MECHANISTIC STUDIES CONCERNING THE NATURE OF ALKYL TRANSFER IN MAIN GROUP ORGANOMETALLIC COMPOUND ADDITIONS TO KETONES

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Chairman

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SUMMARY

The formation of "CH_3MgBr" from magnesium and methyl bromide in ether has been shown to be accompanied by the formation of about 0.2% of a very reactive magnesium hydride species. This hydride has been shown to be responsible for the formation of benzhydrol in reactions of benzophenones using a large excess of "CH_3MgBr". The relationship between the grade of magnesium used to prepare the Grignard reagent and the amount of 2-methylbenzhydrol formed was determined to be due solely to the size of the magnesium turnings and to the rate at which methyl bromide was added to the magnesium. Excess methyl bromide has been shown to destroy the activity of this hydride.

Radical probes were incorporated into the R-group of Grignard reagents such that radical character could be observed as isomerization or cyclization of the particular probe. Reactions between <u>cis</u>-propenylmagnesium bromide, 5-hexenylmagnesium chloride, 1,1-dimethyl-5-hexenylmagnesium chloride and 2,2-dimethyl-5-hexenylmagnesium chloride with benzophenone and 2-methylbenzophenone in diethyl ether, THF and <u>n</u>-butyl ether established that SET character was observable in the reactions of primary and tertiary Grignard reagents with benzophenone. Apparently an intermediate radical anion-radical cation pair is formed, which can collapse to give 1,2-addition product or dissociate to form a radical anion and a free radical within the solvent cage which in turn can collapse to 1,2-addition or conjugate addition

(dependent upon radical reactivity, solvent, and steric factors) or escape the solvent cage to form pinacol.

Trialkylaluminum reagents were found to react with benzophenone via a polar mechanism evidenced by their transfer of 1^{o} alkyl groups to benzophenone preferential to 3^{o} alkyl groups.

Organolithium reagents appear to react through a SET mechanism with benzophenone by virtue of the similarity in the yield and product distribution shown by comparable Grignard and organolithium reactions with benzophenone.

CHAPTER I

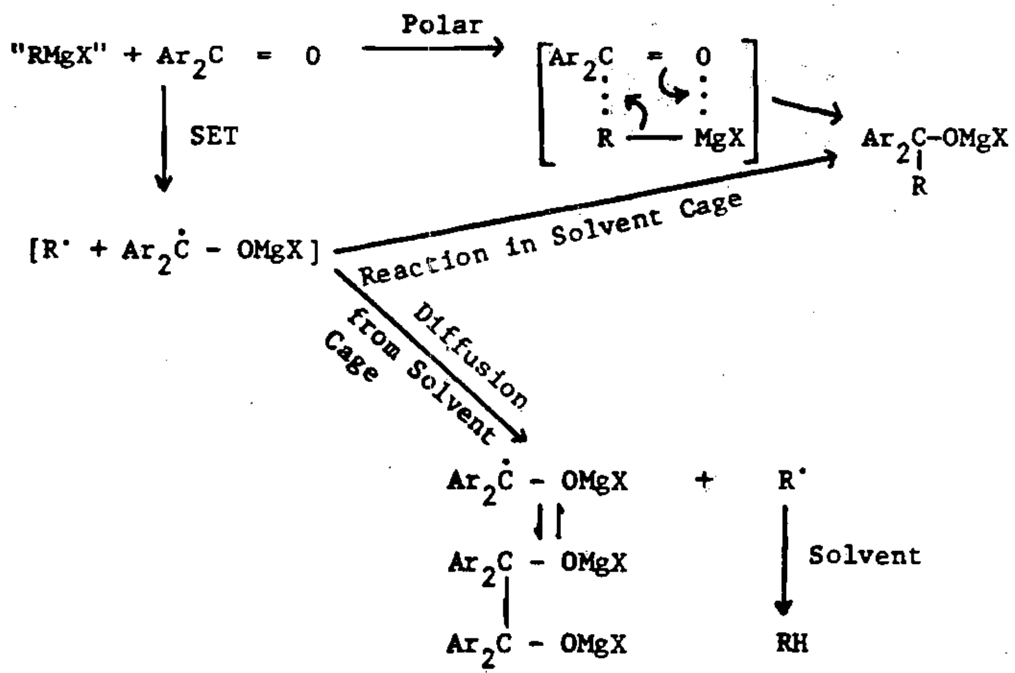
INTRODUCTION

Note

The research presented in this thesis was carried out as part of a team effort in the study of Grignard reaction mechanisms. To present a concise and complete description of this research it is necessary to use some of the work carried out by other members of this team. In each instance proper acknowledgement will be given in parentheses or by footnote. The majority of outside material is drawn from research by Thomas L. Wiesemann. The remainder comes from experiments carried out by Joseph T. Laemmle, R. Scott Smith, Jerry D. Buhler and Irene G. Lopp, who made up the rest of this team of investigators.

Background

The reaction of Grignard reagents with organic substrates (particularly ketones) is well recognized as a very important reaction in synthetic organic chemistry; however, the mechanism of this reaction is not well understood. Questions concerning the nature of the Grignard reagent in solution, the identification of the reactive species, and the kinetic order of the reactive organomagnesium species have been satisfactorily answered over the past several years. In Grignard reactions with ketones the description of the alkyl transfer from the Grignard reagent to the carbonyl carbon atom is the most significant question that remains to be answered. The exact nature of alkyl transfer from the Grignard reagent to the ketone, whether it proceeds by a polar or a single-electron transfer (SET) mechanism has been a source of considerable speculation. As a result of previous studies,[1] we have discussed in detail the polar mechanism whereby methylmagnesium bromide ("CH_3MgBr") reacts with 2-methylbenzophenone[2] (2-MBP) and benzonitrile.[3] However, while this work was being carried out, evidence was presented by several other research groups to indicate that the reaction of Grignard reagents with ketones could and does proceed in some cases by a SET pathway.



(1)

In 1968, Blomberg and Mosher presented evidence supporting a SET pathway in Grignard reactions.[4] In the reaction of "neopentylmagnesium cloride" with benzophenone in THF, not only did they observe 1,2 addition, but they also found benzopinacol and neopentane both in 20% yield. Presumably the neopentane arose from hydrogen abstraction from the solvent by a neopentyl radical. In this study, Blomberg and Mosher also reported observing an ESR signal which they assigned to the ketyl. They suggested a mechanism similar to equation 1, which included both polar and SET pathways as operative in the reaction.

Fauvarque has studied the reaction of R_2Mg compounds with flourenone and benzophenone in various solvents.[5] His ESR observations indicate that ketyl concentration depends on the polarity of the solvent and the ability of the alkyl group to stabilize the radical. Significant amounts of ketyl were observed when dibenzylmagnesium was allowed to react with flourenone in HMPA; however, the same reaction in ether showed only a trace of ketyl to be present. The proposed SET mechanism is similar to that shown in equation 1.

More recently, Holm and Crossland have presented strong evidence for a rate-determining SET step in the reaction of "t-C_4H_9MgCl" with benzophenone in diethyl ether.[6] In reactions with various substituted benzophenones, they obtained pinacol, 1,2-, 1,4-, and 1,-6-addition products. For all of these reactions, however, the Hammett plot of relative rate vs. σ-substituent constant gave a straight line (even when the substituted benzophenone had two or three ortho-methyl groups). In similar reactions using "CH_3MgBr" the presence of only one ortho-methyl group on benzophenone caused significant deviation from the linear free-energy relationship. Although, when added to acetone, "CH_3MgBr" reacts faster than "t-C_4H_9MgCl", Holm and Crossland have pointed out that "t-C_4H_9MgCl" reacts 100 times faster than "CH_3MgBr" toward benzophenone and 100,000 times faster toward the more sterically hindered durlphenyl ketone. Based on this evidence, they proposed that the rate-determining step for the reaction of "$\underline{t}$-C_4H_9MgCl" with benzophenone involves SET to give an intermediate common to all products (similar to equation 1). The SET is then followed by one or more fast steps to give the observed products. On the other hand, they considered it likely that the reaction of "CH_3MgBr" with benzophenone proceeds through a polar pathway.

While carrying out kinetic experiments which established the first-order dependence of the reaction on the Grignard reagent when "CH_3MgBr" was allowed to react with benzophenone, members of this research group made additional observations.[3,4] They found that the amount of addition product observed compared with by-product (benzopinacol and benzhydrol), as well as observed rate constant, was dependent upon the ratio of Grignard reagent to ketone, the "purity" of the magnesium used to prepare the Grignard reagent, and the manner in which the Grignard was prepared (that is, using excess magnesium or excess CH_3Br in the preparation).[7] The formation of pinacol in the reaction of "CH_3MgBr" with benzophenone was shown to be the result of a transition metal catalyzed SET reaction.[8] Iron and other first-row transition metals appear to be the best catalysts. The isolation of erythro and threo pinacols in addition to equilibrium studies relating rates of formation of the two isomers show that although iron salts catalyze electron transfer to form the ketyl, iron is not involved in the formation of the pinacols.

On the other hand, hydrol formation did not correlate at all with the transition metal content of the magnesium. The exact nature and mechanism of this reation was unknown.

Purpose

In light of these observations, we have undertaken a detailed study of the reaction of "CH_3MgBr" with 2-methylbenzophenone with respect to the formation of 2-methylbenzhydrol. The objective of this study was to determine; (1) the nature of the side reaction giving rise to the by-product hydrol, (2) the nature of the impurity involved in this side-reaction and (3) the conditions which determine the extent of hydrol formation.

A study was made of Grignard reactions with benzophenone and 2-MBP using cis-propenylmagnesium chloride, 5-hexenylmagnesium chloride, 1,1-dimethyl-5-hexenylmagnesium chloride and 2,2-dimethyl-5-hexenylmagnesium chloride as free radical probes incorporated into the R-groups of Grignard reagents. The objective of this study was to determine the nature of the alkyl transfer for the reactions of Grignard reagents with benzopheonone by observing the postulated free radical as isomerization or cyclization of the particular probe in the reaction products.

In addition, a study was carried out using 2,2-dimethyl-5-phenyl-4-penten-3-one (benzalpinacolone an αβ-unsaturated ketone which gives only conjugate addition with Grignard reagents) with the aforementioned probes. The objective was to obtain a deeper understanding of the nature and extent of SET in conjugate addition of Grignard reagents to enones.

This study was expanded by incorporating R-group free radical probes into trialkylaluminum and organolithium reagents. Again the objective was to determine the nature of alkyl transfer when these reagents are allowed to react with benzophenone.

CHAPTER II

EXPERIMENTAL

Apparatus

Reactions were performed under nitrogen or argon at the bench using Schlenk tube techniques or in a glove box equipped with a recirculating system using manganese oxide columns to remove oxygen and dry ice-acetone traps to remove solvent vapors.[9] Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Glassware and syringes were flames and cooled under a flow of nitrogen or argon. Ketone, metal salt and internal standard solutions were prepared by weighing the reagent in a tared volumetric flask and diluting with the appropriate solvent.

All melting points are corrected and all boiling points are uncorrected. The proton NMR spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer), Model RMU-7 or a Varian, Model M-66, mass spectrometer. GLPC analyses were carried out on an F and M Model 700 or Model 720 gas chromatograph. The ir spectra were determined with a Perkin-Elmer, Model 621 or Model 257, infrared recording spectrophotometer.

Analytical

Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.[10] Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10 using Eriochrome-Black T as an indicator. Aluminum was determined by adding excess standard EDTA solution to hydrolyzed samples and then back titrating with standard zinc acetate solution at pH 4 using dithizone as an indicator. Lithium reagents were analyzed by the standard Gilman double titration method (titration of total base then titration of total base after reaction with benzyl chloride).[11] Halide was determined by titration with $AgNO_3$ and back titration by KCNS with ferric alum indicator. The amount of active C-Mg and C-Li was determined by titrating the active reagent with dry 2-butanol in xylene using 2,2'-diquinoline as an indicator. Carbon, hydrogen analyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia.

Where organometallic reagents could have more than one isomer, the isomer distribution was determined by hydrolyzing an aliquote of the reagent with a minimum of saturated NH_4Cl solution, addition an internal standard (1-heptene or cyclohexene) and analyzing the resulting hydrocarbons by glpc. Hydrocarbons were identified by comparison with authentic samples. An alternate method used where appropriate involved carbonating a Grignard reagent with freshly crushed dry-ice and determining the isomer composition of the resulting carboxylic acids by NMR analysis versus an internal standard.

Analysis of all products from the reactions of methylmagnesium bromide with benzophenone and 2-methylbenzophenone, from the reactions of _cis_ and _trans_ propenyl magnesium bromide, 5-hexenyl-magnesium chloride, 5-hexenyllithium, tris(5-hexenyl)aluminum, 1,1-dimethyl-5-hexenyl-magnesium chloride, 2,2-dimethyl-5-hexenylmagnesium chloride and dimethyl-_t_-butylaluminum with benzophenone and 2-methylbenzophenone were determined by NMR analysis based upon isolated or synthesized authentic compounds. NMR analyses employed $CDCl_3$ as a solvent with internal Me_4Si.

For the products arising from reaction of methylmagnesium bromide with benzophenone: 1,2-addition was determined by the observation of the methyl group attached to the carbonyl carbon (1.92ppm), benzopinacol was determined by the -OH hydrogen (3.05ppm), and benzhydrol was determined by the hydrogen attached to the carbonyl carbon (5.80ppm).

For the products arising from reaction of methylmagnesium bromide with 2-methylbenzophenone: 1,2-addition was determined by observation of the methyl group attached to the carbonyl carbon (1.85ppm) and the methyl group bound to the ring (1.96ppm), and 2,2'-dimethylbenzopinacol was determined by observation of the -OH hydrogen (2.16ppm) and the methyl group bound to the ring (2.26ppm).

For the products arising from the reaction of _cis_-propenyl-magnesium bromide with benzophenone: 1,2-addition was determined by observation of the allylic methyl group, a doublet of doublets (1.46ppm; J_{ax} = 1.5 Hz, J_{bx} = 7.0 H_z).

For the products arising from the reaction of _trans_-propenyl-magnesium bromide with benzophenone: 1,2-addition was determined by observation of the allylic methyl group a doubles of doublets

(1.77 ppm J_{ax} = 1.5 Hz J_{bx} = 7.0 Hz).

For products arising from the reaction of either 5-hexenylmagnesium chloride, 5-hexenyllithium, or tris(5-hexenyl)aluminum with benzophenone: 1,2-addition straight chain was determined by observation of the chemical shift of vinyl protons (4.75-6.17 ppm) 1,2-addition cyclized was determined by observation of the methylene group attached to the carbonyl carbon, doublet (2.25 ppm; J = 5 Hz).

For the products arising from the reaction of 5-hexenylmagnesium chloride with benzalpinacolone analysis was carried out by glpc using 8% Apiezon L on Chromosorb W (AW, 60/80 mesh on a 10-ft. column at 210°C with a flow rate of 60 ml/min. of helium using benzophenone as the internal standard. The retention times are as follows: 1,4-addition straight chain, 24 min. and the 1,4-addition cyclized, 31 min. All retention times were determined by comparison with authentic compounds.

For the products from the reaction of 1,1-dimethyl-5-hexenylmagnesium chloride with benzophenone: straight chain 1,2-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.67-6.17 ppm) and the gem-dimethyl group attached to the carbonyl carbon (1.11 ppm) cyclized 1,2-addition product was determined by observation of the chemical shift of the gem-dimethyl groups attached to the cyclopentyl ring (two singlets, 0.75 ppm and 0.87 ppm) straight chain 1,6-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.67-6.17 ppm) and the gem-dimethyl group attached to the aromatic ring 1.34 ppm) cyclized 1,6-addition product was determined by observation of the chemical shift of the gem-dimethyl group attached to the cyclopentyl ring (two singlets, 0.88 ppm and 1.07 ppm.

For the products arising from the reaction of 1,1-dimethyl-5-hexenylmagnesium chloride with 2-methylbenzophenone: straight chain 1,2-addition product was determined by observation of the chemical shift of the protons (multiplet, 4.67-6.17 ppm and the gem-dimethyl group attached to the carbonyl carbon (1.15 ppm) cyclized 1,2-addition product was determined by observation of the chemical shift of the gem-dimethyl groups attached to the cyclopentyl ring (two singlets, 0.75 ppm and 0.87 ppm by comparison with the equivalent benzophenone product), straight chain 1,6-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet 4.67-6.17 ppm) and the gem-dimethyl group attached to the substituted aromatic ring (1.33 ppm) cyclized 1,6-addition product was determined by observation of the chemical shift of the gem-dimethyl groups attached to the cyclopentyl ring (two singlets, 0.88 ppm and 1.07 ppm).

For the products arising from the reaction of 1,1-dimethyl-5-hexenylmagnesium chloride with benzalpinacolone analysis was carried out by glpc using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 10-ft. column at 220°C with a flow rate of 69 ml/min. of helium using benzophenone as the internal standard. The retention times are as follows: straight chain 1,4-addition product, 30 min., cyclized 1,4-addition product (6-member ring), 39 min., and cyclized 1,4-addition product (5-member ring), 41 min. All retention times were determined by comparison with authentic compounds.

For the products arising from the reaction of 2,2-dimethyl-5-hexenylmagnesium chloride with benzophenone: straight chain 1,2-addition product was determined by observation of the vinyl protons (multiplet, 4.70-6.17 ppm) and the gem-dimethyl group attached β to the carbonyl carbon (0.78 ppm), cyclized 1,2-addition product was determined by gem-dimethyl group attached to the cyclopentyl ring (two singlets, 0.83 ppm and 1.0 ppm). This analysis is supported by reducing the alkylation products with H_2Pd-C to the hydrocarbons and analyzing the products by glpc versus an internal standard (benzophenone).

For the products arising from the reaction of 2,2-dimethyl-5-hexenylmagnesium chloride with 2-methylbenzophenone: straight chain 1,2-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.7-6.17 ppm) and the gem-dimethyl group attached β to the carbonyl carbon (0.78 ppm), cyclized 1,2-addition product was determined by observation of the chemical shift of the gem-dimethyl group attached to the cyclopentyl ring (two singlets, 0.83 ppm and 1.0 ppm by comparison with equivalent benzophenone product), straight chain 1,6-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.7-6.17 ppm) and the gem-dimethyl group attached β to the substituted ring (0.85 ppm), cyclized 1,6-addition product was determined by observation of the chemical shift of the gem-dimethyl group attached to the cyclopentyl ring (0.80 ppm) and by the methylene group attached to the substituted aromatic ring, a doublet (2.30 ppm; J = 6 Hz). 1,6-Addition products were reduced to the corresponding hydrol with $LiAlH_4$ to facilitate separation from the 1,2-addition products by column chomatography prior to NMR analysis. Thus the chemical shifts for the 1,6-addition products are for the reduced (hydrol) form of the ketone. Comparison of the NMR spectra of the 1,6-addition product from the 3^o Grignard probe with benzophenone indicates that there is little change in the chemical shift values between ketone and hydrol form of the products.

For the products arising from the reaction of 2,2-dimethyl-5-hexenylmagnesium chloride with benzalpinacolone analysis was carried out glpc using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 10-ft. column at 230°C with a flow rate of 60 ml/min. of helium using benzophenone as the internal standard. The retention times are as follows: straight chain 1,4-addition product, 40 min., and cyclized, 1.4-addition products 52 min. All retention times were determined by comparison with authentic compounds.

Materials

Solvents

Fisher reagent grade anhydrous diethyl ether was stored over sodium, then distilled under nitrogen from $LiAlH_4$ and/or sodiumbenzophenone ketyl just prior to use.

Eastman practical grade n-butyl ether, was refluxed over sodium for 24 hours, then distilled under nitrogen from sodium just prior to use.

Fisher reagent grade tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were dried over $NaAlH_4$ and distilled under nitrogen just prior to use.

Fisher reagent grade benzene and laboratory grade hexane and pentane were stirred over concentrated H_2SO_4, washed with Na_2CO_3, then distilled water, dried over anhydrous $MgSO_4$ and distilled from $NaAlH_4$ under nitrogen just prior to use.

Fisher reagent grade carbon tetrachloride and ethylacetate were distilled from P_2O_5 just prior ot use.

Ketones

Eastman highest purity 2-methylbenzophenone (2-MBP), bp. 125-127°C/0.3mm (lit.[12] bp. 134-137/2mm) and benzophenone, mp. 48-49°C (lit.[13] mp. 48.1°C) were distilled under vacuum.

Fisher Certified A.C.S. grade acetone was dried over $MgSO_4$, then filtered, distilled from P_2O_5 and stored over 4A molecular sieves, bp. 56°C (lit.[14] bp. 56.3°C).

Finton 4-*tert*-butylcyclohexanone was sublimed under nitrogen, mp. 43-48°C (lit.[15] mp. 49-50°C).

Eastman highest purity 9-flourenone, mp. 82-85°C (lit.[16] mp. 85°C) was used without further purification.

2,2-dimethyl-5-phenyl-4-penten-3-one (benzalpinacolone) was prepared as previously described from the base catalyzed condensation of benzaldehyde and pinacolone.[17] It was shown to be 99% pure by glpc analysis, mp. 43°C (lit.[17] 42-43°C). An authentic sample of 2,2 dimethyl-5-phenyl-4-penten-3-one was obtained from Gloria Mischuk, a graduate student in the research group of Dr. H. O. House.

Solutions of these ketones were stored in a glove box and shielded from light prior to use.

Alkyl Halides

Methyl bromide (Matheson 99.5% purity) was dried and purified by passing through a 30 cm tube of NaOH pellets and then through a 70 cm tube of Linde 4A molecular sieve. Methyl d_3 bromide (Merck Isotopic Products) was used without further purification. Fisher reagent grade bromobenzene, bp. 156°C (lit.[18] bp. 155-156°C) and <u>tert</u>-butyl chloride, bp. 51-52°C (lit.[19] bp. 51.0°C); Aldrich 6-chloro-1-hexene, bp. 82°C/140 mm (lit.[20] bp. 128-130°C), Chemical Samples 6-bromo-1-hexene, bp. 60°C/32 (lit.[21] bp. 47-51°C/16 mm); 5-bromo-1-pentene bp. 125°C (lit.[22] bp. 124.5-128°C); 4-bromo-1-butene, bp. 99°C (lit.[23] bp. 99-100°C) were distilled from calcium hydride just prior to use. Aldrich 1-bromo-1-propene, bp. 58-62°C (lit.[24] bp. 59-60°C) was fractionally distilled on a Nester-Faust teflon annular spinning band column to give pure <u>cis</u>-1-bromo-1-propene, bp. 60°C. The <u>trans</u>-1-bromo-1-propene could not be obtained pure.

<u>Metal Salts and Metals</u>

$FeCl_3$ (Fisher sublimed) and $NiCl_2$ (Alfa Anhydrous) were opened only in the glove box, and used without further purification. $MnCl_2$, $PbCl_2$, $ZnCl_2$, $Cacl_2$, $AgNO_3$, and KF (Fisher Certified Anhydrous) were used without further purification. $AlCl_3$ (Fisher Certified Anhydrous) was sublimed just prior to use. $HgCl_2$ (Baker Reagent Grade) was dried over P_2O_5 in a vacuum desicator for 24 hours prior to use.

Triply and doubly sublimed magnesium (Dow) was milled with a carbide tool prior to use. ROC/RIC magnesium crystals were used without further purification.

Lithium wire (MC/B) was washed with pentane under an argon flush prior to use.

Lithium dispersion (Alfa), 30% in petrolatum, was washed repeatedly with ether/pentane until clean under an argon atomsphere prior to use.

Organometallic Compounds

Grignard reagent solutions were prepared as previously described[3] unless otherwise indicated.

Grignard reagents in THF were prepared and analyzed in the same manner as Grignard reagents prepared in ether.

Grignard reagents in di-n-butyl ether were prepared by removing the diethyl ether from the Grignard reagent under vacuum after the di-n-butyl ether had been added.

Lithcoa tert-butyllithium and MC/B methyllithium were analyzed prior to use.

Ethyl Corporation trimethylaluminum in ether was obtained from a preparation by S. A. Noding.

$LiAlH_4$ (Alfa Inorganic) was suspended in refluxing ether for 24 hours, then filtered. The clear solutions were standarized by standard aluminum analysis (EDTA titration) prior to use.

Others

Authentic samples of 1-hexene, 1-heptene, cyclohexene, 1,5-hexadiene, cyclohexane, 1,1-dimethylcyclohexane, and methylcyclopentane were obtained from Aldrich Chemical Company. Authentic samples of 6-methyl-1-heptene, methylenecyclopentane, 2-methyl-1,5-heptadiene and 1,1,3-trimethylcyclopentane were obtained from Chemical Samples Company.

Aldrich (99%) diphenylmethane, bp. 264°C (lit.[25] bp. 262-263°C/745 mm); Aldrich (Spectro Grade) nitromethane, bp. 101°C (lit.[26] bp. 98-101°C); Eastman highest purity benzaldehyde, bp. 178-180°C (lit.[27] bp. 73.7°C/21 mm were distilled prior to use.

Aldrich (99%) diisopropylamine, bp. 84°C (lit.[28] bp. 83.9°C) was refluxed over and distilled from calcium hydride prior to use.

Aldrich (99+%) isobutyric acid, bp. 153-154°C (lit.[29] bp. 150-154°C/683 mm was refluxed over and distilled from P_2O_5.

Aldrich (99%) triphenylphosphine mp. 79-81°C (lit.[30] mp. 80.5°C) was dried over P_2O_5 in a vacuum desicator for 48 hours prior to use.

Aldrich (98%) crontonic acid (trans-2-butenoic acid), mp. 71-72°C (lit.[31] mp. 71.4°C) was recrystallized twice from ethanol-water followed by vacuum drying over P_2O_5 for 24 hours.

Aldrich (97%) pinacolone bp. 106°C (lit.[32] bp. 103-107°C) and Aldrich (98%) methylcrotonate, bp. 118-120°C (lit.[33] bp. 119°C/768 mm) were distilled prior to use.

Preparations

Miscellaneous

The preparations of 1-(2-methylphenyl)-1-phenylethylene and 1-(2-methylphenyl)-1-phenyl ethanol were carried out as previously described.[34] The preparation of active magnesium hydride has been previously described.[35] 2,2'-Dimethylbenzopinacol and flourenone pinacol were prepared according to the procedure of Gomberg and Bachmann from the reaction of the appropriate ketone with magnesium and iodine.[36] The preparation of 1,1-dimethyl-5-hexen-1-ol was carried out as previously described by reacting 4-pentenylmagnesium bromide with acetone.[37]

2-Methylbenzhydrol

Thirty mmoles (5.88 gms) of 2-methylbenzophenone was reduced with 15 mmoles of $LiAlH_4$ in ether at 0°. After 4.0 hours at room temperature, the reaction was hydrolyzed with aqueous NH_4Cl and dilute HCl. The ether layer was washed once with aqueous $NaHCO_3$, twice with water, dried with anhydrous $MgSO_4$ and the ether removed under vacuum. The crude solid was recrystallized from hexane, mp. 89.0-90.0°C (lit.[38] mp. 89°C); IR (neat, film) 3330 (OH), 3030 (aromatic CH), 2940 cm^{-1} (aliphatic CH); NMR ($CDCl_3$, TMS) 3 H singlet at 2.26 ppm, broad 1 H singlet at 2.25 ppm, 1 H singlet at 6.05 ppm, 9 H multiplet at 7.12-7.73 ppm.

cis-2-Butenoic Acid

Fifty mmoles (6.05 gms) of cis-1-bromo-1-propene was added to 0.3 gm-atoms (2.08 gms) of lithium metal suspended in THF. After stirring for 5 hours the suspension was poured through a screen into a flask containing freshly crushed dry-ice. The reaction was hydrolyzed with water. The water layer was extracted with ether and the ether layer discarded. The water layer was then acidified with 1:1 HCl, saturated with NaCl and extracted twice with Et_2O. The ether extracts were combined and washed once with water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. The crude oil was recrystallized from cold pentane, mp. 15.0°C (lit.[39] mp. 14.4-14.6°C); IR (neat, film) 3400-2900 (broad OH), 2960 (aliphatic CH), 1700 (C=O), 1660 (cis -

C=C, 1130 (C-O-H), 700 cm^{-1} (cis H-C=C-H): NMR($CDCl_3$, TMS) 3 H doublet of doublets at 2.17 ppm, 1 H multiplet at 6.22-6.83 ppm, 1 H multiplet at 5.67-6.08 and a 1 H singlet at 11.88 ppm.

1,1-Diphenyl-trans-2-buten-1-ol

One hundred mmole (10.0 gm) of methyl crotonate dissolved in ether was added to 200 mmole of phenyllithium in 200 ml of ether at 0^oC. After addition was complete the reaction was allowed to warm to room temperature and then was refluxed for 4 hours. The reaction was hydrolyzed with aqueous NH_4Cl and dilute HCl. The ether layer was washed once with aqueous $NaHCO_3$, twice with water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. The resulting liquid was chromatographed on preparative scale TLC plates (alumina) eluting with 8% ethyl acetate/hexane to give two bands. Band 1, a solid, recrystallized from hexane was identified as 1,2-diphenyl-1-butanone, mp. 72-73^oC (lit.[40] mp. 72.5-73.5^oC); IR (CCl_4) 3033 (aromatic CH), 2930 (aliphatic CH), 1680 cm^{-1} (C=O); NMR ($CDCl_3$, TMS) 3 H doublet at 1.37 ppm, 3 H multiplet at 3.0-3.76 ppm, 10 H multiplet at 7.0-8.13 ppm. Band 2, a liquid was identified as 1,1-diphenyl-trans-2-buten-1-ol, N^D_{25} 1.5858 (lit.[41] N^{25}_D 1.5860); IR (neat, film) 3410 (broad OH), 3030 (aromatic CH), 2920 (aliphatic CH), 1665 (trans C=C), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 3 H doublet of doublets centered at 1.77 ppm, 1 H singlet (broad) at 2.45 ppm, 2 H multiplet at 5.27-6 ppm. 10 H multiplet at 7.0-7.7 ppm, mass spectrum, m/e (rel. intensity) 224 (M^+, 14), 206(8), 105(100), 91(17), 77(38), 69(16), 51(17); Analysis Calculated for $C_{16}H_{16}O$: C, 85.72%; H, 7.14%. Found: C, 85.64%; H 7.17%.

1,1-Diphenyl-cis-2-buten-1-ol

To 7.5 mmoles of cis-1-propenyllithium in 50 ml of THF was added 5.0 mmoles (0.91 gms) of benzophenone in 25 ml of THF. The mixture was allowed to react for 8 hours at 25°C, then hydrolyzed with aqueous NH_4Cl. Et_2O was added and the mixture extracted several times with cold water to remove the THF. The ether layer was dried over anhydrous $MgSO_4$, and the ether removed under vacuum. NMR analysis indicated no trans-isomer was present. High vacuum vapor transfer gave a colorless liquid, N_D^{25} 1.5889 (lit.[41] N_{25}^{D}1.5901); IR 3420 (broad OH), 3030 (aromatic CH), 2925 (aliphatic CH), 1650 (cis C=C), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 3 H doublet of doublets centered at 1.46ppm, 1 H singlet (broad) at 2.45ppm, 2 H multiplet at 5.33-6.25ppm, 10 H multiplet at 7.0-7.70ppm; mass spectrum, m/e (rel. intensity) 224 (M^+,21), 209(17), 183(15), 181(15), 167(19), 165(17), 105(100), 77(36); Analysis, Calculated for $C_{16}H_{16}O$: C, 85.72%; H, 7.14%. Found: C, 85.45%; H, 7.22%.

α-(2,2-Dimethylcyclopentyl)acetophenone

To 4.46 mmoles of 3° probe Grignard reagent (containing 62.7% 1,1-dimethyl-5-hexenylmagnesium chloride, 33.3% 2,2-dimethylcyclopentyl-1-methylmagnesium chloride, and 4.0% 2,2-dimethylcyclohexylmagnesium chloride) in 24 ml of ether was added 4.0 mmole (0.42 gm) of benzaldehyde in 10ml of ether. The mixture was allowed to react for 6 hours, hydrolyzed with aqueous NH_4Cl and extracted with ether. The ether extracts were washed with water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. The resulting liquid was dissolved in 25 ml of acetone and Jones reagent added until an orange color persisited.

The color was discharged with isopropyl alcohol. Following neutralization with sodium bicarbonate, the acetone layer was separated. The aqueous layer was extracted with ether, and the ether and acetone layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under vacuum giving a pale yellow liquid. The reaction products were separated by prepartive glpc on a 6' x ¼" - 10% Carbonwax 20M column at 190°C. The title compound crystallized as it was collected, mp. 29-30°C; IR (neat, film) 3030 (aromatic CH), 2950 (aliphatic CH), 1685 (C=O), 1600 (aromatic C=C), 1450 cm^{-1} (aliphatic CH_2); NMR ($CDCl_3$, TMS) 6 H doublet centered at 0.93ppm, 7 H multiplet at 1.17-2.33ppm, 2 H multiplet centered at 2.86ppm, 5 H multiplet at 7.7-8.17ppm; mass spectrum, m/e (rel. intensity) 216 (M^+, 28), 173(17), 149(18), 120(100), 105(81), 77(31); Analysis, Calculated for $C_{15}H_{20}O$: C, 83.33%; H, 9.26%. Found: C, 83.38% : H, 9.34%.

Diphenyl-(2,2-Dimethylcyclopentylmethylene)carbinol

The α-(2,2-dimethylcyclopentyl) acetonphenone prepared above was dissolved in dry ether and added to an excess of phenylmagnesium bromide in ether. Standard Grignard work up gave a pale yellow liquid, IR (neat, film) 3480 (OH), 3030 (aromatic CH), 2940 (aliphatic CH), 1600 (aromatic C=C), 1450 cm^{-1} (aliphatic CH_2); NMR ($CDCl_3$, TMS) 6 H doublet centered at 0.83ppm, 10 H multiplet at 1.0-2.7ppm, 10 H multiplet at 7.0-7.7ppm; mass spectrum, m/e (rel. intensity) 176 (P-H_2O,<1), 217(8), 183(100), 105(38), 77(9), 55(4).

Further proof of structure was obtained by injecting this compound on a 6' x ¼" carbowax 20M column at 250°C and collecting the olefin dehydration product, 1,1-diphenyl-2-(2,2-dimethylcyclopentyl) ethylene; IR (neat, film) 3035 (aromatic CH), 3020 (olefinic trisub CH), 2940 (aliphatic HC), 1680 (C=C), 1600 cm^{-1} (aromatic C=C); mass spectrum m/e (rel. intensity) 276 (M^+,<1), 261(<1), 227(7), 165(10), 104(17), 85(36), 77(18), 55(100); Analysis, Calculated for $C_{21}H_{24}$: C, 91.3% ; H, 8.70%. Found: C, 91.03% ; H, 8.91%.

1-Chloro-1,1-Dimethyl-5-hexene

To a cold (0^oC) solution of 250 ml of 10% $ZnCl_2$ in concentrated HCl in a separatory funnel was added 100 mmoles (14.6 gm) of 1,1-dimethyl-5-hexen-1-ol. The funnel was stoppered and shaken for 15 minutes. The phases were allowed to separate and the lower acid layer was discarded. The upper organic layer was washed with water, neutralized with sodium bicarbonate, and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$ and the ether removed under vacuum. Distillation gave a colorless liquid bp. 60^oC/23mm; IR (neat, film) 3080 (vinyl CH), 2960 (aliphatic CH), 1645 cm^{-1} (vinyl C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 1.58ppm, 6 H multiplet at 1.67-2.38ppm, 3 H multiplet at 4.86-6.47ppm; mass spectrum, m/e (rel. intenstiy) 146 (M^+ , < 1), 95(30), 69(100), 56(42), 55(46), 54(36), 41(74), 39(40); Analysis, Calculated for $C_8H_{15}Cl$: C, 65.53% ; H, 10.25%. Found: C, 65.67% ; H, 10.32%.

2,2-Dimethyl-5-hexen-1-ol

To 0.5 mole (44.0gms) of isobutyric acid in 700 ml of freshly distilled THF was added 1.0 mole (833 ml 1.2M) of lithium diisopropylamide in hexane at -20^oC. The solution was allowed to warm to room temperature and then warmed to 30^oC for 30 minutes to complete the metalation. To this suspension was added 0.525 moles (70.9 gms) of 4-bromo-1-butene dissolved in 100 ml of THF. The reaction warmed to 55°C and was allowed to mix overnight. The reaction was hydrolyzed with water, extracted with ether (ether layer discarded), acidified with 1:1 hydrochloric acid, and extracted twice with ether. The combined ether extracts were washed twice with water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. The resulting liquid, 2,2-dimethyl-5-hexenoic acid; NMR ($CDCl_3$, TMS) 6 H singlet at 1.22 ppm, 4 H multiplet at 1.33-2.42 ppm, 3 H multiplet at 4.75-6.13 ppm, 1 H singlet at 12.2 ppm, was dissolved in 100 ml of dry ether and added to an excess of $LiAlH_4$ in ether at 0°C. Standard work up gave a colorless liquid: bp. 83-84°C/21 mm also collected a portion at 97°C/45 mm. N_D^{25} 1.4422 (lit.[42] bp. 97-98°C/45 mm; N_D^{25} 1.4425) NMR ($CDCl_3$, TMS) 6 H singlet at 0.82 ppm, 5 H multiplet (contains OH) at 1.15-2.28 ppm, 2 H singlet at 3.30 ppm, 3 H multiplet at 4.78-6.22 ppm, mass spectrum, m/e (rel. intenstiy) 128 (M^+,<1), 110(1), 97(14), 95(7), 81(14), 55(100), 43(20), 41(35), 39(17).

<u>1-Chloro-2,2-Dimethyl-5-hexene</u>

A solution of 0.142 moles (18.1 gms) of 2,2-dimethyl-5-hexen-1-ol and 0.156 moles (40.8 gms) of triphenylphosphine in 300 ml of dry CCl_4 was refluxed for 48 hours. The solution was allowed to cool at room temperature, then hexane added to bring the total volume to 500 ml and filtered. The solvent was removed under vacuum and the resulting liquid redissolved in hexane and filtered. This procedure was repeated until the addition of hexane did not cause a precipitate to form.

The crude liquid was distilled to give a colorless liquid: bp. 77-78°C/44mm (glpc analysis showed the liquid to be contaminated by about 2% alcohol and 2% double bond isomer). Preparative glpc gave a pure, colorless liquid: N_D^{25} 1.44.26; IR (neat, film) 3060 (vinyl CH), 2960 (aliphatic CH), 1645 cm^{-1} (vinyl C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 0.98 ppm, 4 H multiplet at 1.22-2.31 ppm, 2 H singlet at 3.33 ppm, 3 H multiplet at 4.8-6.2 ppm, mass spectrum, m/e (rel. intensity) 146(M^+, 3), 97(100), 95(38), 69(38), 55(85), 41(65), 39(49); Analysis, Calculated for $C_8H_{15}Cl$; C, 65.55%; H, 10.24%. Found: C, 65.75%; H, 10.27%.

1-Propenylmagnesium Bromide

To a 250 ml round bottom flask equipped with a reflux condenser, pressure equalizing addition funnel stoppered with a septum cap, magnetic stirring bar, and attached to a THF/$NaAlH_4$ still was added 0.05 gm-atoms (1.2 gm) of activated[43] triply sublimed magnesium. The entire apparatus was evacuated and flamed, then flushed with nitrogen. Enough dry THF was distilled into the flask to just cover the magnesium. With a syringe, 40 mmoles (4.84 gms) of cis-1-bromo-1-propene was added to the addition funnel. About 0.5 ml of the neat halide was added to the magnesium - THF mixture with stirring. The remainder of the halide was diluted with 50 ml of dry THF. After a two hour induction period the reaction started. Additional THF was distilled into the reaction mixture and additional halide - THF mixture added at a rate such that refluxing did not occur. The reaction was allowed to mix an additional 8 hours after addition of the halide was complete, then allowed to settle until clear. The Grignard reagent was used without being filtered.

The isomer composition of the propenyl Grignard reagent was determined by NMR analysis of the 2-butenoic acids produced by the carbonation of the Grignard reagent. Three propenyl Grignard reagents were prepared by the above procedure and their isomer composition is as follows:

Grignard A (0.015 ± 0.005<u>M</u>) was composed of: 0.142 ± 0.004<u>M</u> (94.7%) <u>cis</u>-propenylmagnesium bromide; 0.008 ± 0.0008<u>M</u> (5.3%) <u>trans</u>-propenylmagnesium bromide.

Grignard B (0.16 ± 0.005<u>M</u>) was composed of 0.07 ± 0.003<u>M</u> (60.6%) <u>cis</u>-propenylmagnesium bromide; 0.063 ± 0.002<u>M</u> (39.4%) <u>trans</u>-propenylmagnesium bromide.

Grignard C (0.41 ± 0.12<u>M</u>) was composed of: 0.16 ± 0.003<u>M</u> (25.2%) <u>cis</u>-propenylmagnesium bromide; 0.314 ± 0.009<u>M</u> (74.8%) <u>trans</u>-propenylmagnesium bromide.

<u>5-Hexenylmagnesium Chloride</u>

To a 250 ml round bottom flask equipped with a reflux condenser, pressure equalizing addition funnel stoppered with a septum cap, magnetic stirring bar, and attached to an ether/$LiAlH_4$ still was added 0.10 gm-atoms (2.4 gm) of activated[43] triply sublimed magnesium. The entire apparatus was evacuated and flamed, then flushed with nitrogen. Enough dry ether was distilled into the flask to just cover the magnesium. With a syringe 74.0 mmoles (12.0 gms) of 1-chloro-5-hexene was added to the addition funnel. About 0.5 ml of the neat halide was added to the magnesium-ether mixture with stirring. The remainder of the halide was diluted with 10 ml of dry ether. After a short induction period the reaction started. Additional ether was distilled into the reaction and additional halide-ether mixture added at a rate such that refluxing was held to a minimum. After addition of the halide was complete the reaction was allowed to mix an additional 8 hours, then allowed to settle until clear. The Grignard reagent was used without being filtered. The isomer composition of the Grignard reagents below were determined by glpc analysis.

Grignard D ($0.34 \pm 0.016\underline{M}$) was composed of : $0.33 \pm 0.015\underline{M}$ (95.9%) 5-hexenylmagnesium chloride; $0.014 \pm 0.001\underline{M}$ (4.1%) cyclopentylmethylmagnesium chloride; cyclohexylmagnesium chloride (none detected).

Grignard E ($0.38 \pm 0.02\underline{M}$) was composed of: $0.32 \pm 0.01\underline{M}$ (83.3%) 5-hexenylmagnesium chloride; $0.064 \pm 0.006\underline{M}$ (16.7%) cyclopentylmethylmagnesium chloride; cyclohexylmagnesium chloride, (none was detected).

This Grignard reagent was also prepared in THF by the above procedure. The isomer composition of this Grignard reagent was determined in the same manner and shown by glpc analysis to be as follows:

Grignard F ($0.286 \pm 0.01\underline{M}$) was composed of: ($0.26 \pm .008\underline{M}$) (90.9%) 5-hexenylmagnesium chloride: $0.026 \pm 0.002\underline{M}$ (9.1%) cyclopentylmethylmagnesium chloride; cyclohexylmagnesium chloride; (none detected).

<u>1,1-Dimethyl-5-hexenylmagnesium Chloride</u>

To a 250 ml round bottom flask equipped with a sidearm stopcock, a reflux condenser, pressure equalizing addition funnel stoppered with a septum cap, magnetic stirring bar, and attached to an ether/$LiAlH_4$ still was added 0.05 gm-atoms (3.6 gms) of activated[43] triply sublimed magnesium. The entire apparatus was flamed under vacuum, then flushed with nitrogen. Enough dry ether was distilled into the flask to just cover the magnesium. Through the sidearm of the flask (under N_2 flush) 0.2 ml of ethyl bromide was added with stirring. After the vigorous reaction had stopped the ether solution was removed by syringe and fresh ether distilled into the flask. This procedure was continued until 90% of the ethylmagnesium bromide was accounted for by acid titration of the removed ether. With a syringe 20 mmoles (2.93 gms) of 1-chloro-1,1-dimethyl-5-hexene was added to the addition funnel. About 0.5 ml of the neat halide was added to the magnesium-ether mixture with stirring. The remaining halide was diluted with 10 ml of dry ether. The reaction started within 10 minutes. Additional ether was distilled into the reaction vessel and additional halide-ether mixture was added at a rate such that refluxing was held to a minimum. The reaction was allowed to stir an additional 8 hours after the addition of the halide was complete, then allowed to settle until clear. The Grignard reagent was used without being filtered. The isomer composition of the Grignard reagents prepared were determined by glpc analysis.

Grignard G ($0.142 \pm 0.006\underline{M}$) was composed of: $0.076 \pm 0.0025\underline{M}$ (53.6%) 1,1-dimethyl-5-hexenylmagnesium chloride; $0.056 \pm 0.0025\underline{M}$ (39.4%) 2,2-dimethyl-cyclopentylmethylmagnesium chloride; $0.010 \pm 0.007\underline{M}$ (7.0%) 2,2-dimethylcyclohexylmagnesium chloride.

Grignard H ($0.31 \pm 0.01\underline{M}$) was composed of: $0.16 \pm 0.005\underline{M}$ (51.6%) 1,1-dimethyl-5-hexenylmagnesium chloride; $0.14 \pm 0.004\underline{M}$ (45.2%) 2,2-dimethylcyclopentymethylmagnesium chloride; $0.01 \pm 0.001\underline{M}$ (3.2%) 2,2-dimethylcyclohenylmagnesium chloride.

Grignard I (0.11 ± 0.0035M) was composed of: 0.061 ± 0.002M (53.5%) 1,1-dimethyl-5-hexenylmagnesium chloride; 0.048 ± 0.001M (42.1%) 2,2-dimethylcyclopentylmethylmagnesium chloride; 0.005 ± 0.0005M (4.4%) 2,2-dimethylcyclohexylmagnesium chloride.

Grignard J (0.24 ± 0.007M) was composed of: 0.15 ± 0.004M (62.5%) 1,1-dimethyl-5-hexenylMgCl; 0.080 ± 0.002M (33.3%) 2,2-dimethylcyclopentylmethylmagnesium chloride 0.010 ± 0.001M (4.2) 2,2-dimethylcyclohexylmagnesium chloride.

1,1-Dimethyl-5-hexenylmagnesium chloride was also prepared in THF by the above procedure and in n-butyl ether as described earlier. The isomer composition of these Grignard reagents was determined in the same manner and shown by glpc analysis to be as follows:

Grignard K in THF (0.266 ± 0.008M) was composed of: 0.12 ± 0.03M (45.1%) 1,1-dimethyl-5-hexenylmagnesium chloride; 0.12 ± 0.003M (45.1%) 2,2-dimethylcyclopentylmethylmagnesium chloride; 0.026 ± 0.002M (9.8%) 2,2-dimethylcyclohexylmagnesium chloride.

Grignard L in n-butyl ether (0.26 ± 0.008M) was composed of: 0.13 ± 0.004M (50.0%); 1,1-dimethyl-5-hexenylmagnesium chloride; 0.12 ± 0.003M (46.2%); 2,2-dimethylcyclopentylmethylmagnesium chloride; 0.01 ± 0.001M (3.8%) 2,2-dimethylcyclohexenylmagnesium chloride.

2,2-Dimethyl-5-hexenylmagnesium Chloride

To a 50 ml round bottom flask equipped with a sidearm stopcock, a reflux condenser, pressure euqalizing addition funnel stoppered with a serum cap, magnetic stirring bar, and attached to an ether/$LiAlH_4$ still was added 0.042 gm-atoms (1.0 gm) of activated[43] triply sublimed magnesium. The entire apparatus was flamed under vacuum, then flushed with nitrogen. Enough dry ether was distilled into the flask to just cover the magnesium. Through the sidearm of the flask (under N_2 flush) 0.2 ml of ethyl bromide was added with stirring. After the vigorous reaction had stopped the ether solution was removed by syringe and fresh ether distilled into the flask. This procedure was continued until 90% of the ethylmagnesium bromide was accounted for by acid titration of the removed ether. About 30 ml of ether was distilled into the flask. To this was added (by syringe through the sidearm) 4.7 mmoles (0.34 gms) of 1-chloro-2,2-dimethyl-5-hexene. The reaction, which never procedes rapidly, was allowed to mix for 3 days, then allowed to settle until clear. The Grignard reagent was used without being filtered. The isomer composition of the Grignard reagents was determined by glpc analysis.

Grignard M ($0.14 \pm 0.004\underline{M}$) was composed of: $0.07 \pm 0.002\underline{M}$ (50.0%) 2,2-dimethyl-5-hexenylmagnesium chloride $0.07 \pm 0.002\underline{M}$ (50.0%) 3,3-dimethylcyclopentylmethylmagnesium chloride.

Grignard N ($0.19 \pm 0.007\underline{M}$) was composed of: $0.04 \pm 0.0025\underline{M}$ (21.1%) 2,2-dimethyl-5-hexenylmagnesium chloride; $0.15 \pm 0.004\underline{M}$ (78.9%) 3,3-dimethylcyclopentylmethylmagnesium chloride.

<u>5-Hexenyllithium</u>

Bis(5-hexenyl)mercury. To a 1.0 liter round bottom flask equipped with a sidearm stopcock, Soxhlet extractor (no cup only glass wool) containing 30 mmoles (8.13 gms) of $HgCl_2$, and a reflux condenser all under nitrogen was added 70 mmoles (130 ml, $0.59\underline{M}$) of 5-hexenylmagnesium chloride (8.5% cyclopentylmethylmagnesium chloride). Approximately 600 ml of freshly distilled dry ether was added through the Soxhlet extractor. The flask was heated to reflux overnight during which time a heavy white precipitate formed. The $HgCl_2$ was completely dissolved in about 6 hours. The solution was filtered under nitrogen, hydrolyzed aqueous NH_4Cl, the ether layer washed with distilled water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. Distillation of the residue gave a colorless liquid, bp. 155-157°C/9mm. NMR ($CDCl_3$, TMS) aliphatic multiplet at 0.8-2.4 ppm, and an olefinic multiplet at 4.67-6.33 ppm, with an aliphatic : olefinic hydrogen ratio of 3.1 : 1.0. Bis-5-hexenylmercury with 8.5% cyclopentylmethyl groups would be expected to have this exact ratio of aliphatic : olefinic hydrogens. This dialkylmercury compound was used without further purification or characterization.

To a 100 ml round bottom flask equipped with a sidearm stopcock and a magnetic stirring bar was added 0.047 gm-atoms (0.33 gms) of (pentane-ether washed) lithium dispersion and 45 ml of ether under an argon atomsphere. The flask was placed in a CCl_4/dry-ice bath (-23°C). To the cold solution was added 8.5 mmoles (3.1 gms) of bis-5-hexenylmercury (8.5% cyclopentylmethylmercury) with stirring. The reaction was allowed to mix for 6 hours, then allowed to settle until clear. The lithium reagent was stored at -78°C when not in use.

The isomer composition of the lithium reagent was shown by glpc analysis to be as follows:

Lithium Reagent A (0.30 ± 0.009<u>M</u>) was composed of: 0.24 ± 0.007<u>M</u> (80.0%) 5-hexenyl Li; 0.06 ± 0.002<u>M</u> (20.0%) cyclopentylmethyl Li.

1,1-Dimethyl-5-hexenyllithium

Bis(1,1-dimethyl-5-hexenyl) mercury. To 250 ml round bottom flask equipped with a sidearm stopcock and a magnetic stirring bar was added 6.0 mmoles (1.63 gms) of $HgCl_2$ and 42 ml of dry ether. This mixture was stirred until the $HgCl_2$ had completely dissolved. To this was added slowly with stirring 12.0 mmoles (60 ml, 0.2 M) of 3^o probe Grignard reagent (Grignard G). The addition of the Grignard reagent resulted in the formation of a white precipitate which quickly turned dark grey and remained dark until the addition was complete. The reaction was allowed to mix over night. The reaction mixture was filtered under nitrogen, hydrolyzed with aqueous NH_4Cl, the ether layer washed with distilled water, dried over anhydrous $MgSO_4$, and the ether removed under vacuum. Distillation of the residue, over a wide boiling range, gave a colorless liquid, bp. 162-185°C/0.3 mm, NMR ($CDCl_3$, TMS) large aliphatic H multiplet at 0.5-2.4ppm and a trace of olefinic H multiplet at 4.68-6.33ppm. There was only a trace of olefin material present remaining in the product. The synthesis of this probe was not continued.

Tris(5-hexenyl)aluminum

To a 50 ml round bottom flask equipped with a magnetic stirring bar, a 3-way stopcock which was attached to a male 24/40 standard taper joint was added 9.1 mmoles (20.7 ml, 0.44M) of 5-hexenylmagnesium chloride (7.0% cyclopentylmagnesium chloride). To this solution was added, with rapid stirring, 3.0 mmoles (2.5 ml, 1.2M) of aluminum chloride in ether at 0°C. The reaction was allowed to warm to room temperature and then stir for 24 hours. The reaction flask was then placed in a centrifuge to facilitate rapid settling of the $MgCl_2$ precipitate. The clear solution was transferred to another flask by syringe. The ether was removed under vacuum and replaced with dry pentane. After the precipitate had settled the clear solution was shown by analysis to have an Al : Mg : Cl ratio of 1.0:0.010:0.02.

The isomer composition of the aluminum reagent was shown by glpc analysis to be as follows:

Aluminum Reagent A (concentration of R_3Al = 0.30/3 = 0.10$\underline{M}$) was composed of: 0.28 ± 0.008$\underline{M}$ (93.3%) 5-hexenylaluminum 0.02 ± 0.001$\underline{M}$ (6.7%) cyclopentylmethylaluminum.

Tris(1,1-dimethyl-5-hexenyl)aluminum

To a 250 ml Schlenk tube (sized to fit a centrifuge) was added 24 mmoles (100 ml, 0.24$\underline{M}$) 3° probe Grignard reagent (62.7% 1,1-dimethyl-5-hexenylmagnesium chloride). To this at 0°C was added with rapid stirring 6.0 mmoles (5.0 ml, 1.2$\underline{M}$) aluminum chloride. Daily analysis indicated that complete reaction required 4 days of stirring. After centrifuging, the clear solution was transferred to another flask by syringe. The ether was removed under vacuum and replaced with dry pentane. After the precipitate had settled the clear solution was shown by analysis to have an Al : Mg : Cl ratio of 1.0:0.015:0.023.

The isomer composition of the aluminum reagent was shown by glpc analysis to be as follows:

Aluminum Reagent B (0.054 ± 0.002$\underline{M}$) was composed of: 0.003 0.0003$\underline{M}$ (5.0%) 1,1-dimethyl-5-hexenylaluminum 0.051 ± 0.002$\underline{M}$ (95.0%)

2,2-dimethylcyclopentylmethylaluminum.

Dimethyl-t-butylaluminum

To a 50 ml round bottom flask equipped with a magnetic stirring bar and a 3-way stopcock which was attached to a male 24/40 standard taper joint, was added 10 mmoles (8.3 ml, 1.2M) of trimethylaluminum in ether and 5.0 mmoles (9.8 ml, 0.51M) of aluminum chloride. The redistribution reaction was allowed to stir for 1 hour. To this solution at $0^{o}C$ with stirring was added 15 mmoles (17.4 ml, 0.86M) of tert-butylmagnesium chloride. The reaction was allowed to warm to room temperature and stirred for 24 hours. The reaction flask was then placed in a centrifuge to facilitate rapid settling of the $MgCl_2$ precipitate. The clear solution was transferred to another flask by syringe. The ether was removed under vacuum and replaced with dry benzene. After the precipitate had settled the clear solution was shown by analysis to have an Al : Mg : Cl ratio of 1.0:0.018:0.020. An aliquot of the trialkylaluminum solution was placed in a preweighed flask equipped with a sidearm stopcock, the solvent was removed under high vacuum to give a colorless liquid, dimethyl-tert-butylaluminum diethyl etherate, NMR (C_6H_6, C_6H_6) 6 H singlet at -0.23ppm, 6 H triplet centered at 1.28ppm, 9 H singlet at 1.36ppm, and a 4 H quartet centered at 3.55ppm. Gas analysis CH_4 : Al was determined to be 2.0:1.0; Analysis, Calculated for $C_{10}H_{25}AlO$: Al, 15.7%. Found: Al, 15.6%.

CH_3MgBr + Active MgH_2 [35]

To a 100 ml round bottom flask equipped with a sidearm stopcock and a magnetic stirring bar was added 0.25 mmoles of MgH_2 under N_2

flush and 120 mmoles (50.4 ml, 2.38M) of methylmagnesium bromide with stirring. After 15 minutes the MgH_2 had completely dissolved. This solution was used for further reactions immediately.

Procedure

Reactions in General

Reactions were carried out in round-bottomed flasks equipped with T-bore stopcocks attached to male 24/40 standard taper joints (allows nitrogen flush while reagents are being added or removed through the stopcock by syringe), and a teflon coated magnetic stirring bar. The appropriate amounts of solvents, organometallic reagents, ketones and catalysts were syringed into the flask under a nitrogen or argon flush. After complete reaction the mixture was hydrolyzed with saturated aqueous NH_4Cl solution under nitrogen atomsphere. In some cases the ether layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent removed under vacuum. In other cases the solvent and other volatile compounds of interest were removed under vacuum and collected in a liquid nitrogen or dry ice-acetone trap.

Reaction of "CH_3MgBr" with 2-Methylbenzophenone (400:1 Grignard; Ketone Ratio) with D_2O Hydrolysis.

To 120 mmoles of "CH_3MgBr" in 79 ml of ether was added 0.3 mmole (1.0 ml, 0.3M) of 2-MBP in ether. After 6 hours, the reaction was hydrolyzed with 99.9% D_2O, the ether layer was separated, dried, and the ether removed under vacuum. The residue was taken up in $CDCl_3$ and gave upon NMR analysis: 57% 2-methylbenzhydrol (no deuterium incorporation), 42% 1-(2-methylpenhyl)-1-phenyl ethanol and 2%

2-methylbenzopinacol.

Reaction of "CD_3MgBr" with 2-Methylbenzophenone (250:1 Grignard: Ketone Ratio).

To 50 mmoles of "CD_3MgBr" in 79 ml of ether was added 0.2 mmoles (1.0 ml, 0.2M) of 2-MBP in ether. After 6 hours, the reaction was hydrolyzed, the ether layer separated, dried, and the ether removed under vacuum. The residue was taken up in $CDCl_3$ and gave upon NMR analysis: 69% Phenyl-(2-methylpenyl)-d_3-methyl carbinol, 20% 2-methyl-benzopinacol, and 11% 2-methylbenzhydrol (no deuterium incorporation).

Reaction of "CH_3MgBr" with 2-MBP (400:1 Grignard:Ketone Ratio) Doping with Metals, Anions and Oxygen.

A separate reaction was carried out for each doping reagent; Fe(III), Ni(II), Ag(I), Na^o, O_2, F^-, Cl^-, Pb(II), Zn(II) and Ca(II). When possible, a solution of the doping reagent (1000 ppm) was added to 120 mmole of "CH_3MgBr" in about 75 ml of ether just prior to the addition of 0.3 mmoles (1.0 ml, 0.3M) of 2-MBP in ether. If the doping reagent was not soluble in ether an approximate amount of the dry solid was added to the flask (in the dry box) followed by the Grignard reagent and then the ketone. Ten ml of O_2 was bubbled into a flask by syringe. After 6 hours, the reactions were carefully hydrolyzed, the ether layers separated, dried, and the ether removed under vacuum. The residues were taken up in $CDCl_3$ and analyzed by NMR.

Reactions Showing the Selectivity of the Magnesium Hydride Reducing Species.

To an ether solution containing 120 mmole of "CH_3MgBr" or "CH_3MgBr" + "MgH_2"[35] was added 0.3 mmole of 2-MBP and 0.3 mmole of acetone. Reactions were carried out for 4 hours, and hydrolysis was followed by vacuum stripping of the volatile portion. Analysis of this portion was obtained by GLC on a 19-ft., 15% diglycerol on 60/80 mesh Chromasorb W column at 60° and a flow rate of 60 ml/min. of helium using 3,3,5-tri-methylcyclohexanone as an internal standard. The retention times for the *tert*-butanol (addition product) and the *i*-propanol (reduction product) were 12 and 15 min., respectively. Extraction of the residue after vacuum stripping gave the rest of the reaction products which were then analyzed in the normal manner.

Reaction Showing the Stereochemistry of Reduction of 4-*tert*-Butylcyclohexanone by the Magnesium Hydride Species.

These reactions were carried out in the normal manner. Analysis was carried out by GLC using 10% FFAP on Diatoport S on a 20-ft. column at 150°C with a flow rate of 20 ml/min., of helium using 3,3,5-tri-methylcyclohexanone as the internal standard. The retention times are as follows: axial alcohol, 30.5 min. and equatorial alcohol, 47 min. and the addition products: axial alcohol, 20 min. and equatorial alcohol, 34 min. All retention times were determined by comparison with authentic compounds.

<u>Reactions Showing the Effect of the Size of Magnesium Shavings and Methyl Bromide Flow Rate on the Percentage of 2-Methylbenzhydrol Formed in Reactions Involving 120 mmoles of "CH_3MgBr" with 0.3 mmole 2-Methylbenzophenone.</u>

Three separate Grignard reagents were prepared, each utilizing the same volume of ether, the same amount of dry methyl bromide (682 ml/min., for 28 min.) and the same weight of Dow doubly sublimed magnesium (28.0 gms). However, the Dow doubly sublimed magnesium was milled with a new carbide tool to obtain fine shavings, medium shavings, and large chips. To 120 mmoles of each of the three "CH_3MgBr" reagents in 79 ml of ether was added 0.3 mmole (1.0 ml, 0.3<u>M</u>) of 2-MBP in ether. After 6 hours, each reaction was hydrolyzed, the ether layer separated, dried and the ether removed under vacuum. The residues were each taken up in $CDCl_3$ and analyzed by NMR.

<u>Reactions of Cis and Trans-Propenylmagnesium Bromide with Benzophenone with and without Doping by 4000ppm $FeCl_3$.</u>

To a THF solution of 1.5 mmoles of <u>cis</u>-propenyl-magnesium bromide (Grignard A) or <u>cis</u>-propenylmagnesium bromide/<u>trans</u>-propenyl-magnesium bromide (Grignard B,C) was added 1.0 mmole (2.0 ml, 0.5<u>M</u>) of benzophenone in THF. In those cases where the reactions were doped, the $FeCl_3$, 0.0075 mmole (0.75 ml, 0.01<u>M</u>) in THF, was added just prior to the addition of the ketone. After 6 hours the reaction was hydrolyzed, extracted with ether, the ether layer separated, dried, and the ether removed under vacuum. The resulting liquid was taken up in $CDCl_3$ and analyzed by NMR.

Reaction of cis-Propenylmagnesium Bromide with 2-Methylanthraquinone (2-MAQ).

To a THF solution of 2.5 mmoles of cis-propenylmagnesium bromide (Grignard A) in 13.75 ml of THF was added 1.0 mmole (6.25 ml, 0.158M) of 2-MAQ in THF. The reaction turned a dark green with the formation of a precipitate. After 6 hours, the reaction was hydrolyzed with the color changing to bright yellow. Standard work-up under nitrogen followed by an oxidation of the liquid residue gave upon NMR analysis a spectrum which appeared to be the di-1,2-adduct of 2-MAQ with no isomerization of the cis-propenyl probe. The liquid residue upon recrystallization or chromatography on silica gel or alumina resulted in the recovery of 2-MAQ.

Reaction of 5-Hexenylmagnesium Chloride in Ether with Benzophenone.

To 1.0 mmole of 5-hexenylmagnesium chloride (Grignard D) in 9.15 ml of ether was added 0.5 mmole (0.85 ml, 0.59M) of benzophenone. After 6 hours, the reaction was hydrolyzed, all volatile compounds were removed under vacuum and collected in a liquid nitrogen trap. GLPC analysis using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at 50°C with a flow rate of 40 ml/min. of helium using cyclohexene as the internal standard indicated the following distribution of hydrocarbons: 0.47 $\pm$ 0.01 mmoles 1-hexene; 0.24 $\pm$ 0.007 mmoles 1,5-hexadiene; 0.029 $\pm$ 0.0002 mmoles methylcyclopentane.

The residue left after vacuum stripping was dissolved in ether, washed with water, the ether layer separated, dried, and the ether removed under vacuum. The remaining liquid was taken up in $CDCl_3$ and analyzed (internal standard CH_3NO_2) by NMR: 0.25 mmoles (51%) of 1,1-diphenyl-5-hepten-1-ol and 0.24 mmoles (49%) of benzhydrol.

From a preparative scale reaction, the non-volatile reaction products were chromatographed on alumina eluting with 8% ethylacetate/hexane. Fraction 1 consisted of a liquid identified as 1,1-diphenyl-5-hepten-1-ol, N_D^{25} 1.5551 ; IR(neat, film) 3480 (broad OH), 3030 (aromatic CH), 2960 (aliphatic CH), 1645 (vinyl c=c), 1600 cm^{-1} (aromatic c=c) ; NMR ($CDCl_3$, TMS) 8 H multiplet at 1.0-2.5 ppm, 1 H broad singlet at 2.13 ppm, 3 H multiplet at 4.75-6.17 ppm, 10 H multiplet at 7.08-7.60 ppm; mass spectrum, m/e (rel. intensity) 266 (M+,<1), 248(1), 183(100), 105(75), 77(33), 41(17); Analysis, Calculated for $C_{19}H_{22}O$: C, 85.71% ; H, 8.27%. Found: C, 85.54% : H, 8.32%.

Fraction 2 consisted of a solid which was recrystallized from ethanol-water to give white crystals of benzhydrol, mp. 66-67°C (lit.[45] 68°C) ; NMR ($CDCl_3$, TMS) 1 H broad singlet at 2.25 ppm, 1 H singlet at 5.80 ppm, 10 H singlet at 7.37 ppm.

Reaction of 5-Hexenylmagnesium Chloride in THF with 2-Methylbenzophenone.

To 5.72 mmole of 5-hexenylmagnesium chloride (Grignard F) in 56 ml of THF was added 1.23 mmoles (1.0 ml, 1.23M) of 2-MBP in THF. The reaction was allowed to run for 6 hours. Application of the same work-up procedure as used in the previous reaction, gave by glpc analysis the following distribution of hydrocarbons:
4.0 ± 0.1 mmoles 1-hexene ; 0.88 ± 0.02 mmoles 1,5-hexadiene ; 0.48 ± 0.01 mmoles methylcyclopentane. NMR analysis by comparison to the

benzophenone addition product and to 2-methylbenzhydrol gave the following; 0.88 mmoles (71.5%) of 2-methylbenzhydrol and 0.35 mmoles (28.5%) of the 1,2-addition product uncyclized.

Reaction of 5-Hexenylmagnesium Chloride in Ether with Benzalpinacolone.

To 8.85 mmoles of 5-hexenylmagnesium chloride (Grignard E) in 83 ml of ether was added 5.0 mmoles (5.0 ml, 1.0 M) of benzalpinacolone in ether. The reaction was allowed to proceed for 6 hours. Application of the same work-up procedure as used in the previous reaction, gave by glpc analysis, the following distribution of hydrocarbons: 3.2 ± 0.1 mmoles 1-hexene; 0.78 ± 0.02 mmoles methylcyclopentane. The non-volatile products of the reaction mixture were analyzed by glpc and isolated by preparative glpc to give two products, the first: 4.14 ± 0.1 mmoles (83.6%) of 1,1,1-trimethyl-4-phenyl-9-decen-3-one, N_D^{25} 1.4940; IR (neat, film) 3030 (aromatic CH), 2940 (aliphatic CH), 1710 cm^{-1} (C=O); NMR ($CDCl_3$, TMS) 9 H singlet at 1.0 ppm, 8 H multiplet at 1.06-1.87 ppm, 2 H distorted doublet at 2.75 ppm, 1 H multiplet at 2.93-3.50 ppm, 3 H multiplet at 4.67-6.17 ppm, 5 H multiplet at 7.0-7.43 ppm; mass spectrum, m/e (rel. intensity) 272(M^+, 3), 216 (27), 190(21), 174(100), 173(67), 132(47), 118(29), 106(47), 105(42), 92(97), 58(33); Analysis, Calculated for $C_{19}H_{28}$) : C, 83.82%; H, 10.29%. Found: C, 83.66%; H, 10.34%.

The second product isolated : 0.81 ± 0.02 mmoles (16.4%) of 1,1,1-trimethyl-4-phenyl-5-cyclopentyl-2-pentanone, mp. 28.5-29.0°C; IR (melt) 3030 (aromatic CH), 2960 (aliphatic CH), 1700 cm^{-1} (C=O): NMR ($CDCl_3$, TMS) 9 H multiplet at 1.0 ppm, 11 H multiplet at 1.06-2.10 ppm, 2 H distorted doublet at 2.71 ppm, 1 H multiplet at

2.93-3.50 ppm, 5 H multiplet at 7.0-7.43 ppm; mass spectrum, m/e (rel. intensity) 274 (M^+, 3), 216(12), 190(22), 174(100), 173(59), 106(25), 105(27), 92(91), 58(33); Analysis, Calculated for $C_{19}H_{28}O$: C, 83.82%; H, 10.29%. Found: C, 83.62%; H, 10.32%.

Reaction of 5-Hexenyllithium in Ether with Benzophenone.

To 1.0 mmole of benzophenone in 13.3 ml of ether, cooled to -45°C wirh dry ice-acetone bath, was added 2.0 mmoles (6.7 ml, 0.30M) of 5-hexenyllithium (Lithium Reagent A) which was at -76°C and was transferred with a syringe which had been packed in dry-ice. The reaction was held at -40 to -42°C in a dry ice - acetonitrile bath for 24 hours. The reaction mixture was hydrolyzed, all volatile compounds removed under vacuum and collected in a liquid nitrogen trap. GLPC analysis using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at 50°C with a flow rate of 40 ml/min. of helium using cyclohexene as the internal standard indicated the following distribution of hydrocarbons: 0.72 0.02 mmole 1-Hexene ; 0.51 0.015 mmole 1,5-hexadiene; 0.30 0.01 mmole methylcyclopentane ; 0.12 0.01 mmole methylene cyclopentane.

The residue left after vacuum stripping was dissolved in ether, washed with water, the ether layer separated, dried, and the ether removed under vacuum. The remaining liquid was taken up in $CDCl_3$ and analyzed (internal standard CH_3NO_2) by NMR: 0.63 mmole (64.3%) of benzhydrol and 0.35 mmole (35.7%) of 1,1-diphenyl-6-hepten-1-ol.

Reaction of tris(5-hexenyl)aluminum Diethyl Etherate in Pentane with Benzophenone.

To 2.75 mmoles of tris(5-hexenyl)aluminum diethyl etherate in 25 ml of pentane was added 1.0 mmole (2.0 ml, 0.5M) of benzophenone in pentane. After 48 hours, the reaction was worked-up as previously described. GLPC analysis indicated the following distribution of hydrocarbons: 6.71 ± 0.1 mmoles 1-hexene; 0.63 ± 0.01 mmole methylcyclopentane ; 0.47 ± 0.01 mmole 1,5-hexadiene ; 0.04 ± 0.004 mmole methylenecyclopentane. NMR analysis gave the following: 0.51 mmole (53.7%) of benzhydrol and 0.44 mmole (46.3%) of 1,1-diphenyl-6-hepten-1-ol.

Reaction of 1,1-Dimethyl-5-hexenylmagnesium Chloride in Ether with Benzophenone.

To 2.28 mmoles of 1,1-Dimethyl-5-hexenylmagnesium Chloride (Grignard I) in 20 ml of ether was added 0.5 mmole (1.92 ml, 0.26M) of benzophenone in ether. The reaction was allowed to run for 6 hours. Application of the same work-up procedure as used in the previous reaction, gave by glpc analysis using 10% TCEP on Distorport S, 60/80 mesh on a 35-ft. column at 50°C with a flow rate of 30 ml/min. of helium using 1-heptene as the internal standard, the following distribution of hydrocarbons : 0.91 ± 0.02 mmole 1,1,2-trimethylcyclopentane; 0.77 ± 0.02 mmole 2-methyl-6-heptene; 0.09 ± 0.005 mmole 1,1-dimethylcyclohexane. NMR analysis gave the following: 0.19 mmole (36.9%) of 1,1-diphenyl-2,2-dimethyl-6-hepten-1-ol; 0.01 mmole (2.0%) of 1,1-diphenyl-2-(2,2-dimethylcyclopentyl) ethanol; 0.23 mmole

(44.6%) of 4-2,2-dimethylcyclopentylmethylene) benzophenone; 0.085 mmole (16.5%) of 4-(1,1-dimethyl-5-hexenyl) benzophenone.

From a preparative scale reaction, the non-volatile reaction products were allowed to react with an excess of $LiAlH_4$, the reaction hydrolyzed, the ether layer separated, dried, and the ether removed under vacuum. The liquid residue was dissolved in hexane and chromatographed on a 4-ft. silica gel column eluting with 8% ethylacetate/hexane at a flow rate of 5 ml/min. at a pressure of 10 psig.

Fraction 1 was eluted with 200 ml of the solvent mixture. NMR analysis indicated that no aromatic protons were present in this fraction.

Fraction 2 was eluted with 175 ml of the solvent mixture. NMR analysis indicated the presence of essentially one compound with traces of a second compound. The second compound is visible as a small doublet centered at 0.83 ppm (J=7Hz) which strongly suggests that this compound is 1,1-diphenyl-2-(2,2-dimethylcyclopentyl) ethanol, which displays a doublet at exactly the same chemical shift. Repeated chromatography of this fraction and collection of late fractions resulted in obtaining pure 1,1-diphenyl-2,2-dimethyl-6-hepten-1-ol as a colorless liquid, N_D^{25} 1.5649; IR(neat, film) 3570 (OH), 3065 (vinyl CHO), 3030 (aromatic CH), 2960 (aliphatic CH), 1645 (vinyl C=C), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 1.08 ppm, 6 H multiplet at 1.23-2.5 ppm, 1 H broad singlet at 2.28 ppm, 3 H multiplet at 4.67-6.17 ppm, 10 H multiplet at 6.83-7.67 ppm; mass spectrum, m/e (rel. intensity) 294 (M^+,<1), 183(100), 105(48), 91(3), 77(19), 69(5), 41(8), 28(14); Analysis

Calculated for $C_{21}H_{26}O$: C, 85.75% ; H, 8.84%. Found: C, 85.46% ; H, 8.91%.

Fraction 3 was eluted with 100 ml of 12% ethylacetate/hexane. NMR analysis indicates the presence of two compounds. Fraction 3 was hydrogenated at 40 psig using 5% Pd-C in ethanol for 12 hours. The resulting hydrocarbon mixture was separated by preparature glpc using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 2.5-ft. column at 210°C with a flow rate of 60 ml/min. of helium. The first compound eluted (retention time 38 min.) was identified as 4-(1,1-dimethyl-5-hexenyl) phenyl(pheny)methane, IR(neat, film) 3030 (aromatic CH), 2960 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 17 H multiplet at 0.80-1.90 ppm which contains a large 6 H singlet at 1.27 ppm, 2 H singlet at 3.98 ppm, 9 H multiplet at 6.85-7.40 ppm; mass spectrum, m/e (rel. intensity) 280 (M^+, 6), 208(15), 209(100), 91(51), 31(11); Analysis, Calculated for $C_{21}H_{28}$: C, 90.00% ; H, 10.00%. Found: C, 90.23% ; H, 9.72%.

The second compound eluted (retention time 63 min.) was identified as 4-(2,2-dimethylcyclopentylmethylene)phenyl(phenyl)methane, IR (neat, film) 3030 (aromatic CH), 2960 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H doublet at 0.91 ppm, 7 H multiplet at 1.17-250 ppm, 2 H distorted doublet at 2.77 ppm, 2 H singlet at 3.93 ppm, 9 H multiplet at 6.85-7.40 ppm; mass spectrum, m/e (rel. intensity) 278 (M^+ , 38), 182 (44), 181(34), 97(100), 96(40), 91(50), 55(67); Analysis, Calculated for $C_{21}H_{26}$: C, 90.65% ; H, 9.35%. Found: C, 90.47% ; H, 9.44%.

It should be noted that the chemical shifts of the gem-dimethyls used for NMR identification in the 1,6-addition products do not change their relative positions in going from ketone to hydrol to hydrocarbon.

Reaction of 1,1-Dimethyl-5-hexenylmagnesium Chloride in Ether with 2-Methylbenzophenone.

To 5.75 mmoles of 1,1-dimethyl-5-hexenylmagnesium chloride (Grignard H) in 55 ml of ether was added 2.0 mmoles (4.0 ml, 0.5M) of 2-methylbenzophenone in ether. The reaction was allowed to run for 6 hours. Application of the same work-up procedure as the previous reaction gave by glpc analysis (same glpc column and conditions) the following distribution of hydrocarbons: 2.44 ± 0.04 mmoles 1,1,2-trimethylcyclopentane; 1.25 ± 0.03 mmoles 2-methyl-6-heptene; 0.17 ± 0.007 mmole 1,1-dimethylcyclohexane; 0.18 ± 0.007 mmole using average response factors of other hydrocarbons for unidentified peak (most probably 2,2-dimethylmethylenecyclopentane). NMR analysis by comparison to the benzophenone addition products gave the following: 0.41 mmole (20.6%) 1,2-addition straight chain; 0.41 mmole (20.6%) 1,6-addition straight chain; 1.0 mmole (50.3%) 1,6-addition cyclized (5 member ring); 0.17 mmole (8.5%) 2-methylbenzhydrol.

Reaction of 1,1-Dimethyl-5-hexenylmagnesium Chloride in THF with Benzophenone.

To 2.66 mmoles of 1,1-dimethyl-5-hexenylmagnesium chloride (Grignard K) in 25 ml of THF was added 1.0 mmole (1.0 ml. 1.0M) of benzophenone in THF. the reaction was allowed to run for 6 hours. Application of the same work-up procedure as used in the previous reaction, gave by glpc analysis (same glpc column and conditions as the previous reaction) the following distribution of hydrocarbons: 1.13 ± 0.03 mmoles 1,1,2-trimethylcyclopentane; 0.26 ± 0.007 mmole 2-methyl-6-heptene; 0.24 ± 0.007 mmole 1,1-dimethylcyclohexane. NMR analysis gave the following: 0.32 mmole (34.3%) of 1,1-diphenyl-2,2-dimethyl-6-hepten-1-01; 0.22 mmole (23.6%) of 1,1-diphenyl-2-(2,2-dimethyl-cyclopentyl) ethanol; 0.076 mmole (8.1%) 4-(1,1-dimethyl-5-hexenyl) benzophenone; 0.317 mmole (34.0%) 4-2,2-dimethylcyclopentyl-methylene) benzophenone.

Reaction of 1,1-Dimethyl-5-hexenlymagnesium Chloride in n-Butyl Ether with Benzophenone.

To 3.0 mmole of 1,1-dimethyl-5-hexenylmagnesium chloride (Grignard L) in n-Bu_2O was added 0.5 mmole (1.0 ml, 0.5M) of benzophenone in n-Bu_2O. The reaction was allowed to run for 6 hours. Application of the same work-up procedure as used in the previous reaction, gave by glpc analysis (same glpc column and conditions as the previous reaction) the following distribution of hydrocarbons: 1.31 ± 0.04 mmoles 1,1,2-trimethylcyclopentane; 1.08 ± 0.03 moles 2-methyl-6-heptene; 0.12 ± 0.006 mmole 1,1-dimethylcyclohexane. NMR analysis gave the following: 0.22 mmole (44.9%) of 1,1-diphenyl-2,2-dimethyl-6-hepten-1-ol; 0.08 mmole (16.3%) of 1,1-diphenyl-2-(2,2-dimethylcyclopentyl) ethanol; 0.06 mmole (12.2%) of 4-(1,1-dimethyl-5-hexenyl) benzophenone; 0.13 mmole (26.6%) of 4-(2,2-dimethylcyclo-pentylmethylene) benzophenone.

Reaction of 1,1-Dimethyl-5-hexenylmagnesium Chloride in Ether with Benzalpinacolone.

To 4.44 mmoles of 1,1-dimethyl-5-hexenylmagnesium chloride (Grignard J) in 41 ml of ether was added 3.0 mmoles (3.0 ml, 1.0M) of benzalpinacolone in ether. The reaction was allowed to run for 6 hours. Application of the same work-up as used in the previous reaction, gave by glpc analysis (same column and conditions as the previous reaction) the following distribution of hydrocarbons: 0.85 ± 0.02 mmole 2-methyl-6-heptene; 0.62 ± 0.02 mmole 1,1,2-trimethylcyclopentane; 0.05 ± 0.002 mmole, 1,1-dimethylcyclohexane. The non-volatile products of the reaction mixture were analyzed by glpc and isolated by preparative glpc (using the same column) to give three products, the first: 1.25 ± 0.03 mmoles (41.9%) of 1,1,1,5,5,-pentamethyl-4-phenyl-9-decene-2-one, mp. 39-40°C; IR (melt) 3030 (aromatic CH), 2950 (aliphatic CH), 1705 (C=0), 1645 (vinyl C=C), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H doublet centered at 0.85 ppm, 9 H singlet at 0.98 ppm, 9 H multiplet scattered between 1.1-3.4 ppm, 3 H multiplet at 4.77-6.17 ppm, 5 H multiplet at 7.0-7.33 ppm; mass spectrum, m/e (rel. intenstiy) 300 (M^+, 1), 285(< 1), 243 (< 1), 231 (1), 190(69), 134(28), 133(100), 105(52), 91(22), 69(44), 57(56), 55(24); Analysis, Calculated for $C_{21}H_{32}O$: C, 84.00% ; H, 10.67%. Found: C, 83.78%; H, 10.72%.

The second product isolated: 1.51 ± 0.04 mmole (50.7%) of 1,1,1-trimethyl-4-phenyl-5-(2,2-dimethylcyclopentyl)-2-pentanone, N_D^{25} 1.4999; IR (neat, film) 3030 (aromatic CH), 2940 (aliphatic CH), 1705 (C=O), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H singlet at

0.72 ppm, 9 H singlet at 0.98 ppm, 9 H multiplet at 1.1-2.35 ppm, 2 H distorted doublet at 2.75 ppm, 1 H multiplet at 3.0-3.5 ppm, 5 H multiplet at 7.0-7.40 ppm; mass spectrum, m/e (rel. intensity) 300 (M^+, 4), 243(18), 225(18), 201(100), 200(98), 189(76), 105(96), 104(51), 97(82), 96(51), 91(98), 69(27), 57(74); Analysis, Calculated for $C_{21}H_{32}O$; C, 84.00%; H, 10.67%. Found: C, 83.70%; H, 10.70%.

The third product: 0.22 ± 0.008 mmole (7.4%) (using the same response factor as for the first two compounds) was not isolated but most probably was 1,1,1-trimethyl-4-phenyl-4-(2,2-dimethylcyclohexyl)-2-butanone.

<u>Reaction of 2,2-Dimethyl-5-hexenylmagnesium Chloride in Ether with Acetone.</u>

To 0.28 mmoles of 2,2-dimethyl-5-hexenylmagnesium chloride (Grignard M) in 1.0 ml of ether was added 0.15 mmole (0.8 ml, 0.188<u>M</u>) of acetone in ether. After 1 hour, the reaction was hydrolyzed with a minimum amount of saturated aqueous NH_4Cl, dried with anhydrous $MgSO_4$, internal standards added and the reaction mixture analyzed by glpc. Using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at 40°C with a flow rate of 30 ml/min. of helium using 1-heptene as the internal standard, gave the following hydrocarbon distribution; 0.14 ± 0.004 mmole 2,2-dimethyl-5-heptene; 0.041 ± 0.001 mmole 1,1,3-trimethylcyclopentane; 0.032 ± 0.001 mmole 3,3-dimethylmethylenecyclopentane. Using 10% Carbowax 20M on Chromosorb W (AW), 60/80 mesh on a 10-ft. column at 50°C with a flow rate of 60 ml/min. of helium using THF as the internal standard gave the following

products: 0.039 ± 0.002 mmole acetone; 0.033 ± 0.002 mmole isopropyl alcohol. Using the same column and flow rate of helium at 150°C using dodecane as the internal standard gave: 0.065 ± 0.002 mmole 1,1-dimethyl-2-(3,3-dimethylcyclopentyl) ethanol.

From a preparative scale reaction 1,1-dimethyl-2-(3,3-dimethylcyclopentyl) ethanol was isolated by preparative glpc to give a colorless liquid, N_D^{25} 1.4489; IR(neat, film) 3380(broad OH), 2950 (aliphatic CH), 1760 cm^{-1} (C=O); NMR ($CDCl_3$, TMS) undistinguishable multiplet at 0.9-2.7 ppm with apparent singlets at 1.0 ppm and 1.22 ppm; mass spectrum, m/e (rel. intensity) 155(13), 137(8), 97(22), 81(31), 59(100), 55(29), 41(18), 32(18), 28(72); Analysis, Calculated for $C_{11}H_{22}O$: C, 77.65%; H, 12.94%. Found: C, 77.52%; H, 13.00%.

This reaction was repeated allowing 72 hours before hydrolysis. The same results were obtained within experimental error.

<u>Reaction of 2,2-Dimethyl-5-hexenylmagnesium Chloride in Ether with Acetone and Benzophenone.</u>

To 2.8 mmoles of 2,2-dimethyl-5-hexenylmagnesium chloride (Grignard M) in 20 ml of ether was added 1.4 mmoles (7.4 ml, 0.188<u>M</u>) of acetone in ether. After 1 hour 1.0 mmole (2.0 ml, 0.5<u>M</u>) of benzophenone in ether was added. After 48 hours, the reaction was hydrolyzed and all volatile compounds removed under vacuum at 65°C and collected in a dry ice-acetone trap. GLPC analysis using the two columns and conditions described in the previous reaction gave: 0.40 ± 0.01 mmole 2,2-dimethyl-5-heptene; 0.29 ± 0.01 mmole 1,1,3-trimethylcyclopentane; 0.16 ± 0.008 mmole 3,3-dimethylmethylene cyclopentane; 0.24 ± 0.01 mmole

acetone; 0.15 ± 0.007 mmole isoproply alcohol; 0.06 0.02 mmole 1,1-dimethyl-2-(3,3-dimethylcyclopentyl) ethanol.

The residue left after vacuum stripping was dissolved in ether, washed with water, the ether layer separated, dried, and the ether removed under vacuum. The reamining liquid was shown by IR to have no (C=0) absorption between 1600-1750 cm^{-1}; NMR analysis indicates; 0.88 mmole (88%) straight chain 1,2-addition product; 0.12 mmole (12%) cyclized 1,2-addition product (by difference between mmoles indicated by vinyl protons and mmoles indicated by aromatic protons).

The non-volatile reaction products were hydrogenated at 40 psig using 5% Pd-C in ethanol for 12 hours. The resulting hydrocarbon mixture was separated by preparative glpc using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 12-ft. column at 220°C with a flow rate of 70 ml/min. of helium. The first compound eluted (retention time 82 min.) was identified as 1,1-diphenyl-3,3-dimethylheptane, IR(neat, film) 3030 (aromatic CH) 2950 (aliphatic CH), 1600 cm^{-1} (aromatic CH); NMR ($CDCl_3$, TMS) 6 H singlet at 0.78 ppm, 9 H multiplet at 0.79-1.8 ppm, 2 H doublet at 2.10 ppm, 1 H triplet at 4.03 ppm, 10 H multiplet at 6.90-7.40 ppm; mass spectrum, m/e (rel. intenstiy) 280 (M^+, 6), 22(4), 168(3), 167(100), 165(14), 152(9), 91(4), 71(8), 57(18), 43(8), 41(5), 28(15); Analysis Calculated for $C_{21}H_{28}$: C, 90.00%; H, 10.00%. Found: C, 89.98%; H, 10.00%.

The second compound eluted (retention time 100 min.) was identified as 1,1-diphenyl-2-(3,3-dimethylcyclopentyl) ethane, IR(neat, film) 3030(aromatic CH), 2945(aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR($CDCl_3$, TMS) 6 H doublet at 0.95 ppm, 9 H multiplet at 1.10-2.35 ppm, 1 H triplet at 3.98 ppm, 10 H multiplet at 6.9-7.45 ppm; mass spectrum, m/e (rel. intensity) 278 (M^+,4), 168(19), 167(100), 166(4), 165(9), 152(8), 91(4), 69(5), 57(8), 55(5), 28(20); Analysis Calculated for $C_{21}H_{26}$: C, 90.51%; H, 9.49%. Found: C, 90.25%; H, 9.67%.

The ratio of peak areas for compound 1: compound 2 were about 90:10 on the preparative glpc chromatogram.

<u>Reaction of 2,2-Dimethyl-5-hexenylmagnesium Chloride in Ether with 2-Methylbenzophenone.</u>

To 9.5 mmoles of 2,2-dimethyl-5-hexenylmagnesium chloride (Grignard N) in 77 ml of ether was added 9.0 mmoles (18.0 ml, 0.5<u>M</u>) of 2-methylbenzophenone in ether. After 6 days, the reaction was hydrolyzed, and all volatile compounds removed under vacuum and collected in a dry ice-acetone trap. GLPC analysis using the Apiezon L column and conditions described in the previous reaction gave the following distribution of hydrocarbons: 0.30 ± 0.01 mmole 1,1,3-trimethylcyclopentane; 0.18 ± 0.01 mmole 2,2-dimethyl-5-hexene; 7.15 ± 0.1 mmole 3,3-dimethylmethylenecyclopentane.

The residue left after vacuum stripping was dissolved in ether, washed with water, the ether layer separated, dried, and the ether removed under vacuum. The remaining liquid was shown by IR to have a (C=O) absorption bond at 1685 cm^{-1}. The non-volatile reaction products were dissolved in ether and added to an excess of $LiAlH_4$. Standard work-up followed by column chromatography (4-ft. alumina column, eluting with 8% ethylacetate/hexane with a final column wash with 12% ethylacetate/hexane gave 3 fractions.

Fraction 1, 1.60 mmole (0.49 gms) was shown by NMR analysis to contain an alcohol and an olefin (dehydration product). Fraction 1 was hydrogenated at 40 psig using 5% Pd-C in ethanol for 5 days. The resulting hydrocarbon product was shown to contain only one product (retention time 43 min.) and was isolated by preparative glpc (using the same preparative column in the previous reaction at 235°C) to give; 1-phenyl-1-(2-methylphenyl)-3,3-dimethylheptane, N_D^{25} 1.5361; IR(neat, film) 3030(aromatic CH), 2950(aliphatic CH) 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 0.78 ppm, 9 H multiplet at 0.85-1.4 ppm, 2 H doublet at 2.08 ppm, 3 H singlet at 2.36 ppm, 1 H triplet at 4.3 ppm, 9 H multiplet at 6.9-7.70 ppm; mass spectrum, m/e (rel. intensity) 294 (M^+, 18), 181(100), 166(12), 165(14), 57(8); Analysis, Calculated for $C_{22}H_{30}$; C, 89.80%; H, 10.20%. Found: C, 89.62%; H, 10.27%.

It should be noted that cyclized 1,2-addition product was not detected.

Fraction 2, was shown by NMR analysis to contain: 0.008 mmole straight chain 1,6-addition product in the reduced hydrol form; 0.18 mmole cyclized 1,6-addition product in the reduced hydrol form (by difference between mmoles indicated by vinyl protons and mmoles indicated by aromatic protons). Fraction 2 was hydrogenated at 40 psig using 5% Pd-C in ethanol for 5 days. The resulting hydrocarbon mixture was separated by preparative glpc using the same column and conditions as above. Repeated injection and collection of peaks was necessary due to the close retention times of the two compounds.

The first compound eluted (retention time 47 min.) was identified as phenyl-2-methyl-4-(2,2-dimethylhexyl)phenylmethane, IR (neat, film) 3030 aromatic CH), 2960 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 0.83 ppm, 9 H multiplet at 0.9-1.6 ppm, 3 H singlet at 2.25 ppm, 2 H singlet at 2.43 ppm, 2 H singlet at 3.98 ppm, 8 H multiplet at 6.7-7.40 ppm; mass spectrum, m/e (rel. intensity) 294(M^+,5), 235(3), 195(8), 194(5), 182(22), 81(100), 167(7), 166(15), 165(19), 57(17); Analysis, Calculated for $C_{22}H_{30}$: C, 89.80%; H, 10.20%. Found: C, 89.71%; H, 10.28%.

The second compound eluted (retention time 48 min.) was identified as phenyl-2-methyl-4-(3,3-dimethylcyclopentylmethylene) phenylmethane, IR (neat, film) 3030 (aromatic CH), 2950 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H singlet at 0.77 ppm, 7 H multiplet at 0.83-1.8 ppm, 3 H singlet at 2.25 ppm, 2 H doublet at 2.3 ppm, 2 H singlet at 3.98 ppm, 8 H multiplet at 6.9-7.5 ppm; mass spectrum m/e (rel. intensity) 292(M^+, 43), 277(9), 235(100), 196(34), 143(30), 105(32), 57(36); Analysis, Calculated for $C_{22}H_{28}$: C, 90.41%; H, 9.59%. Found: C, 90.23%; H, 9.67%.

Fraction 3, was washed off the column with 12% ethylacetate/hexane and shown by NMR analysis to contain 7.15 mmoles of 2-methylbenzhydrol.

<u>Reaction of 2,2-Dimethyl-5-hexenylmagnesium Chloride in Ether with Benzalpinacolone.</u>

To 4.75 mmoles of 2,2-dimethyl-5-hexenylmagnesium chloride (Grignard N) in 42.75 ml of ether was added 4.25 mmole (4.25 ml, 1.0M)

of benzalpinacolone in ether. The reaction was allowed to run for 24 hours. Application of the same work-up procedure as used in the previous reaction gave by glpc analysis the following distribution of hydrocarbons: 0.076 ± 0.003 mmole 2,2-dimethylhexane; 0.44 ± 0.01 mmole 1,1,3-trimethylcyclopentane. The non-volatile products of the reaction mixture were analyzed by glpc and isolated by preparative glpc to give two products, the first: 0.79 ± 0.02 mmole 1,1,1,6,6-pentamethyl-4-phenyl-9-decene-2-one, N_D^{25} 1.4961; IR (neat, film) 3030 (aromatic CH), 2950 (aliphatic CH), 1705 (C=O), 1645 (vinyl C=C), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H doublet at 0.77 ppm, 9 H singlet at 0.98 ppm, 6 h multiplet at 1.10-2.3 ppm, 2 H distorted doublet at 2.7 ppm, 1 H multiplet at 3.37 ppm, 3 H multiplet at 4.67-6.17 ppm, 5 H multiplet at 7.0-7.40 ppm; mass spectrum, m/e (rel. intensity) 300 (M^+,<1), 245(21, 243(10), 146(15), 145(100), 105(18), 104(18), 57(51), 55(25); Analysis, Calculated for $C_{21}H_{32}O$: C, 84.00%; H, 10.67%. Found: C, 83.95%; H, 10.77%.

The second compound isolated; 3.45 ± 0.1 mmole 1,1,1-trimethyl-4-phenyl-5-(3,3-dimethylcyclopentyl)-2-pentanone, N_D^{25} 1.4955; IR (neat, film) 3030 (aromatic CH), 2940 (aliphatic CH), 1705 (C=O), 1600 cm^{-1} (aromatic C=C); NMR ($CDCl_3$, TMS) 6 H doublet at 0.95 ppm, 9 H singlet at 1.02 ppm, 9 H multiplet at 1.1-2.10 ppm, 2 H distorted doublet at 2.73 ppm, 1 H multiplet at 3.33 ppm, 5 H multiplet at 7.1-7.43 ppm; mass spectrum, m/e (rel. intensity) 300 (M^+, 1), 243(12), 225(12), 201(100), 200(80), 189(41), 145(41), 105(76), 104(56), 97(58), 91(95), 57(78), 55(46).

Reaction of tert-Butylmagnesium Chloride in n-Butyl Ether with Benzophenone.

To 3.0 mmoles of t-butylmagnesium chloride in 18 ml of ether was added 29 ml of n-butyl ether. The ether was removed under vacuum (12 ml of n-butyl ether was added due to loss during removal of diethyl ether). To this solution was added 0.5 mmole (1.0 ml, 0.5M) of benzophenone in n-butyl ether. The reaction was allowed to run for 6 hours. Standard Grignard work-up gave by NMR analysis: 0.25 mmole (51%) 1,2-addition product and 0.24 mmole (49%) 1,6-addition product.

Reaction of tert-Butyllithium in Ether with Benzophenone.

Two mmoles of t-butyllithium in hexane was desolvated under vacuum, cooled to -20°C, and 19 ml of cold diethyl ether added. To this solution at -20°C was added 0.5 mmole (1.0 ml, 0.5M) benzophenone in ether. Standard work-up followed by NMR analysis gave: 0.12 mmole (24%) 1,2-addition product and 0.38 mmole (76%) 1,6-addition product.

Reaction of tert-Butyllithium in Hexane with Benzophenone.

To 2.0 mmoles of t-butyllithium in 19 ml of hexane was added 0.5 mmole (1.0 ml, 0.5M) of benzophenone in hexane. Standard work-up followed by NMR analysis gave: 0.23 mmole (46%) 1,2-addition product and 0.27 mmole (54%) 1,6-addition product.

Reaction of Flourenone Ketyl with 2-Methylbenzophenone.

To 1.0 mmole (0.362 gm) of flourenone pinacol in 15 ml of THF was added 2.0 mmoles (1.96 ml, 1.02M) of "CH_3MgBr" in THF. To this yellow solution was added 2.0 mmole (4.0 ml, 0.50M) of 2-methylbenzophenone in THF. After 6 hours, standard work-up followed by NMR analysis indicated the following products: 1.0 mmole flourenone pinacol and 1.0 mmole 2-methlybenzophenone.

Reaction of 2-Methylbenzophenone Ketyl with Flourenone.

To 1.0 mmole (0.394 gm) of 2-methylbenzophenone pinacol in 15 ml of THF was added 2.0 mmoles (1.96 ml, 1.02M) of "CH_3MgBr" in THF. To this blue solution was added 2.0 mmole (4.0 ml, 0.5M) of fluorenone in THF. After 6 hours, standard work-up followed by NMR analysis indicated the following products: 1.96 mmoles of 2-methylbenzophenone; 0.020 mmole 2-methylbenzophenone pinacol; 0.98 mmole flourenone pinacol; 0.044 mmole fluorenone.

Reactions of "CH_3MgBr" and tC_4H_9MgCl" with 2-Methyl-benzophenone in the Presence of Fluorenone Ketyl in Diethyl Ether.

To 0.25 mmole of fluorenone pinacol in ether was added from 0.5 to 3.75 mmoles of "CH_3MgBr" or "t-ButylMgCl". To this solution was added 1.0 mmole of 2-methylbenzophenone. Reactions were carried out for 4 hours followed by standard work-up procedures and NMR analysis.

Reactions of "CH_3MgBr/MgH_2" with Various Substrates.

To 1.0 mmole of "CH_3MgBr" in THF which contains 0.33 mmole of active MgH_2[41] were added in separate reactions 0.5 mmole of the following substrates: 1-bromooctane; benzylchloride; 1-decene; chalcone; 2-methylbenzophenone; 4-t-butylcyclohexanone; and benzonitrile. Reactions were analyzed by NMR (internal standard CH_3NO_2) and by glpc (versus and internal standard) were NMR analysis was not applicable.

Reactions of "HMgBr"[46] with alkenes and Alkynes using bis-Triphenylphosphine Nickel II Chloride Catalyst.

To 0.5 mmole of "HMgBr"[46] in THF was added 0.2 mmole of alkene or alkyne in a test tube capped with a septum stopper in the dry box. To this solution was added by syringe 0.01 mmole (5 mole %) of bis-triphenylphosphine nickel (II) chloride. The reactions were carried out at either room temperature, 0°C (ice/H_2O), -23°C (CCl_4/N_2), -42°C (acetonitotile/N_2) and at -76°C(acetone/dry ice). Reactions were allowed to run for 24 hours before hydrolysis. GLPC analysis was carried out using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at various temperatures and flow rates of helium. Internal standards used were octane, cyclohexane and phenylacetylene.

Reaction of Dimethyl-t-butylaluminum with Benzophenone in Pentane.

To 1.0 mmole of dimethyl-t-butylaluminum in 9.0 ml of pentane was added 0.5 mmole (1.0 ml, 0.5M) of benzophenone in pentane. After 12 hours, the reaction was hydrolyzed with saturated aqueous NH_4Cl, extracted with ether, the layer was separated, dried, the ether removed under vacuum and the remaining residue taken up in $CDCl_3$ and analyzed by NMR. NMR analysis (internal standard CH_3NO_2) indicated 0.10 mmole (20.4%) of methyl-1,2-addition product and 0.39 mmole (79.6%)of benzhydrol.

CHAPTER III

RESULTS AND DISCUSSION

The Nature and mechanism of Hydrol Formation

When "CH_3MgBr" was allowed to react with 2-MBP in large Grignard: ketone ratios, the product distribution varied widely with both the purity of magnesium and the method of preparation of the Grignard reagent (Table 1). The formation of 2-methylbenzhydrol appears to be dependent mainly on the method of preparation of the Grignard reagent. On the other hand, the amount of 2,2'-dimethylbenzopinacol produced has been shown to depend only on the purity of magnesium used.[8] The "other"[47] product listed in the table also depends only on the purity of magnesium.

The various grades of magnesium used in these experiments were analyzed by four different methods. Spark Source Mass Spectroscopy, Emission Spectroscopy, Proton Excited X-ray Spectroscopy, and X-ray Flourescence Spectroscopy. These methods all gave similar results. Analysis by Spark Source Mass Spectroscopy of the transition metal impurities in the various grades of magnesium used in this study are given in Table 1. Multiple regression and correlation analysis[48] was carried out on this data. Although the relationship between the amount of transition metal present in the magnesium metal used to prepare the Grignard reagent and the amount of pinacol and "other" product formed is excellent, the hydrol formed did not correlate at all with the transition metal content of the magnesium.

The Nature and Mechanism of Hydrol Formation

The production of hydrols in reactions of "CH_3MgBr" with ketones is surprising since methyl Grignard reagents, having no β-hydrogen atoms, would generally not be considered capable of such reductions. Nevertheless, we have shown that when "CH_3MgBr" (prepared from Dow doubly sublimed magnesium) is allowed to react with 2-MBP, 2-methylbenzhydrol is formed. The amount of this product observed increases dramatically (Table 2) as the Grignard:ketone ratio increases. It is important to note that the amount of hydrol produced under a given set of conditions has been shown not only to depend on the grade of magnesium (Table 1) used to prepare the Grignard reagent, but also on the particular preparation from the same grade of magnesium. For example, different "CH_3MgBr" solutions, all made from Dow doubly sublimed magnesium using excess magnesium, when allowed to react with 2-MBP formed 2-methylbenzhydrol in yields varying from 36% to 72%. However, for duplicate runs from the same Grignard solution, results are reproducible to within 3%. It has also been shown (Table 1) that preparation of the "CH_3MgBr" from excess methyl bromide greatly decreases the ability of the Grignard reagent to reduce benzophenone.

It is also important to note (Table 2) that when a constant amount of "CH_3MgBr" is allowed to react with decreasing amounts of ketone, the relative amount of 2-methylbenzhydrol produced increases with respect to the initial concentration of ketone; however, the absolute amount of hydrol remains constant (this observation has also been made by Rudolph and Smith[49]). These data indicate that the agent which produces the hydrol is used up stoichimetrically in the reaction.

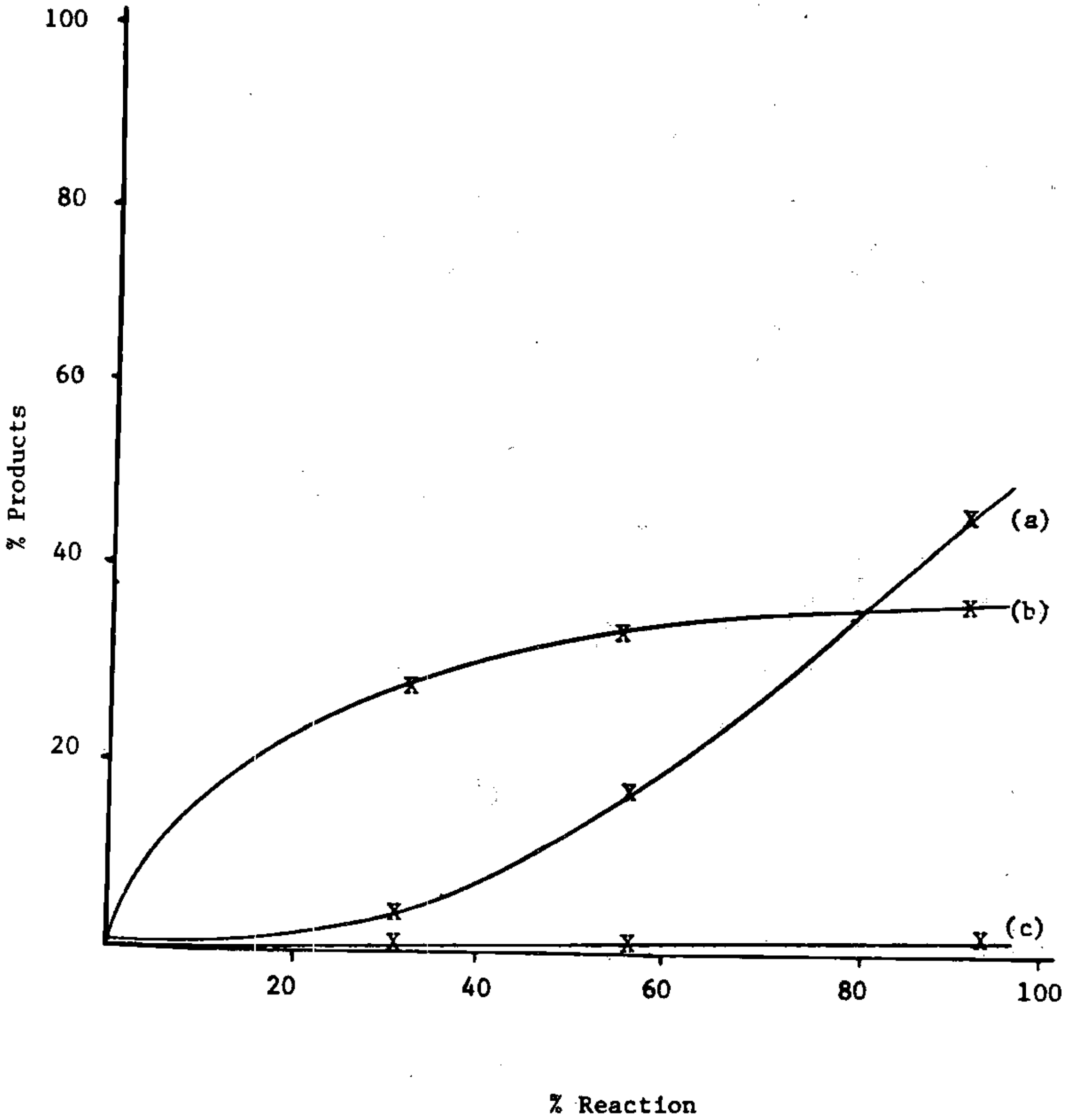


Figure 1. Reaction "CH_3MgBr" (0.50 M) With 2-MBP (0.00125 M) in Diethylether at -30^{o}phenylethanol. (b) 2-methylbenzhydrol. (c) 2,2-dimethylbenzopinacol.

A low temperature product study (by Jerry D. Buhler)[50] makes this point dramatically (Table 3, Figure 1). For example, when "CH_3MgBr" (0.05 M) was allowed to react with 2-MBP (0.00125 M) at - 30° and samples taken with time, the data clearly show that more than one reaction pathway is in operation and that initially the ketone is rapidly reduced to the hydrol before 1,2-addition becomes significant. From these observations, it is clear that the hydrol must be caused by some "impurity" (estimated 0.1-0.2%)[51] in the Grignard reagent.

Experiments (most carried out by Jerry D. Buhler) were run to determine the reaction conditions that affect the formation of hydrol. It was shown that the reagent concentration and the reaction temperature has little effect on the reaction.[50] It was also found that filtering the Grignard reagent before use had no effect on the amount of hydrol formed.[52] The multiple regression and correlation analysis mentioned earlier (in connection with Table 1) showed no correlation between benzhydrol formation and transition metal content of the Grignard reagent.

With these results in mind, attention was turned to an understanding of how the hydrol is formed. A number of pathways appear possible for this reaction. The Grignard reagent could react with the ketone in two successive SET steps to give the dianion which upon hydrolysis would form the hydrol (eq. 2). The Grignard reagent could react in some sort of an alpha-elimination process to give an active hydride species which could serve as the reducing agent (eq. 3). It also is possible that the radical anion (eq. 4) or possibly the dianion (eq. 5) formed in the reaction of the ketone with the Grignard reagent could abstract a hydrogen atom or proton respectively from the solvent before hydrolysis to give the hydrol. Another possibility would be the

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \longrightarrow Ph_2\dot{C}\text{–}OMgBr \longrightarrow Ph_2\ddot{C}\text{–}OMgBr \xrightarrow[H+]{H_2O} Ph_2CHOH \qquad (2)$$

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \longrightarrow CH_2{:} + HMgBr \longrightarrow Ph_2\overset{H}{\overset{|}{C}}\text{–}OmgBr \xrightarrow[H+]{H_2O} Ph_2CHOH \qquad (3)$$

$$Ph_2\dot{C}\text{–}MgBr + (CH_3CH_2)_2O \longrightarrow Ph_2\overset{H}{\overset{|}{C}}\text{–}OMgBr \xrightarrow[H+]{H_2O} Ph_2CHOH \qquad (4)$$

$$Ph_2\ddot{C}\text{–}OMgBr + (CH_3CH_2)_2O \longrightarrow Ph_2\overset{H}{\overset{|}{C}}\text{–}OMgBr \xrightarrow[H+]{H_2O} Ph_2CHOH \qquad (5)$$

$$M\text{–}H + Ph_2C{=}O \longrightarrow Ph_2\overset{H}{\overset{|}{C}}\text{–}OM \xrightarrow[H+]{H_2O} Ph_2CHOH \qquad (6)$$

presence of an active hydride species in the Grignard reagent which could directly reduce the ketone (eq. 6).

An investigation into these possibilities was carried out. When "CH_3MgBr" was allowed to react with 2-MBP in 400:1 ratio and the reaction mixture quenched with 99.9% D_2O, no deuterium incorporation at the α-carbon was observed indicating that the hydrol is not a result of dianion formation followed by hydrolysis. Also when "CD_3MgBr" was allowed to react with 2-MBP no deuterium incorporation at the α-carbon atom was observed indicating the absence of a reaction as described by eq. 3. In a series of experiments (by Thomas L. Wiesemann),[18] the bromomagnesium ketyl was formed by the reaction of "CH_3MgBr" with 2,2'-dimethylbenzopinacol in 2:1 ratio and the resulting solution was altered in ways that produce a solution similar to that which exists in the reaction mixture involving the reaction of "CH_3MgBr" with 2-MBP. In the presence of Grignard:ketyl ratios ranging from 1 to 800, $FeCl_3$ ranging from 0.0 to 0.5 mole percent, and 1,2-addition product ranging from 0.0 to 1.0 equivalent, the ketyl upon hydrolysis yielded only 2,2'-dimethylbenzopinacol. In no case was any 2-methylbenzhydrol detected. These results indicate that neither the ketyl nor the dianion (possibly formed by the reaction of ketyl in excess Grignard reagent with iron catalysis, eqs. 4 and 5) can account for the formation of hydrol in the reaction of "CH_3MgBr" with 2-MBP.

In a separate series of reactions,[18] "CH_3MgBr" was allowed to react with 2-MBP in $(CH_3CD_2)_2O$ (Table 4). An intermediate ketyl may be expected to abstract $D\cdot$ from the alpha position of the solvent while the dianion would be more likely to abstract H^+ from the beta position. When "CH_3MgBr" was prepared in $(CH_3CD_2)_2O$ and the reaction with ketone carried out in the same solvent, all of the hydrol formed contained D on the α-carbon atom of $C_6H_5(C_7H_7)C(D)OH$.[18] This result shows that the hydrogen atom involved in the reduction comes from the ether, and also provides further evidence that the dianion (eq. 5) is not an intermediate. However, when "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ was desolvated and redissolved in $(CH_3CD_2)_2O$ and the resulting solution allowed to react with 2-MBP, all of the hydrol produced was $C_6H_5(C_7H_7)C(H)OH$.[18]

This result demonstrates that the hydrogen abstraction from the ether does not take place when "CH_3MgBr" reacts with the ketone, but during the formation of the "CH_3MgBr". These data strongly indicate once again that the pathways described by eqs. 4 and 5 are not in effect. It appears that the hydrol producing species must be formed during the Grignard preparation step and that this species is more highly reactive as a reducing agent toward ketones than is the Grignard reagent as an alkylating agent (Figure 2). These experiments also indicate that the step involving the formation of the reducing species is radical in nature (since the α-D was abstracted from the ether in spite of the primary deuterium kinetic isotope effect involved.)

Since analysis of Dow doubly sublimed magnesium[19] shows no trace element or combination of trace elements in sufficient quantities (0.2%) to account for the amount of reducing agent necessary to form benzyhydrol in up to 72% yield, it seems that the active reducing agent must be a magnesium hydride species. Although magnesium hydrides have never before been reported as by-products in the formation of a Grignard reagent, several experiments were carried out which demonstrate that indeed this is the case. Table 5 illustrates the striking similarity in reduction selectivity between an equimolar mixture of 2-MBP and acetone with "CH_3MgBr" prepared from Dow doubly sublimed magnesium and reduction of the same mixture with "CH_3MgBr" prepared from ROC/RIC magnesium crystals with added MgH_2. In both cases the reduction product is almost exclusively 2-methylbenzhydrol (98% vs. 94%). These results are very meaningful considering that "CH_3MgBr" prepared from ROC/RIC crystals yields no reduction product without added MgH_2. The fact that considerable reduction is observed in such a large excess of alkylating agent indicates that MgH_2 dissolved in Grignard reagent is a powerful reducing agent toward ketones.

Further evidence that -MgH in the Grignard reagent is the source of the observed reduction is indicated by the similarity in observed stereochemistry when "CH_3MgBr" that gives reduction (Grignard prepared from Dow doubly sublimed magnesium) reduces 4-t-butycyclohexanone compared to "CH_3MgBr" that normally does not give reduction (Grignard prepared from ROC/RIC magnesium) except when MgH_2 is added to the reagent. The data in Table 6 show that the reduction of "CH_3MgBr" (Dow doubly sublimed) with 4-t-butycyclohexanone yields the reduction product in 89:11 ratio (equatorial:axial alcohol). On the other hand, "CH_3MgBr" prepared from ROC/RIC magnesium which normally does not give any reduction product, produces a 79:21 ratio of alcohols (equatorial:axial) when MgH_2 is added. The similarity of the above stereochemistry is even more striking when compared to MgH_2 alone which gives a 32:68 ratio of reduction products.

A number of studies have indicated that Grignard formation is a radical process[53] involving the $CH_3\cdot$, $\cdot Mg^+$, and Br^- species. Combination of these species leads to "CH_3MgBr". From our data it is apparent that up to 0.2% of a radical species must react with ether to form an active hydride species. The following reaction is suggested:

$$CH_3CH_2OCH_2CH_3 + \cdot MgBr \longrightarrow HMgBr + CH_3\dot{C}HOCH_2CH_3 \qquad (7)$$

It was not initially apparent, though, why "CH_3MgBr" prepared from some grades of magnesium led to more hydrol than those samples prepared from other grades under the same reaction conditions (Table 1). Qualitatively it was noticed that the Grignard reagents prepared from large magnesium chips (Ventron chips and ROC/RIC crystals) gave little benzhydrol while those prepared from fine shavings (Dow doubly and triply sublimed) gave much more benzhydrol. In addition it was found that intermediate sized chips (Grignard grade turnings and Dow #5) of magnesium led to intermediate amounts of benzhydrol. A glance at Table 1 clearly indicates that much less hydrol formation is observed when the "CH_3MgBr" is prepared in excess methyl bromide. It became apparent that methyl bromide is capable of reacting with the active hydride species during Grignard reagent formation thus consuming it. In order to test this point, 2-MBP (0.3 mmole) was allowed to react with "CH_3MgBr" (120 mmole - ROC/RIC crystals) to which 0.2 mmole of MgH_2 had been added. The resulting product mixture contained 79% 2-methylbenzhydrol. The same reaction was carried out after addition of six drops of methyl bromide to the Grignard reagent prior to the addition of the Grignard reagent to the ketone. The resulting product mixture contained only 15% 2-methylbenzhydrol. A similar set of experiments was carried out using "CH_3MgBr" prepared from Dow doubly sublimed magnesium with no MgH_2 added. An equivalent set of results was obtained. It is clear, then that methyl bromide is capable of destroying the activity of both the dissolved magnesium hydride species that is formed in the preparation of the Grignard reagent and that added as MgH_2.

The size of the magnesium chips used in the Grignard preparation has a direct bearing on the amount of CH_3Br that builds up in the reaction mixture. Large magnesium chips have a relatively small surface area which allows CH_3Br to build up during the formation of the Grignard reagent, thereby destroying the magnesium hydride species. On the other hand, a much more finely divided grade of magnesium metal would be expected to react with CH_3Br much more rapidly than the larger magnesium chips thus avoiding a buildup of CH_3Br solution. Thus it is expected that the latter finely divided magnesium would produce a Grignard reagent that would result in more reduction of ketone to hydrol. It is also probable that the rate of addition of CH_3Br during the preparation of "CH_3MgBr" would have an important effect on the hydride content of the resulting Grignard reagent. A rapid flow of CH_3Br would tend to cause Grignard reagents of low hydride content and slow CH_3Br addition would tend to form Grignard reagents of high hydride content. In preparation of "CH_3MgBr" for this study, no attempt was made to quantitatively control CH_3Br flow rates. The general procedure was to set the methyl bromide flow rate such that gentle ether reflux was maintained during Grignard formation. This, of course, necessitated the use of higher flow rates when forming "CH_3MgBr" from larger magnesium chips to maintain the same apparent rate of reaction.

In order to investigate the effect of the size of magnesium shavings used to prepare the Grignard reagent and the effect of methyl bromide flow rate, the following experiments were carried out.[54] A block of Dow doubly sublimed magnesium was carefully milled with a new carbide tool to obtain fine shavings (approximately normal size for the Dow doubly sublimed magnesium we had been using) medium shavings (approximately Grignard grade turnings in size) and large chips (approximately

ROC/RIC crystals in size). Methylmagnesium bromide was prepared from magnesium shavings of each size at a constant flow rate of 214 and 682 ml min^{-1} (Table 7). The slower flow rate was set such that gentle ether reflux was maintained in preparation of "CH_3MgBr" employing the fine shavings (i.e., a condition intended to maximize 2-methylbenzhydrol formation). The mass of magnesium was the same to within 0.1 g in all three preparations and the flow time was cut by one-third at the higher flow rate such that the total amount of CH_3Br added was the same in all six preparations. The implications are clear. The percentage of 2-methylbenzhydrol found in the reactions decreases in a regular way at constant CH_3Br flow rate as the size of the magnesium shavings are increased and as the CH_3Br flow rate is increased. Thus the importance of excess CH_3Br during the preparation of the Grignard is very important in determining the amount of MgH_2 remaining in the Grignard reagent after its preparation.

The Nature of Alkyl Transfer in Reactions of Grignard Reagents with Ketones

Now that the mechanisms of hydrol formation and pinacol[8] formation in Grignard reactions with ketones have been determined, the description of the alkyl transfer from the Grignard reagent to the carbonyl carbon atom is the most significant question that remains to be answered. With respect to the nature of this alkyl transfer, Holm and Crossland[6] have presented strong evidence for a rate-determining single electron transfer (SET) step (similar to eq. 1) in the reaction of _t_-BuMgCl with benzophenone in diethyl ether involving the intermediate formation of a "free" radical and radical anion. The ability to "trap" or "observe" the intermediate radical or radical anion would be instrumental in establishing the integrity of the proposed mechanism.

With this in mind, radical probes were incorporated into the R group of Grignard reagents such that free radical character would be observed as isomerization or cyclization of the particular probe. The radical probes studies are illustrated in Table 8.

Cis-Propenylmagnesium Bromide

Should the R group of cis-propenylmagnesium bromide become a "free" radical during the course of a reaction, the cis-propenyl radical would isomerize ($K_{Inversion} \simeq 10^8\ sec^{-1}$)[55] to the thermodynamically more stable trans-propenyl radical resulting in a product with trans stereochemistry.

Three propenyl Grignard reagents of different cis/trans ratios were allowed to react with benzophenone (Table 9). Reactions carried out in excess ketone do not result in isomerization of the propenyl group evidenced by the fact that the starting Grignard reagent cis/trans ratio was exactly reflected in the reaction products. The apparent slight degree of isomerization observed when the reactions are carried out in excess Grignard reagent can be explained by the relative reactivities of the cis and trans isomers. It is found that the trans isomer reacts about twice as fast as the cis isomer with benzophenone. The only effect produced by doping the reactions with Fe salts was the formation of small amounts of pinacol, the alkylation product cis/trans ratios were unaffected.

5-Hexenylmagnesium Chloride

Should the R group of 5-hexenylmagnesium chloride become a "free" radical during the course of a reaction, the 5-hexenyl radical would cyclize ($K_{cyc} \simeq 10^5\ sec^{-1}$)[56,76,77] predominantly to the cyclopentylmethyl radical and to a minor extent to the cyclohexyl radical resulting in products with cyclic R groups. When 5-hexenylmagnesium chloride (1^{o} probe Grignard) was allowed to react with benzophenone in ether only straight chain 1,2-addition products (51%) and benzhydrol (49%) were observed. The benzhydrol was apparently produced by β-hydrogen reduction of the benzophenone by the Grignard reagent. This reaction was further investigated by using a sterically hindered ketone (2-methylbenzophenone) and a more strongly coordinating solvent (THF) in hopes of slowing down the 1,2-addition process such that cyclization might be observed. 5-Hexenylmagnesium chloride in THF when allowed to react with 2-MBP gave straight chain 1,2-addition (28%) and 2-methylbenzhydrol (88%) as products. Thus 1,2-alkylation was slowed down allowing β-hydrogen reduction to become the major reaction pathway.

The absence of isomerization or cyclization in the 1,2-addition products of cis-propenyl-magnesium bromide (a vinylic Grignard) and 5-hexenylmagnesium chloride (a primary Grignard), respectively, with benzophenone indicates that either the reaction is polar or, if SET, no "free" radical character is exhibited (rate of addition is faster than the rate of cyclization of the probe).

1,1-Dimethyl-5-hexenylmagnesium Chloride

Should the R group of 1,1-dimethyl-5-hexenylmagnesium chloride (a tertiary Grignard) become a "free" radical during the course of a reaction, the 1,1-dimethyl-5-hexenyl radical would cyclize ($K_{cyc} \simeq 10^5$ sec^{-1})[56] predominantly to the 2,2-dimethylcyclopentylmethylene radical resulting in products with cyclic R groups. Solutions of 1,1-dimethyl-5-hexenylmagnesium chloride contained from 38-55% of the Grignard reagent as the cyclic isomers. Thus in every reaction the excess Grignard reagent had to be accounted for as the hydrocarbon (hydrolysis product) such that the origin (straight chain or cyclic Grignard reagent) of the alkylation products could be determined. When 1,1-dimethyl-5-hexenylmagnesium chloride (3^o probe Grignard) was allowed to react with benzophenone the hydrocarbon analysis[57,58] indicated that almost 90% of the reaction proceeded through the straight chain isomer. The resulting alkylation products consisted of 61% 1,6-addition and 39% 1,2-addition product. Although very little cyclization of the probe was observed in the 1,2-addition product (2% cyclized 1,2-addition product is accounted for by the amount of cyclized Grignard reagent which reacted) 73% of the 1,6-addition product was cyclized.

The ratio of cyclized to uncyclized 1,6-addition products (73:27) established the radical nature of the 1,6-addition process (heretofore assumed to be a radical process) and indicated that the rate of probe cyclization is comparable to the rate of 1,6-addition product formation. It is important to note that the ratio of 1,6-addition to 1,2-addition products (61:39) indicates that the rate of formation of 1,6-addition product is faster than the rate of 1,2-addition product formation. Thus 1,2-addition product is being formed at a rate slower than that of cyclization of the probe, but little or not cyclization was observed in the 1,2-addition product. Since Holm's results suggest the absence of a polar 1,2-addition reaction, the only reasonable rationalization of these findings is that, after the transfer of the electron from the Grignard reagent to the benzophenone, R· of the Grignard is still tightly bound to the magnesium as a radical cation ($RMgX^{+\cdot}$). Collapse of the radical anion-radical cation pair to form 1,2-addition product would preclude cyclization.

We have also found that the radical anion as well does not appear to be a "free ketyl" in reactions of either primary or tertiary Grignard reagents with benzophenone. Kornblum and co-workers[59] have pointed out that p-dinitrobenzene (p-DNB) is effective as a "radical anion scavenger" which can "short circuit" SET reactions. If the Grignard reaction with benzophenone involves the SET process described by eq. 8 it should be possible for p-DNB to intervene as described by eqs. 9 and 10.

$$RMgX + Ph_2C{=}O \longrightarrow [Ph_2CO]^{\overset{-}{\cdot}} + [RMgX]^{\overset{+}{\cdot}} \longrightarrow \text{Products} \qquad (8)$$

$$p\text{-DNB} + [Ph_2CO]^{\overset{-}{\cdot}} \longrightarrow Ph_2C{=}O + [p\text{-DNB}]^{\overset{-}{\cdot}} \qquad (9)$$

$$[RMgX]^{\overset{+}{\cdot}} \; [p\text{-DNB}]^{\overset{-}{\cdot}} \longrightarrow RMgX + p\text{-DNB} \qquad (10)$$

It was determined by (T. L. Wiesemann)[18] that p-DNB was capable of removing the electron from the ketyl radical anion to regenerate the ketone although not with 100% efficiency. A study was carried out to determine the effect of p-DNB on the reactions of "CH_3MgBr" and "t-BuMgCl" with 2-MBP.[18,60] From the date in Table 11, the reaction of "CH_3MgBr" with 2-MBP in the presence of p-DNB is not significantly slower than the same reaction without p-DNB. The important feature of this data is that p-DNB completely eliminates pinacol formation. The fact that p-DNB prevents pinacol formation, but cannot do the same to the 1,2-addition product, is indicative of a difference in the mechanism leading to these two products. Additional evidence as to the "bound" nature of the R-group radical and ketyl was obtained from ketyl cross over product experiments. Garst and co-workers[61] have shown that benzophenone ketyl is a very effective trap for alkyl free radicals forming predominantly 1,6- and 1,2-addition products. The reaction of excess Grignard reagent with pinacol produces ketyl, but does not react further.[60] The only product upon subsequent hydrolysis is the starting pinacol. Thus by forming ketyl with an excess of Grignard reagent and then adding another ketone it should be possible to conduct a Grignard reaction with a ketone in the presence of a ketyl which could serve as a free radical trap. However, if the ketyl transfers an electron to the ketone, forming a new ketyl and a new ketone followed by subsequent reaction of the Grignard reagent with the new ketone an apparent and erroneous cross-over product would be indicated. This problem is overcome by insuring that the ketone corresponding to the ketyl (fluorenone, Reduction Potential = 1.3v. vs S.C.E.) has a lower reduction potential than the ketone which would be added to the reaction (2-MBP, Reduction Potential = 1.8v vs S.C.E.). This was found to be the case when two equivalents of "CH_3MgBr" were added to one equivalent of fluorenone pinacol to produce the ketyl without an excess of Grignard and 2-MBP was added. Upon subsequent hydrolysis 2-MBP and fluorenone pinacol were the only products. The reverse reaction, fluorenone added to 2-MBP ketyl also gave 2-MBP and fluorenone pinacol but in only 98% yield. The other 2% appeared to be present in the form of a mixed pinacol. Apparently when an appreciable concentration of both ketyls are present, mixed dimagnesium pinacolates form which slows down the exchange process. In any case, the important result was that no 2-MBP ketyl was formed in the reaction of 2-MBP with fluorenone ketyl. (It should be noted that this result does not rule out the possibility of a rapid equilibrium in solution which is simply shifted all the way toward fluorenone pinacol upon hydrolysis. However, if this had been a problem, the existence and/or the extent of the equilibrium probably could have been determined by UV or ESR studies). Thus we postulated that if the Grignard reaction involves the SET process described by eq. 11, it should be possible for fluorenone ketyl to intercept some of the R-group radicals (especially those generated in forming 1,6-addition products with 2-MBP) to form fluorenone addition products as described by eqs. 12 and 13.

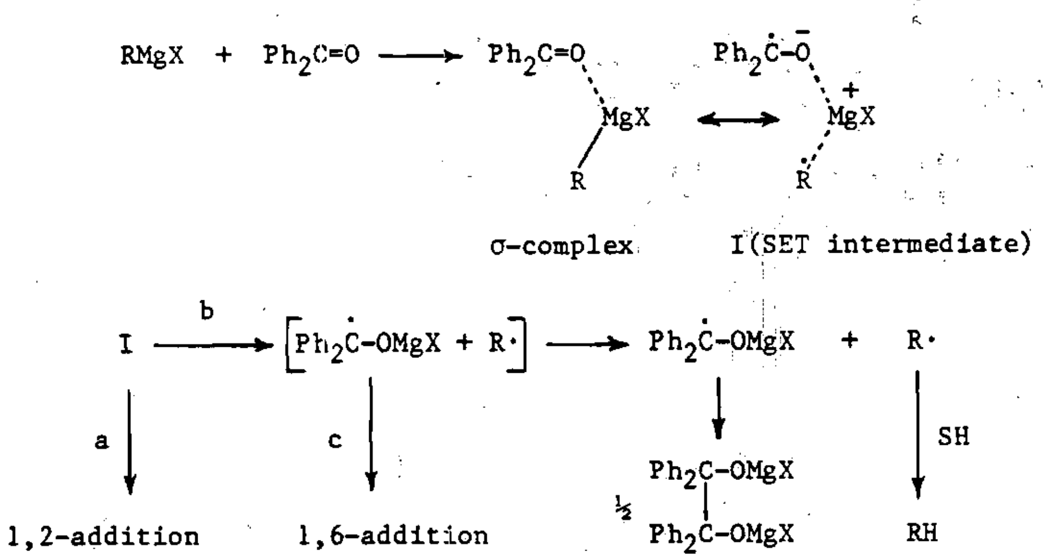
$$RMgX + Ph_2C{=}O \longrightarrow [Ph_2CO]^{\overline{\cdot}} + [RMgX]^{\overset{+}{\cdot}} \longrightarrow \text{Products} \tag{11}$$

$$[RMgX]^{\overset{+}{\cdot}} + [\text{fluore}]^{\overline{\cdot}} \longrightarrow \text{Fluorenone 1,2- and 1,6-addition Products} \tag{12}$$

$$2\ [Ph_2CO]^{\overline{\cdot}} \xrightarrow[\text{hydrolysis}]{\text{after}} \text{benzopinacol} \tag{13}$$

When "CH_3MgBr" was allowed to react with 2-MBP in the presence of fluorenone ketyl (Table 12) the only product observed was the 1,2-addition product of 2-MBP. Also from Table 12, t-butyl 1,2- and 1,6-addition were the only products observed from the reaction of "t-BuMgCl" with 2-MBP in the presence of fluorenone ketyl. These results indicate that while the R-group radical is free enough to cyclize (in the case of 3^{o} probe Grignard) it is not free enought to be trapped by a free radical scavenger.

In light of the "bound" nature of the R-group radical and ketyl it seems necessary for the mechanism of "t-BuMgCl" with benzophenone to involve a radical anion-radical cation pair in which the R-group radical is still tightly bound to the magnesium such that it cannot isomerize or cyclize. This radical anion-radical cation pair (I) may be thought of as originating via the σ complex which is undoubtedly formed very rapidly in a simple acid-base reaction. The radical anion-radical cation pair would then either (a) collapse to 1,2-addition product



(14)

(which would preclude cyclization) or (b) dissociate to form a radical anion and a free radical within the solvent cage which in turn could collapse to conjugate addition products or escape the solvent cage to form benzopinacol as illustrated in eq. 14.

In further investigation of the 3^{o} probe Grignard reaction we wished to determine the effect on the reaction products of increased steric hinderance at the carbonyl carbonyl carbon atom. Thus when the 3^{o} probe Grignard was allowed to react with 2-MBP in ether the resulting hydrocarbon analysis[57,62] indicated that 91% of the reaction proceeded through the straight chain isomer. The alkylation products consisted of 71% 1,6-addition, 21% 1,2-addition and 8% 2-methylbenzhydrol. Although no cyclization was observed in the 1,2-addition product, cyclization was observed for 71% of the 1,6-addition product. In view of our proposed mechanism the increase in 1,6-addition with the concomitant decrease in 1,2-addition could be the result of a slowing down of the collapse of the radical anion-radical cation pair to 1,2-addition product with respect to dissociation to form 1,6-addition product. The 2-methyl group could also be contributing to the rate of dissociation of the radical anion-radical cation pair by destabilizing the complex through steric interference.

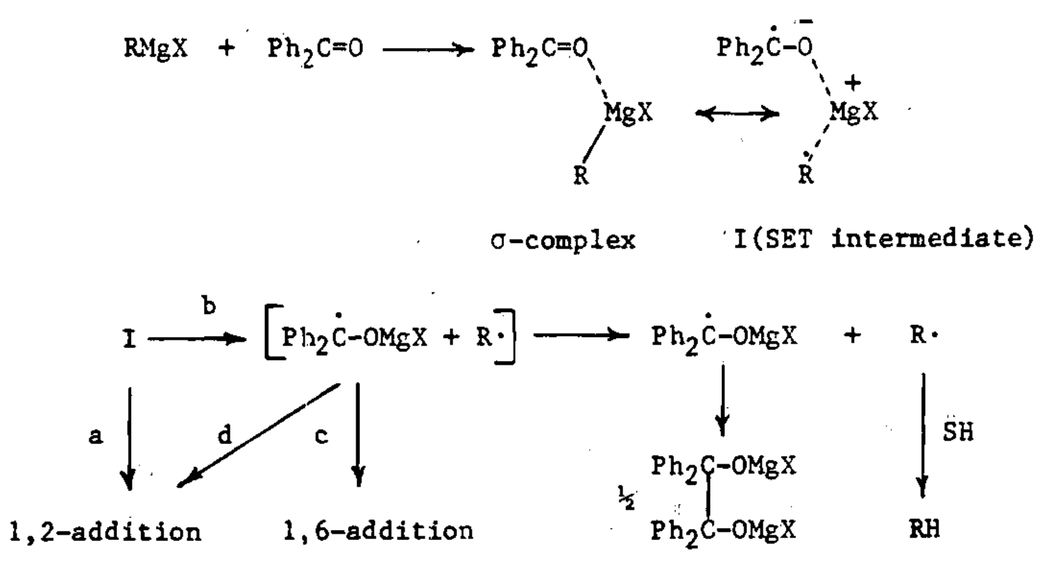
In the reaction of 3^{O} Grignard with benzophenone the effect of changing the solvent basicity and viscosity were determined by employing THF and di-n-butyl ether as reaction solvents. Tetrahydrofuran is a more strongly coordinating solvent than diethyl ether and is about twice as viscous (THF, η_{40}(cP) = 0.389; DiethylEther, η_{40}(cP) = o.194).[17a]

Di-n-butyl ether is less basic than diethyl ether, since basicity is diminished for di-n-alkyl ethers with increasing chain length; however, at the same time its viscosity is more than two and one half times that of diethyl ether (Di-n-Butyl Ether, η_{40} (cP) = 0.506).[17a]

Only 82% of the reaction proceeded through the straight chain isomer when this 3° probe Grignard was allowed to react with benzophenone in di-n-butyl ether.[57,63] The alkylation products consisted of 61% 1,2-addition products and 39% 1,6-addition products. Cyclizied 1,2-addition product accounted for 27% of the 1,2-addition products. However, the absolute yield of cyclized 1,2-addition product matches within experimental error the amount of cyclized Grignard reagent which took part in the reaction. Thus it strongly appears that cyclized 1,2-addition product did not originate from straight chain Grignard reagent. Cyclized 1,6-addition product accounted for 69% of the 1,6-addition product produced in the reaction. Observing the dramatic decrease in the yield of 1,6-addition product in di-n-butyl ether compared to the same reaction in diethyl ether, one would be inclined to attribute this to the increase in solvent viscosity (a slowing down of radical migration to the 6-position). However, if viscosity were the determining factor a large increase in the ratio of cyclized to uncyclized 1,6-addition product would be expected because of the extended lifetime of the radical. This is not what is observed, in fact, the ratio of cyclized to uncyclized 1,6-addition product actually decreases slightly. There are two alternative explanations for this data and both are concerned with the coordinating ability of di-n-butyl ether. In terms of our proposed mechanism, once the electron transfer has occurred the stability of the radical anion-radical cation pair would be very dependent upon the coordinating ability of the solvent to stabilize the ketyl. A poorly coordinating solvent such as di-n-butyl ether would not be expected to stabilize the ketyl very effectively, thus the radical anion-radical cation pair would tend to collapse to 1,2-addition rather than dissociate to ketyl and free radical and in turn to 1,6-addition product.

An alternate explanation is that electron transfer itself is very dependent upon solvent polarity as demonstrated by Fauvarque[5] and suggested by Walborsky.[64] A poorly coordinating solvent such as di-n-butyl ether would not be expected to effectively promote electron transfer, thus allowing a polar reaction to become competitive. It is also interesting to note that 16% of the reaction took place through the cyclic Grignard, but no benzhydrol (from β-hydrogen reduction) was detected. Cyclopentylmethyl Grignard reagent and other Grignard reagents which contain a 3° β-hydrogen (isopropyl and isobutyl Grignard reagents) usually give in excess of 80% benzhydrol on reaction with benzophenone.[65a] When the 3° probe Grignard was allowed to react with benzophenone in THF solvent 91% of the reaction proceeded through the straight chain Grignard reagent.[57,66] The alkylation products consisted of 58% 1,2-addition products and 42% 1,6-addition products. Cyclization was observed in 41% of the 1,2-addition products and in 81% of the 1,6-addition products. Since only 9% of the 3° probe Grignard which reacted was the cyclic isomer then at least 45% of the cyclized 1,2-addition product had to originate from straight chain Grignard reagent. These results produce solid evidence for the reaction of a 3° Grignard reagent with benzophenone that 1,2-addition products can come about through a radical process. This data suggests that the strongly coordinating solvent THF promotes dissociation of the radical anion-radical cation pair through stabilization of the ketyl and then retards migration (viscosity effect) of the alkyl radical to the 6 position evidenced by a decrease in 1,6-addition products (compared to the same reaction in ether). Other viscosity effects observed were an increase in the ratio of cyclized to uncyclized 1,6-addition products (due to the increased lifetime of the radical) and the appearance of cyclized 1,2-addition product which is probably formed via internal return of the dissociated alkyl radical to the carbonyl carbon (solvent viscosity causes longer residence time at the site of radical anion-radical cation pair dissociation).

To be consistent with these new data, it seems necessary for the mechanism described in eq. 14 to involve a second pathway for the formation of 1,2-addition product (path d), that is by reaction of the free alkyl radical (from dissociation of the radical anion-radical cation pair) with the carbonyl carbon of the ketyl within the solvent cage as illustrated in eq. 15.



(15)

Thus far the description of the mechanism of the reaction of a Grignard reagent with benzophenone has dealt with only a 3^{o} Grignard reagent. Only with a 3^{o} Grignard reagent has any evidence of electron transfer been observed. It is possible however,that all Grignard reactions with ketones proceed through a SET pathway by the proposed mechanism (eq. 15). The stability of the radical anion-radical cation complex (I) should be determined by the stabilities of the incipient radical (R·) and the ketyl ($Ph_2\dot{C}-\overline{O}$) and the coordinating ability of the solvent, which in turn would determine the amount of SET character observed in the reaction. With tertiary Grignard reagents, the intermediate complex (I) would be unstable because of the stability of the tert-alkyl radical, thus making path b competitive with path a or even the predominant reaction pathway. The choice between path c and d would be dependent upon solvent viscosity, radical reactivity (1^{o} radicals are more reactive than 3^{o} radicals) and steric considerations. On the other hand, vinylic Grignard reagents, e.g. cis-propenylmagnesium bromide and primary alkyl Grignard reagents, e.g. 5-hexenylmagnesium chloride may react by a polar mechanism or if by SET, form a more stable complex which would collapse via path a to give only 1,2-addition product with no SET character observed (as in the cases reported here).

2,2-Dimethyl-5-hexenylmagnesium Chloride

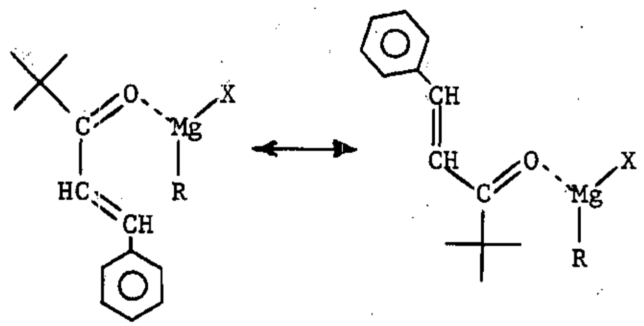
To observe electron transfer character in a reaction between a 1^{o} Grignard reagent and benzophenone, assuming the postulated mechanism to be in effect, it became apparent that the rate of path a (eq. 15) would have to be slowed sufficiently to allow at least partial reaction through path b. When neo-pentylmagnesium bromide is allowed to react with benzophenone, a very slow reaction takes place producing primarily 1,2-addition product, but also about 10% of the 1,6-addition product.[67] This is, the first example of electron transfer behavior displayed in a reaction of a primary Grignard reagent with a ketone. Based on this information a <u>neo</u>-pentyl type probe was prepared (2,2-dimethyl-5-hexenymagnesium chloride, <u>neo</u>-octenyl Grignard) and reacted with benzophenone. The <u>neo</u>-octenyl Grignard reagent when prepared contains a substantial quantity of cyclic (5-membered ring) isomer. Unlike the 3° Grignard probe, the <u>neo</u>-octenyl cyclic Grignard reagent is much more reactive toward benzophenone than is its straight chain isomer. Thus in a reaction with benzophenone large amounts of cyclic 1,2-addition products and benzhydrol are produced before the Grignard of interest has started to react. It was established that by adding one equivalent of acetone to a solution of <u>neo</u>-octenyl Grignard reagent which contains one equivalent of the cyclic Grignard, that the cyclic Grignard reacts completely with the acetone (1,2-addition, β-hydrogen reduction and enolization) leaving the straight chain isomer intact. It was also established that the acetone-cyclic Grignard reagent reaction products had no effect on the stability or stereochemical integrity of the <u>neo</u>-octenyl straight chain Grignard reagent. Thus by pre-reacting out the cyclic Grignard, we were able then to conduct a reaction between the <u>neo</u>-octenyl Grignard and benzophenone. This reaction proceeded 100% through the straight chain isomer.[68,69] The alkylation products consisted of 100% 1,2-addition with cyclization observed in 12% of the 1,2-addition product. This is the first example of electron transfer behavior exhibited in the formation of 1,2-addition product from the reaction of a primary Grignard reagent with a ketone. Thus the increase in steric bulk apparently slowed down the collapse of the radical anion-radical cation complex such that dissociation via path b (eq. 15) and recombination via path d could occur. The absence of 1,6-addition product (path c) is somewhat surprising when compared to the neo-pentyl Grignard reaction with benzophenone which produced about 10% 1,6-addition product. However, when the increased difficulty of migration of the neo-octenyl radical (due to its larger size) is coupled with the fact that we are dealing with a very reactive primary radical (as compared to a tertiary radical) it is possible that internal return (path d) became predominant over migration (path c).

The effect of increased steric hinderance about the carbonyl carbon atom on the formation of 1,2- and 1,6-addition was determined when neo-octenyl Grignard reagent was allowed to react with 2-MBP. The extremely slow reaction produced alkylation products exclusively through the straight chain Grignard reagent.[68,70] The alkylation products consisted of 86% 1,2-addition product and 14% 1,6-addition products. No cyclization was observed in the 1,2-addition product but cyclization was observed in 69% of the 1,6-addition products. With the introduction of a 2-methyl group in benzophenone the product distribution of the reaction was drastically altered. The introduction of a 2-methyl group in benzophenone apparently slowed even more the collapse of the radical anion-radical cation complex (path a) and also provided enough steric interference to prevent internal return (path d) leaving path c as the only alternative.

Benzalpinacolone and the Grignard Reagent Probes

Another member of this research group has previously studied the question of polar versus electron transfer mechanisms in the reactions of Grignard reagents with ketones by incorporating the radical probe into the ketone substrate. This was an attempt to observe the radical anion formed in eq. 1. The ketone probe consisted of a *cis*-enone (2,2,6,6-tetramethylhex-4-ene-3-one) which is rapidly converted to the *trans*-isomer in any reaction involving the transfer of an electron to the enone.[71] The major drawback to the use of the enone as a probe involves the isomerization of the starting "*cis*-enone" through a SET pathway not necessarily along the main reaction pathway, followed by a polar reaction giving what appears to be products of a SET reaction. However, by careful comparison of the various reactions, insight was gained into the mechanism of Grignard reactions with ketones, especially with respect to the mechanism of formation of the 1,2-addition product. By selecting an enone which gives only 1,4-addition (benzalpinacolone, 2,2-dimethyl-4-phenylpent-4-ene-3-one) we hoped by using our Grignard reagent probes to gain insight into the mechanism of formation of 1,4-addition product. Benzalpinacolone when allowed to react with most Grignard reagents produces only 1,4-addition products. This is probably a consequence of steric factors rather than electronic factors. Benzalpinacolone by virture of its conjugated structure, should be a planer molecule. Consequently when complexed by a Grignard reagent, the enone would be expected to have two σ-complex conformations eq. 16. Both of these conformations show a great deal of steric crowding for approach to the carbonyl carbon, thus the preference for 1,4-addition.

When 5-hexenylmagnesium chloride was allowed to react with benzalpinacolone the reaction proceeded about 85% through the straight chain



(16)

isomer and about 15% through the cyclic (5-membered ring) isomer.[72,73] The alkylation products consisted of 84% straight chain 1,4-addition product and 16% cyclized 1,4-addition product. Thus no cyclization of the probe occurred since the ratio of cyclized to uncyclized of the starting Grignard reagent is duplicated within experimental error in the reaction products. The hydrocarbon analysis also supports this conclusion. The absence of cyclization in the 1,4-addition product of 5-hexenylmagnesium chloride with benzalpinacolone indicates that either the reaction is polar or if SET, no "free" radical character is exhibited.

However, when the tertiary Grignard probe was allowed to react with benzalpinacolone, the reaction proceeded 66% through the straight chain isomer, 29% through the cyclic (5-membered ring) isomer and 5% through the cyclic (6-membered ring) isomer.[57,74] The alkylation products consisted of 42% straight chain 1,4-addition, 51% cyclized (5-membered ring) 1,4-addition and 7% cyclized (6-membered ring) 1,4-addition products. Thus 66% straight chain Grignard reacted to produce only 42% straight chain 1,4-addition product, cyclization was observed in 41% of the cyclized 1,4-addition products. The observation of cyclized 1,4-addition product establishes the radical nature of the 1,4-addition process with 3° Grignard reagents while the ratio of cyclized to uncyclized (originating from 3° Grignard reagent, 24:42) establishes the rate of 1,4-addition product formation as comparable with the rate of probe cyclization ($R_{cyc} \approx 10^5 sec^{-1}$).[56]

Extending this study on to the _neo_-octenyl Grignard probe, we find that the reaction of the _neo_-octenyl Grignard reagent with benzalpinacolone proceeded $21.7 \pm 1.7\%$ through the straight chain isomer and $78 \pm 1.7\%$ through the cyclic (5-membered ring) isomer.[68,75] The alkylation products consisted of $18.6 \pm 0.8\%$ cyclized 1,4-addition product. Thus within experimental error a small amount (~3%) of the cyclized 1,4-addition product originated from straight chain Grignard reagent.

These results are so similar to the data collected with the Grignard reagent probes with benzophenone that we are almost forced to draw the same conclusions. It appears that the reactions of Grignard reagents with enones proceeds through an intermediate radical anion-radical cation pair which can collapse to 1,2- or 1,4-addition (dependent upon steric factors) or depending on the stabilities of the incipient radical (R·) and the ketyl, dissociate forming a ketyl and free radical within the solvent cage which can then collapse again to 1,2- or 1,4-addition products depending on steric and electronic (the unpaired electron density for the benzalpinacolone ketyl would probably be divided fairly equally between the carbonyl carbon and the benzyl carbon) factors.

Trialkylaluminum Probe Reactions

The reaction of tris-(5-hexenyl)aluminum diethyl etherate with benzophenone in pentane gave much the same results as the Grignard counterpart with benzophenone. The only products observed were 54% benzhydrol and 46% straight chain 1,2-addition product. The absence of cyclization in the 1,2-addition product indicated that no free radical character was observed, but does not prove that a SET process did not occur. Unfortunately the tris-(1,1-dimethyl-5-hexenyl)aluminum compound could not be prepared such that it was stable to intra-molecular cyclization. However, we did prepare dimethyl-*t*-butylaluminum diethyl etherate such that we could observe which group (primary or tertiary) would be preferentially transferred to the benzophenone. This should be a valid though qualitative experiment to determine if trialkylaluminum compounds display any of the reaction characteristics identified as SET behavior in comparable Grignard reactions. When dimethy-*t*-butylaluminum is allowed to react with benzophenone the products consisted of 20% methyl-1,2-addition product and 80% benzhydrol. Thus with trialkylaluminum compounds the primary alkyl group (methyl) transfers to benzophenone preferential to the tertiary alkyl group. In Grignard reactions tertiary alkyl groups transfer to benzophenone (1,2- and 1,6-addition) preferential to primary alkyl groups via an SET process. Thus it appears that trialkylaluminum diethyl etherates in reactions with benzophenone do not display characteristics attributable to a SET process, but proceed by a polar mechanism.

Organolithium Probe Reactions

The reaction of 5-hexenyllithium with benzophenone in ether produced results very similar to the corresponding Grignard reaction with benzophenone. The products of the reaction consisted of 36% straight chain 1,2-addition product and 64% benzhydrol. The apparent increase in benzhydrol formation as compared to the corresponding Grignard and Aluminum reactions is probably due to the percentage of cyclic lithium reagent (20%) present in the reaction as compared to 4 % and 7% for the Grignard and Aluminum reactions respectively. Unfortunately the 1,1-dimethyl-5-hexenyllithium was not successfully prepared. However, comparison of reactions of "t-BuMgCl" and "t-BuLi" compounds with benzophenone indicate almost identical yields of 1,2- and 1,6-addition products. Thus organolithium compounds appear to be displaying reaction behavior with benzophenone which has been identified as SET in nature as in comparable Grignard reactions.

New Magnesium Hydride Reagents

The reagent CH_3MgBr/MgH_2 (3/1) in THF, was allowed to react in separate reactions with various substrates hoping to find indications of unusual reactivity, selectivity or sterochemistry (Table 13). This project was continued by other members of this research group.

Hydrometallation

The reagent HMgBr in THF with and without Ni catalyst was allowed to react with various aliphatic and aromatic alkenes and alkynes, hoping to find conditions by which HMgBr would hydrometalate carbon-carbon double bonds (Table 14). This project was continued by other members of this research group.

CHAPTER IV

CONCLUSION

The large variation in the amount of hydrol formed from CH_3MgBr prepared from different grades of magnesium has been traced not to the purity of the various grades, but to the size of the crystals or shavings. Those grades of magnesium that consisted of fine shavings gave the most hydrol and those grades of much coarser material gave the least hydrol. We have shown that MgH_2 is normally produced as a by-product (~0.2%) in CH_3MgBr formation and that the MgH_2 is destroyed when allowed to react with excess CH_3Br. Since the reaction of CH_3Br with magnesium (fine shavings) is very rapid, the by-product MgH_2 survives when the reaction is carried out in excess magnesium. On the other hand, the reaction of CH_3Br with magnesium (coarse shavings) is slow and the concentration of CH_3Br builds up in the reaction mixture destroying the by-product MgH_2 even when the reaction is carried out in excess magnesium.

With respect to the mechanism of the reaction of a Grignard reagent with a ketone, the nature of the alkyl transfer from the Grignard reagent to the carbonyl carbon atom has been a source of considerable speculation. This speculation centers around whether the alkyl transfer proceeds by a polar or an electron transfer mechanism. Holm and Crossland[6] concluded from their work that in the reaction of "*t*-BuMgCl" with benzophenone, the 1,2-addition product as well as

1,4-, 1-6 addition product and pinacol all came about through an electron transfer mechanism. It is apparent from this work that their conclusions are basically correct, but in need of some modification. In Light of the "bound" nature of the R-group radical (as evidenced by the flourenone ketyl cross-over product experiments and the absence of cyclization in the 1,2-addition product from the reaction of 3^{o} probe Grignard reagent with benzophenone and 2-methylbenzophenone) and the "bound" nature of the ketyl (as evidenced by the p-DNB radical anion scavenger experiments), a "free radical" and a "free ketyl" apparently do not form in the SET step as was proposed. When a Grignard reagent reacts with a ketone, a radical anion-radical cation pair is formed which can collapse to give 1,2-addition product or dissociate to form a radical anion and a free radical within the solvent cage which in turn can collapse to 1,2-addition product, conjugate addition product or escape the solvent cage to form pinacol. The 1,2-addition products, which form after dissociation of the radical anion-radical cation pair, show free radical character as indicated by the cyclized 1,2-addition products formed from the reaction of 3^{o} Grignard reagent probe with benzophenone in THF and from the reaction of neo-octenyl Grignard reagent probe with benzophenone. The 1,6-addition products, which all come about after dissociation of the radical anion-radical cation pair, show free radical character as evidenced by the cyclized 1,6-addition products formed in all of the reactions which involve the 3^{o} Grignard reagents probe (in all solvents studied) with benzophenone and 2-MBP and also in the reaction of neo-octenyl Grignard reagent probe with 2-MBP. Within the radical anion-radical cation pair, the R-group of the Grignard reagent is still tightly bound to the magnesium and the ketyl is also bound such that it is not free to take part in other reactions. This radical anion-radical cation pair may be thought of as originating via the σ-complex which is undoubtedly formed very rapidly in a simple acid-base reaction. The stabilities of the incipient radical (R·) and the ketyl ($R_2\dot{C}-\overline{O}$) as well as the nature of the solvent determine the stability of the radical anion-radical cation pair which in turn determines the amount of SET character observed in the reaction. With tertiary Grignard reagents and benzophenone, the intermediate complex is relatively unstable owing to the stability of the <u>tert</u>-alkyl radical and the benzophenone ketyl. With primary Grignard reagents and benzophenone, the intermediate forms a more stable complex which collapses to give 1,2-addition product. The radical anion-radical cation complex is also quite sensitive to solvent effects. Poorly coordinating solvents do not promote dissociation of the pair thus resulting in more 1,2-addition (less 1,6-addition). On the other hand a strongly coordinating solvent such as THF leads to dissociation of the radical anion-radical cation pair by stabilizing the ketyl. It also appears that the radical anion-radical cation complex can be sterically hindered toward collapse to give 1,2-addition product. If the sterically hindered complex is relatively stable (such as with a primary Grignard reagent) the overall result is simply a very slow reaction to give mostly 1,2-addition product. However, if the complex is relatively unstable (such as with a tertiary Grignard) the overall result will be an increase in the amount of 1,6-addition product formed.

Although radical character in the reactions of primary and tertiary Grignard reagents with benzophenone has been demonstrated, it is possible that polar and SET mechanisms are competitive, depending principally on the reduction potential of the ketone, the oxidation potential of the Grignard reagent and the solvent. At the two ends of the spectrum, all evidence indicates that the reaction of "_t_-BuMgCl" with benzophenone is SET in nature, whereas the reaction of "CH_3MgBr" with acetone is polar in nature.

Although the study with organolithium reagents was not as complete as it could have been, there were strong indications that organolithium reagents behave very much like Grignard reagents in their reactions with ketones.

Trialkylaluminum reagents were found to transfer 1^{o} alkyl groups preferential to 3^{o} alkyl groups which leads to the conclusion that trialkylaluminum reagents react with benzophenone via a polar mechanism. This is based on the fact that Grignard reagents transfer 3^{o} alkyl groups preferential to 1^{o} alkyl groups to benzophenone by a SET mechanism.

Table 1. Products from the Reactions of Methylmagnesium Bromide (1.50 M) With 2-Methylbenzophenone (0.0375 M) in Diethyl Ether at Room Temperature Effect of Magnesium Purity at 400:1 Grignard to Ketone Ratio.

		Yield %				Elemental Analysis[e] (ppm)											
Grade of Mg	Grignard Prepared In Excess	1,2-Addn.[a]	Pinacol[b]	Hydrol[c]	Other[d]	Ti	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ag	Pb	Na	K
Single Crystal	Mg	68	10	13	9	0	0	70	18	0	0.1	3	48	140	0	0.3	0.4
Dow No. 5	Mg	71	7	13	8	17	0	6	18	0	1.0	6	20	0	0	0.3	0.4
Ventron Chips	Mg	77	14	0	10	0	0	21	22	0.3	0	0.1	56	0	0	0.3	0
D. S.[f]	Mg	62	2	36	0	0	0	0	0.1	0	0	0.1	25	0	0	9	0.9
ROC/RIC	Mg	92	1	4	3	0	0	7	10	0	0	0	73	0	18	0	1
T. S.[f]	Mg	41	1	58	0	0	0	0	0	0.3	0	0	27	0	0	18	16
GGT[f]	Mg	55	19	8	19	0	0	130	140	0	0.1	3	54	0	0	0.3	0
Ventron Chips	CH_3Br	85	10	0	5	0	0	21	22	0.3	0	0.1	56	0	0	0.3	0
ROC/RIC	CH_3Br	94	4	0	2	0	0	7	10	0	0	0	73	0	18	0	1
T. S.[f]	CH_3Br	82	2	4	3	0	0	0	0	0.3	0	0	27	0	0	18	16

a. 1-phenyl-1(2-methylphenyl) ethanol. b. 2,2'-dimethylbenzopinacol. c. 2-methylbenzhydrol. d. apparently 1-(2,6-dimethylphenyl)-1-phenylethanol. e. Analysis by Microtrace Analytical Services, Industry, CA 91746. f. Key: DS = Dow Doubly Sublimed; TS = Dow Triply Sublimed; GGT = Baker, Grignard Grade Turnings.

Table 2. Effect of Grignard to Ketone Ratio on Products from the Reaction of "CH_3MgBr"[a] with 2-Methylbenzophenone in Ether at Room Temperature.[18]

"CH_3MgBr" (moles/li)	2-MBP (moles/li)	"CH_3MgBr" / 2-MBP	% Yield Ketone[b]	% Yield 1,2-Addition[c]	% Yield Pinacol[d]	% Yield Hydrol[e]	Hydrol[3] (moles/li)
0.010	0.99	1:99	xs	100	0	0	0
0.010	0.11	1:11	xs	100	0	0	0
1.50	1.50	1:1	0	100	0	0	0
1.50	0.15	10:1	0	99	0.6	Trace	Trace
1.50	0.015	100:1	0	89	2	9	0.00135
1.50	0.00375	400:1	0	62	2	36	0.00135
1.50	0.001875	800:1	0	40	4	56	0.00105

a. Prepared from doubly sublimed magnesium using excess magnesium.

b. 2-methylbenzophenone.

c. 1-phenyl-1-(2-methylphenyl) ethanol.

d. 2,2'-dimethylbenzopinacol.

e. 2-methylbenzhydrol.

Table 3. Formation of Products with Respect to Time in the Reaction of "CH_3MgBr"[a] (0.50 M) with 2-Methylbenzophenone (0.0125 M) in Et_2O at $-30\,^{\circ}C$.[b]

	% Yield				
Rx Time	Unreacted Ketone (%)	1,2-Addition[c]	Pinacol[d]	2-Methyl-benzhydrol	Hydrol/Addition
10 sec	68	2.7	1.7	28	10.4
1 hr	46	18	2.0	34	1.9
4 hr	10	48	2.3	39	0.81
12 hr	0	56	2.5	41	0.73

a. Prepared from doubly sublimed magnesium using excess magnesium.

b. Analysis by NMR.

c. 1-phenyl-1-(2-methylphenyl) ethanol.

d. 2,2'-dimethylbenzopinacol.

Table 4. Formation of 2-Methylbenzhydrol at 400:1 Grignard to Ketone Ratio[18]

Grignard[a] Formed In	Reaction Carried Out In	% Yield Reduction Product[b]	
		$C_6H_5(C_7H_7)CHOH$	$C_6H_5(C_7H_7)CDOH$
$CH_3CH_2OCH_2CH_3$	$CH_3CH_2OCH_2CH_3$	59	-
$CH_3CD_2OCD_2CH_3$	$CH_3CD_2OCD_2CH_3$	0	27
$CH_3CH_2OCH_2CH_3$	$CH_3CD_2OCD_2CH_3$	65	0

a. CH_3MgBr prepared from Dow doubly sublimed magnesium.

b. Normalized as: % 1,2-addition + % reduction = 100%.

Table 5. Selectivity of Reduction of an Equalmolar Mixture of 2-Methylbenzophenone and Acetone with "CH_3MgBr" and "CH_3MgBr" + MgH_2.[a]

Grade of Magnesium Used To Prepare "CH_3MgBr"	1,2-Addition[b] Products (%)	Reduction Products (%)[b]	
		2-Methylbenzhydrol	Isopropanol
Dow (DS)	74.5	25.0	0.5
ROC/RIC[c]	100.0	0	0
ROC/RIC[c] + MgH_2	74.0	24.5	1.5

a. Millimoles of each ketone = 0.3: mmole CH_3MgBr = 120; mmole MgH_2 = 0.2.

b. Yields normalized as: % 1,2-addition + % reduction = 100%.

c. Grignard prepared in excess CH_3Br.

Table 6. Stereochemistry of Reduction of 4-tert-butycyclohexanone (0.3 mmole) with "CH_3MgBr" (120 mmole) and "CH_3MgBr" + MgH_2.

		Alkylation			Reduction		
Grade Mg Used	mmoles MgH_2	Total[a] Yield	Axial[b] Alcohol(%)	Equatorial[b] Alcohol(%)	Total[a] Yield	Axial[b] Alcohol(%)	Equatorial[b] Alcohol(%)
Dow (DS)	0	84	66	34	16	11	89
ROC/RIC[c]	0	100	59	41	0	-	-
ROC/RIC[c]	0.2	92	62	38	8	21	79
--------	0.3	-	-	-	-	68	32

a. Normalized as: % alkylation alcohols + % reduction alcohols = 100%.

b. Normalized as: % axial alcohol + % equatorial alcohol = 100%.

c. Grignard prepared in excess CH_3Br.

Table 7. Effect of the Size of Magnesium Shavings and Methyl Bromide Flow Rate on the Percentage of 2-Methylbenzhydrol in Reactions Involving 1.5 M Methylmagnesium Bromide[a] with 0.00375 M 2-Methylbenzophenone.

Mg Shaving Size	Flow Rate (cc/min)	% Yield[b] 1,2-Addition	Pinacol	Hydrol
Fine	214[c]	41	ND	59
Fine	682[d]	74	ND	27
Medium	682[d]	84	ND	16
Large	682[d]	91	ND	9

a. All preparations utilized 28 g of Dow doubly sublimed magnesium.

b. Normalized as: % 2-methylbenzhydrol + 1,2-addition = 100%.

c. Flow time = 85 minutes.

d. Flow time = 28 minutes.

Table 8. Grignard Reagent Free Radical Probes

Grignard Probes	Intermediate Radical	Isomerized or Cyclized Radical	Expected 1,2-Addition Product With $Ph_2C{=}O$ For SET Process

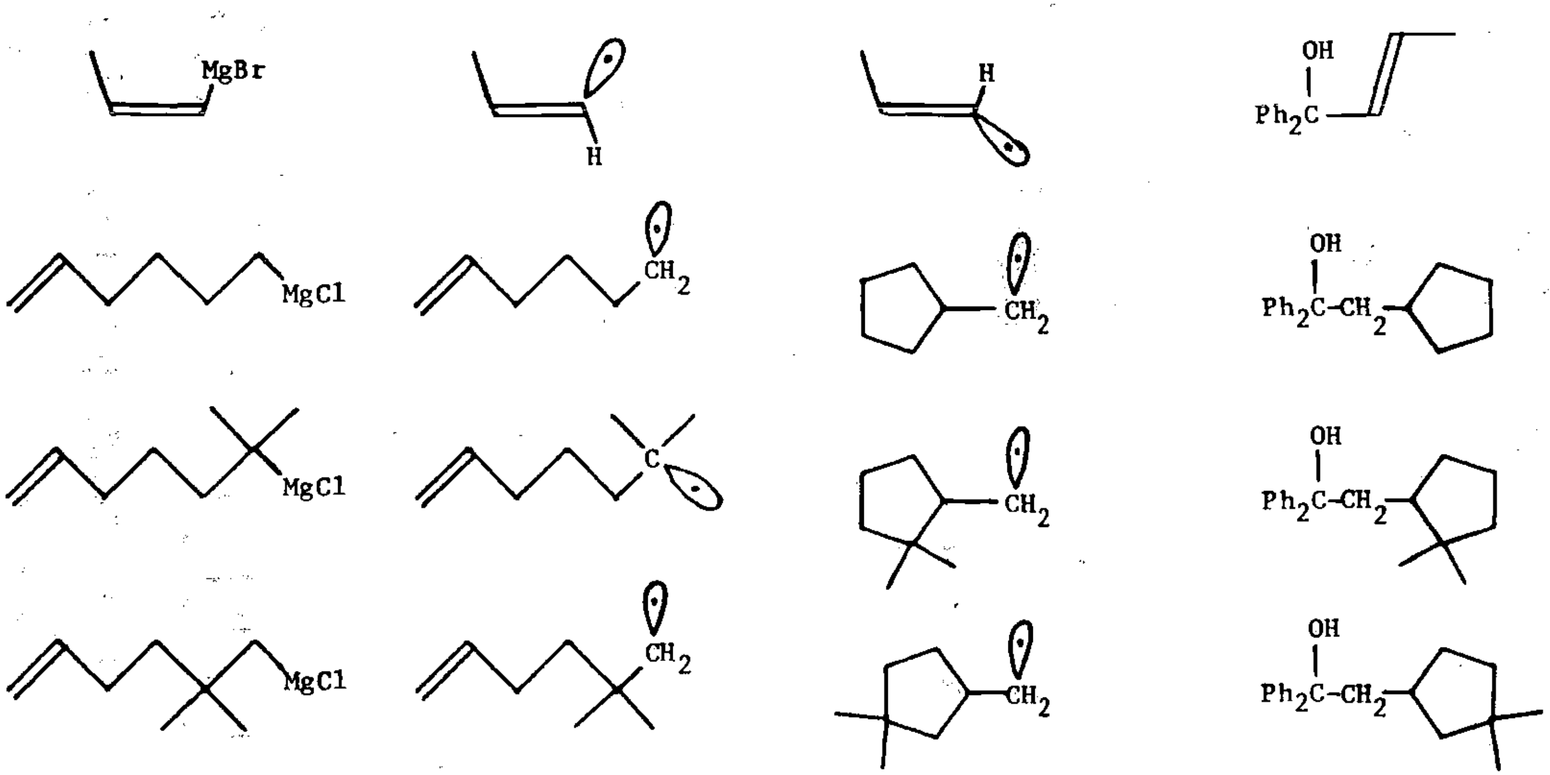


Table 9. Products From the Reaction of Propenylmagnesium Bromide with Benzophenone.

Exp.	Propenyl Isomer cis	Grignard Ratio trans	ppm Fe	G/K Ratio	Products: Total Carbinol[a]	Pinacol[a]	cis-Carbinol[b]	trans-Carbinol[b]
1	95	5	0	0.5	100	0	95.0	5.0
2	60	40	0	0.5	100	0	60.7	39.3
3	29	71	0	0.5	100	0	29.3	70.7
4	95	5	0	1.5	100	0	91.6	8.4
5	95	5	4000	1.5	93.6	6.4	90.8	9.2
6	60	40	0	1.5	100	0	43.3	56.7
7	60	40	4000	1.5	93.5	6.5	41.8	58.2
8	29	71	0	1.5	100	0	18.7	81.3
9	29	71	4000	1.5	92.7	7.3	20.0	80.0

a. Normalized as 100% = % Total Carbinol + % Pinacol.

b. Normalized as 100% = % cis - Carbinol + % trans - Carbinol.

Table 10. Products From the Reaction of "CH_3MgBr"[a] With 2-MBP (0.0167 M) in the Presence or Absence of p-Dinitrobenzene (p-DNB) in Diethylether at Room Temperature.[18]

Exp.	"CH_3MgBr"	% p-DNB	Reaction Time (mins)	% 1,2-Addn.[b]	% Pinacol	% Recovered Ketone	% Recovered p-DNB
1	0.033 M	0	3	23.9	Trace	76.1	-
2	0.033 M	0	9	41.4	4.1	54.9	-
3	0.033 M	0	16	58.6	10.5	31.0	-
4	0.033 M	0	30	63.9	13.1	23.0	-
5	0.100 M	17	5	57.2	0	42.8	17.8
6	0.100 M	17	11	79.6	0	20.4	15.6
7	0.100 M	17	20	91.9	0	8.1	19.4
8	0.100 M	17	40	98.7	0	1.3	13.9

a. Dow doubly sublimed magnesium, but obviously contaminated by a few ppm $FeCl_3$ or other transition metal salt.

b. Normalized as 100% = % 1,2-Addition + % Pinacol + % Ketone.

Table 11. Products From the Reaction of "t-BuMgCl" With 2-MBP (0.0167 M) in the Presence or Absence of p-DNB in Diethylether at Room Temperature.[18]

Exp.	"t-BuMgCl"	% p-DNB	Reaction Time (mins)	% 1,6-Addn.[a]	% 1,2-Addn.	% Pinacol	% Recovered Ketone	% Recovered p-DNB
1	0.033 M	0	3	71.2(78.4)[b]	19.6(21.6)	9.1	0	-
2	0.033 M	0	6	76.4(83.7)	14.9(16.3)	8.7	0	-
3	0.033 M	0	9	73.5(79.7)	18.7(20.3)	7.8	0	-
4	0.033 M	0	18	74.2(83.5)	14.7(16.5)	11.2	0	-
5	0.133 M	12.5	4	83.0	17.0	0	0	0
6	0.133 M	12.5	7	84.3	15.7	0	0	3.1
7	0.133 M	12.5	16	84.0	16.0	0	0	4.6
8	0.133 M	12.5	29	85.0	15.0	0	0	10.5

a. Normalized 100% = % 1,6-Addition + % 1,2-Addition + % Pinacol + % Ketone.

b. Normalized 100% = % 1,6-Addition + % 1,2-Addition.

Table 12. Reactions of CH_3MgBr and t-C_4H_9MgCl with 2-Methylbenzophenone in the Presence of Fluorenone Ketyl in Diethyl Ether.

					Products[a]			
Exp.	Grignard Reagent	Pinacol	RMgX	2-MBP	Recovered Ketone	2-MBP 1,2-Addn.	2-MBP 1,6-Addn.	Fluorenone Alkylation
1	CH_3MgBr	0.017 M	0.034 M	0.067 M	100	0	0	0
2	CH_3MgBr	0.017 M	0.050 M	0.067 M	100	0	0	0
3	CH_3MgBr	0.017 M	0.067 M	0.067 M	100	0	0	0
4	CH_3MgBr	0.017 M	0.083 M	0.067 M	95	5	0	0
5	CH_3MgBr	0.017 M	0.100 M	0.067 M	77	23[b]	0	0
6	CH_3MgBr	0.017 M	0.133 M	0.067 M	50	50[b]	0	0
7	CH_3MgBr	0.017 M	0.250 M	0.067 M	0	100[b]	0	0
8	t-BuMgCl	0.033 M	0.133 M	0.017 M	0	12[b]	88	0
9	t-BuMgCl	0.033 M	0.200 M	0.017 M	0	13[b]	87	0

a. Normalized as: 100% = % Recovered Ketone + % 1,2-Addn. + % 1,6-Addn. + % Fluor. Alkylation.

b. Traces of 2-Methylbenzopinacol present, probably from ppm of Fe present in Mg from which Grignard Reagent was prepared.

Table 13. Products From the Reaction of CH_3MgBr/MgH_2 (3/1) in THF with Various Substrates at a Hydride to Substrate Ratio of 1.32/1.0

Exp.	Substrate	Reaction Products
1	Benzonitrile	Benzaldehyde (95%); Acetophenone (5%)
2	Benzyl chloride	No reaction
3	1-Bromooctane	No reaction
4	4-_t_-Butylcyclohexanone	Alkylation (68%; $^{ax.}$/eq.-OH ^{68}/32) Reduction (32%; $^{ax.}$/eq.-OH ^{62}/38)
5	Chalcone	1,2-Addition and 1,4-Addition (100%); No reduction
6	1-Decene	No reaction
7	2-Methylbenzophenone	Hydrol (75%); 1,2-Addition (25%)

Table 14. Products From the Reaction of HMgBr With Various Unsaturated Hydrocarbon Substrates at a Hydride to Substrate Ratio of 2.5/1.0

Exp.	Substrate	Mole % Ni	Hexane	1-Hexene	1-Hexyne	trans-2-Hexene	Ethyl Benzene	Styrene	Phenyl Acetylene	Mass Balance
1	1-Hexene	-	0.1	80.2	-	0.0	-	-	-	80.3
2	1-Hexene	5	19.9	42.9	-	17.7	-	-	-	80.2
3	1-Hexene	5[a]	11.1	35.8	-	23.2	-	-	-	70.2
4	1-Hexene	5[b]	0.1	92.0	-	0.0	-	-	-	92.0
5	1-Hexene	1	4.0	73.5	-	0.0	-	-	-	77.5
6	1-Hexyne	-	0.0	0.2	82.7	0.0	-	-	-	82.9
7	1-Hexyne	5	0.2	2.5	7.0	0.0	-	-	-	9.8
8	1-Hexyne	1	0.4	0.5	77.0	0.0	-	-	-	78.0
9	Styrene	0	-	-	-	-	0.0	100	-	100
10	Styrene	5	-	-	-	-	43.0	65.0	-	108
11	Styrene	1	-	-	-	-	0.8	57	-	57.8
12	PhC≡CH	5	-	-	-	-	0.0	0.0	0.0	0.0
13	PhC≡CH	1	-	-	-	-	0.0	0.0	0.0	0.0

a. 1.0 equivalent of pyridine added.

b. Reaction conducted at -78°c for 24 hours.

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57. St. Chain refers to the hydrocarbon obtained by hydrolysis of 1,1-dimethyl-5-hexenylmagnesium chloride; Cyclo 5 refers to the hydrocarbon obtained by hydrolysis of 2,2-dimethylcyclopentylmethylmagnesium chloride; Cyclo 6 refers to the hydrocarbon obtained by hydrolysis of 2,2-dimethylcyclohexylmagnesium chloride.

58.

Mmoles of Grignard I Added to the Reaction		Mmoles of Hydrocarbons Recovered from Reaction		Difference
St. Chain	1.22 ± 0.04	St. Chain	0.77 ± 0.02	0.45 ± 0.07
Cyclo 5	0.96 ± 0.02	Cyclo 5	0.91 ± 0.02	0.05 ± 0.04
Cyclo 6	0.10 ± 0.01	Cyclo 6	0.09 ± 0.005	0.01 ± 0.01
	2.28 ± 0.07			0.51 ± 0.12

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62.

Mmoles of Grignard H Added to the Reaction		Mmoles of Hydrocarbons Recovered from Reaction		Difference
St. Chain	2.97 ± 0.09	St. Chain	1.25 ± 0.03	1.72 ± 0.11
Cyclo 5	2.60 ± 0.07	Cyclo 5	2.44 ± 0.04	0.16 ± 0.11
Cyclo 6	0.18 ± 0.02	Cyclo 6	0.17 ± 0.007	0.01 ± 0.09
	5.75 ± 0.18			1.89 ± 0.31

63.

Mmoles of Grignard L added to the Reaction		Mmoles of Hydrocarbons Recovered from Reaction		Difference
St. Chain	1.50 ± 0.04	St. Chain	1.08 ± 0.03	0.42 ± 0.07
Cyclo 5	1.39 ± 0.03	Cyclo 5	1.31 ± 0.04	0.08 ± 0.07
Cyclo 6	0.11 ± 0.01	Cyclo 6	0.12 ± 0.006	- -
	3.00 ± 0.08			0.05 ± 0.14

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65. Unpublished results of T. L. Wiesemann and D. P. Campbell.

66.

Mmoles of Grignard K Added to the Reaction		Mmoles of Hydrocarbon Recovered from Reaction		Difference
St. Chain	1.20 ± 0.03	St. Chain	0.26 ± 0.007	0.94 ± 0.037
Cyclo 5	1.20 ± 0.03	Cyclo 5	1.13 ± 0.03	0.07 ± 0.06
Cyclo 6	0.26 ± 0.02	Cyclo 6	0.24 ± 0.007	0.02 ± 0.027
	2.66 ± 0.08			1.03 ± 0.12

67. These experiments were carried out by R. S. Smith.

68. St. Chain refers to the hydrocarbon obtained by hydrolysis of 2,2-dimethyl-5-hexenylmagnesium chloride; Cyclo 5 refers to the hydrocarbon obtained by hydrolysis of 3,3-dimethylcyclopentylmethylmagnesium chloride; Cyclo-5-olefin refers to the hydrocarbon obtained when Cyclo 5 undergoes β-hydrogen reduction of a ketone; Ace refers to acetone; IPA refers to isopropyl alcohol; 1,2-Add refers to 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol.

69.

Mmoles of Grignard M Added to the Reaction		Mmoles of Hydrocarbons and Other Products Recovered		Difference
St. Chain	1.4 ± 0.04	St. Chain	0.04 ± 0.001	1.0 ± 0.05
Cyclo 5	1.4 ± 0.04	Cyclo 5	0.29 ± 0.01	1.11 ± 0.05
	2.8 ± 0.08			
		Cyclo-5-olefin	0.16 ± 0.01	
Ace	1.4 ± 0.01	Ace	0.24 ± 0.01	-1.11 ± 0.03
		IPA	0.15 ± 0.01	
		1,2-Add	0.96 ± 0.02	

70.

Mmoles of Grignard N Added to the Reaction		Mmoles of Hydrocarbons Recovered from the Reaction		Difference
St. Chain	2.0 ± 0.1	St. Chain	0.18 ± 0.01	1.82 ± 0.11
Cyclo 5	7.5 ± 0.2	Cyclo 5	0.30 ± 0.01	7.20 ± 0.21
	9.5 ± 0.3			
		Cyclo-5-olefin	7.15 ± 0.10	-7.15 ± 0.10

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72. St. Chain refers to the hydrocarbon obtained by hydrolysis of 5-hexenylmagnesium chloride; Cyclo 5 refers to the hydrocarbon obtained by hydrolysis of cyclopentylmethylmagnesium chloride.

73.

Mmoles of Grignard E Added to the Reaction		Mmoles of Hydrocarbons Recovered from the Reaction		Difference
St. Chain	7.37 ± 0.23	St. Chain	3.2 ± 0.1	4.17 ± 0.38
Cyclo 5	1.48 ± 0.14	Cyclo 5	0.78 ± 0.02	0.70 ± 0.16
	8.85 ± 0.37			4.87 ± 0.54

74.

Mmoles of Grignard J Added to the Reaction		Mmoles of Hydrocarbons Recovered from the Reaction		Difference
St. Chain	2.78 ± 0.07	St. Chain	0.85 ± 0.02	1.93 ± 0.09
Cyclo 5	1.47 ± 0.04	Cyclo 5	0.62 ± 0.02	0.85 ± 0.06
Cyclo 6	0.19 ± 0.01	Cyclo 6	0.05 ± 0.002	0.14 ± 0.012
	4.44 ± 0.12			2.92 ± 0.17

75.

Mmoles of Grignard N Added to the Reaction		Mmoles of Hydrocarbons Recovered from the Reaction		Difference
St. Chain	1.0 ± 0.06	St. Chain	0.076 ± 0.003	0.92 ± 0.063
Cyclo 5	3.75 ± 0.01	Cyclo 5	0.44 ± 0.01	3.31 ± 0.11
	4.75 ± 0.16			4.23 ± 0.17

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VITA

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