MAGNESIUM

ANNUAL SURVEY COVERING THE YEAR 1973

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Contents

1. INTRODUCTION

There is no doubt that, as far as organomagnesium chemistry is concerned, on of the most important facts in 1973 is the appearance of Volume 13/2a in the HOUBEN-WEYL series, Methoden der organischen

Chemie [1]. In this volume, in almost 500 pages, Nützel reviews the literature - till the beginning of 1972 - dealing with Mg-organic compounds, besides the literature of organic compounds of Be, Ca, Sr, Ba, Zn and Cd (in cooperation with other authors). After Kharasch's book in English (1954) and Yoffe and Kocheskov's work, originally in Russian, later on translated in English (1965), this new German work is an extremely valuable recent compilation of the chemistry of organomagnesium compounds.

A review has been written by Wardell on the organometallic compounds of Group II with some emphasis on Grignard chemistry [2].

In the series of Specialists' Reports on Organometallic Chemistry, Crosse wrote a seven page review on organomagnesium chemistry in 1971 [3].

Akhrem, Levina and Titov wrote a book on Alkylation of Unsaturated Carbonyl Compounds by Grignard Reagents [4].

In a review on the Chemistry of α-acetylenic ketones, Bol'shedvorskaya and Vereshchagin discussed, among other subjects, the reactions of these unsaturated ketones with Grignard reagents [5].

Bell wrote a three-page, educational, review on the problems, related to the Constitution of Grignard reagents [6].

Maercker wrote a review on NMR-spectroscopic investigations of lithium- and magnesium-organometallic compounds [7]; this review includes some interesting informations on NMR-spectra made during reactions of Grignard compounds, e.g. with the ethereal solvent.

In a series of review articles on solvent effects in organometallic chemistry Petrosyan and Reutov discussed, among other subjects, the solvent effects on the reaction of organomagnesium halides with organic halides [8].

In a review paper Alexandrov discussed, among other subjects, the oxidation reaction of RMgX and of R_2Mg by means of oxygen [9].

The following dissertations have appeared in the U.S.A.:

F.W. Von Rein: Addition of Grignard and organolithium reagents to kynols [10]. Li-Chung Chao: Kinetics and mechanisms of methylmagnesium bromide and dimethylmagnesium addition to benzonitrile [11]. S.N. Ulmer: Preparation, characterization and synthetic utility of organometallic carbonylmagnesium compounds [12]. G.J. Lambert: Grignard reduction reactions. Reduction yield aberrations in the reacti of tert-butyl phenyl ketone with Grignard reagents. Mechanism of be zophenone reduction with the 2-norbornyl Grignard reagent [13]. A.A. Ponaras: Reaction of imine derivatives of α,β-epoxy ketones wi Grignard reagents and sodium borohydrides. Monoalkylation of α,β-unsaturated ketones and synthesis of β-hydroxyketones [14]. L.F. Chan bonneau: Kinetics and mechanism of organolithium and organomagnesiu reagent reaction with ketones [15]. W.F. Erickson: New reactions of amines with Grignard reagents, organolithium reagents and alkali metal hydrides [16]. J.V. Kempf: Reaction of Grignard reagents with nitromethane to form N,N-dialkylhydroxylamine [17].

2. PREPARATION OF ORGANOMAGNESIUM COMPOUNDS

After the report of a violent detonation of the reaction mixture, o tained during the preparation of m-trifluoromethylphenylmagnesium bromide in diethyl ether (Annual Survey 1971, page 4) it is worthwhile to notice that Novotny, Collins and Starks were successful in preparing p-trifluoromethylphenylmagnesium chloride in THF up to th 50 moles scale. The yield was improved from 9% to 75% by use of an entrainment procedure [18].

Rieke and Bales report an improvement of their preparative procedure for highly reactive magnesium (Annual Survey 1972, page 72): magnesium chloride was reduced in boiling THF by potassium in the presenc of potassium iodide [19]. With this reactive magnesium p-chlorotoluene yielded 94% of the corresponding Grignard compound within ten mi nutes at roomtemperature whereas commercial magnesium as well as reactive magnesium, prepared as previously reported, yielded no Grignard reagent at all under the same conditions. Furthermore p-fluorotoluene and 1-chlorobicyclo[2.2.1]heptane also gave organomagnesium compounds in fair yields (70%) with the newly reported reactive magnesium.

In three patents the use of sodiumaluminumalkoxyhydride additives to ethereal solvents is reported for improved preparations of Grignard reagents:

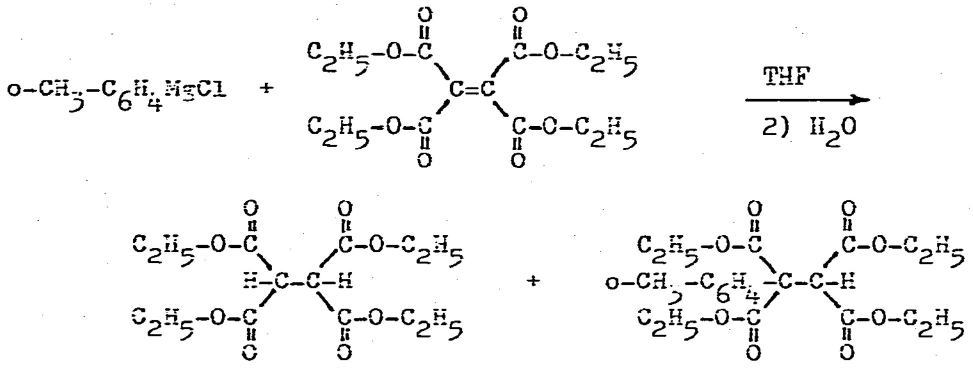
Vit claims the application of $NaAlH(O-CH_2-CH_2-O-CH_3)_3$ [20] as well as of $NaAlH_2(-O-(CH_2)_n-O-CH_3)_2$ (n = 2 or 4) and of $NaAlH_2[-O-(CH_2)_2-N(CH_3)_2]_2$ [21].

Uehara, Hori and Aoyagi, in a Japanese patent, claim the use of compounds of the same type such as $NaAlH_x(-O-R)_{4-x}$ [22].

Concerning the effect of magnesium metal purity as well as of the method of preparation of Grignard reagents on their reactivity the following two reports have to be mentioned:

Ashby, Neumann, Walker , Laemmle and Chao studied reactions of methylmagnesium compounds in diethyl ether with reactants such as (substituted)benzophenones and benzonitrile [23]. In those cases in which large excesses of benzophenone and benzonitrile were employed, no byproducts were detected and the rate constants were found to be independent of the manner in which the Grignard reagent was prepared or of the purity of the metal used. However the reaction of methylmagnesium bromide with benzophenone under pseudo-first-order conditions (in excess methylmagnesium bromide) gives rate constants which do depend on the initial ketone concentration whereas furthermore these reactions give large amounts of non-addition products; these effects are significantly reduced when the purity of the magnesium used for the preparation of the Grignard reagent is increased and were essentially eliminated when ultrapure magnesium was used. Similar results were observed in the reactions with benzonitrile.

House, Melillo and Sauter observed that in the reaction of o-methylphenylmagnesium chloride with the ethyl ester of ethylenetetracarboxylic acid in THF the reduction reaction was completely suppressed when the Grignard compound was prepared from ultrapure magnesium [2



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2

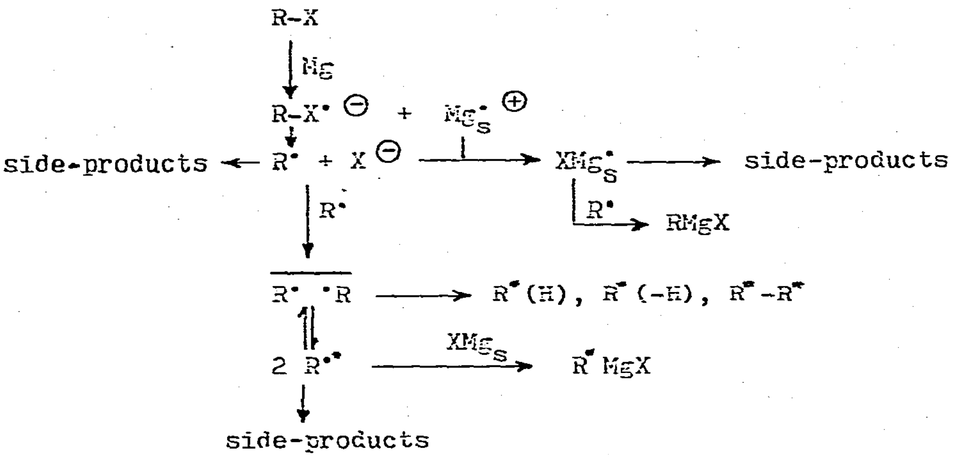
Using "ordinary, Grignard-grade Magnesium" 1 was obtained in 26% yield together with 2 (45% yield); with ultra pure magnesium 2 was exclusively obtained (72% yield).

Reaction of 3-dimethylamino-1-chloropropane with magnesium is considerably facilitated by the use of pure magnesium as was found by Sadet and Rumpf [24A]. Especially magnesium with less than 10^{-6} impurities, prepared by zone-refining, was effective; the Grignard reagent obtained with this metal gave high yields on ketones on reaction with benzonitrile.

2A. Discussion of reactions of organic halides with magnesium

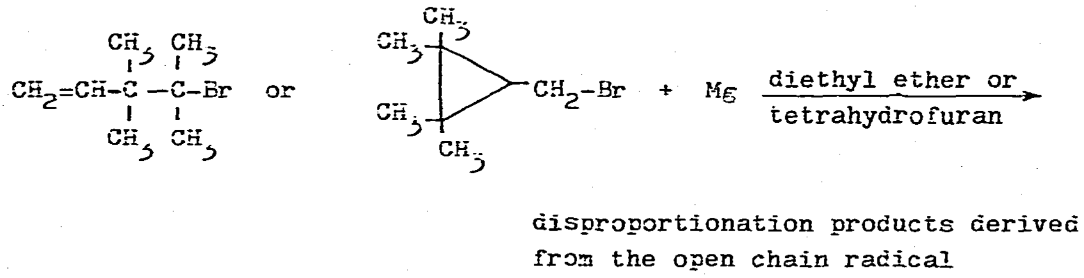
As already briefly mentioned previously (Annual Survey 1972, page 73 Bodewitz, Blomberg and Bickelhaupt studied the Grignard reaction wit the aid of CIDNP [25]. Polarization was observed in the Grignard reagent as well as in byproducts (hydrocarbons and olefins) and, in the reaction of 2-iodopropane in dibutyl ether, also in the starting ha-

Scheme



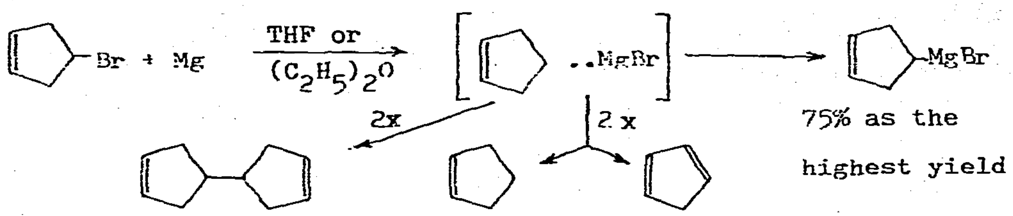
lide. A reaction scheme was proposed in which the first step is the single electron transfer step from the metal to the carbon-halogen bond under the formation of a radical-anion, which rapidly decomposes to form a radical $R^\bullet$ and a halide anion, which reacts with magnesium attached to the surface ($Mg_s^{\bullet\,+}$) to form surface-bound monovalent magnesium halide. In a rapid reaction this magnesium subhalide reacts with $R^\bullet$ to form the Grignard reagent. Although this direct radical combination is regarded to be the main pathway to Grignard formation CIDNP phenomena indicate that RMgX formation also occurs via the radical pair $\overline{R^\bullet\ {}^\bullet R}$, formed from organic radicals which have diffused away from the site of formation. Escape reactions of $R^\bullet$ out of the radical pair are held responsible for the occurrence of polarization in side-products.

Based on the analysis of the products from the reaction of 1-halo-1-methyl-2,2-diphenylcyclopropane (R-X) with magnesium in perdeuterated diethyl ether and tetrahydrofuran solvents, Walborsky and Aronoff obtained further evidence for the radical nature of the Grignard formation reaction [26]. The radical intermediates largely disproportionate on the surface of the metal and not in the solution. In perdeuterated diethyl ether 20.2% hydrocarbon was isolated which contained not more than 6.7% R-D, indicating the "cannibal-nature" of the radical R$^{\bullet}$ which removes hydrogen from other R-entities rather than from the solvent. Although in perdeuterated THF the yield of hydrocarbons was much less (1.0% and 1.4%) the amount of R-D was relatively higher 29.2% and 28.1%. With optically active halides the stereochemical results were consistent with a surface-radical mechanism. It is noteworthy to read that "neither the particle size nor the purity of the magnesium have any effect on the stereochemistry of the reaction". The reaction of the following bromides with magnesium leads ,

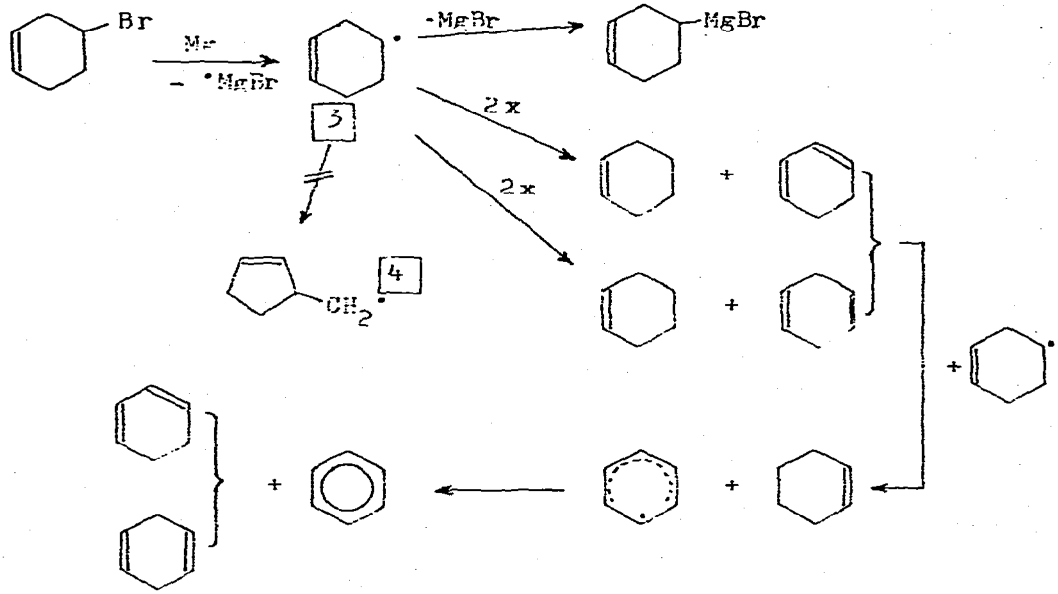


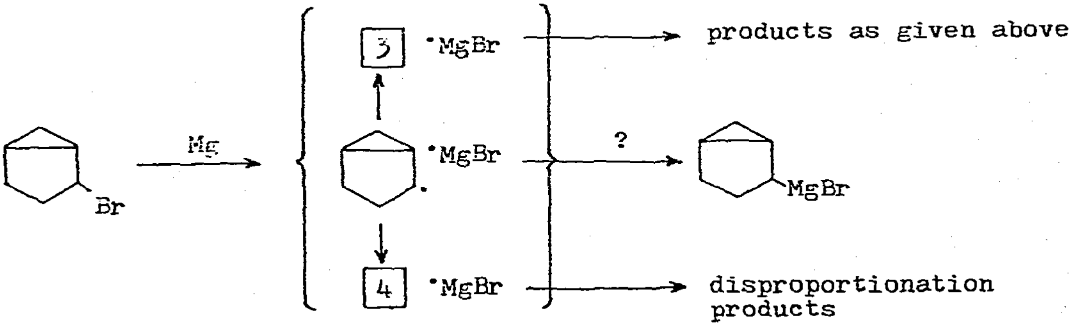
according to Maercker, Güthlein and Wittmayr, exclusively to the formation of disproportionation products in both diethyl ether and tetrahydrofuran [27]. For each of the bromides these products were derived from the open chain radical, formed on reaction with magnesium which evidently is more stable than the cyclopropylcarbinyl radical. From the corresponding chlorides the Grignard compounds could be prepared under normal reaction conditions!

In order to study rearrangements in cyclic Grignard compounds Maercker and Geuss observed the formation of considerable amounts of side products during the Grignard reaction [28]; radicals are held responsible for these products as indicated in the schemes below.



75% as the highest yield

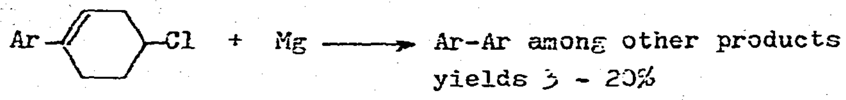




products as given above

disproportionation products

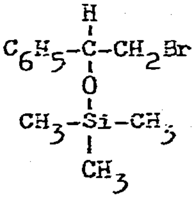
E.A. Hill and Shih observed the formation of biphenyls in the following Grignard reactions [29]:



Ar = phenyl, p-tolyl or m-trifluoromethylphenyl

It is of interest to report some of the results given in the (fine-print) experimental section: for Ar is phenyl, Ar-Ar yields were small (3-4%) but in mixed runs, involving a 4-chlorocyclohexenyl derivative with Ar = m-trifluoromethylphenyl, Ar-Ar yields were particularly high (15-20%) although m-trifluoromethylbiphenyl never was obtained in yields higher than 3%.

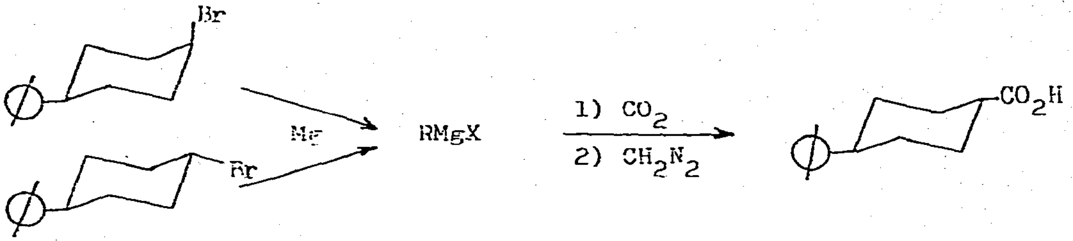
Fostein, Delmond and Pommier interpreted the results, obtained in the reaction of 2-bromoalkoxysilanes with magnesium in diethyl ether, with Walborsky's type of radicals [30]. The relatively "tight" radical pair is held responsible for the formation of coupling products R-R as well as of disproportionation products R(H) and R(-H), whereas the "loose" radical pair leads to the formation of elimination products. In both a coupling and an elimination product from the the following bromides



$$C_6H_5\text{-}CH(OSi(CH_3)_3)\text{-}CH_2Br \xrightarrow{Mg} C_6H_5CH{=}C\underline{H}_2 + \text{other products}$$

$$(CH_3)_3Si\text{-}O\text{-}CH_2\text{-}CH_2Br \xrightarrow{Mg} (CH_3)_3Si\text{-}O\text{-}CH_2\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}CH_2\text{-}O\text{-}Si(CH_3)_3$$

the authors observed polarization in the underlined protons.
Trans- as well as cis-4-phenyl-1-bromocyclohexane react with magnesium to give a Grignard reagent which on carbonation and esterification of the resultant acid mixture gives 99.8% and 98.2% methyl trans-4-phenylcyclohexanate (Novis Smith) [31]:

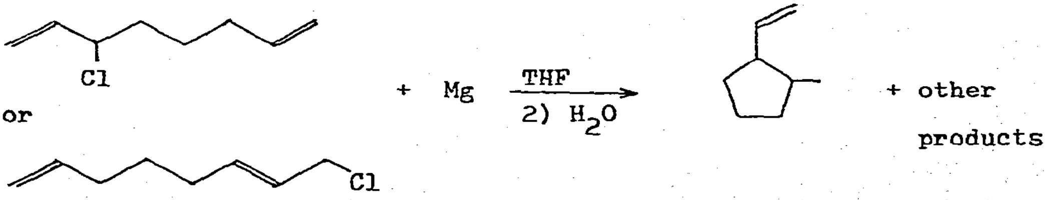


The corresponding reaction with mercury(II) bromide gave 88% of the trans isomer, but according to the author "there are a number of possible intermediates formed during reaction that can explain this slightly lower preference for equatorial bonding".

Although, in general, the presence of impurities in magnesium reduces the yield of Grignard reagent, obtained in the reaction of an alkyl halide with the metal, Allen, Lawler and Ward found that exclusion of oxygen may be more important for minimizing the coupling reaction between R-X and RMgX than it is for preventing oxidation of the Grignard reagent [32]. Reduced heavy metals, the most common impurities in magnesium, are ineffective in catalyzing this coupling reaction. Since in particular the addition of halogens decreases the yield of RMgX, the present investigations suggest that the addition of iodine, as an initiator for the Grignard reaction, may actually decrease the overall yield if low purity magnesium is employed.

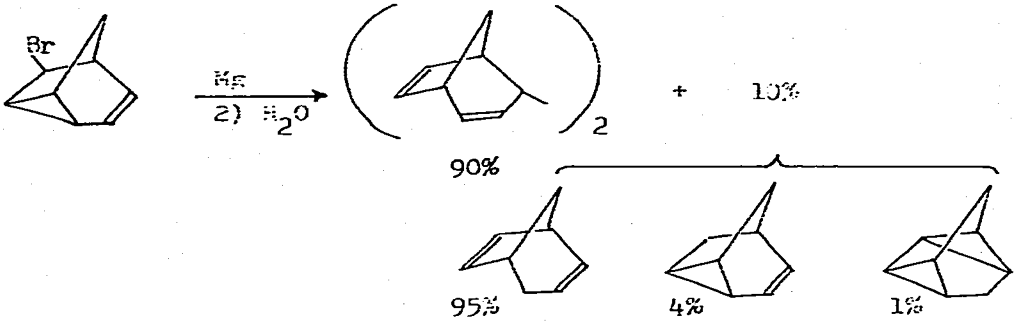
The following reports on (partially) unsuccessful Grignard reactions have been published:

1-halo- or 3-halooctadienes are reported to give increasing amounts of cyclic compounds on reaction with magnesium in THF (Fukutani, Tokizawa and Okada) [33]:

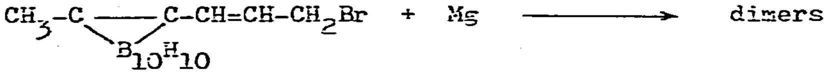


in one case a yield of 53% of vinylcyclopentane (after hydrolysis) is reported.

Sakai reports the formation of hydrocarbons from the reaction of exo-6-bromotricyclo[3.2.1.0^{2,7}]-3-octene with magnesium [34]:

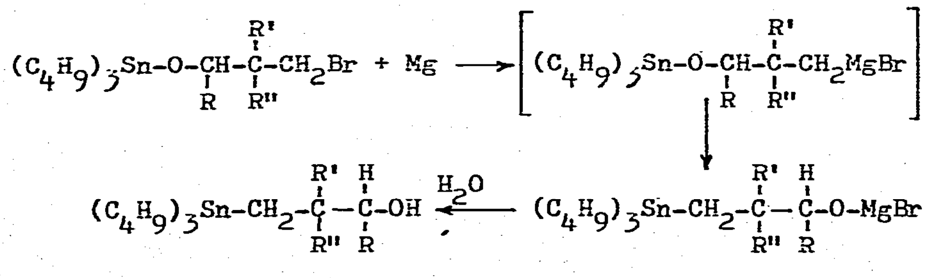


Zakharkin, Babich, Litovcheno and Ivanova observed the formation of dimers (the linear dimer was predominantly formed) in the reactio of 1-(methyl-o-carboranyl)-3-bromopropene with magnesium [35]:



$$CH_3\text{-}\underbrace{C\text{——}C}_{B_{10}H_{10}}\text{-}CH\text{=}CH\text{-}CH_2Br \;+\; Mg \longrightarrow \text{dimers}$$

According to Delmond, Pommier and Valade, 3-haloalkoxytributyltin compounds react with magnesium to form non-isolated Grignard compounds which rearrange (probably intramolecularly) to yield 3-hydroxyalkyltributyltin derivatives in fair to good yields [36]:

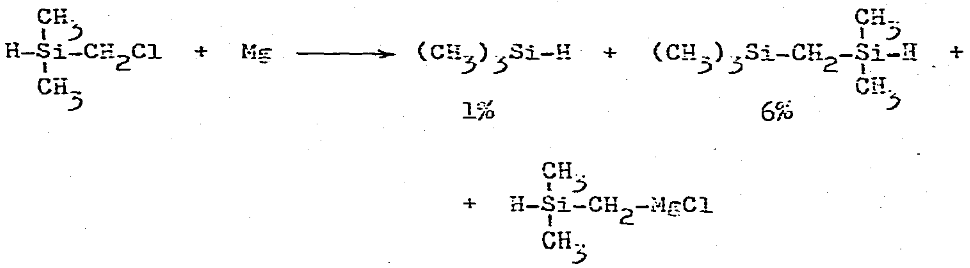


$$(C_4H_9)_3Sn\text{-}O\text{-}\underset{R}{CH}\text{-}\overset{R'}{\underset{R''}{C}}\text{-}CH_2Br + Mg \longrightarrow \left[(C_4H_9)_3Sn\text{-}O\text{-}\underset{R}{CH}\text{-}\overset{R'}{\underset{R''}{C}}\text{-}CH_2MgBr\right]$$

$$\downarrow$$

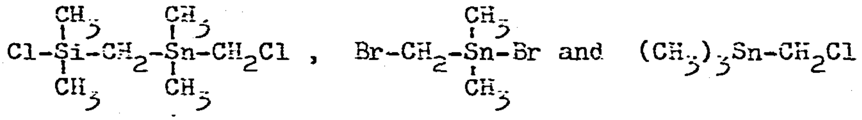
$$(C_4H_9)_3Sn\text{-}CH_2\text{-}\overset{R'}{\underset{R''}{C}}\text{—}\overset{H}{\underset{R}{C}}\text{-}OH \xleftarrow{H_2O} (C_4H_9)_3Sn\text{-}CH_2\text{-}\overset{R'}{\underset{R''}{C}}\text{—}\overset{H}{\underset{R}{C}}\text{-}O\text{-}MgBr$$

Cundy, Lappert and Pearce found sideproducts as indicated below in the reaction mixture of chlorodimethylsilylmethane and magnesium [37]



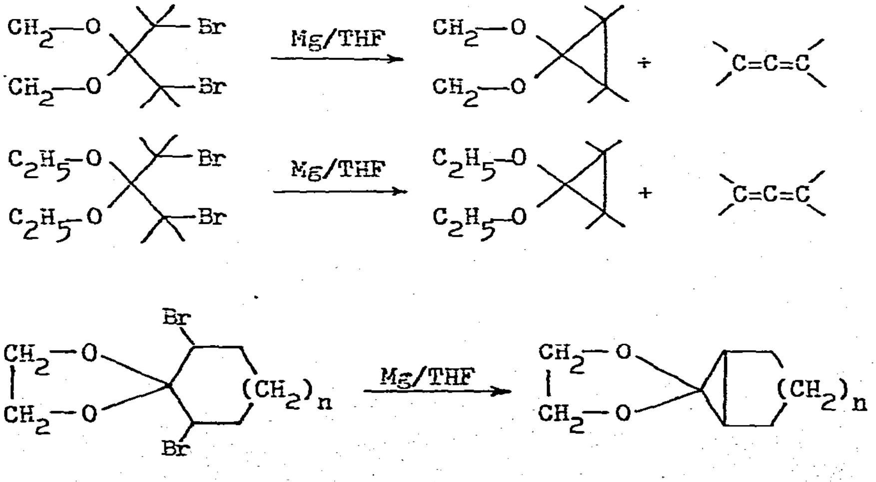
$$H-\overset{CH_3}{\underset{CH_3}{Si}}-CH_2Cl + Mg \longrightarrow \underset{1\%}{(CH_3)_3Si-H} + \underset{6\%}{(CH_3)_3Si-CH_2-\overset{CH_3}{\underset{CH_3}{Si}}-H} + H-\overset{CH_3}{\underset{CH_3}{Si}}-CH_2-MgCl$$

The same type of anomalous products were observed by Buyakov, Gar and Mironov as the results of reactions of the following Si and Sn containing organic halides with magnesium in diethyl ether [38]:

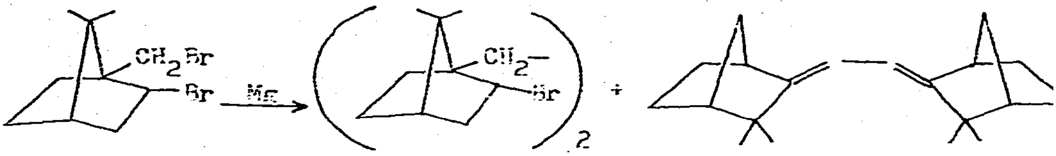


$$Cl-\overset{CH_3}{\underset{CH_3}{Si}}-CH_2-\overset{CH_3}{\underset{CH_3}{Sn}}-CH_2Cl\ ,\quad Br-CH_2-\overset{CH_3}{\underset{CH_3}{Sn}}-Br \text{ and } (CH_3)_3Sn-CH_2Cl$$

The action of magnesium on the ketals of 2-oxo-1,3-dibromoalkanes in THF leads both to cyclopropanes and allenes, as was found by Giusti and Morales [39]; steric factors influence the ratio of the two products. Open ketals yield more allene-derivatives than cyclic ketals:

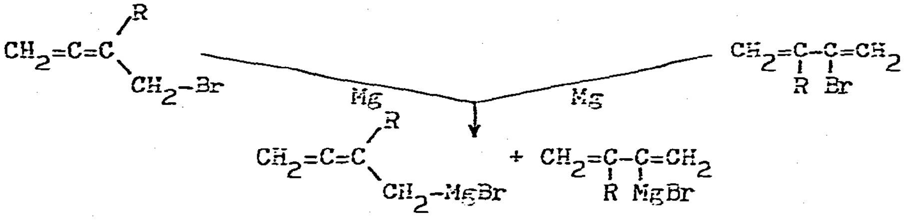


The reaction of the following bicyclic dibromo compound with magnesium yielded no Grignard reagent but only dimerization products (Mehta) [40]:



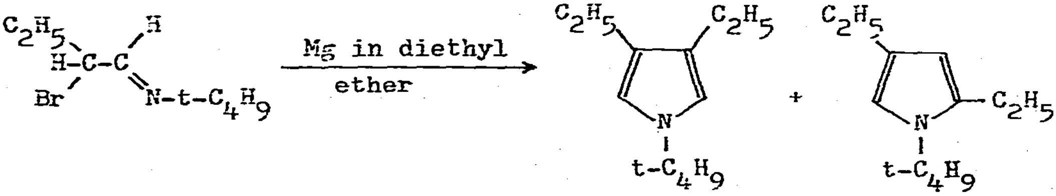
minor product major product

Although the allenic as well as the conjugated dienylic bromo compound, indicated in the equation below, yield both types of Grigna reagents on reaction with magnesium, no equilibrium between these two reagents seems to exist according to Michel and Troyanowsky an contrary to what has been reported erroneously earlier by this surveys author (Annual Survey 1971, p. 15) [41]:



no equilibrium between these two Grignard reagents

Duhamel, Duhamel and Valnot suggest both an ionic and/or a radical mechanism for the interpretation of the results observed in the following reaction [42]:



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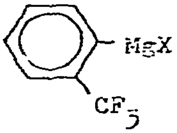
2B. Preparation of organomagnesium compounds

2Bi. Halide substituted organomagnesium compounds

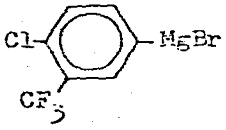
As has already been mentioned in the previous chapter p-trifluoromethylphenylmagnesium chloride was prepared in THF on a 50 moles scale [18].

The following two trifluoromethyl-substituted phenylmagnesium halides were reported:



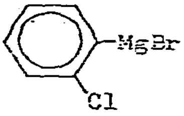
and

ref. [43]



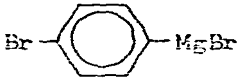
ref. [44]

Other halo-substituted phenylmagnesium halides reported in 1973 were



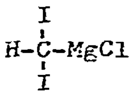
and

ref. [45]



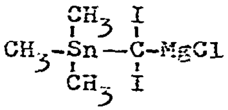
ref. [46]

Seyferth and Lambert Jr. used the following diiodo-Grignard reagents for the synthesis of halogenated organotin compounds [47]:



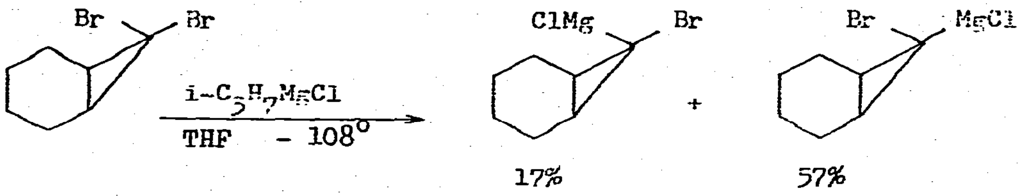
$$H-\overset{I}{\underset{I}{C}}-MgCl$$

and

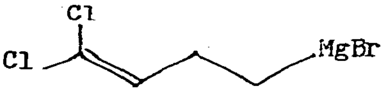


$$CH_3-\overset{CH_3}{\underset{CH_3}{Sn}}-\overset{I}{\underset{I}{C}}-MgCl$$

The same authors observed the formation of two isomeric Grignard reagents by reaction of a gem-dibromocyclopropane derivative with isopropylmagnesium chloride at -108° in THF [48]:



Lansbury and Stewart prepared the dihalo-unsaturated Grignard compound [49]:



Employing the low-temperature (-70°) metal-halogen exchange reacti of Pierce, Meiners and McBee (1953) as an approach to the preparati of n-heptafluoropropylmagnesium bromide, Denson, C.F. Smith and Tamborski synthesized perfluoroaliphatic mono- and di-Grignard reagents from

C_3F_7I, $C_8F_{17}I$, $I(-CF_2-)_3I$, $I(-CF_2-)_8I$, C_3F_7Br, $Br(-CF_2-)_6Br$ and $F_2C=CF_2$

in excellent yields (90-100%) [50]. The choice of the Grignard exchange reagent (either phenylmagnesium bromide or ethylmagnesium bromide) should be based not only on the perfluoroalkyl halide to b reacted, but also on the solvent system employed as well as on the ease of isolating the final perfluorinated product from the exchang product.

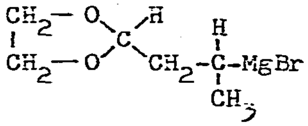
2Bii. Alkoxy_substituted_organomagnesium_compounds

Ethoxymethylmagnesium chloride

$$C_2H_5-O-CH_2-MgCl$$

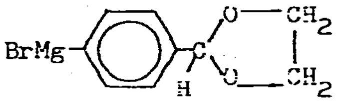
was used by Vartanyan, Avetsyan, Noravyan and Mkrtchyan for the synthesis of 4-hydroxy-4-alkoxymethyl-substituted pyrans [51], whereas De Botton used the same reagent, either in a Barbier-type (in situ) synthesis or in a Grignard-type synthesis, for the preparation of aldehydes [52].

Loozen and Godefroi made use of the ketal-Grignard reagent

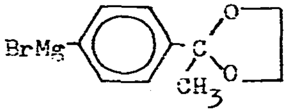


for reactions with heterocyclic aldehydes [53].

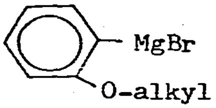
For the synthesis of triarylphosphines with more than one carbonyl-function, Schiemenz and Kaack made use of the following aromatic Grignard reagents [54]:



and

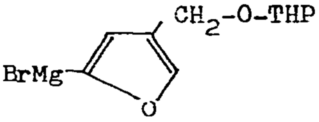


For different synthetic purposes use was made of



ref. [43]

and



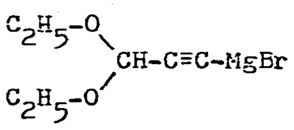
ref. [55]

THP = tetrahydropyranyl

A remarkable number of alkoxy-substituted acetylenic and vinylic organomagnesium halides, of which only the formulas will be given here have been used:

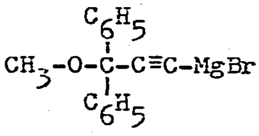
C_2H_5-O-C≡C-MgBr ,

ref. [56]



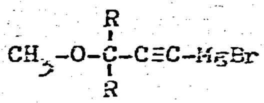
$(C_2H_5\text{-}O)_2CH\text{-}C{\equiv}C\text{-}MgBr$,

ref. [57]



$CH_3\text{-}O\text{-}C(C_6H_5)_2\text{-}C{\equiv}C\text{-}MgBr$

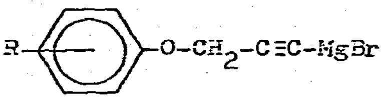
ref. [58]



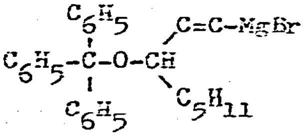
$$CH_3-O-\overset{R}{\underset{R}{C}}-C\equiv C-MgBr$$

R = alkyl; R–R = cycloalkyl

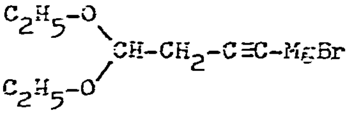
ref. [59]



ref. [60]



ref. [61]

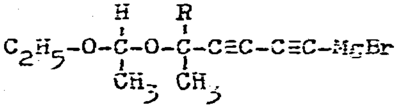


ref. [62]

$R-O-CH=CH-C\equiv C-MgBr$

R = alkyl

ref. [63] and [64]



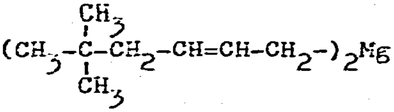
$$C_2H_5-O-\overset{H}{\underset{CH_3}{C}}-O-\overset{R}{\underset{CH_3}{C}}-C\equiv C-C\equiv C-MgBr$$

ref. [65]

2Biii. Organomagnesium compounds containing unsaturated C-C bonds

In a Japanese patent Konishi, Hirata, Takayanagi, Mori, Kamada and Toyoshima claim that a mixture of 1,2-dimethoxyethane and HMPA is superior to THF as a solvent for the preparation of vinylmagnesium chloride [66]. Yields as high as 95% of the unsaturated Grignard compound may be obtained in the solvent mixture!

Glaze and McDaniel prepared bis(neopentylallyl)magnesium by a technique which will be discussed in chapter 2C [67]:

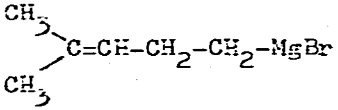


$$(CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-CH=CH-CH_2-)_2Mg$$

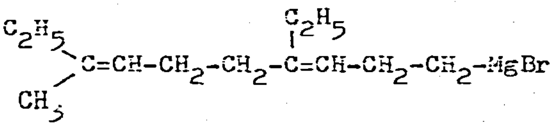
In the same chapter Moreau and Gaudemar's novel synthesis of alkynyl Grignard reagents will be discussed [68]: these French authors prepared the following compounds:

$\mathrm{C_2H_5{-}C{\equiv}C{-}MgBr}$ and $\mathrm{C_4H_9{-}C{\equiv}C{-}MgBr}$

Kuznetsov, Kuznenok, Selens and Svishchuk used unsaturated Grignard reagents for the synthesis of intermediates for the preparation of insect juvenile hormones [69]:



and



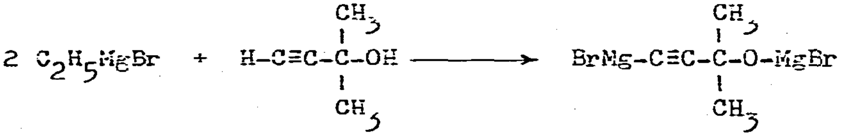
For the synthesis of unsaturated silanes Florensova, Volkova, Maroshin and Kryazhev made use of two acetylenic Grignard reagents [70]

$\mathrm{C_6H_5{-}C{\equiv}C{-}MgBr}$ and $\mathrm{CH_2{=}CH{-}C{\equiv}C{-}MgBr}$

The anomalous reactions of 1-halo- and 3-halooctadienes with magnesium (formation of cyclic Grignard reagents) have been mentioned in Chapter 2A [33].

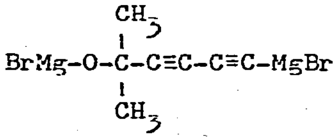
In the same chapter the formation of an allenic Grignard compound, together with a dienylic one, during the reaction of either the allenic halide or the dienylic halide with magnesium was mentioned [41].

Five reports have appeared on the synthetic utility of bromomagnesioalkoxy-substituted acetylenic Grignard reagents:



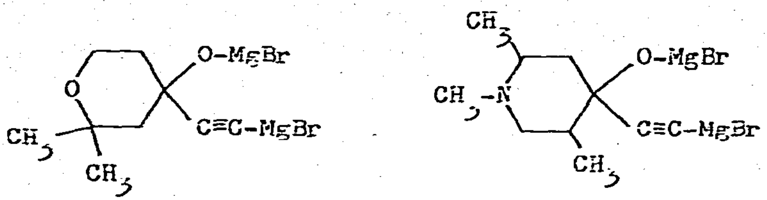
$$\mathrm{2\ C_2H_5MgBr + H{-}C{\equiv}C{-}\underset{CH_3}{\overset{CH_3}{C}}{-}OH \longrightarrow BrMg{-}C{\equiv}C{-}\underset{CH_3}{\overset{CH_3}{C}}{-}O{-}MgBr}$$

ref. [71] and [72]



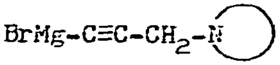
$$\mathrm{BrMg{-}O{-}\underset{CH_3}{\overset{CH_3}{C}}{-}C{\equiv}C{-}C{\equiv}C{-}MgBr}$$

ref. [73]

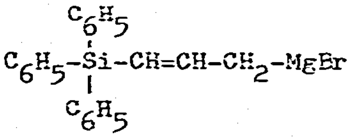


ref. [74] and [75]

In a Japanese patent mention is made of N-heterocyclic substituted acetylenic Grignard compounds [76]:

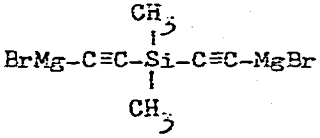


Corriu and Massé synthesized silicon containing allylmagnesium brom des such as [77]



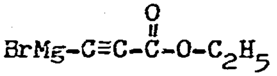
$$C_6H_5-\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{Si}}-CH{=}CH-CH_2-MgBr$$

A bifunctional silicon containing acetylenic Grignard compound was reported by Gverdtsiteli, Melua and Doksopulo [78]:



$$BrMg-C{\equiv}C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{Si}}-C{\equiv}C-MgBr$$

Vodolazskaya and Baukov used a carbethoxy-functional acetylenic Grignard reagent for the synthesis of silicon derivatives [79]:



$$BrMg-C{\equiv}C-\overset{\overset{\displaystyle O}{\|}}{C}-O-C_2H_5$$

Erickson obtained the stable (no cyclization occured) chloroacetylenic Grignard reagent [80]:

$$BrMg-CH_2-CH_2-CH_2-C{\equiv}C-Cl$$

A great number of alkoxy-substituted unsaturated organomagnesium compounds have been mentioned in Chapter 2Bii (references [56] through [65]).

2Biv. Some other organomagnesium compounds

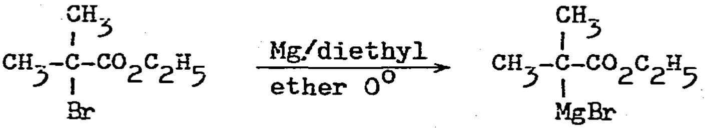
Bell and Scott synthesized

$$CT_3MgI$$

for reactions with 25-oxo-27-norcholecalciferol acetate [81].
Navita, Yasumura and Tsuruta prepared complexes of organomagnesium compounds by reaction of R_2Mg with 2-alkoxy-1-ethanol [82]; the complex, obtained from di-n-butylmagnesium and 2-methoxy-1-ethanol e.g. had the following composition

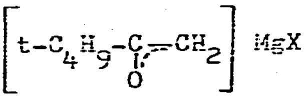
$$n-C_4H_9-Mg-O-CH_2-CH_2-O-CH_3.Mg(-O-CH_2-CH_2-O-CH_3)_2$$

and was highly reactive in styrene polymerization. In such systems ion pairs are produced, separated by the coordinating agent.
Several Grignard reagents containing ester or ketone functions (in such "Grignard reagents" enolate structures predominate) have been used for synthetic or theoretical studies:
The Ivanov reagent, $C_6H_5CH(MgBr)CO_2MgBr$, was used by Ivanov, Kirilov, Petrov and Golemshinski [83].
P.Y. Johnson and Davis prepared the same sort of ester-functional "Grignard reagent" from aliphatic esters [84]:



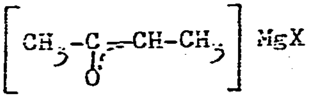
$$CH_3-\overset{CH_3}{\underset{Br}{C}}-CO_2C_2H_5 \xrightarrow[\text{ether } 0^o]{\text{Mg/diethyl}} CH_3-\overset{CH_3}{\underset{MgBr}{C}}-CO_2C_2H_5$$

From the laboratory of Mme Maroni-Barnaud stereochemical investigations have been published for which organomagnesium derivatives of esters and ketones were applied such as:



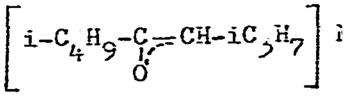
$$\left[t\text{-}C_4H_9\text{-}\underset{O}{C}{=}CH_2\right]MgX$$

ref. [35], [86], [87]



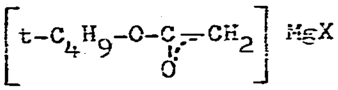
$$\left[CH_3\text{-}\underset{O}{C}{=}CH\text{-}CH_3\right]MgX$$

ref. [85]



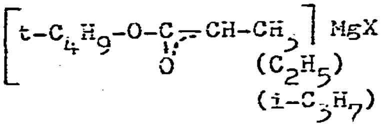
$$\left[i\text{-}C_4H_9\text{-}\underset{O}{C}{=}CH\text{-}iC_3H_7\right]$$

ref. [86]



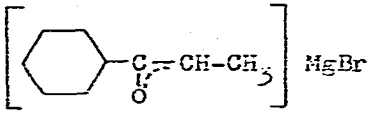
$$\left[t\text{-}C_4H_9\text{-}O\text{-}\underset{O}{C}{=}CH_2\right]MgX$$

ref. [86], [87], [88]

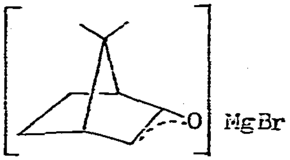


$$\left[t\text{-}C_4H_9\text{-}O\text{-}\underset{O}{C}{=}CH\text{-}CH_3\right]MgX \quad \begin{matrix}(C_2H_5)\\(i\text{-}C_3H_7)\end{matrix}$$

ref. [86], [87], [88], [89]

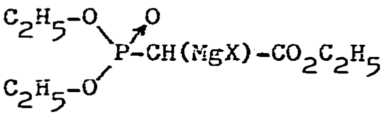


ref. [89]



ref. [89]

Treatment of the diethyl ester of carbethoxymethanephosphonic acid with isopropylmagnesium bromide or with n-propylmagnesium chloride resulted in the formation of the corresponding magnesium derivative as reported by Kirilov and Petrov [90]:

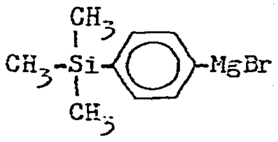


The preparation of a carbethoxy-functional acetylenic Grignard compound has been reported in Chapter 2Biii [79]. Furthermore, in the same chapter mention was made of bromomagnesioalkoxide-substituted Grignard reagents ([71], [72], [73], [74] and [75]) as well as of

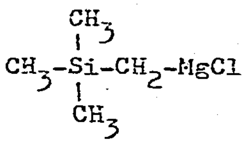
amino-functional acetylenic Grignard reagents ([74] and [76]).
Apart from the silicon-substituted Grignard reagents, reported in previous chapters (in Chapter 2A, [37]; in Chapter 2Biii, [77] and [78]) the following reagents have to be mentioned:
An exiting report is the one by Schumann and Rösch, who claim to have reacted trimethylsilyl chloride (0.5 mole) with magnesium (0.5 gat) in the presence of HMPA (1 mole) to form the silicon-magnesium compound [91]:

$$(CH_3)_3SiCl \;+\; Mg \xrightarrow{HMPA} (CH_3)_3SiMgCl$$

The reaction mixture was heated for two hours at 75° before it was further reacted with phosphorus derivatives (see Chapter 5I). It has not been made clear why this siliconmagnesium compound, the first ever prepared, is so stable under the reaction conditions mentioned above.
Other interesting silicon containing Grignard compounds are


ref. [92]

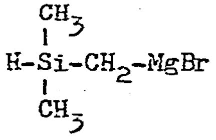
and



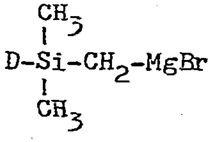
$$(CH_3)_3Si{-}CH_2{-}MgCl$$

ref. [93]

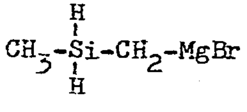
Jarvie and Rowley synthesized and reacted the following silicon-Grignards [94]:



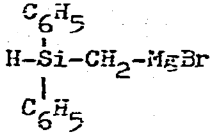
$$H{-}Si(CH_3)_2{-}CH_2{-}MgBr$$



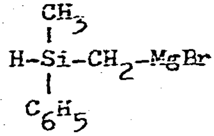
$$D{-}Si(CH_3)_2{-}CH_2{-}MgBr$$



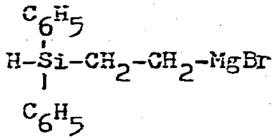
$$CH_3{-}SiH_2{-}CH_2{-}MgBr$$



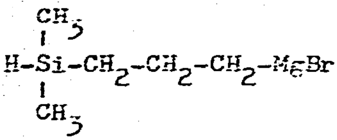
$H\text{-}\overset{C_6H_5}{\underset{C_6H_5}{Si}}\text{-}CH_2\text{-}MgBr$



$H\text{-}\overset{CH_3}{\underset{C_6H_5}{Si}}\text{-}CH_2\text{-}MgBr$

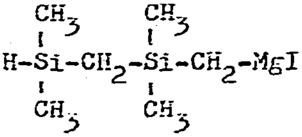


$H\text{-}\overset{C_6H_5}{\underset{C_6H_5}{Si}}\text{-}CH_2\text{-}CH_2\text{-}MgBr$



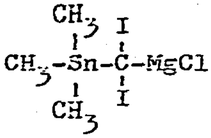
$H\text{-}\overset{CH_3}{\underset{CH_3}{Si}}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}MgBr$

and



$H\text{-}\overset{CH_3}{\underset{CH_3}{Si}}\text{-}CH_2\text{-}\overset{CH_3}{\underset{CH_3}{Si}}\text{-}CH_2\text{-}MgI$

Seyferth and Lambert Jr. [47] as well as Delmond, Pommier and Valade [36] synthesized and reacted the following tin-containing Grignard compounds:



$CH_3\text{-}\overset{CH_3}{\underset{CH_3}{Sn}}\text{-}\overset{I}{\underset{I}{C}}\text{-}MgCl$

and $(n\text{-}C_4H_9)_3Sn\text{-}MgBr$

ref. [47]

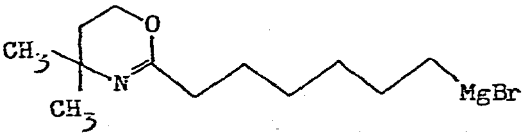
ref. [36]

Kazantsev and Aksartov made use of o-carboranylmagnesium bromide ($o\text{-}R\text{-}C(B_{10}H_{10})C\text{-}MgBr$) in synthesis [95].

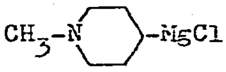
Aside from the trimethylsilyl-Grignard compound mentioned above, Schumann and Rösch also prepared the germanium and tin homologues $(CH_3)_3Ge\text{-}MgCl$ and $(CH_3)_3Sn\text{-}MgCl$ [91].

In an American patent, Williams and Cook claim the preparation of the following "lead-Grignard compound" [96]: $(C_2H_5)_3Pb\text{-}MgCl$

Continuing their work in oxazine-chemistry, Meyers and co-workers (see also Annual Surveys 1969 and 1970) investigated the reactivity of the 2-substituted 4,4-dimethyl-dihydro-1,3-oxazine [97]:



Schroeter, in a German patent, claims the preparation of N-methylpiperidyl-4-magnesium chloride [98]:



Kaiser, Beard and Hauser [99] as well as Koshar and Mitsch [100] prepared sulfonyl-substituted Grignard reagents:

$C_6H_5{-}SO_2{-}CH(MgCl){-}C_6H_5$ ref. [99]

$R_F{-}SO_2{-}CH(MgX){-}R$ ref. [100]

2C. New or uncommon reactions, leading to the formation of organomagnesium compounds

Moreau and Gaudemar prepared acetylenic Grignard compounds from propargylic bromides by the following sequence of reactions [68]:

$$CH_2{=}C{=}CH{-}MgBr \quad + \quad H{-}N< \longrightarrow CH_3{-}C{\equiv}C{-}H \quad + \quad CH_2{=}C{=}CH_2 \quad + \ BrMg{-}N<$$

$$CH_3{-}C{\equiv}C{-}H \quad + \quad BrMg{-}N< \text{or} \ + \quad CH_2{=}C{=}CH{-}MgBr \xrightarrow{\qquad} CH_3{-}C{\equiv}C{-}MgBr$$

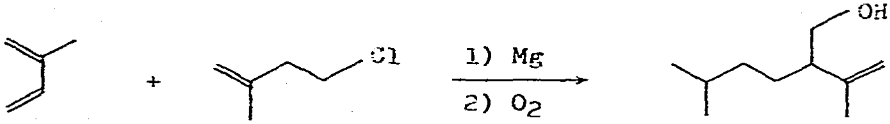
As the starting bromides $CH_3{-}CH(Br){-}C{\equiv}C{-}H$ and $n{-}C_3H_7{-}CH(Br){-}C{\equiv}C{-}H$ were applied.

Glaze and McDaniel prepared bis(neopentylallyl)magnesium by the reaction of anhydrous magnesium chloride with neopentylallyllithium [67]. Bis(neopentylallyl)magnesium is the first hydrocarbon soluble allylic magnesium compound and several contrasts in its properties in hydrocarbon and ethereal solvents are demonstrated by the authors.

Kamienski [101] and Kamienski together with Eastham [102], in American patents, claim the preparation of dialkylmagnesium as well as of mixed alkylarylmagnesium compounds by reactions, similar to those mentioned above: activated magnesium chloride reaction with organometallic compounds. The lithium chloride formed in these processes can be recycled by reaction with sodium and n-butyl or n-amyl chloride.

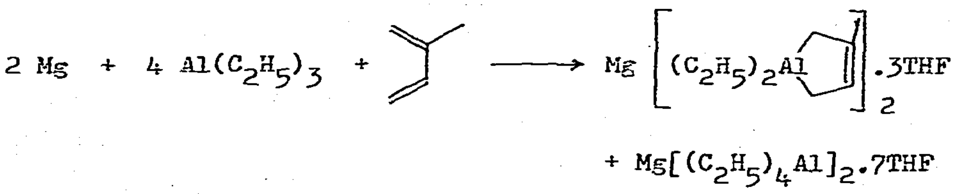
Several reactions of magnesium with unsaturated hydrocarbons, leadi to the formation of organomagnesium compounds, have been reported, mainly in the patent literature:

In two German patents Ramsden claims the synthesis of lavendulol by the reaction of isoprenemagnesium with 4-chloro-2-methyl-2-butene, followed by air oxidation [103] and [104]:



In a U.S. patent Ramsden reports the preparation and reactions of magnesium-olefin compounds [105]. Reactions with aldehydes, oxirane or oxidizing agents yield alcohols and diols; diketones are formed on reaction with nitriles, diacids on reaction with carbon dioxide. Linalool and geraniol were prepared by reaction of magnesium with myrcene, either in the presence of tungsten, zinc or copper salts, followed by oxidation of the intermediates with oxygen [106], or wi cyclopentadiene-type compounds in the presence of a Lewis acid such as boron trifluoride etherate followed by oxidation [107].

The reaction of conjugated dienes with magnesium in the presence of trialkylaluminum compounds leads to the formation of mixed magnesiu aluminum complexes of the following type, as studied by Lehmkuhl, Culjkovic and Nehl [108]:

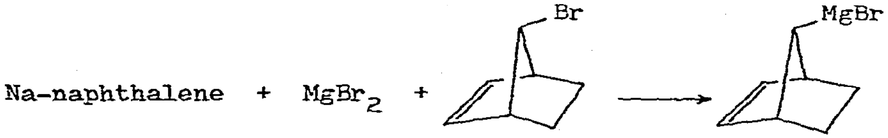


Several other dienes and organoaluminum compounds have been used by the authors.

Magnesium films cause the reduction (selfhydrogenation) of alkynes and 1,2-alkadienes by an interaction between the absorbed molecules and a hydrocarbon residue, strongly held on the surface (Y. Gault) [109]. The author could not find any evidence for the intermediacy of species to diene-magnesium compounds as mentioned above. The hydrocarbon residue on the surface probably is a polymer.

As already reported in Chapter 2Bi, Seyferth and Lambert Jr. prepared α-bromoorganomagnesium compounds by reaction of isopropylmagnesium chloride with a gem-dibromide in THF at -108° [48].

Kennedy, Kuivila, Tien and Considine prepared bromo norbornene-7-magnesium by the peculiar reaction of magnesium bromide with the corresponding bromonorbornene and sodium-naphthalene [110]:



Addition of trimethylstannyl chloride yielded only 9% of the norbornenyltin compound; in a modification of this procedure, in which the formation of the Grignard reagent was by-passed, the trimethyltin halide was added to the reaction mixture instead of magnesium bromide which resulted in the formation of the norbornenyltin derivative in 31% yield. "This may indicate, that trimethyltinchloride is a better trap for the anion than is magnesium bromide" the authors state.

On measuring the pH of dimethoxyethane solutions of magnesium salts with the aid of a hydrogen-electrode, Caillet and Bauer observed the formation of organomagnesium compounds by the following reactions [111]:

$$R^{\ominus} + Mg^{2\oplus} \rightleftharpoons RMg^{\oplus}$$
$$2R^{\ominus} + Mg^{2\oplus} \rightleftharpoons R_2Mg$$

$R^{\ominus}$ stems from the sodium or tetrabutylammonium salts of acids such as acetylacetone, aniline or triphenylmethane.

2D. Reactions with intermediate or "in situ" Grignard compounds

Gravilenko, Fatyushina, L'vova, Kolesov, Kavaksin and Zakharkin report the formation of trimethylgallium by the reaction [112]

$$CH_3I + Mg/Ga \xrightarrow[\text{dibutyl ether}]{\text{diethyl ether or}} (CH_3)_3Ga \qquad (70\%)$$

in which reaction most probably an intermediate methylmagnesium der vative is formed.

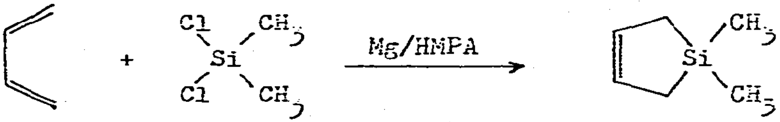
The effect of trace elements in the above mentioned synthesis of trimethylgallium was studied by Gribov, Kozyrkin, Federov, Nokol'skii and Solomatin [113]; the results suggest that the process of preparation of trimethylgallium may serve as a mean of reduction of the contents of the trace elements in the final product.

Williams and Cook, in an American patent, claim the preparation of trimethyl- and triethylleadmagnesium chloride by the following reaction [96]:

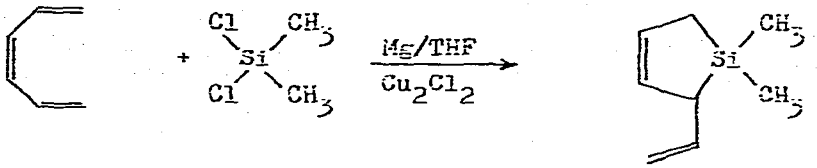
$$R\text{-}Cl + Mg + PbCl_2 \longrightarrow R_3Pb\text{-}MgCl$$

Three more publications appeared from Calas' and Dunoguès' group dealing with the trimethylchlorosilane/magnesium/HMPA reaction with several different substrates; the theoretical problem of an intermediate silyl-Grignard compound becomes important, especially in the

light of Schumann and Rösch' report on the preparation of trimethylsilylmagnesium chloride in HMPA as mentioned in Chapter 2Biv [91].
In one of their publications the French authors report that; for the interpretation of their results, they maintain the model in which the radical-anion develops to a silylated radical, which makes the mechanism analogous to one in which a silylated organomagnesium compound with radical behavior is proposed [114].
Together with Bolourtchian, Biran and Duffaut, Dunoguès and Calas investigated the reaction of the (CH$_3$)$_3$SiCl/Mg/HMPA couple with unsaturated conjugated ketones which leads to the formation of products, resulting from 1,4-disilylation as well as from reductive duplication [114].
Together with Arreguy, Biran and Pisciotti, Dunoguès and Calas studied the reaction of (CH$_3$)$_3$SiCl/Mg/HMPA with conjugated poly-enes [115]. 1,4-addition of trimethylsilyl groups is observed. When dimethyldichlorosilane is used instead of trimethylchlorosilane in reaction with butadiene silacyclopentane is formed:



Finally, together with Jousseaume and Pilot, Dunoguès and Calas studied the reaction of the silylation couple with chlorinated compounds such as chloral, hexachloroacetone and 1,1-dimethyl-2,2,2-trichloro-1-ethanol [116]. The products obtained, indicate the reductive properties of Mg/HMPA towards carbon-chlorine bonds.
Birkofer and Prüstel report the formation of silacyclopentenes by the rather mild reaction of magnesium with dichlorosilanes and 1,3,5-hexatriene in the presence of Cu(I) chloride in refluxing THF [117]:



The authors suggest that a radical-anion mechanism is responsible for the silylation of the triene in the 1,4-position.

De Botton reports the synthesis of aldehydes by means of reactions of terpene-ketones with Grignard compounds, derived from chloromethoxyethane [52]; for this purpose the reactions can be performed either in a Barbier-type fashion (in situ) or in the "normal" Grignard procedure. No differences in yields were observed between the two methods except for the unsaturated terpene ketones such as pulegone, isopulegone or carvone, where the Barbier technique yield less of the desired product.

Katzenellenbogen and Lenox, finally, reported the synthesis of ally carbinols by several methods, among which the "in situ" Grignard technique [118]. With cyclohexanone and cyclopentanone, fenchone an di-tert-butyl ketone the yields were good to excellent. The same pr cedure was unsatisfactory for diisopropyl ketone.

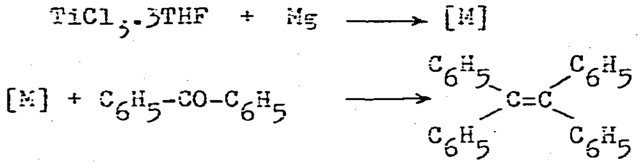
2E. Miscellaneous

Ulmer, Skarstad, Burlitch and Hughes report the preparation of the following pyridine complex of a magnesium-molybdenum-cyclopentadienyl dicarbonyl compound [119]:

$$Mg/Hg \quad + \quad Hg[Mo(CO)_3C_5H_5]_2 \xrightarrow{C_5H_5N} Mg(pyridine)_4[Mo(CO)_3C_5H_5]_2$$

The reduction of hydrocarbon solutions of di-n-butylmagnesium, di-sec-butylmagnesium and di-tert-butylmagnesium by alkali metals has been described by Eastham and Malpass [120]; in general compounds with the formula R_3MgM were obtained. Besides lithium, sodium and potassium also rubidium and caesium were applied. The products were hydrocarbon soluble.

Tyrlik and Wolochowicz obtained a complex of magnesium with titanium (III) chloride in THF which showed highly reductive properties [121]; with ketones dimerization products were obtained:

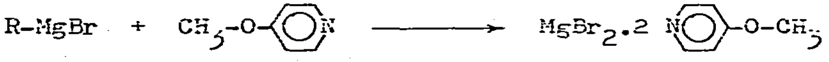


$$TiCl_3 \cdot 3THF + Mg \longrightarrow [M]$$

$$[M] + C_6H_5\text{-}CO\text{-}C_6H_5 \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2$$

In general the yields of such products were excellent; with benzophenone 67%, with benzaldehyde 80%, with acetone 95%. With cyclohexanone the pinacol was obtained.

Thiessen, Desseyn and Alderweireldt obtained pyridine complexes of magnesium bromide on addition of 4-alkoxy-substituted pyridines to solutions of ethyl- or phenylmagnesium bromide [122]:



2F. Analysis of organomagnesium compounds

Karavanov and Lapkin developed a technique for the determination of halomagnesium alkoxyde in a mixture of it with organomagnesium halide as it is obtained on air-oxidation of Grignard solutions [123]: hydrolysis of an aliquot followed by acid titration yields the amount of "basic"-magnesium. Extraction of the hydrolysed portion with benzene and determination of R-OH (from R-O-MgX) by the modified active hydrogen method of Terent'ev, finally yields the analytical data required.

3. PHYSICAL PROPERTIES, STRUCTURE AND MOLECULAR ASSOCIATION OF ORGANOMAGNESIUM COMPOUNDS

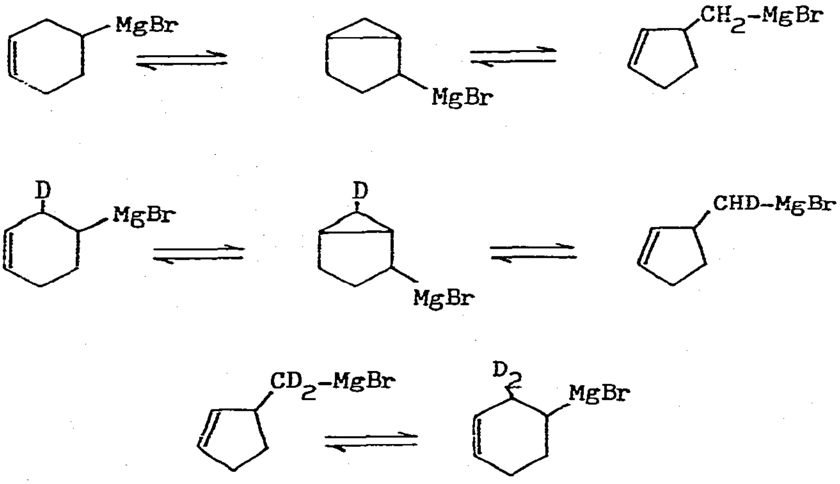
3A. NMR studies of organomagnesium compounds

As already mentioned in Chapter 1 a review on NMR-studies by Maerck has appeared [7]. The paper is chiefly concerned with the methods f routine transference of air and moisture sensitive compounds into N tubes as well as with the preparation of organometallic compounds u der inert atmosphere directly in the sample tube.

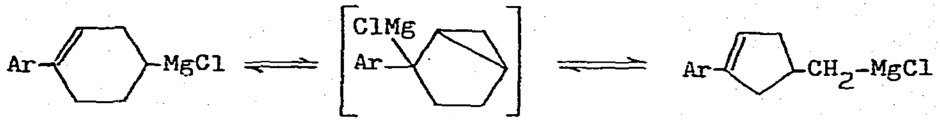
In two separate reports Maercker and coworkers studied the NMR-spectra of the following Grignard compounds in equilibria

ref. [27]

and in reference [28]:

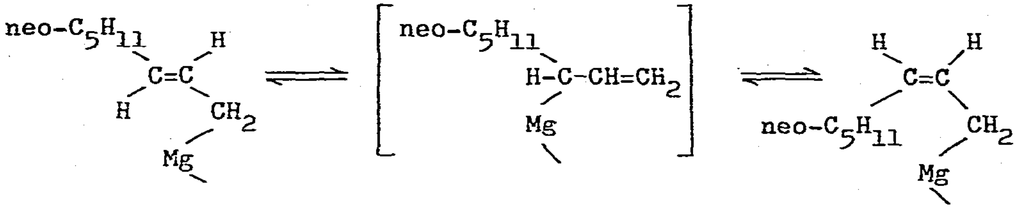


Hill and Shih studied the same sort of equilibrium with the aid of NMR-spectroscopy in sealed tubes; solvent THF, temperature 122^{o} [29



Ar = phenyl, p-tolyl and m-trifluoromethylphenyl

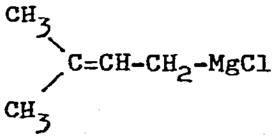
Glaze and McDaniel reported NMR-spectroscopic studies of bis(neopentylallyl)magnesium in THF-d_8 and diethyl ether d_{10} [67]. The results are most conveniently interpreted in terms of a dynamic allyl-system:



At high temperatures, rapid equilibria exist between the trans and cis primary forms and the secondary form which is present only in low concentrations. At lower temperatures, these equilibria are slowed and individual resonances of the trans and cis isomers are observed. It is interesting to note that the isomers are present in nearly equal amounts. No conclusions could be drawn from the NMR-spectra of bis(neopentylallyl)magnesium in n-pentane and in benzene-d_6 since no fine structure in the olefin region could be interpreted.

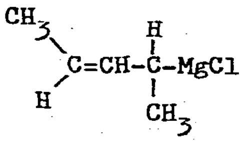
In an analogous study, Hutchinson, Beck, Benkeser and Grutzner determined the structure of substituted allylmagnesium chlorides with the aid of NMR-spectroscopy [124]:

$R\text{-}CH{=}CH\text{-}CH_2MgCl$ with $R = H, CH_3, C_2H_5$, iso-C_3H_7 and tert-C_4H_9



$(CH_3)_2C{=}CH\text{-}CH_2\text{-}MgCl$

and



$CH_3(H)C{=}CH\text{-}CH(CH_3)\text{-}MgCl$

In case the allyl Grignard compound is asymmetric the chemical shif are characteristic for a structure with a primary magnesium atom. I there is any of a compound with secondary magnesium present in the solution, it must be in rapid equilibrium with the primary compound Furthermore a rapid equilibrium between the cis and trans stereoisomers about the double bond is observed; the magnitude of the coupli constants provides a measure of the equilibrium population of the i mers. This equilibrium population could also be obtained by quenchi with acids and the results, obtained by both methods, compare well with each other. For Y-substituted allylmagnesium chlorides the cis/trans ratios were:

R =	methyl	ethyl	iso-propyl	tert-butyl
cis	60	45	30	3
trans	40	55	70	97

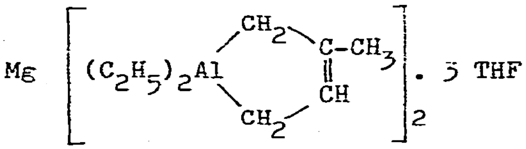
At low temperatures the Schlenk equilibrium was detected and further more, the behavior of the diallylmagnesium compound was found to b similar with the corresponding allylmagnesium chlorides.

Ducom and Brodzky observed changes in the NMR-spectra of solvent mol cules, complexed with diethylmagnesium [125]. By measuring the changes of the chemical shifts of protons both in the basic solvents an in diethylmagnesium in different solvents, the authors observed repl cement of solvents in the complexes with diethylmagnesium on additi of competing bases. Such changes in chemical shifts allowed the dete mination of an order of relative basicities of basic solvents versus diethylmagnesium which showed the following order:

tetrahydrothiophene < isopropyl ether, tri(dimethylamino)phosphine < triethyl amine < dibutyl ether < N-methylpyrrolidine < dioxane dimethoxyethane < 2-methyltetrahydrofuran < tetrahydropyran < tetrahydrofuran < diglyme < tetramethylethylenediamine < HMPA.

Especially the position of triethyl amine in this series is rather surprising.

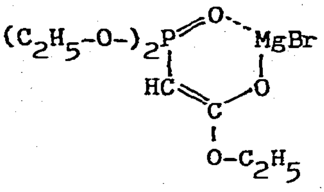
Lehmkuhl, Culjkovic and Nehl reported the NMR-spectra of the mixed organomagnesium-aluminum compound [108]:



The NMR-spectra of diethylmagnesium, complexed with HMPA were measured in diethyl ether as the solvent, by Tomoi and Kakiuchi [126]. The chemical shift of the methylene protons remained unchanged till one molar equivalent of HMPA was added, than changed considerably from 0.60 ppm to 0.85 ppm in the region between one and about two equivalents of HMPA, after which the chemical shift remained constant. Similar experiments with THF and calculations with the aid of the relationship of Narasimhan and Rogers lead to values for the electronegativity of magnesium in diethylmagnesium of 0.94 in diethyl ether, of 0.89 in the presence of 3 molar equivalents of THF and of 0.79 in the presence of 3 molar equivalents of HMPA.

3B Other techniques

Several reports on the determination of the structure of organomagnesium compounds with the aid of infrared spectroscopy have appeared: The infrared spectrum of the bromomagnesium derivatives of carbethoxymethanephosphinic acid indicates, that besides structures as given by $\boxed{5}$, also complexes of magnesium bromide with the acid, as given by $\boxed{6}$, are present in the solid state [90]:



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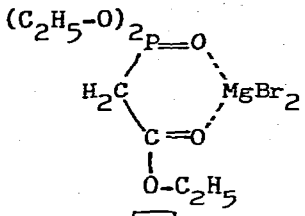
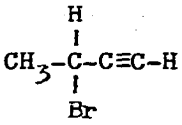
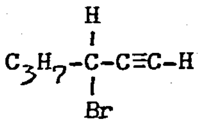


6

Infrared spectroscopic investigations have been reported of Grigna derivatives of the following bromides [68]:



$CH_3-\underset{Br}{\overset{H}{C}}-C\equiv C-H$



$C_3H_7-\underset{Br}{\overset{H}{C}}-C\equiv C-H$

and $D-C\equiv C-CH_2-Br$

The spectra indicate the existence of both the allenyl ($>C=C=\overset{|}{C}-Mg-$) and the propargyl ($-C\equiv C-\underset{|}{\overset{|}{C}}-Mg-$) organomagnesium compounds in diethyl ether solutions.

Kress and Guillermet have studied the infrared spectra of $MgBr_2.2(CH_3)_2O$, $MgBr_2.2(CD_3)_2O$, $MgBr_2.(CD_3)_2O$, $MgCl_2(CH_3)_2O$ and $MgI_2.(CH_3)_2O$ [127]. The spectra suggest a tetra-coordination of magnesium in the complexes and the presence of oxygen as the bridging atom in the 1:1 complexes.

The infrared spectrum of magnesium chloride, trapped in solid Kr at 20 K was studied by White, Calder and Hemple [128]. A linear configuration of the molecule is confirmed.

Electronic spectra of magnesium fluorenide, obtained by reaction of diethylmagnesium with fluorene in diethyl ether in the presence of HMPA have been reported [126]. A solvent separated ion-pair of magnesium fluorenide is observed.

With the aid of electronic spectra Narita, Yasumura and Tsuruta observed the existence of a coordination-agent-separated ion-pair in the product from the reaction of di-n-butylmagnesium with 2-alkoxyethanol [82]. The complex was highly reactive in styrene polymerization; furthermore it could metallate fluorene.

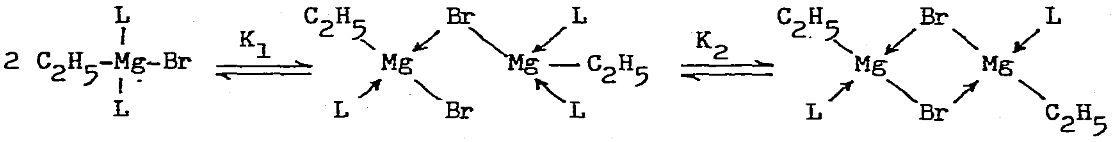
In another study of the carbanionic character of RMgX-HMPA complexes, Tomoi and Kakiuchi studied the reactivities of these systems as initiators in anionic polymerization [129]. The reactivity decreased in the order: benzyl > allyl > aryl > s-alkyl > n-alkyl. The results are explained in terms of both the ease of carbanion formation and activity of the ion formed.

With the aid of ebullioscopic techniques, Jarvie and Rowley determined the degree of association of

$$(CH_3)_2SiH\text{-}CH_2\text{-}MgBr$$

which compound was monomeric in tetrahydrofuran [94].

Vink, Blomberg and Bickelhaupt measured the degree of association of ethylmagnesium bromide in the weakly basic solvent 1-ethoxy-2-methylbutane [130]. Furthermore these authors report the optical rotations of ethylmagnesium bromide in (+)(S)-1-ethoxy-2-methylbutane and benzene. The following equilibria were postulated:



L = 1-ethoxy-2-methylbutane

The values for K_1 and K_2 (103 mole/l and 1.41 mole/l respectively) indicate that the dimer with three solvent molecules is an important constituent of the solution. For each of the three Grignard complexes the molar rotations were calculated.

The enthalpies of reaction of seventeen organic halides with magnesium in diethyl ether were measured by Holm with the aid of a flow-calorimeter [131]. From the values obtained, it can be concluded that the carbon-magnesium bond strength is constant for the various primary alkylmagnesium halides with groups such as ethyl, n-butyl and isobu For methyl and phenyl the value is 11-12 kcal/mole higher; for isop pyl, sec-butyl and tert-butyl it is lower by 5.5 and 15 kcal/mole r pectively. Thus carbon-magnesium bond dissociation energy is lower than for R = benzyl or R = allyl, even though these groups form bon to magnesium which are 8 kcal/mole weaker than the bonds between ma nesium and primary alkyls.

With the aid of pH-measurements with a hydrogen electrode, Caillet Bauer determined the equilibrium of the following reaction in 1,2-d methoxyethane [132]:

$$\text{R-Mg-} \quad + \quad \text{H}^{\oplus}\text{ClO}_4^{\ominus} \xrightleftharpoons{\text{K'}_\text{A}} \text{R-H} \quad + \quad \text{-Mg}^{\oplus}\text{ClO}_4^{\ominus}$$

in which R-H was e.g. tert-butyl alcohol, indene, phenylacetylene o benzene. The results could be applicable

a) for the synthesis of an organomagnesium compound by this displac ment reaction,

b) for the quantitative determination of organomagnesium compounds, and finally

c) for the identification of an organomagnesium compound.

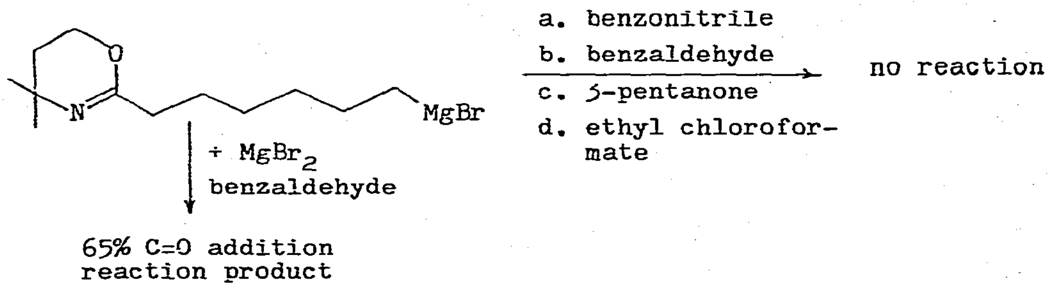
Lehmkuhl, Kintopf and Janssen measured the half-wave-potentials of alkali and of alkaline earth metals in THF by polarography of metal-tetraalkyl aluminates (such as $Mg[Al(C_2H_5)_4]_2$) with a dropping merc ry-electrode [133]. $E_{1/2}$ of magnesium was found to be -0.056V.

3C Structure and reactions

For the nickel(II)-catalyzed cross-coupling reactions of isopropylmagnesium chloride with aromatic halides:

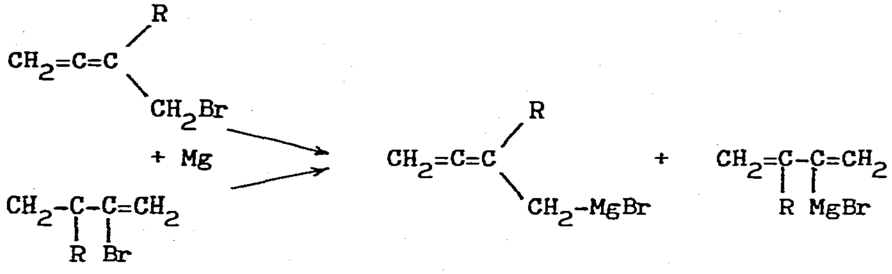
$$i\text{-}C_3H_7MgCl \quad + \quad Ar\text{-}X \quad \xrightarrow{Ni[(CH_3)_2P\text{-}C_2H_4\text{-}P(CH_3)_2]Cl_2} \quad i\text{-}C_3H_7\text{-}Ar \quad + \quad n\text{-}C_3H_7\text{-}Ar \quad + \quad Ar\text{-}H$$

Kiso, Tamao and Kumada observed, that the lability of the leaving halide is practically of no influence on the extent of isomerization. On the other hand isomerization is strongly influenced by the electronic nature of the substituents on the aromatic ring [134]. 1-Bromonaphthalene gave the non-isomerized product as the main compound: 73% versus 19% n-propylnaphthalene and 8% naphthalene. For almost all other aromatic halides, isomerized products were the major ones.
The oxazine-Grignard reagent, reported in Chapter 2Biv [97], failed to react to any appreciable extent with benzaldehyde, benzonitrile, 3-pentanone or ethyl chloroformiate, but on addition of one equivalent of magnesium bromide to the ethereal solution of the Grignard compound its reactivity was enhanced considerably; with benzaldehyde the expected carbonyl addition reaction product was isolated in 65% yield!



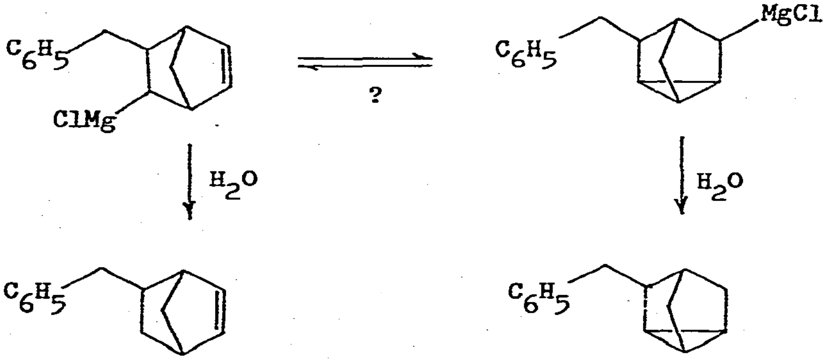
The reactions with ethyl chloroformate or benzonitrile in the presence of magnesium bromide were less effective (35-50% product yield). No reaction occured with 3-pentanone. It was assumed by the authors that the lone electron pairs, present on oxygen or nitrogen were complexing with magnesium which causes reduction of reactivity of the Grignard compound. The purpose of the added salt was twofold: a) to complex with either oxygen or nitrogen, thus releasing the Grignar compound, and b) to enhance the electrophilic nature of the electrophiles.

On hydrolysis of a part of a mixture of the dienylic and allenic Grignard compounds (both formed on reaction of each of the starting bromides [41]):



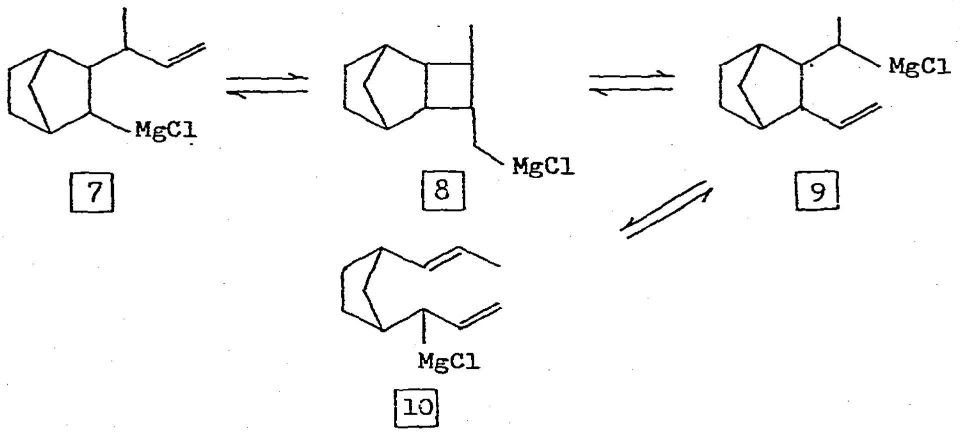
the composition of the remaining Grignard solution changed consider bly, due to the much greater reactivity of the primary Grignard compound. Since no change in this new composition of the solution was observed on standing during several days no equilibrium seems to ex between the two Grignard reagents.

Lehmkuhl, Reinehr, Brandt and Schroth could not establish with certainty the existence of an equilibrium between the following two pol cyclic Grignard compounds [135]:

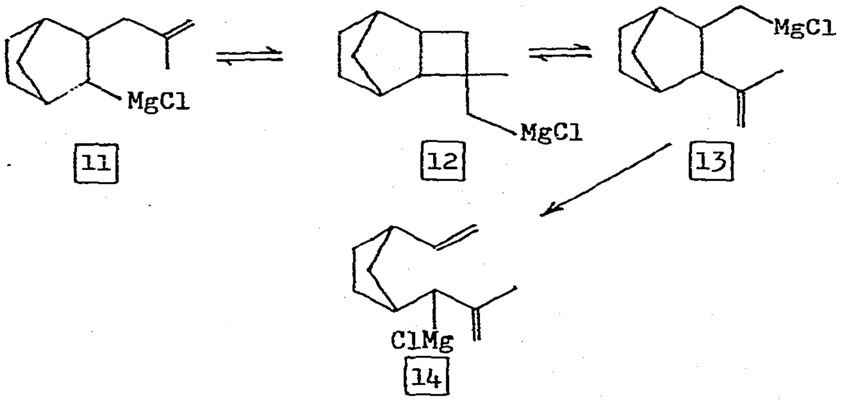


The norbornene derivative could not be distinguished with certainty, the main hydrolysis product being the tricyclic hydrocarbon. It appears that the equilibrium lies far to the right.

For the formation of different products, obtained on hydrolysis of Grignard solutions, formed after heating $\boxed{7}$ and $\boxed{11}$ at 85° for 24 hours, Lehmkuhl and Reinehr formulated the following equilibria [136]:

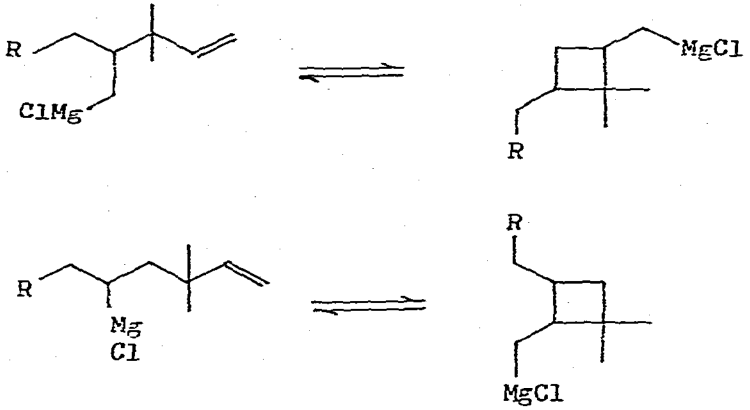


and

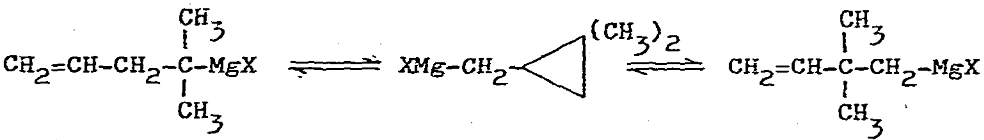


The ringopening from $\boxed{9}$ to $\boxed{10}$ and, analogously from $\boxed{13}$ to $\boxed{14}$ is a novel type of reaction in organometallic chemistry. No five-membered ring opening has been reported previously.

In a third publication dealing with the same type of Grignard chem try, Reinehr, Henneberg, Lehmkuhl and Schroth suggest the existenc of the following equilibria to account for the formation of the pr ducts, isolated on hydrolysis of the Grignard solutions [137]:



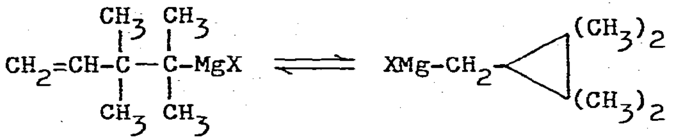
Although the rate of rearrangement of the dimethyl-substituted 3-butenyl-Grignard compound $\boxed{15}$ was slowed down considerably as compared to the rearrangement of the non-substituted organomagnesium compound (half-life time 30h at 70° as compared to 30 h at 27°)



$$\mathrm{CH_2{=}CH{-}CH_2{-}C(CH_3)_2{-}MgX} \rightleftharpoons \mathrm{XMg{-}CH_2{-}C_3H_3(CH_3)_2} \rightleftharpoons \mathrm{CH_2{=}CH{-}C(CH_3)_2{-}CH_2{-}MgX}$$

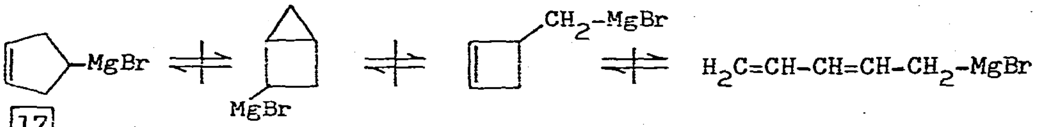
$\boxed{15}$ $\boxed{16}$

the equilibrium still lies almost completely to one side (99.9% of $\boxed{16}$ present in solution; only 0.07% of the cyclopropyl derivative could be detected) as Maercker and co-workers observed. These author obtained the first stable primary cyclopropylmethyl-Grignard by increased substitution [27]:



The equilibrium lies almost completely to the right: 99.9% of the cyclopropyl derivative was present in solution.

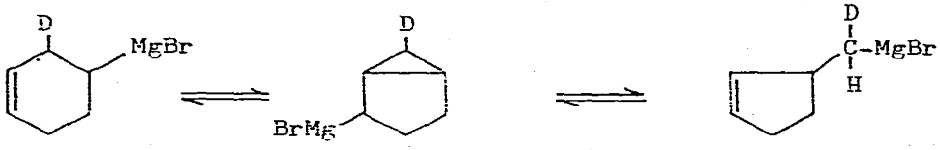
No rearrangements of the following types could be detected by Maercker and coworkers when diethyl ether or THF was used as the solvents [28]:



17

Grignard compound 17 did not undergo decomposition on heating at 80° for 14 days but decomposed at 120° in ten days. It is interesting to read that 17 decomposes readily at roomtemperature when the solvent is removed in vacuum. The same is true for the corresponding di-organomagnesium compound.

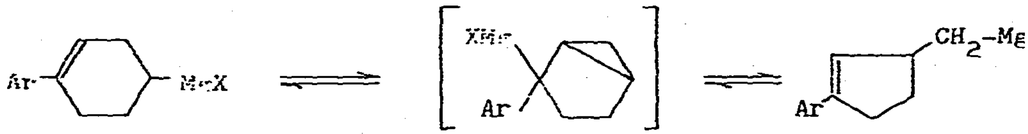
On the other hand, the following equilibrium was observed in diethyl ether as well as in THF at 80° within a few hours:



18 19 20

No NMR-signals from 19 could be detected in the equilibrium mixture that contained about 90% of 20 . The authors made a study of solvent and temperature effects on the position of the equilibrium as well as of thermodynamic secondary isotope effects. The rate of equilibration was measured: in diethyl ether this rate was about ten t mes faster than in THF.

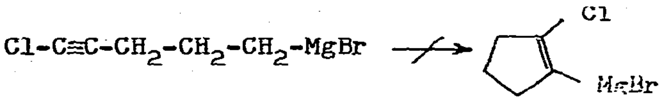
E.A. Hill and Shih studied the same sort of rearrangements with th aid of 1-aryl-substituted-4-chlorocyclohexenylmagnesium halides [2



Ar = phenyl, p-tolyl and m-trifluoromethylphenyl

A noteworthy feature of the results obtained is the slow rate of re arrangement of all three Grignard compounds. Experiments were carri out at 122^{0}! For Ar = phenyl the half life time for rearrangement i 350 h at that temperature. The rate-retarding effect of phenyl-substitution and the modest acceleration by electronwithdrawing groups appear to be best accounted for by a four-center addition mechanism No positive evidence was found for a π-interaction with the carbon magnesium bond in the transition state of the reaction.

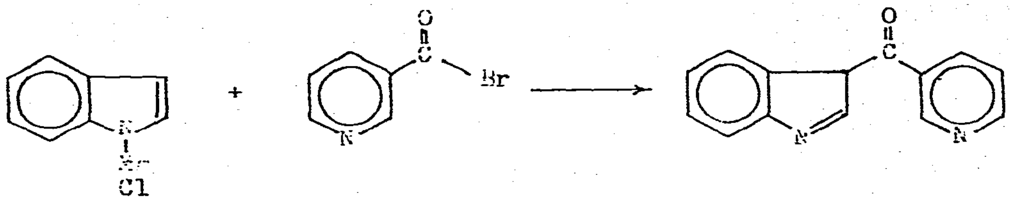
No addition reaction to unsaturated carbon-carbon bond was observe in the following chloro-alkynyl-Grignard reagent [80]:



The only lower boiling product, isolated after hydrolysis was 1-chloro-1-pentyne.

Several reports concerning rearrangements during reactions of organ magnesium compounds have been published.

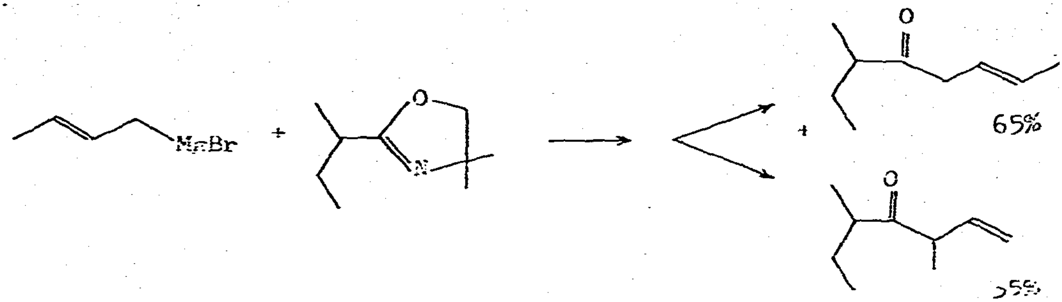
The formation of 3-acylindoles in the reaction of acyl halides with indolylmagnesium chloride, is favored by the use of an excess of the Grignard reagent (Rusinova, Smushkevich and Suvorov) [138]:

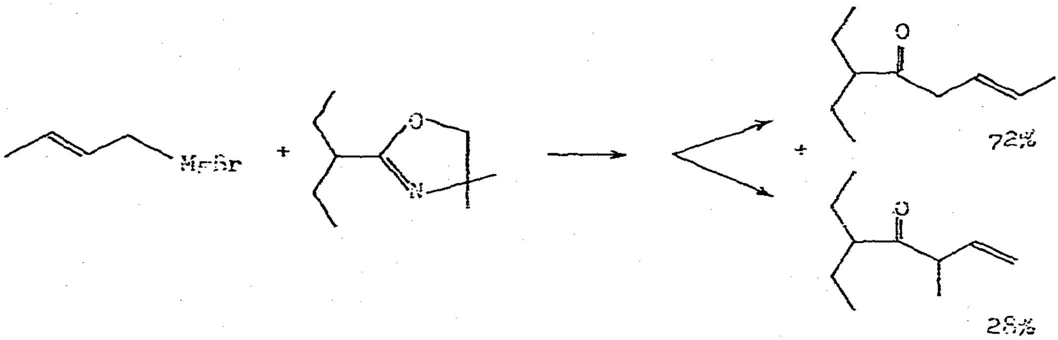


With 10% excess of the Grignard compound only 13% of 3-nicotinoylindole is formed, with 50% excess 60% of the 3-isomer is formed. γ-Triphenylsilylallylmagnesium bromide reacts with either water, carbon dioxide or oxirane to give mainly linear products whereas attack on the γ-position was observed in reactions with benzophenone and trimethylchlorosilane [77]:

$$\begin{tikzcd}
(C_6H_5)_3Si\text{-}CH{=}CH\text{-}CH_2\text{-}MgBr/(C_2H_5)_2O \arrow[r, "H_2O,\ CO_2", "\text{oxiran}"'] \arrow[d, "(C_6H_5)_2C{=}O \\ (CH_3)_3SiCl"] & \text{linear products} \\
\text{products resulting from attack at } \gamma\text{-position}
\end{tikzcd}$$

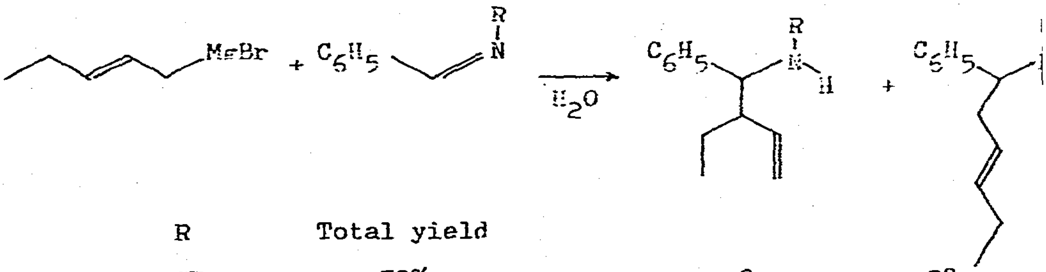
Lion and Dubois studied the reaction of substituted allylmagnesium halides with 4,4-dimethyl-2-substituted-oxazolines and observed the formation of the rearranged and unrearranged product [139], as was concluded from the structures of the unsaturated ketones, obtained after hydrolysis of the primary reaction product:





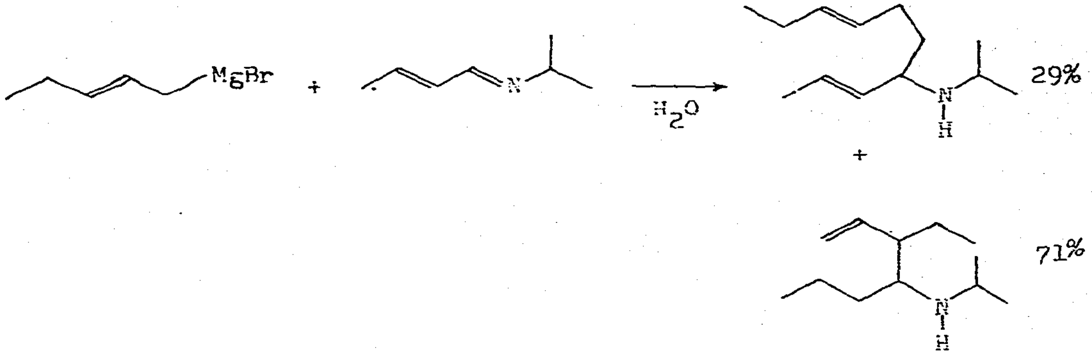
From Mme Miginiac's laboratory several reports have appeared on the stereochemistry of reactions of substituted allylic Grignard reagen with aldimines and unsaturated aldimines:

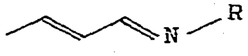
γ-Ethyl-substituted allylmagnesium bromide reacts with N-substitute aldimines as follows (Miginiac and Mauzé) [140]:



R	Total yield			
CH_3	70%	2	:	98
$i-C_3H_7$	88%	6	:	94
$t-C_4H_9$	76%	9	:	91

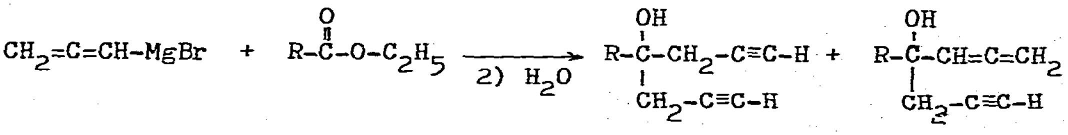
Reactions of the same organomagnesium compound with unsaturated aldi mines lead to a variety of products: 1,2-addition products with and without rearrangement and 1,4-addition products with and without rearrangement (Miginiac and Mauzé) [141] and [142]:



With C_6H_5 (R = CH_3, iso-C_3H_7 or tert-C_4H_9) unrearranged 1,2-addition products were formed mainly, together with unrearranged 1,4-addition product.

The following propargyl-allenyl rearrangements were reported:

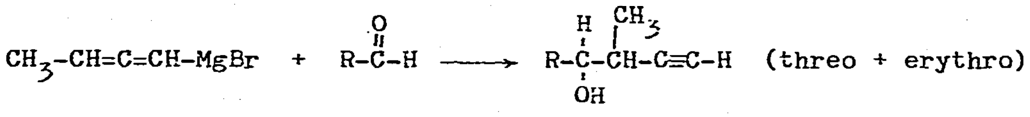
Plouin and Glênat studied the composition of the products, obtained from the reaction of allenylmagnesium bromide with several ethyl esters of aliphatic acids; a comparison was made with the results, obtained with the aid of other techniques among which one included the preparation of the organomagnesium compound in a mixture of diethyl ether and benzene and a reaction temperature as high as the reflux temperature of the solvent mixture [143]:



$$CH_2{=}C{=}CH{-}MgBr \;+\; R{-}\overset{\overset{O}{\|}}{C}{-}O{-}C_2H_5 \xrightarrow[2)\ H_2O]{} \begin{array}{l} \quad OH \\ R{-}\overset{|}{\underset{|}{C}}{-}CH_2{-}C{\equiv}C{-}H \\ \quad CH_2{-}C{\equiv}C{-}H \end{array} + \begin{array}{l} \quad OH \\ R{-}\overset{|}{\underset{|}{C}}{-}CH{=}C{=}CH_2 \\ \quad CH_2{-}C{\equiv}C{-}H \end{array}$$

Working at lower temperatures gave less of the mixed allenyl-alkynylcarbinol. The best products (least contaminated with the mixed carbinol) were obtained by the use of organoaluminum compounds of the same type. Independent of the method applied, ethyl formate and et: benzoate gave only one product, i.e. the dialkynyl carbinol.

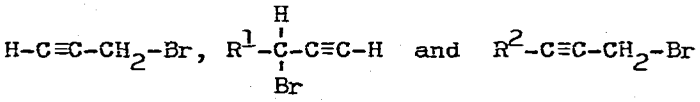
The reaction of the Grignard reagent, derived from 3-bromo-1-butyn -which exists mainly in the allenyl form in solution- with aliphat: aldehydes as well as with benzaldehyde or acetophenone was studied by Sanière-Karila, Capmau and Chodkiewicz [144]



$$CH_3\text{-}CH{=}C{=}CH\text{-}MgBr \;+\; R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \longrightarrow R\text{-}\underset{OH}{\overset{H}{C}}\text{-}\overset{CH_3}{CH}\text{-}C{\equiv}C\text{-}H \quad (\text{threo} + \text{erythro})$$

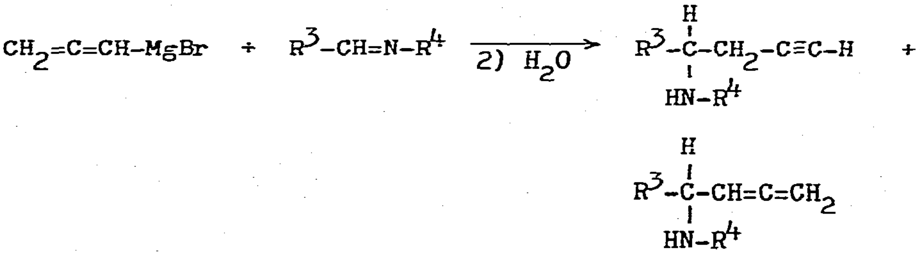
In particular the authors studied the threo-erythro ratios of the different product mixtures.

Two publications appeared from the laboratory of Moreau and Gaudema Organomagnesium compounds, derived from the following alkynyl bromi



$$H\text{-}C{\equiv}C\text{-}CH_2\text{-}Br,\quad R^1\text{-}\underset{Br}{\overset{H}{C}}\text{-}C{\equiv}C\text{-}H \quad \text{and} \quad R^2\text{-}C{\equiv}C\text{-}CH_2\text{-}Br$$

reacted with aldimines, $R^3\text{-}CH{=}N\text{-}R^4$ to give both the alkynyl and the allenyl amines, resulting from addition to the carbon-nitrogen doub bond [145]:

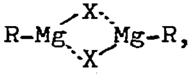


$$CH_2{=}C{=}CH\text{-}MgBr \;+\; R^3\text{-}CH{=}N\text{-}R^4 \xrightarrow[2)\ H_2O]{} R^3\text{-}\underset{HN\text{-}R^4}{\overset{H}{C}}\text{-}CH_2\text{-}C{\equiv}C\text{-}H \;+\; R^3\text{-}\underset{HN\text{-}R^4}{\overset{H}{C}}\text{-}CH{=}C{=}CH_2$$

The rearrangements of the unsaturated Grignard compounds, on reaction with aldimines, leading to the formation of α-acetylenic Grignard compounds have been mentioned in Chapter 2C [68].

3D. Theoretical Calculations

Theoretical calculations on bond breaking enthalpies in CH_3MgF, CH_3MgCl, CH_3MgCH_3 and $(CH_3MgF_3)^{2-}$, made by Astier and Millié, lead to the conclusion that the radical mechanism is energetically more favorable than the ionic mechanism [146]. For each of the first three organomagnesium compounds mentioned, the enthalpy of bond breaking was about 39 kcal/mole, independent of the other bond to the magnesium atom. Ionic bond breaking leads to enthalpies of 244, 182 and 224 kcal/mole respectively. On the other hand, the important role of solvent could be demonstrated: in solutions MgX^+ and CH_3^- are favorably formed. The energies of formation of methylmagnesium fluoride and methylmagnesium chloride were 51 and 58 kcal/mole.

Kato and Tsuruya examined the plausible structures of Grignard reagents on the basis of the energies, obtained by them via the CNDO/2 method, which does not consider the d-AO of the Mg-atom [147]. For sake of simplicity the authors chose methylmagnesium chloride in diethyl ether and calculated the energies of the different species, monomers as well as dimers. The latter seem to be energetically more favored and halogen-bridged dimers,  $R{-}Mg\overset{X}{\underset{X}{\diamond}}Mg{-}R$, are the more stable compounds.

4. MECHANISM OF REACTIONS OF ORGANOMAGNESIUM COMPOUNDS

4A. Reactions with carbonyl compounds

4Ai. Addition and reduction reactions

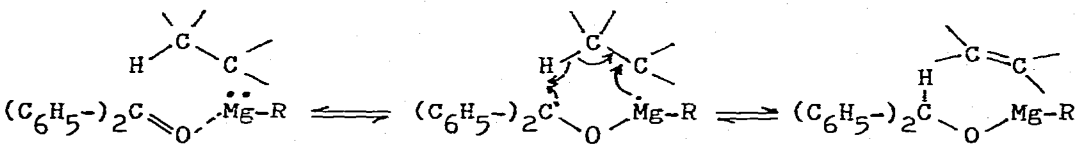
Four different research groups have reported about the mechanism of reactions of organomagnesium reagents with carbonyl compounds.

The influence of the purity of magnesium - applied for the preparation of methylmagnesium compounds - on the amounts of non-addition products as well as on the rate constants of reactions with substituted and non-substituted benzophenone has been mentioned in the troduction to Chapter 2 [23]. When ultra pure magnesium was used, rate data were found to be consistent with a specific mechanism in which both dimethylmagnesium and methylmagnesium bromide react wit the ketone in a first-order fashion. Methylmagnesium bromide, prep red from doubly sublimed magnesium, employing an excess of magnesi gave only 73% addition to benzophenone at low concentrations of ke tone, while a comparable run with a Grignard solution, prepared wi excess bromoethane, gave 92% addition. For single crystal magnesiu for the same type of experiments values of 88% and 95% respectivel were obtained. The new data are consistent with the mechanism established earlier (Ashby and coworkers; Annual Survey 1971, page 43 Annual Survey 1972, page 111).

Contrary to the above-mentioned mechanism, based on the reaction o cyclopentylmagnesium reagents with 4-methylmercaptoacetophenone in diethyl ether, S.G. Smith, Rudolph and Charbonneau propose a mechanism for the reaction with carbonyl compounds in which complex formation precedes product formation [148]: the reaction is first orde in ketone and the kinetic order in organomagnesium compound approac one in dilute solutions and zero at high concentrations. The author extensively studied the ratio of the products formed in addition, reduction and enolization reactions. It is to be noted that the addition of magnesium bromide (up to a $RMgBr/MgBr_2$ ratio of almost one causes an increase in the relative amount of reduction reaction pro duct. With $R_2Mg/MgBr_2 = 4.5$ approximately 67% reduction was observe when $RMgBr/MgBr_2 = 1$ 86% reduction was found.

Using 2,2,5,5-tetradeuterocyclopentylmagnesium bromide, asuming that there is no isotope effect on addition and enolization reactions, the authors calculated a value of 2.0 for the primary kineti isotope effect on the reduction reaction, which differs from the results of a related study by Holm (Annual Survey 1971, page 54). Fro their results Smith and coworkers conclude that a mechanism, involving a biradical intermediate and separate rate-determining and product-determining steps, as proposed by Holm, is not applicable to their data.

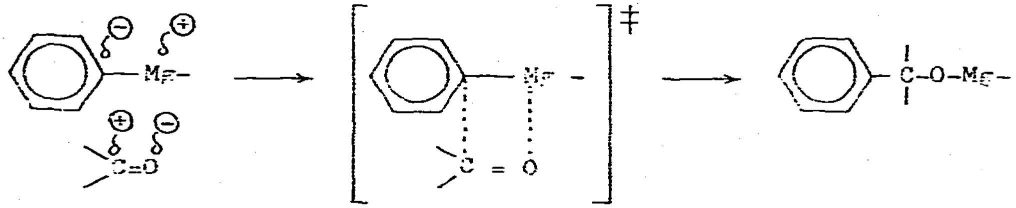
Holm studied the mechanism of the reaction of Grignard compounds with benzophenone in diethyl ether with the aid of deuterated compounds [149]. Kinetic isotope effects of the reaction of β-deuterated ethylmagnesium bromide or tert-butylmagnesium chloride were almost negligibly small (1.01 and 1.0 respectively); at the same time reduction of benzophenone by these Grignard compounds was limited (6% and 0% benzhydrol was formed). For isopropyl-, n-butyl- and isobutylmagnesium bromide, the kinetic isotope effects were 1.16, 1.28 and 1.46 respectively (20%, 55% and 91% reduction products were obtained). This observed correlation would indicate a primary isotope effect, which is associated with the reduction reaction only. Competition between equal amounts of deuterio- and non-deuterio-isobutylmagnesium bromide for a very small amount of benzophenone gave a ratio of benzhydrol to α-deuteriobenzhydrol of 2.4. According to the author the lack of correlation between the two values of the deuterium isotope effect "requires in some way a separation of the rate determining step and the product determining step." Holm therefore comes to the conclusion, that the reaction occurs partly by a single electron transfer mechanism as for example in the following two step mechanism:



Furthermore, interpretation of the results requires separation of a rate determining step if Grignard reagent is in excess, but a one step mechanim is proposed for the reaction with benzophenone in excess.

Three publications from Tuulmets' group have appeared, dealing with the kinetics of ketone reactions with Grignard compounds.

Together with Truuvälja, Tuulmets measured the kinetics of reaction of substituted diphenylmagnesium with benzophenone and with pinacolone in diethyl ether as well as in THF [150]. Pinacolone is slightly less reactive than benzophenone and the reaction is somewhat less susceptible to the inductive effect in the latter case. Considerabl greater influence is exerted by the solvent: with diphenylmagnesium benzophenone reacts 45 times faster in diethyl ether than in THF; for pinacolone this ratio is 25. The authors conclude, that the tra sition state of the reaction is cyclic and that the reaction "may b specified as that of a S_E2i or S_ECi mechanism":



From the activation parameters, obtained, it was concluded that a considerable loss of entropy occurs in the activation which also indicates the formation of a rather rigid, cyclic, activated complex Since the enthalpies of the activation are very low, the authors consider radicals to be formed in these reactions. This led them to the conclusion that "it cannot be excluded that the activated complex,in consequence of a single electron transfer, collapses to free radical that, without leaving the solvent cage, rapidly form the reaction pr ducts. It must be emphasized, however, that this cannot be the only possible explanation of the appearance of free radicals in the course of the reaction".

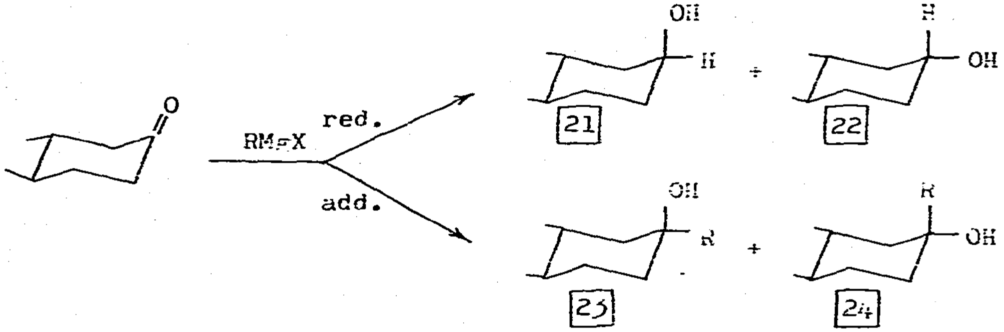
Together with Luuk, Tuulmets determined the rates of reactions of aliphatic ketones, R-CO-CH_3, with isobutylmagnesium bromide (30-50 fold excess over ketone) in diethyl ether at 20° [151]. The yields of reduction reactions were determined which allowed the authors to determine the partial rate constants of the reduction reactions. The dependence of these rates on the structure parameters of the ketones were expressed in a mathematical equation.

In another publication together with Luuk, Tuulmets investigated the kinetics of the reaction of aliphatic ketones, R-CO-CH_3, with isopropylmagnesium bromide (50 fold excess) in diethyl ether at 20° [152]. The yields of addition and reduction reaction products were determined and by substraction of these yields from the initial amount of ketone added, the yields of enolization products could be calculated. Rate constants for the enolization reactions were given: R has little if any effect on the enolization of the methyl group. The transition state of this reaction is an "early one". In order to explain the strong inductive effect of alkyl groups in the Grignard reagent, one has to assume, that the formation of a new C-H bond anticipates the breaking of the C-Mg bond. It appears, therefore, that the mechanisms of Grignard addition, reduction and enolization reactions are very similar.

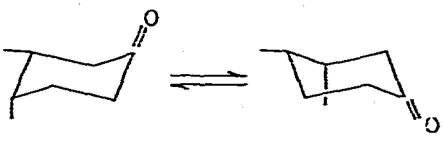
4Aii. Steric course of reactions with carbonyl compounds

In the reaction of methyl- and phenylmagnesium bromide with 2-methyl-, 3-methyl- and 3,4-dimethylcyclopentanone in diethyl ether, Ashby, Laemmle and Roling observed preferential trans-attack leading to the formation of the cis-alcohol [153]. For 3-methylcyclopentanone the cis-trans ratio in the product was 58:42. For methylmagnesium bromide with 2-methylcyclopentanone this ratio was hardly any higher (60:40). With 3,4-dimethylcyclopentanone however both Grignard compounds show preferential trans-attack: 98%.

In two publications, Jasserand, Granger, Girard, Chapat and Rossi discussed the results of the stereochemical outcome of the reactio of aliphatic Grignard compounds with cis- and trans-3,4-dimethylcyclohexanone [154] and [155]. Both the addition and reduction reacti products were analyzed:

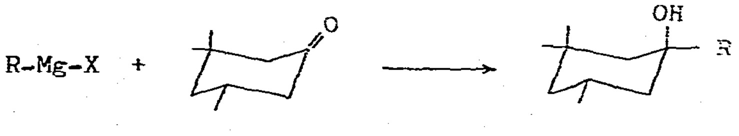


Especially the products derived from the trans isomer show pronounced changes in the ratios of axial and equatorial attack with incre ing bulkiness of the aliphatic radical R. For tert-butylmagnesium chloride e.g. 23 was obtained as the only addition product and 94 of 22 was obtained in the mixture of reduction products. For cis-dimethylcyclohexanone, the effect of the bulkiness of group R was less pronounced and the authors could prove the influence of the pr sence of two conformers of this ketone on the steric course of the nucleophilic attack:



The results were discussed in the light of classical theories eithe dealing with purely steric control on the approach of the nucleophil or dealing with competition between steric and torsional interactio which theories appeared insufficient for the reactions with a substrate which is inhomogeneous in its conformation.

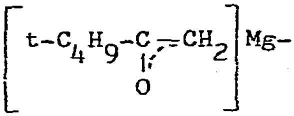
Landor, O'Connor, Tatchell and Blair reacted Grignard compounds with 3,3,5-trimethylcyclohexanone and obtained only one of the two possible tertiairy alcohols (besides reduction products in some instances) [156]:

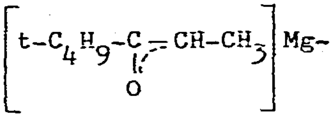


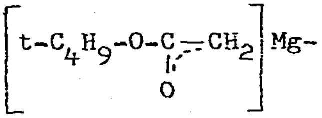
R = methyl, ethyl, vinyl, ethynyl, propyl, allyl, 2-propynyl, isopropyl and tert-butyl

The stereochemistry of reactions of organomagnesium derivatives of esters and ketones (see Chapter 2Biv) with cyclohexanones has been studied by the group of Mme Maroni:

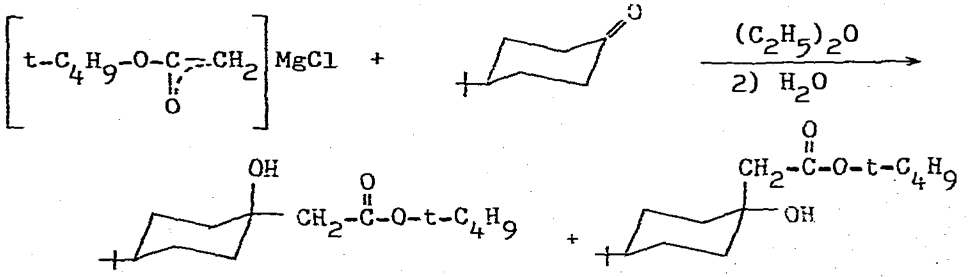
Reactions of enolates of tert-butyl ketones or esters such as


$\left[t\text{-}C_4H_9\text{-}\underset{O}{C}\text{=}CH_2\right]Mg\text{-}$,


$\left[t\text{-}C_4H_9\text{-}\underset{O}{C}\text{=}CH\text{-}CH_3\right]Mg\text{-}$ and

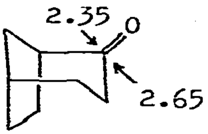

$\left[t\text{-}C_4H_9\text{-}O\text{-}\underset{O}{C}\text{=}CH_2\right]Mg\text{-}$

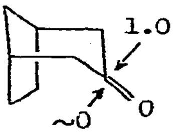
with cyclic ketones, among which mainly 4-tert-butylcyclohexanone and 3,3,5-trimethylcyclohexanone were studied, lead to products formed from equatorial or axial attack on the carbonyl group:



Whereas in diethyl ether β-hydroxy esters are obtained with axial hydroxyl groups, in HMPA the stereochemistry is almost completely t opposite: in the above mentioned reaction the ratios of the two products were 96/4 in diethyl ether and 19/81 in HMPA [86]. The symmetrical magnesium enolates, R_2Mg, also gave quite different stereospecificity [86] and [87]. Remarkable solvent effects were observe apart from the one mentioned in HMPA: a diethyl ether/benzene mixture (10/90) was almost equivalent to diethyl ether alone, but THF and dimethoxymethane caused considerable changes [88]. To the authors' opinion it might well be possible, that C-metallated species are responsible for attack on the axial position, but current theories are not applicable to the results obtained in the new researches. Apart from steric control and torsional strain in the transition state, it seems almost sure that "orbital factors" as well as "hardness and softness" and net charges on the the reacting entities have to be taken into consideration to account for the results obtained [86] and [88].

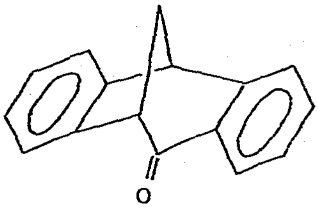
The stereochemistry and relative kinetics of the reaction of methylmagnesium iodide with bicyclo[3,2,1]octan-2one and the corresponding -3-one in diethyl ether at 0^{o} have been studied by Volpi, Biggi and Pietra [157]: the partial relative rates are indicated in the following pictures:

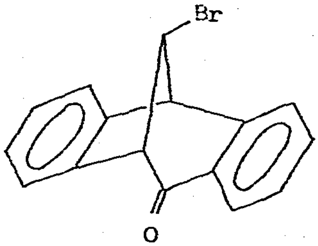




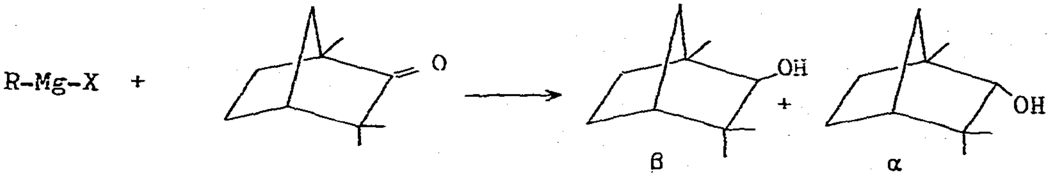
Bicyclo[3,2,1]octane-2-one reacts five times faster with methylmagnesium iodide than the corresponding -3-one.

Avram, Dinulescu, Nenitzescu, Jones, Katritzky and Wyatt discussed the steric effects of the addition of methylmagnesium iodide to the following dibenzobicyclicoctadienones [158]:



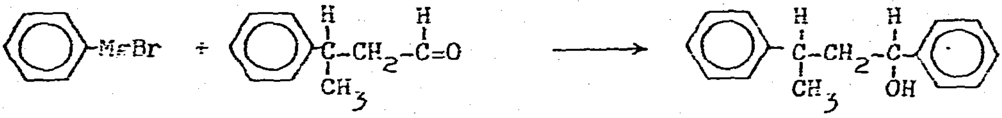


The results, obtained by Korvola, from the reactions of n-propyl-, isopropyl-, n-butyl-, sec-butyl-, tert-butyl- or cyclohexylmagnesium halides in diethyl ether at 40° with fenchone, indicate that α-fenchol is the principle product [159]:

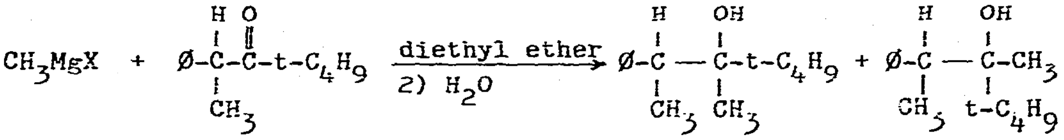


α-/β-fenchol isomer ratios varied between 76/24 (obtained with cyclohexyl Grignards) and 93/7 (with isopropylmagnesium iodide). No significant influence from the halogen was observed on the steric course of the reaction. The fastest reaction was observed with isopropyl Grignard reagents: 100% consumption of fenchone within one hour with isopropylmagnesium chloride (formation of 92% α-isomer). The formation of stereoisomers on reaction of Grignard compounds with non-cyclic carbonyl compounds was reported in the following publications:

Gonzales and Perez Ossorio obtained 51.1% of the threo-isomer in the reaction of phenylmagnesium bromide as indicated below, which value correlated well with the one obtained from theoretical calculations, based on conformation populations of the carbonyl compound and its non-bonded interaction with the reagents [160]:



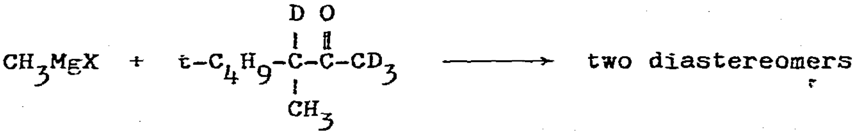
In order to establish the limits of applicability of their model o asymmetric induction, Karabatsos, Zioudrou and Moustakali studied the effect of the tert-butyl group, directly bonded to the carbonyl in addition reactions of methylmagnesium chloride or bromide with tert-butyl-1-phenylethyl ketone [161]:



$$CH_3MgX + \emptyset-\overset{H}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-t-C_4H_9 \xrightarrow[2)\ H_2O]{\text{diethyl ether}} \emptyset-\overset{H}{\underset{CH_3}{C}}-\overset{OH}{\underset{CH_3}{C}}-t-C_4H_9 + \emptyset-\overset{H}{\underset{CH_3}{C}}-\overset{OH}{\underset{t-C_4H_9}{C}}-CH_3$$

One of the diastereomers was formed in 97% or $>99\%$ (for X = Br or Cl respectively), corresponding to $-\Delta\Delta G^{\ddagger}$ values of 1.9 and >2.5 kcal/mole.

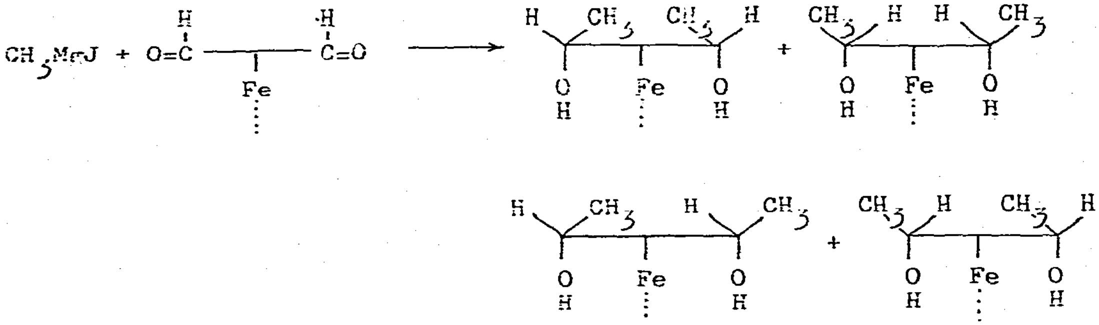
Investigating temperature effects of asymmetric induction Karabatsos, Zioudrou, Chrysochou, Herlem and Nipe studied, among others, reactions of methylmagnesium halides with deuterated 3,4,4-trimethyl 2-pentanone [162]:



$$CH_3MgX + t-C_4H_9-\overset{D}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-CD_3 \longrightarrow \text{two diastereomers}$$

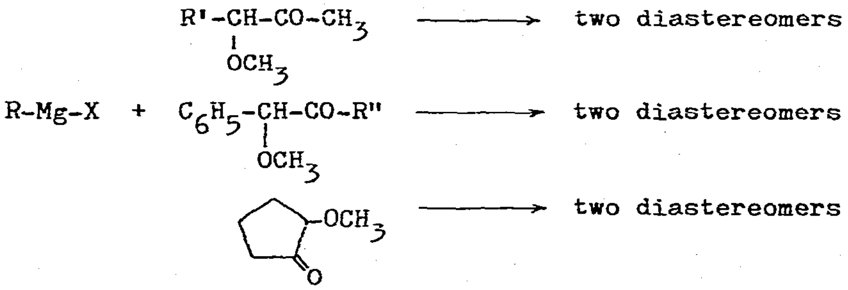
For X = Cl in THF the diastereomer ratio changed from 73.5/26.5 ($\Delta\Delta G^{\ddagger} = -0.690$), obtained from the reaction at 66^{0}, to 35.2/64.8 ($\Delta\Delta G^{\ddagger} = +0.310$) from the reaction at -24^{0}. Enthalpy favors the "wrong" diastereomer. However, methylmagnesium bromide in diethyl ether and in THF, and methylmagnesium iodide in diethyl ether, were normal; i.e. $\Delta\Delta G^{\neq}$ and $\Delta\Delta H^{\neq}$ had the same sign and magnitude. As the authors state "these comments underscore the fact that models of asymmetric induction should be used primarily as starting points for further experimentation and thinking". The authors made use of the Cram model of diastereomeric transition states to explain the results obtained in the reactions of Grignard compounds with alkyl 2-phenylethyl ketones.

Excess methylmagnesium iodide reacts with 1,2-ferrocenedialdehyde to yield the following products (Moise and Mugnier) [163]:



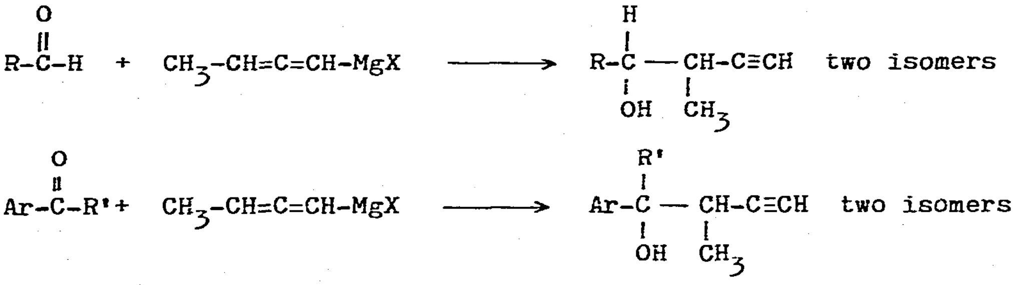
In total 80% of both meso-isomers was obtained and 20% of the racemic mixture of glycols.

Guillerm-Dron, Capmau and Chodkiewicz observed the formation of diastereomers in reactions of organomagnesium compounds with α-methoxy ketones, both of the open chain and the cyclic type [164]:



Among the Grignard compounds used were ethyl-, n-propyl-, 1-propynyl-, 2-propynyl- and 2-phenylethynylmagnesium halides. For R' = iso-C_3H_7 or tert-C_4H_9 only one of the stereoisomers was formed. Variation of the isomer composition was rather great in some reaction investigated; three types of transition states were developed by the authors to account for the steric courses of the reaction studied.

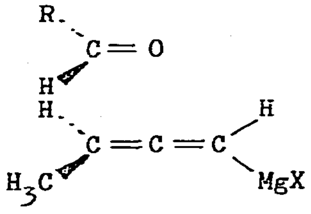
Together with Mme Sanière-Karila, Capmau and Chodkiewicz investigated the composition of the products obtained in the following reactions [144]:



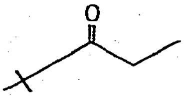
$$R-\overset{O}{\overset{\|}{C}}-H + CH_3-CH=C=CH-MgX \longrightarrow R-\underset{OH}{\overset{H}{C}}-\underset{CH_3}{CH}-C\equiv CH \quad \text{two isomers}$$

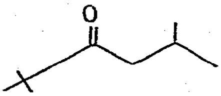
$$Ar-\overset{O}{\overset{\|}{C}}-R' + CH_3-CH=C=CH-MgX \longrightarrow Ar-\underset{OH}{\overset{R'}{C}}-\underset{CH_3}{CH}-C\equiv CH \quad \text{two isomers}$$

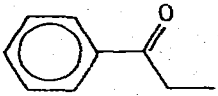
An eclipsed transition state, requiring a S_E2' reaction mechanism, seems to account for the results obtained by the authors:

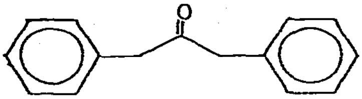


Two more publications from Mme Maroni and coworkers deal with the addition of halomagnesium enolates to enones; with Gorrichon the reaction of several different enolates with benzylideneacetone was investigated [89]: among the ketones from which the enolates were derived mention has to be made of the following ones:





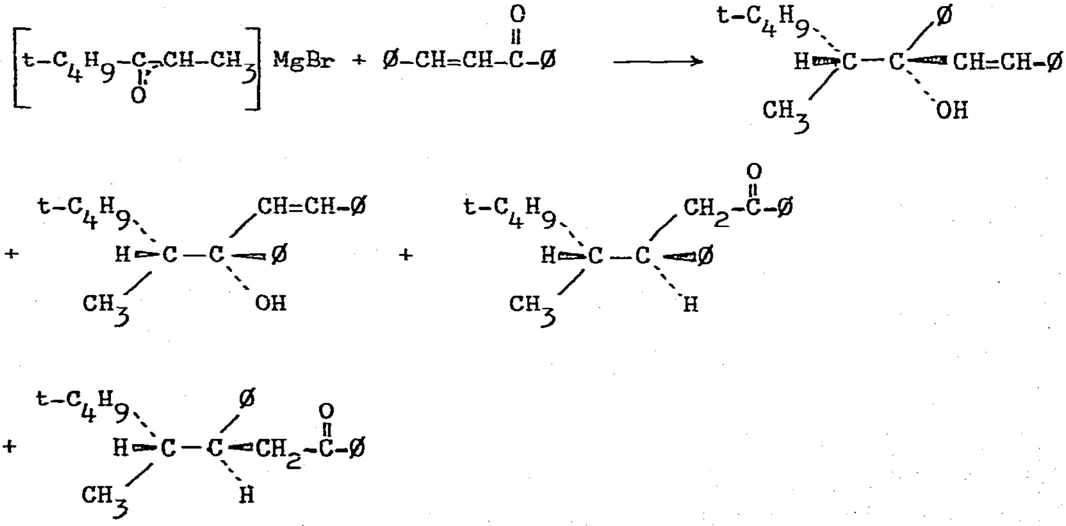




In the products obtained by the authors, i.e. rather sterically crowded δ-diketones, quite often only one of the possible two isomers was observed, indicating a high stereoselectivity. Only in the case of the reaction of the first mentioned ketone enolate was 1,2-addition to the unsaturated ketone observed. In other cases exclusively 1,4-addition was observed.

The question rose to what extent carbon-metalated magnesium compounds participated in these reactions.

Together with Bertrand, Cabrol and Gorrichon-Guigon, reactions with benzalacetophenone were studied [85]. Here again 1,2- and 1,4-addition was possible as well as formation of threo and erythro products:



With R_2Mg only 1,4-addition was observed whereas with halomagnesiu enolates the main product was the 1,2-addition reaction product. More surprising is the observation that in the first 10 minutes of the reaction 1,2-addition is the main reaction whereas after one hour almost 100% 1,4-addition products were isolated, indicating that a reversible reaction occurs.

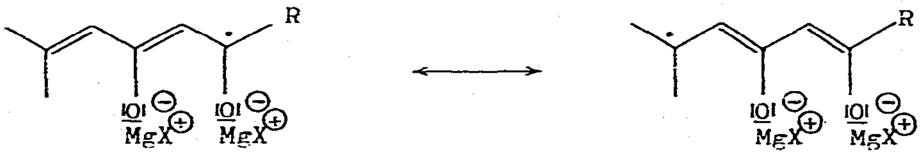
The product yield was 85% after three minutes and the ratio of the two product types was almost 50/50 at that time. This ratio change to 0/100 after three hours. Furthermore the threo/erythro ratio changed in the 1,4-addition product from 15/85 to 84/16 in 24 hour

4B. Radical reactions of organomagnesium compounds

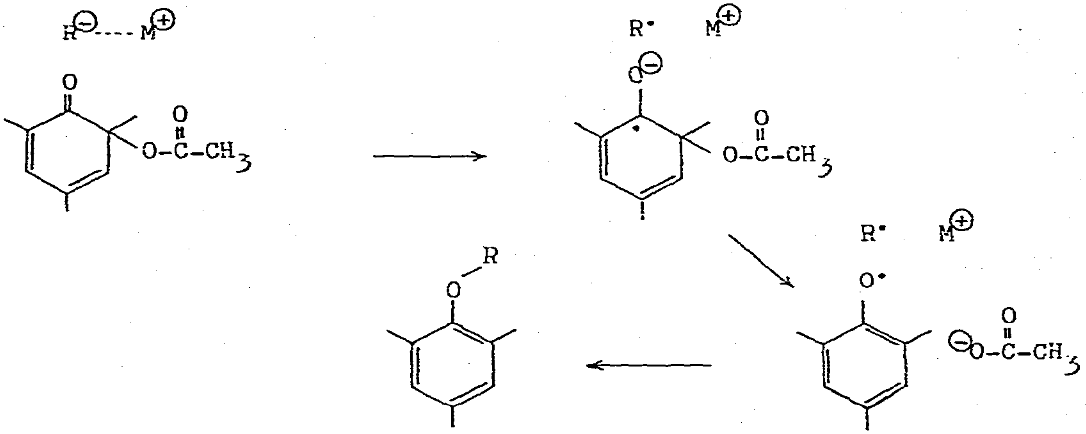
In Chapter 4Ai, Holm's paper on the mechanism of the reaction of benzophenone with deuterated organomagnesium compounds, for which the author proposed - at least partly - the formation of radicals by a single electron transfer, has been discussed [149].

R. Gêlin, S. Gêlin and Dehondt reported more extensively on the reaction of alkyl- and aryl-Grignard compounds with unsaturated β-diketones during which reactions duplication of the diketones occurs, as was published earlier (Annual Survey Magnesium 1971, [135 [165].

With the aid of epr-spectroscopy the authors observed the followin ketyl in the reaction mixture:



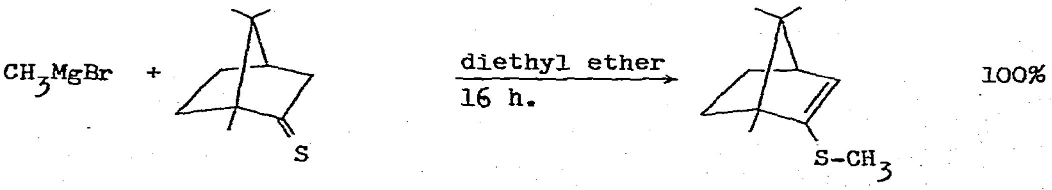
Miller suggests a mechanism, including phenoxy and hydrocarbon radicals, for the reaction of Grignard compounds with ortho-quinol acetates, although it does not seem certain yet, whether radicals are genuine intermediates or whether they simply represent resonance contributors to the transition state of a single step displacement on oxygen [166]:



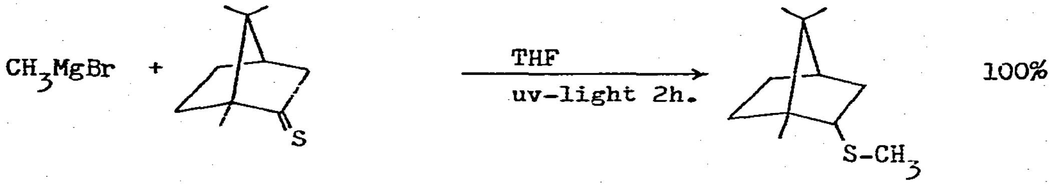
In case the o-quinol acetate is trimethyl substituted, ether formation is less than 0.1% with methylmagnesium bromide, 4% with ethylmagnesium bromide and 28%, 67% and 91% with tert-butyl-, sec-butyl and benzylmagnesium halides respectively!

Dagonneau and Vialle, together with Paquer and Metzner, continued their researches in the field of reactions of Grignard compounds with thioketones where, by means of epr-spectroscopy, radicals have been proved to occur (see also earlier publications, Annual Survey Magnesium 1972).

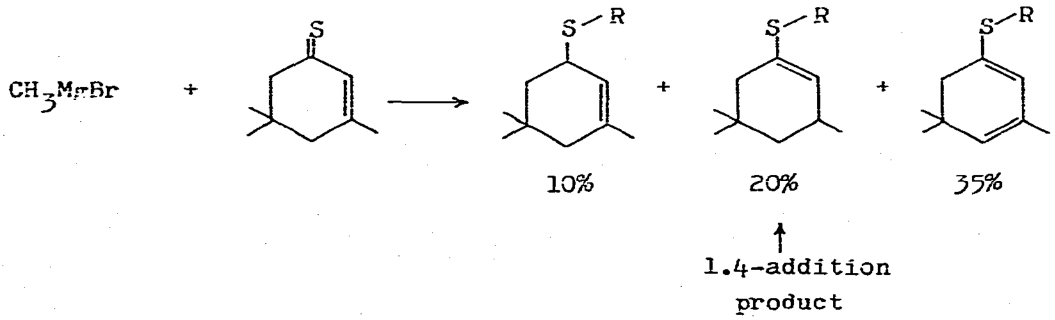
With thiocamphor, methylmagnesium bromide reacts to form the methyl enethiol ether in 100% yield when diethyl ether was used as the solvent [167]:



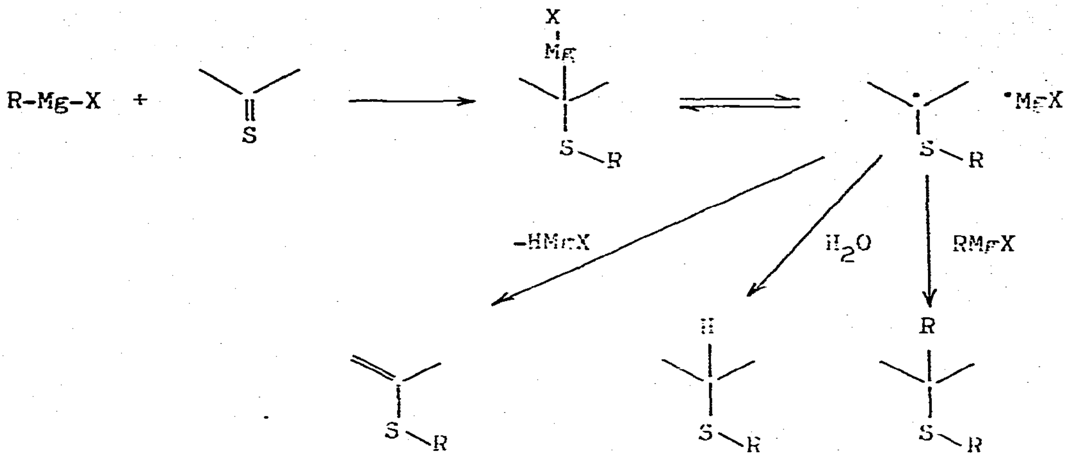
no reaction at all with thiocamphor, but the saturated thioether was obtained quantitatively when the reaction mixture was irradiated with ultraviolet light during two hours:



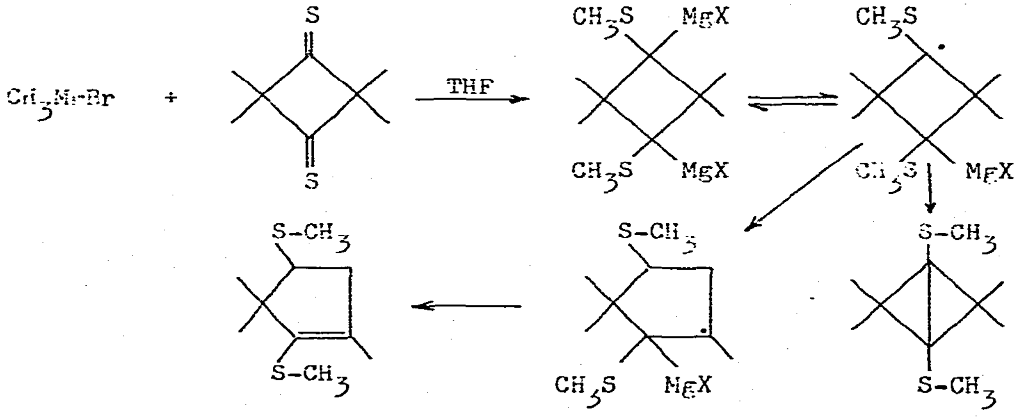
With other cyclic thioketones several products could be isolated; investigation of reactions of unsaturated cyclic thiones with aliphatic Grignard compounds revealed the occurrence of 1,4-conjugate addition, analogous to copper(I) catalyzed reactions with unsaturated ketones [168]. As an illustration the following reaction is given:



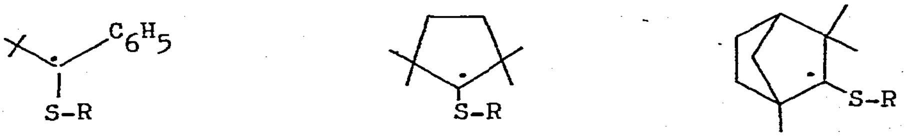
The same authors proposed the following mechanism to account for the formation of different products during the reaction of organomagnesium compounds with thioketones, e.g. with thiopivalone [169]:



With cyclobutane-1,3-dithione a peculiar internal elimination reaction was observed, leading to the formation of a bicyclo[1,1,0]butane derivative [170]:



Dagonneau and Vialle, finally, reported the g-factors as well as the coupling constants of the following radicals [171]:



R = methyl and ethyl

The influence of the purity of magnesium, used for the preparation of Grignard compounds, on the yields of these compounds, has been mentioned in Chapter 2A [32]; radical reactions have been studied of isopropylmagnesium bromide, prepared from magnesium of several grades of purity, with isopropyl bromide under different reaction c conditions. Addition of styrene inhibits catalysis by metal impurities, whereas large CIDNP enhancements are observed for the disproportionation reaction products, C_3H_8 and C_3H_6, demonstrating the intermediacy of isopropyl radicals.

The same authors, Allen, Ward and Lawler, studying the CIDNP spect obtained from the iron-catalyzed reaction of selectively deuterate isopropylmagnesium bromide with selectively deuterated isopropyl bromide, come to the conclusion that free radicals are produced only from the alkyl halide, since CIDNP is observed exclusively in t products, derived from this product [172]:

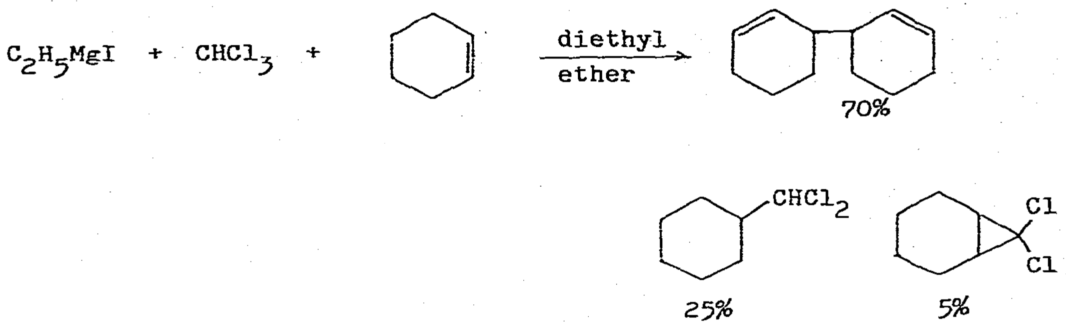
$$(CH_3)_2CH\text{-}MgBr \quad + \quad (CH_3)_2CD\text{-}Br \xrightarrow{FeCl_2} CH_3CD{=}CH_2 \quad + \quad CH_3CH{=}CH_2$$

$$+ \quad C_3H_8 \quad + \text{ coupling products}$$

Only 2-deuteriopropene was polarized; no polarization in undeuterated propene was observed!

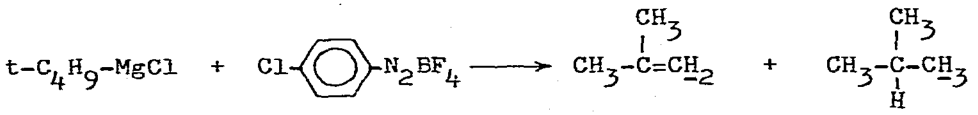
epr-Studies of reactions of triphenylmethylmagnesium chloride with various reagents such as $CuCl_2$, $C_6H_5N_2BF_4$, C_6H_5I, KOH, tritylsodium and others, revealed the formation of triphenylmethyl radicals (Ponomarchuk, Kasukhin and Fieleleeva) [173]. With iodobenzene or with phenylmagnesium bromide, $C_6H_5^{\bullet}$ was also formed. The authors conclud that the one-electron reaction contributes to the reactivity of triphenylmethylmagnesium halides.

Davis, Deady, Finch and Smith report the intermediacy of radicals during the reaction of ethylmagnesium iodide with chloroform in th presence of a large excess of cyclohexene [174]:



It is likely that the products are formed in radical reactions involving the dichloromethyl radical; in none of the reactions evidence was found for products, arising from the formation of the trichloromethyl radical.

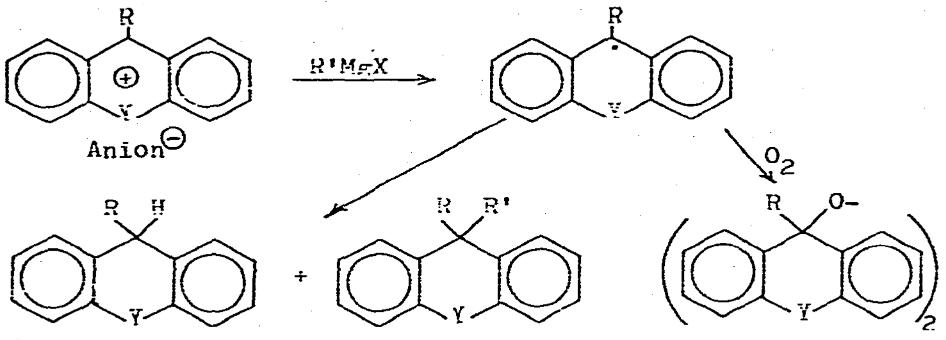
One-electron transfer from tert-butylmagnesium bromide as well as from benzylmagnesium chloride was demonstrated by CIDNP-spectra from reaction mixtures of these Grignard compounds with para-chlorophenyl diazonium tetrafluoroborate (Savin, Temyachev and Kitaev) [175]:



among other products;
polarization observed in the
underlined protons

The observation of polarized absorption by chlorobenzene in the reaction of the same terafluoroborate with benzylmagnesium chloride apparently is connected with the formation of a radical pair, consisting of a benzyl and a chlorophenyl radical.

Hori, Kataoka and coworkers published three papers on the reaction of Grignard compounds with 9-substituted xanthylium, selenoxanthylium and thioxanthylium salts [176], [177] and [178]. By study of the epr-spectra, radical intermediates were detected and analyzed.



Y = O, S or Se

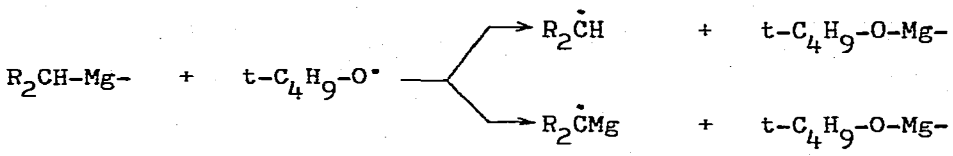
From the products, obtained by reacting Grignard reagents with unsaturated ethers, Mkryan and Gasparyan concluded that radical intermediates occured [179]:

$$\text{R-Mg-X} + \text{t-C}_4\text{H}_9\text{-CH}_2\text{-C}\equiv\text{C-CH}_2\text{-O-R'} \longrightarrow$$

coupling products of
allene, acetylene and
R (alkyl) radicals

Panek reported that many radical anions can easily be prepared by one electron reduction with readily available organometallic compounds in HMPA solution [180]. Benzylmagnesium chloride reduces 10^{-4} M biphenyl to its radical anion quantitatively in less than ten minutes.

Methyl-, ethyl-, n-propyl- and isopropylmagnesium compounds in diethyl ether solution reacted with photochemically generated tert-butoxy radicals to afford epr spectra, consisting of the superposition of the individual spectra of two species with different g-factors (Kuang, Battioni and Kochi) [181]:



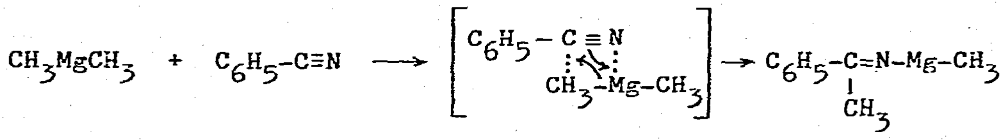
The spectra disappeared on shuttering the light and was not observed in the absence of peroxide. No spectrum of a paramagnetic species, attributable to a magnesium-centered radical, has been observed; if any is formed it must have a fleeting existence, even at -130°.

4C. Miscellaneous reactions

The influence of the purity of magnesium, used for the preparation of methylmagnesium bromide, on the mechanism of reactions with benzonitrile is similar to the influence on reactions of methylmagnesium bromide with benzophenones (see Chapter 4Ai ref. [23]): with ultra pure magnesium no by-products are formed and the pseudo-first-order rate constants are essentially independent of the initial benzonitrile concentration.

The kinetics of the reaction of benzonitrile with methylmagnesium bromide [182] and of dimethylmagnesium in diethyl ether [183] were investigated by the same group (Ashby, Chao and Neumann). When the Grignard reagent was prepared from single crystal magnesium the alkylation product, acetophenone, is obtained quantitatively. The kinetic data show a second-order reaction: first order in the organomagnesium compound and first order in nitrile. The reaction rate decreases markedly on addition of magnesium bromide, indicating that the bimolecular rate constant for reaction with the Grignard compound is considerably smaller than for reaction with dimethylmagnesium: 1.0×10^{-3} versus 17.7×10^{-3}. The initial product formed

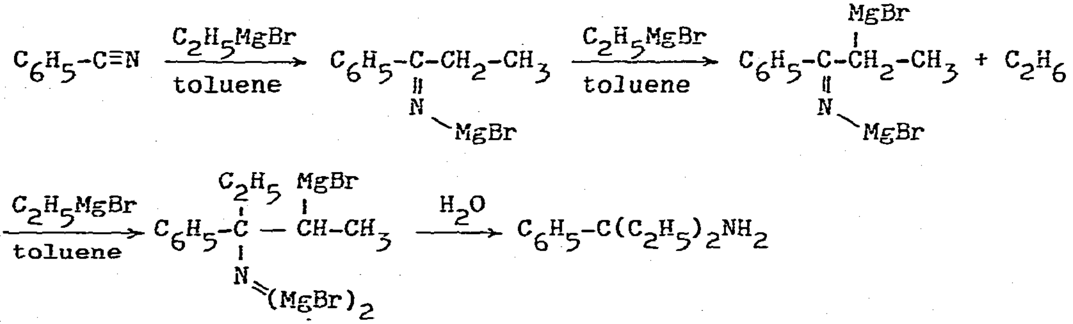
]



$$CH_3MgCH_3 + C_6H_5{-}C{\equiv}N \longrightarrow \left[\begin{array}{c} C_6H_5-C\equiv N \\ \vdots \;\; \vdots \\ CH_3-Mg-CH_3 \end{array}\right] \longrightarrow C_6H_5-\underset{\underset{\displaystyle CH_3}{|}}{C}=N-Mg-CH_3$$

reacts rapidly with magnesium bromide to form methylmagnesium bromide.

Laurent and Alvernhe observed the formation of primary amines in the reaction of nitriles with Grignard reagents in toluene as the main solvent [184]. The Grignard reagents were first prepared in diethyl ether after which toluene is added and the ether removed by distillation; addition of the nitrile at reflux temperature of the reaction mixture yields the amine as given in the following equations, representing the reaction of ethylmagnesium bromide with benzonitrile:



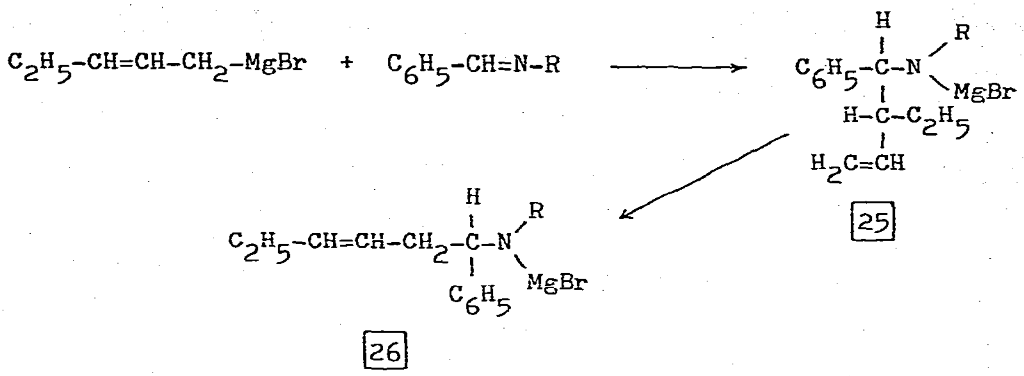
$$C_6H_5-C\equiv N \xrightarrow[\text{toluene}]{C_2H_5MgBr} C_6H_5-\underset{\underset{\displaystyle N\diagdown MgBr}{\|}}{C}-CH_2-CH_3 \xrightarrow[\text{toluene}]{C_2H_5MgBr} C_6H_5-\underset{\underset{\displaystyle N\diagdown MgBr}{\|}}{C}-\overset{\overset{\displaystyle MgBr}{|}}{C}H_2-CH_3 + C_2H_6$$

$$\xrightarrow[\text{toluene}]{C_2H_5MgBr} C_6H_5-\overset{\overset{\displaystyle C_2H_5}{|}}{\underset{\underset{\displaystyle N\diagdown(MgBr)_2}{|}}{C}}-\overset{\overset{\displaystyle MgBr}{|}}{C}H-CH_3 \xrightarrow{H_2O} C_6H_5-C(C_2H_5)_2NH_2$$

For this particular case the yield of the amine was 60%; in the reaction of phenylmagnesium bromide with acetonitrile the main product under these reaction conditions remained the "normal" product acetophenone, whereas the amine was formed for not more than 10%.

From other reactions with nitrogen containing organic compounds reported, those with imines have to be mentioned:

Mme Miginiac and Mauzé observed reversibility of the reaction of bromo 2-pentenylmagnesium with benzaldimines, containing bulky substituents on nitrogen [140]:



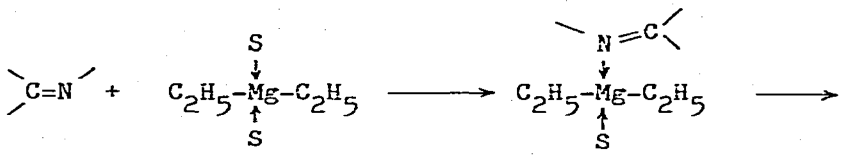
For R = isopropyl, within 24 hours 65% of the unbranched product $\boxed{26}$ is formed versus 6% after 20 minutes. For R = tert-butyl, after 24 hours the reaction mixture contains 92% of $\boxed{26}$ versus 9% of $\boxed{26}$ after 20 minutes. No change at all in the composition of the reaction mixture is observed for R = methyl, but the addition of zinc bromide causes an increase in the amount of this product from 2% to 44% in 24 hours.

For the 1,2-addition reaction of allylic Grignard reagents to unsaturated aldimines the same authors also observed reversibility [141]. In the reaction

$$C_2H_5\text{-}CH{=}CH\text{-}CH_2\text{-}MgBr \quad + \quad C_6H_5\text{-}CH{=}CH\text{-}CH{=}N\text{-}i\text{-}C_3H_7 \longrightarrow \text{1,2-addition}$$

72% addition to the double bond is observed versus 15% 1,4-addition; these percentages were not altered after 24 hours, but the composition of the 1,2-addition reaction products changed from 25% branched + 58% linear products to 0% branched and 86% linear product (relative yield, calculated from the total amount of products obtained). For the 1,4-addition reaction no reversibility could be proved because of the low absolute yields and the difficult separation of the different products.

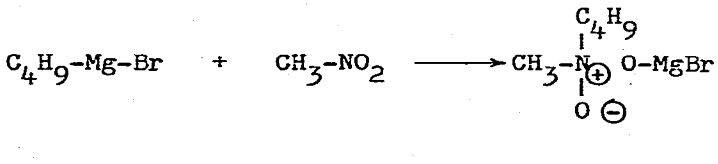
According to Thomas, reactions of diethylmagnesium with benzaldimines proceed via preliminary complex formation between the organomagnes compound and the imines [185]:



Whether reaction occurs within this complex or by attack of a second molecule diethylmagnesium on this complex could not be settled by the author. Considerable solvent effects were observed: the more basic solvents yielded less product in a given length of reaction time. It should be mentioned that one mole of diethylmagnesium reac with two moles of an imine to yield 90% product. It appears that th ethylmagnesium amide, formed by the first attack on the C=N double bond, reacts further with a second molecule of the imine. Finally i has to be mentioned that reduction of the C=N double bond was observed!

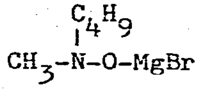
On the other hand, no such reduction was observed by Thomas in the reaction of ethylmagnesium bromide with the same aldimine [186]. Ethylmagnesium bromide appeared more reactive than the symmetrical organomagnesium compound.

The reaction of nitromethane with aliphatic Grignard reagents was studied by Wawzonek and Kempf [187]. Here too, the first step is a complex formation:



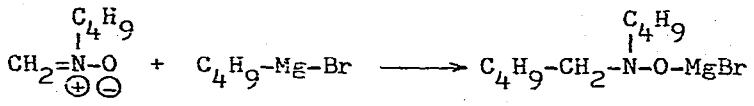
$$C_4H_9\text{-}Mg\text{-}Br + CH_3\text{-}NO_2 \longrightarrow CH_3\text{-}\overset{C_4H_9}{\underset{O\ominus}{N\oplus}}\ O\text{-}MgBr$$

This complex reacts further, either to give the bromomagnesium alkoxide of N-butyl-N-methylhydroxylamine $\boxed{27}$ or the nitrone $\boxed{28}$ which adds a Grignard reagent to form the bromomagnesium alkoxide of N-pentyl-N-butylhydroxylamine:



$CH_3-\overset{\overset{C_4H_9}{|}}{N}-O-MgBr$;

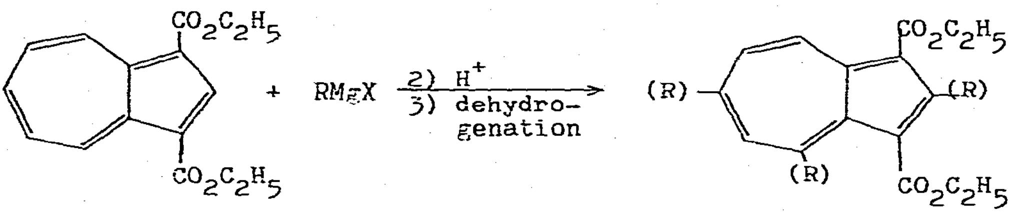
27



$CH_2=\overset{\overset{C_4H_9}{|}}{\underset{\oplus\ominus}{N}}-O + C_4H_9-Mg-Br \longrightarrow C_4H_9-CH_2-\overset{\overset{C_4H_9}{|}}{N}-O-MgBr$

28

Substitution in the azulene system by reaction of Grignard compounds with diethyl azulene-1,3-dicarboxylate, followed by hydrolysis and dehydrogenation, as represented in the following equation, is highly influenced by the steric requirements of the Grignard compound, as observed by Abe, Morita and Takase [188]:

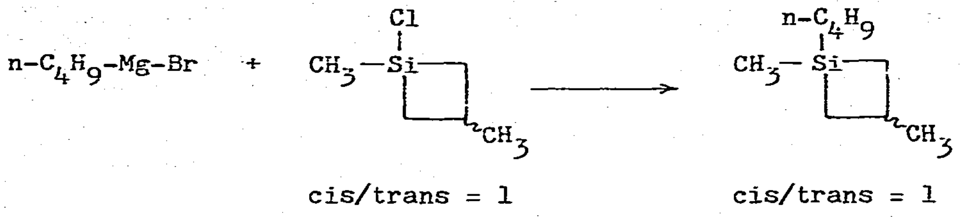


The following results were reported:

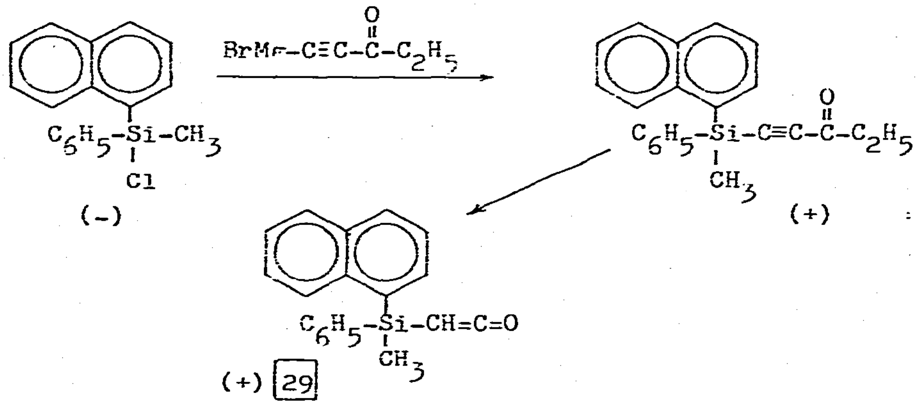
Grignard reagent	2-subst.	4-subst.	6-subst.
CH_3-Mg-I	15 %	5 %	1 %
$C_6H_5-Mg-Br$	10 %	70 %	2 %
$\alpha-C_{10}H_7-Mg-Br$	6 %	45 %	7 %
tert-$C_4H_9-Mg-Br$	-	1 %	23 %

Several publications deal with the stereochemistry of reactions with silicon compounds:

Seyferth, Shih, Dubac, Mazerolles and Serres observed no change in the cis/trans ratio of 1,3-dimethyl-1-silacyclobutane in the reaction of the 1-chloro derivative with n-butylmagnesium bromide [189]:

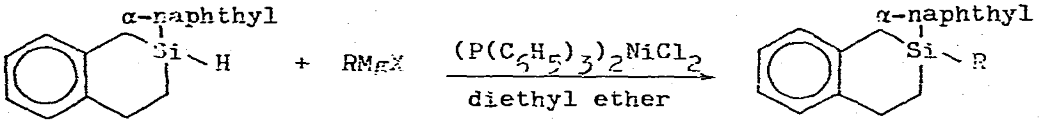


The silyl ketene $\boxed{29}$ was synthesized with an over-all stereospecificity of 50-60 % by Vodolazskaya and Baukov in the reaction of an acetylenic Grignard compound with the chlorosilane given in the following equation [79]:

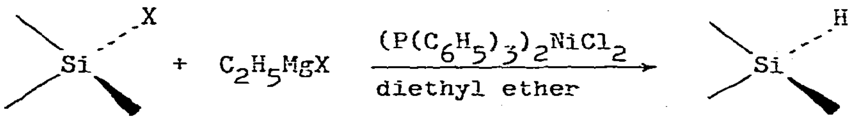


Inversion about the Si atom occurs during the reaction with the organomagnesium compound.

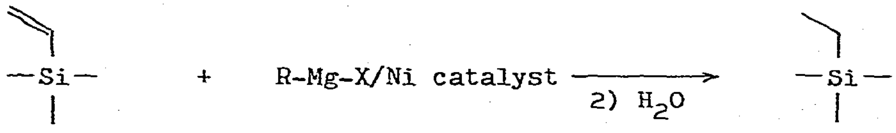
Corriu, Massé and Meunier investigated the stereochemistry of the reactions of the same type of organosilanes with Grignard compounds, catalyzed by triphenylphosphine/nickel(II) chloride [190], [191] and [192] (see also Anual Survey, 1970, ref. [205]). Substitution of a Si-H bond by a Si-C bond with the aid of a Grignard reagent and the nickel(II) catalyst was accomplished only when no reactive β-hydrogen atoms are present in the Grignard compound as is the case for methyl-, allyl-, benzyl- or phenylmagnesium halides. In particular the allyl-Grignard reagent is very reactive [190]. Other nickel catalysts such as $(Acac)_2Ni$ or $NiCl_2$ were much less effective as were salts of other transition metals. The reaction proceeds with retention of configuration:



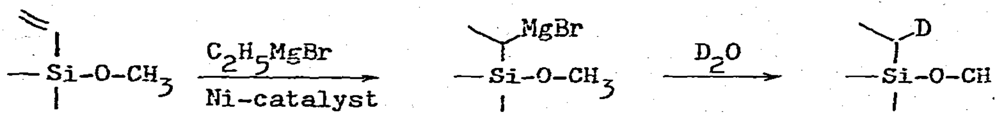
Reducing Grignard reagents (having a reactive β-hydrogen in the organic group) cause the formation of a Si-H bond on reaction with X-substituted silanes, most likely via a Ni-H intermediate [191]:



Retention of configuration was observed in this reaction for X = X = O-CH_3, F or D; inversion was observed for X = Cl. Other Grignard compounds are less effective in this reduction and show the following order: $C_2H_5 > n\text{-}C_3H_7 > iso\text{-}C_3H_7 > n\text{-}C_4H_9 > iso\text{-}C_4H_9$. Remarkable is the reduction of a vinyl silicon derivative by the Grignard-Nickel catalyst combination:



An organomagnesium compound is supposed to be formed as one of the reaction products since deuterolysis of the reaction mixture yields deuterated ethylsilanes:



Furthermore the stereochemistry of these reactions has been studied (see also [192]).

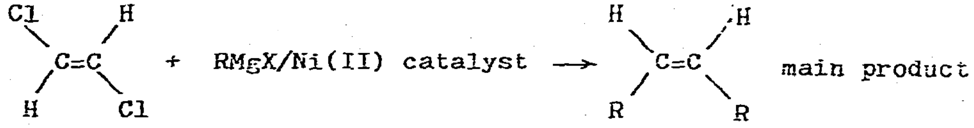
High stereospecificity was observed by Tamao, Zembayashi, Kiso and Kumada in the reaction of phenylmagnesium bromide with cis- and trans-bromostyrene in the presence of $DppNiCl_2$ as a catalyst (Dpp $(C_6H_5)_2P\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}P(C_6H_5)_2$) [193]:

$$C_6H_5\text{-}Mg\text{-}Br \;+\; C_6H_5\text{-}CH{=}CH\text{-}Br \xrightarrow{\text{Ni(II) complex}} C_6H_5\text{-}CH{=}CH\text{-}C_6H_5 \quad \text{100\% yiel}$$

$$\text{100\% trans} \longrightarrow \text{93\% trans + 7\% cis}$$

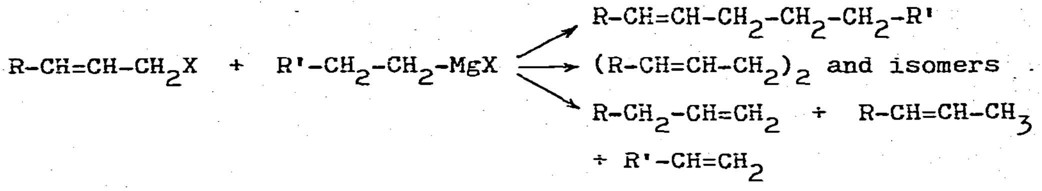
$$\text{100\% cis} \longrightarrow \text{7\% trans + 93\% cis}$$

On the other hand, in the reaction of cis- as well as of trans-1,2-dichloroethene the isomer ratios of the stilbenes formed were equal, the thermodynamically less stable cis-isomer being formed in excess:



According to the authors the high cis-stereoselectivity strongly suggests that an elimination-addition mechanism is operative on nickel. However, in several instances trans-selectivity was observed which obviously requires the intermediacy of other Ni-acetylene complexes than for the cis-stereoselective reactions.

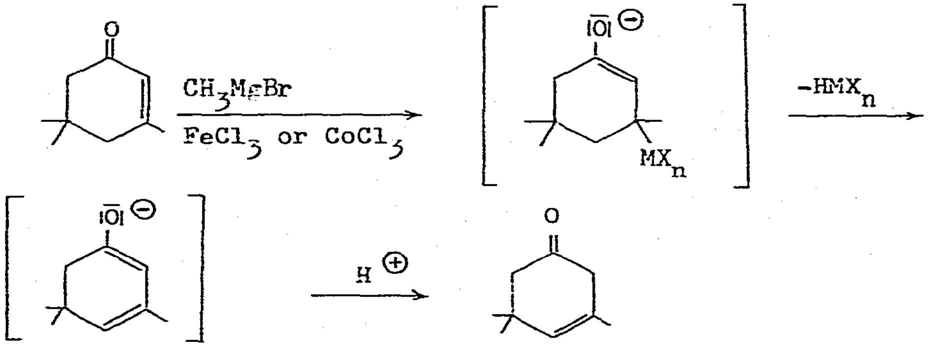
Ohbe and Matsuda continued their investigations on the Kharasch reaction of allylic halides with Grignard reagents in the presence of $FeCl_3$, $CoCl_2$, $NiCl_2$ and $CuCl_2$ (see also Annual Survey 1972, ref. [247]) [194]:



$$R\text{-}CH{=}CH\text{-}CH_2X + R'\text{-}CH_2\text{-}CH_2\text{-}MgX \longrightarrow \begin{cases} R\text{-}CH{=}CH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R' \\ (R\text{-}CH{=}CH\text{-}CH_2)_2 \text{ and isomers} \\ R\text{-}CH_2\text{-}CH{=}CH_2 + R\text{-}CH{=}CH\text{-}CH_3 + R'\text{-}CH{=}CH_2 \end{cases}$$

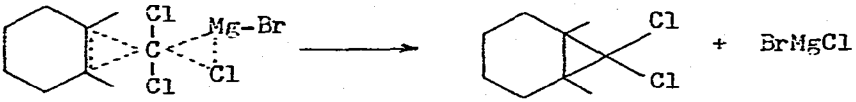
The authors state that, analogous to the view, presented by Tamura and Kochi (Annual Survey 1971, ref. [148] - [153]), the reactive species in the present reactions are reasonably considered to be allylic-metal intermediates; thus the catalytic reaction would be essentially between the allylic-metal intermediate and either allyl halide or Grignard reagent. For Ni and Co catalysts the intermediate may better be described as a π-allyl complex.

According to C.R. Johnson, Herr and Wieland [195] there is a good possibility that the so-called deconjugation reaction of isophorone by combinations of Grignard reagents and iron(III) or cobalt(II) chlorides, may occur via the formation of a metal-alkyl intermediate (see also Meinwald and Hendry, J. Org. Chem. 36 (1971) 1446):



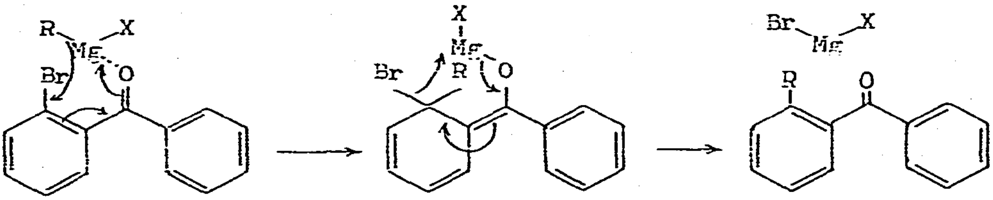
Although ethylmagnesium iodide reacts with chloroform or carbon tetrachloride, in the presence of cyclohexene, under the formation of products which justify the occurrence of radicals as intermediates (Chapter 4B, ref. [174]), the reaction of phenylmagnesium bromide proceeds via a carbenoid intermediate, which reacts with cyclohexe

$$C_6H_5MgBr \; + \; CCl_4 \longrightarrow C_6H_5Cl \; + \; Cl_3C\text{-}MgBr$$

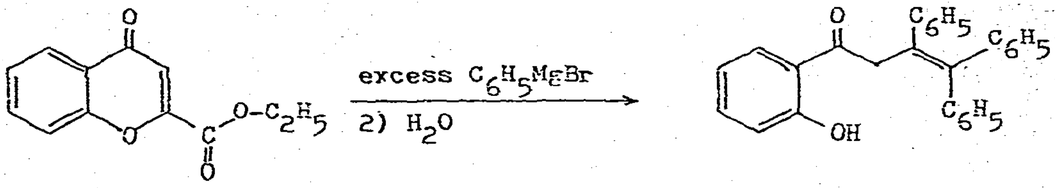


Support for the initial exchange reaction comes from the detection of substantial amounts of chlorobenzene in the reaction mixture. Some halogen rearrangement in the carbenoid intermediate may give a possible explanation of the formation of surprisingly large amou of bromochloro- and dibromobicyclo[4.1.0]heptanes.

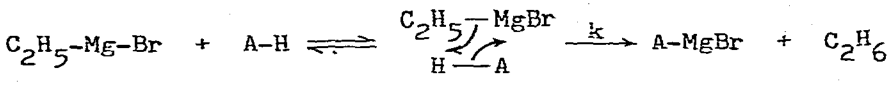
As reported by Bickelhaupt and Jongsma, the reaction of Grignard reagents with 2-bromobenzophenone leads to the formation of substantial amounts of a product which seems to result from a substitution reaction of the Br atom by the organic group of the Grignar reagent, in addition to the normal carbonyl addition reaction product [196]. The authors suggest that occurrence of a ketone-Grignar complex in which nucleophilic substitution takes place:



The reaction of a five fold excess of phenylmagnesium bromide with ethyl chromone-2-carboxylate leads to the formation of 1-(o-hydrox phenyl)-3,4,4-triphenyl-3-buten-1-one, possibly by a reductive fis sion of the ether bond between the atoms in the positions 1 and 2, as proposed by Holmberg and Sjöholm [197]:



Tüzün and Erdik studied the kinetics of the reaction of ethylmagnesium bromide with weak acids such as amines, alcohols and 1-alkynes [198]. The authors propose a S_Ei mechanism for the (Zerewitinoff) reaction:

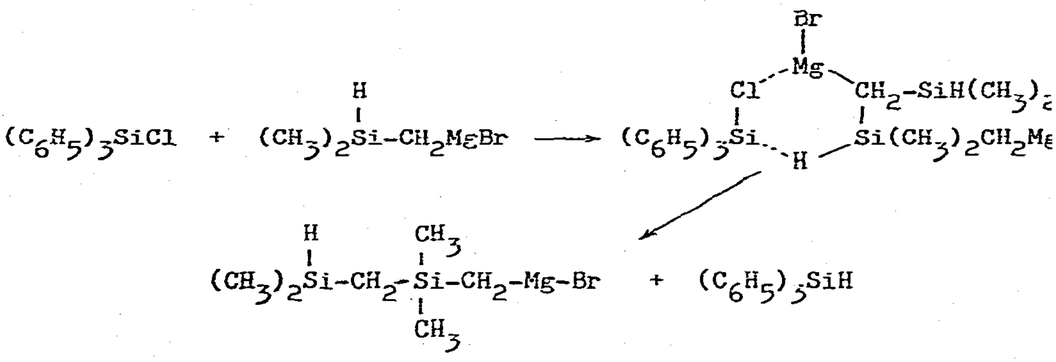


$$C_2H_5\text{-Mg-Br} + \text{A-H} \rightleftharpoons \begin{matrix} C_2H_5 - MgBr \\ H - A \end{matrix} \xrightarrow{k} \text{A-MgBr} + C_2H_6$$

The same authors, in another study, compared the reactivity of alkylmagnesium halides by a kinetic method [199]; the Zerewitinoff reaction rate constants were measured of ethyl-, propyl- and butyl-Grignard compounds with diethylamine in diethyl ether at 25^0. The relative reactivity of alkylmagnesium halides increases in the order $<$ chloride $<$ bromide $<$ iodide. A linear dependence of log k on the number of β-hydrogen atoms in the alkyl group was observed. Finally in this S_Ei reaction, the relative strength of the carbon-metal bond increases in the order tert-butyl $<$ isopropyl $<$ ethyl $<$ sec-butyl $<$ n-butyl $<$ n-propyl $<$ isobutyl $<$ methyl.

Tomoi and Kakiuchi studied the kinetics of the metallation reaction of fluorene by diethylmagnesium in the presence of HMPA [126]. Different reactions occur, depending on the amount of HMPA present, relative to diethylmagnesium. When the ratio $Et_2Mg/HMPA = 1/2$ the order of the reaction was unity in both fluorene and diethylmagnesium; the active species is the complex between Et_2Mg and HMPA. Hydrolysis of magnesium-bis(-1,4-(dimethylalumino)-2-butene) with a 1:1 H_2O/D_2O mixture, reveals an isotope effect whose magnitude indicates that cleavage of the OH (or OD) bond determines the rate of the reaction (Lehmkuhl and Reinehr) [200].

The reduction of triphenylchlorosilane by dimethylsilylmethylmagnesium bromide and by 2-diphenylsilylethylmagnesium bromide in THF gives good third-order kinetics ($k = 4.75 \times 10^{-4}\ l^2.\ mol^{-2}.\ s^{-1}$ an $3.83 \times 10^{-6}\ l^2.\ mol^{-2}.\ s^{-1}$ respectively) which is explained by Jarvie and Rowley with the following reaction scheme which represents a "Swain" type mechanism [94]:

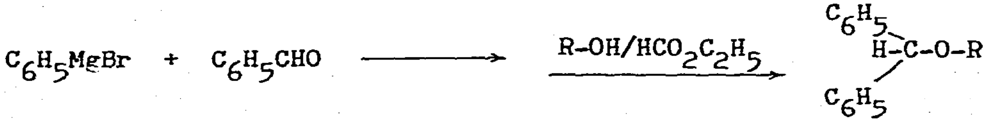


Baryshnikov and Kvasov determined the kinetics of the autoxidation of phenylmagnesium-tert-butoxide, $C_6H_5-Mg-O-t-C_4H_9$, at 0°, 20°, 30° and 40° [201].

5. REACTIONS OF ORGANOMAGNESIUM COMPOUNDS

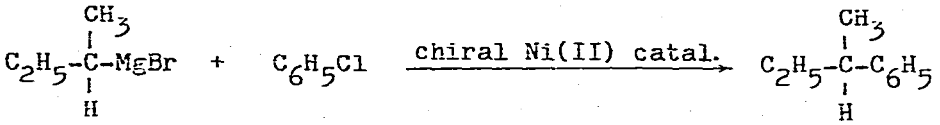
Introduction

Benzhydryl ethers were prepared by Lapkin, Belonovich, Zenkova and Dvinskikh by addition of an alcohol to the reaction mixture, obtaine on addition of phenylmagnesium bromide to benzaldehyde [202]:



$$C_6H_5MgBr + C_6H_5CHO \longrightarrow \xrightarrow{R-OH/HCO_2C_2H_5} (C_6H_5)_2HC-O-R$$

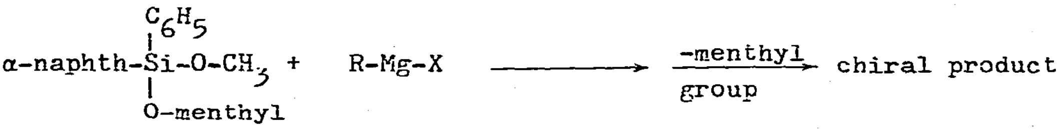
The stereochemistry of reactions of Grignard compounds with carbonyl compounds has been discussed in Chapter 4Aii. Mention has now to be made of asymmetric synthesis with bromo 2-butylmagnesium and bromo 1-phenylethylmagnesium in reactions with vinyl chloride or with phenyl chloride in the presence of a chiral Ni(II)/diphenylphosphine complex as the catalyst [203]. Consiglio and Botteghi report 17% asymmetric synthesis in the following reaction:



$$C_2H_5\text{-}\overset{CH_3}{\underset{H}{C}}\text{-MgBr} + C_6H_5Cl \xrightarrow{\text{chiral Ni(II) catal.}} C_2H_5\text{-}\overset{CH_3}{\underset{H}{C}}\text{-}C_6H_5$$

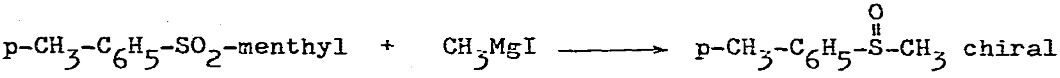
17% optically pure

Asymmetric synthesis in reactions of organomagnesium compounds with chiral substrates which contain menthyl groups were reported for the following reactions:



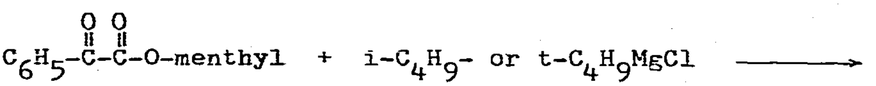
$$\alpha\text{-naphth-}\overset{C_6H_5}{\underset{\text{O-menthyl}}{Si}}\text{-O-}CH_3 + \text{R-Mg-X} \longrightarrow \xrightarrow[\text{group}]{\text{-menthyl}} \text{chiral product}$$

Corriu and Lanneau, Ref. [204]



$$p\text{-}CH_3\text{-}C_6H_5\text{-}SO_2\text{-menthyl} + CH_3MgI \longrightarrow p\text{-}CH_3\text{-}C_6H_5\text{-}\overset{O}{\overset{\|}{S}}\text{-}CH_3 \text{ chiral}$$

Estep and Tavares, Ref. [205].



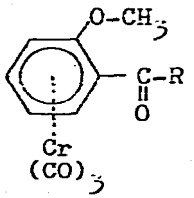
$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-O-menthyl} + i\text{-}C_4H_9\text{- or } t\text{-}C_4H_9MgCl \longrightarrow$$

asymmetric reduction product

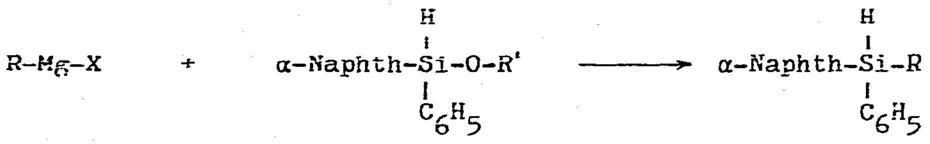
D. Cabaret, ref. [206].

Asymmetric synthesis with chiral substrates were furthermore reported by:

Besancon, Tirouflet, Card and Dusausoy [207] in reactions with chromo-carbonyl compounds:

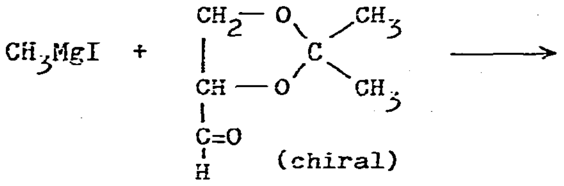


Corriu and Moreau [208] in reactions with asymmetric silicon compounds:



$$R\text{-}Mg\text{-}X + \alpha\text{-Naphth-}\underset{C_6H_5}{\overset{H}{Si}}\text{-}O\text{-}R' \longrightarrow \alpha\text{-Naphth-}\underset{C_6H_5}{\overset{H}{Si}}\text{-}R$$

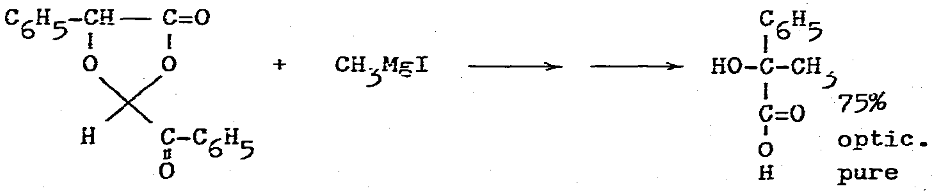
Calinaud and Gelas [209]:



76% erythro and 24% threo isc mer of the C=O addition product

With a similar type of 1,3-dioxolanyl phenyl ketone Meric and Vigneron even obtained products with 97% optical purity [210]; in both instances the optically active substrates were derived from carbohydrates.

Cahier-Rivault and Vigneron obtained 75% optically pure products by reactions of the following chiral 1,3-dioxolanyl ketone with methylmagnesium iodide [211]:



5A. Reactions with aldehydes and ketones

Stereochemistry

In addition to the reports of reactions with carbonyl compounds dealing with the stereochemical aspects as mentioned in chapter 4Aii (ref. [153], [156], [157] and [158]) the publications of Kitahara and Nagakura (reactions with 9-methyl-6-ene-1-cis-decalone) [212] and of Joska, Fajkos and Sorm (reactions with 6-methyl analogs of B-norsteroids) [213] are given here.

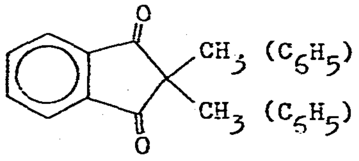
Enolization

Sadet and Rumpf report the formation of products, resulting from condensation of the enolate-anion, formed on attack of chloro 3-dimethylamino-propylmagnesium on aldehydes and ketones, on unreacted ketones and aldehydes [214].

Burnham, Melton and Eisenbraun observed o-methylphenylmagnesium bromide to act as a base in the aldol condensation with tetralone to form the tetralone aldol which reacts further [215].

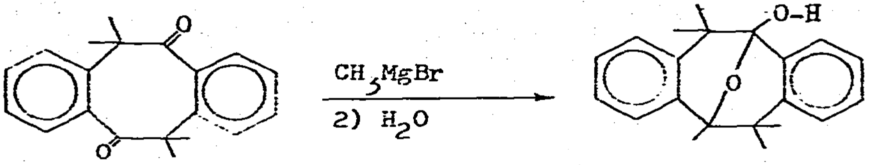
Dicarbonyl compounds

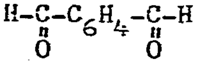
The stereochemical studies of reactions of organomagnesium compounds with ferrocenedialdehyde were reported in Chapter 4Aii [162]. Other dicarbonyl compounds used in reactions with Grignard compounds were:



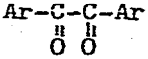
Schoenberg and Mamluk [216]

R.M. Lagidze, A.I. Dvalishvili, L.P. Chigogidze, D.R. Lagidze and Devdariani observed the following hemiacetal formation [217]



 ; Vereshchagin, Kirillova and Demina [218]

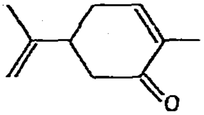
$H-\underset{\|}{\overset{}{C}}-C_6H_4-\underset{\|}{C}-H$ with O beneath each C: $\mathrm{H{-}C(=O){-}C_6H_4{-}C(=O){-}H}$

 ; Badder, Fahmy and Aly [219].

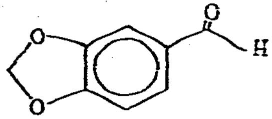
$\mathrm{Ar{-}C(=O){-}C(=O){-}Ar}$

Double addition

Double addition of ketones to the bifunctional Grignard reagent derived from acetylene, Br-Mg-C≡C-Mg-Br, was reported for the followin compounds:

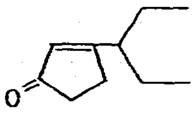


Krupowicz and Sapiecha [220]

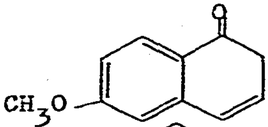


Krupowicz and Sapiecha [221]

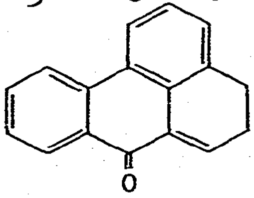
Other ketones



Mironov, Ivanov and Akhrem [222]



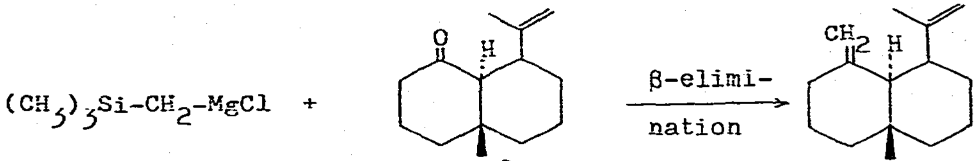
+ C_2H_5-O-C≡C-MgBr ——→ product dehydrates spontaneously [56]



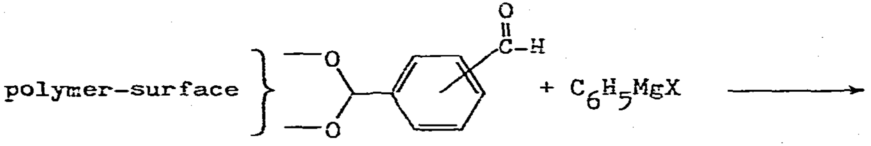
Allen [223].

$(C_6H_5-CH=CH-C_6H_4-)_2C=O + C_6H_5-CH=CH-C_6H_4-MgBr \xrightarrow[2)\ H_2O]{}$

$(C_6H_5-CH=CH-C_6H_4-)_3C-OH$ Myakina and Kotlyarevskii [224].



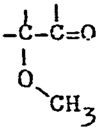
[93]



Hydrolysis of the product gave p- and m-formylphenyl phenylcarbinols (Leznoff and Wong) [225].

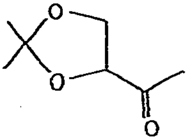
Carbonyl compounds with other functional groups.

Ether or ketal function.

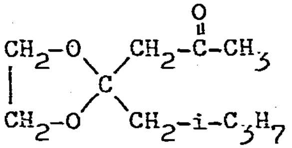


$-\underset{\underset{CH_3}{|}}{\underset{O}{|}}{\overset{|}{C}}-\overset{|}{C}=O$

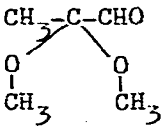
stereochemical investigation reported in Chapter 4Aii [164]



ref. [209];



Vig, Ram and Fig [226]

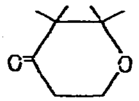


$\underset{\underset{CH_3}{|}}{O}\;\;CH_3-C-CHO\;\;\underset{\underset{CH_3}{|}}{O}$ + $CH\equiv C-MgBr \longrightarrow$ Hahn [227]

Reactions of acetylenic Grignard compounds with di-isopropylidene- or di-benzylidene protected aldehydo-D-ribose were reported by Ogura, Ogiwara, Itoh and Takahashi [228].

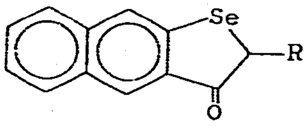
The same type of reactions of protected carbohydrates with Grignard compounds were reported by Brimacombe, Rollins and Thompson [229] as well as by Kiely, Walls and Black [230].

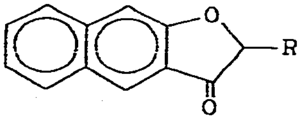
Reactions with pyranone derivatives:



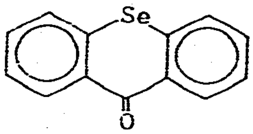
were reported by Vartanyan, Noravyan, Avetsyan and Mkrtchyan [51], Karaev, Movsumzade, Agamirzoev and Askerov [231] and Baranov, Burya and Krivum [232].

Cagniant, Kirsch and Lêgendre studied reactions of the following heterocyclic selena or oxa-ketones [233]:





Protiva, Sindelar, Metys and Metyosova studied similar compounds in their reactions with γ-dimethylaminopropyl Grignards [234]



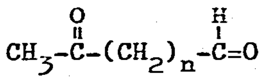
The hydroxy-ketone $\boxed{30}$ reacts normally with methylmagnesium iodide when R= isopropyl or ethyl but produces the tert -carbinol when R = tert-butyl (Esafov, Vshivkov, Markova and Svalova) [235]:

$$CH_3MgI + CH_3-\underset{OH}{\overset{R}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-R' \;\; \boxed{30} \longrightarrow \xrightarrow[2)\ H_2O]{} R-\underset{OH}{\overset{CH_3}{C}}-CH_3$$

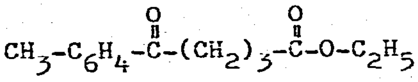
for R = tert-butyl

Second carbonyl function

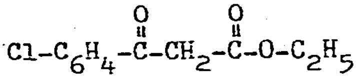
Vaskan and Kovalev studied reactions of Grignard compounds with ten 1,5- or 1,6-ketoaldehydes [236]



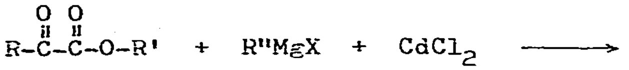
$$CH_3-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{H}{C}=O \qquad n = 5 \text{ or } 6$$



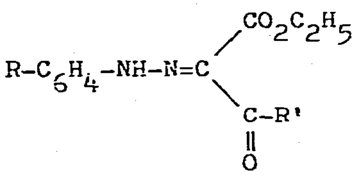
$CH_3-C_6H_4-\overset{O}{\overset{\|}{C}}-(CH_2)_3-\overset{O}{\overset{\|}{C}}-O-C_2H_5$; Vig, Kumar, Salota and Sharma [237].



$Cl-C_6H_4-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O-C_2H_5$; Gallardo [238].

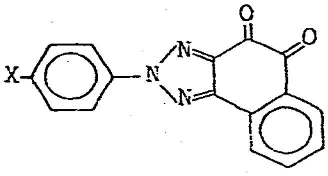


$R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-O-R' + R''MgX + CdCl_2 \longrightarrow$ Karavanov [239].

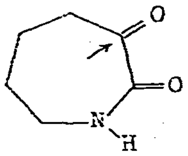


reacts with RMgX to form the normal C=O addition reaction products of the keto carbonyl group (Harhash, Mansour, Elnagdi and Elmoghayer) [240].

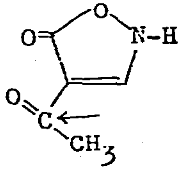
Di-carbonyl addition products were also obtained in reactions of RMgX with the following di-ketone, as reported by Mansour, Ibrahim and Zaher [241].



In the following two compounds Grignard addition occurs to the carbonyl group indicated with an arrow:



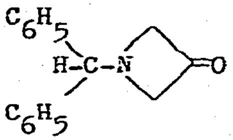
Smirnova and Glushkov [242].



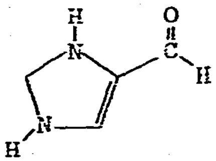
Harhash, Elnagdy and Hussein [243]

Carbonyl-nitrogen functions in combination

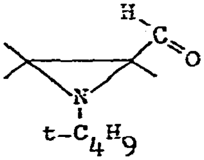
Normal C=O addition occured in reactions of Grignard compounds with the following N-containing substrates:



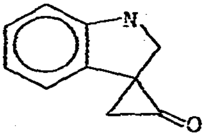
; Chaterjee [244]



; Loozen and Godefroi [53]



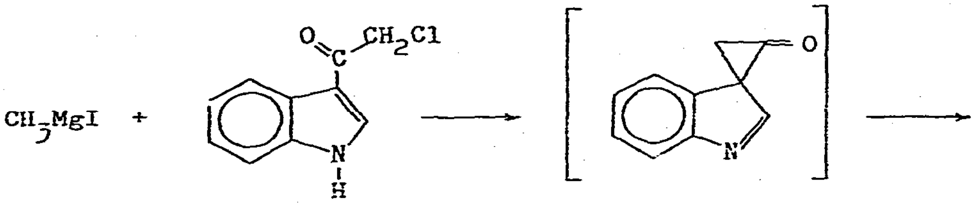
; Wartski and Sierra-Escudero [245]



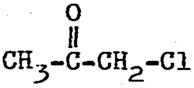
; Bergman and Bäckrell [246]; ringopening of the cyclopropanone ring occurs.

Halosubstituted ketones

The above-mentioned spirocyclopropanone was formed in the following reaction [246]

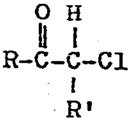


Other α-chloroketones used as substrates were:



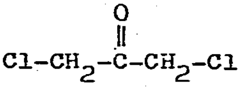
$CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}Cl$

;Shchelkunov and Vasil'eva [57]



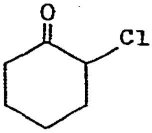
$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}\underset{\underset{R'}{|}}{\overset{\overset{H}{|}}{C}}\text{-}Cl$

; Kuprianova and Tatarchuk [73]

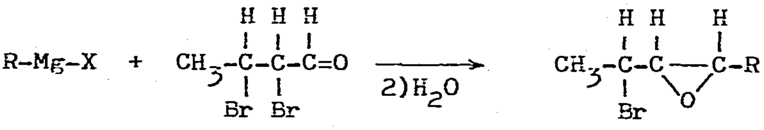


$Cl\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}Cl$

; used by C.R. Johnson and Herr in reactions with bromo 2-magnesiumpropene, leading to the formation of cyclic products [247].



; Karaev, Movsumzade. Amanirziev and Askerov [231]



$R\text{-}Mg\text{-}X + CH_3\text{-}\underset{\underset{Br}{|}}{\overset{\overset{H}{|}}{C}}\text{-}\underset{\underset{Br}{|}}{\overset{\overset{H}{|}}{C}}\text{-}\overset{\overset{H}{|}}{C}{=}O \xrightarrow[2)H_2O]{} CH_3\text{-}\underset{\underset{Br}{|}}{\overset{\overset{H}{|}}{C}}\text{-}\overset{\overset{H}{|}}{C}\text{—}\overset{\overset{H}{|}}{C}\text{-}R$ (epoxide, O bridging)

[71]

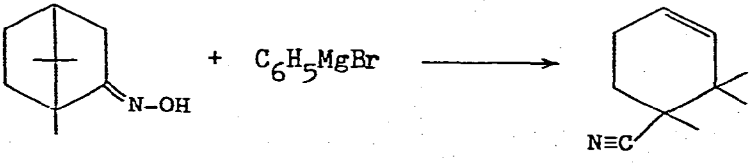
Thioketones

Reactions of thioketones with organomagnesium compounds have been referred to in Chapter 4B: [167], [168] and [169].

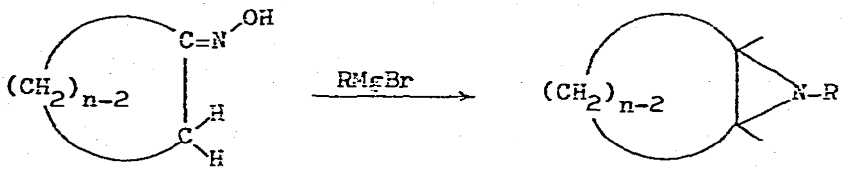
Carbonyl derivatives.

Oximes

Chaabouni and Laurent observed ringopening in the reaction of camphoroxime with phenylmagnesium bromide [248]:



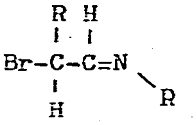
The same authors observed the following reaction with cyclohexanone oxime [249]



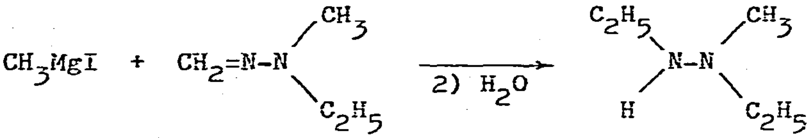
and with other cyclic oximes [250]. Toluene was used as the diluent is these cases.

Imines

The reactions with imines, as studied by Mauzé and Miginiac [140] and by Thomas [185] and [186] have been reported earlier, as were the reactions studied by Moreau and Gaudemar [68] and [145].

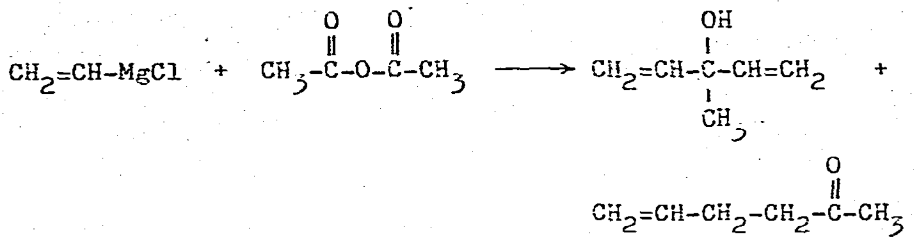
Another oxime studied was  $\mathrm{Br{-}\overset{R}{\underset{H}{C}}{-}\overset{H}{C}{=}N{-}R}$ [42]

Condon, Thakkar and Goldstein observed the following reaction which represents an addition to the C=N double bond [251]



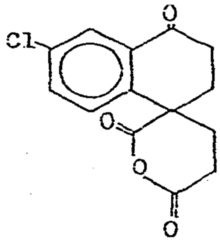
5B. Reactions with acids, esters, lactones, lactams, imines, etc.

Suga, Watanabe, Fujita and Takahashi continued their researches in the field of reactions of vinylmagnesium chloride with acids, anhydrides and their diesters [252]; one of the reactions reported is

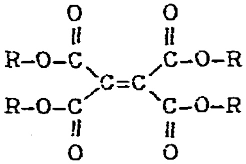


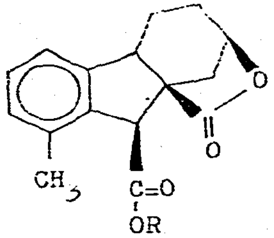
$$CH_2{=}CH{-}MgCl + CH_3{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \longrightarrow CH_2{=}CH{-}\underset{CH_3}{\overset{OH}{C}}{-}CH{=}CH_2 + CH_2{=}CH{-}CH_2{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}CH_3$$

Reactions of aromatic Grignard reagents with trifluoroacetic acid lead to the formation of substituted trifluoroacetophenone [43]. Furthermore reactions were reported with

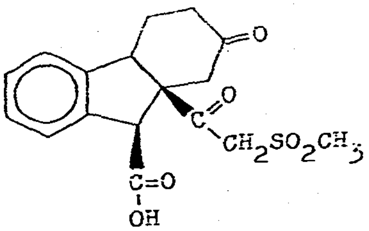


Fateen, Omran and Kaddah [253]





and



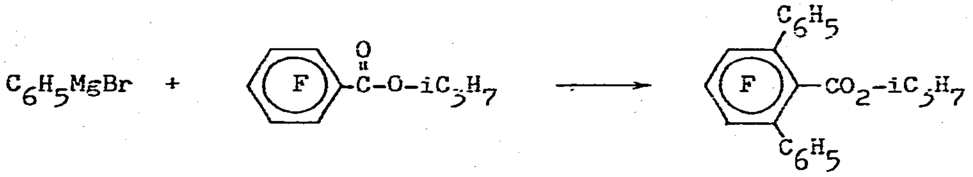
ref. [24]

Esters

CH_3MgI had no specificity in the cleavage of fatty acids in reactions with triglycerides and gave 1,2- and 1,3-diglycerides, 1- and

2- monoglycerides as well as tertiary alcohols (Franzke, Hollstein, Kroll and Noska [254]).

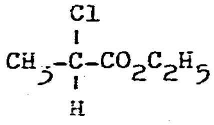
Gerasimova and Baturina got evidence that steric hindrance reduced the reaction of phenylmagnesium bromide with the carboxyl group of esters of pentafluorobenzoic acid, thus leading to substitution in the aromatic ring [255]:



In the reactions of branched alkylmagnesium halides with aliphatic esters in HMPA mainly the least sterically hindered enolates are formed which can be trapped by acylation (Huet, Emptoz and Jubier) [256].

Reactions with oxalic acid esters were investigated by Lapkin and Kashinskii [257] as well as by Karavanov who added cadmium chloride to obtain hydroxyesters [258].

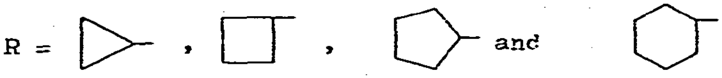
Reactions of alkylmagnesium halides with which was optically active yielded optically active carbinols (Vasi, Nanavati and Patel) [259].



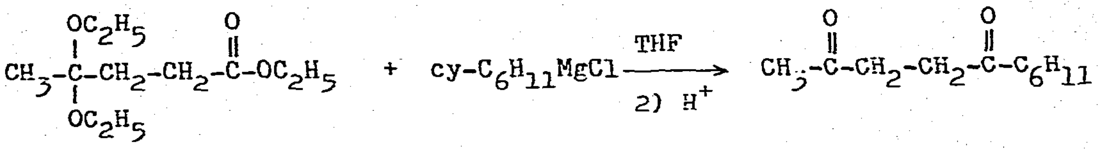
$$CH_3-\overset{\displaystyle Cl}{\underset{\displaystyle H}{C}}-CO_2C_2H_5$$

Ferwanah, Pressler and Reichardt obtained the "expected" ketals in 60-80% yields in the following reactions of orthoesters [260]:

$$R-CH_2-MgBr \quad + \quad CH(-OC_2H_5)_3 \longrightarrow R-CH_2-CH(-OC_2H_5)_2$$

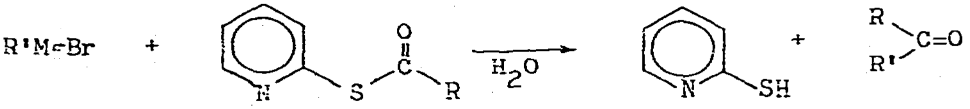


The following reaction was reported in a Japanese patent [261]:

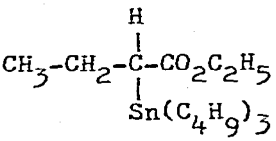


$$CH_3-\underset{OC_2H_5}{\overset{OC_2H_5}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 + cy-C_6H_{11}MgCl \xrightarrow[2)\ H^+]{THF} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_{11}$$

Mukaiyama, Araki and Takei obtained high yields of ketones by the following reactions of S-(2-pyridyl)thioates [262]:

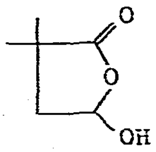


Odic and Pereyre studied reactions of the following tributyltin ester with Grignard reagents [263]; metal exchange reactions seem to take place.



$$CH_3-CH_2-\underset{Sn(C_4H_9)_3}{\overset{H}{C}}-CO_2C_2H_5$$

Des Abbayes, Neveu and Salmon-Legagneur studied reactions of Grignard reagents with the following acid derivatives [264]:



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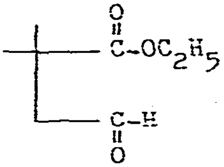

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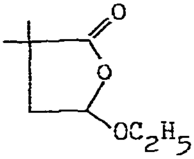

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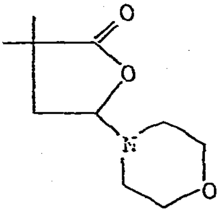
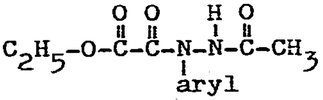
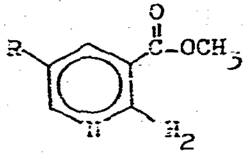


Normal addition to the carboxylate group under formation of tertiary carbinols was reported in the reactions of the following esters with arylmagnesium halides:

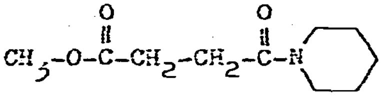


$$C_2H_5-O-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-\underset{aryl}{N}-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-CH_3$$

; Berdinskii and Nezhdanov [265]



; Konshin and Chesnokov [266]

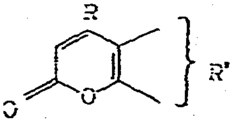


; Shklyaev and Kalugina [267]

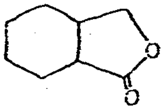
Lactones

Reactions with the following lactones have been published:

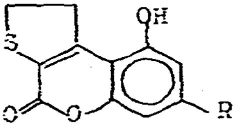
; Chiron and Graff [268]. Yields ring-opened products.



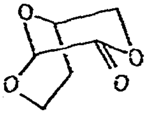
; French Patent [269].



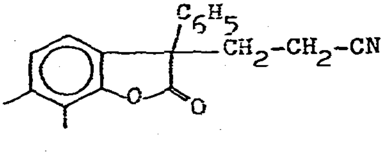
; Nanya, Tsunekawa, Suzuki and Maekawa [270].



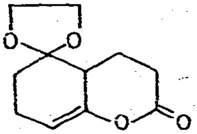
; German Patent [271]



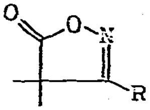
; Calinaud, Gélas and Thiallier [272]



; Ofenberg and Arventiev [273]

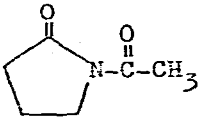


; French Patent [274]



; Petrus, Verducci and Vidal [275]

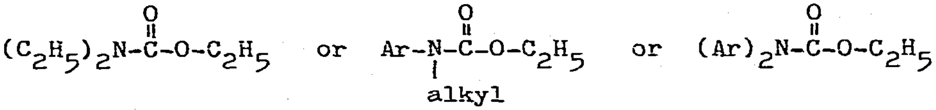
Amides



; Sugden and Chaughan [276]

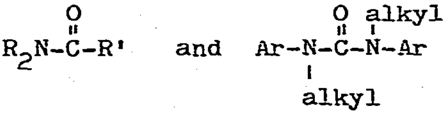
Dialkylformamide, $H-\overset{O}{\overset{\|}{C}}-N(-R)_2$ reacts with secondary Grignard reagents to form C=O addition products which on dehydration yield vinylic amines $\overset{R}{\underset{R}{>}}C=CH-N(-R)_2$; Hansson and Wickberg [277].

N-substituted carbaminic acid esters:



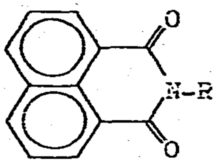
$$(C_2H_5)_2N-\overset{O}{\overset{\|}{C}}-O-C_2H_5 \quad \text{or} \quad Ar-\underset{\text{alkyl}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-O-C_2H_5 \quad \text{or} \quad (Ar)_2N-\overset{O}{\overset{\|}{C}}-O-C_2H_5$$

react with alkylmagnesium bromides to give the following types of products (Wiessel, Suchi, Michman and Patai) [278]:

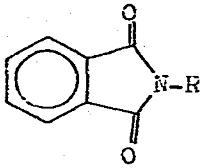


$$R_2N-\overset{O}{\overset{\|}{C}}-R' \quad \text{and} \quad Ar-\underset{\text{alkyl}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{\text{alkyl}}{\overset{|}{N}}-Ar$$

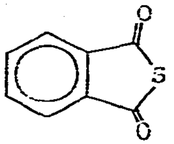
El-Garby Younes and Islam observed mono C=O addition in reactions of imides with Grignard compounds [279] and [280]



and



Omram and Harb finally studied reactions of Grignard reagents with thiophthalic anhydride [281]



5C. Reactions with unsaturated carbonyl compounds, ethers, amines and others

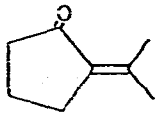
Unsaturated aldehydes, ketones and derivatives.

In Chapter 2D mention has been made of the reaction of "in situ" trimethylsilylmagnesium compounds with unsaturated ketones [114].

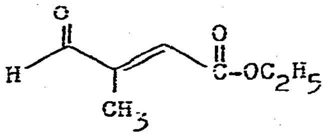
In Chapter 4B the radical character of the reaction of Grignard compounds with unsaturated diketones was discussed [165].

The reaction of unsaturated ketones with bromomagnesium enolates, prepared from ketones (see Chapter 2Biv) leads to the formation of δ-diketones [85] and [89].

The following reactions have been reported:

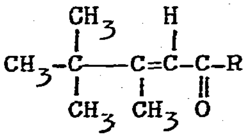


; Bernath, Gruber and Tomoskozi [282]

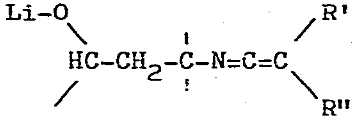


; German Patent [283]

R-CH=CH-CH=N-R' (R' is methyl, isopropyl or tert-butyl) [142]



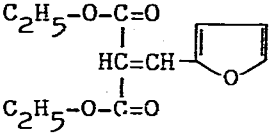
$CH_3-C(CH_3)_2-C(CH_3)=CH-C(=O)-R$ with aromatic Grignard reagents gives normal C=O addition reaction products according to Esafov, Vshivkov, Klepikova Ryzhanovskaya and Tsoi [284].



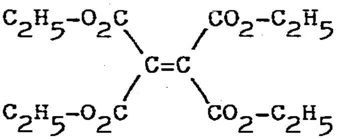
; A.I. Meyers, E.M. Smith and M.S. Ao [285].

Unsaturated esters

Reactions have been reported with the following unsaturated esters:

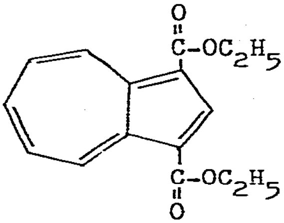


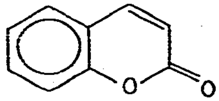
; Holmberg, Olli, Strand and Jalonen [286]; with tert-butylmagnesium chloride reduction, as well as 1,4-, 1,6- and 1,8-addition reaction products were obtained.



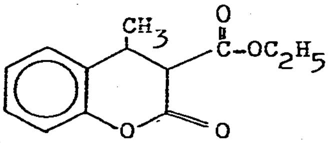
; House, Melillo and Sauter [24].

The stereochemical aspects of the reaction of Grignard reagents with the annulene derivative have been discussed in Chapter 4C [188].

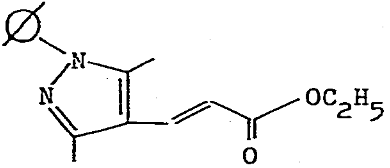




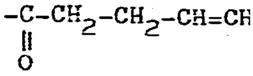
; Aboussali, Royer and Dreux [287]



; Holmberg, Malmström and Wennström [288]



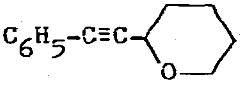
; Finar and Okoh [289]

Watanabe, Suga and Fujita studied the reaction of unsaturated este of different types with vinylmagnesium chloride [290]. Besides normal addition reaction products (leading to tertiary alcohols) the authors observed the formation of butenyl ketones 

$$-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-CH=CH$$

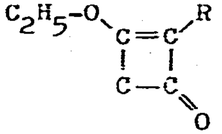
Unsaturated ethers.

The following unsaturated ethers were investigated in reactions wi Grignard reagents.

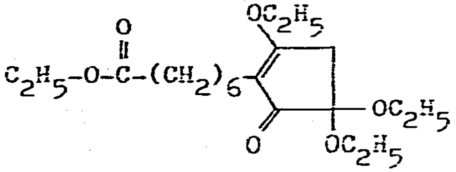


; Nelson and W.J. Miller [291]

$CH_2=CH-C\equiv C-S-R$ (R = methyl or ethyl) which, among other products, yield allenic thioethers (Radchenko and Cherkasov) [292].

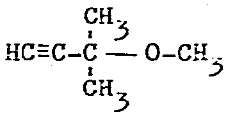


; Ficini, Claeys and Depezay [293]



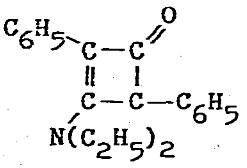
; Van Hulle, Sipido and Van de Walle [294].

The radical nature of the reaction of Grignard compounds with acetylenic ethers has been discussed in Chapter 4B [179].

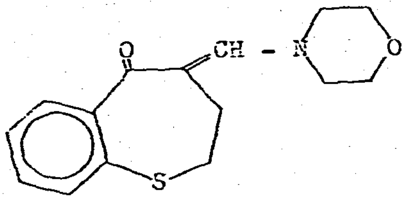


$$HC\equiv C-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-O-CH_3$$

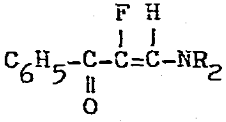
Enamines:



; Ficini, Claeys and Depezay [295].



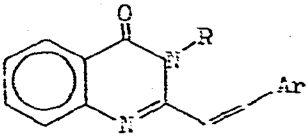
; Traynelis, Sih and Borgneas [296]



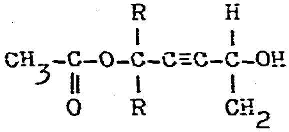
$C_6H_5-\underset{\underset{O}{\|}}{C}-\overset{\overset{F}{|}}{C}=\overset{\overset{H}{|}}{C}-NR_2$

; Elkik and Imbeaux-Oudotte [297]

Finally the following unsaturated compounds have been used:



; Messiha, Doss and Nosseir [298]



$CH_3-\underset{\underset{O}{\|}}{C}-O-\overset{\overset{R}{|}}{\underset{\underset{R}{|}}{C}}-C\equiv C-\overset{\overset{H}{|}}{\underset{\underset{CH_2}{|}}{C}}-OH$

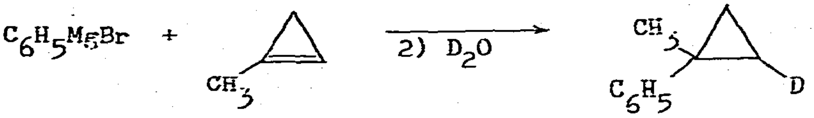
; Baudouy, Gore and Roumestant [299]

$R-CH=CH-NO_2$ reacts with carboranylmagnesium bromide to give C=C addition reaction products [95].

5D. Reactions with double bonds

Lehmkuhl and coworkers have published a series of papers on the reaction of benzylmagnesium chloride and of allylic Grignard reagents with double bonds [135], [136], [137] and [300]. The steric course of these reactions as well as the occurrence of equilibria between the different possible products have been discussed in Chapter 3C. Among the unsaturated systems, studied by the authors were alkenes, including ethene, and norbornene as well as phenylethene.

Nesmeyanova, Rudashevskaya and Kazanskii investigated the stereochemistry of the addition reaction of phenylmagnesium bromide with methylcyclopropene [301]:



Cis-addition appears to occur.

Allylmagnesium bromide gives facile addition to conjugated unsaturated systems such as

$$C_4H_9-CH{=}CH-C{\equiv}C-H$$

as reported by Bernadou, Mauzê and Mme Miginiac [302].

No intramolecular addition to the triple bond occured in

$$Cl-C{\equiv}C-CH_2-CH_2-CH_2-MgBr$$

as was already reported in Chapter 3C [80].

Likewise, Courtois and Mme Miginiac observed no dimerization of allylmagnesium bromide on heating during several hours [303].

Several reports have been published on addition to double and triple bonds, catalyzed by metal salts. These reactions will be summarized in Chapter 5L.

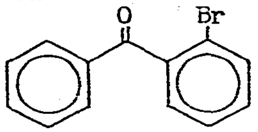
5E. Reactions with organic halides

The reaction of an organic halide with a Grignard reagent is of great importance in the Grignard reaction (reaction of R-X with Mg) itself. The influence of oxygen on the catalysts, present in the magnesium as impurities, has been discussed in Chapter 2 A [32].

The radical character of such reactions in the presence of impurities was discussed in Chapter 4B [172].

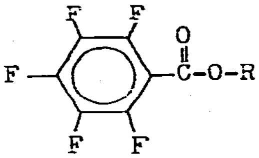
In the same chapter as well as in Chapter 4C a discussion was given of the mechanism of the reactions of Grignard reagents with CCl_4 or with $CHCl_3$ in the presence of cyclohexene [174].

Bickelhaupt and Jongsma observed substitution of the bromine atom in 2-bromobenzophenone



in reactions with methylmagnesium bromide [196].

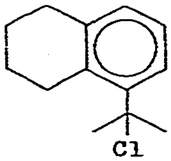
Mono- and disubstitution of fluorine in



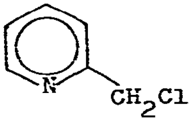
during reactions with phenylmagnesium bromide was reported by Gerasimova and Baturina [255].

Activated halides

Reactions with the following benzylic halides have been reported

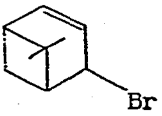


; Burnham, Duncan, Eisenbraun, Keen and Hamming [304]

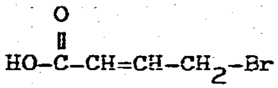


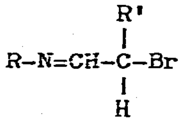
; Mitra, Kulkarni and Joshi [305]

Allylic halides, investigated were:



; Joulain, Moreau and Pfau [306]

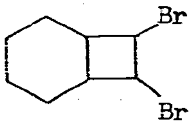

$HO-\overset{\overset{O}{\|}}{C}-CH=CH-CH_2-Br$;Heslinga, Pabon and Van Dorp [307]

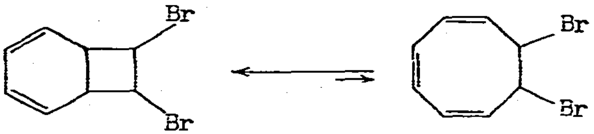

$R-N=CH-\overset{\overset{R'}{|}}{\underset{\underset{H}{|}}{C}}-Br$; Duhamel, Duhamel and Valno [42]

$C_6H_5-CH_2-CH=CH-CH_2-Cl$; USSR Patent [308]

No reaction was observed with the cyclobutyl dibromide 31 so in in the following equilibrium the reaction with Grignard reagents, which was observed by Straub, Rao and Mueller, proceeds via the biallylic cyclooctatriene dibromide although this compound could not be detected in the equilibrium by means of nmr-spectroscopy [309].

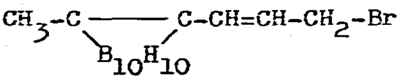
31





Other allylic and propargylic systems studied were:

$Cl-CH_2-CH=CH-CH_2-Cl$; Mesnard and Miginiac [310]

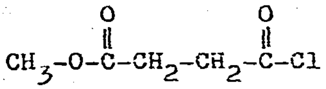

$CH_3-C\underset{B_{10}H_{10}}{\text{———}}C-CH=CH-CH_2-Br$; Zakharkin, Babich, Litovchenko and Ivanova [35]

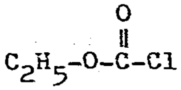
$H-C{\equiv}C-CH_2-Br$; Kurbanov, Dzhurakulov and Kuchkarov [60]

as well as Yamonaka and Ao and Tsuruta [55].

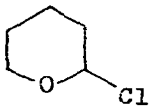
Acyl halides

$R-\underset{\overset{\|}{O}}{C}-Cl$ was studied in reactions with indolemagnesium halides as was discussed in Chapter 3C [138].


$CH_3-O-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\overset{\overset{O}{\|}}{C}-Cl$; Brunet, Paquer and Rioult [311]

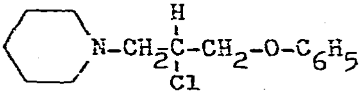

$C_2H_5-O-\overset{\overset{O}{\|}}{C}-Cl$. ; Uhle and Werner [92]

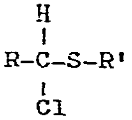
The following haloethers were studied:



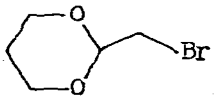
; Nelson and Miller [291]

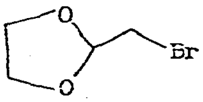
$R-O-CH_2Cl$; Volkov, Nikol'skaya, Levanova and Zarudneva [63] as well as Nikol'skaya, Volkov and Levanova [64].


$N-CH_2-\underset{Cl}{\overset{H}{C}}-CH_2-O-C_6H_5$; German Patent [312]

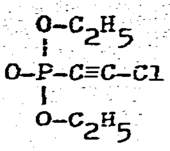

$R-\underset{Cl}{\overset{H}{C}}-S-R'$; Hurd, Moe and Starke [313]

No reaction was observed with the following β-bromo cyclic ketals as reported by Volkov, Skvortsov, Danda and Khudyakova [314]:



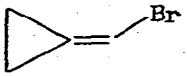


Unsaturated halides

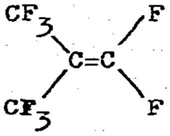


$$O\text{-}\overset{\overset{\displaystyle O\text{-}C_2H_5}{|}}{\underset{\underset{\displaystyle O\text{-}C_2H_5}{|}}{P}}\text{-}C\equiv C\text{-}Cl$$

; Ionin, Mashlyakovskii, Ignat'ev, Timofeeva, Mingaleva, Vorov'ev and Petrov, [315].



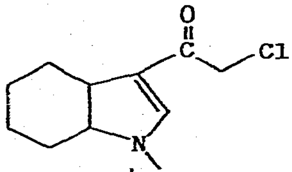
; Heyd and Hanack [316]



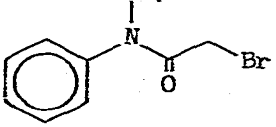
; US Patent [317]

Halocarbonyl compounds

The in situ reaction of trimethylchlorosilane/Mg/HMPA with choroaldehydes has been mentioned in Chapter 2D [116]

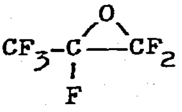


; Bergmann and Bäckrell [246]

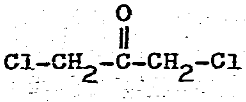


; Mori, Nishimura and Ban [318]

Finally mention has to be made of the reactions with the following compounds



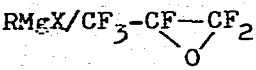
; Watts, Allison, Barthold and Tarrant [319]

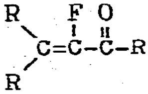


$$Cl\text{-}CH_2\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_2\text{-}Cl$$

; C.R. Johnson and Herr [247].

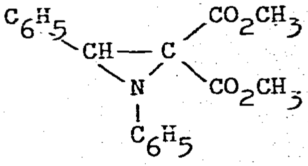
5F. Reactions with oxiranes, oxetanes and azirines

The ratio  $RMgX/CF_3-CF-CF_2$ (with O bridging CF and CF$_2$) strongly influences the product formation

With excess Grignard reagent  $R_2C=CF-C(=O)-R$ is formed [319].

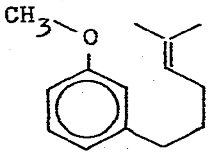
Delmond and Pommier studied the reaction of tributyltinmagnesium halide with oxetane [36].

Vaultier, Danion-Bougot, Danion, Hamelin and Carrier studied the reaction of the azirine [320]:

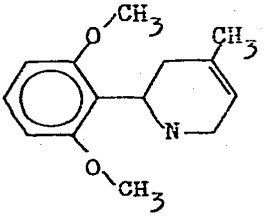


5G. Reactions with ethers, acetals, orthoesters and aminoethers

Heating a solvent-free mixture of methylmagnesium iodide and a phenol ether for several hours at 150-165°, followed by hydrolysis leads to the formation of the phenols:



; Moreau and Rouessac [321]

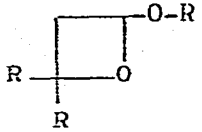


; Razdan, Pars, Zitko, Kane and Thompson [322]

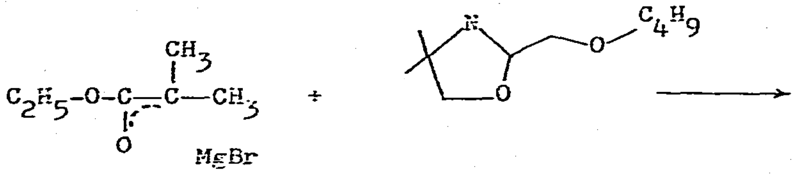
In his review paper on nmr-spectroscopy of organomagnesium compounds Maercker mentions some reactions with ethereal solvents [7].

Furthermore the following reactions were reported

CH_3MgJ or C_6H_5MgBr +



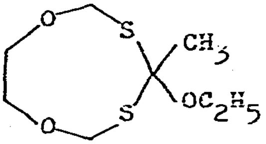
⟶ US Patent [323]



$C_2H_5{-}O{-}C(=O){-}C(CH_3)(MgBr){-}CH_3$ + ⟶

ref. [8

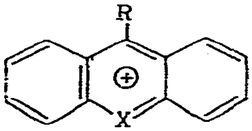
and reactions with



; Abdullaev, Maisa and Alizade [324]

5H. Reactions with heterocyclic compounds

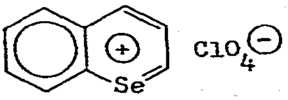
The radical character of reactions of 9-substituted xanthylium, selenoxanthylium and thioxanthylium salts



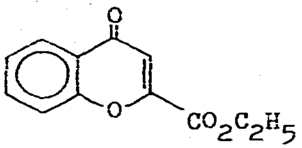
X = O , S or Se

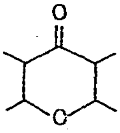
with Grignard reagents has been discussed in Chapter 4B [176], [177] and [178]

Tadino, Christiaens and Renson studied the reaction of phenylmagnesium bromide with the selena homologue of benzopyrilium perchlorate [325].

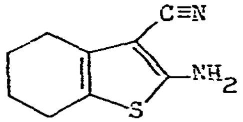


Reactions of chromone and thiopyrone as well as pyrone derivatives with Grignard compounds were reported earlier (Chapter 4C; ref. [197]; Chapter 5A; ref. [232]):

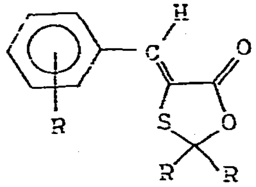




Furthermore the following sulfur-containing heterocyclic compounds were used in reactions with organomagnesium compounds:



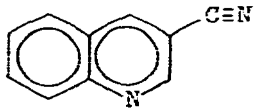
; Heckendorn and Gagneux [326]

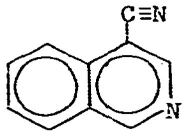


; Harhash, Elnagdi and Abdallah [327]

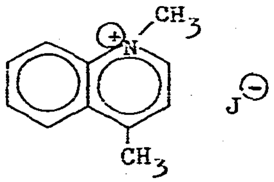
Nitrogen-containing heterocycles

Mononitrogen





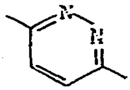
; Matsumori, Ide and Watanabe [328]



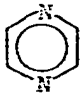
; Surana, Kishore and Joshi [329]

Dinitrogen

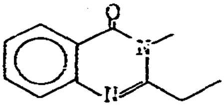
Crossland studied the stereochemical course of the protonation of addition products, formed between Grignard reagents and pyridazines [330] and [331]



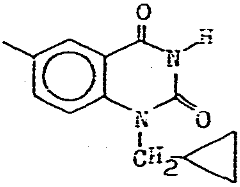
Tas and Kleipool observed substitution of pyrazine on reaction with allylmagnesium chloride [332]



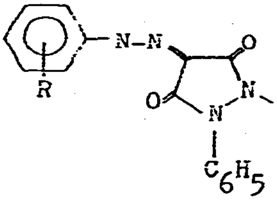
Sammour, Selim, Elkasaby and Abdalla described reactions of Grignard reagents with quinazolone [333]



Yamamoto, Ishizumi, Mori, Inaba and Yamamoto studied reactions of Grignard reagents with quinazolinedione derivatives [334]

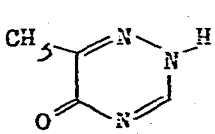


Elnagdi, Shawali and Elokbi reacted the following diazacyclopentanedione with phenylmagnesium bromide [335]

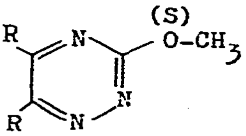


Trinitrogen

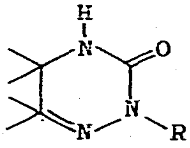
Daunis, Jacquier and Pigière reacted Grignard reagents with the following triazine derivatives:



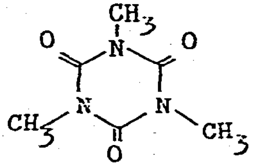
ref. [336]



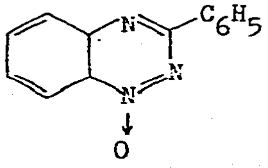
ref. [337]



ref. [338]



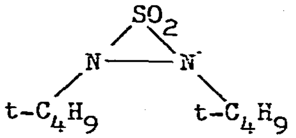
; Etienne, Lonchamboux, Giraudeau and Durand [339]



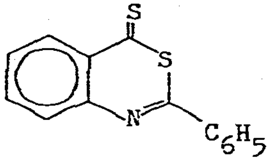
; Igeta, Nakai and Tsuchiya [340]

Mixed heterocyclic compounds

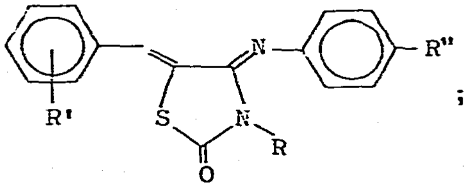
Sulfur-nitrogen



; Timberlake, Hodges and Garner [341]

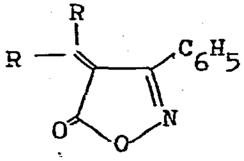


; Sammour, Selim, Fahmy and Elewa [342]

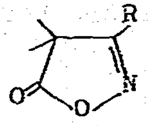


; Kassab, Elnagdi and Hamed [343]

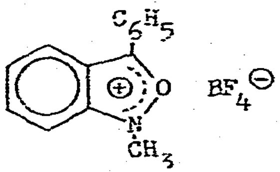
Nitrogen-oxygen mixed heterocycles



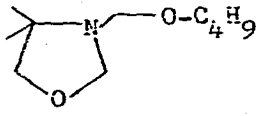
Harhash, Elnagdi, Hussein and Fahmy [344]



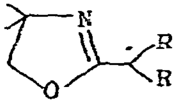
; Petrus, Verducci and Vidal [275]



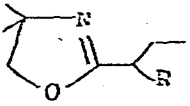
; Nakagawa, Aki and Yamamoto [345]



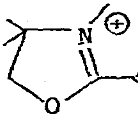
; P.Y. Johnson and Davis [84]



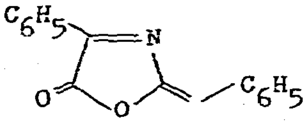
; Lion and Dubois [139]



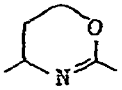
; Lion and Dubois [346]



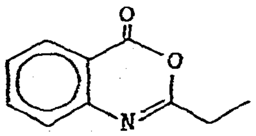
; Lion and Dubois [347]



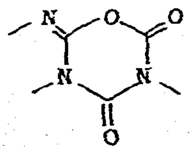
; Adembri, Scotton, Speroni and Tedeschi [348]



; Meyers and coworkers [97]



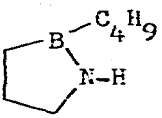
; Sammour and coworkers [333]



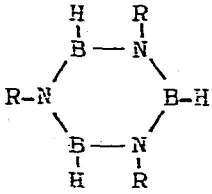
; Etienne and coworkers [339]

5I Reactions with Boron, Nitrogen, Silicon, Phosphorus, Germanium, Sulfur, Arsenic and Antimony compounds

Boron compounds



; Dorokhov, Boldyreva and Mikhailov [349]



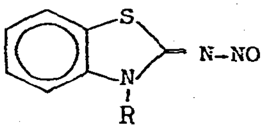
; Powell [350]

Nitrogen derivatives

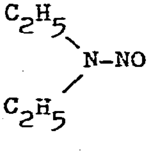
The mechanism of the reaction of n-butylmagnesium bromide with nitromethane was discussed in chapter 4C [187].

The radical character of the reaction of Grignard reagents with para-chlorophenyl diazonium tetrafluoroborate was discussed in chapter 4B [175].

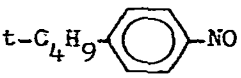
Reactions have been reported with the following nitroso compounds:



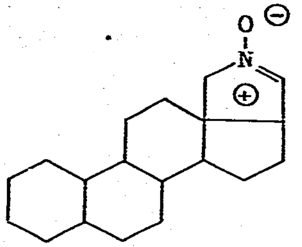
; Akiba, Kawamura, Hisaoka and Inamoto [351]



; Michejda and Schluenz [352]



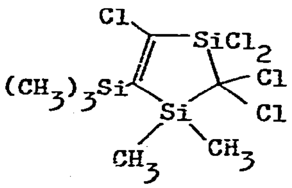
; Brittish Patent [353]

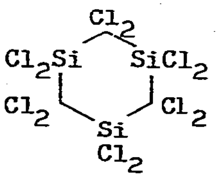


; Alazard and Lusinchi [354]

Silicon derivatives

Fritz, together with Boettinger, Braunagel and Danappel and Matern studied the reactions of di- and trisilacycloalkanes with methylmagnesium chloride [355], [356] and [357]:

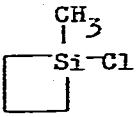




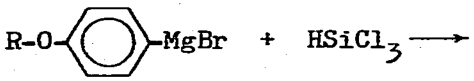
The stereochemical aspects of the reactions of Grignard compounds with silicon compounds have been mentioned in Chapter 4C (ref. [189 [190], [191] and [192]) as well as in Chapter 5Introd. (ref. 204] and [208]).

The formation of unexpected products in the reaction of magnesium with stanna-silanes has been mentioned in Chapter 2A [38].

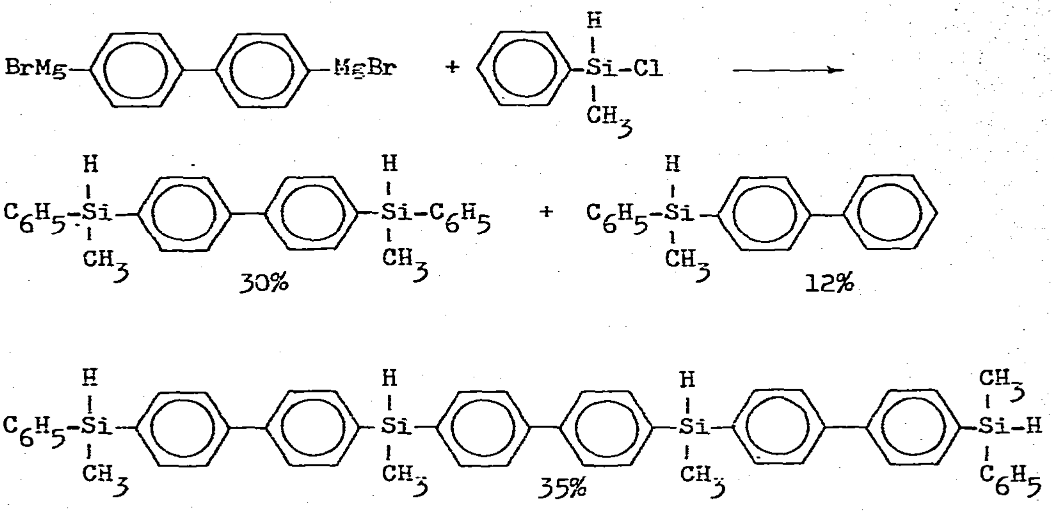
Reactions of Grignard reagents with chlorosilanes of different types have been reported by several groups:



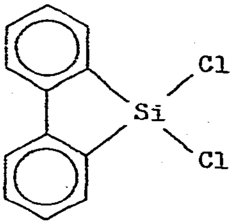
; Nametkin, Vdovin, Poletaev and Ushakov [358].



; Lapkin, Mukhina, Kirillov and Sigova [359]



Gverdtsiteli, Doksopulo and Tabidze [360]

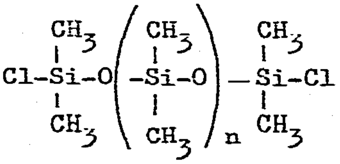


Gverdtsiteli, Chernyshev and Ediberidze [59]

The mechanism of reaction of sila-Grignard reagents with chlorosilanes has been discussed in Chapter 4C [94].

Reactions of acetylenic Grignard reagents with $(CH_3)_3Si-Cl$ and $(CH_3)_3SiF$ have been reported by Florensova and coworkers [70].

Andreev, Streyugina and Levdik reported reactions of aromatic Grignard reagents with chlorosiloxanes [46]

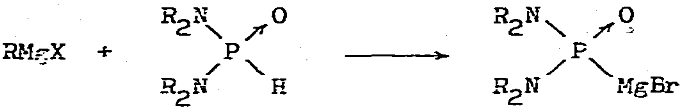


$$\mathrm{Cl{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}O\left(\overset{CH_3}{\underset{CH_3}{-Si-O}}\right)_n{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}Cl}$$

Reaction of phenylmagnesium bromide with phenyltrichlorosilane and other trichlorosilanes, followed by reaction with dimethyldichlorosilane leads to the formation of silicone resins as reported in a German patent [361].

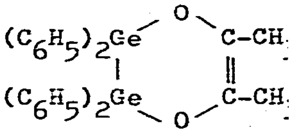
Phosphorus compounds

$(C_6H_5)_{3-n}PCl_n$ was reacted with aromatic Grignard reagents to give the expected phosphorus-containing coupling product [54]. The same type of product was formed in the reaction with $(C_2H_5-O)_2P-Cl$ [83] Nifant'ev and Shilov obtained bromomagnesium tetraalkylphosphorodiamidites by the following reaction [362]:



Trimethylsilylphosphine derivatives were prepared by the reaction of the trimethylsilylmagnesium compound (see Chapter 2Biv !) with chlorophosphorus derivatives such as PCl_3, tert-$C_4H_9PCl_2$ and (tert-$C_4H_9)_2PCl$ [91].

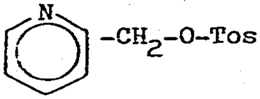
The reaction of dioxadigermacyclohexene with methylmagnesium iodide causes the formation of tetraphenyldimethyldigermane [363].



Sulfur derivatives

Meijer, Vermeer and Brandsma [364] as well as Winther and Senning reported reactions of Grignard reagents with CS_2 [365].

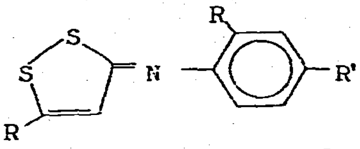
The formation of an asymmetric sulfoxide by the reaction of menthyl (-)(S)-p-toluenesulfinate has been reported in Chapter 5Introd. [205]. The formation of sulfonyl-substituted Grignard reagents by reaction of organomagnesium compounds with sulfones has been mentioned in Chapter 2Biv [99] and [100].



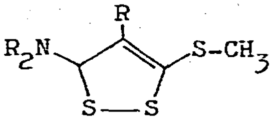
has been applied in reaction with phenylmagnesium bromide [305]

$C_6H_5-S-S-C_6H_5$ was used in reactions with fifteen different Grignard reagents to prepare C_6H_5-S-R [366].

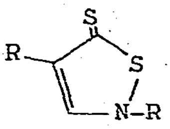
Boberg and Gentzkow used the following sulfur derivatives in reactions with Grignard reagents:



ref. [367]



ref. [368]



ref. [369]

Finally the following arsenic and antimony compounds were used in reactions with Grignard reagents:

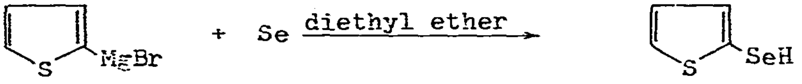
$FAs(C_2F_5)_2$, by Kopaevich, Belen'kii, Mysov, German and Knunyants
[370]

$(C_4H_9)_3SbBr_2$, by Nesmeyanov, Borisov, Norikova, Fedin and Petrovskii [371]

5J Reactions with oxygen, peroxides and selenium

Ol'dekop and Livshits prepared isopropyl and sec-butyl hydroperoxide with 96-97% purity by reaction of the corresponding Grignard reagent with oxygen in diethyl ether at -75^{0}. The yields were between 60 and 80% [372].

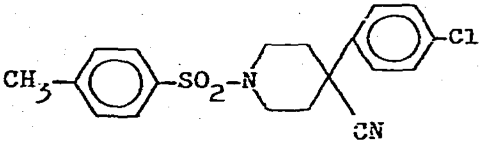
Sindelar, Svatek and Protiva prepared thiopheneselenol as follows [373]:



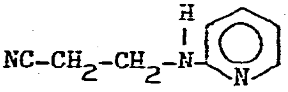
As already mentioned in Chapter 4C the kinetics of the autoxidation of $C_6H_5-Mg-O-t-C_4H_9$ were studied at different temperatures [201]. In Chapter 4B mention was made of investigations on reactions of Grignard reagents with photochemically generated tert-butoxy radicals [181].

5K Reactions with nitriles

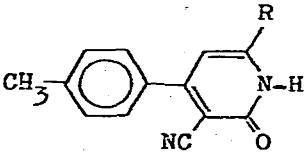
Reactions of Grignard reagents with nitriles, leading to the formation of the usual ketones were reported :



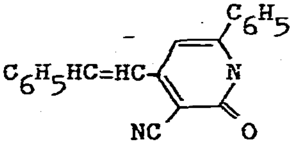
; Rylski, Gajewski and Dabrowska [374]



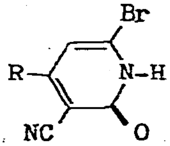
; Reynaud, Mandereau and Nguyen Tri-Xuong [375]



; Sammour, Fahmy, Abd El-Rahman, Khnookh and Abd Elmoez [376]



; Sammour, Raouf, Elkasaby and Hassan [377]

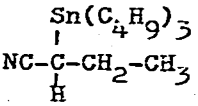


; Jahine, Sayed, Zaher and Sherif [37

In a number of reports abnormal reactions of Grignard reagents with nitriles were given:

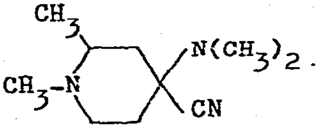
The formation of amines when Grignard reagents were applied at highe temperatures by using toluene as a diluent, has been discussed in Chapter 4C [184].

Odic and Peryre found alkylation products in reactions of methylmagnesium halides and methyl iodide with the following tributyltin-substituted nitrile [263]

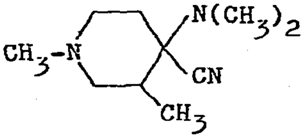


$$NC-\underset{H}{\overset{Sn(C_4H_9)_3}{C}}-CH_2-CH_3$$

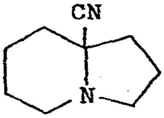
Displacement of the nitrile group by the alkyl group from the Grignard reagent was found as the main reaction of the following nitriles:



; Matyukhin, Malina and Unkovskii [379]



; Unkovskii, Matyukhin, Malina and Urinovich [380]



; Reinecke and Daubert (see Annual Survey 1972; ref. [278]) [381]

51. Reactions with or in the presence of metal salts

a. Preparation of organometallic compounds

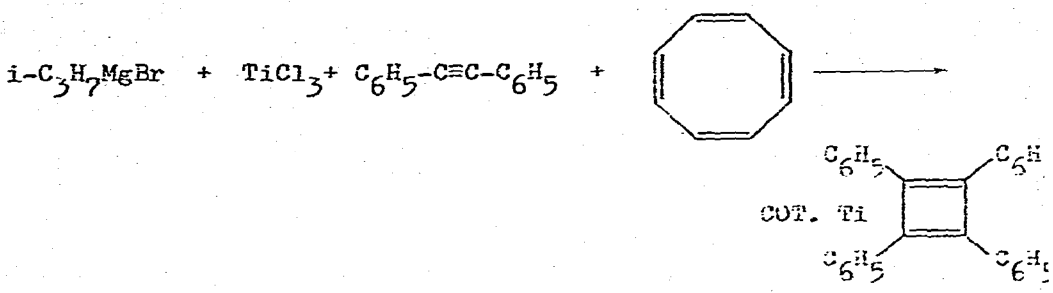
Reactions of organomagnesium compounds with metal salts, mainly the halides, in order to produce organometallic compounds, have been reported with a large number of metals.

$BeCl_2$ or $BeCl_2$.etherate were used to prepare R_2Be with R = alkyl, as studied by Carley, Lowrance and Maughan [382].

Neopentylmagnesium halide reacts with $TiCl_4$ to yield tetraneopentyltitanium. Mowat and Wilkinson [383].

With (cyclopentadienyl)$_2$TiCl$_2$ R-Mg-X (containing silicon or germanium) reacts to form (cyclopentadienyl)$_2$TiR$_2$. Collier, Lappert and Pearce [384].

Van Oven reported the following reaction [385]:



Vanadium tetrachloride, VCl_4, was reacted by Razuvaev, Latyeava, Lineava and Drobotenko [386] as well as by Latyeava, Lineava and Drobotenko [387] with benzylmagnesium chloride under different reaction conditions to obtain, among other products $(benzyl)_4V$.

Mays and Sears reacted methylmagnesium iodide with

$C_5H_5Fe[(C_6H_5)_2P$-CH_2-CH_2-$P(C_6H_5)_2]Cl$ ref. [388]

$GeCl_4$ was used by Kuznetsov, Podzolko, Kovalev and Buslaev [389].

Koblitz and Wilke prepared $(COT)_2ZrR_2$ from the corresponding dichloro compound [390].

Tetraneopentylzirconium was prepared in the same way as the corresponding titanium compound, mentioned above [383].

The same authors investigated niobium salts in their reactions with trimethylsilylmethylmagnesium halides [383].

Furthermore tris(triphenylphosphinyl)rhodium chloride was investigated in reactions with the same organomagnesium halide [37].

In an US patent the preparation of bis(6-methoxynaphthyl)cadmium is claimed [391].

A large number of tin compounds have been reported:

Gielen, DePoorter, Sciot and Topart prepared racemic methylbutylisopropylcyclohexyltin in a series of reactions, starting from tributyltin chloride [392].

Furthermore Gielen, DePoorter, Liberton and Poelinck used different unsaturated, alkyl and aryl Grignard reagents in reactions with R_3SnCl [393].

Seyferth and coworkers used several α-haloorganomagnesium compounds in reactions with trimethyltin chloride [47] and [48].

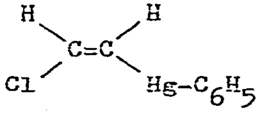
$(C_5H_5)Fe[(C_6H_5)_2P\text{-}CH_2\text{-}CH_2\text{-}P(C_6H_5)_2]SnCl_3$ was used in reaction with methylmagnesium iodide [388].

$(cyC_6H_{11})_3SnCl$ was prepared from $SnCl_4$ and the corrresponding Grignard reagent in toluene as the cosolvent [394].

Also the preparation of hafnium derivatives [384] and tantalium derivatives [385] has been reported.

Tamaki and Kochi prepared methylgold(I) complexes with different ligands [395].

Phenylmagnesium bromide reacts with cis ClCH=CHHgCl to form the corresponding chlorovinylphenylmercury derivative [396]: Nesmeyanov, Prokof'ev, Erdyneev, Borisov and Okhlobystin :



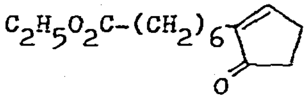
Highly pure mixed tetraalkylleads were prepared by Clinton, Gardner and Kochi in reactions of alkylmagnesium halides with leadacetate [397].

Brandi, Brunelli, Lugli and Mazzei, finally, prepared benzyluranium derivatives by reaction of the corresponding uranium chloride [398].

b. Metal salts as catalysts in reactions of organomagnesium compounds

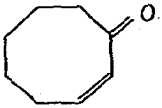
Conjugate addition of organomagnesium compounds to unsaturated carbonyl derivatives was reported by several groups:

For the synthesis of prostaglandines and congeners Schaub and Weiss used tributylphosphine-Cu(I) iodide in the reaction of the appropriate Grignard compound with the following unsaturated cyclic ketone [399].



In another publication Bernady and Weiss used the same catalyst in a similar synthesis [61].

For 1,4-addition of simple alkylmagnesium halides to cyclooctenone Damiano and Diara applied catalysis by copper(I) chloride [400].



Organomagnesium cuprates, having one or more β-hydrogen atoms show no reductive power towards 4-methyl-1-cyclohexenone contrary to the corresponding Grignard reagents. Mainly 1,4-addition was observed (Jallabert and Spassky) [401].

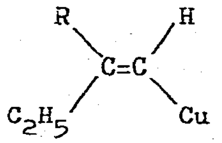
In the same sense Mme Rivière and Tang used organomagnesium cuprates for the investigation of 1,4-addition reactions to unsaturated ketones [402].

Bolt and Zeelen obtained 1,4-addition reaction products with methylmagnesium iodide and 5α-1-estren-3-one, catalyzed by copper(I) bromide, in 82% yield. [403]

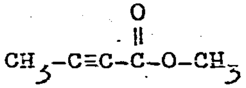
Gocmen and Soussan studied conjugate addition reactions of magnesium compounds mixed with cadmium salts [404].

Addition to and reaction with double and triple carbon-carbon bonds were reported in the following publications:

Ethylmagnesium bromo cuprates, $C_2H_5CuMgBr_2$, react with 1-alkynes to form cis-addition products: Normant, Cahiez, Chuit and Villiéras [405]:



In an US patent the addition to the triple bond in the following acetylenic ester was reported [406]

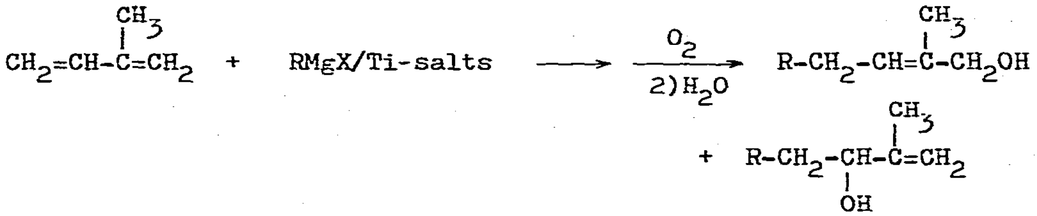


$CH_3-C\equiv C-\overset{O}{\overset{\|}{C}}-O-CH_3$

Addition of arylmagnesium bromides to alkynes, catalyzed by triphenylphosphinenickel(II) chloride was reported by Duboudin and Jousseaume [407]. In several of these reactions the stereospecificity was very high.

The reduction of vinylsilicon derivatives by alkylmagnesium halides in the presence of nickel(II) catalysts has been discussed in Chapter 4C [191].

A Japanese patent mentions the use of mixed titanium chlorides as catalysts in reactions of Grignard compounds with isoprene, followed by air-oxidation, leading to the formation of allylic alcohols [408]:



$$CH_2{=}CH-\overset{CH_3}{\overset{|}{C}}{=}CH_2 \; + \; RMgX/Ti\text{-salts} \longrightarrow \xrightarrow[2)H_2O]{O_2} R-CH_2-CH{=}\overset{CH_3}{\overset{|}{C}}-CH_2OH \; + \; R-CH_2-\underset{OH}{\underset{|}{CH}}-\overset{CH_3}{\overset{|}{C}}{=}CH_2$$

Disproportionation of 1- and 2-pentene by alkylmagnesium halides and tungsten(VI) chloride as the catalyst in benzene/isooctane as the solvent at 25° was reported by Mar'in, Sheboldová, Bol'shinkova, Khidekel and Kalechits [409]. Maximal yields of propene and 1- and 2-butene were obtained with a Mg/W ratio of 70:1.

A considerable number of reports on the metal salt catalyzed reaction of organomagnesium halides with organic halides have appeared in 1973:

The investigation of the mechanism of the iron catalyzed reaction of isopropylmagnesium halides with deuterated isopropyl bromide has been mentioned and discussed in Chapter 4B [172].

The isomerization accompanying the nickel-catalyzed cross-coupling of sec-alkyl Grignard reagents with organic halides was discussed in Chapter 3C [134].

The stereospecific cross-coupling reaction of secondary, racemic, Grignard reagents with unsaturated halides, catalyzed with a chiral nickel complex was mentioned in Chapter 5 Introd. [203]

Kershenbaum, Makovetskii and Dolgoplosk studied the reaction of ethylmagnesium bromide, treated with nickel(II) or cobalt(II) chlorides, with ethyl bromide [410]. Ethane and ethene were formed in equimolecular amounts as well as some butane. Zerovalent Co and Ni complexes are supposed to be formed.

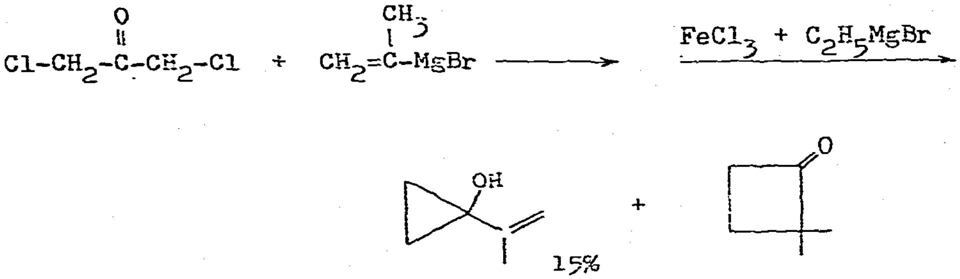
Tamao, Zembayashi, Kiso and Kumada observed stereospecificity in the reaction of Grignard reagents with monohalo olefins, catalyzed by nickel(II) complexes [193]. On the other hand, reactions with 1,2-dihalo olefins proceed non-stereospecifically! In a Japanese patent the same authors claim the preparation of styrene and stilbenes by reaction of the required reagents, catalyzed by dichloro-[1,2-bis(diphenylphosphino)ethane]nickel [411].

The reduction, coupling and isomerization reaction of Grignard reagents with allyl halides in the presence of iron, cobalt, nickel or cuprous salts has been discussed in Chapter 4C [194].

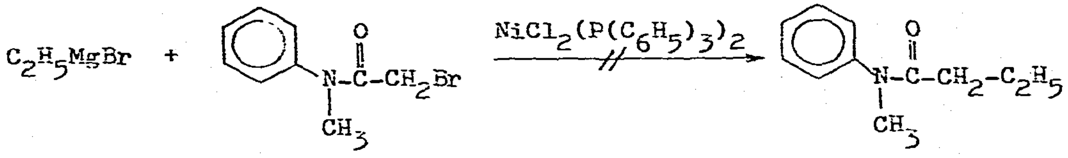
Levy reports the formation of polychlorobiphenyls by reaction of pentachlorophenylmagnesium chloride with chlorophenyl iodides, catalyzed by copper(I) iodide [412].

Thorsett and Stermitz investigated the effect of the ligand in the nickel(II) complex used as the catalyst in the coupling reaction of chloroquinolines and isoquinolines with several types of Grignard reagents. Depending on the catalyst couplingor reduction of Cl could take place. Also preferential coupling sites were observed with polychloro quinolines [413].

The following reaction with iron catalysts was reported [247]:



Mori, Nishimura and Ban did not observe the formation of the cross-coupling product in the following reaction but instead obtained a mixture of several products [318]:



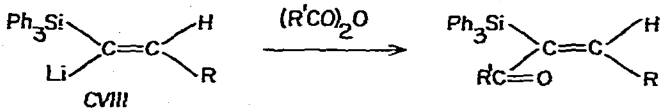
Luong Thi, Mme Rivière and Spassky studied the reaction of alkyl magnesium cuprates with acid chlorides of α-chloro acids [414].

Miscellaneous reactions of Grignard reagents, catalyzed by metal salts.

In Chapter 4C mention has been made of a number of investigations by Corriu and his group on the nickel catalyzed reactions of organomagnesium halides with Si-derivatives [192] and [190]. See also Chapter 5I.

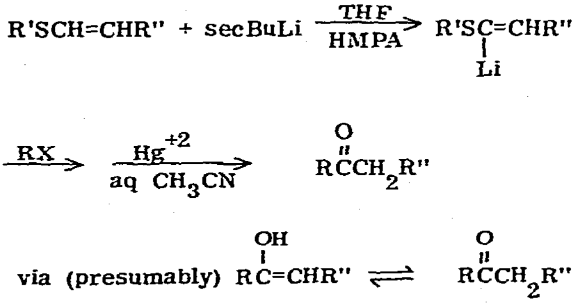
Cadmium chloride was used by Karavanov to modify the reactivity of alkylmagnesium halides towards oxalic acid ester [415] [239].

A new route to α,β-unsaturated ketones having a silyl group attached to the carbon-carbon double bond has been developed [168]. α-Lithiovinyltriphenylsilane (CVIIIa, R = H) and 1-lithio-1-triphenylsilyl-2-phenylethylene-E (CVIIIb, R = Ph) coupled with both acetic (R' = Me) and benzoyl (R' = Ph) anhydrides to provide the corresponding acyl derivatives.



CVIII

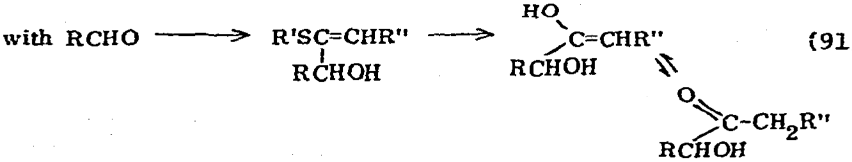
A vinyllithium reagent has been developed which, after alkylation and hydrolysis, afforded good yields of ketones (equation 90) [169]. Treatment of the 1-(alkylthio)vinyllithium intermediate with aldehydes (equation 91) and epoxides (equation 92) similarly gave good yields of the respective acyloins and α,β-unsaturated ketones.



$$R'SCH{=}CHR'' + secBuLi \xrightarrow[HMPA]{THF} R'S\underset{\underset{Li}{|}}{C}{=}CHR'' \qquad (90)$$

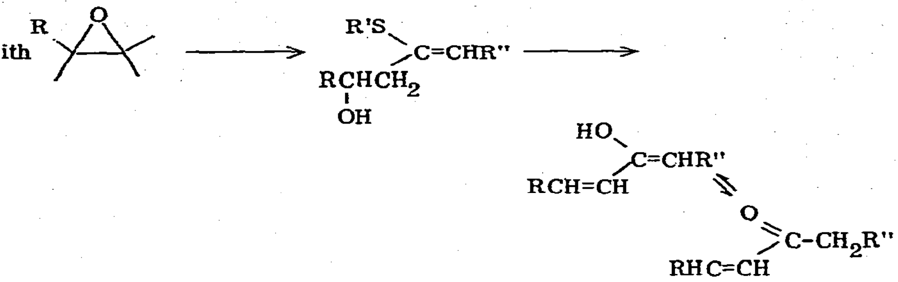
$$\xrightarrow{RX} \xrightarrow[aq\ CH_3CN]{Hg^{+2}} R\overset{\overset{O}{\|}}{C}CH_2R''$$

$$\text{via (presumably) } R\overset{\overset{OH}{|}}{C}{=}CHR'' \rightleftharpoons R\overset{\overset{O}{\|}}{C}CH_2R''$$



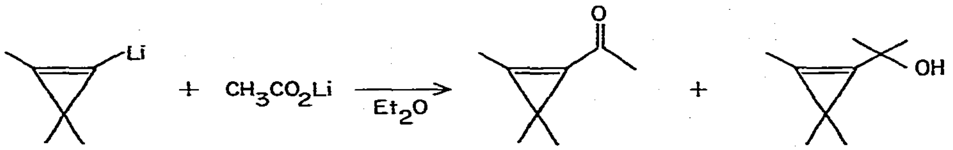
(91)

Nearly quantitative and instantaneous formation of the appropriate 1-metallocyclopropene upon addition of at least one equivalent of alkali amide (M = Li, Na, K) in liquid ammonia has been reported [170]. Mono- and dialkylated cyclowith



(92)

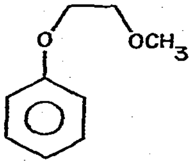
propenes were formed upon alkylation. Standing for 18 hours or much longer produced dimers and trimers of cyclopropene. Among the methods attempted for the preparation of 1-acylcyclopropenes was the alkylation of lithium acetate by the cyclopropenyl lithium intermediate CIX which produced the desired acyl compound CX and the corresponding alcohol (CXI) in a product ratio of 2:1 [171]. When lithio intermediate CIX was treated with dimethylacetamide, a small amount of the alcohol CXI was produced along with the major product, 3,3-dimethyl-2,5-hexanedione.



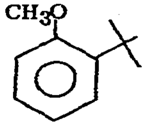
CIX CX CXI

An approximately 14-fold greater extent of lithiation of 1-methoxy-2-phenoxyethane (CXII) over anisole was observed upon competitive metalation in hexane or ether [172]. It was concluded that complexation was a factor in such metalations.

o-tert-Butylanisole (CXIII) has been found to undergo directed metalation at the remaining ortho position to the extent of 7.5% under conditions that gave a 65% yield of ortho metalation in anisole [173]. With TMEDA present a 30% yield of metalation as determined by isolation of the trimethylsilyl derivative was obtained. These results indicated steric interference with the conformation(s) necessary for co-ordination with n-butyllithium in the transition state.

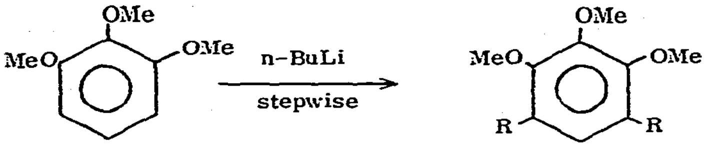


CXII



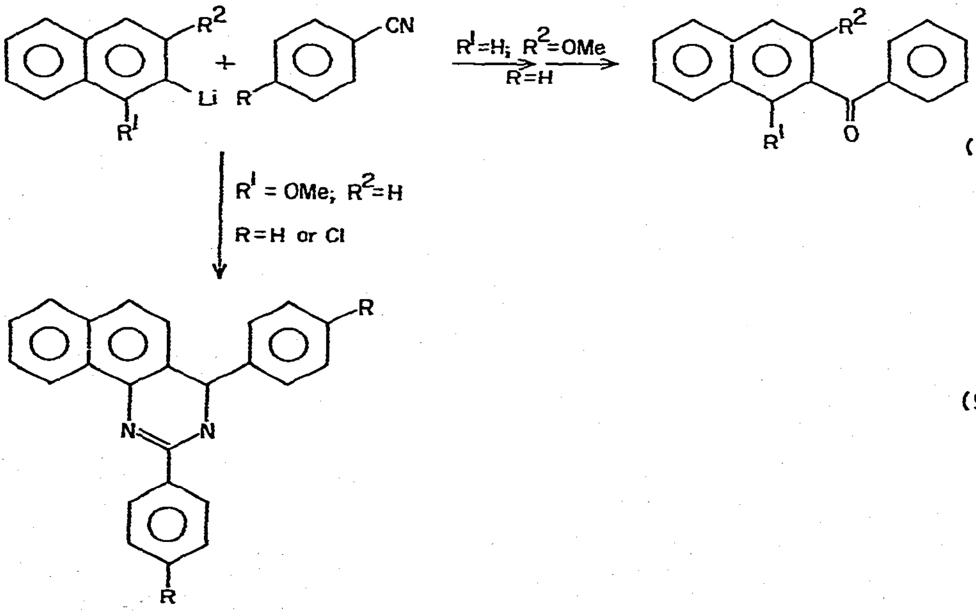
CXIII

Pyrogallol trimethylether has been stepwise metalated and alkylated at the positions ortho to the two methoxy groups (equation 93) [174].



(93)

A novel synthesis of 2,4-diarylbenzo[h]quinazolines beginning with the directed metalation of 1-methoxynaphthalene has been reported (equation 94) [175]. Similar metalation of 2-methoxynaphthalene led only to the benzoylation product (equation 95).

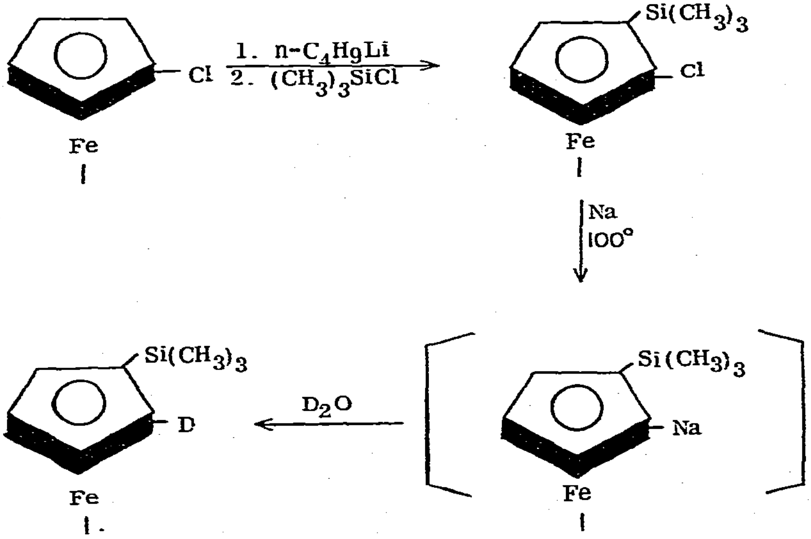


(95)

(94)

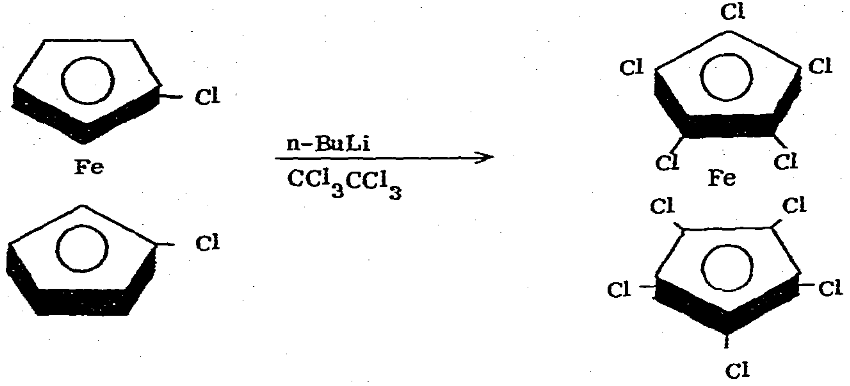
Lithium diisopropylamide metalated the side-chain in N,N-diisopropyl- and N,N-diethyl-o-, m- and p-toluamides [176]. With n-butyllithium, N,N-diethyl-o-toluamide also underwent side-chain metalation, but the m- and p-isomers provided mainly addition to the carbonyl. Lithiation of 1,3-bis(trifluoromethyl)benzene with n-butyllithium occurred at both the 2- and 4-positions while similar metalation of the 1,4-isomer occurred at the 2-position [177]. Sites of metalation were determined by carbonation and subsequent examination of the products by 100 and 220 MHz pmr.

Directed lithiation of chloroferrocene has allowed preparation of the 2-trimethylsilyl derivative [178]. Conversion of the specifically substituted molecule to 2-deuteriotrimethylsilylferrocene (CXIV) has resulted in the identification of the chemical shifts of the 2,5- and 3,4-position protons.



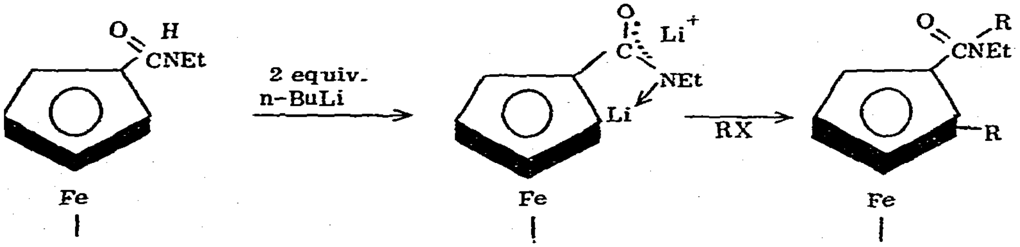
CXIV

Sequential directed metalation of 1,1'-dichloroferrocene has led ultimately to the preparation of decachloroferrocene (equation 96) [179]. A similar route involving seven successive lithiation-chlorination steps was used for the synthesis of the ruthenium analog.



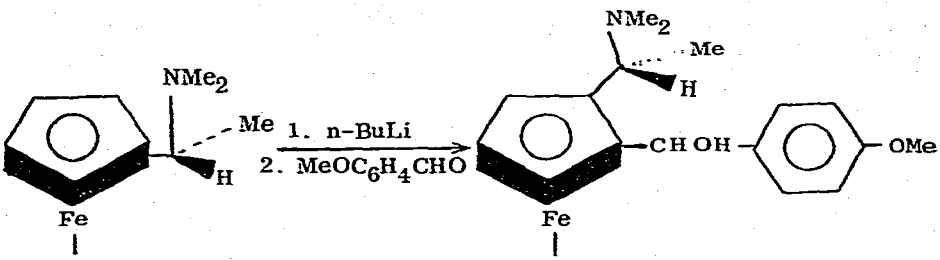
(96)

A series of 2-substituted N-ethylferrocene carboxamides were prepared by directed metalation of N-ethylferrocenecarboxamide (equation 97) [180].



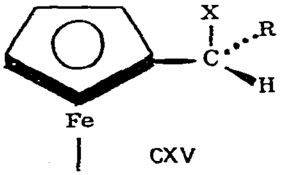
(97)

Directed lithiation of (R)-N,N-dimethyl-1-ferrocenylethylamine followed by condensation with p-anisaldehyde provided asymmetric induction not only at the incipient chiral plane, but also at the incipient chiral carbon (equation 98) [181]. A single crystal X-ray structure of the predominant product from this metalation (S,R,S)-2-(p-methoxyphenyl)hydroxymethyl-N,N-dimethyl-1-ferrocenylethylamine has provided confirmatory evidence for the absolute configurations assigned to a series of 1,2-disubstituted ferrocenes.



(98)

Methoxymethylferrocene (CXV, X= OMe) afforded approximately equal amounts of 2-and 1'-lithiation as determined by derivatization experiments with benzophenone [182]. α-Methoxyethylferrocene (MEF) upon lithiation gave a mixture of all three possible metalation isomers. (+)-MEF, when metalated and condensed with benzophenone, led to the expected mixture of three products, but only the 2-isomer possessed induced ring asymmetry. The activity possessed by this compound was found to be only about 10% of that exhibited by an otherwise identical sample prepared by a route involving asymmetric induction in the ferrocene system where metalation was directed by nitrogen (CXV, $X = NMe_2$).

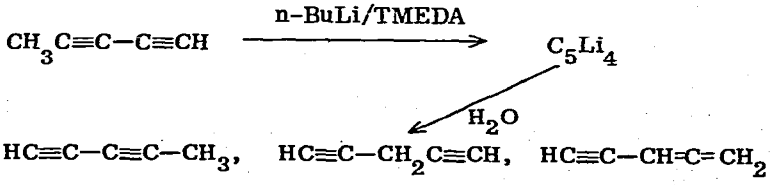


CXV

X = -OMe; R = H

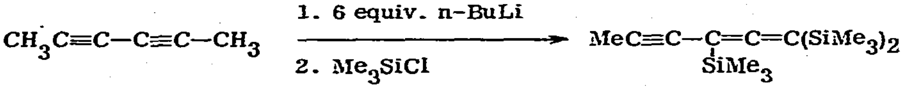
$X = -NMe_2$; R = Me

1,3-Pentadiyne, when treated with n-butyllithium/TMEDA reagent, has been reported to form a tetralithium species which after hydrolysis yielded the three acetylenes shown (equation 99) [183]. An ir spectrum of the C_5Li_4 species suggested that a $Li_2C{=}C{=}C{=}C{=}CLi_2$ structure predominated.



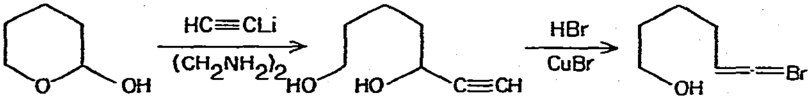
$$CH_3C{\equiv}C{-}C{\equiv}CH \xrightarrow{\text{n-BuLi/TMEDA}} C_5Li_4 \xrightarrow{H_2O} HC{\equiv}C{-}C{\equiv}C{-}CH_3,\ HC{\equiv}C{-}CH_2C{\equiv}CH,\ HC{\equiv}C{-}CH{=}C{=}CH_2 \qquad (99)$$

Hexa -2,4-diyne upon addition of six equivalents of n-butyllithium followed by, after 65 hours, addition of trimethylchlorosilane produced the trisilyl derivative (equation 100) [184]. It was thought the protons were all abstracted from the same carbon. For a shorter metalation period (16 hours) and two equivalents n-butyllithium significant monometalation was observed. Intermediate periods of metalation following otherwise the same procedure brought the unusual cumulene, $Me\underset{SiMe_3}{C}{=}C{=}C{=}C{=}C(SiMe$



$$CH_3C{\equiv}C{-}C{\equiv}C{-}CH_3 \xrightarrow[2.\ Me_3SiCl]{1.\ 6\ equiv.\ n\text{-}BuLi} MeC{\equiv}C{-}\underset{SiMe_3}{C}{=}C{=}C(SiMe_3)_2 \qquad (100)$$

A synthesis of ($\pm$)-undeca-5,6-diene-8,10-diyn-1-ol has been recorded (equation 101) [185]. Novel features of this synthesis were an allenic bromide/butadiynyl(trimethyl)silane coupling reaction and the ring opening reaction of 2-hydroxypyran by lithium acetylide.



(101)

$$\xrightarrow[HMDS]{Me_3SiCl} Me_3SiO(CH_2)_4CH{=}C{=}CHBr \twoheadrightarrow HO(CH_2)_4CH{=}C{=}CH(C{\equiv}C)_2H$$

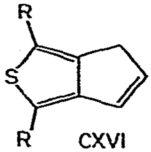
Mg and Li derivatives of phenylacetylene and vinylacetylene were treated with Me_3SiCl and Me_3SiF to afford the expected mono trimethylsilyl derivatives [186].

Ferrocenylacetylene was lithiated and reacted with Et_3SiCl and Et_2SiCl_2 to give $FcC{\equiv}CSiEt_3$ and $(FcC{\equiv}C)_2SiEt_2$, respectively [187].

V. Heterocycles

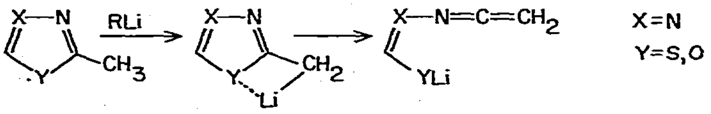
Lithiation of tert-butyl-3-thienyl sulfone afforded mainly the 2,4-dilithio intermediate [188]. This was in contrast to the behavior of tert-butyl phenyl sulfone which formed benzyne under these conditions.

4H-Cyclopenta[c]thiophene (CXVIa,R=H) and its 1,3-dichloro derivative (CXVIb, R=Cl) have been metalated with n-butyllithium [189]. Analysis of carboxylic acids produced by carbonation of the lithio intermediate(s) showed that CXVIa was metalated 70% at the allylic position and 30% at the two thiophene positions. The dichloro compound (CXVIb) was metalated exclusively at the allylic position. HMO calculation of bond orders and charge distribution for the allylic lithio intermediate, a formal Hückel 10-π-electron system, were provided.



CXVI

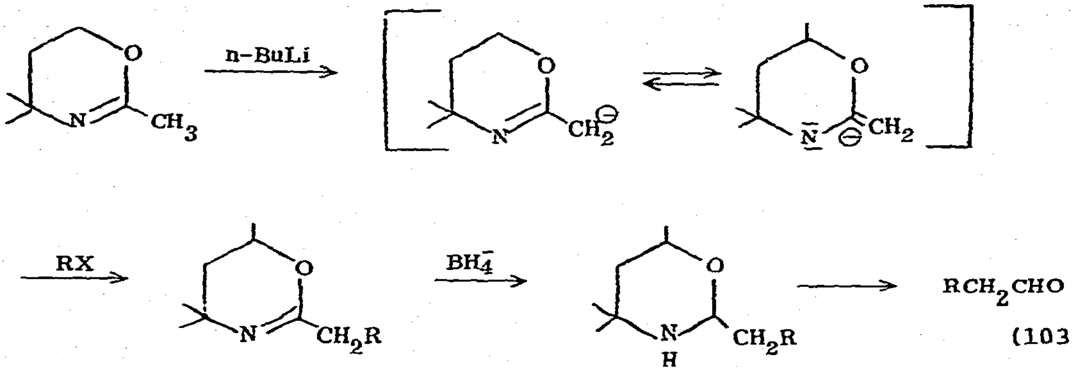
Upon treatment with organolithium reagents thiazoles (Y=S), 1,3,4-thiadiazoles (X=N; Y=S) and 1,3,4-oxadiazoles (X=N; Y=O) all rearranged to the ketenimine structure which could be isolated in a dimer form (equation 102) [190].



(102)

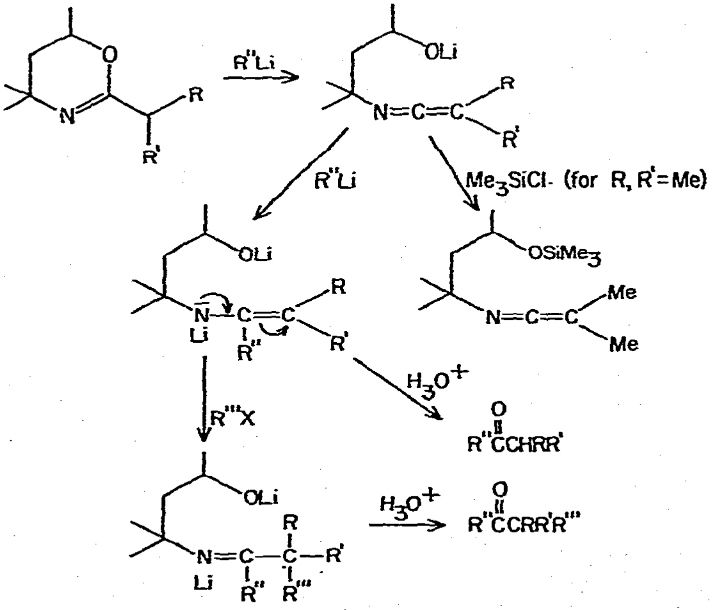
Syntheses via alkylations of dihydro -1,3- oxazines and 2-oxazolines has been extensively studied during 1973. A review of this area has been published [191].

The use of dihydro-1,3-oxazines in the synthesis of substituted acetaldehydes has been reported (equation 103) [192]. The scheme amounts to an aldehyde equivalent to the malonic ester synthesis.



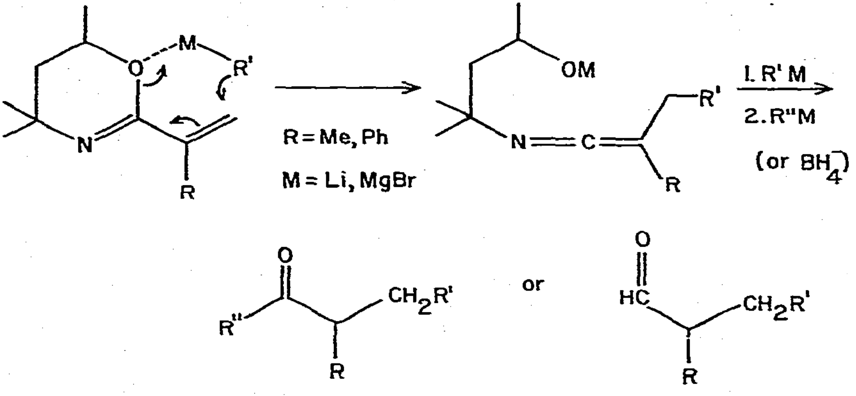
(103)

Starting with 2-isoalkyloxazines, a series of highly substituted ketones could be prepared by treatment with organolithium reagents and alkylation (equation 104) [193]. The presence of a ketone intermediate was varified by isolation of its trimethylsilyl derivative. Essentially the same results have been reported by Lion and Dubois [194].



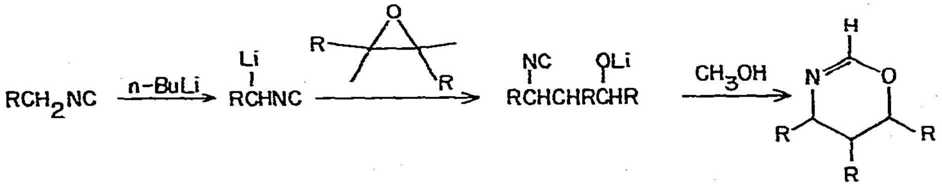
(104)

1,4-Addition of organolithium and Grignard reagents to 2-alkenyloxazines has lead to a synthetic route to α-substituted aldehydes and ketones (equation 105) [195].



(105)

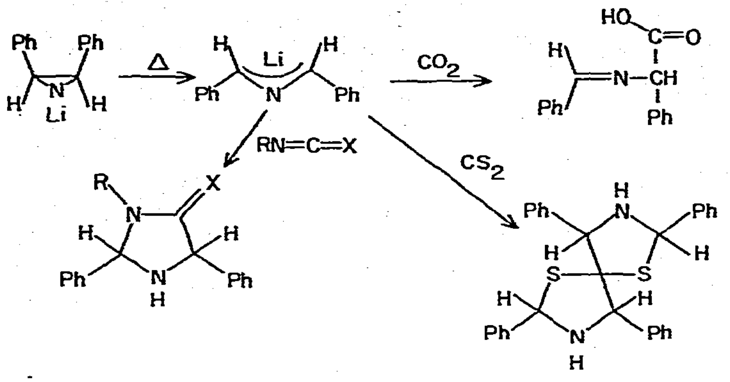
α-Metalation of isocyanides followed by treatment with an epoxide has provided a method for the synthesis of 5,6-dihydro-4H-1,3-oxazines (equation 106) [196].



(106)

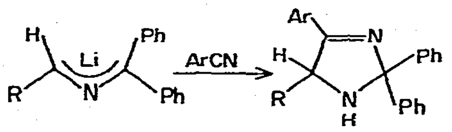
Anionic cycloaddition reactions have been utilized in the synthesis of heterocycles, trans, trans-1,3-diphenyl-2-azaallyllithium, formed by thermal ring cleavage of N-lithio-2,3-diphenylaziridine, has been observed to undergo cycloaddition reactions with CO_2, CS_2, RN=C=X (X=S,O) and $C_6H_{11}N=C=NC_6H_{11}$ to produce a variety of heterocyclic derivatives (equation 107) [197].

Cycloaddition of 1,3-azaallyllithium compounds to nitriles has been found to yield 3-imidazolines or, in some cases, imidazoles (equations 108 and 109) [198].



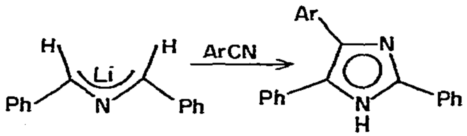
X= S,O

(107



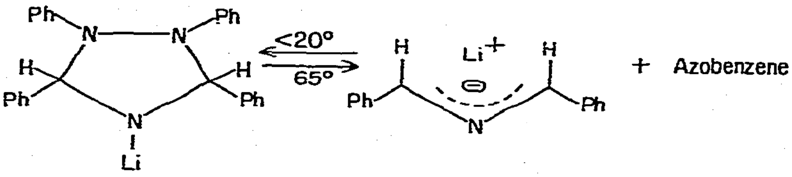
(108)

R=H, Ph



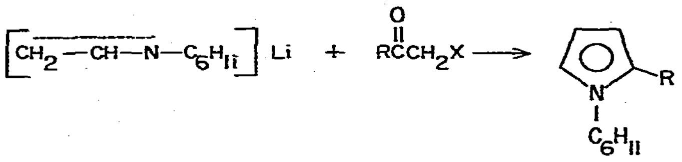
(109)

The reversibility of the cycloaddition reaction shown in equation 110 has been demonstrated. Similar reversibility in the pyrrolidine and pyrazolidine systems were also reported [19



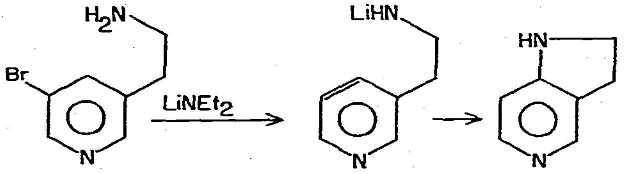
(11

A series of α-haloketones have been reacted with lithiated Schiff bases to afford pyrrole derivatives (equation 111) [200].



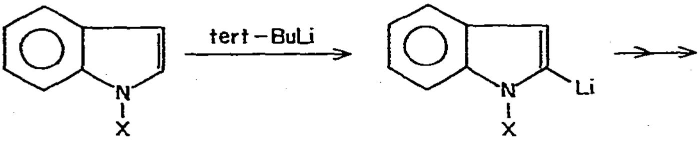
(11

3-(2-Aminoethyl)- (equation 112) and 3-benzoylamino-5-bromopyridine when treated with lithium amides in inert solvents underwent intramolecular cyclization via the respective heteroaryne intermediates [201].



(112)

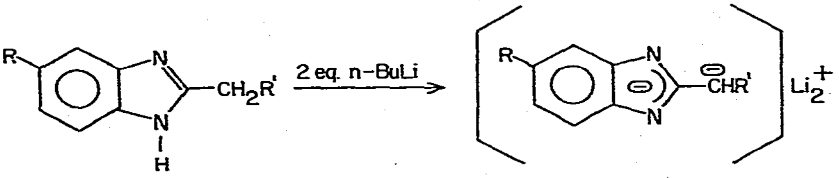
The benzenesulfonyl and methoxymethyl moieties served as N-protecting groups for the lithiation of indole in the 2-position (equation 113) [202]. Reaction of this intermediate with aldehydes, ketones, acid chlorides, esters and nitriles was accomplished. The benzenesulfonyl protecting group was conveniently removed by mild alkaline hydrolysis.



(113)

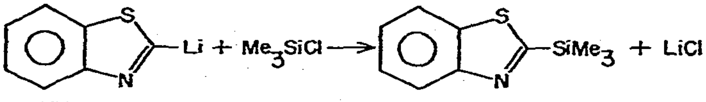
$X = PhSO_2-,\ MeOCH_2-$

Formation of the dilithio derivatives of benzimidazoles allowed reaction with alkyl halides, aldehydes and ketones selectively at the side-chain carbanion site (equation 114) [203].



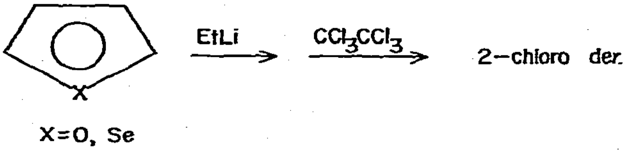
(114)

2-Benzothiazolyl(trimethyl)silane (CXVIII) and a series of di(2-benzothiazolyl)silanes have been prepared by metalation of benzothiazole with n-butyllithium to form the 2-lithiated intermediate CXVII followed by reaction with the appropriate silane. The silicon-carbon bond in these systems was found to be very reactive [204].



CXVII CXVIII

The preferred route to 2- and 3-chloro furan and selenophene was found to be by reaction of the corresponding lithio derivative with hexachloroethane (equation 115 and 116) [205].



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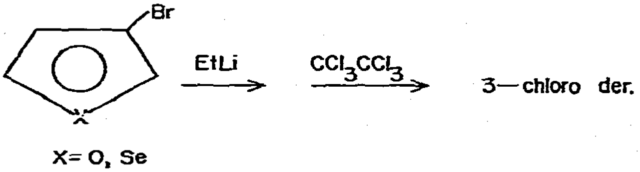
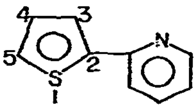


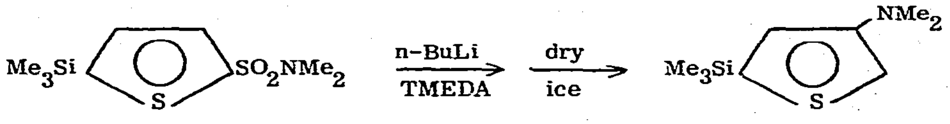
(116)

Metalation of thiophene derivatives has provided some interesting results in 1973. 2-(2'-Thienyl)-pyridine (CXIX) has been observed to undergo metalation not only at the 5-position, but also at the 3-position as determined by derivatization of the mixture of these organolithium intermediates with trimethylchlorosilane [206]. 2-(2'-Thienyl)-quinoline and a pyrimidine derivative of CXIX were also found to exhibit this metalation pattern.



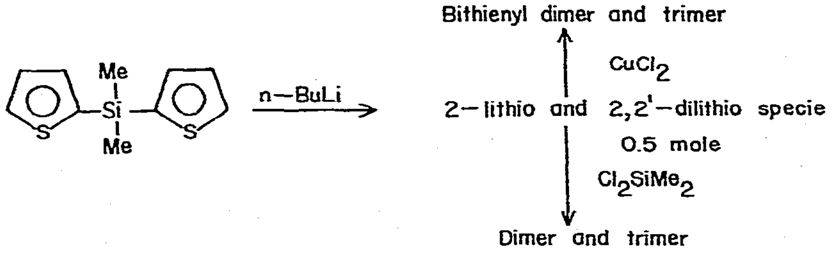
CXIX

Dithiation of 5-trimethylsilyl-2-N,N-dimethylthiophenesulfonamide (CXX) afforded 3-metalation and, in one instance, spontaneous loss of the trimethylsilyl group [207]. When n-butyllithium/ TMEDA reagent was used a rearrangement to produce the amine CXXI was discovered.

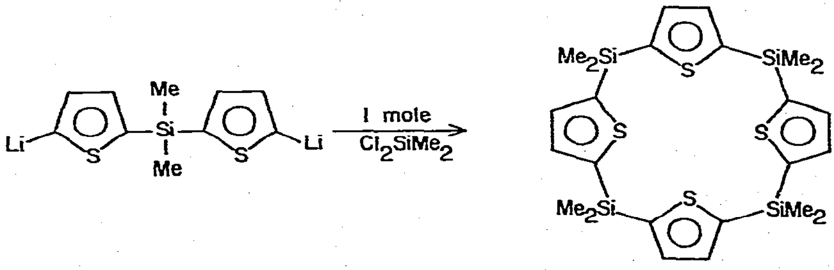


CXX CXXI

Dimethyl-di(2-thienyl)silane was metalated with n-butyllithium to afford a mixture of the 2-lithio- and 2,2'-dilithio intermediates (equation 117) [208]. These were 1) coupled with $CuCl_2$, 2) di- and trimerized with 0.5 mole Cl_2SiMe_2 and 3) transformed into a cyclic dimer with 1.0 mole Cl_2SiMe_2 (equation 118). Nucleophilic substitution of four fluorines on hexafluorobenzene by trichloro-2-thienyllithium in THF has been observed [209]. Tetrakis(trichloro-2-thienyl)difluorobenzene was obtained in good yield. Data to support a contention that the remaining fluorines were para to each other was included.

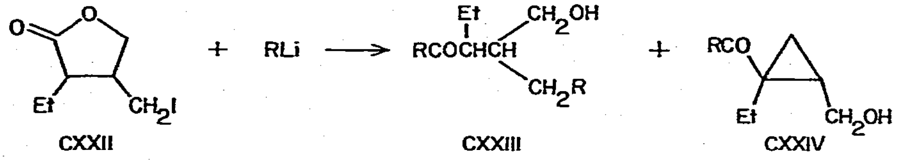


(117)

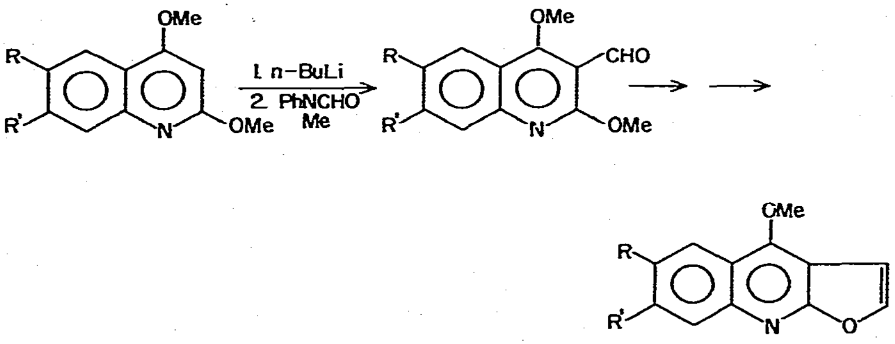


(118)

RLi(R = 5-chloro-1-methyl-2-imidazolyl) in ether was added to the lactone CXXII with the ring-opened product CXXIII being isolated after hydrolysis [210]. Cyclopropane CXXIV was a by-product.

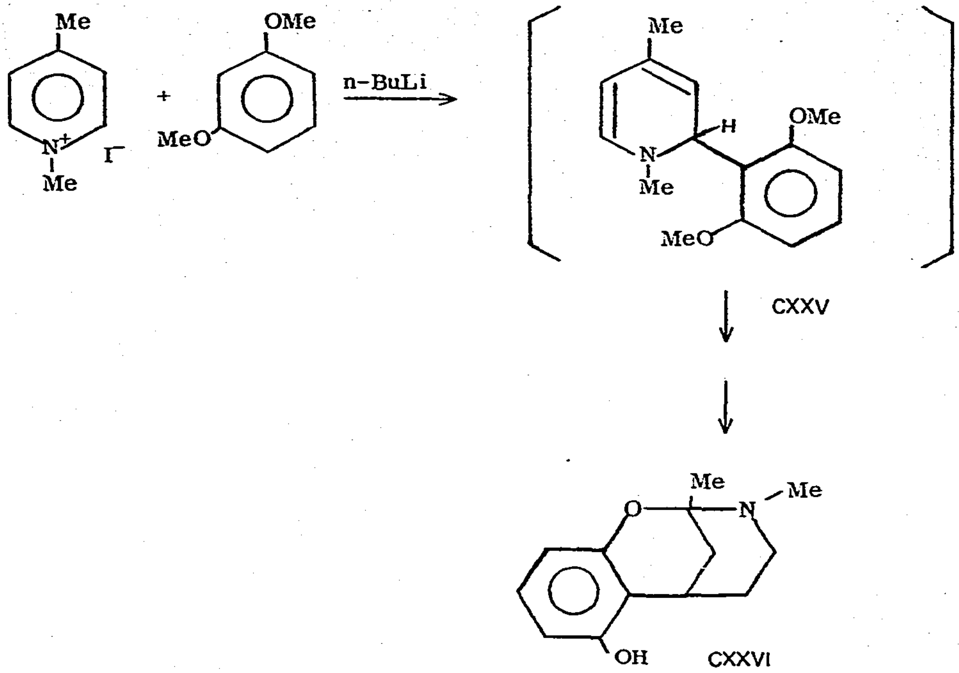


A new synthesis involving directed metalation of a 2,4-dimethoxyquinoline system of the furoquinoline alkaloids, dicatamine(R,R' = H), pteleine(R = OMe,R' = H) and evolitrine (R = H, R' = OMe) has been developed [211]. The method was extended to the synthesis of a b-naphthofuran (equation 119), b-naphthocoumarin and oxaphenalene.



(119)

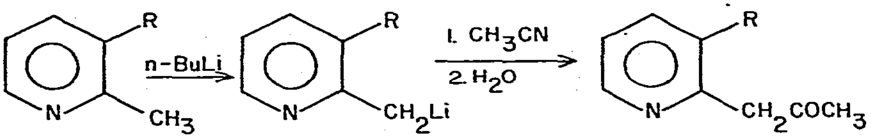
Directed metalation of 1,3-dimethoxybenzene produced the 2-lithio intermediate which, after treatment with 1,4-dimethylpyridinium iodide, afforded a high yield of the crude 1,2-dihydropyridine derivative CXXV [212]. Subsequent reactions in this series culminated in the synthesis of derivatives of 1,5-benzoxazocine and its 1,3-isomer CXXVI.



CXXV

CXXVI

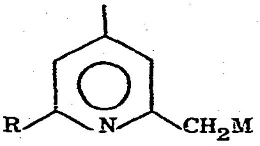
A series of (3-substituted-2-pyridyl)-2-propanones was synthesized by lithiation of the appropriate 3-substituted 2-picoline with n-butyllithium followed by acylation with acetonitrile (equation 120) [213].



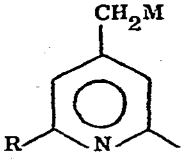
(120)

R = OMe, OEt, $OCHMe_2$, Me

2,4-Lutidine, 2,4,6-collidine and 2,4-dimethylquinoline gave exclusive metalation at the 2-methyl group (CXXVII) with n-butyllithium. On the other hand, with alkali amides in liquid NH_3 or $LiN(i\text{-}Pr)_2$, only metalation at the 4-methyl position (CXXVIII) was observed [214].



CXXVII



CXXVIII

VI. Addition Reactions of Olefins, Carbonyl Compounds and Similar Substrates.

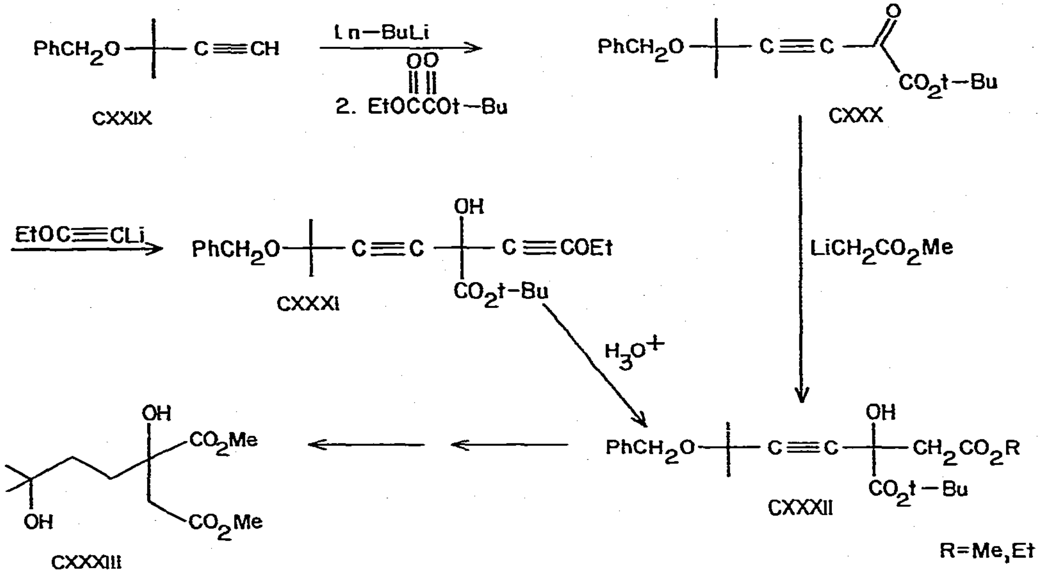
A review article on the addition of alkali metal reagents to unsaturated systems has been published [215].

A study of the reactivity of propynyllithium and propynylsodium in aprotic solvents has resulted in the delineation of conditions that allow a high yield of products to be obtained [216]. A maximum yield (91%) of 1-(1-propynyl) cyclohexanol was obtained from the lithio intermediate and cyclohexanone while the maximum yield (87%) of 2-butynoic acid was obtained from the sodio intermediate and carbon dioxide.

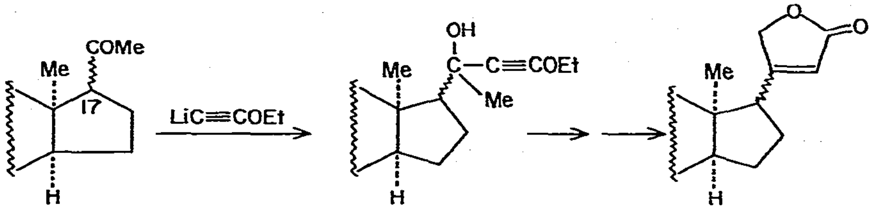
The addition reaction of alkyllithium reagents with aldehydes and ketones was examined in detail [217]. Optimum conditions involved addition of the carbonyl compound to the organolithium species at -78°. Only small losses in yield due to enolization and reduction pathways were discerned for any of the systems. An improved synthesis of carboxamides from addition of organolithium compounds to isocyanates derived from the Curtius reaction has been reported [218].

Addition of excess tert-butylethyloxalate to the lithium salt of the acetylene derivative CXXIX gave the keto ester CXXX which, when reacted with lithium ethoxyacetylide, afforded CXXXI. This compound could be hydrolyzed to the diester CXXXII but this ester could also be prepared directly from keto ester

CXXX by treatment with α-lithio methylacetate. These compounds were found useful in a regiospecific synthesis of the acyl portion of harringtonine CXXXIII [219].

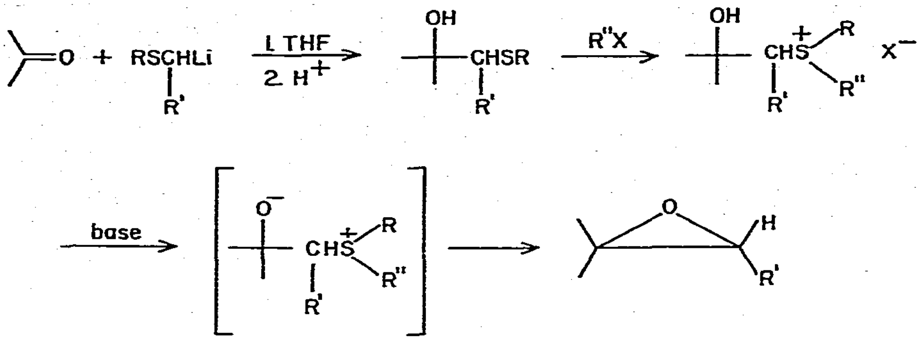


Synthesis of C-17 epimeric 5α, 13α-cardenolides was accomplished by means of the route shown (equation 121) [220].



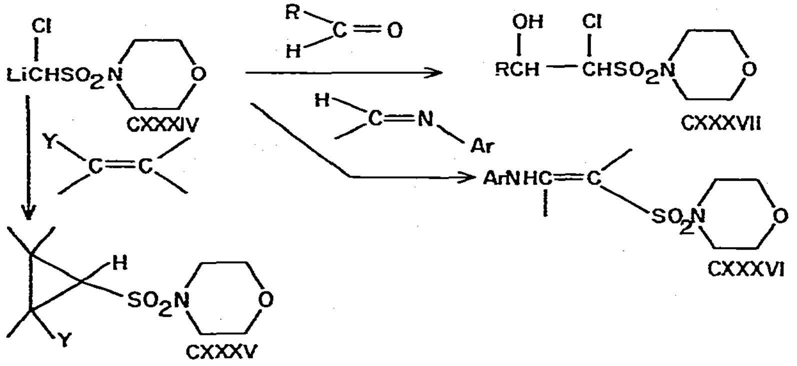
(121)

Treatment of ketones with RSCHR'Li afforded 41 - 100% yields of β-hydroxy sulfides. Alkylation of these sulfides with MeI or $Me_3O^+BF_4^-$ gave the corresponding oxiranes in from 43 to 98% yields (equation 122) [221]. It is advantageous to use this reagent for reaction with highly enolizable and sterically hindered ketones.

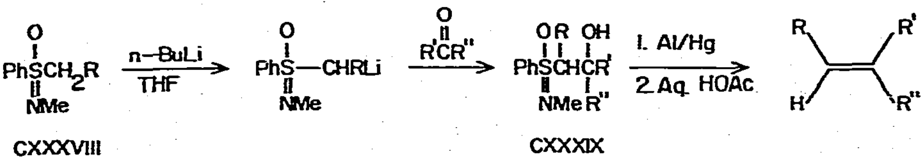


(122

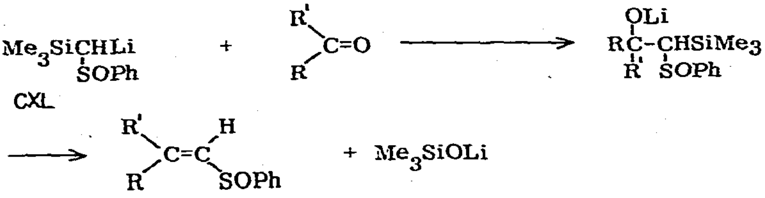
α-Lithiochloromethanesulfonomorpholide (CXXXIV) reacted with CC, CN and CO unsaturated linkages to afford the corresponding cyclopropane (CXXXV), enamine (CXXXVI) and hydroxy derivatives (CXXXVII), respectively [222].



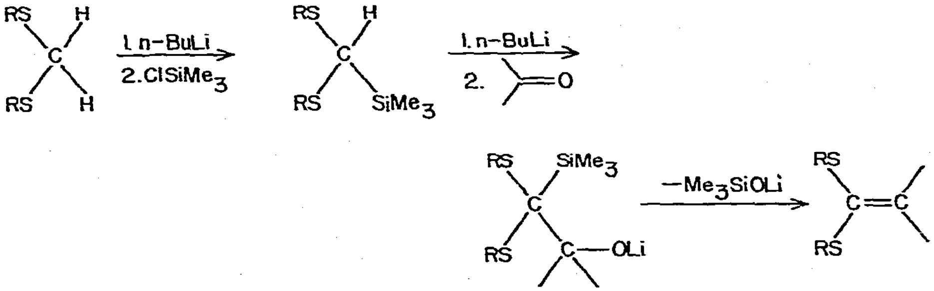
Sulfoximines CXXXVIII (R = H, Me, Pr) have been α-lithiated with n-butyllithium and the lithio intermediate condensed with aldehydes and ketones. Treatment of the resulting β-hydroxysulfoximines CXXXIX with aluminum amalgam followed by aqueous acetic acid provided reductive elimination [223]. A series of 16 olefins was prepared by this technique.



Condensation of the α-lithiosulfoxide intermediate CXL with various carbonyl compounds such as acrolein, adamantanone, benzaldehyde, benzophenone, cinnamaldehyde, cyclohexanone and isobutyraldehyde gave good yields of the corresponding vinylsulfoxides [224].

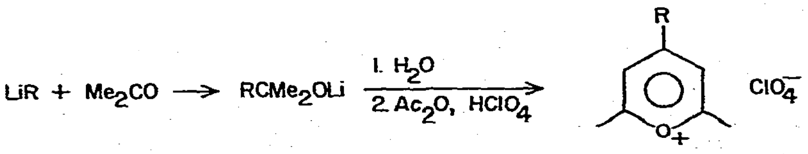


Ketone thioacetals can be prepared in high yield by the reaction of aldehydes, ketones and formamides of secondary amines with 2-lithio-2-(trimethylsilyl)-1,3-dithiane and related intermediates (equation 123) [225].



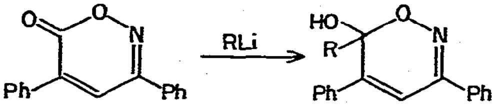
(123)

Condensation of LiR(R = 2-benzothiazolyl and 2-thienyl) with acetone followed by hydrolysis and dissolution in acetic anhydride/perchloric acid afforded 4-substituted 2,6-dimethylpyrylium perchlorates (equation 124) [226]. These were converted into the corresponding pyridines <u>via</u> treatment with ammonia.



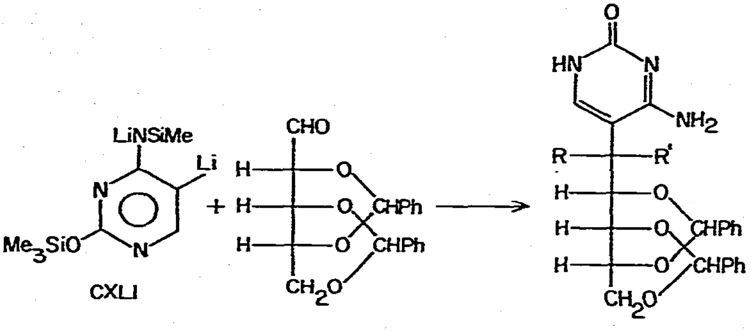
(124)

A series of aryloxazinols (R = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-$EtOC_6H_4$, p-BrC_6H_4, m-MeC_6H_4) has been prepared by the addition of RLi to the parent oxazinone (equation 125) [227].



(125)

Dilithio cytosine derivative CXLI was condensed with 2,4:3,5-di-O-benzylidene-D-ribose to give a mixture of the pentitols CXLIIa (R = H, R' = OH) and CXLIIb (R = OH, R' = H) [228]. Acid hydrolysis provided a mixture of 4-amino-2-hydroxy-5-(β-and α-D-ribofuranosyl)pyrimidines.

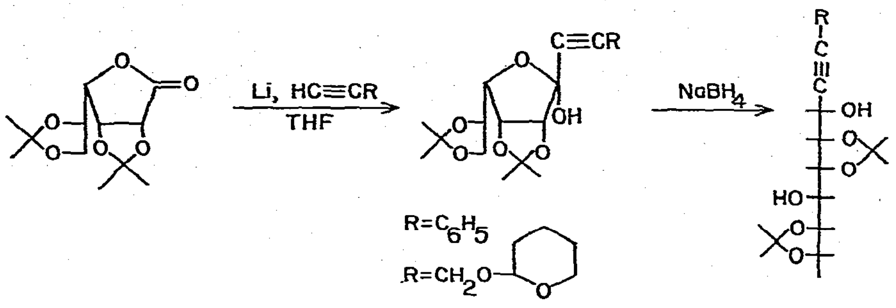


CXLI

CXLII

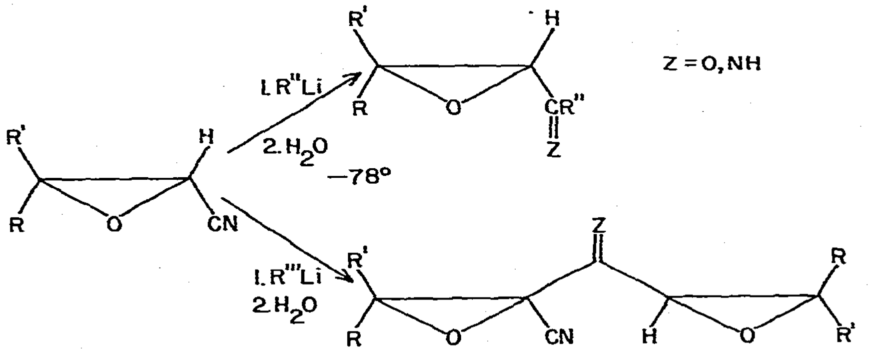
2,3-O-isopropylidene-D-ribonolactone with lithium and PhC≡CH in THF gave a 32% yield of the 1-phenylethynyl derivative CXLIII [229]. Reduction with $NaBH_4$ provided the acyclic heptyne CXLIV. Similarly, 1-octyne-L-glycero-L-talo-3,4,5,6,7,8-hexol derivatives were prepared. Benzothiazole or 1-benzylbenzimidazole upon treatment with lithium in THF afforded 40% 2,2'-bibenzothiazole and 45% 1,1-dibenzyl-2,2'-bibenzimidazole, respectively.

Epoxynitriles upon reaction with organolithium reagents afforded a series of products resulting from addition to the nitrile function (equation 126) [230]. Dimerization of the epoxynitriles was found to compete effectively with addition



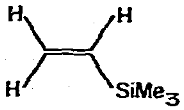
CXLIII CXLIV

in several cases and was attributed to the relative basicities of the organolithium reagents. The weaker bases, MeLi, PhLi, $LiCH_2CN$ and $LiCH_2CO_2Et$ promoted addition while the stronger bases, n-BuLi, $LiCH_2Cl$, $LiCHCl_2$ and $LiCH{=}CH_2$ provided dimerization.

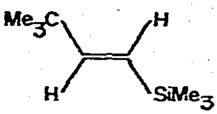


(126)

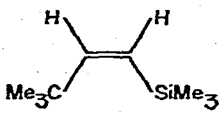
Treatment of vinyltrimethylsilane (CXLV) with tert-butyllithium/TMEDA afforded only addition of the tert-butyllithium reagent to the double bond while similar treatment of the trans isomer CXLVI caused metalation exclusively at the silylmethyl group. Under these same conditions, the cis isomer CXLVII gave a mixture of α-silylvinyl proton and silyl methyl group metalation [231].



CXLV



CXLVI

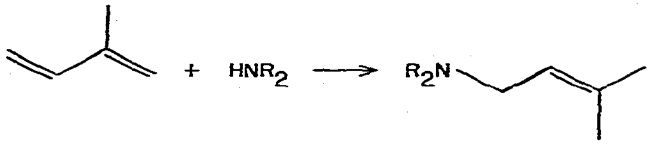


CXLVII

A series of allene amines, $RCH_2CH{=}C{=}CHCH_2NEt_2$ (where R = Et, n-Pr, Me_2CH) have been prepared by the addition of RLi or RCaI to $CH_2{=}CHC{\equiv}CCH_2NEt_2$ [232]. Combining the allyl organometallic agent CXLVIII with aldimines (R = Me, Ph; R' = Me, Me_2CH, Me_3C) afforded reversible 1,2-additon and some 1,4-addition (M = ZnBr, MgBr) [233]. 1,4-Addition was not preferred for these organometallics but was the exclusive pathway when M = Li.

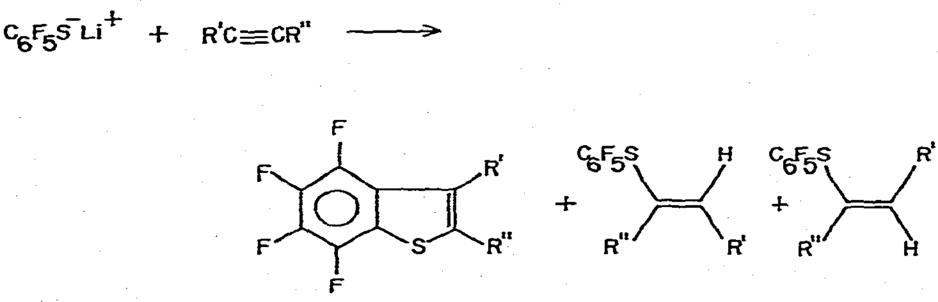
$$RCH{=}CHCH{=}NR' + \underset{\text{CXLVIII}}{EtCH{=}CHCH_2M} \longrightarrow \text{1,2- and 1,4- addition}$$

Alkali naphthalenides (alkali = Li, Na, K) in THF have been reported to effect addition of amines to conjugated olefins (equation 127) [234].



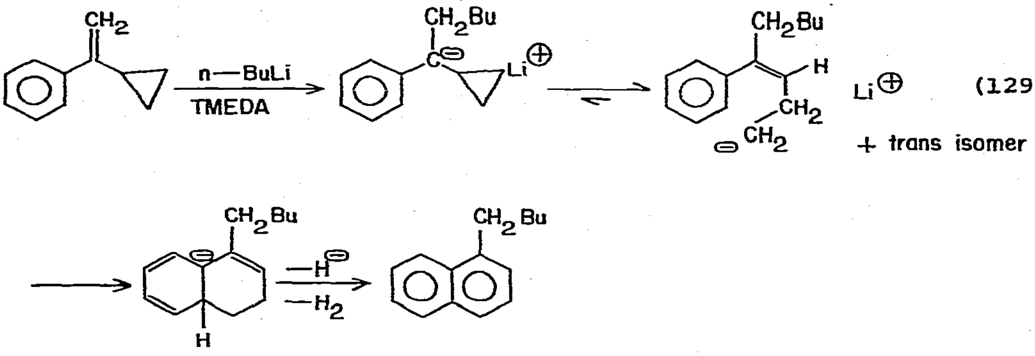
(127

Lithium pentafluorobenzenethiolate was added to various acetylenic compounds to give benzo[b]thiophene derivatives and/or olefins (equation 128) [235].



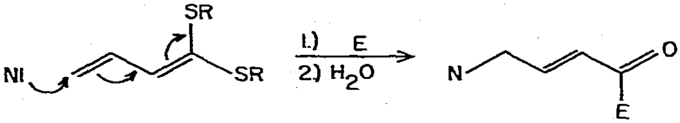
(128)

n-Butyllithium in the presence of TMEDA has been observed to add to α-cyclopropylstyrene to form a cyclopropylcarbinyllithium derivative which undergoes a ring-opening-cyclization-oxidation sequence to give 1-pentylnaphthalene (equation 129) [236].



(129)

A process which allows a Michael-type addition reaction to a four-carbon unsaturated system has been described (equation 130) [237]. The necessary thioacetals can be prepared from 2-lithio-2-(trimethylsilyl)-1,3-dithiane.

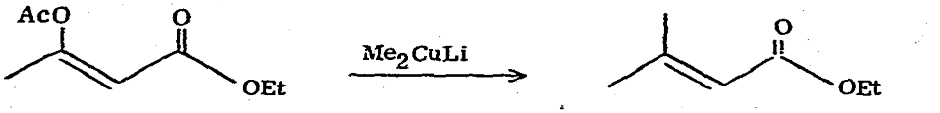


(130)

VII. Copper-Lithium Reagents and Their Reactions

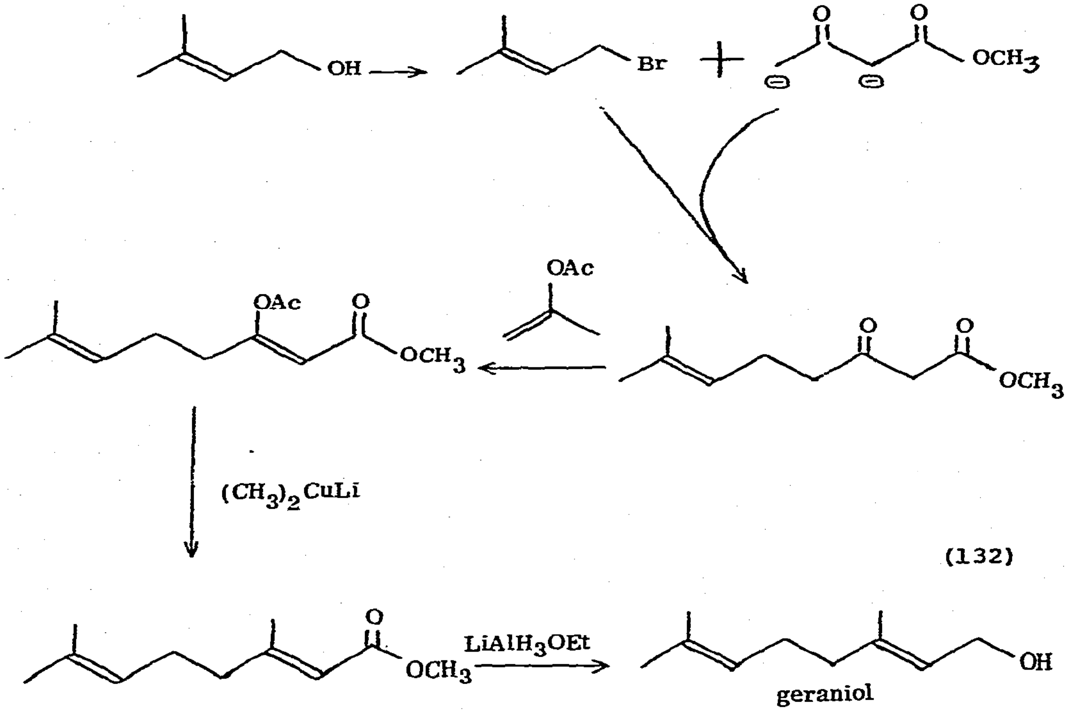
Five new alkylhetero-and arylhetero (alkyl) cuprate(I) reagents, Het(R)CuLi, where Het = t-BuO, PhO, t- BuS, PhS and Et_2N have been prepared [238]. These reagents allow selective alkyl transfer to acid chlorides, α,α-dibromo ketones, alkyl halides and α,β-ethylenic ketones.

Replacement of a β-acetoxy group in a series of α,β-unsaturated carbonyl compounds using Me_2CuLi has been reported (equation 131) [239].



(131

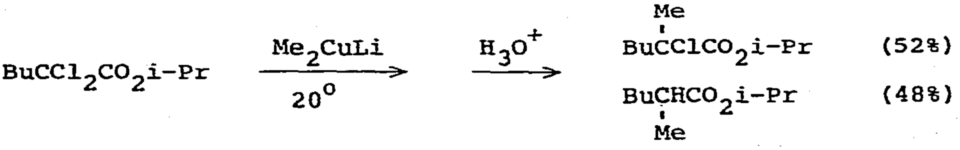
This reaction of lithium dialkylcuprates with β-acetoxy-α,β-unsaturated esters which provides stereoselective synthesis of β-alkyl-α,β-unsaturated esters was successfully utilized in a 5-step synthesis of geraniol (equation 132) [240].



(132)

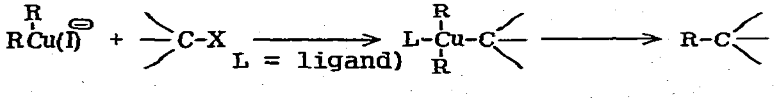
Primary tosylates combined with a wide variety of lithium diorganocuprates (I) to afford substitution products in 70-100% yields [241]. 2-Octyl tosylate reacted with Me_2CuLi to give an 87% yield of 2-methyloctane but other secondary tosylates gave lower yields of the coupling product because of competition by an E_2 process. The coupling reaction of such tosylates was found to proceed at a significantly lower temperature than the analogous couplings with alkyl bromides; in addition the tosylate couplings were noted to proceed faster in ether than in THF. Coupling reactions of difunctional substrates where both functional groups could compete for reagent were examined; preferential reaction at the tosylate of a keto tosylate, some selectivity at the tosylate of a bromo tosylate and little selectivity in an epoxy tosylate were observed.

α,α-Dichloro esters when treated with lithium dimethyl cuprate afforded a mixture of α-chloro-α-methyl ester and the reduced α-methyl ester (equation 133) [242]. At -70° α-chloro ester enolates were produced which upon warming to 20° gave α-methyl ester enolates.



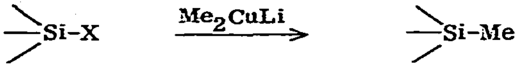
$$\mathrm{BuCCl_2CO_2i\text{-}Pr} \xrightarrow[20^{o}]{\mathrm{Me_2CuLi}} \xrightarrow{\mathrm{H_3O^+}} \begin{array}{ll} \mathrm{Bu\overset{Me}{C}ClCO_2i\text{-}Pr} & (52\%) \\ \mathrm{Bu\underset{Me}{C}HCO_2i\text{-}Pr} & (48\%) \end{array} \qquad (133)$$

(+)-(S)-2-Butyl tosylate or mesylate, when treated with Ph_2CuLi in ether, afforded (-)-(R)-2-phenylbutane of such rotation as to indicate 100% inversion of configuration (equation 134) [243]. Likewise the reaction of Me_2CuLi with *cis* and *trans* -4-*tert*-butylcyclohexyl tosylate and with *endo*-2-norbornyl tosylate also afforded complete inversion but with varying amounts of elimination. With *exo*-2-norbornyl tosylate considerable loss of stereospecificity was discovered. A second-order rate constant of $2.8 \cdot 10^{-3}$ ℓ/mol.sec. was determined for the reaction of n-octyl tosylate with Me_2CuLi in ether at -42°. It was concluded that these transformations proceed by an "Sn2-like" mechanism and that a triorgano Cu(III) intermediate was likely involved.



(134)

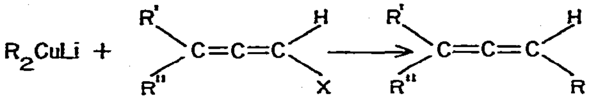
Displacement of a series of substituents from mono- and difunctional silanes has been effected with Me_2CuLi. When the silicon atom was asymmetric, displacement took place with retention of configuration (equation 135) [244].



(135)

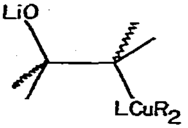
X = H, OMe, F, Cl, OMenthyl

Dialkylcopper lithium reagents at low temperatures can be used to replace a halogen on an allene to produce the alkylated allene (equation 136) [245].



(136)

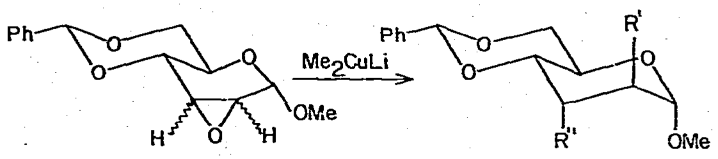
trans-Nucleophilic ring opening of oxiranes can be effectivel accomplished by lithium diorganocuprates [246]. A triorganocopper (III) intermediate CXLIX was discussed. Correspondence was noted on the concept of hard and soft acids and bases with the selectivit of lithium diorganocuprates in reactions containing epoxide and other electrophilic sites.



CXLIX

Epoxides with neighboring oxygen functions (HO, MeO, AcO, EtO_2C) were found to exhibit little regiospecificity in their ring-opening reactions with lithium dimethylcuprate [247].

A stereospecific ring opening cleavage of an oxirane in carbohydrates which utilized Me_2CuLi has been reported (equation 137) [248].



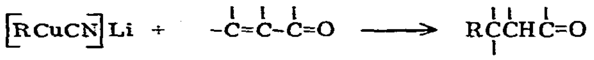
(137)

allo (down) oxide ⟶ R'=Me; R''=OH
manno (up) oxide ⟶ R'=OH; R''=Me

An unsymmetrical lithium cuprate reagent has been prepared which offers the advantage of utilizing only one equivalent of RLi in its preparation (equation 138) [249]. This reagent has been examined in both substitution and conjugate addition reactions (equations 139 and 140).

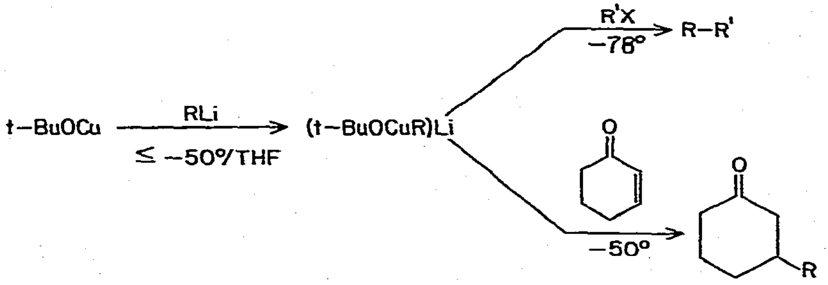
$$CuCN + RLi \longrightarrow [RCuCN]Li \qquad (138)$$

$$[RCuCN]Li + R'Br \longrightarrow R\text{-}R' + CuCN + LiBr \qquad (139)$$



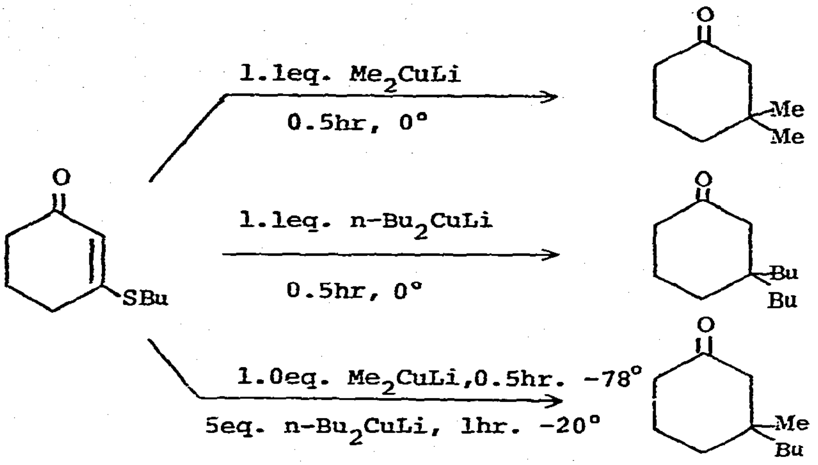
$$[RCuCN]Li + -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \longrightarrow R\underset{|}{\overset{|}{C}}\overset{|}{C}H\overset{|}{C}=O \qquad (140)$$

A new copper lithium reagent, (t-BuOCuR)Li, has been found quite effective in substitution and conjugate addition reactions (equation 141) [250]. This is important in that much lower excesses of this reagent as compared to other such reagents were sufficient for high conversion. Also important was the fact that R in (t-BuOCuR)Li could be a secondary or tertiary alkyl group.



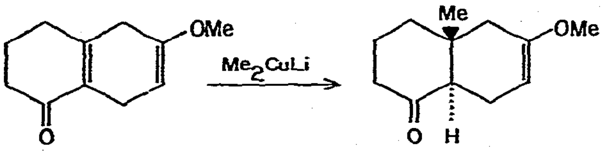
(141)

Conversion of β-alkoxy and β-alkylthio α,β-unsaturated carbonyl compounds into their respective β-alkyl and β,β-dialkyl derivativ has been observed (equation 142) [251].



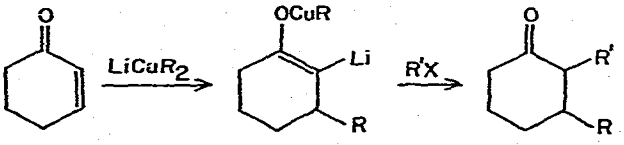
(142

Addition of a methyl group to the α,β-ethylenic ketone system in bicyclic ketone CL was observed to take place stereospecifically in 50% yield to give the trans decalin compound CLI [252]



CL CLI

Unhindered intermediate enolates may be alkylated regiospecifically at the α-carbon (equation 143) [253]. These enolates can be formed by conjugate addition of a lithium organocuprate reagent to an α,β-unsaturated carbonyl system. When the β-position was already substituted, various amounts of equilibration of the α-positions was observed.



(143)