circumstances are those favouring an electron transfer mechanism: the use of magnesium 'ate complexes (see Section 3.3.3) [2] and complexation by crown ethers or cryptands [3] (and also with allyl and benzylmagnesium halides [4]). Electron transfer processes may well be also involved in the reaction of pyridine, an organic halide and magnesium, leading to a 4-alkylpyridine (a rare example of a reaction under "Barbier" conditions giving a different product from the reaction of the preformed Grignard reagent [1]):




In contrast, reactions of organomagnesium compounds with pyridinium salts are more useful than those of organolithium compounds. Unsubstituted pyridinium salts have a somewhat greater tendency towards 4-alkylation than pyridine itself [5], and with a bulky *N*-substituent, 4-alkylation predominates. If the *N*-substituent is also a good leaving group, a viable general synthesis of 4-substituted pyridines results [6].

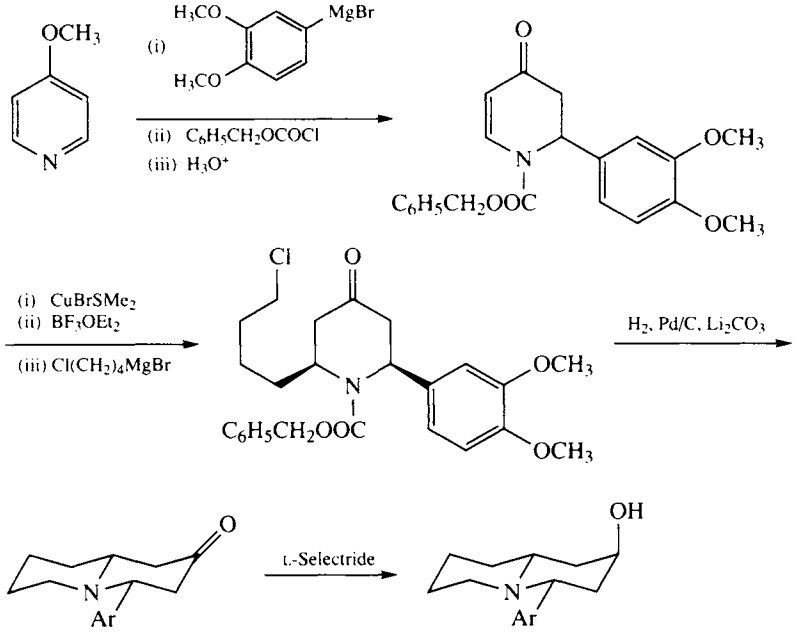


Attack at the 4-position is also promoted by certain 3-substituents, which may also direct the stereochemistry of the attack [7, 8], e.g. [7].




95% (high *de*)

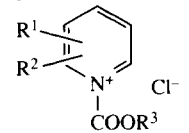
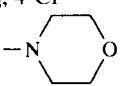
The dihydropyridines resulting from analogous reactions of *N*-acyl- or *N*-alkoxycarbonylpyridinium salts may be isolated and characterized; moreover, they are valuable intermediates in elegant syntheses of alkaloids. What is more, the *N*-alkoxycarbonylpyridinium salts may be generated *in situ* by the reaction of the pyridine with a chloroformate even in the presence of a Grignard reagent [9]. An example is a four-step synthesis of (±)-lasubine II (Scheme 5.2), and a procedure is given for the key step [10].




**Scheme 5.2**

TABLE 5.2

Addition of organomagnesium compounds to *N*-alkoxycarbonylpyridinium salts

| Pyridinium salt,  $R^1$,$R^2$ | $R^3$ | Grignard reagent | Position(s) | Total yield | Ref. |
|---|---|---|---|---|---|
| H | $CH_3$ | $C_6H_5C{\equiv}CMgBr$ | 2 | 98 | [11] |
| H | $CH_3$ | $(CH_3)_2CHMgBr$ | 2 + 4 (37:63) | 99 | [11] |
| H | $C_2H_5$ | $C_6H_5CH_2MgBr$ | 4 | 60[a] | [12] |
| 3-$SiEt_3$ | $C_6H_5$ | $CH_3CH_2CH_2CH_2MgCl$ | 2 + 4 + 6 (14:14:72) | 91 | [13] |
| 3-$SiPr^i_3$ | $C_6H_5$ | $CH_3CH_2CH_2CH_2MgCl$ | 6 | 98 | [13] |
| 3-$SnPr^i_3$ | [b] | $CH_3CH_2CH_2MgCl$ | 6[c] | 72 | [14] |
| 4-$C(CH_3)_3$ | $CH_3CH_2$ | $(CH_2)_3CMgCl$ | 2 | 55 | [15] |
| 4-$OCH_3$[d] | [b] | $C_6H_5MgBr$ | 2[e] | 83 | [16] |
| 4-$OCH_3$ | $C_6H_5CH_2$ | $CH_3CH_2OCH_2CH_2O(CH_2)_4MgCl$ | 2 | 93 | [17] |
| 4-Cl | $C_6H_5$ | n-$C_{11}H_{23}MgBr$ | 2 | Quantitative (crude) | [18] |
| 3,4-di-$CH_3$[f] | $CH_3CH_2$ | $C_6H_5MgBr$ | 2 + 6 (22:78) | 31 | [19] |
| 3,4-di-$CH_3$ | $(CH_3)_2CH$ | $C_6H_5MgBr$ | 2 + 6 (10:90) | 32 | [19] |
| 3,4-di-$CH_3$ | $C_6H_5$ | 2-$CH_3C_6H_4MgBr$ | 6 | 56 | [19] |
| 3-$SiPr^i_3$, 4-$OCH_3$ | [b] | $CH_3MgCl$ | 6 | 92[g] | [16] |
| 3-$SiPr^i_3$, 4-Cl | $C_6H_5$ | $CH_3MgCl$ | 6 | 66 | [13] |
| 3-Cl, 4-  | $C_6H_5$ | $CH_3MgCl$ | 2 | ~ 65 | [20] |

[a]As 4-benzylpyridine. [b](−)-8-Phenylmenthyl. [c]*de* 82%. [d]For another example, see procedure in text. [e]*de* 30%. [f]Exclusive 2-addition to *N*-benzyl- and *N*-methyl-3-4-dimethylpyridinium halides has been reported [21]. [g]*de* 91%.

*N-(Benzyloxycarbonyl)-2-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine* [10]

3,4-Dimethoxyphenylmagnesium bromide is prepared by the reaction of activated magnesium (0.73 g, 30 mmol) with 1-bromo-3,4-dimethoxybenzene (1.5 ml, 12 mmol) in THF (10 ml) [10]. A solution of 4-methoxypyridine (1.0 ml, 10 mmol) in THF (10 ml) is cooled to −23°, and the Grignard reagent is added slowly by cannula. Benzyl chloroformate (1.4 ml, 10 mmol) is added dropwise during 10 min, and the solution is stirred at −23° for 4 h, and then poured into stirred 10% HCl (25 ml). The mixture is stirred for 10 min, and the organic layer is separated. The aqueous layer is extracted with ether (2 × 50 ml) and the combined organic phases are washed with brine (25 ml), dried ($MgSO_4$) and evaporated. Recrystallization of the residue from acetone–hexanes gives the title compound (2.8 g, 75%), m.p. 115–117°.

Further selected examples of reactions of Grignard reagents with *N*-alkoxycarbonylpyridinium salts are listed in Table 5.2. One problem with these reactions is regioselectivity, but this may often be controlled by steric factors; compare, for example, entries 3 and 4 in Table 5.2.

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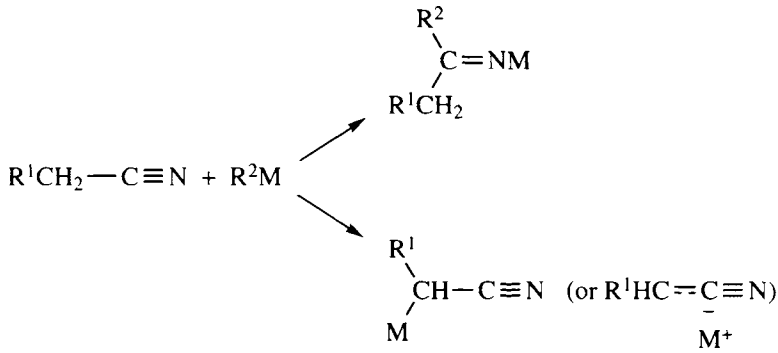
## 5.3 ADDITION TO NITRILES

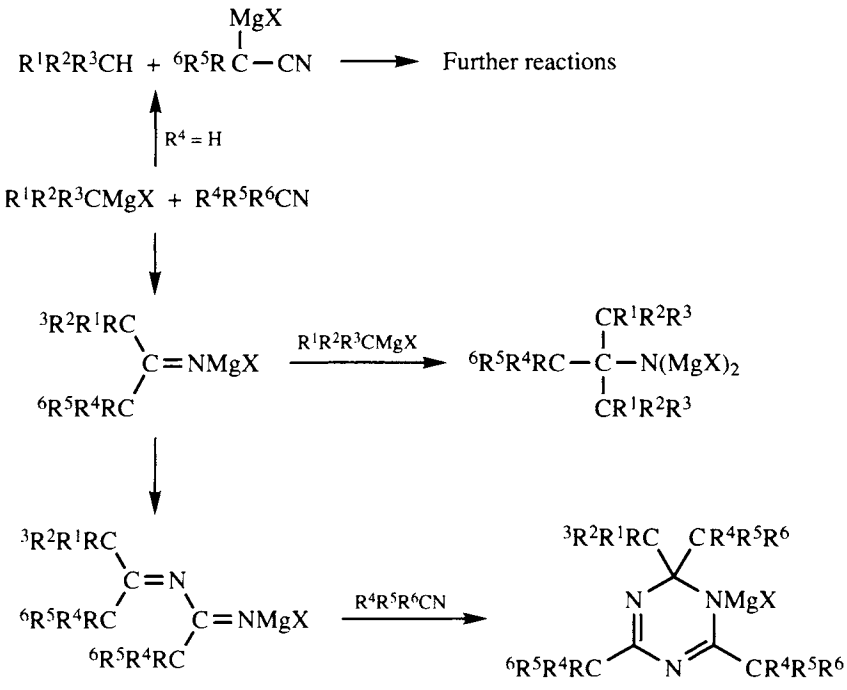
Reactions of organomagnesium and organolithium compounds with nitriles normally proceed via initial addition to the carbon–nitrogen triple bond or via initial α-deprotonation:




(Reduction of nitriles by organomagnesium compounds has not often been reported, though it may well occur, by mechanisms analogous to those for reduction of carbonyl compounds: see p. 112. A few cases are also known in which the cyano group is displaced: see Section 8.3.2). These initial reactions may then be followed by others, involving an excess of either the organomagnesium compound or of the nitrile [E]. These further reactions are of limited usefulness in synthesis, but the more important ones are summarized in Scheme 5.3.

When reactions involving deprotonation are desired, it is better to use reagents such as LDA, though in favourable cases organomagnesium compounds have been employed. For reactions requiring addition to the cyano group, both organomagnesium and organolithium compounds have been used successfully, and it is difficult to predict which will be better in a particular case.

The addition reaction is most commonly used for the synthesis of

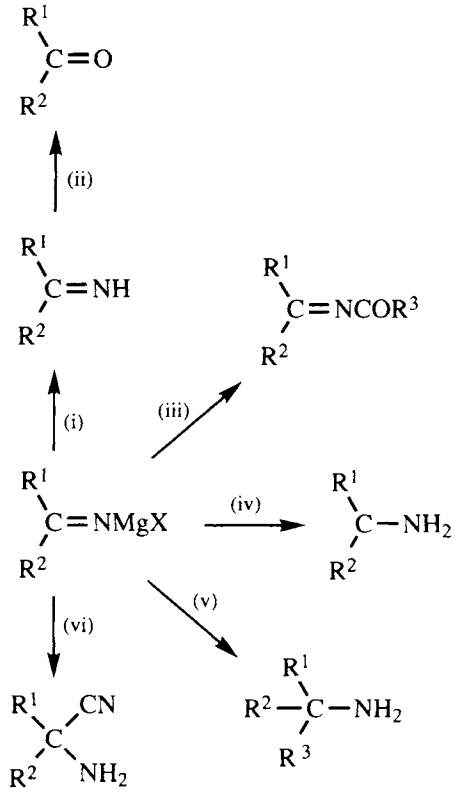



**Scheme 5.3**

ketones, via hydrolysis of the intermediate imine [A]. However, other useful reactions of the adduct include protonation to give the free imine, reaction with other electrophilic reagents to give various *N*-substituted imines, and reduction to give a primary amine. These reactions are summarized in Scheme 5.4. For all of them the key step is the initial addition, and some guidelines for optimizing this step and minimizing side-reactions are as follows:

(i) The rate of the addition is increased, side-reactions reduced, and overall yield improved, by the use of relatively non-donor solvents, such as benzene (HAZARD) containing only one equivalent of ether [1].
(ii) The addition reaction is catalysed by copper(I) salts (though the examples described all involve nitriles lacking α-hydrogens) [2].
(iii) The difference in reactivity between cyano groups and other functional groups is often sufficient to allow selective reactions.

In general, the cyano group is less reactive towards organomagnesium compounds than carbonyl groups [A], but more reactive than epoxides [3].




Reagents: (i) $H^+$; (ii) $H_3O^+$; (iii) $R^3COCl$; (iv) reduction (see below); (v) $R^3Li$ or $CH_2{=}CHCH_2MgX$ [4]; (vi) $CN^-$ [5]

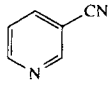
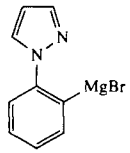
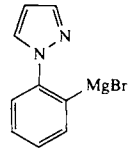
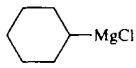
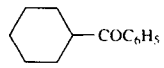
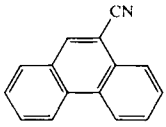
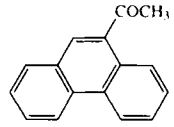
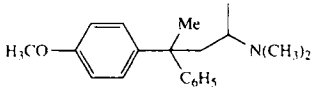
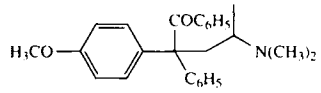
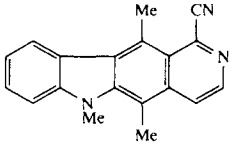
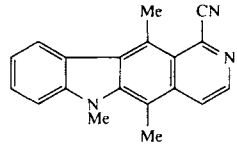
**Scheme 5.4**

By far the most common application of the addition reaction is the synthesis of ketones, by hydrolysis of the intermediate imine *in situ*. Some examples are listed in Table 5.3, and a procedure is given for an intramolecular version.* Numerous examples have been tabulated [A].

*For other intramolecular examples, see Ref. [6].

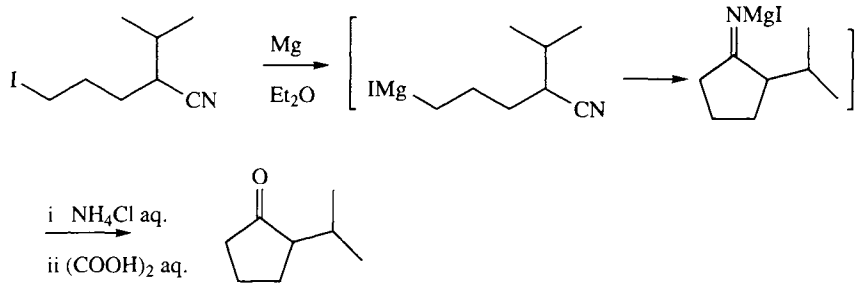
TABLE 5.3

Synthesis of ketones via addition of organomagnesium compounds to nitriles

| Nitrile | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
| $CH_3OCH_2CN$ | $C_6H_5MgBr$ | $CH_3OCH_2COC_6H_5$ (71–78) | [8] |
|  |  |  (72) | [9] |
| $C_6H_5CN$ | $(CH_3)_3CCN$ | $C_6H_5COC(CH_3)_3$ (94)[a] | [2] |
| $C_6H_5CN$ |  |  (98)[a] | [2] |
|  | $CH_3MgI$ |  (52–59) | [10] |
|  | $C_2H_5MgBr$ |  (91) | [11][b] |
|  | $CH_3MgI$ |  (95) | [13] |

[a]Copper(I) bromide catalyst. [b]Related examples have been described [12].

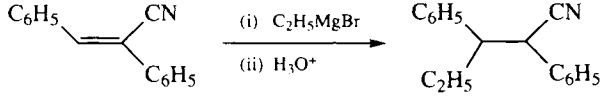
*2-Isopropylcyclopentanone* [7]



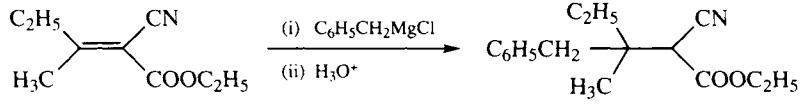

Dry, clean magnesium turnings (1.22 g, 0.05 mol) are placed in a 250 ml three-necked flask, furnished with an atmosphere of argon, and dry ether (10 ml) is added. A mixture of 5-iodo-2-isopropylpentanonitrile (12.55 g, 0.05 mol) and ether (35 ml) is added dropwise. The reaction is initiated by the addition of a few drops of 1,2-dibromoethane. The mixture is stirred gently at 20–25° for 12–15 h, by which time the metal has reacted. Saturated aqueous ammonium chloride (20 ml) is added. The organic layer is separated and washed with sodium hyposulfite solution. The solvent is evaporated from the ether layer. A solution of oxalic acid (10 g) in water (60 ml) is added to the residue and heated under reflux for 4 h. Extraction with ether and distillation gives 2-isopropylcyclopentanone (4.54 g, 72%).

Several other cyclopentanones and cyclohexanones were prepared by analogous reactions [7].

Both 1,2- and 1,4-addition of organomagnesium compounds to α,β-unsaturated nitriles are known [A, 14]. Two examples of the latter reaction are shown here.




~ 85% (with little 1,2-addition product) [14]




92–95% [15]

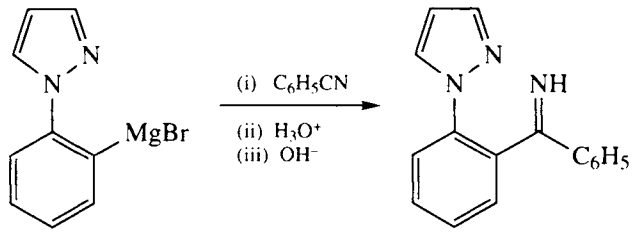
When isolation of the imine is required [16], care has to be taken to minimize contact with aqueous acid, though in some cases the hydrochloride may be obtained even from aqueous acid, as in the following procedure. Where the imine is more sensitive, it may be isolated as the hydrochloride, prepared under anhydrous conditions [16, A], or protonation of the adduct by methanol may be used to furnish the free imine:

$$C_6H_5CN + C_6H_5MgBr \longrightarrow (C_6H_5)_2C{=}NMgBr \xrightarrow{CH_3OH} (C_6H_5)_2C{=}NH$$

61–81% [17]

Other examples of the isolation of free imines have been recently described [18].

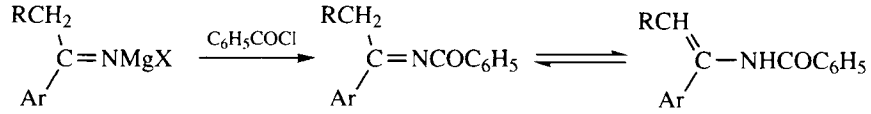
*Phenyl 2-(pyrazol-1-yl)phenyl ketimine* [9]



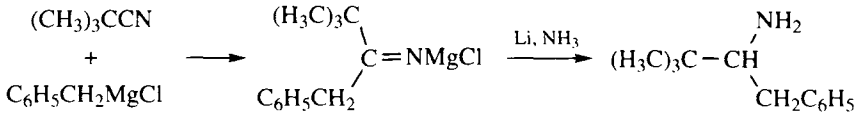

A solution of 2-(pyrazol-1-yl)phenylmagnesium bromide in THF (350 ml) is prepared by metallation of 1-phenylpyrazole (86.5 g, 0.6 mol) by ethylmagnesium bromide [9] and stirred and maintained at 25–30° as a solution of benzonitrile (51.6 g, 0.5 mol) in THF (150 ml) is added rapidly. The mixture is heated under reflux for 6 h, cooled, and poured into a solution of ammonium chloride (120 g) in water (1 litre). The solution is extracted with ether, and the ether phase is extracted with 2 M hydrochloric acid (total 600 ml). (Evaporation of the ether phase then leaves 1-phenylpyrazole (40 g)). The acid extract is (without filtration from the crystals which precipitate) treated with 10 M sodium hydroxide (300 ml) and extracted with ether. Evaporation of the extract gives phenyl 2-(pyrazol-1-yl)phenyl ketimine (99 g, 80% based on benzonitrile), m.p. 106–107°.

Of the other reactions shown in Scheme 5.4, only acylation and reduction have found sufficient use to merit further comment. Acylation proceeds smoothly, and several examples have been described [19, 20]. It

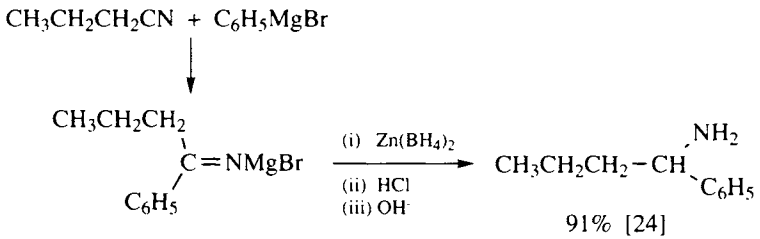
should be noted that when the adduct of a primary alkylmagnesium halide to an aromatic nitrile is benzoylated, the product tautomerizes to the enamide:



*In situ* reduction of the adducts was first accomplished by lithium in liquid ammonia [21]. This method gave good yields, but reduction by sodium or zinc borohydride is also satisfactory, and experimentally more convenient [22–24]. Representative examples are shown in the following equations:



84% [21]



91% [24]

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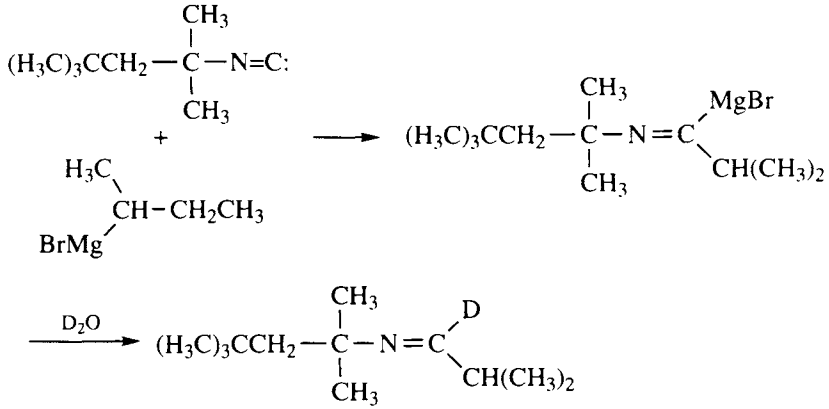
## 5.4 ADDITION TO ISONITRILES

Both organolithium [E, G] and organomagnesium compounds add to isonitriles, lacking α-hydrogen atoms, to give metalloimines, which are masked acyl anion equivalents. Grignard reagents are less reactive than organolithium compounds, and arylmagnesium halides are unsatisfactory, but alkylmagnesium halides give respectable yields [1, 2], as in the following example:




67% [2]

## References

1. G. E. Niznik, W. H. Morrison III and H. M. Walborsky, *J. Org. Chem.* **39**, 600 (1974).
2. G. E. Niznik, W. H. Morrison III and H. M. Walborsky, *Org. Synth.* **Coll. 6**, 751 (1988).

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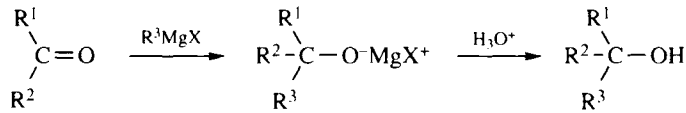
# —6—

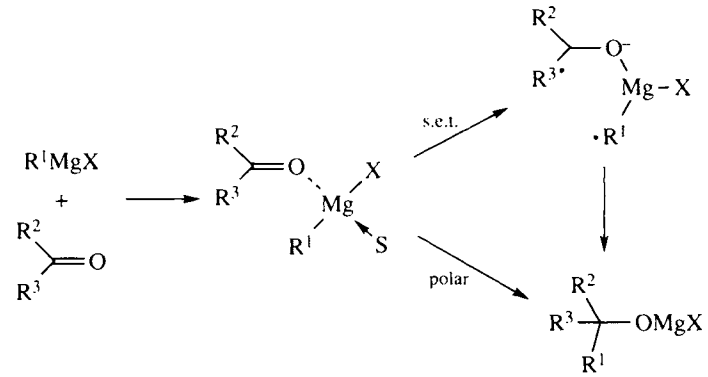
# Addition of Organomagnesium Compounds to Carbonyl Groups

## 6.1 ADDITION TO ALDEHYDES AND KETONES

The addition of organomagnesium compounds to the carbonyl group of aldehydes and ketones has a long history, and remains one of the most important reactions for carbon–carbon bond formation. While the overall reaction is simple, it is susceptible to a number of side-reactions, and its




mechanism may be far from straightforward. The mechanistic complexities are not merely academic, since an appreciation of them may be important in maximizing yields and minimizing side-reactions. Detailed accounts of mechanistic studies are available in reviews [1–3], but some key features are summarized in Scheme 6.1.




(Note that for simplicity only monomeric organomagnesium compounds are represented: the presence of oligomeric species, and the possibility of Schlenk-type equilibria, gives rise to further complexities).

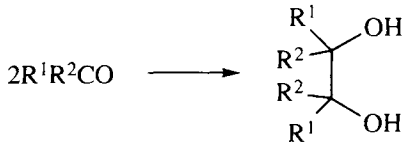
**Scheme 6.1**

It is noteworthy that the initial interaction is depicted as the formation of a carbonyl–organomagnesium complex, i.e. as electrophilic attack by magnesium at the carbonyl oxygen rather than (as described in elementary textbooks) nucleophilic attack by carbon at the carbonyl carbon. Such complex formation is usually fast, but in the presence of strongly coordinating ligands attached to magnesium it is retarded, with consequences for both the rate and the stereochemistry of the reaction.

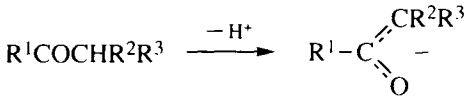
Besides the addition to the carbonyl group, three important side-reactions may occur: reduction of the carbonyl compound to the corresponding alcohol,

$$R^1R^2CO \longrightarrow R^1R^2CHOH$$

bimolecular reduction to a 1,2-diol ("pinacol reduction"),

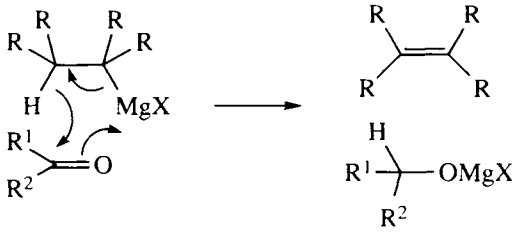


and α-deprotonation ("enolization"),



These side-reactions are rarely of preparative value, so the following discussion is centred on means of minimizing them.

(i) Reduction to the alcohol may take place by at least four routes. The most important is the well-established pathway of β-hydrogen transfer, giving the alcohol together with an alkene derived from the organomagnesium compound [A, 4]:*



*There is evidence for an electron transfer mechanism in some cases [3, 5, 6].

When the organomagnesium compound possesses tertiary (or several secondary) β-hydrogen atoms, and the carbonyl compound is sterically hindered, reduction may be the predominant reaction. This mode of reduction may be suppressed to some extent in the presence of metal salts [A, 7].

Alternative routes to unimolecular reduction include hydrogen abstraction by ketyls (see (ii)), Meerwein–Ponndorf reduction by alkoxides [A][†] and reduction by a reactive form of magnesium hydride [9].

(ii) There is convincing evidence that many addition reactions of organomagnesium compounds to carbonyl groups involve electron transfer pathways (see Scheme 6.1), although the details are controversial [2, 3, 6, 10]. The key intermediate in such pathways is a ketyl or related species; if this intermediate is sufficiently long lived it may react by dimerizing, and hydrolysis on work-up gives a 1,2-diol. This pathway is strongly promoted by the presence of transition metal compounds, even in trace amounts [A, 1] or of free magnesium. However, it can still occur to some extent even with filtered solutions of organomagnesium compounds prepared from highly purified magnesium, particularly with aromatic ketones and in more polar solvents [2, 3, 11, 12].

(iii) Organomagnesium compounds can act as bases as well as nucleophiles, and α-deprotonation is a common side-reaction of their reactions with carbonyl compounds, leading either to recovery of carbonyl compound on work-up or to aldol products. When enolate formation is troublesome, it can be reduced to some extent by the use of less polar media (for example hydrocarbons containing only a small proportion of ethers [13]) or low reaction temperature [14]. An important stratagem is the conversion of the organomagnesium compound *in situ* into an organometallic reagent which is less basic, but retains nucleophilicity (see Chapter 16). Titanium(IV) [15] and cerium(III) [16] salts have been found particularly useful.[*]

The forerunner of the reaction of preformed Grignard reagents with carbonyl compounds was the Barbier synthesis, in which an organic halide, a carbonyl compound, and magnesium react together. After many years of neglect, the Barbier synthesis has been revived. It has been improved, notably by the use of ultrasonic irradiation, and in favourable cases and/or under optimized conditions it can give excellent yields [18, 19]. Examples are noted in the following sections.

[†]Note that the Oppenauer oxidation of product alcohols may also occur [8].

[*]Complications can arise, however [17].

### 6.1.1 Addition to aldehydes

The addition of an organomagnesium compound to an aldehyde is an excellent general method for preparing secondary alcohols, and the side-reactions referred to above are a problem only in particularly unfavourable cases. Large numbers of examples have been tabulated [A] and examples from *Organic Synthesis* are listed in Table 6.1. α,β-Unsaturated aldehydes normally undergo mainly or exclusively 1,2-addition, as in the examples in Table 6.1. The following experimental procedure is typical.

*1-Phenylprop-2-en-1-ol* [32]

$$PhCHO + H_2C{=}CHMgBr \longrightarrow PhCH(OMgBr)CH{=}CH_2$$

$$\xrightarrow{NH_4Cl\ aq} PhCH(OH)CH{=}CH_2$$

Vinylmagnesium bromide (~ 2 M in THF, 0.23 mol) and THF (50 ml) are mixed and cooled to −10° as freshly distilled benzaldehyde (21.2 g, 0.20 mol) is added dropwise during 15 min. The mixture is allowed to warm to 20° and stirred for a further 15 min. The mixture is cooled in ice–water and stirred vigorously as a solution of ammonium chloride (25 g) in water (120 ml) is added. The organic layer is separated and the aqueous layer is extracted twice with ether. The combined organic layers are dried ($MgSO_4$). Most of the solvents are evaporated under reduced pressure, and the residue is distilled to give 1-phenylprop-2-en-1-ol, b.p. 100°/12 mmHg, 23.6 g (88%).

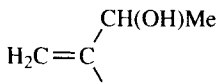
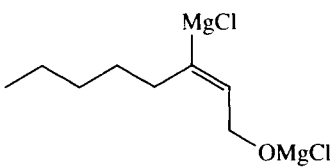
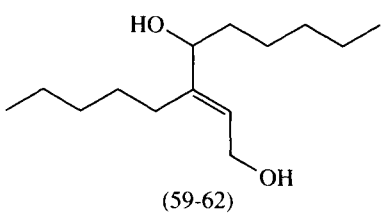
Although the reactivity of aldehydes towards organomagnesium compounds is greater than that of ketones, selective reactions of conventional Grignard reagents with formyl groups in the presence of oxo groups are not usually viable. On the other hand, it has been reported that ligand exchange between organolithium compounds and magnesium carboxylates and sulfonates (see Section 3.4) gives reagents with much greater selectivity [33]:

$$\underset{\text{(equimolar)}}{PhCHO + PhCOMe} \xrightarrow[\text{(from RLi + MgL}_2\text{)}]{\text{RMgL}} \underset{\textbf{(1)}}{PhCH(OH)R} + \underset{\textbf{(2)}}{Ph{-}\overset{\overset{R}{|}}{\underset{\underset{Me}{|}}{C}}{-}OH}$$

Product ratios **(1):(2)** were: 55:54 (MeMgBr), 95:5 (MeMgOTs), 99:1 ($MeMgOCOCMe_3$), 60:40 (BuMgBr), 99:1 (BuMgOTs)

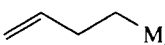
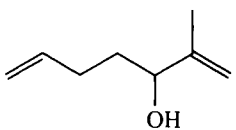
TABLE 6.1

Addition of organomagnesium compounds to aldehydes

| Aldehyde | Organomagnesium compound | Product isolated (yield, %) | Ref. |
|---|---|---|---|
| $(CH_2O)_n$[a] | cyclo-$C_6H_{11}MgCl$ | cyclo-$C_6H_{11}CH_2OH$ (64–69) | [20] |
| MeCHO | $Me_2CHMgBr$ | $Me_2CHCH(OH)Me$ (53–54) | [21] |
| MeCHO | $H_2C{=}CH(MgBr)SiMe_3$ |  (67–78) | [22] |
| MeCHO | 3-$ClC_6H_4MgBr$ | 3-$ClC_6H_4CH(OH)Me$ (82.5–88) | [23] |
|  |  |  (59-62) | [24] |

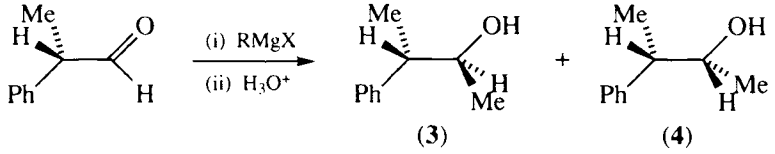
*(continued on next page)*

TABLE 6.1 *(continued from previous page)*

| Aldehyde | Organomagnesium compound | Product isolated (yield, %) | Ref. |
|---|---|---|---|
| $4\text{-}Me_2NC_6H_4CHO$ | $2\text{-}MeOC_6H_4MgBr$ | $(2\text{-}MeOC_6H_4)(4\text{-}Me_2NC_6H_4)CHOH$ (57–58) | [27] |
| $H_2C{=}CHCHO$ | $H_2C{=}CHCH_2MgBr$ | $H_2C{=}CHCH_2CH(OH)CH{=}CH_2$ | [28] |
| MeCH=CHCHO | MeMgCl | MeCH=CHCH(OH)Me (81–86) | [29] |
|  |  |  (59–64) | [28] |
| PhCH=CHCHO | MeMgBr | PhCH=CHCH=$CH_2$[b] (72–75) | [29] |
| PhCH=CHCHO | HC≡CMgBr | PhCH=CHCH(OH)C≡CH (58–69) | [30] |

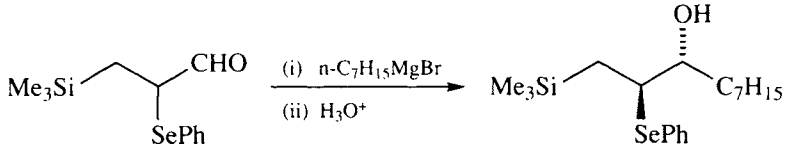
[a]Gas; paraformaldehyde may also be used, but gives lower yields [A]. See also Ref. [31]. [b]From dehydration of the alcohol.

Addition of an organomagnesium compound to an aldehyde gives rise to a new asymmetric carbon atom, and much effort has been devoted to maximizing the stereoselectivity of such additions. Three types of reaction have been studied: diastereoselective addition of organomagnesium compounds to α-chiral aldehydes, diastereoselective addition of chiral organomagnesium compounds to achiral aldehydes and enantioselective additions of achiral organomagnesium compounds to achiral aldehydes in the presence of chiral ligands. Of these, the first is the most important. In his seminal paper [34], Cram attributed the observed diastereoselectivity in the addition of organomagnesium compounds to α-chiral aldehydes to steric approach control. A typical example was the reaction of Grignard reagents with 2-phenylpropanal depicted in Scheme 6.2 (only one enantiomer shown for convenience). For methylmagnesium bromide or iodide the ratio of Cram **(3)** to anti-Cram **(4)** products was approximately 2:1 to 7:3 [34, 35], and for methylmagnesium chloride at −78° the ratio was about 87.5:12.5 [36]. For butylmagnesium chloride at −78° the ratio was about 90.6:9.4, falling to 83.9:16.1 at +22° [31]. These ratios are somewhat lower than those given by methyllithium and butyllithium [36]. A typical example of a Cram-selective reaction is described in the following procedure.




**Scheme 6.2**

*2-(Phenylseleno)-1-(trimethylsilyl)decan-3-ol* [37]




A solution of heptylmagnesium bromide (3 mmol) in THF is stirred under nitrogen at −95° as a solution of 2-(phenylseleno)-3-(trimethylsilyl)propanal (2 mmol) in THF (1 ml) is added during 15 min. The mixture is stirred at −95° for 2.5 h and at −60° for 0.5 h. Saturated aqueous ammonium chloride (2 ml) is added and the mixture is allowed to

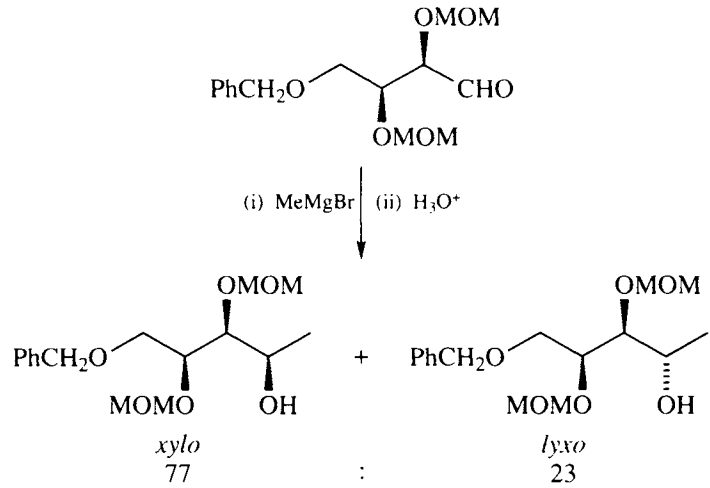
warm to room temperature. Sufficient water is added to dissolve the precipitated salts. The mixture is extracted with ether (4 × 20 ml), and the combined organic extracts are washed with water (10 ml) and brine (10 ml), and dried ($MgSO_4$). Most of the solvents are evaporated, and the residue subjected to chromatography (silica gel, ethyl acetate–light petroleum (5:95)), to give I-2-(phenylseleno)-1-(trimethylsilyl)decan-3-ol (85%) as an oil.

The stereochemistry of the product was established by elimination to give (*E*)-1-(trimethylsilyl)dec-2-ene.

Numerous experiments aimed at enhancing Cram stereoselectivity, or alternatively at reversing it, have been carried out, and the principles governing it have been intensively discussed [36, 38].

For enhancing Cram selectivity, two approaches have proved successful (though some of the quantitative results should perhaps be viewed with some caution [36]): increasing the bulk of the organomagnesium reagent by using compounds such as $RMgNR'_2$, RMgOCOR′ or RMgOR′, where the groups R′ are large [33, 39]; and conversion of the organomagnesium compound *in situ* into another organometallic compound (for a summary of the results for various metals see Ref. [36]).

Two factors may lead to modification or reversal of Cram selectivity: (a) chelation control by neighbouring groups [40], as in the addition of Grignard reagents to a protected L-threose in which the *xylo* product predominated [41], e.g.

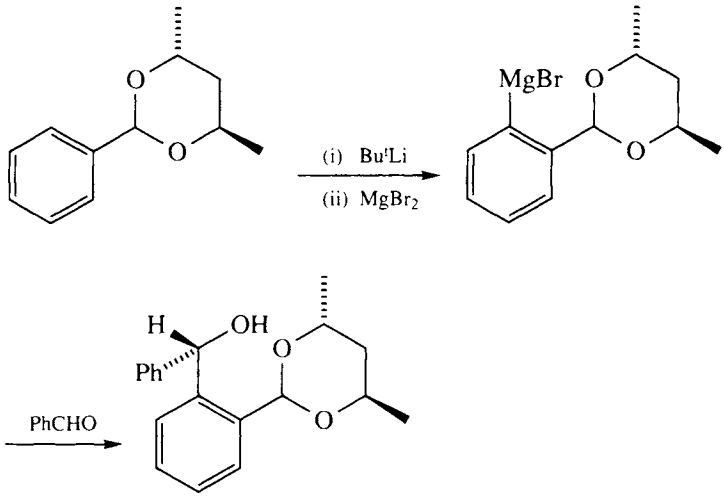



*xylo* 77 : *lyxo* 23

and (b) again conversion of the organomagnesium compound into another organometallic compound [40]. For example, in the reaction of Scheme

6.2, the use of a cuprate reagent ("$Me_2Cu{\cdot}MgBr$") derived from methylmagnesium bromide, in the presence of kryptofixes K-21 or K-22 gave **(3)** and **(4)** in a ratio of 1:2 [42].

The stereochemistry of reactions of aldehydes with chiral organomagnesium compounds has been less extensively studied, but good diastereoselectivity has been reported [43–47]. In the following example, the organomagnesium reagent is more stereoselective than the organolithium compound from which it is prepared (or than a corresponding organotitanium reagent) [44]:




88% *de*

Asymmetric syntheses using reactions of achiral carbonyl compounds with achiral organomagnesium compounds in the presence of recoverable chiral solvating ligands would be very attractive. Unfortunately, only modest enantioselectivities have been achieved so far (see, for example, Refs. [48, 49]) though they are improving [50] — and, surprisingly, reactions with aldehydes are less promising than those with ketones (see below) [51, 52].

Barbier syntheses using aldehydes are somewhat susceptible to side-reactions [18, 53], but can give good yields, as in the following example.

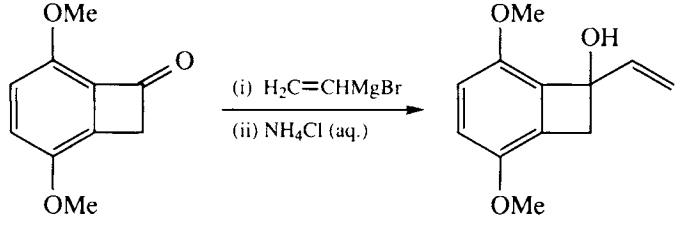
*Barbier synthesis of 1-phenylethanol* [54] Dry benzene (12 ml) (HAZARD), dry THF (3 ml) and magnesium (high purity, preferably sublimed) are placed in a dry reaction vessel fitted with a reflux condenser and a dropping funnel and furnished with an atmosphere of argon. The "Barbier mixture", consisting of freshly distilled benzaldehyde (5.3 g),

freshly distilled iodomethane (8.5 g), benzene (28 ml) and THF (7 ml), is placed in the dropping funnel. The Barbier mixture (~ 2 ml) is added to the reaction flask, and once the reaction has started (slight coloration) the remainder is added during about 90 min, the temperature of the reaction mixture being kept below 40°. Ice-cold saturated aqueous ammonium chloride is added. The organic layer is separated and the aqueous layer is extracted with ether (×3). The combined organic layers are washed well with water, and dried ($Na_2SO_4$). The solvents are evaporated and the residue distilled to give 1-phenylethanol (5.1 g, 85%), b.p. 75°/5 mmHg.

### 6.1.2 Addition to ketones

The addition of organomagnesium compounds to the carbonyl group of ketones is somewhat more susceptible to side-reactions than the corresponding reaction of aldehydes; the carbonyl group is more sterically hindered in the ketones, and generally has lower inherent reactivity. Nevertheless, satisfactory results are usually obtainable. In cases of difficulty, as noted in the introduction to this chapter, the addition reaction is favoured by less polar media (e.g. hydrocarbons containing only small proportions of ethers [13]; see Table 6.2, footnote *g*) and by lower reaction temperatures (see Table 6.2, footnote *e*), and by the addition of salts (see Table 6.2, footnote *c*). Conversion of the organomagnesium compound into another organometallic compound *in situ* may also circumvent side-reactions involving α-deprotonation. Many examples are tabulated in General Ref. [A], and some are listed in Table 6.2. The following procedure is typical.

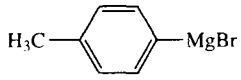
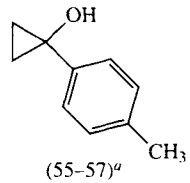
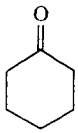
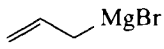
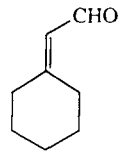
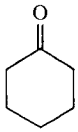
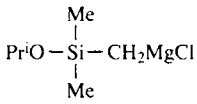
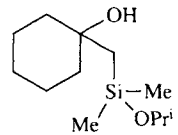
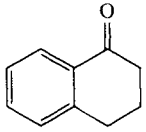
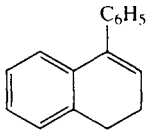
*1-Ethenyl-3,6-dimethoxybenzocyclobuten-1-ol* [61]




In a 25 ml three-necked flask is placed THF (3.0 ml) and vinylmagnesium bromide (~ 1 M in THF, 2.7 mmol), and the mixture is stirred at −10°. A solution of 3,6-dimethoxybenzocyclobutenone (0.10 g, 0.56 mmol) in THF (6 ml) is added dropwise; a deep wine-red coloration forms. The mixture is

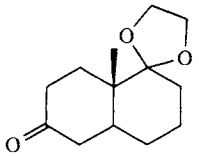
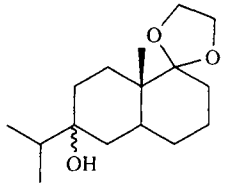
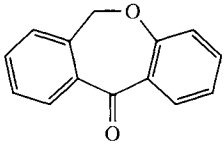
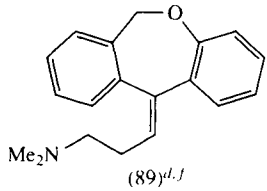
TABLE 6.2

Addition of organomagnesium compounds to ketones

| Ketone | Organomagnesium compound | Product isolated (yield, %) | Ref. |
|---|---|---|---|
| $(ClCH_2)_2CO$ |  |  (55–57)[a] | [55] |
|  |  |  (65)[b] | [56] |
|  |  |  (high) | [57] |
| $(Me_2CH)_2CO$ | $(CH_3CH_2CH_2)_2Mg$ | $(Me_2CH)_2C(OH)CH_2CH_2CH_3$ (up to 97)[c] | [7] |
|  | $C_6H_5MgBr$ |  (42–48)[d] | [58] |
| $(C_6H_5)_2CO$ | $C_6H_5MgCl$ | $(C_6H_5)_2C{=}CHC_6H_5$ (54–59)[d] | [59] |

*(continued on next page)*

TABLE 6.2 *(continued from previous page)*

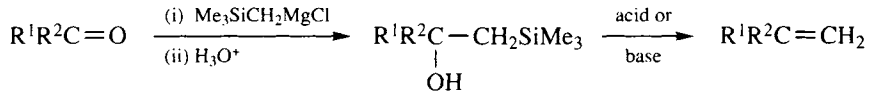
| Ketone | Organomagnesium compound | Product isolated (yield, %) | Ref. |
|---|---|---|---|
|  | $Me_2CHMgBr$ |  (50)[c] | [14] |
|  | $Me_2N(CH_2)_3MgBr$ |  (89)[d,f] | [60] |

[a]By treatment of the adduct with ethylmagnesium bromide and iron(III) chloride followed by acid. [b]By acylation and ozonolysis. [c]In the presence of lithium t-butoxide; with diisopropylmagnesium alone, substantial amounts of reduction are observed. [d]By dehydration of the alcohol. [e]Reaction at −50°; reaction in refluxing ether gave only 5%. [f]Reaction in toluene containing 5% THF.

stirred at −10° for 1.5 h, cooled to −50°, and treated with cold saturated aqueous ammonium chloride; the red colour is immediately discharged. Ether (20 ml) is added, and the mixture is allowed to warm to 0°. The phases are separated, and the aqueous phase is extracted with ether (4 × 5 ml). The combined organic phases are washed with water (10 ml), 5% aqueous sodium hydrogencarbonate (5 ml) and saturated aqueous sodium chloride (10 ml), dried ($MgSO_4$), and evaporated to leave a colourless oil. Flash chromatography (silica, 8:1 petroleum ether–ethyl acetate) gives 1-ethenyl-3,4-dimethoxybenzocyclobuten-1-ol (0.109 g, 88%), m.p. 54–56°.

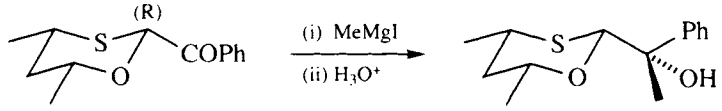
Note that in several examples in Table 6.2 the initial adduct is used for subsequent reactions *in situ*. Peterson olefination [62] and related reactions (General Ref. [E], p. 27) have been performed via organolithium more than via organomagnesium intermediates, but reactions involving

initial addition of the readily available trimethysilylmethylmagnesium chloride (see pp. 22, 29) are useful [62]:



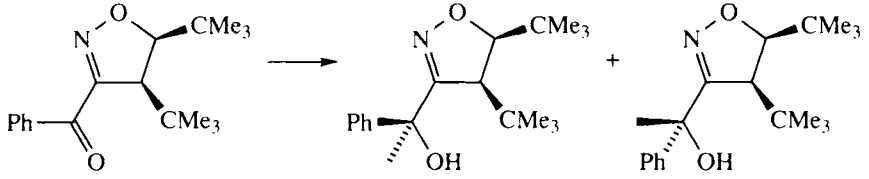
As in the case of aldehydes, Barbier reactions of magnesium, organic halide and ketone can be an alternative to the reactions via preformed organomagnesium compounds [18, 53].

The stereochemistry of addition of organomagnesium compounds to ketones is governed by similar factors to those influencing their addition to aldehydes (see Section 6.1.1). For addition of achiral organomagnesium compounds to α-chiral ketones, steric approach control is commonly observed, but chelation control may also operate [63, 64]. It is noteworthy that a pioneering asymmetric synthesis — one of the first which could be regarded as virtually *stereospecific*, was of this type [65]:



In this case steric approach control and chelation control (preferential magnesium–oxygen complexation) work in concert.

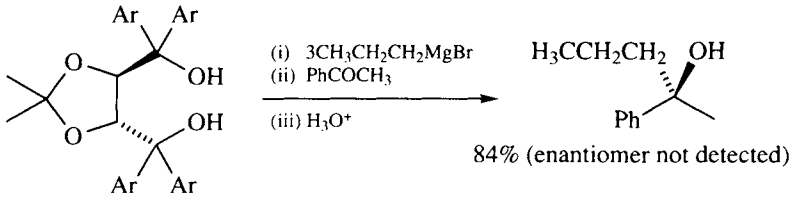
With β- [66] and γ-chiral ketones [67], examples are known where organomagnesium compounds add from the opposite face to organolithium compounds, as illustrated [66].



| | | | |
|---|---|---|---|
| MeMgBr, $CH_2Cl_2$, −78 °C | 7 | : | 93 |
| MeLi, THF, −78 °C | 95 | : | 5 |

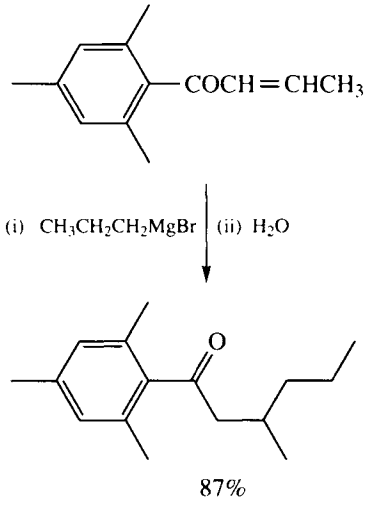
For reactions of chiral organomagnesium compounds with achiral ketones, references already cited in connection with aldehydes (e.g. Ref. [45]) are relevant.

Until recently, attempts to achieve asymmetric syntheses by reactions of achiral carbonyl compounds with achiral organomagnesium compounds in the presence of chiral ligands had met with only limited success (see p. 119). Recently, however, very promising results have been reported involving additions to ketones [52, 68]; "TADDOLs" (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanols, where the aryl groups are phenyl or 2-naphthyl) are particularly effective, as in the following example [52]:




84% (enantiomer not detected)

Organomagnesium compounds show a greater tendency than organolithium compounds towards conjugate addition to α,β-unsaturated ketones [A], and frequently give mixtures of products. Thus, when 1,2-addition is required, organolithium compounds are preferred. Probably the most generally applicable method for achieving 1,4-addition is conversion of the organomagnesium reagent into an organocopper species *in situ*; in many cases stoichiometric conversion is not necessary, and the addition of a catalytic amount of a copper(I) salt is sufficient [69].* Conjugate addition is




87%

*Zinc(II) complexes have also proved effective [70].

also favoured by (a) bulky substituents on the carbonyl carbon, as the example reaction [71], and (b) conditions favouring electron transfer (or electron transfer-induced homolysis [72]) pathways: polar, electron-donating solvents or additives, tertiary organomagnesium compounds and magnesium 'ate complexes [73], electron-accepting substrates.

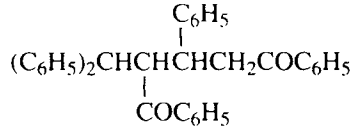
Chalcones commonly undergo 1,4-addition, as in the following procedure.

*1,2,2-Triphenylpropan-1-one* [74]

$$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) } C_6H_5MgBr} (C_6H_5)_2CHCH_2COC_6H_5$$

A solution of phenylmagnesium bromide is prepared from magnesium (0.54 g, 22 mmol) and bromobenzene (2.20 ml, 21 mmol) in diethyl ether (20 ml). The solution is stirred under reflux as a solution of chalcone (1,3-diphenylpropenone) (2.0 g, 10 mmol) in diethyl ether (15 ml) is added dropwise. The mixture is stirred under reflux for 5 min after the addition is complete, and then allowed to cool. 6M-Hydrochloric acid is added dropwise until two clear layers form. The layers are separated and the aqueous layer is extracted with ether (10 ml). The organic layers are combined, dried ($MgSO_4$), and the solvent is evaporated. The residue is recrystallized from methanol (20 ml), to give 1,2,2-triphenylpropan-1-one (1.97 g, 69%), m.p. 92–94°.

Note that in the above procedure the enone is added to an excess of the Grignard reagent. If conditions are employed which permit the simultaneous presence of the enolate resulting from 1,4-addition and the enone. Michael addition of the former to the latter leads to 1,3,5-triphenyl-2-(diphenylmethyl)pentane-1,5-dione **(5)**.

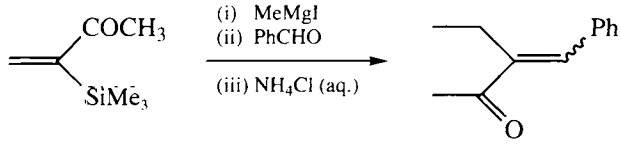


**(5)**

The formation of compound **(5)** is an example of tandem *vicinal* functionalization. An extensive review [75] refers to many examples similarly involving conjugate addition of an organomagnesium compound

(often copper-induced) to an α,β-unsaturated ketone, followed by reaction of the resulting enolate with an electrophile. The following procedure provides a neat example of tandem *vicinal* difunctionalization combined with Peterson olefination.

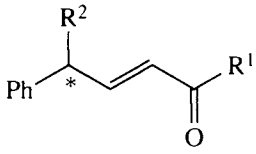
*3-Ethyl-4-phenylbut-3-en-2-one* [76]



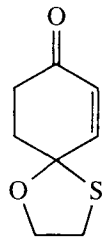

A solution of methylmagnesium iodide (1.2 mmol) in diethyl ether (3 ml) is cooled to −15° and a solution of 3-trimethylsilylbut-3-en-2-one (142 mg, 1 mmol) in diethyl ether (1 ml) is added. The mixture is stirred at −15° for 1 h and a solution of benzaldehyde (127 mg, 1.2 mmol) in diethyl ether (1 ml) is added. The mixture is stirred at −15° for 1 h and at 0° for 0.5 h, and saturated aqueous ammonium chloride is added. The mixture is extracted with ether (2 × 30 ml). The combined extracts are dried ($MgSO_4$) and the solvent is evaporated. Chromatography of the residue (silica, hexane–ethyl acetate 30:1) gives (*Z*)- (10 mg, 6%) and (*E*)-3-ethyl-4-phenylbut-3-en-2-one (67 mg, 39%).

A similar reaction at room temperature gave only the (*E*) isomer (59%).

The stereochemistry of conjugate addition of organomagnesium compounds to α,β-unsaturated ketones is governed by similar considerations to those governing addition to saturated ketones; recent examples include diastereoselective additions to both acyclic **(6)** [77] and cyclic [78] **(7)** enones.

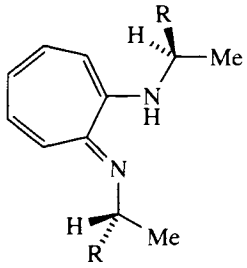



**(6)**

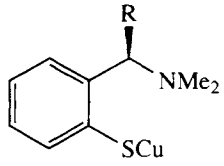



**(7)**

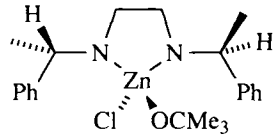
Although in some cases, copper catalysis has little effect on the stereochemistry, some asymmetric induction by chiral copper catalysts such as copper(I) complexes of aminotropone iminates **(8)** [79] or the chiral arylthiocopper compound **(9)** [80] has been achieved. Chiral zinc(II) complexes **(8)** also promote enantioselective conjugate addition [81].




**(8)**



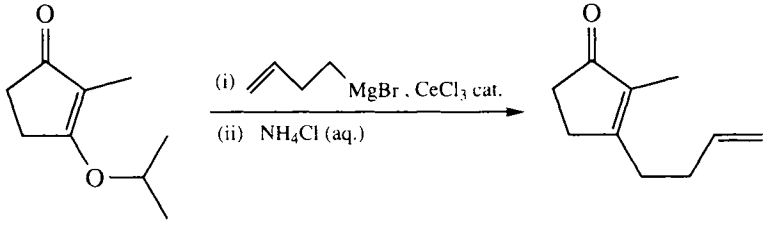

**(9)**




**(10)**

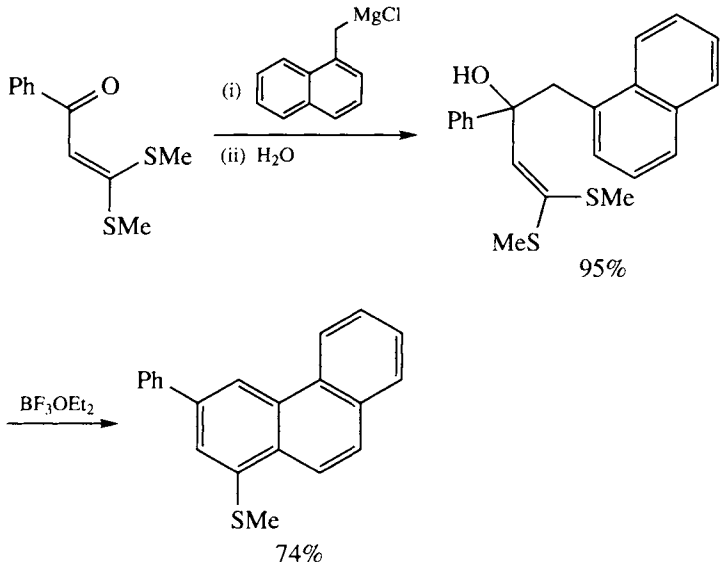
A special case of conjugate addition involves diaryl ketones. As noted in Section 4.2, conjugate addition of organomagnesium compounds may lead to products formally derived from addition to a ring. Such reactions are favoured by conditions promoting electron transfer, particularly when polar addition to the carbonyl group is sterically hindered [3].

One type of reaction of α,β-unsaturated ketones with organomagnesium compounds deserves special comment. β-Alkoxy or β-alkylthio α,β-unsaturated ketones tend to undergo 1,2-addition. This may be followed by elimination, as in the following example [82]:




In other cases, however, the initial adduct is stable, and its hydrolysis product is isolable, and is a useful intermediate for further transformations. For example, the products from reactions of organomagnesium compounds with β-oxoketene dithioacetals may be transformed into a variety of

aromatic and heteroaromatic systems, e.g. [83]:

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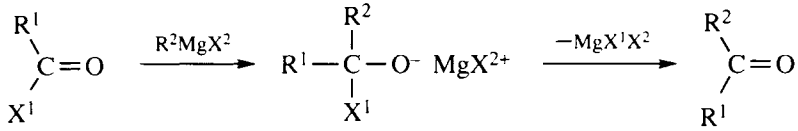
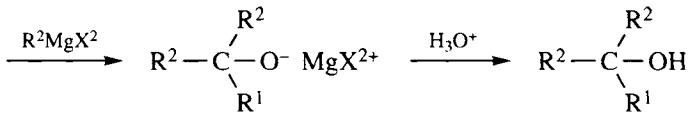
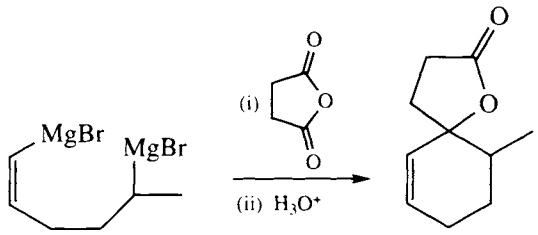
## 6.2 REACTIONS WITH ACYL HALIDES, ANHYDRIDES, ESTERS AND LACTONES

The reactions of organomagnesium compounds with acyl derivatives, $R^1COX$, where X represents a good leaving group, follow a common pattern:

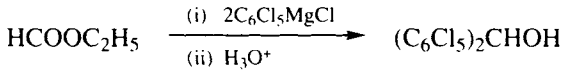




With an excess of the organomagnesium compound, such reactions readily give satisfactory yields of tertiary alcohols (though subject to side-reactions as noted in the introduction to this chapter) [A]; some examples are listed in Table 6.3. Barbier-type reactions may also be used [11]. With formate esters, the reaction gives secondary alcohols, as in entry 3 in Table 6.3 and in the following procedure. Reactions of di-Grignard reagents with lactones and cyclic anhydrides have proved a versatile route to spiro compounds [12, 13], as in the following example [12]:



*Bis(pentachlorophenyl)methanol* [14]

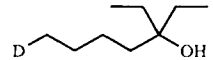
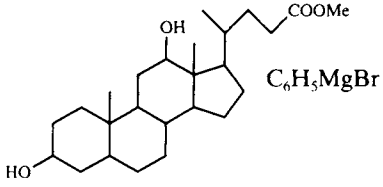
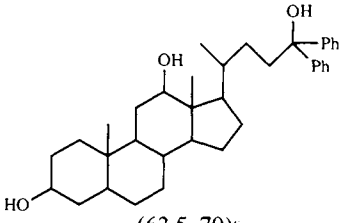
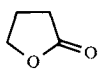
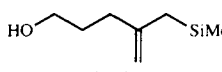
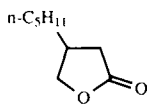
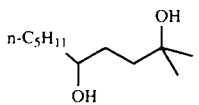


A solution of pentachlorophenylmagnesium chloride* is prepared from hexachlorobenzene (66 g, 0.23 mol) and magnesium (8.44 g, 0.35 mol) in a mixture of THF (150 ml) and benzene (150 ml) (HAZARD: toluene would be preferable). The solution is heated to reflux, and ethyl formate (40 ml, excess) is added by syringe at such a rate that the exothermic reaction maintains refluxing. The mixture is stirred as it is allowed to cool to room temperature during 1 h. Methanol (20 ml) is added, and the solvents are evaporated. The resulting dark-brown residue is washed with hydrochloric acid, methanol and ethyl acetate, and then recrystallized from 4:1 toluene–pyridine, to give bis(pentachlorophenyl)methanol (35 g, 29%).

*See also p. 35.

TABLE 6.3

Syntheses of tertiary alcohols by reactions of organomagnesium compounds with acyl derivatives

| Acyl derivative | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
| $Cl(CH_2)_4COCl$ | $C_2H_5MgBr$ |  (81)[a] | [1] |
| $C_6H_5COCl$ | $C_6H_5MgBr$ | $(C_6H_5)_3COH$ (71–80) | [2] |
| $HCOOC_2H_5$ | n-$C_4H_9MgBr$ | $(n\text{-}C_4H_9)_2CHOH$ (83–85) | [3] |
| $CH_3COOC_2H_5$ | $C_6H_5MgBr$ | $(C_6H_5)_2C{=}CH_2$[b] (67–70) | [4] |
| $C_6H_5COOC_2H_5$ | $C_6H_5MgBr$ | $(C_6H_5)_3COH$ (83–90) | [5] |
|  | $C_6H_5MgBr$ |  (63.5–70)[c] | [6] |
| $(C_2H_5O)_2CO$ | $C_2H_5MgBr$ | $(C_2H_5)_3COH$ (82–88) | [7] |
| $(C_2H_5O)_2CO$ | $(CH_3)_3CCH_2CH_2MgCl$ | $[(CH_3)_3CCH_2CH_2]_3COH$ (95)[d] | [8] |
|  | $Me_3SiCH_2MgCl$ |  (74)[e] | [9] |
|  | $CH_3MgBr$ |  (57) | [10] |

[a]After further reactions *in situ*: (i) Li; (ii) $D_2O$; (iii) $H_3O^+$. [b]From dehydration of alcohol. [c]Yield of subsequent reaction. [d]Crude. [e]$CeCl_3$ added to suppress enolization; product formed by Peterson elimination.

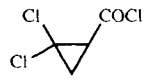
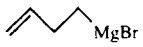
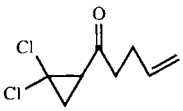
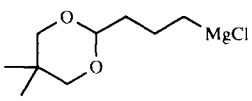
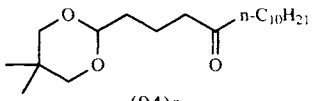
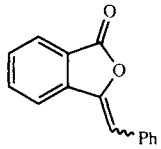
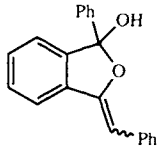
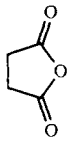
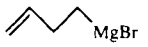
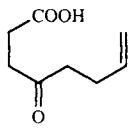
On the other hand, it is often desired to stop the reaction at the first stage, to synthesize a ketone. In this case, special conditions are required, in order to avoid the simultaneous presence of organomagnesium

compound and ketone. Thus, the organomagnesium compound should be added to an excess of the acyl derivative at the lowest possible temperature. Some examples of successful syntheses of ketones from acyl derivatives are listed in Table 6.4, and a procedure follows. In the case of acyl halides an alternative stratagem is the conversion of the organomagnesium compound in to another organometallic reagent *in situ*. Traditionally, cadmium halides have been added to Grignard reagents [A, 20, 21] but copper(I) salts have been extensively used [22]* and

*It has been reported, however, that the use of copper catalysts may lead to more side-reactions [23].

TABLE 6.4

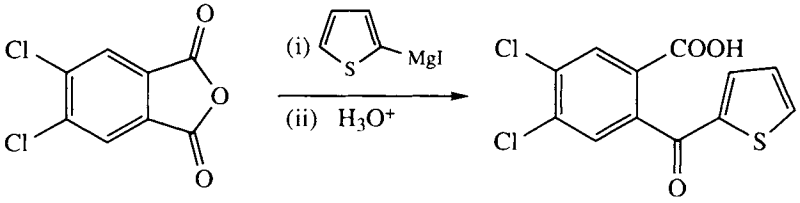
Syntheses of ketones by reactions of organomagnesium compounds with acyl derivatives

| Acyl derivative | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
|  |  |  (64) | [15] |
| $(CH_3)_3CCH_2COCl$ | $(CH_3)_3CH_2MgCl$ | $[(CH_3)_3CCH_2]_2CO$ (90) | [16] |
| $n\text{-}C_{10}H_{21}COCl$ |  |  (94)[a] | [17] |
|  | $C_6H_5MgBr$ |  (60–71) | [18] |
|  |  |  (40)[a] | [19] |

[a]Crude.

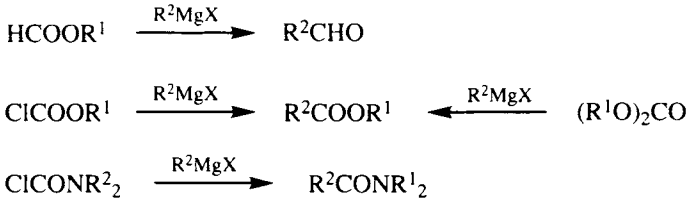
manganese(II) compounds are also effective [24]. Reactions with esters are especially difficult to control, and methods effective with organolithium compounds sometimes fail with organomagnesium compounds [25]. Recently, the 'ate reagent derived from methylmagnesium chloride and two equivalents of lithium bis(trimethylsilyl)amide has been reported as effective for the conversion of a methyl ester to a methyl ketone [26].

*4,5-Dichloro-2-(2-thienoyl)benzoic acid* [27]



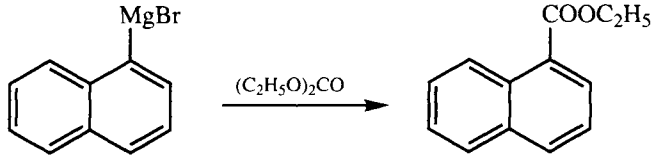

A solution of 2-thienylmagnesium iodide is prepared from 2-iodothiophene (5.5 g, 50 mmol) and magnesium (1.2 g, 50 mmol) in ether (45 ml) [27]. A suspension of 4,5-dichlorophthalic anhydride (10.85 g, 50 mmol) in ether (100 ml) is cooled in an ice bath and stirred vigorously as the Grignard reagent is added slowly. The mixture is stirred vigorously for 24 h, and saturated aqueous ammonium chloride (50 ml) and 6 M hydrochloric acid (10 ml) are added. The aqueous phase is separated and the precipitate formed in the organic phase is dissolved with 15% aqueous sodium carbonate (100 ml). The alkaline extract is separated and acidified by the addition of 6 M hydrochloric acid, dropwise with vigorous stirring, to give the product as a brown precipitate (94%), m.p. 198–199° (from water).

Similar considerations apply to reactions of organomagnesium compounds with formate esters (leading to aldehydes), chloroformates or carbonates (leading to esters) or carbamoyl chlorides (leading to amides):



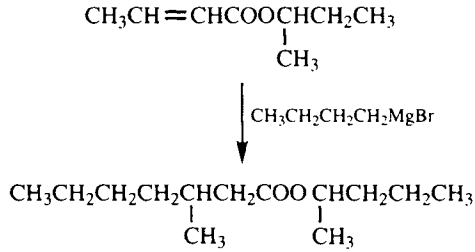

For the synthesis of aldehydes, reactions with formamides are preferable (see Section 6.3), though modest yields have been reported in a few cases [A]. The other reactions can give good yields [A], as in the following procedure, but have been little exploited.

*Ethyl naphthalene-1-carboxylate* [28]




A three-necked flask and a large dropping funnel are used in a standard set-up (see p. 16). A solution of 1-naphthylmagnesium bromide is separately prepared from 1-bromonaphthalene (207 g, 1.0 mol) and magnesium (24.3 g, 1.0 mol) in ether (600 ml) in benzene (550 ml; HAZARD), and transferred to the dropping funnel. In the flask are placed diethyl carbonate (177 g, 1.5 mol) and ether (100 ml). The mixture is stirred as the Grignard reagent is added at such a rate that steady refluxing is maintained. When the addition is complete, stirring is continued for 30 min and then the mixture is allowed to stand overnight. The mixture is poured, with swirling, on to ice (~ 1.5 kg), and cold 30% aqueous sulfuric acid (145 ml) is added slowly. The organic layer is separated and the aqueous layer extracted with ether (100 ml). The combined organic layers are concentrated to about 400 ml and washed with 5% aqueous sodium carbonate (2 × 40 ml) and dried ($CaCl_2$). The solvent is evaporated and the residue distilled at 287–307° and then redistilled under reduced pressure to give ethyl naphthalene-1-carboxylate (136–147 g, 68–75%), b.p. 143–144.5°/3 mmHg.

Reactions of organomagnesium compounds with α,β-unsaturated esters show a somewhat greater tendency to conjugate addition than reactions with α,β-unsaturated ketones (see p. 124). However, copper(I)* catalysis may be beneficial even in cases where conjugate addition is the main uncatalysed reaction [30]:




(68–78% uncatalysed, 80–85% with CuCl catalyst)

For an example of conjugate addition of a Grignard reagent to a cyanoacrylate, see Section 5.3, p. 105.

*Or copper(II) in conjunction with trimethylsilyl chloride [29].

## References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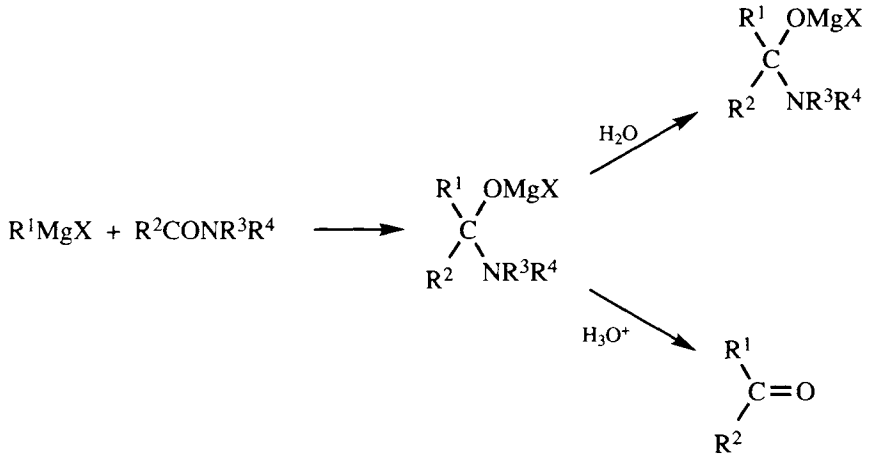
30. See Section 3.1, Ref. [73].

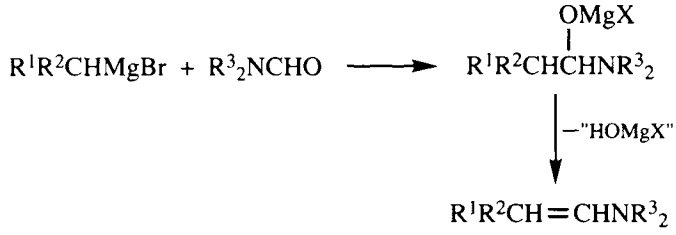

## 6.3 ADDITION TO *N,N*-DISUBSTITUTED AMIDES

Reactions of organomagnesium compounds with *N,N*-disubstituted amides differ from those of other acyl derivatives (Section 6.2) in that the initial adducts are much more stable. However, although examples are known where a carbinolamine may be isolated following careful hydrolysis, acid hydrolysis without special precautions usually gives the

carbonyl compound:




This type of reaction with *N,N*-disubstituted formamides, giving aldehydes, was an early application of Grignard reagents, sometimes known as the Bouveault reaction [A].* Dimethylformamide and *N*-methylformanilide, PhN(Me)CHO, have been most commonly used, but more recently *N*-formylpiperidine and 2-(*N*-formylmethylamino)pyridine have been recommended; examples are listed in Table 6.5, and a recent example of the traditional procedure follows. It should be noted that these reactions are subject to a number of side-reactions [A]. One useful one is the formation of enamines by elimination from the initial adduct [9]:

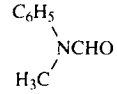
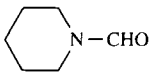
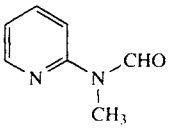
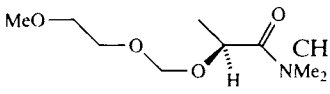
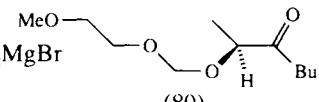
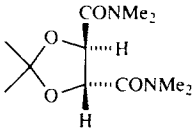
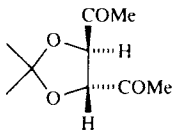
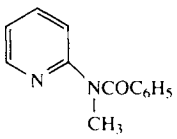
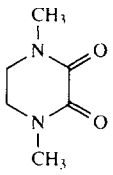
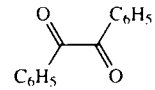
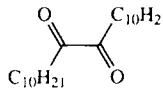



A "Barbier" modification has been described in which aldehydes are prepared by electrolysis of organic halides in DMF with a sacrificial magnesium anode [10].

*For an alternative and often superior synthesis of aldehydes from organomagnesium compounds, by reaction with orthoformates, see Section 8.2.1.

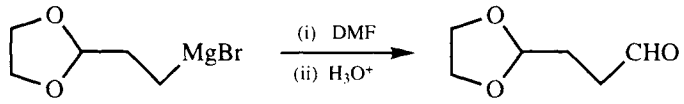
TABLE 6.5

Synthesis of aldehydes and ketones by reactions of organomagnesium compounds with amides

| Amide | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
| $(CH_3)_2NCHO$ | $(CH_3)_2CHCH_2MgCl$ | $(CH_3)_2CHCH_2CHO$ (56) | [1] |
|  | $C_6H_5MgBr$ | $C_6H_5CHO$ (up to 67) | [2] |
|  | $C_6H_5CH_2CH_2MgCl$ | $C_6H_5CH_2CH_2CHO$ (66–72) | [3] |
|  | $C_6H_5MgBr$<br>$C_6H_5CH_2MgCl$<br>$C_6H_5CH{=}CHMgBr$ | $C_6H_5CHO$ (72)<br>$C_6H_5CH_2CHO$ (80)<br>$C_6H_5CH{=}CHCHO$ (70) | [4][a] |
|  | $CH_3CH_2CH_2CH_2MgBr$ |  (80) | [5] |
|  | $CH_3MgCl$ |  (50)[b] | [6] |
|  | $CH_3CH_2MgCl$ | $C_6H_5COCH_2CH_3$ (83) | [7] |
|  | $C_6H_5MgBr$ |  (84) | [8] |
| | n-$C_{10}H_{21}MgBr$ |  (70) | |

[a]Other examples are also described. [b]A little t-alcohol is also obtained.

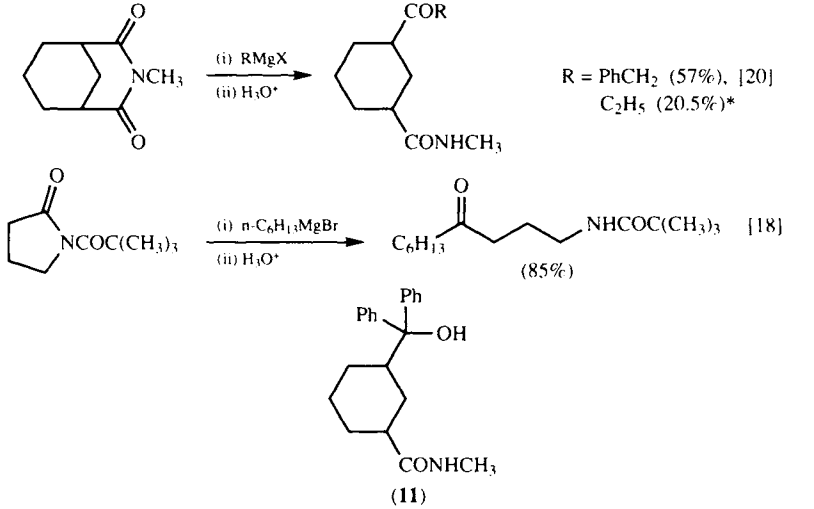
*3-(1,3-Dioxolan-2-yl)propanal* [11]




A Grignard reagent is prepared from 2-(2-bromoethyl)-1,3-dioxolane (20.02 g; 0.111 mol) in THF (120 ml) [12]. Dry DMF (9.5 ml, 0.123 mol) is added with stirring during 10 min, and the mixture is stirred at room temperature for 90 min. A solution of citric acid monohydrate (23.4 g, 0.111 mol) in water (70 ml) is added. The organic layer is separated and the aqueous layer is extracted with ether (5 × 20 ml). The combined organic layers are dried, the solvents are evaporated, and the residue is distilled under reduced pressure to give 3-(1,3-dioxolan-2-yl)propanal (57%), b.p. 85–90° at 18 torr.

The synthesis of ketones from organomagnesium compounds and *N,N*-dialkylamides has been comparatively little exploited, but a few examples are included in Table 6.5. A significant limitation has been the low reactivity of the amides, but this has been overcome by the use of *N*-(2-pyridyl)amides (see penultimate entry in Table 6.5) and especially *N*-methoxyamides (hydroxamates). Examples of the use of the latter are listed in Table 6.6.

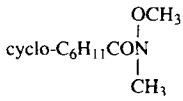
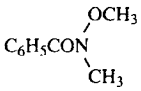
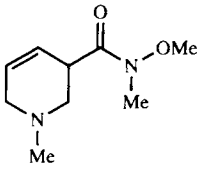
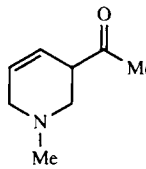
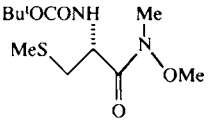
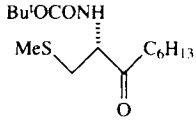
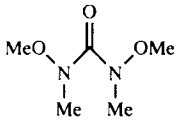
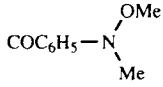
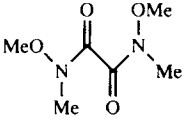
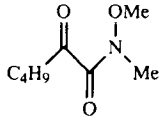
Few examples of reactions of organomagnesium compounds with lactams have been reported [A, E]. On the other hand, reactions with cyclic imides (and carbamate analogues [18, 19]), as illustrated by the following examples, have some promise in synthesis:




*With an excess of phenylmagnesium bromide, the t-alcohol **(11)** was obtained in high yield.

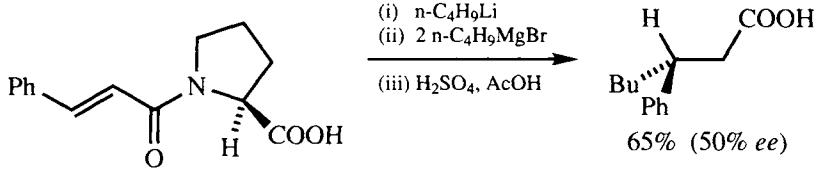
TABLE 6.6

Synthesis of ketones by reactions of organomagnesium compounds with *N*-methoxyamides

| *N*-Methoxyamide | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
|  | $CH_3CH_2CH_2CH_2MgBr$ | cyclo-$C_6H_{11}COCH_2CH_2CH_2CH_3$ (97) | [13][a] |
|  | $CH_3MgBr$ | $C_6H_5COCH_3$ (93–96) | [13] |
|  | $CH_3MgCl$ |  (79) | [14][a] |
|  | n-$C_6H_{13}MgBr$ |  (40)[b, c] | [15] |
|  | $C_6H_5MgBr$ |  (77) | [16][d] |
|  | n-$C_4H_9MgBr$ |  (75) | [17][a,d] |

[a]Other examples are also reported. [b]32% *erythro*, 8% *threo* [c]By reduction with sodium borohydride *in situ*. [d]Sequential reaction with organomagnesium or organolithium compounds used to prepare unsymmetrical ketones [17].

α,β-Unsaturated amides commonly undergo conjugate addition by organomagnesium compounds [A]. In the following example, a modest degree of asymmetric induction was achieved [21]:

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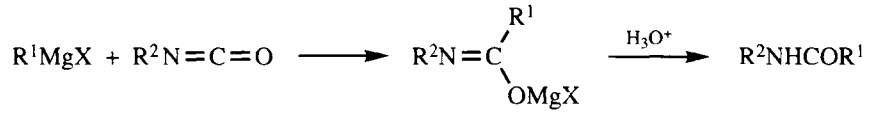
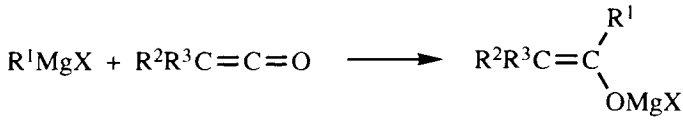
## 6.4 ADDITION TO CUMULATED CARBONYL GROUPS AND CARBOXYLATE IONS

The reaction of Grignard reagents with isocyanates is a good general method for preparing amides [A]:

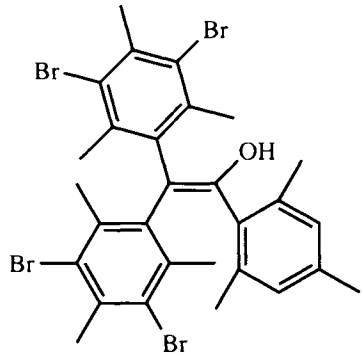


Indeed, the reaction with phenyl- or 1-naphthylisocyanate is sufficiently general to be recommended in traditional schemes for qualitative organic analysis (e.g. Ref [1]), as a general method for characterizing organic halides. However, it has been surprisingly little exploited in synthesis, although a "Barbier" adaptation promoted by sonication has been reported [2].

Analogous reactions of organomagnesium compounds with ketenes, giving enolates, also appear to be general [A]:

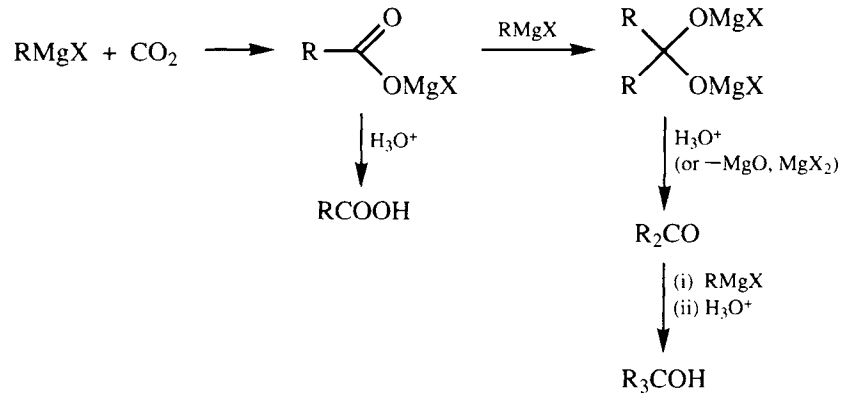


Although they have been very little exploited, one was recently used in the preparation of the isolable hindered enol **(12)** [3].



**(12)**

The reaction of organomagnesium compounds with carbon dioxide to give carboxylates, and thence carboxylic acids, was one of the first to be reported by Grignard [4], and Grignard also observed the important side-reactions leading to ketones and t-alcohols [5]:




In order to maximize the yield of carboxylic acid, the concentration of carbon dioxide should be as high as possible and the temperature as low as possible. These conditions are most commonly achieved by adding the organomagnesium solution to solid carbon dioxide. For routine cases the following procedure is recommended. A wide-mouthed conical flask or a tall beaker is flushed with nitrogen and crushed, fresh, *dry*, solid carbon dioxide is placed in it. It is sometimes advantageous to cover the carbon dioxide with a dry solvent such as ether. The organomagnesium solution is added by syringe, by syphoning or simply by pouring. The mixture is allowed to stand until the excess of carbon dioxide has evaporated, then worked up conventionally, with acidification to liberate the free acid. Several alternative procedures are given in General Ref. [A], which also includes many tabulated examples. Fully described examples from *Organic Syntheses* are listed in Table 6.7. A metal apparatus for large-scale reactions of Grignard reagents with $^{13}CO_2$ has been described [12].

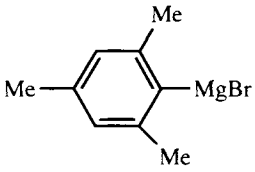
The conditions for the reaction with pentachlorophenylmagnesium chloride are noteworthy. In this case carbon dioxide is passed into the solution without special precautions; steric hindrance slows the reaction with carbon dioxide, but also the side-reactions.

Although the early literature records a number of examples of the synthesis of ketones by reactions of Grignard reagents with carboxylic acids or metal carboxylates [A], this method has been generally found less satisfactory than the corresponding reaction of organolithium compounds [G, 13].* However, it has been reported that reactions of halomagnesium

*Activation of a carboxylic acid by reaction with a chloroenamine is reported to facilitate synthesis of ketones even with acids containing reactive functional groups [14], but detailed confirmation is lacking.

TABLE 6.7

Synthesis of carboxylic acids by reaction of organomagnesium compounds with carbon dioxide

| Organomagnesium compound | Yield of corresponding carboxylic acid (%) | Ref. |
|---|---|---|
| $CH_3CH_2CH(CH_3)MgCl$[a,b] | 76–86 | [6] |
| $(CH_3)_3CMgCl$[b] | up to 70 | [7] |
|  | 84–86 | [8] |
| $C_6Cl_5MgCl$[c] | 77 | [9] |
| 1-$C_{10}H_7MgBr$[b] | 68–70 | [10] |
|  [a] | 60–70 | [11] |

[a]And other examples. [b]Carbon dioxide passed into solution at low temperature. [c]See text.

formates with primary alkyl-, alkenyl- and arylmagnesium halides can give useful yields of aldehydes, provided that *dry* formic acid is used, with THF as the solvent [15] (see also Section 6.3 and 8.2.2):

$$HCOOH + CH_3CH_2MgBr \longrightarrow HCO_2MgBr$$

$$HCO_2MgBr + RMgX \longrightarrow RCH(OMgBr)_2 \xrightarrow{H_2O} RCHO$$

Reactions with other metal carboxylates are also still occasionally used, as in the following example [16]:

$$CF_3CO_2Na + RMgBr \longrightarrow \underset{(40\text{–}50\%)}{CF_3COR}$$

(It should be noted that the reaction of acids such as phenylacetic acid with two equivalents of a Grignard reagent gives "Ivanov reagents", $ArC{=}C(OMgX)_2$ [17].)

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7. See Section 3.1, Ref. [79].
8. See Section 3.1, Ref. [112].
9. See Section 3.1, Ref. [36].
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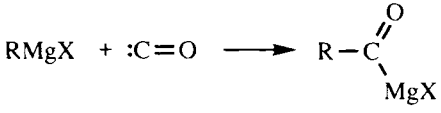
## 6.5 ADDITION TO CARBON MONOXIDE AND METAL CARBONYLS

Organomagnesium compounds are less reactive than organolithium compounds [E] towards carbon monoxide and metal carbonyls. The initial reaction with carbon monoxide is similar — addition to give an acylmagnesium compound:

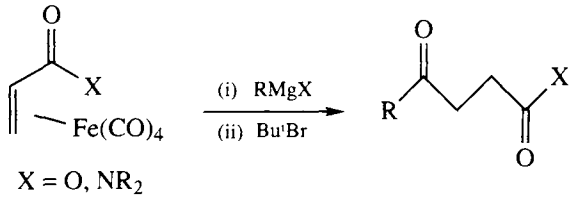


However, many subsequent reactions can occur, and the outcome is not generally useful for synthesis [1, 2].*

Similarly, reactions of organomagnesium compounds with metal carbonyls have not been found useful for synthesizing carbene complexes. On the other hand, reactions of organomagnesium compounds with iron

*Some reactions with acyl halides with magnesium under "Barbier" conditions also appear to involve acylmagnesium intermediates [3].

tetracarbonyl complexes of α,β-unsaturated esters [4] and amides [5] show some promise as a route to 4-oxo-esters and amides:




X = O, $NR_2$

## References

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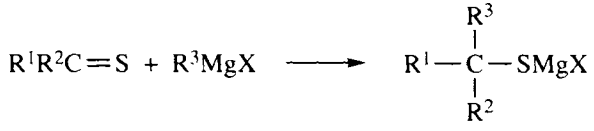
5. A. Pouilhés and S. E. Thomas, *Tetrahedron Lett.* **30**, 2285 (1989).

# —7—

# Carbophilic Addition of Organomagnesium Compounds to Thiocarbonyl Groups

Some reactions of organomagnesium compounds with thiocarbonyl compounds are analogous to those with carbonyl compounds, forming a carbon–carbon bond by attack of the organic group of the organomagnesium compound at the thiocarbonyl carbon; these reactions are the subject of this chapter. Other reactions proceed by "thiophilic addition", giving a new carbon–sulfur bond; these reactions are covered in Section 12.4. The mechanisms of the alternative pathways (and of other reactions not involving addition to the thiocarbonyl group), and the factors governing which pathway is followed, are still imperfectly understood [D, 1]. Nevertheless, some generalizations can be made, though there are exceptions, and the outcome of a given reaction may depend on the experimental conditions.

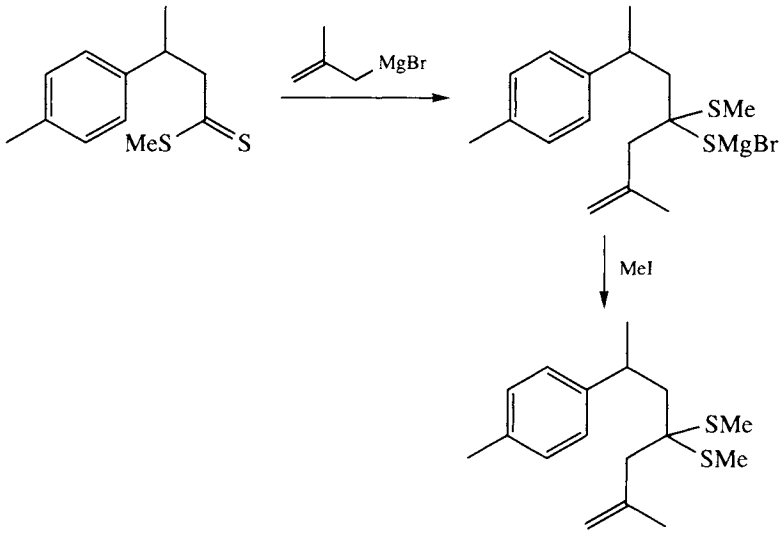
On the whole, reactions of thioketones with vinyl-, allyl-, propargyl-, benzyl-, and, sometimes, methylmagnesium halides proceed by carbophilic addition [1–3] (though subsequent rearrangements to the thiophilic product may occur [2]):



As in the case of ketones, reduction and α-deprotonation may be significant side-reactions.

The same classes of organomagnesium compound tend to react carbophilically with dithioesters [4]. An important difference from the corresponding reactions of carboxylic esters is that the initial adducts are much more stable, and can be trapped, as in the following

example [5]:




Syntheses of dithioesters by the reaction of Grignard reagents with dithiochloroformates have been reported, but the yields were at best modest [5]:*

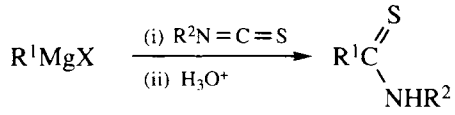
$$RMgX + ClC(S)SCH_2CH_3 \longrightarrow RC(S)SCH_2CH_3$$

Reactions of organomagnesium compounds with α,β-unsaturated dithioesters are somewhat unpredictable, 1,2-, 1,4-carbophilic and thiophilic addition having been observed [6]. With α,β-unsaturated thioamides [7] and imidothioesters [6], however, 1,4-carbophilic addition appears to predominate.

The most generally useful reactions of organomagnesium compounds with thiocarbonyl compounds are those with carbon disulfide and with isothiocyanates. The former can be used to prepare a variety of compounds by further reactions of the dithiocarboxylate initially formed, and the latter is a good general method for synthesizing thioamides:

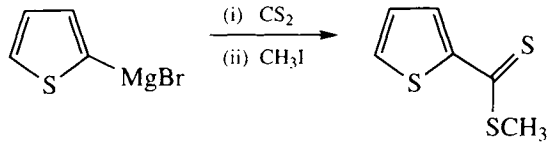
$$RMgX + CS_2 \longrightarrow RCS_2MgX \xrightarrow{E^+} R-C(=S)-SE$$

*The same paper also reports reactions with chlorothioformamides, $ClC(S)NR_2$, but the nature of the products is unclear.




In both cases carbophilic attack predominates, though thiophilic attack can sometimes be a troublesome side-reaction [8]. For reactions with carbon disulfide, THF is preferred as the solvent, and catalysis by copper(I) bromide is often beneficial. Some examples of reactions with carbon disulfide are listed in Table 7.1, and a procedure follows.

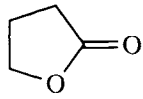
*Methyl thiophene-2-carbodithioate* [8]




A solution of thiophene-2-magnesium bromide is prepared by the reaction of magnesium (5 g) with 2-bromothiophene (16.3 g) in THF (110 ml) [8], and decanted from unreacted magnesium, which is washed with THF (20 ml). The solution is cooled to 20°, and copper(I) bromide and carbon disulfide (10.6 g, excess) are added. The mixture is warmed to about 30°. When the resulting exothermic reaction has subsided, the mixture is heated at 50° for 30 min. Iodomethane (21.3 g) and

TABLE 7.1

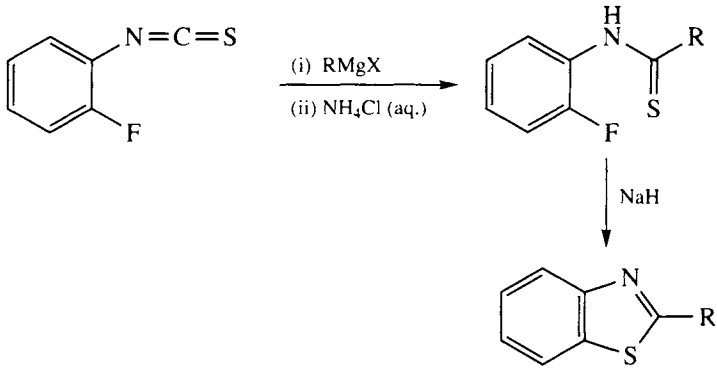
Reactions of organomagnesium compounds with carbon disulfide

| Organomagnesium compound | Reagent added to dithiocarboxylate | Product (yield, %) | Ref. |
|---|---|---|---|
| $CH_3CH_2MgCl$ | $CH_3SSO_2CH_3$ | $CH_3CH_2C(S)SSCH_3$ (95) | [9] |
| $CH_3CH_2MgBr$ | $BrCH_2C{\equiv}CH$ | $CH_3CH_2CS_2CH_2C{\equiv}CH$ (72) | |
| | $BrCH_2CH{=}CH_2$ | $CH_3CH_2CS_2CH_2CH{=}CH_2$ (80) | [10] |
| $C_6H_5MgBr$[a] | $ClCH_2CO_2Na$ | $C_6H_5CS_2CH_2CO_2H$ (40) | [11] |
| $n\text{-}C_7H_{15}MgBr$[a] |  | $n\text{-}C_7H_{15}CS_2(CH_2)_3COOH$ (60) | [12] |

[a]Other examples are also described; yields are variable.

hexametapol (CAUTION: suspected carcinogen) (40 ml) are added and the mixture is heated at 60° for 3 h. The mixture is poured into a solution of potassium cyanide (CAUTION) (4 g) and ammonium chloride (30 g) in water (200 ml), and the resulting mixture is shaken vigorously. The organic layer is separated, and the aqueous layer is extracted with ether (×4). The combined organic layers are washed with water (×4) and dried ($MgSO_4$). The solvent is exaporated under reduced pressure, and the residue is fractionally distilled to give methyl thiophene-2-carbodithioate, b.p. ~ 100° at 0.5 mmHg (> 90% based on the Grignard reagent).

Several early examples of reactions with isothiocyanates have been tabulated [A]; the following more recent example has also been carried out by a "one pot" procedure [13]:

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2. M. Dagonneau, *J. Organomet. Chem.* **80**, 1 (1974).
3. D. Paquer and M. Vazeux, *J. Organomet. Chem.* **140**, 257 (1977).
4. S. Masson, M. Saquet and A. Thuillier, *Tetrahedron* **33**, 2949 (1977).
5. H. Viola and R. Mayer, *Z. Chem.* **16**, 355 (1976).
6. See Section 5.1, Ref. [23b].
7. Y. Tamaru, T. Harada, H. Iwamoto and Z.-I. Yoshida, *J. Am. Chem. Soc.*, **100**, 5221 (1978).
8. See Section 3.1, Ref. [62].
9. R. S. Sukhai and L. Brandsma, *Synthesis*, 971 (1979).
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12. S. R. Ramadas and P. S. Srinivasan, *J. Prakt. Chem.* **319**, 169 (1977).
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# —8—

# Substitution at Carbon by Organomagnesium Compounds

For organic synthesis, a good general method for creating carbon–carbon bonds by formal nucleophilic substitution would be invaluable. Unfortunately the apparently obvious methods, such as reactions of organometallic compounds with organic halides, are often far from satisfactory. Accordingly, many variations on both the nucleophilic component and the leaving group have been tried, and the mechanistic complexities of the reactions — they are rarely straightforward nucleophilic substitutions — have been extensively studied [1]. In this chapter, an attempt is made to summarize the circumstances in which acceptable yields of the desired products have been achieved, without detailed discussion of reaction mechanisms.

### Reference

1. Yu. N. Polivin, R. A. Karakhanov and V. N. Postnov, *Uspekhi Khim.* **59**, 401 (1990).

## 8.1 DISPLACEMENT OF HALIDE

As noted above, the reaction

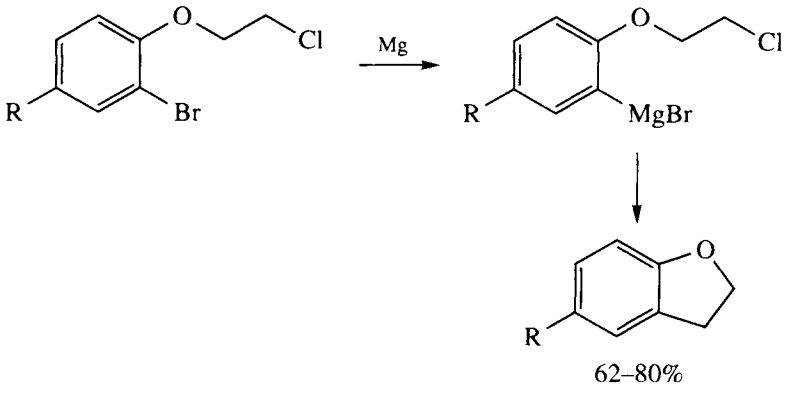
$$R^1MgX^1 + R^2X^2 \longrightarrow R^1\text{-}R^2 + MgX^1X^2$$

has significant limitations, even though organomagnesium compounds are somewhat less susceptible than organolithium compounds [G] to side-reactions involving metal–halogen exchange or deprotonation. The simple, uncatalysed reaction indeed only gives acceptable results for a fairly narrow range of organic halides.

(a) Some primary alkyl bromides and iodides (especially iodo-

methane). Some primary alkyl chlorides may also be satisfactory when the substitution is intramolecular, as in the following example [1]*(see also Table 8.1, entry 1):

*But see Ref. [2].




62–80%

(b) Allyl and benzyl halides (the former often with rearrangement) (e.g. see Ref. [3])*.

*The reaction of magnesium with allyl halides can be a useful method for synthesizing 1,5-dienes by Wurtz-type coupling, e.g. [4].

$$2CH_2{=}CHCH_2Cl + Mg \rightarrow CH_2{=}CHCH_2CH_2CH{=}CH_2$$
(55-65%)

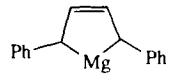
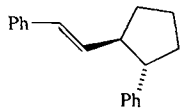
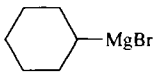
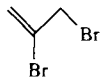
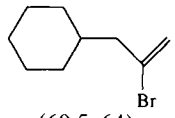
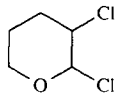
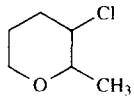
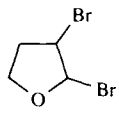
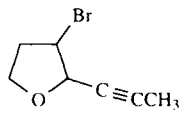
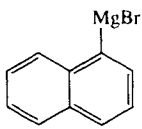
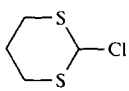
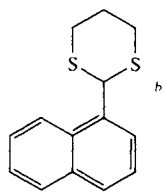
(c) α-Haloethers and thioethers.

Some examples to illustrate these categories are listed in Table 8.1. Many examples of reactions between organomagnesium compounds and organic halides are tabulated in General Ref. [A]; it should be noted, however, that for many of the earlier experiments, transition metals may have been present as impurities in the magnesium used. While under some circumstances transition metal catalysis may be beneficial, under the conditions commonly used in the early experiments it usually led to a proliferation of products. For reactions with primary alkyl and allylic halides, catalysis with copper(I) salts is often beneficial;† examples of such reactions are also shown in Table 8.1 and a procedure follows.

†For reactions involving stoichiometric conversion of organomagnesium compounds into organocopper reagents, see Chapter 16.

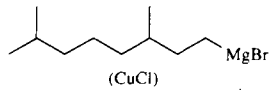
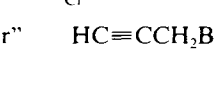
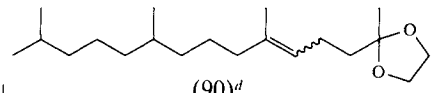
TABLE 8.1

Reactions of organomagnesium compounds with organic halides

| Organomagnesium compound | Halide | Product (yield, %) | Ref. |
|---|---|---|---|
| 1. **Uncatalysed** | | | |
|  | $Cl(CH_2)_3Cl$ |  (81) | [5] |
|  |  |  (60.5–64) | [6] |
| $PhMgBr$ | $ClCH_2OCH_2CH_2Cl$ | $PhCH_2OCH_2CH_2Cl$[a,b] | [7] |
| $CH_3MgBr$ |  |  (65–72) | [8] |
| $H_3CC{\equiv}CMgBr$ |  |  (almost quantitative) | [9] |
|  |  |  (57) | [10] |
| 2. **Copper catalysed** | | | |
|  (CuI) | $n\text{-}C_6H_{14}I$ |  (91) | [11][b,c] |

*(continued on next page)*

TABLE 8.1 *(continued from previous page)*

| Organomagnesium compound | Halide | Product (yield, %) | Ref. |
|---|---|---|---|
| 4-$CH_3C_6H_4MgBr$ (CuBr) | $CH_2Br_2$ | $(4\text{-}CH_3C_6H_4)_2CH_2$ (83)[b] | [12] |
| $C_6H_5CH_2O(CH_2)_{11}MgBr$ ($Li_2CuCl_4$) | $Br(CH_2)_6Br$ | $C_6H_5CH_2O(CH_2)_{17}Br$ (44) | [13] |
| n-$C_6H_{11}C{\equiv}CMgBr$ (CuCl) | $BrCH_2CH{=}CH_2$ | n-$C_6H_{11}C{\equiv}CCH_2CH{=}CH_2$ (high) | [14] |
|  (CuCl) |  |  (90)[d] | [15] |
| "$H_2C{=}C{=}CHMgBr$" (CuCl) | $HC{\equiv}CCH_2Br$ | $H_2C{=}C{=}CHCH{=}C{=}CH_2$ (30–36) | [16] |
| $C_6H_5C{\equiv}CMgBr$ (CuCl) | $HC{\equiv}CCH_2Br$ | $C_6H_5C{\equiv}CCH_2C{\equiv}CH$ (54–75) | [17] |

[a]Reaction with Na/K, then hydrolysis, gave $PhCH_2OH$ (70% overall); by a one-pot procedure the yield was 73%. [b]Other examples also reported. [c]For related examples see Ref. [18]. [d]A 91:1 mixture with unrearranged isomer.

*1-Bromo-4-phenylbutane* [19]

$$C_6H_5MgBr + Br(CH_2)_4Br \xrightarrow[CuBr,LiBr]{} C_6H_5(CH_2)_4Br$$

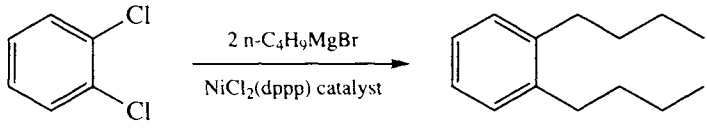
A solution of copper(I) bromide (5 mmol) and lithium bromide (10 mmol) in THF (10 ml) is added to a mixture of 1,4-dibromobutane (300 mmol) and THF (90 ml). The mixture is warmed to 40° and phenylmagnesium bromide (1 M in THF; 100ml) is added dropwise during 1 h, at such a rate that the temperature is maintained at 50–55°. The mixture is stirred at 50° for 1 h and cooled to room temperature. A solution of ammonium chloride (30 g) and potassium cyanide (5 g) (CAUTION) in ice–water (200 ml) is added. The mixture is shaken vigorously. The aqueous layer is separated and extracted with ether (×4). The combined organic solutions are dried ($MgSO_4$) and concentrated under reduced pressure. Fractional distillation gives 1-bromo-4-phenylbutane (85%), b.p. 83°/0.8 mmHg.

Not surprisingly, attempted uncatalysed cross-coupling between organomagnesium compounds and vinylic or aryl halides generally fails, and early studies of transition metal catalysis led to a variety of products, notably derived from homo-coupling (2RMgX → R–R), reduction, and elimination. However, catalysts are now available which lead to good yields of the desired products, though small amounts of homo-coupling and reduction products are also commonly obtained, and rearrangement of the organic group of the organomagnesium compound can also occur. The chemistry of catalysed cross-coupling reactions has been reviewed [20, 21], and only the main features leading to useful syntheses are summarized here.

The most generally applicable catalysts are diphosphine complexes of nickel(II) halides, notably dichloro[1,3-bis(diphenylphosphino)propane]nickel(II), "$NiCl_2$(dppp)", and to a lesser degree analogous palladium(II) complexes. Procedures for the latter, and tables of examples, are included in a companion volume [22]. Many examples are listed in the reviews [20, 21]; a procedure follows, and selected examples, mostly recent, or illustrating the range of products obtainable, are listed in Table. 8.2*.

*Some examples are tabulated in Ref. [33].

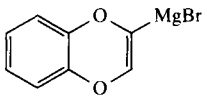
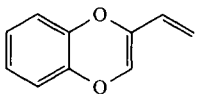
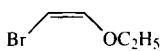
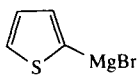
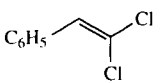
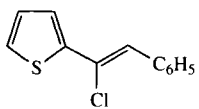
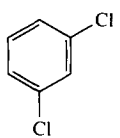
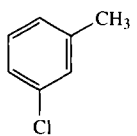
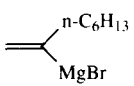
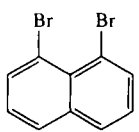
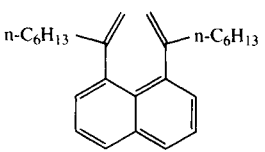
*1,2-Dibutylbenzene* [33]

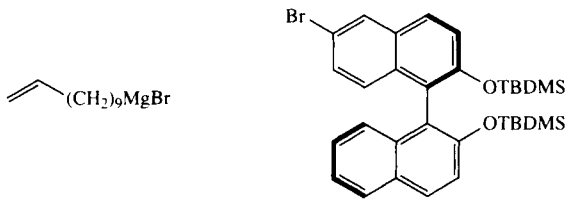



$NiCl_2$(dppp) (~0.25 g), 1,2-dichlorobenzene (29.5 g; 0.201 mol) and diethyl ether (150 ml) are placed in a 1 litre flask, fitted with a pressure-equalizing dropping funnel and furnished with an inert atmosphere. The mixture is cooled in an ice bath and stirred as the Grignard reagent prepared from magnesium (12.2 g, 0.502 mol) and bromobenzene (68.5 g, 0.500 mol) in ether (250 ml) are added during 10 min. The resulting mixture is stirred as it warms to room temperature; within about 30 min an exothermic reaction starts. Stirring is continued at room temperature for 2 h (more ether being added if necessary) and then under reflux for 6 h. The mixture is cooled in an ice bath and stirred as 2 M-hydrochloric acid is added slowly (CAUTION: EXOTHERMIC). The organic layer is separated, and the aqueous layer is extracted with ether (2 × 70 ml). The combined organic layers are washed with water, saturated aqueous sodium

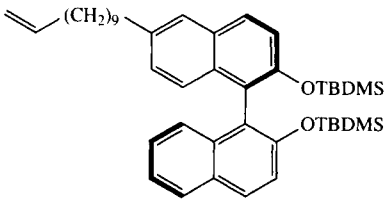
TABLE 8.2

Catalysed cross-coupling of organomagnesium compounds with vinylic and aryl halides

| Organomagnesium compound | Halide | Catalyst[a] | Product (yield, %) | Ref. |
|---|---|---|---|---|
|  |  | $NiCl_2(dppp)$ |  (80)[b] | [23] |
| $C_6H_5MgBr$ |  | $NiCl_2(dppp)$ | $C_6H_5CH{=}CHOC_2H_5$ (70)[b,c] | [24] |
|  |  | $PdCl_2(dppb)$ |  (80) | [25] |
| $CH_3MgCl$ |  | $PdCl_2(dppf)$ |  (93) | [26] |
|  |  | $NiCl_2(dmpe)$ |  (55) | [27] |

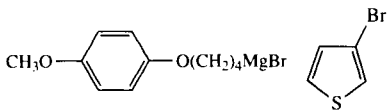



$NiCl_2(dppp)$

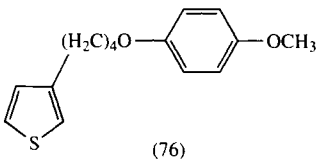



(83)

[28]

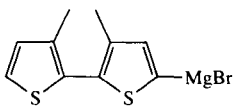


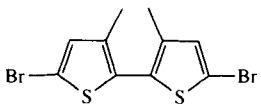

$NiCl_2(dppp)$



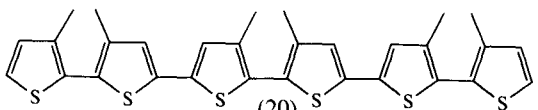

(76)

[29]



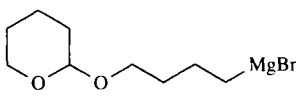



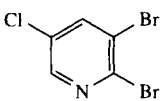

$NiCl_2(dppp)$



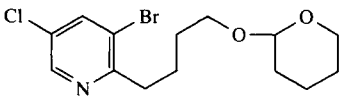

(20)

[30]



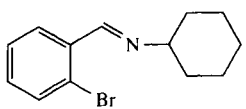

$NiCl_2(dppp)$

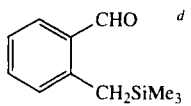



(79)

[31]

$Me_3SiCH_2MgCl$



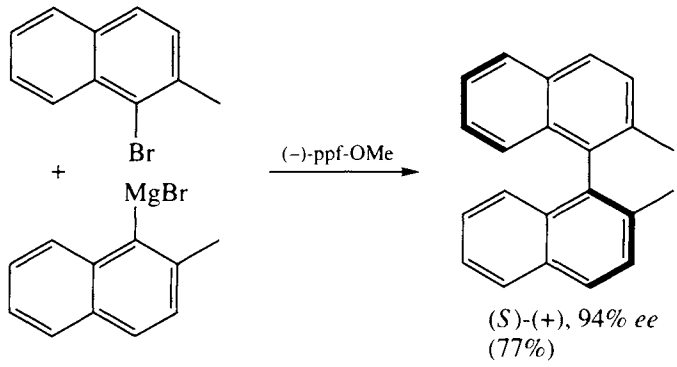

(90)

[32]

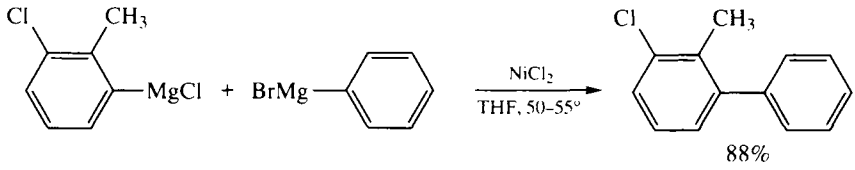
[a] dppp, 1,3-bis(diphenylphosphino)propane; dppb, 1,4-bis(diphenylphosphino)butane; dppf, 1.1′-bis(diphenylphosphino)ferrocene; dmpe, 1,2-bis(dimethylphosphino)ethane; acac, pentane-2,4-dione. [b] Other examples are also described. [c] (*E*):(*Z*) = 42:58. [d] Following hydrolysis on work-up.

hydrogencarbonate, and water, then dried (calcium chloride). The solvent is evaporated and the residue fractionally distilled through an efficient column, to give 1-butyl-2-chlorobenzene (~4 g), b.p. 52–54°/3.5 mmHg, and 1,2-dibutylbenzene (30.0–31.5 g; 79–83%), b.p. 76–80°/3.5 mmHg).

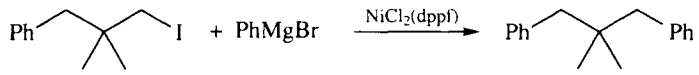
The nature of the phosphine ligand may be critical in certain cases, and some success has been achieved in inducing asymmetry by the use of chiral ligands [5]. A notable recent example is shown in the following scheme [34]:




In contrast, cross-coupling between arylmagnesium chlorides and aryl bromides is catalysed by nickel(II) chloride, without any bidentate ligand [35]:

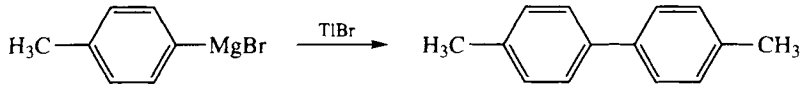



Palladium-catalysed cross-coupling of organomagnesium compounds with alkyl halides is rarely useful (e.g. see [36]), but a satisfactory nickel-catalysed coupling with a neopentyl halide has been reported recently [37]:




Various methods for direct homo-coupling are now available, such as palladium-induced methods [22], so that prior conversion of the halide

into an organomagnesium reagent is often superfluous. Nevertheless, efficient examples have been well described, e.g. [38]:

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17. See Section 3.2, Ref. [16].
18. See Section 3.2, Ref. [62].
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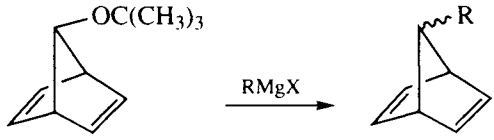
## 8.2 DISPLACEMENT OF OXYGEN FUNCTIONS

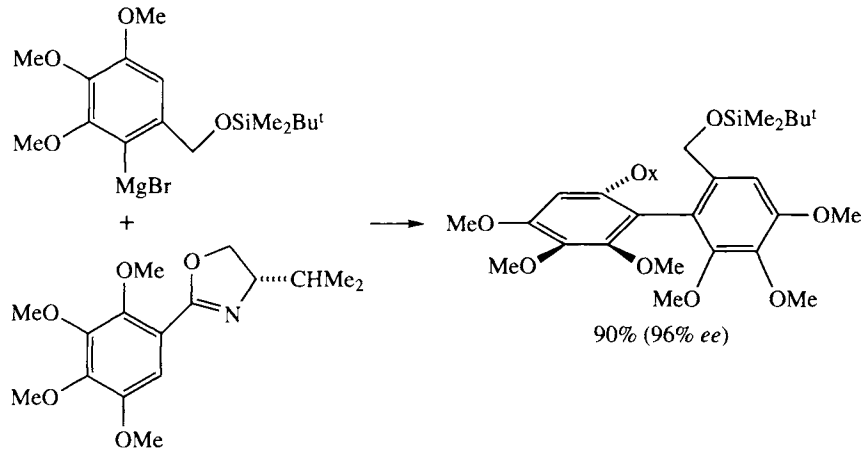
### 8.2.1 Displacement of alkoxide

Simple ethers are, of course, sufficiently inert to organomagnesium compounds to be the most commonly used solvents. Displacement of alkoxide can occur, however, if there are special factors promoting this pathway, such as ring strain (as in the case of oxiranes and oxetanes) and low electron density at the carbon atom to be attacked (as in the cases of acetals and orthoesters, and aromatic rings bearing activating groups). Catalysed reactions with vinyl ethers are also useful, and catalysed reactions with allyl and propargyl ethers have also been reported [E]. The special case of 7-t-butoxynorbornadiene is also noteworthy [1]:

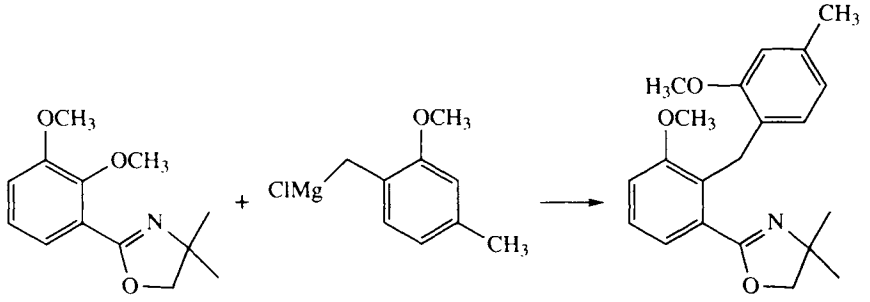



#### *8.2.1.1 Displacement from aryl and vinyl ethers*

Under forcing conditions, alkyl aryl ethers are cleaved by Grignard reagents by displacement of aryloxide [A]. Such reactions are not generally useful in synthesis, but the displacement of *methoxide* from positions *ortho* to alkoxycarbonyl [2] and oxazolinyl groups [3] has been applied to the synthesis of *ortho*-substituted carboxylic acids, and displacement *ortho* to diphenylphosphino groups has also been reported [4]. The following example describes the key step in a synthesis of anthraquinones. Recently, asymmetric induction by a chiral oxazolinyl substituent has been reported [5]:

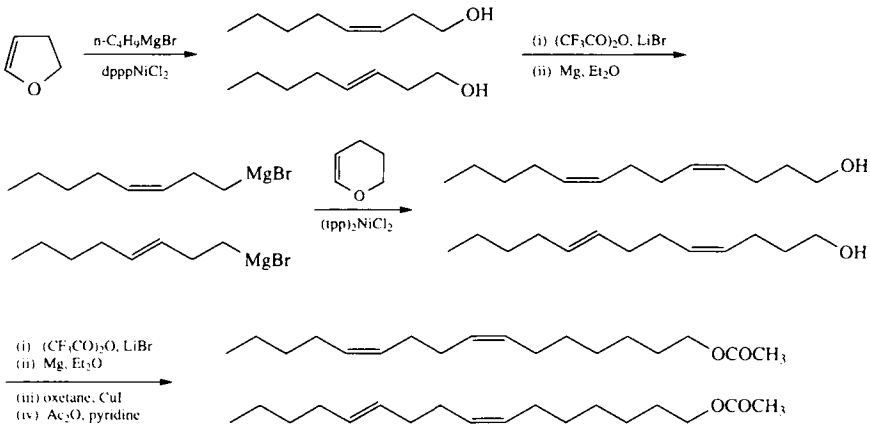



*4,5-Dihydro-2-[2-(2-methoxy-4-methylbenzyl)-3-methoxyphenyl]-4,4-dimethyloxazole* [6]




The Grignard reagent prepared by the reaction of 4-chloromethyl-2-methoxytoluene (2.27 g, 13.3 mmol) with magnesium anthracenide (see p. 40) in THF (50 ml) is added at room temperature to a stirred solution of 4,5-dihydro-(2,3-dimethoxyphenyl)-4,4-dimethyloxazole (3.0 g, 12.7 mmol) in THF (30 ml). The solution is stirred for 18 hours at room temperature and then poured into water. The resulting solution is extracted with ethyl acetate, and the organic extract is thoroughly extracted with 2 M-hydrochloric acid. The combined aqueous extract is basified with aqueous ammonia and extracted with ethyl acetate. The extract contains the product, which may be purified, e.g. by radial chromatography, to give the title compound (2.7 g, 86%), m.p. 155–156.5° (from light petroleum).

Nickel-catalysed displacement of alkoxide from enol ethers shows considerable potential in synthesis. It is particularly applicable to ring-opening of 2,3-dihydrofurans, preferably by long-chain primary alkyl Grignard reagents or Grignard reagents lacking β-hydrogens [7]; 3,4-dihydro-2*H*-pyrans are less reactive, but can give acceptable results [8]. Both reactions are illustrated by the synthesis of the pheromone gossyplure, which occurs in nature as a mixture of (11*Z*) and (11*E*) isomers [9]:

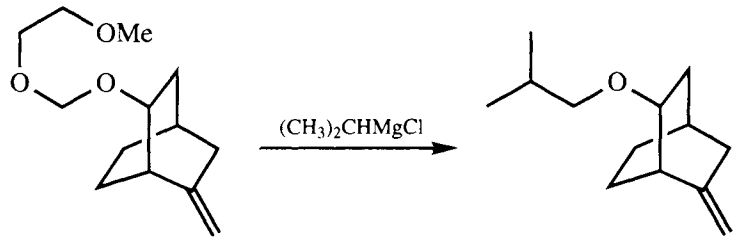



### *8.2.1.2 Displacements from acetals, aminals, orthoesters and related compounds*

Under mild conditions, acetals are sufficiently unreactive towards organomagnesium compounds to serve as protected carbonyl compounds. Under more vigorous conditions, however, displacement of one alkoxy group occurs:

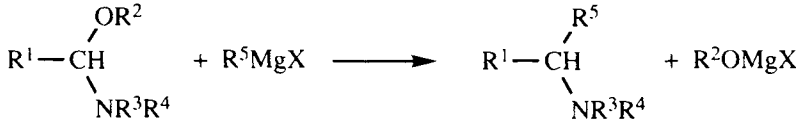

The paper in which the following procedure was described reports several other examples [10], and references to others are given in a review [11]; see also Ref. [12].

*(1S,2R,4R)-2-(Isobutoxy)-6-methylenebicyclo[2.2.2]octane* [10]



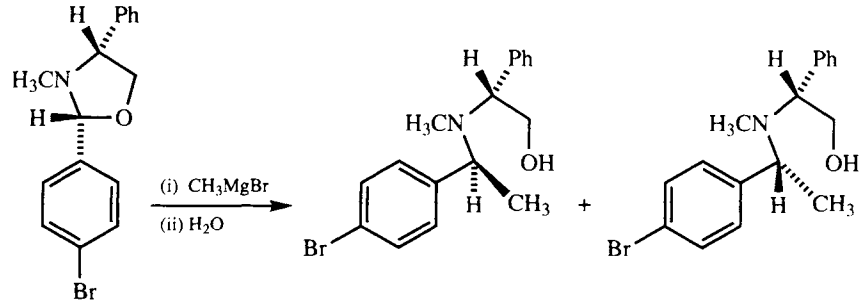

Isopropylmagnesium bromide (2.5 M in ether, 0.36 ml) is added to a solution of (1*S*,2*R*,4*R*)-2-(2-methoxyethoxy)methoxy)-6-methylenebicyclo[2.2.2]octane (68 mg, 0.3 mmol) in toluene (2.0 ml). The mixture is heated under reflux for 15 min (during which time a white precipitate forms). The mixture is cooled to room temperature, and water (10 ml) is added. The product is isolated via ether extraction (×3), chromatography and Kugelrohr distillation (150–160°/30 torr) as a colourless oil (47.2 mg, 81%).

In analogous reaction of aminals, alkoxy rather than dialkylamino groups are normally displaced (for an exception, see Section 8.3.1):

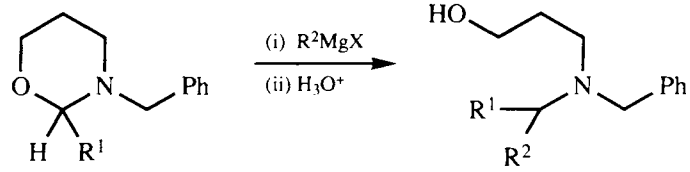



This type of reaction appears to be fairly general [13] (see also Refs. [14] and [15]), but it has particular value for the cleavage of oxazolidines, tetrahydro-1,3-oxazines and related compounds, giving aminoalcohols. A typical procedure follows, and other examples are shown in the following equations. Further examples are reported in the literature [16, 17].

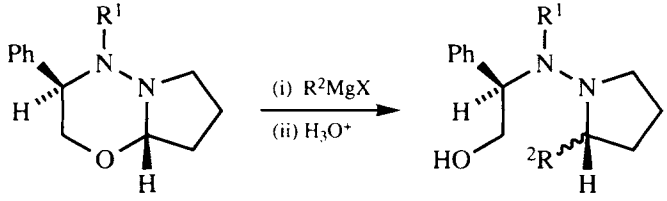
N-*(2-Hydroxy-1-phenylethyl)*-N-*methyl-1-(4-bromophenyl)ethylamine* [16] Methylmagnesium bromide (3 M in ether, 4.8 mmol) is added dropwise to a stirred solution of (2*R*,4*R*)-2-(4-bromophenyl)-*N*-methyl-4-phenyloxazolidine (1.6 mmol) in THF (15 ml) at −10°. The mixture is stirred at room temperature for 20 h. A small amount of water is added, and the resulting suspension is filtered. The filtrate is dried




($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (silica, n-hexane–ether (2:1)) gives the title compound (80.5%) as a mixture of diastereomers.

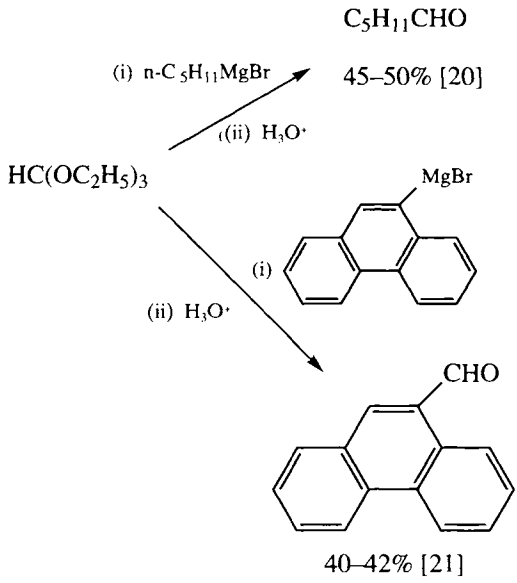



29 examples (80–94%) [18]

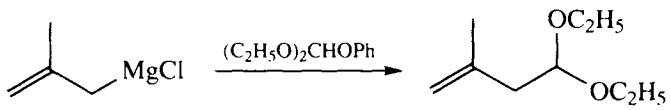



$R^2 = CH_3, C_2H_5, C_6H_5CH_2, C_6H_5$
Both diastereomers. Total 81–88%
[19]

The reaction of Grignard reagents with orthoformates is an old-established alternative to reactions with formates (see Section 6.2) or formamides (see Section 6.3) for the preparation of aldehydes. Many examples are listed in General Ref. [A], and two are fully described in *Organic Syntheses*:




Two high-yielding syntheses of acetals have been more recently described:

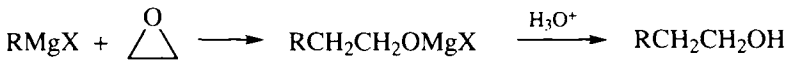



$$RC{\equiv}CMgBr + HC(OC_2H_5)_3 \longrightarrow RC{\equiv}CCH(OC_2H5)_3 + C_2H_5OMgBr$$

'excellent yields' [23]

### *8.2.1.3 Ring-opening of oxiranes, oxetanes and other cyclic ethers*

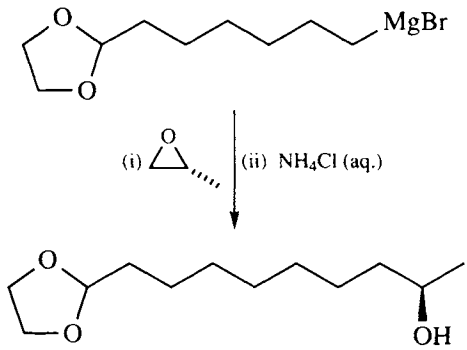
By far the most important reactions in this category are those of oxiranes, and the reaction with the parent compound is a good general method for two-carbon homologation:




The early *Organic Syntheses* procedure for the synthesis of hexan-1-ol [24] is typical, but suffers from the disadvantage of using benzene as a cosolvent, as

do the procedures and many of the examples tabulated in General Ref. [A]. In fact, the reaction proceeds smoothly in ether at room temperature, though the presence of halide may lead to halohydrin as a significant by-product [25]; the use of a higher-boiling cosolvent was an attempt to circumvent this problem by further reaction of the halohydrin with Grignard reagent. Another problem with Grignard reagents can be Lewis acid-catalysed rearrangement. These problems are compounded in reactions with substituted oxiranes; for example, reactions of Grignard reagents with methyloxirane can give as many as six products [26]. The side-reactions promoted by halide may be avoided by the use of dialkylmagnesium compounds rather than Grignard reagents, though the problems with regioselectivity may remain. Catalysis by copper(I) is also reported to be beneficial, facilitating reactions at lower temperatures and thus avoiding the need for higher-boiling solvents. The contrast between the following procedure, the early procedure [24], and the study noted above [26] is noteworthy. Further illustrative examples are listed in Table 8.3

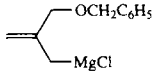
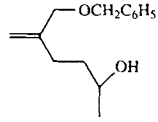
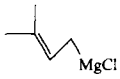
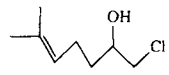
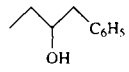
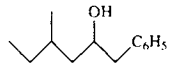
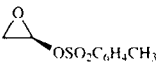
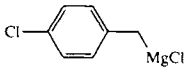
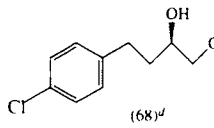
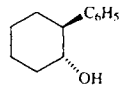
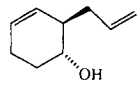
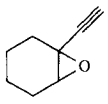
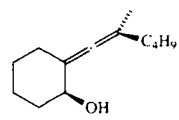
*2-[(*R*)-8-Hydroxynonyl]-1,3-dioxolane* [36]




A Grignard reagent is prepared from 2-(6-bromohexyl)-1,3-dioxolane (2.3 g, 20.0 mmol) and magnesium (0.3 g, 12.3 mmol) in THF (15 ml) and cooled to 0°. A spatula-end of copper(I) iodide is added, and the mixture is stirred at 0° for 30 minutes. Stirring and cooling is continued as a solution of (*R*)-methyloxirane (1.0 ml, 14.0 mmol) in THF (10 ml) is added slowly. After a further 3 h at 0° the mixture is allowed to warm to room temperature. Aqueous ammonium chloride is added, and the organic layer is separated. The aqueous phase is extracted with ether (3 × 50 ml) and the combined organic layers are dried ($MgSO_4$) and distilled, to give 2-[(*R*)-8-hydroxynonyl]1,3-dioxolane (1.8 g, 83%), b.p. 90–95°/0.01 torr.

TABLE 8.3

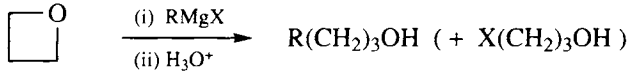
Reactions of organomagnesium compounds with substituted oxiranes

| Oxirane | Organomagnesium compound | Catalyst | Product (yield, %) | Ref. |
|---|---|---|---|---|
|  |  | CuI |  (87)[a] | [27] |
|  |  | CuI |  (66) | [28] |
|  | $(C_2H_5)_2Mg$ | None |  (75)[b] | [29] |
|  | $(s\text{-}C_4H_9)_2Mg$ | None |  (54)[c] | [30] |
|  |  | $Li_2CuCl_4$ |  (68)[d] | [31] |
|  | $C_6H_5MgBr$[e] | |  (80)[f] | [32] |
|  |  | |  (40) | [33] |
|  | n-$C_4H_9MgCl$ | CuBr |  (84)[g] | [34] |

[a]By GLC. [b]$PhCH_2CH(OH)CH_3$ (42%) formed by reduction. [c]With $C_2H_5MgBr$, an approximately equal amount of $PhCH(Et)CH_2OH$ was also obtained. [d]An analogous reaction gave the enantiomer (77%). [e]For other examples, see Ref. [35]. [f]Crude yield almost quantitative. [g]*anti*:*syn* 10:90; with BuMg**Br** and $CuBr{\cdot}PR_3$, *anti* predominates.

An analogous reaction of 2-(5-bromopentyl)-1,3-dithiane is described, giving 2-[(*R*)-7-hydroxyoctyl]-1,3-dithiane (70%).

Reactions of Grignard reagents with oxetane lead to three-carbon homologation; yields are often good, but 3-halogenopropanol may be a significant by-product [37]:



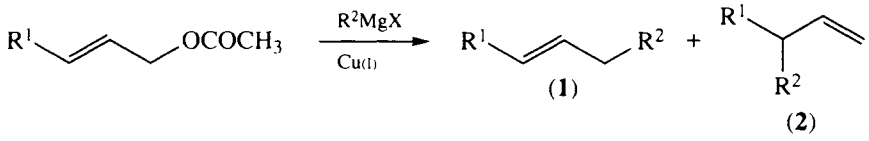

Copper(I) catalysis is also reported to be beneficial for this reaction [9, 36].

Organomagnesium compounds are much less reactive than organolithium compounds [G] towards THF, but the reaction of triphenylmethylmagnesium bromide with THF can give high yields of 5,5,5-triphenylpentan-1-ol [38].

### 8.2.2 Displacement from carboxylate, carbamate and cyanate

The usual reactions of organomagnesium compounds with esters, amides and nitriles are those described in Sections 5.3, 6.2 and 6.3. However, factors such as steric hindrance and stability of leaving group may lead to reactions resulting in overall nucleophilic displacement. Most of them are of limited applicability (see Ref. [39] for examples involving carbamate), but two warrant coverage.

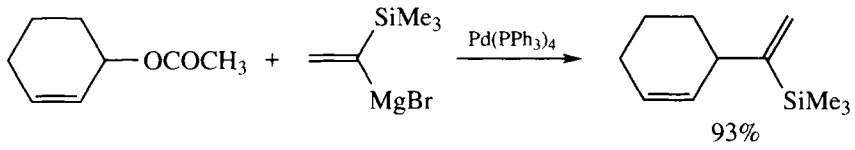
Catalysed reactions of organomagnesium compounds with allylic acetates are potentially useful in synthesis, but lack of regioselectivity may be a problem:




($R^1$ = PhS, PhO, n-$C_3H_7$)

However, a systematic study has demonstrated that the regiochemistry can be controlled [40]: conditions favouring dialkylcuprate as the catalytic intermediate (fast addition of Grignard reagent), low temperature, low concentration of catalyst), favour α-attack, leading to (**1**), whereas conditions favouring formation of alkylcopper (slow addition of Grignard

reagent, higher temperature, higher concentration of catalyst) favour γ-attack, leading to (**2**). For copper(I) cyanide-catalysed reactions there is also a marked solvent effect, ether favouring (**2**) and THF favouring (**1**). Analogous palladium(0)-catalysed reactions have also been reported [41], e.g.




Under the right conditions the reaction of Grignard reagents with organic cyanates, giving after hydrolysis the nitrile corresponding to the Grignard reagent and an alcohol or phenol, is fairly general [42]:

$$R^1OCN + R^2MgX \xrightarrow[(ii)\ H_3O^+]{(i)\ Et_2O} R^2CN + R^1OH$$

Yields are variable, but in favourable cases can be very high; for example, phenyl cyanate and t-butylmagnesium chloride gave pivalonitrile (92%) and phenol (87%).

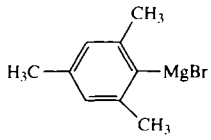
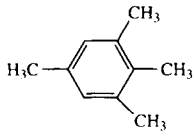
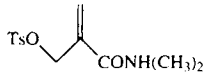
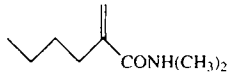
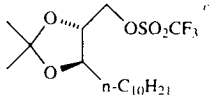
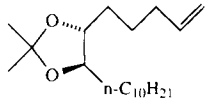
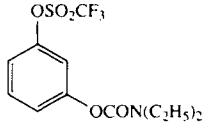
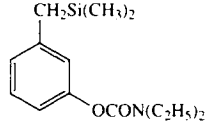
### 8.2.3 Displacement of sulfate, sulfonate and phosphate

Reactions of organomagnesium compounds with dialkyl sulfates or alkyl sulfonates often give satisfactory yields of the products of displacement of sulfate or sulfonate. Side-reactions have been observed, but they can often be avoided; for example, an excess of the sulfate or sulfonate should be used with Grignard reagents, as some is consumed by nucleophilic attack by halide ion [A]. The dialkyl sulfates are reactive, but hazardous. Toluenesulfonates (tosylates) are less reactive, but their reactions are catalysed by copper complexes; the reactions of trifluoromethanesulfonates (triflates) are catalysed by nickel complexes. Reactions of Grignard reagents with secondary tosylates appear to follow an $S_N2$ mechanism, with inversion of configuration [43].

Some illustrative examples of these types of reaction are listed in Table 8.4. Others are listed in General Ref. [A].

TABLE 8.4

Reactions of organomagnesium compounds with sulfates and sulfonates

| Organomagnesium compound | Sulfate/ sulfonate[a] | Catalyst | Product (yield, %) | Ref. |
|---|---|---|---|---|
| $C_6H_5CH_2MgCl$ | $(C_2H_5O)_2SO_2$ | None | $C_6H_5CH_2CH_2CH_3$ (70–75) | [44] |
|  | $(CH_3O)_2SO_2$ | None |  (52-60) | [45] |
| $HC{\equiv}CMgBr$ | $HC{\equiv}CCH_2OTs$ | CuBr | $HC{\equiv}CCH_2C{\equiv}CH$ (~ 60) | [46][b] |
| EtMgBr |  | None |  (73) | [47] |
|  |  | CuBr |  (79) | [48][b] |
| $(CH_3)_3SiCH_2MgCl$ |  | $Ni(acac)_2$ |  (70) | [39][b] |
| $CH_3OCH_2O(CH_2)_4MgBr$ | $TsO(CH_2)_6OTs$ | $Li_2CuCl_3$[d] | $CH_3OCH_2O(CH_2)_{14}OCH_2OCH_3$ (81) | [49][b] |
| $C_6H_5CH_2MgCl$ | $TsOCH_2CH_2CH_2CH_3$ | None | $C_6H_5CH_2CH_2CH_2CH_2CH_3$ (70–75) | [50] |

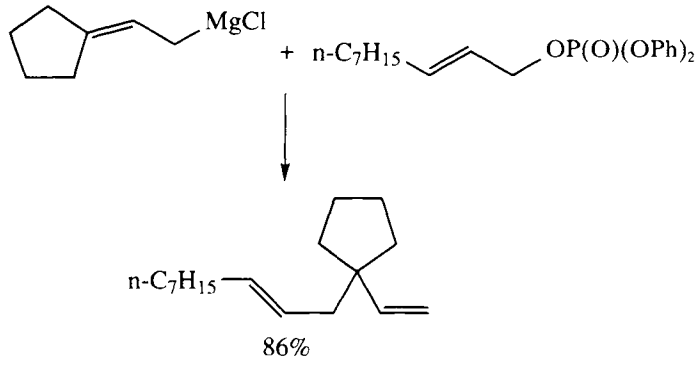
[a]Ts,4-$CH_3C_6H_4SO_2$. [b]Other examples are also described. [c]Prepared *in situ* from the alcohol and triflic anhydride. [d]$Li_2CuCl_4$ gave inferior results.

A few reactions of hindered Grignard reagents with trimethyl phosphate have been reported [51],

$$RMgX + (MeO)_3PO \longrightarrow RMe$$

(R=$Ph_3C$, 77%
R=2,4,6-$Me_3C_6H_2$, 39%)

but the reaction is not very general, although an interesting reaction of an allylic Grignard reagent with an allylic phosphate with rearrangement has recently been described [52], e.g.

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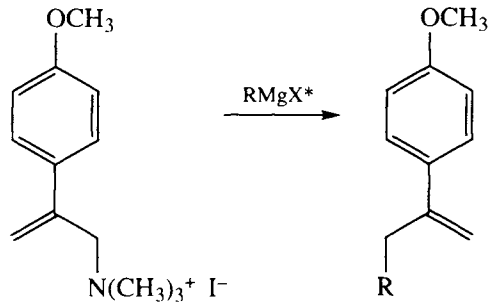
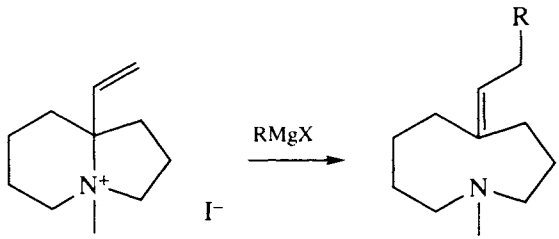
## 8.3 DISPLACEMENT OF NITROGEN, CARBON AND SULFUR FUNCTIONS

### 8.3.1 Displacement of nitrogen functions

Few nitrogen functions are sufficiently good leaving groups to undergo displacement by organomagnesium compounds in preference to other reactions. A few examples of displacement of tetraalkylammonium from quaternized allylic amines have been described, e.g.



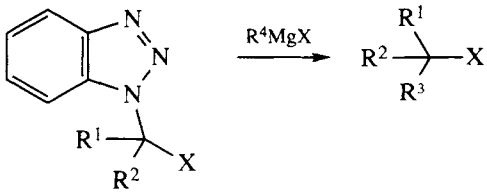

[1]




[2]

*CuI catalyst required with MeMgBr.

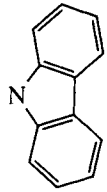
However, systematic studies by Katritzky *et al.* [3] have demonstrated that reactions of 1-substituted benzotriazoles with organomagnesium compounds constitute a versatile method for substitution α to a variety of functional groups, as exemplified in Scheme 8.1. It is noteworthy that the benzotriazolyl group is displaced in preference to alkoxy (contrast the reactions of aminals noted in Section 8.2.1) and other heteroaromatic groups such as carbazolyl. The following procedure is typical.




(Note: one or both of $R^1$, $R^2$ = H usually)

X = $OR^4$ [4–6]

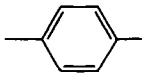
X = $NR^4_2$ [7]

X =  (also pyrrol-1-yl, indol-1-yl, benzimidazol-1-yl) [8, 9]

X = N(OH)COAr* [10]

X = $N{=}CHNR^4_2$ [11]

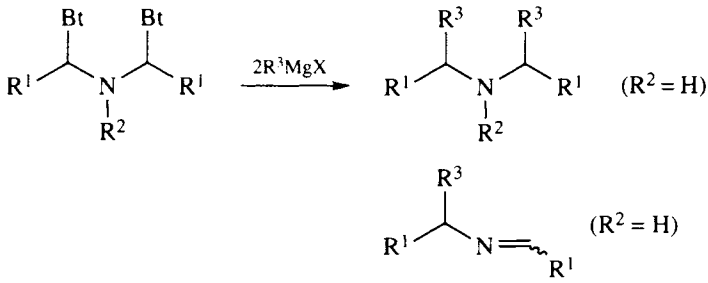
X = $N{=}PPh_3$† [12]

X =  [13]

**Scheme 8.1**

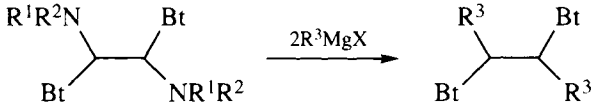
*Product isolated is RCH(OH)NHCOAr.
†Product used *in situ* for aza-Wittig reactions.

The reactions of α,α'-bis-benzotriazolylamines have also been described; tertiary amines undergo disubstitution [14], but secondary amines undergo mainly monosubstitution and elimination, giving imines [15]:



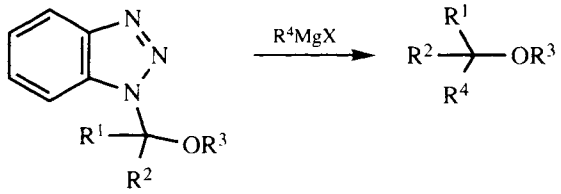

Bt = benzotriazol-1-yl

The reaction has also been applied to the synthesis of vic-diamines [16]:




Bt = benzotriazol-1-yl

*Synthesis of ethers from 1-alkoxymethylbenzotriazoles (general procedure for non-volatile ethers)* [4]



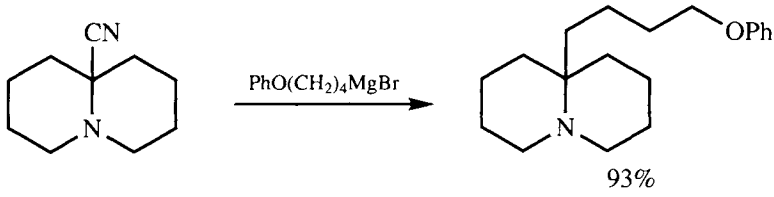

An α-benzotriazolyl ether (50 mmol) and toluene (120 ml) are placed in a 250 ml three-necked flask fitted with a dropping funnel and equipped for distillation and magnetic stirring. The mixture is stirred and heated until the solvent just starts to distil. A solution of Grignard reagent (~100–120 mmol) is added dropwise at such a rate as to balance the rate of distillation. When the addition is complete, distillation is continued until the distillation temperature reaches 100°. The distillation equipment is replaced by a reflux condenser, and the mixture is heated under reflux for 3 hours. The reaction mixture is poured into ice–water and neutralized with acetic acid. The organic layer is separated, washed successively with water, 10% aqueous sodium hydroxide (100 ml) and water, dried (anhydrous sodium sulfate) and evaporated in a rotary evaporator. The crude ether remaining is purified by distillation under reduced pressure or chromatography.

As an example, a reaction of benzylmagnesium chloride with 1-(1-isopropoxybenzyl)benzotriazole gave 1-isopropoxy-1,2-diphenylethane, b.p. 70°/0.04 mmHg (85%).

### 8.3.2 Displacement of carbon functions

Displacement of carbon functions by organomagnesium compounds is rare, but several examples involving loss of cyanide have been reported

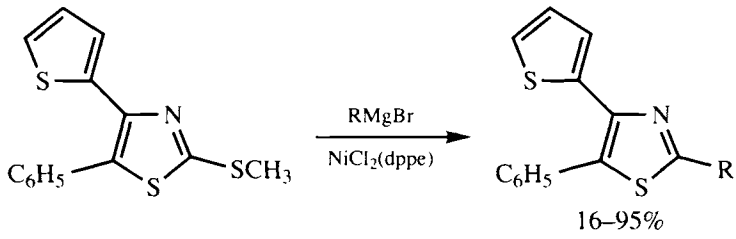
[A, 17]. This reaction of α-aminonitriles is fairly general and has been used in synthesis, as in the following equation [18]:



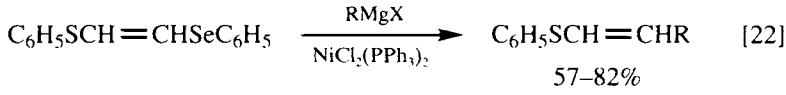

Other examples are described in Refs [19] and [20].

### 8.3.3 Displacement of sulfur functions

Reactions of organomagnesium compounds with thioethers usually take other pathways, and uncatalysed reactions involving displacement of thiolate are rare. On the other hand, several examples of nickel(II)-catalysed reactions have been described, and analogous reactions of selenoethers have also been reported, e.g.



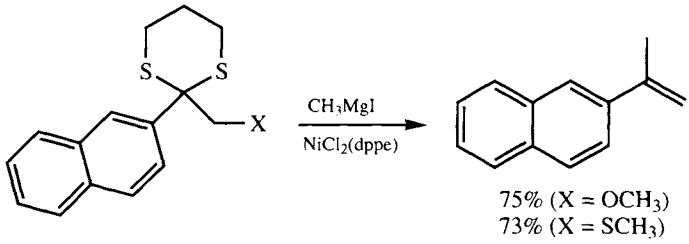

[21]




[22]

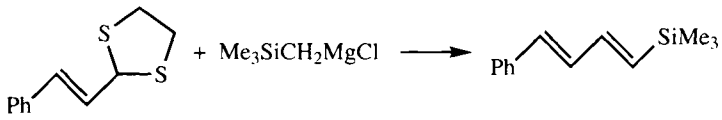
The nickel-catalysed reaction of organomagnesium compounds with dithioacetals, in which the initial substitution leads to elimination, giving a substituted alkene, is potentially useful [23, 24], as in the following procedure. Elimination of β-alkoxy or alkylthio groups from the

dithioketal may also occur [25], e.g.



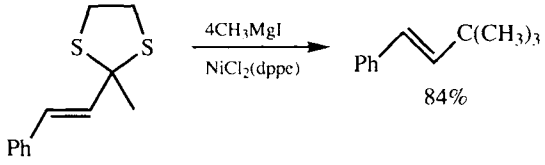

75% (X = $OCH_3$)
73% (X = $SCH_3$)

(E,E)-*1-Phenyl-4-trimethylsilyl-1,3-butadiene* [26]



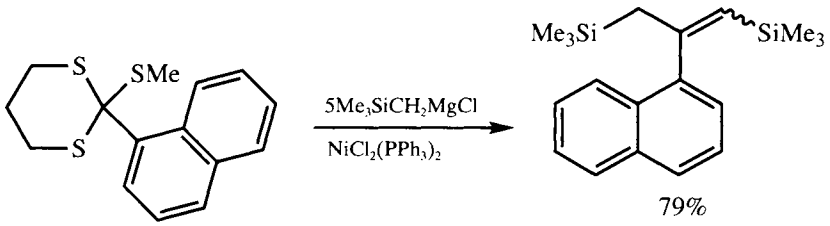

2-(2-Phenylethenyl)-1,3-dithiolane (14.6 g, 70 mmol) and dichlorobis(triphenylphosphine)nickel (2.3 g, 3.5 mmol) are placed in a 1 litre, two-necked flask fitted with a reflux condenser, a septum and a stirrer, and furnished with a nitrogen atmosphere. Dry THF (200 ml) is added, and the mixture is cooled in ice. A solution of trimethylsilylmethylmagnesium chloride (prepared from trimethylsilylmethyl chloride (25.8 g, 0.21 mol) in ether (150ml) [21]) is introduced by cannulation in one portion. The mixture is heated under reflux for 10 h and cooled to room temperature. Saturated aqueous ammonium chloride (200 ml) is added, the organic layer is separated, and the aqueous layer is extracted with ether (2 × 200 ml). The combined organic layers are washed with 10% aqueous sodium hydroxide (2 × 100 ml) and brine (2 × 100 ml), and dried ($MgSO_4$). The solvents are evaporated under reduced pressure and the residue is filtered through a short silica column with hexane (300 ml). The hexane is evaporated under reduced pressure, and the product is distilled at 99–101°/0.6 mmHg as a colourless liquid (12.9 g, 91%) which solidifies on standing.

It should be noted, however, that the regiochemistry of the elimination cannot always be completely controlled [27], and that replacement of both sulfur functions may occur, e.g. [28].

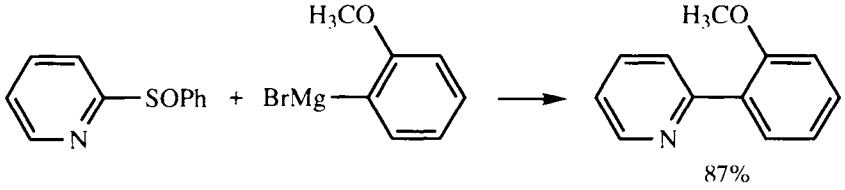



84%

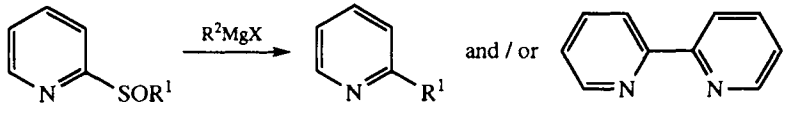
These types of reactions have also been applied to orthothioesters [29] and a tetrathioorthocarbonate [30], e.g. [29].




Reactions of organomagnesium compounds with sulfoxides often result in ligand exchange [31], and may be complicated by α- or *ortho* metallation. However, in some cases, notably with 2-pyridyl aryl sulfoxides, reactions with arylmagnesium halides give useful yields of products from displacement of the aryl sulfoxido group [32, 33], e.g. [32]



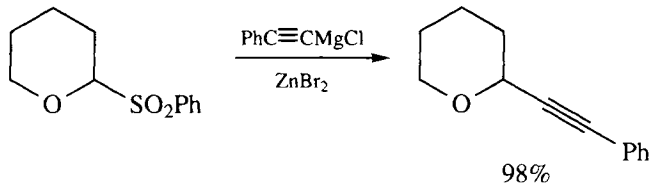

Note, however, that with alkyl sulfoxides or alkylmagnesium halides, products derived formally from loss of SO may be obtained [34] (see also Ref. [35]):




Uncatalysed displacement of sulfonyl groups by organomagnesium compounds is rare (e.g. Ref. [36]), but copper-catalysed coupling with allylic sulfones gives good yields though variable regiochemistry [37, 38]. Nickel-catalysed cross-coupling of arylmagnesium bromides with aryl t-butyl sulfones has also been recently reported; yields were good, but a little homo-coupling also occurred [39].

$$Ar^1SO_2CMe_3 \xrightarrow[Ni(acac)_2]{Ar^2MgBr} Ar^1{-}Ar^2 \ (+Ar^2{-}Ar^{2)}$$

Reactions of organozinc reagents, prepared from organomagnesium compounds *in situ* (see Section 16), with α-sulfonyl ethers and carbamates [40] can give excellent results, e.g. [41].

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41. D. S. Brown and S. V. Ley, *Org. Synth.* **70**, 157 (1992).

# —9—

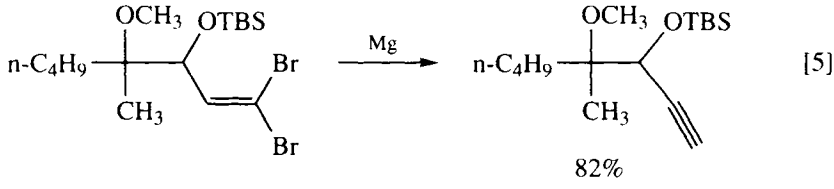
# Carbenoid and Arynoid Reactions of Organomagnesium Compounds

Carbene precursors such as α-halogenoalkylmagnesium compounds and aryne precursors such as *o*-halogenoarylmagnesium compounds are on the whole less readily accessible than the corresponding organolithium compounds, and more thermally stable, so that carbenoid and arynoid reactions based on the organomagnesium intermediates are much less used [1].*

*Similarly, other reactions involving elimination in which the organometallic compound acts as a strong base are rare compared with the corresponding reactions of organolithium compounds [1].

## 9.1 CARBENOID REACTIONS

Although α-halogenoalkylmagnesium compounds have been prepared, particularly by metallation or metal halogen exchange [2], they are usually sufficiently stable to function as carbanion rather than carbene equivalents [3], and even some apparently carbenoid reactions probably involve discrete organomagnesium intermediates [4]. Two examples of carbenoid reactions, the second possibly involving an 'ate complex derived from an α-halogenoalkylithium compound, are shown in the accompanying equations.




[5]

$$(n\text{-}C_4H_9)_2Mg + 2LiCH(Cl)Si(CH_3)_2C_6H_5 \longrightarrow \underset{72\%}{n\text{-}C_4H_9CH_2Si(CH_3)_2C_6H_5} \quad [6]$$

## References

1. See General Ref. [G], Chapter 16.
2. See Section 3.2, Ref. [26].
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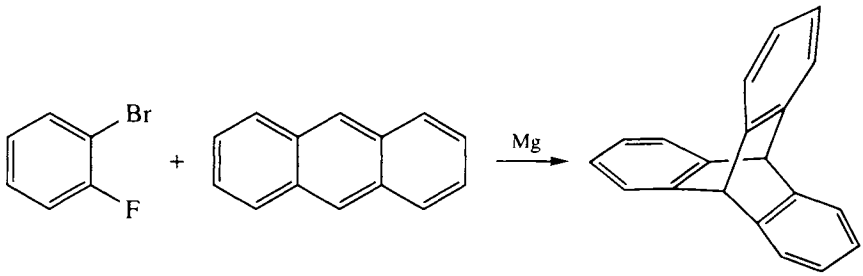
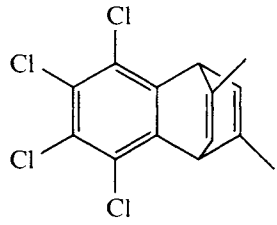
## 9.2 ARYNOID REACTIONS

Wittig's classic synthesis of triptycene presumably involved 2-fluorophenylmagnesium bromide as an intermediate [1]:




28%

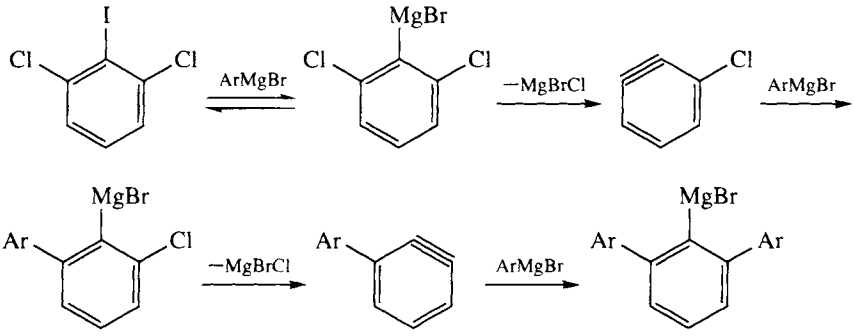
The use of a discrete organomagnesium intermediate, and the greater stability of *o*-halogenoarylmagnesium compounds than *o*-halogenoaryllithium compounds is illustrated by the pentachlorophenyl derivatives. Whereas pentachlorophenyllithium decomposes in boiling benzene to give the tetrachlorobenzyne adduct, pentachlorophenylmagnesium chloride is stable in boiling benzene, though it does give the tetrachlorobenzyne adduct (**1**) in boiling *p*-xylene [2].



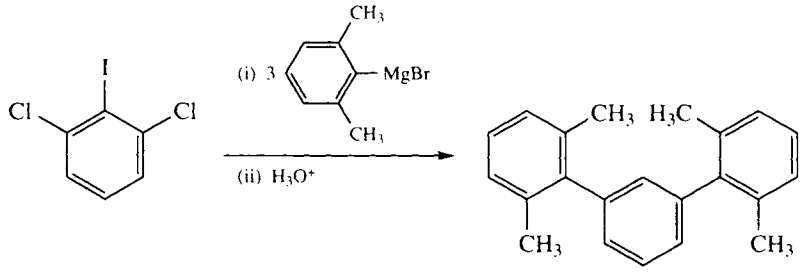

(**1**)

More recently, an ingenious sequence of metal–halogen exchange and elimination reactions has been used to prepare terphenyls from 2,6-

dichloroiodobenzene [3, 4]:



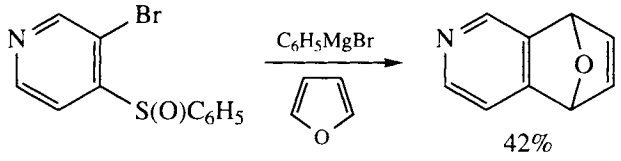

*2,6,2″,6″-Tetramethyl-1,1′:3′1″-terphenyl* [3]




A solution of 2,6-dimethylphenylmagnesium bromide (from bromo-2,6-dimethylbenzene (20.4 g, 110 mmol) and magnesium (2.95 g, 126 mmol)) in THF (300 ml) is heated under reflux under argon as a solution of 2,6-dichloroiodobenzene (10.0 g, 36.7 mmol) in THF (~ 35 ml) is added dropwise, and heating under reflux is continued for 3 h. The mixture is cooled, and 10% hydrochloric acid (40 ml) is added. The mixture is extracted with ether (2 × 100 ml). The extract is dried ($MgSO_4$) and the solvent is evaporated under reduced pressure. The iodo-2,6-dimethylbenzene by-product* is vacuum distilled and the residue is purified by column chromatography (silica, petroleum ether) to give the terphenyl (7.4 g, 70%), m.p. 37–38°.

*Formation of this by-product can be avoided by using vinylmagnesium bromide for the initial metal-halogen exchange [3].

As alternatives to *o*-halogenoarylmagnesium halides, *o*-phenylsulfonylarylmagnesium halides have been used as precursors to arynes, including 3-pyridyne [5]:

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5. See Section 3.2, Ref. [67].

# —10—

# Reactions of Organomagnesium Compounds with Proton Donors

Reactions of organomagnesium compounds with proton donors are usually regarded as a nuisance: destruction of the reagent by adventitious water or an acidic functional group. In some cases, however, the reaction becomes useful: as a means of indirect reduction of organic halides, as a means of isotopic labelling, and when the resulting magnesium compound is the required product. (Note that the reaction with a *carbon* acid results in the formation of a new organomagnesium compound, i.e. metallation; see Section 3.2.1.)

$$RX + Mg \longrightarrow RMgX$$
$$RMgX + HY \longrightarrow RH + MgXY$$
$$RMgX + D(T)Y \longrightarrow RD(T) + MgXY$$

## 10.1 INDIRECT REDUCTION OF HALIDES AND ISOTOPIC LABELLING VIA ORGANOMAGNESIUM COMPOUNDS

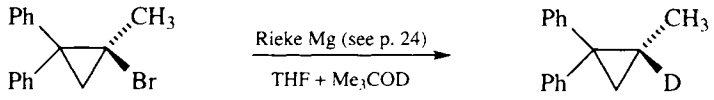
An example of indirect reduction via an organomagnesium compound is a well-described synthesis of n-pentane [1]:

$$CH_3CH_2CH_2CH(Br)CH_3 \xrightarrow{Mg} CH_3CH_2CH_2CH(MgBr)CH_3 \xrightarrow{H_2SO_4} CH_3CH_2CH_2CH_2CH_3$$
$$50\text{–}53\%$$

Examples involving metal–halogen exchange (see Section 3.2.2) rather than reaction with magnesium have also been described, e.g. [2]

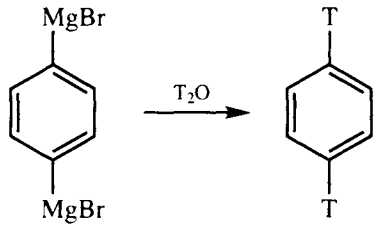
$$C_6Br_6 \xrightarrow{PhMgBr} C_6Br_5MgBr \xrightarrow{H_3O^+} C_6Br_5H$$
$$> 95\%$$

Reaction with deuterium oxide, *O*-deuterated alcohols or acids is commonly used to provide evidence for the formation of organomagnesium compounds (e.g. see Ref. [3]). Although the presence of water normally inhibits the reaction of organic halides with magnesium, it is noteworthy that under appropriate conditions a "Barbier" procedure was successful [4]:




high yield and incorporation

For preparative deuterium or tritium labelling, organomagnesium compounds are less generally used than organolithium compounds, but similar considerations should apply [5]. In the following example a remarkably high degree of tritium incorporation was achieved [6]:




up to 58000 Ci $mol^{-1}$

## References

1. See Section 3.1, Ref. [87].
2. See Section 3.2, Ref. [41].
3. See Section 3.1, Refs [17], [136] and [138].
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5. See General Ref. [G], p. 121.
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## 10.2 PREPARATION OF MAGNESIUM ALKOXIDES, THIOLATES AND AMIDES

Alcohols, phenols, thiols and primary or secondary amines are all sufficiently acidic to donate a proton to an organomagnesium compound. The reaction with an equimolar amount of a Grignard reagent is a clean

route to the halomagnesium salt:

$$R^1MgX + HOR^2\ (SR^2, NR^2R^3) \longrightarrow R^1H + XMgOR^2\ (SR^2, NR^2R^3)$$

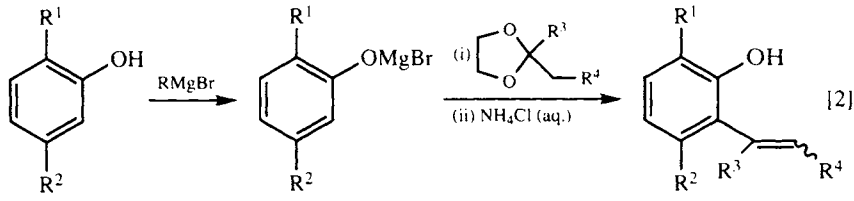
With a dialkylmagnesium compound, one equivalent of the proton donor gives an alkylmagnesium alkoxide (thiolate, amide) (see Section 3.4.4), whereas 0.5 equivalent gives the magnesium alkoxide (thiolate, amide):

$$R^1{}_2Mg + HOR^2\ (SR^2, NR^2R^3) \longrightarrow R^1MgOR^2\ (SR^2, NR^2R^3)$$

$$2R^1{}_2Mg + HOR^2\ (SR^2, NR^2R^3) \longrightarrow Mg(OR^2)_2\ [(SR^2)_2, (NR^2R^3)_2]$$

Some representative examples of the preparation of alkoxides and thiolates are shown in the following schemes, which also show how the products were subsequently used:

$$Cl(CH_2)_nOH \xrightarrow[\text{(ii) Mg}]{\text{(i) RMgCl, THF}} ClMg(CH_2)_nOMgCl \qquad [1]$$



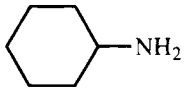
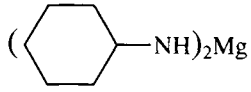
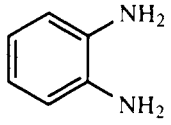
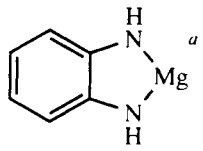
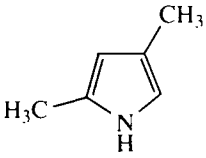
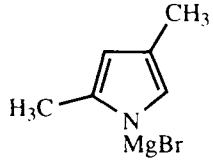

[2]

$$RSH \xrightarrow{EtMgBr} RSMgBr \xrightarrow{(2,4,6\text{-}Me_3C_6H_2)_2BF} (2,4,6\text{-}Me_3C_6H_2)_2B\text{-}SR \qquad [3]$$

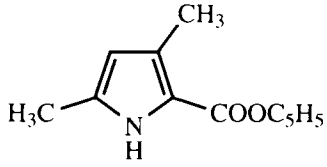
Reactions of organomagnesium compounds with amines give a number of useful reagents. A preparation and use of a bromomagnesium dialkylamide has already been described (see p. 49), and others are listed in Table 10.1. (Note that in most cases the products listed in Table 10.1 were not isolated, and their constitution was not established.) The final entry in Table 10.1 is noteworthy, as bromomagnesio derivatives of pyrroles and indoles may be used as carbon nucleophiles in the synthesis of pyrrole and indole derivatives. In the case of pyrroles, *N*-, 2- and/or 3-substituted products may be obtained, and the conditions favouring one or another have been extensively studied [10]. In the example shown in the

TABLE 10.1

Preparation of magnesium amides

| Amine | Organomagnesium compound | Product | Ref. |
|---|---|---|---|
|  | $Bu^nBu^sMg$ |  | [4] |
| $(C_2H_5)_2NH$ | $C_2H_5MgBr$<br>$Bu^nBu^sMg$ | $(C_2H_5)_2NMgBr$<br>$[(C_2H_5)_2N]_2Mg$ | [5]<br>[4] |
| $(Me_2CH)_2NH$ | $C_2H_5MgBr$<br>$Bu^nBu^sMg$ | $(Me_2CH)_2NMgBr$<br>$[(Me_2CH)_2N]_2Mg$ | [6]<br>[7] |
|  | $Bu^nBu^sMg$ |  [a] | [8] |
|  | $C_2H_5MgBr$ |  | [9] |

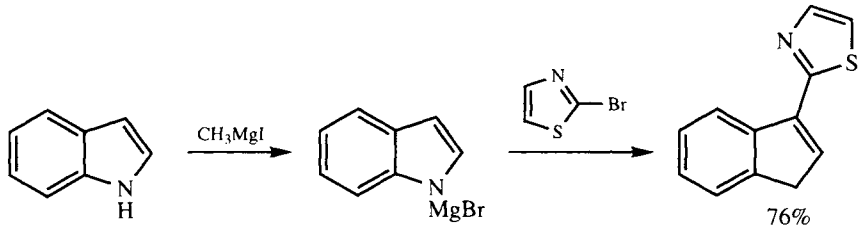
[a] Isolated and characterized as a tetrameric THF complex.



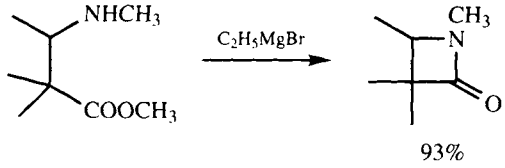
(**1**)

table, reaction with ethyl chloroformate gave the ester (**1**) in 57–58% yield. With *N*-bromomagnesioindole, reaction at the 3-position usually

predominates [10], as in the following recent example [11]:




An application involving cyclization of a magnesium amide furnishes a general synthesis of β-lactams [12, 13], e.g. [12]:




The reaction of a primary aromatic amine with two equivalents of a Grignard reagent can give a bisbromomagnesio derivative. Such reagents have found some applications in synthesis [14, 15].

N, N-*Bis(bromomagnesio)anilines* [14]

$$ArNH_2 + 2C_2H_5MgBr \longrightarrow ArN(MgBr)_2 + 2C_2H_6$$

A solution of ethylmagnesium bromide (30.8 mmol) in THF (20 ml) is stirred at 0° under nitrogen as a solution of the primary aromatic amine (15.8 mmol) in THF (15 ml) is added. The mixture is stirred gently at 55° until evolution of ethane is complete (~ 40 min). (Subsequent reaction with nitroarenes to give azo- and/or azoxybenzenes is described [14].)

The reaction of hydrogen sulfide with two equivalents of ethylmagnesium bromide in ether gives a reagent as a "viscous mass", which is soluble in THF and reacts with alkyl halides in that solvent to give thioethers [16]:

$$H_2S \xrightarrow{2EtMgBr} S(MgBr)_2 \xrightarrow[THF]{2RX} R_2S$$

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# —11—

# Formation of Carbon–Nitrogen Bonds via Organomagnesium Compounds

The conversion of organomagnesium compounds into nitrogen-containing compounds is a desirable functional group transformation, but even the few available methods are variable in their effectiveness. Two types of reaction have been used: reactions with compounds in which nitrogen is bound to a more electronegative atom, and reactions with compounds containing nitrogen–nitrogen multiple bonds. The general subject of "electrophilic amination of carbanions" has been well reviewed [1].

Reactions of organomagnesium compounds with *N*-halogenoamines give variable proportions of halogen compounds and amines (see also Chapter 14):

$$R^1MgX + XNR^2R^3 \longrightarrow R^1NR^2R^3 \text{ and/or } R^1X$$

For the synthesis of amines from organomagnesium compounds. *N*-chloroamines are preferred. Chloramine itself gives good yields with dialkylmagnesium compounds and alkylmagnesium chlorides, but other alkylmagnesium halides and arylmagnesium halides give higher proportions of the halide [A, 1, 2].

The reactions of organomagnesium compounds with *O*-alkylhydroxylamines have been less thoroughly studied than the corresponding reactions of organolithium derivatives [E, G, 1], though good yields of the amine have been reported, particularly with methoxyamine [A]. As in the case of organolithium compounds, at least two equivalents of the organomagnesium compound are required for maximum yield.* More recently, *O*-sulfonyl and *O*-phosphinylhydroxylamines have been used in the synthesis of both primary and tertiary amines [1]:

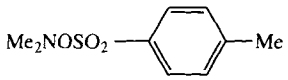
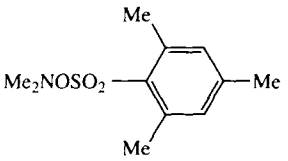
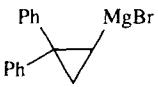
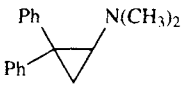
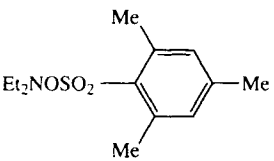
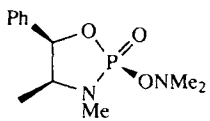
$$R^1{}_2NOSO_2R^2 \xrightarrow{R^3MgX} R^1{}_2NR^3 \xleftarrow{R^3MgX} R^1{}_2NOP(O)R^2{}_2$$

*The use of one equivalent of an expendable organomagnesium compound to avoid this disadvantage (cf. [G]) has not been reported, and the use of "sacrificial" methyllithium was not very successful [3].

Once again, yields are somewhat unpredictable, but in many cases Grignard reagents give higher yields than the corresponding organolithium compounds. Some representative examples are shown in Table 11.1, and a procedure follows.

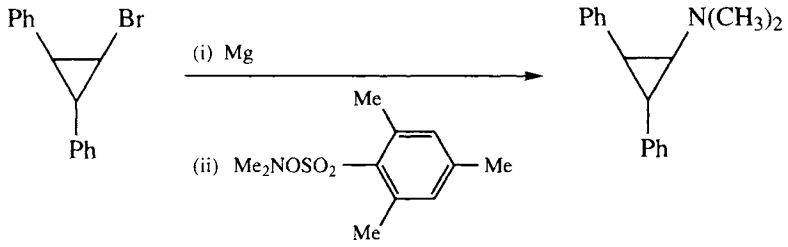
TABLE 11.1

Amination of organomagnesium compounds by *O*-sulfonyl- and *O*-phosphinylhydroxylamines

| Hydroxylamine derivative | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
|  | $C_6H_5MgBr$ | $C_6H_5N(CH_3)_2$ (62) | [4] |
| | cyclo-$C_6H_{13}MgBr$ | cyclo-$C_6H_{13}N(CH_3)_2$ (low) | [4] |
|  |  |  (47) | [5] |
|  | $C_6H_5MgBr$ | $C_6H_5N(C_2H_5)_2$ (42) | [5] |
| | 1-$C_{10}H_8MgBr$ | 1-$C_{10}H_8N(C_2H_5)_2$ (69) | [5] |
| $H_2NOP(O)(C_6H_5)_2$ | $C_6H_5MgBr$ | $C_6H_5NH_2$ (67) | [6] |
| | $C_6H_5MgBr$ | $C_6H_5NH_2$ (22) | [7] |
| | $C_6H_5MgCl$ | $C_6H_5NH_2$ (35) | [7] |
| | n-$C_6H_{13}MgBr$ | n-$C_6H_{13}NH_2$ (27) | [6] |
| | $C_6H_5CH_2MgCl$ | $C_6H_5CH_2NH_2$ (70) | [7] |
|  | $C_6H_5CH(CH_3)MgBr$ | $C_6H_5CH(CH_3)N(CH_3)_2$ (40)[a] | [8] |

[a] 44% *ee*.

*1-Dimethylamino*-cis,trans-*2,3-diphenylcyclopropane* [9]

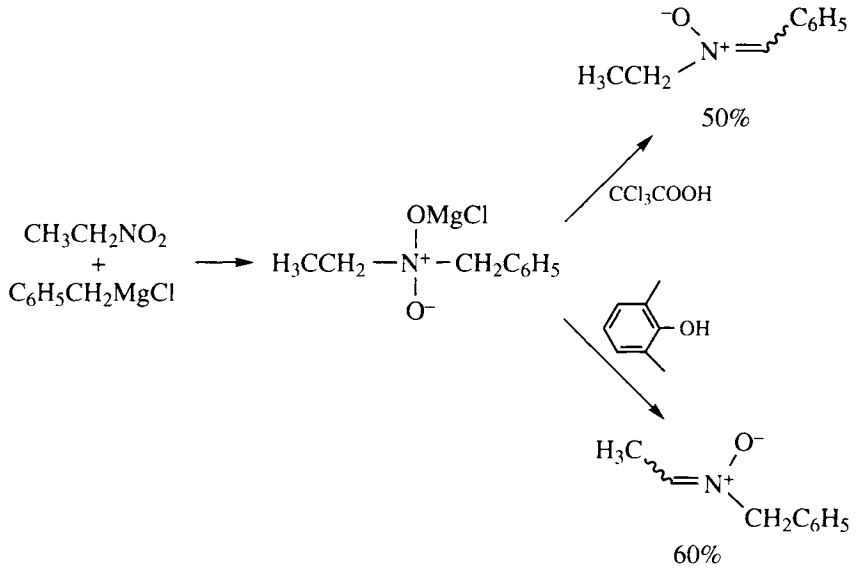



A solution of *cis, trans*-2,3-diphenylcyclopropylmagnesium bromide (70 ml, 6.1 mmol) is prepared from 1-bromo-*cis,trans*-2,3-diphenylcyclopropane (2.46 g, 9.0 mmol) and magnesium (2.46 g, 10.0 mmol) in diethyl ether (80 ml) and added at −10° to a suspension of *N,N*-dimethyl-*O*-mesitylsulfonylhydroxylamine (1.50 g, 6.1 mmol) in THF (20 ml). The mixture is allowed to warm to 25° and stirred for 15 h. Hydrochloric acid (2 M, 20 ml) is added, and the aqueous layer is separated, extracted twice with ether, and basified (2 M NaOH, 20 ml). The resulting alkaline solution is extracted three times with ether. The extract is dried ($MgSO_4$), the solvent is evaporated, and the residue (880 mg, 52%) is recrystallized from ether/pentane to give 1-dimethylamino-*cis,trans*-2,3-diphenylcyclopropane (790 mg, 47%), m.p. 66–68°.

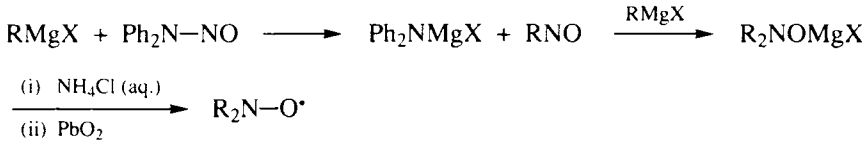
Reactions of organomagnesium compounds with nitroso or nitro compounds are often complicated, and not useful in synthesis, or only represented by isolated examples.* One exception to this generalization involves conjugate addition to α,β-unsaturated and aromatic nitro compounds (see Section 4.2), and two others lead to the formation of carbon–nitrogen bonds.

Reactions of allylic and benzylic Grignard reagents with alkyl nitro compounds can, under the right conditions, provide an acceptable route to nitrones [11]. Lack of regio- and stereoselectivity may be a problem, though the former can be controlled to some extent by varying the acid used for protonation, e.g.

*For example, the preparation of nitrosobenzene by the reaction of phenylmagnesium bromide with nitrosyl chloride was reported as long ago as 1909 [10], but has scarcely been further explored.

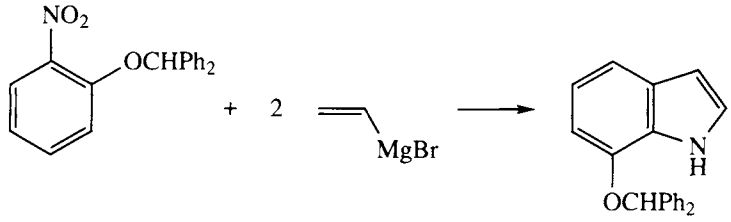



Attempts to extend these reactions to the synthesis of simple hydroxylamines were plagued by deprotonation and redox side-reactions, but recently yields have been much improved by conversion of the Grignard reagent into an organocerium reagent *in situ* [12]; for example, *N*-butyl-*N*-propylhydroxylamine was prepared in 90% yield. Another successful variant utilized *N*-nitrosodiphenylamine to generate a nitroso compound *in situ*. The hydroxylamine salt produced was oxidized *in situ* to give a nitroxide [13]:




Reactions of 1-alkenylmagnesium halides with *ortho*-substituted nitroso- or nitroarenes can lead to indoles [14–17]. The first stage of the complex reaction pathway from nitro compounds is reduction to the nitroso compounds, so the former are usually more readily available starting materials.

*7-(Diphenylmethoxy)indole* [17]




A solution of 2-diphenylmethoxynitrobenzene (3.05 g, 10 mmol) in THF (100 ml) is stirred under nitrogen at −40° as vinylmagnesium bromide (M in THF; 35 ml) is added in portions during a few minutes. The mixture is stirred for 40 min at −40°, and poured into aqueous ammonium chloride (200 ml). The resulting mixture is extracted with ether (2 × 100 ml), and the combined extracts are dried ($Na_2SO_4$) and filtered, and the solvent is evaporated. The residue is purified by chromatography (silica, 12.5% ethyl acetate in hexane) to give 7-diphenylmethoxyindole (1.72 g, 57%), m.p. 112–115°).

A number of reactions of organomagnesium compounds with compounds containing nitrogen–nitrogen multiple bonds give products containing new carbon–nitrogen bonds [A, E], but few of them are useful in synthesis. The main exceptions are reactions with azides, and some reactions of diazonium salts.

Reactions of Grignard reagents with azides, giving triazenes, have been known for many years [A]:

$$R^1MgX + R^2N_3 \longrightarrow R^1N{=}N\text{-}N(MgX)R^2 \longrightarrow R^1N{=}N\text{-}NHR^2 \text{ (or tautomer)}$$

Yields are variable [A], but generally good yields were reported for a more recent study using azidomethyl phenyl sulfide, $PhSCH_2N_3$ [18]. In the examples where $R^1$ = aryl, the triazenes were easily hydrolysed to the corresponding amines, $R^1NH_2$.

Variable yields of azo compounds were also obtained from reactions of Grignard reagents with diazonium salts, but benzenediazonium tetrafluoroborate gave acceptable yields from arylmagnesium bromides or t-butylmagnesium chloride in THF [19]:

$$PhN_2 + BF_4^- \xrightarrow[THF]{RMgX} PhN{=}NR$$

e.g. R = Ph, 66%
R = $Bu^t$, 40%

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# —12—

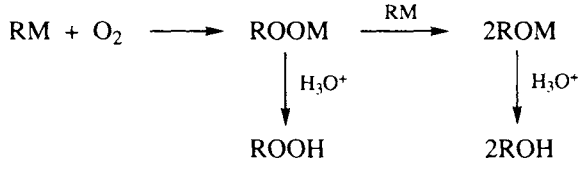
# Formation of Carbon–Oxygen Bonds Via Organomagnesium Compounds

The only effective methods for obtaining carbon–oxygen bonds from organomagnesium compounds involve reactions with compounds containing oxygen–oxygen bonds: dioxygen and peroxides. (Reactions which have been developed for organolithium compounds — with the molybdenum pentoxide–pyridine–hexametapol complex ("MoOPH") and oxaziridines [E, G] — are almost untried for organomagnesium compounds).

## 12.1 REACTION WITH DIOXYGEN

Early investigations of reactions of Grignard reagents with oxygen gave only poor yields of the corresponding alcohols or phenols, and the reaction was generally regarded as a nuisance rather than as useful, though it aroused interest because of the observation of chemiluminescence [A, 1]. Indeed, the uncontrolled reaction tends to give mixtures of products, by complex reaction pathways. However, under controlled conditions it is often possible to obtain useful yields of alcohols or phenols, formed as depicted in Scheme 12.1.*

*Hydroperoxides could probably also be obtained, by analogy with organolithium compounds [E, G].

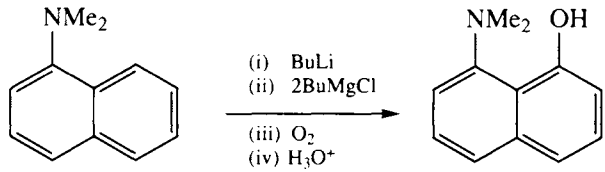



**Scheme 12.1**

In general, (a) yields of alcohols or phenols are better from organomagnesium compounds than from organolithium compounds (though organomagnesium iodides are liable to give iodo compounds as by-products), and (b) alkylmetal compounds give better yields than arylmetal compounds, probably because the second stage of the reaction is faster. Thus, if an organolithium compound is initially available (for example by metallation), it should be converted into the organomagnesium compound by treatment with magnesium bromide (see Section 3.3) before oxidation, and yields of phenols may be improved by co-oxidation with a sacrificial *alkyl*magnesium halide [2]. An example of the application of both these stratagems is provided by the following synthesis of 8-dimethylamino-1-naphthol.*

*An alternative two-step procedure is the oxidation of an organoboron intermediate, prepared from the organomagnesium compound (see Section 15.1).

*8-Dimethylamino-1-naphthol* [3]




(CAUTION: Small detonations occurred during a related procedure, unless the following precautions were observed [4]: the entire amount of Grignard reagent is added before the bubbling is started, and the initial rate of bubbling of oxygen should not exceed two bubbles per second.)

A solution of 1-dimethylaminonaphthalene (CAUTION: possible carcinogen) (0.17 g, 1 mmol) in dry ether (2 ml) is stirred at room temperature as butyllithium (~ 1.7 M in hexane, 4.5 mmol) is added. The mixture is stirred for 48 h and then cooled to 0° and kept at that temperature as butylmagnesium chloride (2 M in ether, 6.8 mmol) is added. After 20 min the mixture is cooled to −5° and maintained at this temperature for 4 h while dry oxygen is passed into the stirred solution. The mixture is poured into a stirred mixture of water (100 ml), acetic acid (10 ml) and zinc powder (1 g), and stirring is continued until effervescence ceases. The mixture is filtered, and the ethereal layer is separated, washed with saturated aqueous sodium hydrogencarbonate

(3 × 50 ml) and water (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residual oil (silica, 17% ether in hexane) gives 8-dimethylamino-1-naphthol (1.52 g, 51%), m.p. 58–59°.

Similar procedures have been used to prepare 4-hydroxydibenzothiophene (48%) [5], 4-hydroxydibenzofuran (50–60%) [6] and 1-hydroxyphenoxathiin-10,10-dioxide (49%) [4].

Recently, the oxidation of dioctylmagnesium with dioxygen to give 1-octanol in high yield has been fully described [7].

### References

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2. D. Ivanoff, *Bull. Soc. Chim. Fr.* **39**, 47 (1926); M. S. Kharasch and W. B. Reynolds, *J. Am. Chem. Soc.* **65**, 501 (1943).
3. A. J. Kirby and J. M. Percy, *Tetrahedron* **44**, 6903 (1988).
4. D. S. Kemp and D. R. Buckler, *J. Org. Chem.* **54**, 3647 (1989).
5. E. Campaigne, L. Hewitt and J. Ashby, *J. Heterocycl. Chem.* **6**, 753 (1969).
6. D. S. Kemp and N. G. Galatakos, *J. Org. Chem.* **51**, 1821 (1986).
7. See Section 3.2, Ref. [56].

## 12.2 REACTIONS WITH PEROXIDES

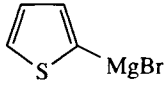
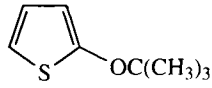
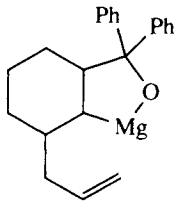
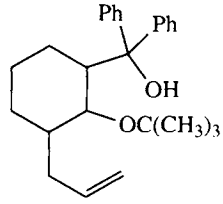
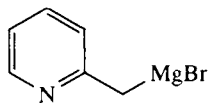
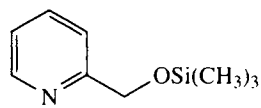
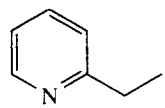
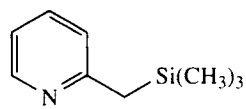
The general reaction between an organomagnesium compound and an organic peroxide is represented by the following equation:

$$R^1MgX + R^2OOR^3 \longrightarrow R^1OR^2 + R^3OMgX \text{ and/or } R^1OR^3 + R^2OMgX$$

The potential problem with regioselectivity is avoided by the use of, for example, a strongly biased peroxide such as a t-butyl peroxyester. Some examples are listed in Table 12.1. A symmetrical peroxide also gives two products (e.g. Table 12.1, entry 4). In the case of bis(trialklylsilyl)peroxides, hydrolysis of the resulting mixture should provide a route to the alcohol or phenol. However, although good yields are often attainable from organolithium compounds, organomagnesium compounds give inferior results [7], and may yields be further lowered by alternative reaction pathways (see Table 12.1, last entry).

TABLE 12.1

Reactions of organomagnesium compounds with peroxides

| Peroxide | Organomagnesium reagent | Product(s) (yield, %) | Ref. |
|---|---|---|---|
| $C_6H_5CO_2OC(CH_3)_3$ | $C_6H_5MgBr$ | $C_6H_5OC(CH_3)_3$ (78–84) | [1] |
| $C_6H_5CO_2OC(CH_3)_3$ |  |  (70–76) | [2] |
| $C_6H_5CO_2OC(CH_3)_3$ |  |  (37) | [3] |
| $C_6H_5CO$–OO–$COC_6H_5$ | $C_6H_5MgBr$ | $C_6H_5COOH$ (85–93)<br>$C_6H_5COOC_6H_5$ (55–60) | [4] |
| $C_6H_5CHOOC(CH_3)_3$<br>$OC_2H_5$ | $C_6H_5MgBr$ | $C_6H_5OC(CH_3)_3$ (63–70) | [5] |
| $(CH_3)_3SiOOSi(CH_3)_3$ |  |  (23)<br>  (18)<br>  (5) | [6] |

## References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2. See Section 3.1, Ref. [61].
3. See Section 4.1, Ref. [22].
4. M. Okubo, K. Maruyama and J. Osugi, *Bull. Chem. Soc. Jpn* **44**, 125 (1971).
5. H. Neumann and D. Seebach, *Chem. Ber.* **111**, 2785 (1978).
6. E. Epifani, S. Florio and L. Troisi, *Tetrahedron* **46**, 4031 (1990).
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# —13—

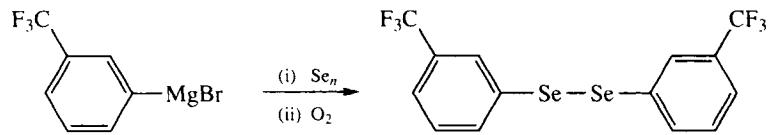
# Formation of Carbon–Sulfur, Carbon–Selenium and Carbon–Tellurium Bonds via Organomagnesium Compounds

In contrast with the dearth of methods for obtaining carbon–oxygen bonds from organomagnesium compounds, there is a variety of methods for obtaining carbon–sulfur bonds. They include reactions with sulfur–sulfur-bonded compounds (including elemental sulfur), reactions involving nucleophilic displacement from sulfur halides and related compounds, reactions with compounds containing sulfur–oxygen double bonds, and thiophilic addition to thiocarbonyl groups (cf. Chapter 7). A few examples have also been reported of analogous syntheses of organoselenium and organotellurium compounds, and these are included where appropriate.

## 13.1 REACTIONS WITH THE ELEMENTS AND COMPOUNDS CONTAINING ELEMENT–ELEMENT BONDS

The reaction of organomagnesium compounds with sulfur (usually mainly $S_8$) can give a range of polysulfides as well as the thiolate. The thiolate is the main product if an excess of sulfur in solution is avoided (see General Ref. [A] for a review of the early work): addition of flowers of sulfur to a Grignard reagent is usually satisfactory. The thiolate may then be hydrolysed to the thiol, or converted *in situ* into other derivatives. Analogous reactions with selenium also give satisfactory yields of selenols or derivatives, and one or two examples of analogous reactions of tellurium have also been reported. Some examples of reactions of all three elements are listed in Table 13.1, and a procedure follows.

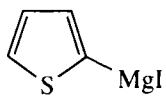
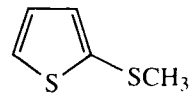
*Bis(3-trifluoromethylphenyl)diselenide* [9]



A solution of 3-trifluoromethylphenylmagnesium bromide is prepared from 3-bromobenzotrifluoride (30.0 g, 0.125 mol) and magnesium turnings (28.1 g, 0.125 mol) in ether (250 ml) (CAUTION: see p. 30), in a 1 litre three-necked flask fitted with a nitrogen inlet, a mechanical stirrer and a dropping funnel, with a sodium hydroxide bubbler attached to the exit tube. The dropping funnel is removed, and powdered black selenium (9.5 g, 0.12 mol) is added to the stirred solution during 10 min, care being taken to avoid the ingress of oxygen. The mixture is stirred for 10 min. Ice (100 g) is added slowly, followed by concentrated HCl (20 ml). The organic layer is separated and washed with water. Methanol (100 ml) is added, and air is bubbled through the solution overnight. The solvents are evaporated and the residue distilled to give bis(3-trifluoromethylphenyl)diselenide (23.2 g, 88%), b.p. 121-123°/0.25 mmHg.

TABLE 13.1

Reactions of organomagnesium compounds with sulfur, selenium and tellurium

| Element | Organomagnesium reagent | Coreagent | Product (yield, %) | Ref. |
|---|---|---|---|---|
| S |  | $CH_3I$ |  (53–60) | [1] |
| | $C_6Br_5MgBr$ | $H_3O^+$ | $C_6Br_5SH$ (58) | [2] |
| | $(C_6H_5)_3CMgBr$ | $H_3O^+$ | $(C_6H_5)_3CSH$ (70) | [3] |
| Se | $C_6H_5MgBr$ | $H_3O^+$ | $C_6H_5SeH$ (57–71) | [4] |
| | $C_6H_5MgBr$ | $Br_2$ | $C_6H_5SeSeC_6H_5$ (64–70) | [5] |
| | $4\text{-}CH_3C_6H_5MgBr$ | $(CH_3)_3SiCl$ | $4\text{-}CH_3C_6H_5SeSiC(CH_3)_3$ (26) | [6] |
| Te | $C_6H_5MgBr$ | $O_2$ | $C_6H_5TeTeC_6H_5$ (50–88) | [7, 8][a] |
| | $4\text{-}CH_3C_6H_5MgBr$ | $(CH_3)_3SiCl$ | $4\text{-}CH_3C_6H_5TeSiC(CH_3)_3$ (27) | [6] |

[a]Other examples are also described; variable yields.

Early work [10] suggested that reactions of Grignard reagent with disulfides resemble those of organolithium compounds:

$$R^1MgX + R^2SSR^2 \longrightarrow R^1SR^2 + R^2SMgX$$

but they have been little used. An example is the cleavage of a thiuram disulfide [11]:

$$(CH_3)_2NCS-S-S-CSN(CH_3)_2 \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) RMgX}} (CH_3)_2NCS-SR \quad 26\text{–}75\%$$

## References


1. See Section 3.1, Ref. [63].
2. See Section 3.2, Ref. [41].
3. W. E. Bachmann and R. F. Cockerill, *J. Am. Chem. Soc.* **55**, 2932 (1955).
4. D. G. Foster, *Org. Synth.* **Coll. 3**, 771 (1955).
5. H. J. Reich, M. L. Cohen and P. S. Clark, *Org. Synth.* **Coll. 6**, 533 (1988).
6. K. Preafcke and C. Weichsel, *Synthesis*, 216 (1980).
7. W. S. Haller and K. J. Irgolic, *J. Organomet. Chem.* **38**, 97 (1972).
8. See Section 2.3, Ref. [8].
9. H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434 (1975).
10. See General Ref. [A], p. 1301.
11. J. R. Grunwell, *J. Org. Chem.* **35**, 1500 (1970).


## 13.2 REACTIONS INVOLVING NUCLEOPHILIC SUBSTITUTION AT THE HETEROATOM

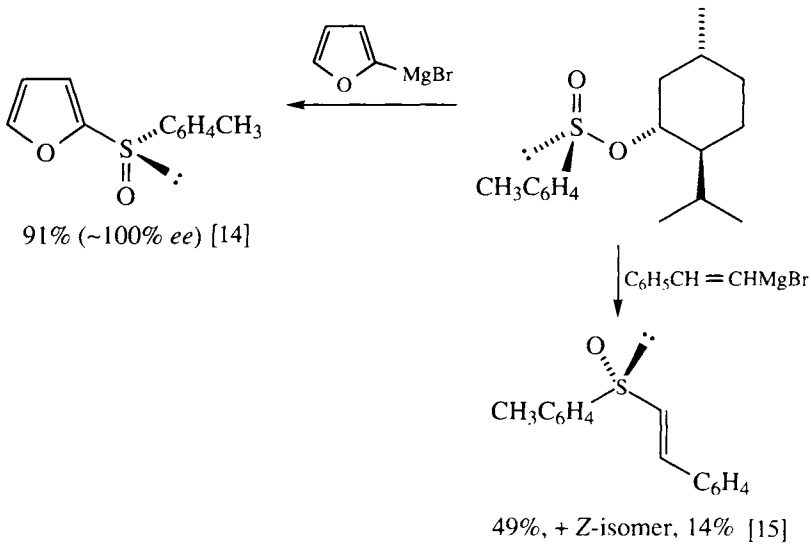
The reactions included here follow the general pattern

$$R^1MgX + R^2EY \longrightarrow R^1ER^2 + MgXY$$

where Y is a good leaving group, most commonly a halogen or an oxygen function, but cyano (in thiocyanates) and in a few cases organic groups furnishing highly stabilized carbanions.* Analogous reactions where the element is in a higher oxidation state, such as sulfonyl halides and tellurium tetrahalides, are also included. Some examples are listed in Table 13.2. Few of these reactions have been extensively used, but those with chiral sulfinates and related compounds have considerable potential for asymmetric synthesis, as exemplified by the following reactions with

*The reactions described in Section 13.1 may also be regarded as special cases.

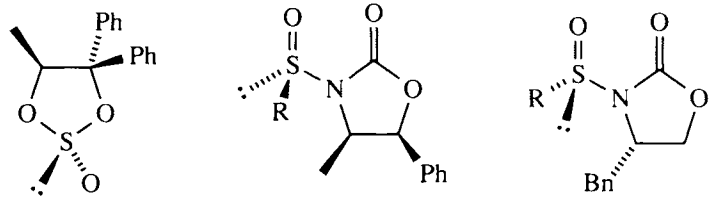
(*S*)-menthyl toluenesulfinate:




91% (~100% *ee*) [14]

49%, + Z-isomer, 14% [15]

Other chiral sulfinyl transfer reagents include a cyclic sulfite (**1**) [16] and sulfinamides (**2**) and (**3**) [17, 18].



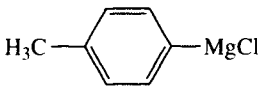
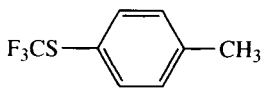
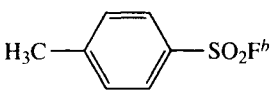
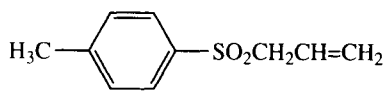
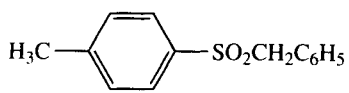

(**1**) (**2**) (**3**)

Although in most cases reactions of organomagnesium compounds with sulfoxides give mixtures resulting from ligand exchange and/or deprotonation, examples have recently been described where decomposition of one displaced ligand results in clean substitution, e.g. [19].

$$C_6H_5S(O)CH{=}CHX \xrightarrow{RMgBr} C_6H_5S(O)R + C_2H_2 + MgBrX$$

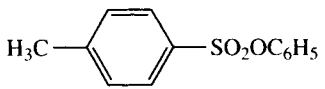
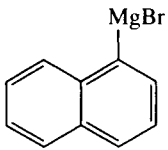
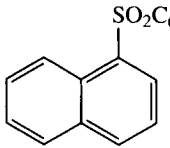
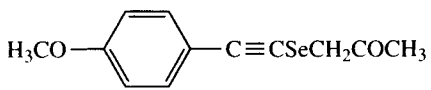
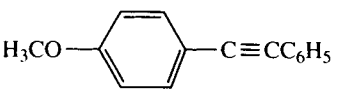
TABLE 13.2

Nucleophilic substitution at sulfur, selenium and tellurium by organomagnesium compounds

| Substrate | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
| $CF_3SCl$ |  |  (34) | [1][a] |
| $C_6H_5S$–$OCH_3$ | $C_6H_5MgBr$ | $(C_6H_5)_2S$ (48) | [2] |
| n-$C_4H_9SCN$ | $C_6H_5MgBr$ | n-$C_4H_9SC_6H_5$ (79) | [3] |
| $NCS(CH_2)_nSCN$ | $CH_3MgI$ | $CH_3S(CH_2)_nSCH_3$ $n$ = 1 (54), 2 (67), 4 (41) | [4] |
| $CH_3SP(S)(C_6H_5)_2$ | n-$C_4H_9MgBr$ | $CH_3S$–n-$C_4H_9$ (almost quantitative) | [5] |
| $SO_2Cl_2$ | $C_6F_5MgCl$ | $C_6F_5SO_2Cl$ (50–60) | [6] |
|  | $H_2C$=$CHCH_2MgCl$ |  (almost quantitative) | [7][c] |
| | $C_6H_5MgBr$ |  (95) | |

*(continued on next page)*

TABLE 13.2 *(continued from previous page)*

| Substrate | Organomagnesium compound | Product (yield, %) | Ref. |
|---|---|---|---|
|  |  |  (71)[d] | [8] |
| $(CF_3SO_2)_2O$ | n-$C_4H_9MgCl$[e] | $CF_3SO_2C_4H_9$ (86) | [9] |
| $(CH_3O)_2SO$ | $(CH_3)_3CMgCl$[f] | $(CH_3)_3CSO{-}OCH_3$ (72) | [10] |
| $(C_6H_5O)_2SO$ | $2C_6H_5MgBr$ | $(C_6H_5)_2SO$ (67–74) | [2] |
| $C_6H_5SeCl$ | $(C_2H_5O)_2P(O)CH_2MgCl$ | $(C_2H_5O)_2P(O)CH_2SeC_6H_5$ (70–85) | [10a] |
|  | $C_6H_5MgBr$ |  (30) | [11] |
| $SeOCl_2$ | $C_6H_5MgBr$ | $(C_6H_5)_3Se^+Br^-$ (37)[g] | [12] |
| $TeCl_4$ | $4(CH_3)_3CMgBr$ | $[(CH_3)_3C]_2Te$ (50)[h] | [13][a] |
| | $(CH_3)_3SiCH_2MgCl$ | $[(CH_3)_3SiCH_2]_4Te$ (76) | [13][a] |

[a]Other examples are described. [b]Sulfonyl chlorides and bromides tend to give mixtures, often containing mainly RHal [A] (see Chapter 14). [c]Other examples are described; other alkyl Grignard reagents, $RCH_2MgX$, tend to give $(ArSO_2)_2CHR$. [d]See also General Ref. [A]; contrast reactions of alkyl sulfonates, which result in displacement at C (see Section 8.2.3). [e]RMgBr, RMgI gave mainly RBr, RI. [f]Other examples are described, but only with t-alkylmagnesium halides. [g]Plus $(C_6H_5)_2Se$ (49.5%); $(C_6H_5)_3SeOMgX$ thought to be an intermediate. [h]By decomposition of the Te(IV) compound.

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## 13.3 REACTIONS WITH SULFUR DIOXIDE AND SULFINIMINES

The reaction of organomagnesium compounds with sulfur dioxide provides a good general method for the preparation of magnesium sulfinates, and thence to various derived compounds (cf. reactions with carbon dioxide: see Section 6.4):

$$RMgX + SO_2 \longrightarrow RSO_2MgX$$

The following procedure [1] is typical, and other similar examples have been described [2] (see also General Ref. [A] for an account of earlier work). An alternative procedure is that described for organolithium compounds (see General Ref. [G], p. 142) [3], in which the Grignard reagent is added to a solution of liquid sulfur dioxide in ether at −78°.

*1-Dodecanesulfinic acid* [1] A Grignard reagent is prepared from 1-bromododecane (125 g, 0.5 mol) in ether (500 ml) and cooled to −35° to

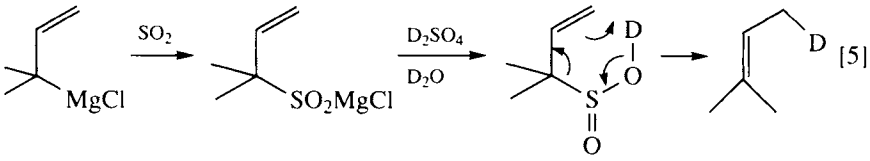
−40° as sulfur dioxide (32 g, 0.5 mol) is added. The reaction mixture is poured into cold aqueous ammonium hydroxide. The resulting suspension is filtered, and the insoluble magnesium dodecanesulfinate is washed thoroughly with water, air dried, and extracted with ether and tetrachloromethane to remove any tetracosane present and then with hot 95% ethanol to remove any magnesium dodecanesulfonate, leaving magnesium 1-dodecanesulfinate dihydrate (105 g, 80%).

Magnesium 1-dodecanesulfinate dihydrate (2.0 g) is ground finely and extracted with boiling 95% ethanol (2 × 50 ml) and ether (2 × 50 ml), and then treated with 2% aqueous hydrochloric acid (100 ml) and ether (50 ml). The ether layer is separated, washed with water (2 × 100 ml) and filtered. The solvent is evaporated under reduced pressure and the residue dried *in vacuo* to give crystalline 1-dodecanesulfinic acid (1.7 g, 96%), m.p. 29–30°.

Reactions in which the sulfinate is used *in situ* are exemplified by the following schemes:

$$(CH_3)_3SiCH_2MgCl \xrightarrow[\text{(ii) } Cl_2]{\text{(i) } SO_2} (CH_3)_3SiCH_2SO_2Cl \quad [4]$$

59%




[5]

It is reported that the reaction of Grignard reagents with selenium dioxide gives diselenides [6].

The reaction of Grignard reagents with sulfimines is the method of choice for preparing sulfinamides [7–9]; mild hydrolysis conditions are necessary for maximum yields [7].

$$R^1N{=}S{=}O \xrightarrow[\text{(ii) 10\% aq. } NH_4Cl]{\text{(i) } R^2MgX} R^1NHSOR^2$$

## References

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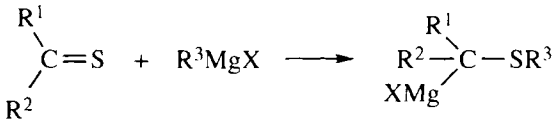
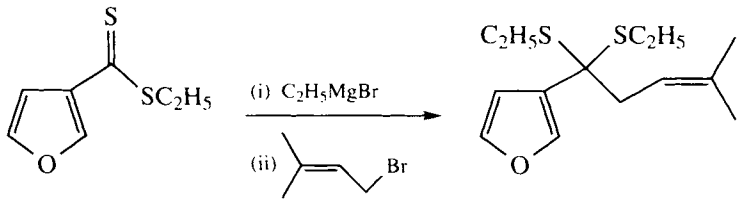
## 13.4 THIOPHILIC ADDITION TO THIOCARBONYL GROUPS

Whereas the reactions of aromatic and unsaturated organomagnesium compounds with thiocarbonyl compounds are analogous to their reactions with carbonyl compounds (see Chapter 7), saturated alkylmagnesium compounds (apart from methyl) tend to react by "thiophilic addition" [1]:



The product is a new organomagnesium compound, which may be used *in situ* for further reactions; reactions with dithioesters are particularly useful, giving functionalized dithioketals [2]. It is interesting to contrast the following example with the reaction involving carbophilic addition described in the same paper (see p. 148) [3].

*1,1-Bis(ethylthio)-1-(3-furyl)-4-methylpent-3-ene (egomaketone dithioketal)* [3]



A solution of ethylmagnesium bromide (0.3 mol) in THF (500 ml) is stirred under nitrogen at −78° as prenyl bromide (36.9 g, 0.25 mol) in THF (40 ml) and ethyl 3-furandithiodicarboxylate (17.2 g, 0.1 mol) are added during 2.5 h. Stirring is continued for 1.5 h and 1:1 water:THF (20 ml) is added carefully. The mixture is allowed to warm to room temperature, and saturated aqueous ammonium chloride is added. The mixture is extracted with pentane, and the organic layer is dried ($Na_2SO_4$). The

solvents and excess prenyl bromide are evaporated *in vacuo* to leave egomaketone dithioketal (27.0 g, quantitative).

The product was hydrolysed to egomaketone (68%) and reduced to perillene (73%) [3].

## References

1. See Chapter 7, Ref. [1].
2. A. I. Meyers, T. A. Tait and D. L. Comins, *Tetrahedron Lett.*, 4657 (1978).
3. See Chapter 7, Ref. [5].

# —14—

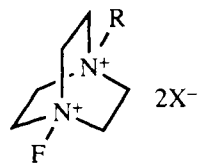
# Formation of Carbon–Halogen Bonds via Organomagnesium Compounds

The reactions described here are useful for replacing one halogen by another, when the organomagnesium compound has been prepared from an organic halide, or for introducing a halogen regiospecifically, when the organomagnesium compound has been obtained by other routes. Both types of reaction are particularly useful with aromatic compounds, where halogen exchange is otherwise difficult, and where regiochemistry different than that of electrophilic aromatic substitution may be obtainable.

## 14.1 FORMATION OF CARBON–FLUORINE BONDS

Because of the difficulty of controlling electrophilic fluorination, and the hazards of working with elemental fluorine*, much effort has been devoted to devising safe, controllable reagents for this purpose. Some earlier reagents such as perchloryl fluoride proved hazardous and/or unpredictable [E, G], but several compounds containing nitrogen–fluorine bonds appear promising [G, 2, 3]. Recently the "Selectfluor" reagents (**1**) have been introduced [4], in particular (**1**) (R = Me, X = $BF_4^-$), which is commercially available. These are relatively non-hazardous and easily stored and handled sources of electrophilic fluorine. Preliminary studies indicate that they react smoothly with Grignard reagents to give the corresponding organic fluorides.

*Even under carefully controlled conditions reactions of organomagnesium compounds with fluorine give only modest yields [1].




(**1**)

*Fluorobenzene* [5] A solution of phenylmagnesium bromide (from bromobenzene (1.57 g, 10 mmol) in ether (50 ml)) is added dropwise during 30 min to a stirred slurry of *N*-fluoroquinuclidinium fluoride (1.49 g, 10 mmol) in ether (15 ml), under an inert atmosphere. An immediate reaction gives a fine white precipitate. The mixture is stirred for 2 h, filtered, and the filtrate added to chloroform, resulting in further precipitation. The mixture is filtered, and the filtrate is concentrated under reduced pressure, and filtered to remove solid quinuclidine. The filtrate is carefully concentrated and the residual liquid is carefully fractionally distilled to give fluorobenzene (0.249 g, 23%), b.p. 84°.

Although the isolated yield from the above preparation was modest, the true yield was higher, and the work-up procedure should be capable of improvement, and the method should be applicable to other organomagnesium compounds [6].

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6. G. S. Lal, U.S. Patent 5,233,074 (1993).

## 14.2 FORMATION OF OTHER CARBON–HALOGEN BONDS

In many cases, reaction of an organomagnesium compound with elemental chlorine, bromine or iodine gives the corresponding organic halogen compound in satisfactory yields*. The main limitations are the risk of halogenation of functional groups (particularly unsaturation), and in the case of iodine, coupling of the organic groups. Chlorination of alkylmagnesium bromides or iodides, and bromination of alkylmagnesium iodides, may lead to halogen scrambling [1]. When side-reactions are troublesome, other sources of "positive halogen" may be used. Those described include *N*-halogen compounds† and arenesulfonyl halides, but reagents described for organolithium compounds [E, G], such as

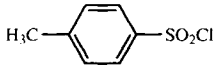
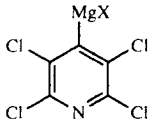
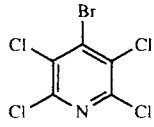
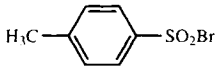
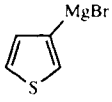
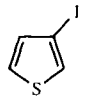
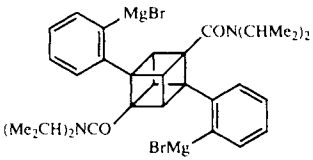
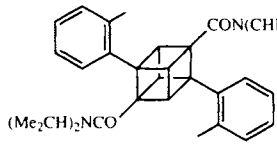
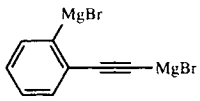
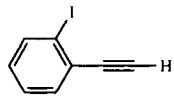
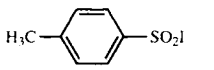
*The reaction with iodine has been used to provide evidence for the formation of Grignard reagents [A, 9].

†Experimental details for the preparation of the organic halides are, however, lacking [2].

hexachloroethane, 1,2-dibromoalkanes and cyanogen bromide, may also be applicable. Examples of reactions of the elements and of sulfonyl halides are listed in Table 14.1. One reagent applicable to alkylmagnesium bromides and iodides but not to alkylmagnesium

TABLE 14.1

Chlorination, bromination and iodination of organomagnesium compounds

| Organomagnesium compound | Reagent | Product (yield, %) | Ref. |
|---|---|---|---|
| $C_6H_5C{\equiv}CMgCl$ | $Cl_2$ | $C_6H_5C{\equiv}CCl$ (85) | [2] |
| $C_6H_5CH_2MgCl$ |  | $C_6H_5CH_2Cl$ (60) | [4] |
|  | $Br_2$ |  | [5] |
| $C_6H_5MgBr$ |  | $C_6H_5Br$ (54) | [4] |
|  | $I_2$ |  (86) | [6] |
|  | $I_2$ |  (~15) | [7] |
|  | $I_2$ |  (71) | [8] |
| $C_6H_5MgBr$ |  | $C_6H_5I$ (65) | [4] |

chlorides or organolithium compounds is triflic anhydride:

$$\text{RMgBr, RMgI} \xrightarrow{(CF_3SO_2)_2O} \text{RBr, RI}$$

The reaction is believed to involve the formation of free halogen [3].

## References


1. L. I. Zakharkin, V. V. Gavrilenko and B. A. Paley, *J. Organometal. Chem.*, **21**, 269 (1970).
2. See General Ref. [A], p. 1243, for a review.
3. X. Creary, *J. Org. Chem.* **45**, 2727 (1980).
4. H. Gilman and R. E. Fothergill, *J. Am. Chem. Soc.* **51**, 3501 (1929).
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6. See Section 3.3, Ref. [14].
7. A. Bashir-Hashemi, H. L. Ammon and C. S. Choi, *J. Org. Chem.* **55**, 416 (1990).
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# —15—

# Synthesis of Organoboron, Organosilicon and Organophosphorus Compounds from Organomagnesium Compounds

The reactions somewhat arbitrarily grouped here may be represented by the general equations:

$$n\mathrm{RMgX} + \mathrm{EY}_m \longrightarrow \mathrm{R}_n\mathrm{EY}_{m-n} + n\mathrm{MgXY}$$

$$n\mathrm{R^1MgX} + \mathrm{R^2}_m\mathrm{EY}_p \longrightarrow \mathrm{R^1}_n\mathrm{R^2}_m\mathrm{EY}_{p-n} + n\mathrm{MgXY}$$

E = B, Si, P and Y = halogen, $\mathrm{OR^3}$ etc.

These syntheses of all three elements have been widely used — those of organoboron compounds often as a prelude to further transformations (see Section 15.4, Ref. [1]), those of organosilicon compounds often to characterize organomagnesium reagents, and those of organophosphorus compounds often to prepare phosphine ligands.

## 15.1 SYNTHESIS OF ORGANOBORON COMPOUNDS

Although alternative methods for preparing organoboron compounds are available (e.g. hydroboration for alkylboron compounds) [1], reactions of organomagnesium compounds (and organolithium compounds [G]) with boron halides, borate esters, etc., remain useful, particularly for arylboron compounds and for compounds with mixed ligands. Some examples are listed in Table 15.1, which includes references to detailed procedures given in a companion volume [1]; some early examples are tabulated in General Ref. [A]. The synthesis of boron heterocycles from "dienylmagnesium compounds" (See Section 3.1.4) is noteworthy. The following procedure is for a variation in which magnesium, an organic halide and boron trifluoride etherate are heated in ether, preferably while being irradiated by ultrasound; this type of procedure is convenient and gives excellent yields even with allyl or benzyl halides [13].

TABLE 15.1

Synthesis of organoboron compounds from organomagnesium compounds

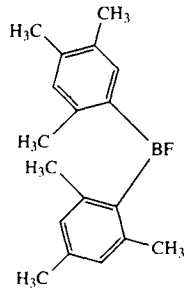
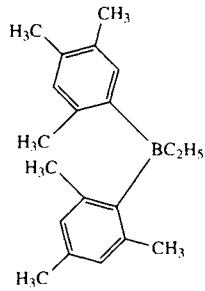
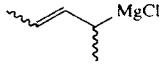
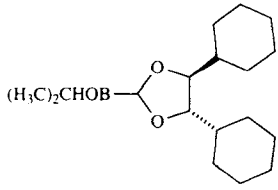
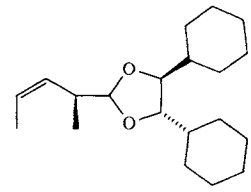
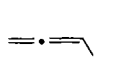
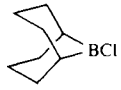
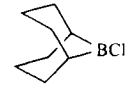
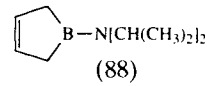
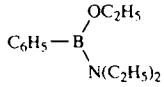
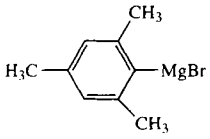
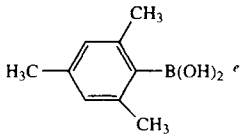
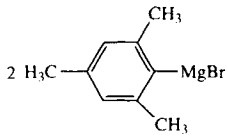
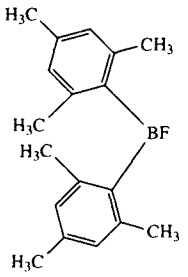
| Organomagnesium compound | Boron reagent | Product (yield, %) | Ref. |
|---|---|---|---|
| $2CH_3MgBr$ | $[(CH_3)_2CHO]_3B$ | $(CH_3)_2CHOB(CH_3)_2$ (70) | [2][a] |
| $C_2H_5MgBr$ |  |  (88) | [3][b] |
| $n\text{-}C_4H_9MgBr$ | $[[(CH_3)_2CH]_2N]_2BCl$ | $C_4H_9B[N[CH(CH_3)_2]]_2$ (84) | [4a] |
|  |  |  (89)[c] | [5] |
|  |  |  (>89) | [6] |
|  | $[(CH_3)_2CH]_2NBCl_2$ |  (88) | [7][d] |
| $n\text{-}C_4H_9MgCl$ | $BCl_3$ | $(n\text{-}C_4H_9)_3B$ (85) | [8] |
| $3C_6H_5MgBr$ | $BF_3{\cdot}O(C_2H_5)_2$ | $(C_6H_5)_3B$ (90) | [9] |
| $C_6H_5MgBr$ |  | $(C_6H_5)_2B\text{–}N(C_2H_5)_2$ (67) | [10] |

TABLE 15.1 *(continued)*

| Organomagnesium compound | Boron reagent | Product (yield, %) | Ref. |
|---|---|---|---|
|  | $B(OCH_3)_3$ |  [c] (70) | [11] |
|  | $BF_3{\cdot}O(C_2H_5)_2$ |  (70) | [12][f] |

[a]Other examples are described. [b]Other examples have been reported [4]. [c]94% *de*! [d]Other examples are described; variable yields, accompanied by polymer. [e]Following hydrolysis. [f]See also Ref. [4].

*Tripropylborane* [13]

$$3CH_3CH_2CH_2Br \xrightarrow{Mg,\ BF_3OEt_2} (CH_3CH_2CH_2)_3B$$

The reaction vessel is designed to fit an ultrasound probe*, and is fitted with a reflux condenser and a septum side-arm, and furnished with an inert atmosphere. Magnesium turnings (0.97 g, 40 mmol), a crystal of iodine, boron trifluoride etherate (1.42 g, 10 mmol) and dry ether (34.5 ml) are introduced into the flask. The ultrasound is switched on, and 1-bromopropane (4.31 g, 35 mmol) is added dropwise via the septum during 5 min, during which time an exothermic reaction starts. After 10 min the ultrasound is switched off and the magnesium salts are allowed to settle. The clear ether layer is transferred to another flask. The magnesium salts

are washed with ether (20 ml) and the washings added to the original ether layer. The solvent is evaporated under reduced pressure, and the residue distilled at 54–56°/12 mmHg to give tripropylborane (1.35 g, 96%).

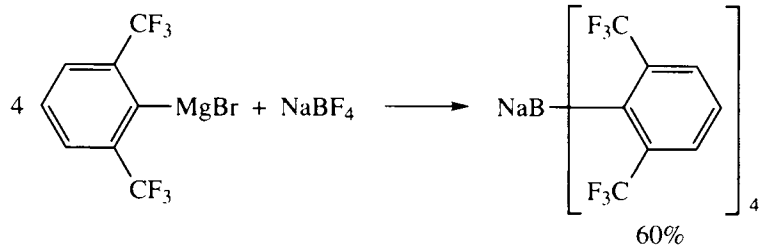
*The paper [13] describes the use of a Tekmar sonic disruptor (250 W, 20 KHz) equipped with a standard horn with tapped end, with the trimer switch on hold and the output control set at 5.

Without ultrasonic irradiation the yield in the above procedure was still high, but the reaction time was 2 h. Ten other examples are reported [13], all with high yields.

The formation of tetraalkylborates by reactions of organomagnesium compounds with trialkylboranes,

$$R^1MgX + R^2{}_3B \longrightarrow XMg[BR^1R^2{}_3]$$

has been comparatively little studied or exploited, and the reactions are more prone to complications arising from ligand exchange or rearrangement than the corresponding reactions of organolithium compounds [1]. However, the preparation of bromomagnesium tetraphenylborate (isolated as sodium tetraphenylborate) from boron trifluoride etherate and an excess of phenylmagnesium bromide has been described [12], and a sodium tetraarylborate has been prepared directly from an arylmagnesium bromide and sodium tetrafluoroborate [4].

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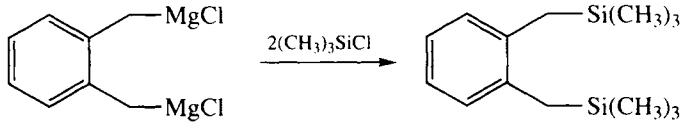
## 15.2 SYNTHESIS OF ORGANOSILICON COMPOUNDS

Much of the early work on the synthesis of organosilicon compounds was based on reactions between Grignard reagents and silicon halides (and to a lesser extent on silicate esters), and much effort was devoted to optimizing stepwise reactions:

$$SiX_4 \xrightarrow{RMgX'} RSiX_3 \xrightarrow{RMgX'} R_2SiX_2 \xrightarrow{RMgX'} R_3SiX \xrightarrow{RMgX'} R_4Si$$

Although these reactions have been largely superseded for the industrial production of simple alkylsilyl halides as precursors to silicones, they, with the analogous organolithium methods [G], remain the principal primary laboratory route to organosilicon compounds [1]. With careful attention to the stoichiometry, the reactions are usually straightforward; when they are sluggish (usually because of steric hindrance), copper(I) catalysis helps [2–4]. Some examples are listed in Table 15.2. The early work has been reviewed in General Ref. [A], which includes some experimental procedures, which are also noted in Table 15.2. The following procedure utilizes a di-Grignard reagent whose preparation is described on p. 34.

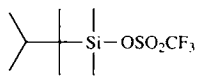
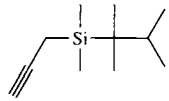
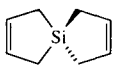
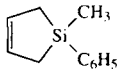
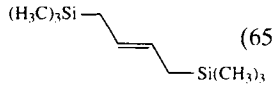
*1,2-Bis(trimethylsilylmethyl)benzene* [21]




A solution of the di-Grignard reagent, prepared as described on p. 34 (but not filtered), is cooled by an ice bath and stirred rapidly as chlorotrimethylsilane (4.4 ml, 35 mmol) is added during 2 h. The mixture is stirred at room temperature for 2 h, and the solvent and excess

TABLE 15.2

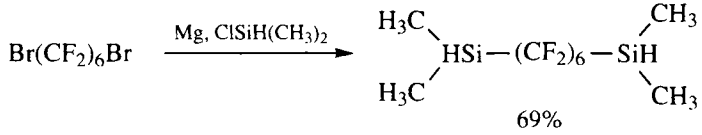
Synthesis of organosilicon compounds from organomagnesium compounds

| Organomagnesium compound | Silicon reagent | Product (yield, %) | Ref. |
|---|---|---|---|
| $HC{\equiv}CMgBr$ | $(CH_3)_3SiCl$ | $HC{\equiv}CSi(CH_3)_3$ (70) | [5] |
| $C_2H_5MgBr$ | $SiCl_4$ | $C_2H_5SiCl_3$ (80) | [6] |
| $2C_2H_5MgBr$ | $SiCl_4$ | $(C_2H_5)_2SiCl_2$ (70) | [6] |
| $3C_2H_5MgBr$ | $HSiCl_3$<br>$Si(OC_2H_5)_4$ | $(C_2H_5)_2SiH$ (77.5)<br>$(C_2H_5)_3SiOSi(C_2H_5)_3$[a] (66) | [7]<br>[8] |
| $3(CH_3)_2CHMgCl$ | $HSiCl_3$ | $[(CH_3)_2CH]_3SiH$ (80) | [9] |
| $n\text{-}C_4H_9MgCl$ | $SiCl_4$ | $(n\text{-}C_4H_9)_4Si$ (79) | [10] |
| $(CH_3)_3CMgCl$ | $(CH_3)_2SiCl_2$[b] | $(CH_3)_3CSi(CH_3)_2Cl$ (74) | [3] |
| $n\text{-}C_{16}H_{33}MgBr$ | $SiCl_4$[b] | $(n\text{-}C_{16}H_{33})_4Si$ (65) | [2] |
| $n\text{-}C_5H_{11}MgCl$ | $SiF_4$ | $(C_5H_{11})_3SiF$ (58) | [11] |
| $BrMg(CH_2)_4MgBr$ | $(CH_3)_3SiCl$ | $(CH_3)_3Si(CH_2)_4Si(CH_3)_3$ (67) | [12] |
| $ClMgOCH_2CH_2CH_2MgCl$ | $(CH_3)_3SiCl$ | $HOCH_2CH_2CH_2Si(CH_3)_3$ (80) | [13] |
| $4CH_2{=}CHCH_2MgBr$ | $SiCl_4$ | $(CH_2{=}CHCH_2)_4Si$ (99) | [14] |
| $CH_2{=}CHMgBr$ | $(CH_3)_3SiCl$ | $CH_2{=}CHSi(CH_3)_3$ (67–78) | [15] |
| $CH_2{=}C{=}CHMgBr$ | $(CH_3)_3SiCl$ | $CH_2{=}C{=}CHSi(CH_3)_3$[c] (high) | [16] |
| |  |  (34) | [17] |
|  | $SiCl_4$ |  (21) | [18] |
| |  |  (78–81) | [19] |
| | $2(CH_3)_3SiCl$ |  (65)[d] | [20] |

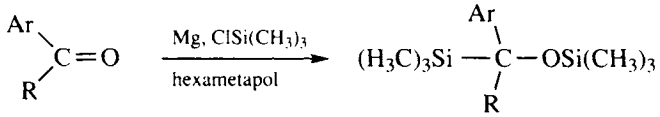
[a] After hydrolysis. [b] CuCN catalyst. [c] Containing a little $HC{\equiv}CCH_2Si(CH_3)_3$. [d] Other examples described, some giving a little (*Z*)-isomer.

chlorotrimethylsilane are evaporated (rotary evaporator). The solid residue is extracted with hexane (3 × 20 ml). The combined extracts are shaken with 1 M HCl (5 ml). The hexane layer is dried ($Na_2CO_3$), filtered and concentrated (rotary evaporator). Distillation then gives 1,2-bis(trimethylsilylmethyl)benzene (up to 2.17 g, 71%), b.p. 60 – 62°/0.1 torr.

A useful alternative to reactions of preformed Grignard reagents is a "Barbier" procedure in which an organic halide, magnesium and a silicon halide react together. In some cases the organomagnesium compound may be an intermediate, and the technique has been particularly employed when the Grignard reagent would be unstable, as in the following example [22]:




In others, however, other pathways are probably involved, for example involving electron transfer mechanisms or silylmagnesium intermediates, and sometimes giving products different from, or unobtainable by, the two-step procedure. For example, reactions of aromatic carbonyl compounds with magnesium and chlorotrimethylsilane in hexametapol result in silylation at both carbonyl carbon and carbonyl oxygen:




Such reactions have been reviewed [23], and a procedure for the preparation of arylsilanes is given in a companion volume [24].

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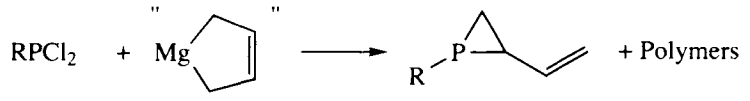
## 15.3 SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS

### 15.3.1 Synthesis of organophosphorus(III) compounds

Reactions of organomagnesium compounds with phosphorus(III) halides and trialkyl phosphites are normally straightforward; the main limitations are steric hindrance, and the instability of the products. Some examples are listed in Table 15.3, and others are tabulated in General Ref. [A].

Reactions of magnesium butadiene (see Section 3.1.4) with alkyldichlorophosphines are reported to give vinylphosphiranes rather than phosphacyclopentenes [11]:

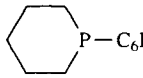
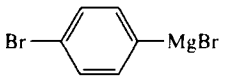
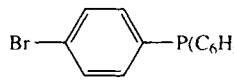
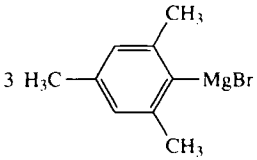
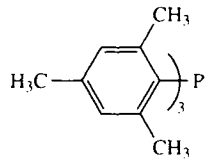



### 15.3.2 Synthesis of organophosphorus(V) compounds

Although many reactions of organomagnesium compounds with phosphorus(V) compounds have been reported [A, 12], few of them have

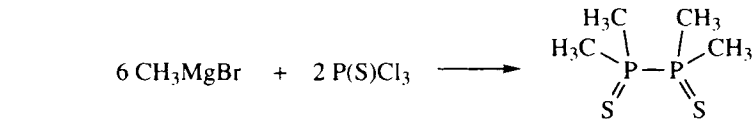
TABLE 15.3

Synthesis of organophosphorus(III) compounds from organomagnesium compounds

| Organomagnesium compound | Phosphorus reagent | Product (yield, %) | Ref. |
|---|---|---|---|
| 3 $CH_3MgBr$[a] | $P(OC_6H_5)_3$ | $(CH_3)_3P$ (80–85) | [1] |
| 2 $CH_3MgCl$ | $H_2C{=}CHPCl_2$ | $H_2C{=}CHP(CH_3)_2$ (35) | [2] |
| | $C_2H_5PCl_2$ | $C_2H_5P(CH_3)_2$ (78) | [2] |
| 2 $(CH_3)_2CHMgCl$[b] | $PCl_3$ | $[(CH_3)_2CH]_2PCl$ (55–60) | [3] |
| n-$C_4H_9MgCl$ | $PCl_3$ | n-$C_4H_9PCl_2$ (45) | [4] |
| 3 n-$C_4H_9MgCl$ | $PCl_3$ | $(n\text{-}C_4H_9)_3P$ (66) | [4] |
| $BrMg(CH_2)_5MgBr$ | $C_6H_5PCl_2$ |  (36) | [5][c] |
| $(CH_3)_2NCH_2CH_2CH_2MgCl$ | $C_6H_5PCl_2$ | $[(CH_3)_2NCH_2CH_2CH_2]_2PC_6H_5$ (65–69) | [7] |
|  | $(C_6H_5)_2PCl$ |  (73–77) | [8] |
|  | $PCl_3$ |  (29)[d] | [9] |
| $(n\text{-}C_8H_{17})_2Mg$ | $PCl_3$ | $(n\text{-}C_8H_{17})_3P$ (84) | [10] |

[a]Dibutyl ether as the solvent. [b]The use of isopropylmagnesium bromide leads to some halogen exchange. [c]It is noteworthy that this old work has scarcely been bettered [6]. [d]Together with tetramesityldiphosphine (6%).

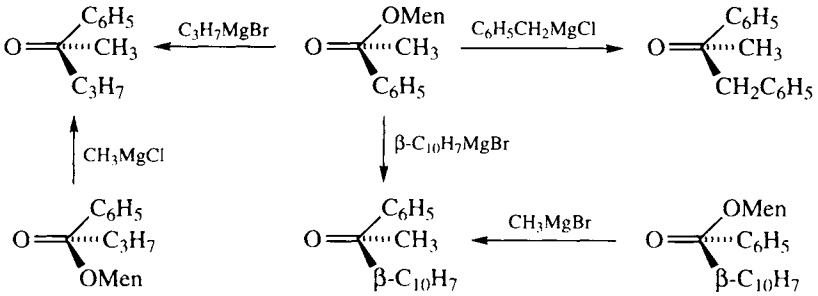
found much use in synthesis*, though one has achieved *Organic Syntheses* status [13]:



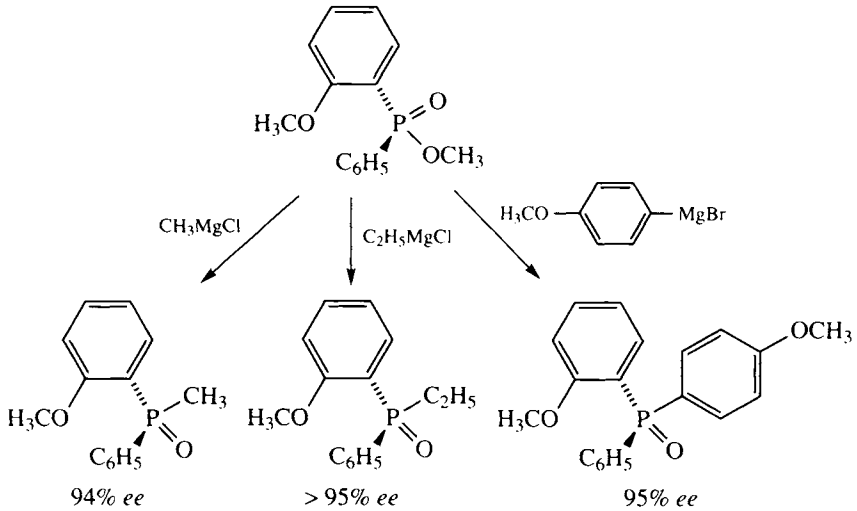
67–74%

*Reactions of phosphates, etc., proceeding by attack at carbon rather than phosphorus, are noted in Section 8.2.3, pp. 170–1.

The major exceptions to this generalization are reactions with chiral phosphinates and related compounds, which provide an important route to chiral phosphine oxides. In these reactions, organomagnesium compounds generally give better stereoselectivity than organolithium compounds, though the latter are more reactive [G, 14b]. The classic work of Mislow and co-workers [14] established that in most cases the reactions proceed with inversion of configuration, as shown in Scheme 15.1, and in the examples shown in Scheme 15.2 [15]. However, *retention* of configuration is sometimes observed, as in the case described in the following procedure [15]; the reasons for such differences are not well understood [15].

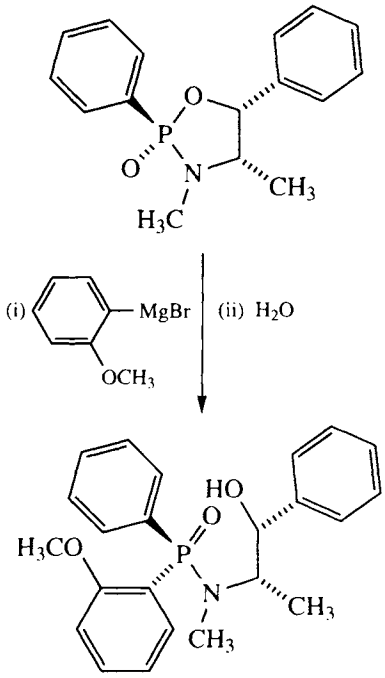



**Scheme 15.1**




**Scheme 15.2**

*(S)-(−)-(2-Hydroxy-1-methyl-2-phenylethyl)-P-2-methoxyphenyl-N-methyl-P-phenylphosphinamide* [15]




A solution of (−)-(2*R*,4*R*,5*S*)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide (10.0 g, 34.8 mmol) in dry THF (150 ml) is stirred at −30° under an inert atmosphere as 2-methoxyphenylmagnesium bromide (0.5 M in THF, 100 ml, 50 mmol) is added via a cannula. The mixture is stirred at −30° for 1 h and at room temperature for 18 h. Water (100 ml) is added cautiously, and the resulting mixture is extracted with dichloromethane (3 × 100 ml). The combined extracts are dried ($MgSO_4$) and concentrated. The white solid thus obtained is recrystallized from toluene (two crops) to give the title compound (9.6 g, 70%), m.p. 195–197°, $[\alpha]_D^{21}$ −14.8°(*c* = 1.0, $CHCl_3$).

## References

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6. J. B. Lambert and H. Sun, *J. Org. Chem.* **42**, 1315 (1977).
7. See Section 3.1, Ref. [84].
8. See Section 3.1, Ref. [92].
9. B. I. Stepanov, E. N. Karpova and A. I. Bokanov, *J. Gen. Chem. USSR* **39**, 1514 (1969).
10. See Section 3.2, Ref. [56].
11. W. J. Richter, *Angew. Chem., Int. Ed. Engl.* **21**, 292 (1982).
12. See Section 8.2, Ref. [51].
13. G. W. Parshall, *Org. Synth.* **Coll. V**, 1016 (1973).
14. O. Korpium, R. A. Lewis, J. Chicos and K. Mislow, *J. Am. Chem. Soc.* **90**, 4842 (1968); R. A. Lewis and K. Mislow, *J. Am. Chem. Soc.* **91**, 7009 (1969).
15. J. M. Brown, J. V. Carey and M. J. H. Russell, *Tetrahedron* **46**, 4877 (1990).

# —16—

# Organomagnesium Compounds in the Synthesis of Other Organometallic Compounds

The reaction of an organomagnesium compound with a derivative — usually the halide — of a less electropositive metal is a very important general method for the synthesis of organometallic compounds:

$$n\text{RMgX} + \text{MY}_m \longrightarrow \text{R}_n\text{MY}_{m-n} + n\text{MgXY}$$

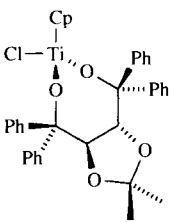
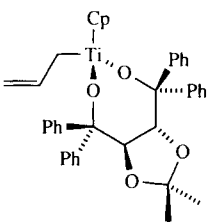
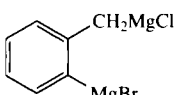
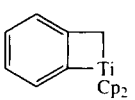
In many cases either an organomagnesium compound or the corresponding organolithium compound (see General Ref. [G]) gives equally satisfactory results. In others, one or the other may be preferable. In general, organomagnesium compounds are less reactive than organolithium compounds, but they are also less basic and poorer one-electron reducing agents, and so less prone to side-reactions arising from these properties. In cases where the organomagnesium compounds themselves are too "hard", organozinc or organoaluminum compounds may be preferable.

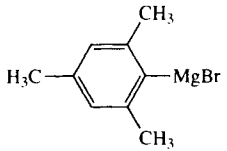
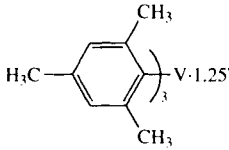
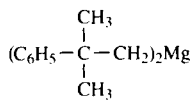
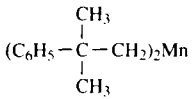
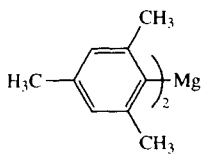
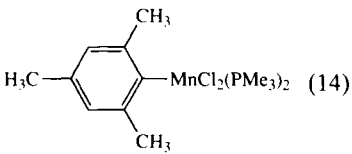
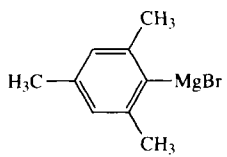
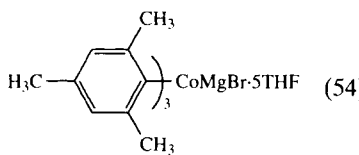
The general equation above may well be an oversimplification, since it takes no account of solvation, association or interactions between the various species. Sometimes well-defined products are isolated; some representative procedures follow, and other well-described examples are listed in Table 16.1, in which the metals are arranged in order of increasing atomic number. Further examples for many of the metals are referred to in Ref. [52]. Frequently, however, metal halides etc., are added to solutions of organomagnesium compounds to give reagents which are used *in situ*, and whose constitution may be conjectural. Some of these reagents have already been mentioned, and leading references to these and others are listed in Table 16.2*.

*Catalysed reactions of organomagnesium compounds, such as the alkylmagnesiation reactions noted in Section 4.1 and the cross-coupling reactions noted in Section 8.1, may also involve other organometallic compounds as intermediates, but only stoichiometric reactions are included here.

TABLE 16.1

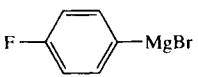
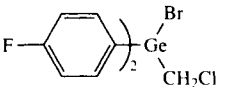
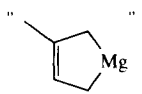
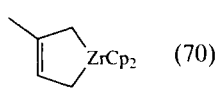
Synthesis of other organometallic compounds from organomagnesium compounds[a]

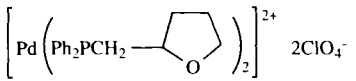
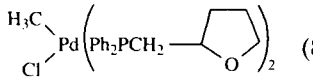
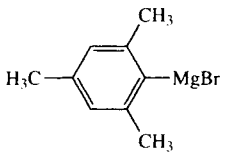
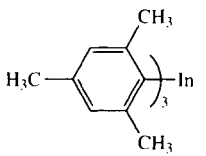
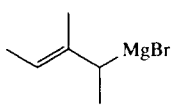
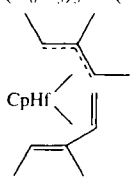
| Organomagnesium compound | Substrate | Product (yield, %) | Ref. | Notes |
|---|---|---|---|---|
| $CH_3MgI$ | $BeCl_2$ | $(CH_3)_2Be$ (85–90) | [1] | |
| "n-$C_4H_9MgI$" | $BeCl_2$ | $(C_4H_9)_2Be$ (41) | [2] | Reaction in benzene avoids problem of removing ether |
| $CH_3CH(CH_3)CH_2MgBr$ | $AlCl_3$ | $[CH_3CH(CH_3)CH_2]_3Al{\cdot}O(C_2H_5)_2$ (~ 51) | [3] | Grignard reagent prepared from optically active bromide |
| $(CH_3)_2CHCH_2CH_2MgBr$ | $AlCl_3$ | $[(CH_3)_2CHCH_2CH_2]_3Al$ (87) | [4] | Reaction in heptane |
| $C_6H_5MgBr$ | $AlCl_3$ | $(C_6H_5)_3Al$ (75) | [4] | Reaction in dodecane |
| Cp*MgCl | $Sc(acac)_3$ | $Cp^*Sc(acac)_2$ (87) | [5] | |
| $CH_3MgCl$ | $TiCl_4$ | $CH_3TiCl_3{\cdot}$bipy (almost quantitative) | [6] | Solid methylmagnesium chloride used |
| $H_2C{=}CHCH_2MgCl$ |  |  (93) | [7] | Other examples are also described |
|  | $Cp_2TiCl_2$ |  (92–94) | [8] | |

| | | | | | |
|---|---|---|---|---|---|
|  | $VCl_3$ |  | (64) | [9] | $Mes_2VCl_2$ also described |
| $H_2C{=}CHCH_2MgCl$ | $CrCl_3$ | $(H_2C{=}CHCH_2)_3Cr$ (69–79) | | [10] | |
|  | $MnCl_2$ |  | (not stated) | [11] | |
|  | $MnCl_2$ |  | (14) | [12] | Mn(III) complex obtained after treatment of reaction mixture with $PMe_3$ followed by oxygen |
| CpMgBr | $FeCl_3$ | $Cp_2Fe$ | | [13] | An historic paper, though other methods for preparing ferrocene are now preferred |
| $CH_3CH_2CH_2MgBr$ | $[CpFe(CO)_2(THF)]^+BF_4^-$ | $CpFe(CO)_2CH_2CH_2CH_3$ (80) | | [14] | |
|  | $CoBr_2$ |  | (54) | [15] | |

*(continued on next page)*

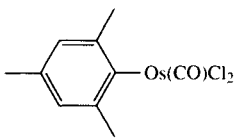
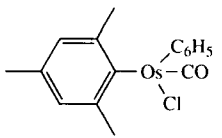
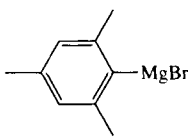
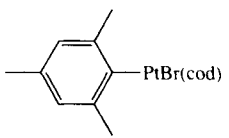
TABLE 16.1 *(continued from previous page)*

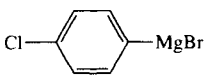
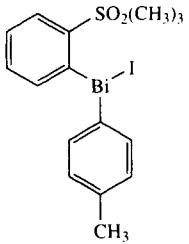
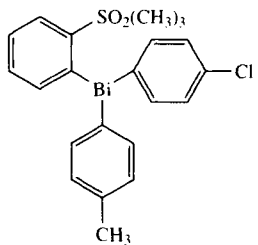
| Organomagnesium compound | Substrate | Product (yield, %) | Ref. | Notes |
|---|---|---|---|---|
| $H_2C{=}CHCH_2MgCl$ | $NiCl_2$ | $(H_2C{=}CHCH_2)_2Ni$ (80) | [16] | |
| $C_6F_5MgBr$ | $Cu_2Br_2$ | $(C_6F_5Cu)_2{\cdot}$(dioxane) (63–80) | [17] | |
| $H_2C{=}CHCH_2MgCl$ | $GeCl_4$ | $(H_2C{=}CHCH_2)_4Ge$ (45) | [18] | A reaction of 3-bromofuran, magnesium and chlorotrimethylgermane under sonication has been reported [19] |
| $n\text{-}C_4H_9MgCl$ | $GeCl_4$ | $(n\text{-}C_4H_9)_3GeCl$ (60) | [4] | |
|  | $Cl_3GeCH_2Cl$ |  (40) | [20] | Note the halogen exchange |
| $C_6H_5MgBr$ | $(C_6H_5)_4AsO$ | $(C_6H_5)_4AsCl{\cdot}HCl$ (74–80) | [21] | After reaction of the intermediate $(C_6H_5)_4AsOMgBr$ with HCl |
|  | $Cp_2ZrCl_2$ |  (70) | [22] | Other examples are also described, including hafnium analogues. A reaction of a diene, magnesium and zirconocene dichloride is thought to proceed via zirconocene rather than an organomagnesium intermediate [23] |

| | | | | |
|---|---|---|---|---|
| $9CH_3MgCl$ | $[MoCp^*Cl_4]_2$ | $MoCp^*(CH_3)_4$ | [24] | |
| $CH_3MgCl$ |  |  (83) | [25] | Other examples are also described |
| $C_6F_5MgBr$ | $PdCl_2(PMe_2Ph)_2$ | $C_6F_5PdCl(PMe_2Ph)_2$ (72) | [26] | |
| $C_6H_5MgBr$ | $CdBr_2$ | $(C_6H_5)_2Cd$ | [27] | Low yield, but after rigorous purification |
| $(CH_3)_3CCH_2MgCl$ | $InI_3$ | $[(CH_3)_3CCH_2]_3In$ (93) | [28] | |
|  | $InCl_3$ |  (90) | [29] | |
| $H_2C{=}CHMgBr$ | $(CH_3)_3SnCl$ | $H_2C{=}CHSn(CH_3)_3$ (64–66) | [30] | |
| $H_2C{=}CHMgBr$ | $(n\text{-}C_4H_9)_2SnCl_2$ | $(n\text{-}C_4H_9)_2Sn(CH{=}CH_2)_2$ (74–91) | [31] | |
| $C_2H_5MgBr$ | $SnCl_4$ | $(C_2H_5)_4Sn$ (89–96) | [32] | |
| $H_2C{=}CHCH_2MgBr$ | $[(n\text{-}C_4H_9)_3Sn]_2O$ | $(n\text{-}C_4H_9)_3SnCH_2CH{=}CH_2$ (94) | [33] | |
| $H_2C{=}CHCH_2MgCl$ | $SnCl_4$ | $(H_2C{=}CHCH_2)_4Sn$ (53) | [34] | |
| $(CH_3)_3CCH_2MgCl$ | $SbCl_3$ | $[(CH_3)_3CCH_2]_3Sb$ (80) | [35] | |
| $C_6H_5MgBr$ | $SbCl_3$ | $(C_6H_5)_3Sb$ (82–90) | [36] | |
|  | $CpHfCl_3$ |  (54) | [37] | |

*(continued on next page)*

TABLE 16.1 *(continued from previous page)*

| Organomagnesium compound | Substrate | Product (yield, %) | Ref. | Notes |
|---|---|---|---|---|
| $CH_3MgI$ | $(\eta 3\text{-}C_3H_5)_3W(PMe_3)Cl$ | $(\eta 3\text{-}C_3H_5)_3W(PMe_3)CH_3$ (66) | [38] | Ethyl and other analogues are also described |
| $H_2C{=}CHCH_2MgBr$ | $W(OC_6H_5)_6$ | $(\eta 3\text{-}C_3H_5)_4W$ (62) | [38] | |
| $(CH_3)_3CCH_2MgCl$ | $(CH_3O)_3WCl_3$ | $[(CH_3)_3CCH_2]_3W{\equiv}C(CH_3)_3$ (80–85) | [39] | |
| $C_6H_5MgBr$ |   |   (55) | [40] | Outcome of related reactions depends on nature of both R and X in RMgX [40, 41] |
| $CH_3MgBr$ | $C_6H_5CH_2Pt(cod)Cl$ | $C_6H_5CH_2PtCH_3(cod)$ (92) | [42] | |
|   | $PtCl_2(cod)$ |   (90) | [42] | Note halogen exchange |
| $H_2C{=}CHMgBr$ | $ClAuPPh_3$ | $H_2C{=}CHAuPPh_3$ (90) | [43] | |
| $(CH_3)_2CHMgCl$ | $HgCl_2$ | $[(CH_3)_2CH]_2Hg$ (87) | [44] | Ethyl and n-propyl analogues prepared similarly |
| $C_2H_5MgBr$ | TlBr | $(C_2H_5)_2TlBr$ (40) | [45] | This method is preferable to that using $TlX_3$ for primary alkyl derivatives, but fails for s-alkyl and aryl derivatives [46]. For a review, see Ref. [47] |

| | | | | |
|---|---|---|---|---|
| $C_2H_5MgBr + C_2H_5I + Mg$ | $PbCl_2$ | $(C_2H_5)_4Pb$ (82) | [48] | For an attempted synthesis of an organolead(II) compound by this route see Ref. [49] |
|  |  |  (95) | [50] | |
| Cp*MgCl | $ThCl_4$ | $Cp^*_2ThCl_2$ (80–85) | [51] | Uranium analogue prepared similarly |

[a]In this table: Cp*, pentamethylcyclopentadienyl; bipy, 2,2'bipyridyl; diox, 1,4-dioxane; cod, cycloocta-1,5-diene.

TABLE 16.2

Organometallic reagents prepared *in situ* from organomagnesium compounds

| Metal | Ref. | Notes |
|---|---|---|
| Ti | [53] | See Section 6.1. See also Ref. [54] for a combination of Ti and Zn |
| Mn | [55] | See Section 6.2 |
| Cu | [56] | See Sections 4.1, 6.1.2 and 6.2 |
| Zn | [54, 57, 58] | See Sections 6.2, 8.2.1 and 8.3. For bimetallic reagents containing Zn, see Section 4.1 |
| Cd | [59] | See Section 6.2 |
| Ce | [60, 61] | See Section 6.1. Ultrasound irradiation is beneficial for the reaction of organolithium compounds with cerium trichloride, and would presumably be so for organomagnesium compounds [62] |
| Yb | [63] | |
| Hg | [64] | |

*Dimethyl(*N,N,N′,N′*-tetramethylethanediamine)nickel* [65]

$$(CH_3)_2Mg{\cdot}TMEDA + Ni(acac)_2(TMEDA) \longrightarrow (CH_3)_2Ni{\cdot}TMEDA$$

Bis(pentane-2,4-dione)(*N,N,N′,N′*-tetramethylethanediamine)nickel (3.73 g, 10.0 mmol) and dimethyl(*N,N,N′,N′*-tetramethylethanediamine)magnesium (1.71 g, 10.0 mmol) are dissolved in toluene (100 ml) at −30°. The resulting solution, initially blue, is kept at −10° for 4 h, after which time it becomes dark red. The suspension is filtered, and the filtrate is cooled to −78°, whereupon fine yellow crystals slowly separate. When crystallization is complete, the mother liquor is siphoned off through a capillary, and the crystals are washed twice with cold pentane and dried *in vacuo* at 20°, to leave the dimethylnickel complex (1.70 g, 83%).

Occasionally the presence of the halide in a Grignard reagent may cause complications, but these can be avoided by the use of the corresponding dialkylmagnesium compound. The above preparation failed with methylmagnesium bromide.

Although halides are the most commonly used substrates, other ligands may also be displaced; some other examples are included in Table 16.1.

*μ-Acetatotriphenyltris(trimethylphosphine)dimolybdenum(II)* [66]

$$Mo_2(OCOCH_3)_4 \xrightarrow[P(CH_3)_3]{(C_6H_5)_2Mg} Mo_2(OCOCH_3)(C_6H_5)_3(PMe_3)_3$$

$\mu_4$-Tetraacetatodimolybdenum (0.57 g, 1.3 mmol) is suspended in ether (50 ml) and trimethylphosphine (1 ml) at 0°, and diphenylmagnesium (0.7 M in ether, 3.8 ml, 2.7 mmol) is added. The resulting blue–green mixture is stirred at 0° for 1 h. Volatile material is evaporated under reduced pressure, and the blue residue is extracted with light petroleum (40 ml). The extract is filtered, concentrated to approximately 20 ml and cooled to −20°. The dark-blue crystals which separate are washed with cold light petroleum (1 ml) and dried *in vacuo* to give the title compound (0.4 g, 46%), m.p. 151–153°.

Analogous syntheses of rhenium, ruthenium and rhodium complexes are also described in Ref. [66].

The following procedure provides a good illustration of a controlled, one-pot, stepwise introduction of ligands.

*t-Butyldimethylantimony* [67]

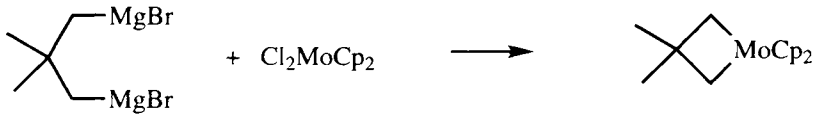
$$SbCl_3 \xrightarrow[(ii)\ 2CH_3MgBr,\ 0°]{(i)\ (CH_3)_3CMgCl,\ -50°} (CH_3)_2SbC(CH_3)_3$$

A solution of antimony trichloride (148.6 g, 0.651 mol) in ether (800 ml) is cooled to −50° and stirred vigorously as t-butylmagnesium chloride (2.0 M in ether, 342 ml) is added dropwise during 3 h. The resulting slurry is stirred at −50° for a further 1 h, allowed to warm to room temperature during about 2 h, stirred at room temperature for a further 1.5 h and recooled to 0°. This temperature is maintained as methylmagnesium bromide (2.7 M, 500 ml) is added dropwise during 3 h. Stirring is continued for 24 h at room temperature and then 3 h under reflux. The mixture is cooled to 0° and stirred as deoxygenated distilled water (500 ml) is added during 2 h. (CAUTION: exothermic reaction; a reflux condenser should be fitted). The resulting mixture is allowed to settle, and the organic layer is transferred to a Schlenk flask, dried ($MgSO_4$), and the solvent is fractionally distilled. The residue is heated at 55°/6 torr, and the air-sensitive product is collected by transfer to a liquid nitrogen trap. Further

purification by fractional distillation gives t-butyldimethylantimony (87.7 g, 64%), b.p. 44°/11 torr.

The following procedure illustrates the use of di-Grignard reagents for the synthesis of metallacycles. In spite of the difficulty in preparing the di-Grignard reagent (see Section 3.1, p. 29), this is one of the most important routes to metallacyclobutanes [69].

*1,1-Bis(cyclopentadienyl)-3,3-dimethyl-1-molybdenacyclobutane* [68]




A solution of 1,3-bis(bromomagnesio)-2,2-dimethylpropane (0.071 mmol) in ether (10 ml) is added to dichlorobis(cyclopentadienyl)molybdenum (21 mg, 0.071 mmol). The ether is evaporated and replaced by THF (10 ml), and the mixture is stirred at room temperature for 3 h. Dioxane (3 ml) is added, and the resulting suspension is filtered. The red–brown filtrate is evaporated to leave the crude title compound (80%), which may be purified by vacuum sublimation.

Organomagnesium compounds show less tendency than organolithium compounds to form the cationic part of 'ate complexes (but see, for example, the cobalt example in Table 16.1). Indeed, even with aluminum the complexes are probably better regarded as mixed aggregates, for example $Mg_2Al_2(CH_3)_8$ [70] and the volatile complexes $[(n\text{-}C_4H_9)_2MgAl(OR)_3]_2$ [71]. It should also be noted that magnesium can also participate in the "anionic" part of 'ate complexes (see Section 3.3.3).

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# Index of Compounds and Methods

All organomagnesium compounds mentioned in the text and tables are indexed, but for some simple alkyl- and arylmagnesium halides only selected entries are included. In general, substrates for reactions of organomagnesium compounds are indexed by the class of compound rather than as individual compounds, and references to routine uses of common substrate classes such as aldehydes and ketones, iodomethane and trimethylsilyl chloride are excluded. Polysubstituted compounds are usually indexed under the parent compound.


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